Supplementary Information:

Mechanistic identification of biofluid metabolite changes as markers of acetaminophen-induced liver toxicity in rats

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Supplementary Captions

Figure S1: Summary of APAP-induced gene and metabolite perturbations in the glycerophospholipid metabolism pathway.

Figure S2: Summary of APAP-induced gene and metabolite perturbations in the arginine and proline metabolism pathway.

Supplementary Table S1: Compilation of kidney metabolic functional tasks

Supplementary Table S2: Global metabolomic profiling analysis of urine

Supplementary Table S3: Compilation of literature data on the uptake/secretion rates for the liver and kidney

Supplementary Table S4: Results of RNA-sequencing analysis for the liver and kidney

Supplementary Table S5: Global metabolomic profiling analysis of blood

Supplementary Table S6: Model comparison and list of potential metabolites in the highly enriched pathways

Supplementary Table S7: Multi-tissue model predictions for blood and urine metabolite changes

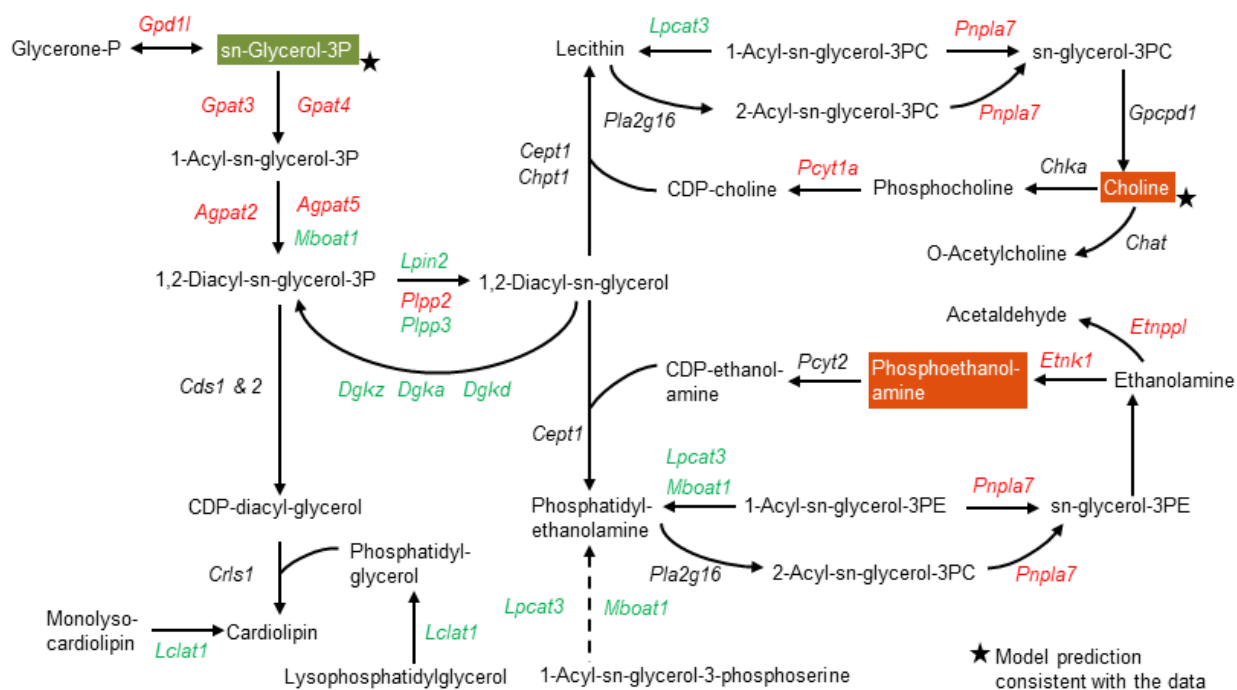**iRnoMTmodel**: SBML version of the rat multi-tissue model

Figure S1: Summary of APAP-induced gene and metabolite perturbations in the glycerophospholipid metabolism pathway. Each arrow indicates the direction of a reaction converting a substrate into a product, with the name of the gene indicated next to the arrow. Upregulated and downregulated genes are shown in red and green, respectively. Increased and decreased metabolites in the plasma are shown in white text with red and green backgrounds, respectively. Stars indicate model predictions consistent with the data. Dashed arrows indicate multiple steps involved in a reaction; the dotted line indicates metabolite precursors involved in other pathways.
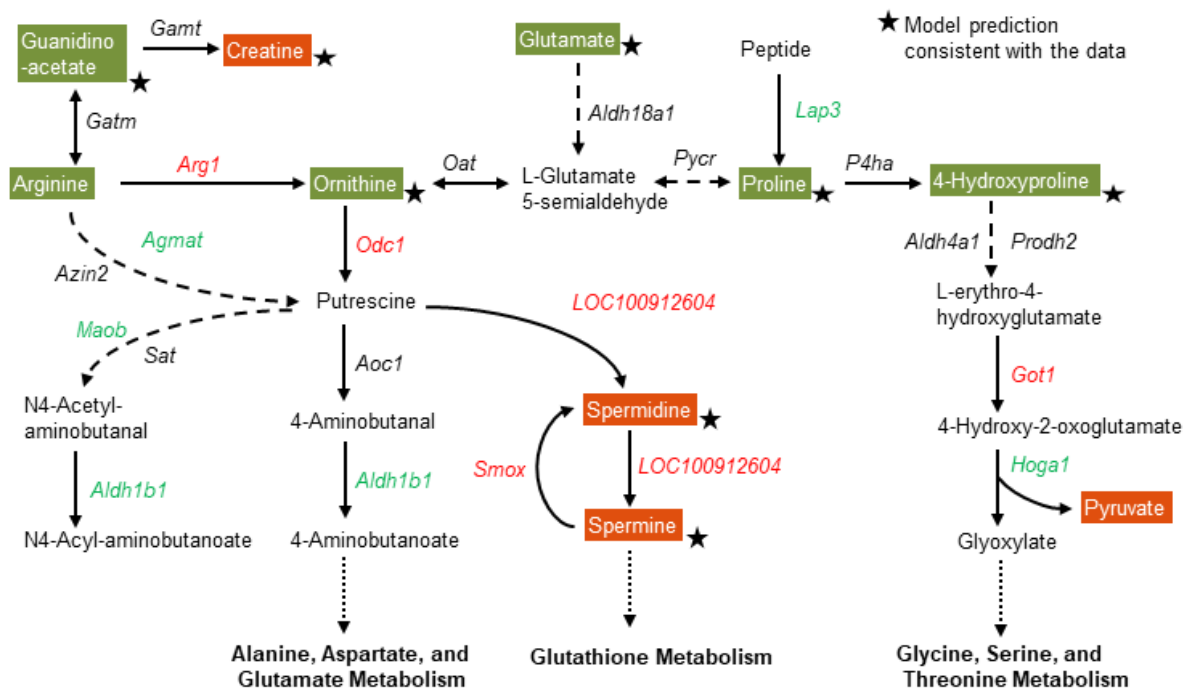
Figure S2: Summary of APAP-induced gene and metabolite perturbations in the arginine and proline metabolism pathway. Each arrow indicates the direction of a reaction converting a substrate into a product, with the name of the gene indicated next to the arrow. Upregulated and downregulated genes are shown in red and green, respectively. Increased and decreased metabolites in the plasma are shown in white text with red and green backgrounds, respectively. Stars indicate model predictions consistent with the data. Dashed arrows indicate multiple steps involved in the reaction; the dotted line indicates metabolite precursors involved in other pathways.