Table 6. Effects of Phenobarbital in Male Humanized Liver Chimeric Mice and Male Wild-type SCID Mice

| Strain of Mouse | Humanized Liver Chimeric Mice (uPA/SCID) [c] | | | SCID Mice[c] |
|---|---|---|---|---|
| Feeding Level (ppm in diet) | 500 | 1000 | 1500 | 1500 |
| (= mg/kg/day) | (69) | (150) | (230) | (220) |
| Survival incidence (Day 7) [e] | 5/5 | 5/5 | 2/5[e] | 5/5 |
| Plasma NaPB level (µg/mL)[e] | 27 | 75 | 120 | 43 |
| MIE: CAR Activation (Day 7) | | | | |
| via KE1 – *CYP2B* mRNA (RT-PCR)[a] | **6.9*** | **7.4*** | **11** | **160*** |
| via KE1 – *CYP3A* mRNA (RT-PCR)[a] | **2.8*** | **3.6*** | **5.2** | **4.0*** |
| Via KE1 - *Ki67* mRNA (RT-PCR) [a] | 0.3* | 0.4 | 0.8 | 0.9 |
| Via KE1 – *GADD45B* mRNA (RT-PCR) [a] | 0.9 | 0.6* | 0.7 | **5.2*** |
| Via AE1 – PROD activity | **6.8*** | **14*** | **14** | **13*** |
| Via AE2: Hepatocyte hypertrophy | **1/5** | **1/5** | **2/2** | **5/5** |
| Via AE3: Absolute liver weight | **1.2*** | **1.2*** | **1.2** | **1.4*** |
| KE2: increased cell prolif., BrdU (Day 7) [b] | 1.9[d] | 1.3 | 1.4 | **4.6*** |

**Legend** (comparative effects vs. untreated controls):
Values are fold-change vs. controls, or incidence for histopathology and survival. * Values statistically significant vs. control ($p<0.05$). Chimeric mice at 1500 ppm had high mortality (n=2 surviving mice) and therefore no statistical analysis was possible. Values considered to be effects of treatment are **shown in bold**.

[a]Gene expression (mRNA) levels were quantified by RT-PCR in liver based upon primers and probe sequences of either human (for chimeric liver) or mouse (for SCID mouse liver). Thus, for example, *CYP2B* mRNA reflects *CYP2B6* in chimeric human livers and *Cyp2b10* in SCID mouse livers.

[b]BrdU was administered by minipump for 24 hours prior to termination. BrdU labelling index was determined for all control and treated groups.

[c]Data are from Yamada et al., 2014. This study also evaluated male CD-1 mice and male Wistar rats at dietary concentrations of 500 – 2500 ppm; results for these groups were similar to those shown for SCID mice (see text for further information).

[d]At 500 ppm in humanized liver chimeric mice, one outlier value was outside of the control range. When this animals' value was excluded, mean BrdU labelling index at 500 ppm was 1.4-fold the control group mean (i.e. similar to the 1000 ppm and 1500 ppm values).

[e]Analysis of phenobarbital in blood indicated the chimeric humanized mice had much higher levels compared to the wild-type SCID mice (or to CD-1 mice) at equivalent ppm dietary dose levels. This likely reflected less induction of metabolism, and is the most likely reason that mortalities occurred at 1500 ppm in the chimeric mice only.