### **­Supplementary Table 2** - Metabolites in hepatic caffeine metabolism.

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| Id | Name (mass) Annotation | Initial Concentration | Concentrations, Comments |
| **caffeine** | **Caffeine**  (1,3,7-trimethylxanthine;  methyltheobromine;  trimethylxanthine;  theine)  C8H10N4O2  Charge: 0  CHEBI:27732  KEGG:C07481 | **0.0021mM** | [**caf**] = **2.1±1.6 (0.1-4.9) µM** (normal subjects, fasting plasma caffeine levels){Wahllaender1985}  [caf] = 17.8±9.4 (0.6-32) µM (shunt, fasting plasma caffeine levels){Wahllaender1985}  [caf] = 12.3±10.5 (0.7-50.6) µM (cirrhosis, fasting plasma caffeine levels){Wahllaender1985}  [caf] = 4.6±4.1 (0.6-17.3) µM (misc liver disease, fasting plasma caffeine levels){Wahllaender1985}    HMDB01847  **[caf] = 78.0 (26.0-129.0) uM (blood)**  Biofluid: Blood, Status: Detected and Quantified, Adult (>18 years old), Sex: Both, Condition: Normal, Reference: McPherson, Richard A., ed. Tietz Clinical Guide to Laboratory |
| **paraxanthine** | **paraxanthine**  (1,7-dimethylxanthine)  C7H8N4O2  Charge: 0  Mw=180.16g/mole  CHEBI:25858  KEGG:C13747 | **0.010mM** | HMDB01860  **[px] = 10.0 (0.30-28.0) uM (blood)** {Yin2004}  Biofluid: Blood, Status: Detected and Quantified, Adult (>18 years old), Sex: Both, Condition: Normal  **[px] = 2.0 – 4.8 µM (serum)** {Klebanoff1999}  359 – 870 ng/ml (serum paraxanthine, pregnant women) |
| **theobromine** | **theobromine**  (3,7-dimethylxanthine;  xantheose;  diurobromine)  C7H8N4O2  Charge: 0  CHEBI:28946  KEGG:C07480 | **0.0011mM** | HMDB02825  **[tb] = 1.1 +/- 0.2 uM (blood)**  Biofluid: Blood, Status: Detected and Quantified, Adult (>18 years old), Sex: Male, Condition: Normal |
| **theophylline** | **theophylline**  C7H8N4O2  Charge: 0  CHEBI:28177  KEGG:C07130 | **0.029mM** | HMDB01889  **[tp] = 29.0 +/- 11.0 uM (blood)**  Biofluid: Blood, Status: Detected and Quantified, Adult (>18 years old), Sex: Both, Condition: Normal |
| **metoprolol** | metoprolol  C15H25NO3  Charge: 0  Mw: 267.36  CHEBI:6904  KEGG:C07202 |  |  |
| **midazolam** | **midazolam**  C18H13ClFN3  Charge: 0  Mw: 325.08  CHEBI:6931  KEGG:C07524 |  |  |
| **omeprazole** | **omeprazole**  C17H19N3O3S  Charge: 0  Mw: 345.41  CHEBI:7772  KEGG:C07324 |  |  |
| **warfarin** | **warfarin**  C19H16O4  Mw: 308.10  CHEBI:10033  KEGG:C01541 |  |  |
| **cyp1a2** | **CYP1A2** |  | Primary |
| **cyp2e1** | **CYP2E1** |  | minor |
| **cyp3a4** | **CYP3A4** |  | minor |
| **cyp3a5** | **CYP3A5** |  | minor |
| **cyp3a7** | **CYP3A7** |  | minor |
| **cyp2c8** | **CYP2C8** |  | minor |
| **cyp2c9** | **CYP2C9** |  | minor |
| **s\_adenosyl\_l\_met** | **S-adenosyl-L-methionine**  C15H23N6O5S  Charge: 1  CHEBI:59789 |  |  |
| **s\_adenosyl\_l\_hcys** | **S-adenosyl-L-homocysteine**  C14H20N6O5S  Charge: 0  CHEBI:27732 |  |  |
| **atp** | **ATP**  C10H12N5O13P3  Charge: -4  (Mw 503.2)  CHEBI:30616  KEGG:C00002 | **2.7mM** (no galactose)  **2.9mM** (1h galactose)  **2.9mM** (1h galactose, GALE inhibition) | [**atp**] = **2.8mM** ([König, et al., 2012](#_ENREF_7))  ([Guynn, et al., 1974](#_ENREF_3))  **[atp] = 2.49±0.12 µmol/gWW** (**~2.77mM**) (rat liver, starved)  **[atp] = 2.56±0.09 µmol/gWW** (**~2.84mM**) (rat liver, fed ad libitum)  **[atp] = 2.32±0.07 µmol/gWW** (**~2.58mM**) (rat liver, meal fed)  **[atp] = 2.42±0.50 µmol/gWW** (**~2.69mM**) (rat liver) ([Keppler, et al., 1969](#_ENREF_5))  ([Keppler, et al., 1970](#_ENREF_6))  **[atp] =2.60 ±0.16µmol/gww** (**~2.89mM**) (starved + galactose 1h, rat, liver)  **[atp] =2.81 ±0.15µmol/gww** (**~3.12mM**) (ethanol, starved + galactose 1h, rat, liver)  **[atp]/[adp] =3.14 ±0.52** (starved + galactose 1h, rat, liver)  **[atp]/[adp] =3.10 ±0.53** (ethanol, starved + galactose 1h, rat, liver) |
| **adp** | **ADP**  C10H12N5O10P2  Charge: -3  (Mw 424.2)  CHEBI:456216  KEGG:C00008 | **1.2mM** (no galactose)  **1.0mM** (1h galactose)  **1.0mM** (1h galactose, GALE inhibition) | [**adp**] = **0.8mM** ([König, et al., 2012](#_ENREF_7))  ([Guynn, et al., 1974](#_ENREF_3))  **[adp] = 1.38±0.08µmol/gWW** (**~1.53mM**) (rat liver, starved)  **[adp] = 1.06±0.03µmol/gWW** (**~1.18mM**) (rat liver, fed ad libitum)  **[adp] = 1.24±0.04µmol/gWW** (**~1.38mM**) (rat liver, meal fed)  **[adp] = 1.08±0.12 µmol/gWW** (**~1.20mM**) (rat liver) ([Keppler, et al., 1969](#_ENREF_5))  ([Keppler, et al., 1970](#_ENREF_6))  **[adp] =0.88 ±0.17µmol/gww** (**~0.98mM**) (starved + galactose 1h, rat, liver)  **[adp] =0.97 ±0.19µmol/gww** (**~1.08mM**) (ethanol, starved + galactose 1h, rat, liver) |
| **utp** | **UTP**  C9H11N2O15P3  Charge: -4  (Mw 480.1)  CHEBI:46398  KEGG:C00075 | **0.27mM** (no galactose) | [**utp**] = **0.27mM** ([König, et al., 2012](#_ENREF_7))  ([Guynn, et al., 1974](#_ENREF_3))  **[utp] = 0.362±0.014 µmol/gWW** (**~0.40mM**) (rat liver, starved)  **[utp] = 0.494±0.038 µmol/gWW** (**~0.55mM**) (rat liver, fed ad libitum)  **[utp] = 0.443±0.039 µmol/gWW** (**~0.49mM**) (rat liver, meal fed) |
| **udp** | **UDP**  C9H11N2O12P2  Charge: -3  (Mw 401.1)  CHEBI:58223  KEGG:C00015 | **0.09mM** (no galactose) | [**udp**] = **0.09mM** ([König, et al., 2012](#_ENREF_7))  **[utp+udp] = 0.35±0.07 µmol/gWW** (**~0.39mM**) (rat liver) ([Keppler, et al., 1969](#_ENREF_5))  **[utp+udp] = 0.35±0.05 µmol/gWW** (**~0.39mM**) (rat liver) ([Keppler and Decker, 1969](#_ENREF_4))  ([Keppler, et al., 1970](#_ENREF_6))  **[utp+udp] =0.34 ±0.05µmol/gww** (**~0.38mM**) (fed, rat, liver)  **[utp+udp] =0.23 ±0.05µmol/gww** (**~0.26mM**) (starved, rat, liver)  **[utp+udp] =0.15 ±0.03µmol/gww** (**~0.17mM**) (starved + galactose 1h, rat, liver)  **[utp+udp] =0.11 ±0.02µmol/gww** (**~0.39mM**) (ethanol, starved + galactose 1h, rat, liver)  Marked decrease in [utp+udp] under galactose challenge. |
| **phos** | **Phosphate**  HO4P  Charge: -2  (Mw 96.0)  CHEBI:43474  KEGG:C00009 | **5.0mM** | [**phos**] = **5.0mM** ([König, et al., 2012](#_ENREF_7))  ([Guynn, et al., 1974](#_ENREF_3))  **[phos] = 4.37±0.16 µmol/gWW** (**~4.86mM**) (rat liver, starved)  **[phos] = 3.64±0.32 µmol/gWW** (**~4.04mM**) (rat liver, fed ad libitum)  **[phos] = 4.41±0.10 µmol/gWW** (**~4.90mM**) (rat liver, meal fed)  **[phos] = 3.18±0.56 µmol/gWW** (**~3.53mM**) (rat liver) ([Keppler and Decker, 1969](#_ENREF_4)) |
| **ppi** | **Pyrophosphate**  HO7P2  Charge: -3  (Mw 175.0)  CHEBI:33019  KEGG:C00013 | **0.008mM** | [**pp**] = **0.008mM** ([König, et al., 2012](#_ENREF_7))  ([Guynn, et al., 1974](#_ENREF_3))  **[pp] = 0.0023±0.0003 µmol/gWW** (**~0.0026mM**) (rat liver, starved)  **[pp] = 0.0038±0.0004 µmol/gWW** (**~0.0042mM**) (rat liver, fed ad libitum)  **[pp] = 0.0049±0.0006 µmol/gWW** (**~0.0054mM**) (rat liver, meal fed)  **[pp] = 0.0065±0.00086 µmol/gWW** (**~0.0072mM**) (rat total liver) |
| **nadp** | **NADP**  C21H25N7O17P3  Charge: -3  (Mw 740.4)  CHEBI:58349  KEGG:C00006 | **0.1mM** |  |
| **nadph** | **NADPH**  C21H26N7O17P3  Charge: -4  (Mw 741.4)  CHEBI:57783  KEGG:C00005 | **0.1mM** |  |
| **h2o** | **H2O**  H2O  Charge: 0  CHEBI:15377  KEGG:C00001 | - | Boundary species, included for mass and charge bilance. |
| **hydron** | **H+**  H  Charge: +1  (Mw 1.0)  CHEBI:15378  KEGG:C00080 | - | Boundary species, included for mass and charge bilance. |
| **co2** | **CO2**  CO2  Charge: 0  (Mw 44.0)  CHEBI:16526  KEGG:C00011 | - | Boundary species, included for mass and charge bilance. |
| **o2** | **O2**  O2  Charge: 0  (Mw 32.0)  CHEBI:15379  KEGG:C00007 | - | Boundary species, included for mass and charge bilance. |
| **h2** | **H2**  H2  Charge: 0  (Mw 2.0)  CHEBI:18276  KEGG:C00282 | - | Boundary species, included for mass and charge bilance. |

## **References**

Diepenbrock, F.*, et al.* (1992) Colorimetric determination of galactose and galactose-1-phosphate from dried blood, *Clinical biochemistry*, **25**, 37-39.

Fridovich-Keil, J.L. (2006) Galactosemia: the good, the bad, and the unknown, *Journal of cellular physiology*, **209**, 701-705.

Guynn, R.W.*, et al.* (1974) The concentration and control of cytoplasmic free inorganic pyrophosphate in rat liver in vivo, *The Biochemical journal*, **140**, 369-375.

Keppler, D. and Decker, K. (1969) Studies on the mechanism of galactosamine-1-phosphate and its inhibition of UDP-glucose pyrophosphorylase, *European journal of biochemistry / FEBS*, **10**, 219-225.

Keppler, D.*, et al.* (1969) Changes in uridine nucleotides during liver perfusion with D-galactosamine, *FEBS letters*, **4**, 278-280.

Keppler, D., Rudigier, J. and Decker, K. (1970) Trapping of uridine phosphates by D-galactose in ethanol-treated liver, *FEBS letters*, **11**, 193-196.

König, M., Bulik, S. and Holzhütter, H.G. (2012) Quantifying the contribution of the liver to glucose homeostasis: a detailed kinetic model of human hepatic glucose metabolism, *PLoS computational biology*, **8**, e1002577.

Lai, K.*, et al.* (2003) GALT deficiency causes UDP-hexose deficit in human galactosemic cells, *Glycobiology*, **13**, 285-294.

Leslie, N.D. (2003) Insights into the pathogenesis of galactosemia, *Annual review of nutrition*, **23**, 59-80.

Orfanos, A.P., Jinks, D.C. and Guthrie, R. (1986) Microassay for estimation of galactose and galactose-1-phosphate in dried blood specimens, *Clinical biochemistry*, **19**, 225-228.

Quan-Ma, R.*, et al.* (1966) Galactitol in the tissues of a galactosemic child, *Am J Dis Child*, **112**, 477-478.

Schadewaldt, P.*, et al.* (2000) Analysis of concentration and (13)C enrichment of D-galactose in human plasma, *Clinical chemistry*, **46**, 612-619.

Segal, S. (1995) Defective galactosylation in galactosemia: is low cell UDPgalactose an explanation?, *European journal of pediatrics*, **154**, S65-71.

Segal, S. and Rogers, S. (1971) Nucleotide inhibition of mammalian liver galactose-I-phosphate uridylyltransferase, *Biochimica et biophysica acta*, **250**, 351-360.

Wang, Z.J.*, et al.* (2001) Proton magnetic resonance spectroscopy of brain metabolites in galactosemia, *Annals of neurology*, **50**, 266-269.

Wells, W.W.*, et al.* (1965) The Isolation and Identification of Galactitol from the Brains of Galactosemia Patients, *The Journal of biological chemistry*, **240**, 1002-1004.

Yamaguchi, A.*, et al.* (1989) Microassay for screening newborns for galactosemia with use of a fluorometric microplate reader, *Clinical chemistry*, **35**, 1962-1964.