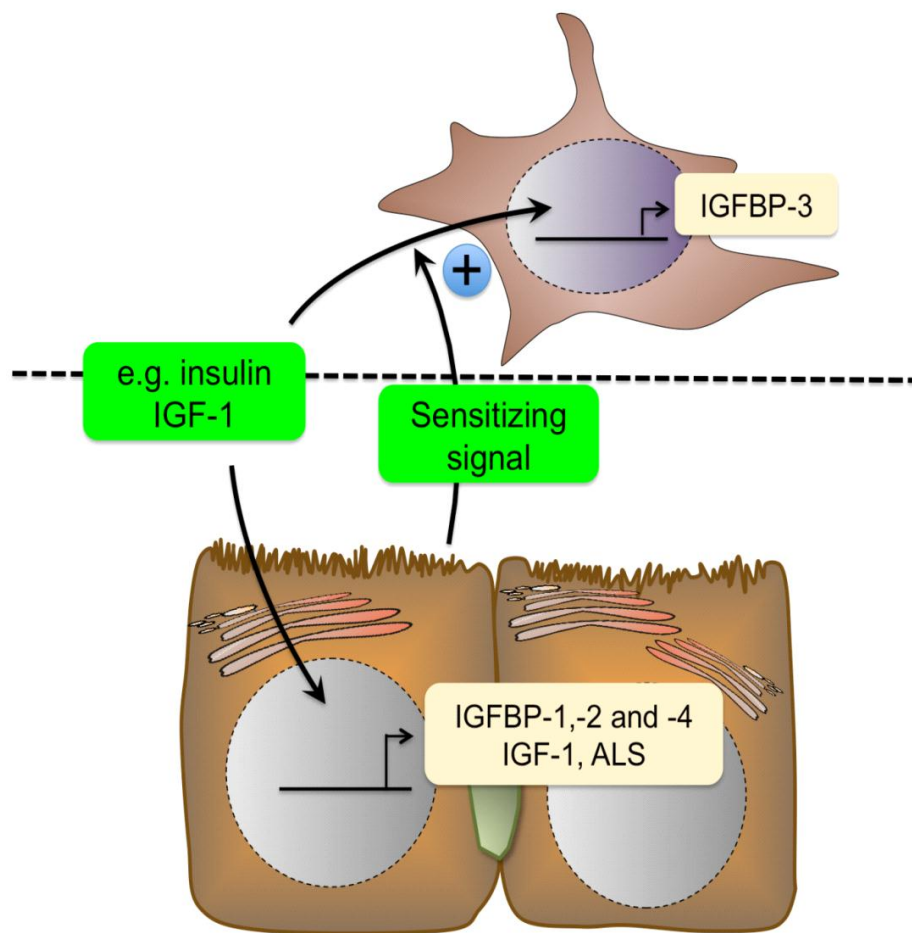
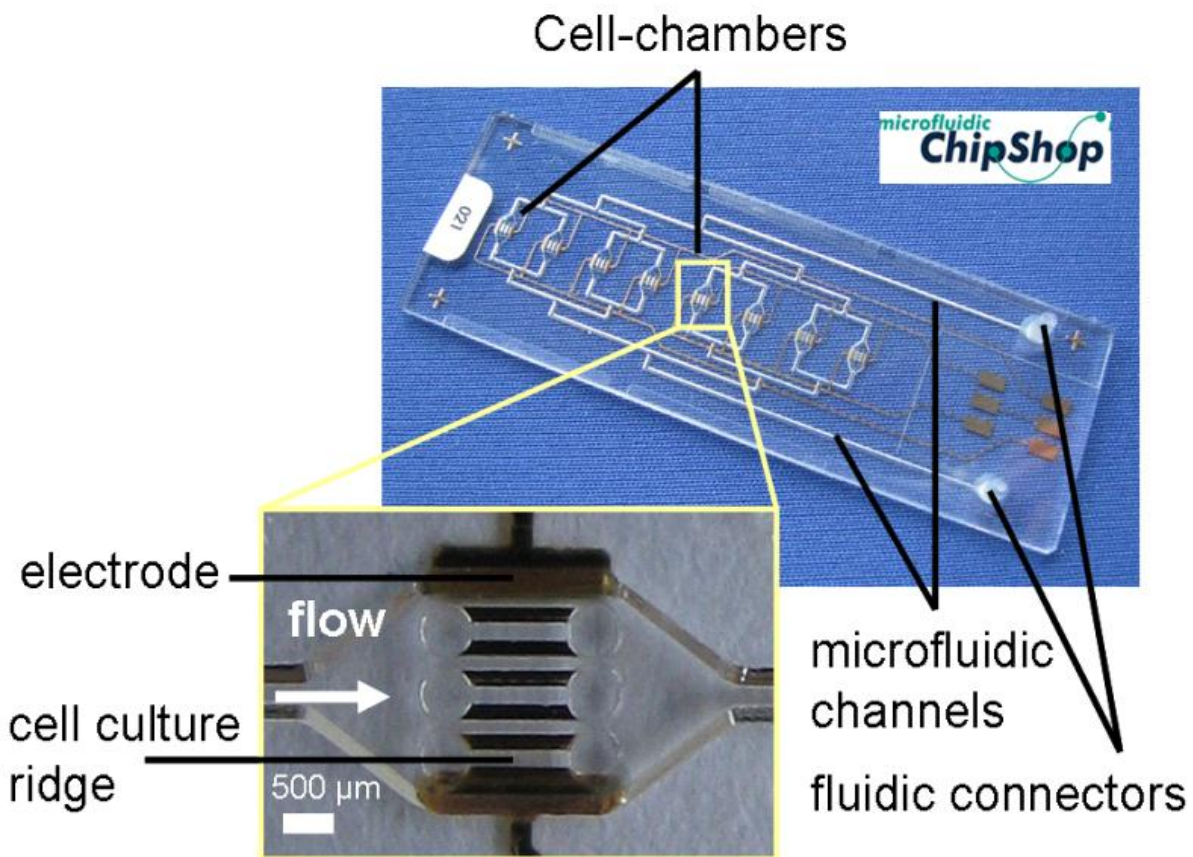


**Fig. S1.** Regulation of the cell type-specific production of IGF-1 and IGFBP1 to 4 by intercellular feedback loops between hepatocytes and macrophages. Co-culture experiments have analyzed the production of insulin like growth factor (IGF-1) and the IGF binding proteins (IGFBP) bind IGF and modulate its activity together with the acid labile subunit (ALS). Thereby, in the liver, IGFBP3 is almost exclusively produced by non-parenchymal cells by liver macrophages but not by hepatocytes. By contrast, IGF-1, ALS and IGBP1, 2 and 4 are produced by hepatocytes in response to stimulation with insulin or IGF1. Most interestingly, in liver macrophages, production of IGFBP3, which is considered to be the major interaction partner of circulating IGF, requires a hepatocyte-derived soluble signal in order to be sufficient.

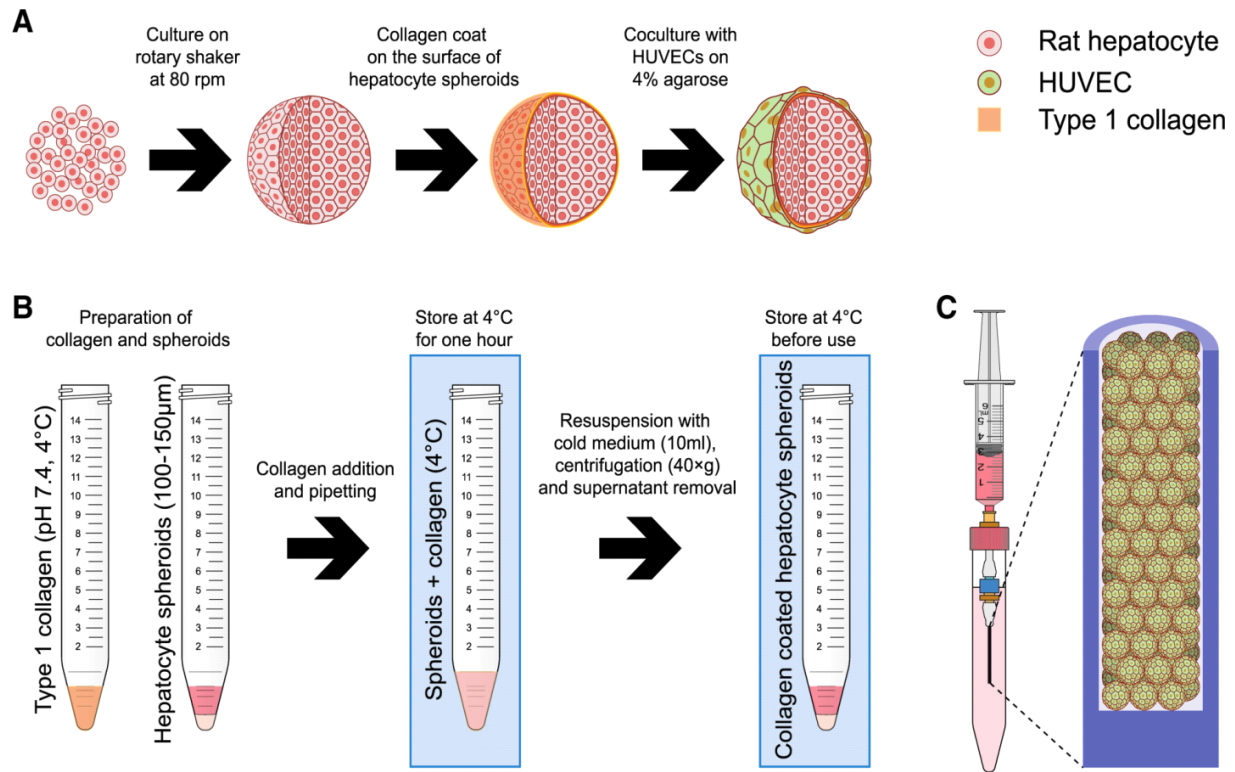


**Fig. S2.** Injection-molded design of the HepaChip® microfluidic device for 3D-assembly of liver cells (Schutte et al., 2011a). The Chip consists of branching microfluidic channels draining the cell-chambers.

Electrodes contact the cell-chambers to apply an electric field. Liver cells assemble towards the ridges by positive dielectrophoresis.

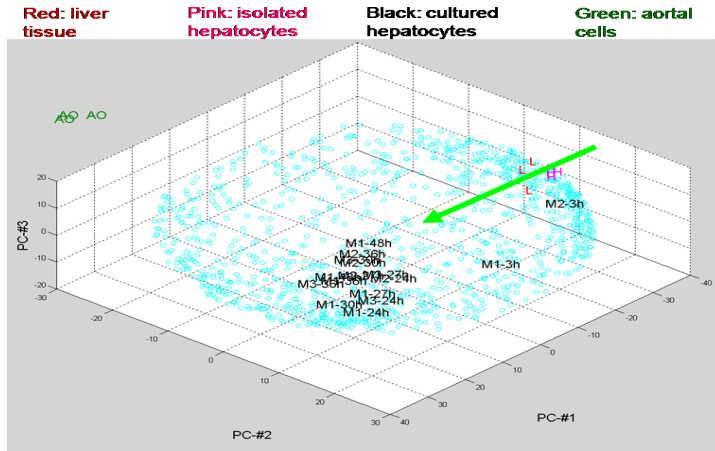


**Fig. S3.** Formation of extended vascularized liver constructs by fusion of hepatocyte spheroids coated with endothelial cells. (A) Hepatocyte spheroids were formed, coated with a collagen I layer and subsequently coated with human umbilical vein endothelial cells (HUVEC). (B) Detailed procedure for the spheroids coating with collagen. (C) HUVEC-decorated hepatocyte spheroids were inoculated into the hollow fiber and centrifuged to pack into the hollow fiber (from [Inamori et al., 2009](#)).

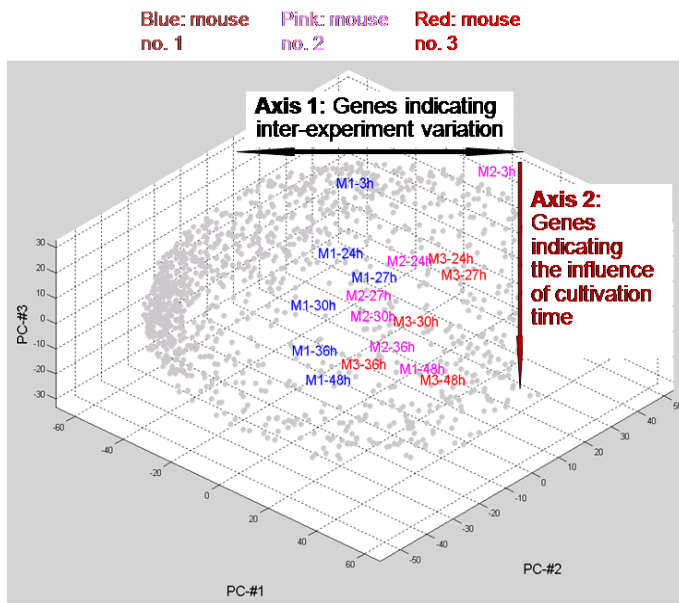


**Fig. S4.** Gene expression alterations of cultured mouse (C57BL6/N) hepatocytes. RNA was obtained from liver tissue, freshly isolated hepatocytes immediately after attachment and from cultured hepatocytes harvested after 3 to 48 h in culture. Analysis was performed by Affymetrix gene arrays. Overall gene expression alterations were visualized by principle component analysis (PCA). (A) The difference in overall gene expression between liver tissue of 3 mice (L) and freshly isolated hepatocytes (H) is relatively small. The major alterations in gene expression occur during the first 24 h in culture. In order to allow comparison of the hepatocytes to a completely different cell type, aortal cells (AO) were included into the PCA. (B) PCA analysis of the genes altered during the culture period. Hepatocytes obtained from the three mice are indicated by different colors. Axis 2 indicates genes whose expression is altered during the culture period of 3, 24, 27, 30, 36 and 48 h (from Zellmer et al. (2010)).

(a)

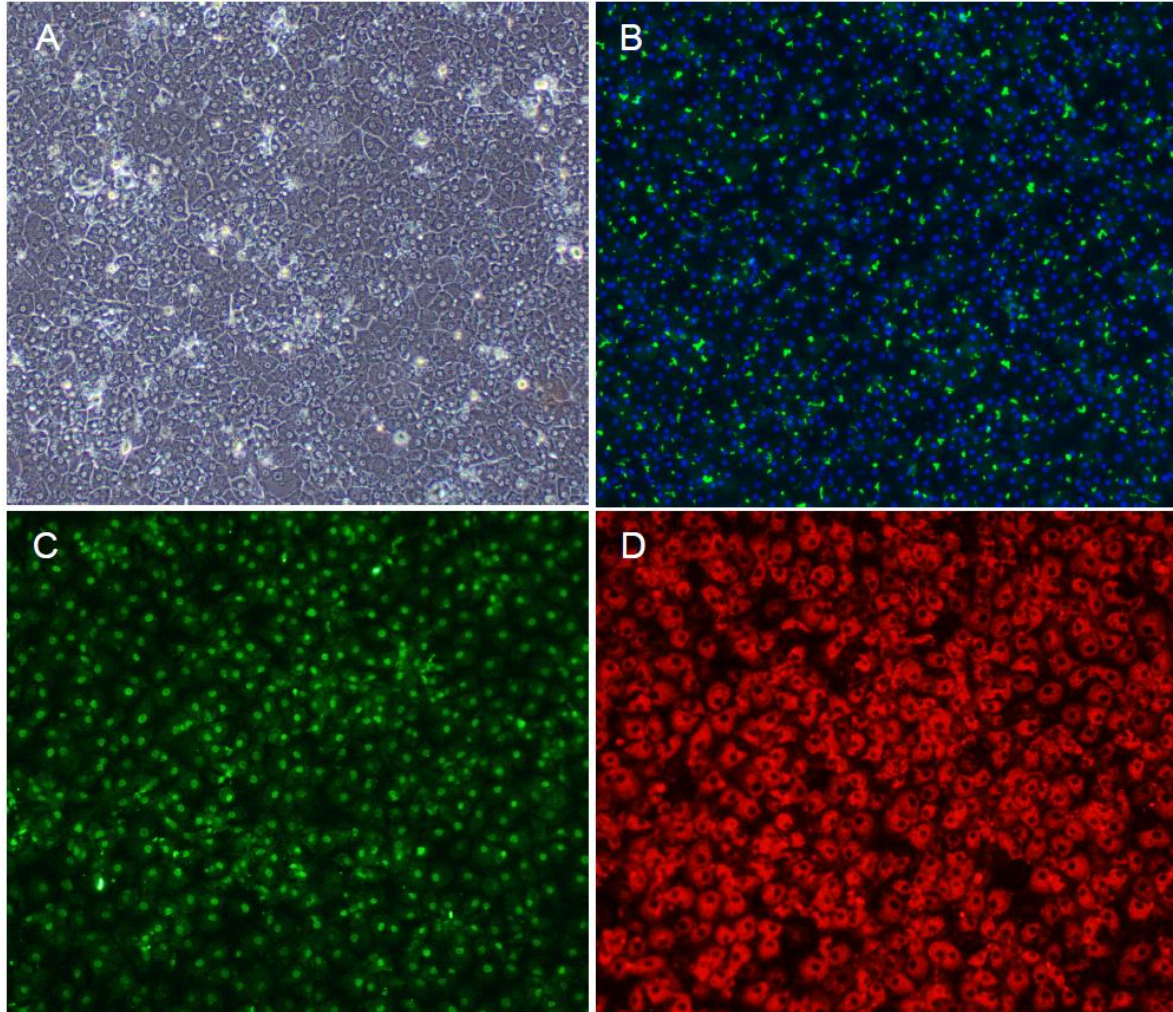


(b)

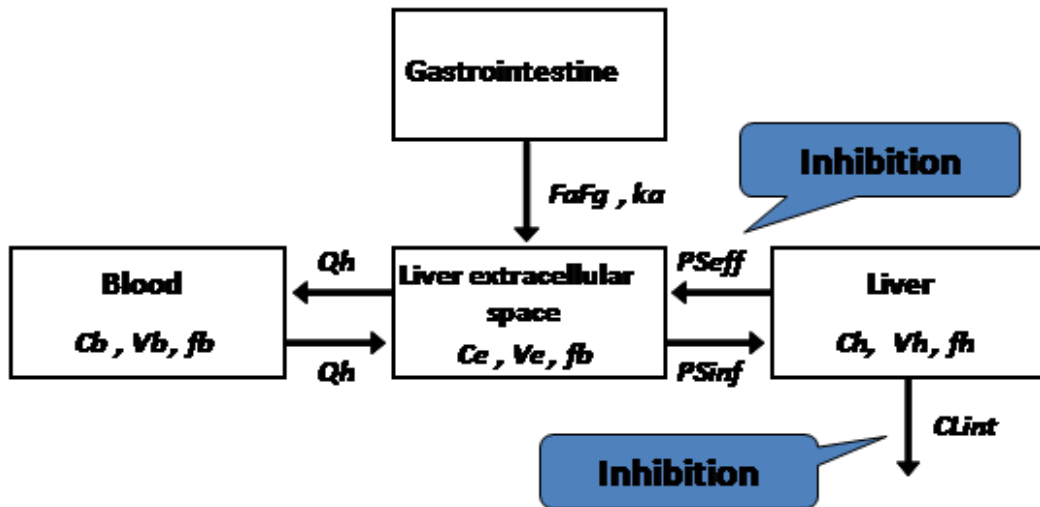


**Fig. S5.** iPS-derived iCell hepatocytes exhibit adult hepatocyte characteristics: (A) Phase contrast of iCell hepatocytes on Collagen-coated plates after 4 days post-seeding. (B) CDFDA staining showing

functional bile canaliculi and a polarized epithelial layer of hepatocytes. (C) Immunohistochemical staining of the human transcription factor HNF4a, shown in green. (D) Immunohistochemical staining of human Albumin, shown in red.



**Fig. S6.** A simple PBPK model for the simulation of DDIs involving the inhibition of hepatic uptake and metabolism/excretion.



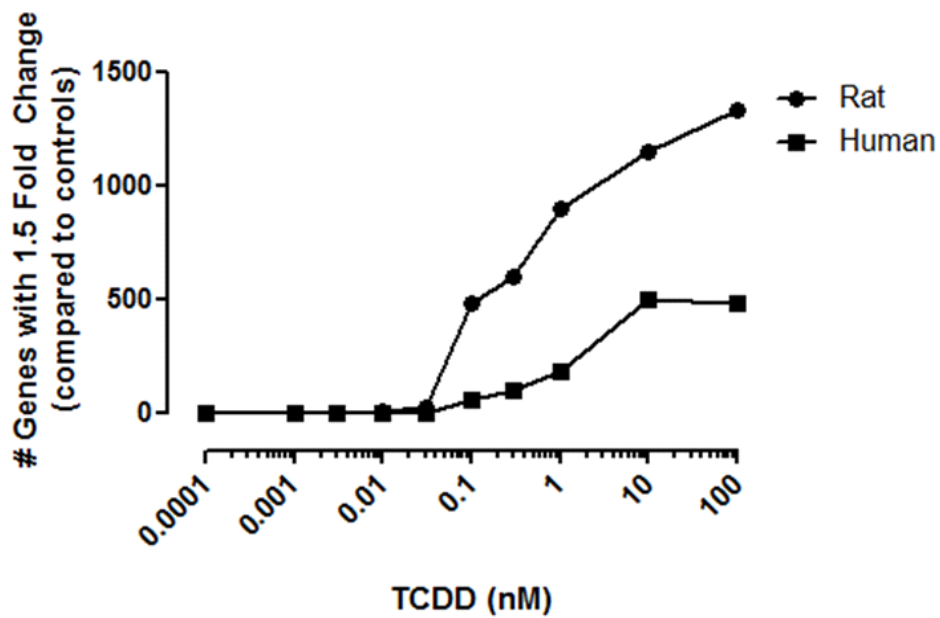
<b>Qh</b>	<b>86.9</b>	<b>L/hr</b>
<b>Ve</b>	<b>0.469</b>	<b>L</b>
<b>Vh</b>	<b>1.22</b>	<b>L</b>
<b>Vb</b>	<b>10</b>	<b>L</b>
<b>ka</b>	<b>2.5</b>	<b>hr<sup>-1</sup></b>
<b>FaFg</b>	<b>1</b>	
<b>Dose</b>	<b>250</b>	<b>μg</b>

$$V_b \frac{dC_b}{dt} = Q_h C_e - Q_h C_b$$

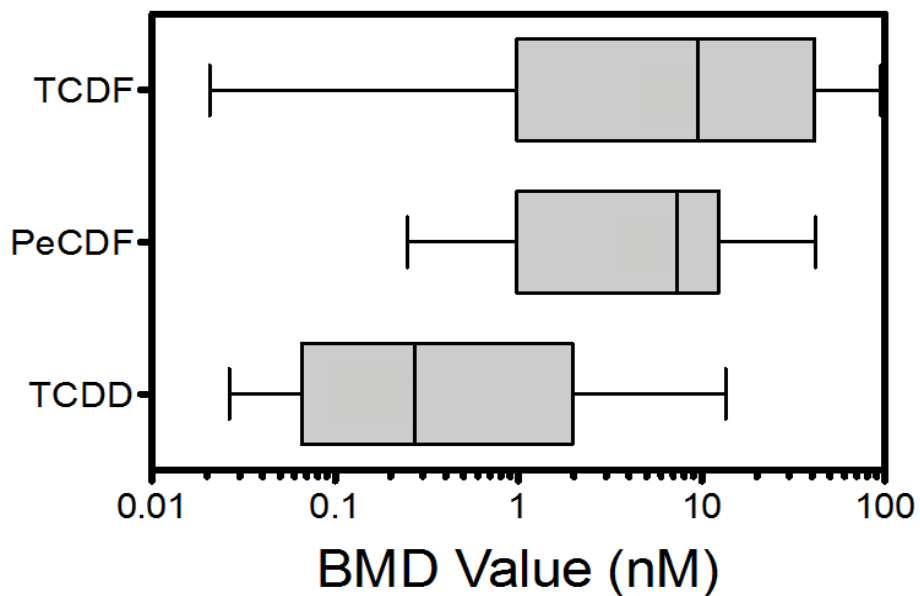
$$V_e \frac{dC_e}{dt} = Q_h C_b - Q_h C_e - f_b P_{Sinf} C_e + f_h P_{Seff} C_h + k_a F_a F_g D \exp(-k_a t)$$

$$V_h \frac{dC_h}{dt} = f_b P_{Sinf} C_e - f_h P_{Seff} C_h - f_h C_{Lint} C_h$$

**Fig. S7.** Orthologous and non-orthologous genes that exhibit a 1.5-fold or greater change in transcriptional activation after exposure to TCDD.

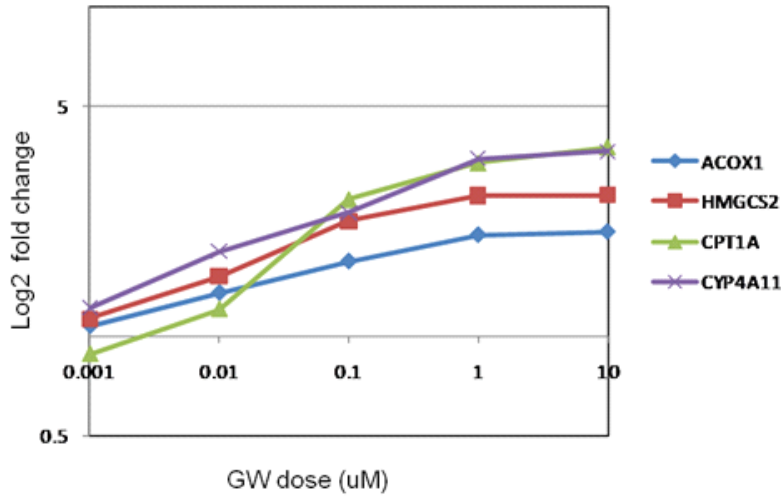


**Fig. S8.** Median BMD estimates for gene expression changes to TCDF, 4-PeCDF and TCDD exposure in primary rat hepatocytes.



**Fig. S9.** Dose-response of selected PPAR $\alpha$ -responsive genes in primary human hepatocytes. (A) Fold changes from transcriptomics studies at 72 h. (B) Validation of gene expression with qRT-PCR measurements. Values are represented as fold of mean 2 h controls.

(A)



(B)

