

# 行政院國家科學委員會補助專題研究計畫成果報告

## 環境職業生殖危害（三）— 台灣地區男性氯乙烯聚合工人配偶受孕所需時間 及其下一代出生異常之研究(2/2)

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計畫主持人：陳保中

共同主持人：鄭尊仁

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### Environmental and occupational reproductive hazards (3) - Time-to-pregnancy among the wives and adverse birth outcomes among the offspring of male polyvinyl chloride workers in Taiwan (2/2)

計畫編號：NSC 90-2320-B-002-124

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主持人：陳保中

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執行機構及單位名稱：台灣大學公共衛生學院職業醫學與工業衛生研究所

#### 一、中文摘要

雖然國內氯乙烯聚合工人世代曾發表過肝功能異常、肝硬化或肝癌、及基因傷害相關的論文，但並不曾探討氯乙烯單體對生殖系統及下一代的影響；男性氯乙烯單體暴露工人曾被報導會導致性慾下降及影響精子生成，但對於是否會影響下一代健康並無一致的結論；因此值得進一步探討男性氯乙烯聚合工人世代的生育能力及對下一代出生異常的影響。本研究分為受孕所需時間及異常出生結果兩部份，懷孕所需時間研究部份為一回溯性世代研究，主要探討男性氯乙烯聚合工人配偶受孕所需時間及異常懷孕狀況如自然流產及死產等，連結台灣結婚登記資料庫共有416位男性氯乙烯聚合工人在最近15年內結婚，本研究第一年完成了93位配偶的面訪問卷；初步資料分析僅在高暴露（大於5 ppm）有較低的相對受孕比。至於異常出生結果研究部份亦是一回溯性世代研究，主要探討男性氯乙烯聚合工人下一代異常出生結果如低出生體重兒、早產兒、及先天缺陷等，在目前已完成的資料連鎖中，在1978至1997年男性工人配偶共有4,706位活產嬰兒，發現暴露組有10位新生而死亡及15位嬰兒死亡發生而非暴露組並無任何嬰兒死亡個案發生。但在648位有暴露資訊的嬰兒中，並無較高的低出生嬰兒或早產兒危險性發生。

**關鍵詞：**氯乙烯單體、世代研究、受孕所需時間、自然流產、死產、低出生體重兒、早產兒、先天缺陷、基因多形性。

#### Abstract

Although there were several published works on abnormal liver functions, liver cirrhosis or cancer, and genetic damages of Taiwan polyvinyl chloride (PVC) cohort, the potential effect of vinyl chloride monomer (VCM) exposure on reproduction has not yet been studied. Male VCM-exposed workers have been

reported loss of libido and reduced spermatogenesis but the effect of male VCM exposure on next generation was inconclusive. Now it is a chance to investigate the effect of male VCM exposure on fecundability measured by time to pregnancy and adverse birth outcomes in Taiwan PVC cohort. This study includes two sub-studies: time-to-pregnancy and adverse birth outcome. The time-to-pregnancy sub-study is designed as a retrospective cohort study to investigate fecundability measured by waiting time to pregnancy and pregnancy outcomes such as spontaneous abortion and stillbirth among the wives of male PVC workers. We recruited 416 valid male workers that married within recent 15 years according to Taiwan marriage registration database. In the first year of this study, 93 wives of male PVC workers participated and finished a face-to-face questionnaire interview. The current analysis consisted of 210 valid pregnancies only. In the preliminary analysis, we found that relative fecundability ratio of the high exposed group (more than 5 ppm) was less than that of non-exposed group although it is not statistically significant. The adverse birth outcome sub-study is designed as a retrospective cohort study to investigate adverse birth outcomes such as low birth weight, prematurity, and infant death with congenital anomalies among the offspring of male PVC workers. We utilized 3925 male PVC workers that have valid national identification numbers to link Taiwan birth registration database during 1978-97. A total of 4,706 livebirths was identified to assess adverse birth outcomes among the offspring of male polyvinyl chloride workers. There were nine newborn deaths and 14 infant deaths among exposed group with unknown exposure level but no case was found in the non-exposed group. However, we could not analyze them further due to few infant deaths. Among 648 births with known exposure level, there was no

significant difference among different exposure groups, either by exposure levels or duration of employment.

**Keywords:** vinyl chloride monomer, cohort studies, time to pregnancy, infant death, low birth weight, and preterm birth.

## 二、緣由與目的

Polyvinyl chloride (PVC) polymerization process beginning in 1950s has become one of the major industries in Taiwan with an annual production of more than one million tons [1]. Many workers were exposed to high concentration of vinyl chloride monomer (VCM), which could cause liver cancers, particularly angiosarcoma of the liver [2-6]. Vinyl chloride has thus classified by the International Agency for Research on Cancer (IARC) as group I carcinogen [7].

It has been proved that VCM exposure of male workers may result in cancer or chromosomal damage, potentially increasing individual risk of liver cancer. However, germ line mutation may lead to infertility, adverse pregnancy outcomes, or heritable alterations expressed in future generations. This area has not been conclusive.

Infante and colleagues noted increased reporting of fetal loss by wives of VCM-exposed workers in a cross-sectional survey of PVC polymerization workers [8]. This study has been criticized because its methods of data collection and reporting were indirect [9] because data on spontaneous abortions obtained directly the workers' wives would have been preferable [10]. Two independent studies failed to find increased spontaneous abortions among wives of vinyl chloride workers [11,12]. No significant increase of spontaneous abortions was seen in a group of 44 female workers exposed to vinyl chloride and other plastics [13].

Data on the potential human teratogenicity of VCM are inconclusive [14-16]. High rates of congenital anomalies of the central nervous system have been reported in communities with PVC polymerization plants [8,16-18]. In subsequent studies, malformations were seen, but there was no relationship with parental occupation or residential distance from the source of vinyl chloride [19,20]. There is insufficient evidence to conclude that VCM is a human teratogen [21].

A literature review on the effects of human paternal VCM exposure on the unborn was inconclusive [15]. VCM has been reported to affect male reproduction. Loss of libido was reported in 37 male workers [14]. Men exposed to VCM levels as low as 30 mg/m<sup>3</sup> for 5 years had effects on spermatogenesis [22].

VCM has not been teratogenic in laboratory

animals. It was fetotoxic in rats exposed to an airborne concentration of 500 ppm, and caused increased post-implantation mortality in fetal rats exposed to 1500 ppm [23]. VCM was not teratogenic in rodents or rabbits exposed to airborne concentrations as high as 2,500 ppm [24]. It was not teratogenic in rats, mice, or rabbits.

However, animal studies suggest decreased male fertility. Male rats exposed to an airborne concentration of 1000 ppm for 6 hours per day for 55 days prior to mating had lowered fertility [22]. Increased pre-implantation mortality was seen in embryonic mice when the males were exposed to a very high airborne level of 30,000 ppm for 5 days prior to mating [22]. Decreased female fertility was seen in rats exposed to an airborne concentration of 250 ppm for 55 days prior to mating [22]. Also, considerable transfer of VCM to amniotic fluid and fetal blood was demonstrated in pregnant rats [14].

Excess birth defects, fetal loss, loss of male libido, and decreased spermatogenesis have been linked with occupational and/or environmental VCM exposure, but these effects have not been conclusively confirmed. Therefore, the actual human reproductive hazard is unknown. Nevertheless, the ever-expanding literature on the mutagenic effects of VCM in microbial and mammalian test system raises concern about possible genetic or reproductive effects, although teratogenicity has not been identified in animal systems.

Although there were several published works on abnormal liver functions [25], liver cirrhosis or cancer [26,27], and genetic damages [28-31] of Taiwan PVC cohort, the potential effect of VCM exposure on reproduction has not yet been studied. In the previous section, male VCM-exposed workers have been reported loss of libido [14] and reduced spermatogenesis [22] but the effect of male preconceptional VCM exposure on next generation was inconclusive [15]. Now it is a chance to investigate the effect of male VCM exposure on fecundability measured by time to pregnancy and adverse birth outcomes in Taiwan PVC cohort. The objective of this study is to assess waiting time to pregnancy among the wives of male polyvinyl chloride workers in Taiwan and to assess adverse birth outcomes among offspring of male polyvinyl chloride workers in Taiwan.

## 三、材料與方法

### 1. Establishment of the PVC cohort

The cohort consisted of 4,011 male and 85 female workers from six PVC polymerization plants. All female employees were office workers and, therefore, they were excluded from the study. The name list was collected from Bureau of Labor Insurance (BLI) where workers' information including national identification number (ID), date of birth, gender, dates of employment and discharge, and job

title was maintained. However, 2% national ID of these workers was not available [27]. As each factory, which employs more than 5 workers, is compulsory to join the national labor insurance by law, the inclusion of our cohort for PVC workers should be comprehensive. In addition, their life styles, occupational and medical histories were also obtained through the annually medical surveillance between 1988 and 1998.

## 2. Time-to-pregnancy study

### (1) Study design and subjects

This sub-study is designed as a retrospective cohort study to investigate fecundability measured by waiting time to pregnancy and pregnancy outcomes such as spontaneous abortion and stillbirth among the wives of male PVC workers. First, we linked male PVC workers to the factory personnel records and Taiwan Ministry of the Interior (MOI) marriage registration database to identify married PVC workers and to establish the PVC marriage cohort. Because valid data on time to pregnancy at a group level can be derived retrospectively with duration of 14 years or more [32,33], we only recruited the male PVC workers who were married within 15 years to reduce the potential recall bias. This valid PVC marriage cohort included 416 male workers who married during 1986-2000 and whose wives approximately gave more than 800 pregnancies in total. We interviewed their wives to collect detailed pregnancy history and other potential confounding factors, and collected specimen from these male married workers to analyze their genetic polymorphisms. These pregnancies was divided into those conceived before the start of employment and those conceived at least 3 months after the start of employment. The latter was grouped into pregnancies to low (less than 1 ppm), middle (1-5 ppm), and high VCM-exposed fathers (more than 5 ppm). Finally, we analyzed the fecundability and pregnancy data among the different groups according to the dose of VCM exposure during 3 months before conception. Furthermore, we will analyze the modification effect of genetic polymorphisms on fecundability and pregnancy outcomes.

### (2) Questionnaire interview

We used a questionnaire to face-to-face interview the wives of the married PVC workers and to collect detailed pregnancy history, especially for waiting time to pregnancy, and other potential confounding factors [33,34]. The key question on the waiting time to pregnancy was phrased as follows: "How many months did it take you to get pregnant?" that is, how many months were you having sexual intercourse without using any method of birth control? [35] They were asked about the last method of birth control for each pregnancy. If they had used an intrauterine device or oral contraceptives, they were asked how many months before each pregnancy they had stopped.

There also were questions on lifestyle factors

such as smoking, use of alcohol, tea or other caffeine beverages during each pregnancy for both of spouse. Information was requested on the husband's possible illness or some other conditions that could have handicapped his ability to become a father, such as parotitis, orchitis, varicocele, and major systemic diseases. The pregnancy history in wives for this study, information on pelvic inflammatory diseases, endometriosis, major abdominal surgery history, treatment for menstrual irregularity and infertility, age at menarche, menstrual regularity, the duration of the menstrual cycle also were collected by the questionnaire. Additional data on work status, and the main work tasks of the wife were collected for the 12 months preceding the pregnancy. Information on men's work history was collected in the PVC cohort database [27].

### (3) Exposure assessment

VCM exposure levels for these study subjects were based on previously published work [36,37]. Briefly, personal and area sampling was conducted to obtain the dose of VCM-exposure according to the method recommended by the US National Institute of Occupational Safety and Health (NIOSH) [38]. Time weighted average VCM exposure levels were assigned to each job category of workers. The assessment of VCM exposure will be adopted if the husband had the same job at the beginning of the time to pregnancy of his wife as during 80 days (the estimated period of spermatogenesis) before the beginning of the studied pregnancy.

The likelihood of VCM exposure was categorized as follows: those to non-exposed fathers (pregnancies conceived before the start of husband employed in the PVC factories or pregnancies conceived after the start of husband employment in the PVC factories but did not expose to VCM), those to low (less than 1 ppm), middle (1 to 5 ppm), and high VCM-exposed fathers (higher than 5 ppm). The duration of employment in the PVC factories was grouped into short (<5 years) and long ( $\geq 5$  years) duration. The exposure assessment was made as blindly as possible in relation to the outcome variable.

### (4) Participation and exclusion criteria

For the analysis of time-to-pregnancy data, couples that had known etiologies of infertility were excluded such as wife had been operated on because of infertility, wife had endometriosis or obstruction of the fallopian tube, husband's parotitis, diabetes, orchitis or hydrocele testis as a child. Wives who could not determine their time to pregnancy were excluded. For the analysis of spontaneous abortion and stillbirth, pregnancies ending in induced abortion, or ectopic or molar pregnancy were excluded. Wives who had systemic diseases such diabetes, hypertension, or syphilis infection were excluded.

### (5) Confounding variables

The following potential confounding variables selected for their biological relevance were included in the analysis for time-to-pregnancy data: age, work status, use of tea, smoking, and use of alcohol in either men or their wives; age at pregnancy, regularity of menses and menarche of wives, severe cold or medication during pregnancy. Known or suspected risk factors for spontaneous abortion and stillbirth: age, work status, smoking either in men or their wives, age at pregnancy, pregnancy history, and socioeconomic status. Pregnancy start year and location also were identified as confounders during the analysis.

#### (6) Statistical analysis

Data on time to pregnancy was analyzed by using the discrete proportional hazard regression with the Statistical Analysis System (SAS) PHREG procedure [39]. Proportional hazards are assumed during the continuous fertile periods within menstrual cycles. Under this assumption, the discrete proportional hazard model is reasoned, and the outcome variable is interpretable as an incidence density ratio (IDR). As pregnancy is a desired outcome, we used the phrase fecundability density ratio (FDR) in place of IDR of pregnancies. The 95% confidence intervals (95% CI) were calculated.

Data on spontaneous abortion and stillbirth was first estimated the relative risk obtained by dividing the rate in the exposed group by the rate in the unexposed group. Potential confounding factors were identified and controlled by Mantel-Haenszel stratification and logistic regression. For the logistic regression, we used the SAS logistic regression procedure [39]. The relative risk estimated in logistic regression is the odds ratio and the 95% confidence intervals (95% CI) were calculated.

Most of the potential confounding factors were analyzed as dichotomous, but also multilevel and continuous. Age was forced into the model. The other variables in the final models were selected on the basis of priori knowledge of known and suspected risk factors and their association with outcome variables in the models. We checked that the exclusion of other variables from the model has no essential effect on the results.

### 3. Adverse birth outcome study

#### (1) Study design and subjects

This sub-study is designed as a retrospective cohort study to investigate adverse birth outcomes such as low birth weight, prematurity, and infant death with congenital anomalies among the offspring of male PVC workers. First, we utilized 3925 male PVC workers that have valid national identification numbers to link Taiwan birth registration database during 1978-97. A total of 4,706 legitimate livebirths was identified to assess adverse birth outcomes among the offspring of male polyvinyl chloride workers. These births will be divided into those conceived

before the start of employment and those conceived at least 3 months after the start of employment. The latter will be grouped into births to low (less than 1 ppm), middle (1-5 ppm), and high VCM-exposed fathers (more than 5 ppm). Moreover, we will link these exposed group and non-exposed groups to Taiwan death registration database to obtain infant deaths with congenital anomalies. Finally, we will analyze adverse birth outcomes among the different groups according to the dose of VCM exposure during 3 months before conception.

#### (2) Data sources

##### 1) Taiwan birth registration database

Information on adverse birth outcomes was obtained from Taiwan birth registration database, which is responsible by Ministry of the Interior. For each birth, detailed demographic information, including national identification number, sex, date of birth, parity, multiplicity, gestational age, birth weight, and place of birth; and parent's national identification numbers, dates of birth, levels of education, industries and occupations, and residential 'Li' (village) were recorded. The system has been completely computerized since 1978.

##### 2) Taiwan death registration database

Information on infant death with congenital anomalies was obtained from Taiwan death registration database, which is responsible by the Bureau of Vital Statistics of Taiwan Provincial Department of Health. For each death, detailed demographic information, including personal identification number, sex, date of birth, date of death, cause of death, place of death, and residential district (town) were recorded. The International Classification of Disease, Injury, and Causes of Death [9th revision (ICD-9)] is used to code the cause of death, and the system has been completely computerized since 1971.

However, we found some data defects inside this database, such as the accuracy of causes of death and ICD coding errors; they don't have national identification numbers before 1975; national identification number errors including missed some numbers, checking number errors, and duplicates; these files don't include the death cases of delayed notification; and the problem of emigration and missing persons. Thus, we will use the other death registration database, which is responsible by Ministry of the Interior since 1978.

#### (3) Exposure assessment

Exposure assessment has been described in the time-to-pregnancy sub-study.

#### (4) Confounding variables

Known or suspected risk factors for LBW and prematurity should be identified and control in the models. However, Taiwan birth registration database only offered the baby's sex, parity, multiplicity, and

both parents' ages, levels of education, industries and occupations, and marital status. However, Chen and colleagues suggested that education is a more favorable socioeconomic indicator in Taiwan for examining birth outcome than is occupation or family income [40]. Pregnancy start year and location will be also identified as confounders during the analysis.

#### (5) Statistical analysis

Low birthweight refers to babies with birthweight below 2,500 gm and prematurity to babies born before 37 completed weeks (259 days) of gestation, as measured from the first day of the LMP. Data on these outcomes and infant death with congenital anomalies will first be estimated the relative risk obtained by dividing the rate in the exposed group by the rate in the unexposed group. Potential confounding factors will be identified and controlled by Mantel-Haenszel stratification and logistic regression. For the logistic regression, we will use the SAS logistic regression procedure [39]. For the nested (matched) case-control sub-study, conditional logistic regression will be applied to identify and control potential confounding factors. The relative risk estimated in logistic regression is the odds ratio and the 95% confidence intervals (95% CI) will be calculated.

Most of the potential confounding factors will be analyzed as dichotomous, but also multilevel and continuous. Age will be forced into the model. The other variables in the final models will be selected on the basis of priori knowledge of known and suspected risk factors and their association with outcome variables in the models. We will check that the exclusion of other variables from the model has no essential effect on the results.

## 四、結果與討論

### 1. Time-to-pregnancy study

In our PVC cohort in Taiwan, we recruited 416 valid male workers that married within recent 15 years according to Taiwan marriage registration database, which is responsible by Ministry of the Interior. In the first year of this study, we only obtained the addresses of 125 workers among those. A total of 93 wives of male PVC workers participated and finished a face-to-face questionnaire interview until now. The current study samples consisted of 210 valid pregnancies. In the preliminary analysis, we found that relative fecundability ratio of the high exposed group was less than that of non-exposed group although it is not statistically significant. (Table 1)

Table 1. Adjusted fecundability density ratio (FDR) by paternal vinyl chloride monomers (VCM) exposure at the beginning of time to pregnancy (TTP)

Variables	N	FDR	95% CI
<u>Paternal factors</u>			
VCM exposure group			
Low (<1 ppm)	144	1.00	-
Middle (1-5 ppm)	50	1.31	0.92-1.88

Variables	N	FDR	95% CI
High (>5 ppm)	16	0.63	0.35-1.16
<u>Education</u>			
College	104	1.00	-
High school	90	1.07	0.74-1.54
Junior school	16	0.70	0.39-1.27
<u>Smoking (cigarettes/day)</u>			
0	126	1.00	-
1-10	52	0.79	0.56-1.13
10-20	32	0.73	0.47-1.14
<u>Maternal factors</u>			
<u>Education</u>			
College	65	1.00	-
High school	99	0.96	0.67-1.38
Junior school	46	0.65	0.40-1.07
<u>Age (years)</u>			
≤23	19	1.32	0.79-2.21
24-33	173	1.00	-
≥34	18	1.44	0.83-2.49
<u>Coffee or tea</u>			
None	182	1.00	-
Coffee	11	0.49	0.24-1.01
Tea	17	0.75	0.43-1.30
<u>Gravidity</u>			
1 <sup>th</sup>	52	1.00	-
2 <sup>th</sup>	64	0.63	0.43-0.92
3 <sup>th</sup> & above	94	0.65	0.44-0.96

### 2. Adverse birth outcome study

In the adverse birth outcome sub-study, we utilized 3925 male PVC workers that have valid national identification numbers to link Taiwan birth registration database during 1978-97. A total of 4,706 livebirths was identified to assess adverse birth outcomes among the offspring of male polyvinyl chloride workers in Taiwan. There were 10 newborn deaths and 15 infant deaths among exposed group but no case was found in the non-exposed group. Due to few infant deaths, we could not analyze them further. (Table 2) Among 648 births with known exposure level, there was no significantly higher risk for low birthweight or preterm birth among different exposure groups, either by exposure levels or duration of employment. (Table 3)

Table 2. Birth outcomes by paternal vinyl chloride monomers (VCM) exposure at the beginning of time to pregnancy (TTP)

Birth outcome	1-5			Exposed <sup>a</sup>	Non-exposed
	<1 ppm	ppm	≥5 ppm		
Total	340	144	164	3232	826
Male	169	77	85	1668	415
Female	171	67	79	1564	411
LBW	11	3	7	139	34
PTD	13	5	7	117	24
Newborn death	-	1	-	9	-
Infant death	-	1	-	14	-

<sup>a</sup> Exposed but unknown exposure level.

Table 3. Adjusted relative risk (RR) for low birthweight and preterm birth by paternal vinyl chloride monomers (VCM) exposure at the beginning of time to pregnancy (TTP)<sup>a</sup>

VCM exposure group	Total	Case	RR	95% CI
<b>Low birthweight</b>				
<5 ppm, <5 years	275	9	1	1
<5 ppm, ≥5 years	199	2	0.30	0.06-1.48
≥5 ppm, <5 years	108	5	1.45	0.46-4.54
≥5 ppm, ≥5 years	54	2	0.96	0.18-5.01
<b>Preterm birth</b>				
<5 ppm, <5 years	275	11	1	1
<5 ppm, ≥5 years	199	5	0.49	0.16-1.53
≥5 ppm, <5 years	108	6	1.31	0.45-3.78
≥5 ppm, ≥5 years	54	1	0.30	0.04-2.60

<sup>a</sup> Adjusted for maternal age, education, infant gender, parity, and the year at the beginning of TTP

## 五、計畫成果自評

The analysis demonstrated that there was a possible effect of male PVC workers who exposed more than 5 ppm VCM on their spouse's fecundability. Although there were 15 infant deaths among exposed groups but no case was found in the non-exposed group. However, there was no significant effect on low birthweight or preterm birth under in our study population. We need further study to elucidate the relation between VCM exposure and TTP or adverse birth outcomes. These results will be published in international academic journals

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