



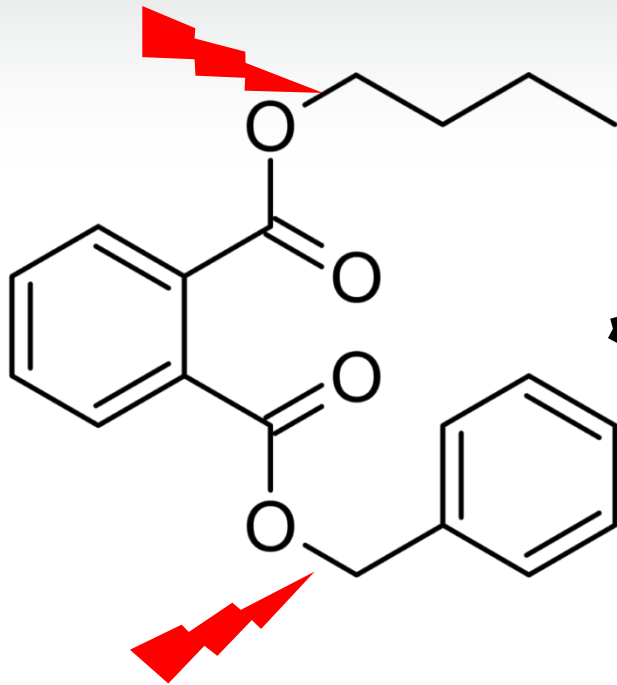
Science Question 4 – Mechanistic data

Rebecca Clewell, PhD
Associate Director
Institute for Chemical Safety Sciences
The Hamner Institutes for Health Sciences

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ACC High Phthalate Panel

Butylbenzyl phthalate metabolism

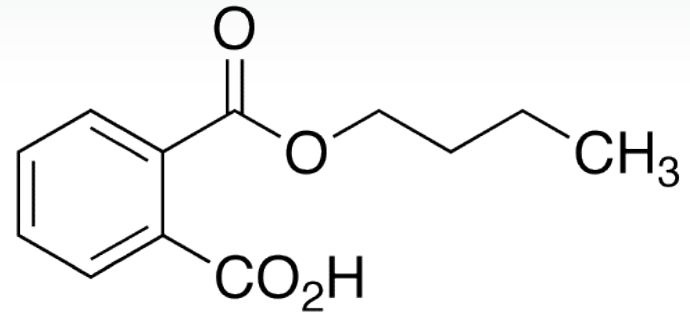
Butylbenzyl phthalate
(BBP)



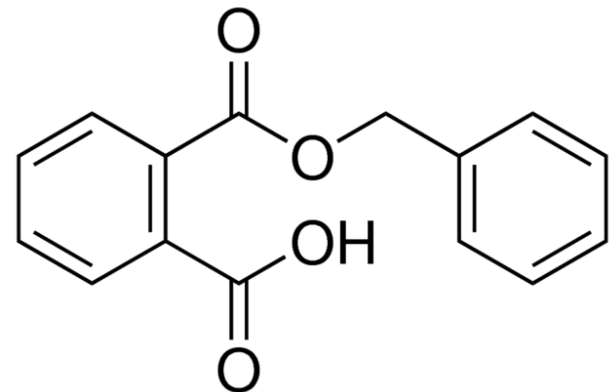
Intestinal
lipases

ACTIVE METABOLITES:

Monobutyl phthalate
(MBP)

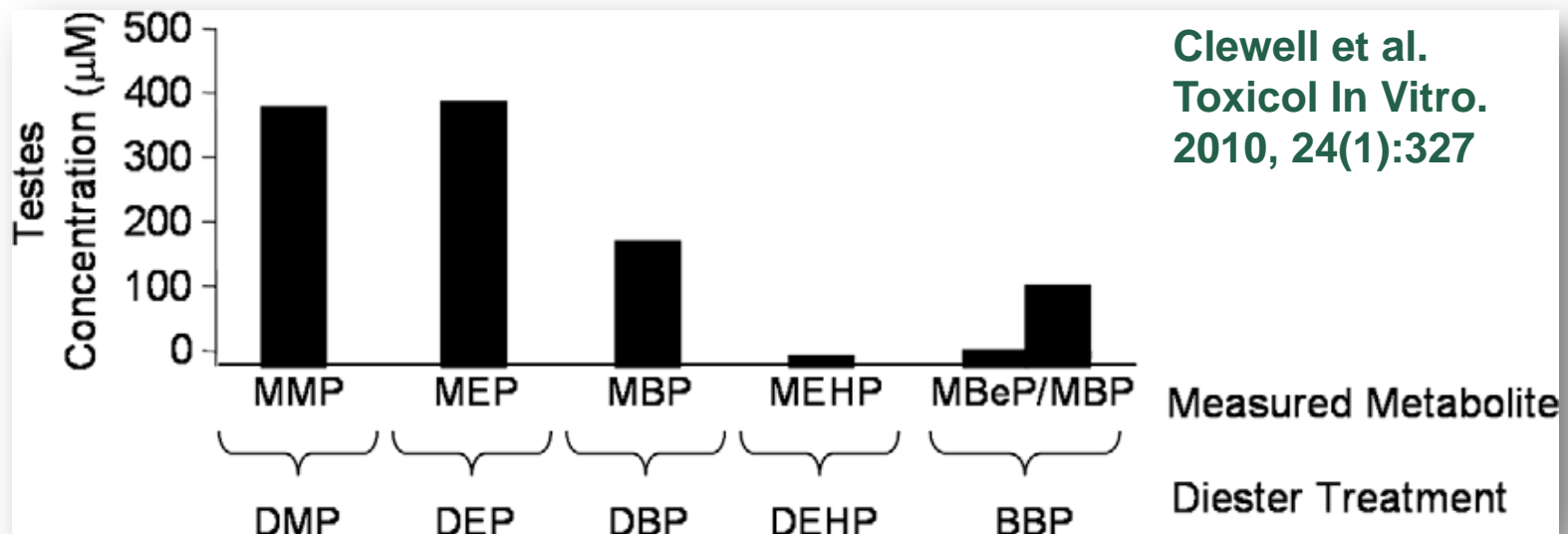


Monobenzyl phthalate
(MBeP)



Butylbenzyl phthalate metabolism

- Human metabolism favors monobenzyl phthalate
 - 6% excreted as MBP vs 78% as MBeP (Anderson et al., 2001)
 - Takahara et al. Biol Pharm Bull. 2014;37(4):703
- Rat metabolism favors monobutyl phthalate
 - 5:1 MBP vs MBeP



Measured monoester concentrations in the fetal testes from dams given daily oral doses of diester from GD 12–19.

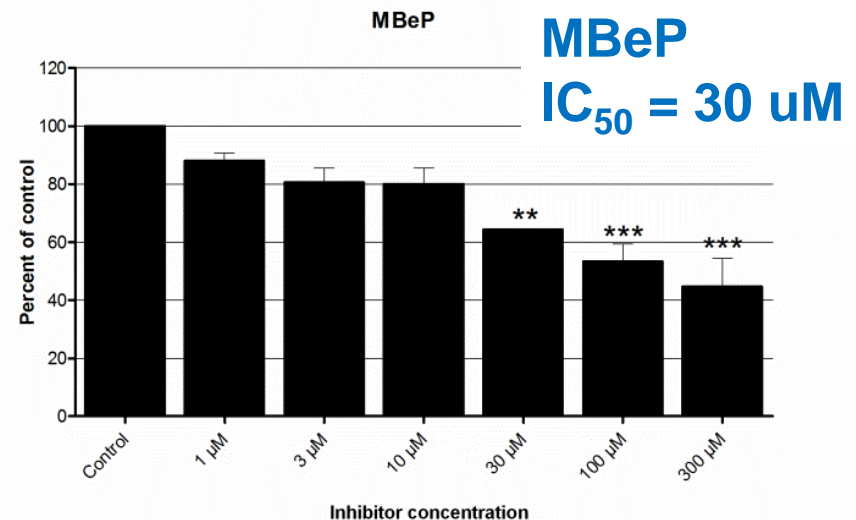
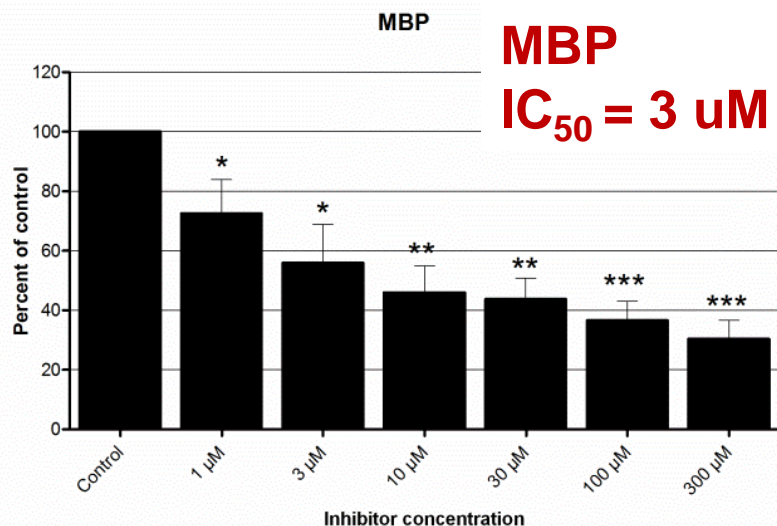
Testes were collected 2 h after final dose. Bars represent mean + SD from 3 fetuses of 2–3 dams.

Metabolite antiandrogenic activity

- R2C rat cell in vitro assay mimics in vivo antiandrogenicity

TESTOSTERONE INHIBITION <i>IN VITRO</i> VS. <i>IN VIVO</i>		
	IC ₅₀ (μM)	
	<i>In vivo</i> (fetal rat testes) ^a	<i>In vitro</i> (R2Cs)
MBP	3	3
MEHP	7	6
MEP	>306 ^b	205

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



- Kinetic and potency data indicate that in vivo BBP studies overestimate human risk

– Majority of effect is from MBP, which is a minor metabolite in the human

Data to be added to BBP mechanistic data table

- Clewell RA, Campbell JL, Ross SM, Gaido KW, Clewell HJ 3rd, Andersen ME. (2010). Assessing the relevance of in vitro measures of phthalate inhibition of steroidogenesis for in vivo response. *Toxicol In Vitro*. 2010 Feb;24(1):327-34. doi: 10.1016/j.tiv.2009.08.003.
- Balbuena P, Campbell J Jr, Clewell HJ 3rd, Clewell RA. (2013). Evaluation of a predictive in vitro Leydig cell assay for anti-androgenicity of phthalate esters in the rat. *Toxicol In Vitro*. 2013 Sep;27(6):1711-8. doi: 10.1016/j.tiv.2013.03.015.