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Elevated Cholinesterase Activity and Increased Urinary Excretion of Inorganic Fluorides in the Workers Producing Fluorine-Containing Plastic (Polytetrafluoroethylene)

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Fluoropolymers are widely used in thermal and electrical industries. Polytetrafluoroethylene (PTFE) plastic is a typical one. During its production, workers are occupationally exposed to many organic fluorides, especially tetrafluoroethylene, chlorodifluoromethane, PTFE and its thermal decomposition products. Of these compounds, it has been documented (Bernard et al., 1983) that following inhalation of combustion products of PTFE the focal hemorrhages, edema, fibrin deposition in lungs and renal infarcts were observed in rats. Odum and Green (1984) have demonstrated a marked damage to proximal tubule of kidney with no effects on the liver in rats exposed to 6000 ppm tetrafluoroethylene for 6 hr. The investigations of the hazards of these compounds to workers have been mainly focused on acute toxicity. There have been some reports that polymers and its pyrolysis caused polymer fume fever and pulmonary edema (Harris, 1951; Eliabeth, 1973; William et al., 1974; Robert, 1977; Williams et al., 1987). In practice, workers engaged in PTFE manufacture are chronically exposed to the above-mentioned chemicals, but little was known about the hazards ascribed to these chemicals (Wang, 1986). To clarify the influences of the exposed chemicals on health in PTFE production we conducted a mass survey investigation in a PTFE production factory. As a result, in addition to the nephrotoxicity characterized by elevated ALP and NAG activities in urine (manuscript in preparation, Zhaofa Xu et al), more interestingly, we have also found a reversible increase in cholinesterase (ChE) activity and enhanced urinary excretion of inorganic fluorides in workers engaged in PTFE production. We report here these findings and discuss their physiological significance.

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MATERIALS AND METHODS

All subjects investigated have been employed in a PTFE production factory. According to their status of occupational exposure, the workers were classified into the following groups. **Exposed group:** This group included 129 workers (47 male and 82 female) who have worked in the workplaces producing tetrafluoroethylene and PTFE. Because of technical limitation in our laboratory we could not measure the concentrations of the exposed chemicals in the air of the workplaces. The mean age and duration of exposure in this group were 33.5 years and more than eight months, respectively. **Group removed from exposure:** This group consisted of 32 workers who had been exposed to the organic fluorides in the workplaces similar to the exposed group for over a year, but now have been separated from occupational exposure for more than a year. The average age was 32.1 years, mean duration of exposure and length of time removed from exposure were 2.2 years and 1.8 years, respectively. **Control group:** 74 subjects (32 male and 42 female) were chosen as control group. They have been employed in the offices and dining room at same factory for more than a year and have never been exposed to the chemicals described above. The mean age in this group was 34 years and other conditions resemble the other two groups.

10 ml urine samples were collected before starting a working day and the concentration of inorganic fluorides was detected using fluoride ion selective electrode method (Pharmacy Society of Japan, 1980). The concentration was expressed as mg/l urine.

Blood samples were taken by venipuncture into hepairinized tubes before starting a working day. The ChE activities in whole blood, erythrocyte and plasma were measured simultaneously within 4 hr according to the colorimetric method described by Tomokuni et al (1985) using acetylthiocholine iodide (Sigma chemical Co) as the substrates. The ChE activities were calculated as micromole thiocholine/min/ml whole blood.

RESULTS AND DISCUSSION

As shown in Table 1 and Table 2, the concentration of urinary inorganic fluorides in the exposed group was significantly higher than that in control group ($p < 0.01$). Although in the exposed group the concentration in the males was higher than that in the females, the difference was not statistically significant. Unfortunately, being inadequate in the initial design of study we failed to measure the concentration in the group removed from the exposure. These results at least showed that occupational

Table 1. Concentrations of Inorganic Fluorides in the Urine of the Exposed and Control Groups

Group	Cases	Concentration(mg/l)(Mean±SD)
Control	74	1.05±0.50
Exposed	129	1.35±0.66[a]

a:significant difference from the control group, $p<0.01$.

Table 2. Concentrations of Urinary Inorganic Fluorides in the Males and Females of the Exposed Group

Sex	Cases	Concentration(mg/l)(Mean±SD)
Male	47	1.43±0.68
Female	82	1.28±0.64

There was no significant difference between the males and the females.

exposure to organic fluorides during PTFE production can enhance the excretion of inorganic fluorides in the urine in the exposed workers. Wang (1986) also observed a high excretion of inorganic fluorides in the urine. He suggested that the concentration of inorganic fluorides in the urine was considered as an exposure indicator. Our result was in agreement with his findings. However considering the fact that during PTFE production the workers are exposed to many organic fluorides, except a part of excretion as inorganic fluoride in urine, majority of these organic fluorides are not metabolized, only a little was converted to other organic forms and excreted through urine (Odum and Green, 1984., Arthur, 1988). In this study, we have found that the concentration of inorganic fluorides in the urine was not significantly related to years of exposure reflecting the exposure intensity (data not shown). We therefore suggested that although the concentration of inorganic fluorides could be recognized as an exposure indicator, its exactitude was limited.

Table 3 shows that the ChE activities of whole blood, erythrocytes and plasma in the exposed group, and the ChE activities of whole blood and erythrocytes in the removed group were significantly higher than those in the control group. In addition, the ChE activities of

Table 3. Cholinesterase(ChE) Activities in the Three Groups

Group	Cases	ChE Activity(Mean±SD)		
		Whole Blood	Erythrocyte	Plasma
Exposed	129	7.03±1.34[a,c]	5.36±1.32[a]	1.64±0.59[a,c]
Removed	32	6.34±1.24[b]	5.07±1.11[b]	1.33±0.57
Control	74	5.70±1.41	4.56±0.98	1.22±0.70

The ChE activity is expressed as micromole thiocholine/min/ml whole blood.
a:significant difference from the control, $p<0.01$.
b:significant difference from the control, $p<0.05$.
c:significant difference from the removed group, $p<0.05$.

Table 4. ChE activities in the Males and Females of the Exposed Group.

Sex	Cases	ChE Activity(Mean±SD)		
		Whole blood	Erythrocyte	Plasma
Male	47	7.39±1.44[a]	5.79±1.12[a]	1.58±0.67[a]
Female	82	6.85±1.27	5.18±1.26	1.67±0.53

The ChE activity is expressed as micromole thiocholine/min/ml whole blood.
a:significant difference from the females, $p<0.05$.

whole blood and plasma in the exposed group were statistically higher than those in the removed group. The ChE activities in whole blood, erythrocytes and plasma were elevated by 23.2%, 17.5% and 33.7% respectively in the exposed group, and by 11.2%, 11.2% and 8.7% respectively in the removed group compared with the control group. The results observed in this study indicate that occupational exposure to fluorine-containing organic compounds can increase the ChE activities in workers and after removal from exposure, the elevated ChE activities tends to go back to normal levels, especially with regards to the ChE activity in the plasma. Furthermore, we also analyzed influences of some factors including sex, age, smoking, drinking and duration of exposure, on the ChE activity. As seen in Table 4, we found that only sex influences the ChE

activities. The ChE activities of whole blood and plasma in the males of the exposed group were remarkably increased compared with those in the females ($p<0.05$). The percent enhancements of the ChE activities of the whole blood, erythrocyte and plasma in the exposed group were 27.2%, 22.5% and 47.9% respectively for the males, and were 21.1%, 17.5% and 35.2% respectively for the females.

The physiological importance and mechanism involved in the elevated ChE activities in the exposed workers is still unclear. Adlard et al(1972) have reported that acetylcholinesterase (AChE) activity in adult rat cerebellum was elevated after X-irradiation in infancy and this change was not accompanied by histological alterations. they suggested therefore that the increased AChE activity after early irradiation represents a relative sparing of cholinergic neurons. Bruin (1976) reviewed that after X-irradiation the AChE activity was first enhanced and then was inhibited, thus it was considered that the elevated AChE activity in the early state is ascribed to a protective response. More recently, Jacob et al (1981) and Fatranska et al (1987) have demonstrated that both X-ray irradiation and cold stress induced the increases in AChE activity in the brain. In our study, in those occupationally exposed to organic fluorides during PTFE production the ChE activities in whole blood and erythrocytes were elevated slightly to moderately, and after removal from exposure the activities can recover. Therefore, we propose that the elevated ChE activities of the whole blood, erythrocytes in the workers engaged in PTFE production were attributed to a protective mechanism.

With regard to the ChE activity in plasma, Bruin (1976) viewed that both increase and decrease in serum (or plasma) reflect the liver injury induced by chemicals. On the other hand, Kutty et al (1977) and Ryhanen et al (1984) have suggested that the ChE activity was somehow associated with lipid and lipoprotein metabolism. Abiola et al (1991) however have not found a similar association in the agricultural organophosphate applicators. In the present study, we have demonstrated that the change of the ChE activity in plasma paralleled the activities in the whole blood and erythrocytes and that both the increase and recovery of the ChE activity in plasma were more obvious and rapid than the ChE activities in the whole blood and erythrocytes. Additionally, in our study (data not shown) and previous investigation in animals (Odum and Green, 1984) hepatoxicity due to tetrafluoroethylene was not established. According to these results, We supposed that the enhanced ChE activity in plasma appeared to be a compensatory or protective response in liver.

The present study demonstrated that occupational exposure to organic fluorides during PTFE production resulted in a reversible increase in ChE activities of whole blood, erythrocyte and plasma which may reflect a protective response in the exposed workers. In addition, the urinary excretion of inorganic fluoride was increased in the exposed workers and this could be considered as an exposure indicator to a limited extent.

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