

Table 2. Phenobarbital Dose-Response and Time Concordance – Male CD-1 Mice:

Key Events / Associative Events ^a	Dose Levels (mg/kg/day) of Phenobarbital and Effects – Male CD-1 Mice ^a				
	0.15	1.5	10-15 ^b	75	150
MIE: CAR Activation (Day 2)					
via KE1 – <i>Cyp2b10</i> mRNA (RT-PCR)	-	-	+ (65)	+ (168)	+ (522)
via KE1 - <i>Ki67</i> mRNA ^c	-	-	-	+ (7.4)	+ (14.4)
via KE1 - <i>Tsc22</i> mRNA ^c	-	-	+ (-1.8)	+ (-1.7)	+ (-1.8)
via AE1 – PROD activity (Day 2)	-	+ (1.6)	+ (4.1)	+ (6.9)	+ (8.4)
via AE2 – Hepatocyte hypertrophy (Day7)	-	-	+ (3/4)	+ (4/4)	+ (4/4)
via AE3 – Relative Liver wt. (Day 7)	-	-	-	+ (1.2)	+ (1.5)
KE2: increased cell prolif., BrdU (Day 2)	-	-	+ (2.3)	+ (4.0)	+ (8.1)
Increased cell prolif., BrdU (Day 7)	-	-	-	+ (4.0)	+ (6.5)
KE2: increased cell proliferation, (Day 2):	-	-	-	+ (2/4)	+ (4/4)
Seen as increased mitotic figures (Day 7):	-	-	+ (1/4)	+ (2/4)	-
KE3: clonal expansion, increased altered foci (Months) ^d	ND	ND	ND ^d	ND ^d	ND ^d
AO: Liver adenomas, carcinomas (18 – 24 Months) in CD-1 mice ^e	ND	ND	- ^e	+ ^e	+ ^e

Legend (comparative effects vs. untreated controls):

+ Positive; - Negative; ± Equivocal. ND Not determined. Values in parentheses are fold-change vs. control, or incidence per group for histopathology findings (n=4).

^aUnless otherwise indicated, data are obtained from a large dose-response study in male CD-1 mice exposed via the diet for 2 or 7 days (Geter et al., 2014).

^bDose level of 15 mg/kg/day was tested in Geter et al., 2014 and a dose level of 10 mg/kg/day was a NOAEL for tumor response in CD-1 mice (Whysner et al., 1996).

^cGene expression of *Ki67* and *Tsc22* on Day 2 from microarrays as presented in Supplemental Data Files (Geter et al., 2014). Genomic pathways for cell cycle/cell proliferation were also changed significantly in the 75 and 150 mg/kg/day dose groups, as discussed in the text.

^dClonal expansion, altered foci – were not determined (ND) in CD-1 mouse long-term studies (Whysner et al., 1996),

^eCD-1 mice were exposed to phenobarbital for 2 years, and increased liver tumors were reported at 75 and 150 mg/kg/day, but a NOAEL for tumors occurred at 10 mg/kg/day (Whysner et al., 1996).