Estimation of caffeine intake from analysis of caffeine metabolites in wastewater

Gracia-Lor, E.; Rousis, N.I.; Zuccato, E.; Bade, R.; Baz-Lomba, J.A.; Castrignanò, E.; Causanilles, A.; Hernández, F.; Kasprzyk-Hordern, B.; Kinyua, J.; McCall, A.-K.; van Nuijs, A.L.N.; Plósz, B.G.; Ramin, P.; Ryu, Y.; Santos, M.M.; Thomas, K.; de Voogt, P.; Yang, Z.; Castiglioni, S.

DOI
10.1016/j.scitotenv.2017.07.258

Publication date
2017

Document Version
Other version

Published in
Science of the Total Environment

License
Article 25fa Dutch Copyright Act (https://www.openaccess.nl/en/in-the-netherlands/you-share-we-take-care)

SUPPLEMENTAL INFORMATION

ESTIMATION OF CAFFEINE INTAKE FROM ANALYSIS OF CAFFEINE METABOLITES IN WASTEWATER

Emma Gracia-Lor[a,b*], Nikolaos I. Rousis[a], Ettore Zuccato[a], Richard Bade[b,c], Jose Antonio Baz-Lomba[d,e], Erika Castrignanò[f], Ana Causanilles[g], Félix Hernández[b], Barbara Kasprzyk-Hordern[f], Juliet Kinyua[h], Ann-Kathrin McCall[i], Alexander L.N. van Nuijs[h], Benedek G. Plósz[j,k], Pedram Ramin[j,l], Yeonsuk Ryu[d,e], Miguel M. Santos[m,n], Kevin Thomas[d,o], Pim de Voogt[g,p], Zhugen Yang[f,q] and Sara Castiglioni[a]*

[a]IRCCS – Istituto di Ricerche Farmacologiche "Mario Negri", Department of Environmental Health Sciences, Via La Masa 19, 20156, Milan, Italy

[b]Research Institute for Pesticides and Water, University Jaume I, Avda. Sos Baynat s/n, E-12071, Castellon, Spain

[c]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia 5000, Australia

[d]Norwegian Institute for Water Research (NIVA), Gaustadalléen 21, 0349 Oslo, Norway

[e] Faculty of Medicine, University of Oslo, PO box 1078 Blindern, 0316, Oslo, Norway

[f]University of Bath, Department of Chemistry, Faculty of Science, Bath BA2 7AY, United Kingdom

[g]KWR Watercycle Research Institute, Chemical Water Quality and Health, P.O. Box 1072, 3430 BB, Nieuwegein, The Netherlands

[h]Toxicological Center, Department of Pharmaceutical Sciences, Campus Drie Eiken, University of Antwerp, Universiteitsplein 1, 2610 Antwerp, Belgium

[i]Eawag, Swiss Federal Institute of Aquatic Science and Technology, CH-8600, Dübendorf, Switzerland

[j]Department of Environmental Engineering, Technical University of Denmark, Bygningstorvet, Building 115, DK-2800 Kgs. Lyngby, Denmark

[k]Department of Chemical Engineering, University of Bath, Claverton Down, Bath BA2 7AY, UK

[l]Department of Chemical and Biochemical Engineering, Technical University of Denmark, Søltofts Plads, Building 229, DK-2800 Kgs. Lyngby, Denmark

[m]CIMAR/CIIMAR-Interdisciplinary Centre of Marine and Environmental Research, University of Porto, Avenida General Norton de Matos, S/N, 4450-208 Matosinhos, Portugal

[n]FCUP – Department of Biology, Faculty of Sciences, University of Porto, Rua do Campo Alegre, 4169-007 Porto, Portugal

[o]Queensland Alliance for Environmental Health Sciences (QAEHS), University of Queensland, 39 Kessels Road Coopers Plains, Queensland 4108 Australia

[p]Institute for Biodiversity and Ecosystem Dynamics, University of Amsterdam, P.O. Box 94248, 1090 GE, Amsterdam, The Netherlands

[q]Division of Biomedical Engineering, School of Engineering, University of Glasgow, Glasgow G12 8LT United Kingdom

***Corresponding author:**

E-mail addresses: lor@uji.es (E. Gracia-Lor), sara.castiglioni@marionegri.it (S. Castiglioni)

Table of Contents

Table S1. Excretory profile of caffeine and its metabolites

Table S2. Main characteristics of the wastewater treatment plants (WWTPs) investigated

Table S3. Precursor and products ions of the analyzed compounds with the associated collision energies

Table S4. Linearities, recoveries, repeatibilities and quantification limits

Table S1. Excretory profile of caffeine and its metabolites

Caffeine (1,3,7-trimethylxanthine)

References	Dose	Subjects treated	Duration (h)	Caffeine excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	1.8	
(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	3.7	1
(Callahan et al., 1982)	5 mg/kg (^{14}C-labeled caffeine)	10	48	1.1	0.59
(Callahan et al., 1983)	5 mg/kg (2-^{14}C)caffeine	4 males 4 females oral contraceptives 4 ovulating females	96	1.46 2.61 1.33	0.4 1.19 0.45
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	1.93 2.35	0.57 2.05
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	3.3 2.0	1.4 1.1
(Carrillo and Benitez, 1994)	300 mg	107	24	1.4	0.07

Paraxanthine (1,7-dimethylxanthine)

References	Dose	Subjects treated	Duration (h)	Paraxanthine excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	5	
(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	7.1	1.7
(Callahan et al., 1982)	5 mg/kg (^{14}C-labeled caffeine)	10	48	5.7	1.64
(Callahan et al.,	5 mg/kg (2-^{14}C)caffeine	4 males	96	5.39	1.63

1983)		4 females oral contraceptives 4 ovulating females		5.49 3.45	0.26 0.18
(Grant et al., 1983)	300 mg	68	24	4.8	2.4
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	3.37 3.49	1.47 1.87
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	5.8 4.7	1.1 0.9
(Carrillo and Benitez, 1994)	300 mg	107	24	4.08	0.18

1-methylxanthine

References	Dose	Subjects treated	Duration (h)	1-methylxanthine excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	16	
(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	10	3
(Callahan et al., 1982)	5 mg/kg (^{14}C-labeled caffeine)	10	48	16.31	3.76
(Callahan et al., 1983)	5 mg/kg (2-^{14}C)caffeine	4 males 4 females oral contraceptives 4 ovulating females	96	14.88 9.32 12.28	1.94 1.44 4.75
(Grant et al., 1983)	300 mg	68	24	10.1	4.1
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	8.9 9.48	5.4 3.7
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	7.3 11.4	3.4 2.1
(Carrillo and Benitez, 1994)	300 mg	107	24	9.13	0.4

7-methylxanthine

References	Dose	Subjects treated	Duration (h)	7-methylxanthine excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	8.5	
(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	4	1.6
(Callahan et al., 1983)	5 mg/kg (2-^{14}C)caffeine	4 males 4 females oral contraceptives 4 ovulating females	96	1.84 1.81 2.17	0.5 0.25 0.45
(Grant et al., 1983)	300 mg	68	24	2.5	1.4
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	2.32 2.4	1.18 1.45
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	5 4	2.6 0.3
(Carrillo and Benitez, 1994)	300 mg	107	24	3.11	0.21

1-methyluric acid

References	Dose	Subjects treated	Duration (h)	1-methyluric acid excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	51	
(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	21	8
(Callahan et al., 1982)	5 mg/kg (^{14}C-labeled caffeine)	10	48	25.55	5.2
(Callahan et al., 1983)	5 mg/kg (2-^{14}C)caffeine	4 males 4 females oral contraceptives 4 ovulating females	96	19.89 11.06 16.14	3.9 1.95 4.79
(Grant et al., 1983)	300 mg	68	24	11.8	5

(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	38.12 22.05	14.23 4.69
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	9.4 19.5	3.7 5.3
(Carrillo and Benitez, 1994)	300 mg	107	24	16.49	0.84

1,7-dimethyluric acid

References	Dose	Subjects treated	Duration (h)	1,7-dimethyluric acid excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	8.5	
(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	7.3	1
(Callahan et al., 1982)	5 mg/kg (^{14}C-labeled caffeine)	10	48	4.32	1.64
(Callahan et al., 1983)	5 mg/kg (2-^{14}C)caffeine	4 males 4 females oral contraceptives 4 ovulating females	96	6.19 9 6.05	3.31 2.04 2.63
(Grant et al., 1983)	300 mg	68	24	6	1.9
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	12.56 7.81	1.99 3.36
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	9.3 7.2	2.9 2.1
(Carrillo and Benitez, 1994)	300 mg	107	24	6.57	0.22

Theophylline (1,3-dimethylxanthine)

References	Dose	Subjects treated	Duration (h)	Theophylline excretion (%)	SD
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	0.48 0.77	0.31 0.69
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	1.6 0.8	0.5 0.4
(Carrillo and Benitez, 1994)	300 mg	107	24	0.5	0.04

Theobromine (3,7-dimethylxanthine)

References	Dose	Subjects treated	Duration (h)	Theobromine excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	3.2	
(Callahan et al., 1982)	5 mg/kg (^{14}C-labeled caffeine)	10	48	1.57	0.46
(Callahan et al., 1983)	5 mg/kg (2-^{14}C)caffeine	4 males 4 females oral contraceptives 4 ovulating females	96	1.21 1.18 0.92	0.29 0.23 0.54
(Grant et al., 1983)	300 mg	68	24	1.1	0.6
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	1.22 2.04	0.79 1.96
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	4.3 1.4	3.4 0.6
(Carrillo and Benitez, 1994)	300 mg	107	24	1.28	0.1

1,3-dimethyluric acid

References	Dose	Subjects treated	Duration (h)	1,3-dimethyluric acid excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	4	
(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	2.9	1
(Callahan et al., 1982)	5 mg/kg (^{14}C-labeled caffeine)	10	48	2.05	0.31
(Grant et al., 1983)	300 mg	68	24	1.2	0.4
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	3.37 2.73	0.89 0.86
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	2.6 1.6	0.9 0.5
(Carrillo and Benitez, 1994)	300 mg	107	24	1.31	0.04

3,7-dimethyluric acid

References	Dose	Subjects treated	Duration (h)	3,7-dimethyluric acid excretion (%)	SD
(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	1.2	0.5
(Carrillo and Benitez, 1994)	300 mg	98	24	0.16	0.13

3-methylxanthine

References	Dose	Subjects treated	Duration (h)	3-methylxanthine excretion (%)	SD
(Latini et al., 1981)	5 mg/kg	4	72	3.5	

(Dan-Shya et al., 1983)	Theophylline (7.5 mg/kg) and caffeine (7.5 mg/kg) 2 weeks later	6	60	2.3	0.3
(Callahan et al., 1982)	5 mg/kg (^{14}C-labeled caffeine)	10	48	2.09 1.98 2.12	0.56 0.24 0.51
(Grant et al., 1983)	300 mg	68	24	1.5	0.7
(Blanchard et al., 1985)	5 mg/kg	5 (elderly) 7 (young)	24	0.94 1.93	0.51 0.91
(Scott et al., 1986)	123-369 mg 300-750 mg	15 pregnant 9 female	24	5.6 2.6	3.2 0.7
(Carrillo and Benitez, 1994)	300 mg	107	24	1.7	0.11

Table S2. Main characteristics of the wastewater treatment plants (WWTPs) investigated

WWTPs investigated (country)	Mean daily flow rate (m^3/day)	Population served by WWTP	Sampling dates (2015)
Bristol (UK)	209,289	886,650	10 – 16 March
Brussels (Belgium)	251,830	954,000	18 – 24 March
Castellón (Spain)	42,372	180,000	25 – 31 March
Copenhagen (Denmark)	144,558	530,000	10 – 16 March
Lugano (Switzerland)	44,386	103,560	25 – 31 March
Milan (Italy)	437,726	1,100,000	10 – 16 March
Oslo (Norway)	276,235	580,000	11 – 17 March
Porto (Portugal)	31,560	150,000	23 – 29 April
Utrecht (The Netherlands)	46,743	300,000	4 – 10 March
Zurich (Switzerland)	180,088	410,000	18 – 24 March

Table S3. Precursor and products ions of the analyzed compounds with the associated collision energies

Compound	Precursor ion (*m/z*)	Product ion 1 (*m/z*) and collision energy (eV)	Product ion 2 (*m/z*) and collision energy (eV)
caffeine	195.1	138 (25)	110 (30)
caffeine-$_3C^{13}$	198.1	140 (25)	-
Paraxanthine (1,7-dimethylxanthine)	181.1	124 (26)	96 (32)
1-methylxanthine	167.1	110 (25)	82 (33)
7-methylxanthine	167.1	124 (24)	150 (24)
1-methyluric acid	182.1	70.1 (30)	126.0 (24)
1,7-dimethyluric acid	197.1	140.1 (25)	69.1 (35)
1,7-dimethyluric acid-d_3	200.1	140.1 (25)	-

Table S4. Linearities, recoveries, repeatability and quantification limits

Compound	Linearity range (ng/mL)	Coefficient of correlation (r^2)	Recovery (%)	Repeatability RSD (%)	MQL (ng/L)
Caffeine*	0-600	0.9989	88	12	3.6
Paraxanthine (1,7-dimethylxanthine)*	0-600	0.9996	76	5	6.6
1-methylxanthine*	0-600	0.9996	72	14	6.1
7-methylxanthine*	0-600	0.9999	64	10	28.5
1-methyluric acid	0-600	0.9988	68	14	220
1,7-dimethyluric acid	0-600	0.9990	87	4	185

*(Senta et al., 2015)

REFERENCES

Blanchard, J., Sawers, S., Jonkman, J., Tang-Liu, D., 1985. Comparison of the urinary metabolite profile of caffeine in young and elderly males. Br. J. Clin. Pharmacol. 19, 225–232. doi:10.1111/j.1365-2125.1985.tb02635.x

Callahan, M.M., Robertson, R.S., Branfman, a. R., McComish, M.F., Yesair, D.W., 1983. Comparison of caffeine metabolism in three nonsmoking populations after oral administration of radiolabeled caffeine. Drug Metab. Dispos. 11, 211–217.

Callahan, M.M., Robertson, R.S., M.J., A., Branfman, A.R., McComish, M.F., Yesair, D.W., 1982. Human metabolism of [1-methyl-14C]- and [2-14C]caffeine after oral administration. Drug Metab. Dispos. 10, 417–423.

Carrillo, J.A., Benitez, J., 1994. Caffeine metabolism in a healthy Spanish population: N-Acetylator phenotype and oxidation pathways. Clin. Pharmacol. Ther. 293–304.

Dan-Shya, D., Tang-Liu, D., Williams, R., Riegelman, S., 1983. Disposition of caffeine and its metabolites in man. J. Pharmacol. Exp. Ther. 224, 180–185.

Grant, D.M., Tang, B.K., Kalow, W., 1983. Variability in caffeine metabolism. Clin. Pharmacol. Ther. 33, 591–602. doi:10.1038/clpt.1983.80

Latini, R., Bonati, M., Marzi, E., Garattini, S., 1981. Urinary excretion of an uracilic metabolite from caffeine y rat, monkey and man. Toxicol. Lett. 7, 267–272.

Scott, N.R., Chakraborty, J., Marks, V., 1986. Urinary metabolites of caffeine in pregnant women. Br. J. Clin. Pharmacol. 22, 475–778.

Senta, I., Gracia-Lor, E., Borsotti, A., Zuccato, E., Castiglioni, S., 2015. Wastewater analysis to monitor use of caffeine and nicotine and evaluation of their metabolites as biomarkers for population size assessment. Water Res. 74, 23–33. doi:10.1016/j.watres.2015.02.002