



IPA

Institute for Prevention and Occupational Medicine
of the German Social Accident Insurance
Institute of the Ruhr-Universität Bochum

Internal burden caused by endocrine disruptors present in the environment and at the workplace

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INRS/ISSA 2016 SYMPOSIUM:

**CHEMICALS WITH SPECIAL HAZARDS: OCCUPATIONAL RISKS AND PREVENTION
ENDOCRINE DISRUPTORS AND SENSITISING SUBSTANCES**

01-03 June 2016 – Paris, France



**RUHR
UNIVERSITÄT
BOCHUM**

RUB

Biological Monitoring:

- ➔ via all routes and sources
- ➔ no/low contamination (*spec. metabolites*)

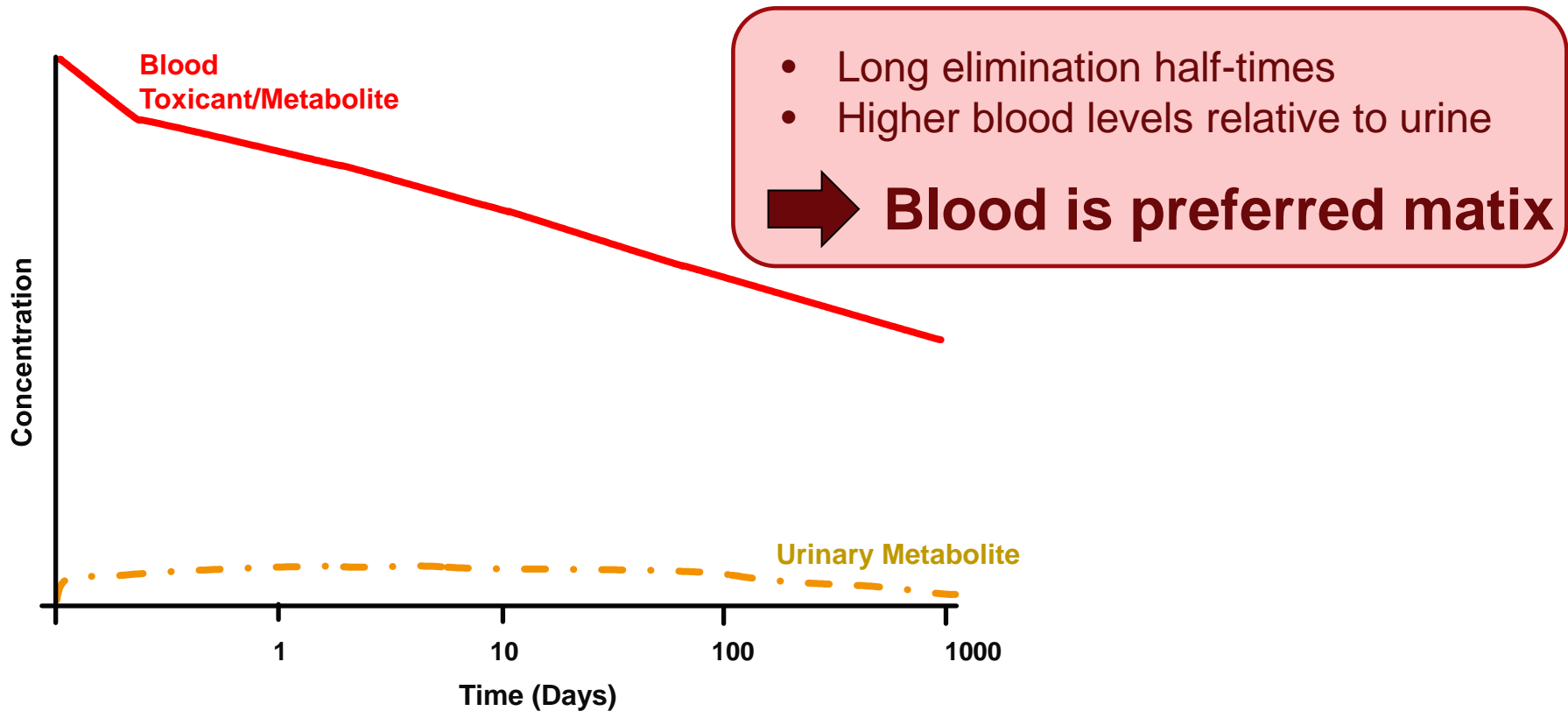
Biological Monitoring! *Integral and robust exposure assessment*

 Back-calculation of daily intake
 ~~Comparison with health/toxicity benchmarks~~
chemicals that actually entered the human body
(TDI, RfD, NOAEL ...)

 *via all routes and sources*
~~Realistic risk assessment~~ (single chemical)

 *no/low of contamination (spec metabolites)*
~~Cumulative risk assessment~~ (multiple chemicals)

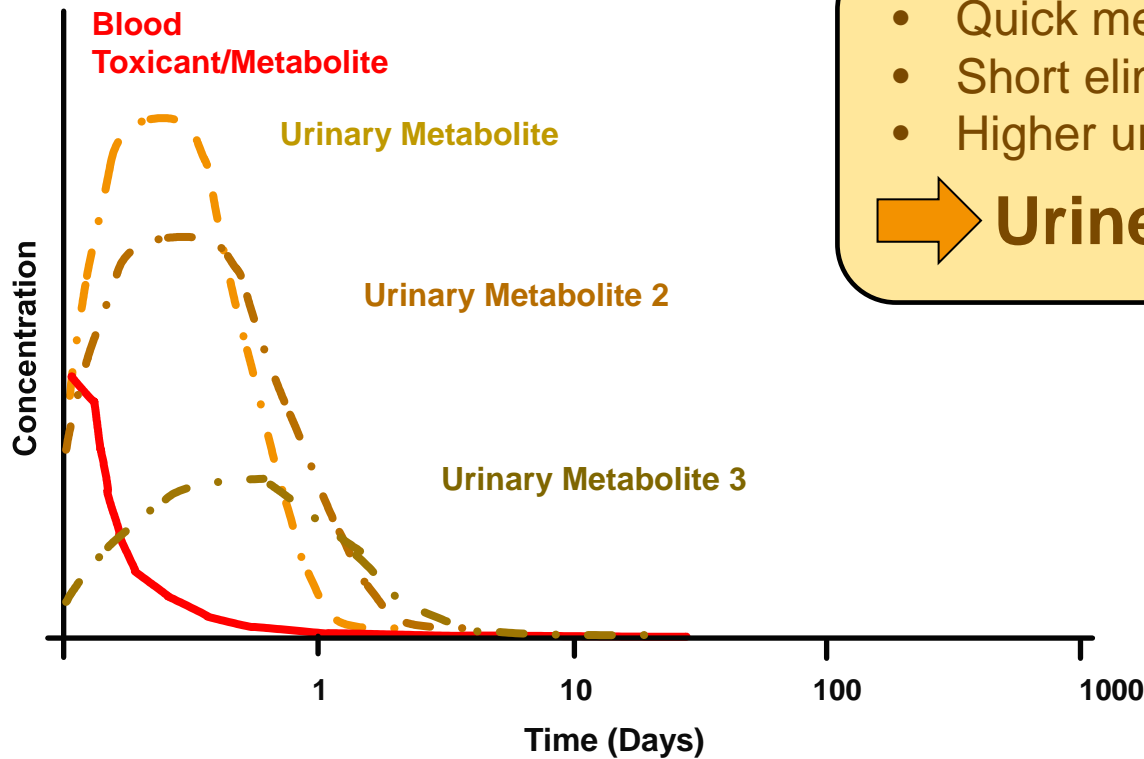
Toxikokinetics: persistent chemicals



Slides taken from ISEA/ISES Wesolowski Award Presentation, Paris 2006:
Biomonitoring: An Integral Part of Exposure Analysis
Larry L. Needham, Ph.D., CDC, Atlanta

Needham and Sexton. JEAAE 10: 611-629 (2000)
Henderson et al. Crit Rev Toxicol 20: 65-82 (1989)

Toxikokinetics: non-persistent chemicals



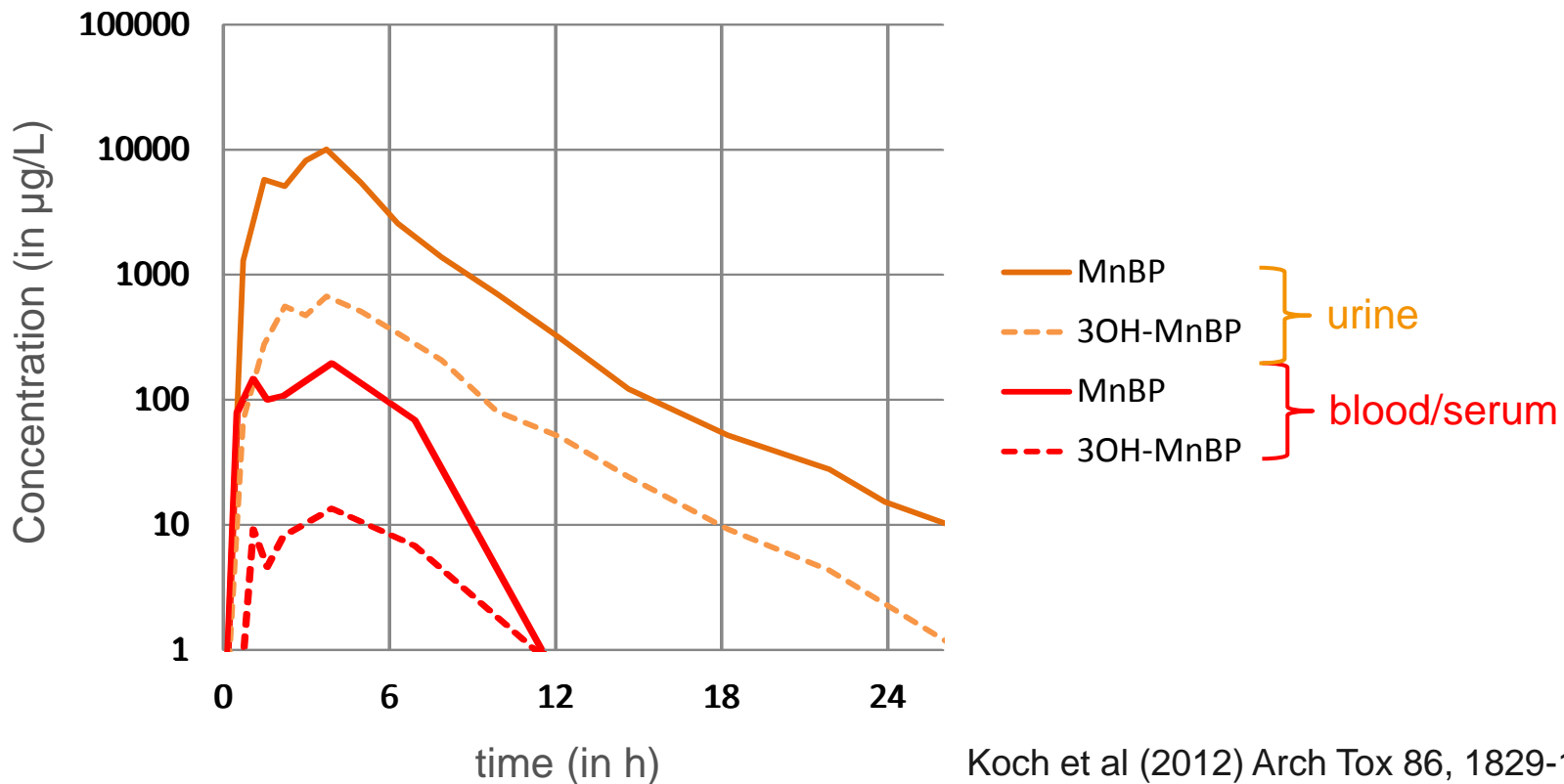
- Quick metabolisation
 - Short elimination half-times
 - Higher urine levels relative to blood
- ➔ **Urine is preferred matrix**

Slides taken from ISEA/ISES Wesolowski Award Presentation, Paris 2006:
Biomonitoring: An Integral Part of Exposure Analysis
Larry L. Needham, Ph.D., CDC, Atlanta

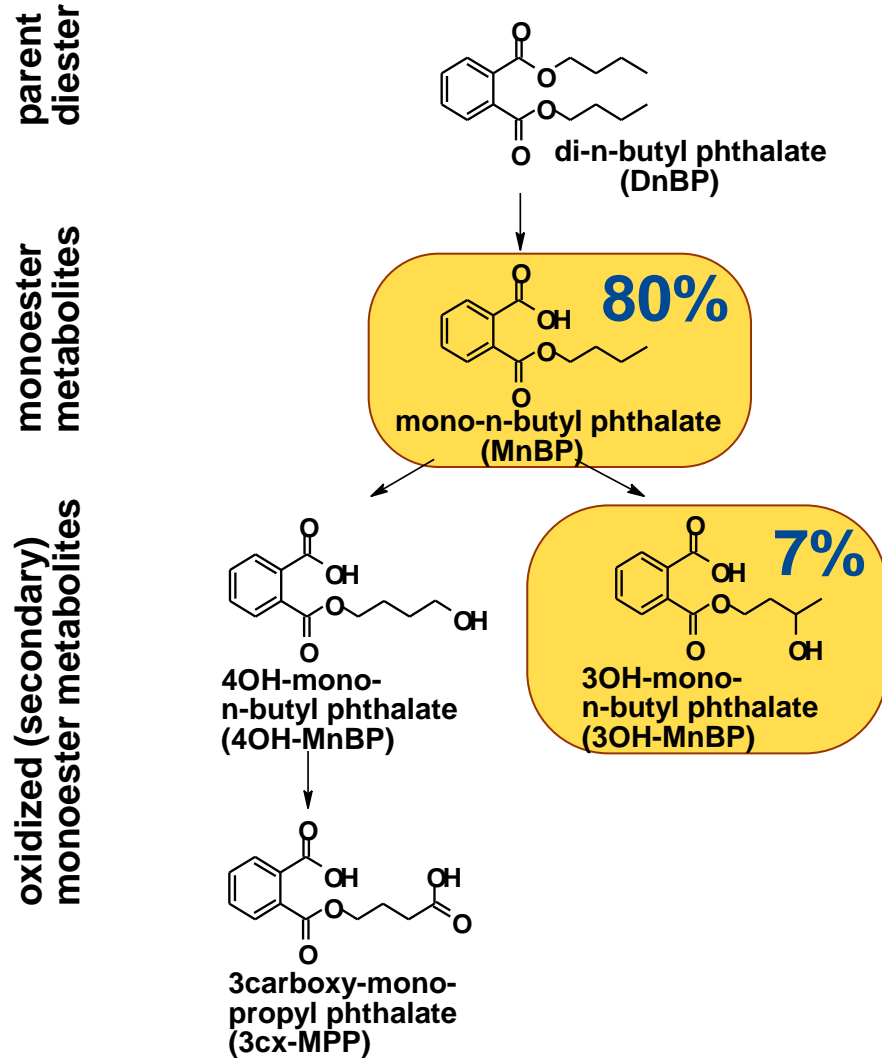
Needham and Sexton. JEAE 10: 611-629 (2000)
Henderson et al. Crit Rev Toxicol 20: 65-82 (1989)

Toxikokinetics: Di-n-butyl phthalate (DnBP)

5mg D4-DnBuP (oral, one human volunteer)

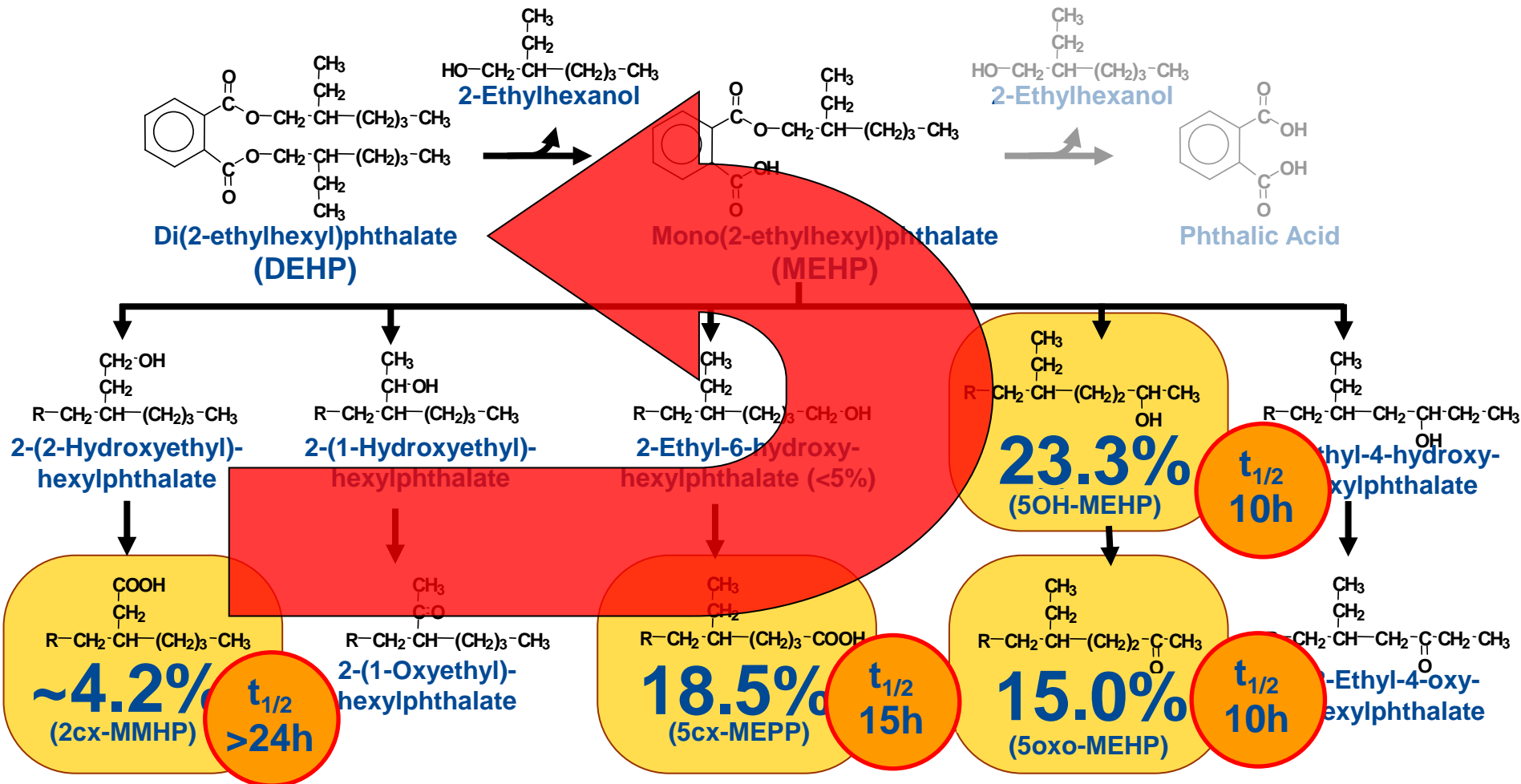


Koch et al (2012) Arch Tox 86, 1829-1839.
Lorber and Koch (2013) Environ Int 59, 469-477.



Koch et al (2012) Arch Tox 86, 1829-1839.
Lorber and Koch (2013) Environ Int 59, 469-477.

Biomarkers for DEHP



Koch et al. (2004) Arch Toxicol 78, 123-130.
 Koch et al. (2005) Arch Toxicol 79, 367-376.

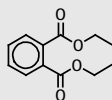
low-molecular weight phthalates

parent phthalate

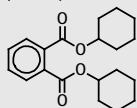
Dimethyl phthalate (DMP)



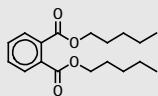
Diethyl phthalate (DEP)



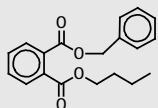
Di-cyclohexyl phthalate (DCHP)



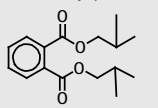
Di-n-pentyl phthalate (DnPeP)



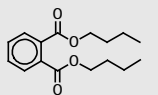
Butyl-benzyl phthalate (BBzP)



Di-iso-butyl phthalate (DiBP)



Di-n-butyl phthalate (DnBP)

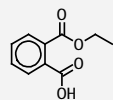


**primary metabolite
(hydrolytic monoester)**

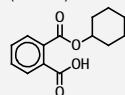
Mono-methyl phthalate (MMP)



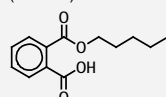
Mono-ethyl phthalate (MEP)



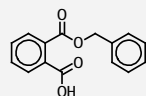
Mono-cyclohexyl phthalate (MCHP)



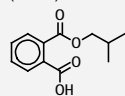
Mono-n-pentyl phthalate (MnPeP)



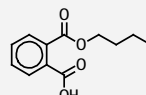
Mono-benzyl phthalate (MBzP)



Mono-iso-butyl phthalate (MiBP)



Mono-n-butyl phthalate (MnBP)



**secondary metabolite
(oxidised monoester)**

n.a.

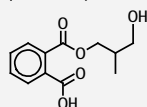
n.a.

n.a.

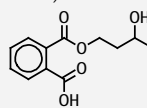
n.a.

n.a.

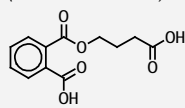
3OH-Mono-methylpropyl phthalate (OH-MiBP)



3OH-Mono-n-butyl phthalate (OH-MnBP)



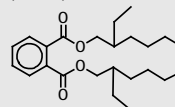
3carboxy-Mono-propyl phthalate (3cx-MiBP or MCPP)



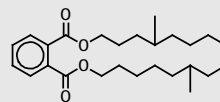
high-molecular weight phthalates

parent phthalate

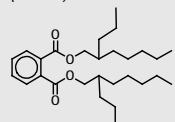
Di(2-ethylhexyl) phthalate (DEHP)



Di-iso-nonyl phthalate (DiINP)[†]

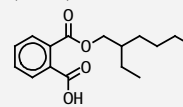


Di-iso-decyl phthalate (DiIDP)[†] and Dipropylheptyl phthalate (DPHP)

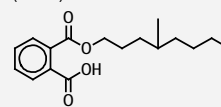


**primary metabolite
(hydrolytic monoester)**

Mono(2-ethylhexyl) phthalate (MEHP)

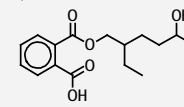


Mono-iso-nonyl phthalate (MiINP)[†]

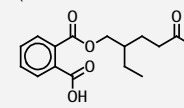


**secondary metabolite
(oxidised monoester)**

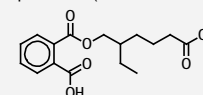
5OH-Mono(2-ethylhexyl) phthalate (5OH-MEHP or MEHHP)



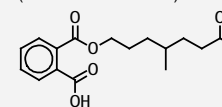
5oxo-Mono(2-ethylhexyl) phthalate (5oxo-MEHP or MEOHP)



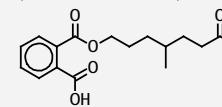
5carboxy-Mono(2-ethylhexyl) phthalate (5cx-MEPP or MECPP)



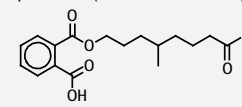
7OH-Mono-methyloctyl phthalate (OH-MiNP or MHiNP)



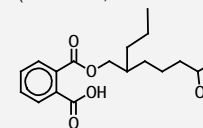
7oxo-Mono-methyloctyl phthalate (oxo-MiNP or MOiNP)



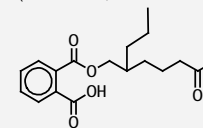
7carboxy-Mono-methylheptyl phthalate (cx-MiNP or MCIOP)



6OH-Mono-propylheptyl phthalate (OH-MPHP, OH-MiDP or MHiDP)



6oxo-Mono-propylheptyl phthalate (oxo-MPHP, oxo-MiDP or MOiDP)



EU Classification

Phthalate	Chain-length
DMP	1
DEP	2
DiBP	4
DnBP	4
BBzP	4-6
D-i/n-PeP	5
D-i/n-HexP	6
DEHP	8
DiNP	8-10
DnOP	8
DiDP	9-11
DPHP	10

H360D: May damage the unborn child

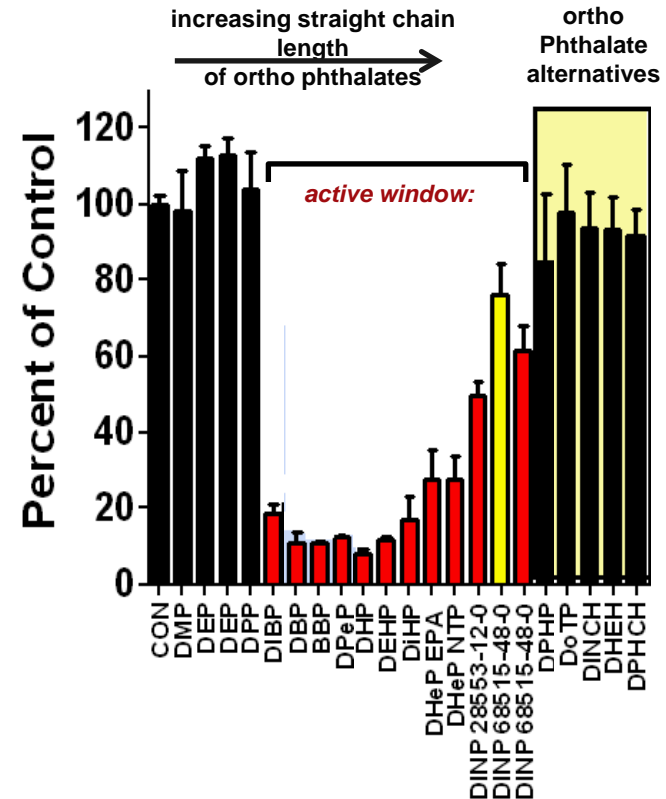
H360F: May damage fertility ; H360f: Suspected of damaging fertility

EU Classification

Phthalate	Chain-length	Classification (year)
DMP	1	-
DEP	2	-
DiBP	4	Repr. 1B (2009)
DnBP	4	Repr. 1B (2001)
BBzP	4-6	Repr. 1B (2001)
D-i/n-PeP	5	Repr. 1B (2004)
D-i/n-HexP	6	Repr. 1B (2013)
DEHP	8	Repr. 1B (2001)
DiNP	8-10	-
DnOP	8	-
DiDP	9-11	-
DPHP	10	-

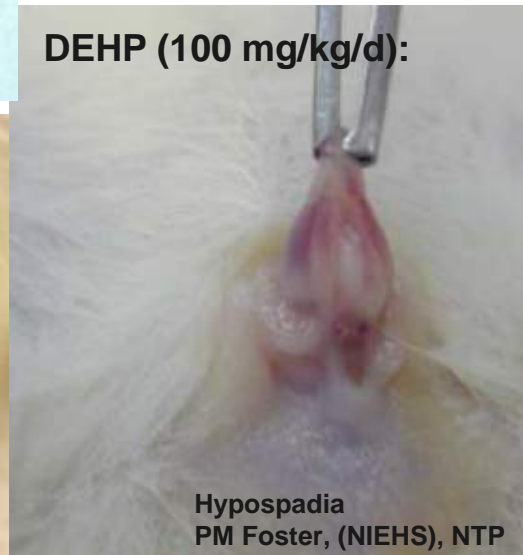
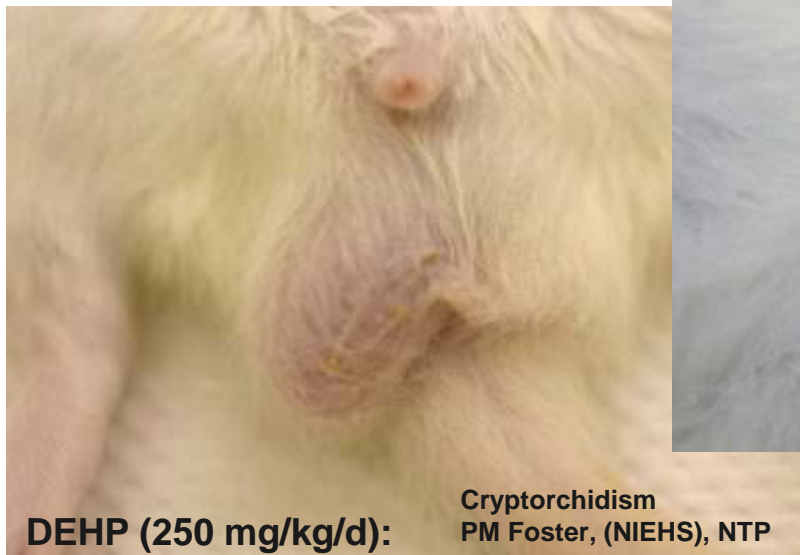
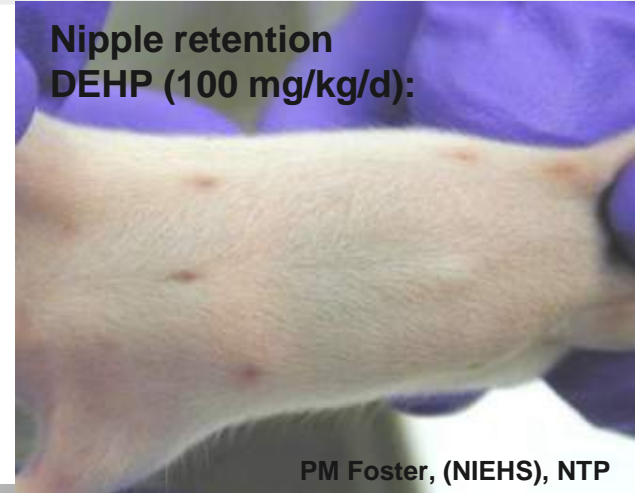
H360D: May damage the unborn child
H360F: May damage fertility

Potency Reduction of Testicular Testosterone Production



(Furr et al. (2014) *Tox Sci* 140:403-424.
Earl Gray, personal communication)

The 'Phthalate-Syndrome'



Phthalate Exposures

(general population)

German Environmental Specimen Bank



Collection of human samples (24h urines) since the early 1980's

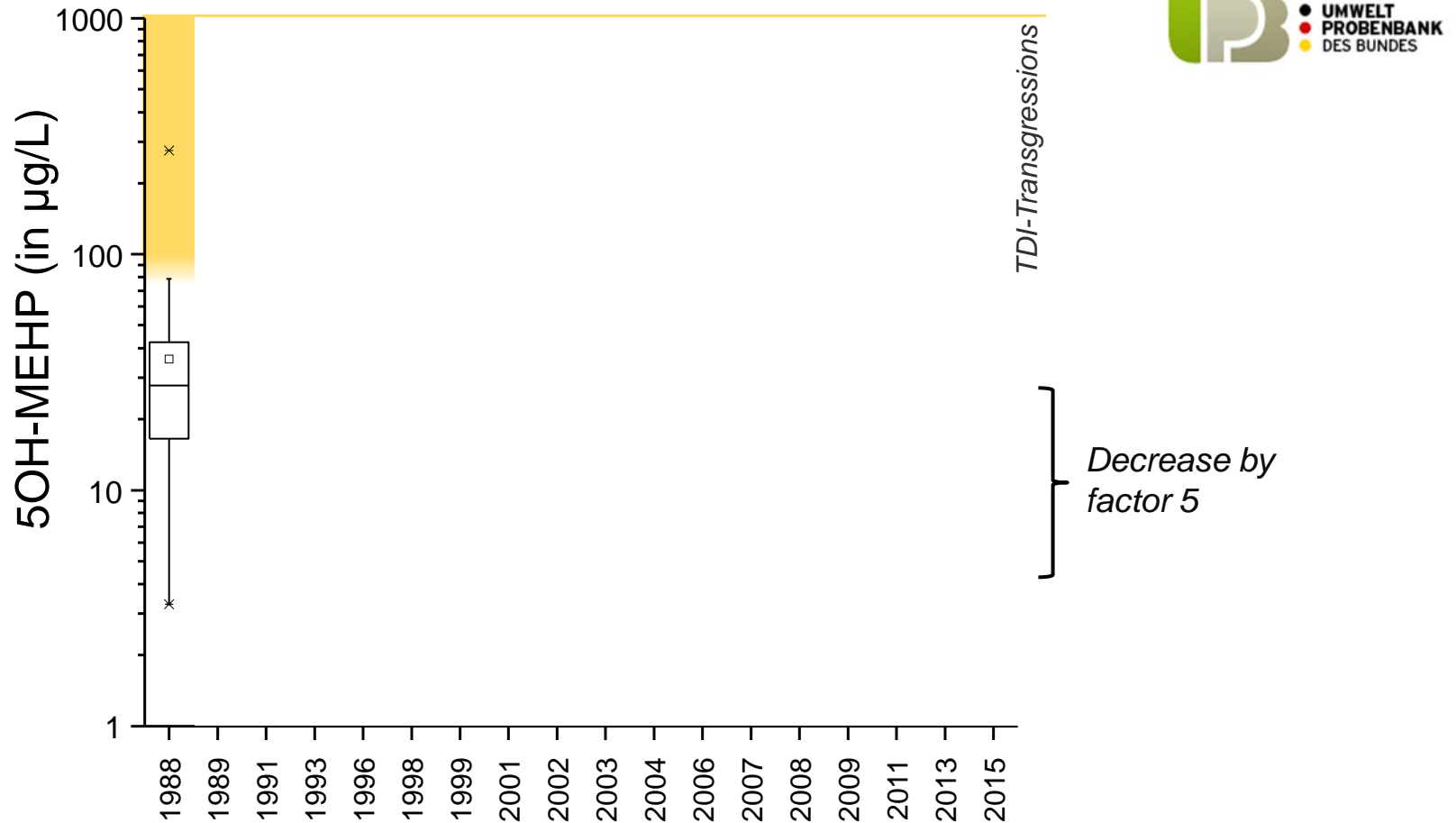


⇒ Time trend analyses

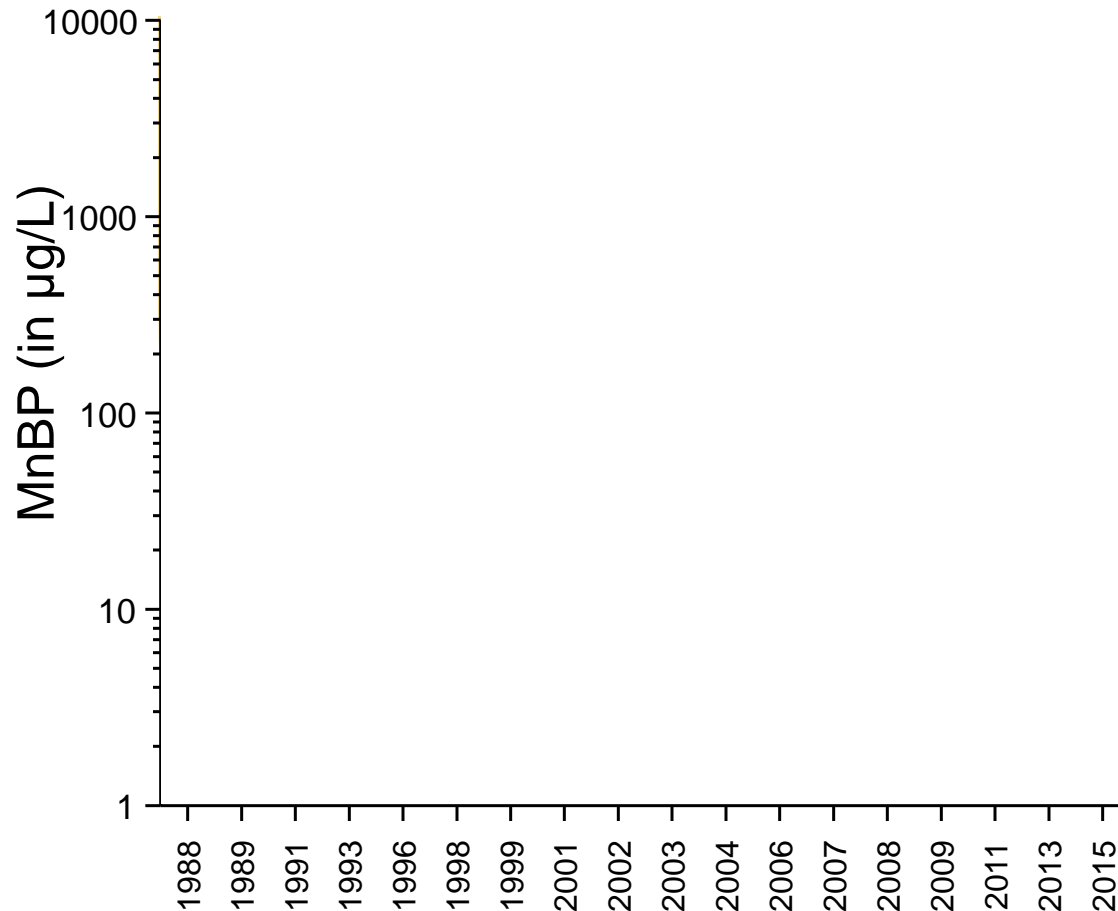
⇒ Daily intake calculations / risk assessment

Umweltprobenbank Münster

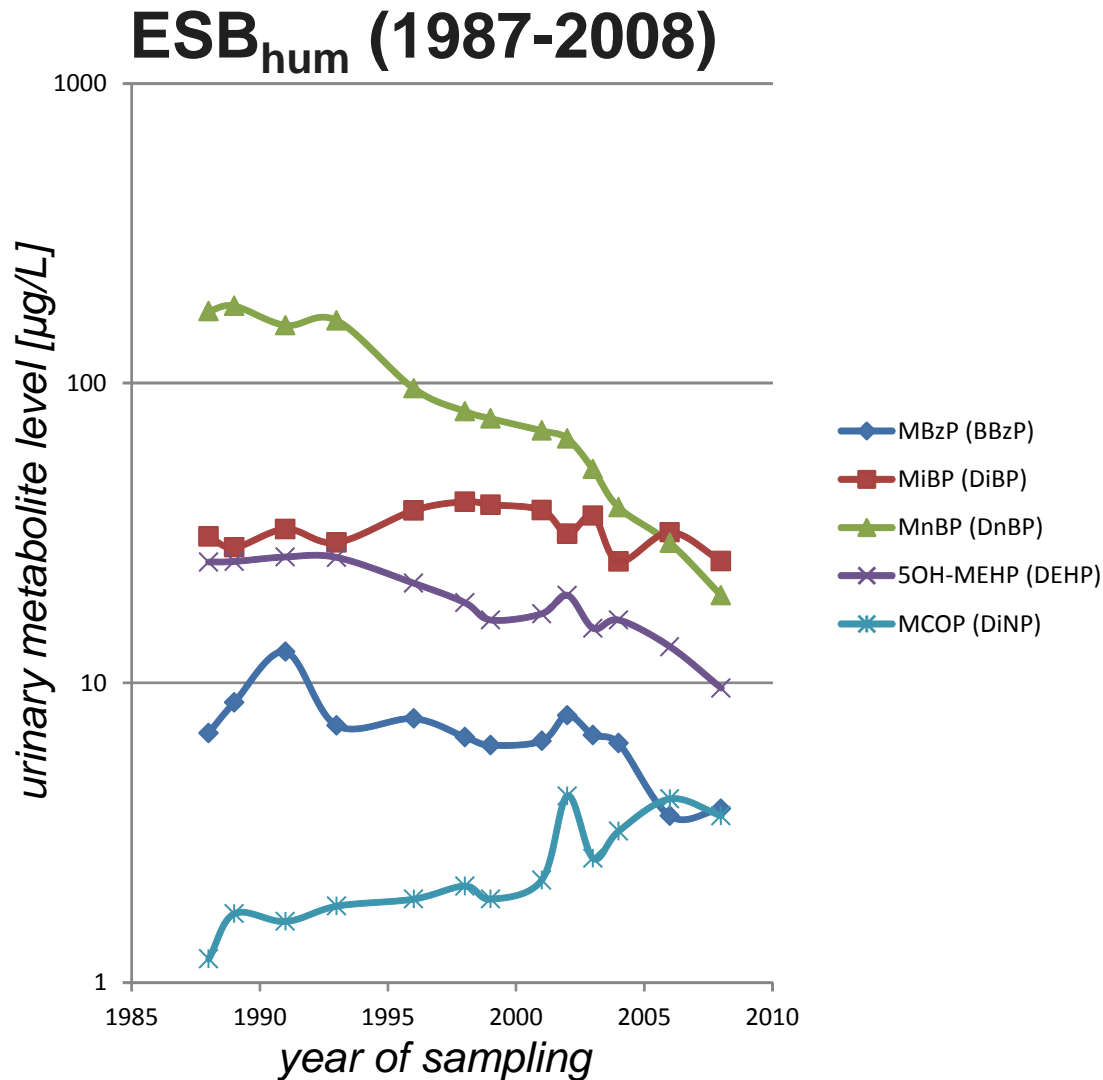
Time Trend DEHP Exposure



Time Trend DnBP Exposure



Decrease by
factor 10

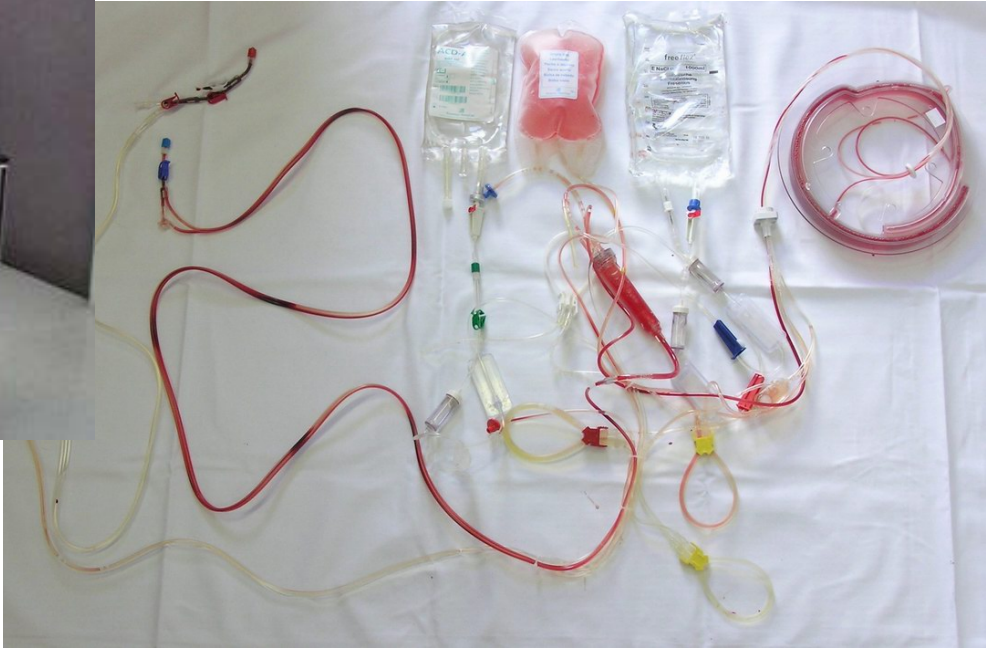
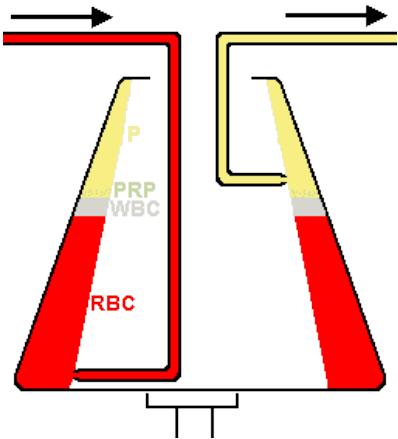


Wittassek et al. (2007)
IJHEH 210(3-4):319-333.

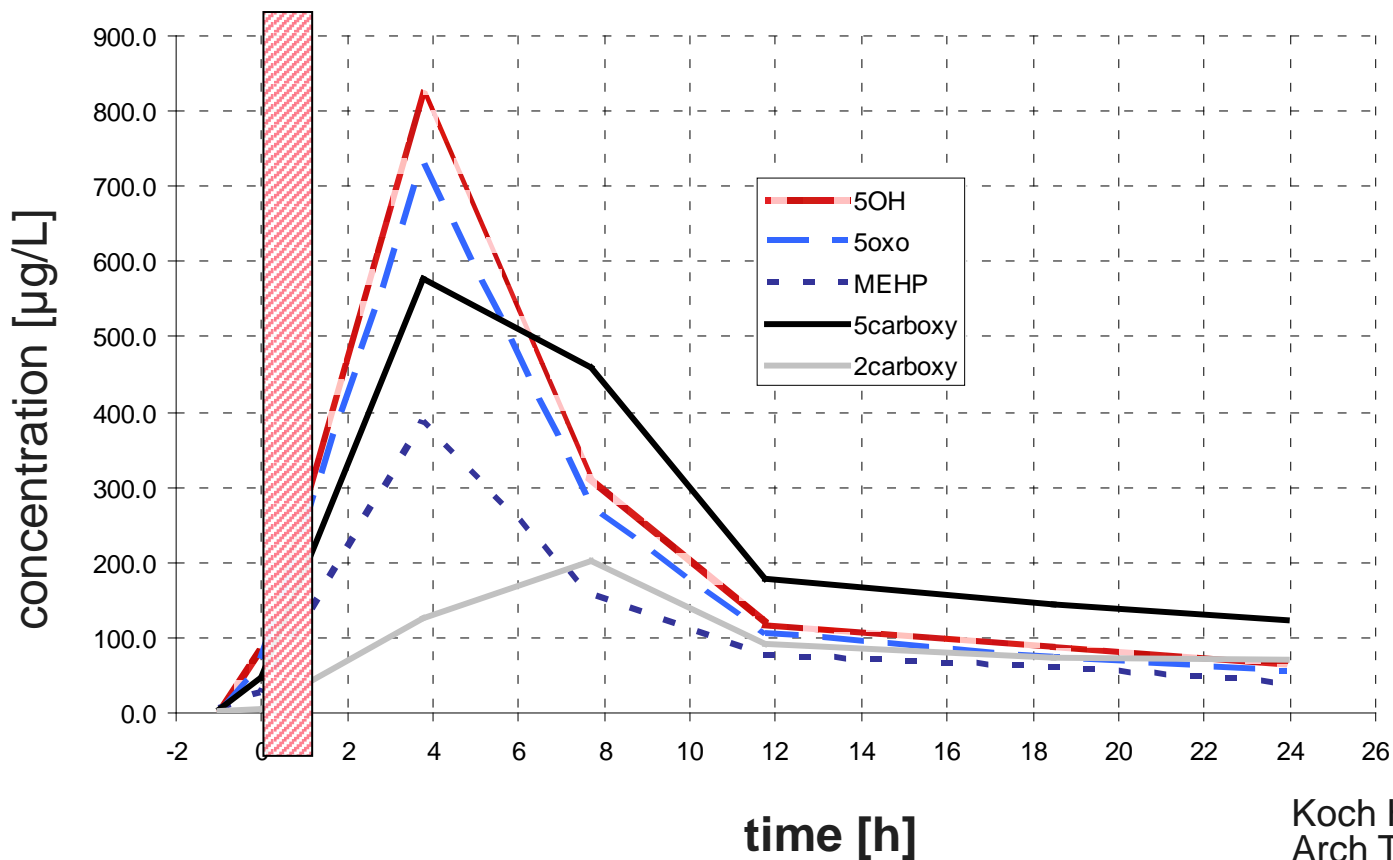
Göen et al. (2011)
IJHEH 215(1):36-45.

Koch et al. (in preparation)
IJHEH

Apheresis / Platelet Donors

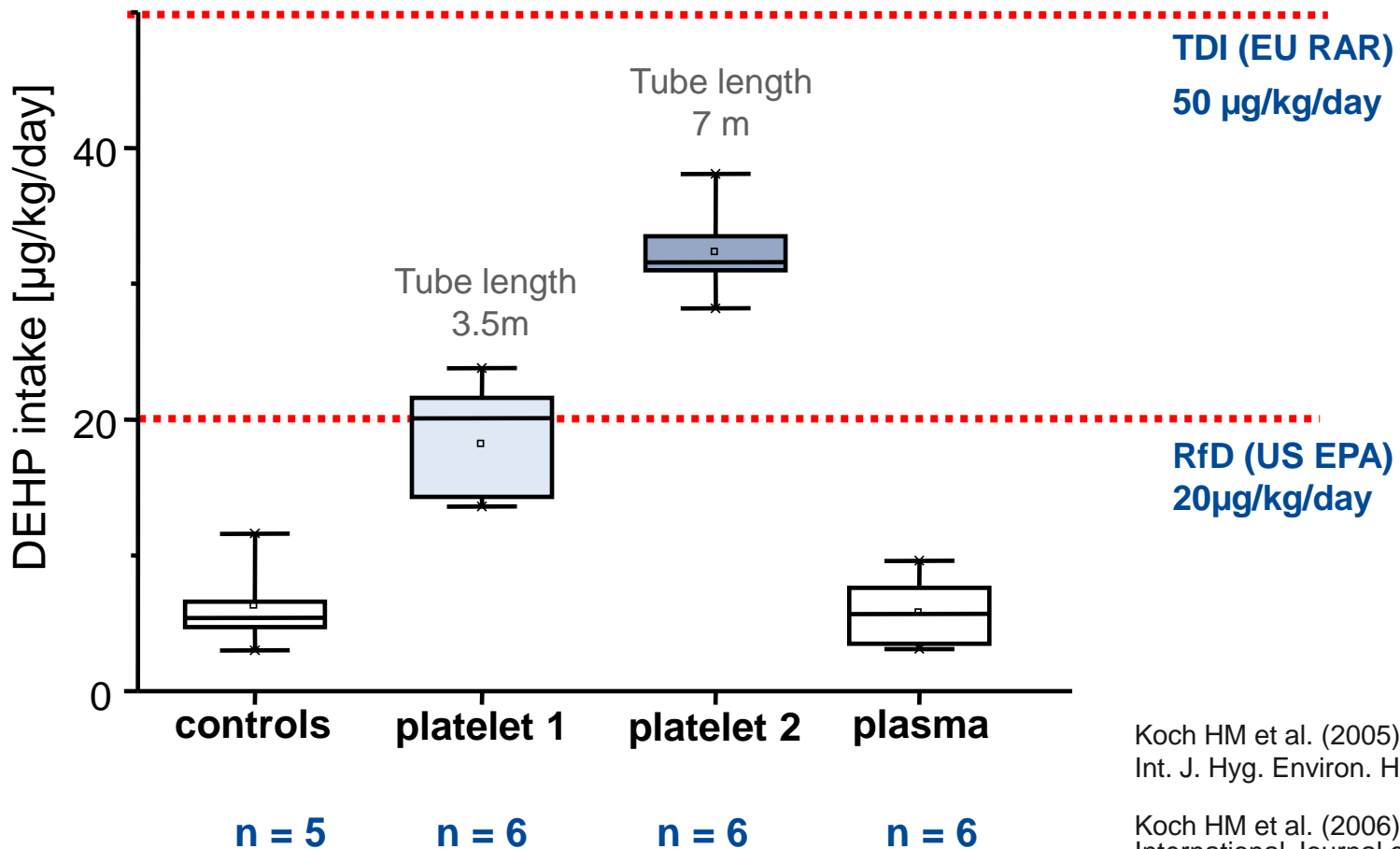


Apheresis / Platelet Donors



Koch HM et al (2006)
Arch Toxicol 79(12), 689-693.

Apheresis / Platelet Donors



Koch HM et al. (2005)
Int. J. Hyg. Environ. Health 208(6), 489-498.

Koch HM et al. (2006)
International Journal of Andrology 29, 155-165.

DEHP in NICUs / preterm infants

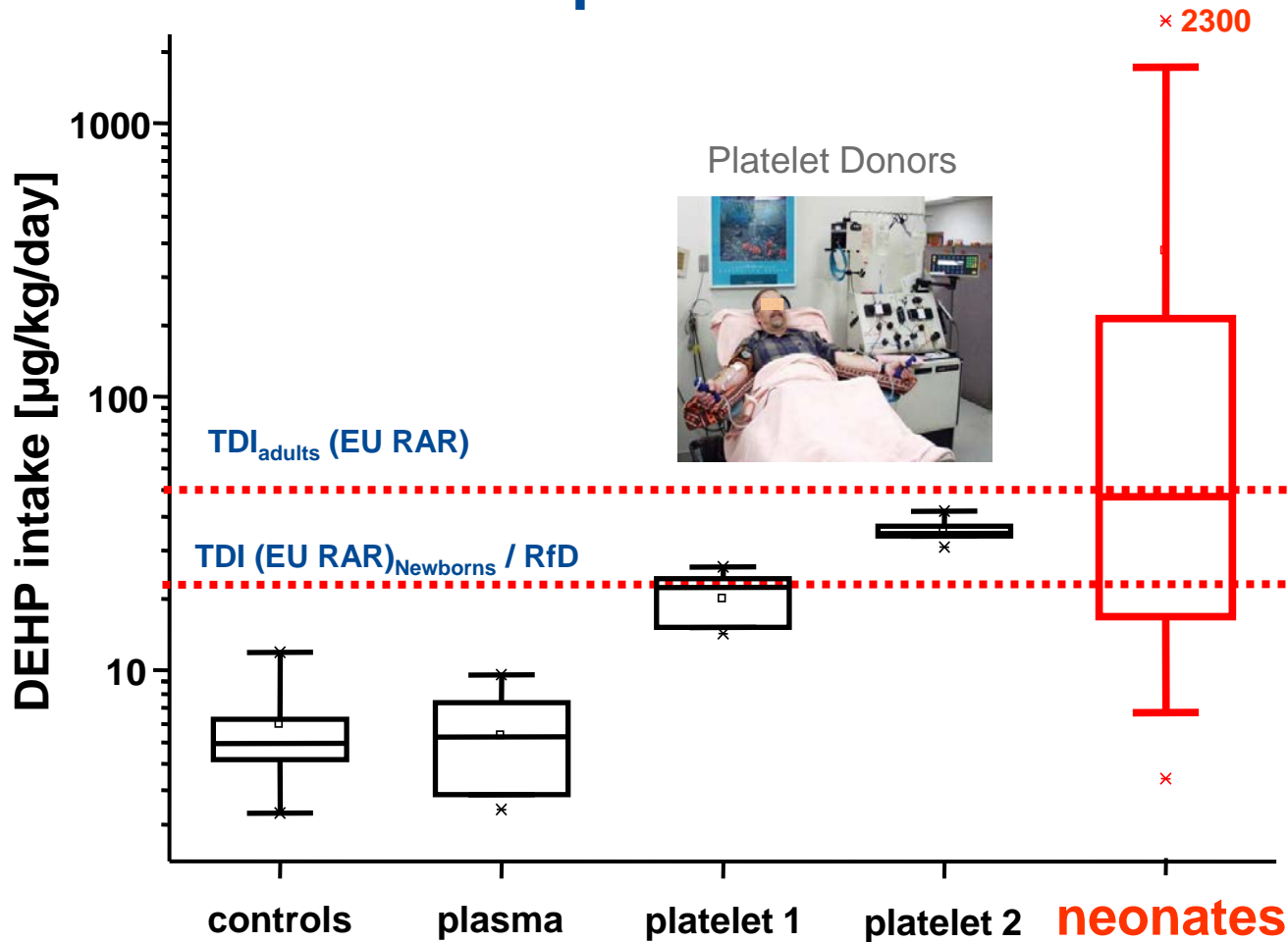


Infants	:	46 (premature: 42)
Gestational age	:	25 - 40 weeks
Age	:	2 - 31 days
Weight of birth	:	490 – 4200g (mean: 1976g)
Gender	:	26 male, 20 female

Fusch G et al. (2005)
Z Geburtshilfe Neonatol 209 (S1), V20

Koch HM et al. (2006)
Int J Andrology 29(1), 155-165.

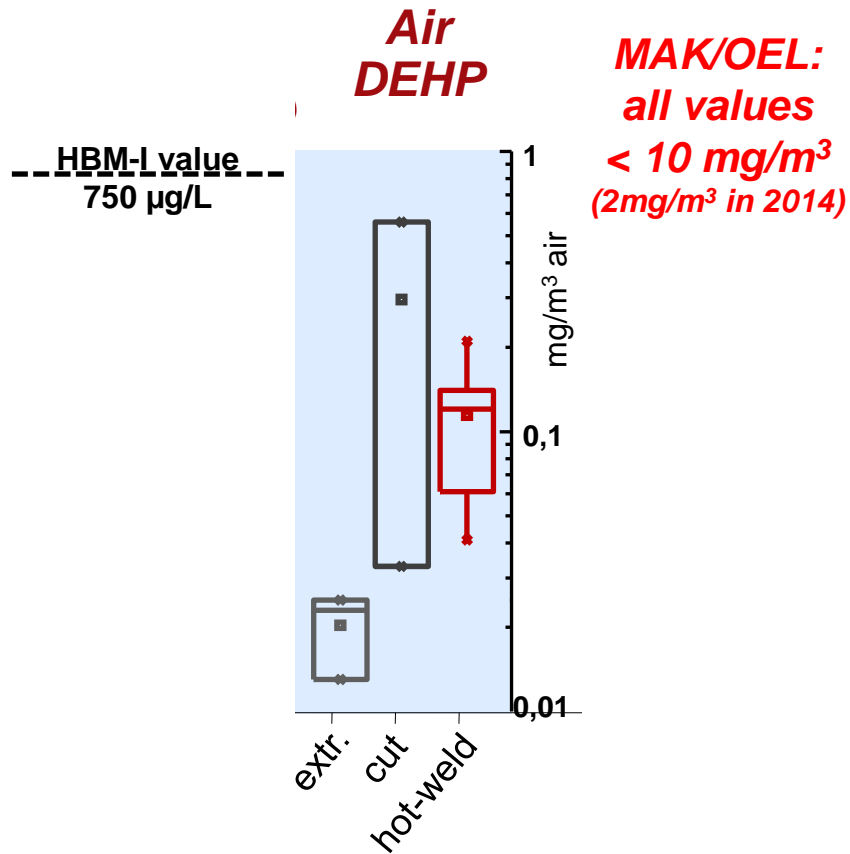
DEHP in NICUs / preterm infants



Fusch G et al. (2005)
Z Geburtshilfe Neonatol 209 (S1), V20

Koch HM et al. (2006)
Int J Andrology 29(1), 155-165.

Production of flexible tubes and hoses

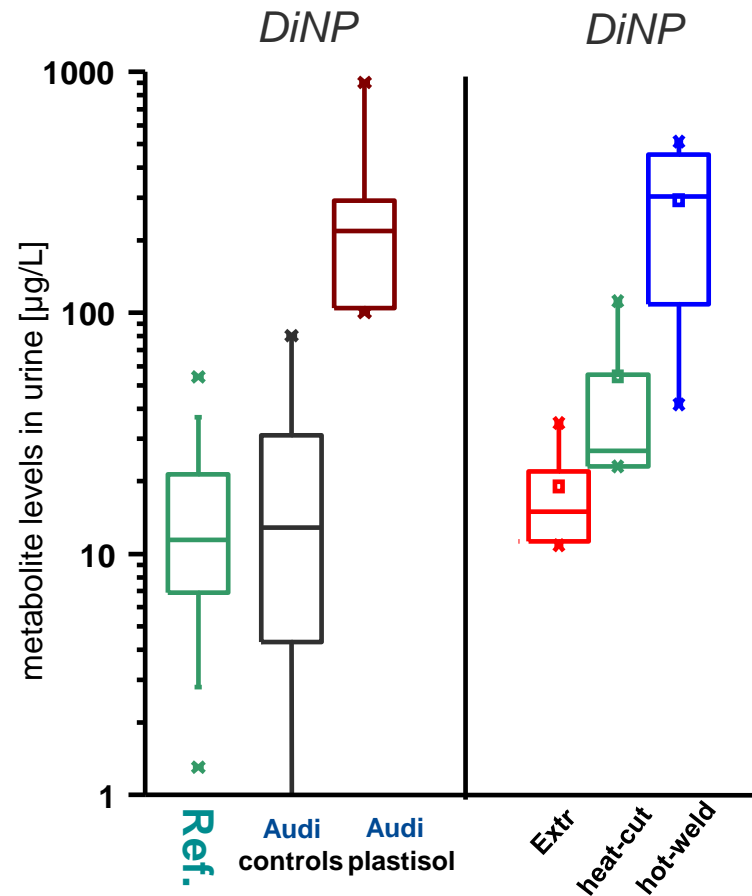
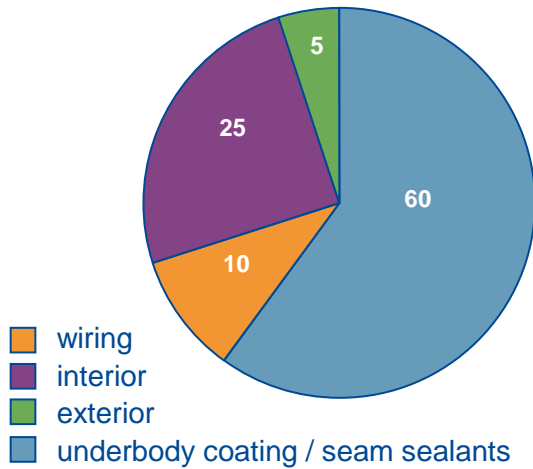


Wire reinforced hoses (hot-welding)

Plastisol/Underbody Coating

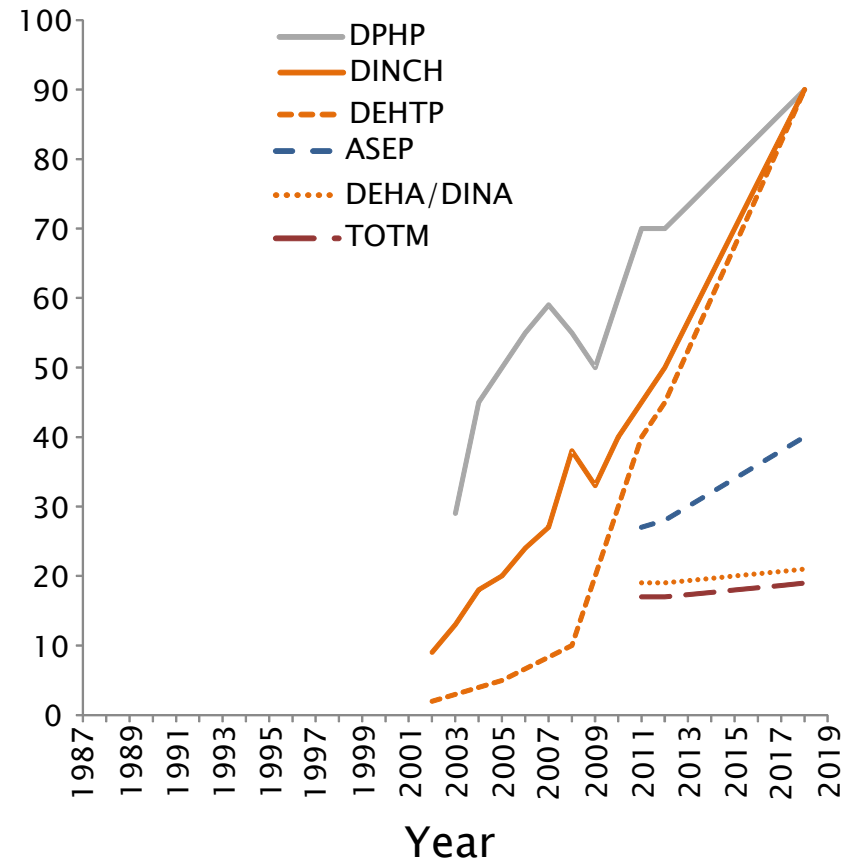
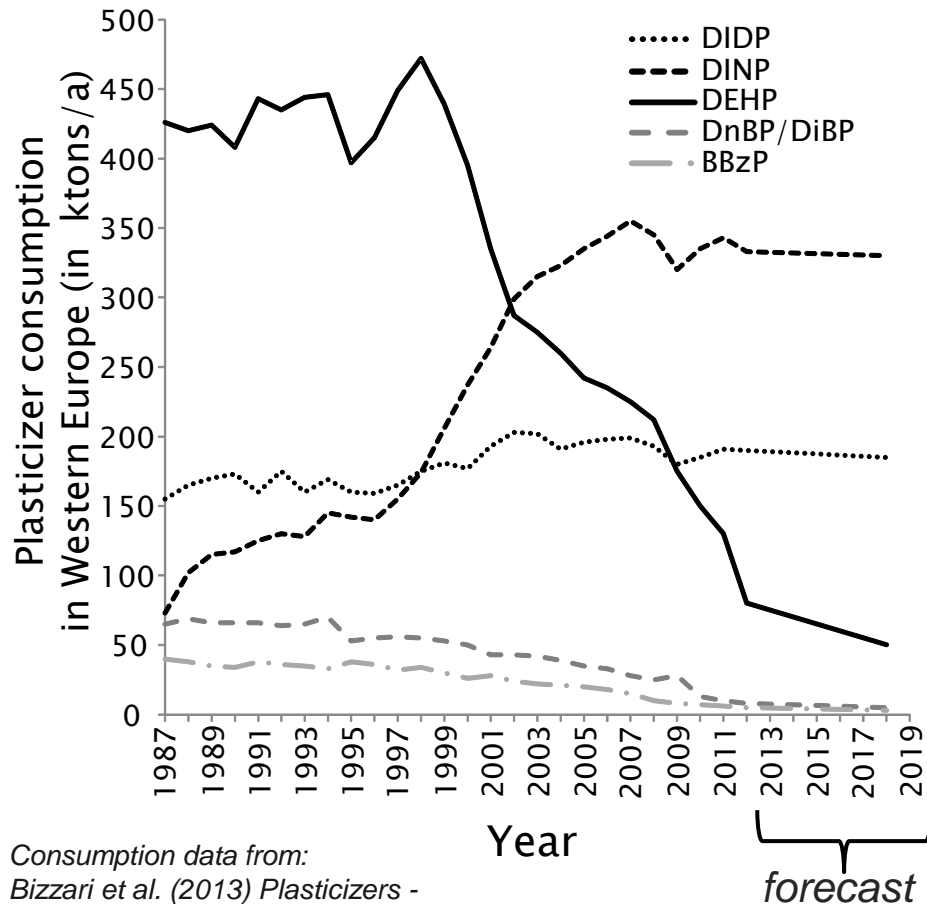


PVC/Phthalates in automobiles

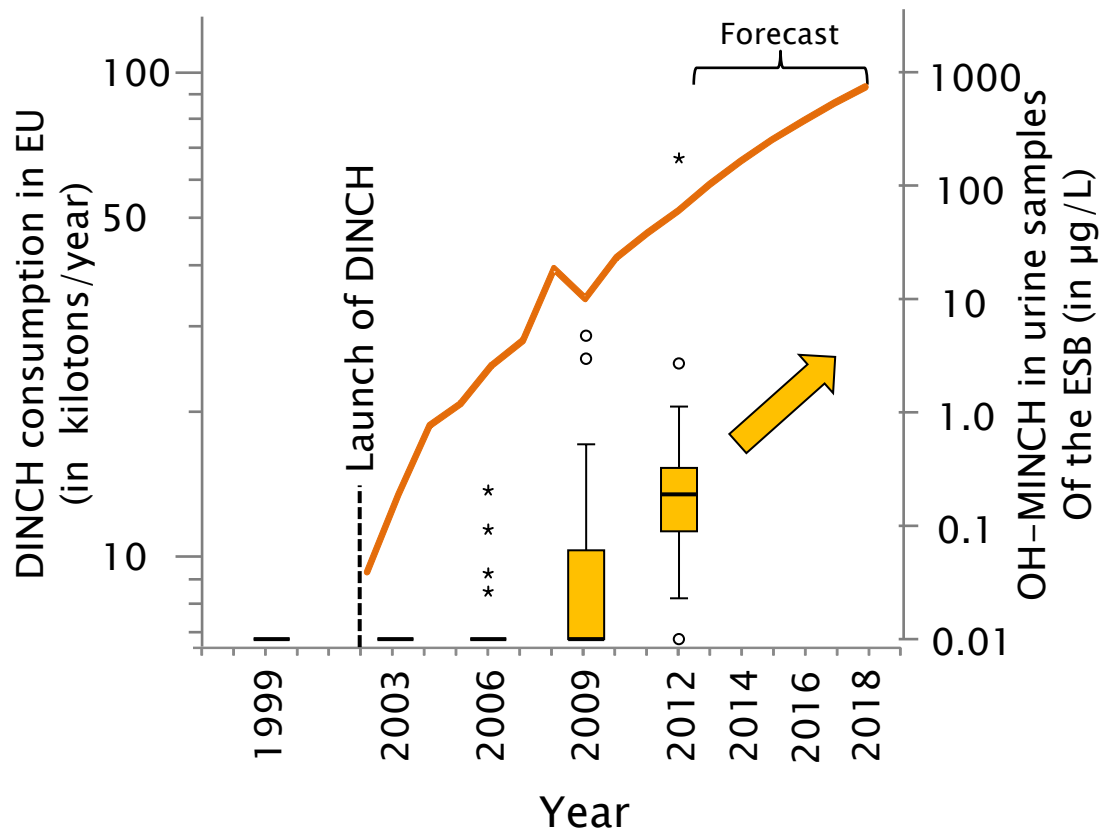


Koch HM et al. (2012)
Toxicol Lett. 213(1):100-6.

Rapidly changing phthalate/plasticiser market



Hexamoll® DINCH®

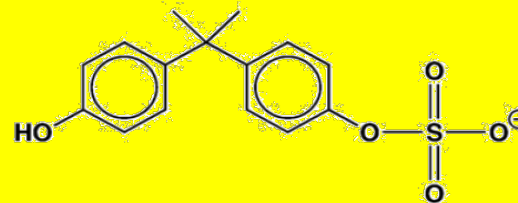
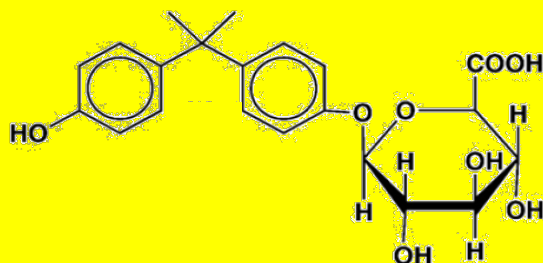
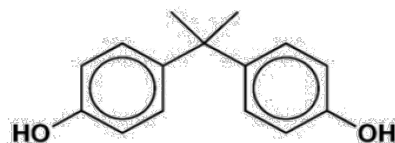


Exposure to DINCH is omnipresent and increasing

But:
Current exposure far below TDI / HBM I

Koch et al. (2013) Arch Tox 87, 799–806.
Schütze et al. (2014) IJHEH 217, 421-426.
Schütze et al. (2015) Chemosphere 128, 216–224

Bisphenol A (BPA) : Biomarker



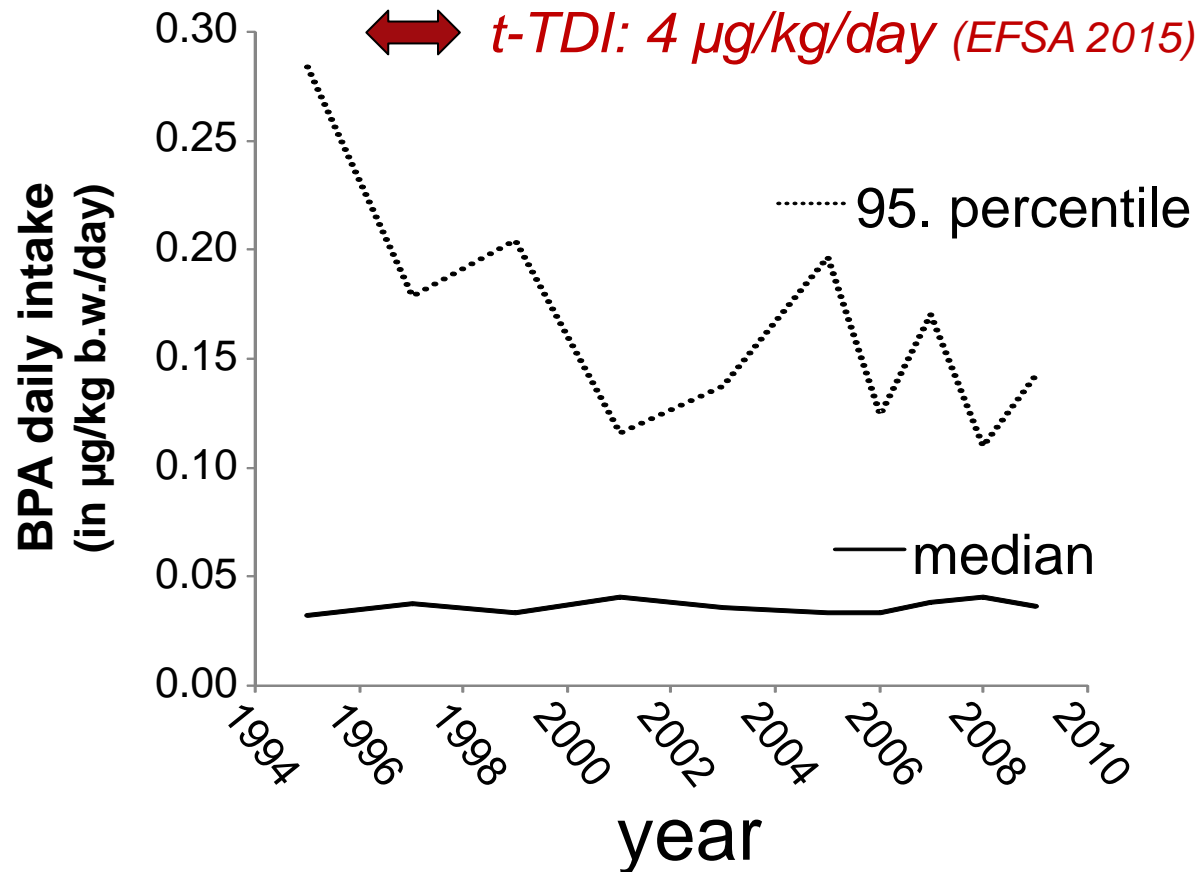
< 24 h

- fast conjugation (close to 100%)
- fast elimination in urine

- blood levels very low
- contamination issues with BPA an blood

*Calafat AM et al. (2015)
Environ Health Perspect. 123 (7), A166-A168*

Bisphenol A (BPA) : Population Data



Comparable data from
US (NHANES)
and Canada (CHMS)

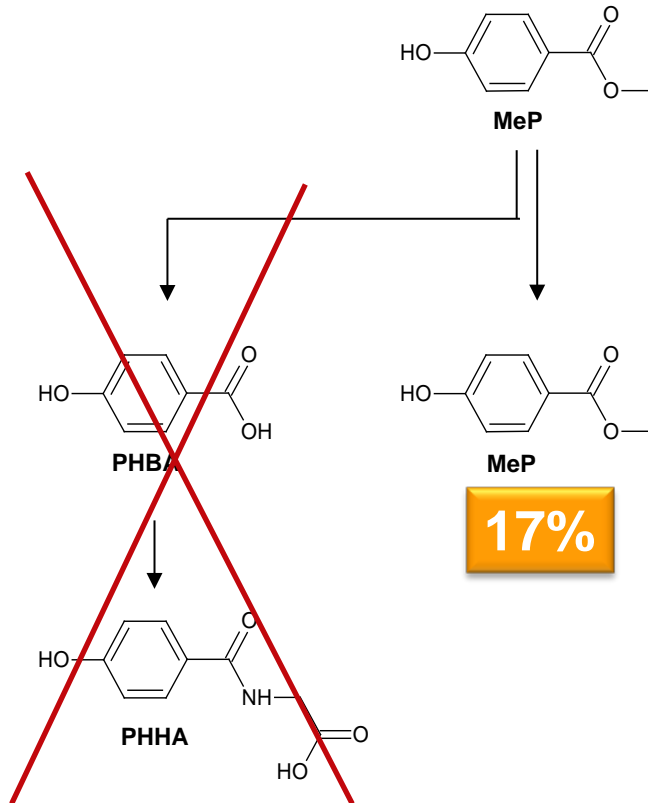
Koch HM et al. (2012)
J Expo Sci Env Epidem 22: 610–616.

Covaci A et al. (2015)
Environmental Research 141: 77-85.

Christensen KL et al. (2012)
Environment International 50: 7-14.

HBM-Commission (2012)
Bundesgesundheitsbl 55:1215–1231.

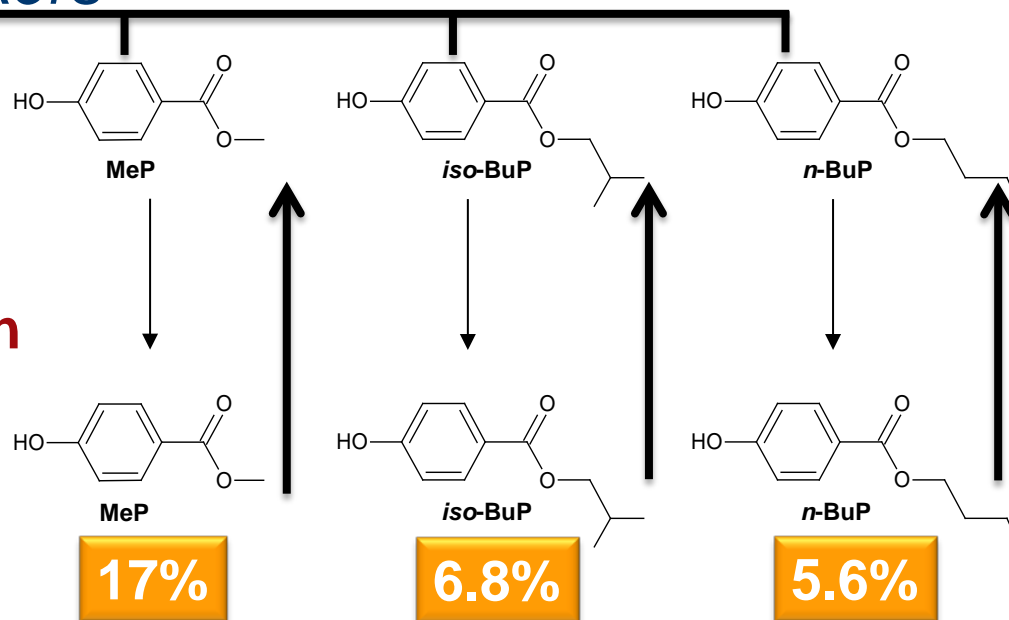
Parabens : Biomarkers



Moos RK et al (e-pub 2015) Arch Tox

Parabens : Biomarkers

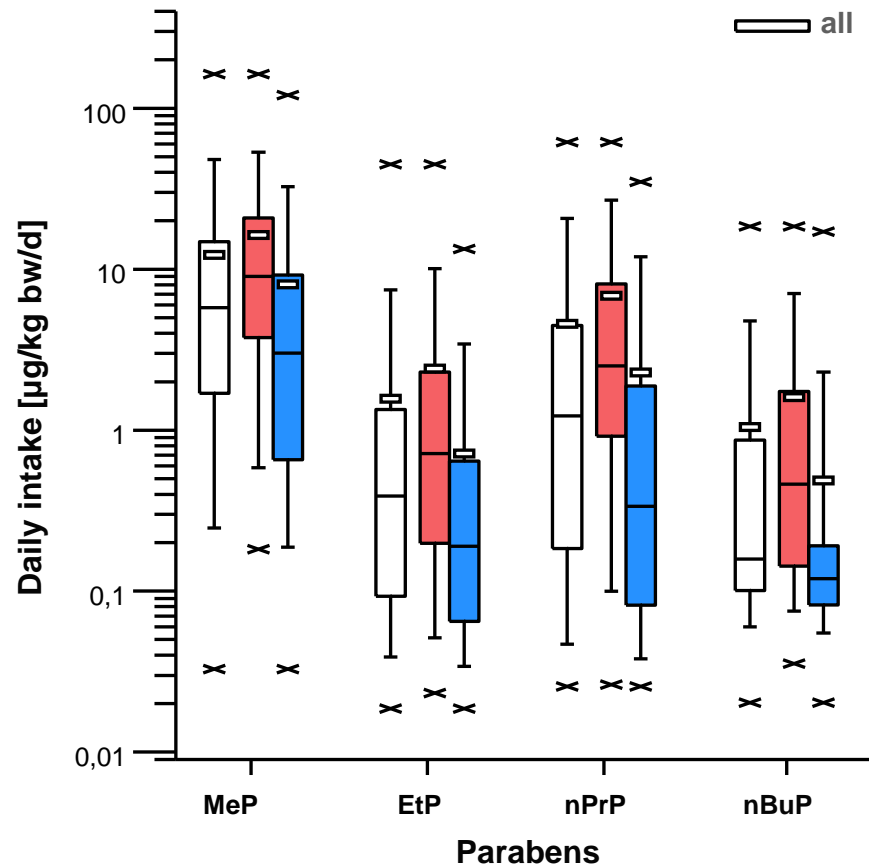
- **dose extrapolation**
(daily intakes)
- **risk assessment**



Urinary metabolite excretion factors

Moos RK et al (e-pub 2015) Arch Tox

Parabens : Population Data



Moos RK et al. (submitted)

J Expo Sci Environ Epidemiol.

Moos RK et al. (e-pub 2015)

Arch Toxicology.

Moos RK et al. (2015)

Int J Hyg Environ Health 218: 666-674.

Koch HM et al. (2014)

Tox Letters 231: 261-269.



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Internal burden caused by endocrine disruptors present in the environment and at the workplace

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INRS/ISSA 2016 SYMPOSIUM:

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ENDOCRINE DISRUPTORS AND SENSITISING SUBSTANCES**

01-03 June 2016 – Paris, France

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