Effects of Occupational and Nonoccupational Factors on Liver Function Tests in Workers Exposed to Solvent Mixtures

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ABSTRACT. A total of 368 workers from six paint-manufacturing factories participated in this study. The workers were classified according to type of exposure: direct, intermittent, and no exposure. The workers' liver-function tests were influenced greatly by gender, hepatitis B, alcohol consumption, and body mass index. Both the serum concentration and the odds of abnormality of total serum bile acids were elevated among the directly exposed group. The authors concluded that analysis of covariance should take into account occupational and nonoccupational factors on liver-function tests to avoid any errors. Total serum bile acids also indicated liver dysfunction from solvent exposure.

THE INCIDENCE of acute liver injury from hepatotoxic chemicals has been reduced in recent decades. Long-term, low-level, and/or interacting occupational and environmental exposures may produce liver injury,[1–2] but how to identify such injury is a major problem. The sensitivity and specificity of conventional liver-function tests are low in chronic low-grade or latent liver dysfunction caused by chemicals.[3–7] In most epidemiological studies, researchers have not controlled for nonoccupational factors (e.g., alcohol consumptions, body mass index, viral hepatitis). How one is to monitor liver injury caused by chemical exposure in the workplace is an unsolved problem.[8–11]

Edling and Tagesson[4] measured serum bile acids to indicate chemical exposure, but their use remains controversial in detecting effects of chemical exposure[12] because other risk factors have gone uncontrolled.[13–15] In this study, we examined biochemical indicators of liver function and confounding factors among solvent-exposed workers.

Materials and Method

Subjects and data collection. During the period of time from September 1992 to February 1993, 6 of 7 paint-manufacturing factories staffed with at least 30 employees each participated in this study. The surveillance program was completed by 402 of the 514 workers. We excluded an additional 34 because they had worked less than 1 y, and their working conditions could not be identified, thus leaving 368 workers for analysis.

Each employee underwent physical examination, liver-function tests, and serological tests for viral hepatitis B and C. Trained interviews administered question-

naires that contained questions about medical history, occupation, alcohol consumption, and medication taken. During the morning, we drew a 10-ml blood sample from the cubital vein of each fasting worker. We then centrifuged the sample to obtain the serum. We stored the samples at 4° C, and they were analyzed within 3 d of storage.

We used a Hitachi 7050 autoanalyzer (Tokyo, Japan) to measure total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, r-glutamyltransferase, and total serum bile acids. We measured the concentration of total serum bile acids by an enzymatic method (Enzabile [Oslo, Norway]). We used enzyme immunoassay (Austria-II, Abbott Laboratories [Chicago, Illinois]) to perform markers for hepatitis B and C.

Of the 124 workers who were directly exposed to solvents, 111 workers voluntarily carried Drager passive personal air samplers during a complete work day. Employees who were not exposed directly to solvents voluntarily agreed to perform air-sampling procedures. Workers were divided into the following three groups: (1) direct exposure (mixing, grinding, dilution, and tinting departments); (2) intermittent exposure (departments of research and development, machine maintenance, and field supervision); and (3) no exposure (administration, storage management, manufacturers of water-soluble paint, and others). We analyzed all air samples by gas chromatography within 1 wk of collection. We expressed the air concentration of each solvent as the time weighted average (TWA), after which we divided it individually by the threshold limit value (TLV) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH), to obtain a fraction. We defined the hygienic effect as the sum of the fractions of the TLVs represented by each solvent.

Data analysis. We used multiple linear regression analysis to evaluate the change in liver-function tests in accordance with indicators of occupational and nonoccupational factors. We analyzed data with and without logarithmic transformation of serum level of liver-function tests. We also fitted a multiple logistic regression model to evaluate the prevalence odds ratio of abnormality of liver-function tests and its relationship with various factors.

Table 1.—Air Concentrations (ppm) of Detected Solvents Measured by Passive Personal Sampling in Different Departments at Paint-Manufacturing Factories in Northern Taiwan

Work department	Toluene Median (range)	Xylene Median (range)	Butyl acetate Median (range)	8-h TWA hygienic effect Median (range)
		Directly exposed		
Mixing (n = 29)*	3 (0–15)	4 (0–19)	2 (0–16)	0.16 (0.03–1.46)
Grinding and dilution (n = 18)	14 (0–107)	16 (1–108)	5 (0–40)	0.4 (0.02–1.51)
Tinting (n = 25)	2 (0–232)	5 (0–391)	2 (0–19)	0.11 (0.01–4.9)
Filling (n = 39)	12 (0–57)	14 (1–89)	4 (0–15)	0.28 (0.01–1.8)
		Intermittently exposed		
Research and development (n = 49)	0 (0–15)	1 (0–6)	0 (0–4)	0.03 (0–0.77)
Machine maintenance (n = 5)	1 (0–16)	0 (0)	2 (0–16)	0.02 (0–0.25)
Field supervision (n = 8)	1 (0–3)	3 (0–5)	4 (0–12)	0.03 (0–0.1)
		Nonexposed		
Other†	0 (0–2)	0 (0–3)	0 (0–4)	0 (0–0.1)

Notes: Benzene, *n*-hexane, acetone, and methylisobutyl ketone (MIBK) were all measured but are not shown here because of their infrequent use. Their medians were always below detection limits.

*Numbers (n) of samples obtained.

†Includes departments of administration, manufacturing of water-soluble paint, storage management, and others.

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Table 2.—Demographic Characteristics of Paint-Manufacturing Workers, Stratified by Exposure Pattern

Characteristics	Exposure pattern		
	No exposure	Intermittent	Direct
Total workers (*n*)	129	115	124
No. of male workers	82	80	103
Percentage of male workers	64	70	83
Age			
Median	36	33	41
Range	17–68	17–67	17–68
Duration of employment (y)			
Median	3	3	4
Range	1–47	1–34	1–33
No. of smokers (% of male workers)*	40 (49)	45 (56)	60 (58)
No. (%) who consumed > 20 g/d	8 (6)	5 (4)	9 (7)
No. (%) who took medication during the past 2 wk	13 (10)	9 (8)	19 (15)
No. (%) of HBsAg† carriers	14 (11)	17 (15)	21 (17)
No. (%) with hepatitis C	2 (2)	6 (5)	5 (4)

*None of the female workers smoked.
†HBsAg = hepatitis B surface antigen.

Results

The air concentrations of solvents for each paint-production process and work department are summarized in Table 1. Workers of paint-manufacturing plants were exposed to solvent mixtures, of which xylene and toluene were the major components. The demographic characteristics are compared in Table 2. The directly exposed workers included a significantly higher percentage of males, who were older and who were employed longer. None of the female workers smoked. There were no statistical differences among the three groups with respect to any other characteristic.

In linear multivariate analysis, both logarithmic transformation and no transformation of the dependent variables showed a similar trend; therefore, only the nontransformed ones are shown in Table 3. Hepatitis B infection appeared to be the most significant indicator for change of all liver-function tests, except r-glutamyltransferase. Alcohol consumption that exceeded 20 g/d, or a body mass index greater than 25 kg/m^3, was associated with increased levels of alanine aminotransferase, r-glutamyltransferase, and total serum bile acids. Alcohol consumption that exceeded 20 g/d also increased aspartate aminotransferase. Male workers had higher enzyme activities of total bilirubin, alkaline phosphatase, and r-glutamyltransferase. Solvent exposure appeared to increase serum concentrations of alkaline phosphatase and total serum bile acids.

The results of multiple logistic regression showed that solvent exposure significantly increased the prevalence odds ratio of abnormality of total serum bile acids—but not of alkaline phosphatase—among the direct-exposure group (Table 4).

Discussion

Changes in liver-function tests were influenced widely by nonoccupational factors. Hepatitis B and alcohol consumption played the most prominent roles in these changes. Both the serum concentrations and the odds of abnormality of total serum bile acids were elevated among the direct-exposure group. These findings suggest that when analysis of covariance is performed, one should take into account occupational and nonoccupational factors on liver-function tests to avoid errors (i.e., changes of any single or combined liver-function test among workers exposed to chemicals must be interpreted carefully).

Given that the serum concentration and odds of abnormality of total serum bile acids were elevated significantly among the direct-exposure group, it follows that total serum bile acids might indicate liver dysfunction from solvent exposure. In addition, because the changes in total serum bile acids were not influenced by duration of exposure, total serum bile acids might indicate acute, rather than chronic, effects on liver function. Researchers need to conduct long-term follow-up studies of these work populations for which total serum bile acid results are available to clarify the significance of these total serum bile acid changes.

In our previous study,[16] r-glutamyltransferase activity increased independently with severity of solvent exposure, but there was no difference in total serum bile acid concentrations between different exposure groups. Perhaps this difference can be explained by the fact that, in the previous study, all workers were exposed directly, to some extent, to solvent mixtures. However, 66% of the workers included in our present study were exposed

Table 3.—Effects of Various Nonoccupational Confounders and of Solvent Exposure on Serum Indicators of Biochemical Functions, Analyzed by Multiple Linear Regression

Independent variable	Dependent variable	TBIL *b*(*SE*) partial R^2	ALP *b*(*SE*) partial R^2	ALT *b*(*SE*) partial R^2	AST *b*(*SE*) partial R^2	GGT *b*(*SE*) partial R^2	TBA *b*(*SE*) partial R^2
Sex	Female = 0, male = 1	0.31 (0.05)* 0.098	35 (6)* 0.121	NS	NS	11 (4)* 0.022	NS
Age (y)	age < 35 vs. 35 ≤ age ≤ 50	0.11 (0.04)* 0.020	NS	NS	NS	NS	NS
	age > 50 vs. 35 ≤ age ≤ 50	NS	25 (8)* 0.018	NS	NS	NS	NS
Alcohol (g/d)	≤ 20: 0, > 20: 1	NS	NS	26 (11)* 0.018	28 (8)* 0.037	34 (7)* 0.070	8 (2)* 0.077
Medication	no: 0, yes: 1	NS	NS	NS	NS	NS	NS
HBsAg	negative: 0, positive: 1	0.13 (0.06)* 0.011	21 (7)* 0.020	32 (7)* 0.058	20 (5)* 0.040	NS	3 (1)* 0.027
Anti-HCV	negative: 0, positive: 1	NS	NS	29 (14)* 0.012	NS	NS	NS
BMI	< 25kg/m^2: 0 ≥25kg/m^2: 1	NS	NS	12 (6)* 0.011	NS	25 (4)* 0.133	2 (1)* 0.012
Solvents exposure	No exposure and intermittent exposure: 0 Direct exposure: 1	NS	8 (3)* 0.015	NS	NS	NS	1.2 (0.5)* 0.020
Duration of employment	years	NS	NS	NS	NS	NS	NS
Total R^2 of modeling		0.129	0.174	0.099	0.077	0.224	0.136

Notes: The number below each regression coefficient (*b*) indicates the partial sum of squares (partial R^2) determined by the regression. NS = not significant, TBIL = total bilirubin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, GGT = r-glutamyltransferase, TBA = total bile acids, HBsAg = hepatitis B surface antigen, Anti-HCV = hepatitis C antibody, and BMI = body mass index.
*p value of coefficient < .05.
†The variable of duration of employment was applied only to the direct-exposure group (n = 124).

Table 4.—Effects of Various Potential Confounders and of Solvent Exposure on Odds Ratios of Abnormalities of Alkaline Phosphatase and Total Serum Bile Acids, Analyzed by Multiple Logistic Regression

Independent variable	Dependent variable	ALP (U/l)* Odds ratio (95% CI)	TBA (µmol/l)* Odds ratio (95% CI)
Sex	Female = 1, male = 2	11† (2, 78)	NS
Age (y)	age < 35 vs. 35 ≤ age ≤ 50	NS	NS
	age > 50 vs. 35 ≤ age ≤ 50	NS	NS
Alcohol (g/d)	≤ 20 g/d: 0, > 20 g/d: 1	NS	3.7† (1.4, 9.8)
Medication	no: 0, yes: 1	NS	NS
HBsAg	negative: 0, positive: 1	3.3† (1.5, 7.3)	3.0† (1.4, 6.6)
Anti-HCV	negative: 0, positive: 1	NS	NS
BMI	kg/m^2	NS	NS
Solvent exposure	No exposure and intermittent exposure: 0 Direct exposure: 1	NS	2.2† (1.5, 3.3)
Duration of employment‡	years	NS	NS

Notes: Total number of workers in this analysis was 368. NS = not significant, ALP = alkaline phosphatase, TBA = total bile acids, HBsAg = hepatitis B surface antigen, Anti-HCV = hepatitis C antibody, BMI = body mass index, and 95% CI = 95% confidence interval.
*Cut-off values: 240 U/l for ALP and 8.4 µmol/l for TBA.
†p < .05.
‡The variable duration of employment was applied to only the direct-exposure group (n = 124).

intermittently or not at all. The odds of abnormal total serum bile acid concentrations among directly exposed workers were similar in the two studies (i.e., 12.4% versus 11.3%, respectively); however, corresponding values for intermittently exposed and nonexposed workers in the current study were significantly lower than those of the earlier study. Also, in the previous study, we did not take body mass index into account, whereas body mass index was the most important predictor for changes in r-glutamyltransferase activity in this study. This fact might explain the inconsistent results between these two studies with respect to analysis of r-glutamyltransferase. We recommend that in future studies of r-glutamyltransferase, researchers take body mass index into account.

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