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HAMNER INSTITUTES FOR HEALTH SCIENCES

# Science Question 2 – Considering phthalate syndrome effects as a single outcome

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# “Phthalate syndrome”

- “Phthalate syndrome”
  - Mainly classified by antiandrogen effects
    - Leads back to human relevance
  - Is misleading
    - Is this truly a phthalate-specific phenomenon?
    - Not all phthalates cause these effects
- Cumulative risk assessment
  - For chemicals with similar modes of action – how do we perform a cumulative risk assessment?
- Must account for differences in **dose** (kinetics) and **potency** (pharmacodynamics)
  - Using phthalate antiandrogenicity as a prototype...

- R2C in vitro rat cell assay mimics in vivo antiandrogenicity of phthalates

Balbuena et al. *Toxicol In Vitro*. 2013, 27(6):1711

- Use in vitro assay to determine relative potency factor (MBP equivalent) for all relevant metabolites

$$RPF = \frac{IC_{50}(MBP)}{IC_{50}(\text{test phthalate})} \longrightarrow \frac{IC_{50}(MBP)}{IC_{50}(MEHP)} = \frac{2.98}{5.64} = 0.53 = RPF_{(MEHP)}$$

- Use NHANES data (2005) to estimate exposure to all relevant metabolites

Balbuena, P., Campbell, J, Clewell, H.J, Clewell, R.A. 2013). Estimation of Cumulative Risk from Exposure to Phthalates Using NHANES Exposure Data and an *In Vitro* Potency Assay. *The Toxicologist*. 132(1). 2461.

# Estimating Cumulative Phthalate Risk

COMPOUND	Percentile	Conc. in Urine ( $\mu\text{g/g}$ creatinine)	Daily Intake ( $\mu\text{Mol/d}$ )	RPF	MBP equivalent Intake ( $\mu\text{Mol/day}$ )	DBP Equivalent Intake ( $\text{mg/kg/day}$ )	% Total Risk directly from DBP	MoE vs RfD = 0.1 ( $\text{mg/kg/d}$ )
Mono butyl phthalate (MBP)	50	21.5	0.1016	1	0.1016			
	95	91.5	0.4323	1	0.4323			
Mono-2-ethylhexyl phthalate (MEHP)	50	4.43	0.0167	0.53	0.0089			
	95	35.1	0.1324	0.53	0.0702			
5-hydroxy MEHP	50	17.6	0.0628	0.194	0.0122			
	95	160	0.5708	0.194	0.1107			
5-oxo MEHP	50	12.5	0.0449	0.029	0.0013			
	95	92.3	0.3315	0.029	0.0096			
Mono-ethyl phthalate (MEP)	50	171	0.9255	0.0145	0.0134			
	95	1430	7.7397	0.0145	0.1122			
Mono-methyl phthalate (MMP)	50	1.45	0.0085	0.0042	0.0000			
	95	10	0.0583	0.0042	0.0002			
Mono (2-octyl) phthalate (MnOP)	50	< LOD		0.125	0.0000			
	95	3.1	0.0117	0.125	0.0015			
Mono benzyl phthalate (MBzP)	50	15.1	0.0714	0.109	0.0078			
	95	95.8	0.4531	0.109	0.0494			
<b>Total:</b>	<b>50<sup>th</sup> %ile</b>				<b>0.1452</b>	<b>0.00067</b>	<b>70%</b>	<b>148</b>
	<b>95<sup>th</sup> %ile</b>				<b>0.7861</b>	<b>0.00365</b>	<b>55%</b>	<b>28</b>

Balbuena, al. (2013). The Toxicologist. 132(1). 2461.