修車工人苯暴露與白血病—個案討論與文獻回顧

成大醫院R2簡玉雯

Brief History

- 49 y/o male, HBV carrier
- Exersional dyspnea since May, 2012
- 高雄長庚CV OPD on 2012/8/1, Hb: 5.6, WBC: 2700, PLT:113000
- Bone marrow biopsy on 2012/8/14 : **AML, M2, chromosome +8**
- Induction C/T with D3A7 (2012/10/30-11/5)→complete remission→post remission C/T with Ara-C x 6 dose (2012/12/15)
- 2013/1/22: Dr. 王榮德' OPD
- Expired later

Occupational History

- 汽車修理約35年，近十年自營
- 工作時間：10 hr/day, 6 d/week
- 工作內容：
  - 用化油劑、清潔劑擦拭零件
  - 徒手用汽油在鐵盆中清洗零件，一次約十多分，一週約3-4次
  - 拆汽油濾清器和汽油幫浦常常
  - 無手套、口罩等防護
- 公會小姐說已經好幾個人得血癌

Occupational exposure & leukemia

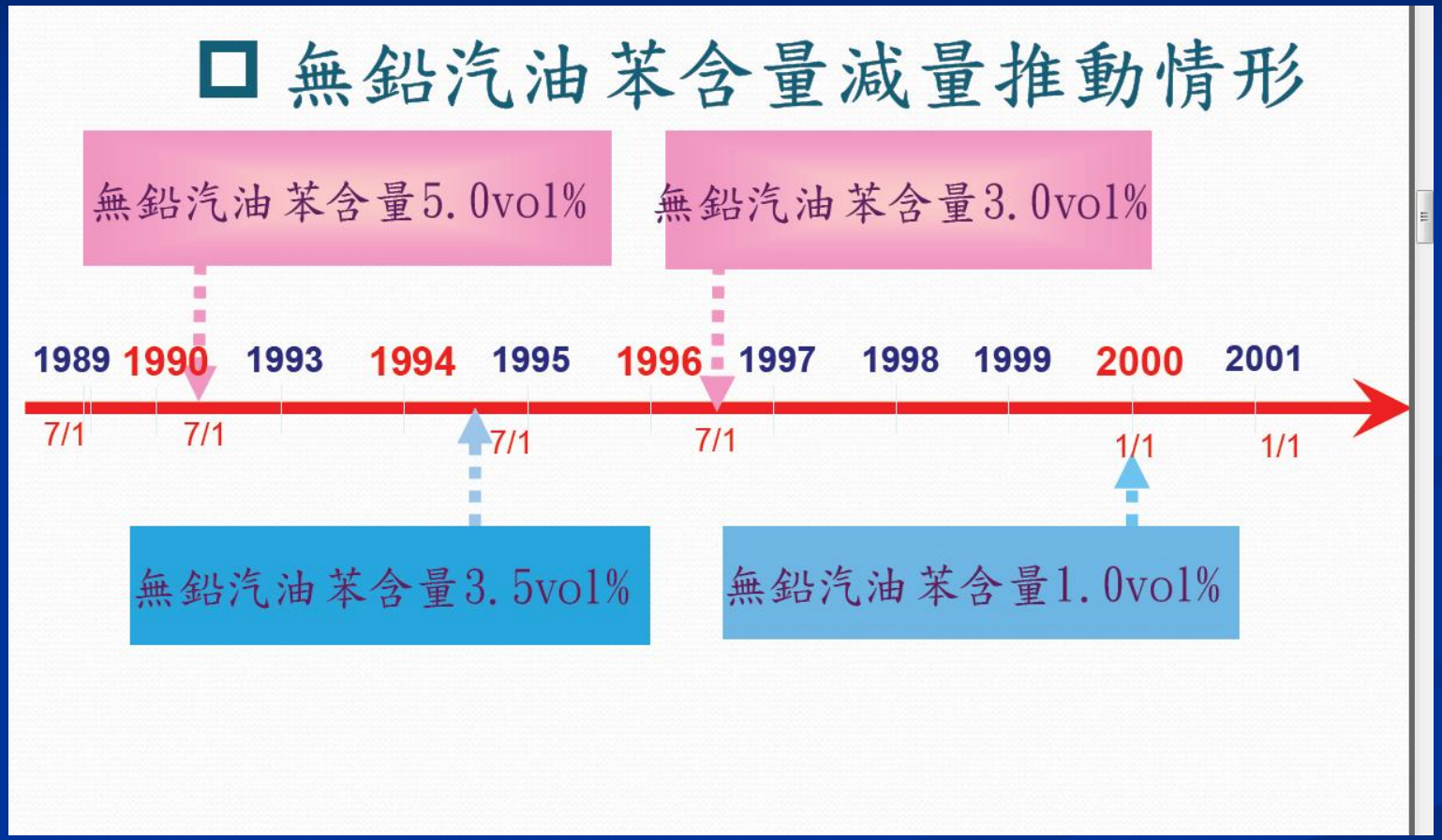
- Strong: Ionizing radiation, Ethylene oxide (環氧乙烷), **benzene**

	Tumour sites or types with sufficient evidence in humans	Tumour sites or types with limited evidence in humans	Evidence of genotoxicity as the main mechanism
Aromatic amines			
4-Aminobiphenyl	Urinary bladder	--	Strong
Benzidine	Urinary bladder	--	Strong
Dyes metabolised to benzidine	--	--	Strong*
4,4'-Methylenebis(2-chloroaniline)	--	--	Strong*
2-Naphthylamine	Urinary bladder	--	Strong
Ortho-toluidine	Urinary bladder	--	Moderate
Auramine production	Urinary bladder	--	Weak/lack of data†
Magenta production	Urinary bladder	--	Weak/lack of data†
PAH-related exposures			
Benzo[a]pyrene	--	--	Strong*
Soot (chimney sweeping)	Skin, lung	Urinary bladder	Moderate
Coal gasification	Lung	--	Strong
Coal-tar distillation	Skin	--	Strong
Coke production	Lung	--	Strong
Coal-tar pitches (paving, roofing)	Lung	Urinary bladder	Strong
Aluminium production	Lung, urinary bladder	--	Weak/moderate†‡
Other chemicals			
Aflatoxins	Hepatocellular carcinoma	--	Strong
Benzene	ANLL	ALL**, CLL**, MM**, NHL**	Strong
Bis(chloromethyl)ether/chloromethyl methylether	Lung	--	Moderate/strong

Benzene and chromosomal change in AML

- Exposure to benzene has been associated with higher level of the chromosomal changes commonly observed in AML, including 5q-/-5 or 7q-/-7, +8, and t(8;21) in the blood cells of highly exposed workers.

□ 無鉛汽油苯含量減量推動情形



Automobile Mechanics & benzene

- Mechanics' benzene exposures have recently been reported to range from 0.01 to 13.6 mg/m3, with the vast majority of measurements well below the current OSHA standard of 1 p.p.m. (3.2 mg/m3)
- Possible **dermal exposure** to benzene has been virtually ignored despite knowledge that mechanics sometimes washed their hands with gasoline and even siphoned gasoline by mouth
- Dermal route may be the source of as much as 80% of the benzene levels measured in blood following repair work involving direct contact with gasoline

Ann Occup Hyg. 2002 Jul;46(5):489-500.

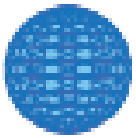
Risk assessment

- Risk assessment in 1989: AML can be caused by excessive benzene exposure, meaning a peak benzene exposure greater than 20 ppm or an estimated cumulative benzene exposure greater than 250 ppm-years.
- Very High exposure:

  400-1000 ppm-years: RR = 9

  > 1000 ppm-years: RR = 83

Khalade et al. Environmental Health 2010, 9:31
http://www.ehjournal.net/content/9/1/31



ENVIRONMENTAL HEALTH

RESEARCH Open Access

Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis

Abdul Khalade[1], Maritta S Jaakkola[2], Eero Pukkala[3,4] and Jouni JK Jaakkola*[1,5]

Abstract

Background: A substantial number of epidemiologic studies have provided estimates of the relation between exposure to benzene at work and the risk of leukemia, but the results have been heterogeneous. To bridge this gap in knowledge, we synthesized the existing epidemiologic evidence on the relation between occupational exposure to benzene and the risk of leukemia, including all types combined and the four main subgroups acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML).

Methods: A systematic literature review was carried out using two databases 'Medline' and 'Embase' from 1950 through to July 2009. We selected articles which provided information that can be used to estimate the relation between benzene exposure and cancer risk (effect size).

Results: In total 15 studies were identified in the search, providing 16 effect estimates for the main analysis. The summary effect size for any leukemia from the fixed-effects model was 1.40 (95% CI, 1.23-1.57), but the study-specific estimates were strongly heterogeneous ($I^2 = 56.5\%$, Q stat = 34.47, $p = 0.003$). The random-effects model yielded a summary- effect size estimate of 1.72 (95% CI, 1.37-2.17). Effect estimates from 9 studies were based on cumulative exposures. In these studies the risk of leukemia increased with a dose-response pattern with a summary-effect estimate of 1.64 (95% CI, 1.13-2.39) for low (< 40 ppm-years), 1.90 (95% CI, 1.26-2.89) for medium (40-99.9 ppm-years), and 2.62 (95% CI, 1.57-4.39) for high exposure category (> 100 ppm-years). In a meta-regression, the trend was statistically significant ($P = 0.015$). Use of cumulative exposure eliminated heterogeneity. The risk of AML also increased from low (1.94, 95% CI, 0.95-3.95), medium (2.32, 95% CI, 0.91-5.94) to high exposure category (3.20, 95% CI, 1.09-9.45), but the trend was not statistically significant.

Conclusions: Our study provides consistent evidence that exposure to benzene at work increases the risk of leukemia with a dose-response pattern. There was some evidence of an increased risk of AML and CLL. The meta-analysis indicated a lack of association between benzene exposure and the risk of CML.

Table S3- Summary of effect size for the relation between benzene exposure and risk of leukemia and dose-response analysis

	Model		Heterogeneity statistics			
	Fixed-effects model (ES [95% CI])	**Random-effects model (ES [95% CI])**	**I^2 Index (%)**	**Q**	**(n)**	***P* value**
Leukemia						
Single stratum including total population	1.40 (1.23-1.57)	1.72 (1.37-2.17)	56.5	34.47	(16)	0.003
Dose response analysis						
Low (>0 to < 40 ppm-years)	1.64 (1.13-2.39) 66 cases*	1.64 (1.13-2.39)	0.0	4.47	(8)	0.725
Medium (40 to < 100 ppm-years)	1.90 (1.26-2.89) 44 cases*	1.90 (1.26-2.89)	0.0	4.23	(6)	0.516
High (100 - ppm-years)	2.62 (1.57-4.39) 33 cases*	2.62 (1.57-4.39)	0.0	1.27	(7)	0.973
No dose available	1.25 (1.09-1.44)	1.50 (1.12-2.02)	63.5	16.44	(7)	0.012
Acute myeloid leukemia						
Single stratum including total population	1.38 (1.15-1.64)	1.70 (1.22-2.36)	51.4	16.46	(9)	0.036
Dose response analysis						
Low (>0 to < 40 ppm-years)	1.94 (0.95-3.95) 18 cases*	1.94 (0.95-3.95)	0.0	1.27	(4)	0.737
Medium (40 to <100 ppm-years)	2.32 (0.91-5.94) 8 cases*	2.32 (0.70-7.72)	38.7	1.63	(2)	0.202
High (100 - ppm-years)	3.20 (1.09-9.45) 12 cases*	3.20 (1.09-9.45)	0.0	0.24	(2)	0.624
No dose available	1.28 (1.06-1.54)	1.48 (1.04-2.11)	57.3	9.37	(5)	0.053

Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. Environ Health. 2010 Jun 28;9:31. doi: 10.1186/1476-069X-9-31.

Exposure Limits

- American Conference of Governmental Industrial Hygienists (ACGIH)
  - 100ppm(1946), 25ppm (1948), 10 ppm (1977),
  - Since 1997: 0.5 ppm (STEL: 2.5 ppm)
- Occupational Safety and Health Administration (OSHA):
  - Since 1987: TWA 1 ppm, STEL 5 ppm
- Taiwan: TWA: 1 ppm, STEL: 2 ppm

修車廠作業員工揮發性有機物質暴露評估 - 1999

表 4-4-4　作業別個人 VOCs 暴露濃度量測結果(μg/m³)

VOCs	引擎修護組 (N=39)	鈑金組 (N=10)	噴漆組 (N=11)
MTBE	20.21±7.32* [ND~4493.52]	19.17±4.58 [ND~226.64]	6.08±4.95 [ND~234.94]
Benzene	52.42±2.34 [4.05~323.42]	25.72±4.07 [ND~94.96]	30.68±4.57 [ND~118.91]
Toluene	484.30±7.24 [ND~11212.47]	553.72±10.47 [ND~16818.96]	1059.11±11.22 [ND~20796.55]
Ethylbenzene	139.75±3.80 [ND~2953.42]	96.85±8.13 [ND~815.46]	297.36±10.47 [ND~3648.63]
m- & p-Xylene+	89.42±5.13 [ND~1388.19]	116.32±5.50 [ND~1413.53]	339.37±5.75 [19.68~3617.07]
o-Xylene	89.07±3.80 [ND~965.66]	85.52±5.01 [ND~1023.40]	182.34±8.13 [ND~2570.17]
1,2,4-Trimethylbenzene+	8.75±4.33 [ND~225.22]	15.08±3.48 [ND~121.53]	37.13±3.71 [ND~493.43]
1,3,5-Trimethylbenzene	62.62±4.85 [ND~1123.58]	28.76±3.92 [ND~388.32]	129.82±3.76 [ND~1289.94]
總 VOCs	1505.01±3.49 [124.06~13321.62]	1467.39±5.29 [107.50~18701.57]	2846.58±4.05 [138.09~30478.71]

*GM±GSD [Range]

+經 ANOVA 統計分析作業別之個人暴露濃度差異，$p<0.05$。

Exposure from air: 0.016 ppm x 35 years = 0.57 ppm-year

A Quantitative Method for Estimating Dermal Benzene Absorption from Benzene-containing Hydrocarbon Liquids

STEPHEN E. PETTY, MARK NICAS, ANTHONY A. BOIARSKI

This study examines a method for estimating the dermal absorption of benzene contained in hydrocarbon liquids that contact the skin. This method applies to crude oil, gasoline, organic solvents, penetrants, and oils. The flux of benzene through occluded skin as a function of the percent vol/vol benzene in the liquid is derived by fitting a curve to experimental data; the function is supralinear at benzene concentrations ≤ 5% vol/vol. When a liquid other than pure benzene is on nonoccluded skin, benzene may preferentially evaporate from the liquid, which thereby decreases the benzene flux. We present a time-averaging method here for estimating the reduced dermal flux during evaporation. Example calculations are presented for benzene at 2% vol/vol in gasoline, and for benzene at 0.1% vol/vol in a less volatile liquid. We also discuss other factors affecting dermal absorption. *Key words*: benzene; dermal; exposure; modeling; quantification; flux; gasoline; mineral spirits; crude oil

INT J OCCUP ENVIRON HEALTH 2011;17:287–300

centration in the hydrocarbon liquid; 2) the composition of the liquid; 3) the condition and body location/area of the skin; and 4) the duration of exposure.[1] Although inhalation of benzene vapor has traditionally received the most attention, more consideration is now being given to dermal exposures to benzene,[2,3] and to chemical contaminants, in general.[4,5]

For example, Sahmel, Boeniger, and Fehrenbacher[5] estimated benzene dermal absorption for automotive repair workers who used gasoline containing 2% benzene. They calculated that approximately 92% of the total daily benzene absorbed dose was due to dermal exposure. In making this estimate, they assumed that 1% of the benzene in the volume of gasoline contacting the skin was absorbed. The 1% value was based, in part, on the observations that 0.13% of pure benzene placed in a nonoccluded manner on human palmar skin is absorbed; damaged primate skin permits fivefold more benzene absorption *in vivo* than does nondamaged skin; and workers with frequent hand contact

Int J Occup Environ Health. 2011 Oct-Dec;17(4):287-300.

Dermal Absorption

- DA (mg) = 0.024 x $(\%C_B)^{0.6616}$ x (Surface area, cm^2)

  x F_{abs} x (Time, hr)

  → 3675 mg = 1 ppm-year

  - 徒手用汽油在鐵盆中清洗零件，一次約十多分，一週約3-4次，共35年

    → 26.4 ppm-year

  - 拆汽油濾清器和汽油幫浦常常被汽油噴濺全身

    → Duration? Surface area? Frequency

Back to the case

- 疾病的證據: **AML, M2, chromosome +8**
- 暴露的證據:
  - Inhalation: 0.016 ppm x 35 year = 0.57 ppm-year
  - Dermal exposure: > 26.7 ppm-year
- 時序性
- 流行病學: 40-100 ppm-year
- 排除其他因素: smoking(-), family history (-), no radiation exposure

- Thank you for your attention

慢性苯中毒診斷認定基準

主要基準

一、具職業苯暴露史及符合時序性。暴露證據須確認工作中暴露於液態或蒸氣苯。

二、臨床症候或徵象並無特異性，嚴重者可能出現血液系統病變症狀。常有頭痛、頭暈、噁心、倦怠等症狀，並可能伴有易感染和(或)出血傾向。

三、血液檢查出現病變。符合下列之一者：(a)白血球計數低於 4000/uL 或嗜中性白血球計數低於 2000/uL，伴血小板計數低於 60×10^3/uL；(b)白血球計數低於 3000/uL 或嗜中性白血球計數低於 1500/uL。

四、骨髓檢查出現病變。符合下列之一者：全血細胞減少症、再生不良性貧血、骨髓形成不良症候群、白血病。

五、排除其他非苯可能造成上述血液病變的原因。

輔助基準

一、同一工作環境，其他工作者也有類似血液症狀或疾病。

二、生物偵測顯示尿中苯的代謝物 S-Phenylmercapturic acid 及 t,t Muconic acid 測定值增高。

三、作業環境空氣採樣測定之苯濃度可能引起血液疾病。苯八小時之時量平均濃度 1 ppm。

Type	Name	Cytogenetics	Percentage of adult AML patients
M0	Minimally differentiated acute myeloblastic leukemia		5%[4]
M1	acute myeloblastic leukemia, without maturation		15%[4]
M2	acute myeloblastic leukemia, with granulocytic maturation	t(8;21)(q22;q22), t(6;9)	25%[4]
M3	promyelocytic, or acute promyelocytic leukemia (APL)	t(15;17)	10%[4]
M4	acute myelomonocytic leukemia	inv(16)(p13q22), del(16q)	20%[4]
M4eo	myelomonocytic together with bone marrow eosinophilia	inv(16), t(16;16)	5%[4]
M5	acute monoblastic leukemia (M5a) or acute monocytic leukemia (M5b)	del (11q), t(9;11), t(11;19)	10%[4]
M6	acute erythroid leukemias, including erythroleukemia (M6a) and very rare pure erythroid leukemia (M6b)		5%[4]
M7	acute megakaryoblastic leukemia	t(1;22)	5%[4]

SECTION 1: PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME: 3M™ Carburetor Cleaner, 08796
MANUFACTURER: 3M
DIVISION: Automotive Aftermarket

ADDRESS: 3M Center, St. Paul, MN 55144-1000

EMERGENCY PHONE: 1-800-364-3577 or (651) 737-6501 (24 hours)

Issue Date: 10/08/12
Supercedes Date: 05/06/11

Document Group: 25-9065-1

Product Use:
Intended Use: Automotive
Specific Use: Automotive Engine Cleaning Solvent

SECTION 2: INGREDIENTS

Ingredient	C.A.S. No.	% by Wt
TOLUENE	108-88-3	35 - 45
ACETONE	67-64-1	20 - 30
METHYL ALCOHOL	67-56-1	10 - 15
PROPANE	74-98-6	10 - 15
DIACETONE ALCOHOL	123-42-2	5 - 10

Benzene

- C6H6
- 在常溫下爲無色揮發性液體，蒸氣壓約75 mmHg
- 熔點攝氏5.5度，沸點爲攝氏80.1度
- 良好的溶劑、去漬劑和清潔劑，先前常被用於油漆、油墨及黏合劑之使用，已漸被甲苯等較低毒性之溶劑取代。
- 許多有機化物的製造原料：

  - 苯乙烯（styrene）：可做手提箱、膠盔、汽車零件
  - 環已烷（cyclohexane）：可做尼龍、合成纖維、工業塑膠
  - 酚（phenol）：可做酚醛樹脂、電氣塑膠
  - 硝基苯（nitrobenzene）：可做火藥
  - 氯苯（chlorobenzine）：可做藥物、農藥等。

Benzene

- 石化工業、橡膠工業、製鞋業、鋼鐵業、印刷業、塑膠業
- 接著劑、化妝品、香水、染料、肥皂、藥品、殺蟲劑、火藥、油漆去污等方面。
- 無鉛汽油中含有1-2% (USA)或≦5% (UK)的苯。
- 香煙中也含苯，一天一包血中苯濃度爲工作於1ppm苯濃度之作業環境的1/30。

代謝途徑

- 由呼吸道和皮膚吸收
- 吸收後主要分佈於脂肪及骨髓組織，30-50%由呼吸道排出
- 其餘由肝臟經酵素cytochrome P-450 代謝成有毒的活性氧自由基產物 (dihydroxyl metabolites)，例如benzoquinone，進入細胞核與DNA鍵結， 這個作用可能與血液癌症的發生有關。

Chronic lymphocytic leukemia						
Single stratum including total population	1.31 (1.09-1.57)	1.31 (1.09-1.57)	0.0	8.86	(10)	0.450
Dose response analysis						
Low (0< 40 ppm-years)	1.83 (0.75-4.48) 13 cases*	1.86 (0.71-4.86)	13.1	1.15	(2)	0.283
Medium (40- 99 ppm-years)	1.67 (0.86-3.24) 15 cases*	1.67 (0.86-3.24)	0.0	0.23	(3)	0.893
High (100 - ppm-years)	3.50 (0.90-13.2) 9 cases*	N/A			(1)	
No dose available	1.24 (1.02-1.50)	1.24 (1.02-1.50)	0.0	4.79	(6)	0.442
Chronic myeloid leukemia						
Single stratum including total population	1.05 (0.83-1.34)	1.05 (0.83-1.34)	0.0	1.69	(6)	0.890
No dose available	1.06 (0.83-1.35)	1.06 (0.83-1.35)	0.0	1.54	(5)	0.819

*Number of cases