生命的隱形殺手

－環境荷爾蒙





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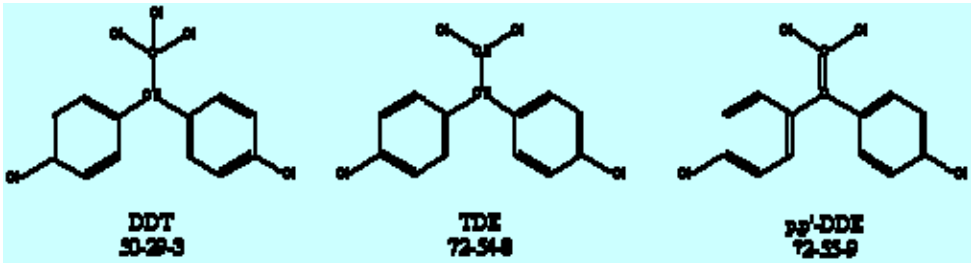
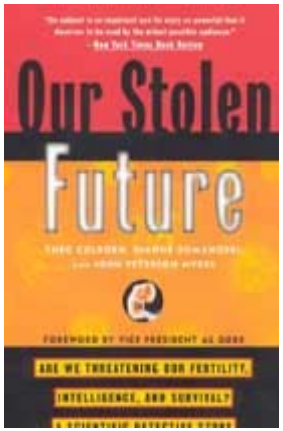
中華民國104年08月17日

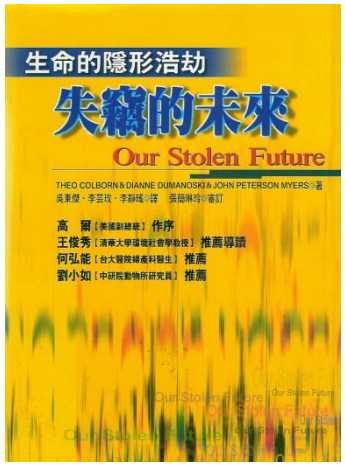
化學致癌物 → 癌症

- **Rachel Carson and Her "Silent Spring" (1962)**
  - 殺蟲劑
  - **(e.g., dichloro-diphenyl trichloroethane: DDT)**



內分泌干擾物質 ⟹ 生長發育危害





- Theo Colborn and Her "Our Stolen Future" (1996)
- 戴奧辛及多氯聯苯(Dioxins and PCBs)
- 內分泌干擾物質假說 (Endocrine disruptor hypothesis)

內分泌干擾物質 ⟶ 生殖系統危害

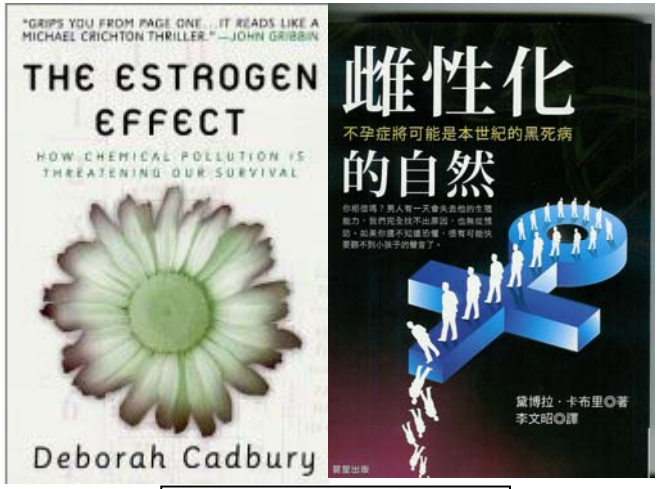
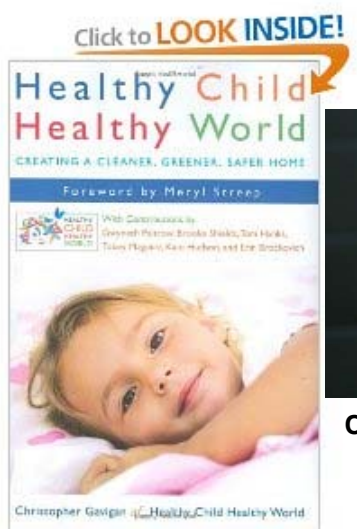


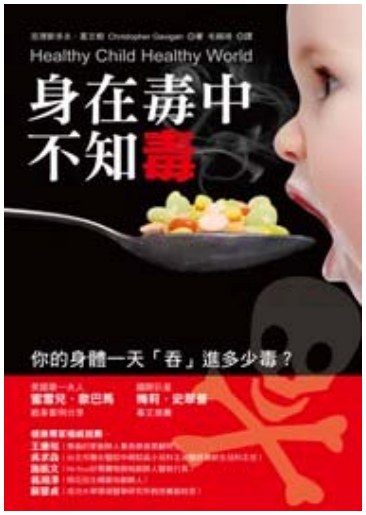

Photo by Jerry Bauer

- **The Estrogen Effect: How Chemical Pollution Is Threatening Our Survival (2000)**
- **鄰苯二甲酸酯(Phthalates)**
- **雌激素效應-不孕症**

如何創造健康的生活環境？



Christopher Gavigan



- **Healthy Child Healthy World: Creating a Cleaner, Greener, Safer Home**
- 為孩子打造無毒的成長環境
- 如何安心選購食材，讓家人吃得健康
- 聰明挑選家具、建材，室內空氣不含毒
- 善用天然清潔用品，環境不再愈清愈毒
- 選擇無毒的美容護膚品，身體才能真正的清潔
- 如何讓寵物免受化學產品的毒害

生殖系統危害現象

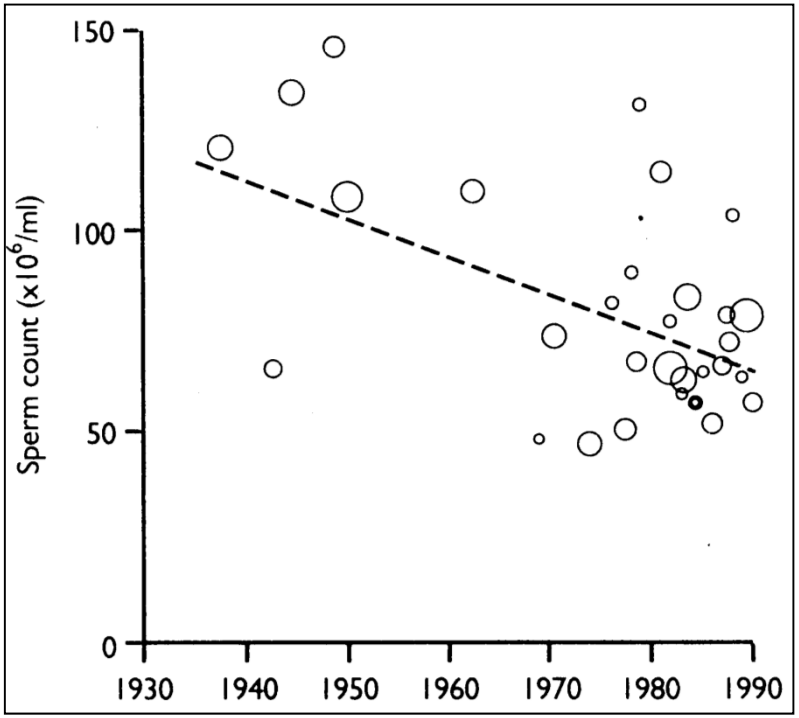


Fig. 1938-1990年61篇研究所載每毫升精液平均精子數之分布趨勢

<Carlson E et al., 1992>

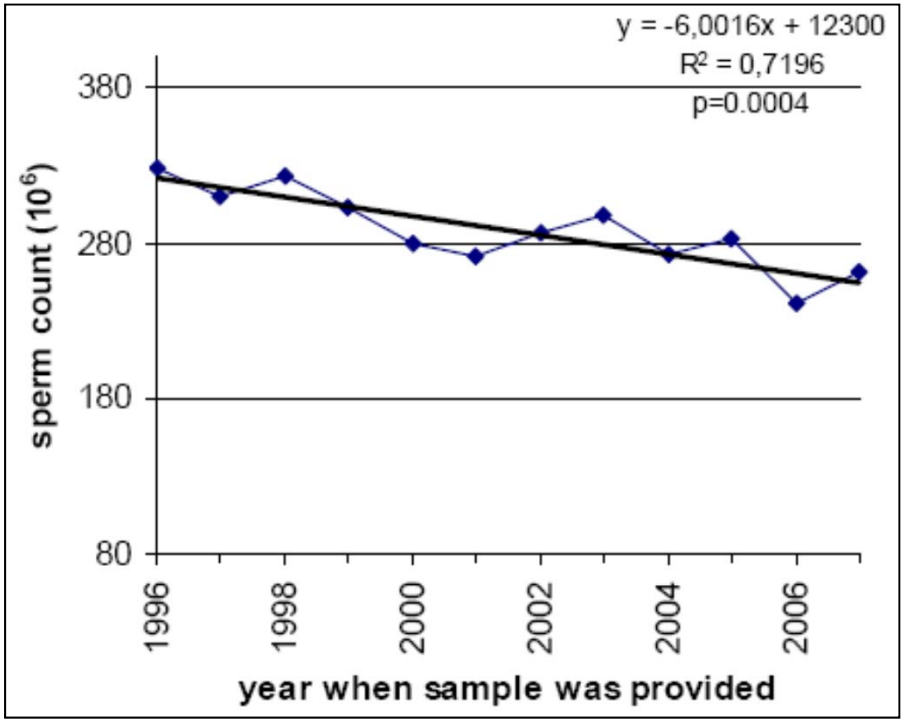
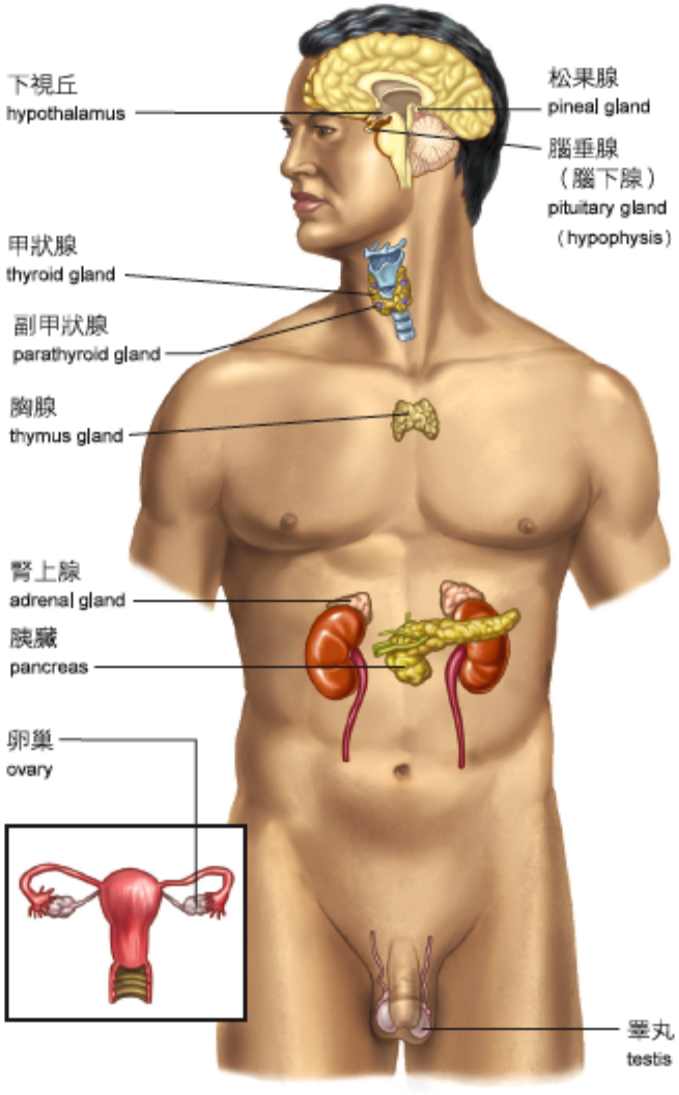


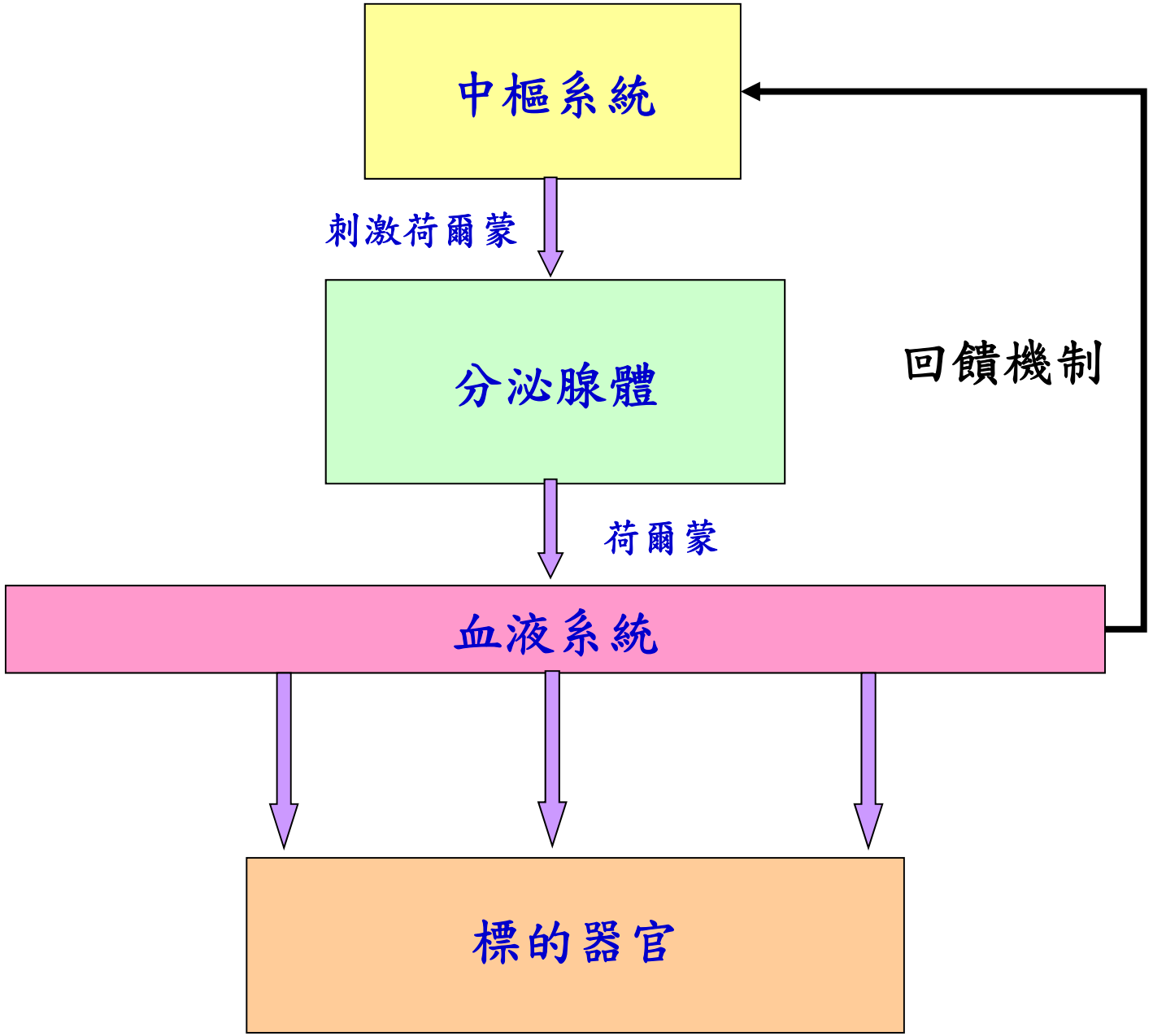
Fig. 1996-2008年突尼西亞1835位男性每毫升精液平均精子數之分布趨勢

<Feki1 et al., 2009>

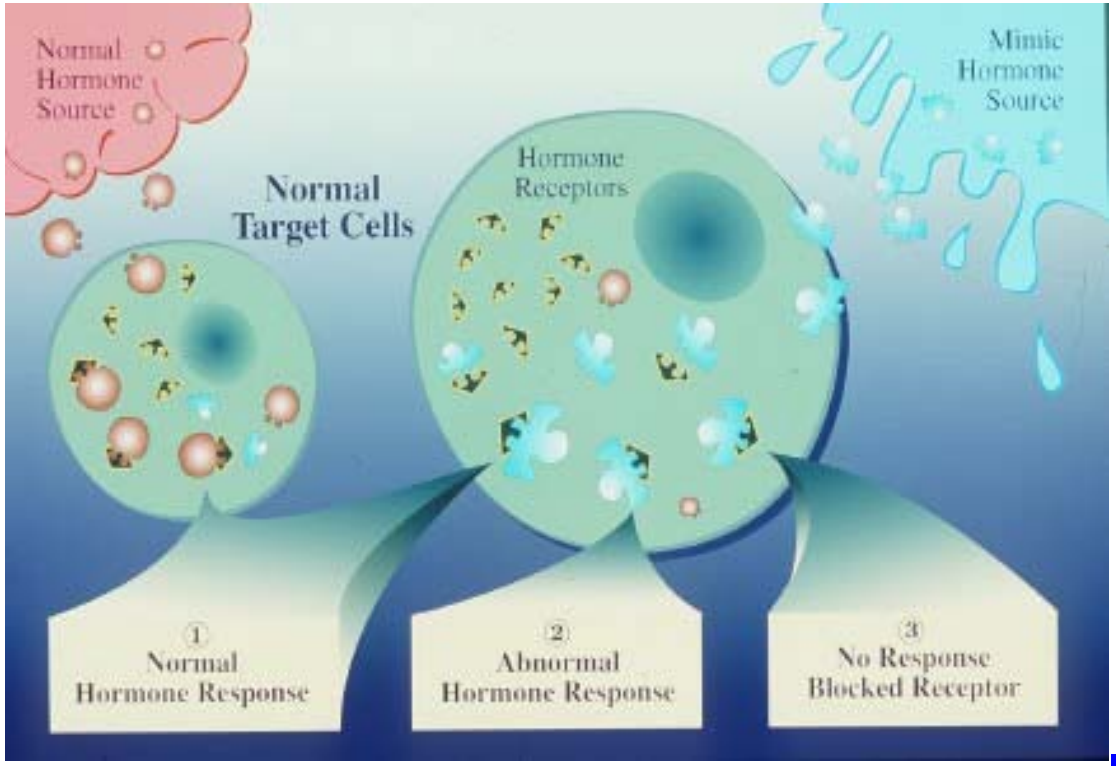
內分泌系統



- 內分泌系統(Endocrine)是負責調控動物體內各種生理恒定，及生長發育功能正常運作的系統，由分泌荷爾蒙的無管腺體所組成。荷爾蒙又稱為激素，是一種化學傳導物質，自腺體分泌出來後，藉由體液或進入血液經由循環系統運送到標的器官而產生作用 。


中樞系統
刺激荷爾蒙
分泌腺體
回饋機制
荷爾蒙
血液系統
標的器官

Endocrine Disruptor Hypothesis (by Theo Colborn)



- 外因性干擾生物體內分泌作用之化學物質，可模擬類似天然的荷爾蒙，欺騙身體而造成體內對荷爾蒙的過度作用，或可能直接刺激或抑制內分泌系統或誘導造成內分泌系統的失調
- 這些物質即稱為內分泌干擾物質或環境荷爾蒙

環境荷爾蒙 (by Taisen Iguchi)

「内分泌干擾物質」

(Endocrine Disrupting Chemicals, EDCs)

1997 NHK 電視節目

井口泰泉 教授

環境荷爾蒙

(Environmental Hormones)

Examples of Known Endocrine Disrupting Chemicals (EDCs)

- 農藥：可氯丹、**DDT**
- 環境污染物：戴奧辛/呋喃
- 工業產品：多氯聯苯、壬基酚、雙酚**A**、多溴二苯醚、有機錫（三丁基錫、三苯醋錫）、鄰苯二甲酸酯、重金屬（鉛、汞）、有機溶劑（丙酮、丁酮）
- 藥物：二乙基烯雌酚（**DES**）、口服避孕藥
- 植物型雌性激素
- 世界各國或組織已彙整國內已管制之**EDCs**達**104**種，尚有數十種可疑者仍在測試中。

持久性有機污染物

- **Persistent organic pollutants（POPs）**

所謂持久性有機污染物係指某些有機化合物在環境中之分解性低，可持續留累積存於環境中，且易經由食物鏈產生生物濃縮，最終具有對人體健康及生態環境產生不良效應之危險性。

已知之持久性有機污染物

- ★ Aldrin
- ★ Chlordane
- ★ DDT
- ★ Dieldrin
- ★ Endrin
- ★ Heptachlor
- ★ Hexachlorobenzene
- ★ Mirex
- ★ Toxaphehene
- ★ Dioxins
- ★ Furans
- ★ PCBs
- ★ α－六氯環己烷
- ★ β－六氯環己烷
- ★ 六溴聯苯醚和七溴聯苯醚
- ★ 四溴聯苯醚和五溴聯苯醚
- ★ 十氯酮
- ★ 六溴聯苯
- ★ 靈丹
- ★ 五氯苯
- ★ 全氟辛烷磺酸、全氟辛烷磺酸鹽和全氟辛基磺酰氟

戴奧辛/呋喃

內分泌干擾效應：國內研究結果

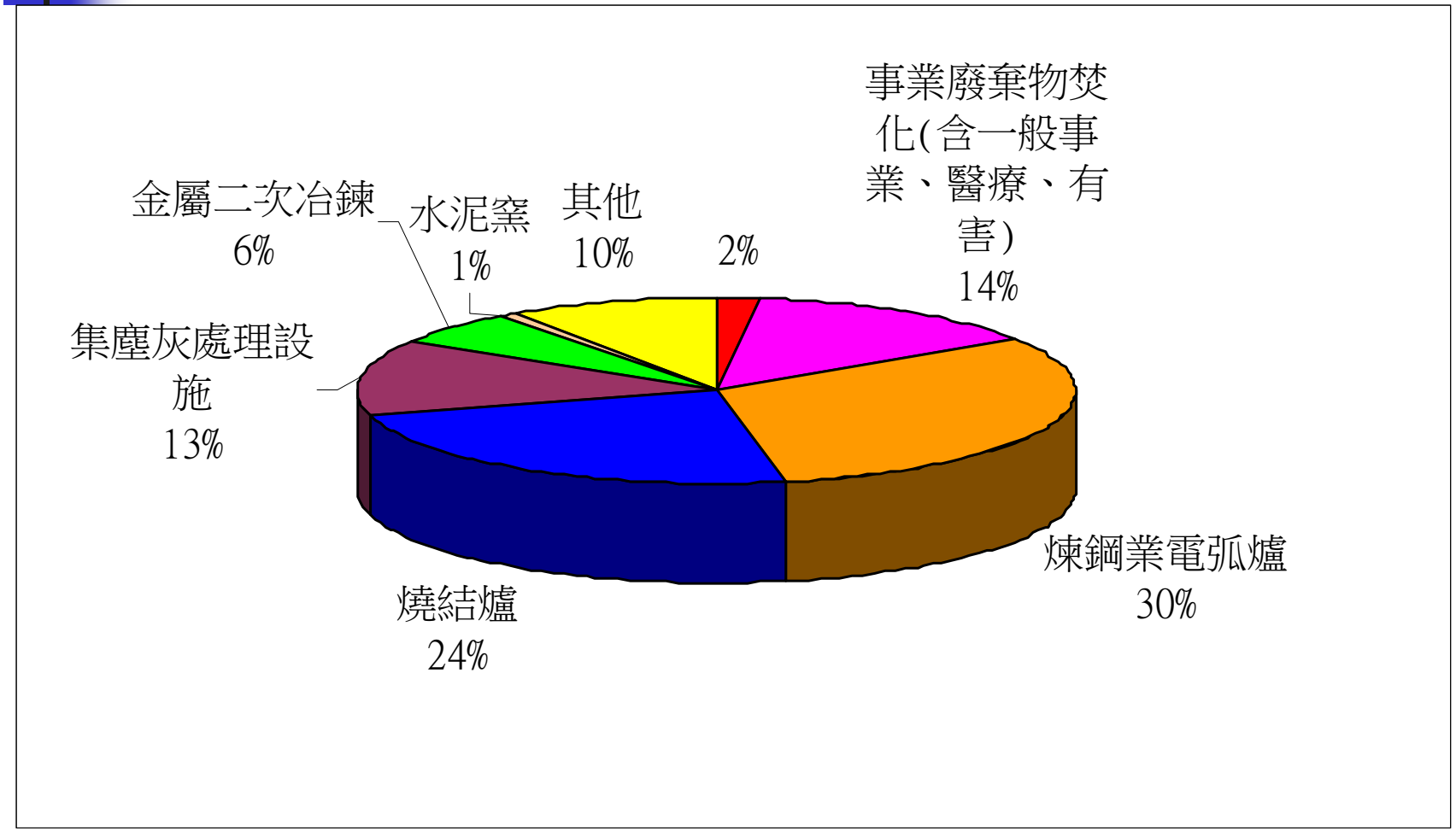
多氯戴奧辛/呋喃之毒性

多氯戴奧辛/呋喃 (polychlorodibenzo-*p*-dioxins and dibenzofurans，PCDD/Fs)

對人體健康與動植物生態的不良影響在文獻中已有明確之記載，依據文獻所載其毒性包括：

1. 皮膚毒性：如痤瘡出現、色素沈積。
2. 神經系統毒性：如週圍神經傳導緩慢。
3. 肝毒性：如肝臟腫大、肝功能異常。
4. 致癌性：如軟組織、惡性淋巴腫瘤。
5. 生殖系統毒性：如中毒者第二代多為女性胎兒。
6. 內分泌干擾毒性：如血糖異常、胰島素阻抗

台灣地區PCDD/Fs 之排放來源



戴奧辛之暴露途徑

- 戴奧辛存在空氣、土壤與底泥，可經由呼吸和食入進入人體。以下則是人體暴露於戴奧辛的可能途徑：
  - ✓ 透過呼吸進入：燃燒行為(森林大火)、機動車輛的排煙及焚化爐、金屬冶煉業排放廢氣。
  - ✓ 透過飲食進入：就人體而言，大約有95％以上之暴露來自食物，尤其是魚類、肉類、及乳製品等。
  - ✓ 水源污染：戴奧辛在水中的溶解性極低，大部分會被水中底泥所吸附，所以在水中含量極為微量。

戴奧辛/呋喃與飯前血糖之關係

- 一般民眾

Table 2
Levels of serum PCDD/Fs and biochemical findings in the study population

	Serum PCDD/Fs in 4 quartile[†]				
	<25% N=258	25–50% N=259	50–75% N=259	>75% N=257	p value
GLU, mg/dl	**92.7(21.0)**	**94.1(24.9)**	**97.0(33.3)**	**102.2(40.8)**	**0.003***
TP, IU/L	7.4(0.9)	7.3(0.8)	7.2(0.6)	7.6(4.3)	0.325
ALB, mg/dl	**4.44(0.55)**	**4.33(0.48)**	**4.24(0.38)**	**4.29(0.43)**	**<0.0001****
BUN, mg/dl	**14.2(3.3)**	**15.0(4.4)**	**15.3(3.9)**	**15.8(3.8)**	**0.0003****
CREA, mg/dl	**0.93(0.18)**	**0.91(0.27)**	**0.85(0.20)**	**0.88(0.21)**	**0.0003****
UA, mg/dl	**6.5(1.7)**	**6.2(1.7)**	**6.1(1.7)**	**6.2(1.8)**	**0.019***
CHOL, mg/dl	190.2(39.4)	194.0(39.5)	195.9(40.1)	195.8(40.1)	0.326
TG, mg/dl	136.0(133.9)	134.1(128.5)	117.8(90.7)	129.6(111.0)	0.289
GOT, IU/L	24.5(17.2)	23.9(24.7)	22.0(9.9)	23.1(11.0)	0.360
GPT, IU/L	25.9(20.3)	23.1(19.6)	23.8(17.8)	24.4(15.0)	0.359
GGT, IU/L	33.6(48.0)	30.5(35.8)	29.2(36.7)	33.9(37.2)	0.471
T-BIL, mg/dl	0.8(0.3)	0.8(0.3)	0.7(0.3)	0.8(0.3)	0.135
ALP, IU/L	71.5(30.8)	68.6(20.4)	66.0(20.5)	68.8(23.4)	0.076

Bold data entries represent the significant differences or significant correlations (p<0.05) found.
Data are mean (standard deviation).
*p value<0.05, **p value<0.001.
[†](1) <25%: serum PCDD/Fs level <11.13 pg I-TEQ/g lipid, (2) 25–50%: 11.13 ≤ serum PCDD/Fs level <15.29 pg I-TEQ/g lipid, (3) 50–75%: 15.29 ≤ serum PCDD/Fs level ≥21.08 pg -TEQ/g lipid, (4) >75%: serum PCDD/Fs level >21.08 pg I-TEQ/g lipid.

Hsiu-Ling Chen et al., Science of the Total Environment, 2006

戴奧辛/呋喃與飯前血糖之關係

- 高污染民眾

TABLE 2. Levels of Serum PCDD/Fs, Insulin Resistance (HOMA-IR), and Pancreatic β-Cell Function (HOMA-β) in Nondiabetic Participants

	Serum PCDD/F Quartile[a]				
	<25th (n = 305)	25th–<50th (n = 310)	50th–<75th (n = 311)	≥75th (n = 308)	P_{trend}
BMI (kg/m^2), mean (SD)	23.9 (3.9)	24.1 (3.9)	24.3 (3.6)	25.0 (3.7)	<0.001
Waist circumference (cm), mean (SD)	80.9 (11.0)	81.0 (11.2)	82.0 (10.8)	85.4 (10.7)	<0.001
Fasting glucose (mg/dL), mean (SD)	89.3 (9.6)	90.2 (9.1)	92.2 (10.6)	94.3 (12.1)	<0.001
Fasting glucose (abnormal), no. (%)	16 (11.5)	29 (13.9)	59 (21.2)	85 (28.2)	<0.001
Insulin resistance, mean (SD)	1.49 (1.14)	1.51 (1.00)	1.72 (1.18)	2.16 (1.49)	<0.001
Pancreatic β-cell function, mean (SD)	101.6 (106.5)	97.7 (92.1)	103.2 (86.3)	114.0 (89.1)	0.09

[a]Quartiles of serum PCDD/F levels (pg WHO_{98}-TEQ_{DF}/g lipid): (1) <25th, <13.1; (2) 25th to <50th, 13.1 to 20.4; (3) 50th to <75th, 20.5 to <33.8; (4) ≥75th, ≥33.9.

Jung-Wei Chang et al., Epidemiology, 2010

戴奧辛/呋喃與胰島素阻抗之關係

- 高污染民眾

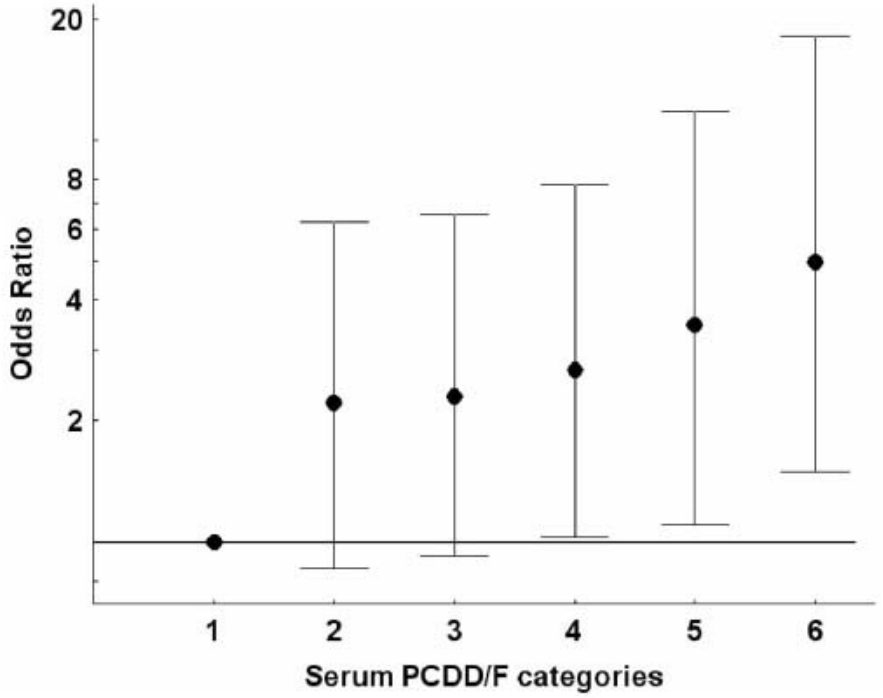


FIGURE. Adjusted odds ratios (filled circles) and 95% CIs (vertical bars) for insulin resistance according to percentile categories of serum PCDD/F levels (pg WHO_{98}-TEQ_{DF}/g lipid): (1) <10th: <9.6 (reference category), (2) 10th to <25th: 9.6 to 13.0, (3) 25th to <50th: 13.1 to 20.4, (4) 50th to <75th: 20.5 to 33.8, (5) 75th to <90th: 33.9 to 54.0, (6) ≥90th: ≥54.1. The odds ratios are adjusted for age, sex, BMI, smoking, weight control, physical activity, and family history of diabetes.

Jung-Wei Chang et al., Epidemiology, 2010

戴奧辛/呋喃、汞交互作用對胰島素阻抗之影響 – 高污染民眾

Table 4
Association between serum PCDD/F, blood mercury levels, and the risk of insulin resistance.

Variables	Total	HOMA-IR			HOMA β-cell		
		No. (%)	OR	95% CI	No. (%)	OR	95% CI
Age (years)							
<40	451	68 (15.1)	1	Referent	86 (19.1)	1	Referent
40–60	659	190 (28.8)	2.19	1.49, 3.22	191 (29.0)	1.56	1.09, 2.25
>60	339	79 (23.3)	1.36	0.78, 2.37	78 (23.0)	0.89	0.52, 1.51
Gender							
men	758	200 (26.4)	1	Referent	204 (26.9)	1	Referent
women	691	137 (19.8)	0.72	0.55, 0.94	151 (21.9)	0.78	0.60, 1.01
Waist circumference (cm)							
men ≤ 90 and women ≤ 80	851	110 (12.9)	1	Referent	134 (15.7)	1	Referent
men ≤ 90 and women ≤ 80	598	227 (38.0)	3.97	3.01, 5.23	221 (37.0)	3.27	2.51, 4.27
Diastolic BP (mmHg)							
≤85	1172	230 (19.6)	1	Referent	262 (22.4)	1	Referent
>85	277	107 (38.6)	1.83	1.36, 2.48	93 (33.6)	1.29	0.95, 1.75
Dioxin[†]/mercury[‡]							
1st tertile/1st tertile	207	12 (5.8)	1	Referent	32 (2.2)	1	Referent
1st tertile/2nd tertile	153	23 (15.0)	2.64	1.20, 6.07	31 (2.1)	1.23	0.68, 2.23
1st tertile/3rd tertile	119	33 (27.7)	4.94	2.23, 11.69	33 (2.3)	1.51	0.78, 2.93
2nd tertile/1st tertile	150	25 (16.7)	4.89	2.09, 12.20	29 (2.0)	1.20	0.63, 2.27
2nd tertile/2nd tertile	154	36 (23.4)	4.34	1.98, 10.07	33 (2.3)	1.05	0.54, 2.03
2nd tertile/3rd tertile	183	65 (35.5)	6.42	3.15, 14.03	57 (3.9)	1.77	0.94, 3.39
3rd tertile/1st tertile	126	28 (22.2)	6.19	2.21, 18.08	28 (1.9)	1.45	0.62, 3.42
3rd tertile/2nd tertile	174	44 (25.3)	8.62	3.57, 21.93	55 (3.8)	1.97	0.95, 4.22
3rd tertile/3rd tertile	183	71 (38.8)	11.00	4.87, 26.63	57 (3.9)	1.54	0.77, 3.11

Abbreviations: OR = odds ratio; CI = confidence interval.

† Serum PCDD/F levels indicate: 1st tertile: <15.9 pg WHO_{98}-TEQ_{DF}/g lipid; 2nd tertile: 15.9 ≤ serum PCDD/F levels < 30.3 pg WHO_{98}-TEQ_{DF}/g lipid; 3rd tertile: 30.3 pg WHO_{98}-TEQ_{DF}/g lipid ≤ serum PCDD/F levels.

‡ Blood Hg level indicates: 1st tertile: <7.2 μg/L; 2nd tertile: 7.2 ≤ blood Hg level < 11.4 μg/L; 3rd tertile: 11.4 μg/L ≤ blood Hg level.

Jung-Wei Chang et al., Journal of hazardous materials, 2010

戴奧辛/呋喃與心血管疾病之關係

- 高污染民眾

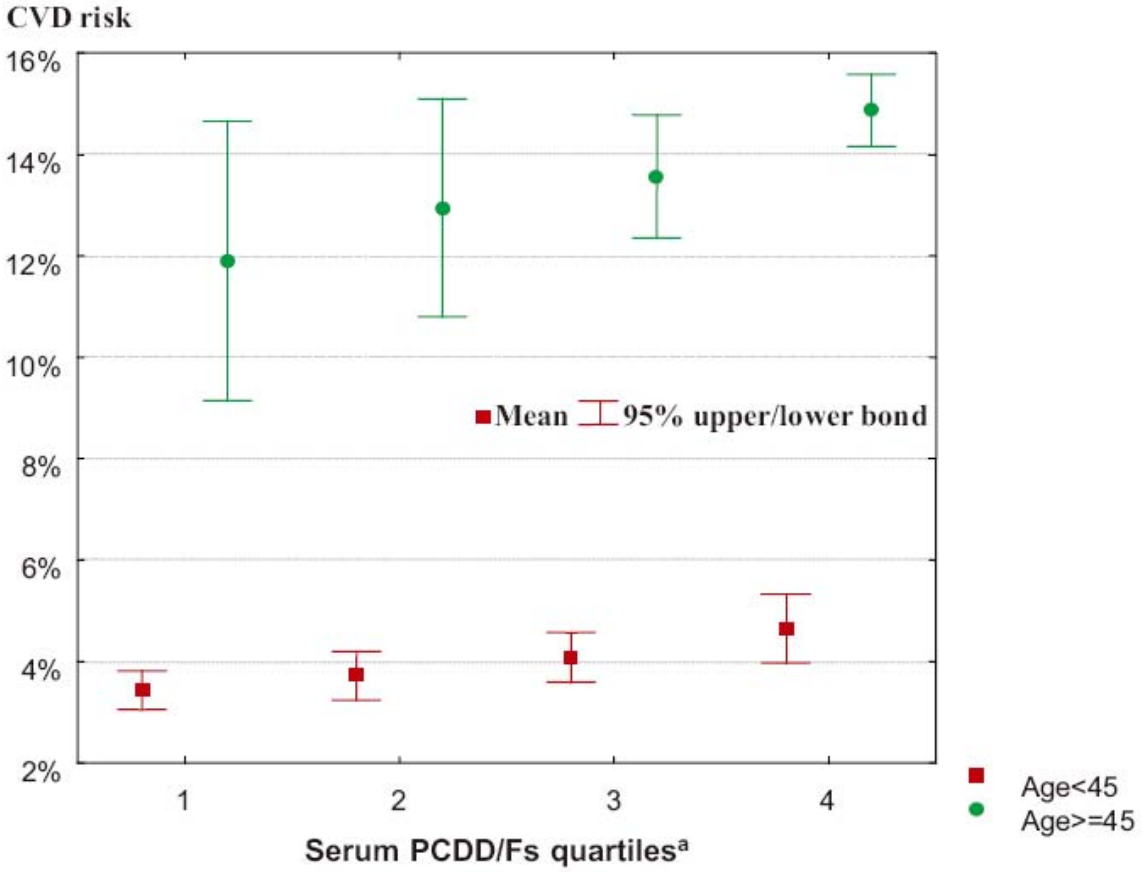


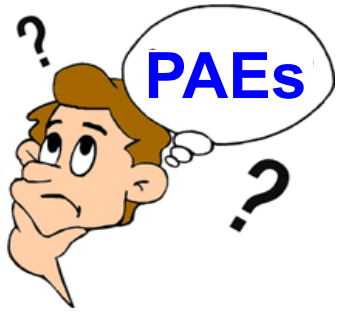
Fig. 1. Differences in CVD risk with the same serum PCDD/F levels in the 30–45- and 45–74-year-old groups. [a]Quartiles of serum PCDD/F levels: (1) < 25th, < 9.86; (2) 25th to < 50th, 9.86–13.8; (3) 50th to < 75th, 13.8 to < 21.2; (4) ≥ 75th, ≥ 21.2. pg WHO_{98}-TEQ_{DF}/g lipid.

Jung-Wei Chang et al., Journal of hazardous materials, 2011

鄰苯二甲酸酯

對孕婦及胎兒內分泌干擾效應：國內研究結果

什麼是Phthalates (PAEs)?



- ✓ 鄰苯二甲酸酯是鄰苯二甲酸(Phthalate acid) 的酯化衍生物，為常見的塑膠塑化劑。所謂塑化劑是指在塑膠原料加工時，添加塑化劑可以改變塑膠成形時的物理性質，使其物理性質變為較為柔軟，易於加工；或是添加塑化劑後，可使得塑膠成品具有柔軟、易於彎曲、摺疊的性質。

Phthalic acid

Phthalic anhydride

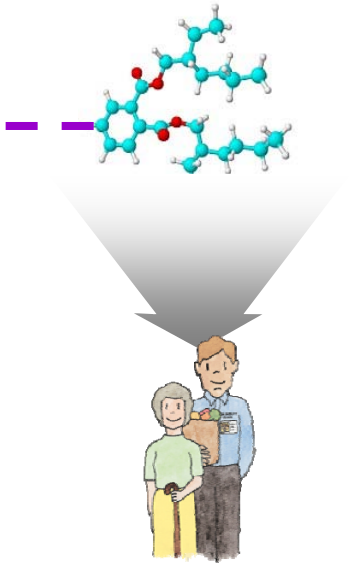
General chemical structure of phthalate ester

PAEs 的用途

- *塑膠塑化劑*
- *化妝品、香水之定香劑*

- 塑膠製品
- 化妝品、香水或具香味商品
- 建築材料
- 電線電纜外皮

Ω 保鮮膜
Ω 汽車內裝
Ω 醫療器材如輸液管、血袋
Ω 玩具



Ref.: Api, 2001; ATSDR, 1995, 2001, 2002; Kavlock et al.,2002, 2006.

✓ 鄰苯二甲酸酯類主要用途

PAEs 種類	主要應用產品
DEHP	建材(地板、壁紙、電線外層)、汽車產品(座椅、內裝、PVC 地墊)、衣服(鞋、雨衣)、食品包裝、兒童產品(玩具、奶嘴)、醫療用品(輸血袋、導管、氧氣罩、注射針筒)、香水、PVC 吸管、電容器、殺蟲劑、真空幫浦油
DBP	主要用於乳膠接合劑(latex adhesive)、纖維塑膠(cellulose plastic)、染料的溶劑、PVC 的塑化劑、體香劑、美髮藥品、指甲油、香水、印刷用油墨、醫療用品(PVC 假牙)、玩具、浴簾
BBP	大量使用於乙烯地板(vinyl tile)、食物運送帶(food conveyor belt)、地毯(carpet tile)、人造皮革(artificial leather)、防水布(tarpaulin)、汽車飾件(automotive trim)、密封條(Weather stripping)、交通錐(traffic cone)、黏著劑(adhesives)、美髮藥品、香水、印刷用油墨
DEP	香水、化妝品、保養品、沐浴用品、鬍後水、體香劑、美髮藥品等
DMP	纖維素酯膜塑膠之可塑劑、美髮藥品
DINP (Di-isononyl phthalate)	PVC 遮板、PVC 襯墊、PVC 管線、PVC 壁紙、PVC 玩具、PVC 吸管、PVC 運輸帶、紡織品、手套

✓ 鄰苯二甲酸酯於化妝品中的檢出率及濃度

PAEs 化合物	2002 美國 (n=72)		
	檢出率 (%)	平均濃度 (檢出最大濃度) (mg/kg)	產品
檢出任一 PAEs	72	-	體香劑，香水，髮膠，美髮慕絲，美髮噴霧，手部及身體乳液，指甲油
DEHP	4	11 (25)	香水
DBP	8	275 (890)	指甲油，美髮噴霧， 體香劑
BBP	6	14 (46)	香水，美髮噴霧
DEP	71	4,700 (280,000)	香水，體香劑，髮膠，美髮慕絲，美髮噴霧，手部及身體乳液
DMP	1	33 (33)	體香劑

資料來源：*Houlihan et al., 2002*

✓ 鄰苯二甲酸酯於化妝品中的檢出率及濃度

PAEs 化合物	2005 美國 (n=48)		
	檢出率 (%)	平均濃度 (檢出最大濃度) (ppm)	產品
檢出任一 PAEs	67	-	身體乳液，美髮噴霧，體香劑，香水，潤膚乳液，髮膠，美髮慕絲，沐浴露，洗髮精，護手霜，指甲油
DEHP	0	ND (<10ppm)	-
DBP	21	10,733 (59,815)	美髮噴霧，體香劑，指甲油
BBP	4	75 (107)	美髮噴霧，指甲油
DEP	58	2,993 (38,663)	香水，身體乳液，美髮噴霧，體香劑，潤膚乳液，髮膠，美髮慕絲，沐浴露，護手霜，指甲油
DMP	6	5,199 (15,395)	指甲油

資料來源：*Houlihan et al., 2005*

✓ 鄰苯二甲酸酯於化妝品中的檢出率及濃度

PAEs 化合物	2002 歐洲 (n=34)		
	檢出率 (%)	平均濃度 (檢出最大濃度) (mg/kg)	產品
檢出任一 PAEs	79		體香劑，香水，美髮慕絲，髮膠，美髮噴霧
DEHP	29	9.3 (24)	體香劑，香水，美髮慕絲，美髮噴霧
DBP	24	22 (150)	體香劑，香水，美髮慕絲，美髮噴霧
BBP	6	5.4 (6.6)	美髮噴霧
DEP	68	2,200 (19,000)	體香劑，香水，美髮慕絲，髮膠，美髮噴霧
DMP	3	2.2 (2.2)	香水
DNOP	21	1.4 (1.6)	體香劑

資料來源：*Joseph, 2002*

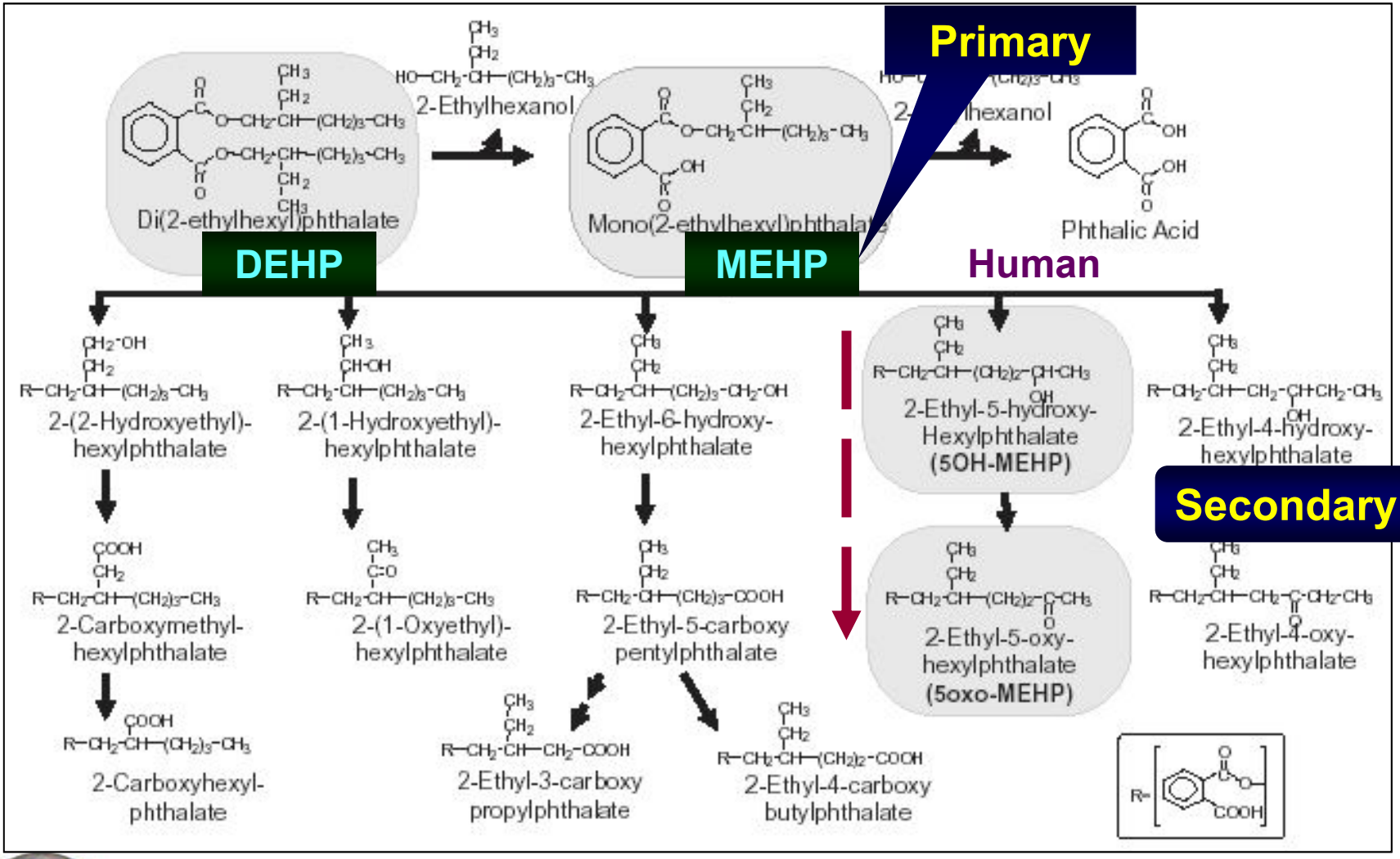
PAEs 的暴露途徑


Food
食物攝入
Personal care products
皮膚吸收
Building products
呼吸攝入
皮膚吸收
Cosmetics

PAEs 的暴露途徑

- PAEs與塑膠以非共價鍵結方式混合，極易自塑膠中釋出。
- 國人外食人口多，很多食物加工、包裝、盛裝和加熱過程都可能用到塑膠製品，造成DEHP趁機溶出滲入食物。
- 食物處理工人戴手套雖可防範食物遭細菌汙染，卻會釋出DEHP，食物以塑膠製品盛裝並加熱，更會大量釋出。
- 過去針對超商便當的研究，也發現超商便當經加熱會大量溶出DEHP，便當材質多為PVC，一個重量四百公克的便當加熱後，DEHP濃度達每日建議攝取量的63.1%-92.2%。
- 國人又常以塑膠袋裝填滾燙熱食，只要溫度超過六十度，就會溶出塑化劑。

PAEs 的代謝途徑



-Albro, et al., 1982; ATSDR, 1993, Schmid, et al., 1985c.

研究目的

Part I: 孕婦鄰苯二甲酸酯暴露會干擾體內甲狀腺荷爾蒙分泌嗎？

Human Reproduction 22, 2715-2722 (2007)

Associations between urinary phthalate monoesters and thyroid hormones in pregnant women

Po-Chin Huang[1], Pao-Lin Kuo[2], Yue-Liang Guo[3], Pao-Chi Liao[1] and Ching-Chang Lee[1,4]

- 量測孕婦尿液中鄰苯二甲酸酯代謝物含量
- 量測孕婦血液中甲狀腺荷爾蒙含量
- 檢核二者之相關性

研究目的

Part II: 孕婦鄰苯二甲酸酯暴露會影響新生兒健康狀態嗎？

***- Environment International* (2008).**

Environment International 35 (2009) 14–20

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ELSEVIER

Association between prenatal exposure to phthalates and the health of newborns☆

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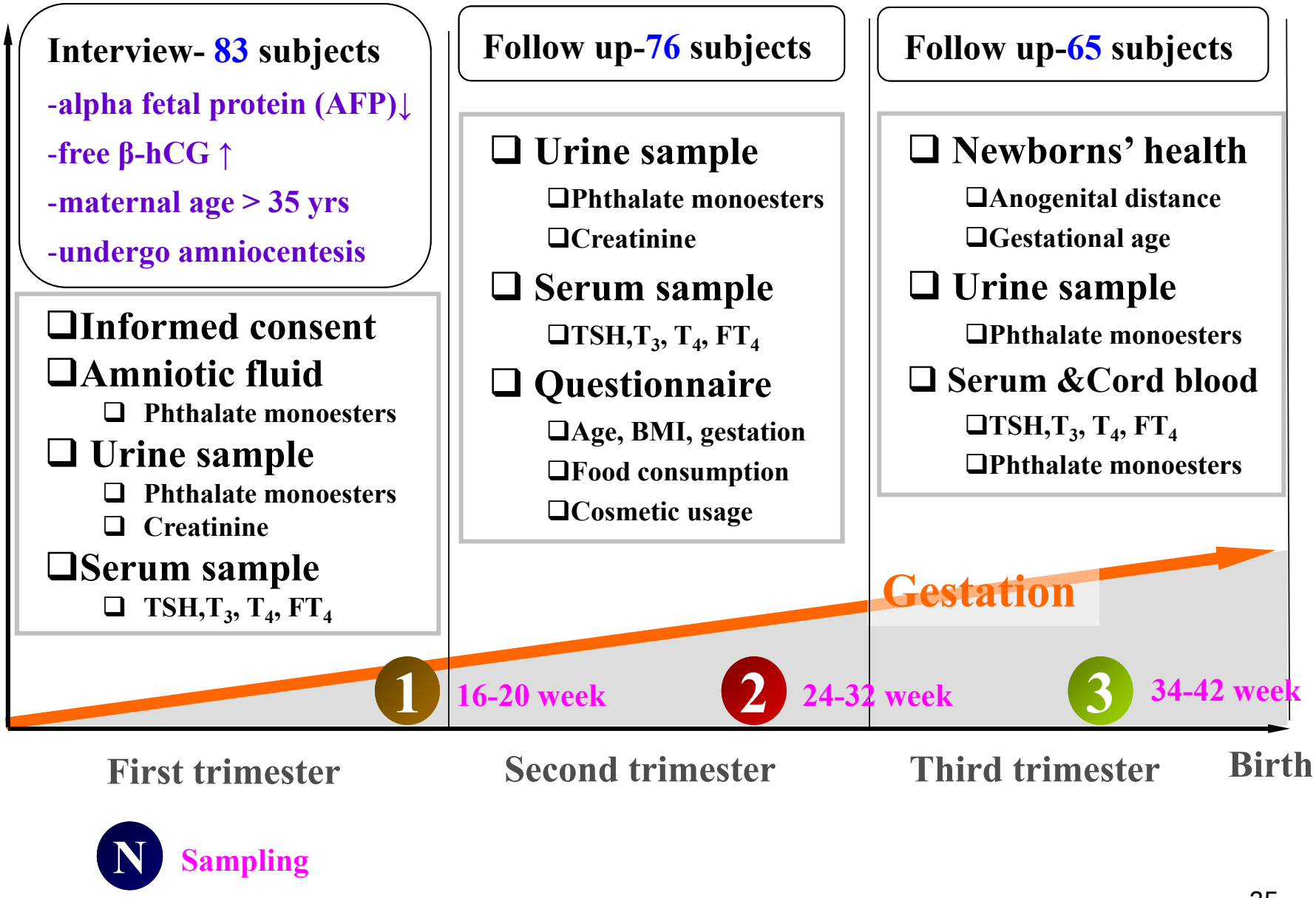
[a] Department of Environmental and Occupational Health, Medical College, National Cheng Kung University, Tainan, Taiwan
[b] Department of Obstetrics and Gynecology, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan
[c] Department of Pediatrics, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan
[d] Sustainable Environment Research Center, National Cheng Kung University, Tainan, Taiwan

- 量測孕婦羊水中鄰苯二甲酸酯代謝物含量
- 量測新生兒健康指標
- 檢核二者之相關性

材料與方法


Interview- 83 subjects
-alpha fetal protein (AFP)↓
-free β-hCG ↑
-maternal age > 35 yrs
-undergo amniocentesis
❑Informed consent
❑Amniotic fluid
❑ Phthalate monoesters
❑ Urine sample
❑ Phthalate monoesters
❑ Creatinine
❑Serum sample
❑ TSH,T3, T4, FT4
Follow up-76 subjects
❑ Urine sample
❑Phthalate monoesters
❑Creatinine
❑ Serum sample
❑TSH,T3, T4, FT4
❑ Questionnaire
❑Age, BMI, gestation
❑Food consumption
❑Cosmetic usage
Follow up-65 subjects
❑ Newborns' health
❑Anogenital distance
❑Gestational age
❑ Urine sample
❑Phthalate monoesters
❑ Serum &Cord blood
❑TSH,T3, T4, FT4
❑Phthalate monoesters
Gestation
1
16-20 week
2
24-32 week
3
34-42 week
First trimester
Second trimester
Third trimester
Birth
N
Sampling

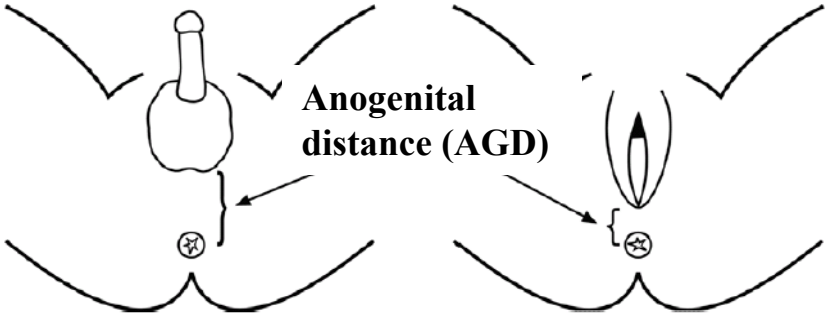
量測指標

- 甲狀腺荷爾蒙
  - Thyroid stimulating hormone (TSH)
  - Thyroxin (T_4)
  - Triiodotyronine (T_3)
  - Free thyroxin (FT_4)
- 問卷
  - Age, BMI, gestation age, Smoking, Medical care etc.
  - Food consumption
  - Cosmetic usage
  - Personal care product usage
  - Building characteristics

- 新生兒體格檢查
  - Anogenital distance (AGD)
  - Birth weight
  - Birth height
  - Gestational age
  - Anogenital index (AGI)

AGI-W= AGD/ birth weight.

AGI-L= AGD/ birth length.



-Salazar-Martinez et al., 2004.

結 果 與 討 論

Table I-1 受檢孕婦基本資料 (*n* = 76).

特性	平均值 ± 標準偏差
Age (years)	33.6 ± 3.3
Body mass index (BMI)	20.9 ± 2.5
Duration of gestation (weeks)	27.9 ± 2.3
Pregnancies and births	
Number of current pregnancy	1.9 ± 1.0
Number of current birth	1.5 ± 0.6
Smoking status (*n*/%)	
Active smoker	0/0
Passive smoker	14/18.4
Non-smoker	62/81.6
Alcohol drinker (*n*/%)	0/0
New decoration of living/ working place during previous 1 year (*n*/%) [a]	
Home	
Moving to new decorated house	7/9.2
Just decorated	4/5.3
Workplace	
Moving to new decorated workplace	2/2.6
Just decorated	6/7.9
Medical care during previous 3 months (*n*/%)	
Blood transfusion	3/3.9
Intravenous drip	3/3.9
Oxygen mask	1/1.3

[a] Moving to new decorated house or workplace means moved into a new building. Just decorated means the place you live or work have decorated recently such as painting or changing the floor.

Table I-2 台灣孕婦尿液中PAE代謝物含量分布 (μg/g creatinine).

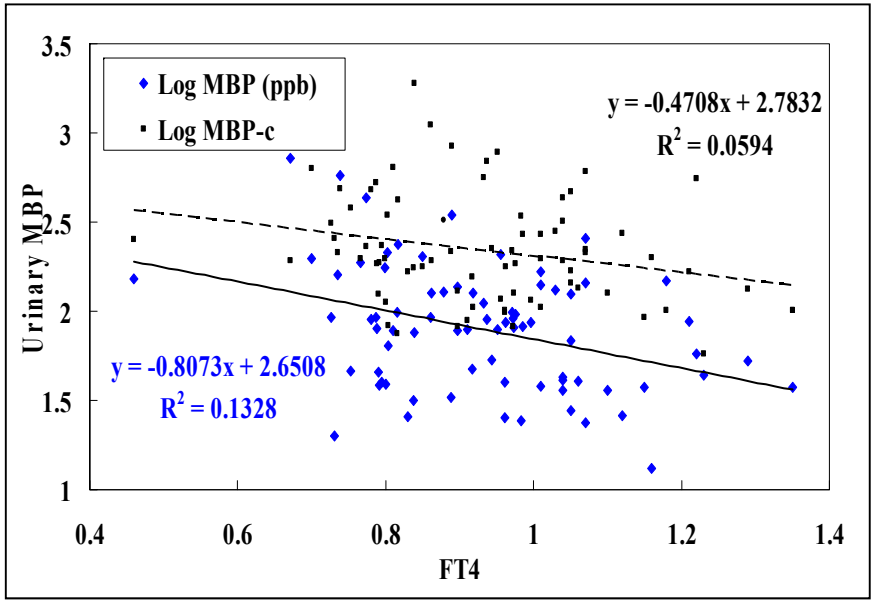
Urinary phthalate monoesters[a]	Percentile								Median (range)		
	n	Min	5th	25th	50th	75th	95th	Max	US pregnant women[c]		US female population[d]
Creatine unadjusted (ng/ml)[b]											
MBP	76	13.2	21.6	40.6	81.8	131.0	368.0	580.0	–	> 2.5	30.0 (5.8-167)
MBzP	76	0.9	0.9	0.9	0.9	0.9	33.4	35.3	–	< 10↑	16.0 (2.4-103)
MEP	76	0.7	2.20	13.1	27.7	52.4	2346.0	5466.0	–	< 6	174.0 (28-2230)
MEHP	76	5.85	7.21	13.1	20.6	38.6	273.0	381.0	–	> 6.5	3.0 (ND-21.6)
MMP	76	0.7	0.7	0.7	4.3	14.7	87.8	237.2	–		–
Creatinine-adjusted (μg/g creatinine)											
MBP	76	57.8	88.9	127.0	195.0	339.0	839.0	1901.0	42.6 (21.3–105)	> 4.5	28.6 (10.6–131)
MBzP	76	0.5	0.8	2.0	3.7	6.0	24.0	69.9	12.1 (5.6–120)	< 4	14.7 (4.84–80.0)
MEP	76	5.0	8.3	27.0	68.0	205.0	4414.0	13 299.0	236 (26.7–5520)	< 3.5	157 (42.7–1920)
MEHP	76	12.2	15.8	31.4	60.8	121.0	885.0	1251.0	4.6 (1.8–449)	> 13	3.33 (ND–16.3)
MMP	76	0.4	0.9	3.7	10.8	34.9	263.0	363.0	–		–

[a]MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MEP, monoethyl phthalate; MEHP, mono-2-ethylhexyl phthalate and MMP, monomethyl phthalate. [b]Detection limit (LOD) of phthalate monoesters were: MBP, 5; MBzP, 1.8; MEP, 1.4; MEHP, 0.9; MMP, 1.4 ng/ml, respectively. Half of LOD was calculated as the detected value below the LOD. [c]New York pregnant women 18–35 years old ($n = 25$). [d]Data from NHANES 1999–2000 included children age 6 and older) ($n = 1326$, range: 10th–95th percentile).

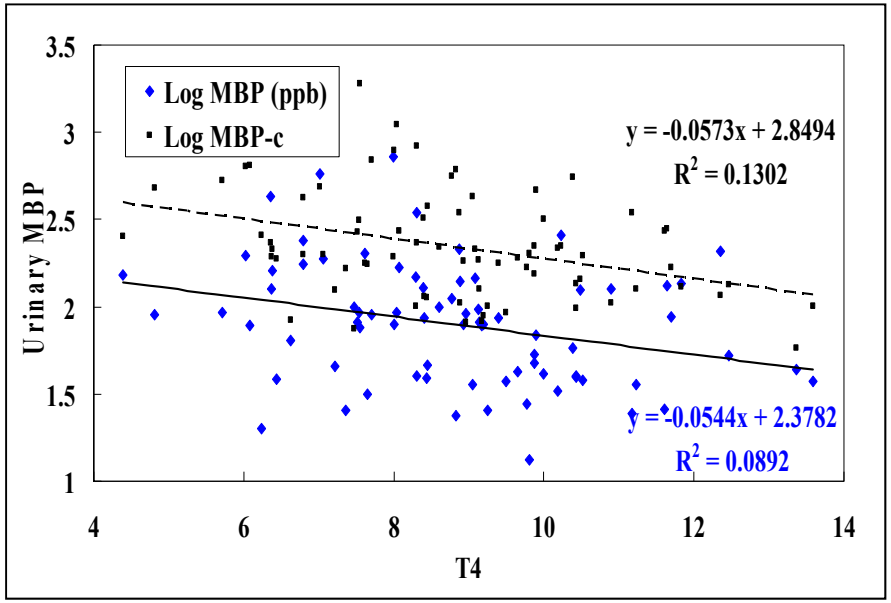
Table I-3 台灣孕婦血清中甲狀腺荷爾蒙含量分布

Hormones [a]	Percentile					Reference range
	Min	5th	50th	95th	Max	
T_3 (ng/dL)	72.6	86.3	132.0	209.0	246.0	84.6-202.0
T_4 (μg/dL)	4.39	5.31	8.85	11.2	13.6	5.13-14.1
Free T_4 (ng/dL)	0.46	0.69	0.93	1.25	1.35	0.93-1.7
TSH (μ IU/mL)	0.22	0.31	1.06	3.4	5.19	0.27-4.2

[a]The analytic sensitivities of T_3, T_4, free T_4, and TSH were 19.5 ng/dL, 0.42 μg/dL, 0.023 ng/dL and 0.014 μlU/mL, respectively; the coefficient variations of T_3, T_4, free T_4, and TSH were 2.9%, 4.2%, 3.1%, and 3.0%, respectively.



A



B

Figure I-1. 孕婦第二週產期尿液中 MBP-c含量與(A) free thyroxine (FT_4), (B) thyroxine (T_4) 之相關性

Table I-4. 以多變項複回歸檢定血清中 FT_4 and T_4 含量與尿液中PAEs代謝物含量之相關性結果

Variables	FT_4 (pmole/l)		T_4(nmole/l)	
	Estimate	Prob>|t|	Estimate	Prob>|t|
Intercept	1.270	0.013	2.362	0.001
Age	0.024	0.886	-0.321	0.177
BMI	0.088	0.579	0.348	0.120
Gestational age	-0.117	0.598	-0.066	0.831
MBP	-0.110	<0.001	-0.112	0.003
MEP	0.026	0.124	0.013	0.398
MEHP	-0.015	0.474	-0.007	0.814
MBzP	0.022	0.232	0.032	0.224
MMP	0.016	0.165	0.015	0.347

[a] One outlier was excluded because of hypothyroidism (n=75).

→Multiple regression: FT_4：R^2=0.24, T_4：R^2=0.187

Table II-1 男性與女性新生兒體格檢查結果 (*n* = 65).

Health status	男嬰 (n=33)	女嬰 (n=32)	P-value[3]
Birth weight (g)	3171 (1678-4260)	3002 (2000-3935)	0.156
Birth length (cm)	49.6 (42.0-56.0)	48.3 (42.5-53.5)	0.023*
Gestational age (weeks)	39.0 (35.3-41.7)	38.4 (33.6-40.3)	0.020*
Ano-genital distance (AGD) (mm)[1]	23 (10-36) >	16 (7-23)	<0.001*
AGI-W(mm/kg)[2]	7.16 (3.18-13.09)	5.37 (2.30-8.96)	0.001*
AGI-L ($\times 10^3$)[2]	4.55 (2.17 -7.35)	3.29 (1.41 -5.07)	<0.001*

[1] The AGD of two girls and boys, respectively, were not available.

[2] AGI=ano-genital index; AGI-W= AGD/birth weight; AGI-L=AGD/ birth length.

[3] *: $p<0.05$

Table II-2 男嬰與女嬰羊水中PAEs代謝物含量分布(ng/mL, n=64)[1].

Female infants	Min	10th	50th	90th	Max
MBP	39.3	45.6	85.5	134.6	192.0
MEHP	ND[2]	5.0	24.0	91.1	148.0
MEP	ND	ND	ND	3.9	6.5
MBzP	ND	ND	ND	84.1	233.0
MMP	ND	ND	ND	ND	2.92
Male infants	**Min**	**10th**	**50th**	**90th**	**Max**
MBP	28.4	44.3	81.3	127.8	145.0
MEHP	ND[2]	2.6	22.1	100.6	110.0
MEP	ND	ND	ND	4.4	7.7
MBzP	ND	ND	ND	87.9	104.0
MMP	ND	ND	ND	ND	ND

[1]One amniotic fluid sample was failed during analysis.

[2]ND=not detected, detection limit of MMP, MEP, MBP, MBzP and MEHP were as follow: 1.4, 1.0, 1.4, 1.4, 0.9 ng/mL

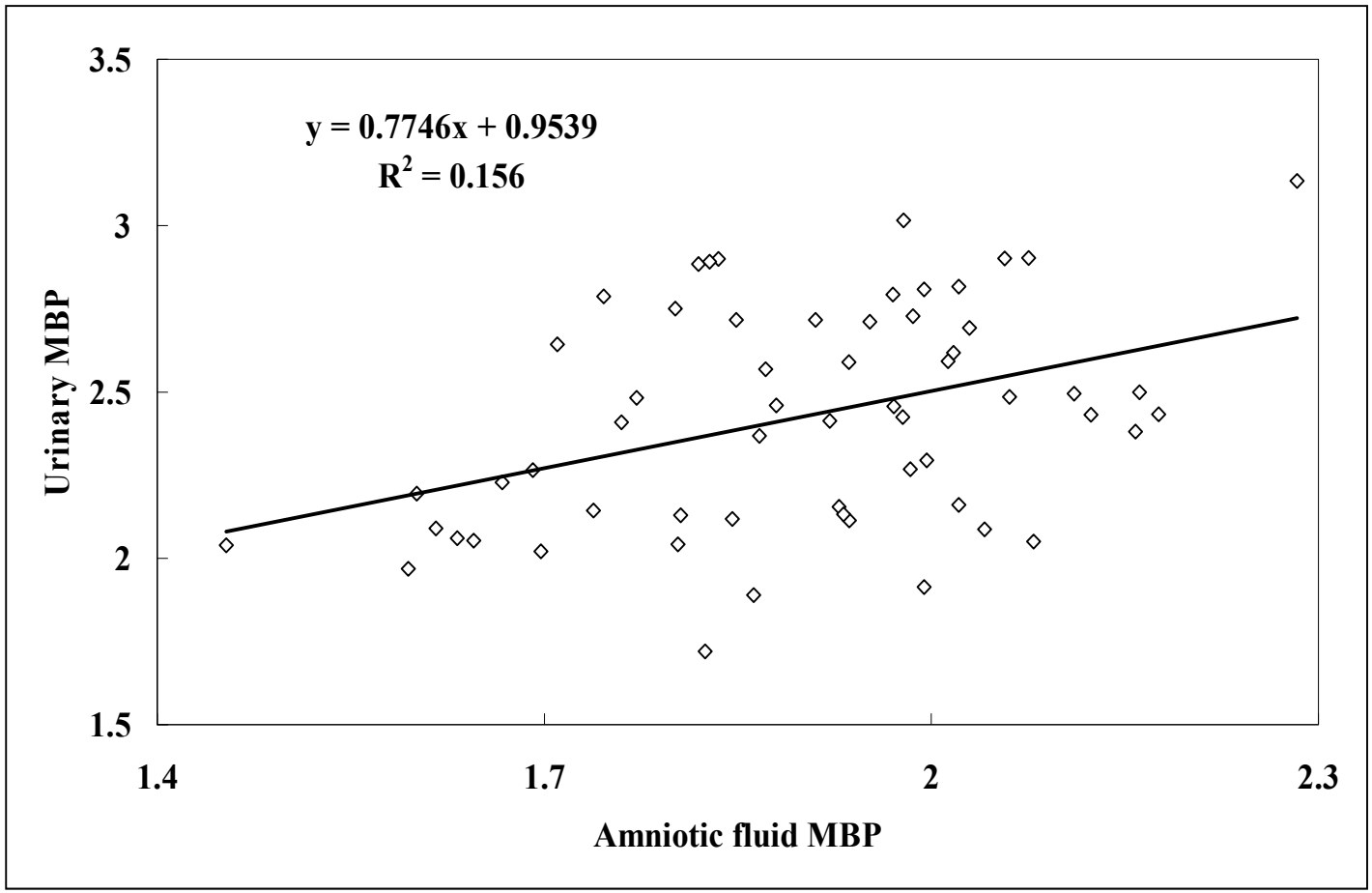


Figure II-1 孕婦尿液中MBP含量與羊水中MBP含量之相關性 (n=59).

Table II-3 以孕婦羊水中MBP及MEHP中位數分高低濃度組後女嬰健康指標之分布及比較 ($n = 31$).

Health status in female infants	MBP-AF[2]			MEHP-AF[3]		
	Low[4] (n=15)	High[4] (n=16)	P-value[1]	Low[4] (n=15)	High[4] (n=16)	P-value[1]
Birth weight (g)	2810±439	3172±398	0.031*	2918±448	3061±467	0.527
Birth length (cm)	47.3±2.3	49.2±1.7	0.018*	48.1±2.1	48.6±2.4	0.138
Gestational age (weeks)	38.1±1.5	38.7±1.0	0.205	38.4±0.9	38.4±1.6	0.591
AGD (mm)	17.6±4.0	13.9±3.8	0.024*	17.0±4.1	14.2±4.1	0.109
AGI-W (mm/kg)	6.2±1.6	4.5±1.5	0.007*	6.0±1.4	4.7±1.8	0.016*
AGI-L ($\times 10^3$)	3.7±0.9	2.8±0.8	0.008*	3.6±0.8	2.9±0.9	0.015*

[1]Wilcoxon Rank Sum Test, *: $p < 0.05$;
[2]AGD data were lacking for one female newborn in each group.
[3]AGD data were lacking for two female newborns in the high MEHP-AF group.
[4]Median levels of amniotic fluid MBP in low and high group were 67 and 104 ng/mL, respectively; those of MEHP were 9.5 and 38.8 ng/mL, respectively.

Table II-4. 以孕婦羊水中MBP及MEHP中位數分高低濃度組後男嬰健康指標之分布及比較 ($n = 313$).

Health status in male infants	MBP			MEHP		
	Low (n=16)	High (n=17)	P-value	Low (n=16)	High (n=17)	P-value
Birth weight (g)	3146±481	3194±469	0.640	3213±440	3131±515	0.815
Birth length (cm)	49.2±2.5	50.0±2.8	0.705	49.4±2.4	49.7±3.0	0.971
Gestational age (weeks)	39.1±1.0	38.9±1.4	0.396	39.1±0.9	38.9±1.5	0.787
AGD (mm)	21.2±6.5	24.1±5.7	0.234	23.3±6.8	22.2±5.6	0.606
AGI-W (mm/kg)	6.6±2.1	7.7±2.2	0.206	7.4±2.6	6.9±1.7	0.635
AGI-L ($\times 10^3$)	4.3±1.2	4.8±1.2	0.304	4.7±1.4	4.4±1.0	0.649

[1] One male infant of each group in MBP-AF and MEHP-AF, respectively, were lack of AGD.

羊水中 MBP與女嬰生產時之AGI呈現顯著負相關

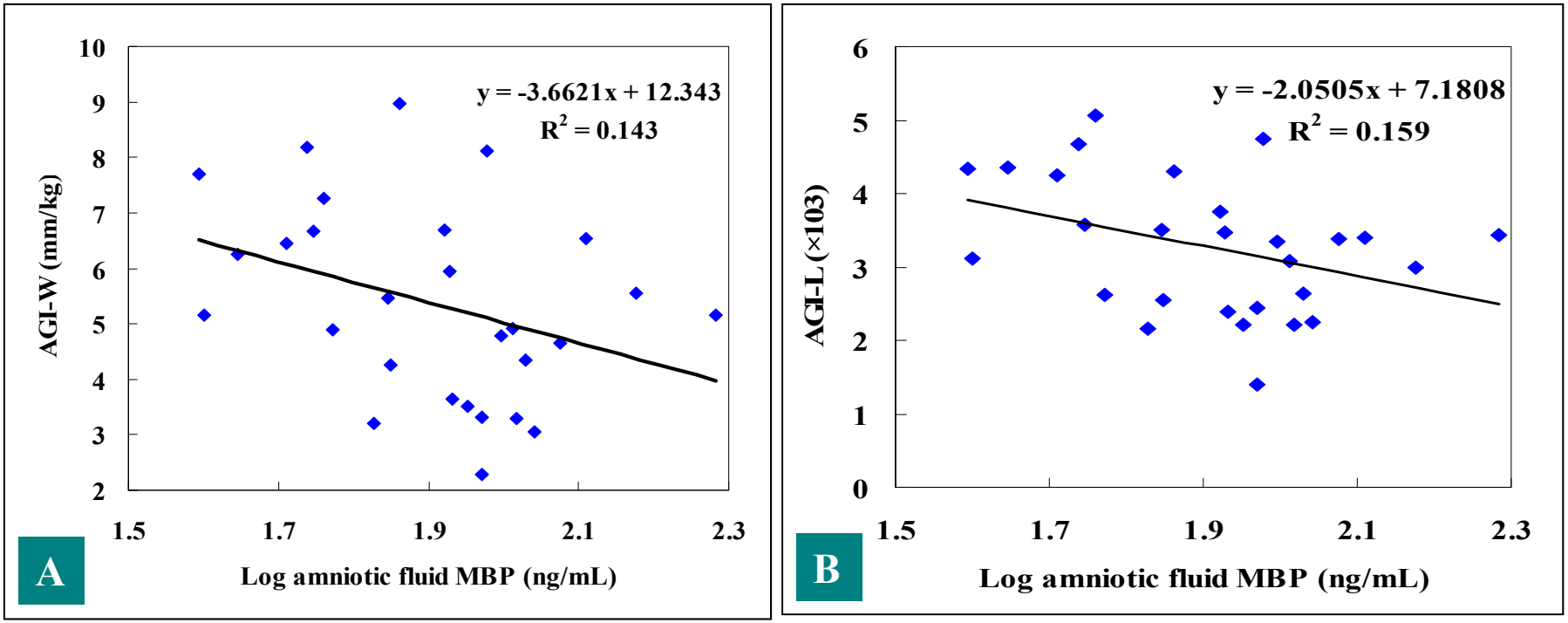


Figure II-2 (A) 羊水中 MBP 與女嬰生產時AGI-W之線性回歸 (n=29, R^2=0.14, p=0.043);
(B) 羊水中 MBP 與女嬰生產時AGI-L之線性回歸 (n=29, R^2=0.16, p=0.032).

鄰苯二甲酸酯

對兒童內分泌干擾效應：國內研究結果

The definition of puberty and precious puberty

- **Puberty is a complex process involving the activation and maturation of the hypothalamic-pituitary-gonadal (HPG) axis.**

- **The timing of puberty in humans approximates 10 years in girls and 11.5-12 years in boys. However, it may range from as young as 8 to 13 years in girls and from 9 to 14 years in boys.**

  (Grumbach and Styne, 1998)

- **Premature sexual development in the human female is presently defined as the appearance of any physical change characteristic of puberty with onset before 8 years of age.**

  (Sippel, 1994)

Prevalence of precocious puberty

- Precocious puberty has a prevalence of 1 in 5,000 children and exists in girls more than boys by a ratio of 10:1. (Nebesio & Pescovitz, 2005; Partsch & Sippell, 2001)

- The prevalence of PP was 20 to 23 per 10 000 in girls, whereas the prevalence was five-fold lower for boys (<5 per 10 000) in Denmark.

(Teilmann et al., 2005)

Follow-up problems of precocious puberty

- Though girls who experience premature puberty grow faster than their peers due to accelerated bone growth, they fail to reach the normal adult height.

(Carel, 2006 ; Partsch & Sippell)

- Early menarche has been linked to greater risk of breast cancer as an adult; therefore, precocious onset would seem to increase that risk.

(Wang, Needham, & Barr, 2005; Zuckerman, 2001)

- Studies indicate that girls who become sexually mature at earlier ages are more likely to engage in risk-taking behaviors such as smoking, using alcohol or drugs, and engaging in unprotected sex.

(Committee on Adolescent Health Care, 2006; Flanigan, 2003; Zuckerman, 2001)

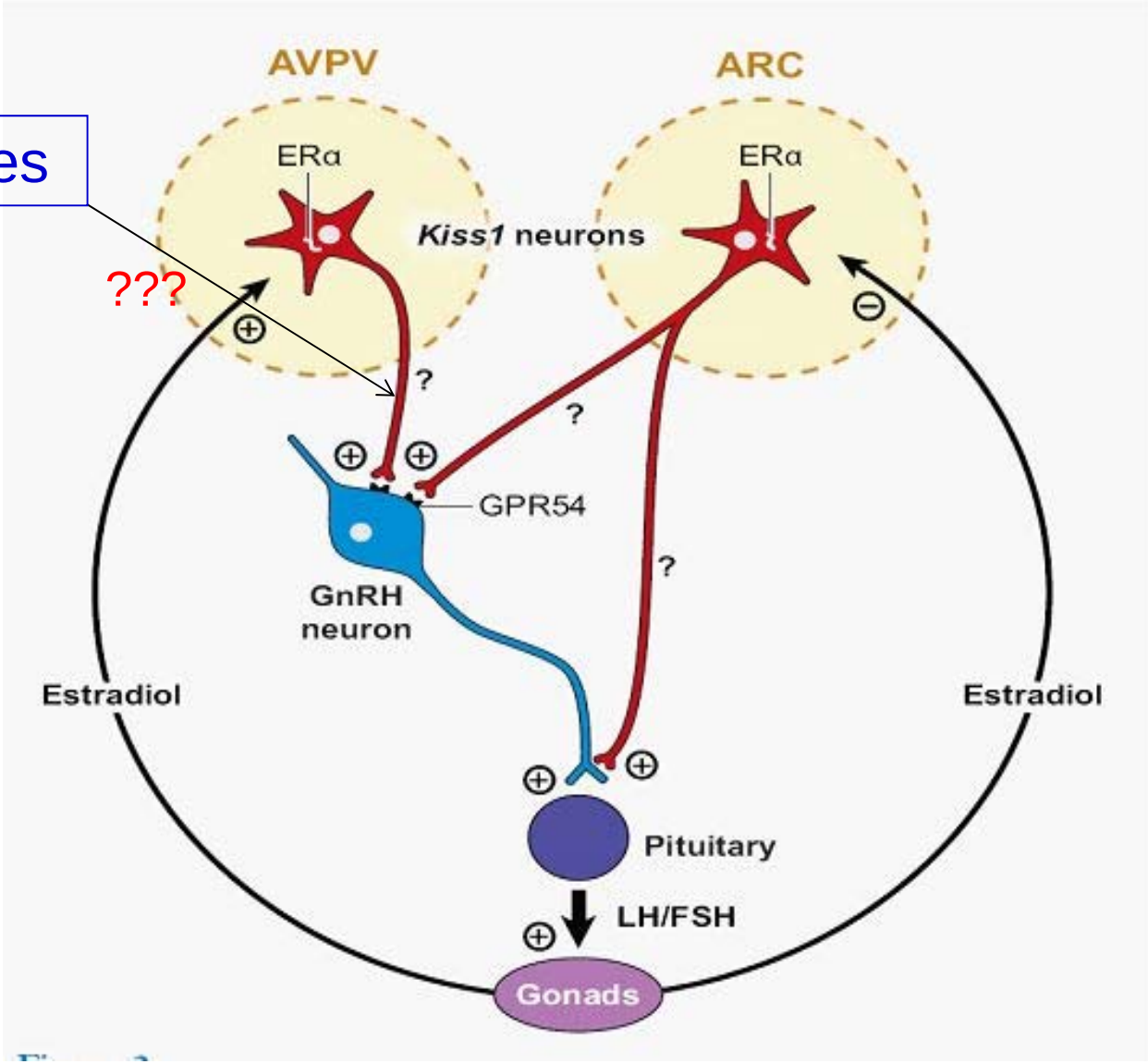
What factors are suspected to trigger the earlier onset of sexual maturation?

- The ethnic, genetic, pediatric obesity, environmental toxins that disrupt endocrine function, psychosocial stress, and early exposure to an increasingly sexualized society explanations for the earlier onset of sexual maturation.

(Lemonick, 2000)

The regulation pathway of sexual hormone in female

Phthalates



Objectives

- To investigate the association and possible mechanism between exposure to phthalates and female puberty.
- To investigate the relationships between urinary monoester metabolites and the PAE levels in house dust for precocious puberty and normal girls,
- To develop effective intervention strategies to decrease the phthalates exposure for children.

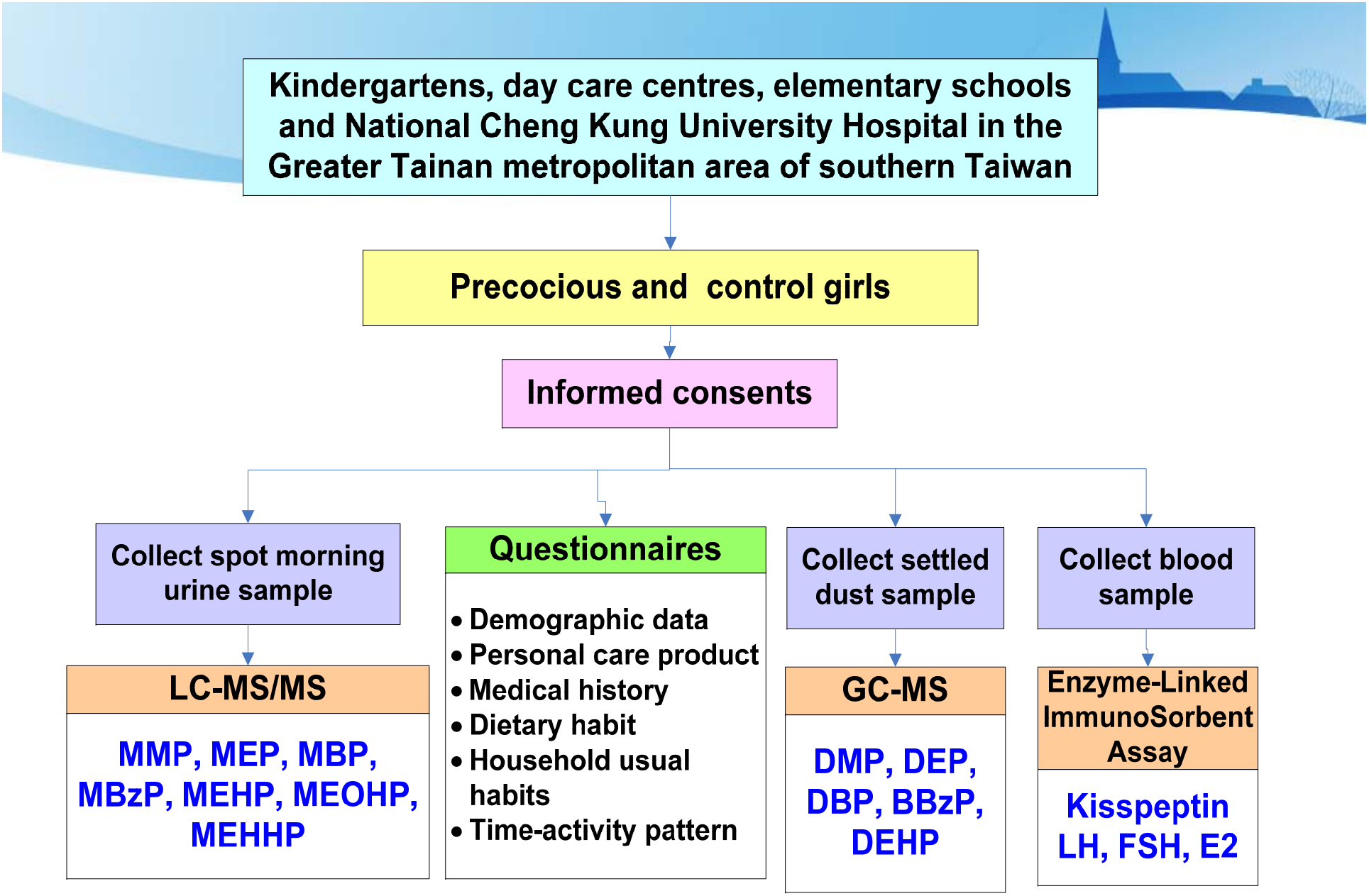
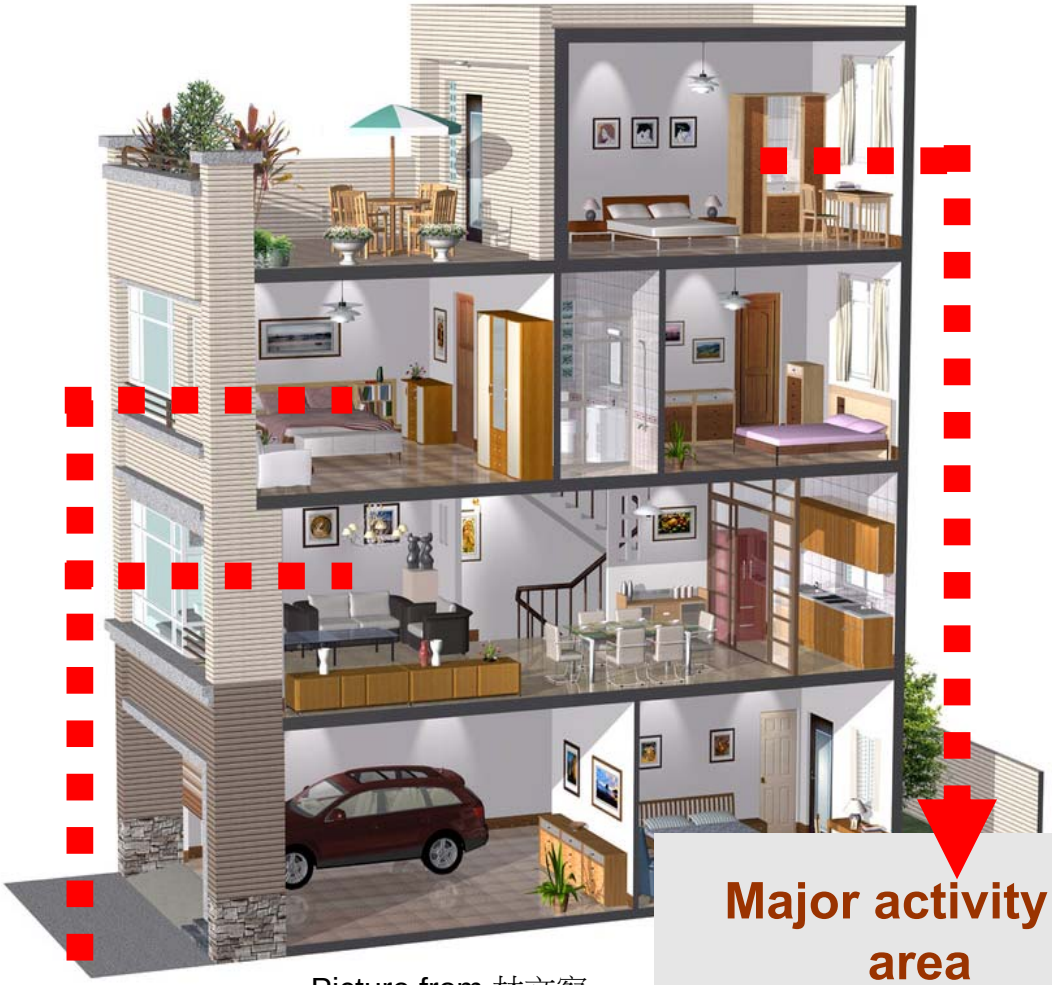


Fig 1 The framework of this study

Sampling strategy for dust- 5 samples



Picture from 林文察

	Bed (or sofa)	Floor	Upper floor
Major activity area (Sleeping room)	Sample 1	Sample 2	Sample 5
Minor activity area (Parents' room, living room, playroom *et al*.)	Sample 3	Sample 4	

Dust collection

- Using aluminum-made collector & cellulose filter
- Covering with aluminum foil and then sealing by parafilm after collecting enough dust sample

Questionnaires for phthalates exposure evaluation

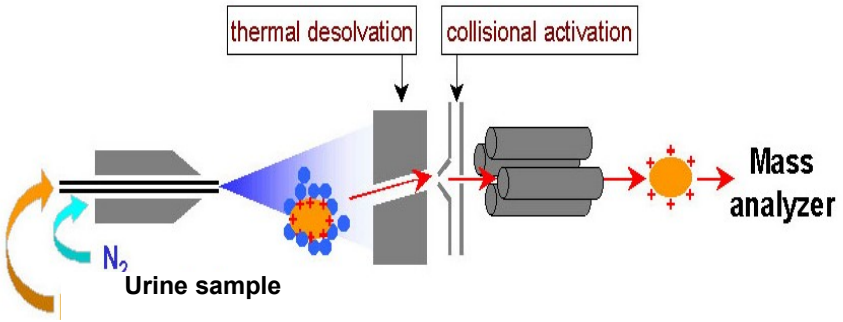
- **Dietary patterns**
  - Category: Main food (rice、noodles, etc.), Vegetable (cabbages、water celery, etc.), Meat (pork, poultry, etc.), Fruits, Snack and Nutritional supplement.
- **Household usual habits**
  - Cleaning frequency, cleaning products, cooking habits *et al.*
- **Time-activity pattern and medical history**
- **Personal care products**
  - Children's habit
    - Body lotion, shampoo, shower cream, soap, hair spray, nail polish, perfume *et al.*
  - Maternal habits
    - Perfume, cosmetics, lipstick *et al.*

Analysis of phthalate metabolites

- **Phthalate metabolites**
  - monomethyl phthalate (MMP)
  - monoethyl phthalate (MEP)
  - monobutyl phthalate (MBP)
  - monobenzyl phthalate (MBzP)
  - mono-2-ethylhexyl phthalate (MEHP)
  - mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
  - mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)

- **Analytical method**

Electrospray ionization mass spectrometry (ESI MS)



1 mL sample thawed, sonicated

↓

250 µL ammonium acetate (1M, pH=6.5)
50 µL $^{13}C_4$-labeled standard (100 ng/mL)
5 µL β-glucuronidase (200 unit/mL)

↓

Incubation at 37°C for 90 min

↓

1 mL acidic buffer 0.14 M NaH_2PO_4

↓

Loaded to SPE cartridge (3 mL/60 mg)

↓

Washed with 2 mL formic acid (0.1M) and 1 mL H_2O

↓

Eluted with 2 mL ACN, 2 mL ethyl acetate

↓

The residue was resuspended in H_2O (1mL)

Results and discussions

Table 1 The demographic characteristics of girls with CPP and prepubescent control girls.

Item	Control Group (*n* = 31)	CPP Group(*n* = 73)	*p*-value[b]
Age (years)[a]	6.8 (2.2-8.3)	8.1 (2.5-11.5)	<0.001
Age at diagnosis (years)[a]	-	7.0 (1.3-8.5)	-
Height (cm)[a]	120.8 (90.0-136.7)	129.6 (83.0-152.1)	<0.001
Weight (kg)[a]	22.6 (12.0-35.1)	29.0 (9.9-55.3)	<0.001
BMI (kg/m^2)[a]	16.0 (12.9-21.1)	16.8 (11.9-24.8)	0.05
FATHER'S EDUCATION LEVEL (*n*)			
High school	6	27	0.16
College	19	32	
Graduate school	4	12	
MOTHER'S EDUCATION LEVEL (*n*)			
High school	8	32	
College	19	36	0.25
Graduate school	2	3	
FAMILY'S MONTHLY INCOME (*n*)			
Less than 70,000 NT$	16	42	0.71
More than 70,000 NT$	13	29	

Abbreviations: [CPP] girls with central precocious puberty, [Control] prepubescent control girls, [BMI] body mass index, [NT$] New Taiwan Dollar . [a]Values are median (range); [b]continuous variables were tested using Mann–Whitney U-Tests, and categorical variables using Fisher's Exact Tests.

Results and discussions

Table 2 Unadjusted and adjusted-creatinine concentrations of urinary phthalate monoesters in girls with central precocious puberty (CPP) and prepubescent control girls.

	Control Group (*n* = 29)	CPP Group (*n* = 71)	*p*-value	NHANES 1999-2008
CREATININE UNADJUSTED (ng/ml)				
MMP	4.53 (0.70-14.1)	6.95 (0.70-48.3)	0.033	< LOD-1.90
MEP	7.87 (0.50-332)	19.1 (0.50-558)	<0.001	45.2-53.9
MBP	40.2 (9.93-163)	60.4 (6.14-1324)	0.049	28.7-40.0
MBzP	2.45 (0.70-18.4)	6.22 (0.70-167)	0.002	17.6-29.0
MEHP	5.10 (0.45-125)	8.23 (0.45-85.1)	0.002	2.20-4.90
MEHHP[e]	27.6 (13.8-106)	59.6 (15.4-432)	0.004	27.0-36.5
MEOHP[e]	25.0 (13.6-92.7)	56.9 (11.2-392)	0.004	16.6-25.8
CREATININE-ADJUSTED (μg/g creatinine)				
MMP	6.34 (0.94-31.3)	8.10 (0.83-128)	0.141	< LOD-2.32
MEP	11.3 (1.06-337)	25.4 (1.21-379)	0.001	50.1-57.4
MBP	67.2 (20.5-275)	94.6 (22.3-910)	0.195	33.9-39.1
MBzP	3.74 (0.95-50.4)	9.00 (1.14-172)	0.005	20.7-27.8
MEHP	9.04 (0.95-185)	10.8 (4.03-69.3)	0.059	2.80-5.38
MEHHP[e]	27.7 (12.3-202)	57.4 (24.5-291)	0.002	31.4-37.0
MEOHP[e]	25.8 (13.8-177)	52.0 (21.9-244)	0.001	18.5-25.3

Results and discussions

Table 3 Average levels [range] of kisspeptin and clinical examinations results of girls with central precocious puberty (CPP) and prepubescent control girls in this study.

		CPP Group (*n* = 40)			
	Control Group (*n* = 11)	Thel+LHRH$^-$ Subgroup (*n* = 13)	LHRH$^+$ Subgroup (*n* = 12)	Leup/Men Subgroup (*n* = 15)	*p*-value[a]
Age (years)	7.4 [6.1-8.3]	7.0 [2.5-9.1]	8.9 [7.7-10.6]	9.0 [4.6-11.5]	<0.001
Kisspeptin (pmol/l)	1.95 [1.69-2.18]	1.97 [1.39-2.51]	2.16 [1.71-2.61]	2.29 [1.92-2.86]	0.022
Bone age (years)	-	6.6 [1.75-9.0]	10.3 [8.8-12]	10.7 [5.0-12.5]	<0.001[b]
Basal LH (mIU/ml)	<0.15	0.25 [<0.15-1.84]	0.99 [<0.15-2.54]	1.03 [<0.15-8.65]	0.003
Basal FSH (mIU/ml)	1.65 [1.11-2.31]	2.96 [1.37-8.14]	4.81 [1.42-8.31]	2.66 [0.92-8.29]	0.006
Basal E_2 (mIU/ml)	<8	4.88 [<8-15.5]	10.5 [<8-19.0]	16.6 [<8-102]	0.032
Peak LH (mIU/ml)	-	5.43 [3.11-7.89]	21.2 [10.9-51.8]	27.6 [9.72-90.2]	<0.001[b]

[a] Kruskal- Wallis Test: *p*-value for the difference between the four groups; [b] Kruskal- Wallis Test: *p*-value for the difference between the CPP subgroups.

Results and discussions

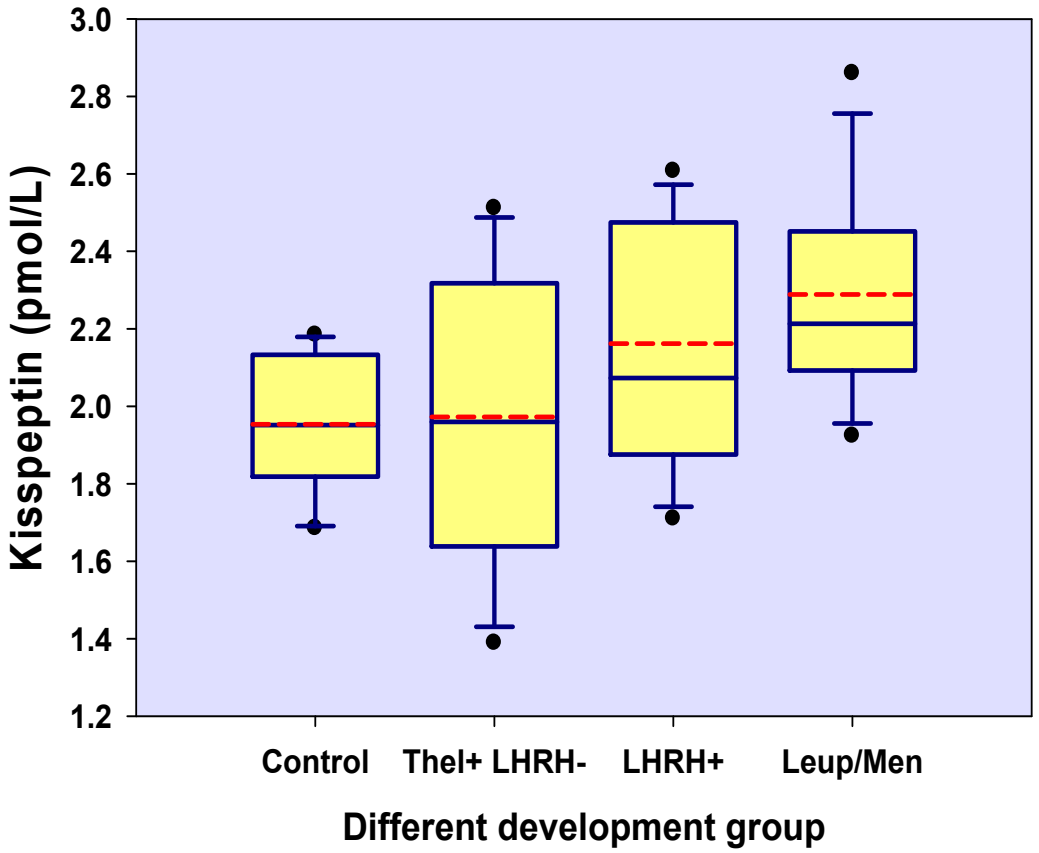
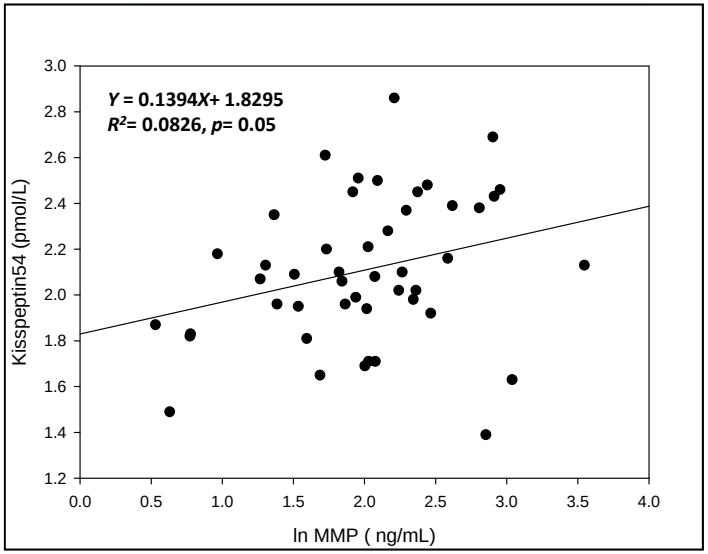
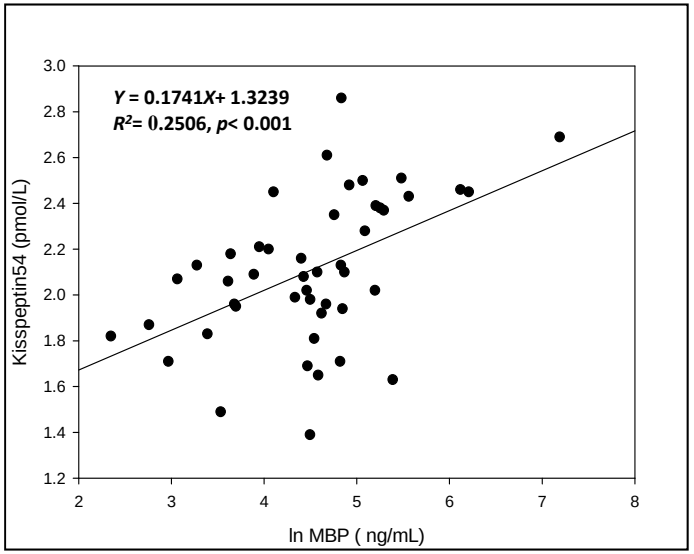
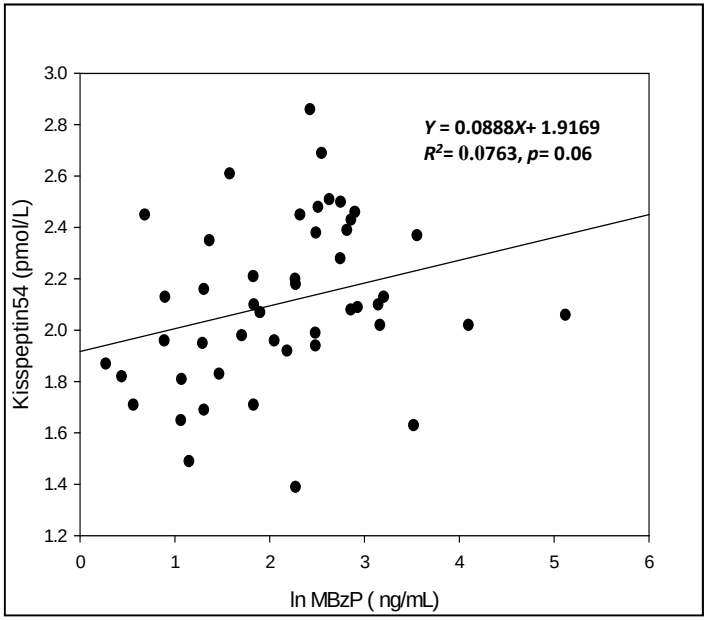


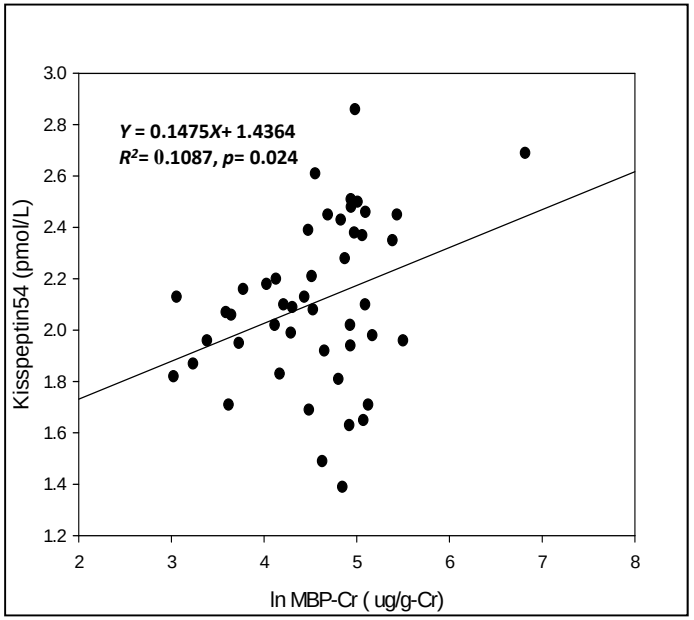
Figure 1. Box plot of kisspeptin distribution in different development groups. 1: Control Group (*n* = 11); 2: CCP subgroup Thel+ LHRH−: premature thelarche and a negative LHRH test result (*n* = 13); 3: CCP subgroup LHRH+: positive LHRH test result (*n* = 12); 4: CCP subgroup Leup/Men: being treated with leuprorelin acetate or had experienced menarche (*n* = 15). Dotted line: the mean level of kisspeptin-54 in each group. (P_{trend} among the four groups after adjusting for age = 0.005)

Results and discussions









探討鄰苯二甲酸酯類暴露與女童性早熟發生之相關性及環境控管介入研究

Results (Intervention strategies)

介入項目	限制使用細項
健康食品及藥物的使用	基於用藥倫理及個人健康考量，本項只紀錄但不限制女童使用，但若與健康無相關者，則仍勸說暫停使用一個禮拜
化妝品及個人衛生用品的使用	限制精油、香水、乳液、指甲油的使用，沐浴乳及洗髮乳則記錄使用量及使用頻率
塑膠容器的使用	限制塑膠碗、保鮮盒、市售飲料、PVC杯水的使用
微波食物的食用	限制微波便當及微波剩菜(覆蓋保鮮膜)的使用
塑膠袋或保鮮膜包裝食物的食用	限制塑膠袋或保鮮膜包裝食物的食用
建材的接觸及洗手習慣	詳實紀錄接觸巧拼、地板玩耍及吃東西前未洗手的時間或次數
時間活動模式	若有上述行為發生則詳實紀錄發生時間及使用量

介入期程：一個星期

Intervention strategy

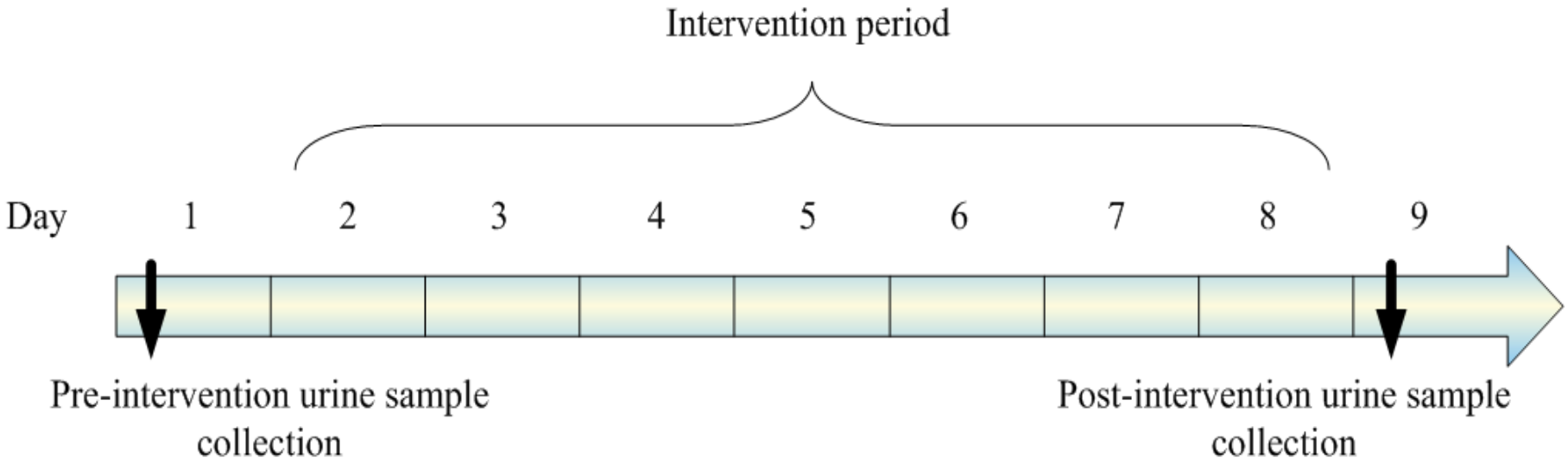


Figure Intervention design and timing of sample collection in this study.

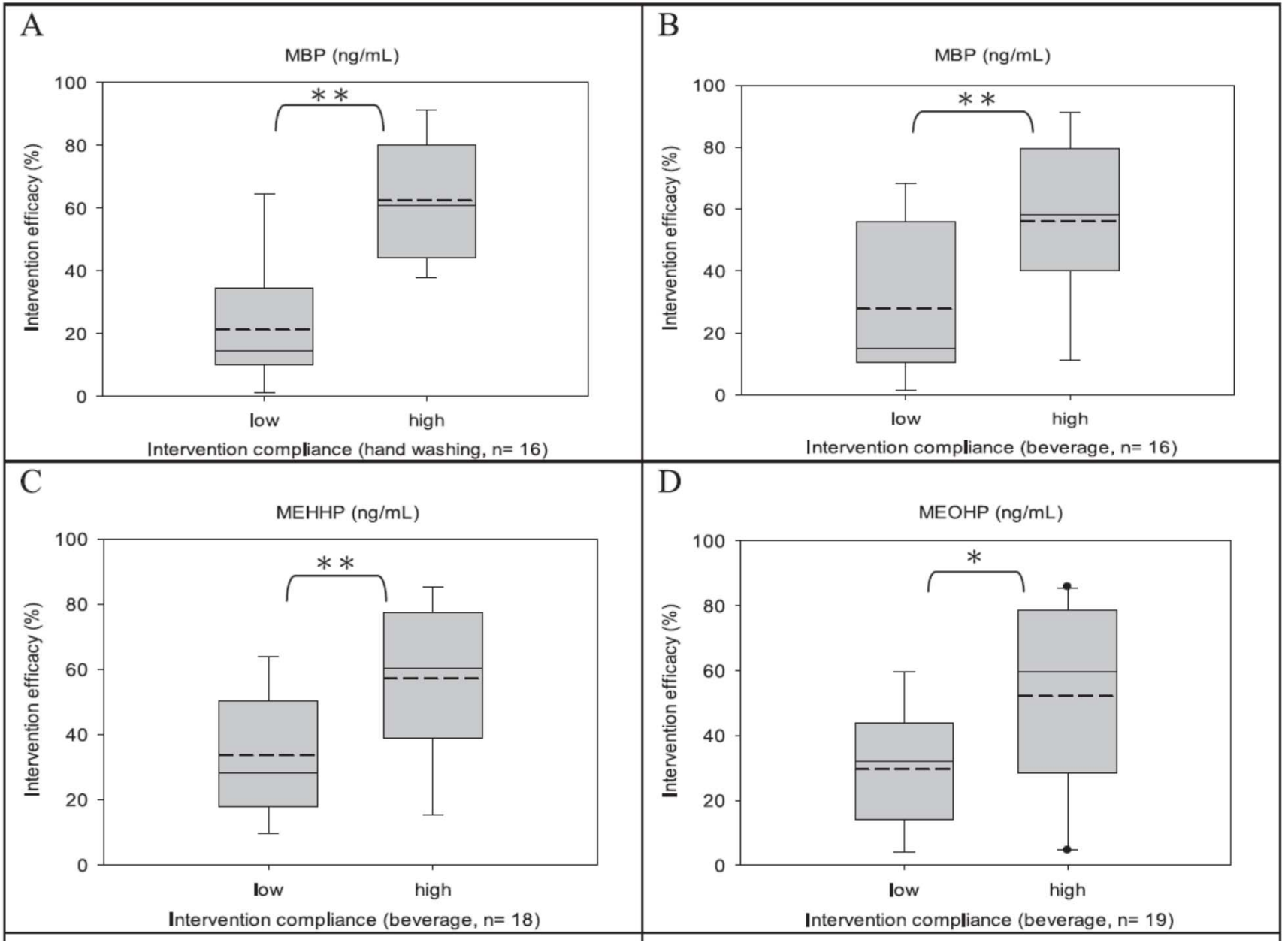
Results and discussions

Table Subjects who follow intervention guideline resulted in declining the level of urinary phthalate metabolites in this study.

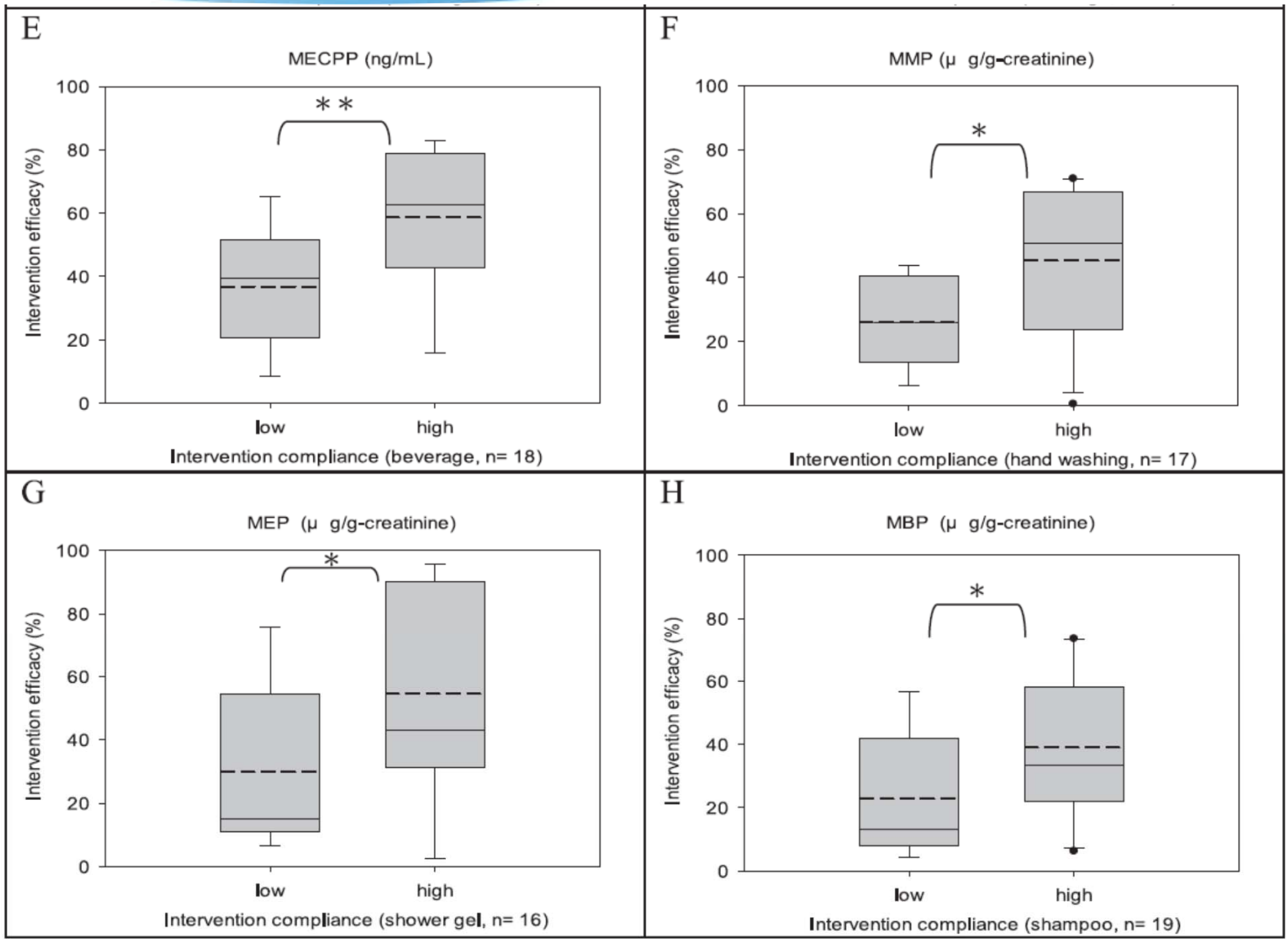
	Phthalate concentration (ng/mL)			Phthalate concentration (ug/g-creatinine)		
	Pre-I	Post-I	$P^{\#}$	Pre-I	Post-I	$P^{\#}$
MMP (n=18)	10.9 (2.38-29.1)	5.63 (2.18-16.4)	<0.001*	9.36 (3.49-29.7)	6.84 (3.02-17.3)	0.003*
MEP (n=15)	75.9 (14.0-710)	25.0 (3.91-154)	0.001*	68.8 (9.08-650)	31.5 (7.43-200)	0.001*
MBP(n=16)	164 (41.2-927)	80.2 (24.7-147)	<0.001*	129 (55.5-277)	95.2 (38.8-157)	0.013*
MBzP (n=19)	7.81 (0.39-85.6)	3.36 (0.29-17.3)	<0.001*	8.26 (1.87-58.2)	4.15 (1.25-17.8)	<0.001*
MEHP(n=19)	13.8 (4.11-84.6)	7.0 (2.51-31.1)	<0.001*	11.9 (3.43-38.3)	8.21 (3.42-24.7)	0.011*
MEOHP (n=19)	51.6 (15.1-563)	26.2 (12.5-79.6)	<0.001*	43.2 (19.8-207)	30.5 (15.5-85.6)	0.01*
MEHHP (n=18)	101 (29.9-1082)	49.0 (22.8-187)	<0.001*	87.0 (32.9-398)	58.1 (29.1-202)	0.005*
MECCP (n=18)	109 (28.5-871)	50.9 (20.3-187)	<0.001*	84.5 (34.7-320)	58.1 (30.1-161)	0.006*

: Wilcoxon Signed Ranks Test; † : Pair T Test; * : P<0.05

Results and discussions



Results and discussions



要怎麼降低或避免塑化劑的暴露？

- 避免喝塑膠杯裝市售飲料的習慣，儘量自己帶不銹鋼杯或馬克杯。
- 避免以塑膠袋、塑膠容器盛裝熱食或微波加熱，平常的生活中也減少使用塑膠袋。
- 養成吃東西前洗手的習慣，避免因手接觸室內灰塵而食入塑化劑。
- 避免用保鮮膜包覆食物進行微波或蒸煮。
- 兒童應避免在PVC地板上吃東西、玩耍，也不要直接睡在PVC地板上。在PVC地板上活動後，要保有洗手的習慣，並避免幼童將手放置口中。
- 室內環境應定期吸塵以維持乾淨，電器不用時應拔除插頭以避免經常在高熱狀態下逸散塑化劑。
- 多使用含天然成分或不含塑化劑之香水、化妝品及個人衛生用品。
- 避免長期吃單一種類的高脂食品，例如：可以交替食用豬肉、牛肉、雞肉或以魚類替代，都可以降低塑化劑的可能暴露。
- 多喝白開水，多攝取新鮮蔬果，少吃高脂食物，並保持心情愉悅


Thanks for your attention!
Comments!