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氯乙烯工人世代生物標記研究(1/2)

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氯乙烯工人世代生物標記研究(1/2)

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前言

氯乙烯單體是重要的塑膠工業原料，過去的研究顯示氯乙烯的暴露可導致肝癌及氯乙烯疾病，例如骨末端溶骨症、鞏皮症等，本研究室建立的氯乙烯工人世代系列研究中發現，台灣氯乙烯聚合工人其肝細胞癌標準死亡比有顯著相關；我們的研究也發現，大部分罹患肝硬化或肝癌的氯乙烯暴露工人，具有 B 型肝炎病毒(hepatitis B virus)感染，我們的結果也發現職業性氯乙烯暴露與 B 型肝炎病毒感染對於肝硬化或肝癌的發展，可能具有協同性交互作用存在。

目前作業場所中氯乙烯暴露濃度已大幅降低，除了傳統的健康檢查可篩檢肝臟疾病外，應用早期的臨床肝功能效應指標，可早期測度氯乙烯所可能造成的肝臟損傷，另外，台灣地區 B 型肝炎盛行造成肝癌高居國內第一死因，氯乙烯與 B 型肝炎對肝功能損傷之交互作用影響值得進一步研究。

研究目的

本研究將整合自 1988 年起於台灣所建立的氯乙烯工人世代，重建其累積暴露劑量資料庫，並且驗證氯乙烯暴露與肝功能指標，包括血清天門東酸轉胺基胺(aspirate animotransferase, AST)、胺基丙酸轉胺基胺(alanine aminotransferase, ALT)是否有劑量反應關係；同時驗證 B 型肝炎病毒與氯乙烯暴露是否對肝功能(ALT、AST)有協同性交互作用存在，並進一步檢視 B 型肝炎表面抗原(HBsAg)及 HBeAg 個別的角色。

文獻探討

血清天門東酸轉胺基胺(aspirate animotransferase, AST)、胺基丙酸轉胺基胺(alanine aminotransferase, ALT)已被廣泛應用於肝功能傷害檢查，職業因子與非職業因子都可能與肝功能異常有關 [1]。非職業性因子中，B 型肝炎與 C 型肝炎病毒感染與酒精攝取對血清轉胺基胺具有協同作用[2][3]。然而，職業性化學暴露與 B 型肝炎與 C 型肝炎對於肝功能酵素是否具有協同作用並不清楚，這個議題在 B 型肝炎盛行的台灣地區相當重要。

本研究室長期追蹤氯乙烯世代工人世代的肝功能異常情形，包括氯乙烯單體製造廠及聚氯乙烯工廠之工人。不論是氯乙烯單體(vinyl chloride monomer, VCM, CAS No. 75-01-4)或是合成氯乙烯單體的原料二氯乙烷(1.2-ethylene dicholoride, EDC, CAS No. 107-06-2)暴露都會可能造成肝功能異常[6][7]，從我們過去的研究中發現，暴露於氯乙烯或是二氯乙烷的工人中，同時有 B 型肝炎感染的工人較沒有 B 型肝炎感染的工人有較高的血清轉胺基胺異常，然而因為樣本數較少而無法達成結論，因此我們利用重新建立的氯乙烯工人世代資料庫，將 1995 年至 1997 年進行體檢的 5 家聚氯乙烯工廠員工，及 4 家氯乙烯單體製造廠員工納入研究以增加樣本數。同時，文獻指出具有 HBeAg 的工人其血清轉胺基胺異常率也較高[8]，因此我們進一步檢視 HBeAg 與職業性化學暴露對血清轉胺基胺的交互作用。

研究方法

研究世代

我們根據勞工保險資料，從分別的六家氯乙烯聚合工廠，建立了由 4,096 名工人組成的職業世代，所有的詳細資料包括身份證字號、生日、性別、職業變動及退休等資料都加以記錄。台大職衛所自 1988 年起定期的針對氯乙烯聚合工廠工人進行體檢追蹤，超過 1500 名工人在他們任職期間接受過至少一次的健康檢查，詳細的職業史、酒精攝取、吸菸、及疾病史都由訪員詳細記錄，每位工人都接受生化檢查及腹部超音波檢查。所有血液檢體採集後都適當儲存於-80 ℃冰箱。

研究對象

共 568 名男性員工納入本研究，包括 292 名來自五家氯乙烯聚合工廠的員工，及 276 名來自兩家氯乙烯製造廠的員工。其中，11 人是辦公室文書職員，3 人是警衛，大部分的工人在我們之前的研究中，用以評估化學暴露與肝功能、基因毒性之相關[6][7][9]。

所有工人接受訪員問卷調查，詳細調查其吸菸、飲酒、藥物使用、疾病史與職業史。其中酒精攝取以酒精含量及飲酒頻率重新標準化計算，以每週攝取超過 80 克酒精者定義為具有飲酒習慣。以資料收集半年內，每天至少抽一根菸者定義為具有吸菸習慣者。

暴露評估

以個人暴露資料計算二氯乙烷及氯乙烯之八小時日時量容許濃度(TWA)[8][9]，缺少個人採樣資料時則以作業環境測定資料代替。工作場所遠離二氯乙烷及氯乙烯作業現場的警衛及辦公室人員定義為對照組，暴露值定為 0ppm。在考慮混和暴露分組時，參考 NIOSH 之建議值作為標準，二氯乙烷之八小時日時量容許濃度為 1ppm，氯乙烯單體之八小時日時量容許濃度亦為 1ppm，兩種化學物質的混合暴露危害計算方式則參考 ACGIH 之方法：

$$C1/T1 + C2/T2$$

其值設為混合暴露指標，其中，C 是測得的 TWA，T 則是可允許的暴露標準，於本研究二氯乙烷及氯乙烯都定為 1ppm。混合暴露指標低於 1 的工人定義為低暴露組，介於 1 至 5 之間的工人定義為中暴露組，大於 5 的工人則定義為高暴露組。

生化檢查及 B 型肝炎病毒標記

肝功能指標，包括血清天門東酸轉胺基胺(aspirate animotransferase, AST)、胺基丙酸轉胺基胺(alanine aminotransferase, ALT)在台大醫院，以 Hitachi 7050 自動分析儀 (Hitachi Co. Tokyo, Japan)進行分析，B 型肝炎病毒表面抗原(HBsAg)及 C 型肝炎病毒抗體(anti-HCV)以酵素免疫分析法(EIA, Abbott Laboratories,

Chicago, IL, USA)進行分析，B 型肝炎病毒表面抗原為陽性之工人再以 ELISA 進行 HBeAg 分析。肝功能異常值判斷由台大醫院定義，1995 年 AST、ALT 異常定為 31，1996-1997 年，AST 異常為 36，ALT 異常為 41。HBsAg 陽性者定義為 B 型肝炎感染陽性工人，C 型肝炎病毒陽性者定義為 C 型肝炎感染陽性工人。因 C 型肝炎感染者數目很少，併入 B 型肝炎帶原進行分析。身體質量指數(body mass index, BMI)定義為體重除以身高的平方。

統計分析

以 PC/SAS 統計套裝軟體(SAS Institute Inc., Cary, NC, USA)進行分析，χ^2 test 檢定吸菸、飲酒等因子以及 B 型肝炎狀態，於氯乙烯暴露各組間是否分佈不同。ALT、AST 異常在各變相間關係以多變項統計分析，最後以 multiple logistic regression model 估計 ALT、AST 異常在不同氯乙烯暴露組別(低、中、高)、B 型肝炎感染(有、無)、飲酒習慣(有、無)及 BMI (>25 vs. <25)之間的勝算比(odds ratio, OR)。在不同氯乙烯暴露組別(低、中、高)中，ALT、AST 異常勝算比進一步以 HBeAg 及 HBsAg 狀態 (-/-, -/+, 及+/+)加以評估。P 值設定於 0.05，定義小於 0.05 統計顯著差異。

結果與討論

研究對象之人口基本學資料表列於表一。氯乙烯暴露之 TWA 中位數為 0.67ppm (0.0-73.8ppm)，二氯乙烯暴露之 TWA 中位數為 0.35ppm (0.0-30.5ppm)。大部分的工人(83.6%)年紀小於 50 歲，29.8%的工人 BMI 大於 25，11.1%的工人平均每週攝取酒精超過 80 克，17.3%的工人 HBsAg 為陽性，3.5%的工人 HBeAg 為陽性。高暴露組相較於低、中暴露組有較多工人具有飲酒習慣，而低暴露組平均年齡較其他兩組為高，其他相關因子包括吸菸、BMI、HBsAg、HBeAg、及 anti-HCV 低、中、高暴露三組皆無統計上顯著差異。

總體而言，共有 112 名工人(19.7%)有較高之 ALT、AST，高、中、低暴露三組中，各有 22.4%、20.4%、18.6%的工人有 ALT、AST 之異常，高暴露組的工人其 ALT、AST 異常率高於其他兩組，但未達統計上顯著差異。

在 multiple logistic regression 分析中發現(表二)，AST 與 BMI 及 B 型肝炎感染有關，ALT 亦已相同趨勢，但 ALT 與 C 型肝炎感染之關係並不顯著。同時，化學暴露的增加也與 ALT、AST 異常有關，但未達統計上顯著差異。

化學暴露與各因子對血清轉胺基酶之交互作用列於表三。分析後發現，化學性暴露與 B 型肝炎感染對血清轉胺基酶之交互作用達統計上顯著差異，當工人不具有 B 型肝炎感染時，血清轉胺基酶在各暴露組中並無差異，而當工人具有 B 型肝炎病毒感染時，ALT、AST 的升高具有劑量效應關係。所有工人中，高暴露組又有 B 型肝炎感染的工人，其 AST 異常之勝算比(OR, 10.6; 95% CI, 3.6-31.5)，與 ALT 異常之勝算比(OR, 6.4; 95% CI, 2.1-19.1)最高。而在有 B 型肝炎感染的工人中，高暴露組的工人亦具有最高之 AST、ALT 異常(OR, 6.2; 95% CI, 1.8-21.4;

OR, 6.5; 95% CI, 1.8-23.6)。

進一步將 HBsAg 陽性者分為 HBeAg 陽性、HBeAg 陰性兩組，進行分析(圖一)。在校正年齡、飲酒及 BMI 後，高暴露組中同時具有 HBsAg 陽性及 HBeAg 陽性的工人有較高之 AST 異常 (OR, 7.1; 95% CI, 0.6-81.2)及 ALT 異常(OR, 21.0; 95% CI, 1.4-320.7)。高暴露組中具有 HBsAg 陽性、HBeAg 陰性的工人相較於低暴露組，有較高之 AST 異常 (OR, 5.1; 95% CI, 1.1-24.3)及 ALT 異常(OR, 3.7; 95% CI, 0.7-20.0)。同時我們發現，對 HBsAg 陰性之工人而言，化學暴露並不會增加他們肝功能異常的風險，而 HBeAg 陽性的高暴露組工人，其 AST 異常 (OR, 29.5; 95% CI, 5.2-166.0)及 ALT 異常(OR, 25.6; 95% CI, 3.9-168.0)風險最高。ALT、AST 異常升高的頻率與 B 型肝炎感染嚴重度之交互作用，在高暴露組中有顯著趨勢 (Mental extension test for trend, $p<0.01$)。

在不同的暴露分組中，不論工人飲酒與否，其 AST、ALT 異常率並無顯著差異。有趣的是我們發現，經過校正肝炎感染、年齡及 BMI 後，具有肝炎病毒感染，並有飲酒習慣者其 AST 異常 (OR, 9.1; 95% CI, 2.4-34.1)及 ALT 異常(OR, 2.9; 95% CI, 0.9-10.1)高於沒有肝炎病毒感染的飲酒者。肝炎病毒感染酒精攝取對 AST 的正向交互作用達統計上顯著差異。

目前已完成資料收集、世代重建及資料分析進度，在我們的初步研究發現，混合暴露於氯乙烯及二氯乙烷與肝炎病毒感染對於肝功能傷害具有正向的協同作用，對有可能暴露於肝毒性物質工人需依其肝炎感染狀況評估其配工，並定期進行肝功能追蹤。

References

1 Chen JD, Wang JD, Tsai SY, et al. Effects of occupational and nonoccupational factors on liver function tests in workers exposed to solvent mixtures. *Arch Environ Health* 1997;**52**:270-4.

2 Villa E, Rubbiani L, Barchi T, et al. Susceptibility of chronic symptomless HBsAg Carriers to ethanol-induced hepatic damage. *Lancet* 1982;**2**:1243-4.

3 Nevins CL, Malaty H, Velez ME, et al. Interaction of alcohol and hepatitis C virus infection on severity of liver disease. *Dig Dis Sci* 1999;**44**:1236-42.

4 Chen DS. Natural history of chronic hepatitis B virus infection: new light on old story. *J Gastroenterol Hepato* 1993;**8**:470-5.

5 Huang KY, Lin SR. Nationwide vaccination: A success story in Taiwan. *Vaccine* 2000;**18**:S35-8.

6 Huang CY, Huang KL, Cheng TJ, et al. The GSTT1 and CYP2E1 genotypes are possible factors causing vinyl chloride induced abnormal liver function. *Arch Toxicol* 1997;**71**:482-8.

7 Cheng TJ, Huang ML, You NC, et al. Abnormal liver function in workers exposed to low levels of ethylene dichloride and vinyl chloride monomer. *J Occup Environ Med* 1999;**41**:1128-33.

8 Chu CM, Sheen IS, Lin SM, et al. Sex difference in chronic hepatitis B virus infection: studies of serum HBeAg and alanine aminotransferase levels in 10,431 asymptomatic Chinese HBsAg carriers. *Clin Infect Dis* 1993;**16**:709-13.

9 Cheng TJ, Chou PY, Huang ML, et al. Increased lymphocyte sister chromatid exchange frequency in workers with exposure to low level of ethylene dichloride. *Mutat Res* 2000;**470**:109-14.

TABLE 1

Frequency distribution of basic characteristics in percentage (%) among 568 male workers stratified by exposure categories

Characteristic	Chemical exposure			
	High (≥ 5) (n=76) (%)	Moderate (≥1 and < 5) (n=191) (%)	Low (<1) (n=301) (%)	Total (N=568) (%)
Manufacturing factory				
PVC	67.1	64.4	39.2	51.4**
VCM	32.9	25.6	60.8	48.6**
Age ≥ 40 years	46.1	46.1	59.1	53.0*
Duration of employment ≥ 15 years	43.4	45.0	56.5	50.9*
Body mass index ≥ 25.0 kg/m^2	29.0	33.0	27.9	29.8
Current cigarette smoking (yes)	48.7	43.5	36.9	40.7
Alcohol drinking (yes)	23.7	8.4	9.6	11.1**
Positive hepatitis B surface antigen (HBsAg)	19.7	15.7	17.6	17.3
Positive hepatitis B e antigen (HBeAg)	7.9	1.6	3.7	3.5
Positive anti-hepatitis C antibody (Anti-HCV)	1.3	4.7	3.7	3.7

* $p < 0.05$; ** $p < 0.01$ by χ^2 test.

TABLE 2

Odds ratio (OR) with 95% confidence intervals (C.I.) of multiple logistic regression modeling adjusted for major determinants: including body mass index (BMI), chemical exposure, hepatitis B surface antigen (HBsAg), anti-hepatitis C antibody (Anti-HCV), drinking, and smoking

		AST	ALT
Determinants	Definition	OR (95% C.I.)	OR (95% C.I.)
Age (years)	≥ 40.0 *ν* < 40.0	0.8 (0.5-1.5)	0.6 (0.4-1.0)
BMI (Kg/M^2)	≥ 25.0 *ν* < 25.0	2.2 (1.2-3.9)*	3.5 (2.2-5.5)*
Chemical exposure	High *ν* Low	1.3 (0.6-2.9)	1.4 (0.7-2.6)
	Moderate *ν* Low	0.8 (0.4-1.5)	1.0 (0.6-1.6)
HBsAg	Positive *ν* Negative	3.5 (1.9-6.4)*	2.5 (1.5-4.2)*
Anti-HCV	Positive *ν* Negative	5.9 (2.2-15.9)*	2.3 (0.8-6.3)
Drinking	Yes *ν* No	1.3 (0.6-3.0)	0.9 (0.5-1.9)
Smoking	Yes *ν* No	1.1 (0.6-2.1)	1.0 (0.6-1.6)

* $p < 0.01$ by χ^2 test.

TABLE 3

Frequencies and adjusted Odds ratio (OR) with 95% confidence intervals (C.I.) of abnormal serum aminotransferase activity stratified by exposure classification and hepatitis virus infection. All odds ratios were adjusted for age, body mass index and alcohol drinking.

	AST (n=58)			ALT (n=103)		
Category	%	OR (95%CI)†	OR (95% CI)‡	%	OR (95% CI)†	OR (95% CI)‡
HBsAg (+) or Anti-HCV (+)						
High Exposure	56.3	10.6 (3.6-31.5)*	6.2 (1.8-21.4)*	62.5	6.4 (2.1-19.1)*	6.5 (1.8-23.6)*
Moderate Exposure	23.5	3.0 (1.1-8.0)	1.6 (0.4-5.7)	35.3	2.1 (0.9-5.0)	2.3 (0.7-7.5)
Low Exposure	15.9	2.3 (0.9-5.4)	1.0 (Referent)	19.0	1.4 (0.7-3.0)	1.0 (Referent)
HBsAg (-) and Anti-HCV (-)						
High Exposure	1.7	0.5 (0.1-1.5)		11.7	0.5 (0.2-1.3)	
Moderate Exposure	5.7	0.6 (0.3-1.6)		14.6	0.7 (0.4-1.3)	
Low Exposure	8.8	1.0 (Referent)		16.4	1.0 (Referent)	

* $p < 0.01$ by Mantel-Haenszel χ^2 test for trend analysis

† The referent group (OR=1) refers to workers with low chemical exposure and negative hepatitis virus infection.

‡ The referent group (OR=1) refers to workers with low chemical exposure and positive hepatitis virus infection.

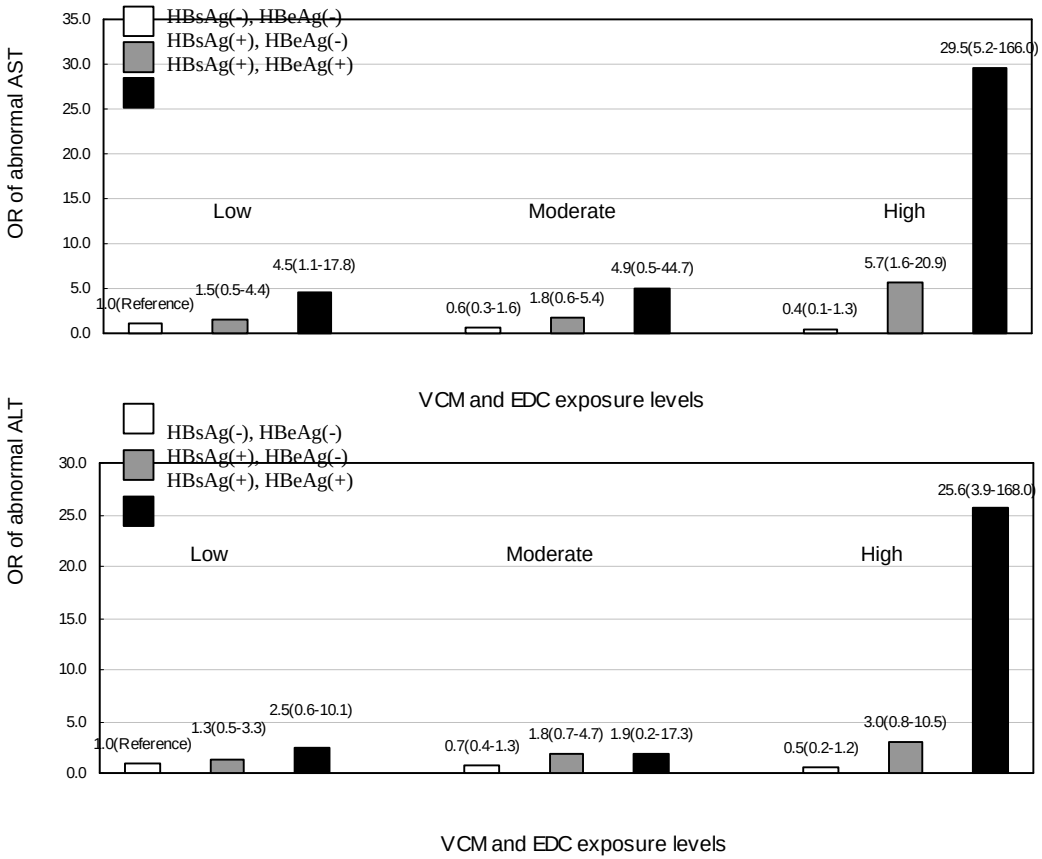

Figure 1

Odds ratio (OR) with 95% confidence intervals (CI) of abnormal AST (top) and ALT (bottom) among workers with different categories of exposure and hepatitis B infection; adjusted with age, drinking, Anti-HCV and BMI. The reference group (OR=1.0) refers to workers with low chemical exposure and negative hepatitis B infection.

參加 ISEE 年會報告

12th conference of the international society of exposure analysis (ISEA)

14th conference of the international society for environmental epidemiology (ISEE)

August 11-15, 2002

Vancouver, BC, Canada

主題：

Linking exposures and health: innovations and interactions

本年度 ISEE/ISEA 年會於加拿大溫哥華舉行，內容包含環境衛生領域重要議題，例如空氣污染、兒童健康、飲水、環境職業癌症及流行病學方法等。本人目前著重於空氣污染相關研究，特別針對空氣污染部分做一描述。

空氣污染目前探討的範圍很廣，主要是微粒及氣相物的健康效應探討。在固態污染物以氣動粒徑(aerodynamic diameter)小於 10 μm 的微粒（PM_{10}）、氣動粒徑(aerodynamic diameter)小於 2.5μm 的微粒（$PM_{2.5}$）等一系列研究發現微粒造成的相關健康效應。在傳統流行病學的架構上，研究者以固定測站爲暴露源，利用醫院就診資料、死亡率及罹病率資料進行統計分析，發現懸浮微粒對於老年人的影響較大，特別是本身已患有心肺疾病者的影響更爲明顯。空氣污染中微粒濃度的增高可造成數天後人口死亡率之增高，其中以心臟血管疾病與呼吸系統死死因有較高相關性，同時增加心血管與呼吸道相關疾病的住院治療、氣喘患者病情的惡化、呼吸道症狀的增加、造成肺功能下降、活動的限制和學童缺席率的增加。

然而隨著研究的進展，流行病學學者發現現有之研究及統計架構不足以充分解釋空氣污染與健康效應的相關議題，因此本次大會對於流行病學方法應用於空氣污染與健康效應之展望進行廣泛的討論。在空污與健康效應相關研究中，研究者必須同時結合多種污染物，包括懸浮微粒 (PM_{10}、$PM_{2.5\text{-}10}$、$PM_{2.5}$)、SO_2、NOx、O_3、PAHs、CO 等，並同時考量懸浮微粒之成分 (sulfate、nitrate 及金屬成分)對於個體健康的效應，這些氣相污染物有時與 PM 之高度相關，使得因果關係不易確定，將來從單一污染物到多重污染物的研究，對空氣污染與健康危害相關可進一步瞭解，因此研究者在處理統計模式時必須以更審慎的方式考量

各污染物的效應(正向/負向)，及生物上之可能機制；同時，過去大部分的研究僅能以中央測站 (central monitoring site)之暴露資料代表周圍居民之暴露，爲更準確的估計其個人暴露與健康效應之因果關係，新的統計方法加入了以 GIS 系統定位附近居民之地理相關，再綜合擴散模式、氣象資料、交通模式及人口活動分佈加以推估個人的暴露；此外，許多研究方向亦著重於評估測站資料與個人採樣暴露資料之相關性，以及室內空氣品質對於懸浮微粒濃度的貢獻。

微粒與心血管疾病是本次大會相當重要的議題。雖然目前大家相信微粒與心肺血管疾病的相關，但是到底是微粒哪一種因子，真正造成危害目前並不清楚，到底是短期效應數小時或是一天內的延遲效應目前仍然不清楚，當然其機轉也還有待討論 ，要如何進一步探討其相關，會中有許多討論，像是 cross-over, time-series 哪一個研究設計較好、有無比較好的 Biomaker 來當作暴露或早期效應指標或是接近疾病的指標，會中有 US EPA 支持的 PM panel 研究，嘗試比較個人暴露、室內、室外及監測站空氣污染物在不同季節、甚至成分做初步比較，將來可提進一步暴露評估資訊。

在流行病學研究方面，各國以疾病爲指標的研究結果相當一致，然而在心跳速率變異性 (Heart rate variability, HRV)方面的研究則相差甚多，對於微粒影響 HRV 的程度引發討論，到底 HRV 是否有暴露上的延遲效應 (time-lag)或是在暴露後數小時即可發生變化，目前並不清楚，心臟科醫師對此量測目前仍有存疑，所以這方面的研究有待進一步證實，似乎個人的評估較難看出差別，有待進一步探討。

有關空氣污染方面，除 0-3 天的延續效應相關探討，一天之內數小時相關的探討也很重要，有報告指出於 6 小時之內，微粒可對心血管疾病產生影響，這些研究可解釋到底是自主神經或是肺發炎反應的延續效應。

另外對於空氣污染的易感性族群的相關探討也引發討論。今日大部分國家已立法控制污染源排放，大幅降低空氣中污染物的濃度，然而在流行病學研究中發現，低濃度的污染物仍會對敏感的族群造成健康影響，除了本來即有心肺疾病之個體外，糖尿病患者暴露微粒後似乎比較容易患有心臟病，而女性又比男性容易受懸浮微粒影響，在系統性的疾病動物實驗建立後，預期明年會有更多這方面的探討。

Synergistic effect by hepatitis virus infection and occupational exposures to vinyl chloride monomer and ethylene dichloride on serum aminotransferase activity

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Short running head: Chemical-viral interaction on serum aminotransferases

Key words: serum aminotransferase; hepatitis virus infection; occupational chemical exposure

Abbreviation: AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B e antigen; anti-HCV, anti-hepatitis C antibody; VCM, vinyl chloride monomer; EDC, 1,2-ethylene dichloride; PEL, permissible exposure level; TWA, time weighted average; PVC, polyvinyl chloride; GSH, glutathione

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Main Messages

- Hepatitis virus infection and increased body mass index are important non-occupational factors that increase serum aminotransferase in asymptomatic chemical workers.
- Hepatitis virus infection has synergistic effect with exposure to vinyl chloride monomer and 1,2-ethylene dichloride on serum aminotransferase activity.
- Synergistic effect between hepatitis virus infection and chemical exposures on serum aminotransferase is more prominent in workers with positive HBeAg as compared to those with positive HBsAg but without HBeAg.

Policy implications

- Assessment of fitness for work should be considered in workers with hepatitis B and C infection, when they have potential exposure to hepatotoxin at workplace.
- In countries where hepatitis B and C virus infection is prevalent, more stringent occupational standard is needed to protect workers exposed to hepatotoxin.

Abstract

Objectives --To study the synergistic effect of occupational chemical exposure with hepatitis virus infection on serum aminotransferase activity.

Methods --A total of 568 male workers who were employed in 5 polyvinyl chloride (PVC) or 4 vinyl chloride monomer (VCM) manufacturing factories were included for analysis. Information relating to current job title, alcohol consumption and cigarette smoking was obtained by an interviewer-administered questionnaire. Exposure level of chemical mixtures was classified by hygienic effect (a summation of personal time weighted average / reference permissible exposure level of each chemical) into high, moderate and low exposure groups. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), and anti-hepatitis C antibody were assayed.

Results -- Hepatitis virus infection and increased body mass index were associated with abnormal serum aminotransferase activity. We also found that in workers with hepatitis virus infection, those with high exposure had a higher prevalence of abnormal AST and ALT as compared to low exposure group (odds ratio, 6.2, 6.5; $p<0.01$). While among those without hepatitis virus infection, the differences of prevalence of abnormal AST and ALT were not statistically significant between different chemical exposure groups. But there was a significant trend of increasing risks of elevated AST and ALT in moderate and high exposure groups with hepatitis virus infection. Such a synergistic effect was more prominent among HBeAg-positive workers.

Conclusions --We conclude that mixed exposures to EDC and VCM have positive synergistic effect with hepatitis virus infection on liver damage. Assessment of fitness for work should be

considered in workers with hepatitis B and C infection, when they have potential exposure to hepatotoxin at workplace. Furthermore, in countries where hepatitis B and C virus infection is prevalent, more stringent occupational standard is needed to protect workers exposed to hepatotoxin.

Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) have been used extensively in the assessment of the liver damage. Abnormal serum aminotransferases have been associated with occupational and non-occupational factors.[1] Among nonoccupational hepatotoxins, hepatitis B and C virus infection have synergistic effects with alcohol consumption on serum aminotransferases.[2][3] However, it is not clear whether occupational chemical exposure and hepatitis B and C have synergistic effects on these hepatic enzymes or not. This question is needed to be resolved for the assessment of fitness of work, particularly in population with high prevalence of hepatitis B infection, including Taiwan.[4][5]

We have followed vinyl chloride monomer (VCM) and polyvinyl chloride (PVC) manufacturing workers for their liver disorders in the past decade. Either VCM (CAS No. 75-01-4) or 1,2-ethylene dichloride (EDC; CAS No. 107-06-2) exposure has been associated with serum aminotransferase abnormalities in our previous studies.[6][7] In the above studies, it seems that exposed workers with hepatitis B infection tend to have higher risk of abnormal serum aminotransferase as compared to those without hepatitis B infection. However, it was difficult to draw a conclusion because of the small number of subjects with abnormal serum aminotransferase. To increase the power of detection for the interaction between hepatitis virus infection and occupational chemical exposure, we included workers from both PVC and VCM manufacturing plants, who received medical examination between 1995 and 1997. Since workers with hepatitis B e antigen (HBeAg) also had higher prevalence of serum aminotransferase abnormality,[8] the interaction between HBeAg and occupational chemical exposure on serum aminotransferase was further assessed.

Methods

STUDY POPULATION

A total of 617 workers were eligible. Because 49 workers had incomplete data, 568 (92%) workers from 5 PVC (n = 292) and 4 VCM (n = 276) manufacturing factories were included for the analysis. Among them, 11 workers were office workers, who stayed indoor during most of their working hours, and 3 workers were guards who stayed away from the manufacturing site. Most of these workers have been presented in previous studies to investigate the relationship between external chemical exposures and liver function or genotoxicity, or the effects of metabolic genotypes on liver function or genotoxicity.[6][7][9]

After informed consent was obtained, all study subjects were surveyed by an interviewer-administered questionnaire to obtain information on smoking, alcohol consumption, medicines, and medical and occupational histories. Alcohol consumption was calculated from drinking frequency and alcohol content of each beverage consumed. Those who drank at least once and had alcohol consumption with a minimum of 80 grams intake per week in past one month were defined as having drinking habit. Smoking behavior was defined as having smoked at least one cigarette per day within the preceding 6 months of data collection.

EXPOSURE ASSESSMENT

EDC is used in the production of VCM, and VCM is subsequently used for the polymerization to manufacture PVC. In VCM manufacturing plants, workers were exposed to both EDC and VCM, while workers in PVC plants were exposed to VCM only. Detailed occupational history included job title, daily activity and use of respirator in the current and

previous jobs. Personal samplings were conducted to calculated EDC and VCM time weighted average (TWA) for each category of work.[9][10] If personal sampling data was not available, data of area sampling was used. Office workers and guards were presumably exposed to extreme low concentration of chemicals, thus 0 ppm of VCM and EDC were assumed as their TWA. To consider the combined effect of EDC and VCM, the hygienic effect was calculated by using the model of $(C_1/T_1) + (C_2/T_2)$, where C was the measured TWA and T was the permissible exposure levels or equivalents for each chemical. One ppm was used for both EDC and VCM in this study, which has been adopted by many institutions. Our previous study also found that EDC and VCM cause abnormal liver aminotransferase around 1 ppm. [7] Workers with hygienic effects below 1 were classified into the low exposure group. Workers with hygienic effects between 1 to 5 were classified into the moderate exposure group, and workers with exposures greater than 5 were classified into the high exposure group.

BIOCHEMICAL TESTS AND HEPATITIS VIRUS MARKERS

Markers of liver damage, including AST and ALT, were analyzed with a Hitachi 7050 autoanalyzer (Hitachi Co, Tokyo, Japan) at National Taiwan University Hospital (NTUH). Hepatitis B virus surface antigen (HBsAg) and anti-hepatitis C virus antibody (anti-HCV) were determined by enzyme-linked immunoassay (EIA, Abbott Laboratories, Chicago, IL, USA), respectively. HBeAg was also assayed with ELISA method in workers with positive HBsAg. Abnormal results for serum aminotransferases were defined as having values greater than reference provided by NTUH. In 1995, it was 31 for both ALT and AST. In 1996 and 1997, it was 37 for AST, and 41 for ALT. Subjects with positive hepatitis B infection were defined as

having positive HBsAg, and subjects with positive hepatitis C infection were defined as having positive anti-HCV. Since the number of subjects exhibiting a positive titer for anti-HCV was small, HBsAg and anti-HCV were grouped together as hepatitis virus infection. BMI was calculated as weight in kilograms divided by the square of height in meters.

STATISTICAL ANALYSIS

PC/SAS statistical package (SAS Institute Inc., Cary, NC, USA) was used for the statistical analysis. χ^2 test was used to compare the differences of age, employment duration, hepatitis virus infections, body mass index and alcohol consumption between different exposure groups. Crude comparisons of abnormal AST and ALT by variables of interests were conducted in the univariate analysis. Subsequently, a multiple logistic regression model was used to determine the odds ratio (OR) of abnormal AST and ALT levels for different exposure groups (high, moderate and low chemical exposure), hepatitis virus infection (yes and no), body mass index ($\geq$ 25.0 and <25.0 kg/m^2) and habitual drinking (yes and no). OR of abnormal AST and ALT levels on different exposure groups stratified by hepatitis B and C virus infection was also calculated after controlling for potential confounders including age, BMI and alcohol drinking. OR of abnormal AST and ALT on the chemical exposure (low, moderate and high) was further calculated by HBeAg and HBsAg status (-/-, -/+, and +/+, respectively). All the *p*-values were quoted two-sided, and those values < 0.05 were regarded as statistically significant.

Results

DESCRIPTIVE STATISTICS

The basic characteristics of study subjects stratified by different exposure groups are summarized in Table 1. The median TWA of VCM is 0.67 (range from 0.0 to 73.8) ppm and EDC is 0.35 (from 0.0 to 30.5) ppm. Most workers (83.6%) were less than 50 years of age, 29.8% of workers had BMI greater than 25, 11.1% of workers consumed more than 80 grams of alcohol per week, 17.3% of workers had HBsAg, and 3.5% of workers had HBeAg. High exposure group had more habitual drinkers than moderate and low exposure groups. Low exposure group was older than moderate and high exposure groups. All other characteristics of cigarette smoking, BMI, HBeAg, HBsAg and Anti-HCV were not statistically significant between these three exposure groups.

Overall, 112 workers (19.7%) showed elevations of AST or ALT. There were 22.4%, 20.4, and 18.6% of workers who having abnormal AST or ALT among high, moderate and low exposure groups. Workers of high exposure had more cases of abnormal AST or ALT when comparing with other workers, but this did not reach a statistical significance.

MULTIPLE LOGISTIC REGRESSION ANALYSIS

Multiple logistic regression analysis in Table 2 revealed that AST was associated with BMI and hepatitis virus infection. ALT also had similar findings but the association with hepatitis C infection and ALT did not reach a statistical significance. Increased chemical exposure was also associated with abnormal ALT or AST, but this association did not reach a statistical significance.

INTERACTION ANALYSIS OF FACTORS ON SERUM AMINOTRANSFERASE

The interactions between chemical exposure and each potential factor (hepatitis virus infection, BMI and alcohol drinking) on serum aminotransferase were calculated. Significant interactions were observed for chemical exposure and hepatitis virus infection (Table 3). When workers didn't have hepatitis virus infection, all serum aminotransferases showed no difference among different exposure groups. The dose-dependent effects of chemicals on AST and ALT were found when workers had hepatitis virus infection. Workers who had high chemical exposure and hepatitis virus infection had the highest risk on abnormal AST (OR, 10.6; 95% CI, 3.6-31.5) and ALT (OR, 6.4; 95% CI, 2.1-19.1) when comparing with workers who were low chemical exposure and lacked hepatitis virus infection. If we confined the analysis for those with hepatitis virus infection, high exposure group had the highest risk of abnormal AST (OR, 6.2; 95% CI, 1.8-21.4) and ALT (OR, 6.5; 95% CI, 1.8-23.6) when comparing with low exposure group.

Further analysis was also performed when workers with positive HBsAg were divided into 2 groups according to the presence of HBeAg status (Figure 1). After adjustment for age, drinking, and BMI, significant higher risks of abnormal AST (OR, 7.1; 95% CI, 0.6-81.2) and ALT (OR, 21.0; 95% CI, 1.4-320.7) were observed in high exposure group compared with low exposure group among workers with both HBsAg and HBeAg. Among workers who had positive HBsAg but did not have positive HBeAg, higher risk of abnormal AST (OR, 5.1; 95% CI, 1.1-24.3) or ALT (OR, 3.7; 95% CI, 0.7-20.0) was observed in high exposure group when comparing with low exposure group. Moreover, among workers without HBsAg, chemical exposure didn't increase the risk of abnormal liver function. Workers who had positive HBeAg and high chemical exposure had the highest risk of abnormal AST (OR, 29.5; 95% CI, 5.2-166.0)

and ALT (OR, 25.6; 95% CI, 3.9-168.0) when comparing with low exposed workers without HBsAg. There is a statistically significant trend (Mantel extension test for trend, $p<0.01$) for increased frequency of abnormal AST and ALT along with severity of hepatitis virus infection among high exposure group.

Among workers whether consuming alcohol or not, prevalence of abnormal AST and ALT was not observed between different chemical exposure groups. It is interesting to observe that, after adjusted with hepatitis virus infection, age, and BMI, drinkers with hepatitis virus infection had higher rates of abnormal AST (OR, 9.1; 95% CI, 2.4-34.1) and ALT (OR, 2.9; 95% CI, 0.9-10.1) as compared to those without hepatitis virus infection and habitual drinking. The positive interaction effect of hepatitis virus infection and alcohol consumption on AST reached a statistical significance.

Discussion

The results reveal that occupational chemical exposure had positive interaction with hepatitis B and/or C infection on serum AST and ALT. This synergistic effect was the most obvious in workers with positive HBeAg. However, a statistical association may not indicate a causal association. As the most commonly reported determinants for elevation of AST and/or ALT, including BMI, alcohol, and age, were all controlled; we suspected that such an association might be causal.

Hepatitis B and/or C infection have been associated with elevated serum aminotransferase activities.[11] Our results reveal similar findings, although the association between anti-HCV and ALT was not statistically significant. This is probably due to small

numbers of workers with anti-HCV. Increased BMI is also associated with increased ALT and AST in our study (table 2). Increased BMI is a common etiology of abnormal liver function tests for healthy workers.[6][7][12] Our results corroborate such an association. Alcohol consumption has been reported to be associated with abnormal liver function,[11] but our results didn't show this relationship. This is most likely due to relative small amount of alcohol consumption by theses workers. Lack of association between alcohol consumption with abnormal ALT and AST was also observed in several studies conducted in Taiwanese workers.[10][15] A study conducted in Italy showed that those consumed 80 gm each day had greater risk of developing abnormal liver function among chronic symptomless HBV carriers.[2] Positive synergism was also observed between HCV infection and alcohol consumption.[3] Our study also revealed that HBV and HCV infection exacerbated the effect of alcohol on AST, although the effects of alcohol on ALT was less prominent. Again, this could result from the small amount of alcohol consumption in our study subjects. Additionally, AST elevation is usually more prominent than ALT in alcoholic hepatitis.[13][14] Thus, the relationship between abnormal serum aminotransferases and nonoccupational factors in our study is consistent with previous studies.

A recent study also showed that the relationship between occupational dimethylformamide exposure and abnormal liver function were enhanced in those with HBV infection.[15] Here, we demonstrated that VCM and EDC together could also have a more than additive interaction with HBV and HCV infection. Further analysis in our study indicated that workers with HBeAg were more likely to have abnormal ALT and AST as compared to those with HBsAg alone, when they were exposed to occupational chemicals. As both VCM and EDC were reported to be hazardous to the liver, detection of such an effect is not surprised and the

mechanism should be clarified.

Previous human and animal studies indicated that glutathione (GSH) depletion can be caused by hepatitis virus infection.[16][17][18] Glutathione S-transferases (GST) and glutathione play an important role in the metabolism of EDC and VCM, of which the electrophilic intermediate metabolites are conjugated with GSH to be detoxified.[19][20] Thus, GSH depletion caused by hepatitis virus infection may lead to an accumulation of active intermediate metabolites of EDC and VCM, then exacerbate EDC and VCM-induced hepatotoxicity. Previous study that conducted with 1,1-Dichloroethylene showed correlations between hepatocellular damage and magnitudes of both covalent binding and GSH depletion also supported this proposed hypothesis.[21] Our recent study also suggests that the GSTT1 genotype may play an important role on liver aminotransferase abnormality caused by vinyl chloride.[6] In patients with positive HBeAg, there is more active HBV replication and inflammation, which can reduce the level of GSH.[22] Therefore, they are at a high risk of showing elevation for AST and ALT, as showed in figure 1. We conclude that subjects with hepatitis B and/or C virus infections are more likely to be damaged by hepatotoxic agents, such a potential synergistic effect may be caused by GSH depletion after hepatitis virus infection.

Studies conducted in human and rats also found that ethanol significantly decreased the glutathione concentrations,[23][24][25] of which the synergistic hepatotoxic effect between alcohol and hepatitis virus infection could be also resulted from potential overloading of the oxidative damage through the generation of reactive intermediate and decreased radical scavenging.

It is our concern that VCM or EDC workers with HBV and/or HCV infections may not

be well protected under current occupational standards. We suggest workers with HBeAg not to be involved in works exposed to hepatotoxins. For workers with anti-HCV and abnormal serum aminotransferases, we also advise them not be exposed to hepatotoxin. Workers with positive HBsAg but negative HBeAg need to be closely followed for their serum aminotransferases, if exposed to higher levels of VCM or EDC. Most of all, more stringent occupational standard is needed to protect workers exposed to hepatotoxin in countries where hepatitis B and C virus infection is prevalent.

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References

10 Chen JD, Wang JD, Tsai SY, et al. Effects of occupational and nonoccupational factors on liver function tests in workers exposed to solvent mixtures. *Arch Environ Health* 1997;**52**:270-4.

11 Villa E, Rubbiani L, Barchi T, et al. Susceptibility of chronic symptomless HBsAg Carriers to ethanol-induced hepatic damage. *Lancet* 1982;**2**:1243-4.

12 Nevins CL, Malaty H, Velez ME, et al. Interaction of alcohol and hepatitis C virus infection on severity of liver disease. *Dig Dis Sci* 1999;**44**:1236-42.

13 Chen DS. Natural history of chronic hepatitis B virus infection: new light on old story. *J Gastroenterol Hepato* 1993;**8**:470-5.

14 Huang KY, Lin SR. Nationwide vaccination: A success story in Taiwan. *Vaccine* 2000;**18**:S35-8.

15 Huang CY, Huang KL, Cheng TJ, et al. The GSTT1 and CYP2E1 genotypes are possible factors causing vinyl chloride induced abnormal liver function. *Arch Toxicol* 1997;**71**:482-8.

16 Cheng TJ, Huang ML, You NC, et al. Abnormal liver function in workers exposed to low levels of ethylene dichloride and vinyl chloride monomer. *J Occup Environ Med* 1999;**41**:1128-33.

17 Chu CM, Sheen IS, Lin SM, et al. Sex difference in chronic hepatitis B virus infection: studies of serum HBeAg and alanine aminotransferase levels in 10,431 asymptomatic Chinese HBsAg carriers. *Clin Infect Dis* 1993;**16**:709-13.

18 Cheng TJ, Chou PY, Huang ML, et al. Increased lymphocyte sister chromatid exchange

frequency in workers with exposure to low level of ethylene dichloride. *Mutat Res* 2000;**470**:109-14.

19 Du CL, Kuo ML, Chang HL, et al. Changes in lymphocyte single strand breakage and liver function of workers exposed to vinyl chloride monomer. *Toxicol Lett* 1995;**77**:379-85.

20 Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *N Engl J Med* 2000;**342**:1266-71.

21 Salvaggio A, Periti M, Miano L, et al. Body mass index and liver enzyme activity in serum. *Clin Chem* 1991;**37**:720-3.

22 Clermont RJ, Chalmers TC. The transaminase tests in liver disease. *Medicine* 1967;**46**:197-207.

23 Sorbi D, Boynton J, Lindor KD. The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. *Am J Gastroenterol* 1999;**94**:1018-22.

24 Luo JC, Kuo HW, Cheng TJ, et al. Abnormal liver function associated with occupational exposure to dimethylformamide and hepatitis B virus. *J Occup Environ Med* 2001;**43**:474-82.

25 Swietek K, Juszczyk J. Reduced glutathione concentration in erythrocytes of patients with acute and chronic viral hepatitis. *J Viral Hepat* 1997;**4**:139-41.

26 Barbaro G, Di Lorenzo G, Soldini M, et al. Hepatic glutathione deficiency in chronic hepatitis C: quantitative evaluation in patients who are HIV positive and HIV negative and correlations with plasmatic and lymphocytic concentrations and with the activity of the liver disease. *Am J Gastroenterol* 1996;**91**:2569-73.

27 De Flora S, Hietanen E, Bartsch H, et al. Enhanced metabolic activation of chemical hepatocarcinogens in woodchucks infected with hepatitis B virus. *Carcinogenesis* 1989;**10**:1099-106.

28 ATSDR (Agency for Toxic Substances and Disease Registry). *Toxicological profile for vinyl chloride – Update.* Atlanta, Georgia: ATSDR, 1997.

29 World Health Organisation. *Environmental Health Criteria 176 1,2-Dichloroethane, Second Edition.* Geneva: WHO, 1995.

30 Dowsley TF, Forkert PG, Benesch LA, et al. Reaction of glutathione with the electrophilic metabolites of 1,1-dichloroethylene. *Chem Biol Interact* 1995;**95**:227-44.

31 Kaneko S, Miller RH, Di Bisceglie AM, et al. Detection of hepatitis B virus DNA in serum by polymerase chain reaction. Application for clinical diagnosis. *Gastroenterology* 1990;**99**: 799-804.

32 Michelet F, Gueguen R, Leroy P, et al. Blood and plasma glutathione measured in healthy subjects by HPLC: relation to sex, aging, biological variables, and life habits. *Clin Chem* 1995;**41**:1509-17.

33 Oh SI, Kim CI, Chun HJ, et al. Chronic ethanol consumption affects glutathione status in rat liver. *J Nutr* 1998;**128**:758-63.

34 Vendemiale G. Grattagliano I. Signorile A, et al. Ethanol-induced changes of intracellular thiol compartmentation and protein redox status in the rat liver: effect of tauroursodeoxycholate. *J Hepatol* 1998;**28**:46-53

TABLE 1

Frequency distribution of basic characteristics in percentage (%) among 568 male workers stratified by exposure categories

Characteristic	Chemical exposure			
	High (≥ 5) (n=76) (%)	Moderate (≥1 and < 5) (n=191) (%)	Low (<1) (n=301) (%)	Total (N=568) (%)
Manufacturing factory				
PVC	67.1	64.4	39.2	51.4**
VCM	32.9	25.6	60.8	48.6**
Age ≥ 40 years	46.1	46.1	59.1	53.0*
Duration of employment ≥ 15 years	43.4	45.0	56.5	50.9*
Body mass index ≥ 25.0 kg/m^2	29.0	33.0	27.9	29.8
Current cigarette smoking (yes)	48.7	43.5	36.9	40.7
Alcohol drinking (yes)	23.7	8.4	9.6	11.1**
Positive hepatitis B surface antigen (HBsAg)	19.7	15.7	17.6	17.3
Positive hepatitis B e antigen (HBeAg)	7.9	1.6	3.7	3.5
Positive anti-hepatitis C antibody (Anti-HCV)	1.3	4.7	3.7	3.7

* $p < 0.05$; ** $p < 0.01$ by χ^2 test.

TABLE 2

Odds ratio (OR) with 95% confidence intervals (C.I.) of multiple logistic regression modeling adjuste determinants: including body mass index (BMI), chemical exposure, hepatitis B surface antigen (HBs antibody (Anti-HCV), drinking, and smoking

		AST
Determinants	Definition	OR (95% C.I.)
Age (years)	≥ 40.0 ν < 40.0	0.8 (0.5-1.5)
BMI (Kg/M^2)	≥ 25.0 ν < 25.0	2.2 (1.2-3.9)*
Chemical exposure	High ν Low	1.3 (0.6-2.9)
	Moderate ν Low	0.8 (0.4-1.5)
HBsAg	Positive ν Negative	3.5 (1.9-6.4)*
Anti-HCV	Positive ν Negative	5.9 (2.2-15.9)*
Drinking	Yes ν No	1.3 (0.6-3.0)
Smoking	Yes ν No	1.1 (0.6-2.1)

* $p < 0.01$ by χ^2 test.

TABLE 3

Frequencies and adjusted Odds ratio (OR) with 95% confidence intervals (C.I.) of abnormal serum a activity stratified by exposure classification and hepatitis virus infection. All odds ratios were adjuste index and alcohol drinking.

	AST (n=58)			A (n=	
Category	%	OR (95%CI)†	OR (95% CI)‡	%	OR (95% C
HBsAg (+) or Anti-HCV (+)					
High Exposure	56.3	10.6 (3.6-31.5)*	6.2 (1.8-21.4)*	62.5	6.4 (2.1-19.
Moderate Exposure	23.5	3.0 (1.1-8.0)	1.6 (0.4-5.7)	35.3	2.1 (0.9-5.0
Low Exposure	15.9	2.3 (0.9-5.4)	1.0 (Referent)	19.0	1.4 (0.7-3.0
HBsAg (-) and Anti-HCV (-)					
High Exposure	1.7	0.5 (0.1-1.5)		11.7	0.5 (0.2-1.3
Moderate Exposure	5.7	0.6 (0.3-1.6)		14.6	0.7 (0.4-1.3
Low Exposure	8.8	1.0 (Referent)		16.4	1.0 (Referer

* $p < 0.01$ by Mantel-Haenszel χ^2 test for trend analysis

† The referent group (OR=1) refers to workers with low chemical exposure and negative hepatitis virus infection.

‡ The referent group (OR=1) refers to workers with low chemical exposure and positive hepatitis virus infection.

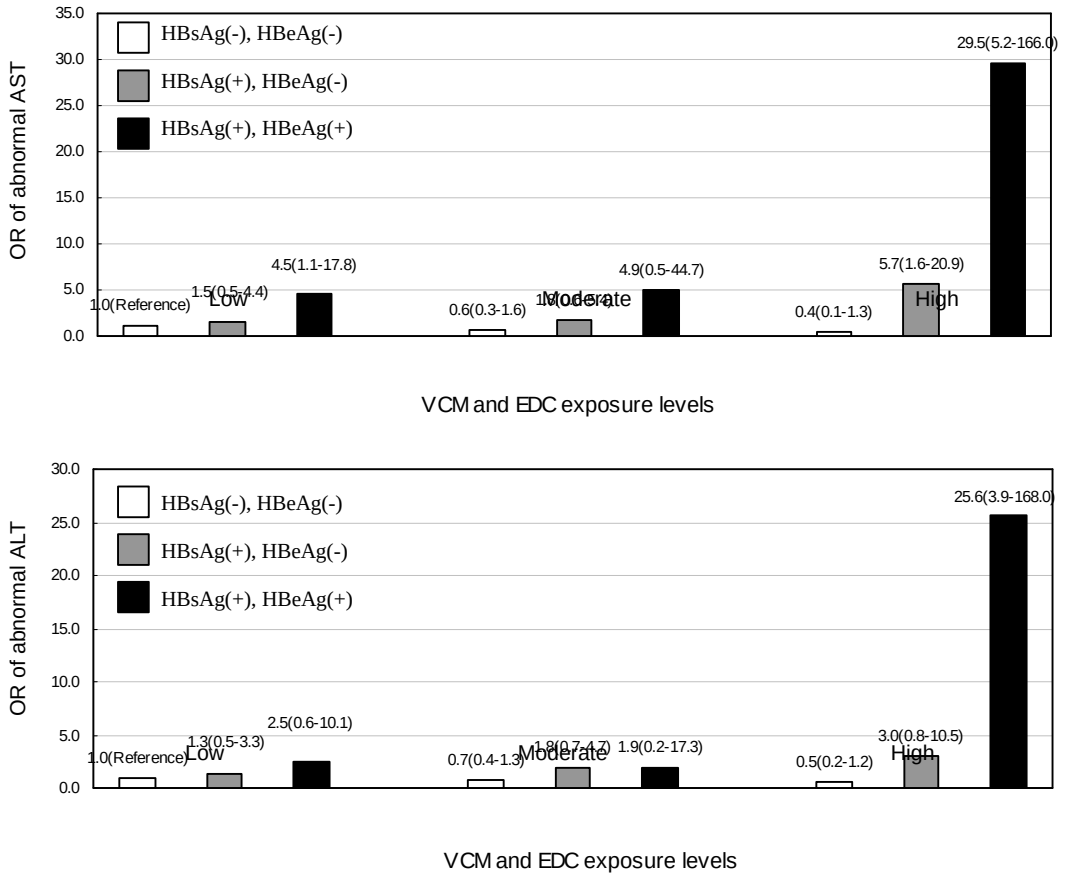

Figure 1

Odds ratio (OR) with 95% confidence intervals (CI) of abnormal AST (top) and ALT (bottom) among workers with different categories of exposure and hepatitis B infection; adjusted with age, drinking, Anti-HCV and BMI. The reference group (OR=1.0) refers to workers with low chemical exposure and negative hepatitis B infection.