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Original Article

장기-저농도로 10년 이상 노출된 작업환경측정 근로자들의 간-담도계, 신장, 혈액-순환기 기능 지표들의 유의한 변화

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Significant Variation in the Indicators for Liver-biliary, Renal, and Blood-circulatory Function among Workers with Long-Term Low-Level Exposure to Chemicals over 10 Years or More Working at Environment Monitoring

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ABSTRACT

This study aims to evaluate the body burden of workers in work environment monitoring with long-term (more than 10 years) low-level exposure to various chemicals. The subject workers were a total of 26 men and women who performed work environment monitoring tasks as the exposure group and those who did not perform such work among their co-workers at the same company as the control group. The exposure to various chemicals was examined through liver and biliary function with 12 indicators, renal function with four indicators, and blood and circulatory function with 16 indicators. The exposure group had significant variation compared to the control group for the indicators of serum GPT, ϒ-GTP, and total bilirubin for liver and biliary function, indicators of creatinine and uric acid for renal function, and indicators for neutral fats, red blood cell count, platelet count, hemoglobin, and hematocrit for blood and circulatory function. Long-term exposure to various chemicals at low levels might affect the variation of the indicators for liver and biliary, renal and blood, and circulatory function of workers. If low-concentration exposure to different hazardous chemicals occurs over a long period of more than 10 years, it could be a harmful factor to the health of workers who measure the working environment.

본 연구는 저농도로 장기간(10년 이상) 작업장에서 사용하는 다양한 화학물질에 노출된 작업환경측정 근로자의 체내 부하를 평가하는 것이다. 노출군은 작업환경측정 업무를 수행하는 남자 및 여자 근로자 16명이며, 대조군은 동일 회사 동료 중 작업환경측정을 수행하지 않는 근로자 10명으로서 총 26명을 연구 대상으로 하였다. 다양한 화학물질 노출에 대한 체내 지표는 간-담도 기능에 12개 지표, 신기능에 4개 지표, 혈액 및 순환기능에 16개 지표를 사용하였다. 간-담도 기능에서는 혈청 GPT, ϒ-GTP, 총 빌리루빈, 신기능에서는 크레아티닌과 요산, 혈액 및 순환기능에서는 중성지방, 적혈구수, 혈소판수, 헤모글로빈과 헤마토크릿 지표에서 노출군과 대조군이 유의한 차이를 나타내었다. 다양한 화학물질에 10년 이상 장기간 저농도로 노출되는 작업환경측정 근로자의 경우 간-담도 기능, 신기능 및 혈액 및 순환 기능 지표에 유의한 변화가 나타날 수 있다. 서로 다른 유해 화학 물질에 10년이상 장기간에 걸쳐 저농도 노출이 발생하더라도 작업환경측정 작업근로자들의 건강에 유해요인으로 작용할 수 있다.

Key words: chemicals, long-term low-level, exposure, liver, renal function

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I. Introduction

It has been thought that exposure to various substances below the exposure limit such as below the exposure limit for TLV-TWA or NOAEL (no observed adverse effect level) would be safe in general view. But exposure to these various chemicals below the exposure limits might be harmful (Kortenkamp et al., 2007). And also health hazards might be occurred when additive, potentiation, and antagonism for chemical metabolism on low concentrations of various chemicals (Ikeda, 1988).

On the exposure status, some workers of specific occupation were continuously exposed to various chemicals at comparatively low-level below the exposure limit. These exposure pattern have been reported with constant interest from the past in South Korea. Especially in workers engaged in laboratory or measuring the work environment, who are exposed to various substances at low level during their work. And they also have been exposed to various types of organic solvents, heavy metals, or other chemicals. Their exposure showed health disorders, for example, various nervous disorders in MCS patient of general people and reproductive disfunction in laboratory workers, neuropathy in agricultural workers (Axelsson et al., 1984; Prasher et al., 2002; Winder, 2002; Morata, 2003; Hojo et al., 2008; Snijder et al., 2012; Campo et al., 2013; Pose-Juan et al., 2016; Park et al., 2017; MOEL, 2021; Zhu et al., 2023; Chen et al., 2024).

In the case of workers on the work environment monitoring in Korea, hazardous factors are measured and analyzed using various measuring devices in the workplace. Their exposure patterns had not exposed to daily regularly same kinds of chemicals but usually exposed to daily different various chemicals. Exposure term were probably daily 2-3 hours which is comparatively lower than that of employees in their company (Phee and Hwang, 2003).

A little report has been available from exposure to various chemicals at long-term low-level about the focus of indicators related in hematology and clinical chemistry. Therefore, this study analyzes the variation of the indicators for workers on the work environment monitoring and examines the health effect.

II. Method

1. Subjected workers of exposed and control group

This study was conducted on employees who belong to one regional industrial health center of the association in Korea. The subjected workers were engaged more than 10 years in work environment monitoring who received annually work health checkups from 2016 to 2020. The subjected workers were constituted exposed and control group. Exposed group was workers for work environment measurement and worker's health checkup for potentially exposed to the various chemicals in the workshop. It is also exposed to high noise and dust in the workshop. Control group was the employee in the same center of exposed group. The control was mainly office workers who had not exposed directly various chemicals in workshops. Among the total 26 subjected workers of this study, 16 workers were in the exposed group and 10 workers were in the control group.

2. Exposed chemicals and indicators of health evaluation

The chemicals potentially exposed to the exposure group of this study at low level were 84 organic compounds, 22 metals and its compounds, 13 acids and alkalis, and 9 gaseous substances, a total of 128 species as shown in Table 1. Among them, special management materials by Industrial Safety and Health Act in Korea were N,N-dimethylacetamide, dimethylformamide, ethylene

Table 1. Multiple chemicals to which the subject workers were exposed

Chemicals (carcinogenicity)

Organic compounds

1 Acetone
2 Acetonitrile
3 Acrylic amid* (1B)
4 Acrylonitrile* (1B)
5 Aniline (2)
6 Benzene*(1A)
7 1-bromopropane* (2)
8 2-bromopropane* (2)
9 1,3-butadiene* (1A)
10 2-butanol
11 2-butoxyethanol (2)
12 2,2-butoxyethethyl acetate (2)
13 Carbon disulfide
14 Chlorobenzene (2)
15 Chloroform (2)
16 Cresol
17 Cyclohexane
18 Cyclohexanol
19 Cyclohexanone (2)
20 1,2-dichloroethene (2)
21 Cyclohexene
22 1,1-dichloro-1-fluoroethane
23 Dichloromethane (2)
24 Diethanolamine (2)
25 Diethyl ether
26 Diethylamine
27 2-diethylamino ethanol
28 Diethylenetriamine
29 Diisobutylketone
30 Dimethylformamide*
31 1,4-dioxane (2)
32 Epichlorohydrin*(1B)
33 1,2-epoxypropane*(1B)
34 2-ethoxyethanol*
35 2-ethoxyethylacetate *
36 Ethanolamine
37 Ethyl acetate
38 Ethyl acrylate (2)
39 Ethylbenzene (2)
40 Ethylene dichloride (1B)*
41 Ethylene glycol
42 Formaldehyde*(1A)
43 Glutaraldehyde
44 Hexamethylene diisocyanate
45 Isoamyl acetate
46 Isobutyl acetate
47 Isobutyl alcohol
48 Isopropyl acetate
49 Isopropyl alcohol
50 Maleic anhydride
51 Methanol
52 2-methoxyethanol*
53 2-methoxyethyl acetate*
54 Methyl acetate
55 Methyl chloride (2)
56 Methyl chloroform
57 Methyl ethyl ketone
58 Methyl isobutyl ketone (2)
59 Methyl n-amyl ketone
60 Methyl n-butyl ketone
61 Methylene diphenyl diisocyanate (2)
62 n-Butanol
63 N-butyl acetate
64 n-heptane
65 n-hexane
66 N-propyl acetate
67 N,N-dimethylacetamide*
68 N,N-dimethylaniline (2)
69 p-dihydroxybenzene (2)
70 Perchloroethylene* (1B)
71 Phenol*
72 Phthalic anhydride
73 Pyridine (2)
74 Stoddard solvent* (1B)
75 Styrene (2)
76 Tetrahydrofuran (2)
77 Toluene
78 Toluene-2,4-diisocyanate (2)
79 Toluene-2,6-diisocyanate (2)
80 Trichloroacetic acid (2)
81 Trichloroethylene* (1A)
82 Triethylamine
83 Vinyl acetate (2)
84 Xylene

Metals and its compounds

1 Aluminum
2 Antimone* (2)
3 Barium
4 Cadmium* (1A)
5 Chromium
6 Chrome hexavalent* (1A)
7 Cobalt
8 Copper
9 Iodine
10 Iron
11 Lead* (1B)
12 Magnesium oxide
13 Manganese
14 Mercury*
15 Nickel* (1A)
16 Silver
17 Tin
18 Titanium dioxide
19 Tungsten
20 Vanadium pentoxide
21 Zinc
22 Zirconium

Acid and Alkali

1 Acetic acid
2 Acrylic acid
3 Formic acid
4 Hydrogen chloride
5 Hydrogen fluoride
6 Hydrogen peroxide (2)
7 Nitric acid
8 Phosphoric acid
9 Potassium cyanide
10 Potassium hydroxide
11 Sodium cyanide
12 Sodium hydroxide
13 Sulfuric acid* (1A)

Gaseous

1 Ammonia
2 Carbon monoxide
3 Chlorine
4 Ethylene oxide* (1A)
5 Hydrogen cyanide
6 Hydrogen sulfide
7 Nitrogen dioxide
8 Nitrogen monoxide
9 Sulfur dioxide

* Special management materials under the Industrial Safety and Health Act in South Korea: Carcinogenic, germ cell mutagenic, and reproductive toxic substances under the Enforcement Regulation, which are marked as special management substances (Korean Law Infromation Center, 2024).

dichloride, 2-methoxyethanol, 2-methoxyethyl acetate, benzene, 1,3-butadiene, 1-bromopropane, 2-bromopropane, stoddard solvent, acrylonitrile, acrylic amide, 2-ethoxyethanol, 2-ethoxyethylacetate, 1,2-epoxypropane, epichlorohydrin, trichloroethylene, perchloroethylene, phenol, formaldehyde for organic compounds, lead, nickel, mercury, antimine, cadmium, chrome hexavalent for metals, sulfuric acid for acids and alkalis, and ethylene oxide for gaseous substances. The special management materials are substances that can cause serious health disorders such as carcinogenic, reproductive cell mutagenic, reproductive toxicity. Carcinogens were classified by GHS classification, e.g., 1A; known to have carcinogenic potential for humans, 1B; presumed human carcinogens, 2; suspected human carcinogens (Table 1). Biological exposure indices for multiple chemical exposure were 12 types of indicators of liver and biliary function, 4 types of renal function and 16 types of blood and circulatory function.

3. Data analysis

Exposed chemicals and health checkup data in the annual work environment measurement results of this study were classified into exposure groups and control groups. The database was established using MS-Excel. The geometric mean (GM), geometric standard deviation (GSD) of the exposed and non-exposed groups were calculated using the established database. IBM SPSS Statistics ver. 25 (IBM Corp., USA) was used for statistical analysis, and t-test was used to compare the mean values of the exposure group and control group to confirm that there was a significant difference in the exposure group.

4. Institutional Review Board

Regarding the entire content of this study, it was implemented after deliberation by the Institutional Review Board of the Catholic University of Busan (CUPIRB-2020-042).

Ⅲ. Results

1. Exposure indices from various chemical exposure

1) Effects for liver and biliary function

For liver and biliary function, the 12 indices (serum GOT, serum GPT, Y-GTP, total protein, albumin, globulin, AG-index, total bilirubin, direct bilirubin, indirect bilirubin, ALP and LDH) were used. The serum GPT was 28.07 U/L in exposure group, and the control group was 13.71 U/L, indicating a higher GM of exposure group, which was statistically significant (p<0.01). Y-GTP also showed significantly different between exposed and control group that the GM of the exposure group was 31.50 U/L, 13.94 U/L in control group (p<0.05). The GM of the total bilirubin was 0.98 mg/dL in exposure group and 0.69 mg/dL in control group, which showed statistically significant (p<0.05). But the serum GOT, exposure group was 28.46 U/L, and the control group was 18.00 U/L. The exposure group had higher GM than that of the control group, but it was not statistically significant (p=0.052). Total protein, albumin,

Table 2. Exposure effect indices for liver and biliary function [GM(GSD)]

	Exposure	Control
Serum GOT (U/L)	28.46(1.43)	18.00(1.36)
Serum GPT (U/L)**	28.07(1.87)	13.71(1.60)
Y-GTP (U/L)*	31.50(2.12)	13.94(1.52)
Total protein (g/dL)	7.39(1.05)	7.40(1.03)
Albumin (g/dL)	4.60(1.08)	4.54(1.05)
Globulin (g/dL)	2.77(1.09)	2.86(1.06)
AG-index	1.66(1.14)	1.59(1.10)
Total bilirubin (mg/dL)*	0.98(1.41)	0.69(1.34)
Direct bilirubin (mg/dL)	0.20(1.58)	0.14(1.44)
Indirect bilirubin (mg/dL)	0.76(1.45)	0.542(1.38)
ALP (IU/L)	78.47(1.79)	52.46(1.23)
LDH (IU/L)	292.56(1.43)	294.65(1.16)

There were 16 workers in the exposure group and 10 in the control group.
* p<0.05, ** p<0.01

AG-index, direct bilirubin, Indirect bilirubin, ALP, LDH were not showed significantly different GM between exposure and control group (p>0.05).

2) Effects for renal function

To confirm the exposure effect of chemicals on renal function, four indicators (creatine, e-GFR, BC ratio, and uric acid) were compared GM between exposed and control group. GM, GSD of the exposure and control group are shown in Table 3. In case of creatine, the GM of the exposed group was 0.87 mg/dL and that of control group was 0.69 mg/dL, indicating a high GM of the exposed group (p<0.01). In uric acid, the exposure group was 7.03 mg/dL, and control group was 4.20 mg/dL as the GM, which was significantly higher in the exposure group (p<0.01). For e-GFR, exposure group was 94.71 as GM, 107.27 in the control group, and the BC ratio 15.14 for the exposure group and 15.47 for the control group, indicating no difference in GM between the two groups (p>0.05).

3) Effects for blood and circulatory function

Table 4 shows 16 indices for blood and circulatory function. The neural fats were 121.47 mg/dL in exposed group, and 77.17 mg/dL in control group, and the exposure group was significantly higher than that of the control group (p<0.05). However, blood sugar, total cholesterol, HDL cholesterol, LDL cholesterol, CPK were not significantly different between exposed and control group. In the GM of blood sugar, the exposure group was 96.65 mg/dL and the control group was 93.08 mg/dL, and there was no difference in GM between groups (p>0.05). The GM of the total cholesterol was 196.90 mg/dL in exposure group and 179.07 mg/dL in control group. HDL cholesterol was 54.26 mg/dL in exposure group and 58.62 mg/dL the control group. LDL cholesterol was 107.94 mg/dL in exposure group and 101.04 mg/dL in control group. CPK was 162.69 IU/L in exposure group and 70.14 IU/L in control group.

To determine the exposure effect in blood function, red blood cell count, white blood cell count, platelet count, hemoglobin, hematocrit, monocyte, neurophil, eosinophil, lymphocyte, and basophil were included as exposure indices. The exposure group of the red blood cell count was 483.53 million/mm^3, and the control group was

Table 3. Exposure effect indices for renal function [GM(GSD)]

	Exposure	Control
Creatinine (mg/dL)**	0.87(1.28)	0.69(1.16)
e-GFR	94.71(1.19)	107.27(1.19)
BC ratio	15.14(1.22)	15.47(1.14)
Uric acid (mg/dL)**	7.03(1.33)	4.20(1.24)

There were 16 workers in the exposure group and 10 in the control group.
** p<0.01

Table 4. Exposure effect indices for blood and circulatory function [GM(GSD)]

	Exposure	Control
Blood sugar (mg/dL)	96.65(1.10)	93.08(1.09)
Total cholesterol (mg/dL)	196.90(1.27)	179.07(1.22)
Neutral fats (mg/dL)*	121.47(2.41)	77.17(1.46)
HDL cholesterol (mg/dL)	54.26(1.25)	58.62(1.30)
LDL cholesterol (mg/dL)	107.94(1.41)	101.04(1.34)
CPK (IU/L)	162.69(1.88)	70.14(1.39)
Red blood cell count (10^4 count/mm^3)*	483.53(1.08)	455.50(1.07)
White blood cell count (10^3 count/mm^3)	5.66(1.28)	6.28(1.29)
Platelet count (10^4 count/mm^3)*	24.14(1.24)	29.68(1.19)
Hemoglobin (g/dL)**	14.91(1.09)	13.19(1.10)
Hematocrit (%)*	43.04(1.08)	39.55(1.08)
Monocyte (%)	6.75(1.27)	5.64(1.34)
Neutrophil (%)	53.28(1.17)	56.76(1.16)
Eosinophil (%)	2.61(2.03)	2.32(2.47)
Lymphocyte (%)	34.73(1.23)	31.76(1.34)
Basophil (%)	0.49(2.05)	0.75(1.76)

There were 16 workers in the exposure group and 10 in the control group.
* p<0.05, ** p<0.01

455.50 million/mm^3, indicating that the exposure group was high (p<0.05). Platelet count was 24.14 million/mm^3 in exposed group and control group was 29.68 million/mm^3, which was lower than that of the control group (p<0.05). Hemoglobin showed a GM of 14.91 g/dL of exposure group and the control group was 13.19 g/dL (p<0.01). And hematocrit was 43.04 % of exposure group and the control group was 39.55 % (p<0.01). However, the indices for blood function, white blood cell count, monocyte, neutrophil, eosinophil, lymphocyte and basophil's were showing no difference between two groups.

Ⅳ. Discussion

In this study, significant difference of indicators to liver and biliary function (serum GPT, Ɣ-GTP, total bilirubin), and to renal function (creatine, uric acid), and to blood function (neutral fats, red blood cell count, platelet count, hemoglobin showed to more than 10 years of working period between exposed and control group. The results of this study were compared with previous reports (Table 5). All the reports in Table 5 were expressed at low level exposure of various chemicals and their health effects. Their reported symptoms related to various chemicals exposure were mainly neurological, renal, and reproductive disorders from epidemiological or human experimental studies (Prasher et al., 2002; Lee et al., 2003; Snijder et al., 2012; Hojo et al., 2008; Campo et al., 2013; Jayasumana et al., 2015; Andersson et al., 2016; Soomro et al., 2023). Among them, nervous system disorders appear to have occurred after exposure to substances presumed to be organic solvent mixtures (greater perceived odor intensities, more unpleasantness as autonomic nervous system disorder, palpitation, insomnia, dizziness with headache, memory impairment, euphoria, and depression as central nervous system disorder, and hearing loss as auditory nerves disorder), and renal and reproductive disorders had something in common with exposure to heavy metals and insecticides mixtures (Wu et al., 2024). On the other hand, animal experiments by simultaneous sub-chronic exposure to low concentrations of chemicals showed quite characteristic findings (Jonker et al., 1996; Groten et al., 1997). Jonker et al. (1996) examined the nephrotoxicants (mixture of hexachloro-1,3-butadiene, mercuric chloride, trichloroethylene, 1,1,2-trichloro-3,3-trifluoro-1-propene) at the exposure level of lowest-observed-nephrotoxic-effect level (LONEL), no-observed-nephrotoxic-effect level (NONEL) and NONEL/4 for 4-wk feeding as sub-chronic toxicity test. Co-exposure at the NONEL exposure level showed increased renal weight (Jonker et al., 1996). As similar animal sub-chronic experiment, Groten et al. (1997) examined nine chemicals exposure to find out whether simultaneous administration for 4-week oral/inhalatory study in male Wistar rats. Exposure levels were minimum-observed-adverse-effect level (MOAEL), NOAEL, or 1/3 NOAEL. Only very few adverse effects were encountered in the NOAEL group. In the main part many effects on hematology and clinical chemistry were encountered at the MOAEL although, the authors concluded that simultaneous exposure to these chemicals does not additivity effect only with sub-chronic exposure (Groten et al., 1997). MOAEL exposure level confirmed similar findings in variation of hematological, clinical chemistry, and biochemical indices as increase in renal weights, hepatocellular hypertrophy, decreased plasma triglyceride, altered ALP enzyme activity.

Since this study has the characteristics of a pilot study, the total number of subjects is small and has possibly overlapped with aging factors due to age increase. However, it is meaningful in that it confirmed the health burden of long-term work exposure of workers measuring the working environment in Korea. More research is needed on the long-term low-level exposure of workers.

Table 5. Previous studies on low-level chemical exposure and their hazard effect in humans and animals

Exposure status	Chemicals	Identified symptoms	Target system
Chamber experiment (Andersson et al., 2016)	n-Butanol	Perceived odor intensities, unpleasantness	Autonomic nervous system
Human life environment (Hojo et al., 2008)	Diesel or gasoline exhaust, tobacco smoke, insecticides, paint or paint thinner, cleaning products, fragrances, tar or asphalt, nail polish or hairspray, new furnishings	Allergic disease	Nervous system
Chronic exposure to multi-solvents (Lee et al., 2003)	Toluene, automobile exhaust, paint, gasoline	Palpitation, insomnia, dizziness with headache, memory impairment, euphoria while working, and depression during the weekend	Central nervous system
Manufacturing and combustion products (Campo et al., 2013)	Styrene, toluene, carbon disulfide and ethylbenzene mixtures Pb and Mn metals	Hearing loss	Auditory nerves
Simultaneous exposure (Prasher et al., 2002)	Solvents and noise	Hearing loss	Auditory nerves
Environmental exposure (Jayasumana et al., 2015)	19 heavy metals and pesticide-glyphosate	Agricultural nephropathy	Renal
Agriculture and horticultural trade (Snijder et al., 2012)	Pb or pesticide exposure	Fertility problems of couples	Reproductive toxicity
Environmental exposure (Soomro et al., 2023)	Phthalates, bisphenols, perfluoroalkyl acids, non-essential metals and trace minerals	Pregnancy induced hypertension	Reproductive toxicity
NONEL (Jonker et al., 1996)	Hexachloro-1,3-butadiene, Mercuric chloride, Trichloroethylene, 1,1,2-trichloro-3,3,3-trifluoro-1-propene	Increased renal weight	Renal toxicities
MOAEL (Groten et al., 1997)	Dichloromethane, formaldehyde, aspirin, di(2-ethylhexyl) phthalate, cadmium chloride, stannous chloride, butyl hydroxyanisol, loperamide, and spermine	Increase in renal weights, hepatocellular hypertrophy, decreased plasma triglyceride, altered ALP enzyme activity	Variation of hematology, clinical chemistry, biochemistry

V. Conclusion

To confirm the exposure effect among workers with more than 10 years of long-term low-level exposure to various chemicals, the exposure effects indices of liver and biliary, renal, and blood and circulatory function were evaluated by case-control study. In the case of the exposed group of workers, significant variation was confirmed in some of the indicators of liver and biliary, renal, blood and circulatory function. If low-concentration exposure to different hazardous chemicals occurs over a long period of more than 10 years, it could be a harmful factor for the health of workers who measure the working environment.

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