Table 4. TCPOBOP Effects and Time Concordance – Male C57BL/6 Mice

Key Events / Associative Events	3 mg/kg ip, One dose (Tojima et al., 2012) [b]	3 mg/kg ip daily (Huang et al., 2005) [f,g] & (Wei et al., 2000) [e]	3 mg/kg ip every 2 weeks (Diwan et al., 1992) [c,d]	3 mg/kg gavage, every 2 weeks (Diwan et al., 1992) [c,d]
MIE: CAR Activation:				
via KE1: *Cyp2b10* mRNA	+ (1 day) (151-fold)	+ (3 days) [g]	ND	ND
via KE1: *Cdc20* mRNA	+ (37-fold)			
via KE1: *Gadd45b* mRNA	+ (14-fold)			
via AE1 – BROD activity	ND	ND	+ (28 days) (82-fold) [d]	+ (28 days) (62-fold) [d]
via AE2 - Hepatocyte hypertrophy (Day 29)[d]	ND	ND	+ (28 days) [d]	+ (28 days) [d]
via AE3 – Relative Liver wt.	ND	+ (3 days) [e,g] + (30 weeks) (1.6-fold) [f]	+ (28 days) (1.9-fold) [d]	+ (28 days) (1.7-fold) [d]
KE2: increased cell proliferation, [BrdU or PCNA]	ND	+ (3 days) [e] BrdU + (3 days) [g] + (30 weeks) [f] PCNA	ND	ND
KE3: clonal expansions, hyperplasia, increased altered foci (Months)	ND	ND	+ (eosinophilic foci) (60 weeks) [c]	+ (eosinophilic foci) (60 weeks) [c]
AO: Liver adenomas, carcinomas	ND	+ (44%) (30 weeks) [f]	+ (71%) [a, c] (60 weeks)	+ (67%) [a, c] (60 weeks)

Legend (comparative effects vs. untreated controls):
+ Positive; - Negative; ± Equivocal. ND Not determined.

[a]Percent incidence of mice with tumors is shown after 60 weeks. Incidence in vehicle control group was 0%.

[b]In Tojima et al. (2012), C57BL/6 mice (wild type) and various knockout mouse strains (CAR KO, PXR KO and double CAR/PXR KO) were treated with 1 x 3 mg/kg TCPOBOP ip, and sacrificed 12 h later. Fold-change values for gene expression in WT mice vs. control mice are shown based on microarray results.

[c]In Diwan et al. (1992), C57BL/6NCr mice exposed to 3 mg/kg TCPOBOP in corn oil once every 2 weeks, by intraperitoneal (ip) or oral gavage dosing for up to 30 weeks (a maximum of 12 applications), and then continued untreated and on control diet until termination at 60 weeks (Diwan et al., 1992). In the same study, separate groups treated in the same manner also received a single dose of the initiator N-nitrosodiethylamine (NDEA) prior to starting TCPOBOP treatment (data not reported in Table above).

[d]Also in Diwan et al. (1992): C57BL/6NCr mice were treated with two doses of 3 mg/kg TCPOBOP by ip or oral gavage 14 days apart, and were sacrificed after 2 weeks (28 days).

[e]In Wei et al. (2000), C57BL6 mice or CAR KO mice on this background were treated with 3 mg/kg TCPOBOP in corn oil by i.p. injection for 3 days. The indicated effects were absent in the CAR KO mice (Wei et al., 2000).

[f]In Huang et al. (2005), C57BL6 mice or CAR KO mice on this background were treated with 3 mg/kg TCPOBOP in corn oil by i.p. injection every 2 weeks for 24 weeks of **chronic dosing** (termination at 30 wks, in Huang et al., 2005, Table 1, Fig. 2, suppl Figure 2)). No correlating effects in CAR KO mice on: liver wt., hypertrophy, octoploidy, cell proliferation (PCNA, Suppl Fig 2B), ↓ apoptosis (TUNEL), *Cyp2b10* mRNA, *Mdm2* mRNA or protein, and liver tumors.

[g]Also, in Huang et al. (2005), C57BL6 mice or CAR KO mice on this background were treated with 3 mg/kg TCPOBOP in corn oil by i.p. injection daily for 3 days (**acute study**) (Huang et al., 2005 Fig. 1, 3, 4, 5; suppl Figure 3).