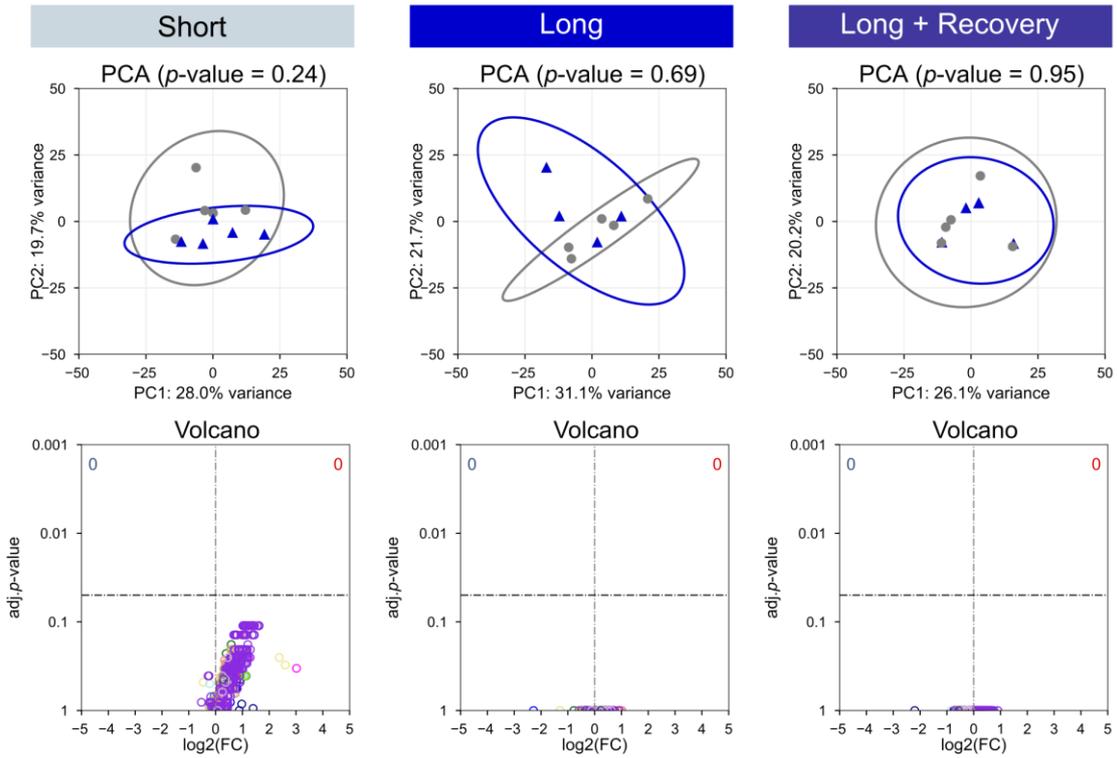


## Supplementary Materials:

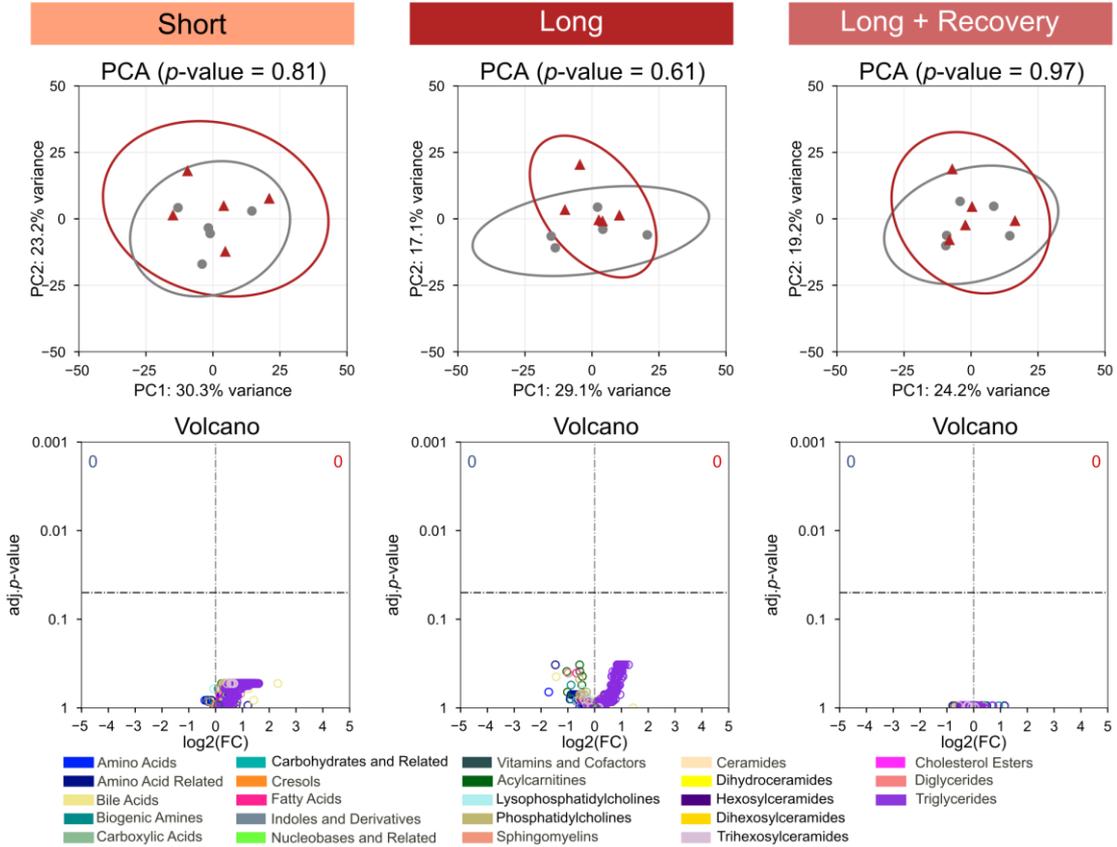
**Table S1.** Metabolites were detected and quantified in different sample types.

Metabolites classes	Thyroid gland	Liver	Plasma
Alkaloids		1	
Amine Oxides		1	
Amino Acids	20	19	20
Amino Acid Related	18	23	44
Bile Acids	8	11	2
Biogenic Amines	6	7	4
Carbohydrates and Related	1	1	19
Carboxylic Acids	1	5	1
Cresols	1	1	
Fatty Acids	7	5	34
Hormones and Related			26
Indoles and Derivatives	2	4	
Nucleobases and Related	2	2	12
Vitamins and Cofactors	1	1	15
Acylcarnitines	14	12	14
Lysophosphatidylcholines	9	10	22
Phosphatidylcholines	65	48	18
Sphingomyelins	15	9	27
Ceramides	26	12	13
Dihydroceramides	2		
Hexosylceramides	16	3	
Dihexosylceramides	8	1	
Trihexosylceramides	6	1	
Cholesterol Esters	4	2	6
Diglycerides	24	8	1
Triglycerides	234	145	32
Cholesterol			1
Complex Lipids, Fatty Acids and Related			9
Energy Metabolism and Related			16
Miscellaneous			12
Lysophosphatidylethanolamine			7
Phosphatidylethanolamine			16
Unknown			37
<b>Total</b>	<b>490</b>	<b>332</b>	<b>408</b>

(a): Effect of Phenytoin with low dose on Thyroid

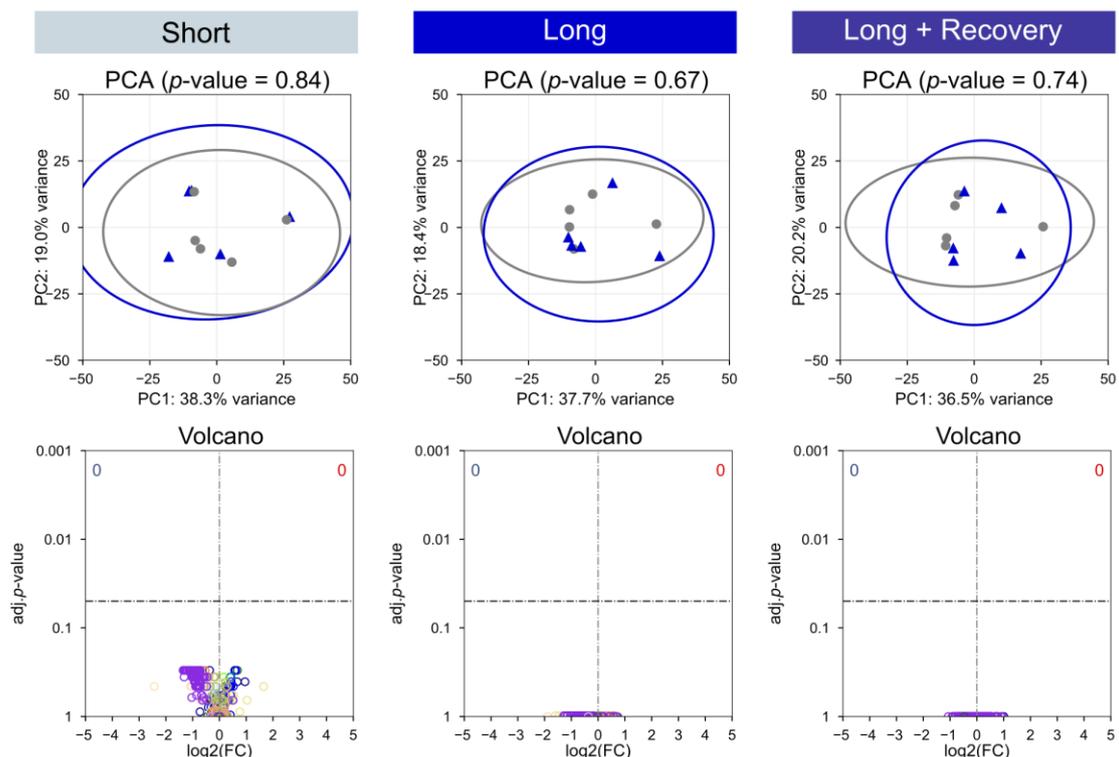


(b): Effect of Phenytoin with high dose on Thyroid

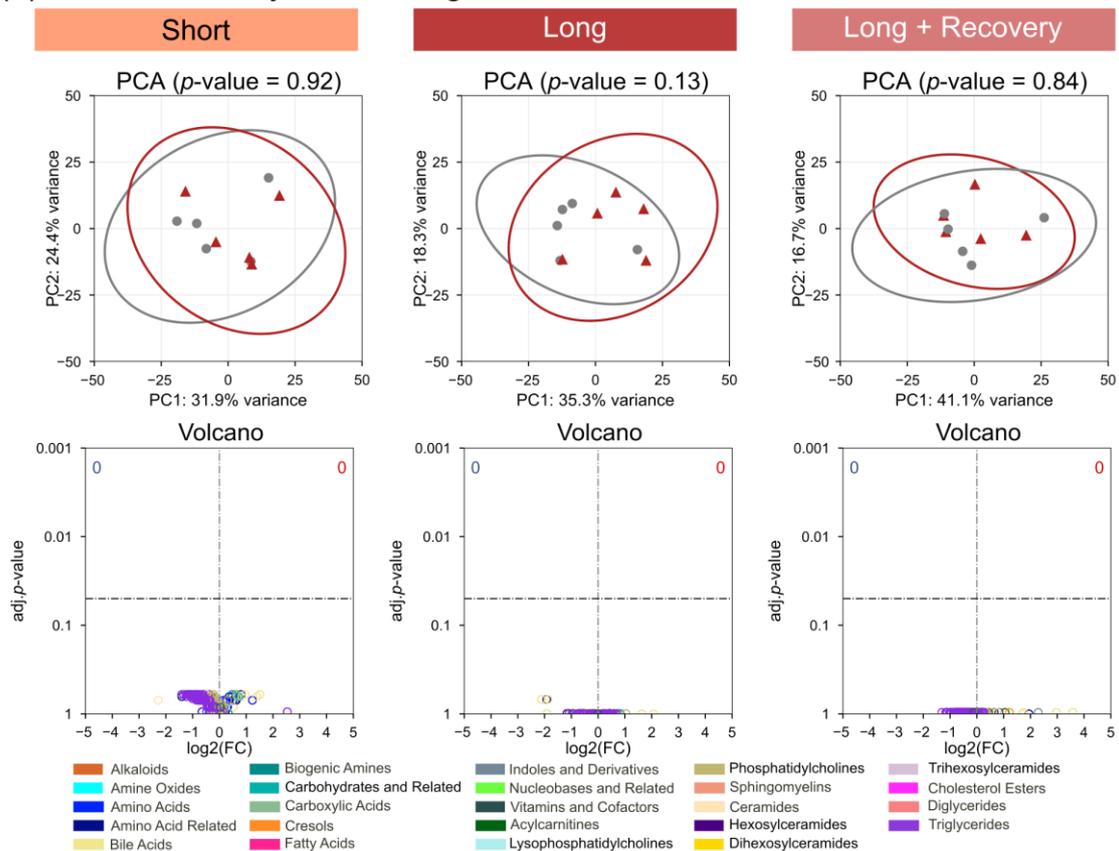


**Figure S1.** Low (a) and high-dose (b) phenytoin-associated changes on the metabolome of the thyroid gland after short-term (2 weeks) and long-term drug administration (4 weeks), as well as an additional 2-week recovery phase after long-term exposure. Differences in global metabolome profiles between treatments (blue and red representing low and high-dose, respectively) to controls (grey) were analyzed by PCA, with their significance determined by PERMANOVA. Differences in metabolite concentrations are visualized in a volcano plot depicting log<sub>2</sub> fold changes of treatment versus control with their significance calculated by the Mann-Whitney U test and P-values corrected for multiple testing using the Benjamini-Hochberg method.

(a): Effect of Phenytoin with low dose on Liver



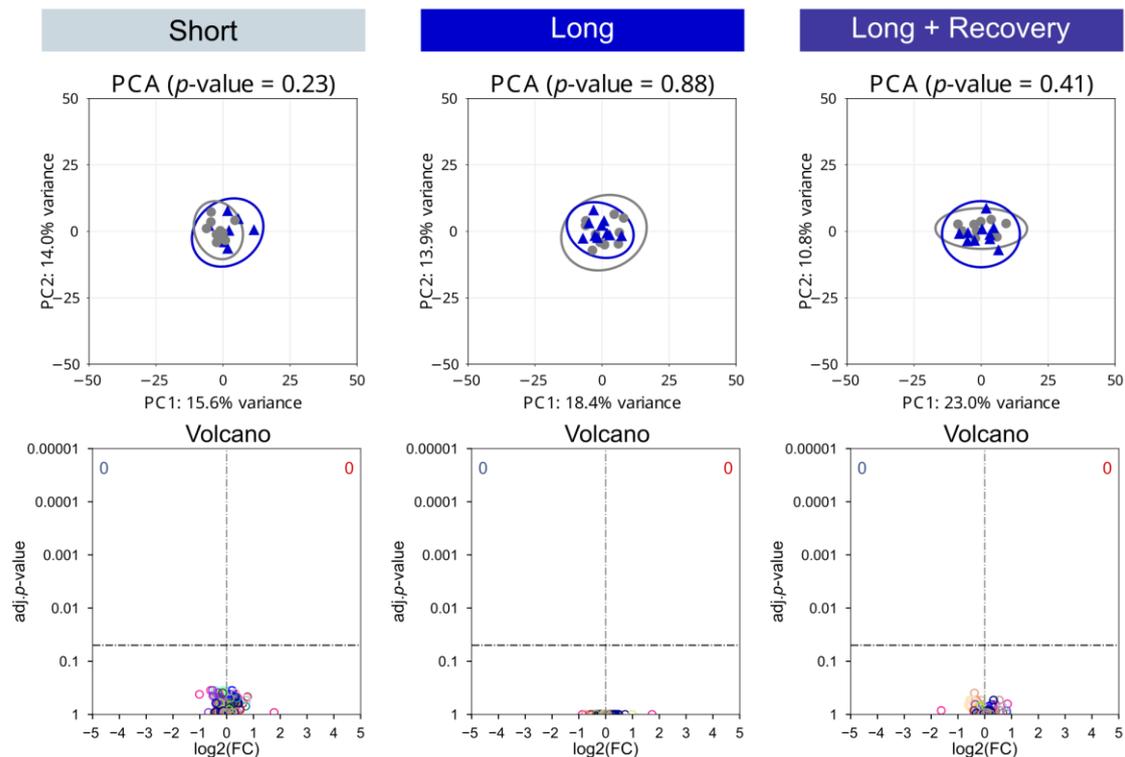
(b): Effect of Phenytoin with high dose on Liver



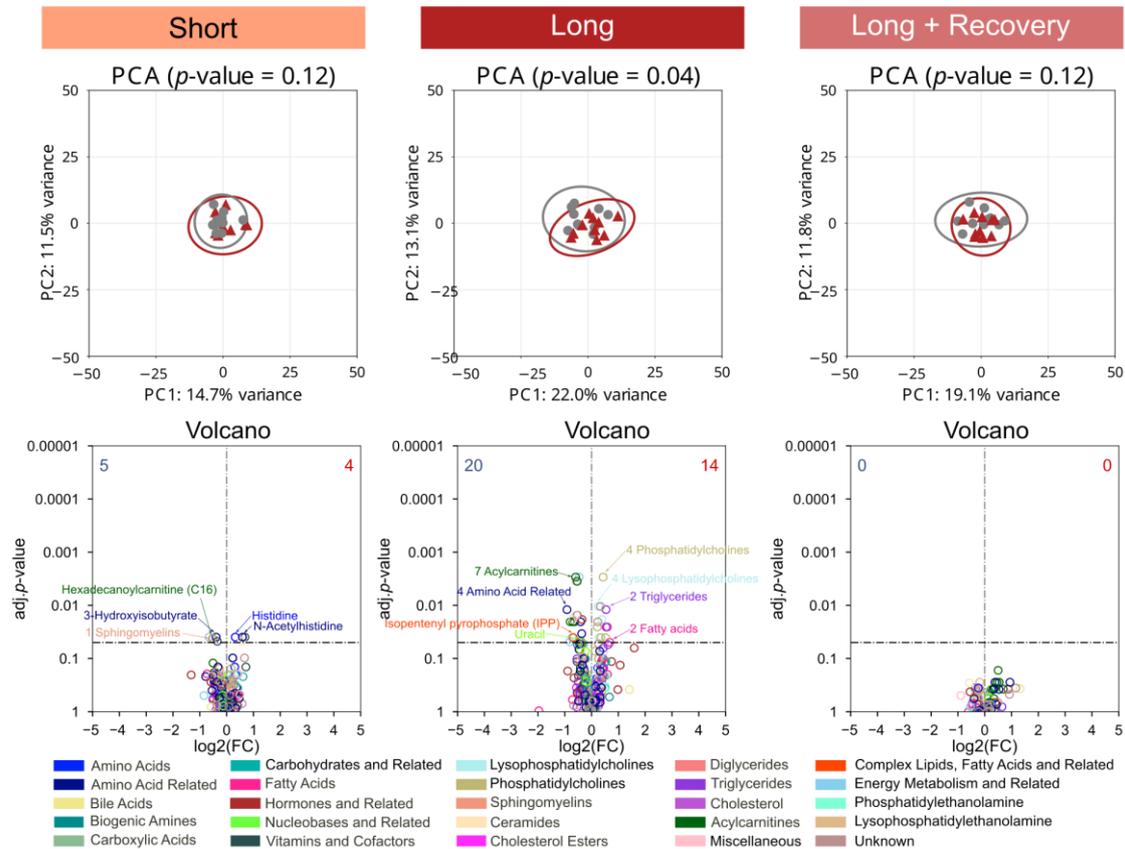
**Figure S2.** Low (a) and high-dose (b) phenytoin-associated changes on the metabolome of the liver after short-term (2 weeks) and long-term drug administration (4 weeks), as well as an additional 2-week recovery phase after long-term exposure. Differences in global metabolome profiles between

treatments (blue and red representing low and high-dose, respectively) to controls (grey) were analyzed by PCA, with their significance determined by PER-MANOVA. Differences in metabolite concentrations are visualized in a volcano plot depicting log<sub>2</sub> fold changes of treatment versus control with their significance calculated by the Mann-Whitney U test and P-values corrected for multiple testing using the Benjamini-Hochberg method.

(a): Effect of Phenytoin with low dose on Plasma



(b): Effect of Phenytoin with high dose on Plasma



**Figure S3.** Low (a) and high-dose (b) phenytoin-associated changes on the plasma metabolome after short-term (2 weeks) and long-term drug administration (4 weeks), as well as an additional 2-week recovery phase after long-term exposure. Differences in global metabolome profiles between

treatments (blue and red representing low and high-dose, respectively) to controls (grey) were analyzed by PCA, with their significance determined by PERMANOVA. Differences in metabolite concentrations are visualized in a volcano plot depicting log<sub>2</sub> fold changes of treatment versus control with their significance calculated by the Mann-Whitney U test and P-values corrected for multiple testing using the Benjamini-Hochberg method.