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A Preliminary Study on Indoor Air Quality for the Development of Risk Assessment Methods for Central Nervous System Disturbances

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Abstract

The present study aimed to identify the air pollutants associated with central nervous system (CNS) disturbances through a survey of indoor air pollutants and manifestation of CNS diseases, and to establish a risk assessment method and risk management measures for CNS disturbances caused by these pollutants. A patient cohort consisting of patients suffering from CNS diseases was selected and a health risk assessment was performed for fine dust ($PM_{2.5}$) and 17 heavy metals/ other elements in the indoor air of the residences of survey subjects. The study results showed statistically significant differences in fine dust concentrations according to the region in which the surveys were conducted.

Keywords: CNS disturbances, PM2.5, risk assessment.

1. Introduction

With increasing concerns over the impact of environmental pollution on the human body, the South Korean government has conducted various studies on this topic and has implemented different policies and to reduce environmental pollution. However, public perception on this subject, which is related to public trust gained through communicating and providing comprehensive, scientific, and quantitative information on the effects of environmental pollution, is still very negative. A health risk assessment method can serve as a scientific and rational methodology to satisfy the uncertain environmental issues and social and cultural demands (USEPA, 1992).

Air pollution is a major environmental pollution issue; it poses a major threat to the health and welfare of citizens of emerging economies, and indoor and outdoor air pollution levels in developing countries have reached alarming levels. The main air pollutants are sulfur oxides (SOx), nitrogen oxides (NOx), carbon monoxide (CO), suspended particulate matter (SPMs), and hydrocarbons (HCs). Industries, power plants, and automobiles emit countless outdoor pollutants, while the sources of indoor air pollution are in-home combustion activities and the inflow of outdoor pollutants. Some studies have reported that high concentrations of SPM, NOx, and HC are associated with an increased prevalence of cardiovascular diseases and respiratory diseases such as tuberculosis and asthma. This form of air pollution is not only a public health threat, but can also result in reduced visibility and economic losses by causing damage to buildings, materials, and machinery, in addition to its negative effects on plants and animals (Hopke, 1998; Sharma & Patil, 1992, 1994; Sharma, 2007).

Korea has recently experienced an increase in the levels of fine dust particles because of an increase in the number of automobiles that emit such particles, as well as the hazardous air pollutants originating from China's industrialization and yellow sand phenomenon. This phenomenon has emerged as a social environmental issue related to deterioration of public health. Concurrently, studies on fine dust concentrations and their health impact have also emerged as a social environmental issue. The majority of studies on the association between fine dust and health have focused on acute exposure via short-term assessments of health changes, including changes in the number of deaths and hospitalizations, and changes in pulmonary function in relation to short-term changes in the concentration of fine dust pollution. More than 40 studies have assessed the association between fine particles and respiratory symptoms or pulmonary function (Pope et al., 2000). Most of these studies focused on asthma and asthma exacerbations. One of the best-known studies on the long-term health impact of fine dust exposure was

presented by Pope et al. (2002), which examined the associations between fine dust ($PM_{2.5}$) and cardiac and respiratory diseases. That study conducted a linkage analysis of health impact and air pollution data collected over 16 years from 500,000 people residing in 116 cities throughout the US. The results showed that mortality and health risks associated with lung cancer and heart disease increased proportionately with increasing concentrations of fine dust.

Most of these studies have assessed the health impact of fine dust in air in the outdoor environment. However, modern urbanites spend most of their day in various indoor environments (Yang et al., 2011), especially in their homes. Therefore, studies on the health impact of fine dusts in indoor environments, especially in the home, are equally important. These problems have been recognized in Korea recently. Atmospheric pollution from fine dust in indoor environments can cause nervous system (CNS) disturbances and has a direct impact on brain structure through cellular, molecular, and inflammatory pathways. The strong associations between ischemic stroke and chronic exposure to atmospheric pollutants and between multiple sclerosis and second-hand smoke exposure are examples of the relationship between nervous system disorders and air pollution. Accordingly, the present study is a part of an exposure assessment study that aims to identify environmental risk factors in indoor air. The study forms part of the Korea Ministry of Environment's environmental health research and development project cohort study that was started in 2014 to examine the association between manifestations of CNS disorders and environmental air pollutants and to identify CNS disturbance-causing air pollutants.

In the first year of the study, fine dust and heavy metal data from particulate and gaseous air pollutant surveys were used to assess the subjects' health risk levels from exposure to home indoor air pollution. The study thus aimed to provide the basic data for identification of potential indoor air environmental risk factors that may cause CNS disorders, and to determine the limits of detection.

2. Methods

2.1. Subject Groups

The subjects in the present study were divided into 4 major groups. Namdong Industrial Complex in Incheon, an industrial zone with severe atmospheric and indoor air pollution, and Seoul, the capital of Korea and its biggest city, were selected as cohort areas. Ganghwa region, known to have much cleaner air than other regions, was selected as the control area. Moreover, in order to conduct a more aggressive study for identification of the association between air pollutants and CNS, a patient cohort consisting of patients diagnosed with CNS-related disorders from Seoul Samsung Medical Center was selected. The cohorts were established in May 2014 and have subsequently been expanded.

In the present study, at least 10 subjects were selected from each cohort (Incheon Namdong Industrial Complex cohort: n = 13, Seoul cohort: n = 10, patient cohort: n = 12, Ganghwa cohort: n = 10) and surveys were conducted on the concentrations of hazardous pollutants in the air in these subjects' residences.

2.2. Surveyed Pollutants and Survey Period

In order to identify the types of hazardous environmental pollutants involved in the manifestation of CNS disorders, surveys were conducted on particulate matter PM_{10} and $PM_{2.5}$, 16 heavy metal and other elements (Ti, V, Cr, Mn, Ni, Cu, Zn, Sr, Mo, Cd, Sn, Sb, Pb), 10 aldehydes (formaldehyde, acetaldehyde, acrolein, propionldehyde, crotonaldehyde, butyrldehyde, benzaldehyde, iso-valeraldehyde, valeraldehyde), 17 total volatile organic compounds (TVOCs) and individual VOCs (dichloromethane, methylethylketone, isobutylketone, chloroform, 1,2-dichloroethane, methyl isobutylketone, benzene, carbon tetrachloride, trichloroethylene, n-butylacetate, toluene, butylbenzene, m.p-xylene, strene, o-xylene, aniline), and 11 organophosphate herbicides and pyrethroid pesticides (dichlorvos, chloropyrifos, diazinon, malathion, parathion, smithion, cinerin I, jasmolin I, degraded pyrethrin I, cinerin II, jasmolin II). A health risk assessment was performed for the levels $PM_{2.5}$ and the 17 heavy metal and other elements. The samples were collected from the Seoul and Ganghwa cohorts in the fall (September through November 2014) and winter (December 2014 through February 2015) months, and the collected samples were analyzed for each facility. For the Incheon and patient cohorts, samples were collected and analyzed during the winter (December 2014 through February 2015) months in each facility. Fine dust samples were collected over a continuous 8-h period via a Mini-Volume Air Sampler (Model 4.1 Airmetrics Co., USA) with a flow rate of 2–7 L/min, using GF/C (Cat NO. 1822047, Whatman) filter paper with pore size of 1.2 μm and diameter of 47 mm.

Filter papers that had collected heavy metal samples were pretreated using a microwave system (ETHOS EASY, MILESTONE, Italy), in accordance with EPA Method 3051A. Then, 10 μg/mL of standard material (Cat No. ICP-MS-CAL2-1, AccuTrace™ Reference Standard, USA) was used to analyze the concentration of the heavy metals with an inductively coupled plasma mass spectrometer (iCAP Q, ThermoElemental, USA).

Table 1. Pretreatment conditions of the samples

Category	step 1	→	step 2	→	step 3
Time (min)	0		10		20
Temperature (℃)	25	18 ℃/min	180	Maintain	180
Pressure (kW)	0	0.17 kW/min	1.7	Maintain	1.7

2.3 Health Risk Assessment

Three rules had to be established before conducting the health risk assessment. First, the health issues caused by the pollutants, which are generally identified by hazard identification that may involve grouping of pollutants, were established. Second, the surveys had to aim to determine the amount of exposure in terms of the levels of pollutants inhaled by a person. Third, the relationship of health issues associated with levels of other pollutants had to be established. The risk (R_i) of health problems in the exposed population was determined by uniformly linking these data, calculated using the equation below:

$$R_i = dose \times toxicity \tag{1}$$

The dose is defined as the amount of substance that can interfere with the metabolic process by penetrating the outer layer of the tissues, while the potential dose represents the amount of substance inhaled (USEPA, 2002). The potential dose can be calculated by using a function equation of the potential average daily dose (ADD_{pot}). In the present study, ADD_{pot} was dependent on the inhalation rate and concentration of pollutants ($PM_{2.5}$ or the 17 heavy metal and other elements) and was adjusted for body weight as a function of time, as per the equation shown below:

$$ADD_{pot} = \frac{(C \times IR \times ED)}{(BW \times AT)} \tag{2}$$

where C represents the concentration of the pollutant (μg/m^3); IR represents respiratory rate (m^3/day); ED represents the exposure duration (day); BW represents body weight (kg); and AT represents the average number of days of exposure (day). *Toxicity* in Equation (1) is a reference value of the capability to cause harm to living tissues. Substances with high toxicity can cause tissue damage when even a small amount is introduced, whereas substances with low toxicity may not cause tissue damage even if large amounts are introduced. Therefore, the definition of toxicity is dependent on the dose of the toxic substance, the inflow pathway of the substance (inhalation in the present study), the concentration distribution of the substance, the form and seriousness of the health impact, and the time required for the health impact to occur. The toxicity value related to health impact when exposure is through inhalation can be assessed using one of two terms: the unit risk (UR) or the inhalation slop factor (ISF). ISF can be derived as shown below:

$$ISF = \frac{UR \times BW}{inhalation\ rate} \tag{3}$$

The ISF represents a conservative estimate of the probability of increased health impact relative to exposure time to a unit of pollutant. Therefore, the equation for risk (Equation 1) can be also expressed as shown below (Zanobetti et al., 2000):

$$R_i = ADD_{pot} \times ISF \tag{4}$$

If exposure to a specific carcinogen continues, equation (4) above provides the estimated probability of lung cancer occurring over a lifetime. Therefore, to explain this exposure time, average time (AT) must be revised to the average life span. Consequently, Equation (2) can be converted to determine the potential lifetime average daily dose ($LADD_{pot}$) for cancer-related health risk assessments, as shown below:

$$LADD_{pot} = \frac{(C \times IR \times ED)}{(BW \times lifetime)} \tag{5}$$

Accordingly, the risk of cancer (R_{ic}) is as follows:

$$R_{ic} = LADD_{pot} \times ISF = \frac{(C \times ED \times UR)}{lifetime} \tag{6}$$

In general, the risk of cancer can vary according to the specific stage of life. In other words, the risk of cancer from early exposure is typically higher than the risk from similar exposure occurring later in life (US EPA, 1997). Specific differences in cancer risk from exposure to chemicals in air can be attributed to the amount of exposure, and the intake (inhalation rate), metabolism, and absorption rates. Therefore, it is necessary to include the exposure levels measured at all stages of life (infancy, childhood, and adulthood) in accordance with US Environmental Protection Agency's (EPA) Child-Specific Exposure Factors Handbook (2002). Accordingly, the present study calculated cancer risks at these stages using age-dependent adjustment factors (ADAFs). For example, the ADAF for subjects under 2 years of age was adjusted to 10 and that for subjects aged 2 to 15 years was adjusted to 3, while no adjustment was made for subjects ≥ 16 years.

The health risk assessment in the present study was performed according to the 4-step procedure as proposed by Covello and Merkhofer (1993) and the National Research Council (NRC, 1983). The procedures employed in each step are as follows:

Steps 1 and 2 involved risk identification and dose-response assessment. In Table 1, data surveys of integrated risk information system (IRIS) within the Toxicology Occupational Medicine and Environmental Series (TOMES) Plus were used to present reference values of the heavy metals detected in facilities and regions surveyed in the present study. These values were derived from cancer potency classification, UR, and NOAEL (no observed adverse effect levels) or LOAEL (low observed adverse effect levels) values according to weighting of evidence for cancer; this is a US EPA classification system. Moreover, the extrapolation method, route of exposure, and form of cancer were presented using the same method. Of the surveyed data, only heavy metals and other elements with a known UR were selected as pollutants to be assessed for health risk assessment in the present study. Hence, cancer-related health risk assessment based was performed on exposure to those heavy metals/ other elements. Cases involving $PM_{2.5}$ were presented as risks associated with emergency room visits (ERV) for asthma. Numerous studies have evaluated the health impact of fine dust particles ($PM_{2.5}$) in relation to asthma, but very few have assessed the risk associated with ERV for asthma in pediatric patients (≤ 18 years) (Norris et al. 1999; Tolbert et al. 2000). The present study assessed the health risk resulting from fine dust exposure as the risk of ERV due to manifestation of pediatric asthma. The UR used for the ERV from fine dust exposure was 0.01% or 1% per unit increase ($\mu g/m^3$), which was the result reported by Levy et al. (2002).

For step 3, which consisted of exposure assessments, the prerequisites were calculation of exposure amount and construction of exposure scenarios using exposure coefficients (body weight, respiratory rate, life expectancy, and exposure frequency) that reflect the various characteristics of the exposed population. In the present study, the exposure amount was measured and exposure scenarios were constructed using the exposure coefficients of each study subject according to domestic and foreign data (Table 2). The present study used a mean body weight of 60 kg, based on the mean values of 68.8 kg and 56.0 kg for Korean men and women, respectively, as suggested by the Korean Ministry of Environment's exposure assessment guideline (2001). Moreover, a log-normal distribution of body weight was assumed based on data from the Korean Ministry of Environment and previous studies (MOE 2001; Roy 1994). The US EPA stipulates a respiratory rate of 20 m^3/day for health risk assessments. Given the lack of survey data related to the respiratory rate in Korea, the present study used the average respiratory rate established by the US EPA. Consequently, respiratory rate exposure coefficients were set as 20 m^3/day for central tendency exposure (CTE) and 30 m^3/day for reasonable maximum exposure (RME). In addition, the distribution of respiratory rate was assumed to be triangular, and the respiratory rates from adequate activity, resting activity, and light activity, as presented in the study by Adams (1993), were used as the maximum, minimum, and optimal values, respectively, of the triangular distribution. Statistics Korea publishes average life span data as residual life expectancy (RLE) for each age group. The RLE represents the surviving age, calculated as the number of years a person who has reached a certain age is expected to survive. Thus, the average RLE of newborns can be defined as average life expectancy. Although various research institutes publish data on life span and RLE, most cite data from Statistics Korea (MOE 2001). Thus, the present study used the life expectancies presented by Statistics Korea in 2013 (78.5 years for men and 85.1 years for women) as a basis for choosing 80 years as the life expectancy exposure coefficient value. Moreover, singular values were used for the probability distribution of life expectancy. Exposure duration was assumed as being from birth to death, and exposure was assumed to occur on an average of 300–330 days per year. The exposure duration was assumed to have a log-normal distribution with a mean of 300 days and standard deviation of 19 days. Approximately 13 h was assumed as the CTE exposure frequency of indoor dwelling time, which was based on the mean home dwelling time (men, 742.0 min; women, 864.6 min) from published results on daily activity details, activity locations, and time spent in each location, surveyed from 838 adults throughout Korea as a part of Korean Ministry of Environment's exposure assessment guideline (2001), while RME exposure frequency was assumed to be 23 h, which was the mean value of the top 95% confidence

interval values (men: 1322.2 min, women: 1440.0 min). Exposure frequency was assumed to follow a normal distribution. For exposure concentration, the arithmetic mean and standard deviation were calculated for each pollutant surveyed in the indoor air of the residences of the study subjects. The arithmetic mean of the CTE concentration was used, while the arithmetic mean plus 3 × standard deviations was used for the RME concentration (so as to use the top 99.7% value of the overall concentration range). The concentration distribution of the pollutants was assumed to follow a normal distribution.

Risk determination, the final step, was performed in two major steps. The risk of ERV due to fine dust exposure was assessed for children (≤ 18 years), as presented in the risk identification step. For heavy metals, the average daily dose (calculated using the equations given earlier) was used to calculate the excess cancer risk of each pollutant.

2.4 Uncertainty Analysis

For the health risk assessment, to resolve the uncertainty and variability in all input variables occurring because of the input of single data, statistical probability distribution was substituted for each variable to calculate the probabilistic risk. Moreover, to express the influence of such uncertainty and variability, the 5% and 95% values were used to present the uncertainty interval (UI). Further, the 95% value was divided by the 5% value to obtain the uncertainty coefficient. The uncertainty analysis was performed using Crystal Ball 2000 (Decisioneeting Inc.), in which 10,000 iterations were performed according to the Latin Hypercube approach (Iman and Conover, 1980).

Table 2. Quantitative estimate of carcinogenic and non-carcinogenic risk from inhalational pollutant exposure

Heavy metal	Carcinogenic class / non-carcinogenic health effect	UR $(\mu g/m^3)^{-1}$	Extrapolation method	Study type	Tumor type	RfC (mg/m^3)	NOAEL /LOAEL (mg/m^3)	UF	MF	Reference
Cr^{6+}	A/Lactate dehydrogenase in bronchoalveolar lavage fluid	1.2×10^{-2}	Multistage, extra risk	Occupational exposure/Rat subchronic study	Lung cancer	1×10^{-4}	0.034	300	1	Mancuso, 1975. Glaser et al., 1990. Malsch et al., 1994.
Ni (refinery dust)	A	2.4×10^{-4}	Additive and multiplicative	refinery workers	Lung cancer	-	-	-	-	Enterline and Marsh, 1982.
Cd	B1	1.8×10^{-3}	Two stage; only first affected by exposure; extra risk	Exposure in the workplace	Lung, trachea, and bronchus cancer	-	-	-	-	Thun et al., 1985
Mn	D/Impairment of neuro-behavioral function	-	-			5×10^{-5}	0.15	1000	1	Roels et al., 1987.

UR, unit risk; RfC, reference concentration; NOAEL, no observed adverse effect levels; LOAEL, low observed adverse effect levels; UF, uncertainty factor; MF; modify factor; A, human carcinogens; B2, probable human carcinogen; C, possible human carcinogen; D, not classifiable as human carcinogen.

Table 3. Fixed assumptions and probability densities used as inputs for risk estimates

Parameter		Unit	CTE	RME	Distribution type	Distribution parameters	Source
Body weight	Adult	kg	60	60	log-normal	mean: 60	MOE, 2001.
						sd: 5	Judgment.
	Child	kg	36	36	log-normal	mean: 36	USEPA, 1989.
						sd: 3	Judgment.
Exposure duration		day/year	300	330	log-normal	mean: 300	Judgment.
						sd: 19	
Exposure frequency		(h/24 h)	0.54	0.96	normal	mean: 0.54	Judgment.
						sd: 0.15	MOE, 2001.
Lifetime		year	80	80	point	80	MOE, 2001.
Inhalation		m^3/day	20	30	triangle	max: 46.3	MOE, 2001.
						min: 13.0	Adams, 1993.
						likeliest: 34.8	Judgment.

sd, standard deviation.

3. Results

3.1 Concentration Distribution Characteristics of Fine Dust and Heavy Metals

Table 3 shows the mean concentrations of fine dust and carcinogenic heavy metals in residential indoor air of the cohorts and control subjects surveyed. Statistically significant differences were found among concentrations of fine dust in the survey regions. The highest concentration of fine dust was noted in the patient cohort (21.4 ± 11.6 μg/m^3). No statistically significant differences were found in the mean concentrations between the cohorts and the control group; the cohorts and control values were 23.4 ± 12.5 and 24.1 ± 11.6, respectively. With respect to heavy metals, Cd were found to exist in concentrations below the limit of detection in the residential indoor air of each cohort group and the control group. On the other hand, Cr was detected in the residential indoor air of all cohort groups surveyed, but was below the limit of detection in 3 of the 10 control group residential spaces during the first sample collection. The Seoul cohort showed the highest concentration (804.4 ± 195.0 ng/m^3). The mean Cr concentrations in cohort and control group residences were 642.8 ± 280.2 ng/m^3 and 722.4 ± 220.4 ng/m^3, respectively, but this difference was not statistically significant. Among the cohort groups, Ni was detected in 20 residential spaces in the Seoul cohort and in 7 out of 10 residential spaces in the control group. In the Seoul and patient cohorts, Ni was below the limit of detection in all residential spaces surveyed. The mean Ni concentrations in the cohort and control groups were 24.1 ± 9.4 ng/m^3 and 21.2 ± 2.5 ng/m^3, respectively, with no statistically significant difference.

Table 4. The mean concentrations of fine dust ($PM_{2.5}$) and carcinogenic heavy metals from residential indoor air of the cohorts and control subjects

Pollutant	**Cohort/Control**	**Region**	***n***	**mean**	**sd**	**p-value**[a]	**p-value**[b]
$PM_{2.5}$ (μg/m^3)	Cohort	Incheon Namdong	13	27.3	12.3	> 0.05	< 0.05
		Seoul	20	16.1	9.6		
		Patient	12	31.4	11.0		
	Control	Ganghwa	20	24.1	11.6		
Cr (ng/m^3)	Cohort	Incheon Namdong	10	426.7	288.0	>0.05	< 0.05
		Seoul	20	804.4	195.0		
		Patient	12	535.7	233.2		
	Control	Ganghwa	7	722.4	220.4		

Ni (ng/m^3)	Cohort	Incheon Namdong	–	–	–
		Seoul	20	24.1	9.4
		Patient	–	–	–
	Control	Ganghwa	7	21.2	2.5
Cd (ng/m^3)	Cohort	Incheon Namdong	–	–	–
		Seoul	–	–	–
		Patient	–	–	–
	Control	Ganghwa	–	–	–

[a] Student's *t*-test; [b] ANOVA. sd, standard deviation.

3.2 ERV Risk Assessment

In our assessment of the increase in ERV for asthma exacerbations in children, the patient cohort showed the highest increase in ERV under the CTE and RME exposure situations, with values of 14.0% and 56.0%, respectively. In contrast, the Seoul cohort showed the lowest increase in risk under the CTE and RME exposure situations, with values of 1.5% and 16.1%, respectively. As shown above, under the CTE exposure situation, the control group and all cohorts except the Seoul cohort showed ≥ 10% increase in risk of ERV for children with asthma according to the unit increase in fine dust; this demonstrated that concentrations of fine dust in these regions were strongly associated with respiratory symptoms, or asthma, in these children. Moreover, the Seoul cohort, which showed the lowest increase in risk, had a 7% increase in risk under the CTE exposure situation, but under the RME exposure situation, the increased risk was ≥ 30%. Thus, we believe that the cohort groups in this region are also susceptible to fine dust-related increases in the incidence of respiratory diseases among children.

UI was wider for the Incheon Namdong and patient cohorts (21.4% and 21.0%, respectively), whereas the Seoul cohort showed the narrowest UI (14.6%). The patient cohort had the lowest uncertainty coefficient (5.5), indicating that it had the lowest uncertainty, while the Seoul cohort had the highest uncertainty coefficient (10.7); this was still a low uncertainty coefficient. These findings indirectly suggest that the uncertainty was low in the calculated results for the rate of increase in the risk of ERV for pediatric asthma exacerbations due to exposure to fine dust in the indoor air of residential environments surveyed.

Table 5. Asthma risk

Category	Region	Fixed point		Monte Carlo		
		CTE (%)	RME (%)	Uncertainty Interval (%)		Uncertainty coefficient
				5%	95%	
Cohort	Incheon Namdong	12.1	55.7	3.1	24.5	7.9
	Seoul	7.0	39.0	1.5	16.1	10.7
	Patient	14.0	56.0	4.7	25.7	5.5
Control	Ganghwa	11.0	51.1	2.5	21.9	8.8

3.3 Cancer Risk Assessment

Table 5 shows the results of point estimate analysis for excess cancer risk according to exposure to Cr^{6+}, a carcinogenic heavy metal that contains $PM_{2.5}$, in the residential indoor air of the cohort and control groups. It also displays the results of the uncertainty analysis and the uncertainty coefficients calculated according to the Monte Carlo system. Total Cr was assessed by converting the concentration of Cr^{6+} to a total Cr concentration. Kang et al. (2009) reported that Cr^{6+} comprised 0.7–2.4% of the total Cr content in industrial complexes in Korea, lower than the 3–8% Cr^{6+} content found in the air of cities in overseas countries (Scorecard, 2007). Given that the objective of the present study was to assess health impacts and to provide basic data needed to establish management measures, we used a value of 2.4%, the highest content reported by Kang et al. The Seoul cohort showed the highest excess cancer risk (1.0×10^{-4}) under the CTE exposure situation. The other three groups also showed high excess cancer rates, exceeding 1.0×10^{-5}. The uncertainty coefficient value for the Seoul and Ganghwa cohort groups did not

exceed 5, while the patient cohort group also showed a low uncertainty coefficient value (7.2), indicating low uncertainty in the calculated results. However, the Incheon Namdong cohort's uncertainty coefficient was 13.4. These findings suggest that efforts should be taken in future surveys to minimize the uncertainty of the Incheon Namdong cohort.

Table 6. Cancer risk

Category	Region	Fixed point		Monte Carlo		
		CTE (%)	RME (%)	Uncertainty Interval (%)		Uncertainty coefficient
				5%	95%	
Cohort	Incheon Namdong	5.5E-5	3.2E-4	9.7E-6	1.3E-4	13.4
	Seoul	1.0E-4	2.5E-4	4.5E-5	1.7E-4	3.8
	Patient	6.8E-5	2.6E-4	1.8E-5	1.3E-4	7.2
Control	Ganghwa	9.2E-5	2.7E-4	3.5E-5	1.6E-4	4.6

4. Discussion

The present study is a part of the Korean Ministry of Environment's environmental health research and development project cohort study. The study aims to identify CNS-causing air pollutants through investigation of the association between indoor air pollutants and occurrence of CNS disorders and to establish risk assessment methods for causes of CNS disturbance and to develop risk management measures. Worldwide, there is currently a paucity of data on the types and concentrations of indoor air pollutants that contribute to CNS disorders. Moreover, risk assessment methods for potential manifestations of CNS disorders have not yet been established. To this end, the present study surveyed various hazardous indoor air pollutants such as particulate matter, heavy metals, aldehydes, TVOCs and individual VOCs, and organophosphate herbicides and pyrethroid pesticides to identify hazardous indoor air pollutants associated with manifestations of CNS disorders. The study also performed health risk assessments related to fine dust ($PM_{2.5}$) and heavy metals in order to provide basic data needed to establish methods for assessing the risk of CNS disorders.

Studies designs used to assess the health impact of dust exposure include epidemiological studies with long-term follow-up to identify causal relationships between dust exposure and disease, and toxicological studies using animal models. However, these methods are limited as they require long-term follow-up. Moreover, use of a short-term scientific health risk assessment method to establish environmental public health policies for Korea and abroad is difficult because of the absence of toxicity values. Hence, the present study used a method for assessing pediatric asthma-related ERV risk due to fine dust exposure and presented data on calculated ERV risk based on the survey results on fine dust ($PM_{2.5}$). The assessment method used in the present study included a specific age group and involved asthma, a typical condition that occurs with exposure to fine dust, and is thus somewhat different from health risk assessment methods involving hazardous chemical pollutants. The present study also took into account the fact that the prevalence of many CNS disorders (especially dementia, Parkinson's disease, and stroke) is higher in certain age groups (i.e.; elderly). CNS-related risk assessment methods should also be conducted on a specific age groups, just as the ERV risk assessment was. This should be considered when establishing future CNS risk assessment methods.

To assess the potential onset of CNS disorders due to long-term exposure to hazardous air pollutants, it would be ideal to determine the accumulated exposure dose from long-term exposure to hazardous pollutants. Thus, it would be ideal to apply the method used to measure accumulated exposure through lifetime average exposure dose as presented by Covello and Merkhofer (1993) and the NRC (1983), and to examine the association between the calculated accumulated exposure dose and CNS disorders. As a prelude to such a study, the present study conducted health risk assessments of heavy metals, well-known carcinogens among all hazardous air pollutants surveyed. The study aimed to provide the basic data needed to assess the associations between CNS disorders and hazardous air pollutants and to establish potential risk assessment methods for the onset of CNS disorders caused by such hazardous air pollutants.

An increase in ERV risk of ≥ 10% under the CTE exposure environment was found in the control group and in two of the cohorts (not in the Seoul cohort), indicating that the risk of respiratory diseases caused by fine dust in these regions was high. Even the Seoul cohort, that had a relatively lower risk under the CTE exposure environment, had

a ≥ 30% increase in risk under the RME exposure environment. These findings indicate that continued long-term surveys and monitoring are needed for $PM_{2.5}$ found in the residential indoor air where the cohorts and control group reside, and that $PM_{2.5}$ is a major air pollutant that must be taken into account in future assessments of its association with CNS disorders.

The 16 heavy metals/ other elements (Ti, V, Cr, Mn, Ni, Cu, Zn, Sr, Mo, Cd, Sn, Sb, Pb) that were detected in the component analysis of $PM_{2.5}$ collected for the study were quantified. Cr^{6+}, Ni, and Cd had a UR by inhalation in IRIS and were thus selected for further study. Moreover, since Cr^{6+} was detected in all 3 cohorts and in the control group, it was chosen as the only heavy metal used to calculate the excess cancer risk. In the status survey, Cd were found at level below the limit of detection in the cohort and control groups; they were determined to be not significantly involved in the manifestation of CNS disorders. In addition, Ni was detected in only the control group and the Seoul cohort; it was thus also determined to be not significantly involved in the manifestation of CNS disorders. On the other hand, Cr^{6+} showed a high excess cancer risk that exceeded 10^{-5} in all cohorts and in the control group. It was thus determined to be a hazardous air pollutant that requires continued long-term surveys and monitoring in indoor air, just like $PM_{2.5}$, but more so than other heavy metals. The present study used total Cr concentration as the basis and used the results from preceding studies to convert this value to Cr^{6+} concentration for the health risk assessment. However, the uncertainty involved in the process of converting Cr^{6+} concentrations using the results from precedent studies can increase the uncertainty of the final values. To increase the reliability of the final study results, reducing such uncertainty is important. In other words, excess cancer risk associated with exposure to Cr^{6+} was high in all cohort and control groups, and for the ultimate goal of this study (to derive reliable results through linkage analysis with potential manifestation of CNS disorders) it would be ideal to take into account highly reliable pollutant exposure concentration values and to transition from a Cr concentration study to a selective Cr^{6+} concentration study.

The process of assessing the health impacts of exposure to hazardous pollutants includes high levels of uncertainty and variability. Identification of this uncertainty and variability is important in health impact assessments. The US EPA (1997) recommends the Monte Carlo analysis as a useful statistical technique to identify such uncertainty and variability. Uncertainties that can occur can be divided into three major categories; scenario uncertainty, parameter uncertainty, and model uncertainty. Scenario uncertainty refers to the uncertainty that arises from missing information or incomplete data in fully defining the exposure or dose. Parameter uncertainty refers to parameter-related uncertainty. Mode uncertainty refers to uncertainty that arises from insufficiency in scientific theories needed for causal inference (US EPA, 1997). In exposure assessments, uncertainty and variability are always inherent in the exposure variables. Variability is caused by differences in the respiratory rate, body weight, exposure frequency, and exposure duration, and also appears from differences in hazard pollutant concentration and responses within the human body, such as genetic differences in terms of the immunity of the receptor to chemicals. Although such variability can be better distinguished with accumulation of more data, it cannot be eliminated or reduced. Uncertainty is introduced by specific variables, the probability distribution model, and the perception of the model (e.g., the mean and standard deviation of log-normal distribution), as well as insufficient hazard pollutant concentration data and low precision. However, unlike variability, it can be reduced by accumulating more data. Uncertainty and variability of the data are added as probability density functions in the Monte Carlo analysis and are reflected in the results, while uncertainty of exposure variables makes it possible for quantitative interpretation of the risk results, such as over- or under-estimation. Generally, for consideration of uncertainty in concentrations linked to regional characteristics, along with sample collection and analysis, the 95% upper confidence level is recommended. Moreover, by repeatedly performing probabilistic analyses on the 95% upper confidence level, mean, and 95% lower confidence level, three risk distributions can be obtained. Therefore, the confidence interval of risk estimate according to uncertainty in concentrations can be calculated (Ashok 1997; US EPA, 1882). Unlike the Monte Carlo analysis, point estimate analysis cannot express the uncertainty and variability of the input variables. However, CTE and RME risks can be calculated for expression of variability (US EPA, 1992).

In an effort to minimize uncertainties that can occur in future studies, the present study calculated the risks associated with CTE and RME in the point estimate analysis, while in the probability analysis the Monte Carlo system was applied in presenting 95% lower confidence level and 95% upper confidence level values, along with uncertainty coefficients. The uncertainty coefficients for the increase in ERV risk from exposure to $PM_{2.5}$ showed low values (range: 5.5–10.7) while excess cancer risk from exposure to Cr^{6+} also showed low values (range: 3.8–13.4). With respect to cases that are determined to require further minimization of uncertainty (that can occur while proceeding with this epidemiological study) to increase the reliability of the results derived, the Seoul cohort for ERV and Incheon Namdong cohort for Cr^{6+} showed uncertainty coefficients that exceeded 10. Therefore, efforts

should be taken to minimize the uncertainties in these two cohorts, more so than in the other cohorts or in the control group.

In conclusion, the present study aimed to identify air pollutants that cause CNS disturbances by surveying the association between indoor air pollutants and manifestation of CNS disorders, and to establish a CNS disturbance-causing risk assessment method and risk management measures for these pollutants. To achieve these objectives, the present study began in May 2014 and will span 5 years. The study also aimed to provide the basic data needed for an appropriate methodology to assess risks related to CNS disorders by presenting assessment methods for excess cancer risk from exposure to hazardous pollutants, increased ERV risk, uncertainty analysis, and methods for applying the derived results by deriving highly reliable measures. In the present study, the total Cr concentration was used, calculated from the Cr^{6+} concentration based on results from previous studies on health risk assessments. However, uncertainty can arise during the process of converting Cr^{6+} concentrations, increasing the degree of uncertainty in the final results. Therefore, to increase the reliability of the study results, it would be ideal to convert future study methods from a total Cr concentration survey to a selective Cr^{6+} concentration survey.

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Competing Interests Statement

The authors declare that they have no competing or potential conflicts of interest.

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