Question 3: Biological relevant level of change in fetal testicular testosterone

Comment: IRIS discussion on the significance of fetal testicular testosterone levels should expand to include consideration of not just the biologically relevant *level of change* but the *biologically relevant species* in which BBP or its metabolites have been observed to produce a change in fetal testicular hormone function.

Table 3-19 of Preliminary Materials for IRIS Review of BBP

8 studies – all rat studies

All 8 studies showed decrements in some reproductive parameters in offspring

2 looked at fetal testicular testosterone (reduced)

1 looked at young adult serum testosterone (increased)

1 looked at adult and weanling serum testosterone (reduced)

IRIS Tables 3-18 through 3-25 present studies showing changes in reproductive targets as a result of BBP exposure, either gestational or transgenerational

30 studies are referenced: 2 were mouse studies; all others rat studies

Mouse studies show less sensitivity to BBP treatment that rats

Mouse studies were NTP (1990) and Saillenfait, et al., 2003.

NTP 1990 study was a segment II dietary study in CD-1 mice.

Maternal and developmental NOAEL: = 182 mg/kg/day

Doses of 910 and 2330 mg/kg/day produced maternal toxicity (↓weight gain, 15% and 29% and relative organ wt changes)

Embryofetal effects, ↑resorptions and fetal death, external and skeletal malformations, exencephaly, short tail, cardiovascular defects, rib defects, ↓fetal weight.

Saillenfait Mice – oral: 280-1690 mg/kg/day

The LOAEL = 560mg/kg/day and reported exencephaly, anal atresia and absent or vestigial tail

Also a rabbit seg II study by Monsanto, 1978.

0, 3 and 10 mg/kg/da No effects, including no maternal toxicity.

Ratio of monoester formed following oral dosing

	MBuP	MBzP
Rat	3	1
Human	1	3

Anderson, WAC, et al., (2001) Food Additives and Contaminants, 18:12, 1068-1074

Eigenberg, DA, et al., (1986) J Toxicol Env Health, 17, 445-456

Nativelle, C., et al., (1999) Food Chem Toxicol, 37, 905-917

Last Thoughts

We are aware of data indicating that male reproductive tract developmental effects mediated by fetal testicular testosterone in rats treated with BBP are likely to be species-dependent and that this effect has not been seen in mouse or human models.

We are also aware of epidemiological studies focusing on BBP exposure and adverse health outcomes, for which results are inconsistent.

Taken together, the level of consistency in studies in different settings using different methods may not be sufficient to establish the biologically relevant level of change in fetal testicular testosterone.