【S-4】

APPLICATION OF METABOLITE PROFILE KINETICS FOR EXPOSURE AND RISK ASSESSMENT

Byung Mu Lee

Division of Toxicology, College of Pharmacy, Sungkyunkwan University, Suwon, Gyeonggi-do, 440-746, South Korea

Chemical toxicants are metabolically converted to numerous metabolites in the body.Toxicokinetic characteristics of metabolites could be therefore used as biomarker of exposure for human risk assessment. Biologically based dose response (BBDR) model was proposed for future direction of risk assessment. However, this area has not been developed well enough for human application. Benzo(a)pyrene (BP), for example, is a well-known environmental carcinogen and may produce more than 100 metabolites and BPDE-DNA adduct, a covalently bound form of DNA with benzo(a)pyrene diolepoxides (BPDEs), has been applied to qualitatively or quantitaively estimate human exposure to BP. In addition, di(2-ethylhexyl) phthalate (DEHP), a widely used plasticizer in the polymer industry, is one of endocrine-disrupting chemicals (EDCs) and has been monitored in humans using urinary or serum concentrations of DEHP or its monomer MEHP for exposure and risk assessment. However, it is difficult to estimate the actual level of toxicants using these biomarkers in humans using. This presentation will discuss a methodology of exposure and risk assessment by application of metabolic profiling kinetics.

APPLICATION OF METABOLITE PROFILING KINETICS FOR EXPOSURE AND RISK ASSESSMENT

Byung Mu Lee

College of Pharmacy,
Division of Toxicology
SungKyunKwan University, Korea
成均館大學校 since 1392

Risk Assessment Procedure

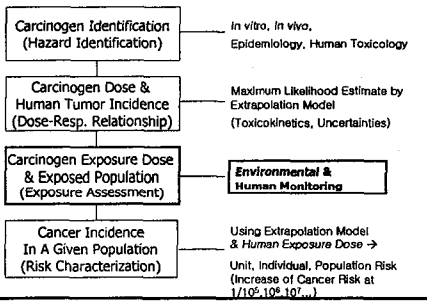
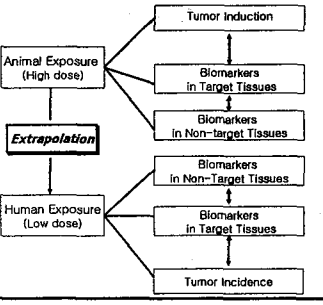


Table 1. Environmental vs Human Monitoring

Environmental Monitoring	Human Monitoring
• Data in the environment not in humans	• Total human exposure level
• Variation depends on the time & location of sampling	• Assessment in the target molecules in humans
• Unknown sources of human exposure	• Reflection of human variation in toxicokinetics
• Impossibility to measure total exposure levels in humans	• Reflection of human susceptibility
• Difficulty predicting actual exposure period	• Applicability of stage-specific biomarker during disease progress to risk assessment
• No consideration of toxicokinetics in humans	• Reflection of additive, potentiation, & antagonism in humans
• Not accurate exposure assessment for risk assessment	• Accurate exposure assessment for risk assesment

Extrapolation of Biomarkers from Animal Studies to Humans for Cancer Risk Assessment



Models Used in Risk Extrapolation

Statistical or Distribution Models

Log-Probit
Logit
Weibull

Mechanistic Models

One-Hit, Multi-Hit
Multistage
Linearized Multistage
Stochastic Two-Stage Model
Moolgavkar-Venson-Knudson (MVK)

Model Enhancement

Time to Tumor Response
Physiologically Based Toxicokinetic Models (PBTK)

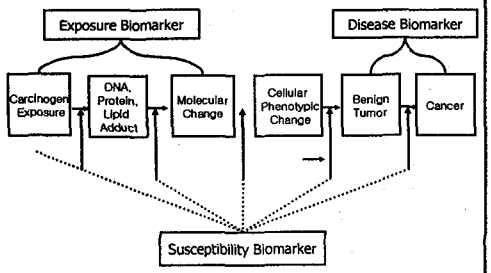
What is Biomarkers ?

Definition: **Biomarkers are defined as intermediate end points or measurable markers of cellular, molecular or chemical events associated with exposure to toxicants or disease progress**

Characteristics:

- **Appear earlier than disease development**
- **Appear frequently before disease development**
- **Are directly associated with disease progression**
- **Need inexpensive, accurate, and easy methods for detection**

Biomarkers During the Chemical Carcinogenesis



Requirements of Exposure Biomarkers for Risk Assessment

- Chemical Specific
- Sensitive
- Applicable
- Non-invasive (if possible)
- Simple
- Inexpensive
- Reproducible
- Dose-dependent !! → Chemicals & Metabolites
  DNA, Protein-adducts

(Omics data from gene/protein are NOT applicable)

- Time-dependent

Biomarkers for exposure & risk assessment

- **Quantitative Biomarkers**
  - Metabolites, DNA, lipid, & protein adducts
- **Qualitative Biomarkers**
  - DNA, lipid, & protein adducts, (Omics data?)

Biomarkers for Human Monitoring

DNA adducts: Advantage – DNA is a critical target in carcinogenesis
– Detection of DNA adduts in target tissues
– Successful application to many carcinogens

Disadvantage – Difficult to obtain human tissues
(5-20ug/ml blood, require large volumes(45ml))
– Variable due to repair

Protein adducts: Advantage – Surrogate markers for DNA adducts. DN
and
protein adduts are proportional f
chemicals
– Large amount of samples a
obtainable
(Hb: 140-160mg/ml, Albumin: 5
60mg/ml blood)
– Chronic exposure(4 months, Hb) d
to no repair

Biomarkers for Human Monitoring

Lipid Adducts: Advantage – Large amount of samples are obtainable
– High affinity with many toxicants
– Surrogate markers for DNA and protein adducts
– Higher adduct formation

Disadvantage – No sufficient data in humans
– No repair

(Kwack, S.J. & Lee, B.M., Carcinogenesis, 21:629-632, 2000)

Biomarkers for Human Monitoring & Exposure Assessment

- Metabolites:
  - BP → BP-OH
  - DEHP → MEHP
    2-ethyl-5-oxyhexyl phthalate (5oxo-MEHP: MEOHP)
    2-(2-hydroxyethyl)hexyl phthalate (MHEHP)
  - DBP → MBP
  - Benzene → Phenol
  - Phenol → Phenol
  - Aflatoxin → Aflatoxicol
  - Cd → Cd
  - Toluene → Hippuric acid
  - Styrene → Mandelic acid

Biological Samples for Exposure Assessment

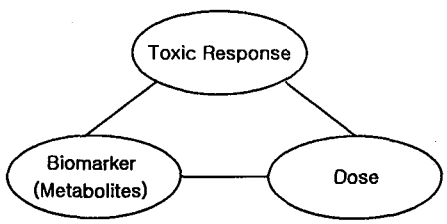
- Blood, cord blood
- Urine
- Hair
- Saliva
- Nail
- Sweat
- Milk
- Feces, etc

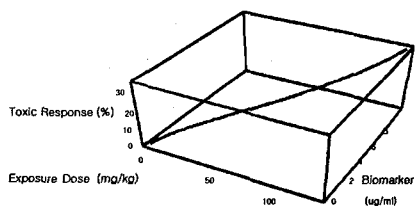
Validation of Biomarker & Application: Exposure Assessment

1) *In vitro* Validation: betw/n animal & human cells
2) *In vivo* Validation: target tissue vs. blood or urine

3) Development of Exposure Assessment Model
4) Accurate Risk Assessment Using Validated Biomarkers

Interrelation between Biomarker(Metabolites), Dose & Toxic Response





A Three-Dimensional Inter-Relationship between Biomarker (metabolites), Exposure Dose & Toxic Response

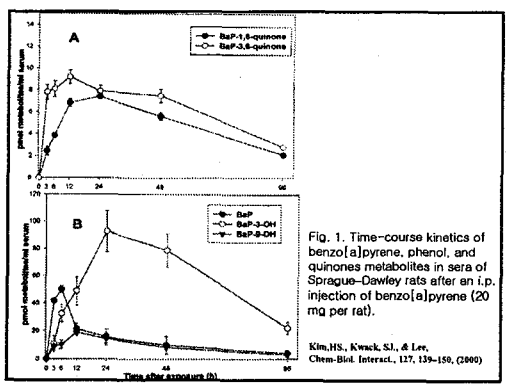


Fig. 1. Time-course kinetics of benzo[a]pyrene, phenol, and quinones metabolites in sera of Sprague-Dawley rats after an i.p. injection of benzo[a]pyrene (20 mg per rat).

Kim,HS., Kwack, SJ., & Lee, Chem-Biol. Interact., 127, 139-150, (2000)

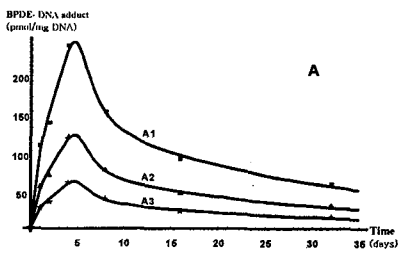


Figure 5. Kinetic Patterns of BPDE-DNA Adducts in the Lung after Single (A1~3) Exposure to BP

: Curves for A1 and A3 are simulated, and A2 is based on the experimental data

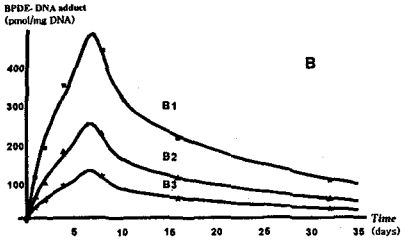


Figure 6. Kinetic Patterns of BPDE-DNA Adducts in the Lung after Continuous (B1~3) Exposure to BP

: Curves for B1 and B3 are simulated, and B2 is based on the experimental data

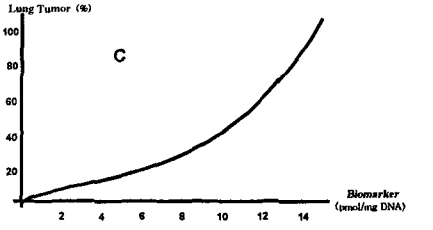


Figure 10. Dose-Response Relationships of Lung Tumor (%) and Biomarker (pmol/mg blood DNA) (C)

: Data source for lung tumor (Ross et al., 1995)

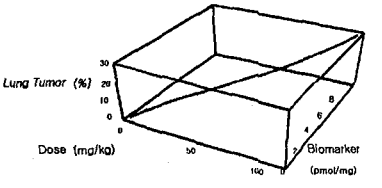


Figure 11. A Three-Dimensional Inter-Relationship between Biomarker, Exposure Dose and Lung Tumor Induction

Table 3. Daily aflatoxin B1 exposure & calculated liver cancer incidence in Koreans *(Choi et al., J. Biochem. Mol. Biol. 29(2), 105-110, 1996)*

	Urinary AFB_1 equivalents (ng/ml)[a]	Urinary AFB_1 equivalents (ng/kg/day)[b]	AFB_1 intake (ng/kg/day)[c]	Calculated[d] incidence
Male (88)	0.86±1.39	18.11±33.01[e]	240.20±438.67	41.56
Female(11)	0.16±0.09	3.82±2.65	50.35±29.88	26.84
Total (100)	0.78±1.39	17.80±40.09	219.07±420.08	40.68

[a] Data are expressed as equivalents of AFB_1 quantitated by ELISA in ml urine. AFB_1 equivalents are used because antisera R101 majorly reacts w/ AFB_1, but the data may be possibly affected by its cross reactivity w/ aflatoxicol H

[b] Daily AFB_1 excretion in urine was estimated assuming that a total volume of urinary excretion was 1,200 ml/day/person (b.w., kg).

[c] Daily AFB_1 intake was estimated from urinary AFB_1 assuming that 7.6% of AFB_1 intake was excreted in urines.

[d] Liver cancer incidence per 100,000 was calculated by the application of AFB_1 intake levels to the linear regression model of Y=21.6X-10.04 with a correlation coefficient of 0.99 ($p<0.001$) obtained from epidemiological data (Zhu et al., 1987; Sabbioni et al., 1987; Groopman et al., 1992).

[e] Statistically different from female by Mann-Whitney Rank Sum Test ($p<0.001$).

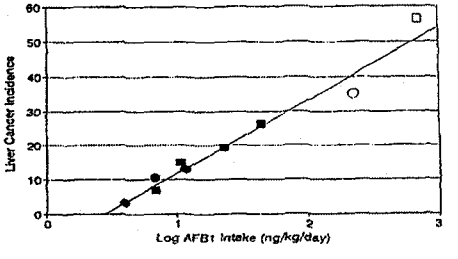


Fig. 1. A linear regression model of Y=21.67X-10.04 developed from epidemiological data of Kenya (●), Swaziland (■), Mozambique (○), & China (□). The correlation coefficient was 0.99 ($p<0.001$) [Y represents liver cancer incidence per 100,000 & X for AFB1 intake (ng/kg/day)] (Sabbioni et al., 1987; Zhu et al., 1987; Groopman et al., 1992)

(Choi et al., J. Biochem. Mol. Biol. 29(2), 105-110, 1996)

Exposure & Risk Assessment of Phthalates from Cosmetics

- Perfume, manicure, hair products, deorderants: 102
  - Domestic products: 27
  - Foreign products: 75

→ detection levels are not significant

(Koo & Lee, JTEH, 67: 1901-1914 (2004))

Table 1. Urinary concentrations of phthalate esters determined by HPLC in humans (㎍/ml urine)

Phthalate	Children (aged 11-12)			Women[a] (aged 20-73)		
	N[a]	Mean	95[th]	N	Mean	95[th]
DEHP	150[b] (149)[c]	0.0095	0.0198	150(147)	0.0125	0.0234
DEP	150(20)	0.0138	0.0996	150(26)	0.0098	0.0497
DBP	150(146)	0.0585	0.0941	150(143)	0.0494	0.1197
BBP	150(24)	0.0015	0.0092	150(7)	0.0004	<LOD[d]
MEHP	150(32)	0.0133	0.0441	150(81)	0.0413	0.1375

[a]Hospital visitors. [b]Sample size for analytical subjects.
[c]Number of samples detected.
[d]LOD (DEHP: 0.004, DEP: 0.0005, DBP: 0.0005, BBP: 0.0005, MEHP: 0.012 ㎍/ml).

(Koo & Lee, J. Toxicol. Environ. Health, 67:1367-1392 (2005))

Estimation of the daily intake of DEHP

Model 1

$$\textit{Daily Intake}(㎍/kg\ bw/day) = \frac{UE\ (㎍/g) \times CE\ (mg/kg\ bw/day)}{F_{UE} \times 1000\ (mg/g)} \times \frac{MW_d}{MW_m}$$

(David *et al.*, 2002)

UE : Urinary excretion of phthalate monomer in microgram per gram creatinine
CE : Creatinine excretion rate normalized by the body weight
F_{UE} : Molar fraction of the urinary excreted monoester related to the ingested diester
MW_d : molar weights of the diester
MW_m : molar weights of the monoester

Model 2

$$\textit{Daily Intake}(㎍/kg\ bw/day) = (T_M \times 5) / \text{Body weight (kg)} / \text{day}$$

(Schmid & Schlatter, 1985; Sjoberg *et al.*, 1985)

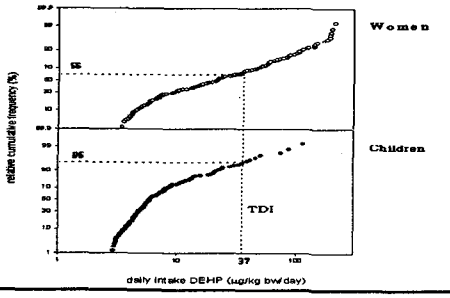
T_M : Total MEHP excretion level ($T_M = M \times V$)
M : MEHP levels in the urine (㎍/ml)
V : Total urinary excretion vol. per day (1200ml)

Table 2. Comparison of the estimated daily exposure of DEHP (㎍/kg bw/day)

Kohn *et al.* (2000) (*NHANES III, 1988-1994*)[a]		*Koch et al.* (2003)		*Our results* (2005)					
Model 1		Model 1		Model 1			Model 2		
All[b] (n=289)	Women[c] (n=97)	Females[d] (n=34)	Males[e] (n=25)	Children[f] (n=150)	Women[g] (n=150)	Men[h] (n=105)	*Children*	*Women*	*Men*
0.71	0.71	12.5	16.9	6.0	37.2	7.3[i]	2.1	4.4	1.08

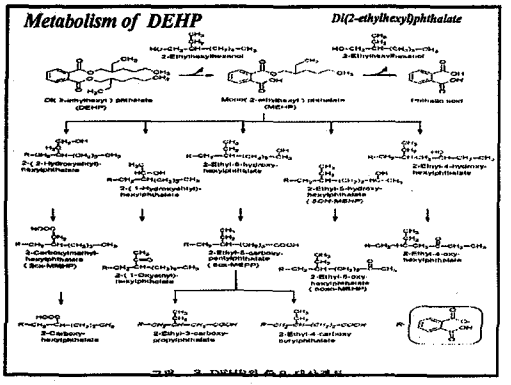
a : Median value
b : General population aged 20-60 years (gender distribution : 56% female, 44% male) (n=289)
c : Women aged 20-40 years (n=97)
d : Females aged 18-40 years (n=34)
e : Males aged 18-40 years (n=25)
f : Children aged 11-12 years (n=150)
g : Women aged 20-73 years (n=150)
h : Men aged 18-38 years (n=105)
i : 일일 노출량 산출시 성인의 일반적인 creatinine 수치 적용

Relative cumulative frequencies for the daily DEHP intake within each collective of women & children



I. 프탈레이트 생체지표 및 노출량산출 연구

- DEHP 단회 노출 및 노출량산출
- DBP 단회 노출 및 노출량산출
- DEHP/DBP 복합노출지표 및 노출량산출
- PA 단회 노출 및 노출량산출
- DEHP 반복 노출 지표 및 노출량 산출



DEHP 단회 노출 및 노출량산출

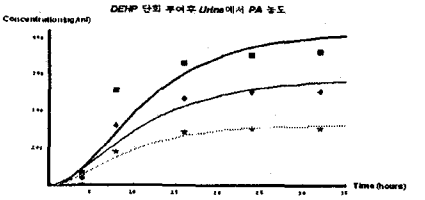


그림 1a. Urinary PA concentration s after single oral administration of DEHP
(200 초록, 1000 적색 , 5000 청색 mg/kg)

1a) DEHP 일회 경구투여 4시간 후의 뇨중 PA농도(x1) 와 노출량 (Y1)과의 상관관계식 (Eq. 1a)

$$Y1 = 0.119(-1+e^{0.112x1}) \quad \text{--------- (Eq. 1a)}$$

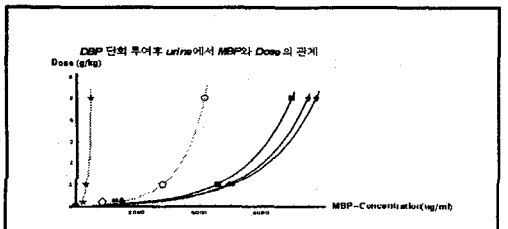


그림 6a DBP 단독 투여후 시간에 따른 뇨 중 MBP 농도와 노출량과의 상관 관계식
위의 그래프는 시간대별(4,8,16,24,32)로 차례로 표시되었음

6a) DBP 일회 경구투여 32시간 후의 뇨중 MBP농도(x6) 와 노출량 (Y6)과의 상관관계식 (Eq. 6a)

$$Y6 = 0.056(-1+e^{0.000585x6}) \quad \text{--------- (Eq. 6a)}$$

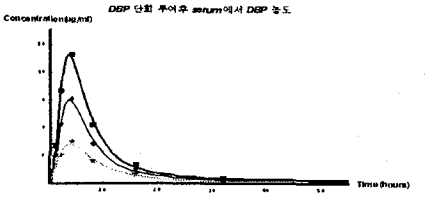


그림 7b. Serum DBP concentration s after single oral administration of DBP
(200 초록, 1000 적색 , 5000 청색 mg/kg)

7b) DBP 일회 경구투여 2시간 후의 혈중 DBP농도(x7) 와 노출량 (Y7)과의 상관관계식 (Eq.7b)

$$Y7 = 0.0673(-1+e^{0.1296x7}) \quad \text{--------- (Eq. 7b)}$$

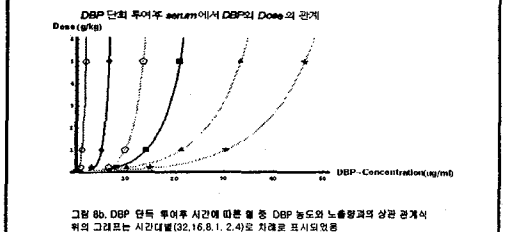


그림 8b. DBP 단독 투여후 시간에 따른 혈 중 DBP 농도와 노출량과의 상관 관계식
위의 그래프는 시간대별(32,16,8,1, 2,4)로 차례로 표시되었음

8b) DBP 일회 경구투여 8시간 후의 혈중 DBP농도(x8) 와 노출량 (Y8)과의 상관관계식 (Eq.8b)

$$Y8 = 0.0256(-1+e^{0.236x8}) \quad \text{--------- (Eq. 8b)}$$

DEHP/DBP 단회 노출 및 노출량산출

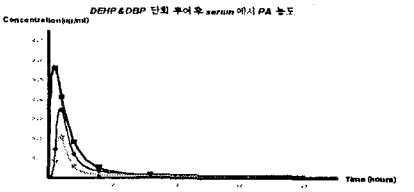


그림 9b. Serum PA concentration s after single oral administration of
the mixture of DEHP and DBP (200 초록, 1000 적색 , 5000 청색 mg/kg)

9b) DEHP 와 DBP의 복합물질 일회 경구투여 4시간 후의 혈중 PA농도(x9) 와 노출량 (Y9)과의 상관관계식 (Eq. 9b)

$$Y9 = 0.051(-1+e^{24.85x9}) \quad \text{--------- (Eq. 9b)}$$

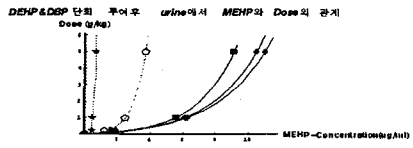


그림 12a DEHP/DBP 단독 투여후 시간에 따른 뇨 중 MEHP 농도와 노출량과의 상관 관계식
위의 그래프는 시간대별(4, 8, 16 ,24, 32)로 차례로 표시되었음

12a) DEHP 와 DBP의 복합물질일회 경구투여 32시간 후의 뇨중 MEHP농도(x12) 와 노출량 (Y12)과의 상관관계식 (Eq. 12a)

$$Y12 = 0.165(-1+e^{0.313x12}) \quad \text{--------- (Eq. 12a)}$$

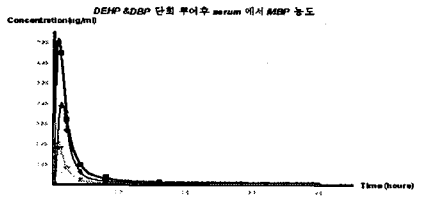


그림 13b. Serum MBP concentration s after single oral administration of the mixture of DEHP and DBP (200 초록, 1000 적색 , 5000 청색 mg/kg)

13b) DEHP 와 DBP의 복합물질 일회 경구투여 1시간 후의 혈중 MBP농도(x13) 와 노출량 (Y13)과의 상관관계식 (Eq. 13b)

$$Y13 = 0.11(-1+e^{0.00596x13}) \quad \text{--------- (Eq. 13b)}$$

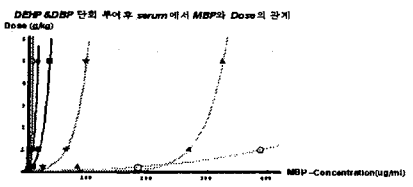


그림 14b DEHP/DBP 단독 투여후 시간에 따른 혈 중 MBP 농도와 노출량과의 상관 관계식
위의 그래프는 시간대별(32,16,8, 4, 2, 1)로 차례로 표시되었음

14b) DEHP 와 DBP의 복합물질 일회 경구투여 4시간 후의 혈중 MBP농도(x14) 와 노출량 (Y14)과의 상관관계식 (Eq. 14b)

$$Y14 = 0.049(-1+e^{0.048x14}) \quad \text{--------- (Eq. 14b)}$$

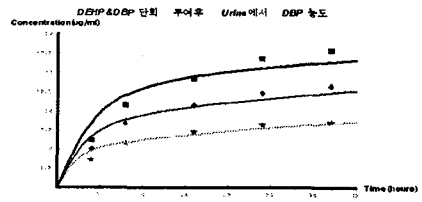


그림 15a. Urinary DBP concentration s after single oral administration of the mixture of DEHP and DBP (200 초록, 1000 적색 , 5000 청색 mg/kg)

15a) DEHP 와 DBP의 복합물질일회 경구투여 8시간 후의 뇨중 DBP농도(x15) 와 노출량 (Y15)과의 상관관계식 (Eq. 15a)

$$Y15 = 0.0029(-1+e^{0.69x15}) \quad \text{--------- (Eq. 15a)}$$

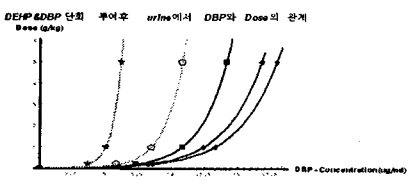


그림 16a DEHP/DBP 단독 투여후 시간에 따른 뇨 중 DBP 농도와 노출량과의 상관 관계식
위의 그래프는 시간대별(4, 8,16, 24, 32)로 차례로 표시되었음

16a) DEHP 와 DBP의 복합물질일회 경구투여 24시간 후의 뇨중 DBP농도(x16) 와 노출량 (Y16)과의 상관관계식 (Eq. 16a)

$$Y16 = 0.0105(-1+e^{0.368x16}) \quad \text{--------- (Eq. 16a)}$$

DEHP 반복 노출 지표 및 노출량 산출

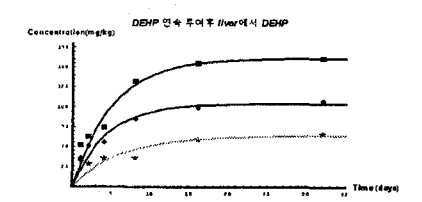


그림21c . Liver DEHP concentrations after continuous oral administration of DEHP (333 low , 1000 mid , 3000 high mg/kg)

21c) DEHP 32일간 경구 반복투여 2일후 간조직중 DEHP농도(x21) 와 노출량 (Y21)과의 상관관계식 (Eq. 21c)

$$Y21 = 0.01024(-1+e^{0.091x21}) \quad \text{--------- (Eq. 21c)}$$

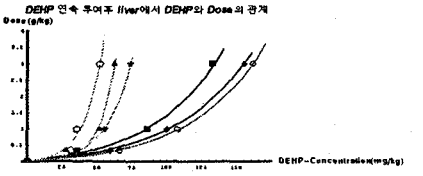


그림 22c. DEHP 연속 투여 후 시간에 따른 간조직 중 DEHP 농도와 노출량 과의 상관 관계식
위의 그래프는 시간대별(1, 2, 4, 8, 16, 32일)로 차례로 표시되었음

22c) DEHP 32일간 경구 반복투여 16일후 간조직중 DEHP농도(x22) 와 노출량 (Y22)과의 상관관계식 (Eq. 22c)

$$Y22 = 0.191(-1+e^{0.0182x22}) \quad \text{--------} \quad \text{(Eq. 22c)}$$

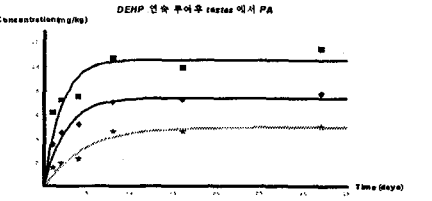


그림23d . Testes PA concentrations after continuous oral administration of DEHP
(333 low , 1000 mid , 3000 high mg/kg)

23d) DEHP 32일간 경구 반복투여 4일후 고환 조직중 PA농도(x23) 와 노출량 (Y23)과의 상관관계식 (Eq. 23d)

$$Y23 = 0.141(-1+e^{0.41x23}) \quad \text{--------} \quad \text{(Eq. 23d)}$$

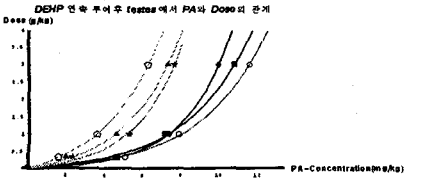


그림 24d. DEHP 연속 투여 후 시간에 따른 고환 조직 중 PA 농도와 노출량 과의 상관 관계식
위의 그래프는 시간대별(1, 2, 4, 8, 16, 32일)로 차례로 표시되었음

24d) DEHP 32일간 경구 반복투여 32일후 고환 조직중 PA농도(x24) 와 노출량 (Y24)과의 상관관계식 (Eq. 24d)

$$Y24 = 0.113(-1+e^{0.269x24}) \quad \text{--------} \quad \text{(Eq. 24d)}$$

II. 프탈레이트의 Toxicokinetic 연구 및 Tissue distribution

- DEHP 단회 노출시 Toxicokinetic 연구 및 Tissue distribution
- DBP 단회 노출시 Toxicokinetic 연구 및 Tissue distribution
- DEHP/DBP 복합물질 단회 노출시 Toxicokinetic 연구 및 Tissue distribution
- PA 단회 노출 Toxicokinetic 연구
- 32일간 DEHP 반복 노출시 Tissue distribution

DEHP 단회 노출시 Toxicokinetic 연구 및 Tissue distribution

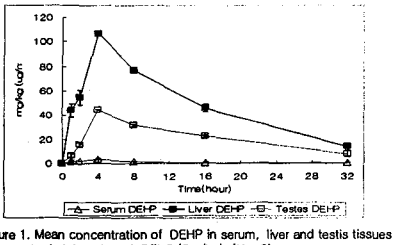


Figure 1. Mean concentration of DEHP in serum, liver and testis tissues after oral administration of DEHP (5 g/kg) (N = 3).

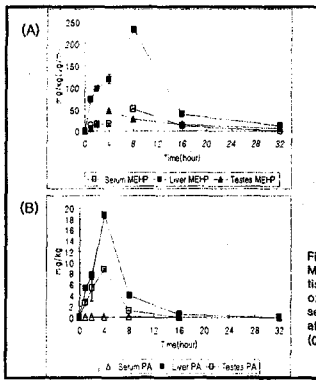


Figure 2. Mean concentration of (A) MEHP in serum, urine, liver and testis tissues after oral administration of DEHP (1 g/kg) and (B) PA in serum, urine, liver and testis tissues after oral administration of DEHP (0.2 g/kg) .

Table 1. Toxicokinetics parameters in plasma determined using noncompartmental analysis of the time course of DEHP, MEHP and PA following oral administration of 200, 1000 and 5000 mg/kg DEHP as single dose.

Parameters	DEHP	MEHP	PA
200 mg/kg DEHP			
Tmax (hr)	4±0.00	8±0.00	8±0.00
Cmax (㎍/㎖)	1.18±0.06	21.40±0.30	0.11±0.01
Ke (1/hr)	0.08±0.01	0.23±0.04	0.11±0.01
$t_{1/2}$ (hr)	8.70±0.95	3.09±0.60	6.37±0.10
AUC (㎍*hr/㎖)	14.15±1.00	182.20±7.42	1.28±0.05
Vz/F (㎖)	20460.25±3672.30	-	-
Cl/F (㎖/hr)	1624.22±115.14	-	-
MRT (hr)	14.39±1.78	8.06±0.31	10.43±0.44

Parameters	DEHP	MEHP	PA
1000 mg/kg DEHP			
Tmax (hr)	4±0.00	8±0.00	8±0.00
Cmax (㎍/㎖)	1.91± 0.00	51.19± 0.02	0.15± 0.00
Ke (1/hr)	0.09± 0.01	0.20± 0.00	0.10± 0.01
$t_{1/2}$ (hr)	7.91±0.06	3.49± 0.00	6.89± 0.00
AUC (㎍*hr/㎖)	25.00±0.74	542.89± 0.00	2.09± 0.00
Vz/F (㎖)	50950.55±1588.39	-	-
Cl/F (㎖/hr)	4464.41±103.21	-	-
MRT (hr)	9.39±0.52	9.66±0.12	11.88±1.25
5000 mg/kg DEHP			
Tmax (hr)	4±0.00	8±0.00	8±0.00
Cmax (㎍/㎖)	3.34±0.30	109.74±10.22	0.23±0.05
Ke (1/hr)	0.08±0.01	0.16±0.064	0.10±0.01
$t_{1/2}$ (hr)	8.40±0.75	4.59±1.60	7.16±0.74
AUC (㎍*hr/㎖)	37.68±2.67	1243.33±91.48	3.34±0.19
Vz/F (㎖)	181305.59±6879.8	-	-
Cl/F (㎖/hr)	14992.04±773.39	-	-
MRT (hr)	12.65±0.97	9.95±1.31	13.00±0.85

DBP 단회 노출시 Toxicokinetic 연구 및 Tissue distribution

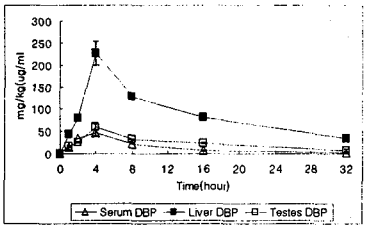


Figure 3.Mean concentration of DBP in serum, liver and testis tissues after oral administration of DBP (5 g/kg).

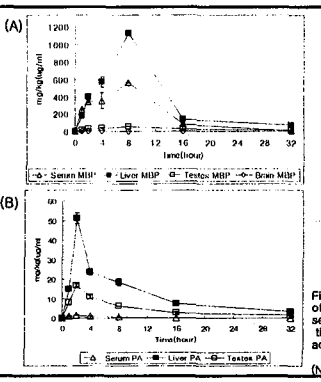


Figure 4. Mean concentration of (A) MBP (B) PA in serum, liver and testis tissues after oral administration of DBP (1 g/kg) (N = 3).

Table 2. Toxicokinetics parameters in plasma determined using noncompartmental analysis of the time course of DBP, MBP and PA following oral administration of 200, 1000 and 5000 mg/kg DBP as single dose.

Parameters	DBP	MBP	PA
200mg/kg DBP			
Tmax (hr)	4±0.00	8±0.00	5.18±2.75
Cmax (㎍/㎖)	14.92±0.59	124.22±7.47	0.49±0.11
Ke (1/hr)	0.10±0.00	0.18±0.01	0.13±0.04
$t_{1/2}$ (hr)	6.85±0.12	3.87±0.02	5.18±2.75
AUC (㎍*hr/㎖)	166.28±8.67	1138.17±7.20	2.99±0.21
Vz/F (㎖)	1606.61±94.50	-	-
Cl/F (㎖/hr)	162.61±6.74	-	-
MRT (hr)	10.45±0.21	7.39±0.51	6.66±2.57

Parameters	DBP	MBP	PA
1000 mg/kg DBP			
Tmax (hr)	4±0.00	8±0.00	6.68±1.70
Cmax (㎍/㎖)	3.50±0.01	562.63±0.23	1.03±0.16
Ke (1/hr)	0.09±0.01	0.19±0.04	0.10±0.02
$t_{1/2}$ (hr)	7.99±1.12	3.68±0.73	6.68±1.70
AUC (㎍*hr/㎖)	389.45±16.04	6260.73±142.44	7.80±1.65
Vz/F (㎖)	3468.64±342.18	-	-
Cl/F (㎖/hr)	301.86±42.97	-	-
MRT (hr)	12.31±1.64	8.16±0.18	9.15±1.46
5000 mg/kg DBP			
Tmax (hr)	4±0.00	6±2.83	7.25±2.19
Cmax (㎍/㎖)	46.34±7.38	1099.24±366.23	1.23±0.16
Ke (1/hr)	0.08±0.00	0.18±0.01	0.10±0.03
$t_{1/2}$ (hr)	8.71±0.22	3.96±0.20	7.25±2.19
AUC (㎍*hr/㎖)	601.18±21.52	15600.99±1565.38	11.71±2.88
Vz/F (㎖)	14084.29±71.87	-	-
Cl/F (㎖/hr)	1120.98±30.13	-	-
MRT (hr)	13.36±0.34	8.21±0.30	10.17±1.93

DEHP/DBP 복합 물질 단회 노출시 Toxicokinetic 연구 및 Tissue distribution

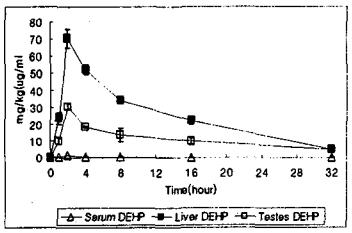


Figure 5. Mean concentration of DEHP in serum, liver and testis tissues after oral administration of the mixture of DEHP and DBP (1 g/kg) (N = 3).

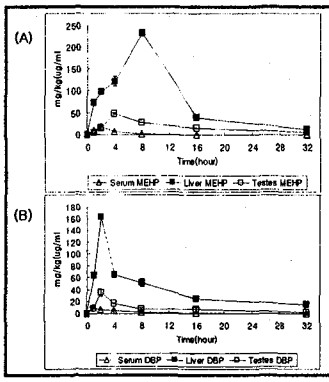


Figure 6.
Mean concentration of (A) MEHP and (B) DBP in serum, liver and testis tissues after oral administration of the mixture of DEHP and DBP (1 g.kg) (N = 3).

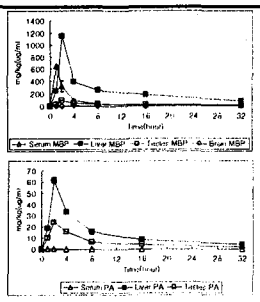


Figure 7. Mean concentration of (A) MBP and (B) PA in serum, liver and testis tissues after oral administration of the mixture of DEHP and DBP (5 g/kg) (N = 3).

PA 단회 노출시 Toxicokinetic 연구

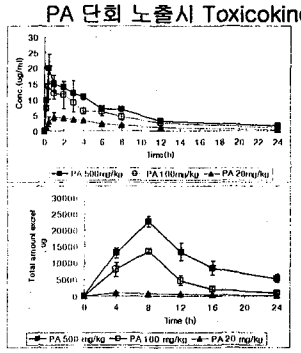
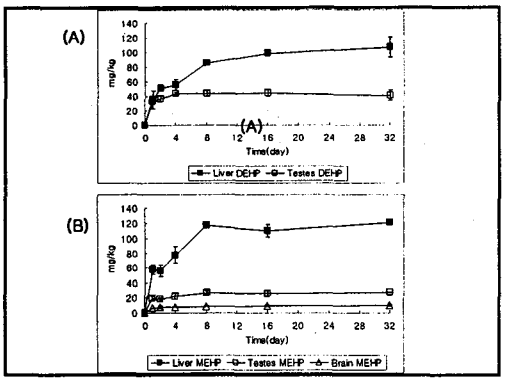


Figure 8.
Time-dependent (A) serum concentration and (B) urinary volume of phthalic acid (PA) following single oral administration of 20, 100, or 500 ㎎/㎏ PA to rats.

Table 3. Toxicokinetics parameters in plasma determined using noncompartmental analysis of the time course of PA following oral administration of 20, 100 and 500 mg/kg PA as single dose.

32일간 DEHP 반복 노출시 Tissue distribution

Table 4. Tissue distribution of phthalate and its metabolite in rats after multiple oral administration of DEHP



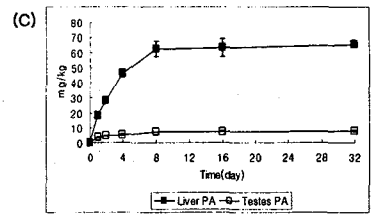


Figure 9. Mean concentration of (A) DEHP, (B) MEHP (C) PA in liver, testis and Brain tissues after multiple oral administration of DEHP (1 g/kg)

Conclusions

- Metabolite profiling kinetics is a new and promising approach for human exposure & risk assessment
- Dose-response relationship betw/n biomarkers & toxicant exposure is a crucial & key factor for biomarker (metabolite) selection
- Simulation of biomarker (metabolite) kinetics for chronic exposure can be obtainable from single treatment, but need validation
- Biologically based dose-response (BBDR) models for exposure to mixture chemicals need to be developed for human exposure assessment
- BBDR models using metabolic kinetics may be applicable to human exposure & risk assessment with employment of safety factor

After Risk Assessment

- Risk Perception
- Risk Communication
- Risk Management – Setting Legal Limits & Application
- Control of Toxicant Exposure

There is no zero risk in our environment !!