Consideration of Non-Oral Route of Administration

BPA Metabolism & Route of Administration

- Unconjugated ("free") BPA biologically active form
- Oral studies considered most relevant for human risks
- BPA glucuronidated in gut and liver
- Adult rodents metabolize BPA more quickly following oral administration compared to subcutaneous (sc) injection
  - Limits utility of sc injection studies in adults
- Neonatal rats metabolize BPA less efficiently than adults at a given administered dose
  - Immaturity of relevant enzyme systems
- Evidence for immaturity of relevant enzymes systems in human fetuses and infants

NTP Consideration of SC Administration Studies

- The NTP considered studies that used sc injection to *neonatal* animals useful in the evaluation
- SC route of administration to adult animals - including pregnant dams – was used only for identifying potential hazards

Age-Dependent Metabolism in Rats

- Reduced detection and liver microsomal activity in fetuses and young animals of the principle UDP-glucuronosyltransferase (UGT2B1) that metabolizes BPA in rats (Matsumoto *et al.* 2002)
- Neonatal rats have higher concentrations of unconjugated BPA than adults at the same oral dose (Domoradzki *et al.* 2004)

	PND 4		PND 7		PND 21		Adult	
	M	F	M	F	M	F	M	F
10 mg/kg								
Cmax (μg/g plasma)	48.3	10.2	1.1	1.4	0.2	0.2	0.024	0.063
1 mg/kg								
Cmax (μg/g plasma)	0.03	0.06	0.04	0.08	0.005	0.006	ND	ND

2013-times higher at PND 4

162-times higher at PND 4

ND = Not determined

Modified Table 2 from: Domoradzki JY *et al.* 2004. Age and dose dependency of the pharmacokinetics and metabolism of bisphenol A in neonatal Sprague-Dawley rats following oral administration. Toxicol Sci 77(2):230-242.

Age-Dependent Metabolism in Rats

- Neonatal animals have a longer half-life (Domoradzki *et al.* 2004)

	PND 4		PND 7		PND 21		Adult	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**
10 mg/kg								
Half-life (h)	17[a]	6.7	11.4	8.5	4.3	6.6	<< 1	<<1
1 mg/kg								
Half-life (h)	7.2	7.3	21.8[a]	8.8	ND	ND	ND	ND

ND = Not determined

[a] Half-life determinations were based on pooled plasma samples through 24 h and, therefore, these estimates may not be reliable

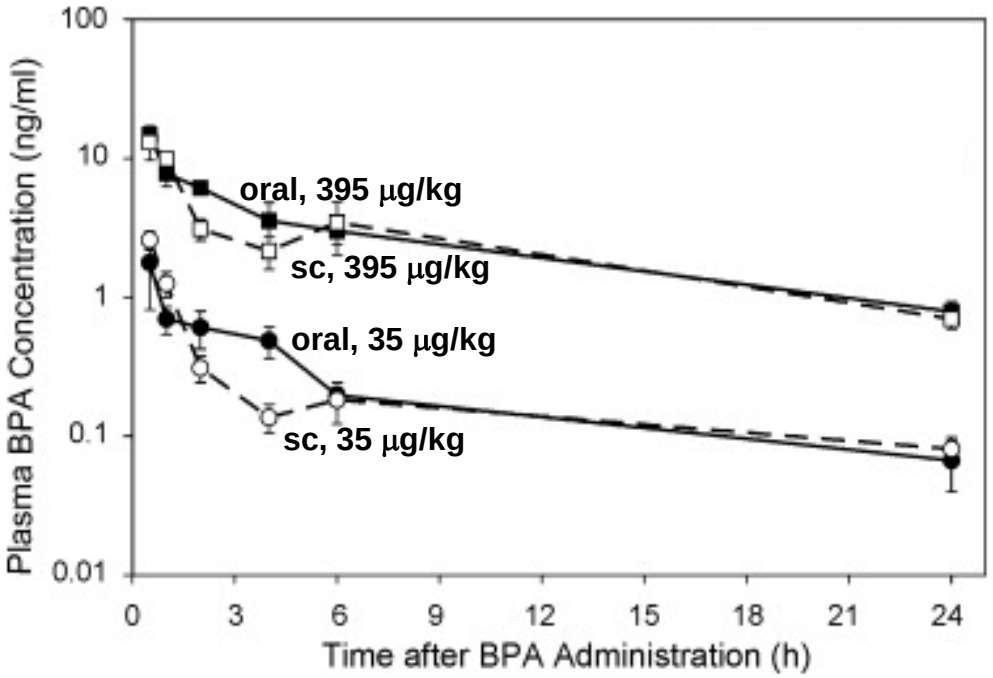
Modified Table 2 from: Domoradzki JY *et al*. 2004. Age and dose dependency of the pharmacokinetics and metabolism of bisphenol A in neonatal Sprague-Dawley rats following oral administration. Toxicol Sci 77(2):230-242.

Age-Dependent Metabolism in Rats

- Neonatal rats do metabolize BPA
  - More efficient metabolism at lower doses (Domoradzki *et al.* 2004)
- Uncertainty on whether the degree of metabolism in neonatal animals is “sufficient” at doses relevant to human exposure
- Less efficient first pass metabolism in neonates suggests that metabolic differences due to route of administration may be less apparent during this life stage

Impact of Route of Administration in Neonatal Mice

- Taylor *et al.* (2008) treated neonatal female mice with low doses of BPA by oral and sc routes of administration
- Concentrations of "free" BPA (radioactivity attributed to unconjugated BPA) were similar



Modified Figure 2 from: Taylor JA *et al*. (2008) *Reprod Toxicol.* No effect of route of exposure (oral; subcutaneous injection) on plasma bisphenol A throughout 24h after administration in neonatal female mice. 25(2): 169-176

Draft NTP Brief Compared to Other Evaluations

- Non-oral route of administration assumed to produce "irrelevantly" high concentrations of unconjugated BPA compared to oral dosing
  - The CERHR Expert Panel considered sc administration studies to be of "limited utility" if otherwise well-conducted
- NTP considers that sc injection studies to neonates are useful
  - Based on Domoradzki *et al.* 2004 and supported by Taylor *et al*. 2008

Questions and Discussion