

~~~~~ Conference of Taiwan Maternal and Infant Cohort Study ~~~~~

# 婦女與嬰幼兒易感族群生殖生長發育之 健康危害評估專題系列研討會 (III)

## Conference of Taiwan Maternal and Infant Cohort Study (III)

# 大會手冊

時 間：2019 年 4 月 11 日(星期四)~4 月 12 日(星期五)

地 點：花蓮慈濟大學 福田樓 H210 教室

主辦單位：科技部生命科學研究推動中心

高雄醫學大學環境醫學研究中心

花蓮慈濟大學公共衛生學系

國家衛生研究院國家環境醫學研究所

陽明大學環境與職業衛生研究所

協辦單位：高雄醫學大學附設中和紀念醫院家庭醫學科

高雄醫學大學公共衛生學系



婦女與嬰幼兒易感族群生殖生長發育之健康危害評估專題系列研討會 (III)  
Conference of Taiwan Maternal and Infant Cohort Study (III)

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# 大會一般資訊 / General Information

地址：花蓮市中央路三段 701 號福田樓 3 樓 <慈濟大學公衛系>

(福田樓位置在大門口左手邊的操場旁)

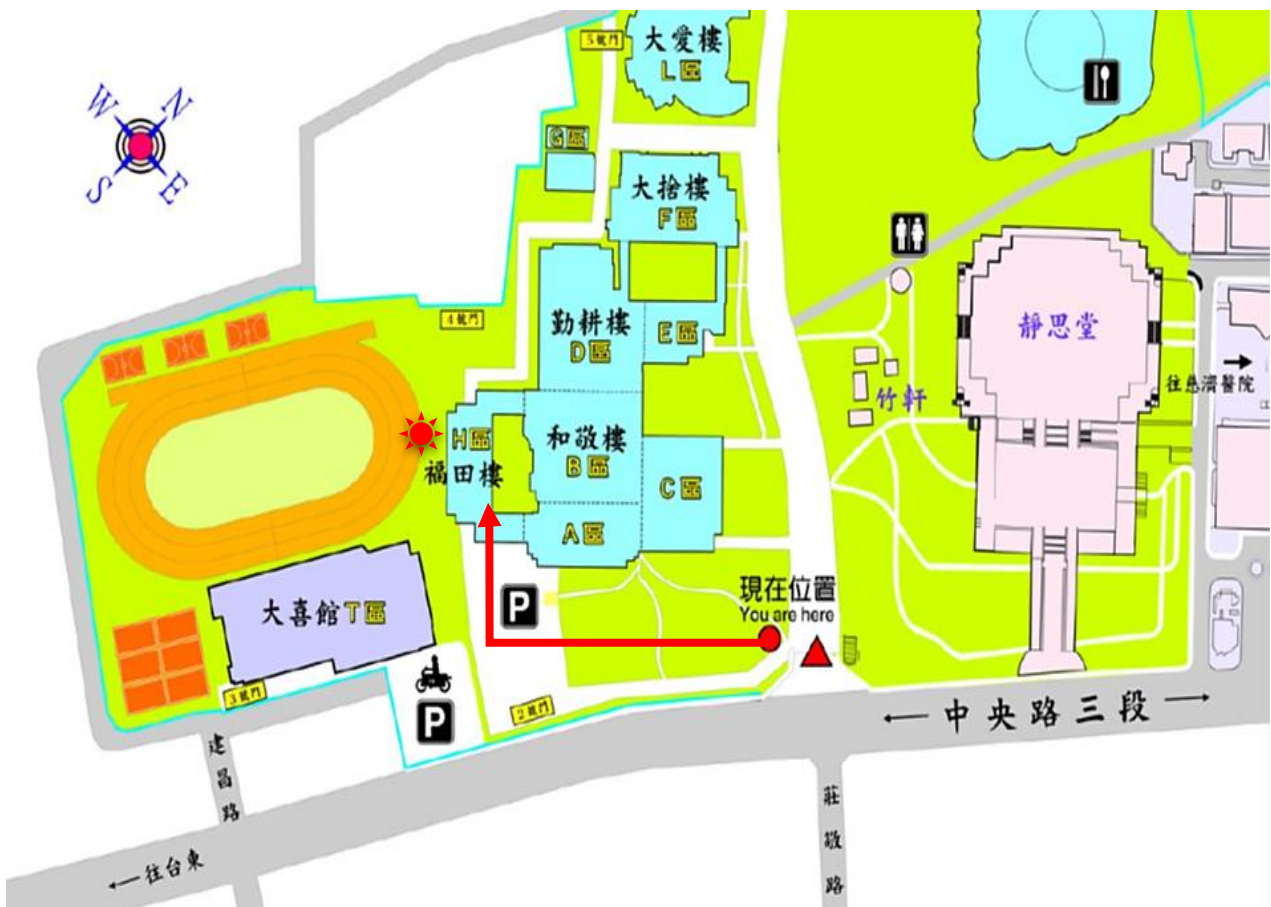
交通方式：

騎車

※慈濟大學大門口便有許多機車停車格

開車

※若您當天開車可直接由大門進入學校停車場，請向警衛說明您是參與本研討會。



# 序言

鑒於 2011 年不肖商人將塑化劑不當摻入各項保健食品及加工食品中作為起雲劑，造成懷孕期婦女及孩童誤食含高劑量塑化劑之重大食安事件。塑化劑屬於鄰苯二甲酸酯類 (phthalates, PAEs) 之化學物質，因具有類似人體荷爾蒙之作用，會干擾原本的內分泌系統平衡。這些「內分泌干擾物」，被歸類為環境荷爾蒙一旦進入人類體內，即便是極低濃度的暴露量，亦可對細胞產生危害作用。特別是對孕期胚胎分化以致嬰幼兒生長初期影響最大，其危害包括神經系統發育缺陷、免疫與生殖系統不全，甚至引發突變性畸胎。環境常見的化學物質除了塑化劑以外，雙酚 A 因結構類似雌性激素，被歸為環境荷爾蒙的一種。含雙酚 A 的塑膠製品常因刮痕、磨損，導致高溫加熱、酸鹼、酒精、微波處理或強力清潔劑等作用下，能導致雙酚 A 釋出，污染食物或飲料進入人體。此外，美耐皿餐為台灣餐飲業常見之餐具，是外食族群經常會接觸使用之餐具。研究發現美耐皿餐具遇到高溫、酸等作用，會釋出三聚氰胺，增加外食者的慢性三聚氰胺暴露風險。近年來發現，空氣污染也會對人產生不良影響，除肺臟、心血管功能外，對孕婦、幼兒等易感族群更會引發過敏相關症狀。台灣常見的環境及食安危害化學物質，包括：環境荷爾蒙污染物 (例如：塑化劑、雙酚 A (BPA)、壬基苯酚類化合物 (NP))、重金屬、農藥、丙烯酰胺以及三聚氰等，以食品、食品容器、奶瓶、兒童玩具、農產品、建材等形式，環繞在我們的食、衣、住、行上，稍有不慎就會誤食，尤其對易感性族群包括孕婦及其子代、兒童的健康有巨大影響。

為周延評估環境毒素(包括環境荷爾蒙以及其他環境污染物等)暴露對孕婦及其子代健康之影響，由高雄醫學大學(南部)、陽明大學(北部)、國家衛生研究院(中部)以及慈濟大學(東部)共同組成「台灣婦幼出生世代研究」團隊 (Taiwan Maternal and Infant Cohort Study, TMICs)，長期追蹤研究孕婦與其子代健康調查並建立長期追蹤之世代研究資料庫，以釐清環境污染物(例如：塑化劑等環境荷爾蒙)以及食安因子對孕婦及子代之危害程度與影響機制。高雄醫學大學對於環境醫學持續的進行推展，並藉由本次研討會邀請國內知名專家學者，以主學術研究題式方式，對生活環境污染物及易感族群健康的影響進行交流及討論。希冀合作聯盟能帶動環境衛生專業、學界及醫界的交流，並修訂規劃相關公共衛生標準及預防策略，更新環境污染物對人體每日耐受量參考值，以預防或減低環境污染物的健康危害與經濟影響，增進社會福祉。

高雄醫學大學環境醫學研究中心  
謹誌

# 大會議程/Conference Program

2019 年 4 月 11 日(星期四) – 第一天

婦女與嬰幼兒易感族群生殖生長發育之健康危害評估專題系列研討會(III)  
Conference of Taiwan Maternal and Infant Cohort Study (III)

時間: 2019 年 4 月 11 日(星期四) – 第一天

地點: 花蓮慈濟大學 第一教學研討室

| 時間          | 講題                                                                                                                                                                                                                     | 主持人                         |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| 14:10-14:30 | 報到                                                                                                                                                                                                                     |                             |
| 14:30-15:10 | The relationship between melamine and phthalate exposure and urinary biomarkers of renal injury and oxidative stress in pregnant women<br>懷孕婦女三聚氰胺與塑化劑暴露與氧化傷害指標及早期腎臟傷害指標之相關性探討<br><b>吳佳芳</b> 助理研究員<br>(高雄醫學大學環境醫學研究中心) | 吳明蒼教授<br>高雄醫學大學<br>環境醫學研究中心 |
| 15:10-15:50 | Ten years progress in the Taiwan Birth Panel Study<br>台灣出生世代長期追蹤研究的十年進展<br><b>陳美惠</b> 主治醫師<br>(國家衛生研究院群體健康科學研究所)                                                                                                       |                             |

2019 年 4 月 12 日(星期五)-第二天

婦女與嬰幼兒易感族群生殖生長發育之健康危害評估專題系列研討會(III)  
Conference of Taiwan Maternal and Infant Cohort Study (III)

時間: 2019 年 4 月 12 日(星期五) - 第二天

地點: 花蓮慈濟大學 H210 教室

| 時間          | 講題                                                                                                                                                                                              | 主持人                           |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| 09:00-09:30 | 報到                                                                                                                                                                                              |                               |
| 上午          |                                                                                                                                                                                                 |                               |
| 09:30-9:40  | 長官致詞                                                                                                                                                                                            |                               |
| 09:40-10:20 | New Trimester-specific Reference Ranges for Clinical Biochemical Tests in Taiwanese Pregnant Women-Cohort of TMICS<br>建立台灣第三孕期臨床生化檢測值之臨床參考範圍-台灣婦幼世代研究聯盟<br><b>吳明蒼教授</b><br>(高雄醫學大學環境醫學研究中心)     | 謝佳容助理教授<br>慈濟大學<br>公共衛生學系     |
| 10:20-10:40 | 中場休息-茶敘時間                                                                                                                                                                                       |                               |
| 10:40-11:20 | Maternal and children exposure to immunotoxic metals and atopic disease status<br>母親和兒童暴露於免疫毒性金屬與異位性疾病的關聯<br><b>王淑麗研究員</b><br>(國家衛生研究院國家環境醫學研究所)                                                | 陳美蓮教授<br>國立陽明大學<br>環境與職業衛生研究所 |
| 11:20-12:00 | Birth Cohort Consortium of Asia (BiCCA): Current Children's Environmental Health Issues in Asia and Future Perspectives<br>亞洲出生世代聯盟：當前在亞洲的兒童環境健康問題及未來展望<br><b>陳保中教授</b><br>(國立台灣大學職業醫學與工業衛生研究所) |                               |
| 12:00-13:30 | 午餐時間 (壁報展示)                                                                                                                                                                                     |                               |

|             |                                                                                                                                                                                                               |                                                |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| 12:00-13:30 | 午餐時間 (壁報展示)                                                                                                                                                                                                   |                                                |
| 下午          |                                                                                                                                                                                                               |                                                |
| 13:30-14:10 | <p>Prenatal bisphenol A exposure and birth outcomes: a nationwide survey by Taiwan Maternal and Infant Cohort Study (TMICS)</p> <p>全國性孕婦產前雙酚 A 暴露特性與相關出生結果</p> <p><b>陳美蓮教授</b></p> <p>(陽明大學醫學院環境與職業衛生研究所)</p> | <p>陳保中教授</p> <p>國立台灣大學</p> <p>職業醫學與工業衛生研究所</p> |
| 14:10-14:50 | <p>Characterization of phthalate exposure among pregnancy women in Taiwan: distribution, temporal variability, and predictors</p> <p>孕婦塑化劑暴露特性與影響因素探討</p> <p><b>謝佳容助理教授</b></p> <p>(慈濟大學公共衛生學系)</p>           |                                                |
| 14:50-15:10 | 中場休息-茶敘時間                                                                                                                                                                                                     |                                                |
| 15:10-15:50 | <p>Air Pollution during Pregnancy and Allergic Sensitization at Birth</p> <p>孕期空氣污染與胎兒過敏生物指標之相關性</p> <p><b>李佩珍副教授</b></p> <p>(台北護理健康大學健康事業管理系)</p>                                                            | <p>王淑麗研究員</p> <p>國家衛生研究院</p> <p>國家環境醫學研究所</p>  |
| 15:50-16:30 | <p>Environmental metals and multiple organ dysfunction</p> <p>環境金屬與多重器官失能之相關性</p> <p><b>蔡宗霖博士後研究員</b></p> <p>(國家衛生研究院國家環境醫學研究所)</p>                                                                           |                                                |
| 16:30-16:50 | <p>頒獎 &amp; 總結</p>                                                                                                                                                                                            | <p>吳明蒼教授</p> <p>高雄醫學大學</p> <p>環境醫學研究中心</p>     |

## 演講者簡介與摘要

## Invited speakers and abstracts





## 演講者簡介與摘要 / Invited speakers and abstracts

### 一、基本資料：

|      |                                |        |                                                        |
|------|--------------------------------|--------|--------------------------------------------------------|
| 中文姓名 | 吳佳芳                            | 英文姓名   | Wu Chia-Fang<br>(Last Name) (First Name) (Middle Name) |
| 聯絡地址 | 高雄市三民區十全一路 100 號高醫大濟世大樓 CS721A |        |                                                        |
| 聯絡電話 | (公) 07-3121101-2141#42         |        |                                                        |
| 傳真號碼 | 07-3221806                     | E-mail | Chiafangwu27@gmail.com                                 |

### 二、主要學歷

| 學校名稱   | 國別   | 主修學門系所    | 學位 | 起訖年月(西元年/月)           |
|--------|------|-----------|----|-----------------------|
| 高雄醫學大學 | 中華民國 | 職業安全衛生研究所 | 博士 | 自 2005 / 9 至 2010 / 7 |
| 高雄醫學大學 | 中華民國 | 職業安全衛生研究所 | 碩士 | 自 2002 / 9 至 2004 / 6 |
| 中山醫學大學 | 中華民國 | 公共衛生學系    | 學士 | 自 1998 / 9 至 2002 / 6 |

### 三、現職及與專長相關之經歷

| 服務機構     | 服務部門／系所               | 職稱     | 起訖年月(西元年/月)           |
|----------|-----------------------|--------|-----------------------|
| 現職：      |                       |        |                       |
| 高雄醫學大學   | 環境醫學研究中心              | 助理研究員  | 自 2017 / 8 ~ 迄今       |
| 經歷：      |                       |        |                       |
| 美國明尼蘇達大學 | Masonic Cancer Center | 訪問學者   | 2018 / 6              |
| 高雄醫學大學   | 公共衛生學系                | 博士後研究員 | 自 2010 / 8 至 2017 / 7 |
| 高雄醫學大學   | 職業安全衛生研究所             | 兼任研究助理 | 自 2009 / 8 至 2010 / 7 |
| 國家衛生研究院  | 環境衛生與職業醫學研究組          | 兼任研究助理 | 自 2005 / 9 至 2009 / 7 |
| 國家衛生研究院  | 環境衛生與職業醫學研究組          | 研究助理   | 自 2004 / 7 至 2005 / 8 |

### 四、專長

|                |         |         |         |
|----------------|---------|---------|---------|
| 1. 環境職業/分子流行病學 | 2. 生物偵測 | 3. 質譜分析 | 4. 生物統計 |
|----------------|---------|---------|---------|

# 懷孕婦女三聚氰胺與塑化劑暴露與氧化傷害指標及早期腎臟傷害指標之

## 相關性探討

吳佳芳 助研究員

高雄醫學大學 環境醫學研究中心

我們的研究團隊先前研究全台灣 2011 塑化劑事件的申訴者，發現環境中三聚氰胺暴露，會使得孩童暴露於來自污染食品高劑量的鄰苯二甲酸二(2-乙基己基)酯對其白蛋白尿影響更嚴重，暗示兩化學物質暴露對孩童的腎臟功能具有交互作用影響。然而，目前尚未有其他的流行病學研究證實。本研究使用我們的研究團隊聯合全台灣北中南東部的科學家，於 2011 年底建立一個涵蓋全台灣出生世代的學術合作(台灣婦幼世代研究聯盟)，檢測孕婦第三孕期尿液中的三聚氰胺及十一種塑化劑代謝物、氧化傷害指標 8-OHdG 及早期腎臟傷害指標(微白蛋白、N-乙醯葡糖胺)。孕婦日常生活中接觸到三聚氰胺及塑膠相關產品的機會很高，而懷孕期間孕婦的環境暴露對自身的健康影響及胎兒的發育皆很重要，藉此研究以了解環境暴露對孕婦健康的影響。

# **The relationship between melamine and phthalate exposure and urinary biomarkers of oxidative stress and renal injury in pregnant women**

Chia-Fang Wu, PhD

Research Center for Environmental Medicine, Kaohsiung Medical University, Kaohsiung,  
Taiwan

The melamine and phthalate are still ubiquitously present in our environment even after two large deliberate food contamination scandals happened in 2008 and 2011. By using one nationwide cohort of 2011 Taiwan food scandal, our research team found the significant dose-response relationship of both urine melamine levels and DEHP exposure with microalbuminuria in children, suggesting the interactive effect of these two common environmental chemicals on early renal damage. To our best knowledge, no one has explored this link in pregnant women. Thus, the aim of this study is to investigate the effect of maternal melamine and phthalate exposure on markers of oxidative stress and early renal damage among the pregnant women themselves. We used our established nationwide birth cohort, named as Taiwan Maternal & Infant Cohort Study (TMICS), since October, 2012. The pregnant women received routine pre-birth examinations in their 3<sup>rd</sup> trimester (weeks 29 to 40). The urine sample was used for the measurement of melamine, 11 phthalate metabolites, 8-oxo-2'-deoxyguanosine (8-OHdG) as oxidative stress markers, N-acetyl-b-glucosaminidase (NAG) and microalbumin as early renal injury markers. We will continue use this nationwide cohort to elucidate the association.

## 演講者簡介與摘要 / Invited speakers and abstracts

陳美惠 (Mei-Huei Chen)

現職：

|                          |        |           |
|--------------------------|--------|-----------|
| 財團法人國家衛生研究院<br>群體健康科學研究所 | 主治醫師   | 2016年6月迄今 |
| 臺灣大學醫學院小兒部               | 兼任助理教授 | 2014年8月迄今 |

學歷：

| 學校名稱   | 系            | 所 | 學位  | 畢(肄)業起迄年月       |
|--------|--------------|---|-----|-----------------|
| 國立臺灣大學 | 職業醫學與工業衛生研究所 |   | 博士  | 2007年9月至2013年12 |
| 國立臺灣大學 | 醫學系          |   | 醫學士 | 1993年9月至2000年6  |

經歷：

| 機關名稱            | 職稱       | 起迄年月            |
|-----------------|----------|-----------------|
| 臺大醫院兒童醫院        | 兼任主治醫師   | 2006年7月~迄今      |
| 臺大醫院雲林分院        | 小兒部主治醫師  | 2013年8月至2016年5月 |
| 韓國梨花女子大學醫學院     | 研修博士生    | 2011年1月至2011年7月 |
| 財團法人天主教耕莘醫院永和分院 | 小兒科主治醫師  | 2006年7月至2013年7月 |
| 臺大醫院            | 新生兒科研修醫師 | 2004年7月至2006年6月 |
| 臺大醫院            | 小兒部住院醫師  | 2001年7月至2004年6月 |

專長：

|       |        |  |
|-------|--------|--|
| 新生兒科學 | 兒童環境健康 |  |
|-------|--------|--|

## 台灣出生世代長期追蹤研究的十年進展

陳美惠 主治醫師

國家衛生研究院群體健康科學研究所

臺灣出生世代長期追蹤研究(Taiwan Birth Panel Study)自 2004 年建立迄今仍持續追蹤，研究目標是針對低劑量、產前或產後環境汙染物暴露和遺傳修飾對「環境相關的兒童疾病」的發生與進展的影響。主要的健康指標包括胎兒和兒童的成長、神經發育、行為問題和異位性皮膚炎以及肺功能。我們招募了 486 對配對的母親與新生兒，並在嬰兒第 4、6 個月和第 1、2、3、5、7 和 9 歲時進行追蹤。研究測量的環境汙染物，包括可替寧 (cotinine)、重金屬 (如鉛、錳和汞)、全氟烷基物質(perfluoroalkyl substances，簡稱 PFAS)、鄰苯二甲酸鹽 (phthalate)和 酚類化合物 (phenolic compounds)。近期的研究聚焦在青春期前的兒童健康，研究發現產前全氟辛烷磺酸 (PFOS) 對胎兒生長的負面影響會隨著兒童的成長而減少，且存在性別差異性。產前 PFOS 暴露對於出生體重較輕和過敏的兒童 (相較健康兒童)，其 9 歲時肺功能有下降的趨勢。塑化劑的後天暴露對兒童 9 歲時的肺功能也存在相似的負面影響，例如單乙基酯 (MEP)。此外，研究發現青春期前 MEP 的暴露與兒童超重或肥胖有關，尤其是男孩的身體質量指數 (BMI) 的 z score。通過上述研究，我們得出結論，產前環境汙染物的暴露可能會對青春期前的兒童產生長期影響，而同一時間點暴露於數種環境汙染物的影響也不容忽視，未來需要進一步探索環境汙染物對青春期發育變化的影響。

## **Ten years progress in the Taiwan Birth Panel Study**

Mei-Huei Chen, PhD

Institute of Population Health Sciences, National Health Research Institutes

The Taiwan Birth Panel Study (TBPS) is an ongoing cohort study that was conducted since 2004. The primary goals are to examine the low-level, prenatal or postnatal exposure and genetic modification effect on the initiation and progress of “environmentally-related childhood diseases”. The main health outcomes are focused on fetal and child growth, neurodevelopment, behavior problems and atopic dermatitis as well as lung function. We enrolled 486 mother-infant pairs at birth and subsequently followed children at age of 4, 6 months and 1, 2, 3, 5, 7 and 9 years. Various environmental pollutants including cotinine, heavy metals (as lead, manganese, and mercury), perfluoroalkyl substances, phthalate and phenolic compounds had been measured. Our recent discovery focused on child health before puberty. We found that the negative impact of prenatal perfluorooctyl sulfonate (PFOS) on fetal growth diminished as children grow up to 8 years of age, and modest effect of gender specific manner. There were trends noted between prenatal PFOS exposure and decreasing lung function at age 9 of children with lower birth weight or allergy. While similar effect on lung function was observed with concurrent exposure to phthalate, such as mono-ethyl phthalate (MEP) at age 9. In addition, we found that concurrent MEP exposure was associated with increment of body mass index (BMI) z-score and pediatric overweight or obesity during pre-puberty stage, particularly in boys. With aforementioned studies we conclude that prenatal environmental pollutants exposure could have long term impact on children before puberty while the impact of concurrent exposure could not be ignored. Further follow-up to explore the change of puberty development is warranted.

## 演講者簡介與摘要 / Invited speakers and abstracts

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| 美國哈佛大學        | 公共衛生學院               | 博士後研究員 | 自 1997/04 至 2000/02 |

### 4. 專長

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# 建立台灣第三孕期臨床生化檢測值之臨床參考範圍-台灣婦幼世代研究

## 聯盟

吳明蒼 教授

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懷孕將導致血液生化檢測值發生變化，但少有為孕婦提供血液生化檢測值的參考區間。若沒有參考區間，將增加誤將正常變化解釋為病理性的風險。據我們所知，目前尚無實驗室為臍帶血測量提供參考區間。本研究目的在建立台灣孕婦第三孕期和臍帶血中重要生化檢測值的參考區間。我們針對台灣婦幼世代研究聯盟 (TMICS) 提供的第三孕期的血液樣本進行檢測，並對其分娩時提供的臍帶血樣本進行分析，參考區間以第 2.5 和第 97.5 百分位當作正常範圍。研究結果發現許多常見激素，尤其是雌激素(Estradiol)，黃體素(progesterone)和睪固酮(testosterone)的正常值在懷孕期間會發生顯著變化；而且本研究也提供多項生化數值的參考區間表以做為臨床上照顧孕婦和新生兒健康的參考數值。



## **New Trimester-specific Reference Ranges for Clinical Biochemical Tests in Taiwanese Pregnant Women-Cohort of TMICS**

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Although most laboratories are well aware that pregnancy induces changes in normal laboratory values, they rarely provide healthy reference intervals for pregnant women. Without adequate reference intervals, there is an increased risk of missing important changes due to pathological conditions and increased risk of erroneously interpreting normal changes as a pathological. This study aims to establish reference intervals for important biochemical parameters pregnant women in Taiwan during their third trimester and from cord blood. We performed laboratory analysis of all blood samples provided by the enrollees from Taiwan Maternal and Infant Birth Cohort Study (TMICS) during their third trimesters and cord blood samples provided by them during delivery. Our reference intervals were based on the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentile of the data as the normal range. We found that the normal values for many common hormones, especially estradiol, progesterone, and testosterone, shift during pregnancy. In addition, and the table of reference intervals of important parameters we present in this study can serve a quick reference for clinicians caring for the pregnant woman and newborn infants.

## 演講者簡介與摘要 / Invited speakers and abstracts

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| 國防醫學大學                      | 公共衛生學系       | 合聘教授   | 自 2013/08 至         |
| 美國國家衛生研究院                   | 環境衛生科學研究所    | 訪問學者   | 自 2012/07 至2013/12  |
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## 母親和兒童暴露於免疫毒性金屬與異位性疾病的關聯

王淑麗 研究員

國家衛生研究院 國家環境醫學研究所

先前研究發現生命早期暴露於某些金屬，特別是無機砷，與免疫機能異常、和肺功能下降有顯著相關，吾人運用 出生世代的 15 年追蹤研究，探討出生前後無機砷得暴露和兒童過敏性疾病的相關性，並且運用較大規模的樣本，來評估出生時的免疫球蛋白 E 與出生前各金屬暴露的相關性。

有異位性皮膚炎、氣喘或過敏性鼻炎任一的兒童，比起正常的，均有顯著高的免疫球蛋白 E。運用混合線性模式分析，兒童的無機砷總量（2-11 歲）超過中位數的，比低於中位數歲的，有顯著較高的過敏性鼻炎（8-14 歲）（OR = 2.72, 95%信賴區間，1.21-5.69，調控性別、父母過敏，母乳喂養，ETS，產前砷暴露和產後鄰苯二甲酸酯暴露）。在父母有過敏的兒童中，產前砷暴露與兒童哮喘有顯著正相關。當孕婦尿液金屬濃度增加時，過敏母親的新生兒臍帶血 IgE 超過  $\geq 0.42$  kU/L 的比值顯著增加[Cd：OR = 2.92 (95%CI 1.01 - 8.42)；Cu：OR = 3.12 (95%CI 1.10 - 8.87)；Ni：OR = 1.99 (95%CI 1.00 - 3.95)；Tl：OR = 2.58 (95%CI 1.08 - 6.18) 超過中位數與其餘者相比]。研究顯示不同異位性疾病，有不同的機制和預防策略。

## **Maternal and children exposure to immunotoxic metals and atopic disease status**

Julie Shu-Li Wang, PhD

National Institute of Environmental Health Sciences, National Health Research Institutes

Early life exposure to certain metals, particularly for inorganic arsenic, have been found associated with impaired immune function and decreased lung function in children. Using birth cohort approach, we evaluated prenatal and childhood exposure to inorganic arsenic and their associations with atopic diseases in a 15-year follow-up birth cohort study in central Taiwan. Other metals were also evaluated on the association with cord blood IgE. Children with any allergic symptom of dermatitis, asthma, or rhinitis tended to have higher blood IgE as compared to the normal ones. Using Linear Mixed Model, Children with total inorganic arsenic over the median in 2-11 years had significantly higher Odds Ratio for allergic rhinitis aged 8-14 years than those below the median (OR= 2.72, 95% Confidence interval, 1.21-5.69) adjusted for sex, parental allergy, breast feeding, ETS, prenatal arsenic exposure, and postnatal phthalate exposure. The increased prenatal arsenic exposure was associated with increased OR of asthma in children with parental allergy. Children postnatal arsenic exposure was associated with allergic rhinitis disregarding parental allergic status. Newborns of mothers with allergy had increased odds ratio of high cord blood IgE ( $\geq 0.42$  kU/L) when maternal urine metal concentration increased [Cd: OR = 2.92 (95% CI 1.01 – 8.42); Cu: OR = 3.12 (95% CI 1.10 – 8.87); Ni: OR = 1.99 (95% CI 1.00 – 3.95); Tl: OR = 2.58 (95% CI 1.08 – 6.18) for over the median as compared to the lower group]. There appeared different mechanism and prevention strategies for the atopic diseases.

## 演講者簡介與摘要 / Invited speakers and abstracts

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| 2014- | 台灣流行病學會                     | 常務理事 |
| 2018- | 國際職業衛生學會職場生殖危害科學委員會(RHICOH) | 秘書   |
| 2012- | 亞洲出生世代研究聯盟(BiCCA)           | 執行委員 |

### 學歷

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## 專長

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## 亞洲出生世代聯盟：當前在亞洲的兒童環境健康問題及未來展望

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環境是影響兒童健康的重要因素，不僅在受孕期或是幼兒期，甚至可能對往後的健康造成深遠影響。然而，在亞洲的兒童不僅面臨傳統的環境危害，還有新興兒科疾病。因此，有必要建立亞洲出生世代研究合作平台，促進兒童環境健康發展。亞洲出生世代聯盟(Birth Cohort Consortium of Asia, BiCCA)於2011年由臺灣出生世代追蹤調查研究(Taiwan Birth Panel Study, TBPS)、韓國母子環境健康研究(Mothers and Children's Environmental Health Study, MOCEH)及日本北海道環境與兒童健康研究(Hokkaido Study on Environment and Children' Health, Hokkaido Study)共同創立，相關的研究成果已公開，截至2017年10月止，亞洲出生世代聯盟共計有13個國家包含27個出生世代研究團隊、將近80,000名母子研究對象加入。然地理分布不均，且使用的量測評估工具亦無統一標準，部分環境毒物已被確認，但對關鍵環境問題的探索並不全面。指標性及針對性的合作研究有助於找出關鍵問題，現已持續進行中。亞洲出生世代聯盟為亞洲國家提供一個資訊交流的平台，跨領域合作及先進技術應用將有助於確認具體的區域環境威脅並改善亞洲兒童的健康狀況。



## **Birth Cohort Consortium of Asia (BiCCA): Current Children's Environmental Health Issues in Asia and Future Perspectives**

Pau-Chung Chen, PhD

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Environment is an important factor influencing children's health, not only at early life but also may lead to adverse consequences on later health. However, children in Asia are facing both traditional environmental hazards and new pediatric morbidities. A collaboration platform of Asian birth cohort studies to promote children's environmental health is warranted. The Birth Cohort Consortium of Asia (BiCCA) was co-established in 2011 by the principal investigators of three birth cohorts in Asia including the Taiwan Birth Panel Study (TBPS), the Mothers and Children's Environmental Health Study (MOCEH), and the Hokkaido Study on Environment and Children' Health (Hokkaido Study). The related information to environmental exposure and health outcome from participating cohorts has put on public. Up to date (October 2017), BiCCA includes 27 birth cohorts with approximately 80,000-study subject that were conducted in 13 Asian countries. The geographical distribution of the cohort studies is uneven and assessment tools are diverse. Certain environmental neurotoxins have been identified; however, the exploration to critical environmental issues is not comprehensive. Targeted research collaboration is warranted and still ongoing. The BiCCA provide an information exchange platform for birth cohort in Asian countries. Multidisciplinary collaboration and state-of-art technologies application should initiate to identify specific regional environmental threats and improve the health of children in Asia.

## 演講者簡介與摘要 / Invited speakers and abstracts

### 學經歷

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| 現任：國立陽明大學環境保護暨安全衛生中心 |     |     | 主任              | 2015/08~迄今      |  |
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| 曾任：國立陽明大學醫學院         |     |     | 副院長             | 2009/08~2015/01 |  |
| 國立陽明大學               |     |     | 副教務長            | 2011/02~2012/7  |  |
| 國立陽明大學環境與職業衛生研究所     |     |     | 教授              | 1999/08~2018/1  |  |
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| 國立陽明大學環境衛生研究所        |     |     | 副教授             | 1998/07~1999/08 |  |
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| 國立陽明大學社會醫學科及公共衛生研究所  |     |     | 副教授             | 1992/06~1998/07 |  |

## 全國性孕婦產前雙酚 A 暴露特性與相關出生結果

陳美蓮 特聘教授

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雙酚 A (Bisphenol A, BPA) 主要用於生產聚合聚碳酸酯(Polycarbonate)和環氧樹脂(Epoxy resin)，廣泛存在於各類日常生活用品中。BPA 已被證實為內分泌干擾物質，具雌激素作用，動物胚胎時期 BPA 的暴露可能影響未來的發育及成長。然而，各國針對孕婦產前 BPA 暴露及其新生兒出生狀況的流行病學調查研究，仍顯示相當不一致的研究結果。因此，本研究利用台灣北、中、南、東地區的孕婦及其新生兒世代研究 (Taiwan Maternal and Infant Cohort Study, TMICS)，探討我國孕婦產前 BPA 暴露特性以及對其新生兒的影響。目前已完成 555 位孕婦妊娠第三期尿液 BPA 分析，使用廣義加成模型 (Generalized additive model, GAM) 非線性迴歸 (penalized spline regression) 及複迴歸分別探討孕婦產前 BPA 暴露對新生兒體長、體重、頭圍、胸圍之關係，並評估 BPA 對男嬰及女嬰相關生殖指標，如：肛門到生殖器距離 (Anogenital distance, AGD)、陰莖長度及寬度之關係。孕婦尿液 BPA 檢出率為 83.1%，尿液肌酸酐校正後幾何平均濃度為 0.95  $\mu\text{g/g cre.}$ ，其中以北區 (1.50  $\mu\text{g/g cre.}$ ) 及南區 (1.60  $\mu\text{g/g cre.}$ ) 孕婦 BPA 尿液濃度較高。孕婦 BPA 濃度經自然對數轉換後，與新生兒標準化頭圍具顯著負相關 ( $\beta = -0.05$ ,  $p = 0.03$ )。以 BPA 濃度中位數分組後，孕婦 BPA 濃度較高者，其出生男嬰肛門中心至陰囊基底部的距離 ( $\beta = 2.06 \text{ cm}$ ,  $p = 0.03$ ) 及肛門到生殖器距離 ( $\beta = 2.84 \text{ cm}$ ,  $p = 0.01$ ) 皆顯著較高。本研究結果顯示孕婦 BPA 暴露可能影響新生兒頭圍及男嬰肛門到生殖器距離。

# **Prenatal bisphenol A exposure and birth outcomes: a nationwide survey by Taiwan Maternal and Infant Cohort Study (TMICS)**

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Animal studies have suggested that in utero exposure to bisphenol A (BPA) may increase the risk of pregnancy failure and embryonic death, impair growth, and low birth weight among offspring. However, the associations between prenatal BPA exposure and birth outcomes were inconsistent in several human cohort studies. Therefore, this study (Taiwan Maternal and Infant Cohort Study, TMICS) investigated the exposure profile of BPA among pregnant women in Taiwan and determined whether maternal BPA exposure influences birth outcomes and reproductive indices. A total of 555 pregnant women were enrolled in this study from 2012 to 2016. All participants completed a structured questionnaire and their urine specimens were collected. The urinary concentrations of BPA in the third-trimester were measured using the ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-TOF/MS). An individual's z-score of birth weight, length, and head circumference were calculated using the mean and standard deviation from the population. A log-transformed quantity of BPA was used and incorporated into the generalized additive model (GAM)-penalized regression splines to determine the non-linear effects on birth outcomes. A multivariable regression model was employed to determine the effects of BPA exposure on birth outcomes and sex-specific reproductive indices. The detection rate of BPA in maternal urine was 83.1% and the geometric mean was 0.95  $\mu\text{g/g cre.}$ . The high maternal BPA concentrations were observed in northern (1.50  $\mu\text{g/g cre.}$ ) and southern (1.60  $\mu\text{g/g cre.}$ ) Taiwan. When the prenatal BPA concentration increased by 1 log-transformed unit, the z score of head circumference significantly decreased 0.05 (p value=0.03). Pregnant women in the group with BPA above the median had a significantly high anogenital distance (AGD, posterior of penis to center of anus distance,  $\beta=2.06$  cm, p value=0.03) and anoscrotal distance (ASD, posterior of scrotum to center of anus distance,  $\beta=2.84$  cm, p value=0.01) comparing to group with BPA lower than the median. This study demonstrated the BPA exposure profile of pregnant women in Taiwan. The significant association between maternal BPA exposure and anogenital distance should be considered.

## 演講者簡介與摘要 / Invited speakers and abstracts

### 一、基本資料

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|------------------------------|----|-------------------|-------------------------------|
| 國立台灣大學公共衛生學院<br>職業醫學與工業衛生研究所 | 博士 | 2005/09 - 2010/09 | 環境流行病學、兒童環境健康、<br>職業衛生、職業流行病學 |
| 國立台灣大學公共衛生學院<br>職業醫學與工業衛生研究所 | 碩士 | 2003/09 - 2005/06 | 公共衛生                          |

### 三. 現職及與專長相關之經歷

| 服務機構及單位                         | 職稱     | 起迄年月              |
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| 現任：慈濟大學 公共衛生學系                  | 助理教授   | 2012/2-迄今         |
| 曾任：<br>國立臺灣大學公共衛生學院職業醫學與工業衛生研究所 | 博士後研究員 | 2010/10 - 2012/01 |

### 四、專長

|        |        |      |        |
|--------|--------|------|--------|
| 環境流行病學 | 兒童環境健康 | 職業衛生 | 職業流行病學 |
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## 台灣孕婦塑化劑暴露影響因素探討

謝佳容 助理教授

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塑化劑是一群高生產量的合成化學物質，因為其使用量大且人類日常生活中廣泛的接觸，所以近年來備受關注，故本研究將探討台灣孕婦塑化劑暴露之影響因素。本研究於 2012-2015 年間於台灣北中南東的九家醫院收集孕產婦共計 1676 位，我們於第三孕程進行問卷調查收集孕婦懷孕期間個人護理產品、飲食習慣及使用塑膠包裝食品之習慣調查，以及收集三個孕程孕婦的尿液，用以分析尿液中 11 種塑化劑代謝物的濃度，並將其分為低分子量與高分子量塑化劑代謝物。利用 GEE 模式探討個人護理產品、飲食習慣及使用塑膠包裝食品之習慣與尿液中塑化劑代謝物濃度之關係。研究結果發現日常照護產品之使用與孕尿液中塑化劑濃度有關，特別是駐留類日常照護用品之使用。其中，孕婦尿液中 MEP 及 MBzP 濃度的增加與駐留類日常照護用品之使用有關，特別是化妝水、唇膏、精油與乳液。此外，沖洗類日常照護用品之使用，如洗面乳，反而能降低部分塑化劑的濃度。使用塑膠包裝食品與攝食牛奶與 DEHP 代謝物濃度的增加有關。而蛋類的攝取也與 MEP 濃度的增加有關。我們的研究指出個人護理產品之使用與使用塑膠包裝食品與孕婦尿液中塑化劑濃度有關，建議懷孕婦女應減少其使用以降低塑化劑的暴露。

# **Characterization of phthalate exposure among pregnancy women in Taiwan**

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Phthalates are a group of high-production-volume synthetic chemicals with widespread human exposure and harmful to infant's health through women's exposure during pregnancy. The objective of this study is to characterize of phthalate exposure among pregnancy women in Taiwan. In years 2012-2015, we conducted a birth cohort study named the Taiwan Mother Infant Cohort Study (TMICs) in Taiwan. We had recruited study population from 9 collaborative medical centers and/or hospitals located in northern, central, southern, and eastern Taiwan. A total of 1676 pregnancy women were recruited in this study. We only included participants if they contributed more than two urine samples and completed the questionnaire. Spot urine samples were collected at each trimester, and levels of eleven phthalate metabolites were measured by liquid chromatography tandem mass spectrometry. We collected their behavior information about personal care products, food consumption and food containers during pregnancy. The association between exposure-related behaviors and urinary phthalate metabolites was assessed using GEE models. Levels of several phthalate metabolites were significantly associated with the use of PCPs, especially leave-on PCPs. The mono- ethyl phthalate (MEP) was significantly associations with increasing frequencies of use of skin toners (11.7%; 95% CI: 1.5%, 22.9%), lipsticks (13.2%; 95% CI: 4.6%, 22.5%), essential oils (21.8%; 95% CI: 9.1%, 36.0%) and egg consumption (24.7%; 95% CI: 2.7%, 51.3%). Additionally, the concentration of DEHP was positively associated with use of plastic food containers (65.5%; 95% CI: 14.5%, 139.1%) and dairy products (11.6%; 95% CI: 2.6%, 21.5%). These results indicate exposure-related behaviors (use of personal care products, food consumption and food containers) were associated with urinary phthalate metabolites. These finding can be utilized to prevent pregnant women from excess exposures to phthalates to the future.

## 演講者簡介與摘要 / Invited speakers and abstracts

### 壹、基本資料

|      |                              |        |                          |
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### 貳、主要學歷

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| 科羅拉多州立大學 | 美國 | 環境科學   | 碩士 | 2005/08 – 2007/05 |
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### 參、現職及教學經歷

| 服務機關                                              | 服務部門／系所                       | 職稱       | 起訖年月              |
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| 經歷：<br>國立臺北護理健康大學                                 | 健康事業管理系                       | 助理教授     | 2013/02 – 2016/01 |
| 經歷：<br>University of California<br>at Los Angeles | Department of<br>Epidemiology | Post-doc | 2011/03 – 2013/01 |



## 孕期空氣污染與胎兒過敏生物指標之相關性

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近二十年來，台灣兒童過敏性疾病的盛行率持續增加。造成過敏性疾病增加的原因可能與環境污染之曝露有相關，過去許多環境流行病學的研究指出，兒童時期空氣污染的曝露與其日後過敏性疾病的發生有關，例如：氣喘。然而，少數研究在探討生命更早期的空氣污染曝露例如：胎兒時期，會不會影響胎兒時期的免疫系統發育，進而增加兒童時期過敏性疾病的發生風險。為此，本研究利用台灣出生世代(Taiwan Maternal and Infant Cohort Study, TMICS)來探討懷孕時期空氣污染曝露與臍帶血過敏原 IgE (cord blood immunoglobulin, IgE)濃度之相關性。TMICS 出生世代針對將近兩千名的婦女與小孩配對進行追蹤研究，從孕婦懷孕時期開始進行基本問卷與環境資料的蒐集。本研究將使用其中 524 名孕婦所蒐集的臍帶血進行過敏原 IgE 的量測。空氣污染曝露評估則利用分位數貝氏最大熵(quantile-based Bayesian Maximum Entropy, QBME)模型與土地利用迴歸模型(land use regression model)，結合環保署在全台灣的空氣污染監測站資料來評估戶外空氣污染的曝露濃度，並且利用線性迴歸與邏輯迴歸模型，來分析孕婦在不同孕期空氣污染的曝露與臍帶血過敏原 IgE 濃度之相關性。本研究發現在控制 O<sub>3</sub>, CO, 以及 SO<sub>2</sub> 濃度後，本研究發現第一孕期或者全孕期每四分位差 PM<sub>2.5</sub> 空氣污染的增加，IgE 濃度超過 0.9 IU/ml 的風險則分別增加了 1.38 倍(95% CI=0.98-1.95)與 1.40 倍(95% CI=0.97-2.04)。而其他空氣污染物(例如：O<sub>3</sub>, CO, SO<sub>2</sub>)則與臍帶血 IgE 濃度的增加沒有相關。利用台灣出生世代，本研究發現孕期 PM<sub>2.5</sub> 的曝露可能會影響到胎兒免疫系統的發育，進而增加兒童時期過敏性疾病的發生風險。期望本研究結果能提供孕婦敏感性群體減少空氣污染曝露，用以減少其子帶過敏性疾病發生風險之參考。

## **Air Pollution during Pregnancy and Allergic Sensitization at Birth**

Pei-Chen Lee, PhD

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The prevalence of childhood allergic diseases has been increased over the past two decades in Taiwan. It has been suggested that environmental contaminants or exposures may contribute to the disease aetiology. Cumulative studies have shown that air pollution exposure during childhood is associated with the development of allergic diseases such as asthma. However, little is known about whether air pollution during pregnancy may influence fetal immune system. Here, by utilizing a prospective birth cohort study (the Taiwan Maternal and Infant Cohort Study (TMICS)); we aimed to investigate whether ambient air pollution exposure during pregnancy is associated with cord blood immunoglobulin E (IgE) concentration – Th2 pathway to allergic asthma. The TMICS recruited approximately 2000 mother–infant pairs in Taiwan and collected extensive information including environmental exposure data, and maternal lifestyle during pregnancy. Maternal specimens, including urine and blood during pregnancy, and cord blood were also collected. We included 524 participants with cord blood IgE concentration available into our final analysis. We used quantile-based Bayesian maximum entropy model and land use regression model, to estimate trimesters and entire pregnancy ambient air pollution exposures. Based on logistic regression models we estimated odds ratios (ORs) and 95% confidence intervals (CIs) for increased IgE from air pollutant exposures during pregnancy. In multi-pollutant model (i.e., model also adjusted for other pollutants), the first trimester and whole pregnancy period, PM<sub>2.5</sub> exposure remained positively associated with elevated cord blood IgE concentration (IgE above 0.9 IU/ml, the odds ratio per PM<sub>2.5</sub> interquartile range increased were 1.38, 95% CI=0.98-1.95, and 1.40, 95% CI=0.97-2.04, respectively). Other pollutants were not associated with elevated cord blood IgE. This birth cohort study suggests that PM<sub>2.5</sub> exposure during pregnancy may influence fetal immune system development, which may contribute to increased risk of developing allergic diseases in childhood.

## 演講者簡介與摘要 / Invited speakers and abstracts

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2017/8 至今

### 研究興趣

1. 環境醫學, 2. 金屬暴露, 3. 生物與健康資料探勘

## 環境金屬與多重器官失能之相關性

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金屬在日常生活被廣泛地利用，因此可能經由不同的暴露途徑進入人體；雖然一般民眾的暴露情況相較於職業暴露來得低，但相關研究仍發現中、低暴露於某些毒性金屬下仍會影響健康並增加引起疾病的風險。因此毒性金屬暴露造成一般民眾多重器官失能以及慢性健康的影響是值得探討的重要議題。本橫斷式研究主要目的為探討金屬暴露（鉛、鎘、鉻、汞）與多重器官失能（第二型糖尿病、腎功能、骨質疏鬆）之間的相關性；分析 2005 至 2008 年台灣營養健康狀況變遷調查之 19 歲以上成人資料，以感應耦合電漿質譜儀分析尿液中的金屬濃度，並使用冷蒸氣原子吸收光譜儀分析紅血球中的汞濃度來評估重金屬暴露。經統計模型分析後發現，紅血球中的汞濃度增加與第二型糖尿病盛行風險有正相關。腎功能方面，尿中鉻或尿中鉛的濃度在校正相關變項後每增加一倍暴露濃度，估計腎絲球過濾率呈現顯著下降；而在高鎘暴露的族群也顯著地發現到尿中鉻或尿中鉛濃度每增加一倍暴露濃度與估計腎絲球過濾率下降有關。最後，高尿鉛濃度與骨質減少/骨質疏鬆也有顯著正相關。這項研究發現紅血球中汞濃度升高與糖尿病的風險有關。鉻暴露和腎功能降低有顯著的相關性，合併鎘的暴露則更明顯；本研究也是第一次發現到鉻、鉛和鎘的共同暴露可能與台灣成年人腎功能（腎絲球過濾率）下降有關。另外也觀察到成人中，特別是女性，較高的尿中鉛濃度可能會增加骨質減少和骨質疏鬆的機率。經由上述結論可發現低濃度的多元素暴露可能與一般族群的健康影響有關。

## **Environmental metals and multiple organ dysfunction**

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Metal may enter human body through different exposure routes due to its many uses in diverse products. Although the general population might have lower exposure than occupational workers, it has proved in recent studies that even middle or low exposure to certain toxic metals may induce adverse effects on health or increase the risk of disease. Thus it is important to investigate the exposure to toxic metal and the related multiple organ dysfunction or chronic health effects in the general population. This cross-sectional study investigated the association between exposure to metals (lead, cadmium, chromium or mercury) and multiple organ dysfunction (diabetes, renal function or bone health) in adults aged  $\geq 19$  years from the Nutrition and Health Survey in Taiwan (2005–2008). Urinary heavy metals and red blood cell mercury were measured by inductively coupled plasma-mass spectrometry and cold vapor atomic absorption spectrometry respectively. After potential confounders were well considered in statistical models, a significant association between elevated red blood cell mercury and prevalence of type 2 diabetes was observed (OR=1.64, 95% CI: 1.14–2.35). For every doubling of urinary chromium or lead, there was a significant decrease in estimated glomerular filtration rate after adjusting for relative factors (chromium:  $-5.99$  mL/min/1.73 m<sup>2</sup>; lead:  $-6.61$  mL/min/1.73 m<sup>2</sup>). Among participants in the highest tertile of cadmium exposure, the estimated glomerular filtration rate decreased with elevated urinary chromium or lead level, respectively. In addition, the highest tertile of urinary lead levels was observed to positively associate with odds ratio of osteopenia/osteoporosis (OR=2.30, 95% CI: 1.19–4.48) in the multivariable regression analysis. This study found that elevated mercury level in red blood cells is significantly associated with the prevalence of type 2 diabetes. A significant association between chromium exposure and decreased renal function was observed. Moreover, the results also demonstrated for the first time that co-exposure to chromium, lead and cadmium is probably associated with a further decline in renal function assessed by glomerular filtration rate in Taiwanese adults. Furthermore, the finding also supports that adults with higher urinary lead levels may have increased risk of osteopenia/osteoporosis, particularly in women. These findings indicate that the low level of multi-element exposure may associate with harmful health effect in general population.

# 海報論文摘要

## Poster abstracts



## 台灣婦幼世代研究聯盟：塑化劑暴露及其風險評估

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2011年5月，台灣爆發塑化劑摻入起雲劑之重大食品安全事件，特別是DEHP (di-(2-ethylhexyl) phthalate) 被故意添加到兒童常用的各種食品中，包括益生菌及保健食品等。為此，來自台灣北部、中部、南部和東部的流行病學家組成「台灣婦幼世代研究聯盟」(Taiwan Maternal & Infant Cohort Study, TMICS)，建立一個涵蓋全台灣出生世代的學術合作，以執行全國性前瞻世代研究，調查食安問題爆發後，環境塑化劑暴露對懷孕母親及其孩童的健康影響。從2012年10月至2015年5月間，已收集來自台灣北部(3所大型醫院)、中部(3所)、南部(2所)和東部(1所)共9間醫院的1631名懷孕母親，完成其第三孕期尿液中十一種塑化劑代謝物的檢測及問卷資料，並提供血清、DNA等不同檢體的保存。目前懷孕母親的平均年齡(±標準差)為31.38(±4.56)歲。新生兒的男女比例約為1:1。TMICS團隊將持續追蹤這些孩童達三歲後的健康狀況。此外，TMICS團隊亦已規劃由我們已收集貯存的母親-胎兒配對之各種不同檢體，持續量測其他環境污染物的濃度，包括有機磷農藥(organophosphate pesticides)、壬基酚(nonylphenol)、雙酚A(bisphenol A)、重金屬(heavy metals)、三聚氰胺(melamine)和丙烯醯胺(acrylamide)，希望對人群免於新興環境污染物之暴露有所貢獻，進而增加這個世代研究的價值。

## **Cohort Profile: The Taiwan Maternal and Infant Cohort Study (TMICS) of phthalate exposure and health risk assessment**

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In 2011, news broke in Taiwan that phthalates, especially di-(2-ethylhexyl) phthalate (DEHP), were deliberately added to a variety of foods commonly consumed by children there. In response, epidemiologists from northern, central, southern and eastern Taiwan established a birth cohort consortium and conducted a nationwide prospective birth cohort study known as the Taiwan Maternal & Infant Cohort Study (TMICS) to investigate environmental phthalate exposure and its effects on maternal and child health after this food scandal. Between October 2012 and May 2015, 1631 pregnant women in their third trimester from nine hospitals located in northern (n = 3), central (n = 3), southern (n = 2), and eastern Taiwan (n = 1) were recruited, administered questionnaires, and asked to provide blood samples and urine samples for the measurement of concentrations of eleven phthalate metabolites. Subjects had a mean age ( $\pm$ SD) of 31.38 ( $\pm$ 4.56) years. Later, the male/female ratio of their newborns was found to be about 1: 1. The TMICS plans to follow-up these children at age of three and afterwards. Additionally, although not the main goal of this particular study, TMICS also plans to keep the urine and blood samples of these mothers and children for subsequent measurement of concentrations of other environmental contaminants, including organophosphate pesticides, nonylphenol, bisphenol A, heavy metals, melamine and acrylamide, thereby increasing the value of this cohort.



## 双黄 1 號(薑黃素葉黃素複方)之層析分析及抗發炎活性研究

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薑黃為亞洲國家常見的藥用植物，特別是在印度及巴基斯坦等國，傳統上可用來治療各種慢性或自體免疫相關疾病。薑黃及其主要活性成分—薑黃素在過去十幾年中已被開發成許多保健食品，在台灣、中國、日本、韓國、馬來西亞和新加坡等國也相當受到歡迎，然而過去卻很少業者嘗試將薑黃素與其他保健產品結合。為了研究薑黃與其他生物活性化合物的協同作用，本團隊開發了一種由薑黃素與葉黃素所組成的營養保健品 YD01，主要用於治療眼部與發炎相關疾病。薑黃素是一種二烯酰甲烷衍生物，對癌症、糖尿病、心血管、腎臟、神經和眼部疾病皆具有顯著的生物活性，而葉黃素則是從萬壽菊(*Tagetes erecta*)中所萃取出來的活性化合物，具有抗氧化、抗發炎和免疫調節等藥理作用。薑黃素已與白藜蘆醇，槲皮素，蘿蔔硫素，視黃酸和葉酸等其他植物化學成分組合使用來治療多種癌症。而薑黃素與葉黃素組合物的治療功效和藥理作用則尚處於起步階段。因此在本次研究中，我們評估了 YD01 (薑黃素—葉黃素複合物)的抗發炎活性，並發現其能顯著抑制人類腎近端小管細胞(HK-2 cell line)因高糖度所誘導的 NF-κB 的磷酸化和總表現量。此外，本研究也針對 YD01 建立一種快速且便利的 HPLC 及 UPLC 分析，並可應用於其他薑黃相關的產品(CL1-6)。

# **Chromatographic Analysis of YD01 (Curcumin-lutein Complex) and Evaluation of its Anti-inflammatory Activities in Human Renal Proximal Tubular HK-2 cells**

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Turmeric, rhizomes of *Curcuma longa*, is a medical herb traditionally used in Asian countries especially India and Pakistan against various chronic and autoimmune illnesses. The herb and its main active component, curcumin, were developed as nutraceuticals, which gained popularity in Taiwan, China, Japan, Korea, Malaysia, and Singapore in the last couple of decades. However, few attempts were made to combine curcumin with other biologically active secondary metabolites in nutraceuticals. To investigate this arena, a nutraceutical composed of curcumin and lutein, YD01, was recently developed for eye disorders and inflammatory diseases. Curcumin, a diferuloylmethane derivative, demonstrated significant biological activities against cancers, diabetes, cardiovascular, kidney, neurological, and ocular diseases. Lutein, a xanthophyll derivative which is extracted from marigold (*Tagetes erecta*), exhibited potent antioxidant, anti-inflammatory, and immunomodulatory properties. Curcumin has been used in combination with other phytochemicals such as resveratrol, quercetin, sulforaphane, retinoic acid, and folates to target different types of cancers. However, the multifaceted therapeutic and pharmacologic effects of curcumin when given in combination with lutein are still in their infancy. We evaluated the anti-inflammatory activity of YD01 (curcumin-lutein complex) which significantly inhibited the phosphorylation and total expression of NF- $\kappa$ B induced by high glucose in human renal proximal tubular HK-2 cells. We also developed a simple and efficient protocol for the analysis of YD01 using HPLC and UPLC. The developed protocol was applied for the analysis of other commercial turmeric products (CL1-6).

## 毛細管電泳法診斷血友病第八凝血因子內顯子 22 反轉之基因分析

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本研究之關鍵在於運用反向轉移聚合酶連鎖反應(Inverse-shifting polymerase chain reaction, IS-PCR)及短端注入毛細管電泳法(Short-end injection CE)，可以迅速並準確的診斷第八凝血因子基因之 intron 22 inversion Type 1 (Inv22-1)及 Type 2 (Inv22-2)。A 型血友病(hemophilia A, HA)係缺乏第八凝血因子蛋白質所導致的 X 連鎖隱性遺傳出血性疾病，其發生率相當高(約 1/5000-10000)。目前為止 A 型血友病仍無法治癒，其中 40-50% 重度 A 型血友病患者基因缺陷為 intron 22 inversion，其中 Inv22-1 的發生率高於 Inv22-2。因此本研究目的為開發一簡單且可靠診斷 A 型血友病 Type 1 及 Type 2 的分析方法。為了改善過去分析 Inv22 基因型的效率，本研究將設計 5 組引子，用來區分野生型、Inv22-1、Inv22-2 及帶因者。405、457 及 512 bp 的 PCR 產物代表野生型；333、457 及 584 bp 代表 Inv22-1；385、405 及 584 bp 的 PCR 產物代表 Inv22-2；333、405、457、512 及 584 bp 代表 Inv22-1 帶因者；385、405、457、512 及 584 bp 代表 Inv22-2 帶因者。兩種基因型的帶因者之間只有 333 bp (Inv22-1)和 385 bp (Inv22-2)的差異。本研究利用毛細管凝膠電泳進行分析，總分析時間僅需 5 分鐘。分離電壓設定為 8 kV，溫度設定為 25°C，分離條件為 1 X TBE 緩衝溶液含有 0.4% (w/v) HPMC 及 1 μM YO-PROs-1 Iodide。本研究方法成功分析 50 位 HA 受試者及 7 位 HA 帶因者，其中 35 位 HA 受試者基因突變類型為非 intron 22 inversion；14 位 HA 受試者為 Inv22-1；1 位 HA 受試者為 Inv22-2。為確保研究結果的準確性，本研究將隨機挑選 7 個受試者樣品(含 5 位 HA 受試者及 2 位 HA 帶因者)，CE 結果與 DNA 定序分析結果相符合，證實本方法具有高準確性。

# **Separation of intron 22 inversion type 1 and 2 of hemophilia A by modified inverse-shifting polymerase chain reaction and capillary gel electrophoresis**

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An inverse-shifting polymerase chain reaction (IS-PCR) combined with short-end capillary gel electro- phoresis (CGE) was developed for genotyping of intron 22 inversion Type 1 (Inv22-1) and Type 2 (Inv22-2) of hemophilia A (HA). Severe HA cases are affected by intron 22 inversion around 45–50%. Inv22-1 has higher frequency than Inv22-2. The aim of this study is to distinguish them by genotyping. In order to improve Inv22 genotyping efficiency, five primers were designed for applying to differentiate the wild type, Inv22-1, Inv22-2 and carrier. Three amplicons of 405, 457 and 512 bp were recognized for wild type; 333, 457 and 584 bp for Inv22-1; 385, 405 and 584 bp for Inv22-2. The Inv22-1 carrier has 5-amplicons including 333, 405, 457, 512, 584 bp and Inv22-2 carrier is differentiated by 385, 405, 457, 512 and 584 bp. The amplicons between Inv22-1 and Inv22-2 carriers are only different in 333 bp for Inv22-1 carrier and 385 bp for Inv22-2 carrier. Capillary gel electrophoresis (CGE) was used for separation within 5 min. The separation voltage was set at 8 kV (cathode at detector), and the temperature was kept at 25°C. The sieving matrix was 89 mM Tris, 89 mM boric acid, 2 mM EDTA containing 0.4% (w/v) HPMC and 1 µM of YO-PROs-1 Iodide. Total of 50 HA patients (including 35 non-Inv22, 14 Inv22-1, and 1 Inv22-2 patients) and 7 HA carriers were diagnosed in the application. Seven random samples (5 patients and 2 carriers) were subjected to comparison and gave identical results of DNA sequencing and this modified IS-PCR.

### 第三孕期臨床生化檢測值參考範圍的訂定-台灣婦幼世代研究聯盟

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參考區間是健康人的特定生化檢測值的上下範圍，並為實驗室測試提供了基本框架。雖然多數實驗室都清楚地意識到懷孕會引起生化檢測值的變化，但它們很少為孕婦提供參考區間。許多常見激素，尤其是雌激素(Estradiol)，黃體素(progesterone)和睪固酮(testosterone)的正常值在懷孕期間發生變化。除非在評估孕婦的生化檢測值時考慮到這些正常的妊娠相關改變，否則妊娠的生理適應可能會被誤解為病理性的，或者它們可能掩蓋其他病症。當評估新生兒的健康狀況時，我們在此呈現的臍帶血參考範圍也可以被臨床醫生用作參考值。我們在本研究中提供的重要生化檢測項目的參考區間表可以為臨床醫生照顧孕婦和新生兒提供簡便快速的參考值。

## **New Trimester-specific Reference Ranges for Clinical Biochemical Tests in Taiwanese Pregnant Women-Cohort of TMICS**

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Reference intervals, upper and lower ranges of specific physiologic measurement among healthy people, provide a basic framework for laboratory testing. Although most laboratories are well aware that pregnancy induces changes in normal laboratory values, they rarely provide healthy reference intervals for pregnant women. The normal values for many common hormones, especially estradiol, progesterone, and testosterone, shift during pregnancy. Unless these normal, gestation-related alterations are taken into account when evaluating laboratory values in a pregnant woman, physiologic adaptations of pregnancy can be misinterpreted as pathologic or they can mask other pathologies. The cord blood ranges we present herein can also be used by clinicians as reference values when evaluating the health status of newborns. The table of reference intervals of important parameters we present in this study can serve a quick reference for clinicians caring for the pregnant woman and newborn infants.

## 有機磷農藥暴露與兒童神經發育的關係

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有機磷農藥 (Organophosphate pesticides, OPs) 是台灣農業使用最多的農藥，通常會在一般大眾身上檢測到尤其是孕婦及兒童。OPs 已被證實為內分泌干擾物，而內分泌干擾物可能影響人類的神經發育。因此，本研究的目的是評估 2 歲兒童的 OPs 暴露情形，及暴露濃度與兒童神經發育影響之間的關係。在前瞻性研究有 280 對母親與孩童，從每位參與者收集產前及產後尿液樣本，並使用 GC/MS 分析 OPs 代謝物：DMP、DMTP、DMDTP、DEP、DETP 和 DEDTP。2 歲兒童的認知行為使用貝利嬰兒發展量表(Bayley-III)評估，使用 Mann-Whitney U test 探討 OPs 暴露與 Bayley-III 量表評分的相關性。目前尿液樣本還在檢測中，初步數據為 56 名 2 歲兒童。DMP、DMTP、DMDTP、DEP、DETP 和 DEDTP 的檢出率分別為 80.4%，69.6%，64.3%，64.3%，62.5% 和 75%。調整肌酐酸濃度後，DMP、DMTP、DMDTP、DEP、DETP、DEDTP、DMs、DEs 和 DAP 的中位數(nmol/g creatinine)分別為 153.14, 53.32, 52.13, 19.24, 141.65, 192.17, 308.8, 311.6 和 702.11，暴露濃度與其他國家相比較高。兒童的認知行為評分包含認知、語言和運動分數，經由 Mann-Whitney U test，DEs 較高者具有顯著較低的運動分數(p=0.037)，但在 OPs 暴露和認知或是語言分數沒有發現顯著的關係。本研究結果顯示 OPs 暴露可能會影響幼兒的認知行為。

# Association between Organophosphate Pesticides Exposure and Neurodevelopment Effects in Children

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Organophosphate pesticides (OPs) are the most heavily used pesticides in agriculture in Taiwan. Therefore, they are commonly detected in general public and affect the neural development in pregnant women and children. We assess the OPs exposure of children in 2 years of age and examine the association between the children's cognitive function and OPs concentration. The urine samples of prenatal and postnatal were collected from 280 mother-child pairs and metabolites of OPs were analyzed by gas chromatography–mass spectrometry. Six analytes were measured including dimethylphosphate (DMP), dimethylthiophosphate (DMTP), dimethyldithiophosphate (DMDTP), diethylphosphate (DEP), diethylthiophosphate (DETP), and diethyldithiophosphate (DEDTP) and created a combined concentration measure for dimethyl compounds (DMs) consisting of the DMP, DMTP, and DMDTP, for diethyl compounds (DEs) consisting of the DEP, DETP, and DEDTP and six dialkyl phosphate (DAPs). The Bayley Scales of Infant and Toddler Development (Bayley-III) was used to assess children's cognitive function. The association between OPs exposure and Bayley-III scale score was determined by using the Mann-Whitney U test. 56 children of the cohort shown the respectively rates for DMP, DMTP, DMDTP, DEP, DETP, and DEDTP are 80.4%, 69.6%, 64.3%, 64.3%, 62.5%, and 75%. After adjusting by urine creatinine, the median (nmol/g creatinine) of urinary DMP, DMTP, DMDTP, DEP, DETP, DEDTP, DMs, DEs, and DAPs are 153.14, 53.32, 52.13, 19.24, 141.65, 192.17, 308.8, 311.6, and 702.11. The concentrations are considerably higher than that in other countries. Children's cognitive, language and motor function are scale by Bayley-III. In Mann-Whitney U test, the higher levels of DEs had significantly lower motor score ( $p=0.037$ ), but no significance between the exposure and either cognitive or language. The limited sample size suggests that Taipei children are commonly exposed to OPs and OPs exposure might affect the cognitive behavior of young children. This report will present more data to verify the results. The predictors of OPs concentrations, such as dietary pattern will also be included.



## 孕婦暴露雙酚 A 與其出生結果之關係

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雙酚 A (BPA) 通常用於日常商品中，例如罐頭和聚碳酸酯 (polycarbonated) 瓶的內塗層。雙酚 A 是一種會影響正常人體激素的內分泌干擾物質 (EDs)，可能會對人體健康產生不良影響。產前暴露於雙酚 A 已證實會通過胎盤影響胎兒。因此，評估胎兒在懷孕期間接觸雙酚 A 的潛在健康風險是非常重要的。本研究的目的是 (1) 評估孕婦尿中雙酚 A 濃度 (2) 調查產前雙酚 A 暴露與出生結果之間的關係。利用台灣北、中、南、東地區的孕婦及其新生兒世代研究 (Taiwan Maternal and Infant Cohort Study, TMICS) 收集之 117 位孕婦資料。在妊娠晚期收集母親尿液樣本，並使用問卷收集參與者的社會人口特徵，飲食習慣和醫療條件。有關胎兒出生結果的信息來自出生時之醫療記錄。使用邏輯回歸模型探討孕婦體內 BPA 濃度與胎兒出生結果之間的關聯。雙酚 A 的檢出率為 99%；濃度範圍 ( $\mu\text{g/g}$ ) 為 0.16 至 46.90。雙酚 A 中位濃度為  $3.11 \mu\text{g/g cre.}$ 。按中位數將暴露水平分為兩組後，較高暴露組的孕婦體重下降 (OR=0.57, 95% CI=0.271-1.193)、胸圍較小 (OR=0.70, 95% CI=0.335-1.47) 和新生兒出生時胎齡較短的風險增加 (OR=0.46, 95% CI=0.191-1.114)。然而，在統計學中，BPA 濃度與出生結果之間沒有顯著相關 ( $P < 0.05$ )。

## **Association between exposure to Bisphenol A in pregnant women and its association with birth outcomes**

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Bisphenol A (BPA) is commonly used in consumer products, such as inner coatings of cans and polycarbonated bottles. BPA is considered an endocrine disrupting substance (EDs) in pregnant women and fetuses via the placenta. Therefore, it is important to evaluate the potential health risk of fetal exposure to BPA during pregnancy. The aims of this study were (1) to determine the urinary concentration of BPA in pregnant women, and (2) to investigate the association between BPA exposure during pregnancy and birth outcomes. The urine samples were collected in the third trimester and questionnaires from 117 pregnant women of the Taiwan Maternal- Infant Cohort Study (TMICS). BPA concentrations in urine were determined by mass spectrometer and were adjusted with urinary creatinine. The association between maternal concentrations of BPA and birth outcomes was estimated using the logistic regression model. The detection rate of BPA is 99%; the concentration ranges ( $\mu\text{g/g}$ ) from 0.16 to 46.90. The mean (SD) BPA levels are 5.37(6.42)  $\mu\text{g/g}$  creatinine and the median BPA levels are 3.11  $\mu\text{g/g}$  creatinine. After stratifying the exposure levels into two groups by median, pregnant women in higher exposure group would have an increased risk of lower body weight (OR=0.57, 95%CI=0.271-1.193), smaller chest circumference (OR=0.70, 95%CI=0.335-1.47) and shorter gestational age at birth newborn (OR=0.46, 95%CI=0.191-1.114). However, there are no associations between BPA concentration and birth outcomes reach a significant level ( $P<0.05$ ) in statistics. Women who have higher BPA concentrations tend to give birth to a lower body weight, smaller chest circumference or shorter gestational age at birth newborn. More data will be included to verify the results. This study will evaluate the potential health risk of fetal exposure to BPA during pregnancy in Taiwan.

## 人體血液與尿液中有機磷、類除蟲菊類的生物標記比較

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殺蟲劑的普及造就現今生活的便利，也增加了民眾暴露的風險。傳統的有機磷殺蟲劑（Organophosphate、OP）因為毒性較強且代謝半衰期長，主要用於農業病蟲害防治；而人工合成的類除蟲菊殺蟲劑（Pyrethroid、PYR），因其相對毒性低且半衰期短，為目前一般市售環境用藥及部分農藥中的主要成分，也是民眾最容易暴露的殺蟲劑類型。一般殺蟲劑暴露評估研究所使用的生物標記多為尿液，因為無侵入性且易於取得；但因代謝物不具特異性，因此無法追蹤原始的殺蟲劑類型。因此本研究欲比較血液中殺蟲劑原始類型與尿液中的代謝產物之關聯，以確認兩者作為生物標記的適用性。研究通過研究倫理審查後，採集 35 位受測者的血液與尿液樣本，以氣相層析質譜儀進行血樣中 10 種最普遍的殺蟲劑分析（OP：Chlopyrifos、Terbufos；PYR：Cypermethrin、Cyphenothrin、Imiprothrin、Metofluthrin、Permethrin、Phenothrin、Prallethrin、Tetramethrin），以及尿樣中多種代謝物的分析（OP 代謝物：DMP、DMTP、DMDTP、DEP、DETP、DEDTP；PYR 代謝物：3-PBA、cis-DBCA、cis-DCCA、trans-DCCA、trans-CDCA、FPBA）。實驗結果發現，血液中 OP 以 Chlopyrifos 偵測量最高（平均值±標準差：83.26±13.25 µg/L），而 PYR 則以 Cypermethrin 為最多（146.35±8.33 µg/L）。尿液中 OP 及 PYR 代謝物之偵測濃度，彼此之間較為接近，分別以 DMP 和 trans-DCCA 為最高。將每人血液中的 OP 和 PYR 以莫耳濃度（µmol/L）加總，再將尿液中兩類的代謝物以莫耳濃度加總，進行 35 人的血液與尿液中的生物標記比較。結果發現無論是 OP 與其代謝物（ $r = 0.786$ ）或是 PYR 與其代謝物（ $r = 0.848$ ），相關性高且達統計顯著標準（ $P < 0.001$ ）。因此本研究得到結論如下：在經常性殺蟲劑暴露的情況下，血液樣本與尿液樣本皆為暴露評估合適的生物標記，血液樣本更適用於需知原始成分的評估研究。

## Comparison between Blood and Urinary Biomarkers of Organophosphates and Pyrethroids

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Prevalent use of insecticides enriches the modern life, but increases the risk of human exposure to insecticides. Traditional organophosphates (OPs) are usually used in agriculture because of the high toxicity and long half-lives. Pyrethroids (PYRs) have become popular recently in environmental and agricultural use for its relatively low toxicity and short half-lives, and also been the major insecticides to which people are exposed. The common biomonitoring samples are urine, which is not invasive and easy to get; the metabolites in urine, however, are not specific to trace the original compounds. Thus, this study was to correlate the original compounds of insecticides analyzed from blood samples to metabolites in urine samples, and to confirm the availability of these two biomonitoring approaches. After getting the approval from the research ethic committee, we collected blood and urine samples from 35 subjects and analyzed them for 10 common insecticides using gas chromatography-mass spectrometry. The insecticides for blood analysis were OP's chlorpyrifos and terbufos, and PYR's cypermethrin, cyphenothrin, imiprothrin, metofluthrin, permethrin, phenothrin, prallethrin, and tetramethrin; urinary metabolites were DMP, DMTP, DMDTP, DEP, DETP, and DEDTP for OP metabolites, and 3-PBA, cis-DBCA, cis-DCCA, trans-DCCA, trans-CDCA, and FPBA for PYR metabolites. The result of blood analysis indicated that chlorpyrifos (OP) was the highest (mean±SD = 83.26 ± 13.25 µg/L), whereas cypermethrin (PYR) reached the top (146.35 ± 8.33 µg/L). The proportions of urinary metabolites were relatively close to one another, with DMP and trans-DCCA being the highest for OP and PYR metabolites, respectively. Each subject's insecticides in blood and metabolites in urine were summed up by conversion to molar concentrations (µmol/L). The correlations were highly significant (P < 0.001) between insecticides in blood and metabolites in urine for OP (r = 0.786) and PYR (r = 0.848), suggesting that blood samples could be used as well as urine samples for biomonitoring. Therefore, blood samples could be particularly useful for studies that need to know the original ingredients of insecticides.

# 產前鄰苯二甲酸酯類暴露對新生兒 IgE 濃度之影響：台灣母親與胎兒

## 世代研究

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鄰苯二甲酸酯類(phthalate ester, PAEs)是一種被大量使用於日常生活用品中之塑化劑, 其暴露會影響孩童的內分泌系統、免疫反應、生長以及疾病的發生。然而。鮮少有研究探討出生前 PAE 暴露對新生兒免疫反應之影響, 因此本研究乃利用出生世代研究來探討出生前 PAEs 暴露與新生兒臍帶血中 IgE 濃度之關聯。運用在 2012 年建立之「台灣母親與胎兒世代研究」, 於台灣北、中、南、東部的九家醫院, 共邀請了 1,677 對孕婦參與研究。研究中利用液相層析串聯質譜儀(LC-MS/MS)分析孕婦第三孕期尿液中 11 種塑化劑代謝物濃度以作為新生兒出生前塑化劑暴露指標, 並運用酵素連結免疫吸附分析法(ELISA)檢測新生兒臍帶血中 IgE 濃度, 而後使用斯皮爾曼相關性分析與多變項回歸分析進行統計檢定。本研究共有 589 對完成問卷訪視與母親尿中塑化劑代謝物檢測及臍帶血 IgE 分析的母親-新生兒對納入研究, 初步結果顯示, 孕婦尿中 MnBP、MEHHP、MEOHP 等塑化劑代謝物濃度乃與新生兒臍帶血中 IgE 濃度成顯著負相關。在考慮可能的干擾因素後, 並以母親過敏性疾病史進行分層分析顯示, 在母親無過敏性疾病病史的新生兒中, 母親尿中 MEHHP [ $\beta$  (95% CI) = -0.421 (-0.679 ~ -0.163)]、MEOHP [ $\beta$  (95% CI) = -0.391 (-0.633 ~ -0.148)]乃與新生兒臍帶血中 IgE 濃度成顯著負相關; 而在母親曾有過敏性疾病病史的新生兒中, 則母親尿中 MnBP 濃度也與新生兒臍帶血中 IgE 濃度成顯著負相關[ $\beta$  (95% CI) = -0.590 (-1.141 ~ -0.039)]。出生前塑化劑暴露乃會影響新生兒臍帶血中 IgE 濃度, 母親尿中 DnBP 與 DEHP 代謝物濃度越高的新生兒, 其臍帶血中的 IgE 濃度越低。

## **Association between in-utero phthalate exposure and cord blood IgE levels: Taiwan Mother and Infant Cohort Study**

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Phthalate esters (PAE) are widely used plasticizers and solvents that are added to many consumer products used in our daily life. PAE exposure is related to endocrine system, immune response, growth, and disease development in children. However, there is limited study about prenatal PAE exposure and immune response in newborns. We therefore aim to investigate the relationship between prenatal phthalate exposure and cord blood IgE (cbIgE) levels from a longitudinal birth cohort study. We invited 1,617 pregnant women from 9 hospitals/medical centers located in the north, middle, south, and east of Taiwan to participate “Taiwan Mother and Infant Cohort Study” conducted in 2012. Eleven urinary concentrations of phthalate metabolites in pregnant women were evaluated by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and were considered as in-utero phthalate exposure levels of newborns. CbIgE levels were measured by enzyme-linked immunosorbent assay (ELISA). We applied Spearman’s correlation and multiple regression analysis for statistical testing. A total of 589 mother-infant pairs with questionnaire and completed measurements of phthalate metabolites and cbIgE were recruited in present study. The concentrations of MnBP, MEHHP, and MEOHP were negatively associated with cbIgE levels. After adjustment for potential confounders and stratified by maternal atopy, among newborn without maternal atopy, MEHHP and MEOHP were negatively associated with cbIgE levels ( $\beta$  [95% CI] = -0.421 [-0.679 ~ -0.163] and -0.391 [-0.633 ~ -0.148], respectively). Moreover, a negative association was found between MnBP concentration and cbIgE levels in newborn with maternal atopy ( $\beta$  [95% CI] = -0.590 [-1.141 ~ -0.039]). In-utero phthalate exposure was associated with cord blood IgE levels. Lower cord blood IgE levels was found in newborns with higher in-utero DEHP exposure.

## 母親金屬暴露與臍帶血中免疫球蛋白 E 增加之相關性探討

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過去研究發現金屬暴露（如鉻、鎘或鉛）可能與免疫生物標誌以及兒童過敏有關，而兒童過敏性疾病（如氣喘）的盛行率在全球也有增加的趨勢；臍帶血中的免疫球蛋白 E (IgE) 則被認為可能是早期階段過敏原導致後續過敏疾病的預測因子。探討懷孕婦女暴露於金屬與臍帶血中 IgE 濃度之間的相關性。自 2012 年至 2013 年間，在台灣北、中、南和東部地區的 9 家醫院所招募的 426 對孕婦及其新生兒為研究對象。每位孕婦皆收集問卷資料和檢體，並在生產時收集臍帶血樣本；其中母親尿液使用感應耦合電漿質譜儀 (ICP-MS) 分析金屬濃度 (鎘、銅、鎳、鉍)，並使用 UniCAP IgE 測定系統對臍帶血 IgE 濃度進行定量。臍帶血 IgE 依據中位數濃度 0.42 kU/L 區分高低兩組。臍帶血 IgE 濃度高的新生兒多為男孩、出生身長略低；在進一步以母親過敏狀態分層後，母親過敏且高臍帶血 IgE 的新生兒具有顯著較低的出生體重。在統計模型中對兒童性別、孕婦教育程度和環境二手菸暴露 (ETS) 進行校正後，母親有過敏的新生兒在母體尿液金屬濃度增加時，臍帶血中 IgE 的勝算比也顯著增加 [ 鎘：OR = 2.92 (95% CI 1.01 - 8.42)；銅：OR = 3.12 (95% CI 1.10 - 8.87)；鎳：OR = 1.99 (95% CI 1.00 - 3.95)；鉍：OR = 2.58 (95% CI 1.08 - 6.18)]。沒有過敏的母親其新生兒臍帶血 IgE 則沒有觀察到類似的結果。有過敏疾患的母親如果金屬暴露濃度高可能會增加子代高臍帶血 IgE 濃度的勝算比。產前暴露被認為可在早期氣喘的發展中透過表觀遺傳的編程而產生作用；由於臍帶血 IgE 增加可能是過敏性的一項指標，因此確認孕婦是否有金屬暴露的風險以及對其子代進行過敏性疾患的初級預防之介入相當重要。

# Maternal Exposure to Metals Associated with Increased Cord Blood Immunoglobulin E

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Previous studies reported metal exposure might (such as chromium, cadmium and lead) associate with immune biomarkers and child allergy. The prevalence of child's allergic disease, such as asthma, has been increased worldwide. Cord blood immunoglobulin E (IgE) was considered a predictor of allergen sensitization in early life stage. In order to investigate the association between maternal exposure to metals and cord blood IgE. A total of 426 pairs of pregnant women and their newborns recruited from 9 hospitals distributed in northern, central, southern, and eastern parts of Taiwan during 2012 to 2013. The questionnaire and specimen were collected from each pregnant woman, and cord blood specimen was collected at the delivery. Maternal urine was used to analyze metal concentration (cadmium, Cd; copper, Cu; nickel, Ni; thallium, Tl) using inductively coupled plasma mass spectrometry (ICP-MS), and cord blood IgE levels was quantified using UniCAP IgE assay system. The high or low cord blood IgE was categorized according to the median concentration of 0.42 kU/L. Newborns with high cord blood IgE were more boys and had slightly lower birth height. In further stratification by maternal allergic status, newborns with high cord blood IgE of mother with allergy had significantly lower birth weight. After adjustment for child's sex, maternal education and environmental tobacco smoke (ETS) at pregnancy in statistical model, newborns of mothers with allergy had increased odds ratio of high cord blood IgE when maternal urine metal concentration increased [Cd: OR = 2.92 (95% CI 1.01 – 8.42); Cu: OR = 3.12 (95% CI 1.10 – 8.87); Ni: OR = 1.99 (95% CI 1.00 – 3.95); Tl: OR = 2.58 (95% CI 1.08 – 6.18)]. Newborns of mothers without allergy did not observed similar results. Offspring of allergic mothers with high exposure to metals have increased odds ratio of high cord blood IgE. Prenatal exposure was considered to play a role in the development of asthma in the early life through epigenetic programming. As increased cord blood IgE might be an indicator of atopy thus it is important to identify pregnant women at risk of metal exposure and interventions for the primary prevention of allergic disease on their offspring.