

Table 3. Phenobarbital Dose-Response and Time Concordance – Male C57BL/10J Mice

Key Events / Associative Events	Dietary Dose Levels (ppm) of Phenobarbital and Effects – Male C57BL/10J Mice ^a				
	100 (11)	200 (22)	400 (44)	700 (78)	1000 (113)
Feeding Level (ppm in diet) ^a (= mg/kg/day) ^a	100 (11)	200 (22)	400 (44)	700 (78)	1000 (113)
AE2 - Hepatocyte hypertrophy (Day 29) ^c	-	+	+	+	+
AE3 – Relative Liver wt. (Day 29) ^a	-	+ (1.2)	+ (1.3)	+ (1.3)	+ (1.6)
KE2: increased cell proliferation (Day 3) (Day 8) (Day 15) (Day 29)	- - - -	- - - -	- - - -	- + (11.3) - -	+ (6.8) + (8.9) +(3.6) -
KE3: clonal expansion, increased altered foci (99 weeks) – eosinophilic, clear cell. ^a	ND	-	ND	ND	+
AO: Liver adenomas, carcinomas (99 weeks) ^a	ND	-	ND	ND	+
Additional Data – C57BL/6J strain ^b MIE: CAR Activation (Immediate – Day 4) ^b				(80 mg/kg/day)	
via KE1: Altered gene expression secondary to CAR activation (Day 4) <i>Cyp2b10</i>	ND	ND	ND	+ (100)	ND
<i>Ki67</i>	ND	ND	ND	+ (6.2)	ND
<i>Tsc22</i>	ND	ND	ND	+ (-1.9)	ND
via AE1 – PROD activity (Day 4)	ND	ND	ND	+ (240)	ND

Legend (comparative effects vs. untreated controls):

+ Positive; - Negative; ± Equivocal. ND Not determined. Values in parentheses are fold-change vs. controls.

^aUnless otherwise indicated, data are from a short-term study (3, 8, 15 and 29 days) or a 99-week dietary study (200 and 1000 ppm in diet) in C57BL/10J male mice treated with PB (Jones et al., 2009). Achieved dose levels (mg/kg/day) were stated in the manuscript for 99-week treatment groups (200 and 1000 ppm), and were estimated for other groups (100, 400, 700 ppm) based on the average dose level ratio ($[\text{ppm}]/[\text{mg/kg/day}] = 9$) for 200 and 1000 ppm groups.

^bStudy in C57BL/6J wild type mice treated with PB (80 mg/kg/day PB, ip x 4 days, in Ross et al., 2010). The C57BL/6J and C57BL/10J mice are closely related genetically (Doran, 2016)

^cIn Jones et al. (2009), liver enlargement and centrilobular hepatocyte hypertrophy were observed at 200 – 1000 ppm in diet from Days 3 – 29, but the actual incidence data were not reported.