Supplementary Figure captions:

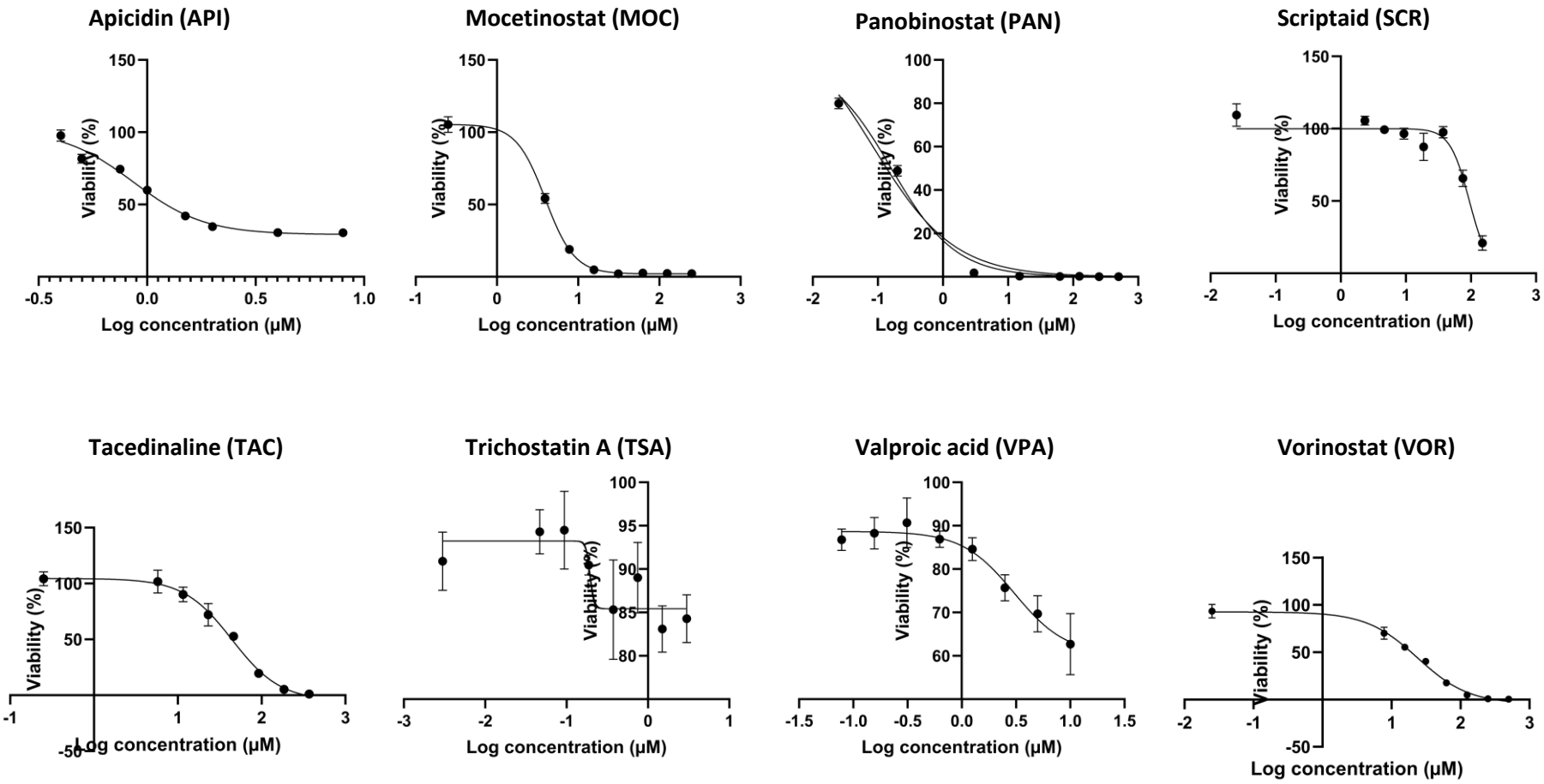
Supplementary Fig. S1 Viability results of the HDACi test chemicals using the CellTiter-Glo Luminescence Viability Assay kit (n = 1). The viability results for the non-HDACi test chemicals were based on our previously published studies (Buick et al., 2021; Ates et al., 2018)

Supplementary Fig. S2 Principal component analysis (PCA) depicting TGx-HDACi-HepaRG classification results for 23 test chemicals. HDACi chemicals are shown in panels: (2A) apicidin (API); (2B) mocetinostat (MOC); (2C) panobinostat (PAN); (2D) scriptaid (SCR); (2E) tacedinaline (TAC); (2F) trichostatin A (TSA); (2G) vorinostat (VOR); and, (2H) valproic acid (VPA). Non-HDACi chemicals are shown in panels: (2I) 2-deoxy-D-glucose (2DG); (2J) aflatoxin B1 (AFB1); (2K) cytosine arabinoside (AraC); (2L) benzo[a]pyrene (BaP); (2M) cisplatin (CISP); (2N) cyclophosphamide (CP); (2O) N-ethyl-N-nitrosourea (ENU); (2P) eugenol (EUG); (2Q) glycidol (GLY); (2R) methyl methanesulfonate (MMSa from Buick et al., 2021); (2S) methyl methanesulfonate (MMSb from Ates et al., 2018); (2T) N-nitrosodimethylamine (NDMA); (2U) propyl gallate (PG); (2V) urea; and, (2W) zidovudine (ZDV). PCA using the TGx-HDACi-HepaRG biomarker for HepaRG cells exposed to the training set of chemicals (red font = HDACi training set; blue font = non-HDACi training set) and for human HepaRG cells exposed to 23 test chemicals at five increasing concentrations (C1-C5) in a 72 hour repeat exposure design (green font = additional concentrations of test HDACi agents and black font = additional concentrations of non-HDACi agents). The line drawn at 0 on the PCA plot divides the HDACi and non-HDACi agents and was used for classification.

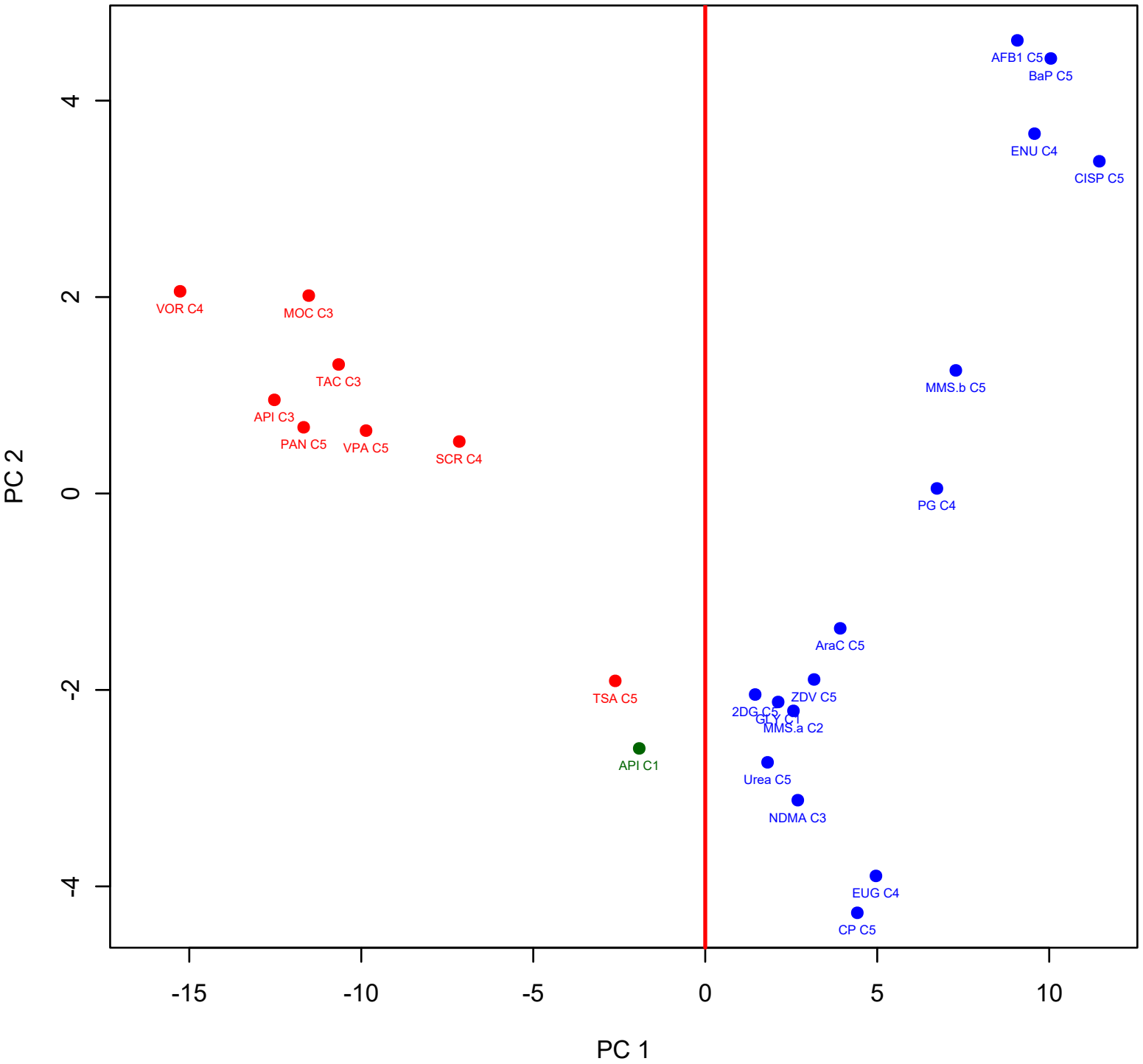
Supplementary Fig. S3 Hierarchical clustering (HC) depicting TGx-HDACi-HepaRG classification results for 23 test chemicals. HDACi chemicals are shown in panels: (3A) apicidin (API); (3B) mocetinostat (MOC); (3C) panobinostat (PAN); (3D) scriptaid (SCR); (3E) tacedinaline (TAC); (3F) trichostatin A (TSA); (3G) vorinostat (VOR); and, (3H) valproic acid (VPA). Non-HDACi chemicals are shown in panels: (3I) 2-deoxy-D-glucose (2DG); (3J) aflatoxin B1 (AFB1); (3K) cytosine arabinoside (AraC); (3L) benzo[a]pyrene (BaP); (3M) cisplatin (CISP); (3N) cyclophosphamide (CP); (3O) N-ethyl-N-nitrosourea (ENU); (3P) eugenol (EUG); (3Q) glycidol (GLY); (3R) methyl methanesulfonate (MMSa from Buick et al., 2021); (3S) methyl methanesulfonate (MMSb from Ates et al., 2018); (3T) N-nitrosodimethylamine (NDMA); (3U) propyl gallate (PG); (3V) urea; and, (3W) zidovudine (ZDV). Hierarchical clustering of the chemicals based on TGx-HDACi-HepaRG classification analysis are shown with color-coding as indicated for PCA. The main branch on the dendrogram separates the HDACi and non-HDACi agents and was used for classification of the test agent.

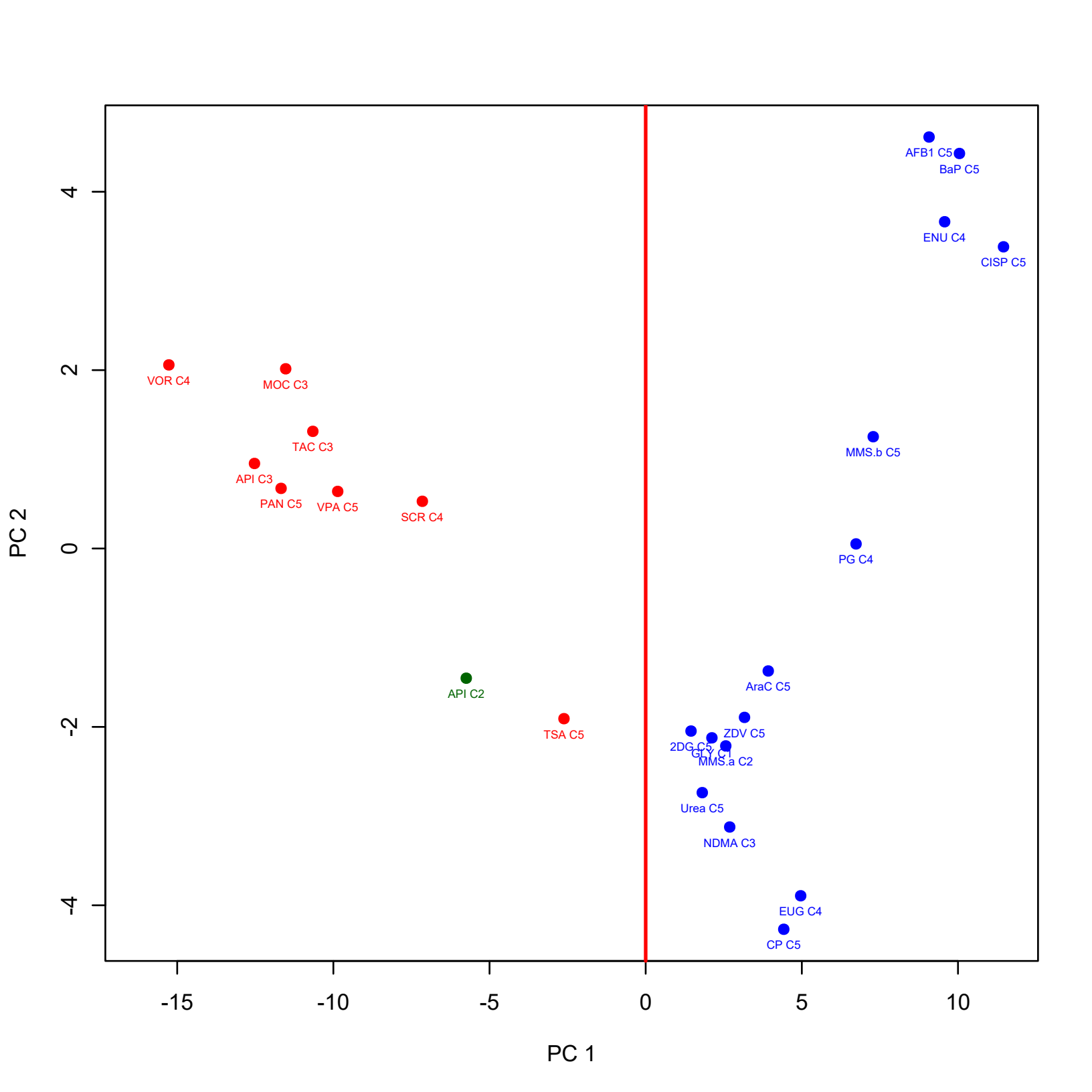
Article title: A Transcriptomic Biomarker to Classify Chemical-Induced Histone Deacetylase Inhibition in Human HepaRG Cells
Journal Name: Archives of Toxicology
Author Names: Julie K. Buick, Eunnara Cho, Anouck Thienpont, Andrew Williams, Birgit Mertens, Vera Rogiers, Tamara Vanhaecke, Carole L. Yauk, Matthew J. Meier
Corresponding Author Affiliation and E-mail Address: Matthew Meier, Research Scientist; Environmental Health Science and Research Bureau, Health Canada; matthew.meier@hc-sc.gc.ca

Supplementary Figure 1



Supplementary Figure 2A: Apicidin (API) Concentrations 1-5 (C1-C5)

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Urea C5
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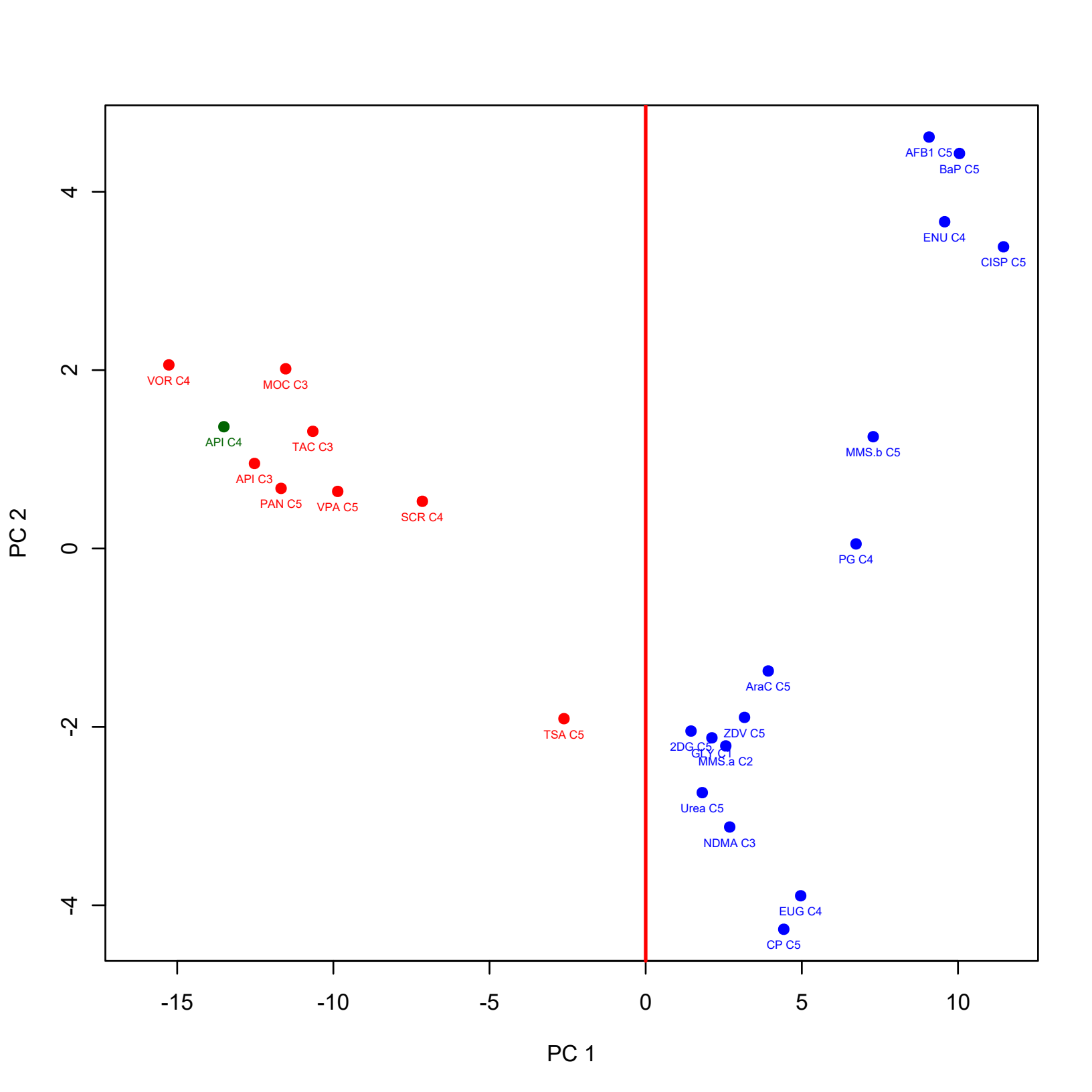
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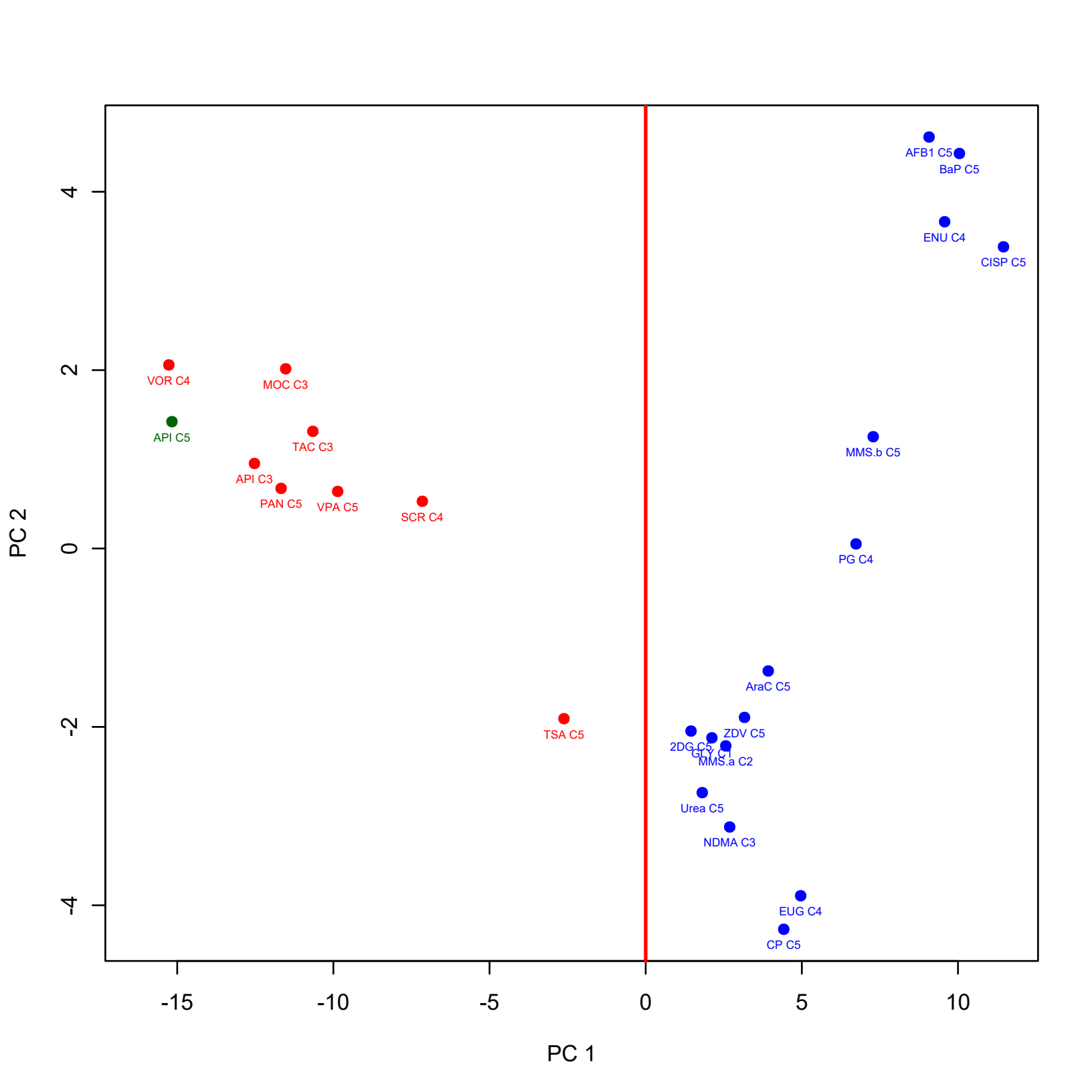
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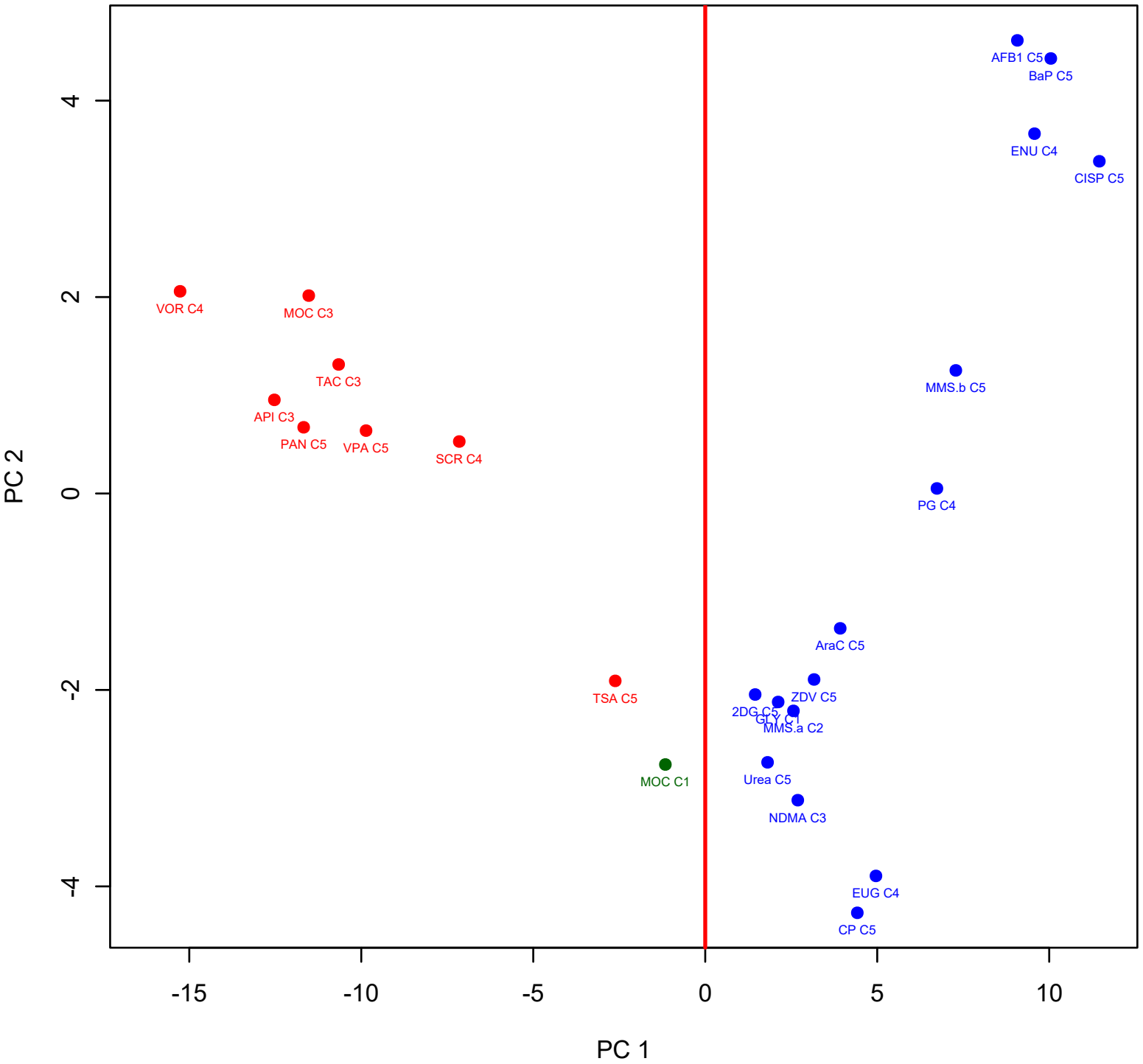
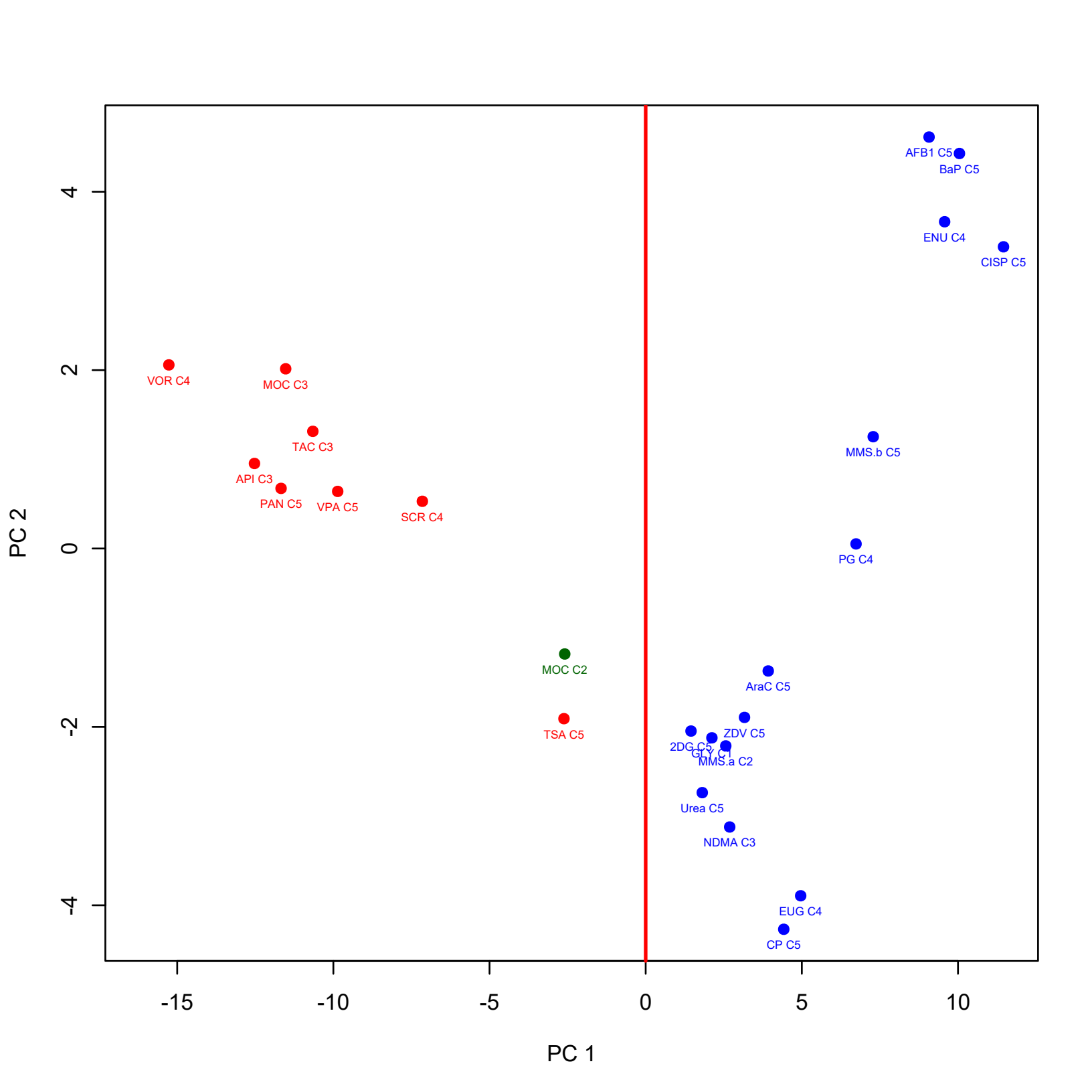
Supplementary Figure 2B: Mocetinostat (MOC) Concentrations 1-5 (C1-C5)

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PG C4
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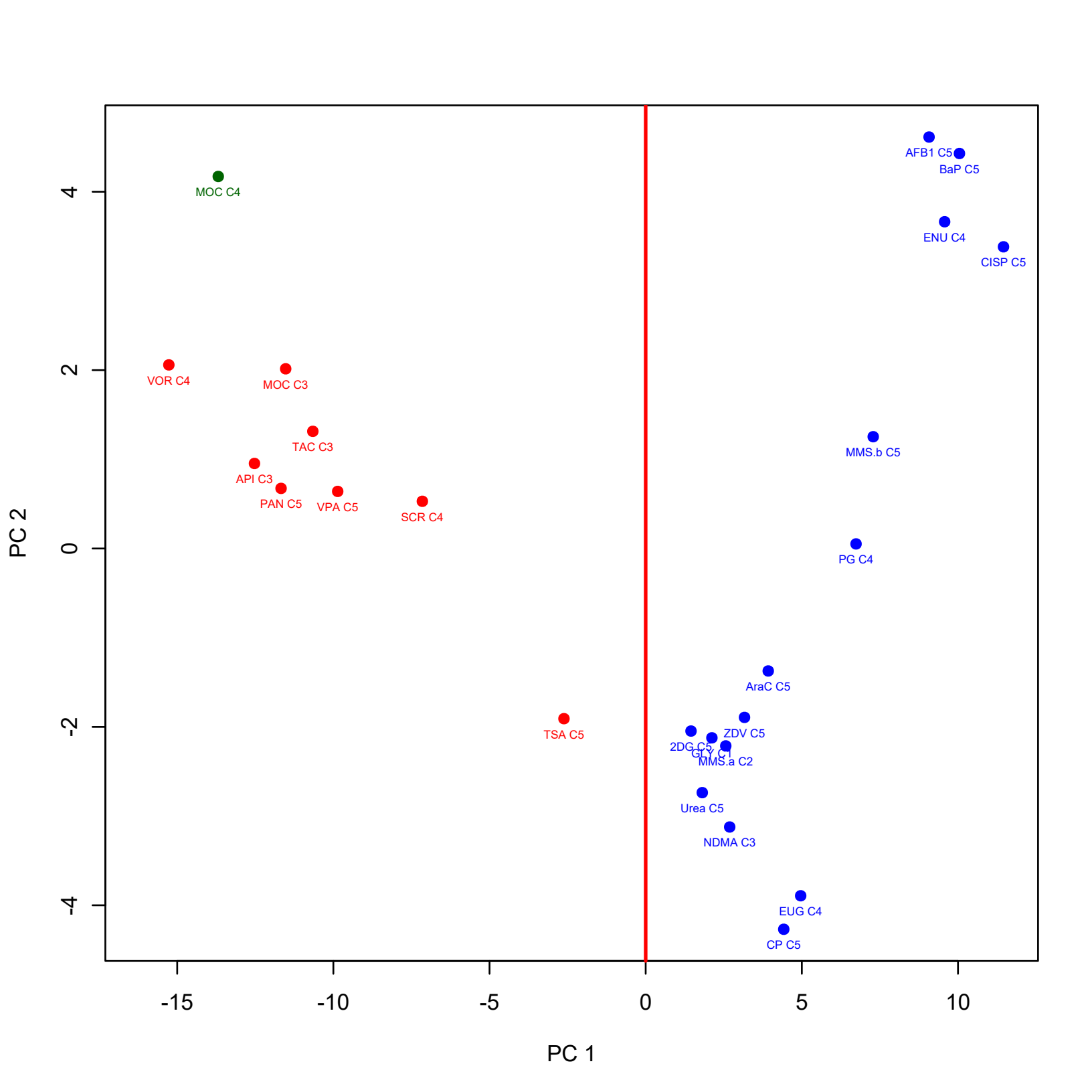
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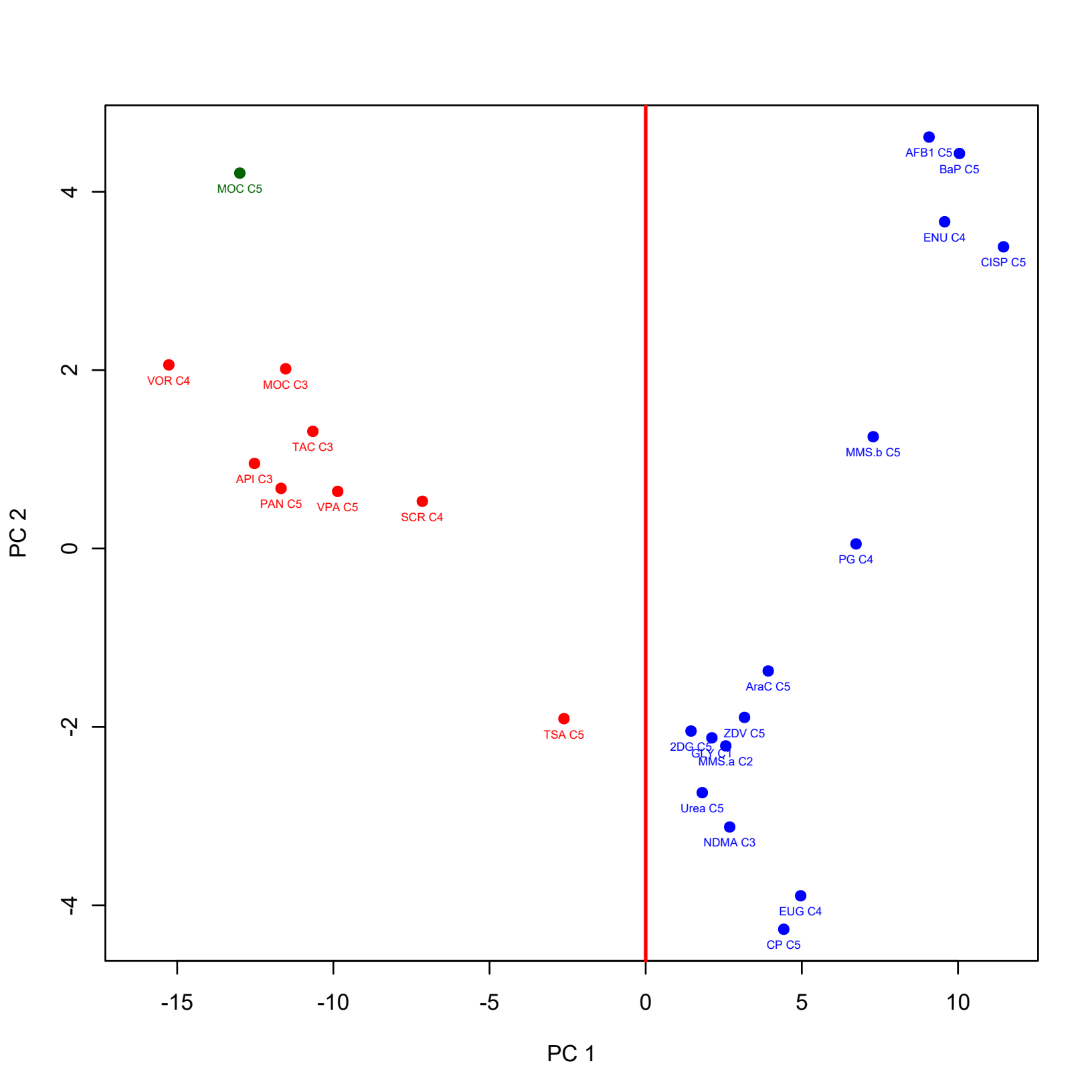
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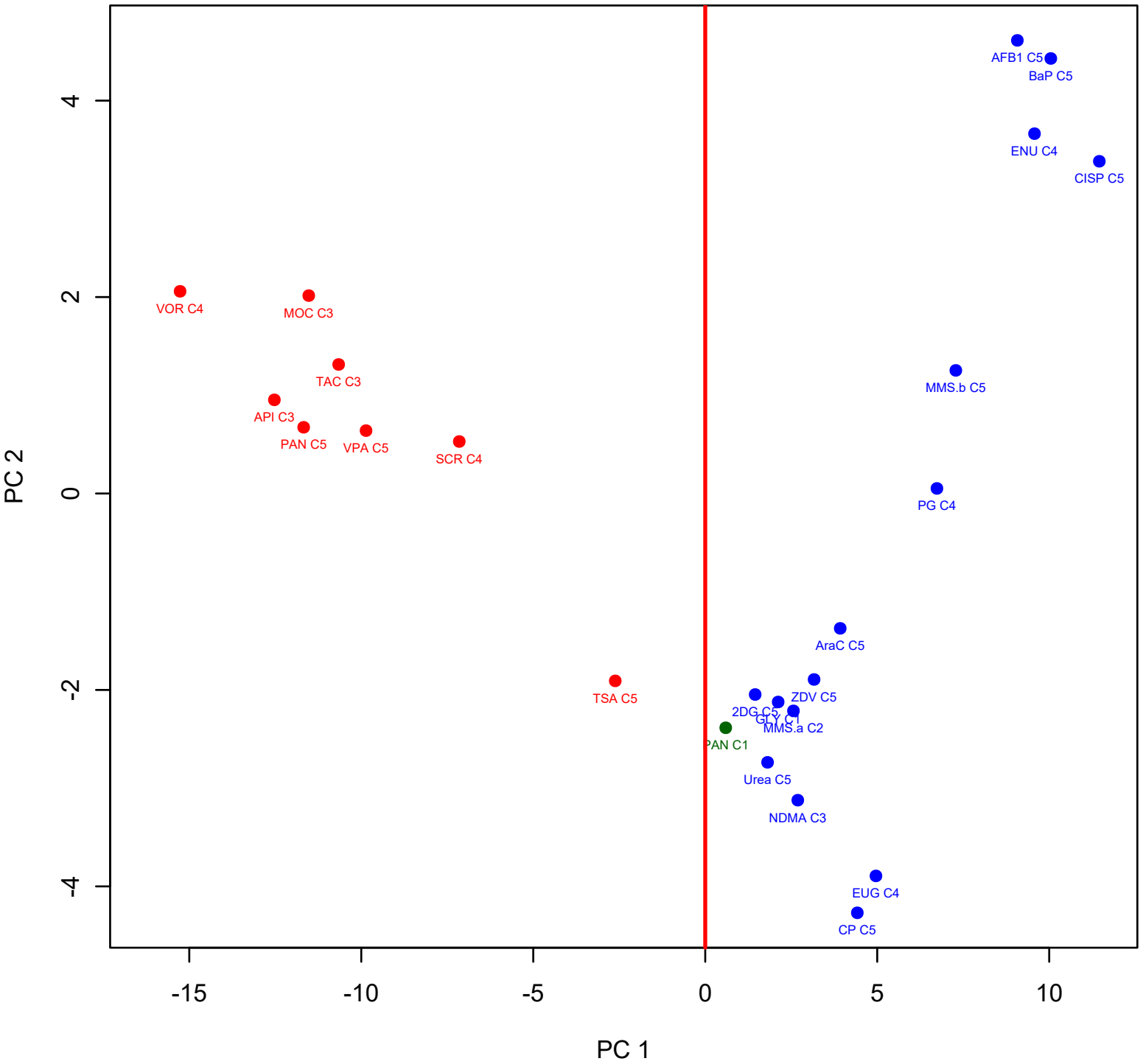
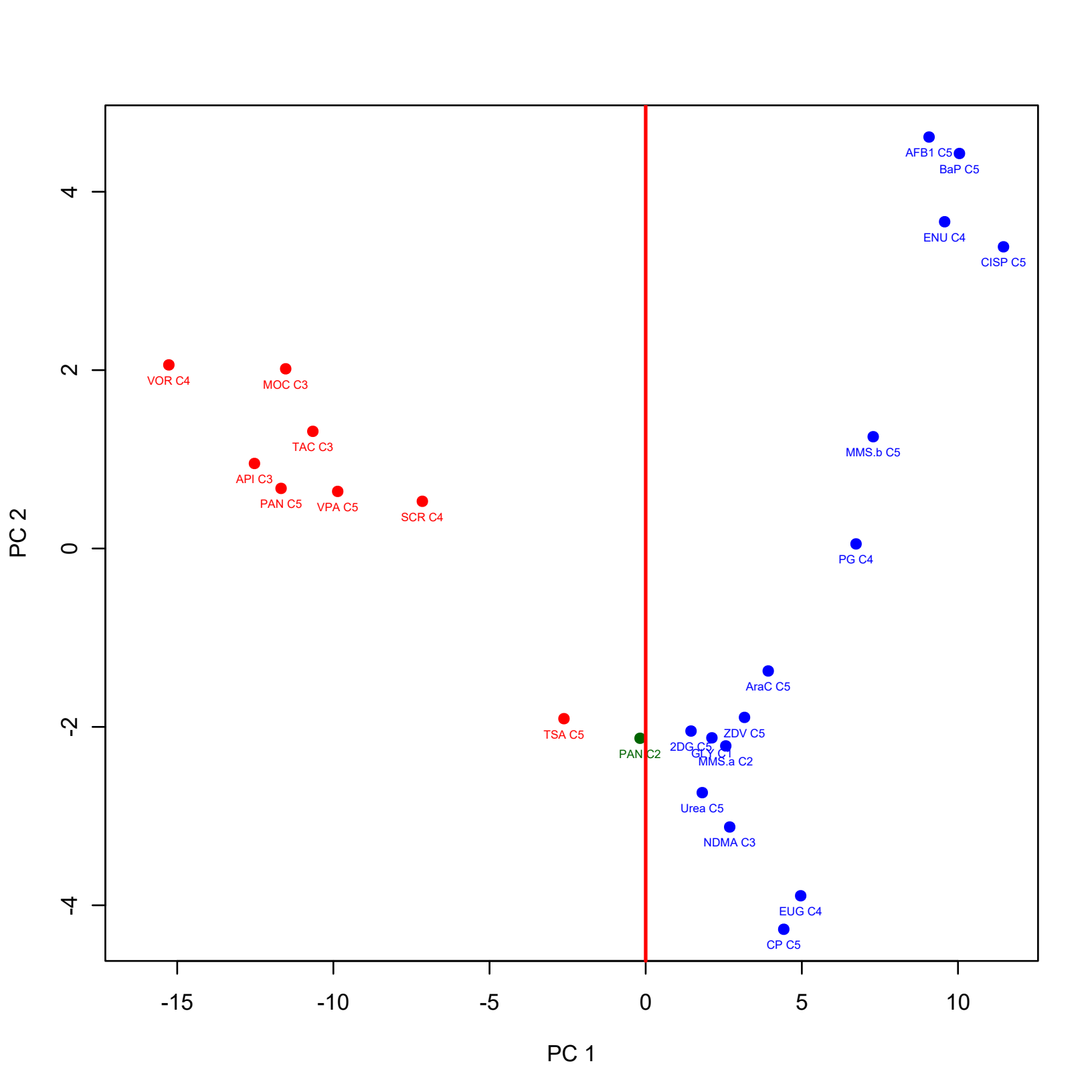
Supplementary Figure 2C: Panobinostat (PAN) Concentrations 1-5 (C1-C5)

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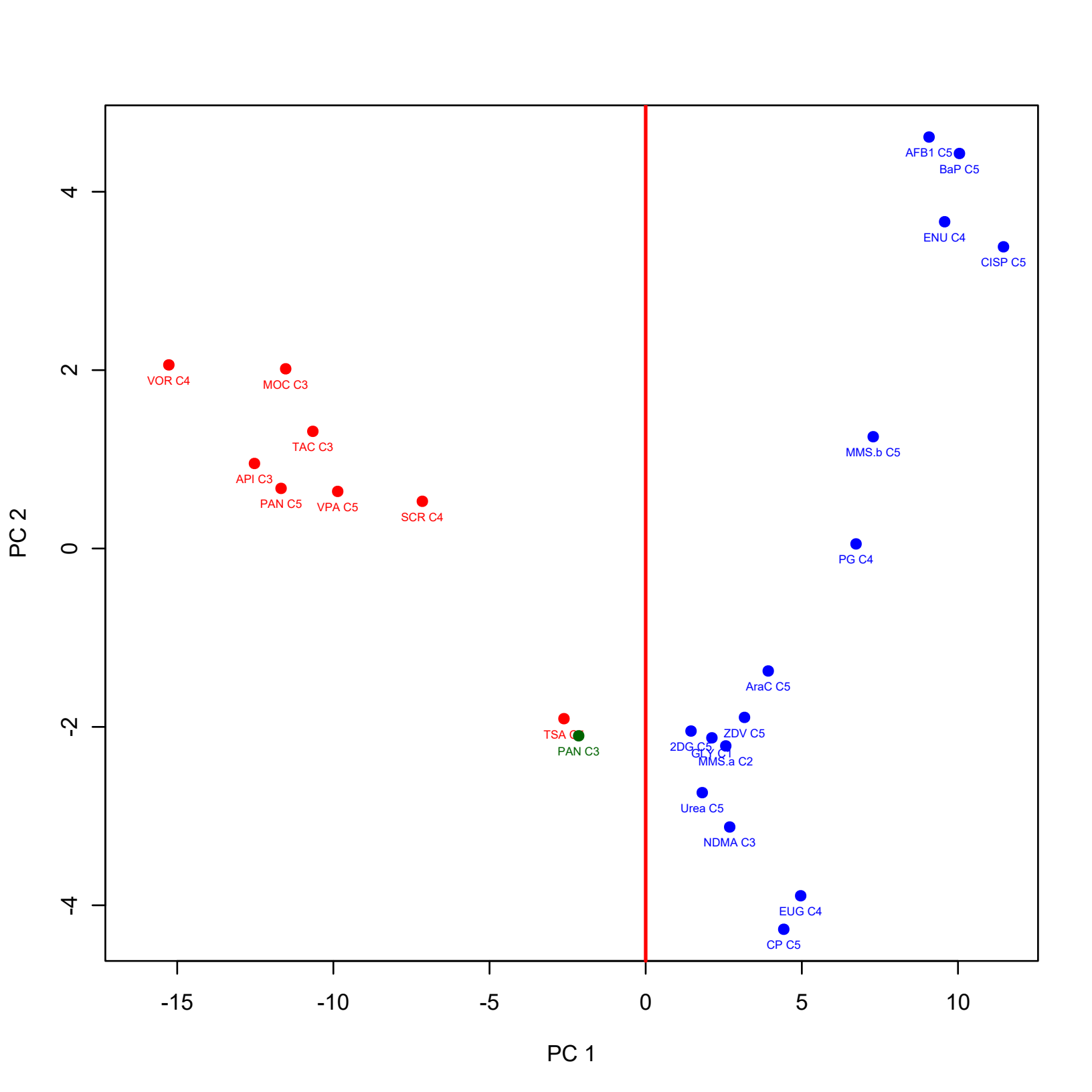
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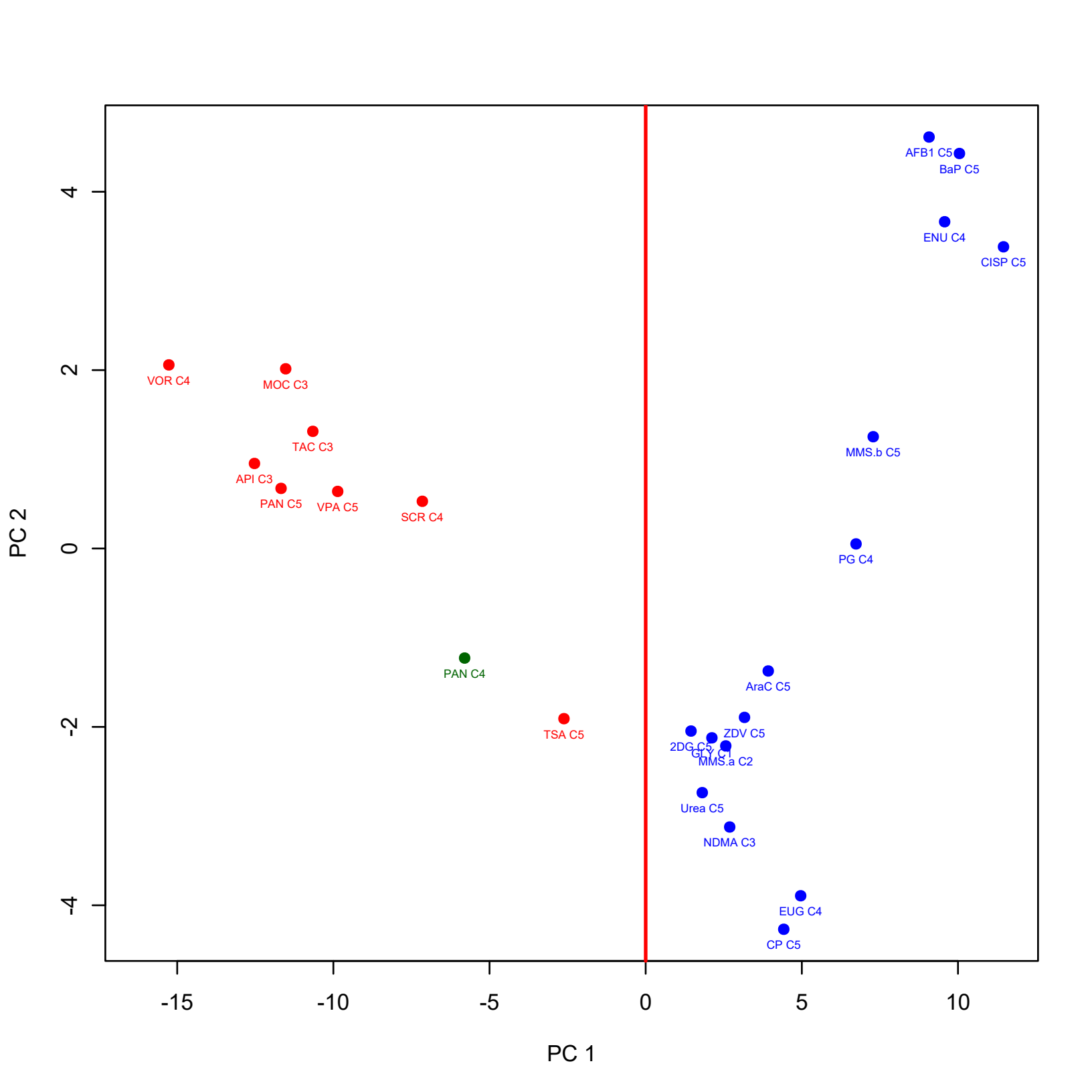
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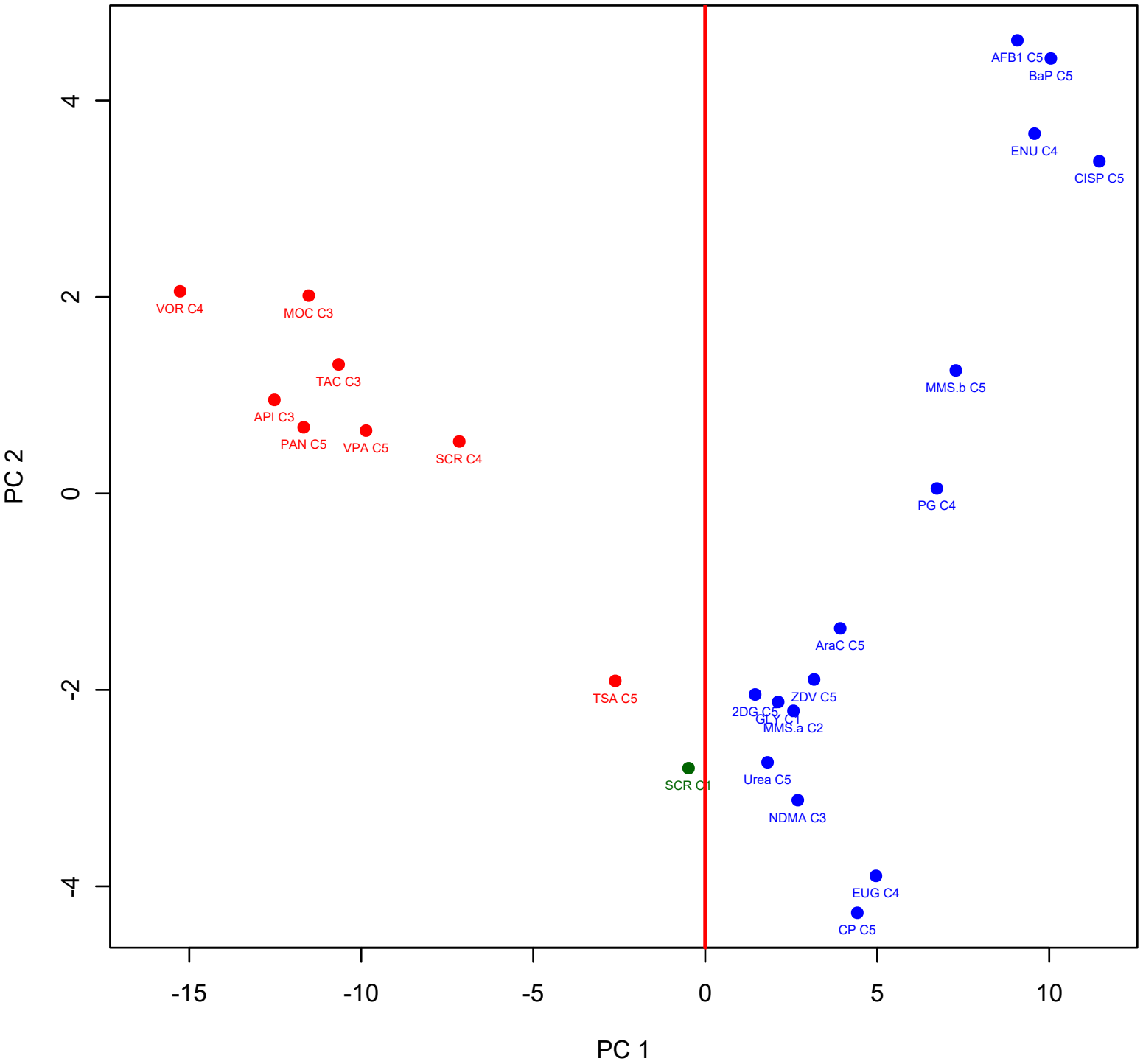
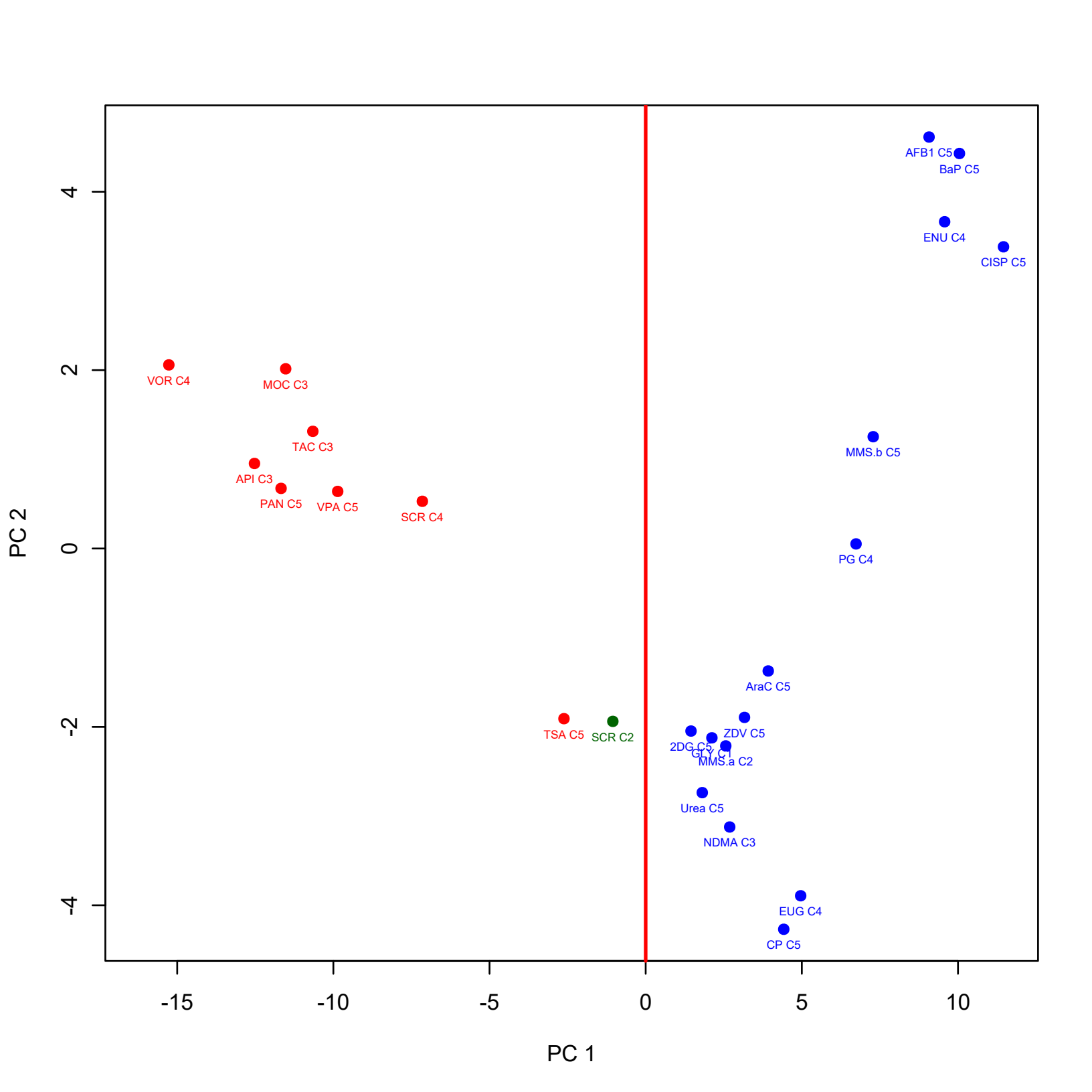
Supplementary Figure 2D: Scriptaid (SCR) Concentrations 1-5 (C1-C5)

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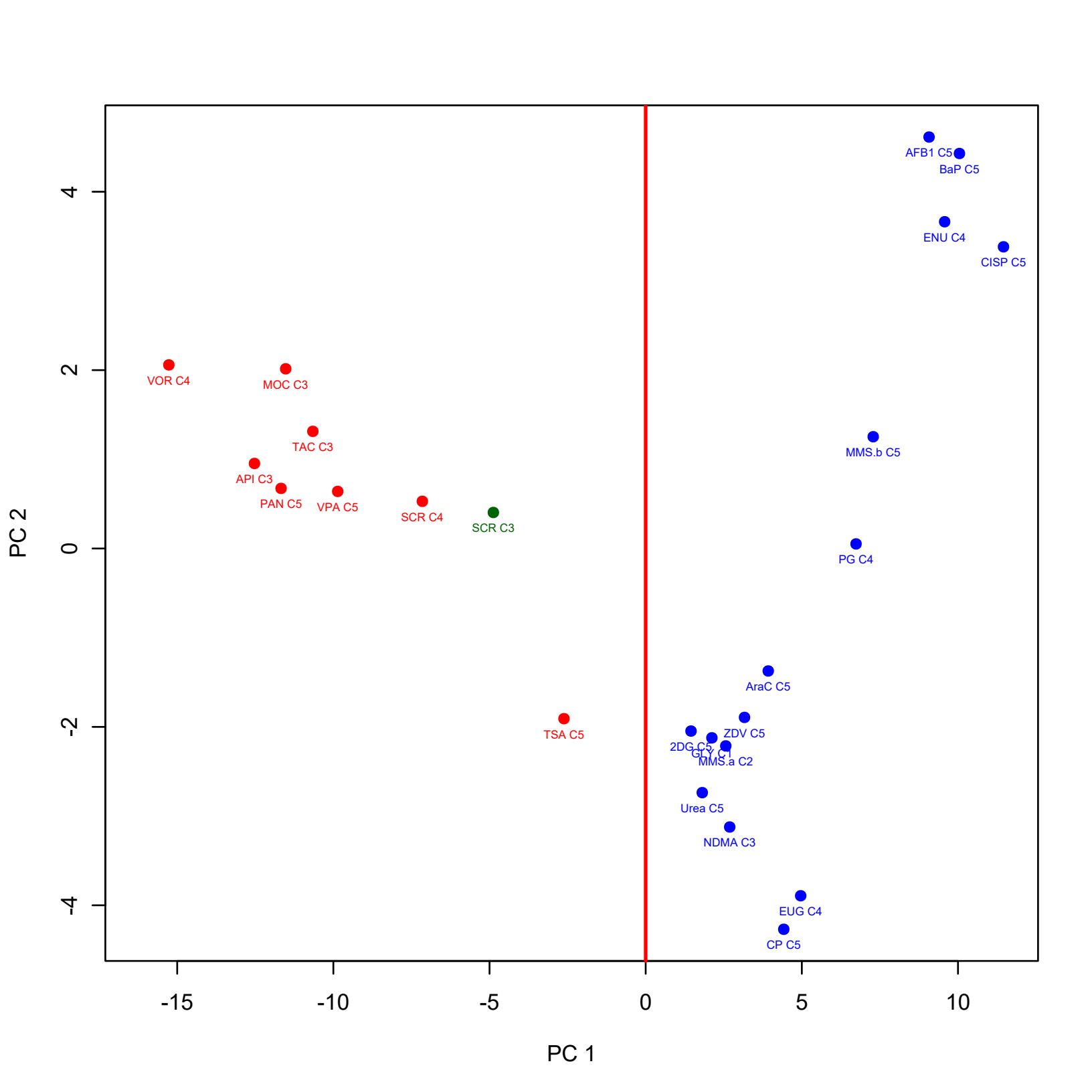
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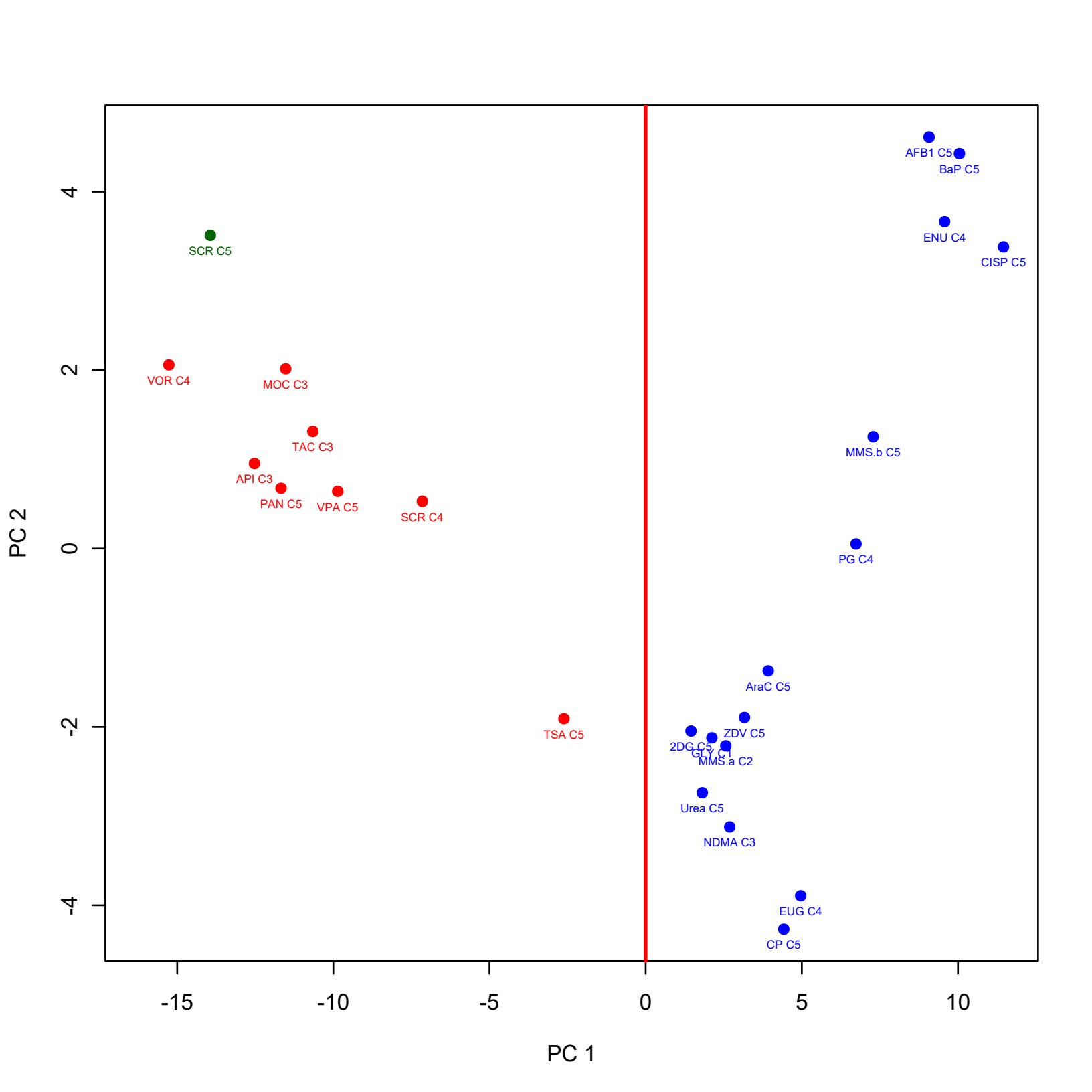
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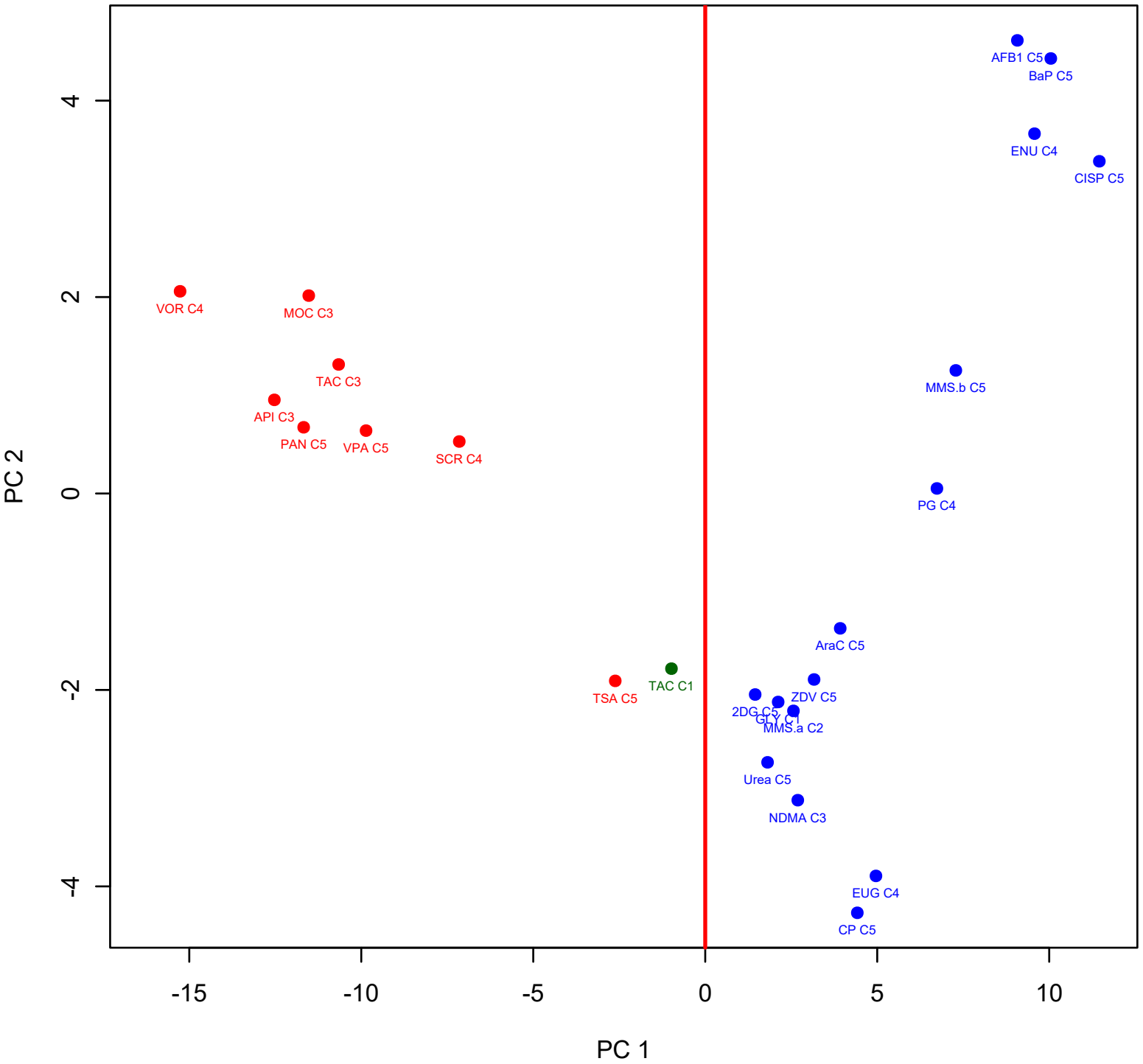
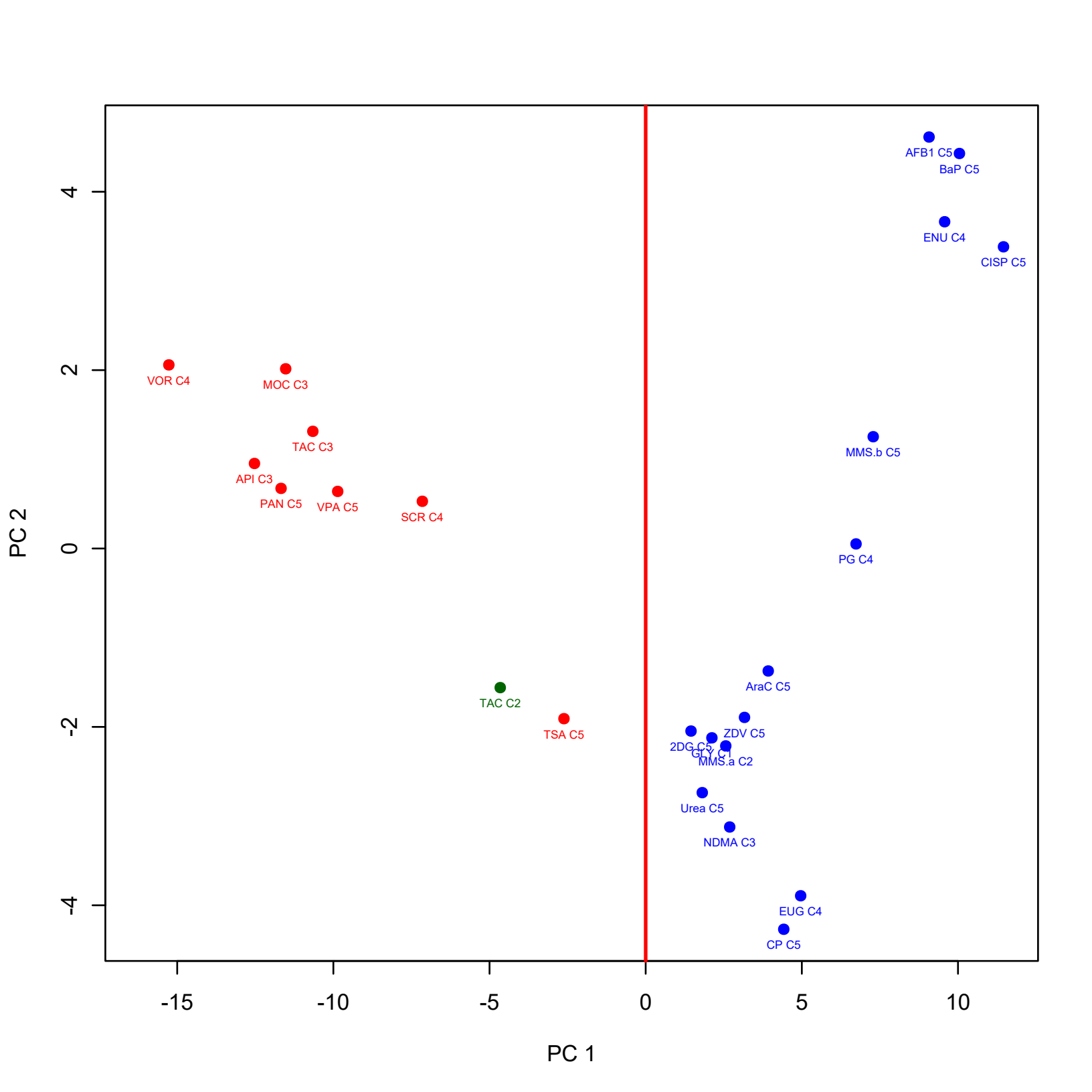
Supplementary Figure 2E: Tacedinaline (TAC) Concentrations 1-5 (C1-C5)

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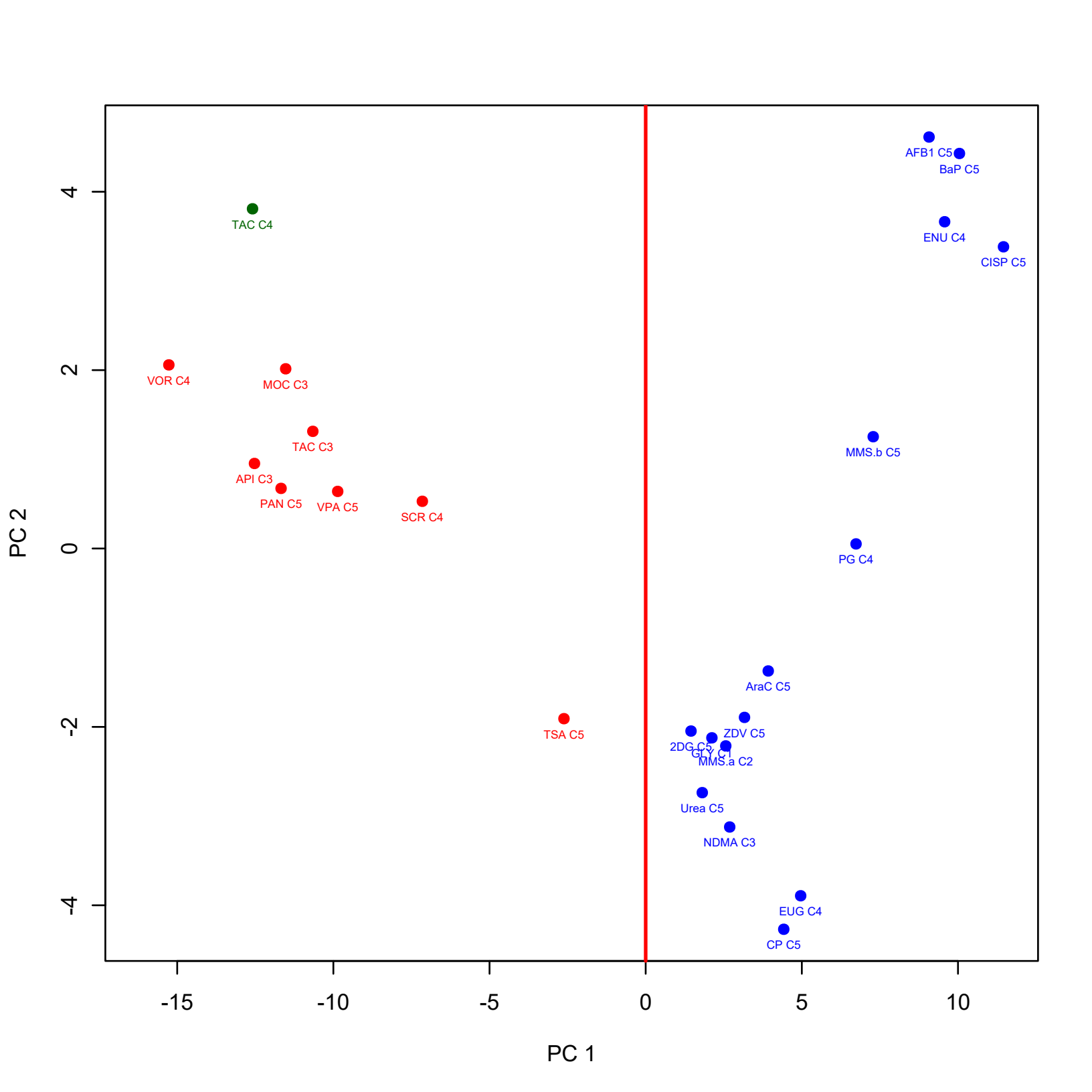
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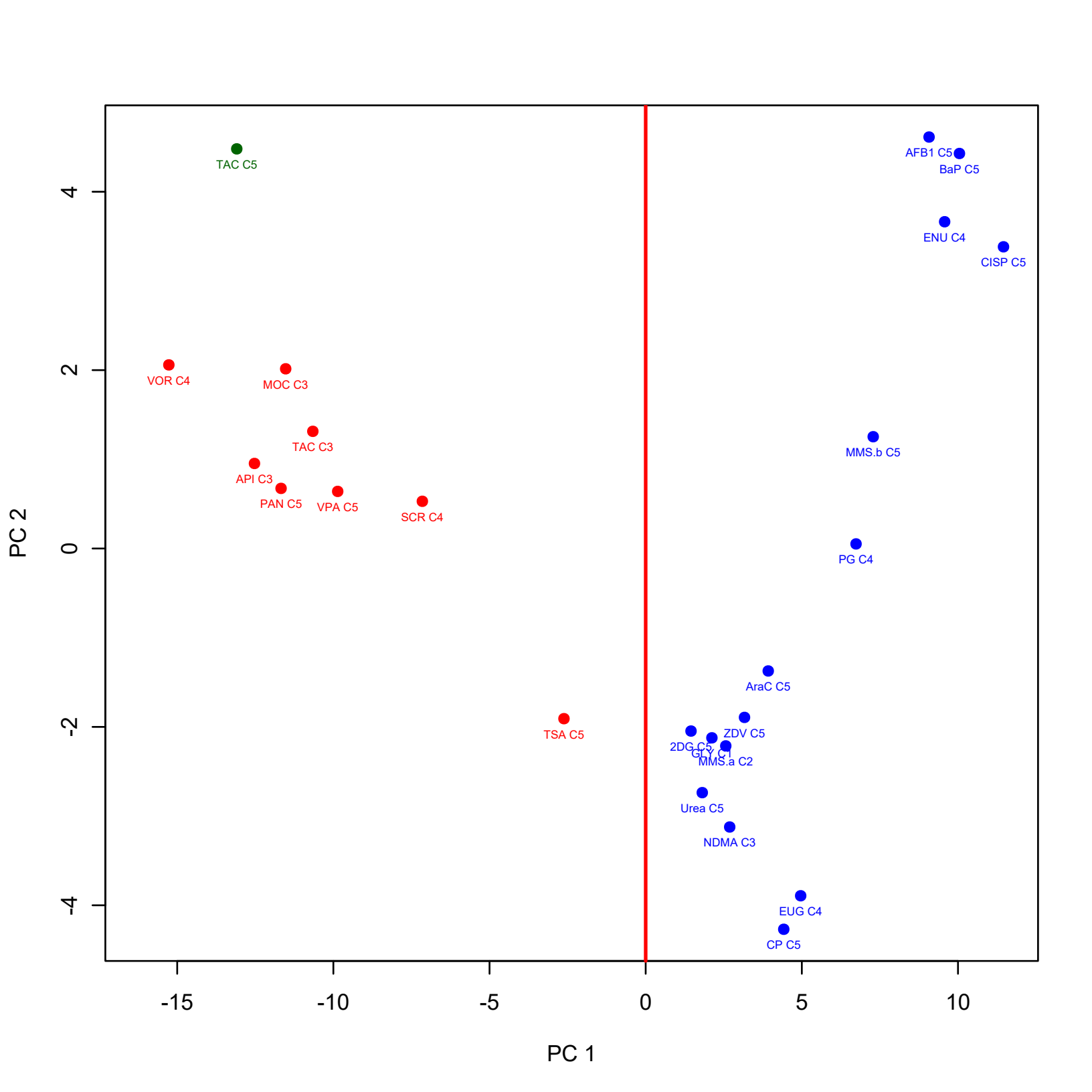
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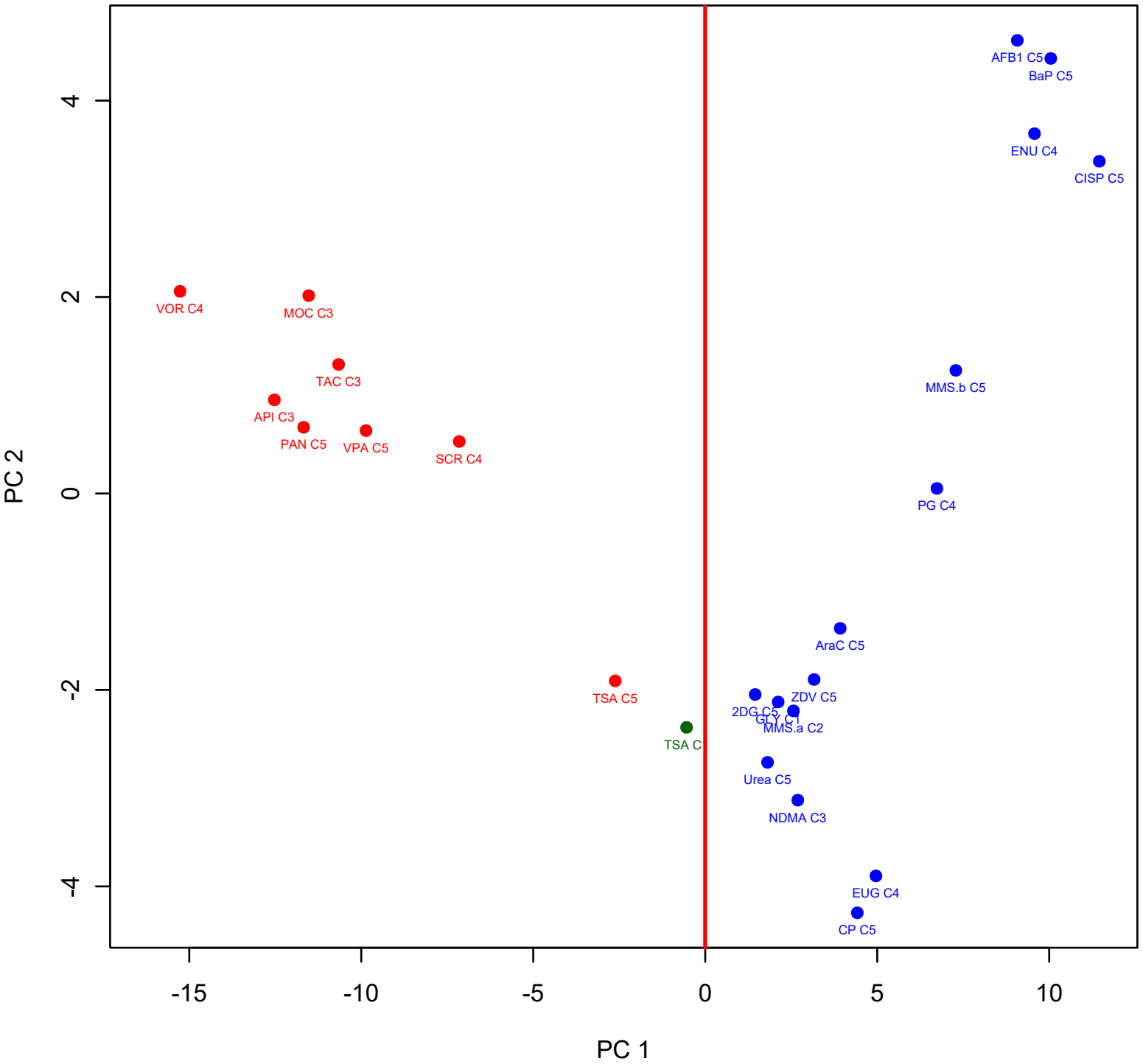
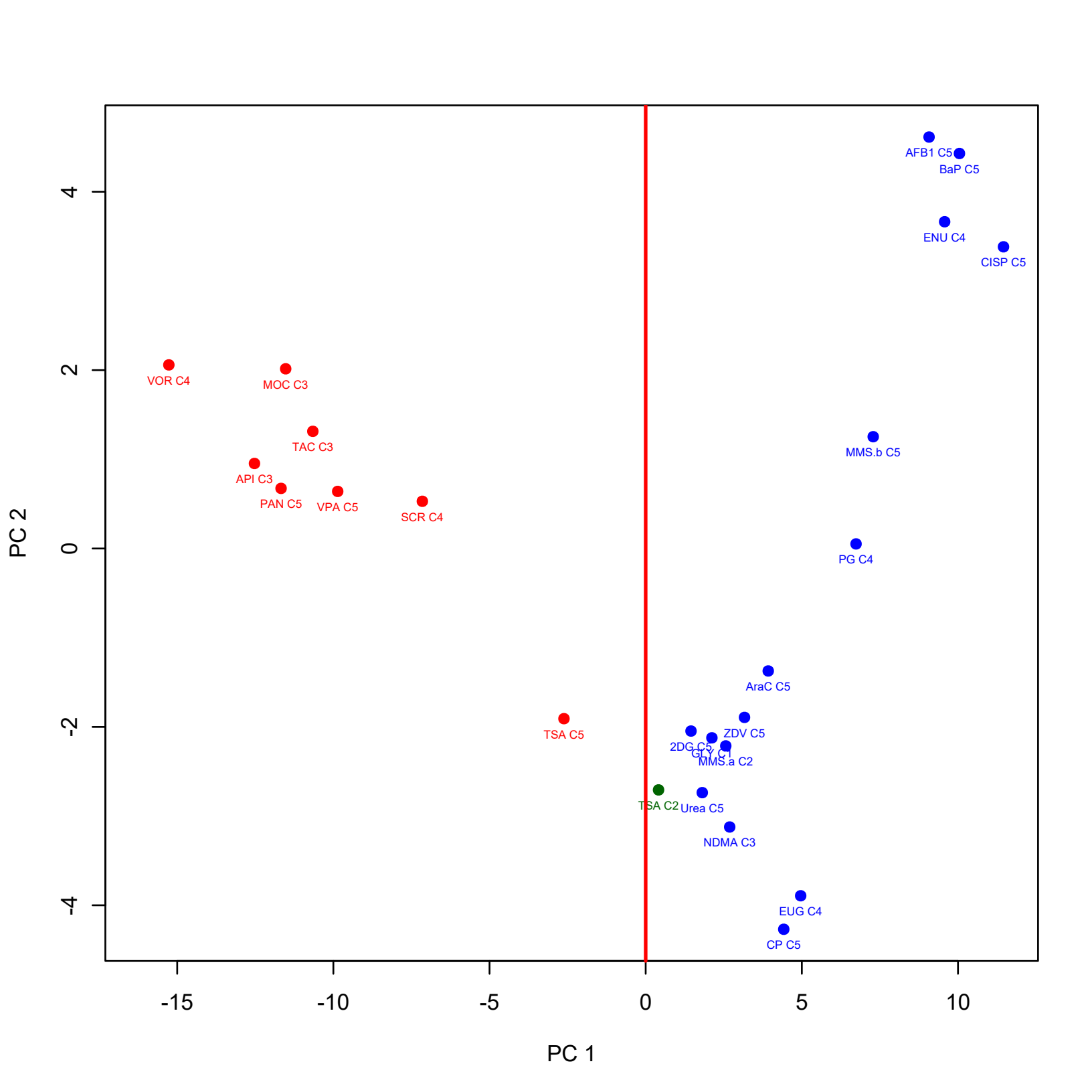
Supplementary Figure 2F: Trichostatin A (TSA) Concentrations 1-5 (C1-C5)

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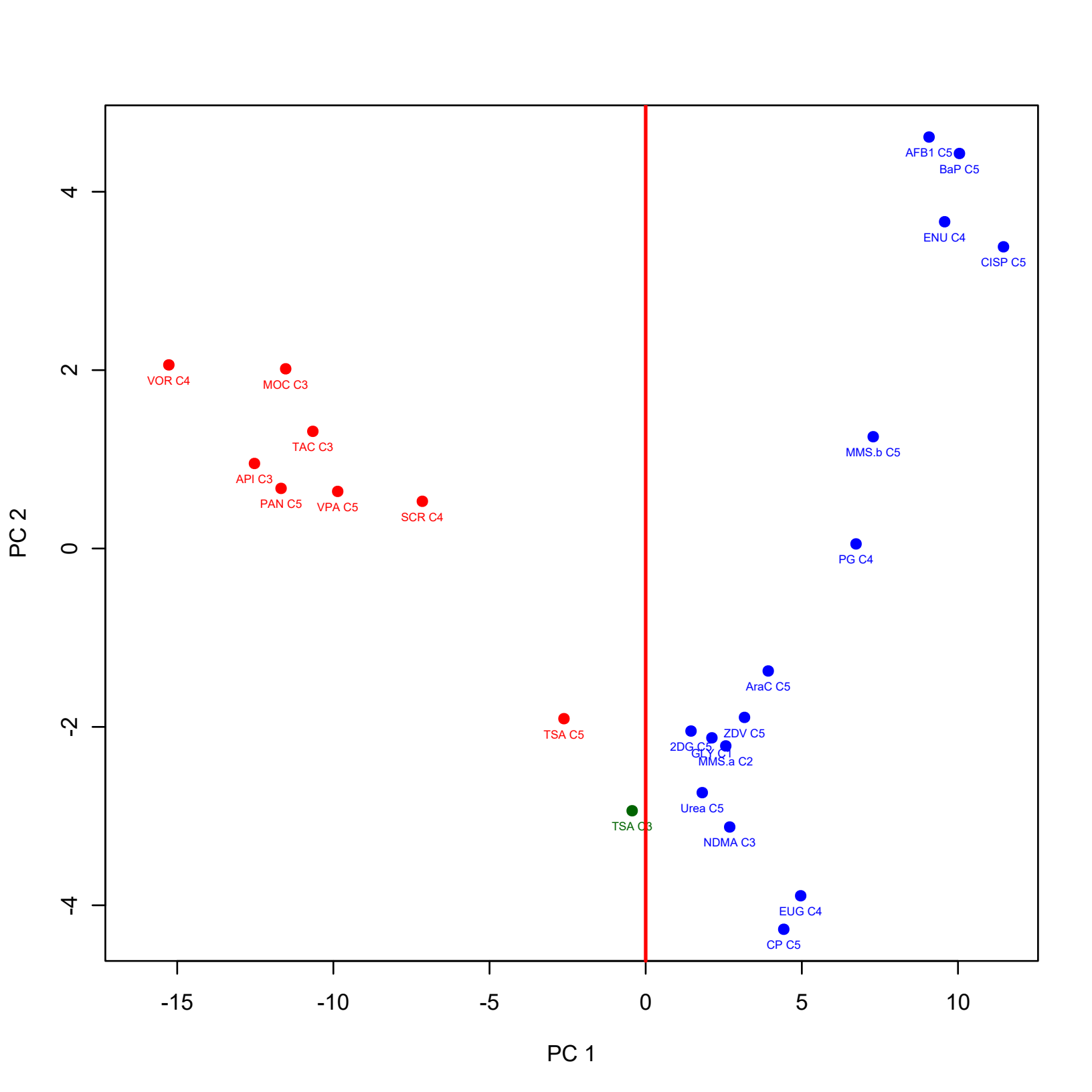
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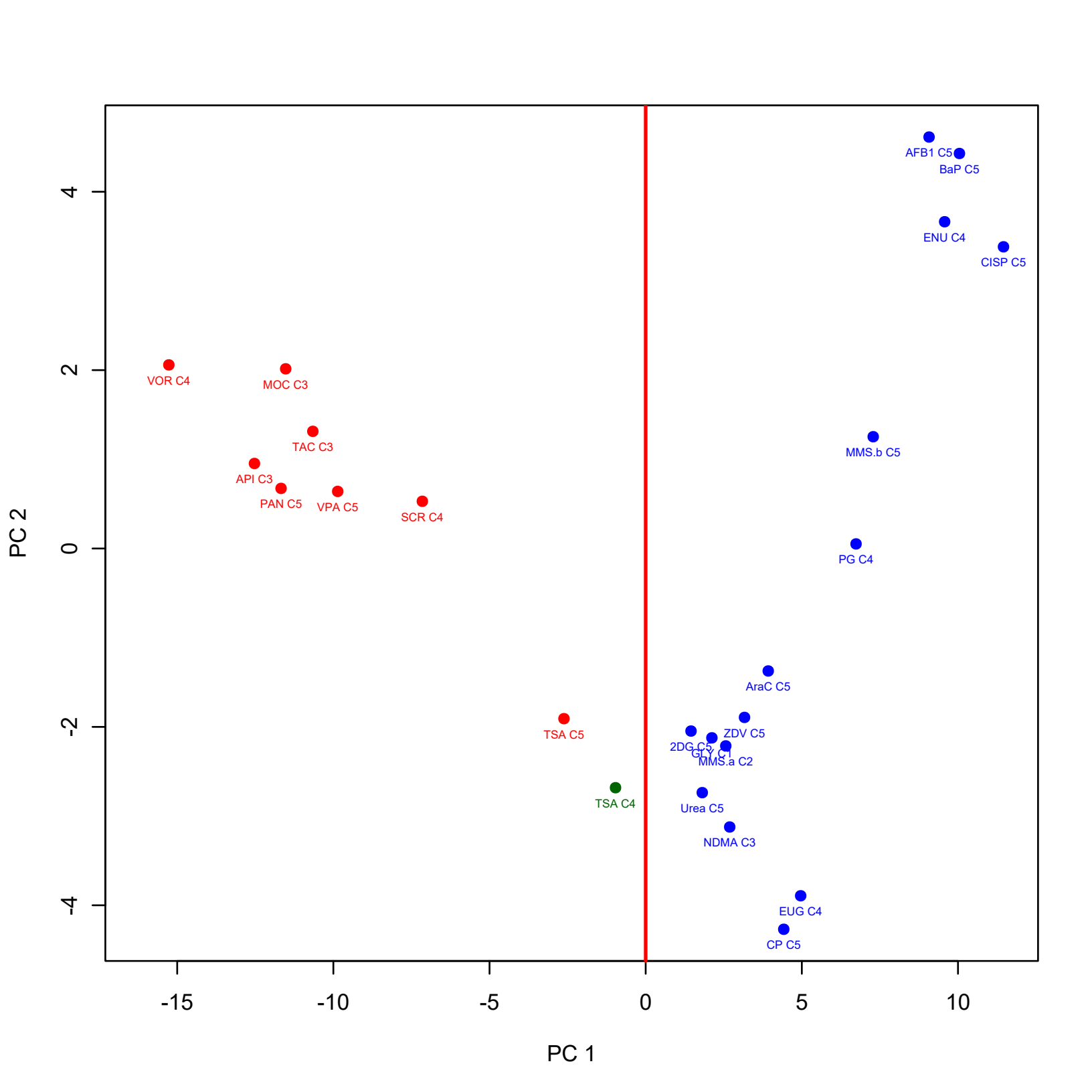
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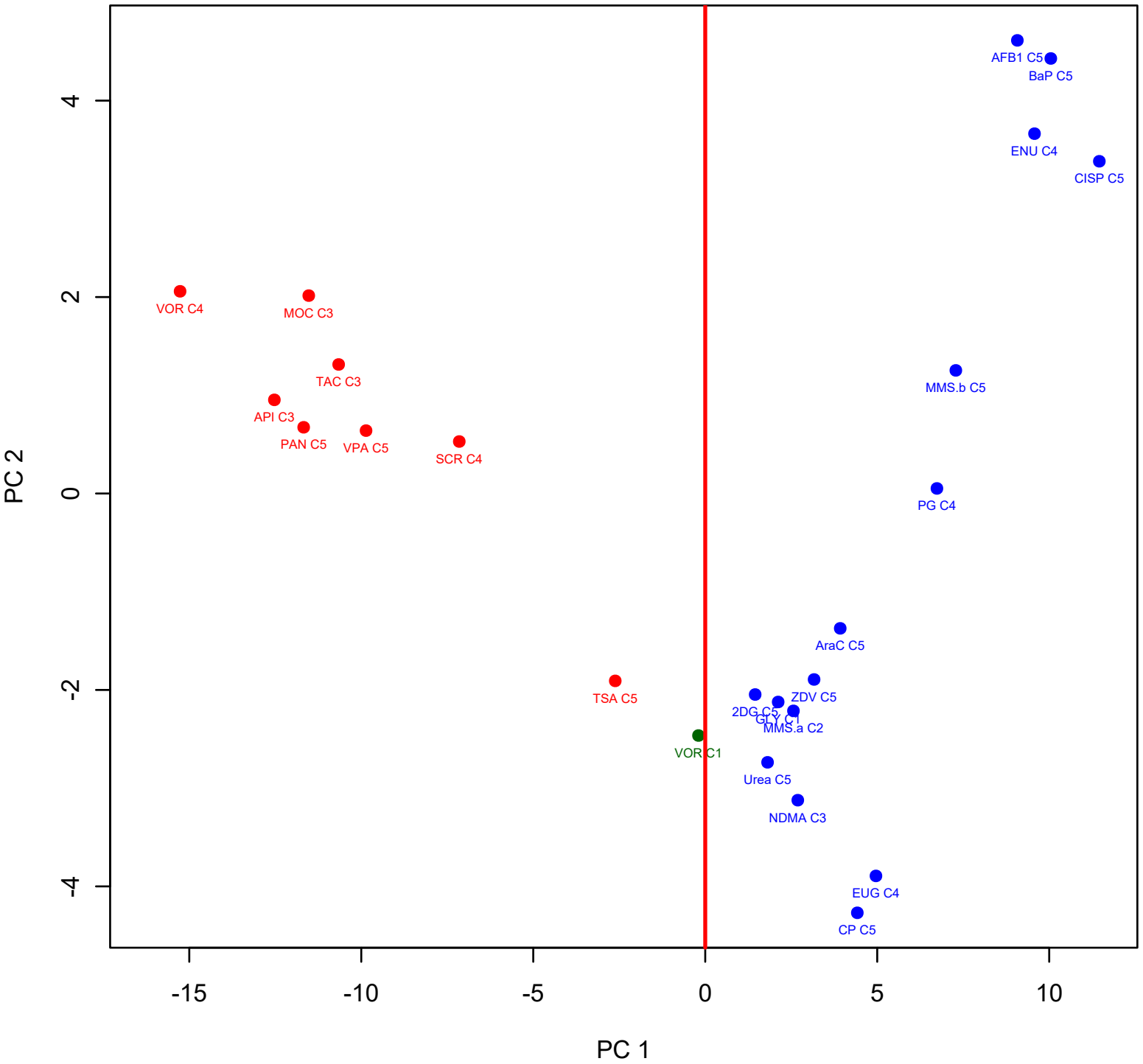
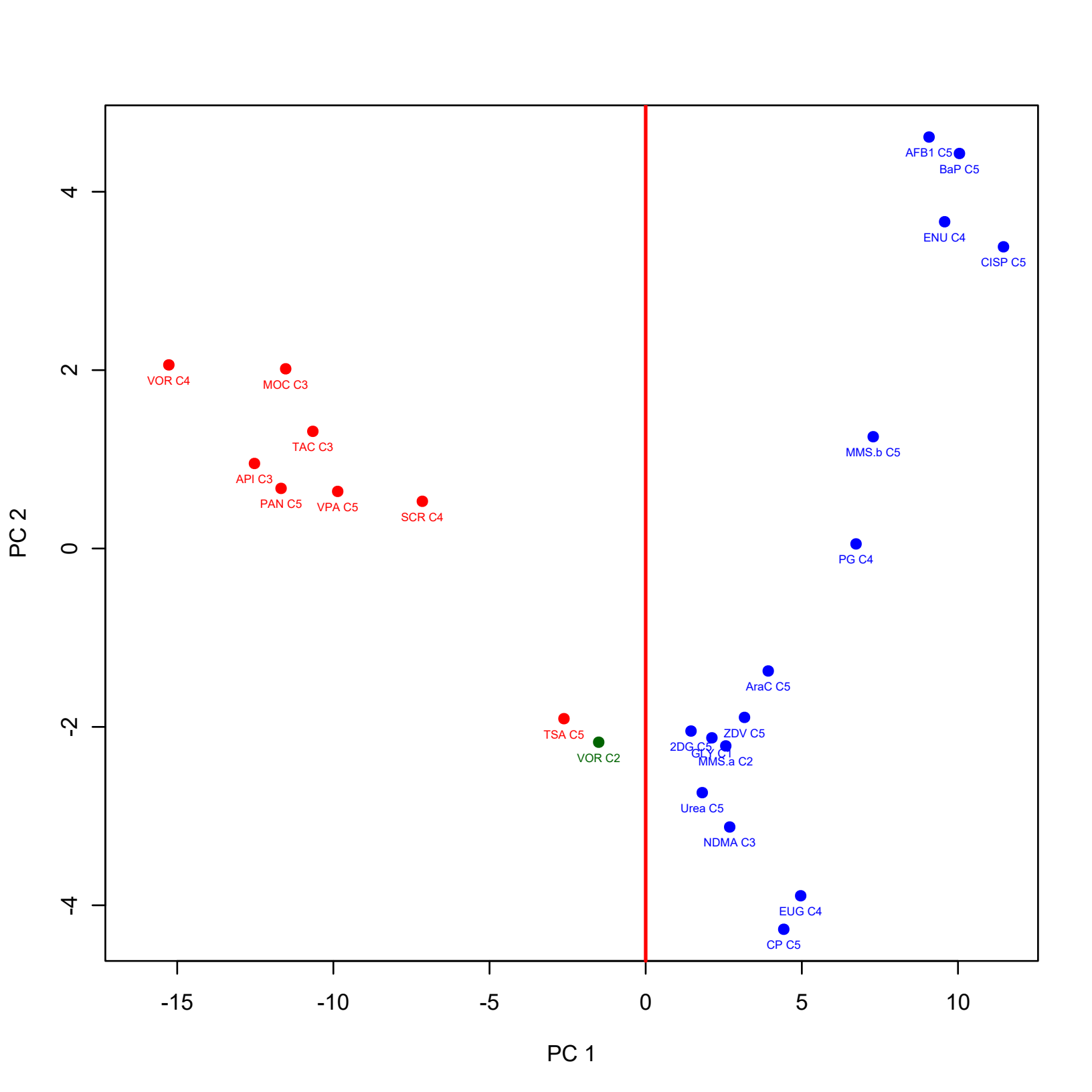
Supplementary Figure 2G: Vorinostat (VOR) Concentrations 1-5 (C1-C5)

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VPA C5
SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
VOR C2
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
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PC 2
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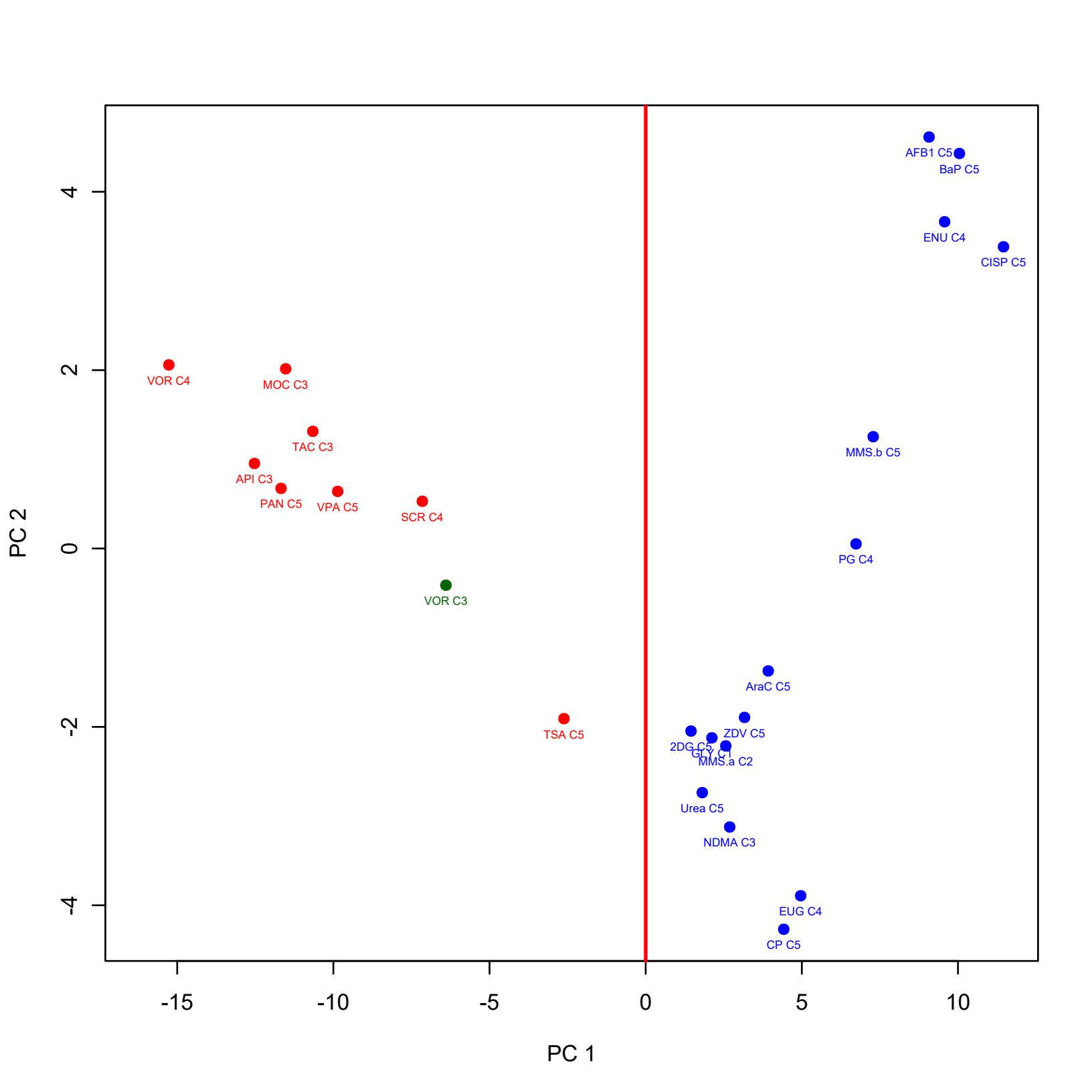
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SCR C4
MMS.b C5
PG C4
VOR C3
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
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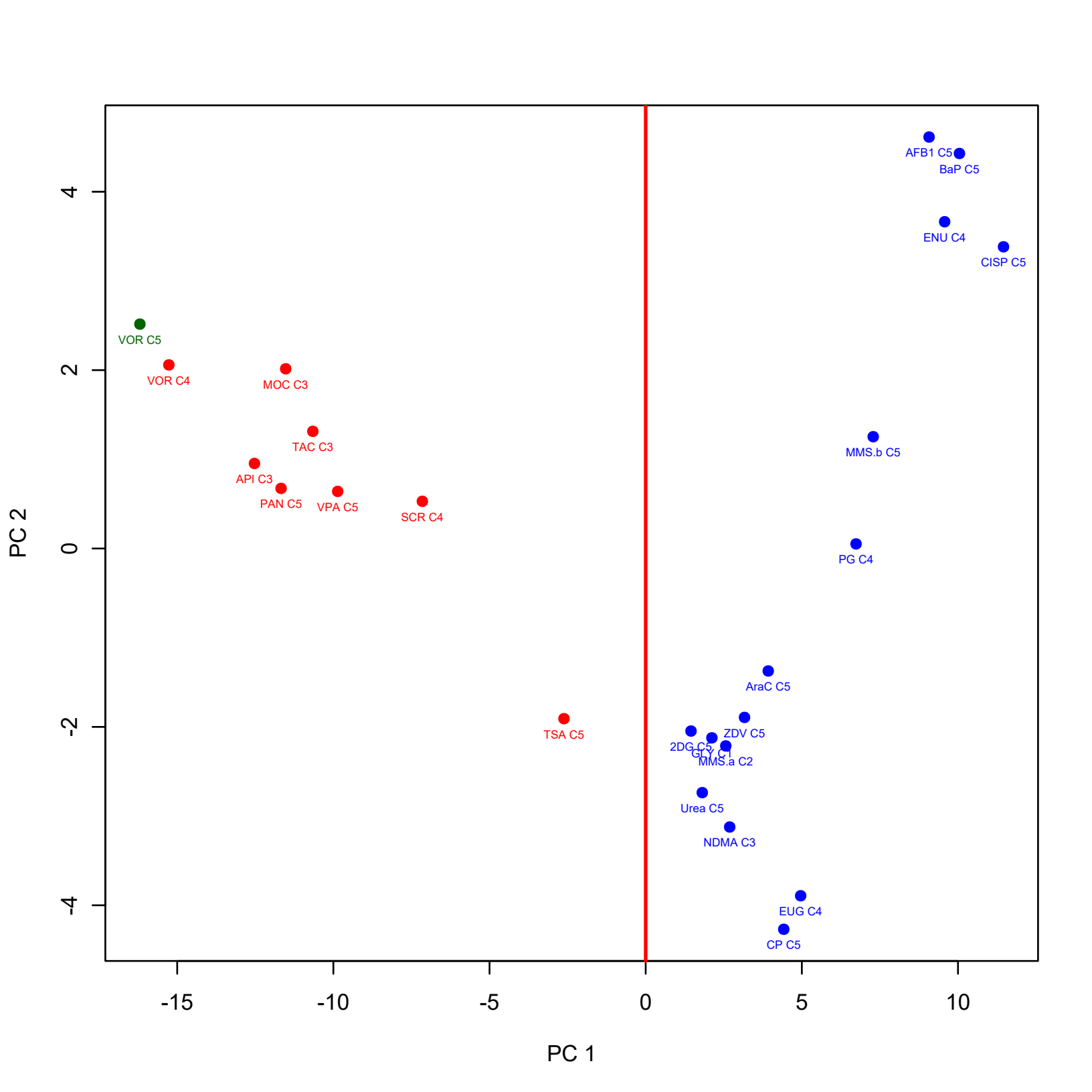
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API C3
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SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
PC 1
PC 2
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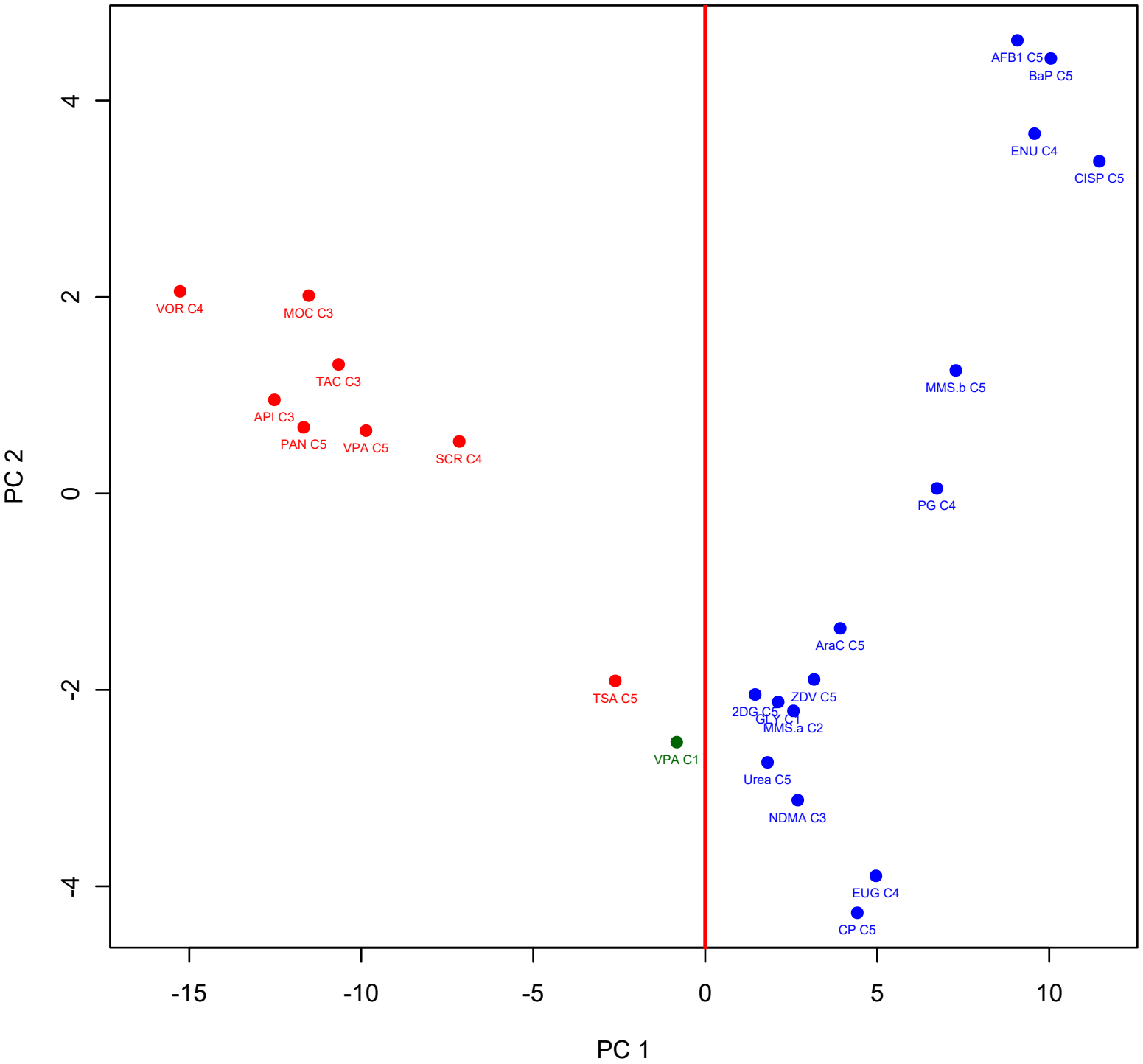
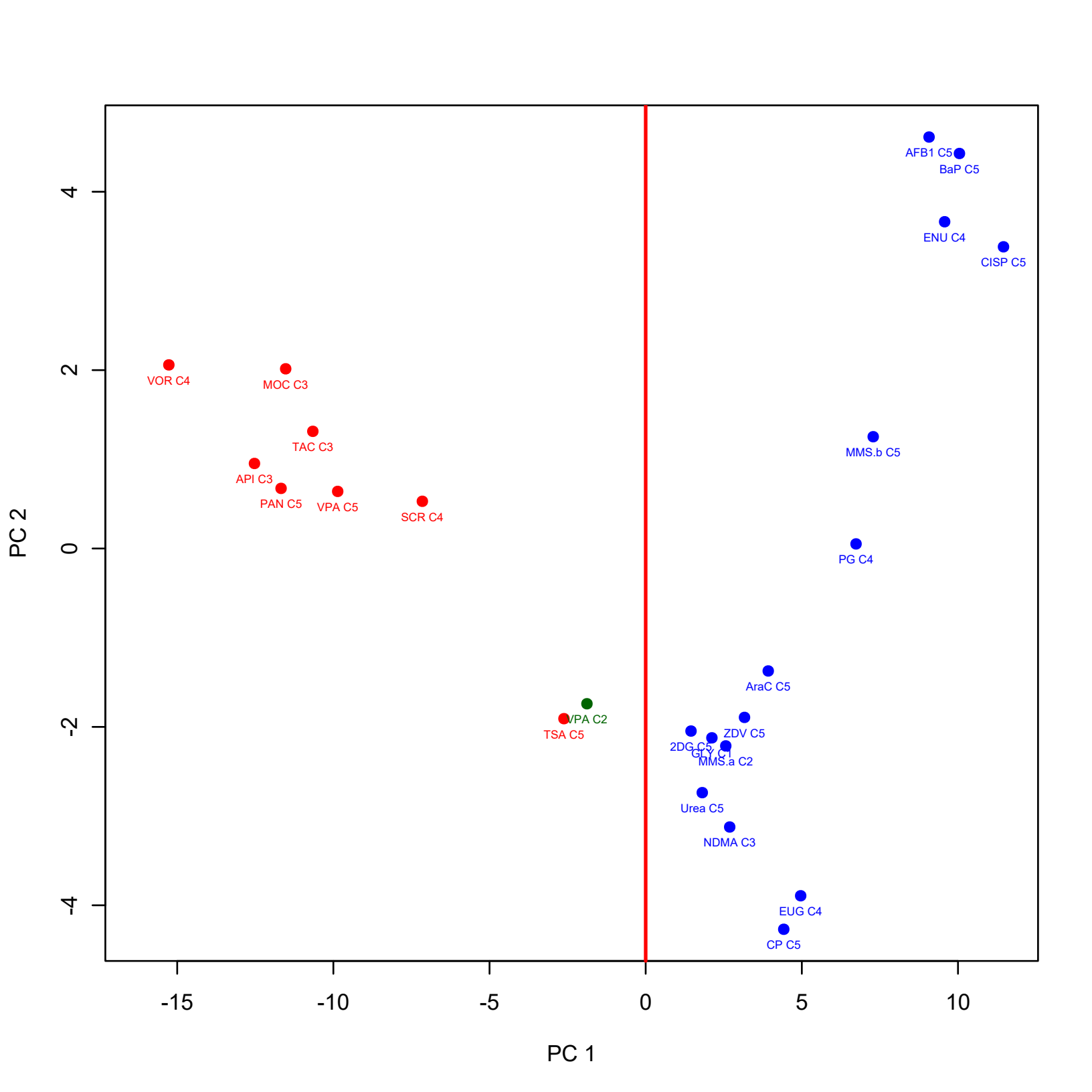
Supplementary Figure 2H: Valproic acid (VPA) Concentrations 1-5 (C1-C5)

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PG C4
AraC C5
VPA C2
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
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PC 2
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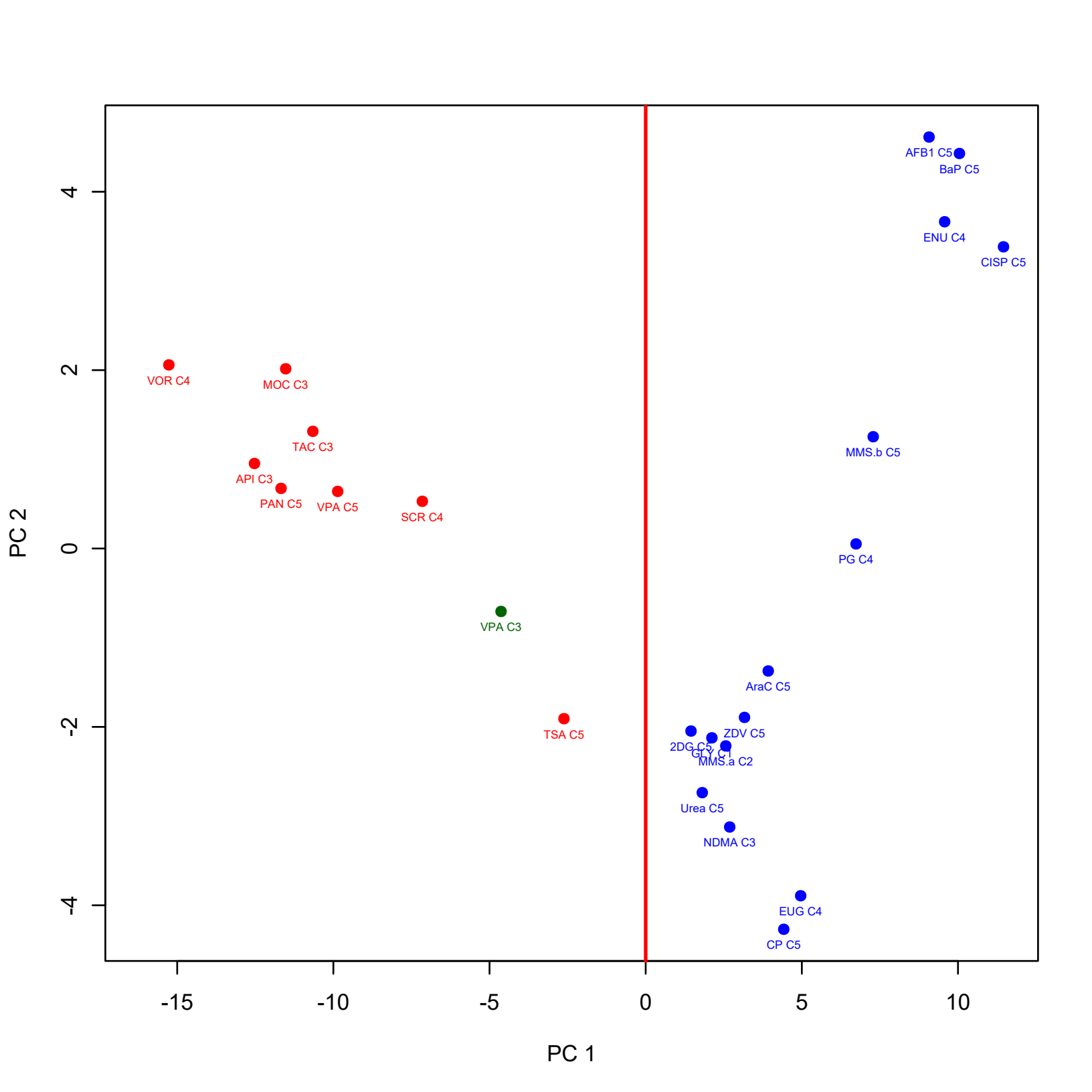
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MMS.b C5
PG C4
VPA C3
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
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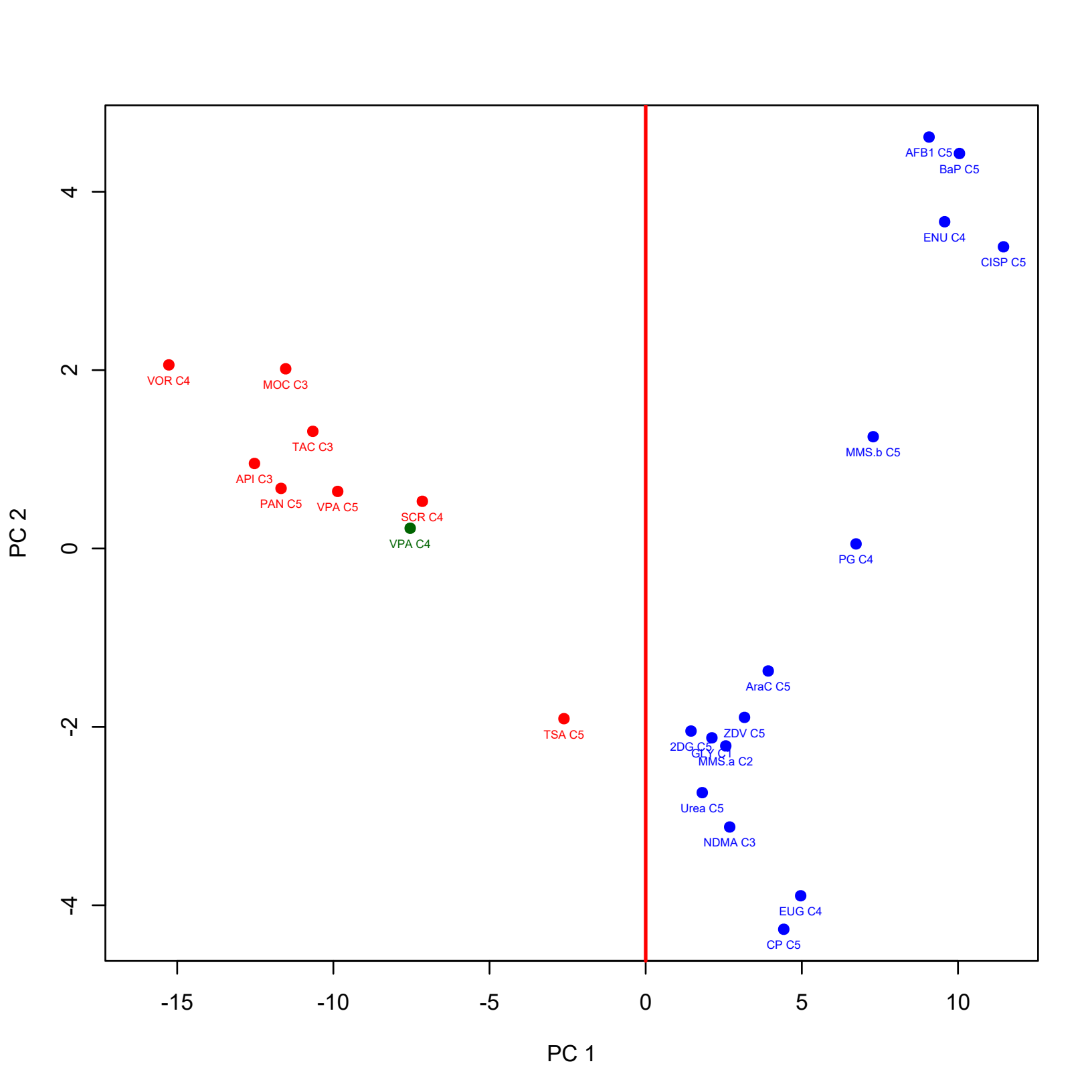
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PAN C5
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VPA C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
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PC 2
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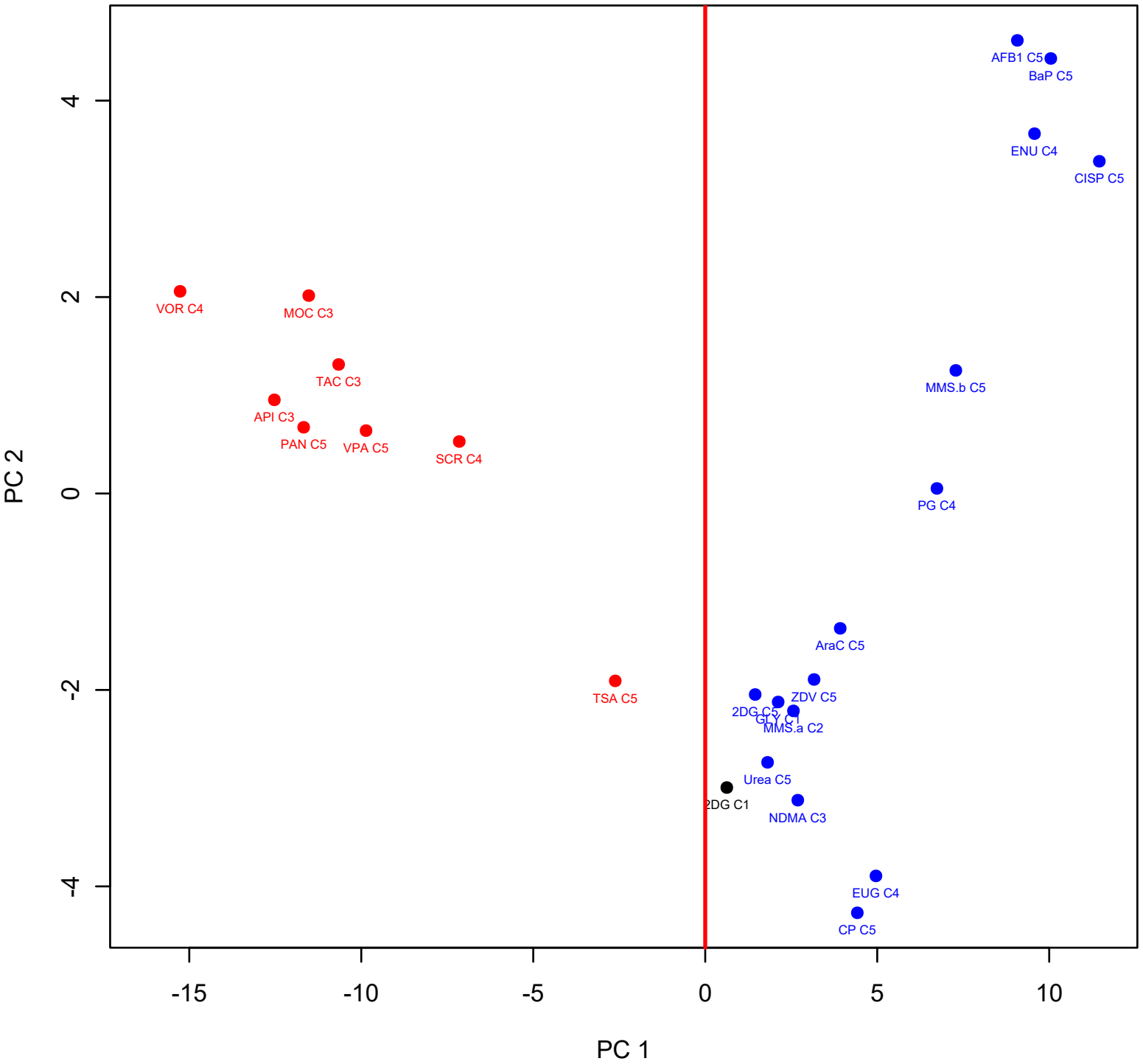
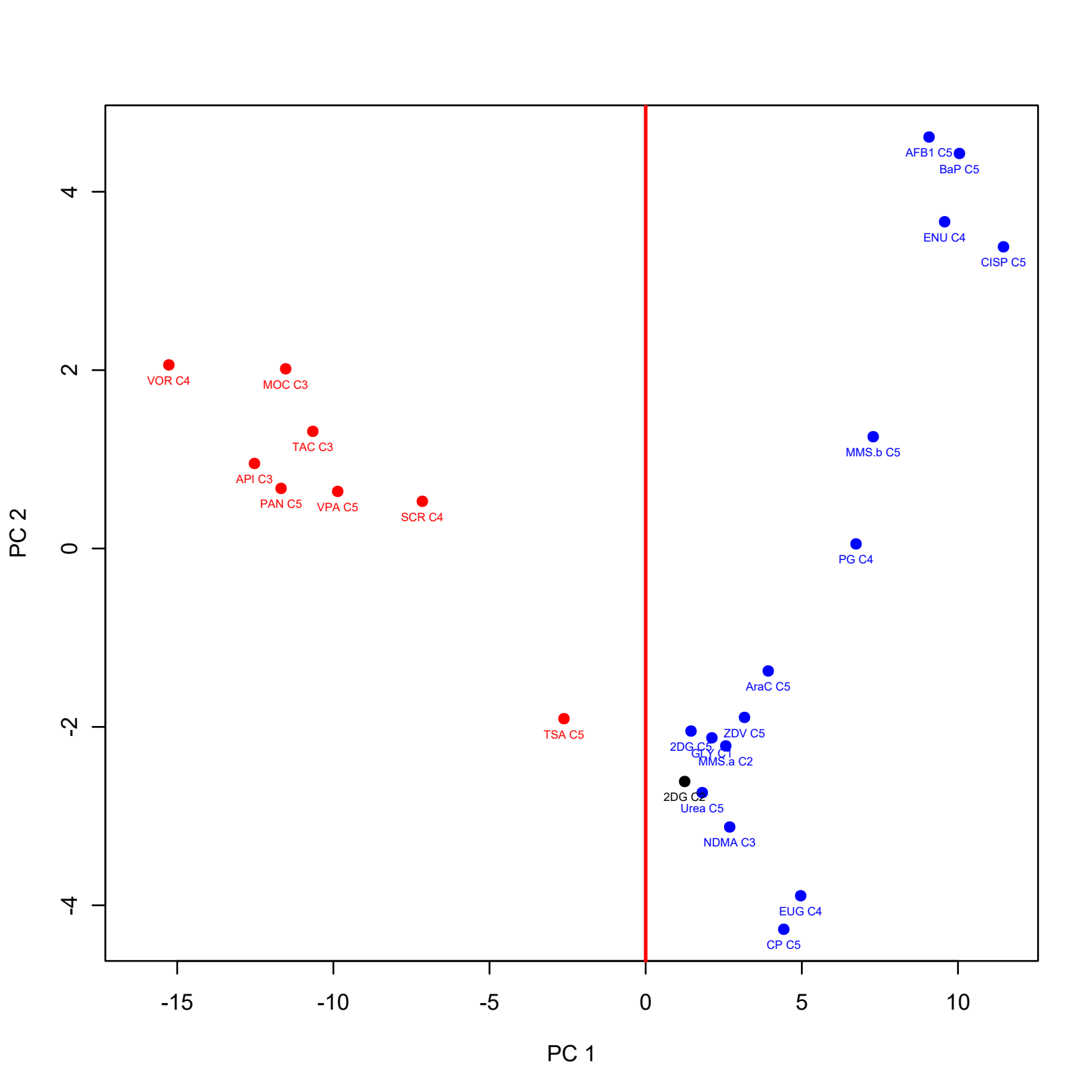
-4

Supplementary Figure 2I: 2-Deoxy-D-glucose (2DG) Concentrations 1-5 (C1-C5)

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MMS.b C5
PG C4
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TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
2DG C2
Urea C5
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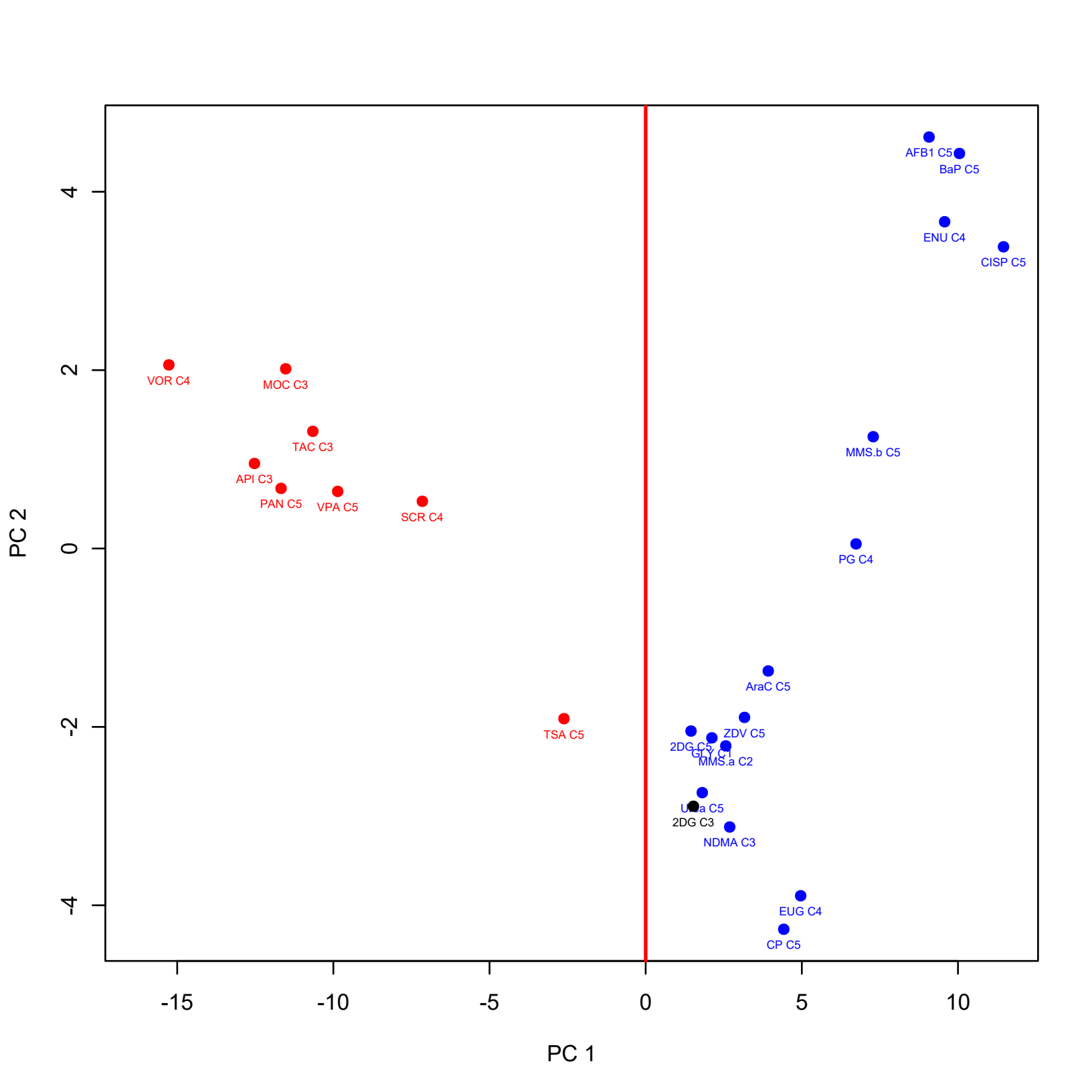
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PG C4
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TSA C5
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GLY C1
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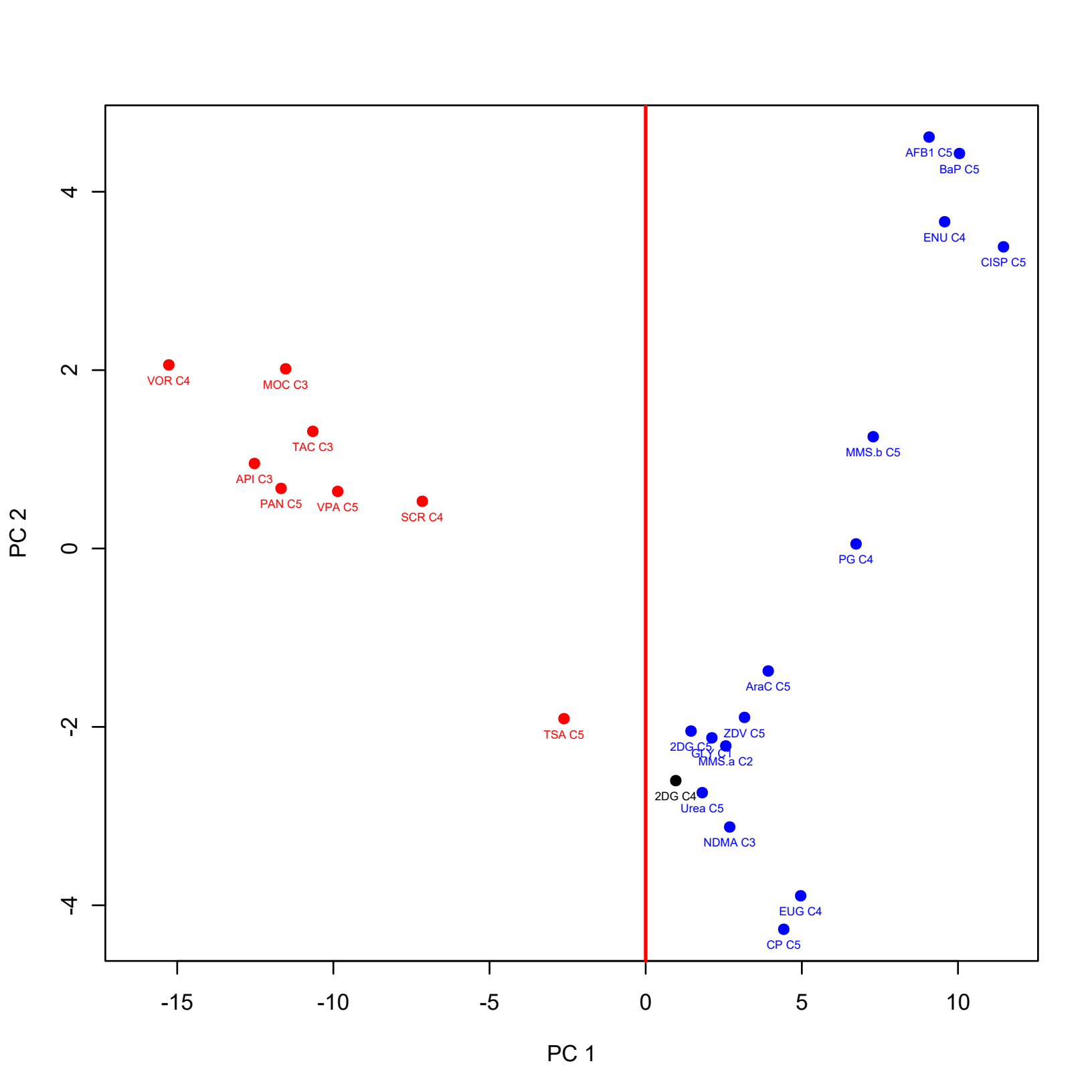
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SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
2DG C4
Urea C5
NDMA C3
EUG C4
CP C5
PC 2
PC 1
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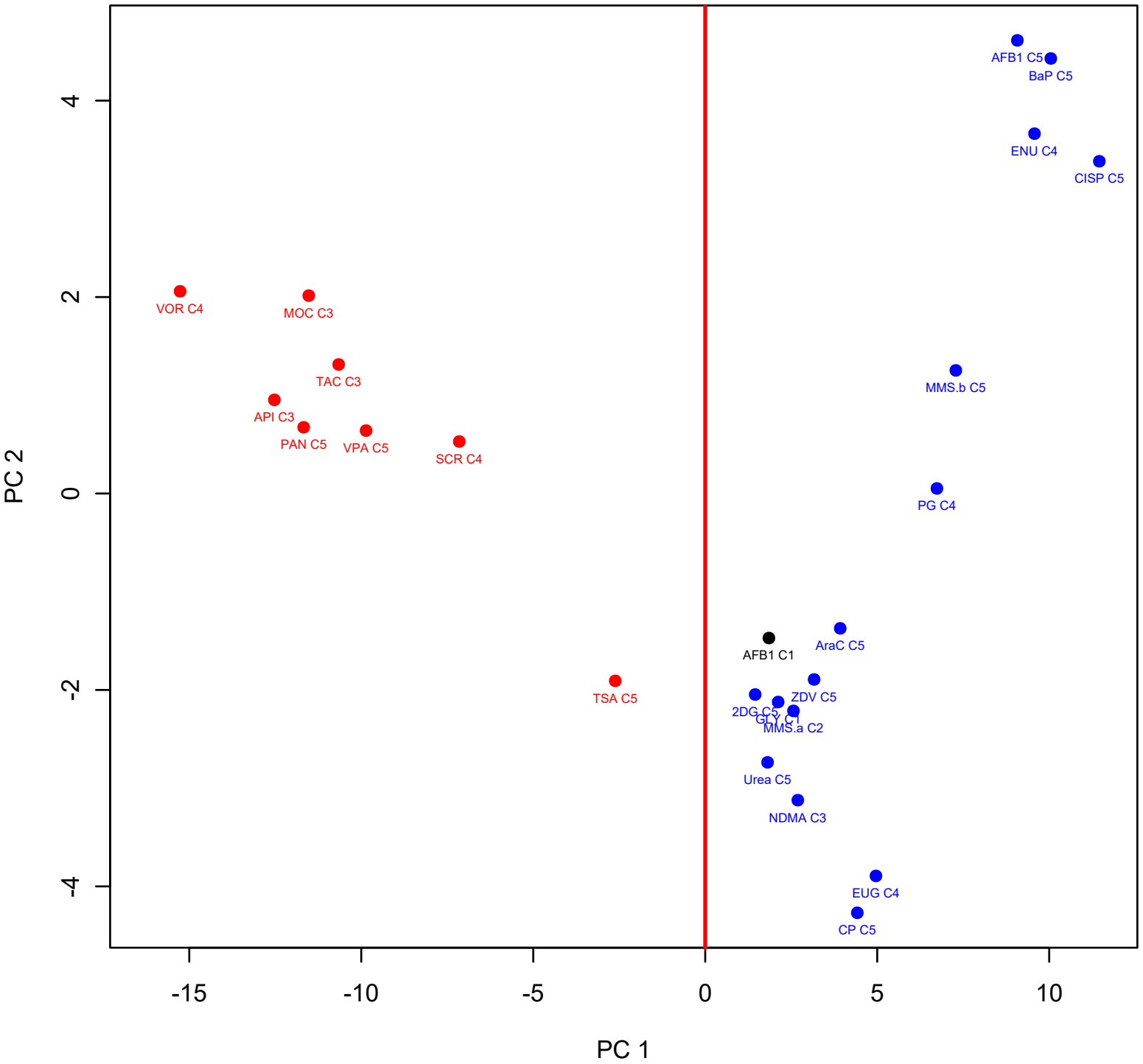
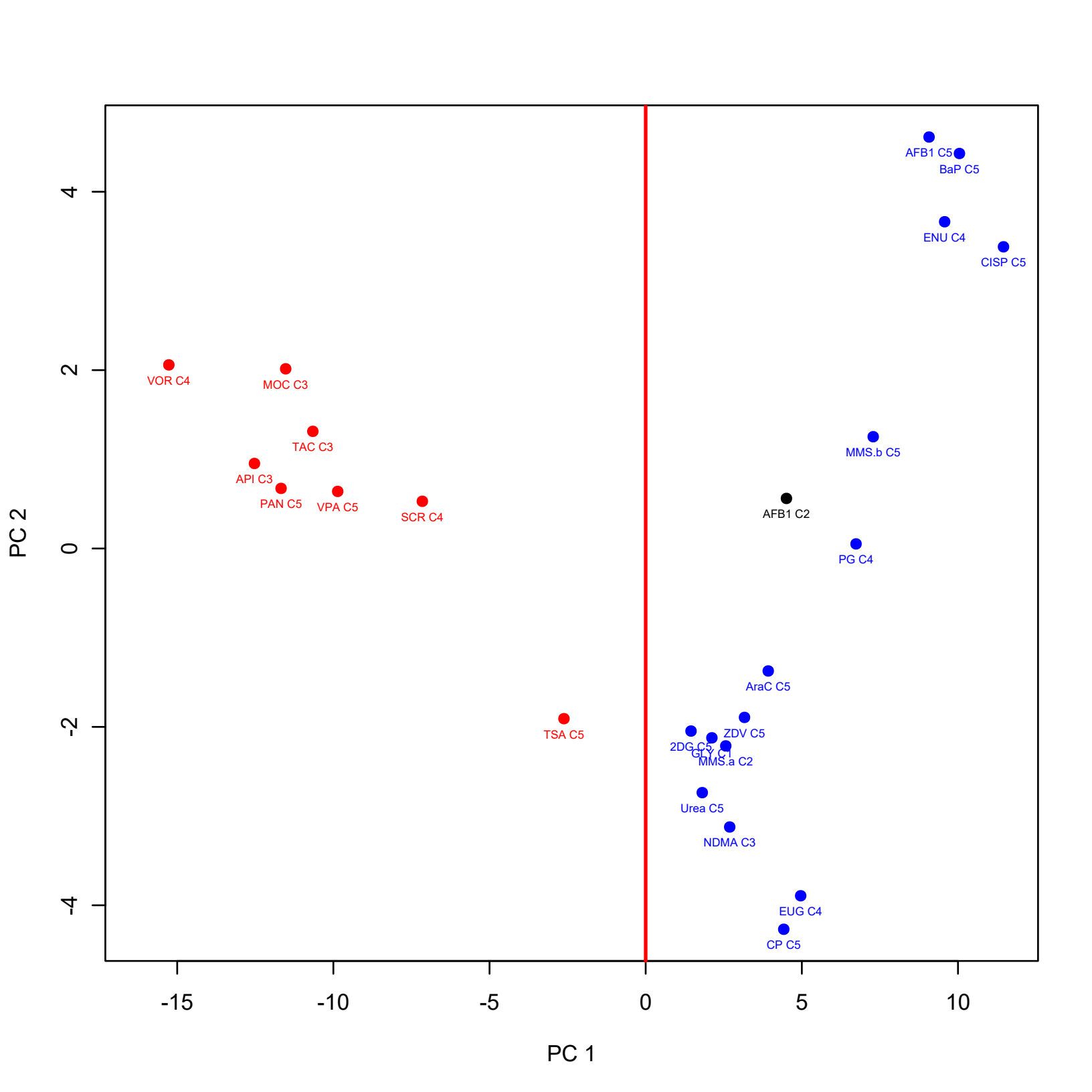
Supplementary Figure 2J: Aflatoxin B1 (AFB1) Concentrations 1-5 (C1-C5)

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AFB1 C2
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
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Urea C5
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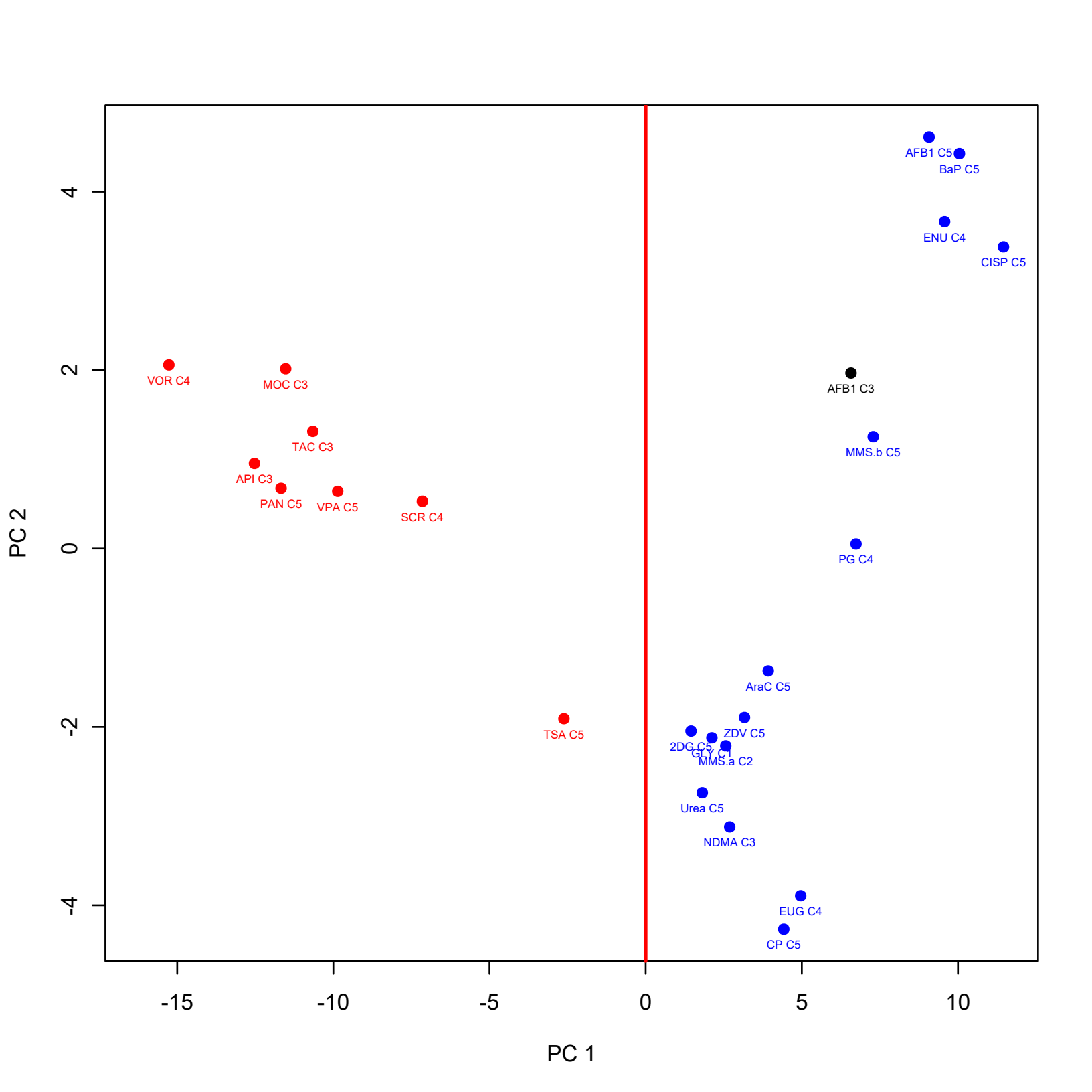
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PAN C5
VPA C5
SCR C4
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
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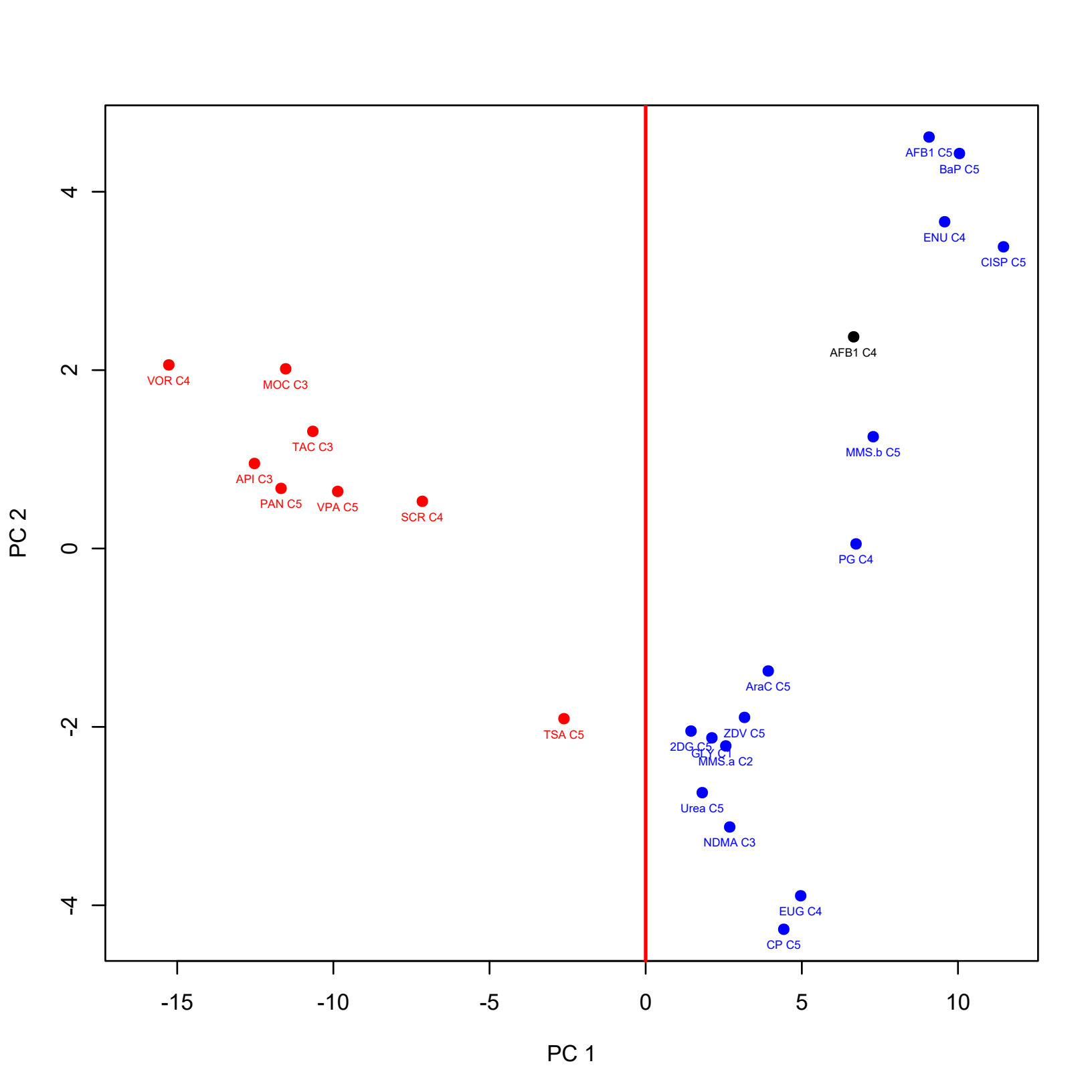
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ZDV C5
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GLY C1
MMS.a C2
Urea C5
NDMA C3
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CP C5
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MOC C3
TAC C3
API C3
PAN C5
VPA C5
SCR C4
TSA C5
PC 1
PC 2
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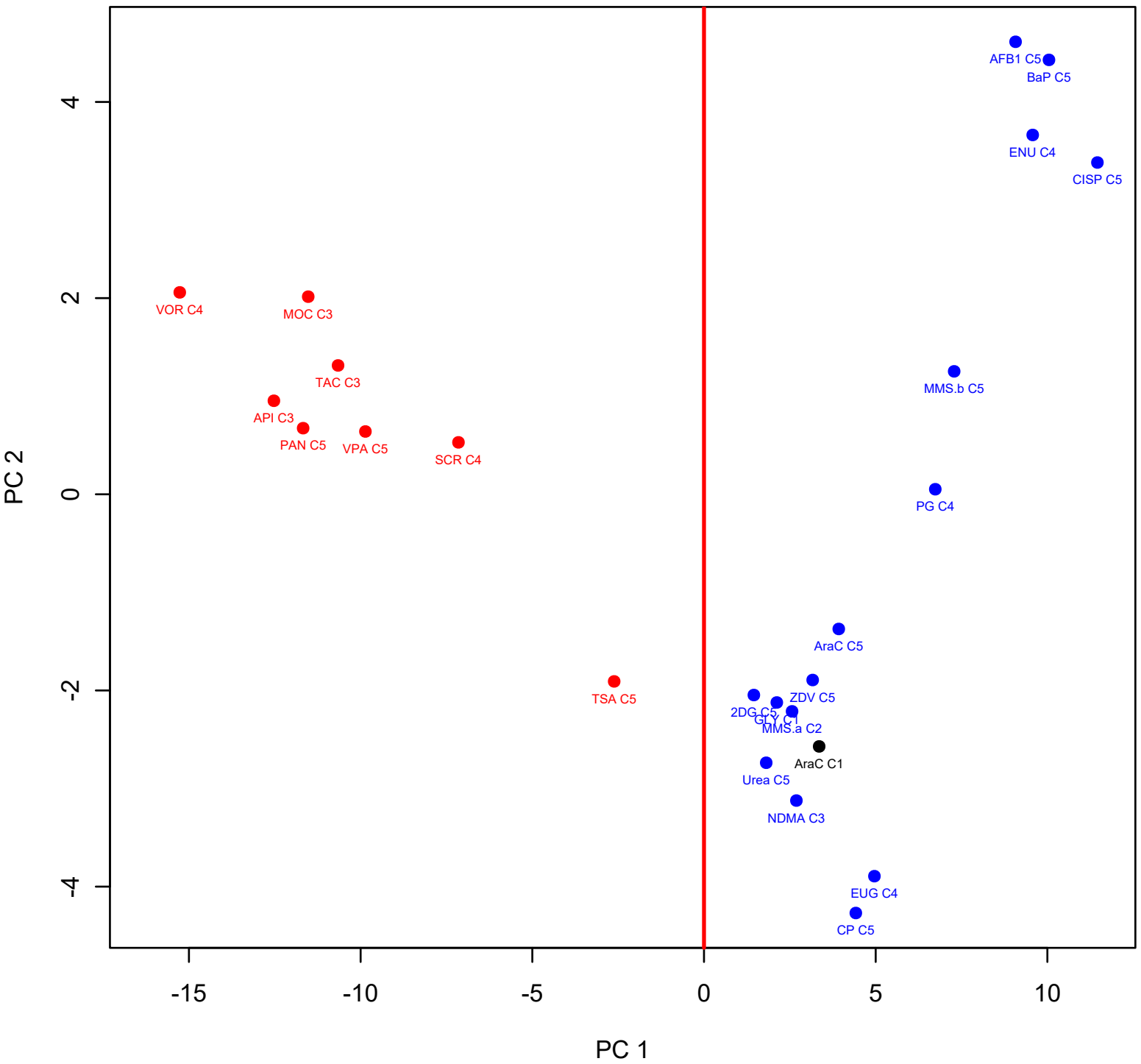
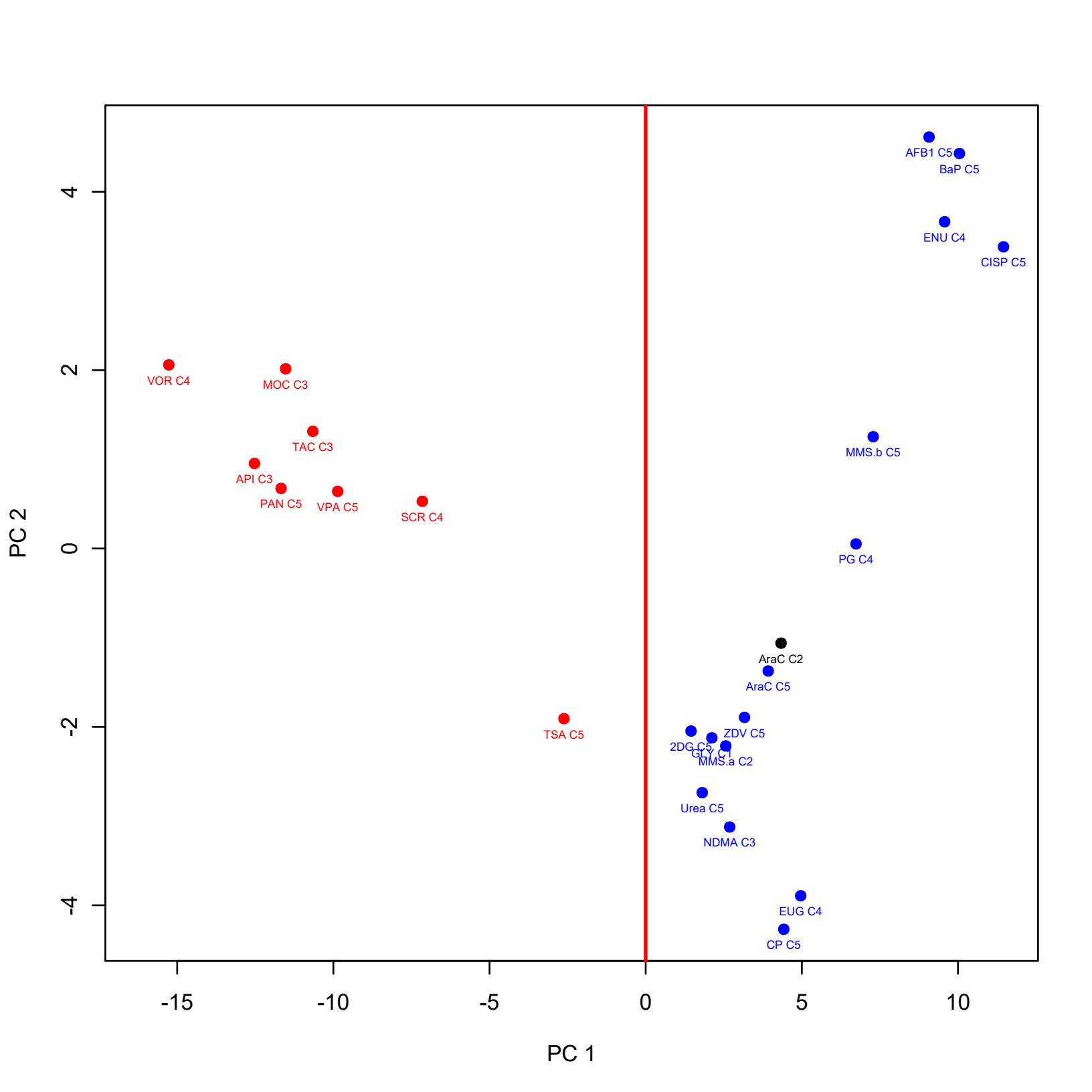
Supplementary Figure 2K: Cytosine arabinoside (AraC) Concentrations 1-5 (C1-C5)

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PG C4
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AraC C5
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Urea C5
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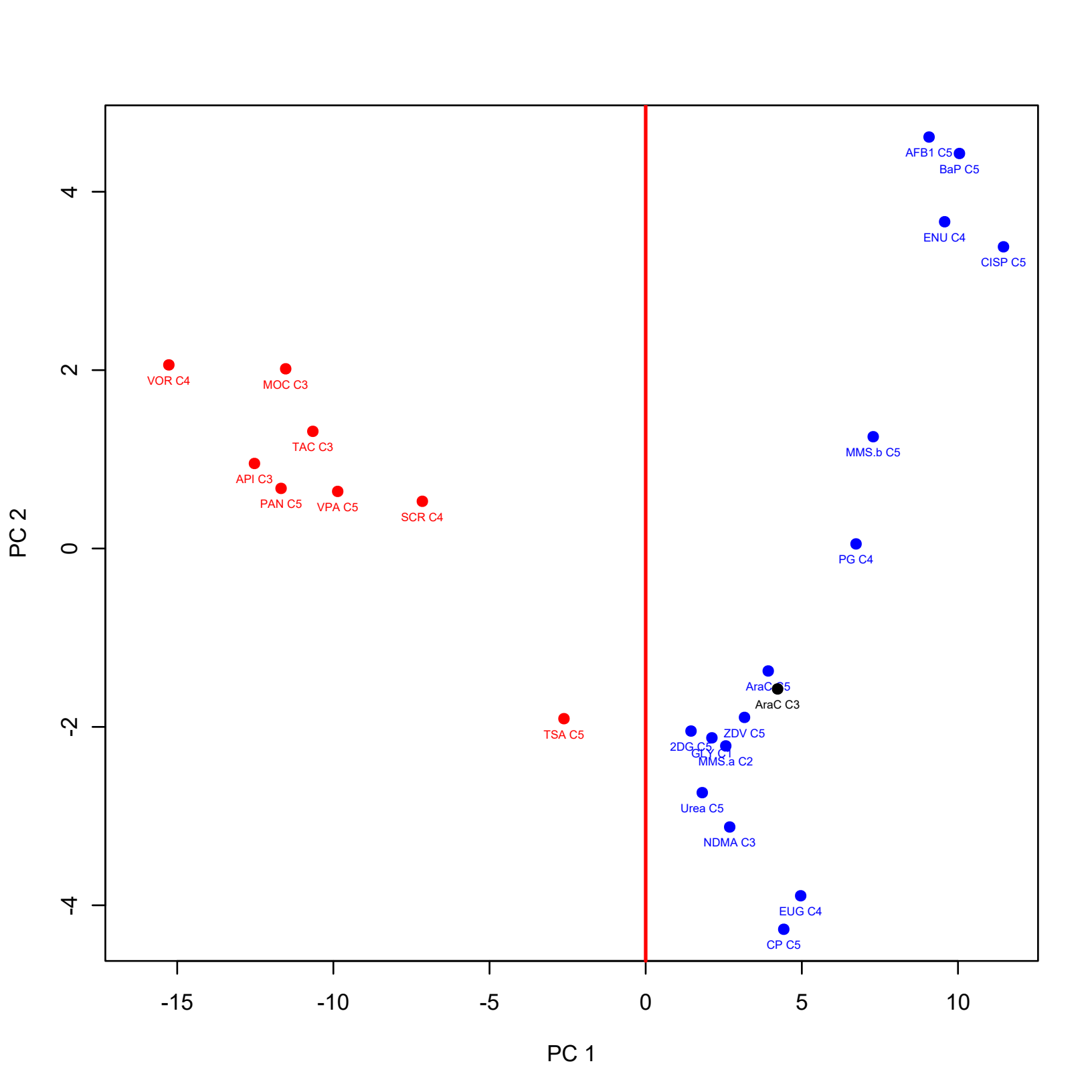
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TSA C5
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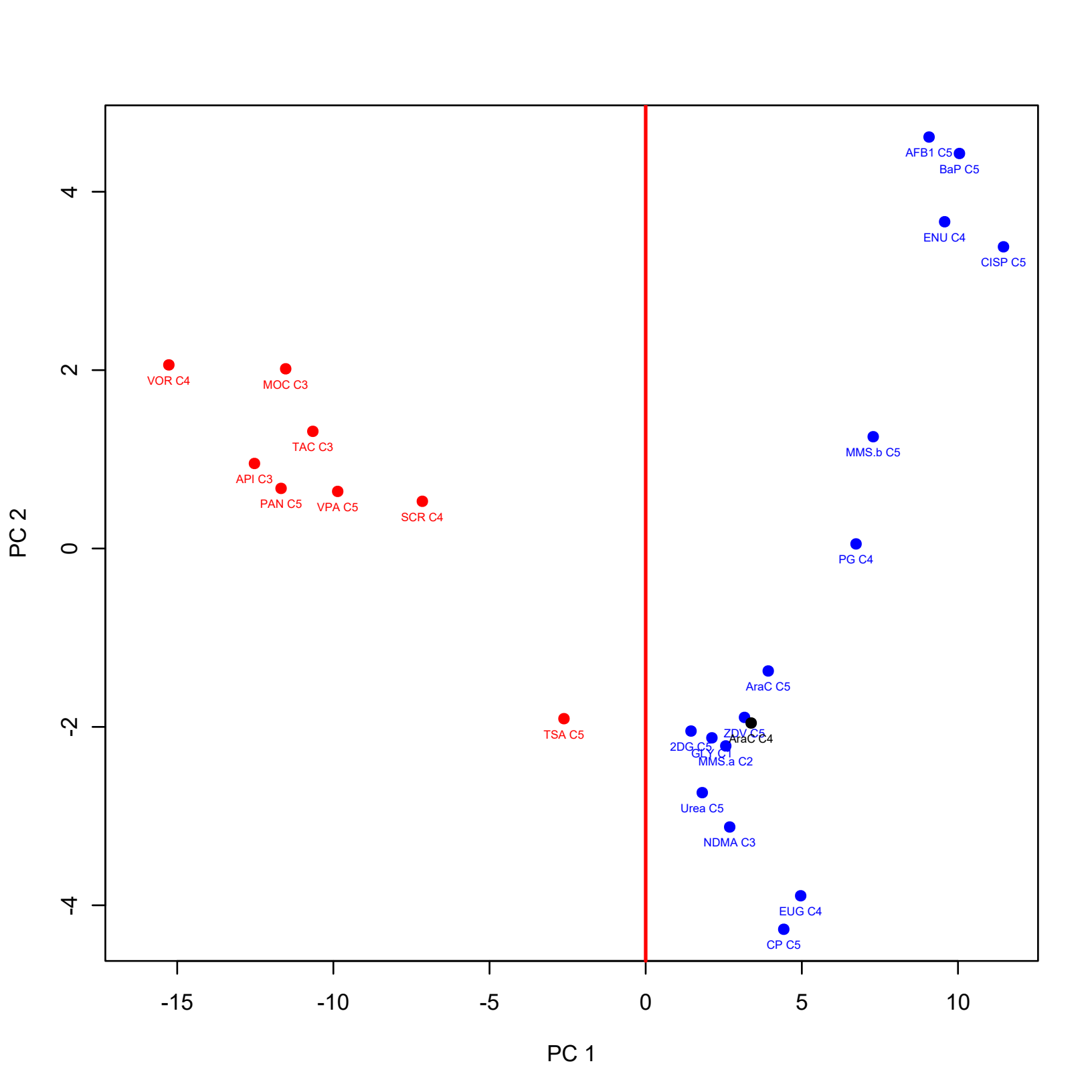
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NDMA C3
EUG C4
CP C5
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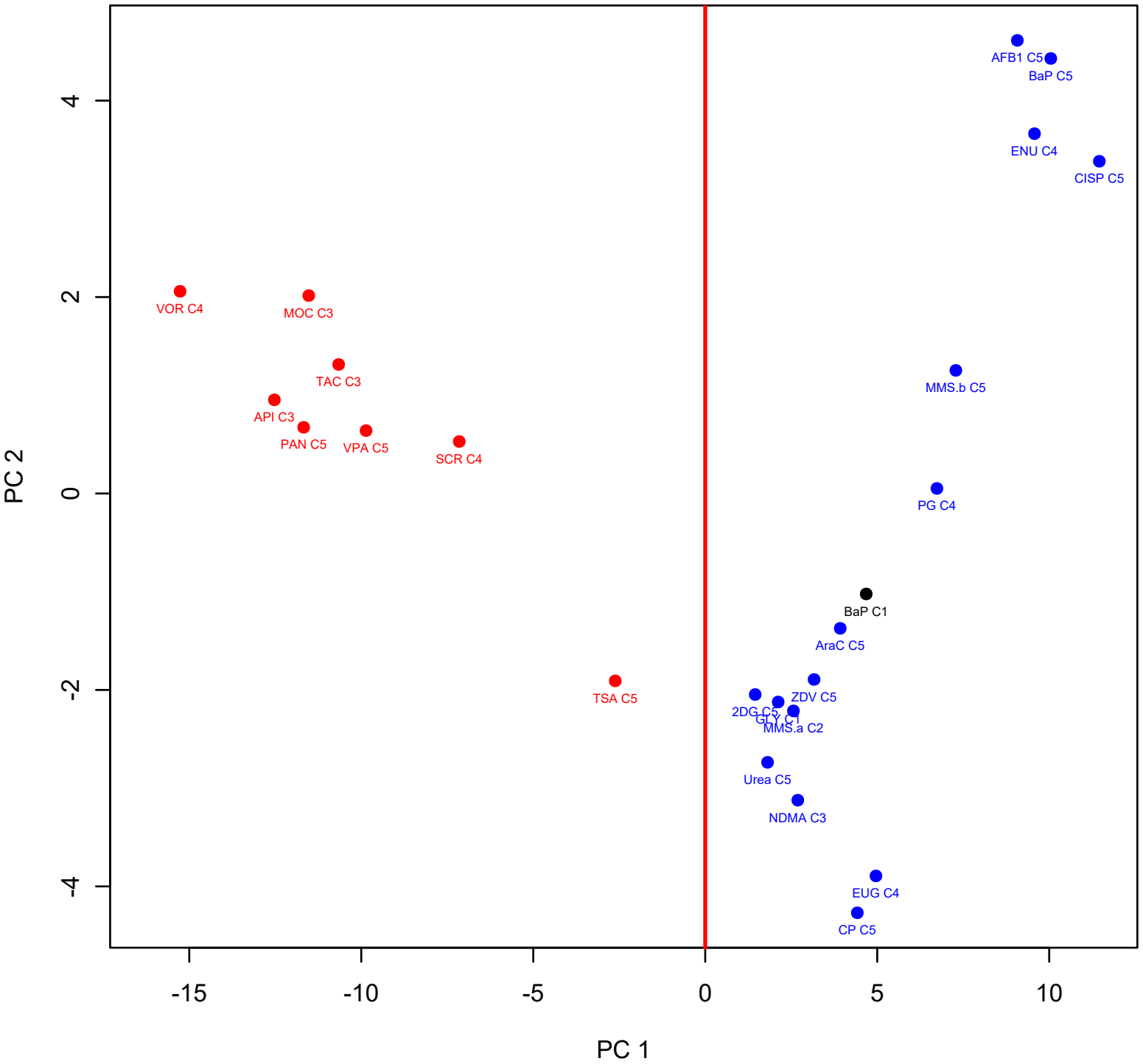
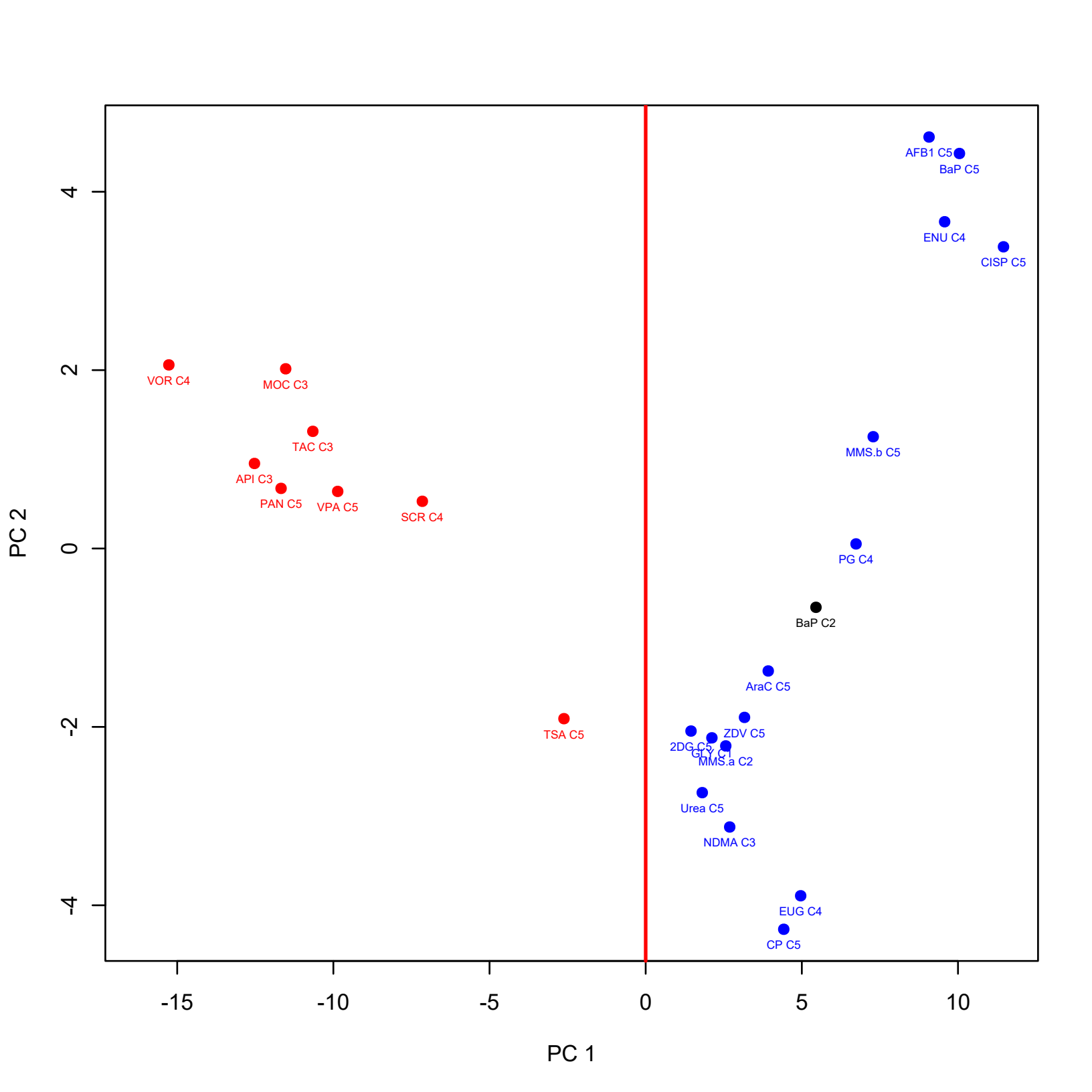
Supplementary Figure 2L: Benzo[a]pyrene (BaP) Concentrations 1-5 (C1-C5)

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MMS.b C5
PG C4
BaP C2
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
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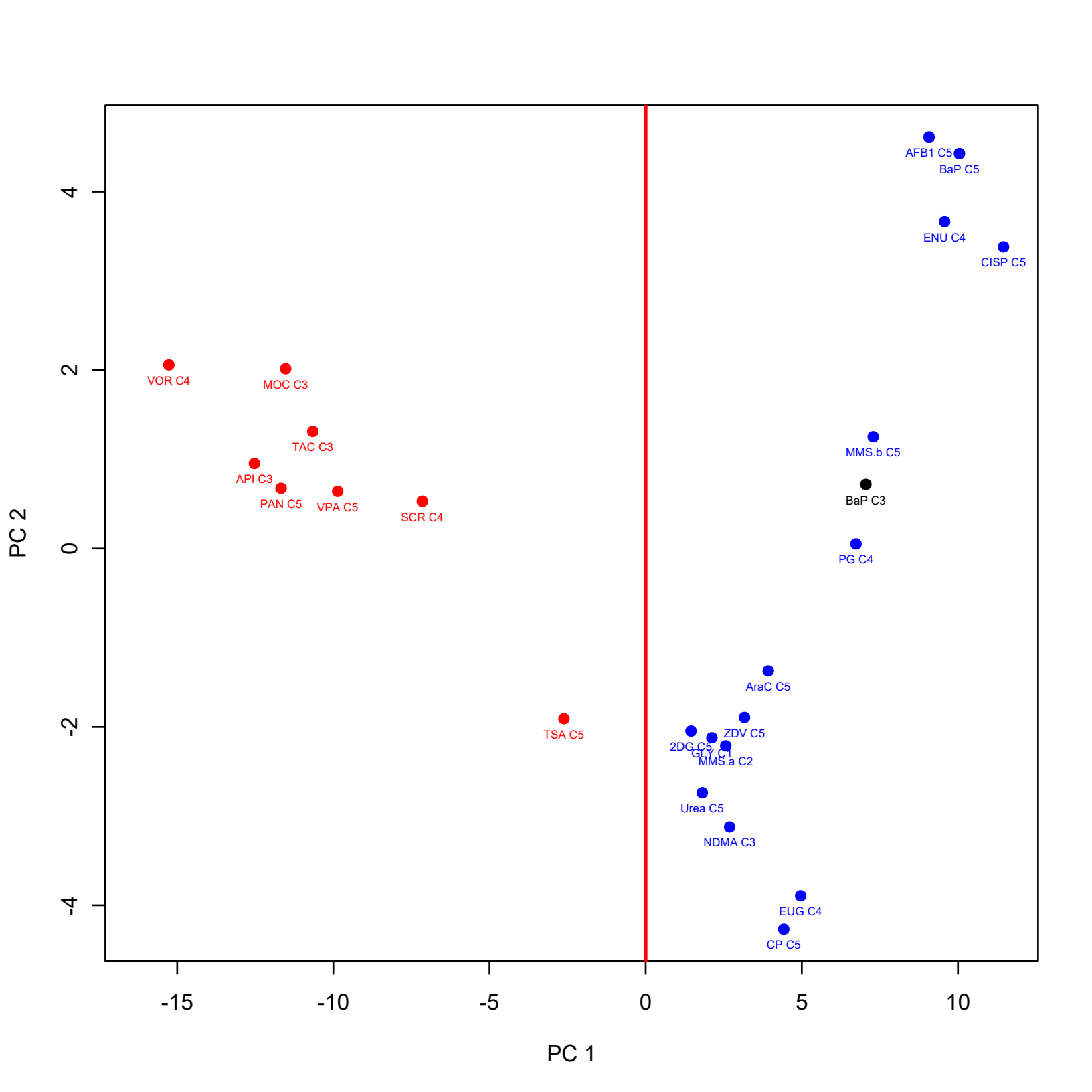
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TSA C5
ZDV C5
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GLY C1
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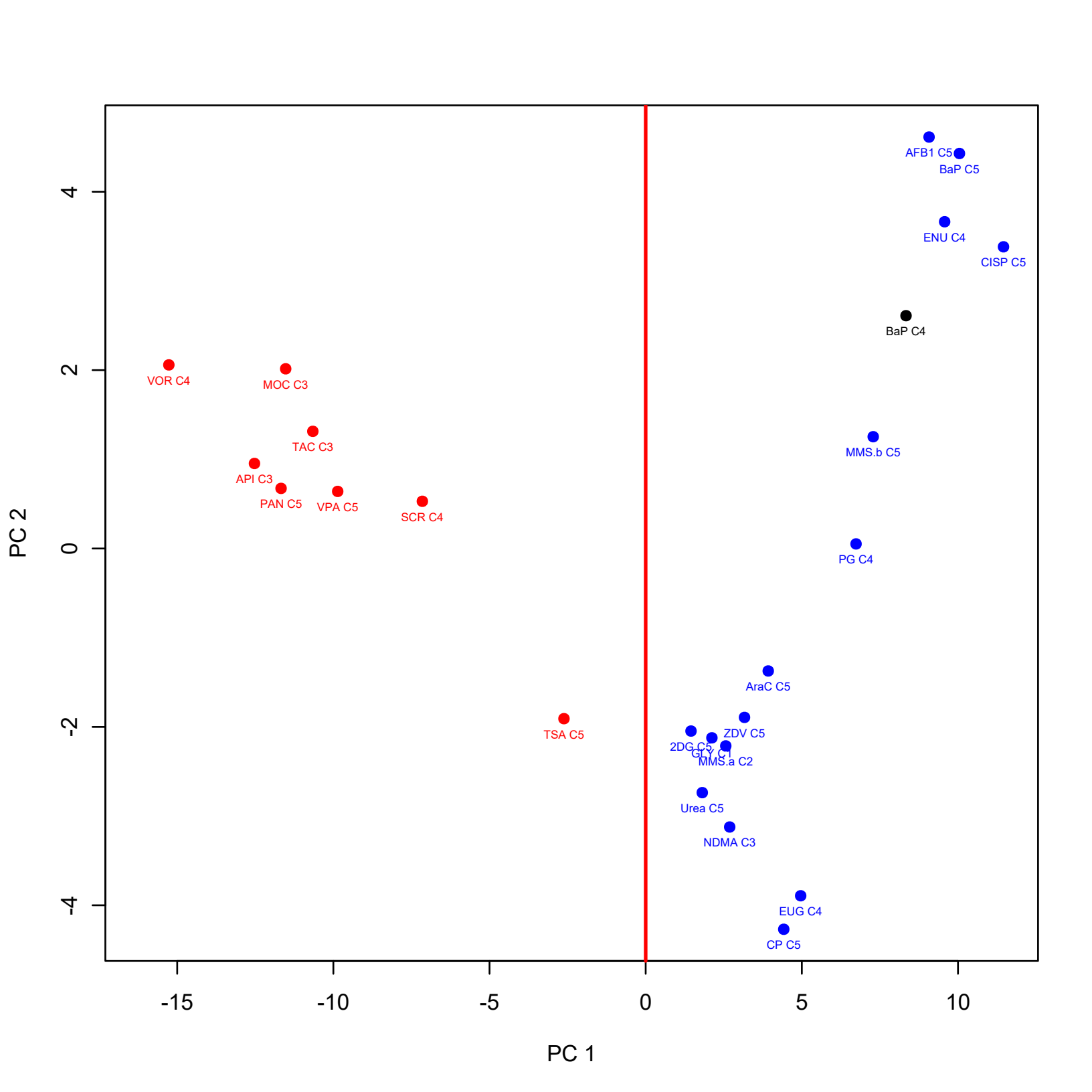
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SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
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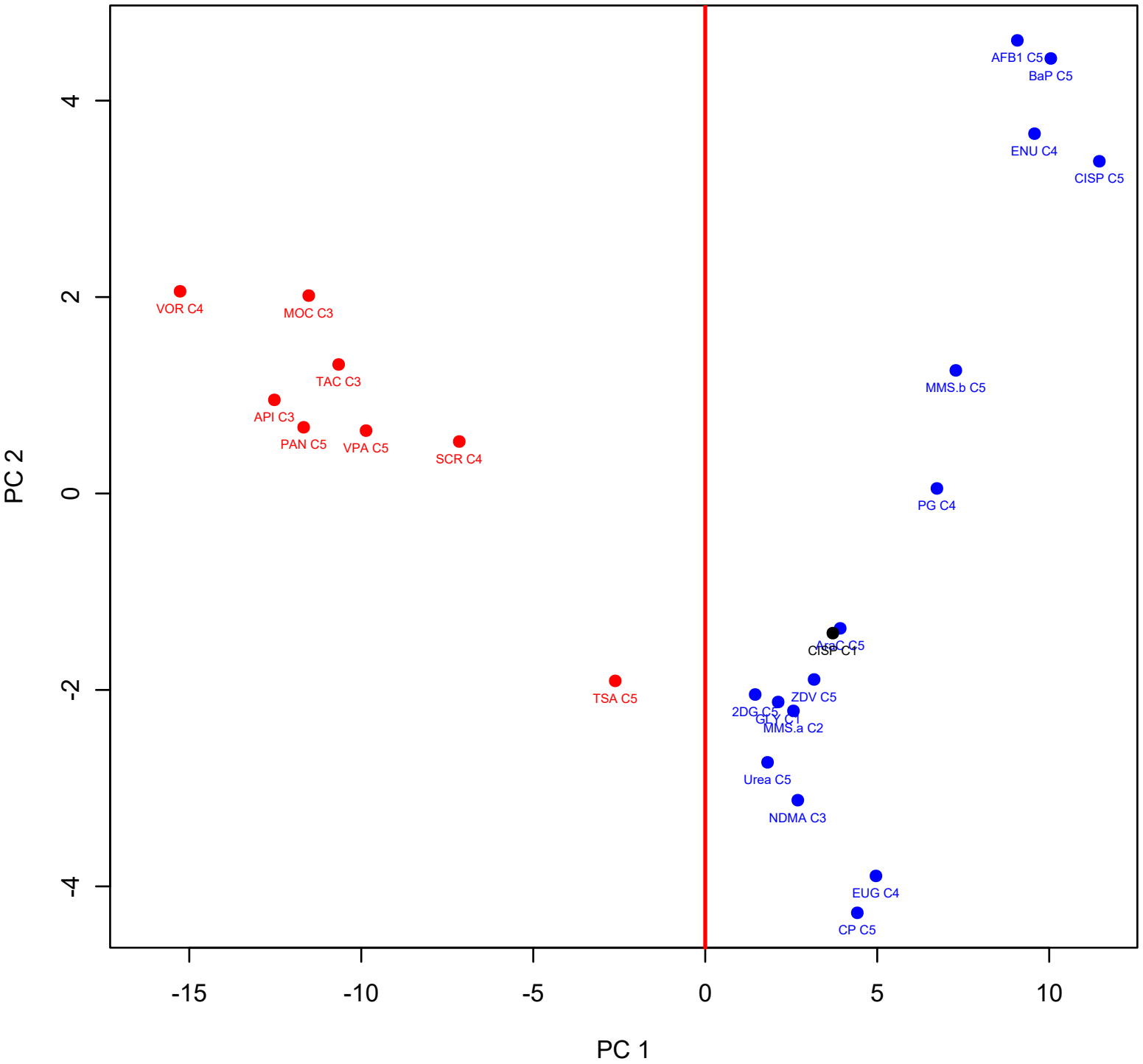
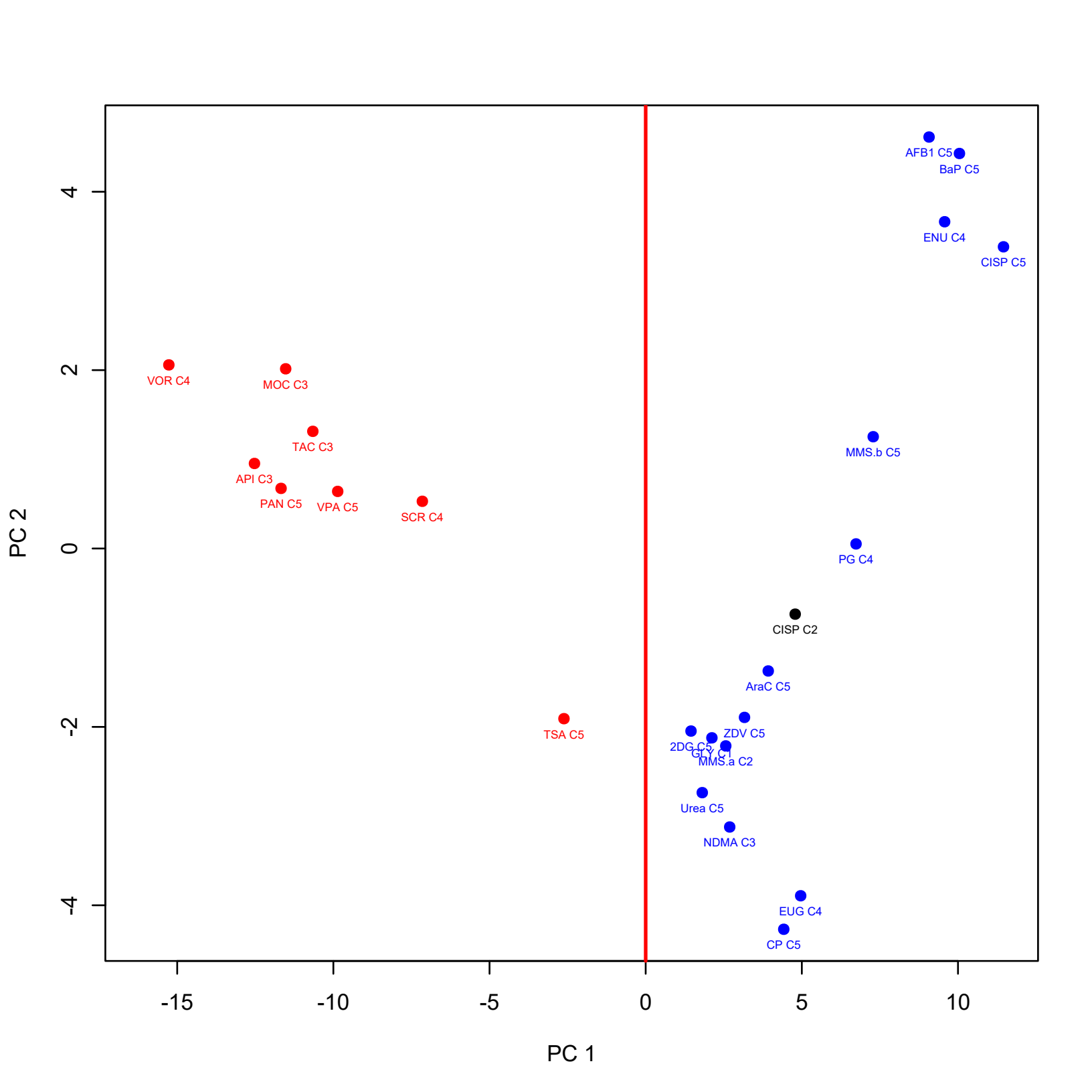
Supplementary Figure 2M: Cisplatin (CISP) Concentrations 1-5 (C1-C5)

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MMS.b C5
PG C4
CISP C2
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
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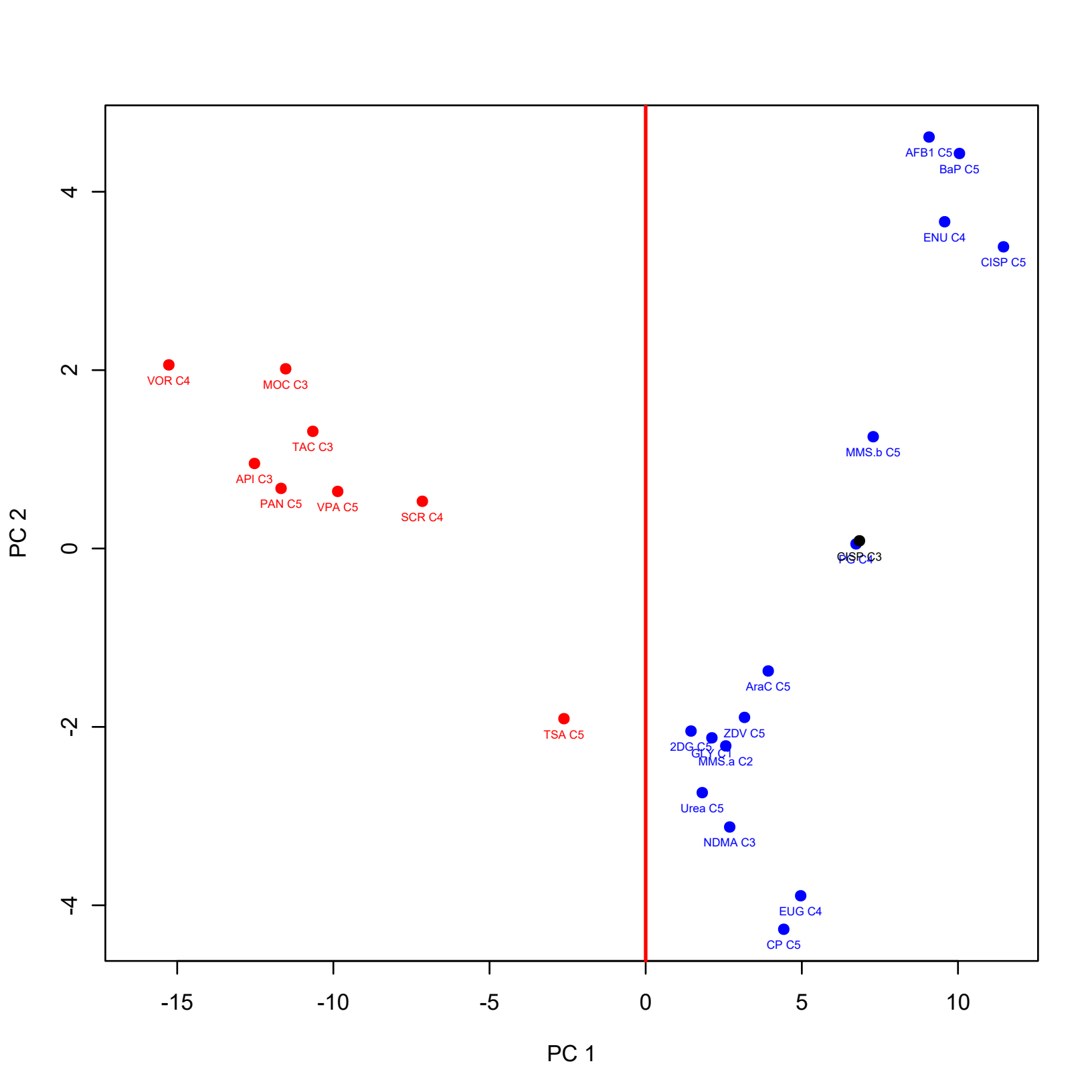
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ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
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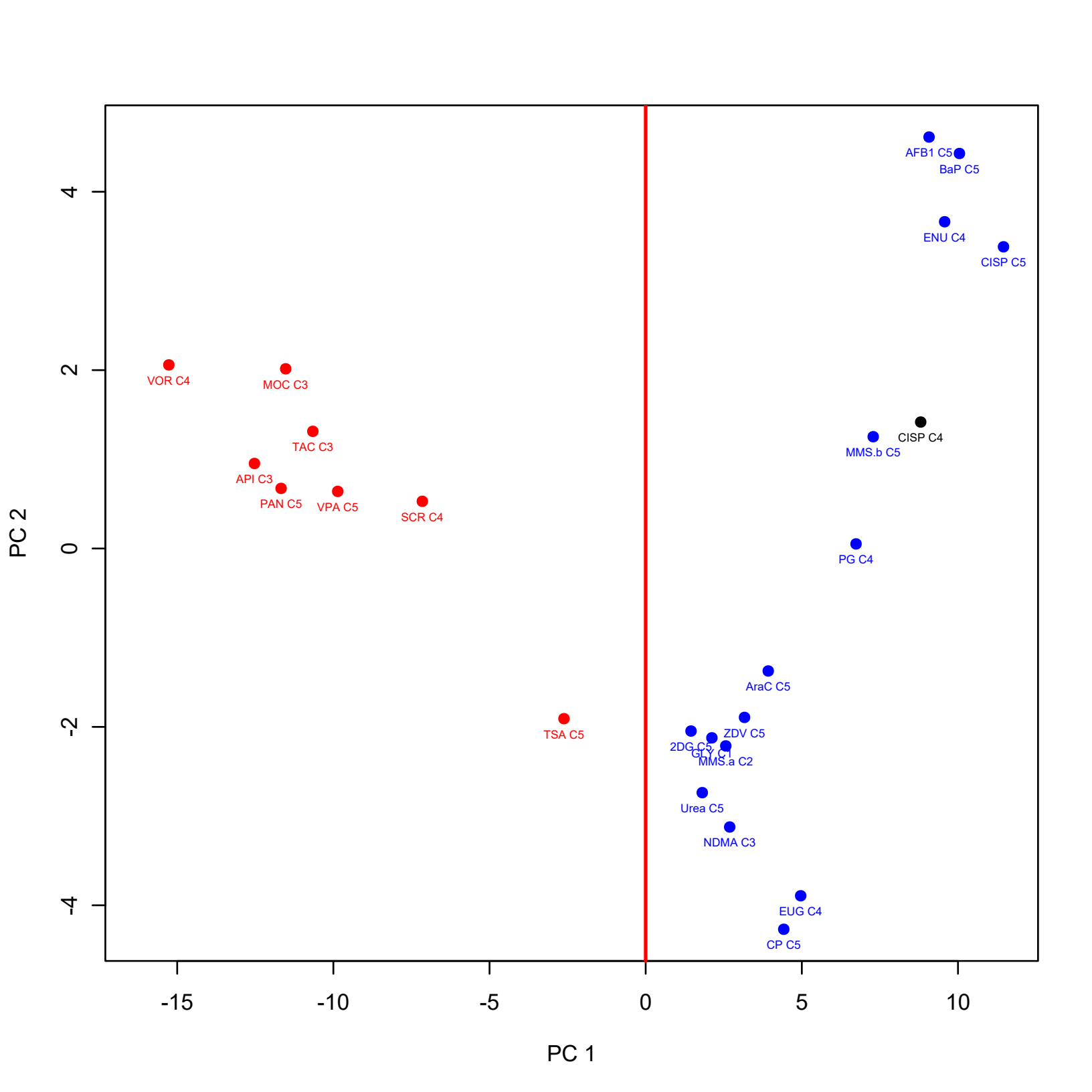
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SCR C4
CISP C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
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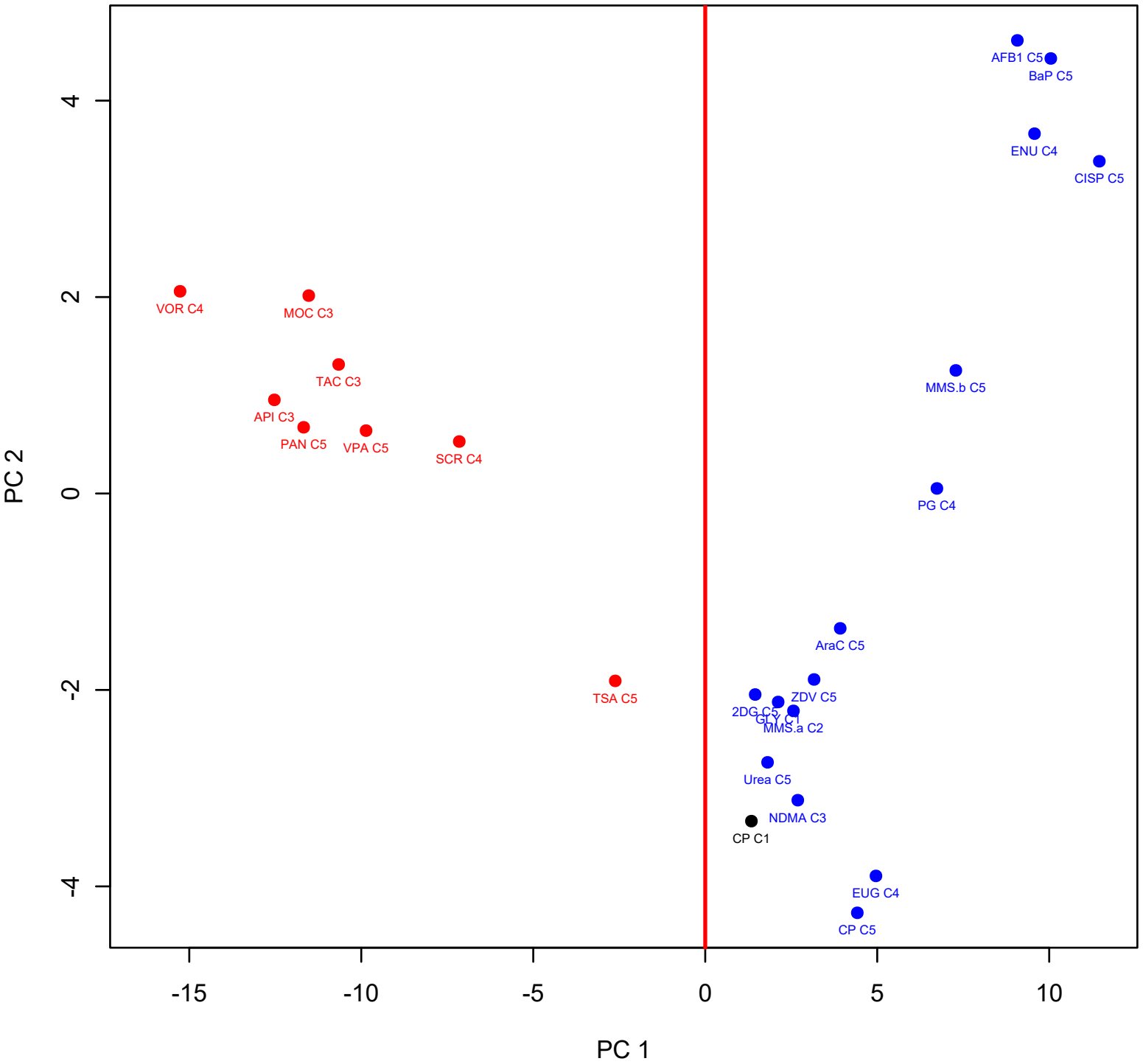
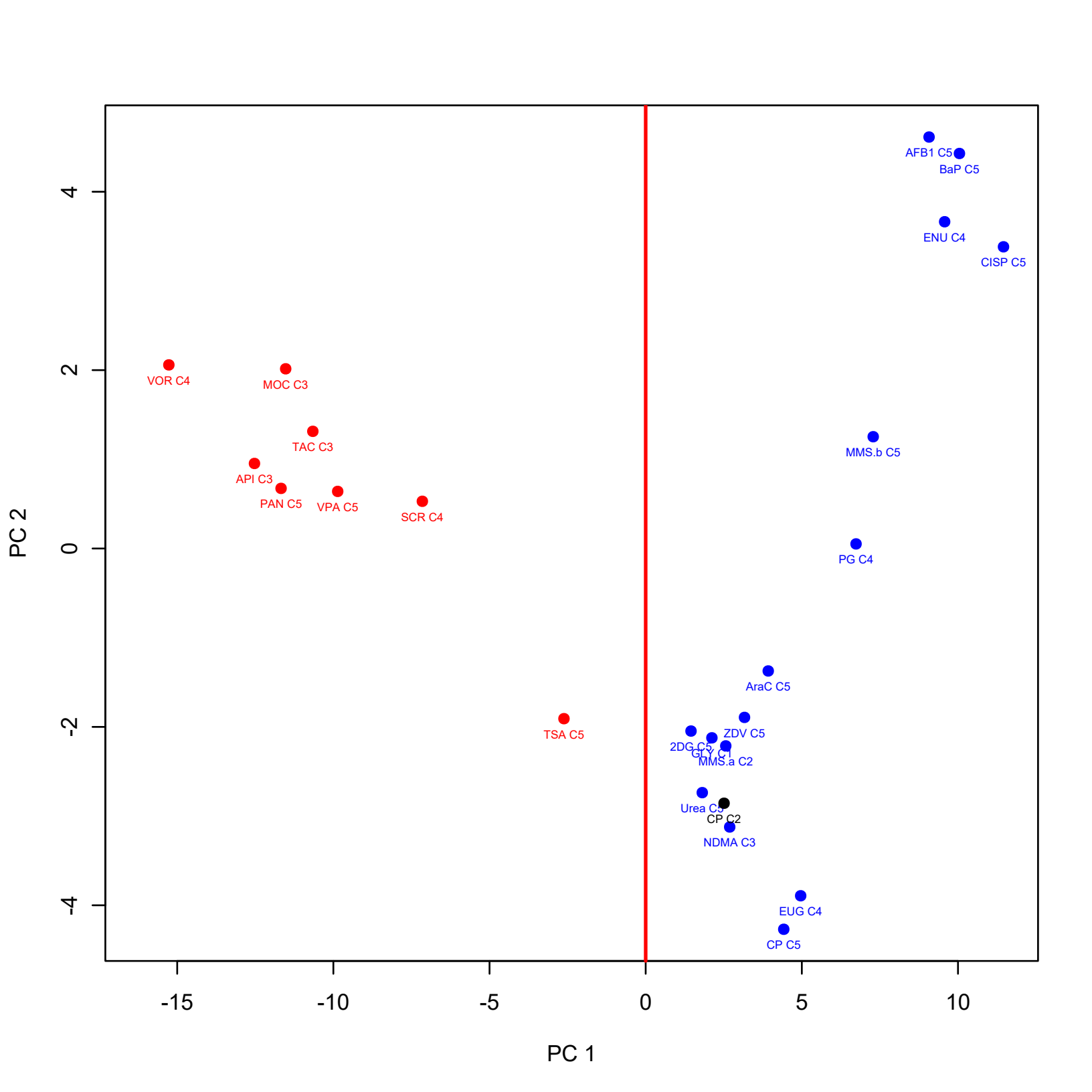
Supplementary Figure 2N: Cyclophosphamide (CP) Concentrations 1-5 (C1-C5)

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SCR C4
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PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
CP C2
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EUG C4
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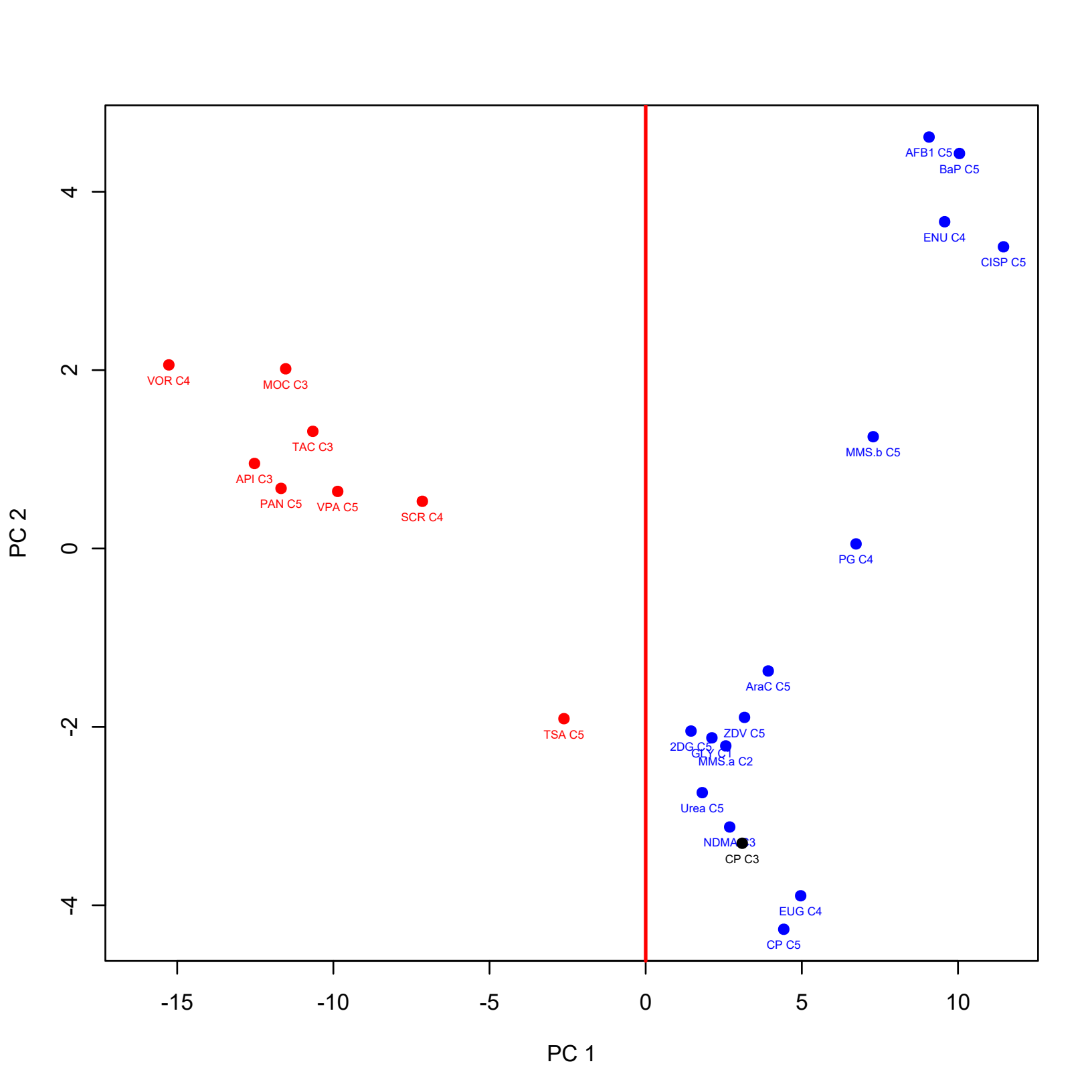
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PG C4
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Urea C5
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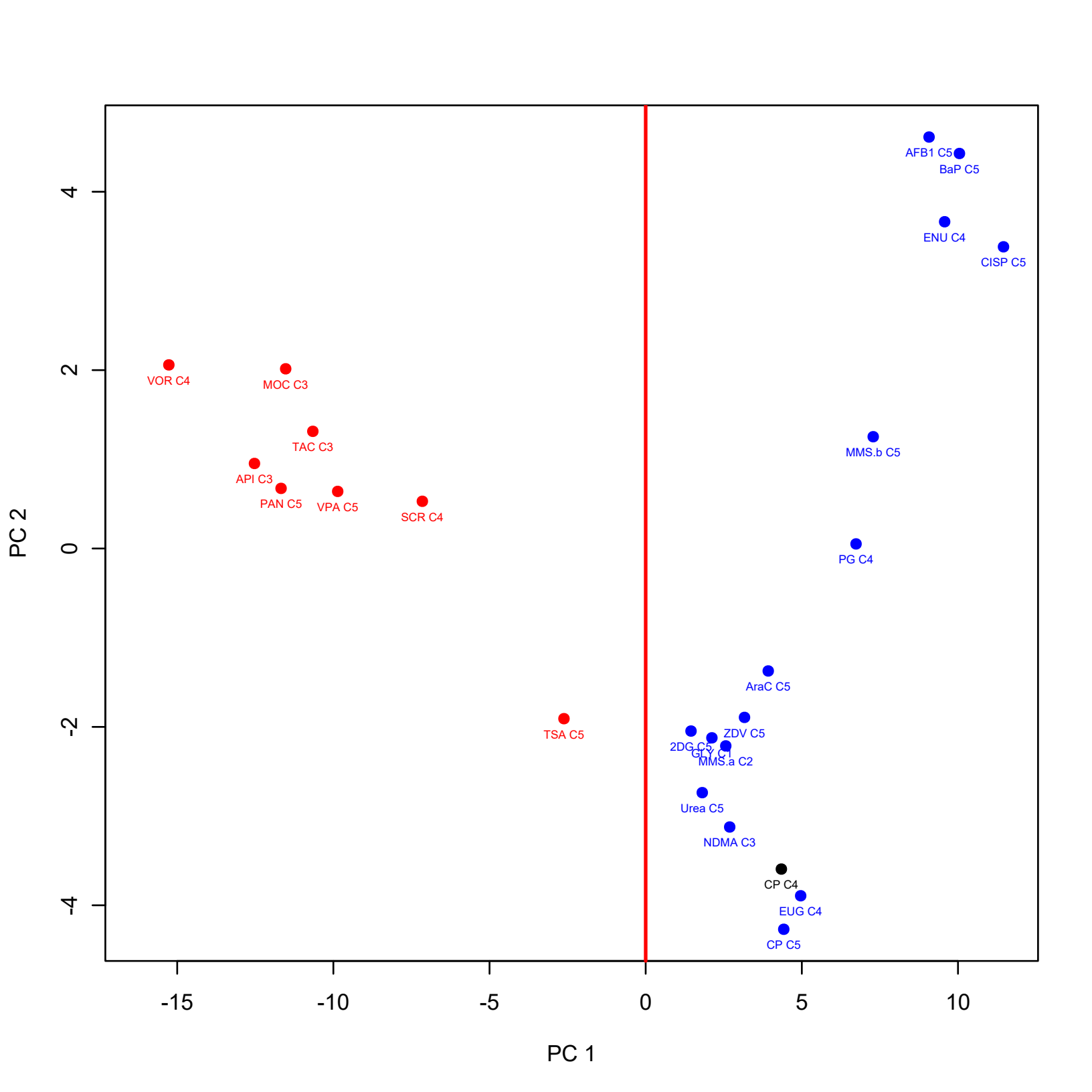
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MMS.b C5
PG C4
AraC C5
TSA C5
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MMS.a C2
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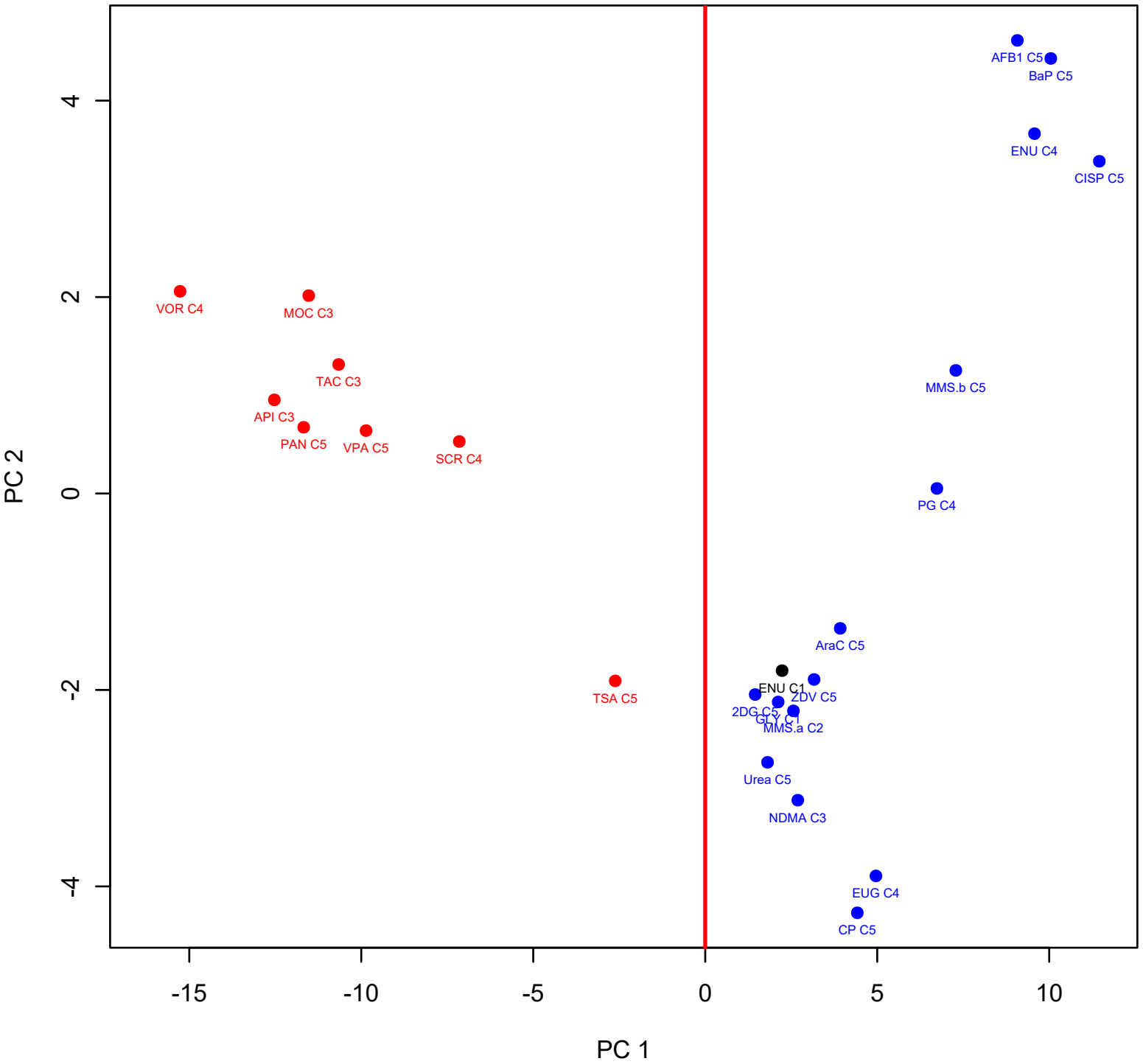
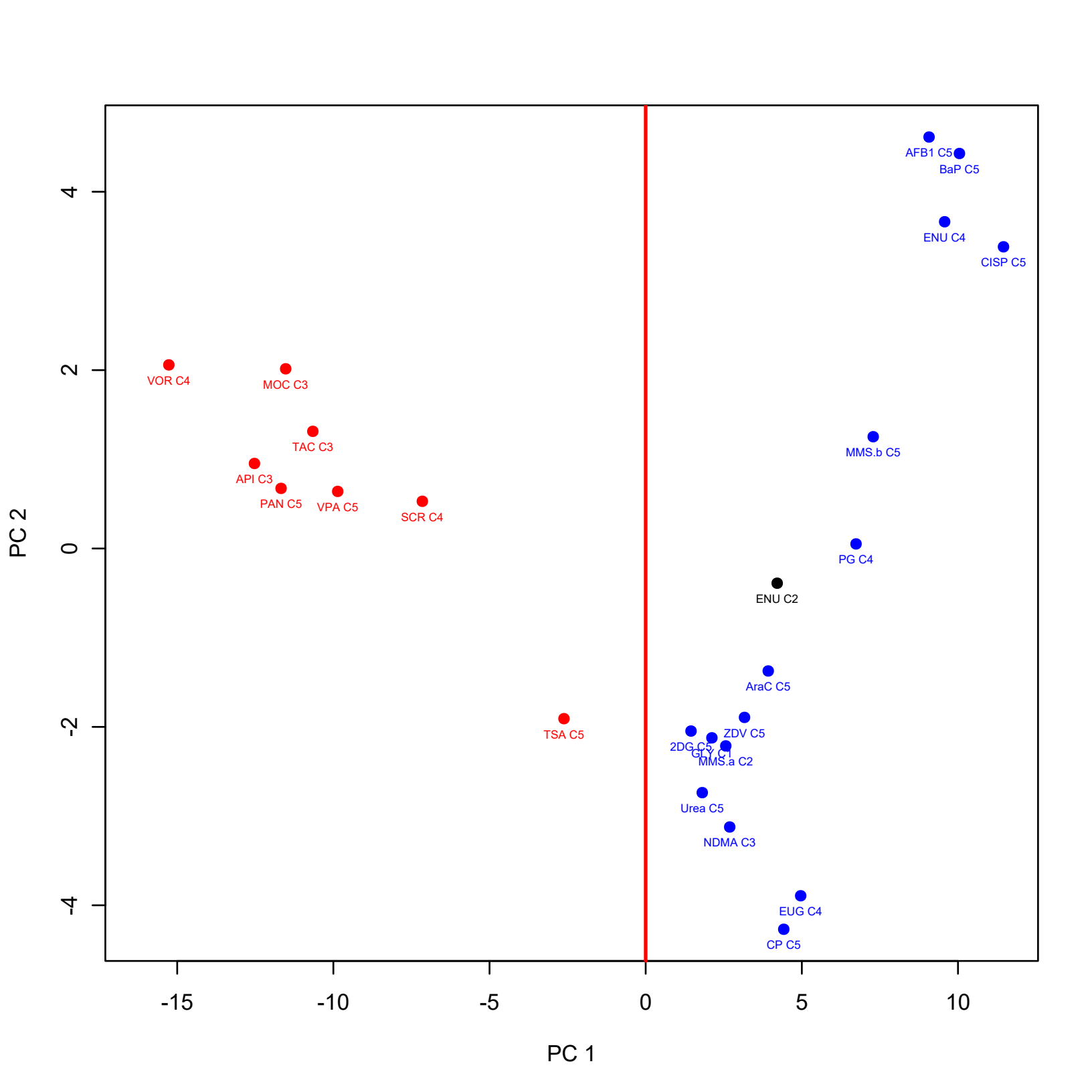
Supplementary Figure 2O: N-Nitroso-N-ethylurea (ENU) Concentrations 1-5 (C1-C5)

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MMS.b C5
PG C4
ENU C2
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
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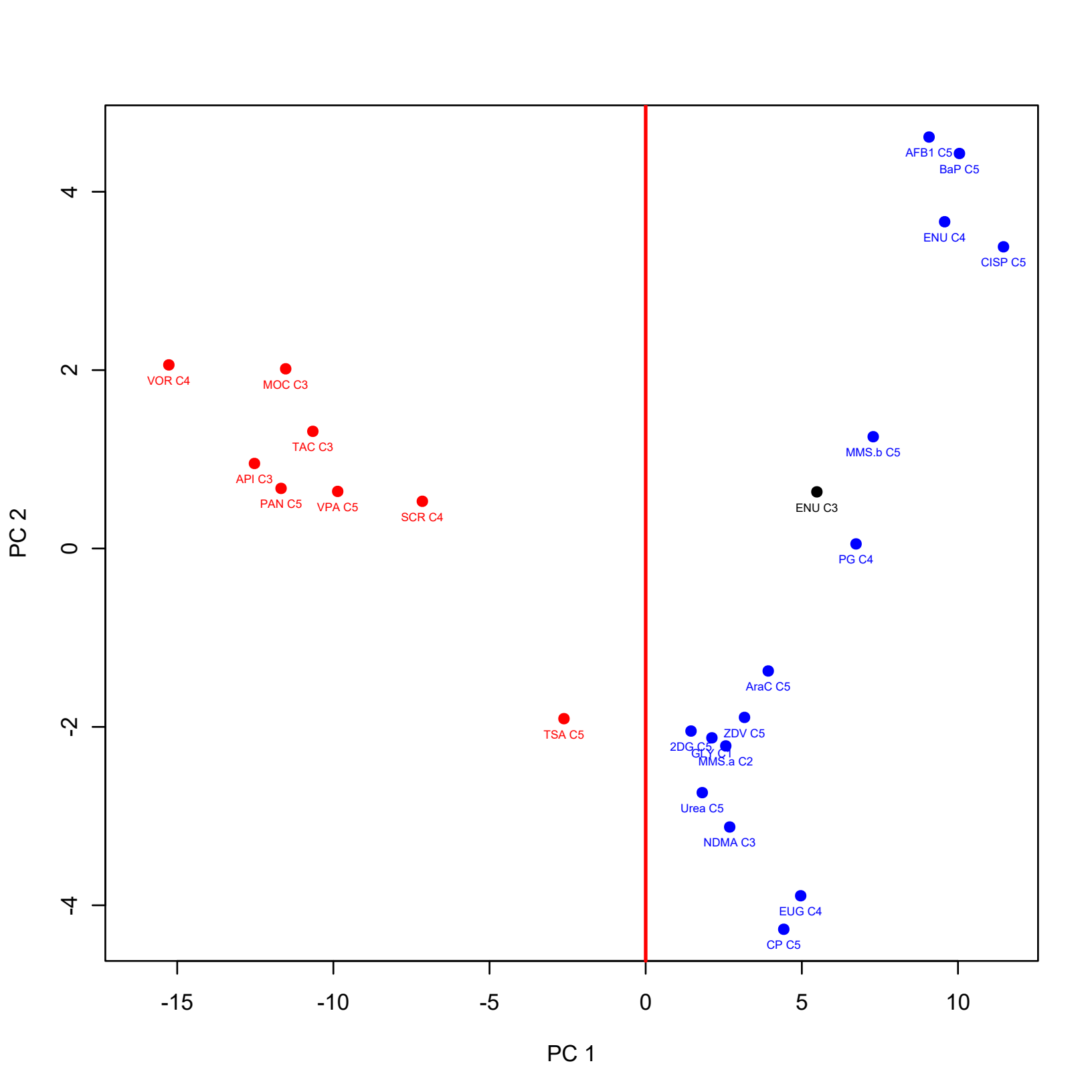
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TSA C5
ZDV C5
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MMS.a C2
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NDMA C3
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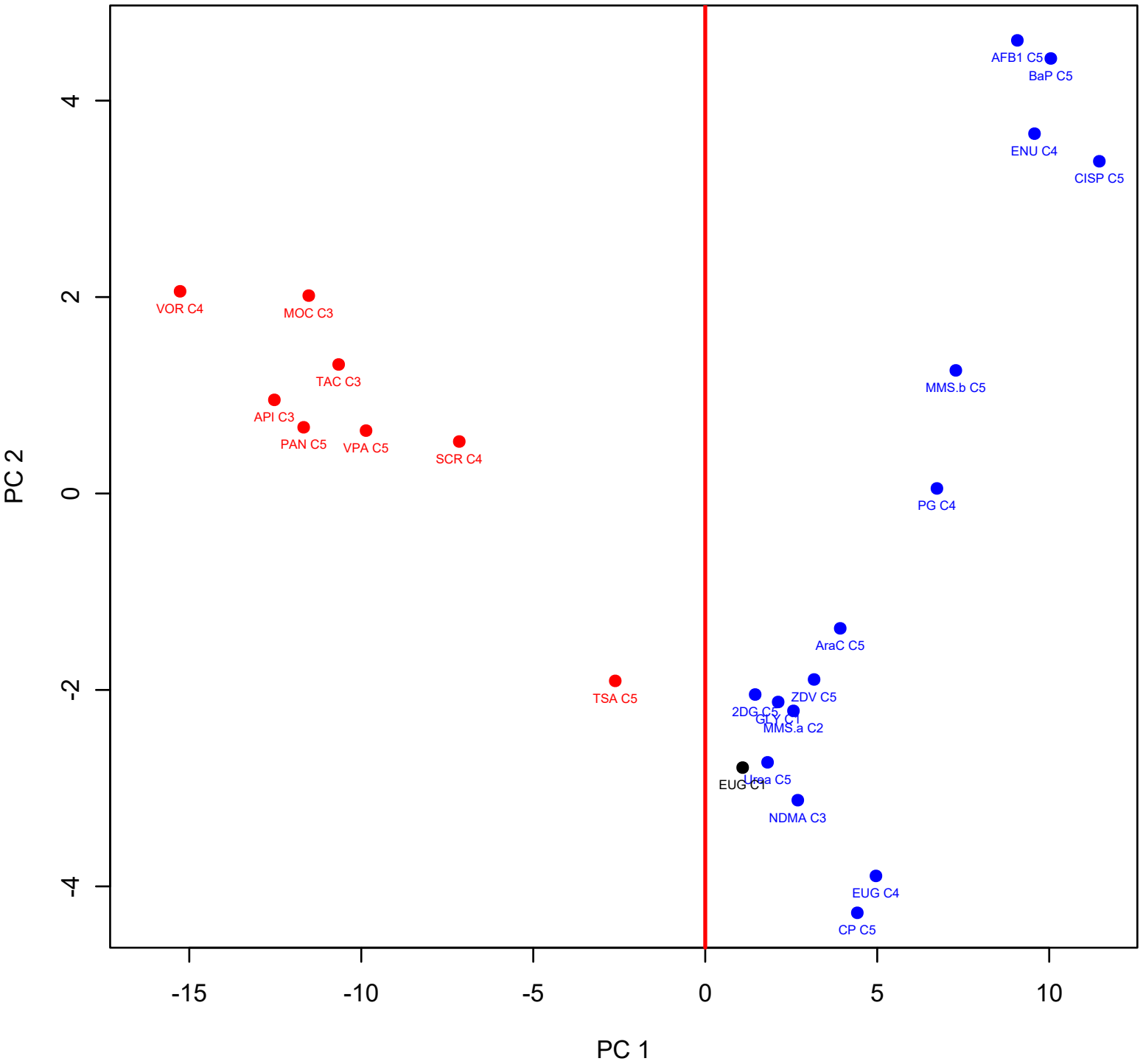
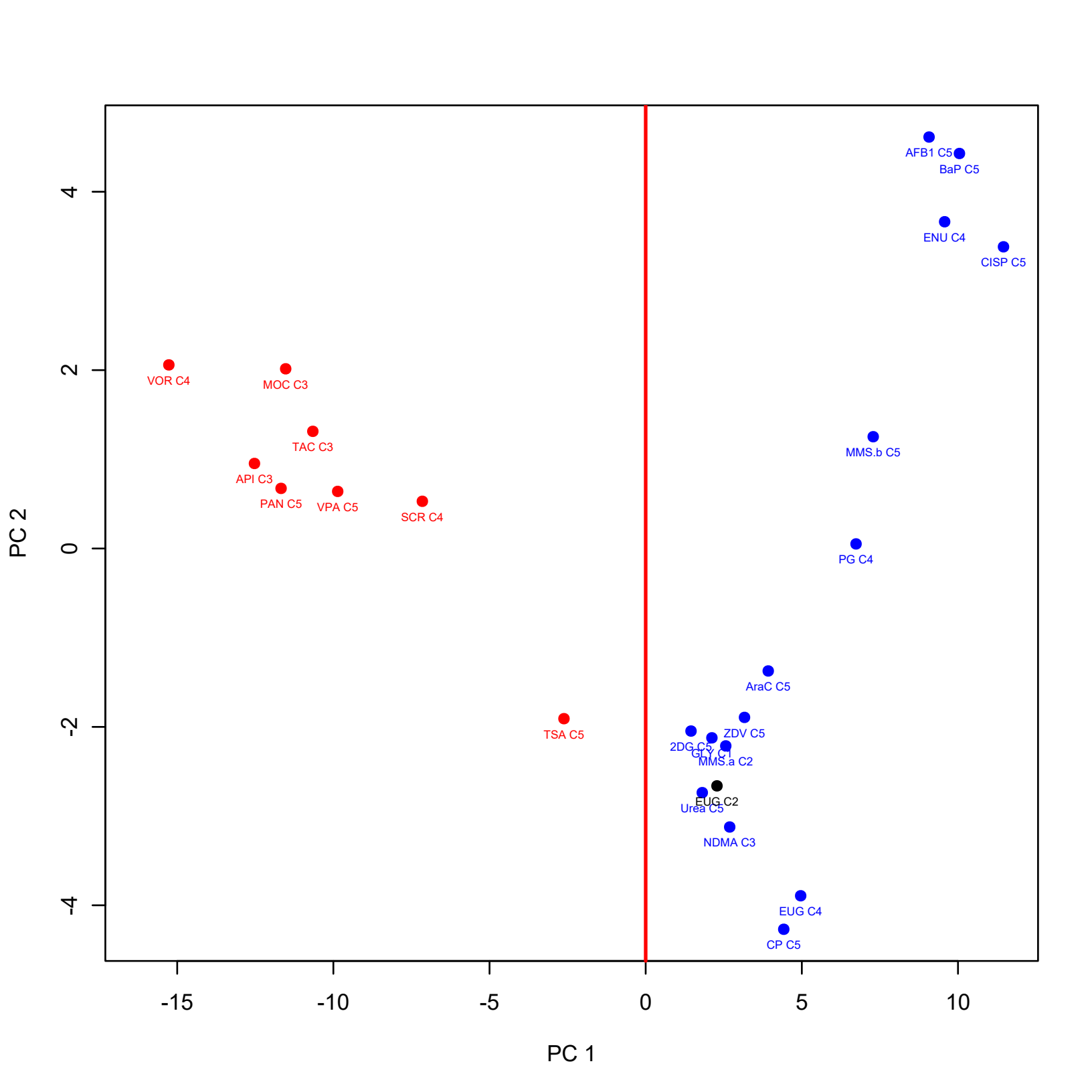
Supplementary Figure 2P: Eugenol (EUG) Concentrations 1-5 (C1-C5)

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MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
EUG C2
Urea C5
NDMA C3
EUG C4
CP C5
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PC 2
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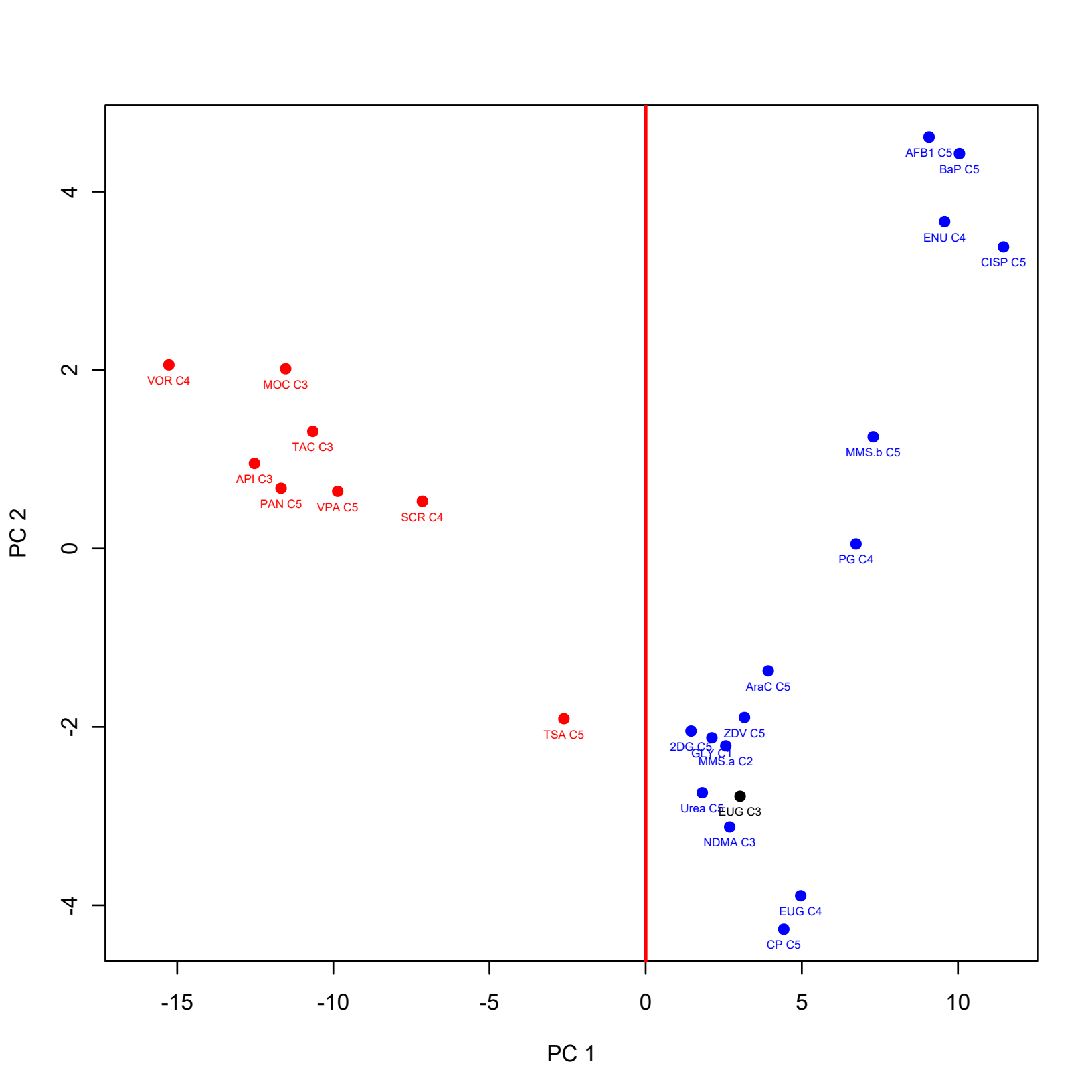
-4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MMS.b C5
PG C4
AraC C5
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2DG C5
GLY C1
MMS.a C2
Urea C5
EUG C3
NDMA C3
EUG C4
CP C5
PC 1
PC 2
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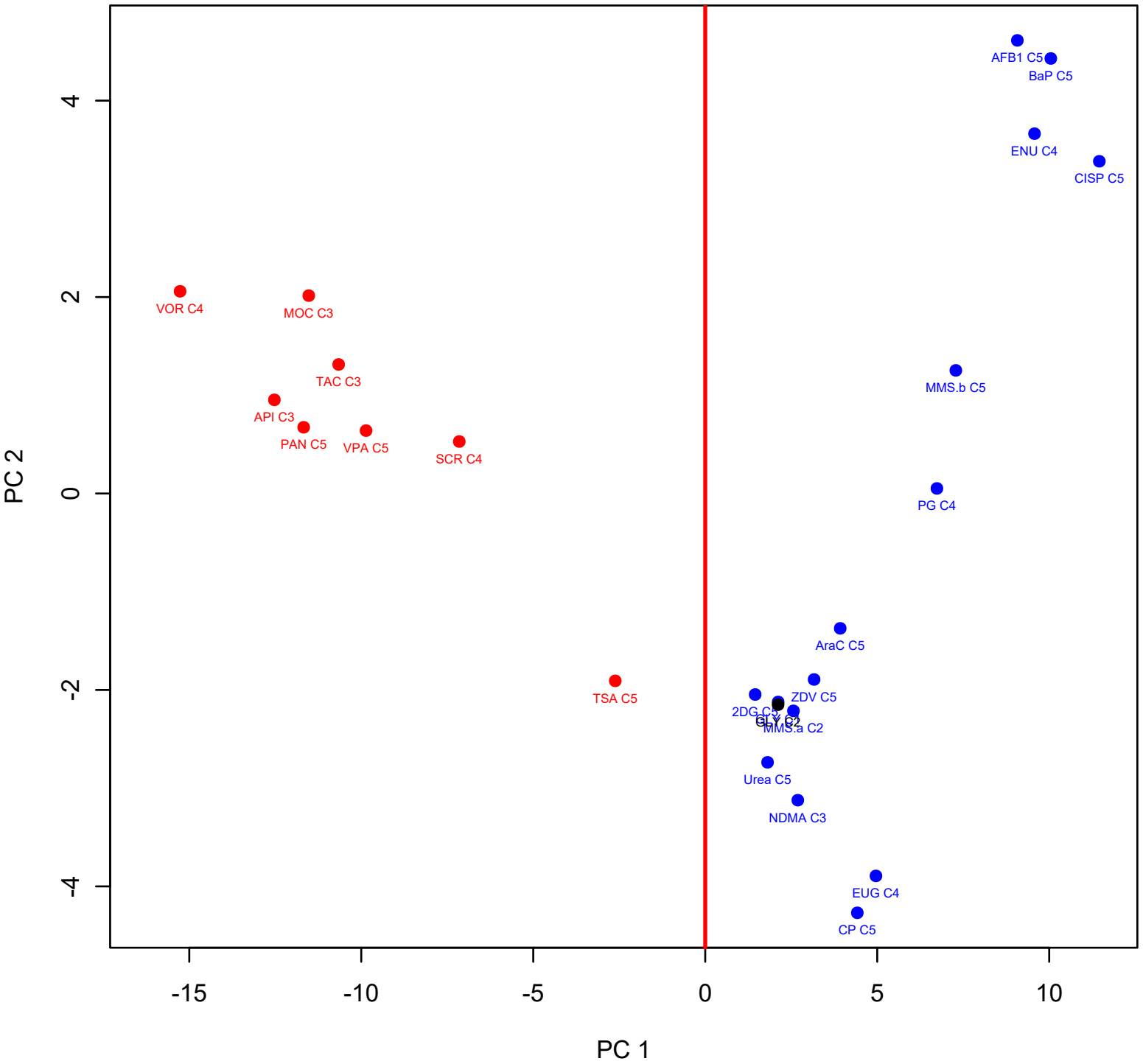
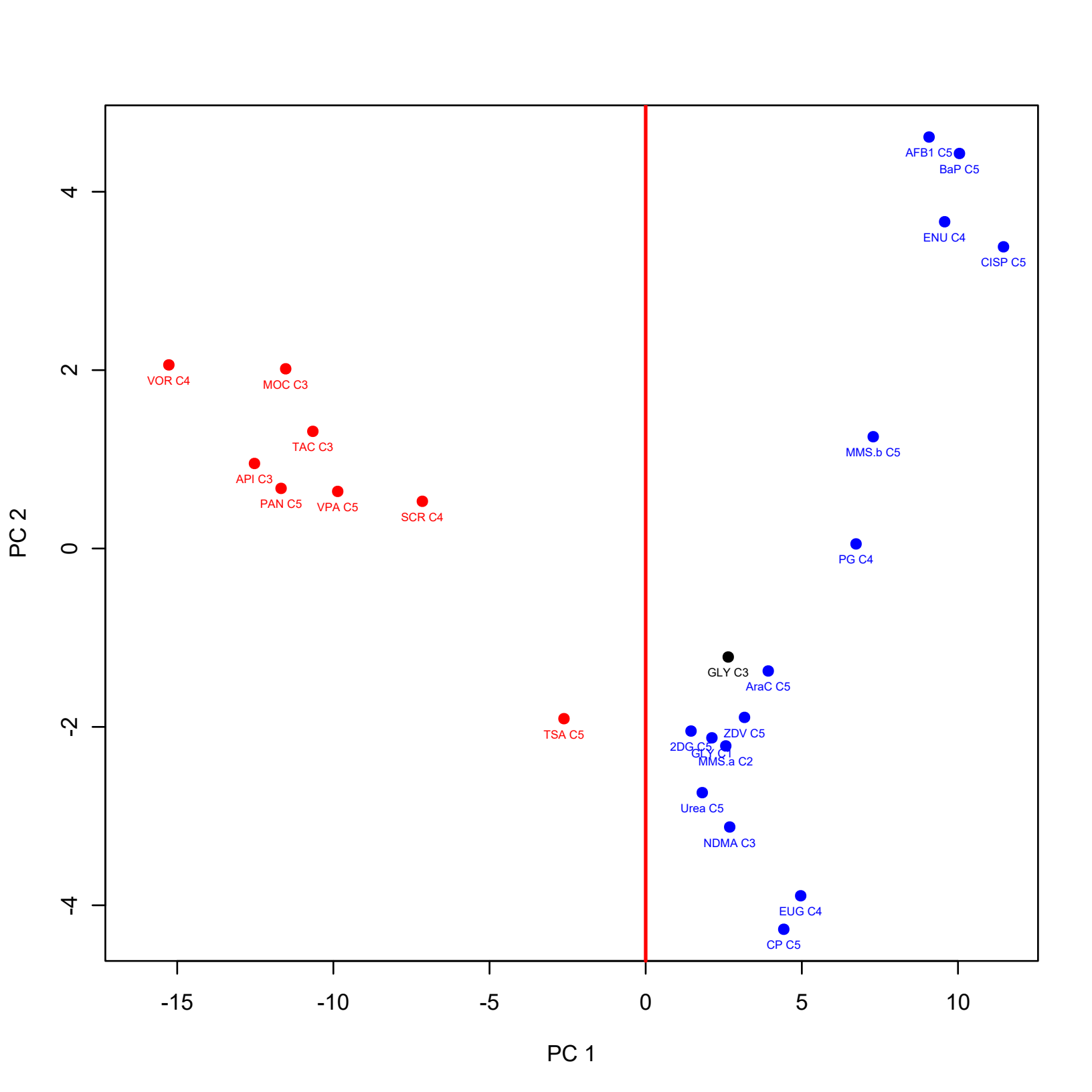
-4

Supplementary Figure 2Q: Glycidol (GLY) Concentrations 1-5 (C1-C5)

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VOR C4
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TAC C3
API C3
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VPA C5
SCR C4
MMS.b C5
PG C4
GLY C3
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
PC 1
PC 2
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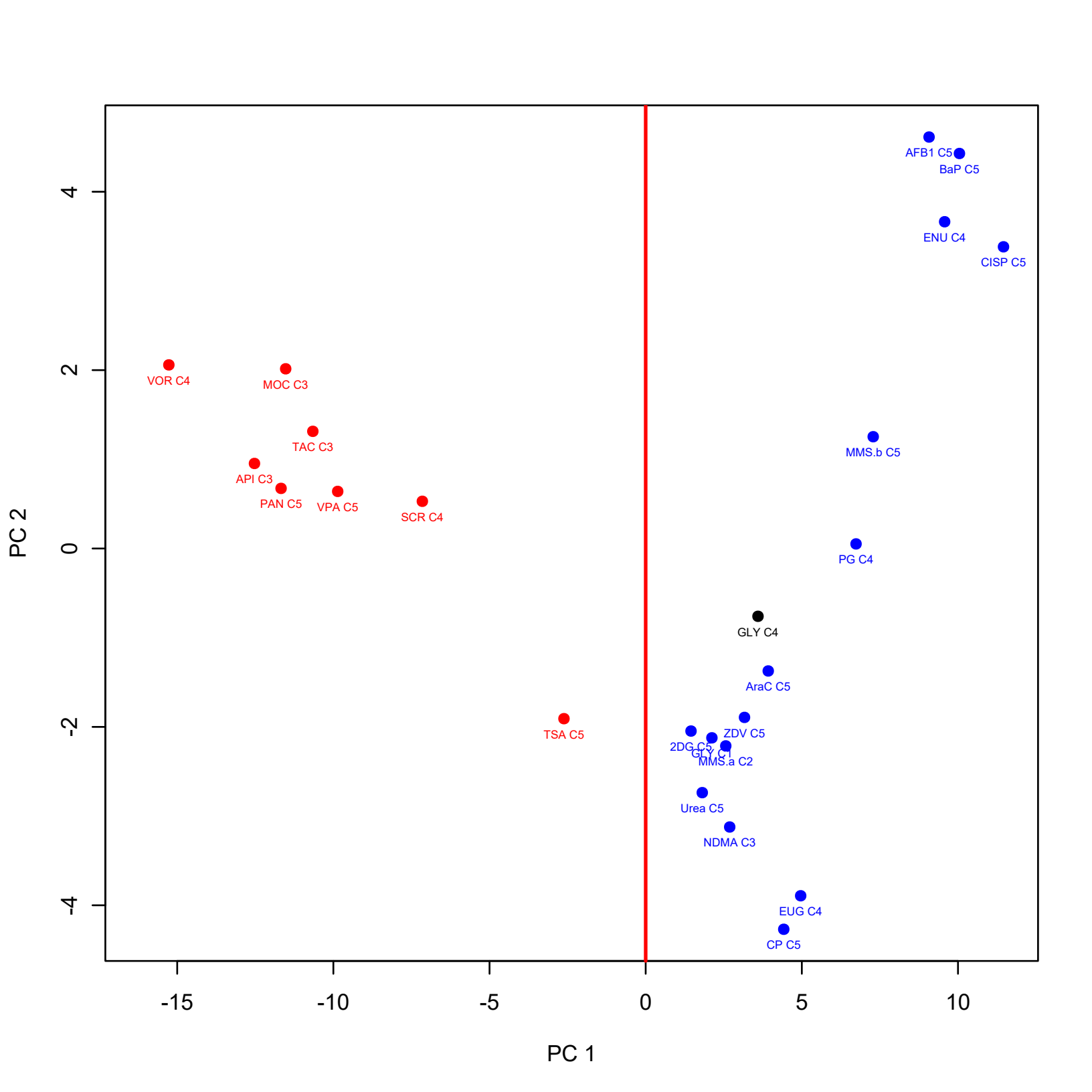
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API C3
PAN C5
VPA C5
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MMS.b C5
PG C4
GLY C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
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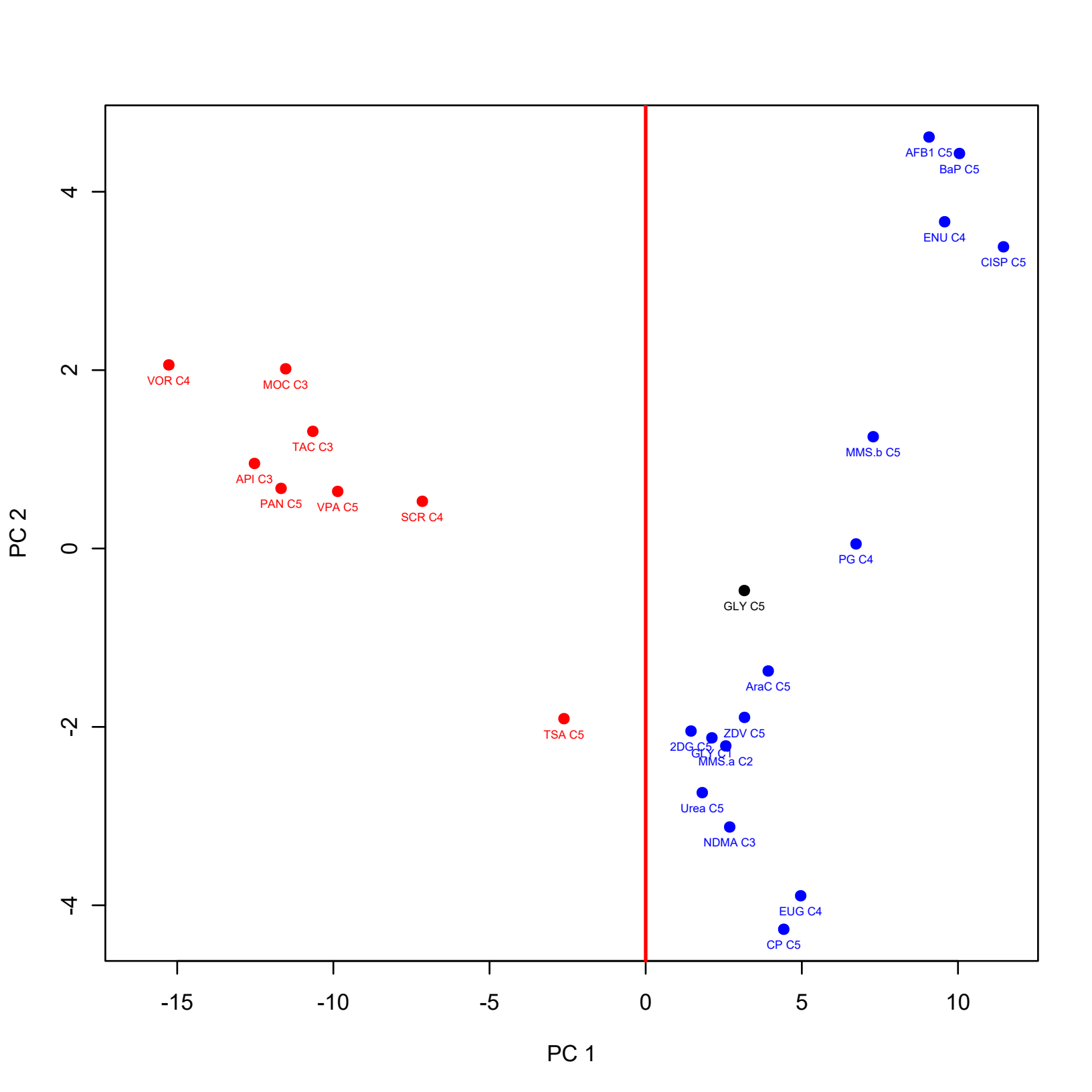
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PG C4
GLY C5
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TSA C5
ZDV C5
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MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
PC 2
PC 1
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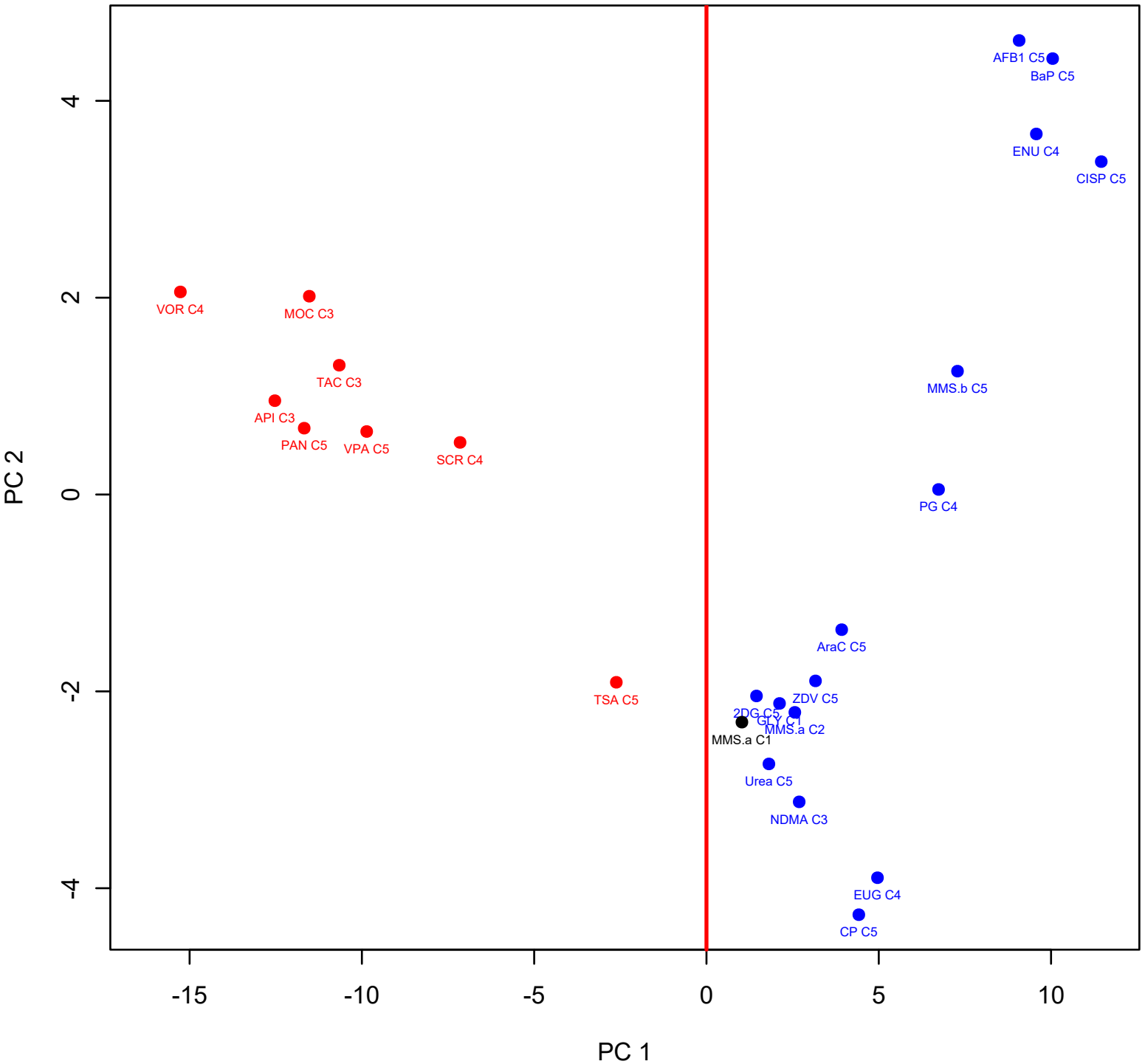
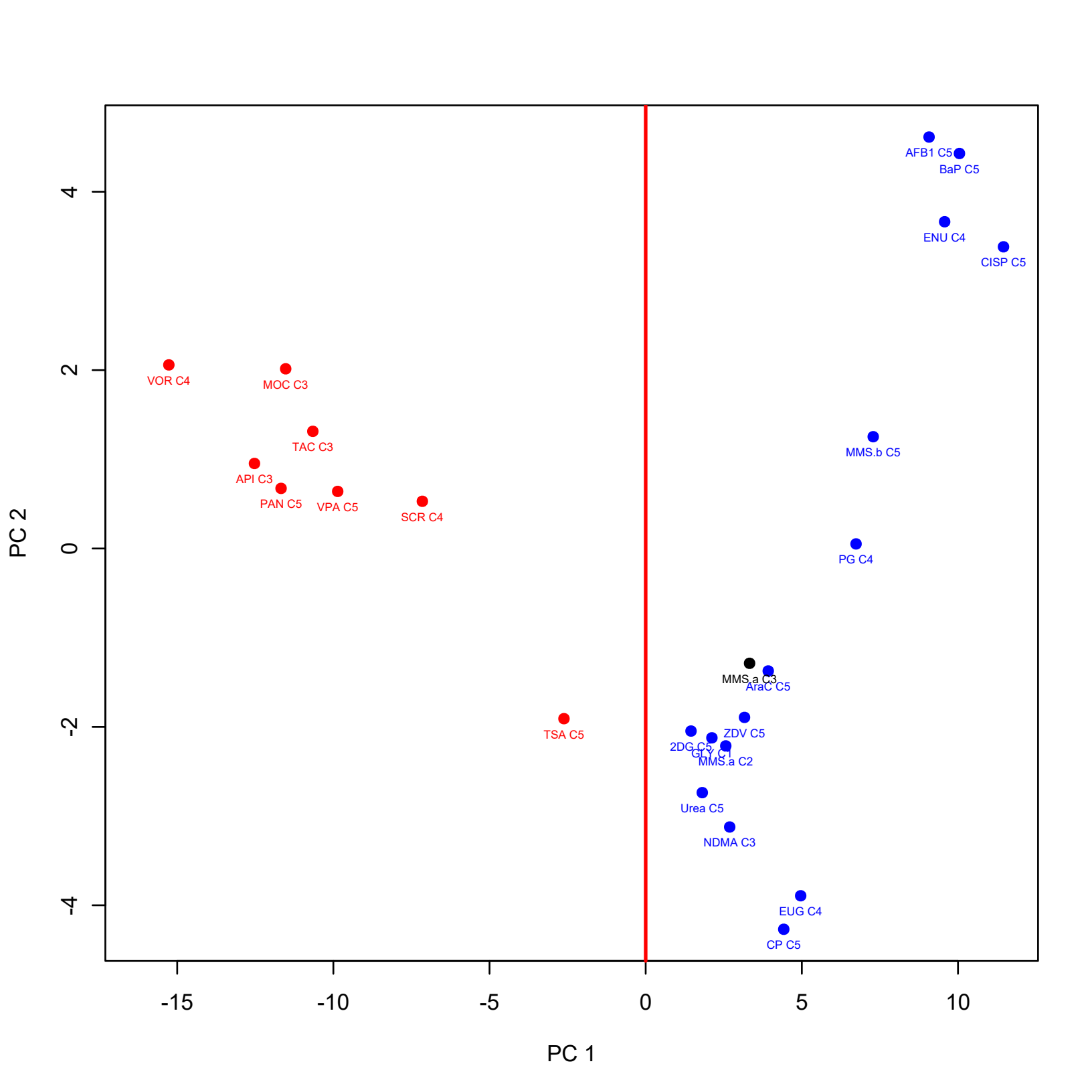
Supplementary Figure 2R: Methyl Methanesulfonate[a] (MMS.a) Concentrations 1-5 (C1-C5)

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API C3
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VPA C5
SCR C4
MMS.b C5
PG C4
MMS.a C3
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
PC 2
PC 1
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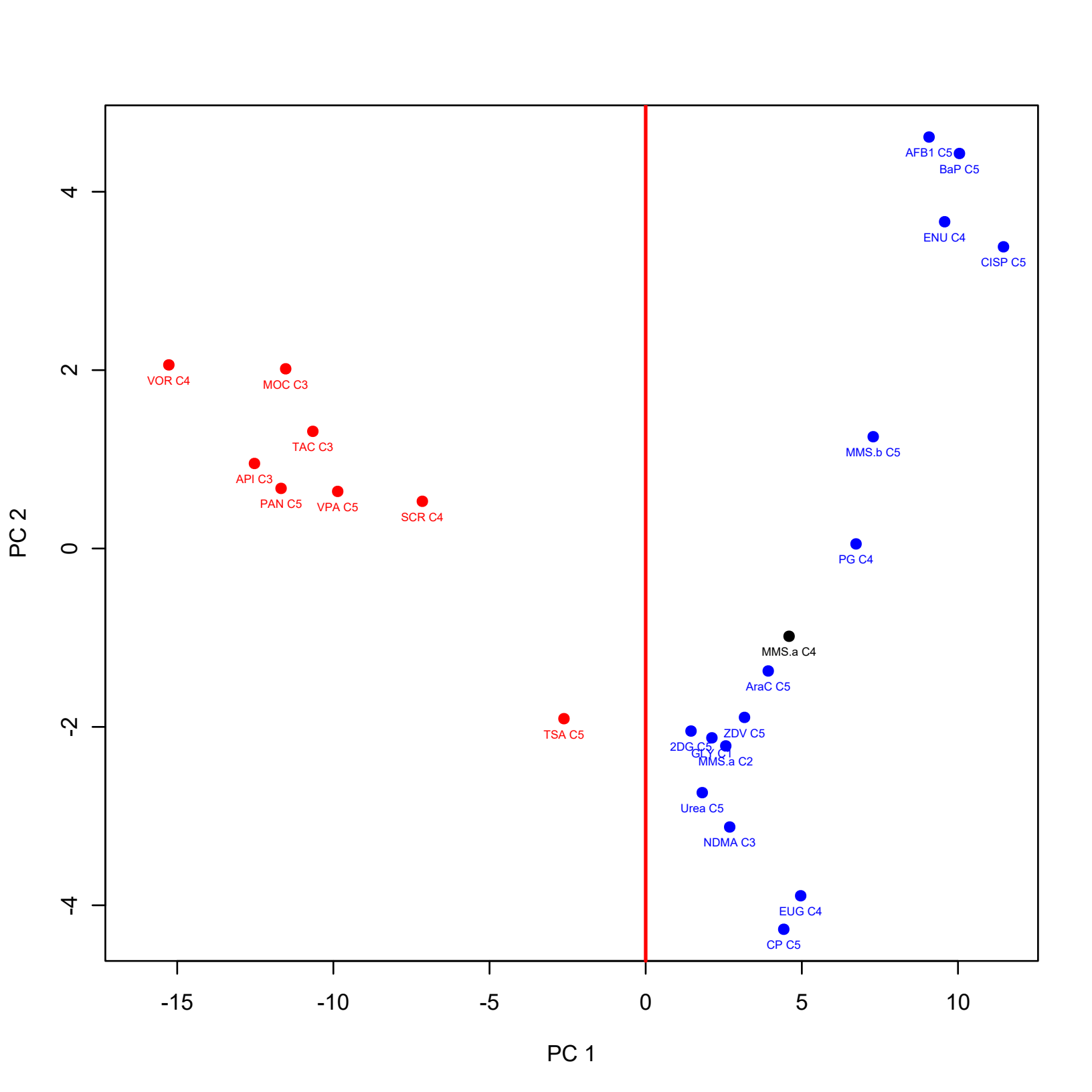
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TAC C3
API C3
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SCR C4
MMS.b C5
PG C4
MMS.a C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
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CP C5
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PC 2
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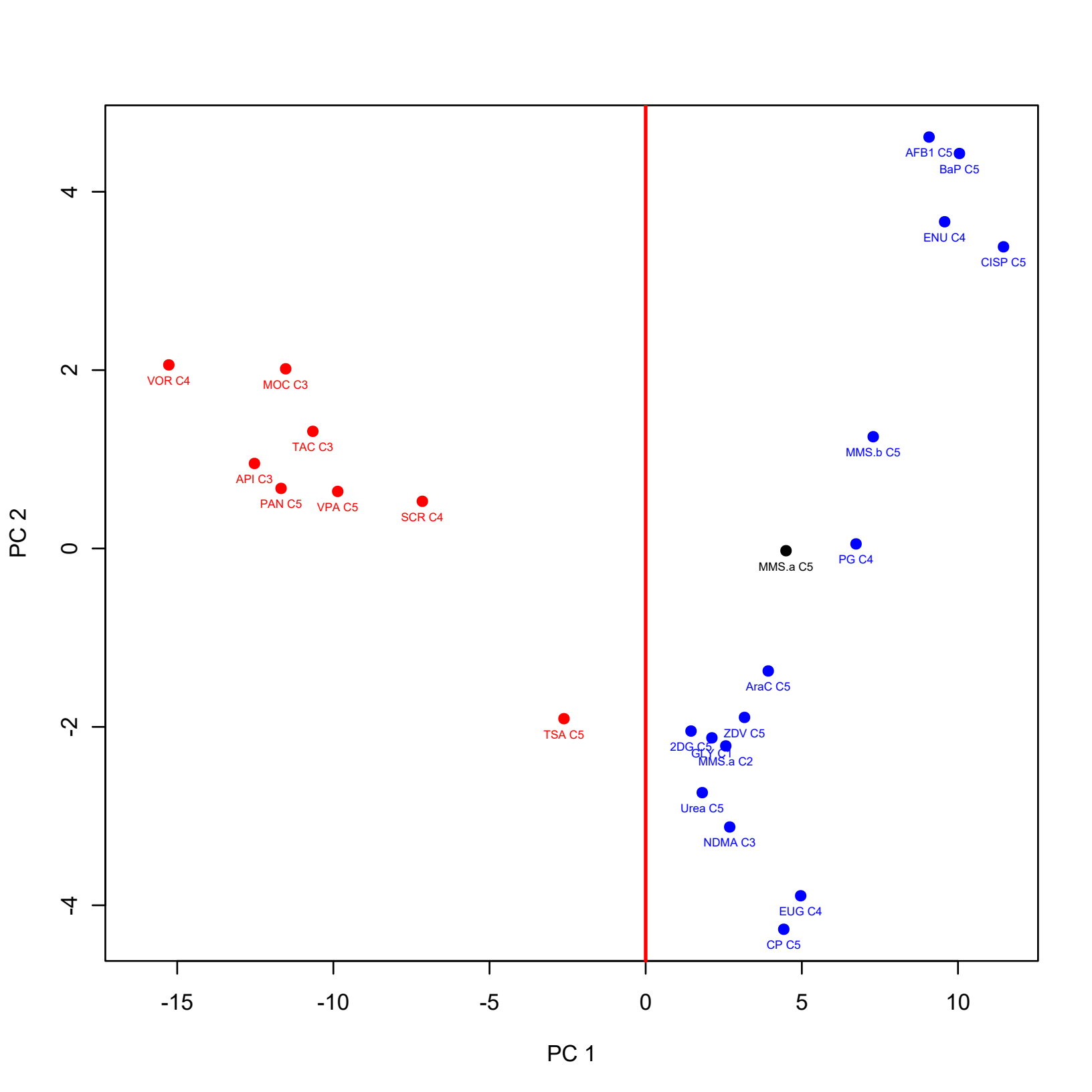
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API C3
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MMS.b C5
MMS.a C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
PC 2
PC 1
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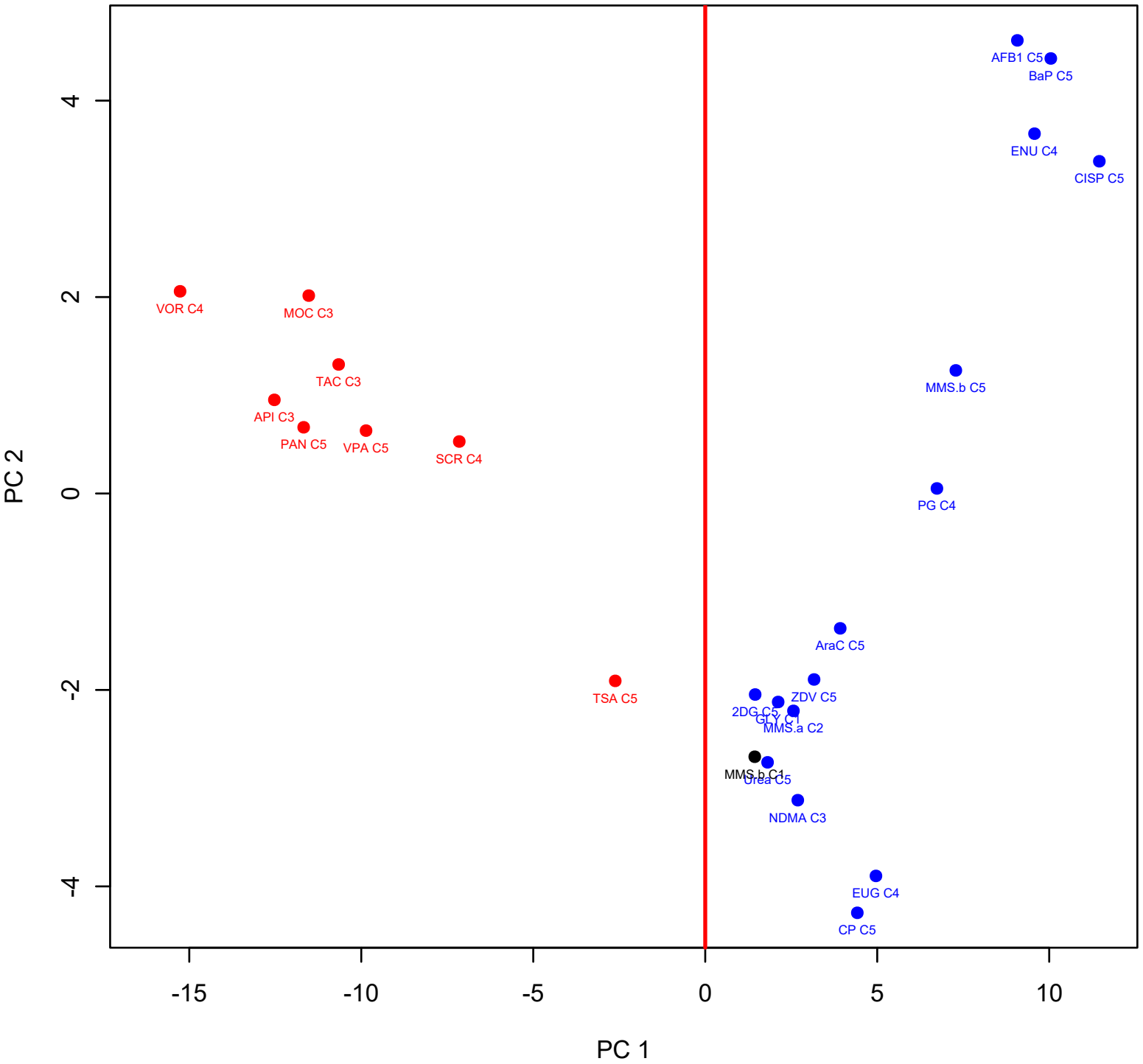
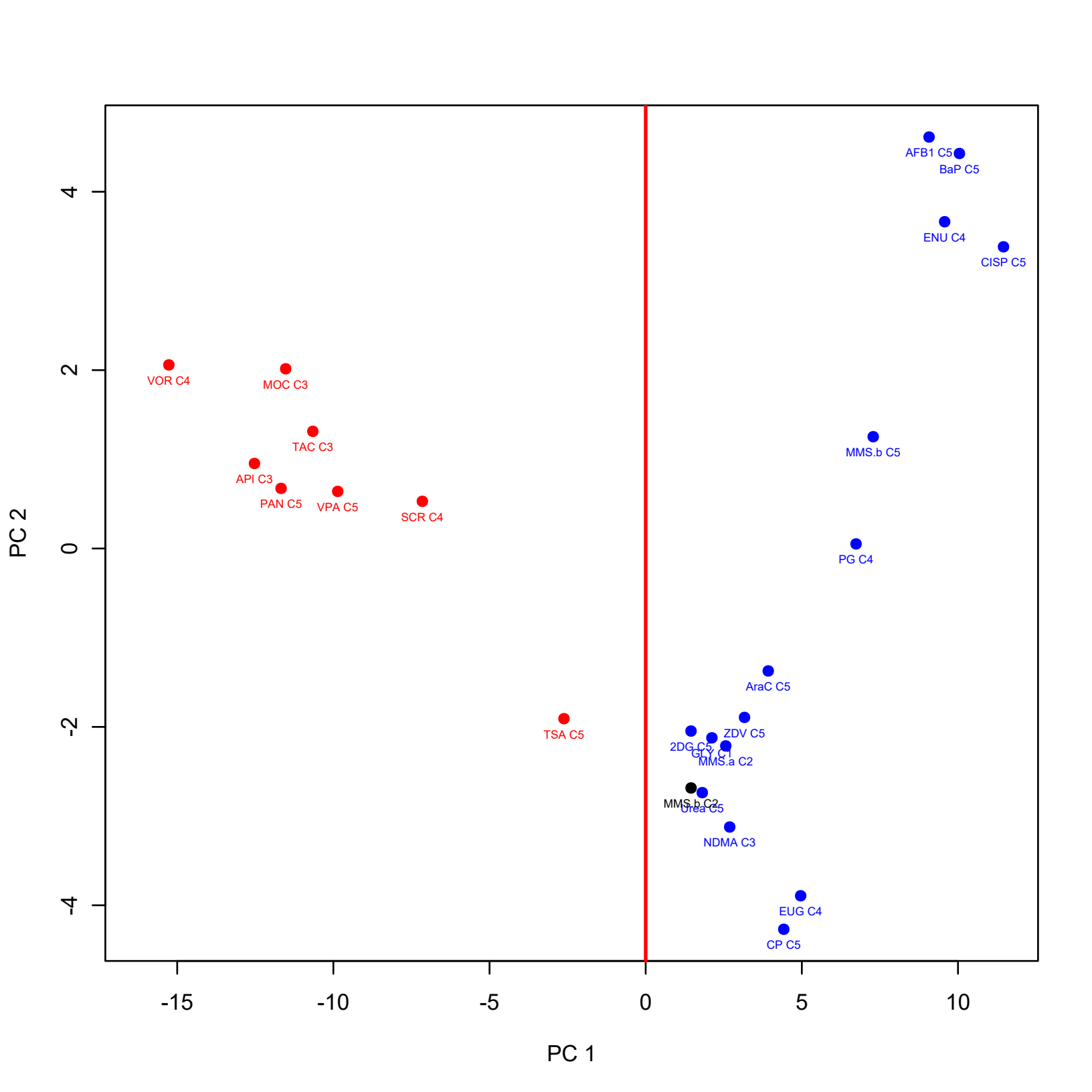
Supplementary Figure 2S: Methyl Methanesulfonate[b] (MMS.b) Concentrations 1-5 (C1-C5)

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GLY C1
MMS.a C2
MMS.b C2
Urea C5
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CP C5
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PC 2
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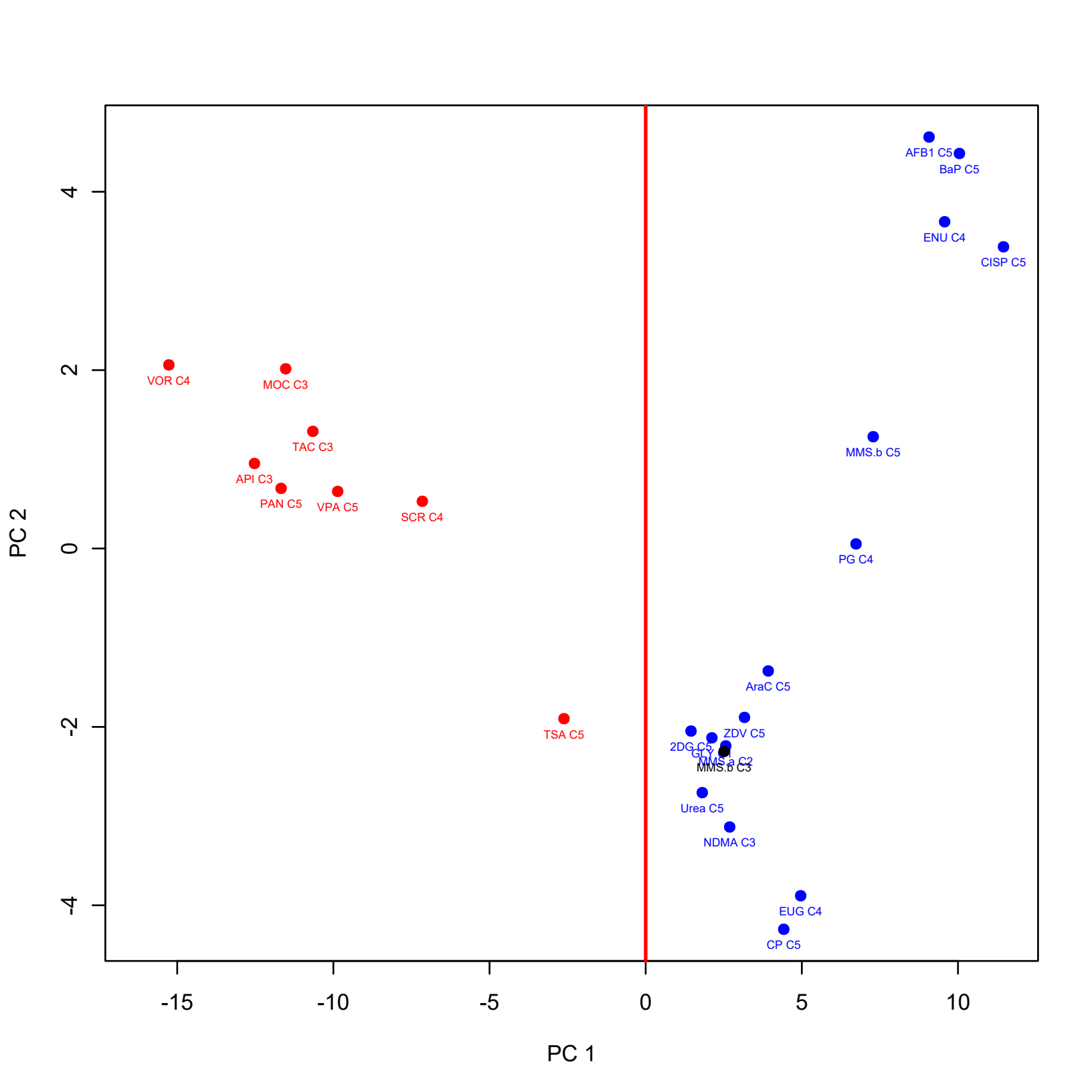
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PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY
MMS.a C2
MMS.b C3
Urea C5
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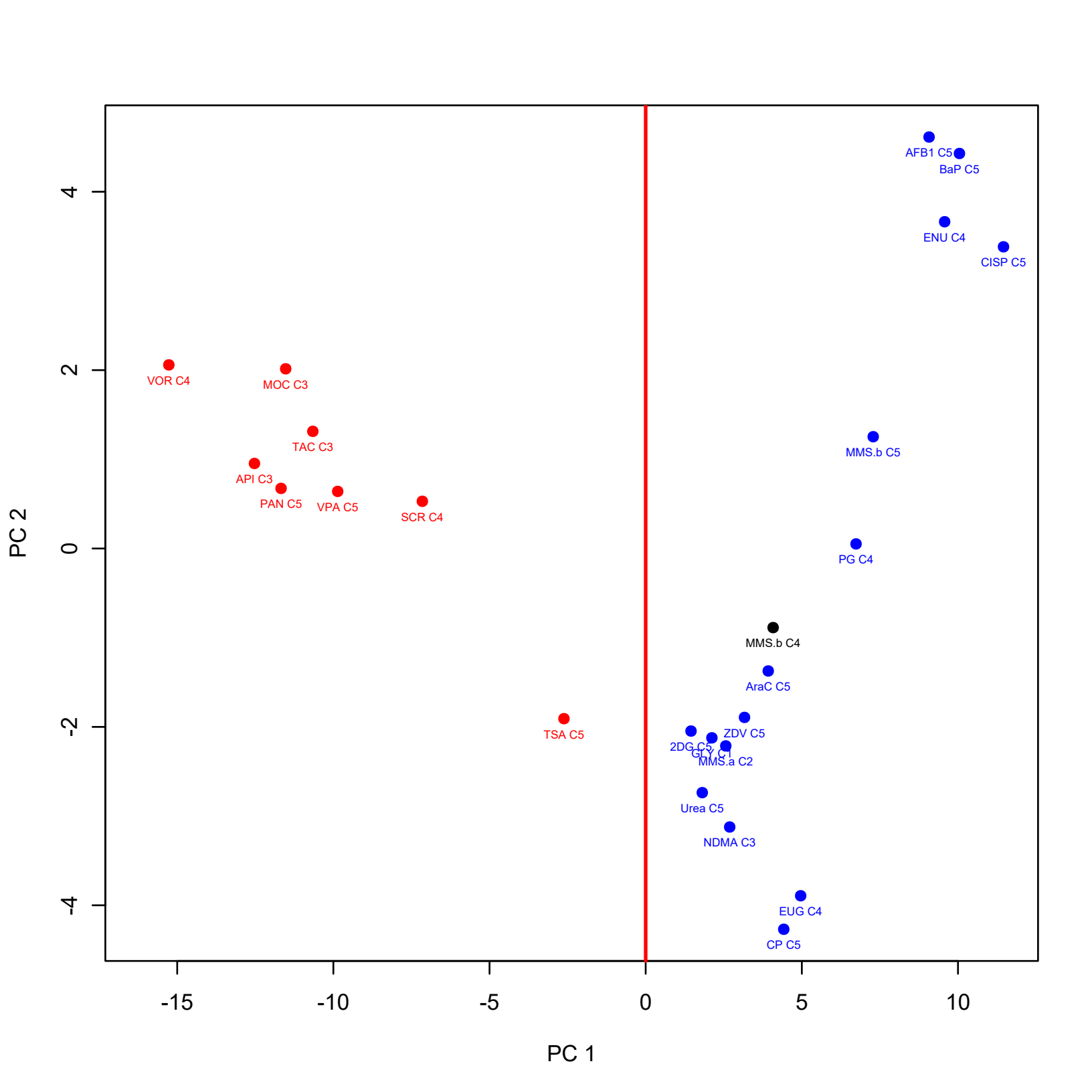
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MMS.b C5
PG C4
MMS.b C4
AraC C5
TSA C5
ZDV C5
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GLY C1
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Urea C5
NDMA C3
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CP C5
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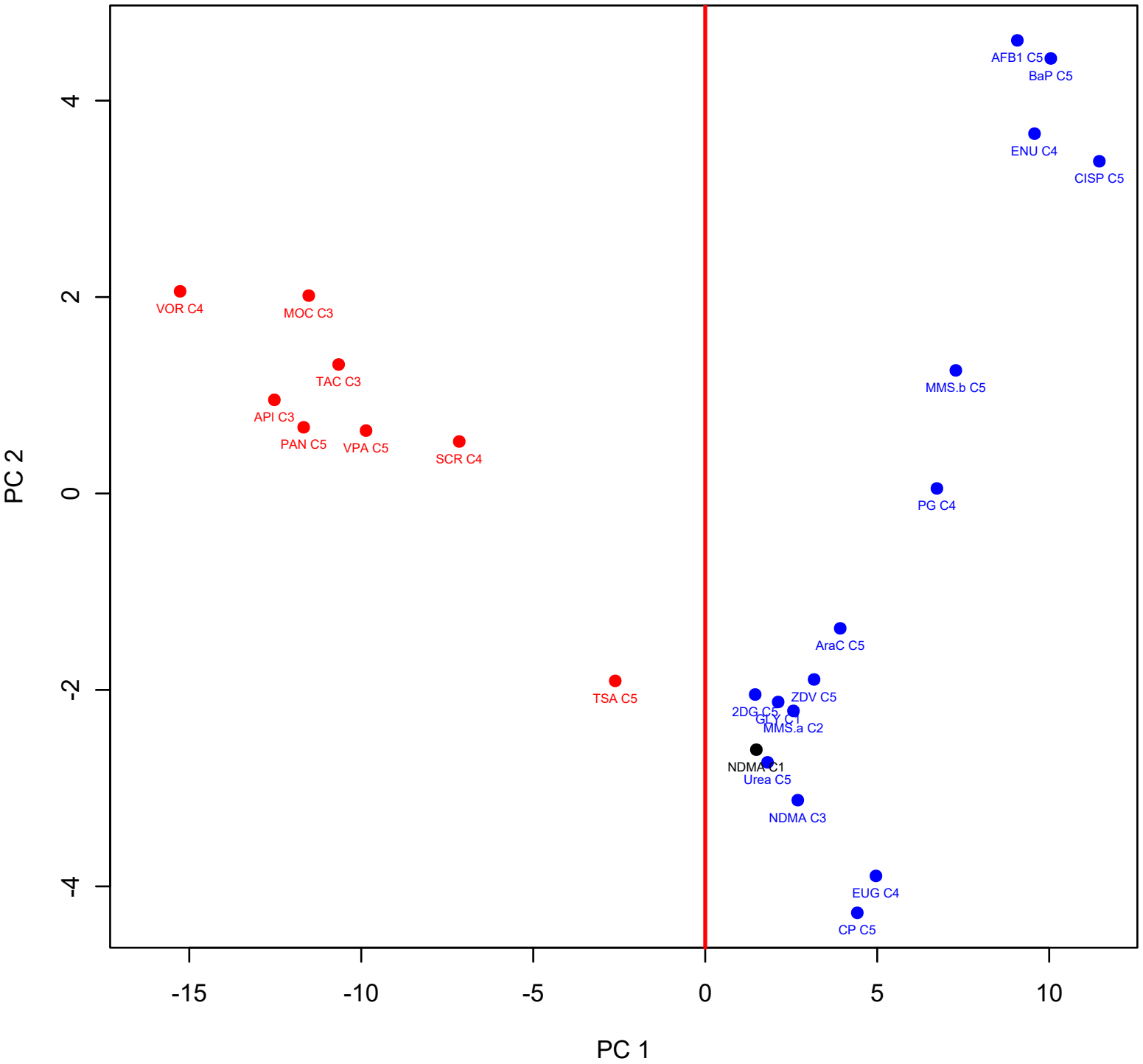
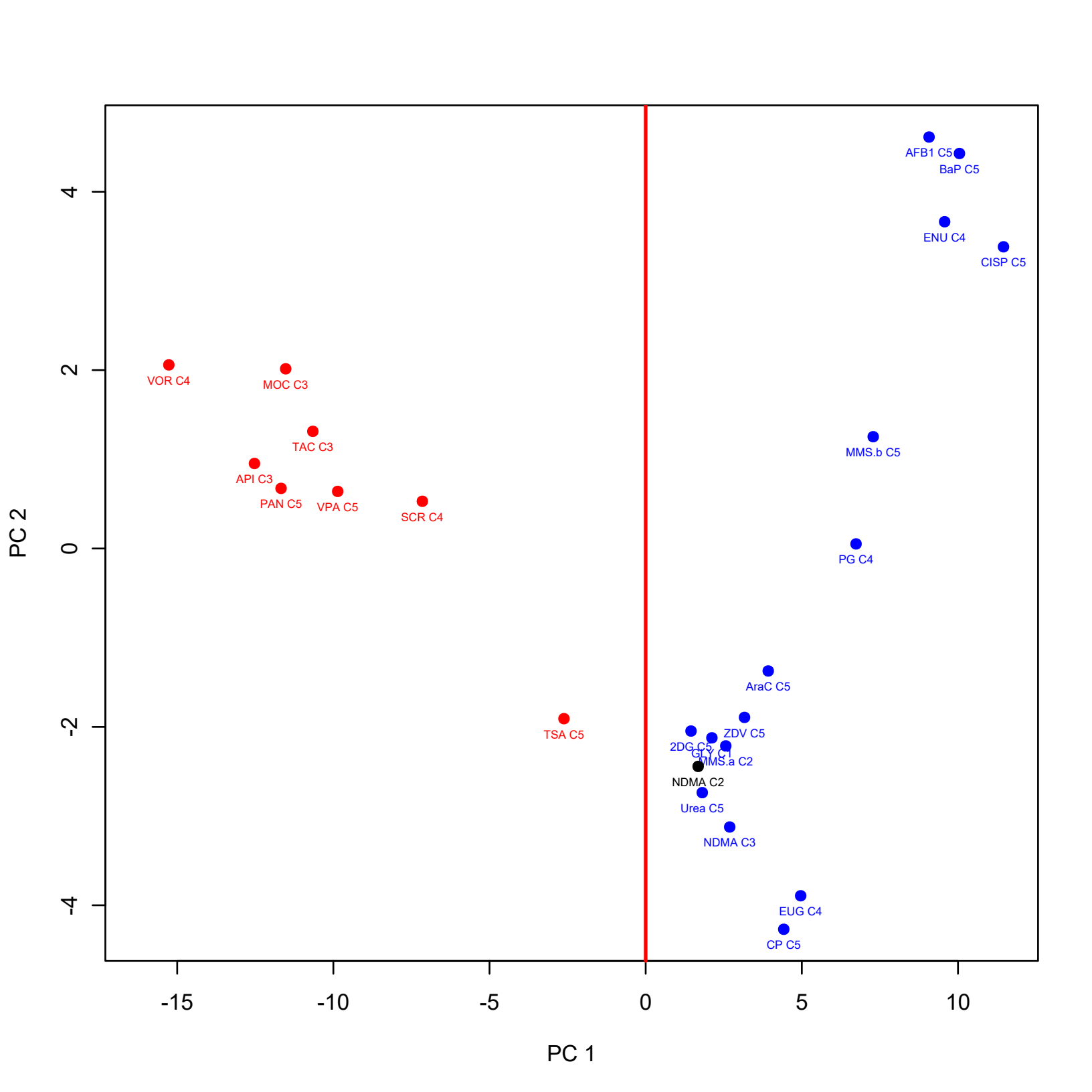
Supplementary Figure 2T: N-Nitrosodimethylamine (NDMA) Concentrations 1-5 (C1-C5)

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MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
NDMA C2
Urea C5
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CP C5
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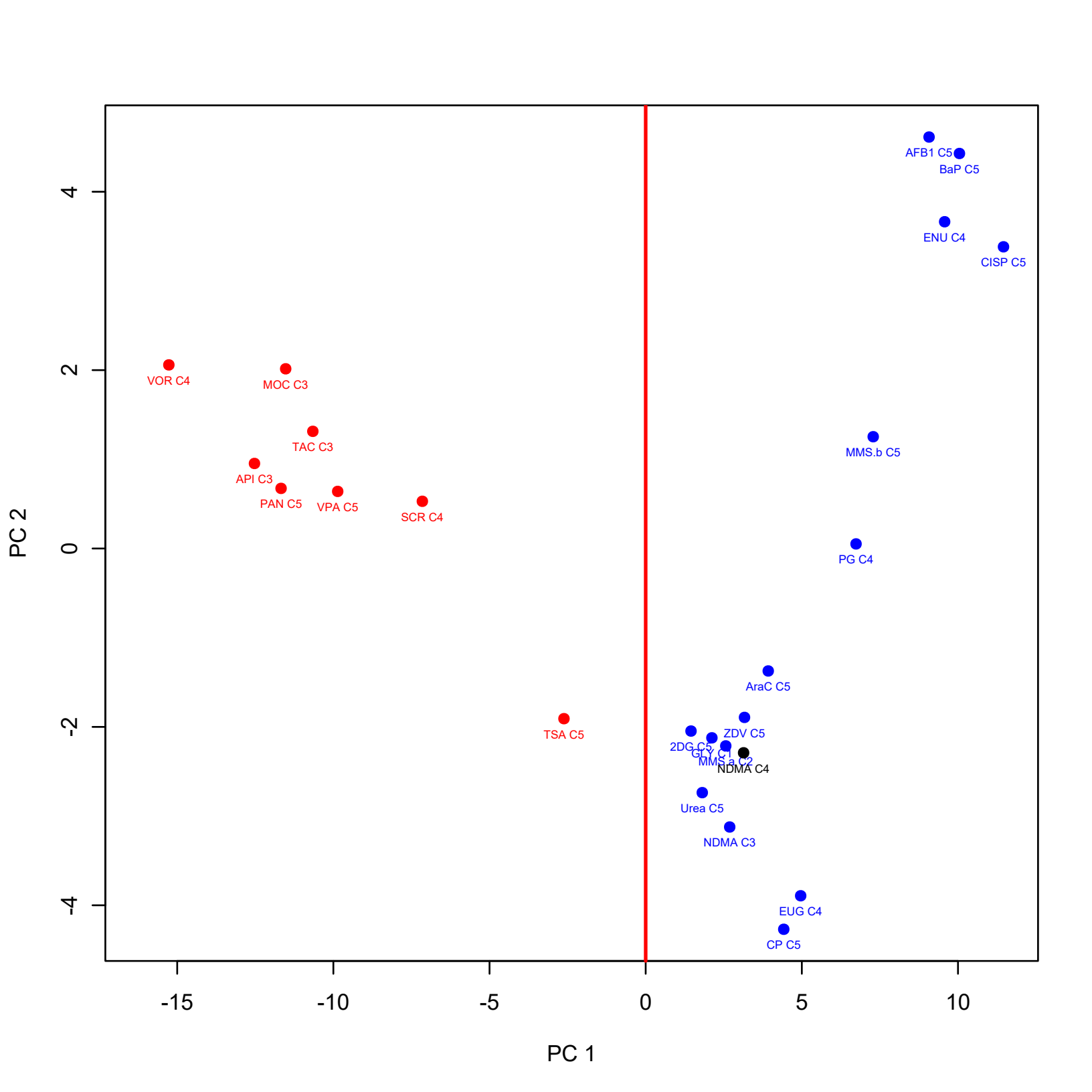
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AraC C5
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ZDV C5
2DG C5
GLY C1
MMS.a C2
NDMA C4
Urea C5
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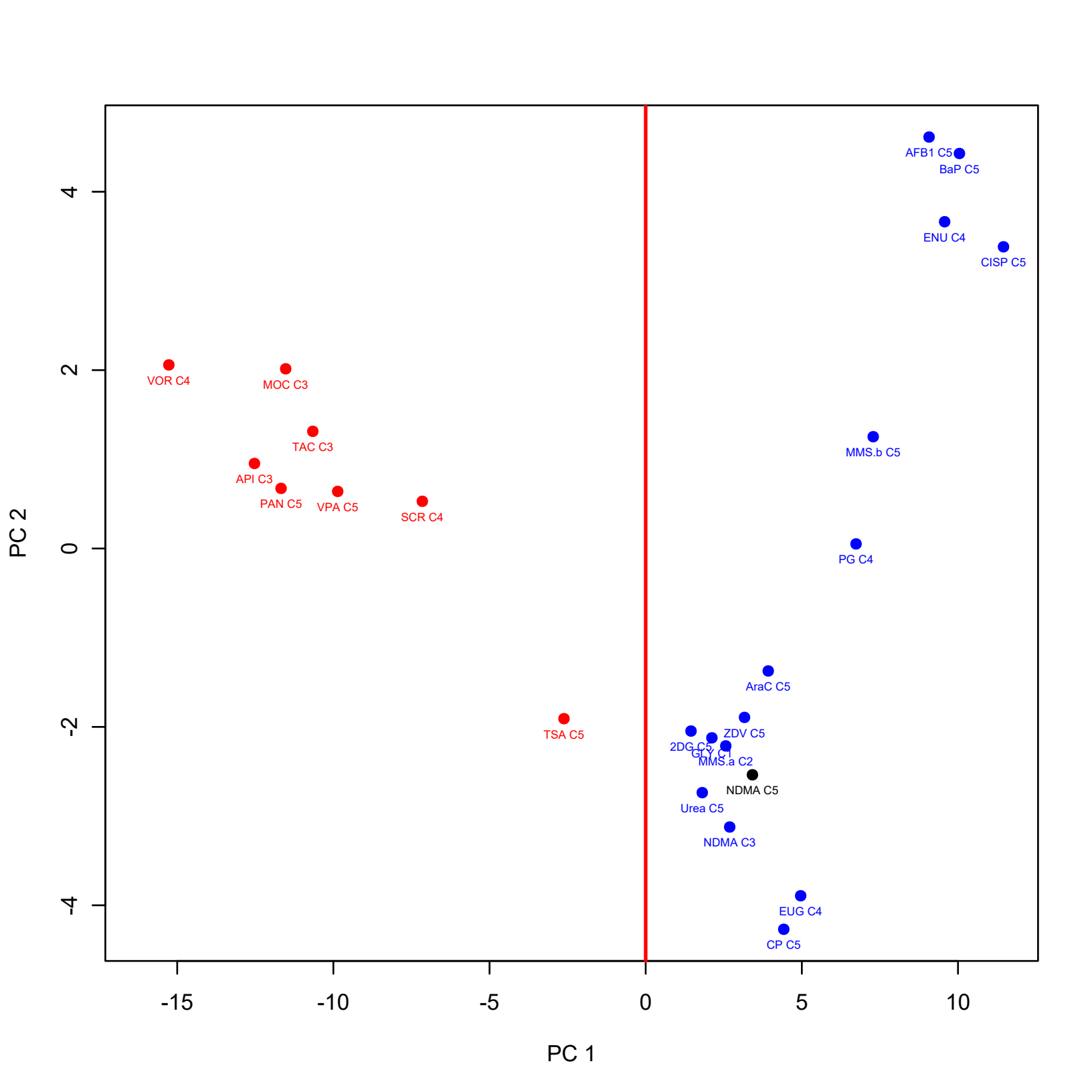
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ZDV C5
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Urea C5
NDMA C3
EUG C4
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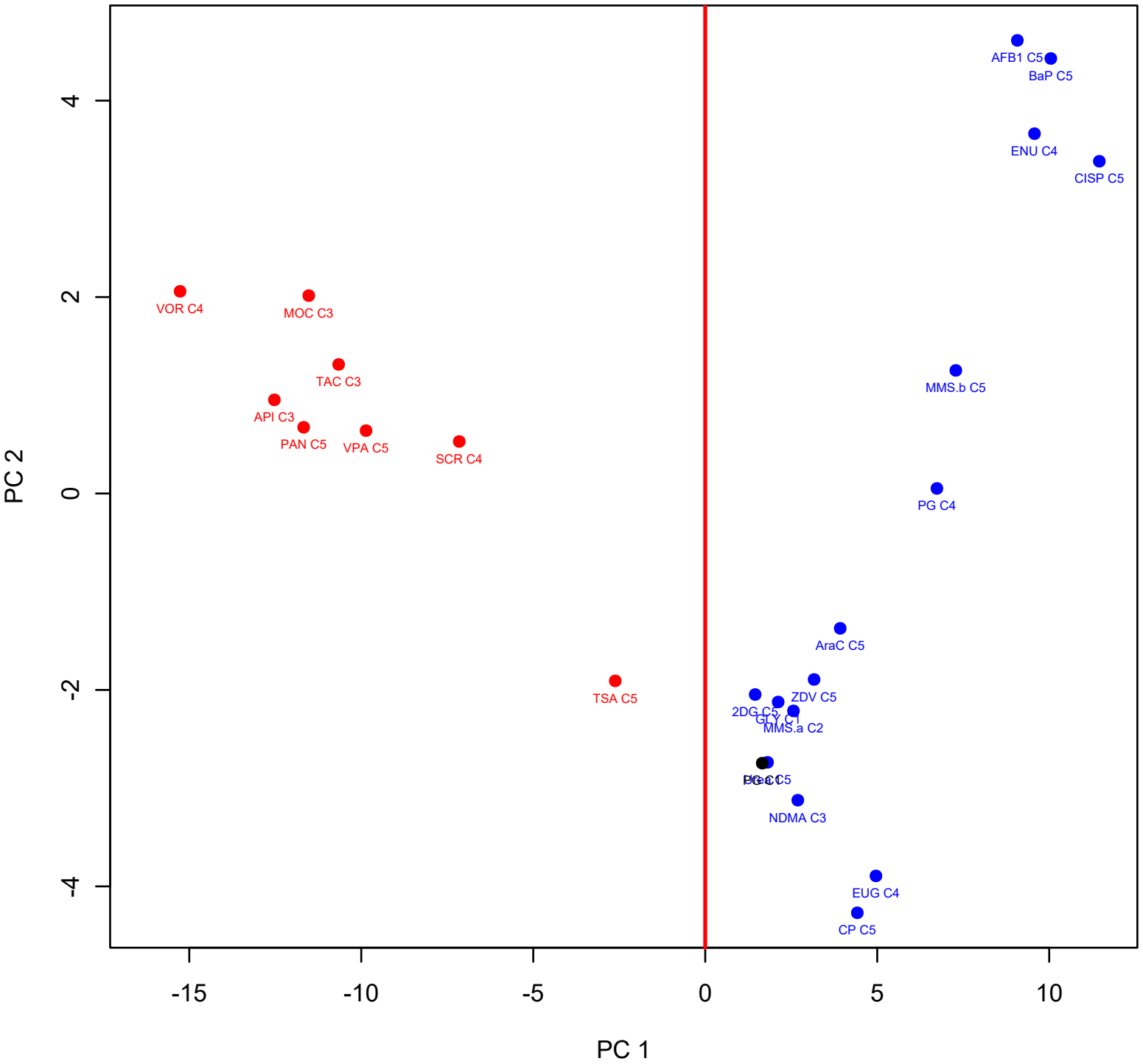
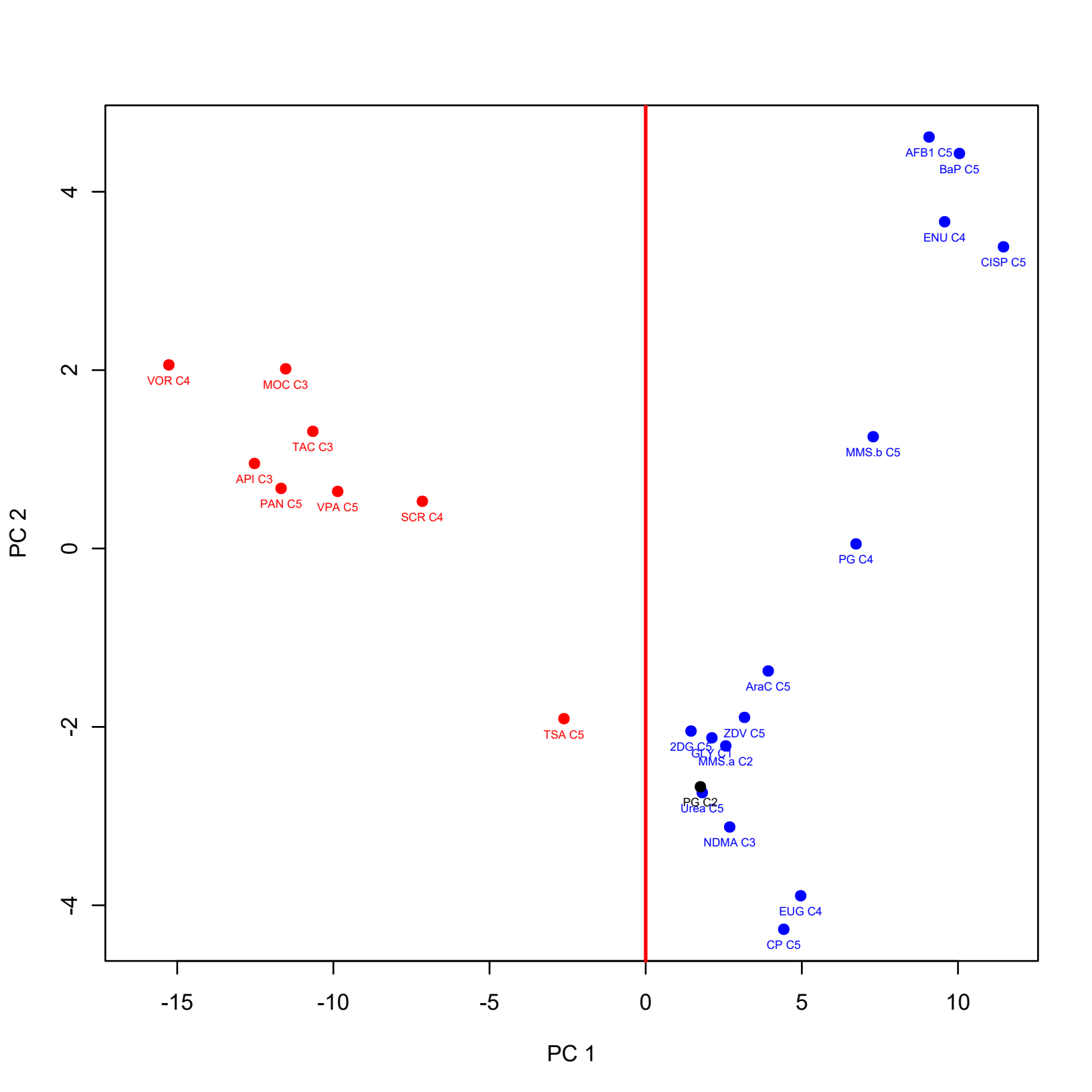
Supplementary Figure 2U: Propyl Gallate (PG) Concentrations 1-5 (C1-C5)

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PG C4
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TSA C5
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GLY C1
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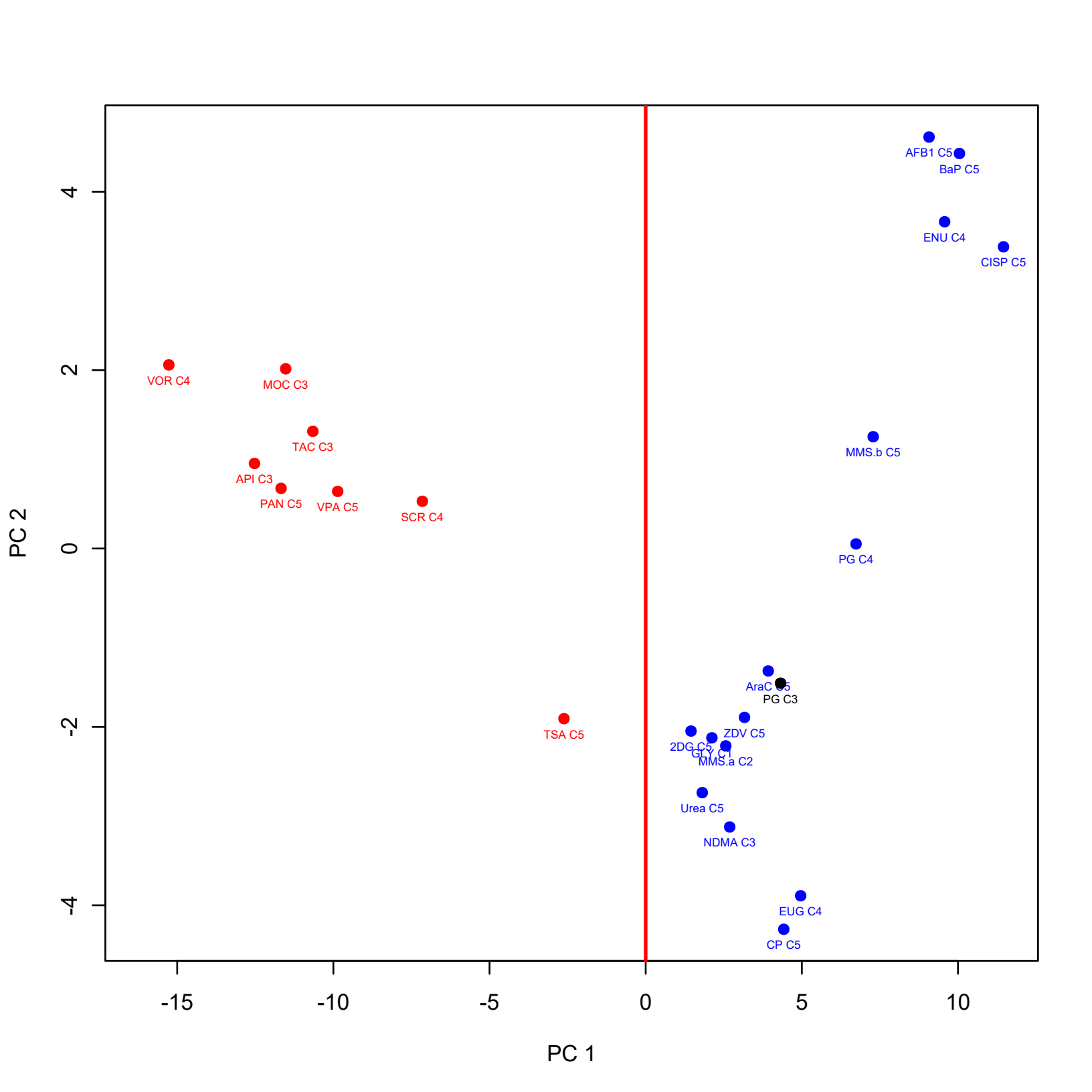
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ZDV C5
2DG C5
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Urea C5
NDMA C3
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CP C5
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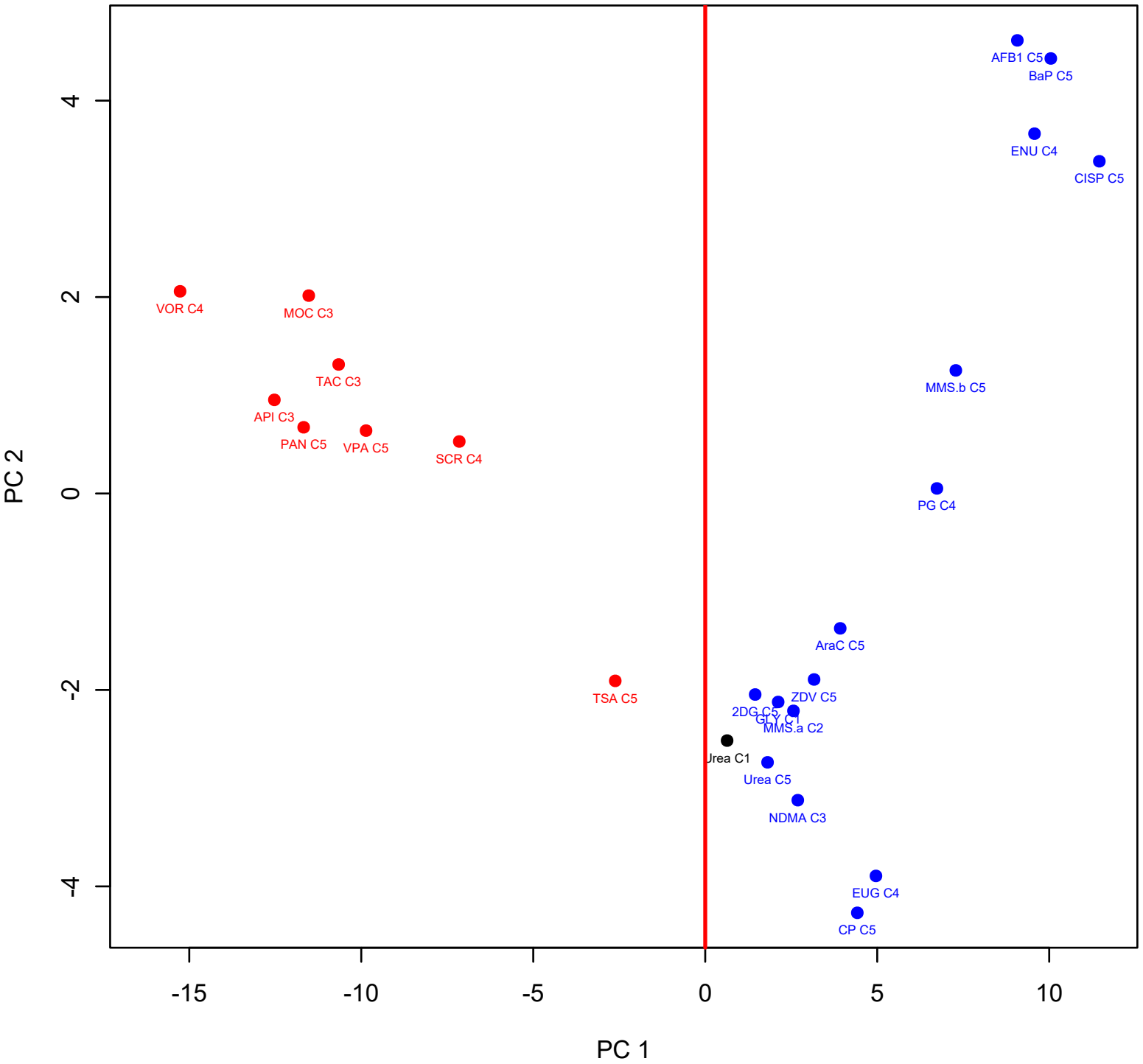
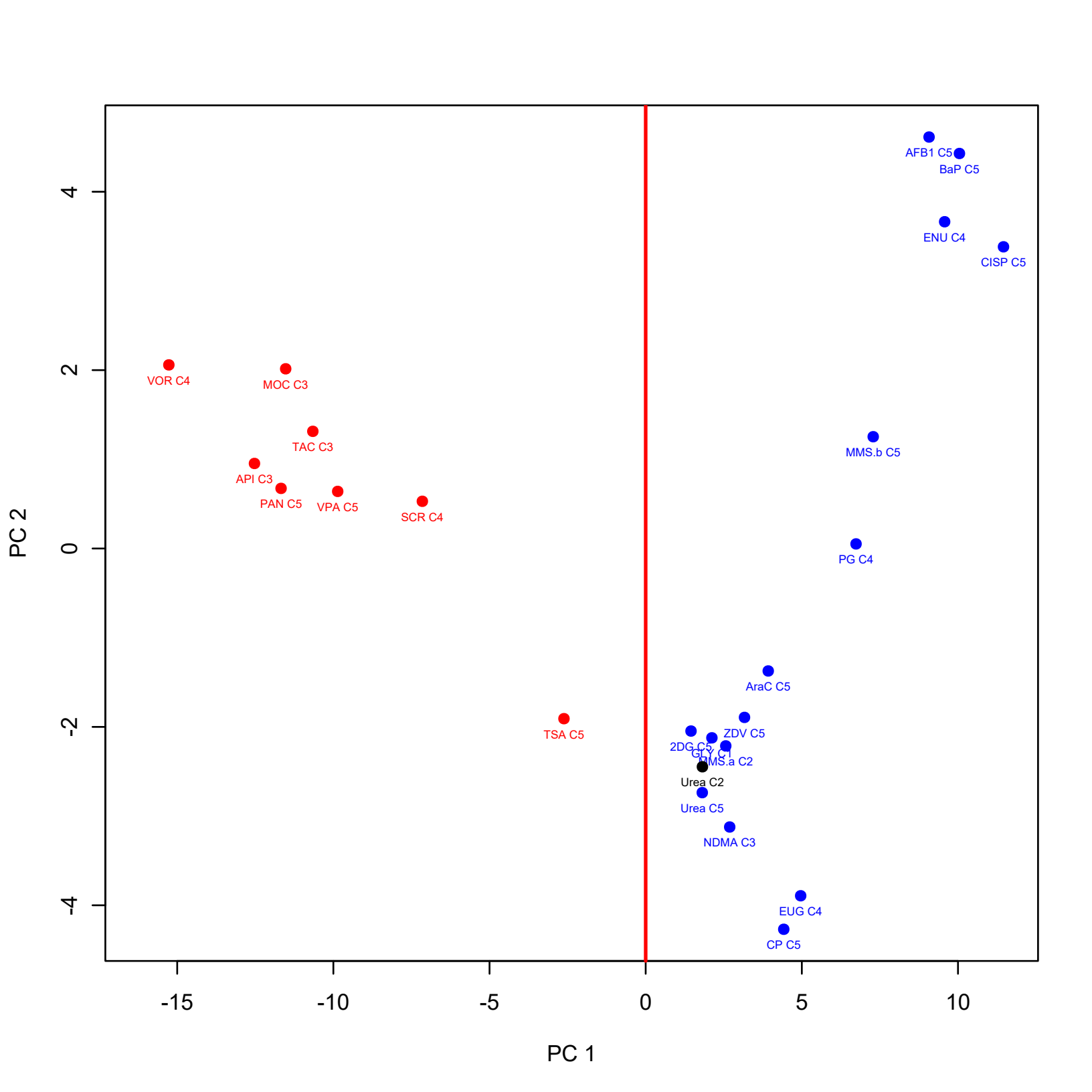
Supplementary Figure 2V: Urea Concentrations 1-5 (C1-C5)

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ENU C4
CISP C5
VOR C4
MOC C3
TAC C3
API C3
PAN C5
VPA C5
SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C2
Urea C5
NDMA C3
EUG C4
CP C5
PC 1
PC 2
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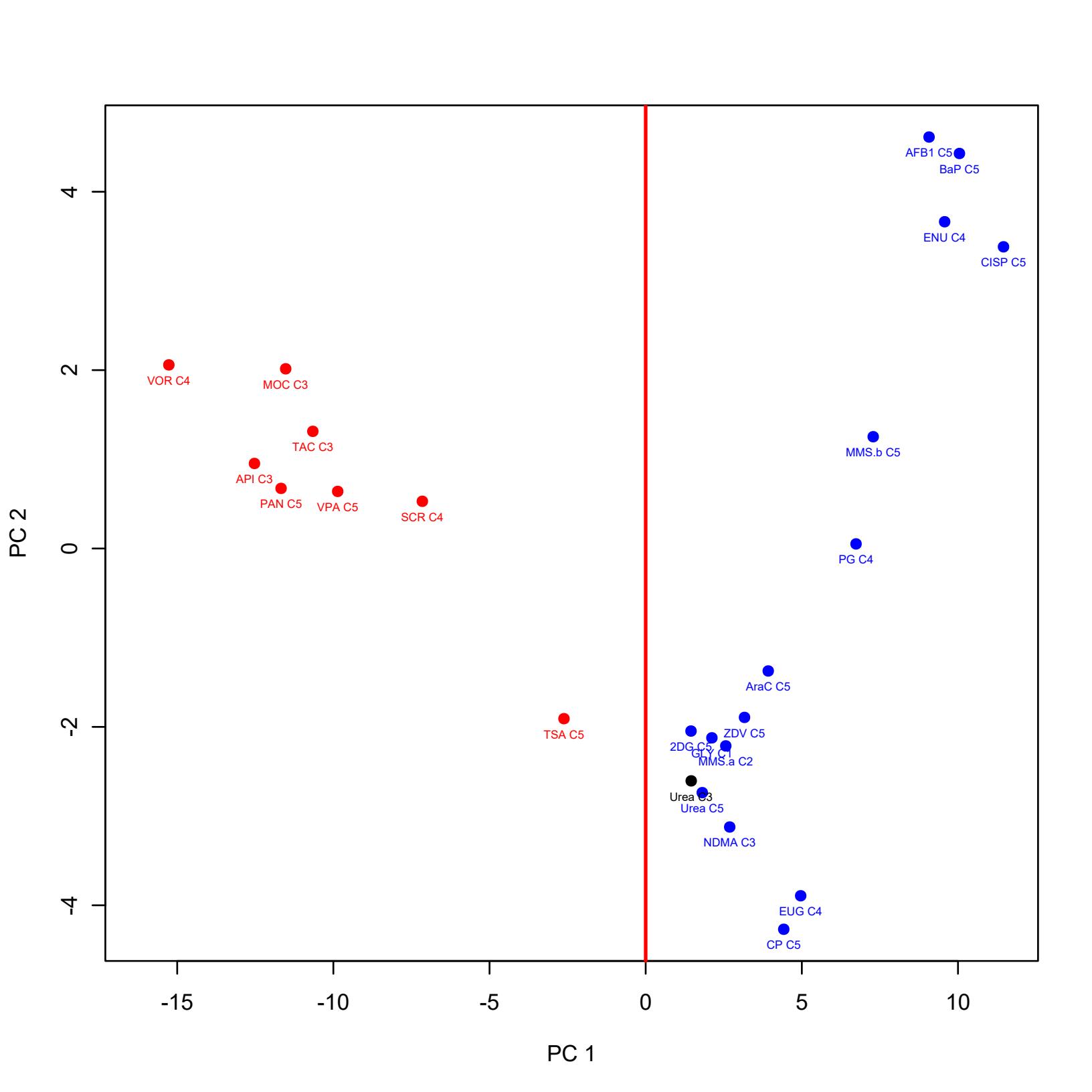
-10
-5
0
5
10
4
2
0
-2
-4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BaP C5
ENU C4
CISP C5
VOR C4
MOC C3
TAC C3
API C3
PAN C5
VPA C5
SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C3
Urea C5
NDMA C3
EUG C4
CP C5
PC 2
PC 1
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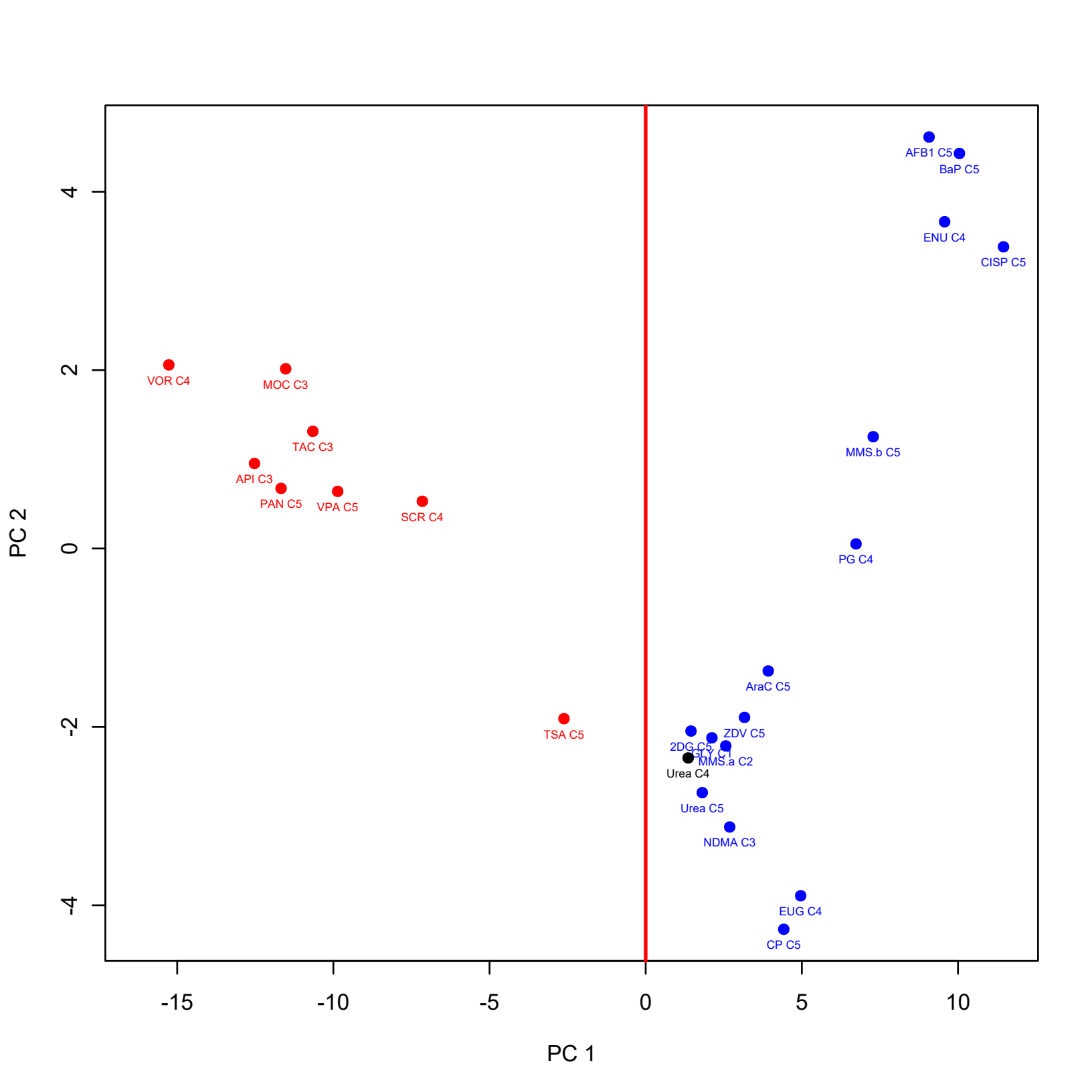
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BaP C5
ENU C4
CISP C5
VOR C4
MOC C3
TAC C3
API C3
PAN C5
VPA C5
SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
GCV C1
MMS.a C2
Urea C4
Urea C5
NDMA C3
EUG C4
CP C5
PC 1
PC 2
-15
-10
-5
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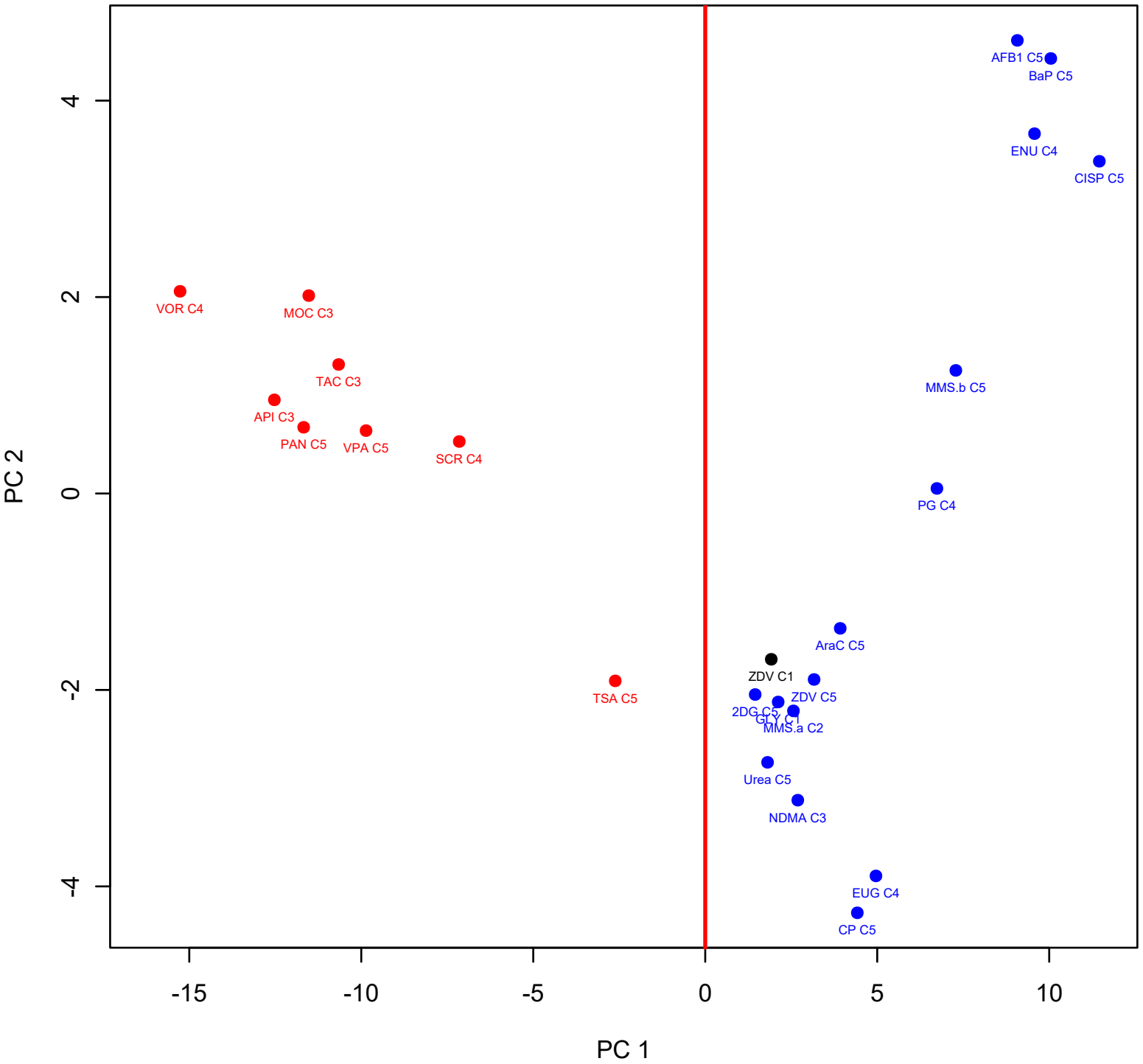
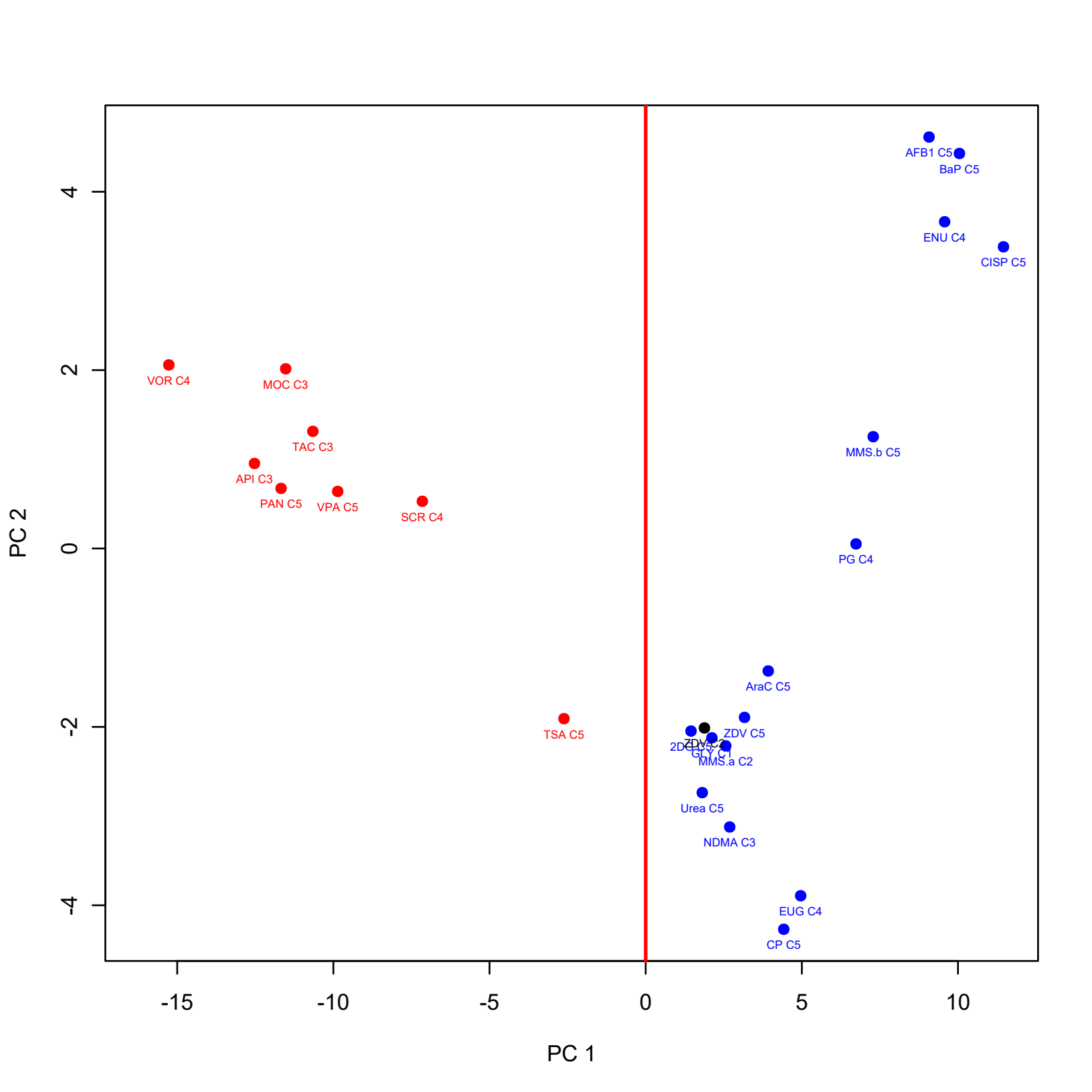
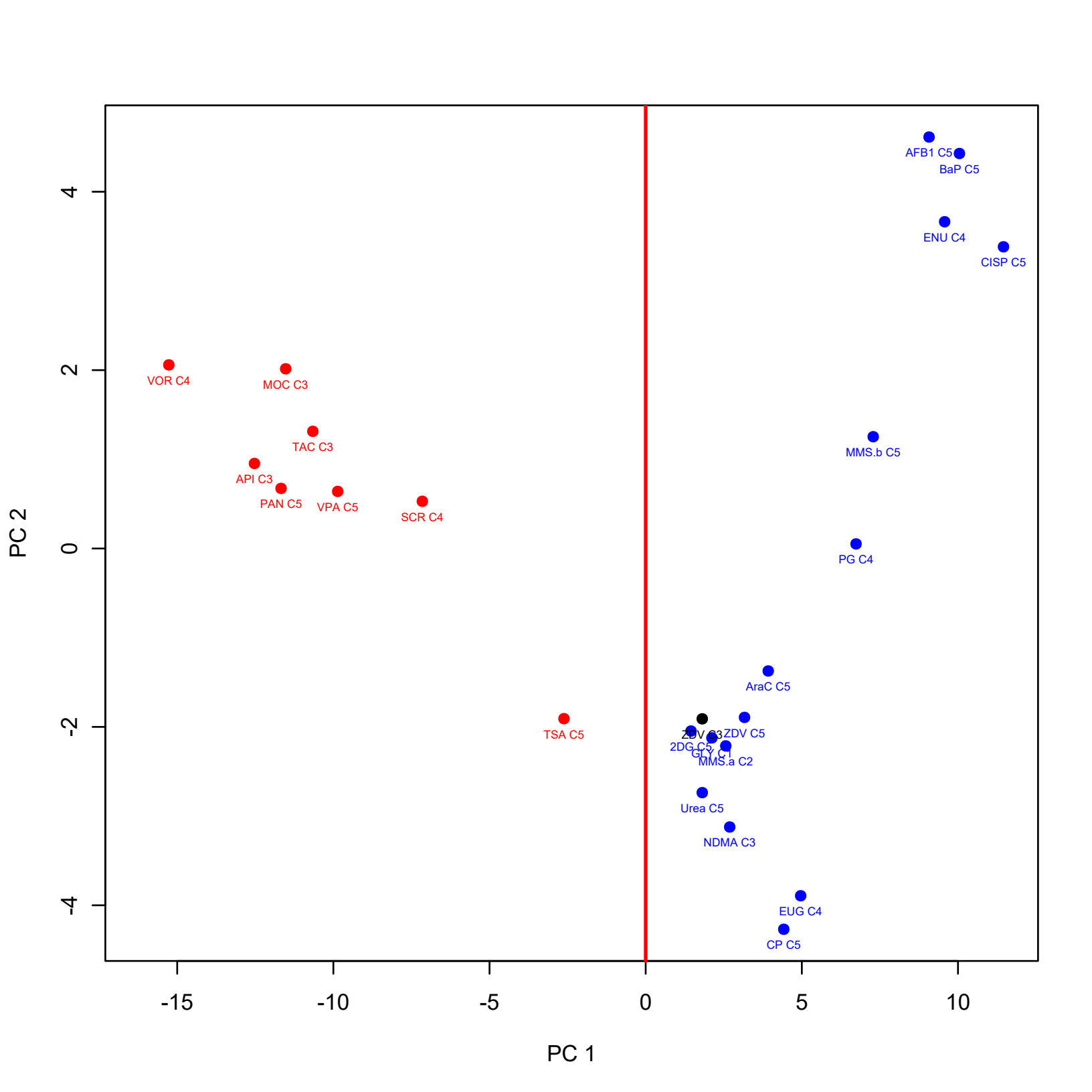
5
10
4
2
0
-2
-4

Supplementary Figure 2W: Zidovudine (ZDV) Concentrations 1-5 (C1-C5)




AFB1 C5
BaP C5
ENU C4
CISP C5
VOR C4
MOC C3
TAC C3
API C3
PAN C5
VPA C5
SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C5
2DG C5
ZDV C2
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
PC 2
PC 1
4
2
0
-2
-4
-15
-10
-5
0
5
10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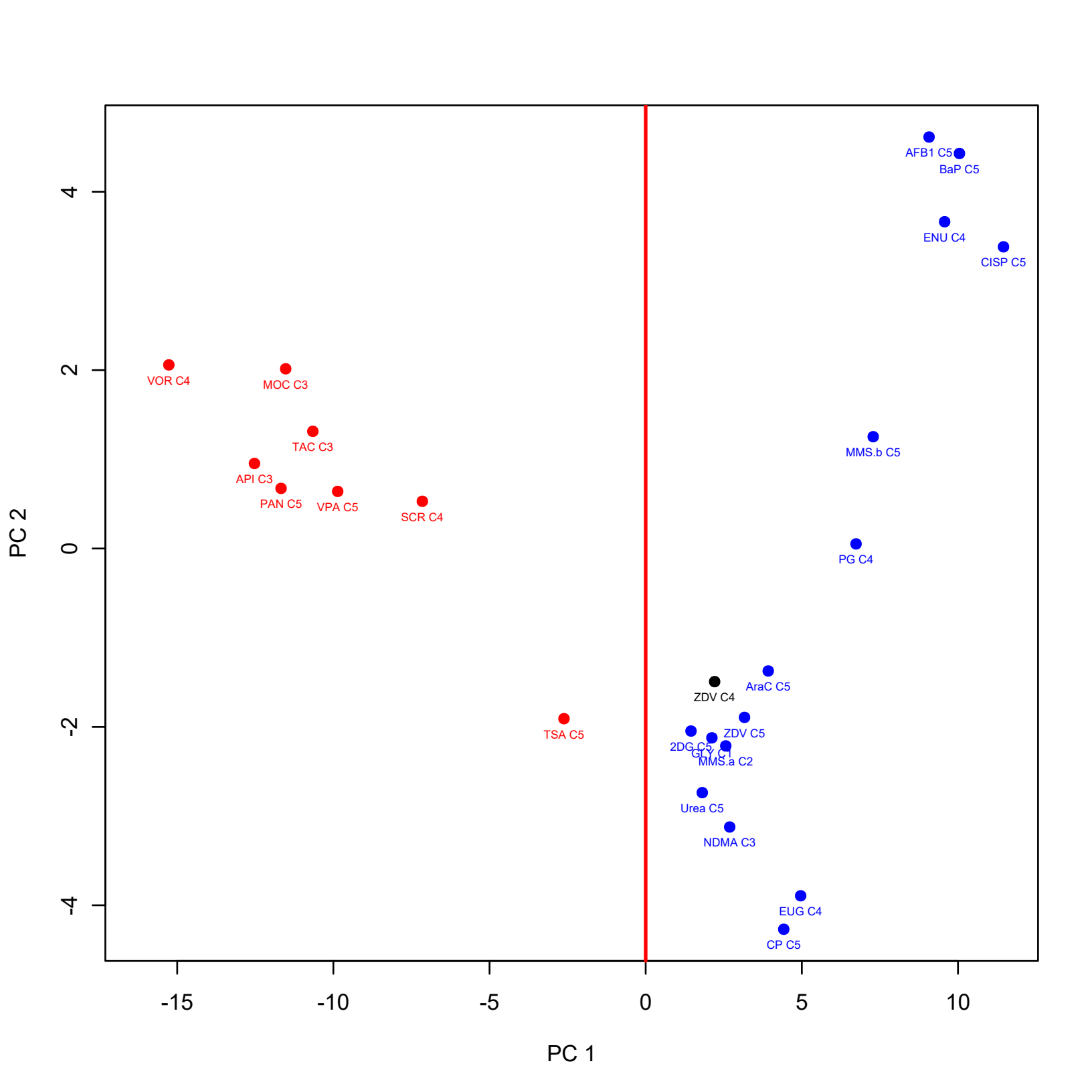
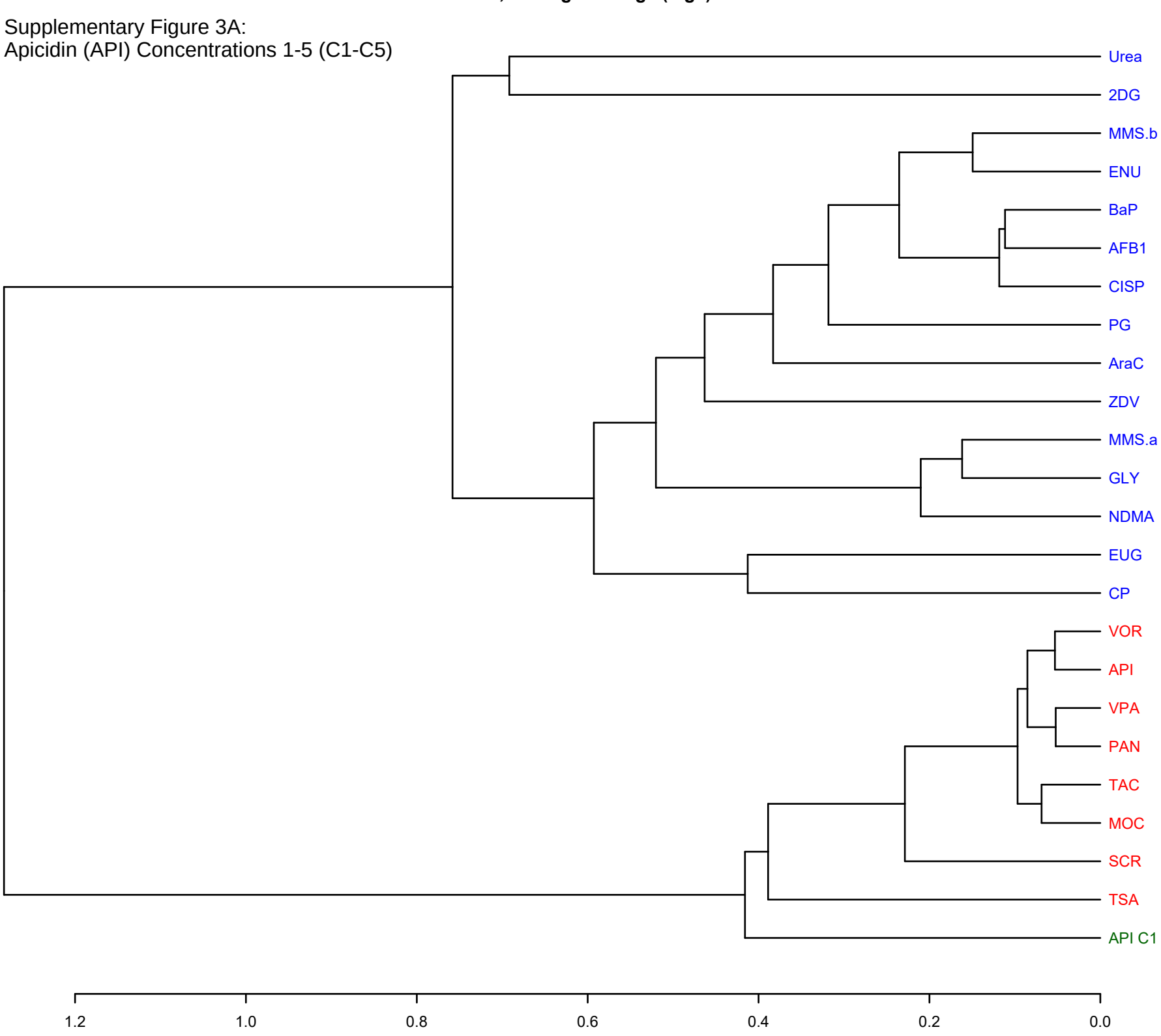
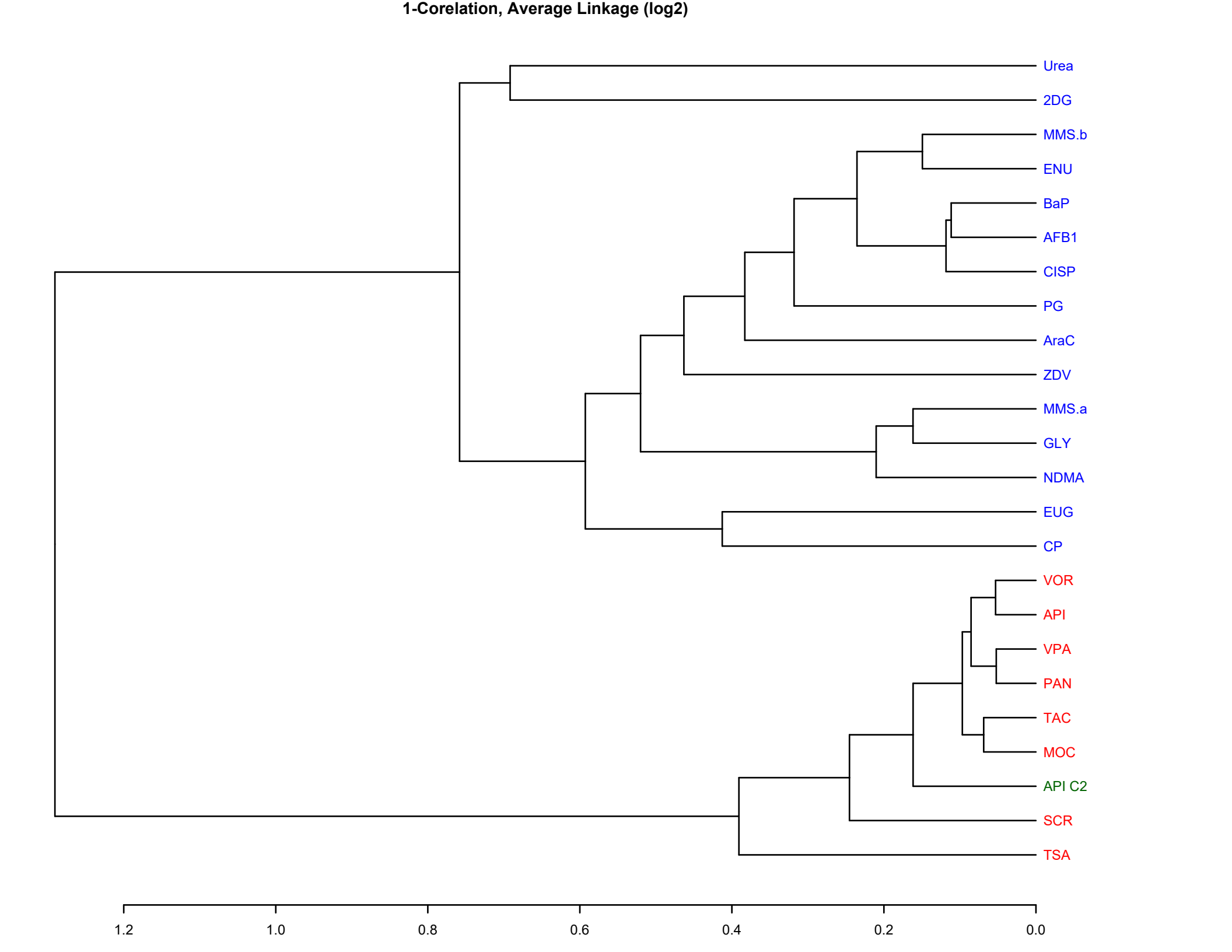
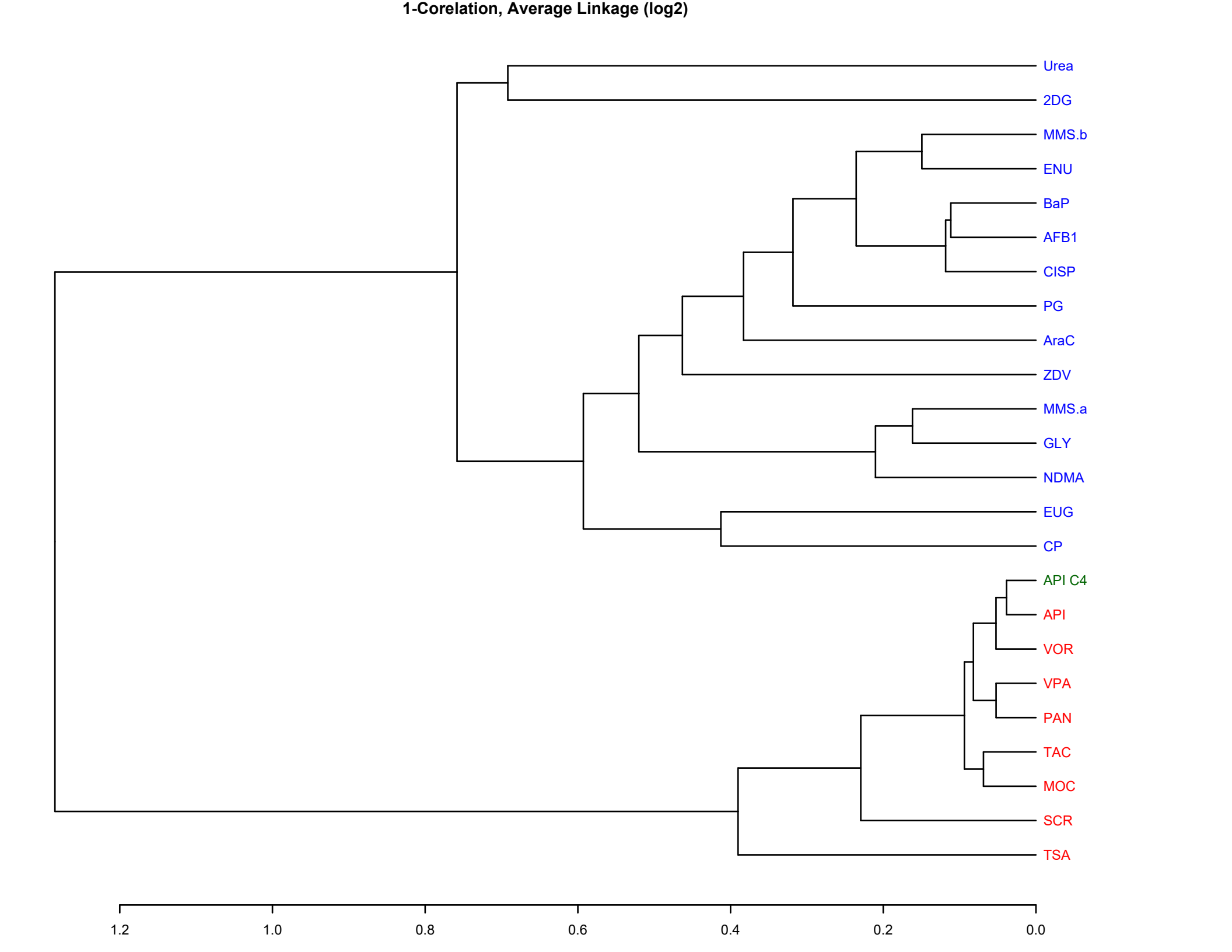
BaP C5
ENU C4
CISP C5
VOR C4
MOC C3
TAC C3
API C3
PAN C5
VPA C5
SCR C4
MMS.b C5
PG C4
AraC C5
TSA C5
ZDV C3
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
PC 1
PC 2
-15
-10
-5
0
5
10
4
2
0
-2
-4

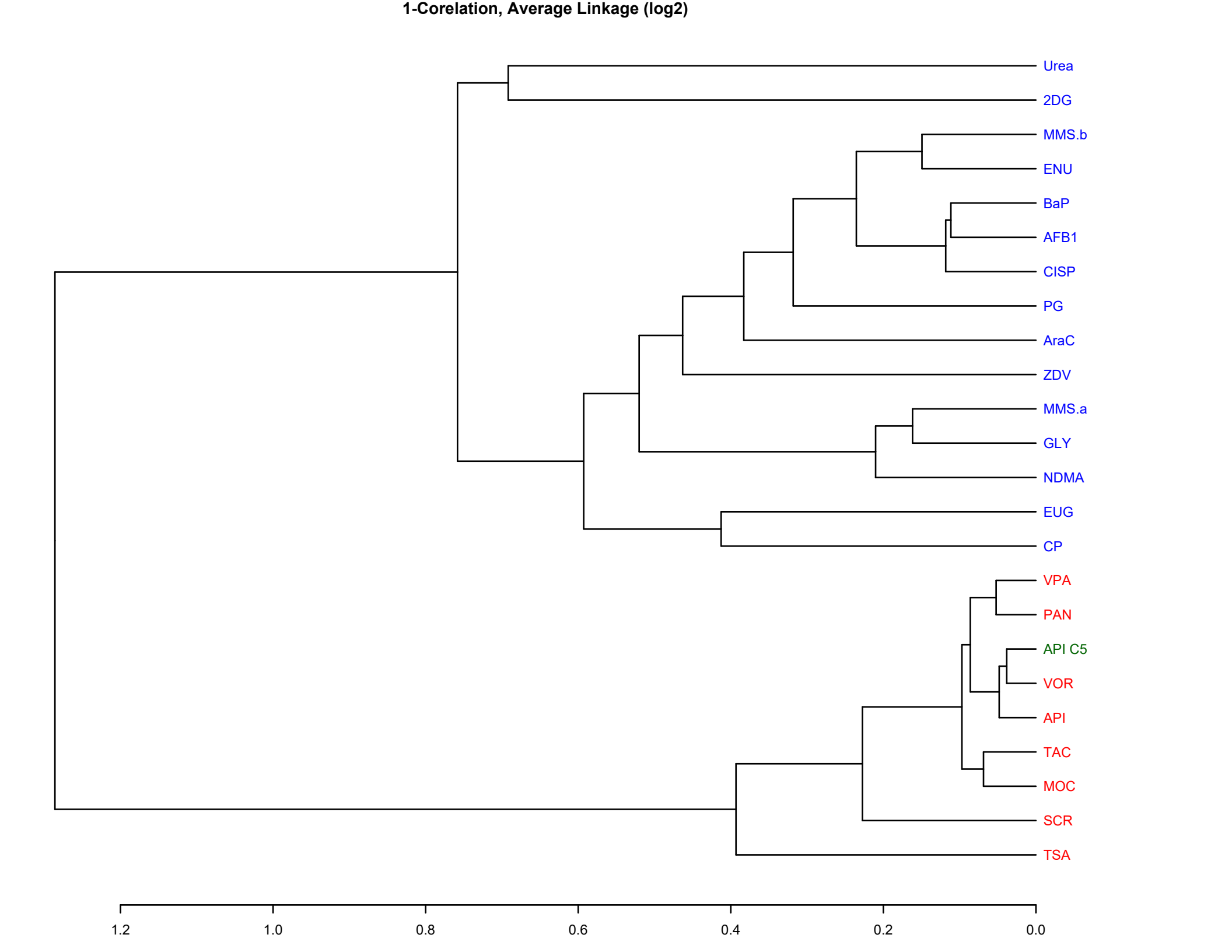

AFB1 C5
BaP C5
ENU C4
CISP C5
MMS.b C5
PG C4
AraC C5
ZDV C4
ZDV C5
2DG C5
GLY C1
MMS.a C2
Urea C5
NDMA C3
EUG C4
CP C5
TSA C5
VOR C4
MOC C3
TAC C3
API C3
PAN C5
VPA C5
SCR C4
PC 1
PC 2
-15
-10
-5
0
5
10
4
2
0
-2
-4

Supplementary Figure 3A:
Apicidin (API) Concentrations 1-5 (C1-C5)

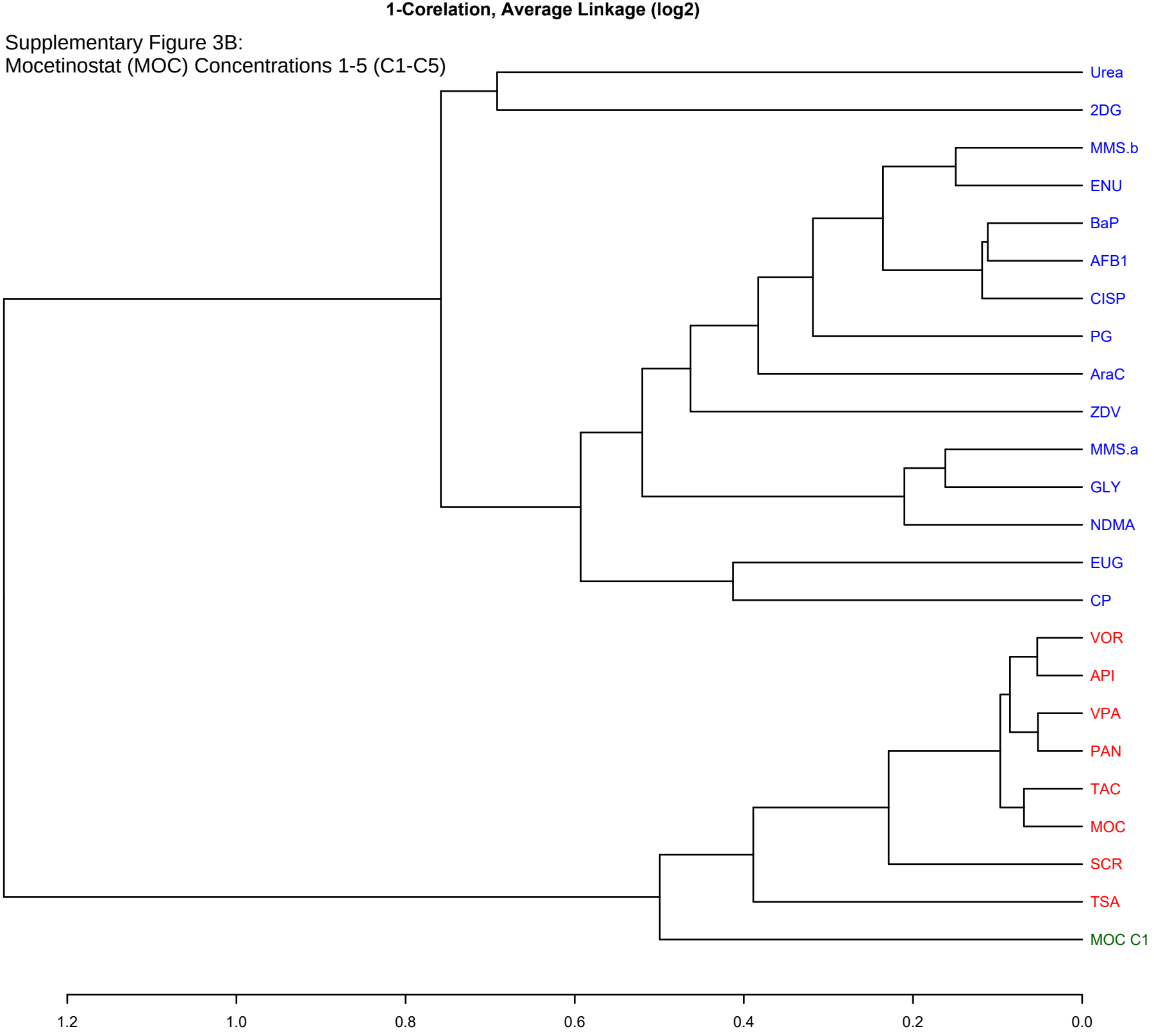


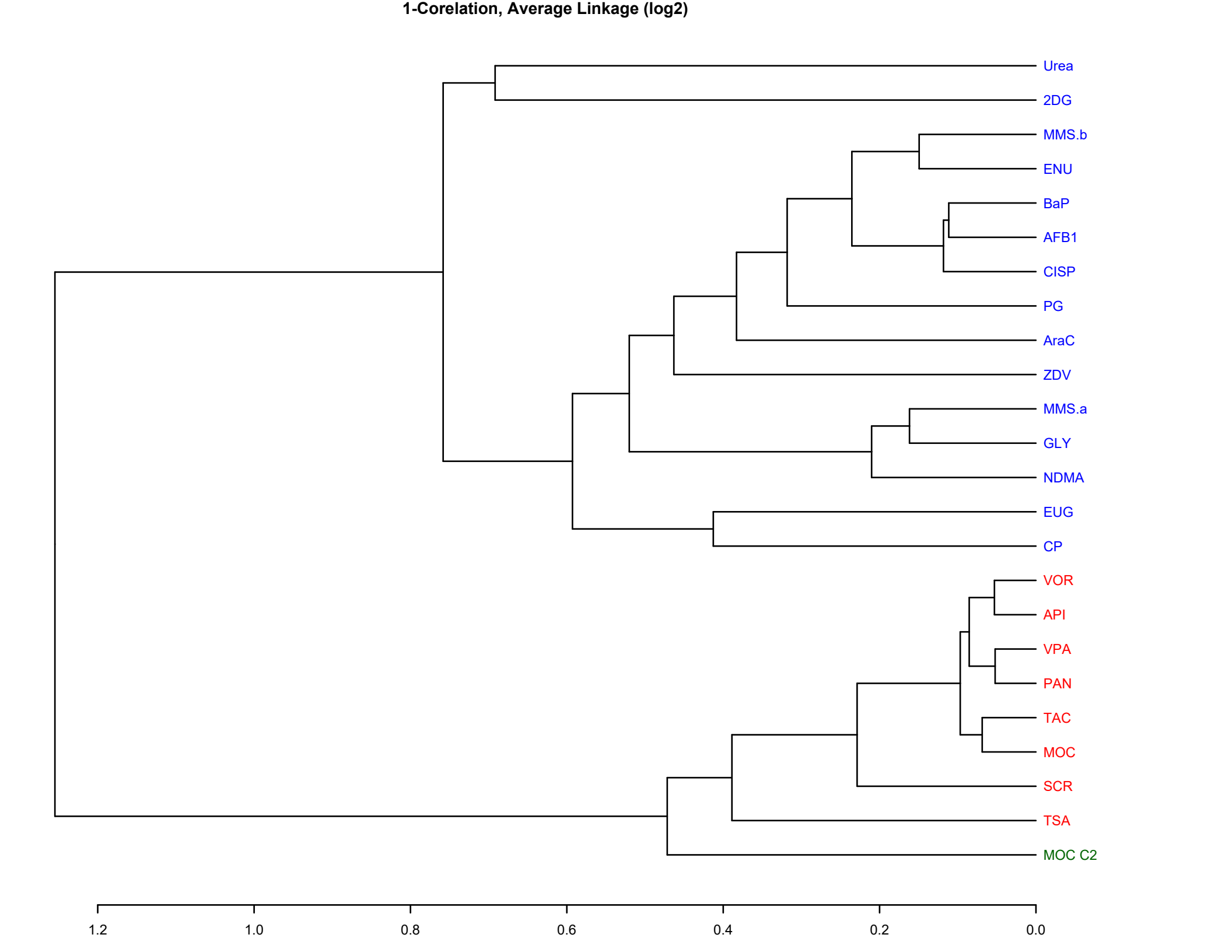

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
API C2
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

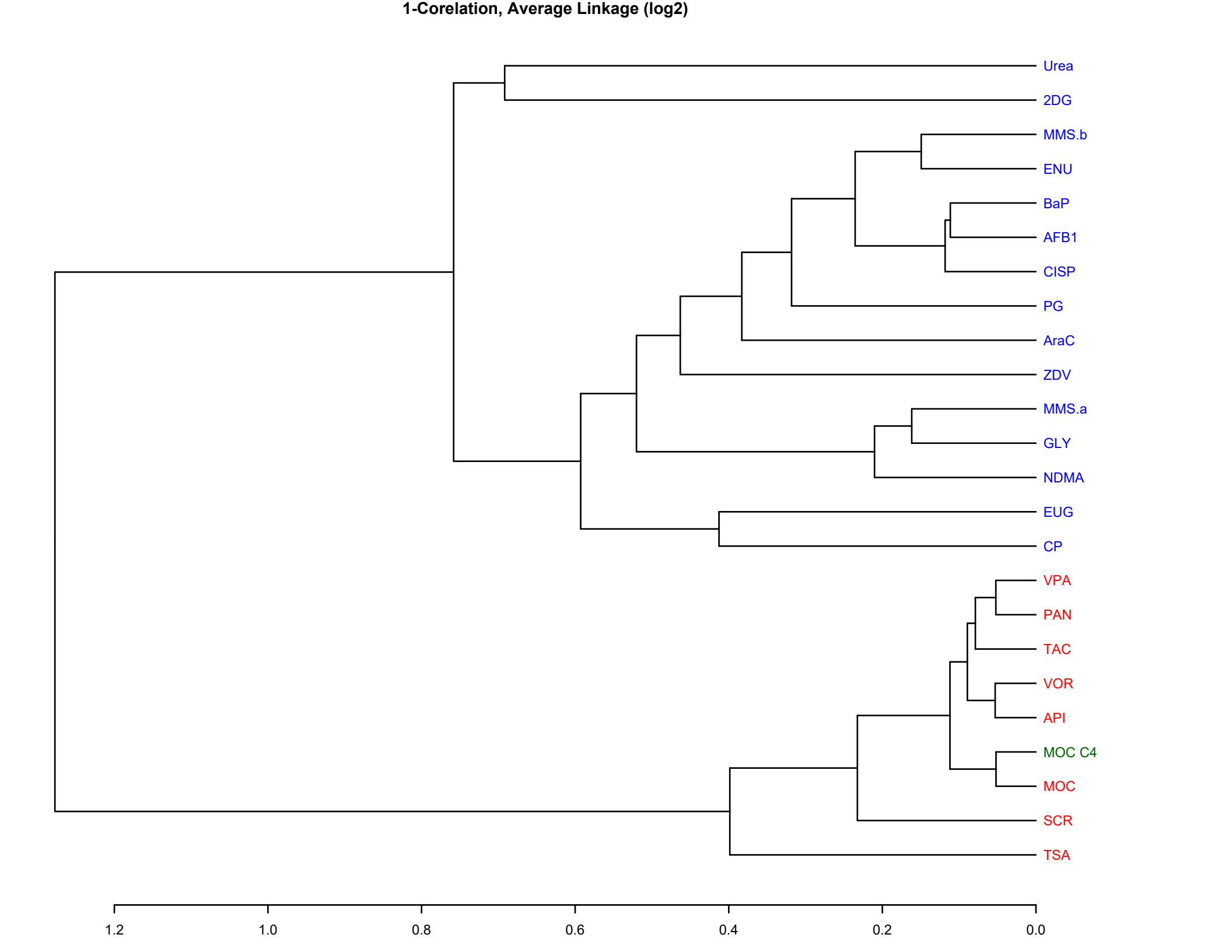

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
API C4
API
VOR
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

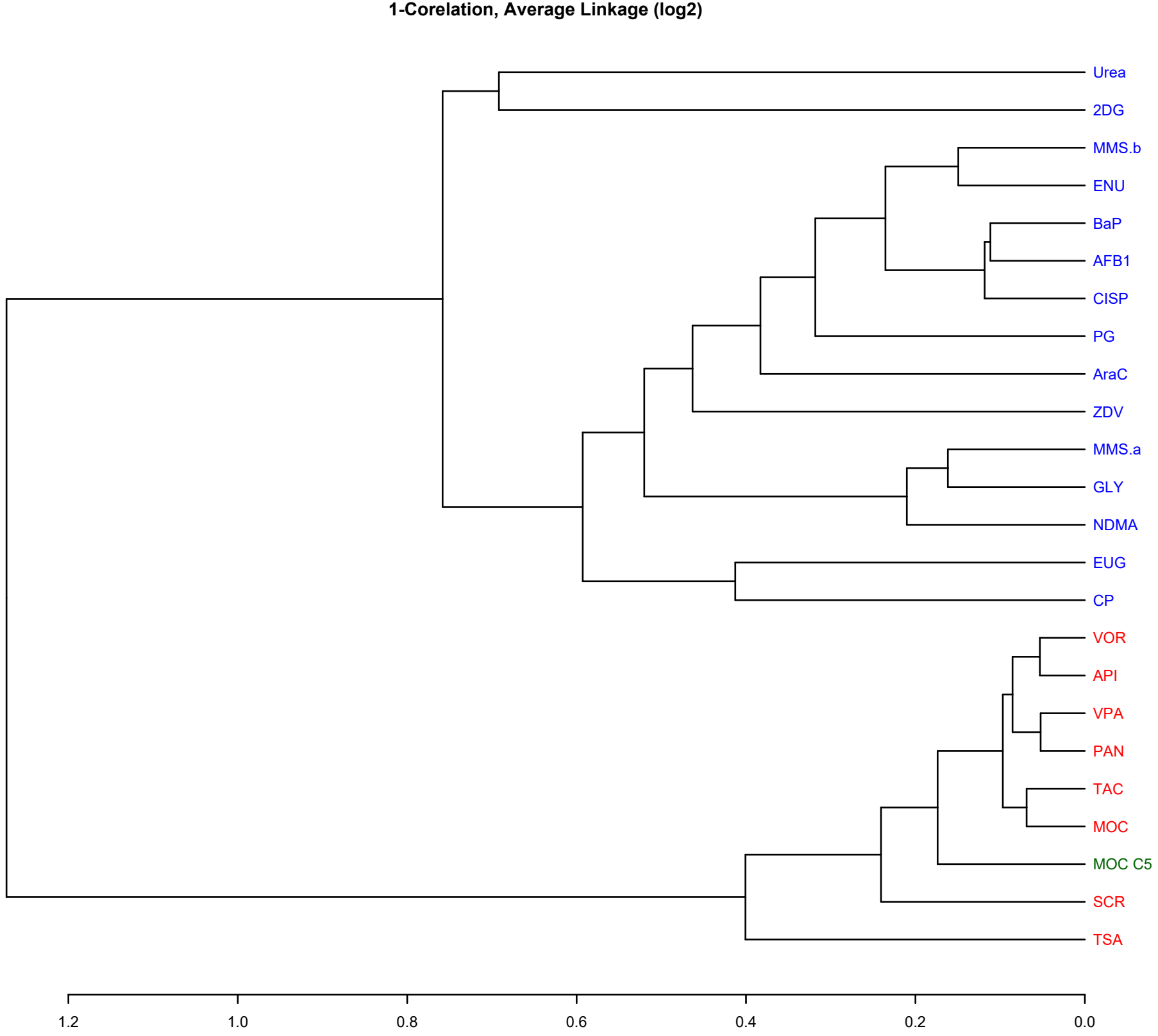

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VPA
PAN
API C5
VOR
API
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3B:
Mocetinostat (MOC) Concentrations 1-5 (C1-C5)

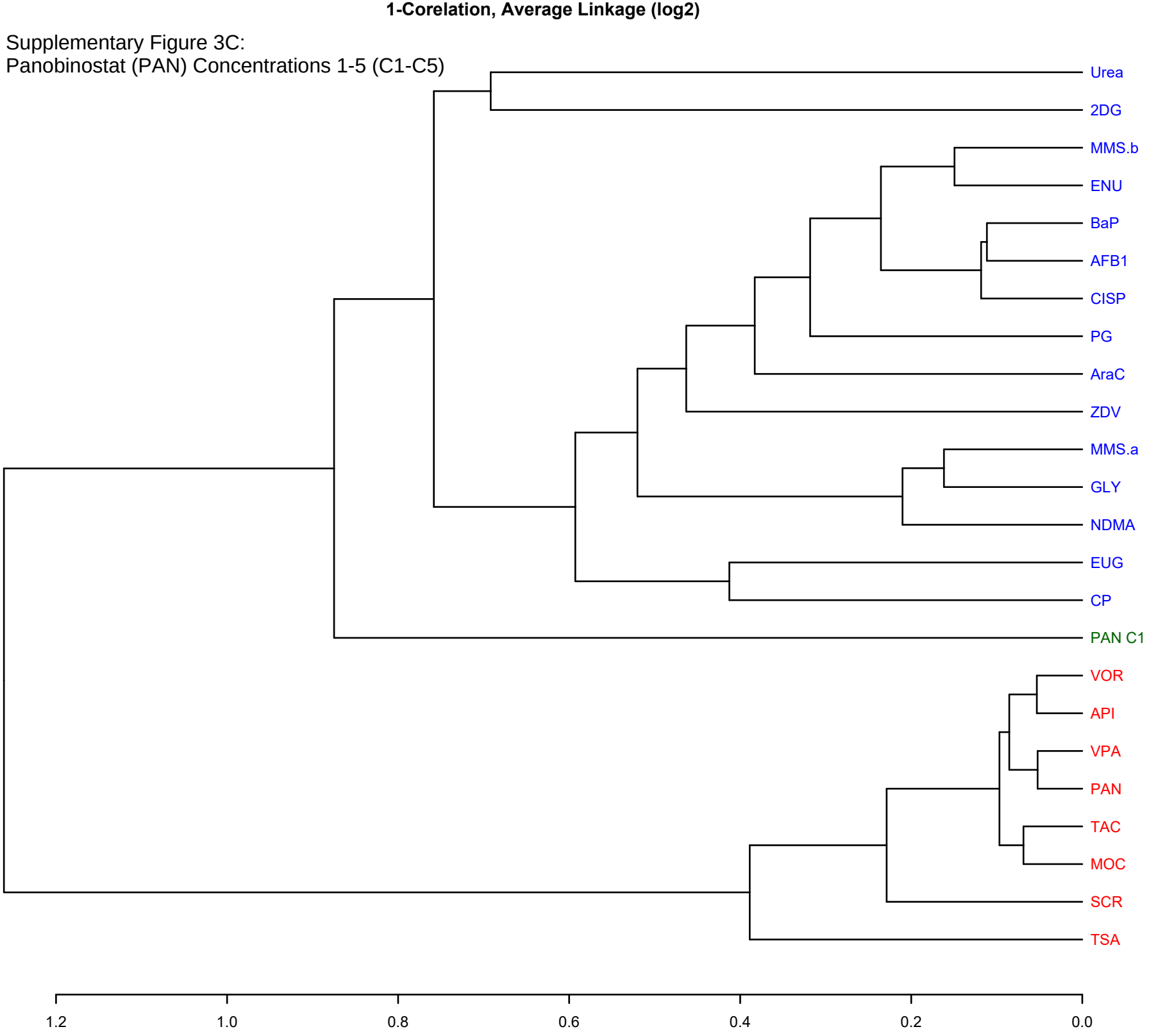


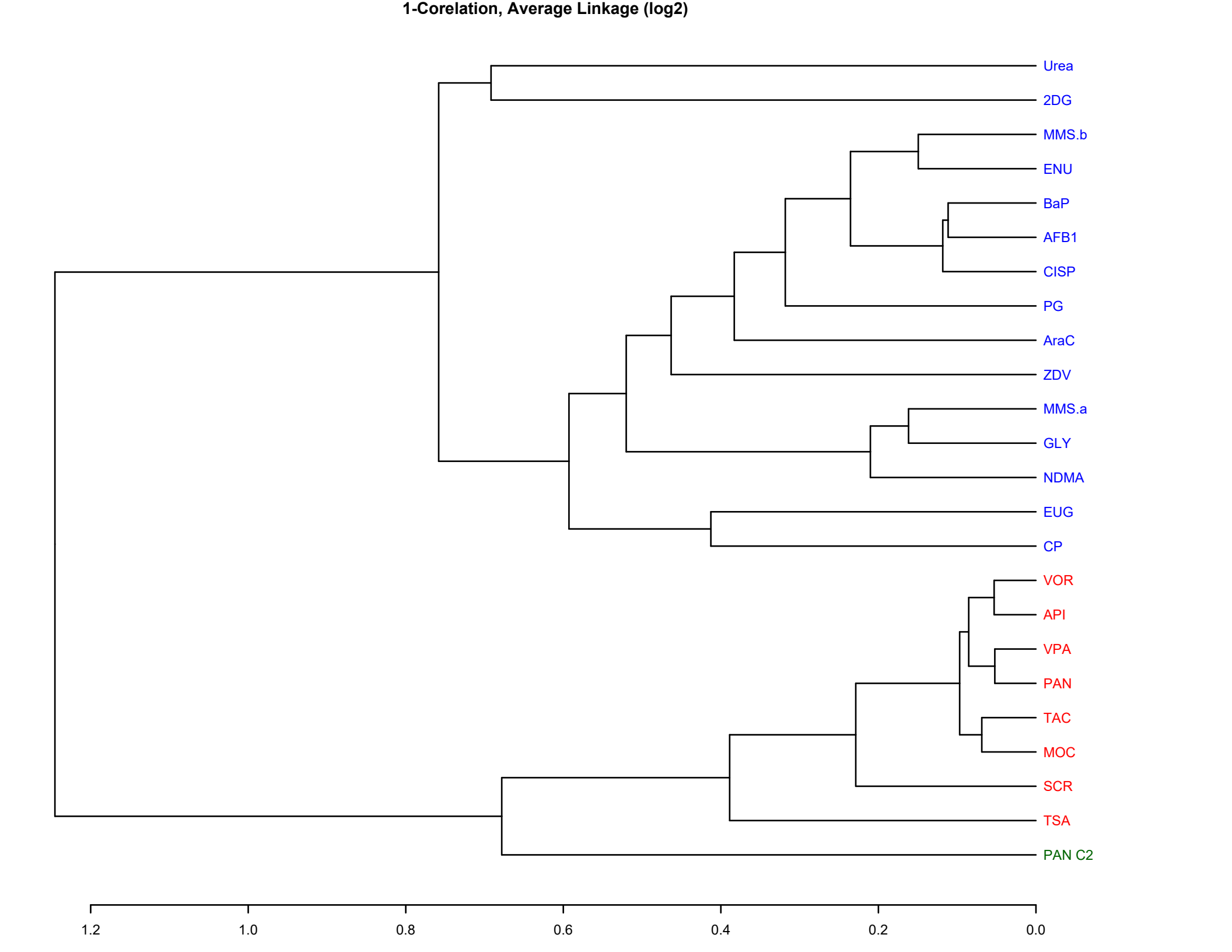

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
MOC C2
1.2
1.0
0.8
0.6
0.4
0.2
0.0

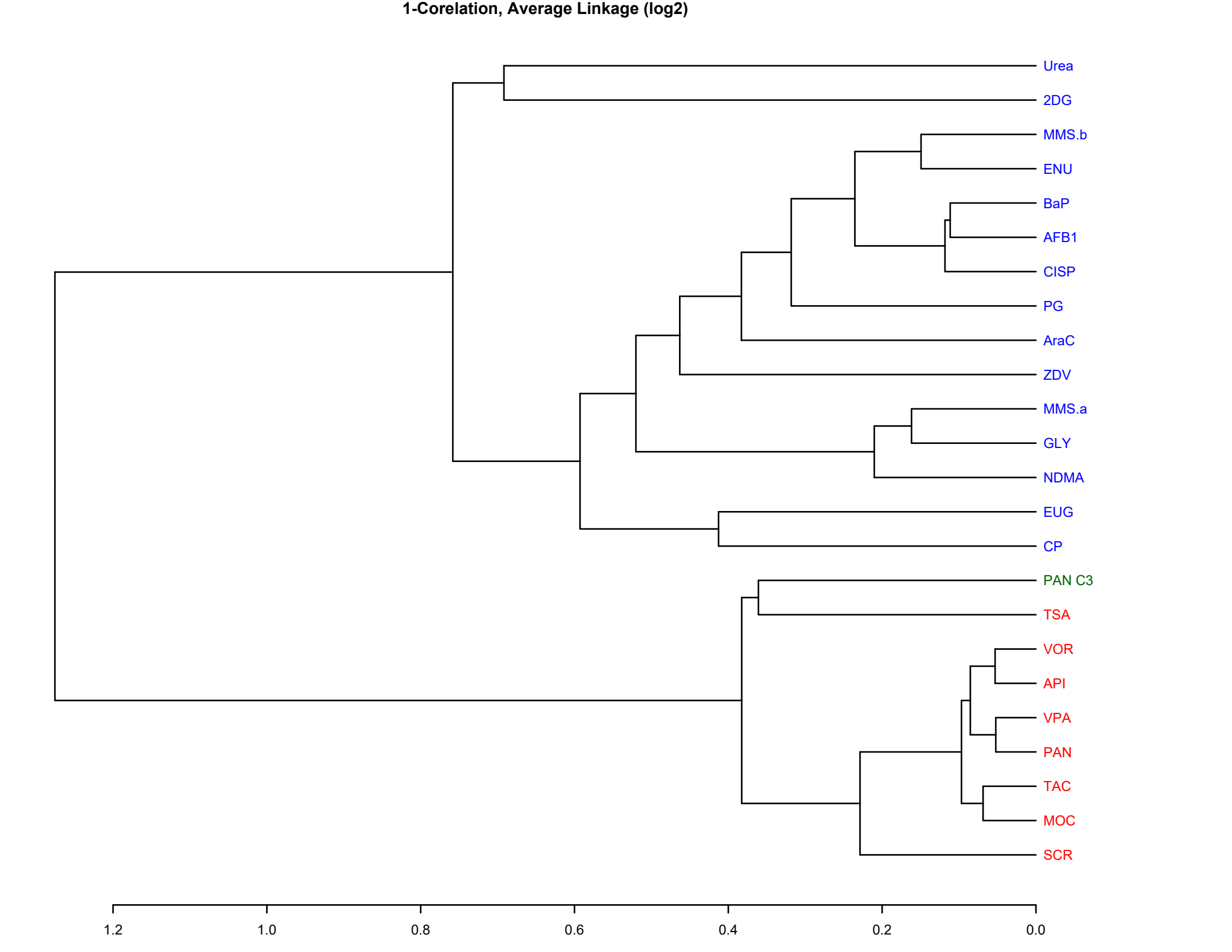

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VPA
PAN
TAC
VOR
API
MOC C4
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

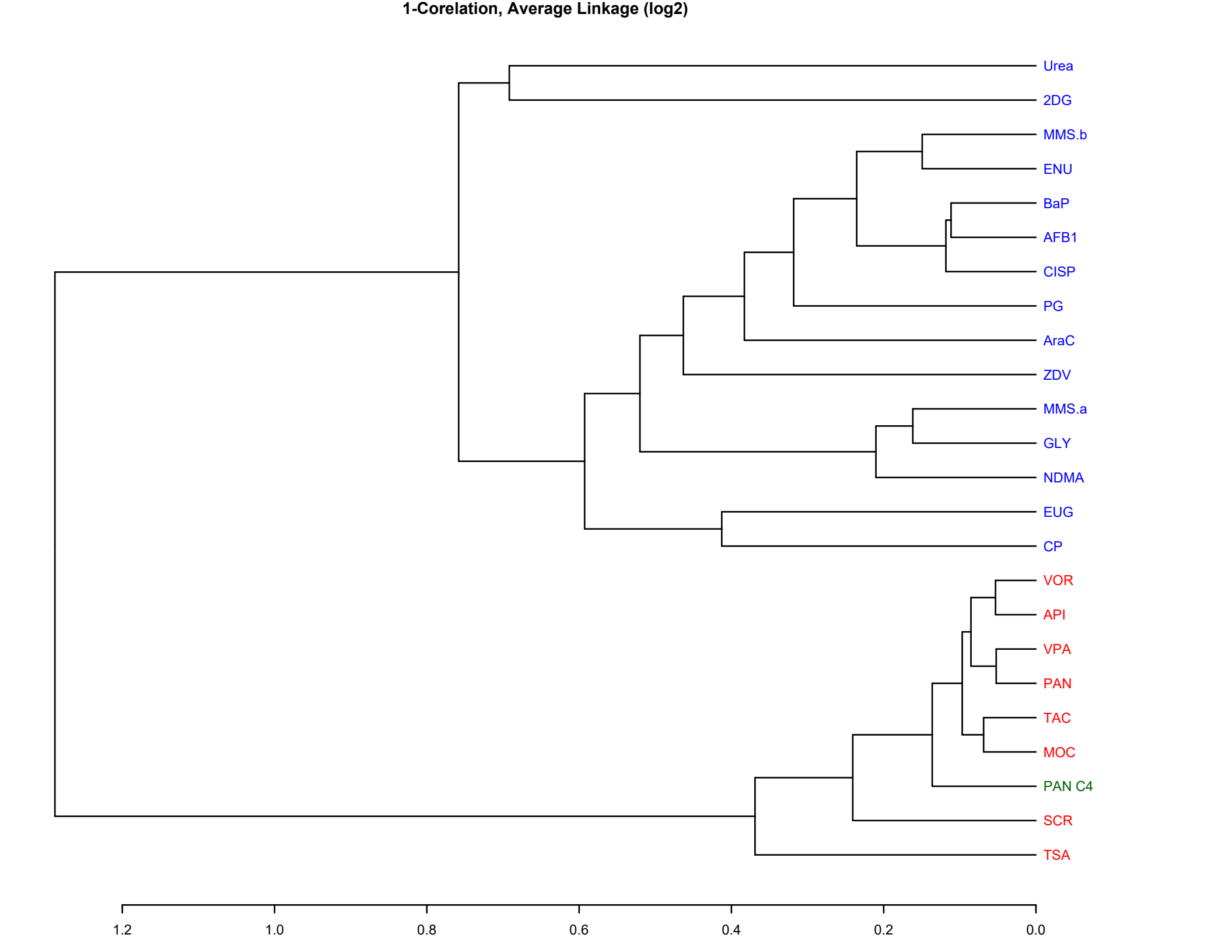

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
MOC C5
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3C:
Panobinostat (PAN) Concentrations 1-5 (C1-C5)

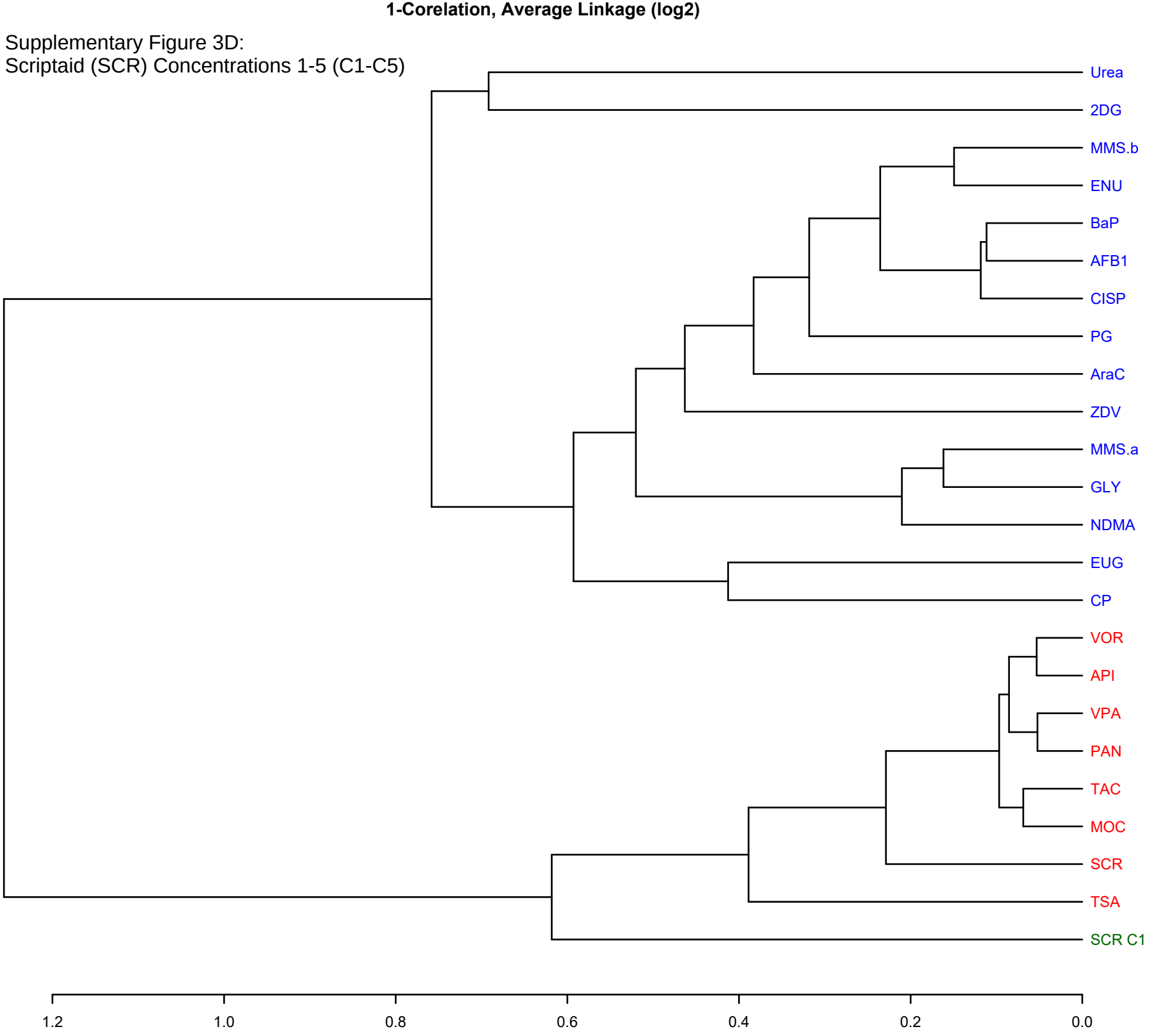


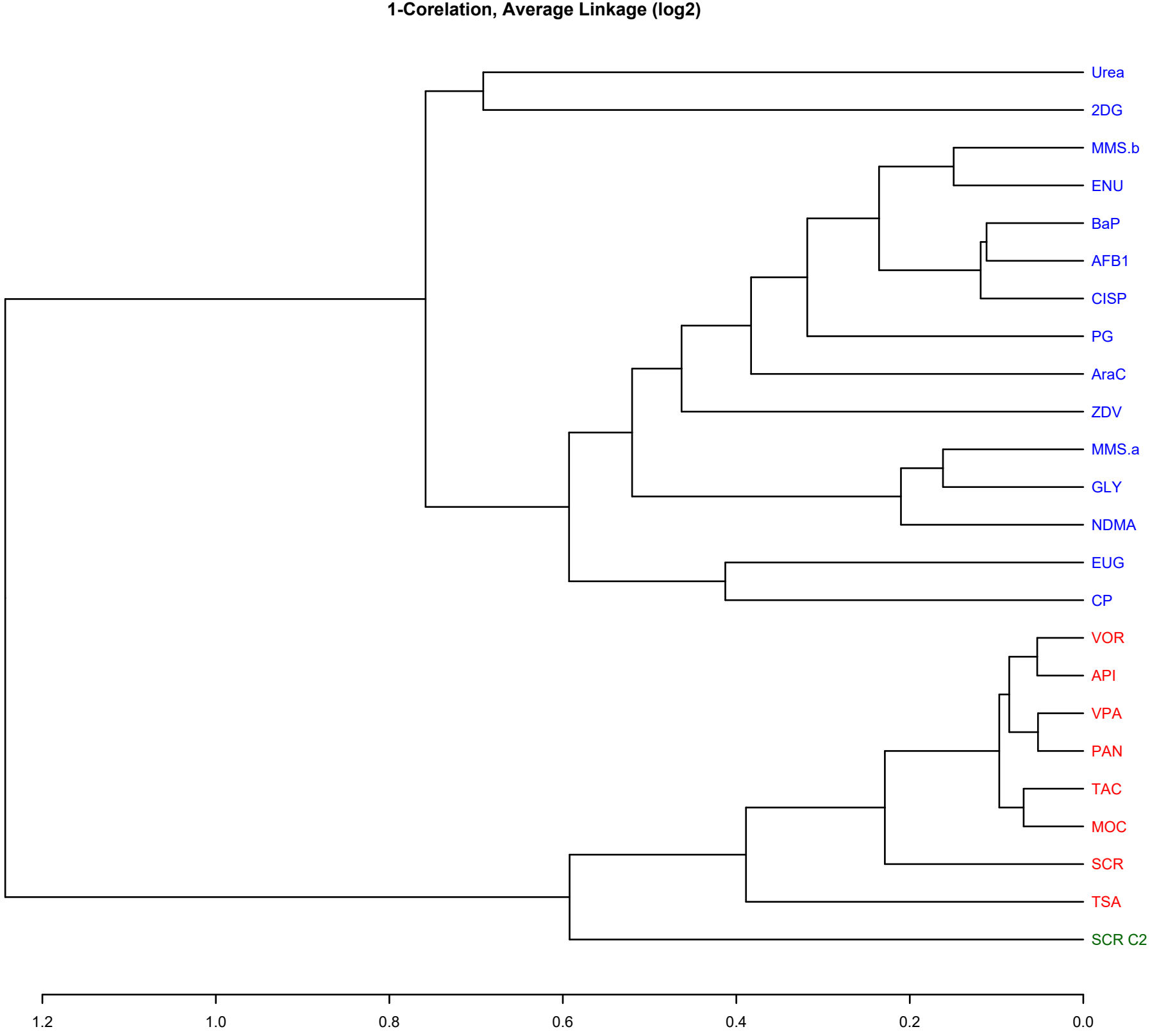

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
PAN C2
1.2
1.0
0.8
0.6
0.4
0.2
0.0

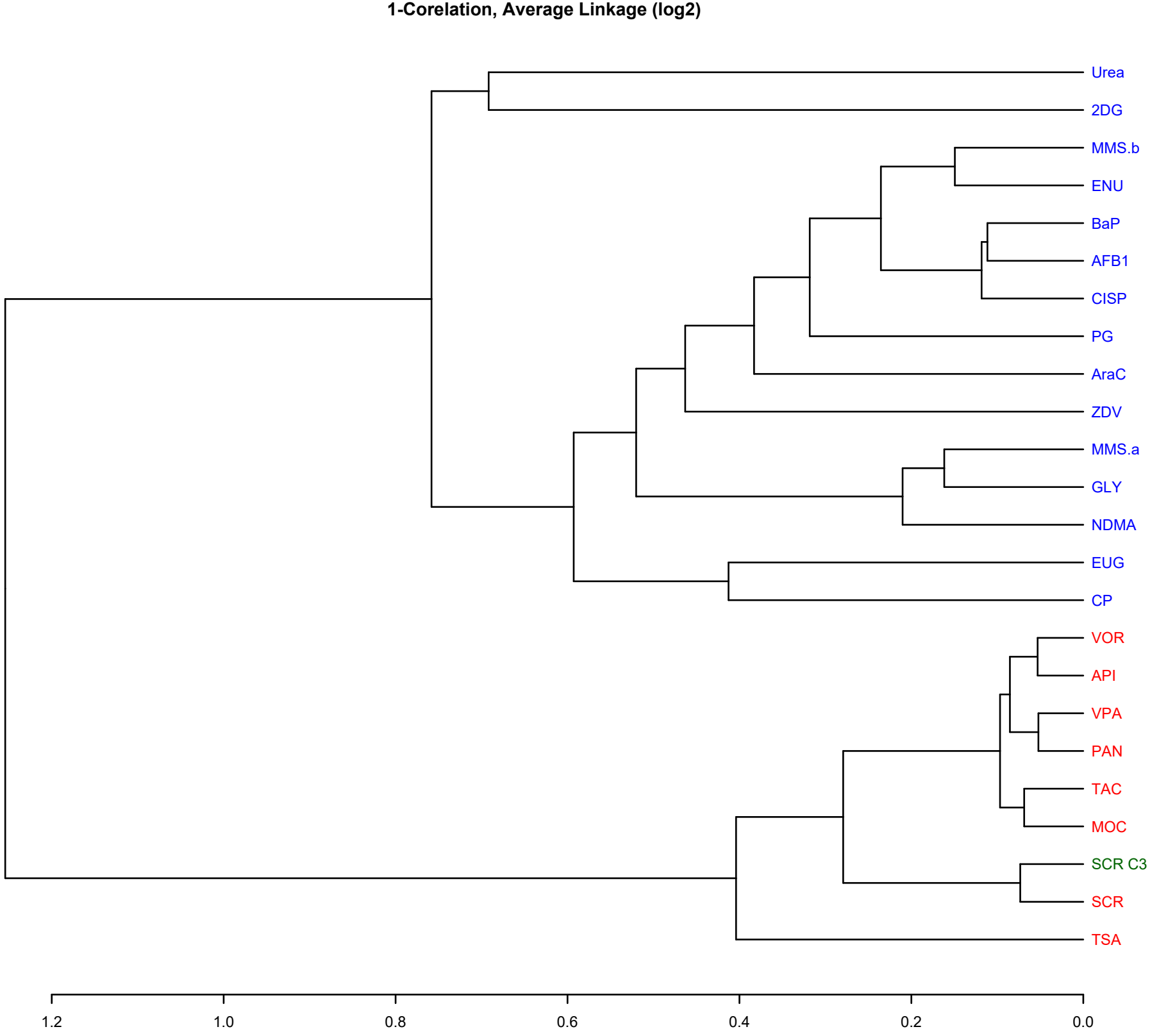

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
PAN C3
TSA
VOR
API
VPA
PAN
TAC
MOC
SCR
1.2
1.0
0.8
0.6
0.4
0.2
0.0

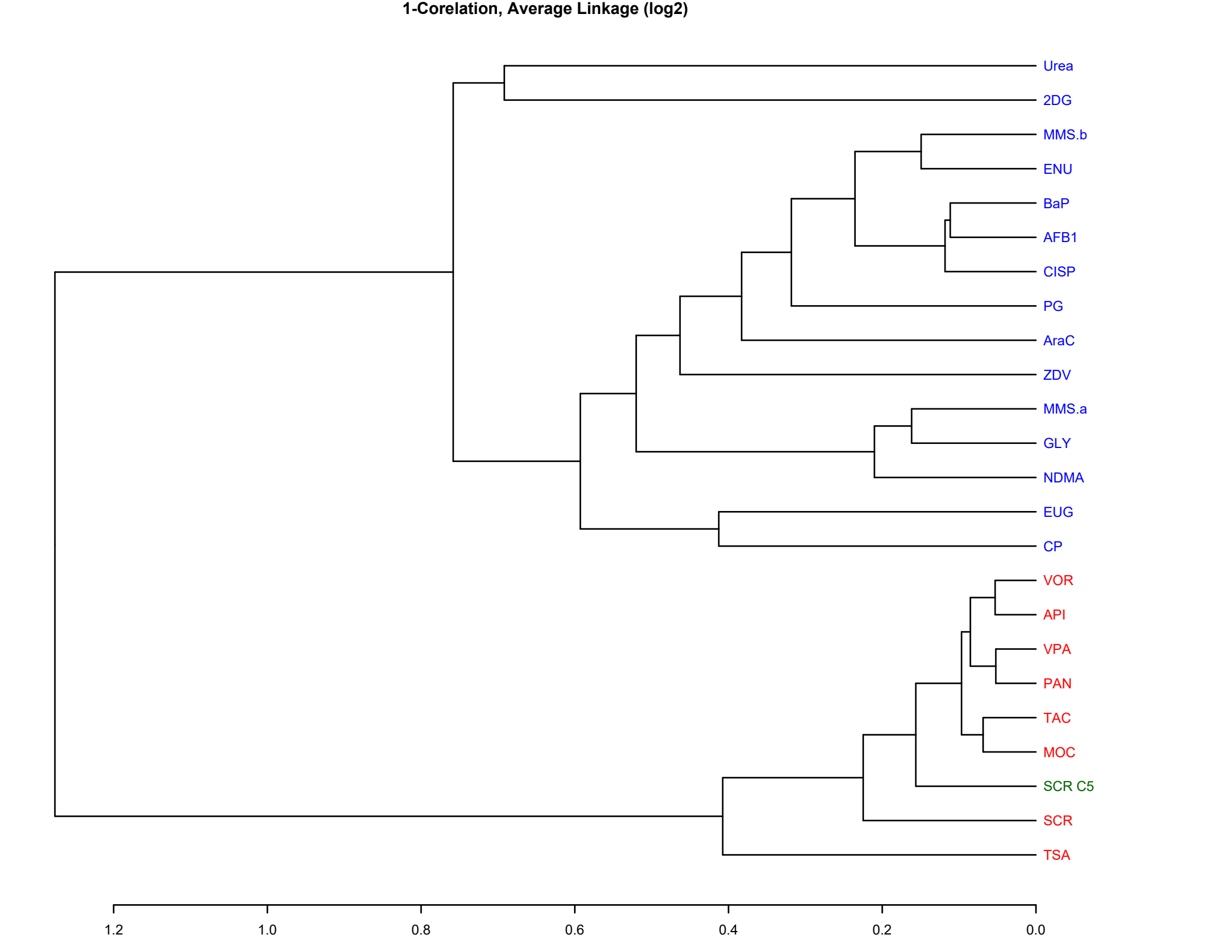

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
PAN C4
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3D:
Scriptaid (SCR) Concentrations 1-5 (C1-C5)

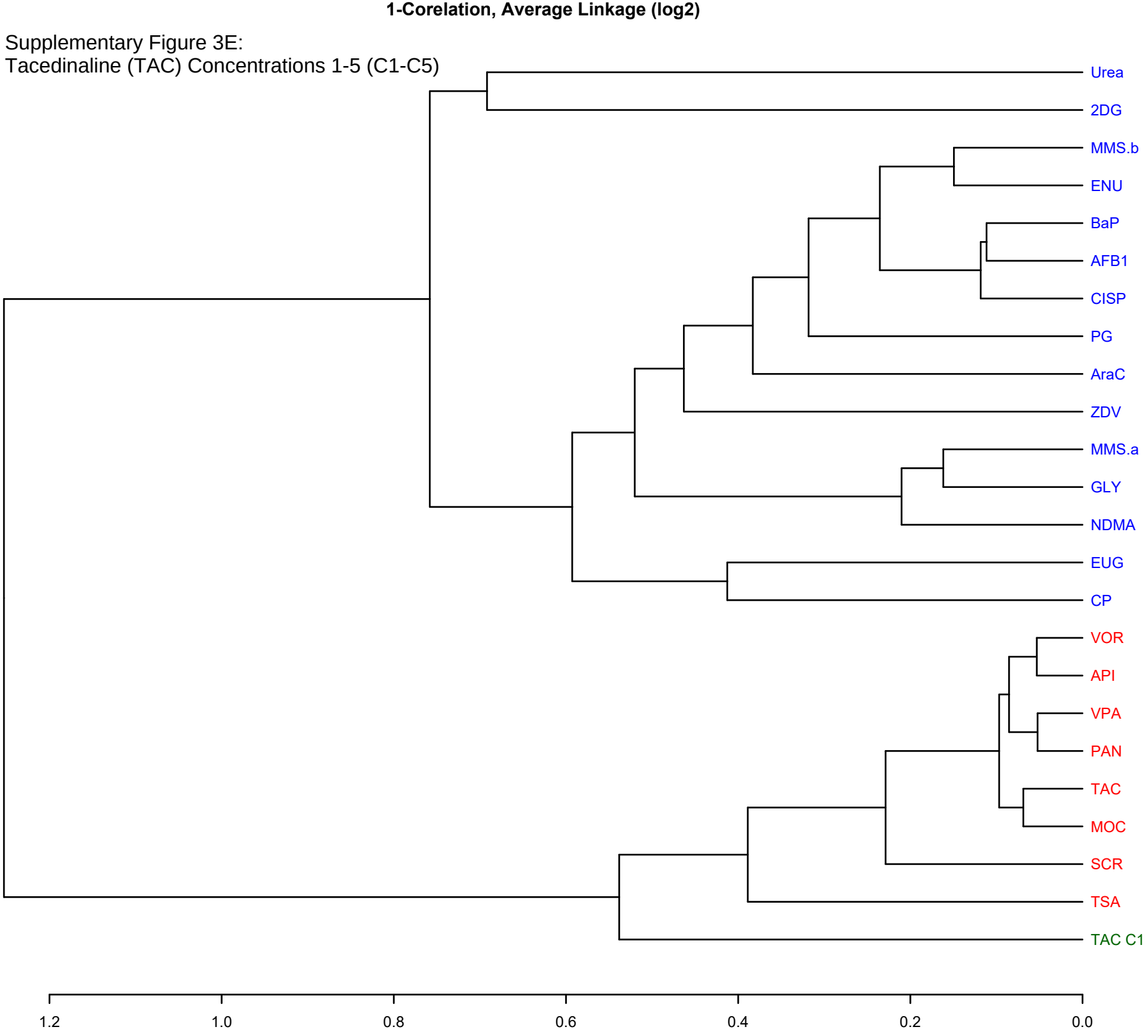


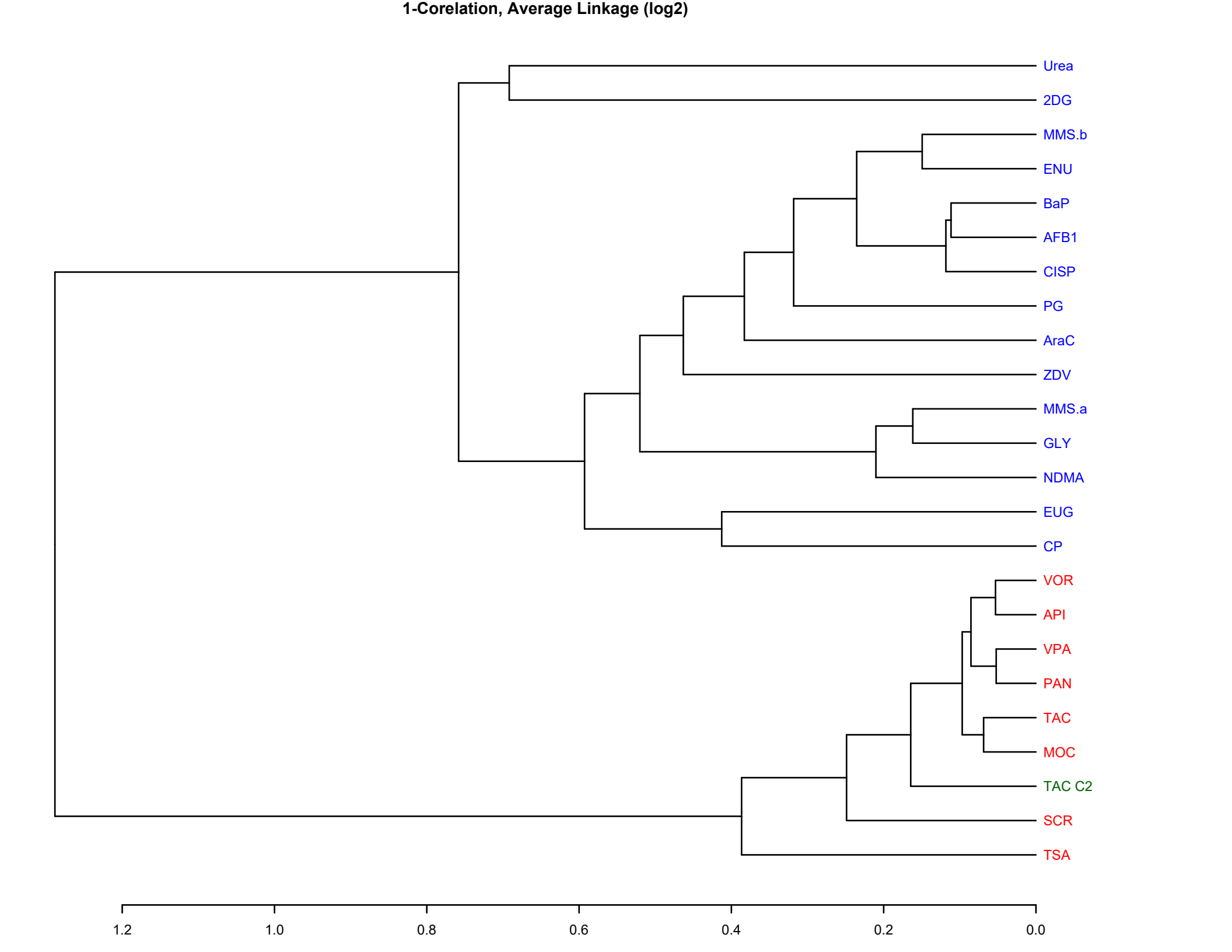

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
SCR C2
1.2
1.0
0.8
0.6
0.4
0.2
0.0

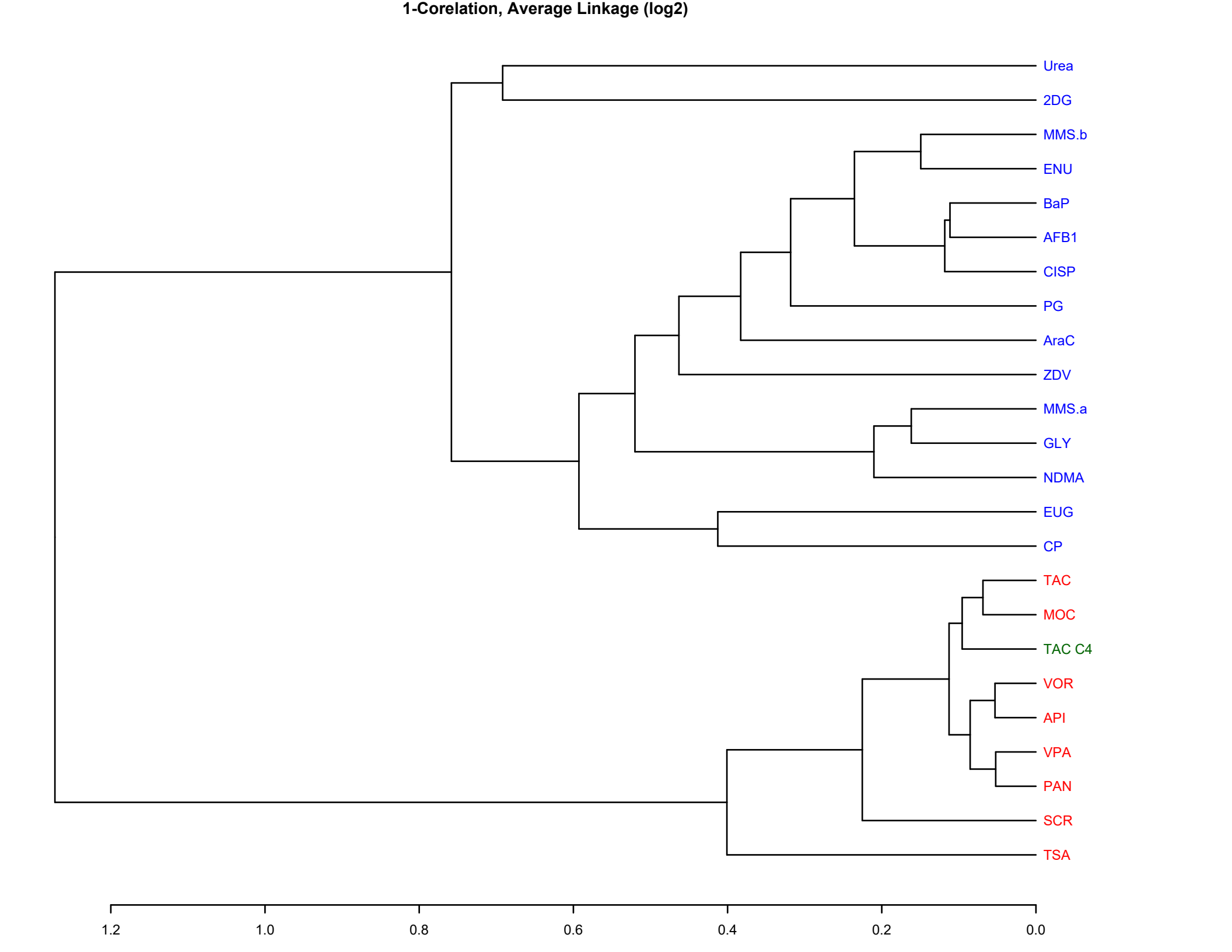

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR C3
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

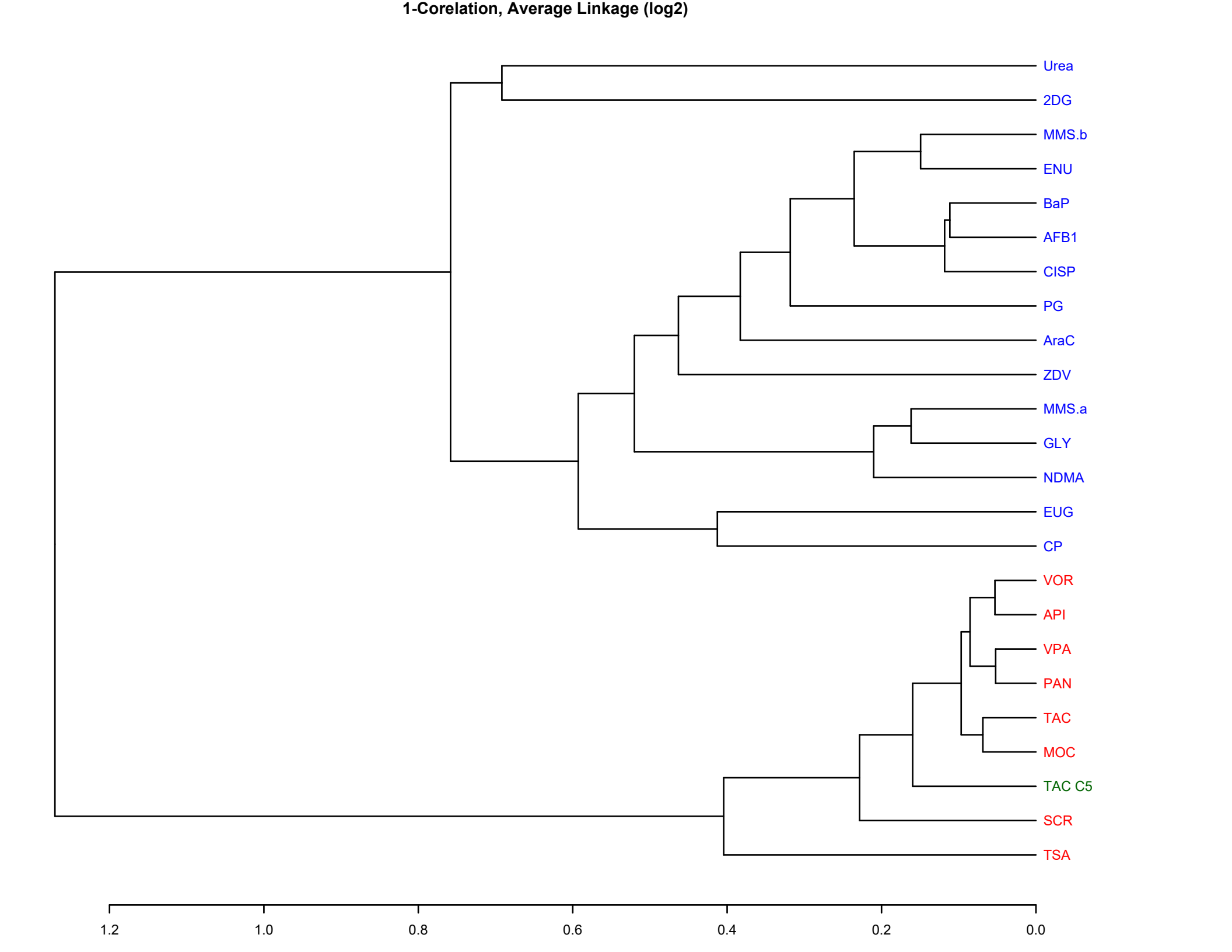

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR C5
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3E:
Tacedinaline (TAC) Concentrations 1-5 (C1-C5)

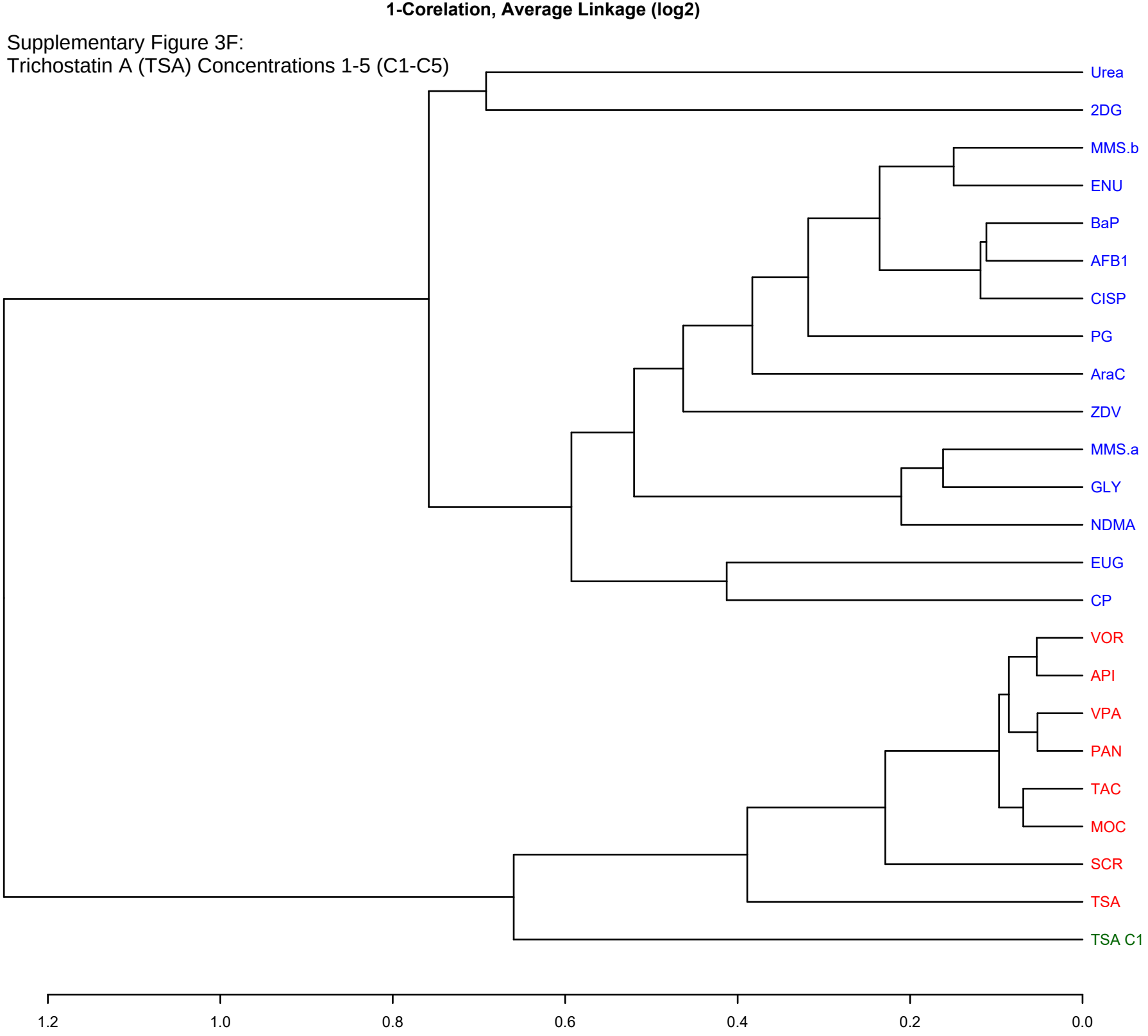


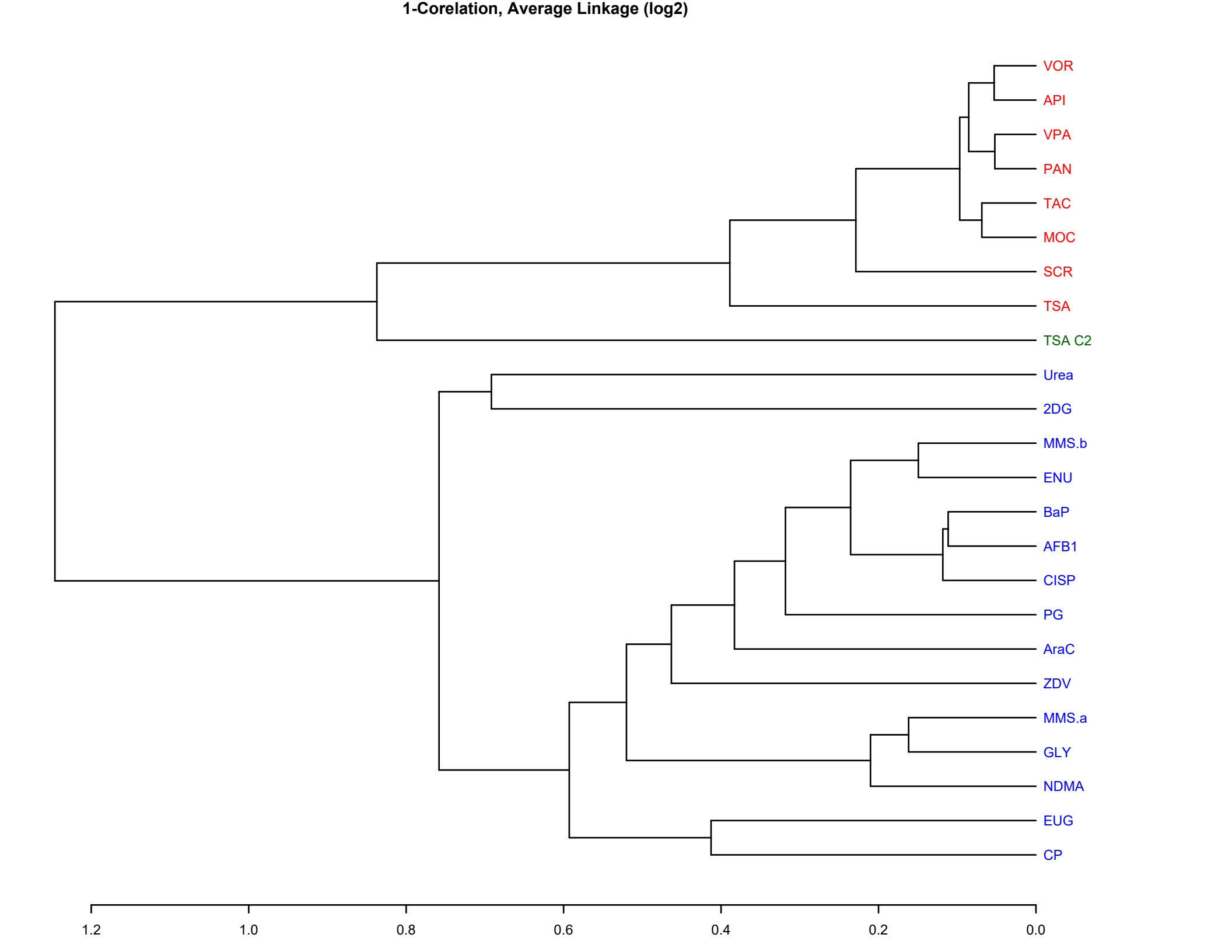

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
TAC C2
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

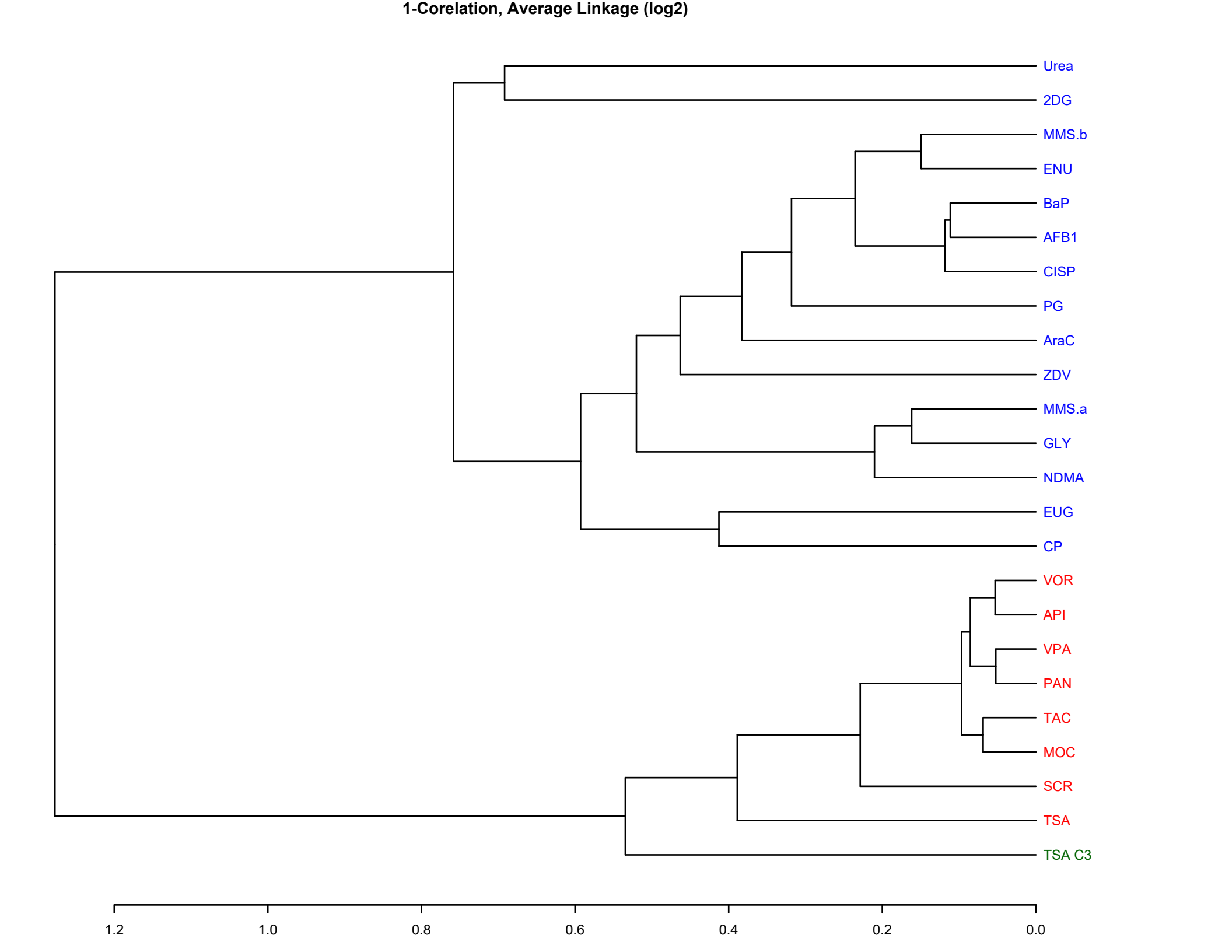

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
TAC
MOC
TAC C4
VOR
API
VPA
PAN
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

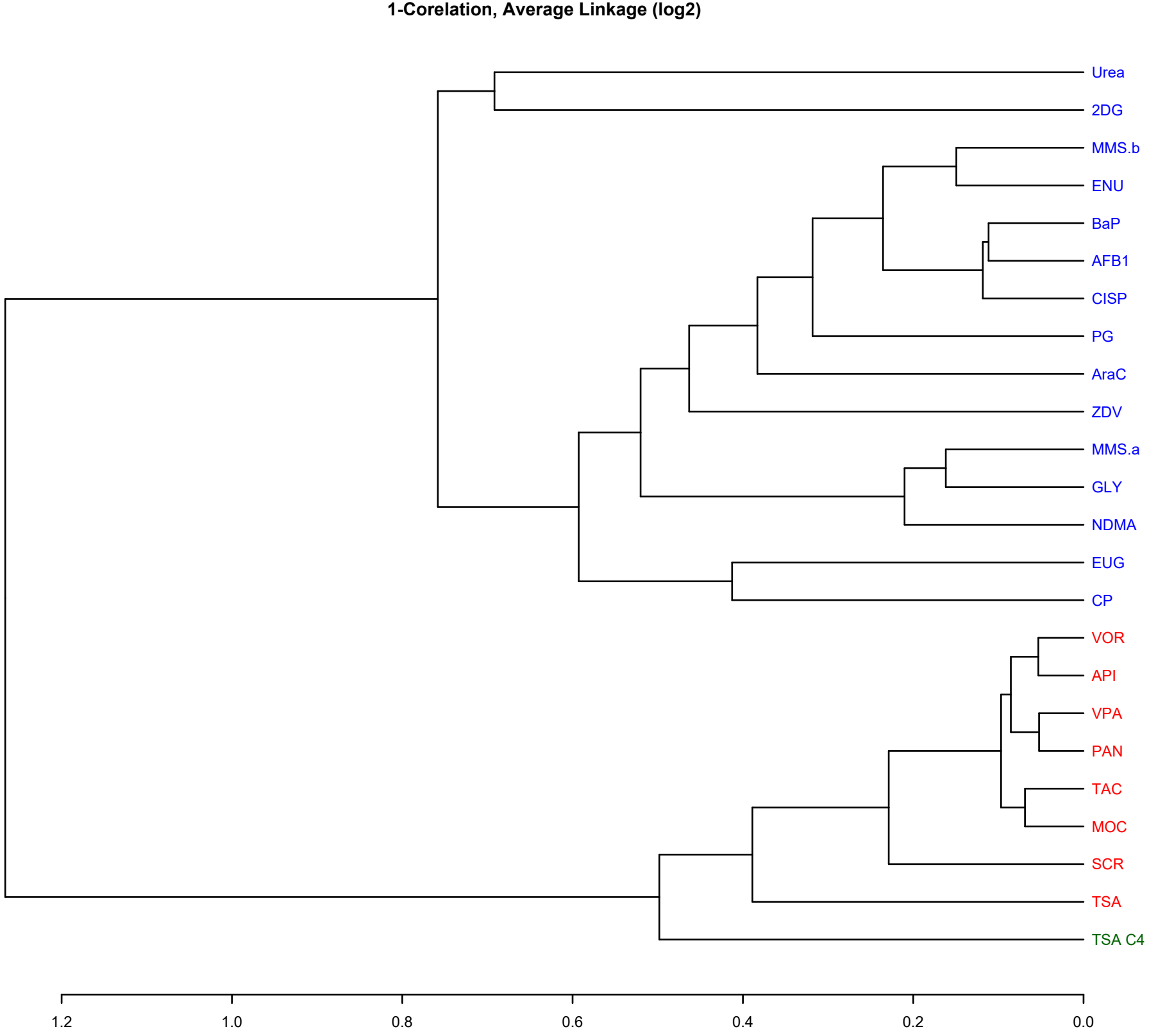

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
TAC C5
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3F:
Trichostatin A (TSA) Concentrations 1-5 (C1-C5)

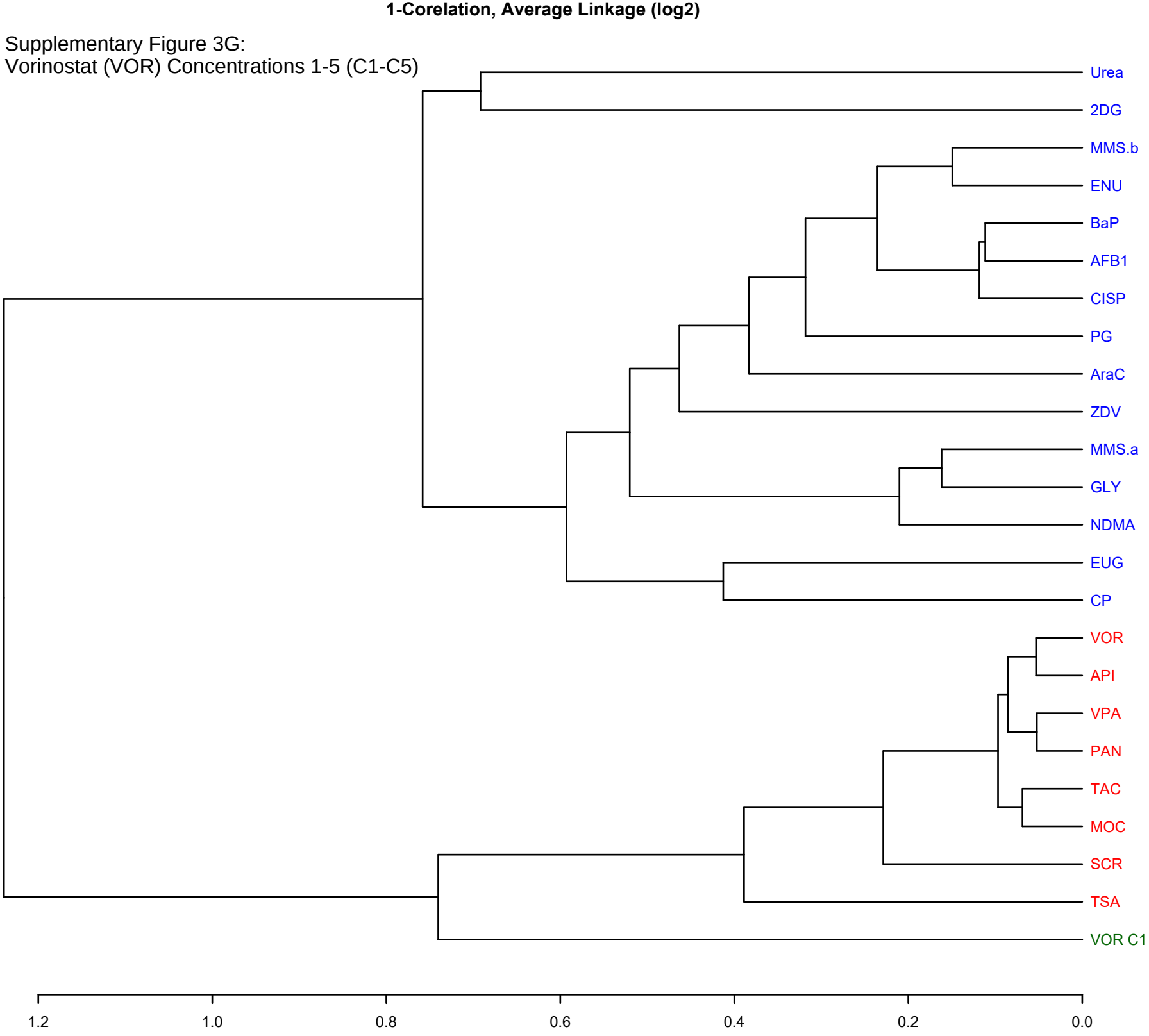


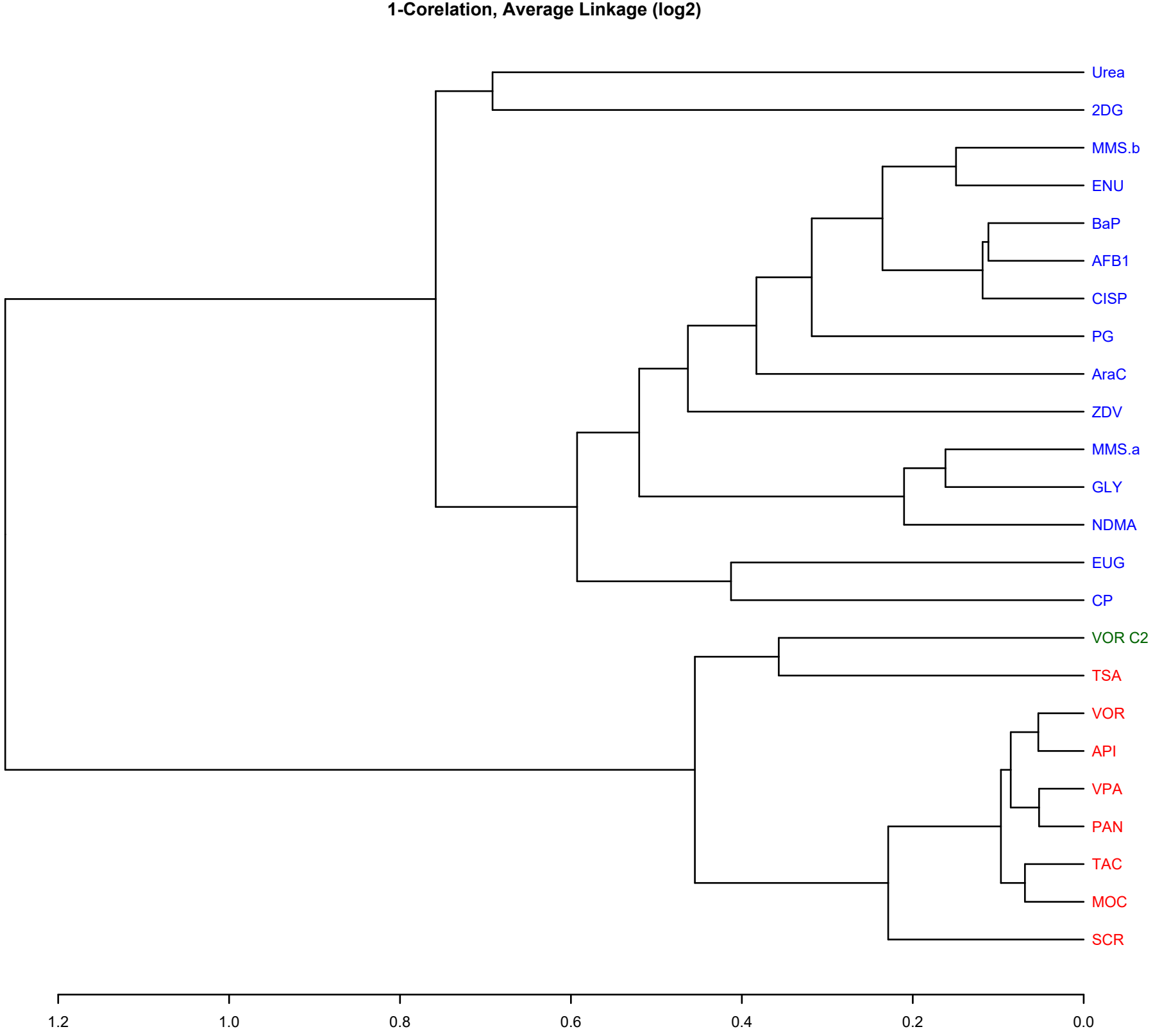

1-Corelation, Average Linkage (log2)
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
TSA C2
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
1.2
1.0
0.8
0.6
0.4
0.2
0.0

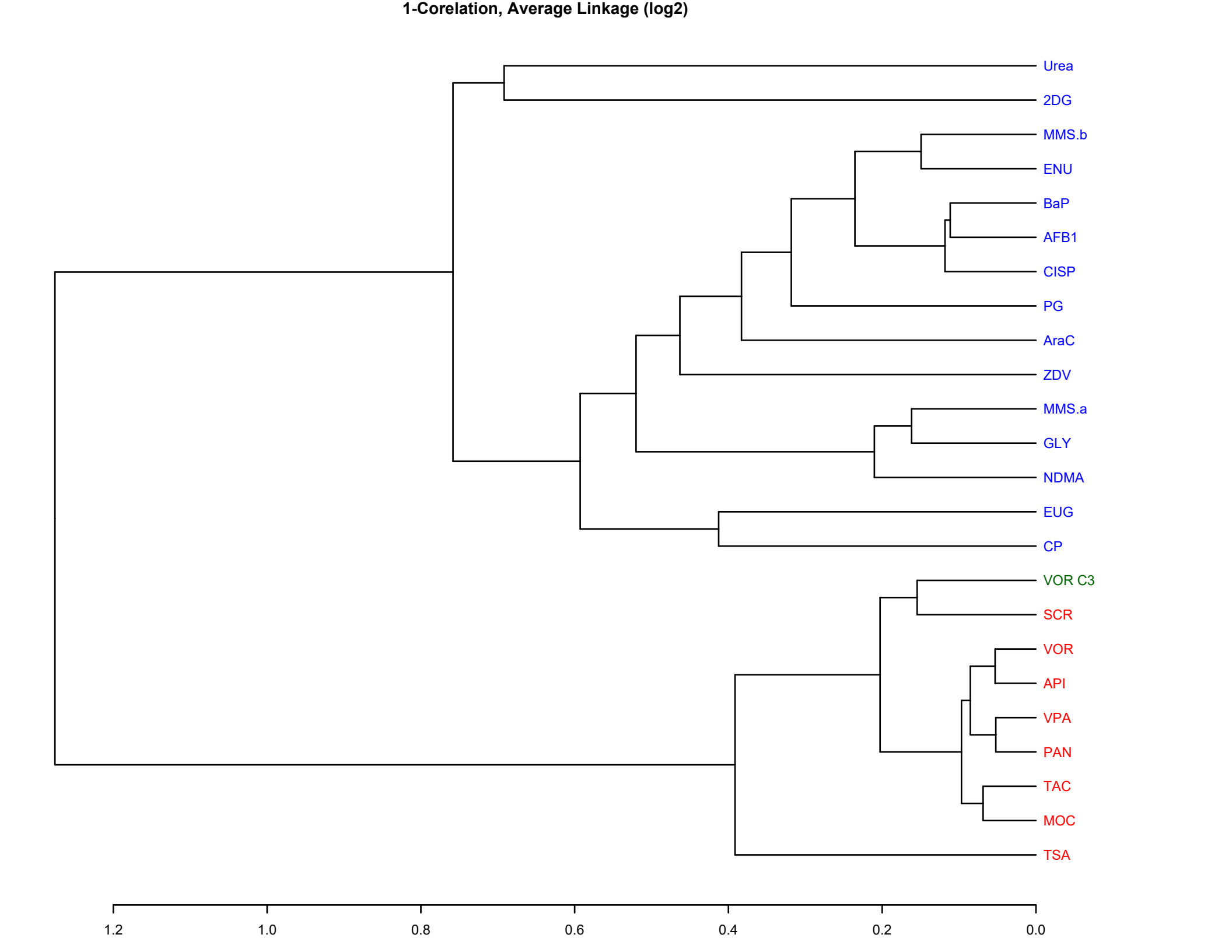

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
TSA C3
1.2
1.0
0.8
0.6
0.4
0.2
0.0

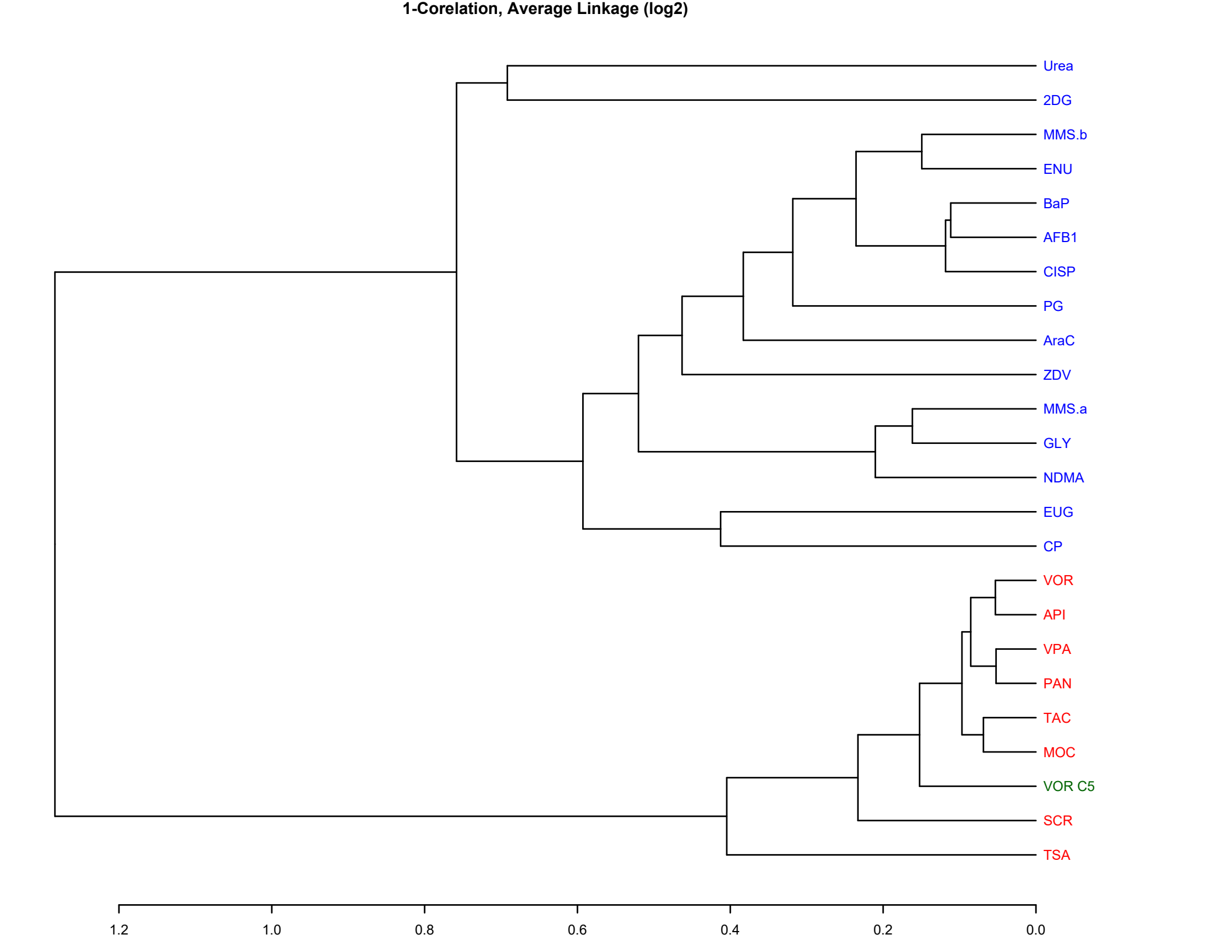

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
TSA C4
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3G:
Vorinostat (VOR) Concentrations 1-5 (C1-C5)

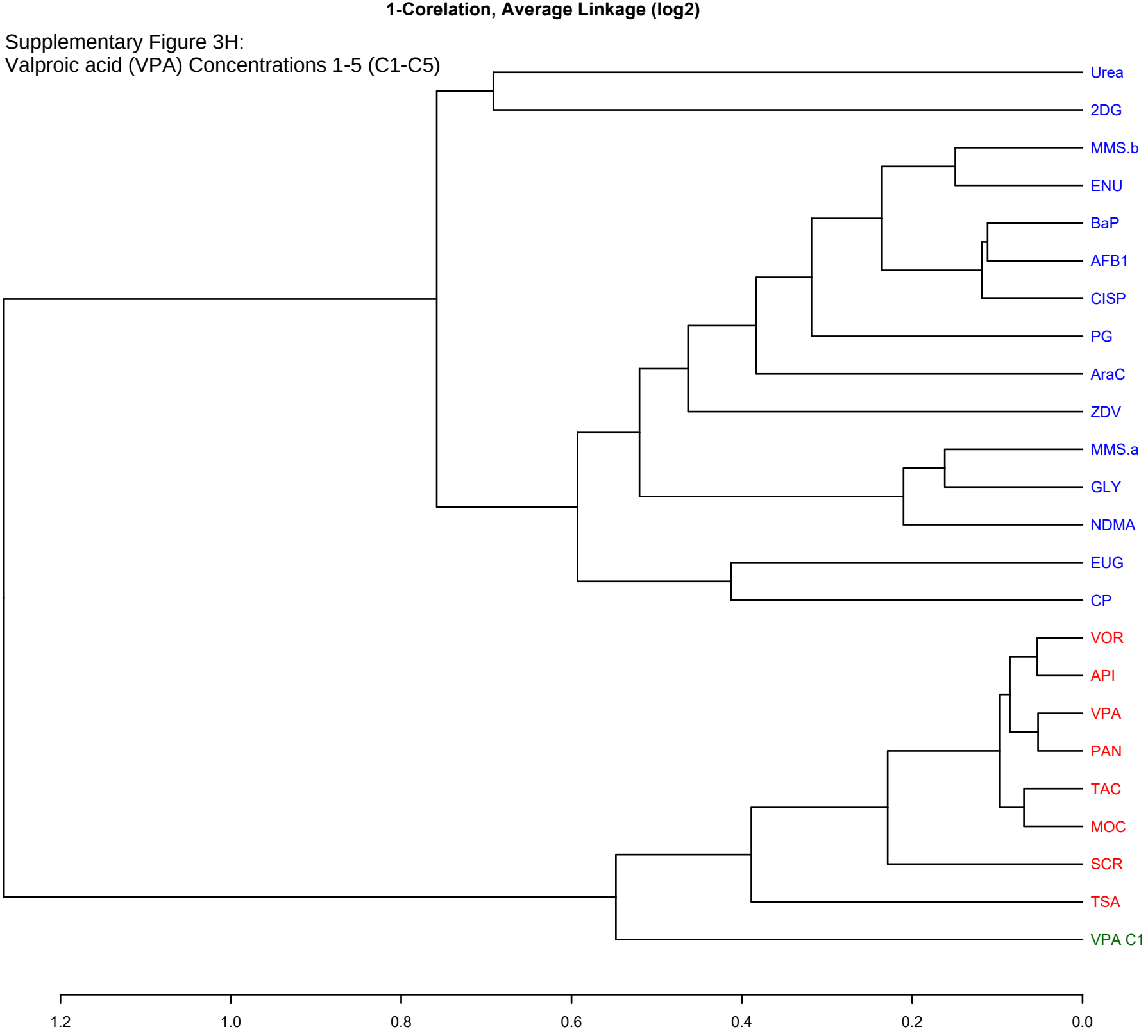


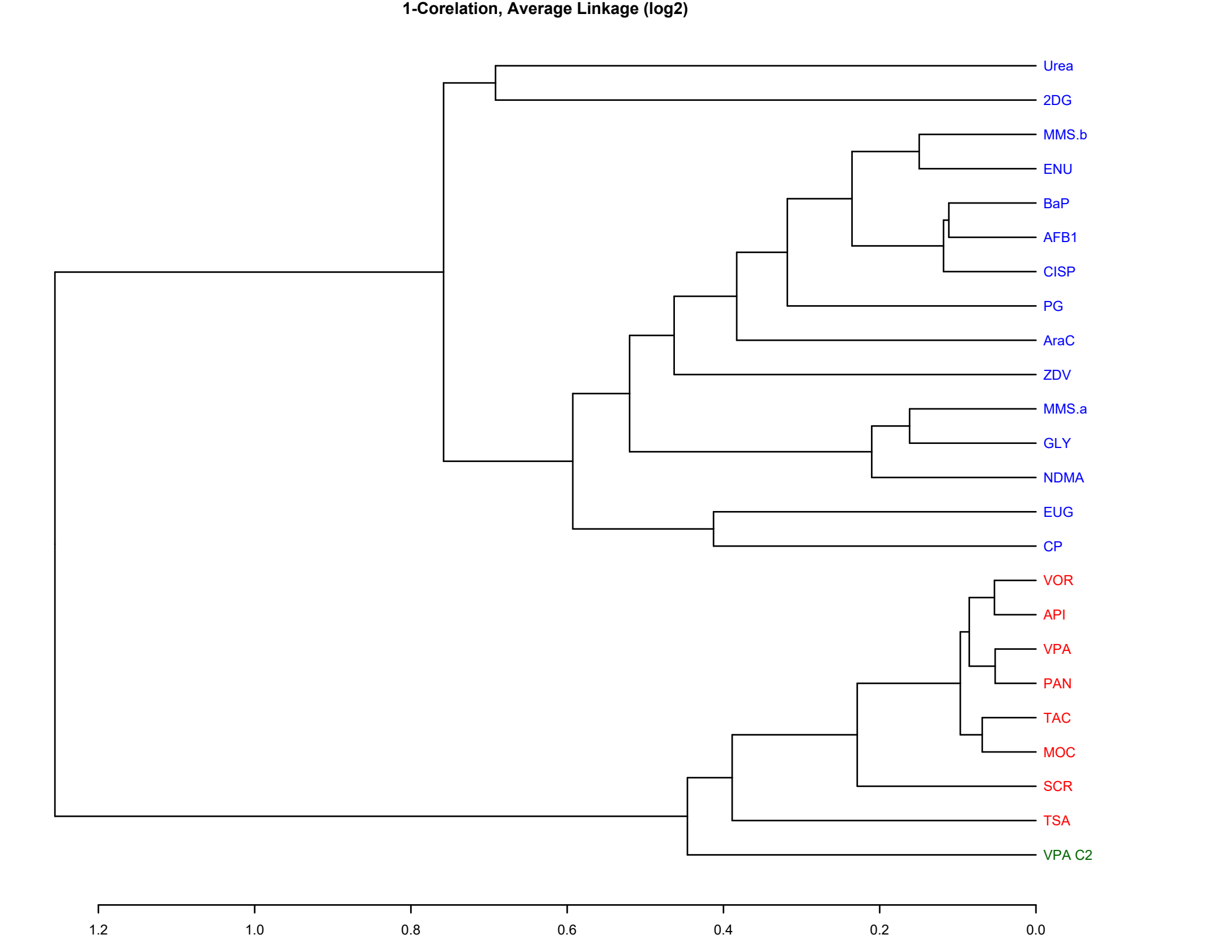

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR C2
TSA
VOR
API
VPA
PAN
TAC
MOC
SCR
1.2
1.0
0.8
0.6
0.4
0.2
0.0

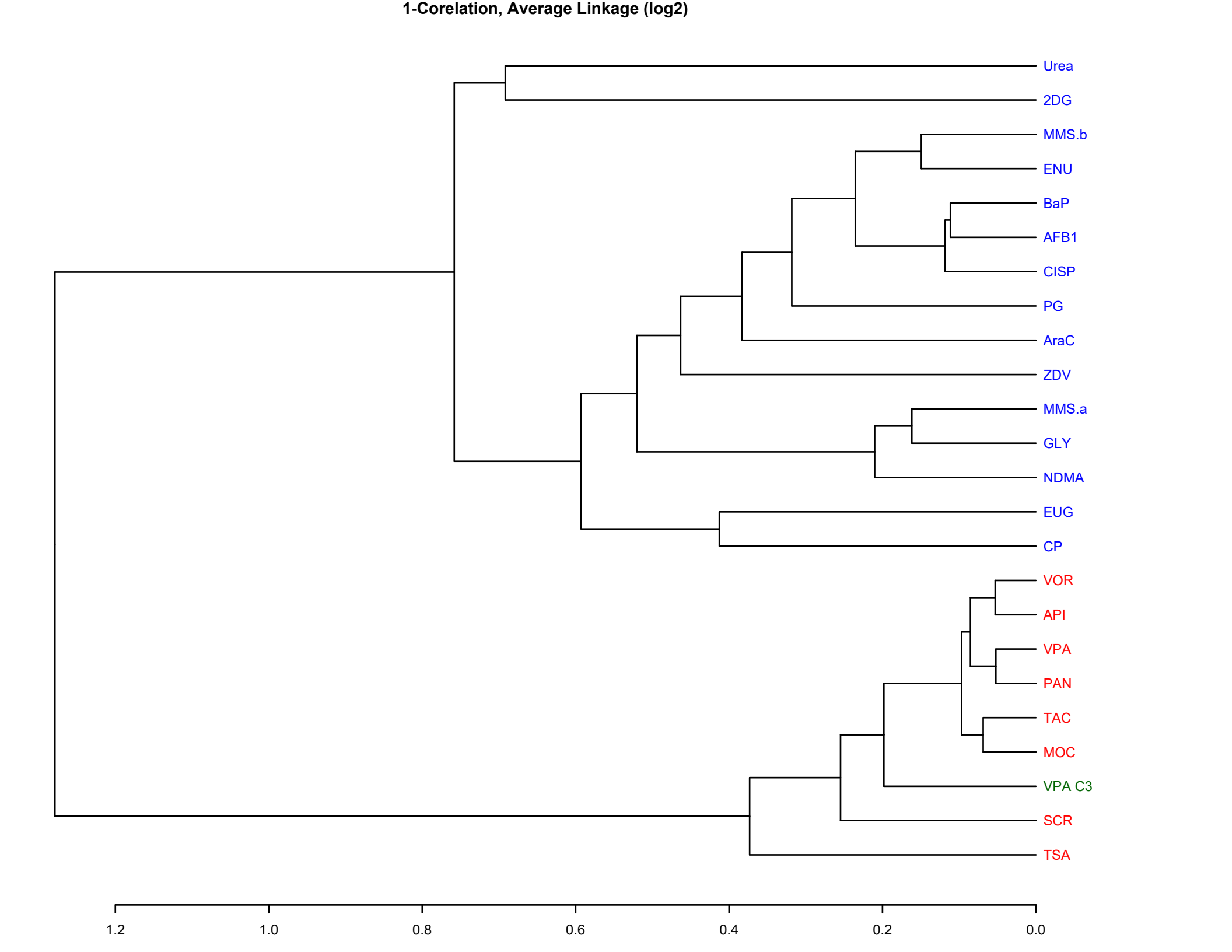

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR C3
SCR
VOR
API
VPA
PAN
TAC
MOC
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

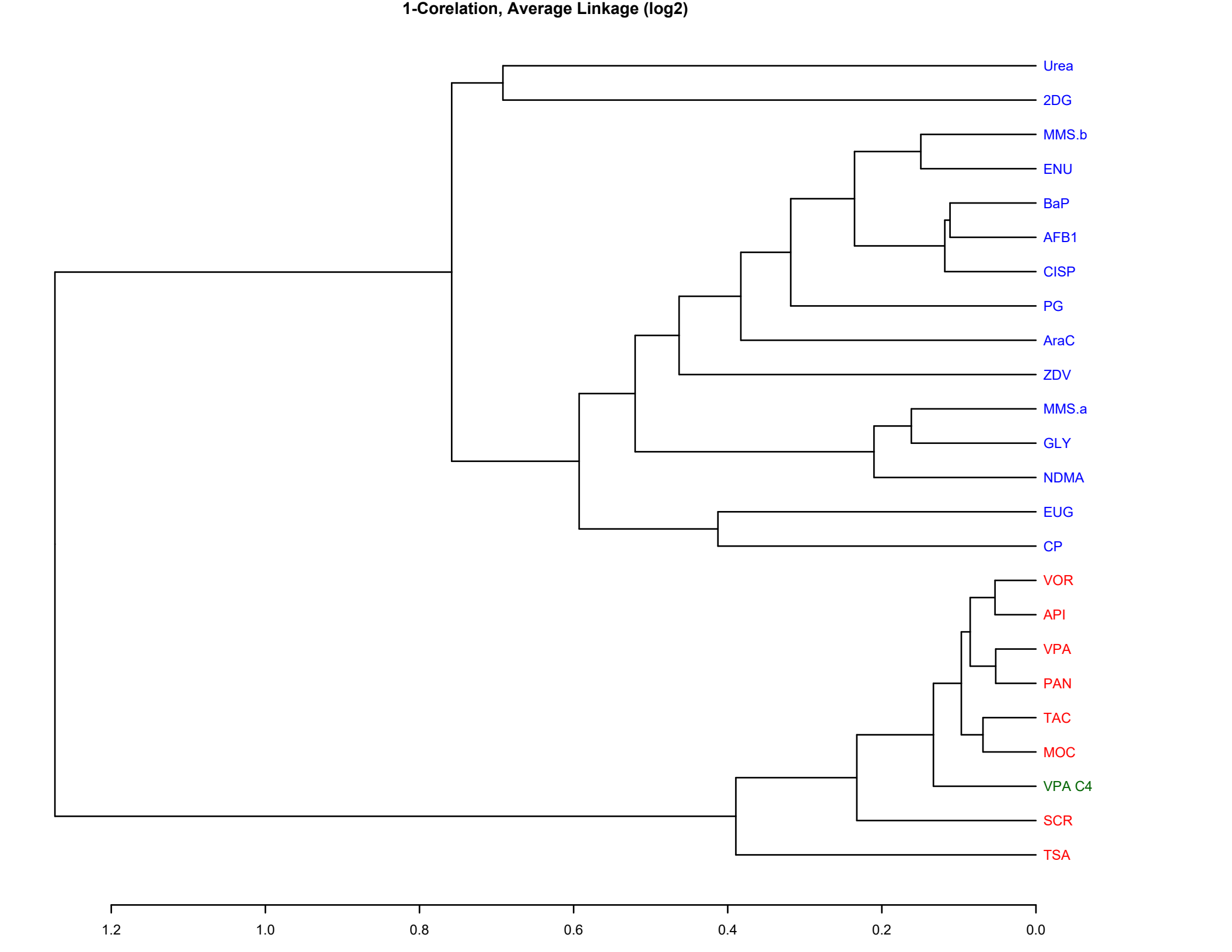

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
VOR C5
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3H:
Valproic acid (VPA) Concentrations 1-5 (C1-C5)

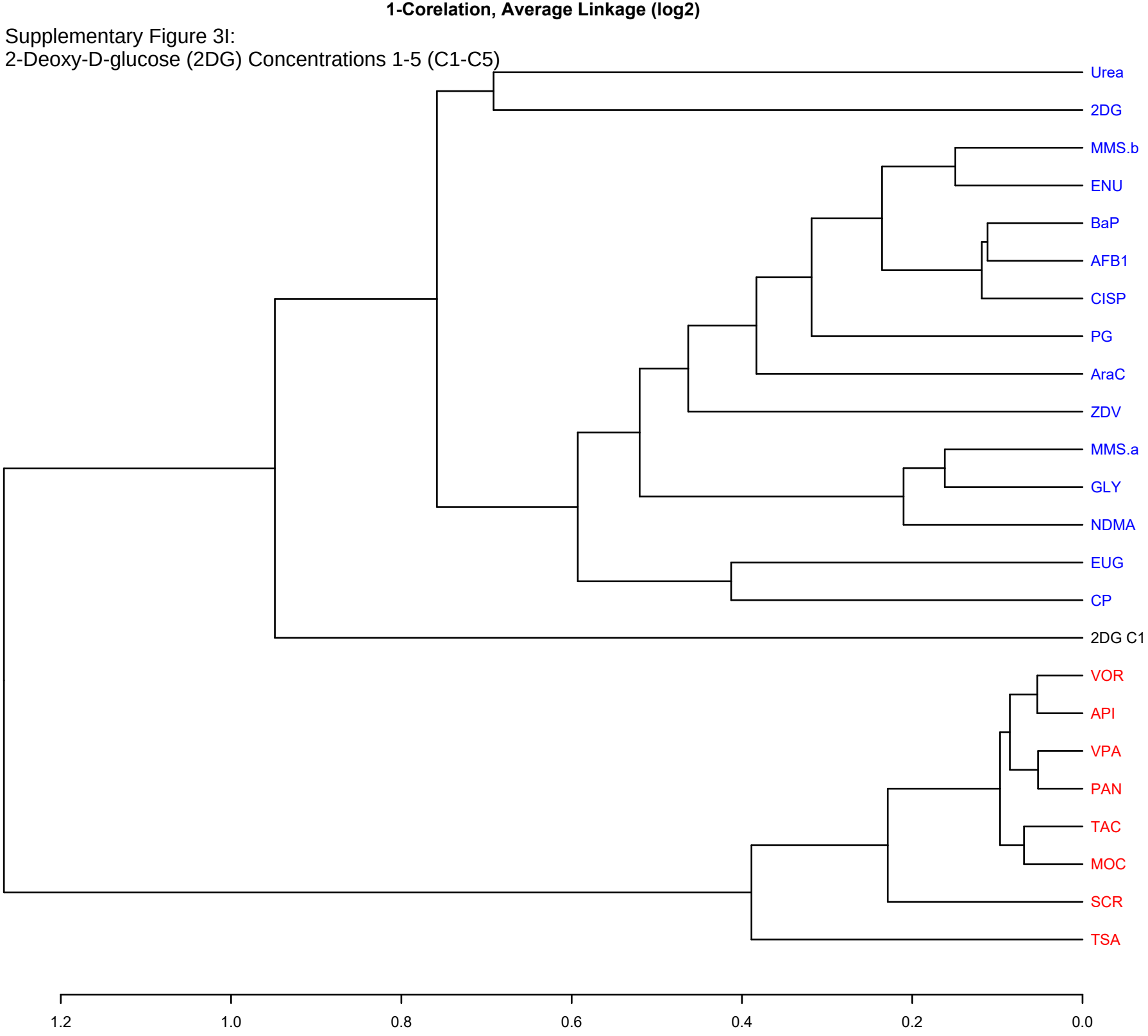


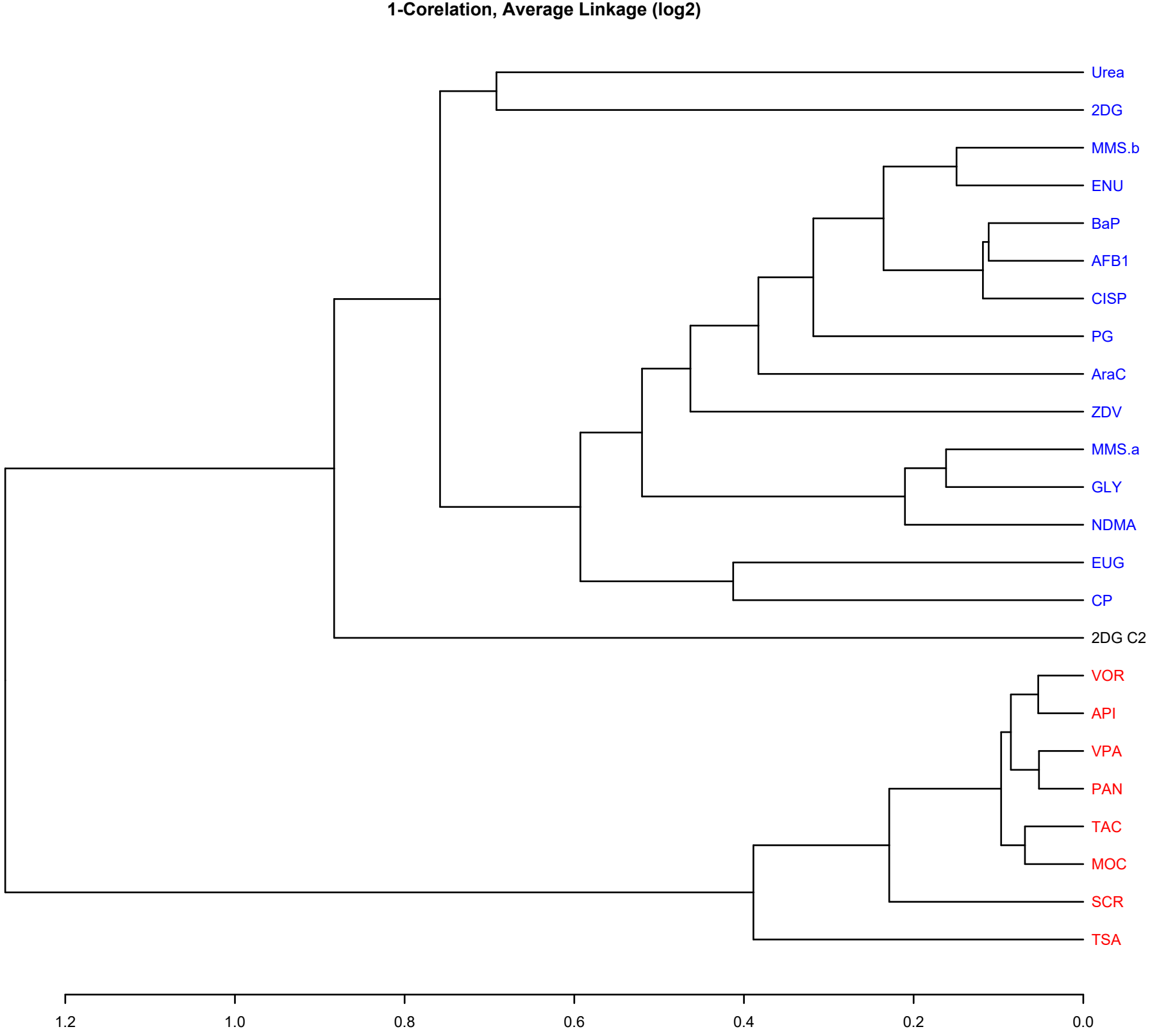

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
VPA C2
1.2
1.0
0.8
0.6
0.4
0.2
0.0

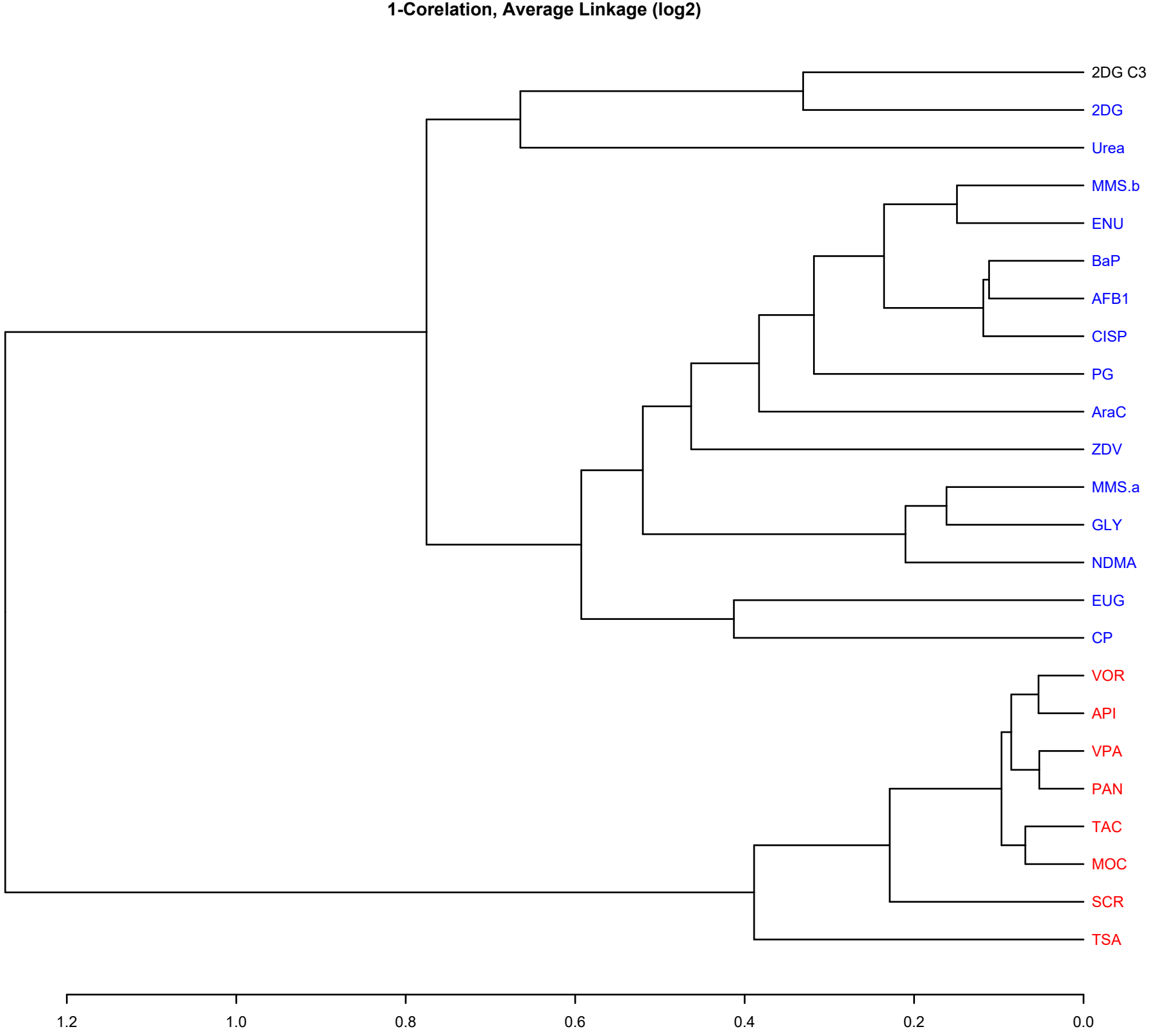

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
VPA C3
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

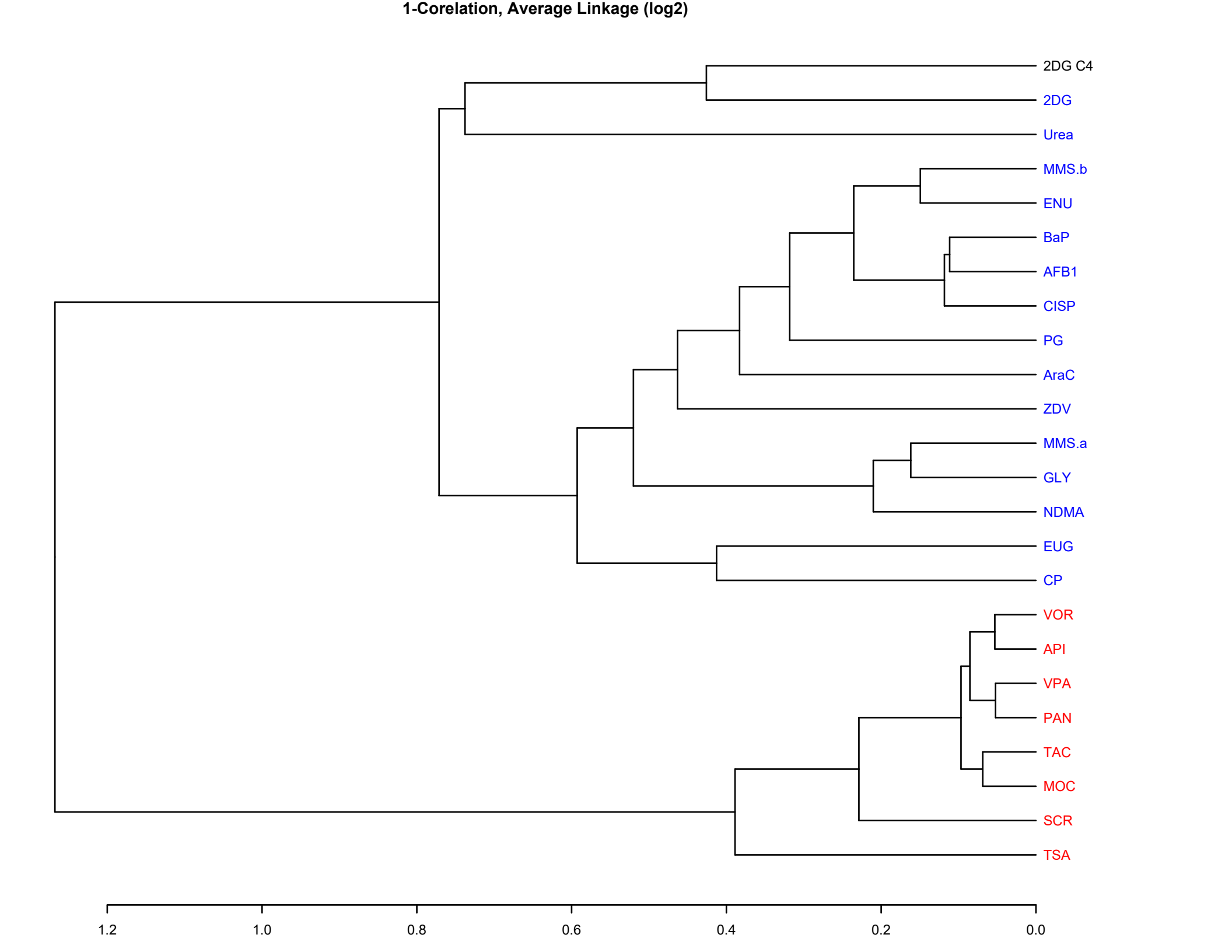

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
VPA C4
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3I:
2-Deoxy-D-glucose (2DG) Concentrations 1-5 (C1-C5)

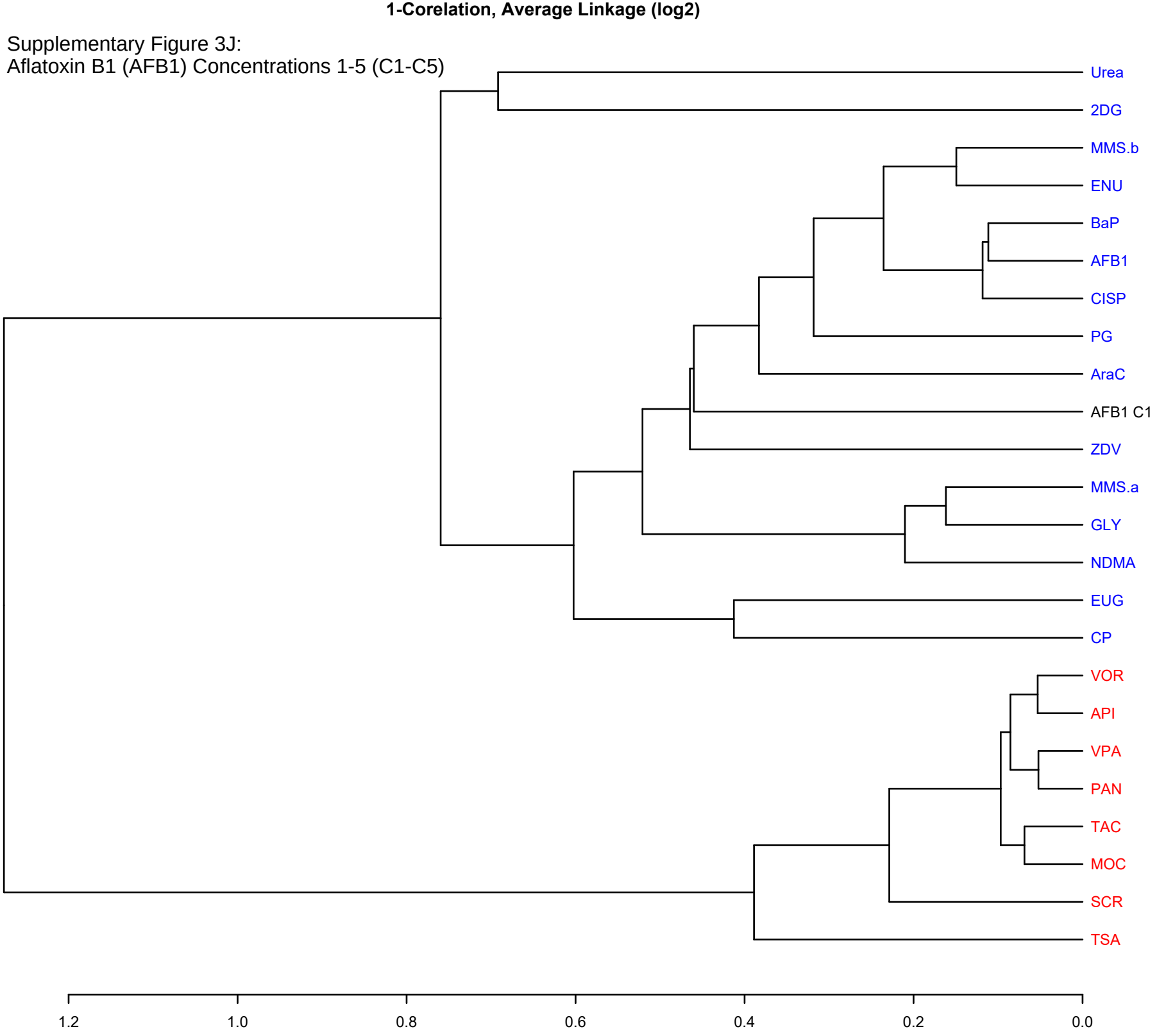


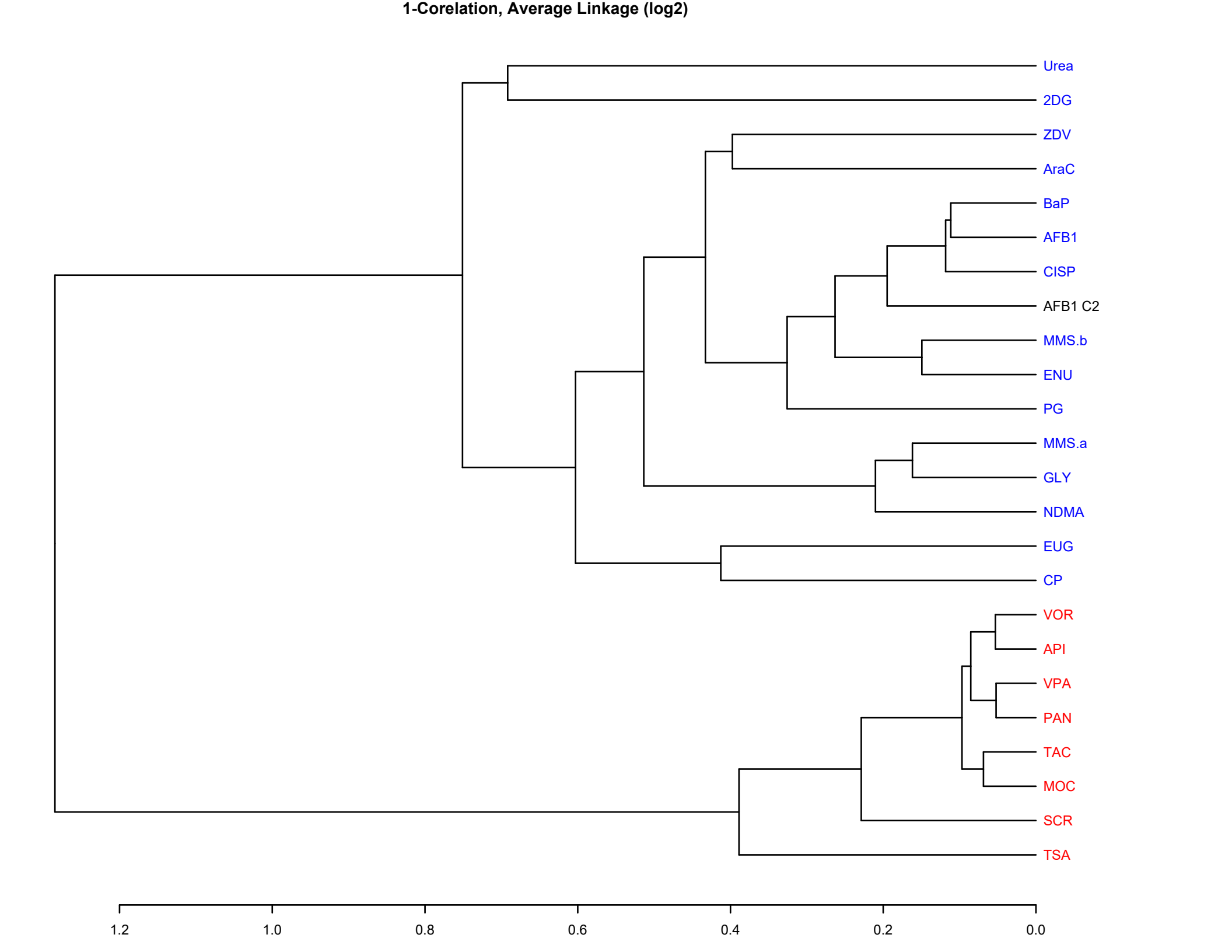

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
2DG C2
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

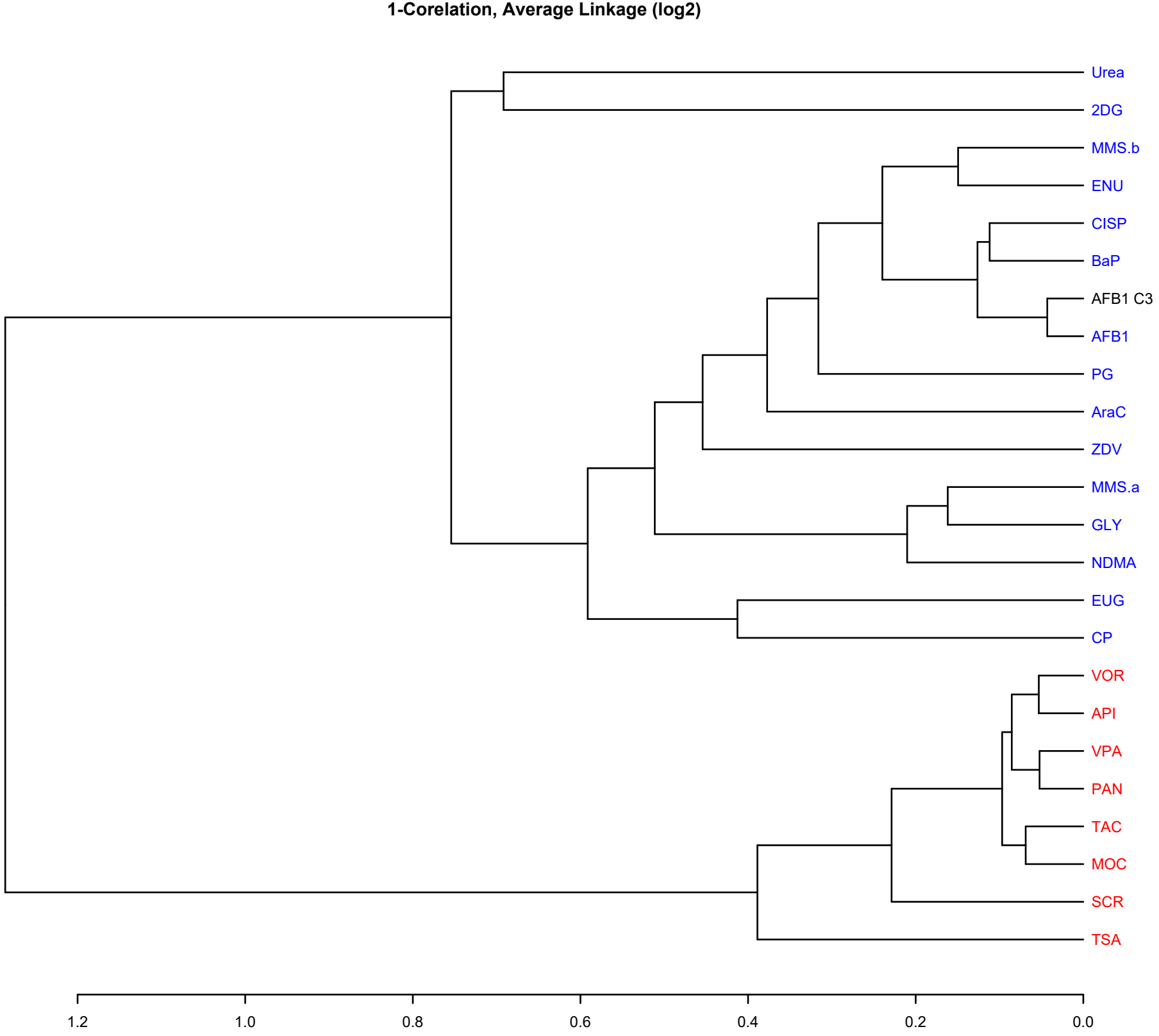

1-Corelation, Average Linkage (log2)
2DG C3
2DG
Urea
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

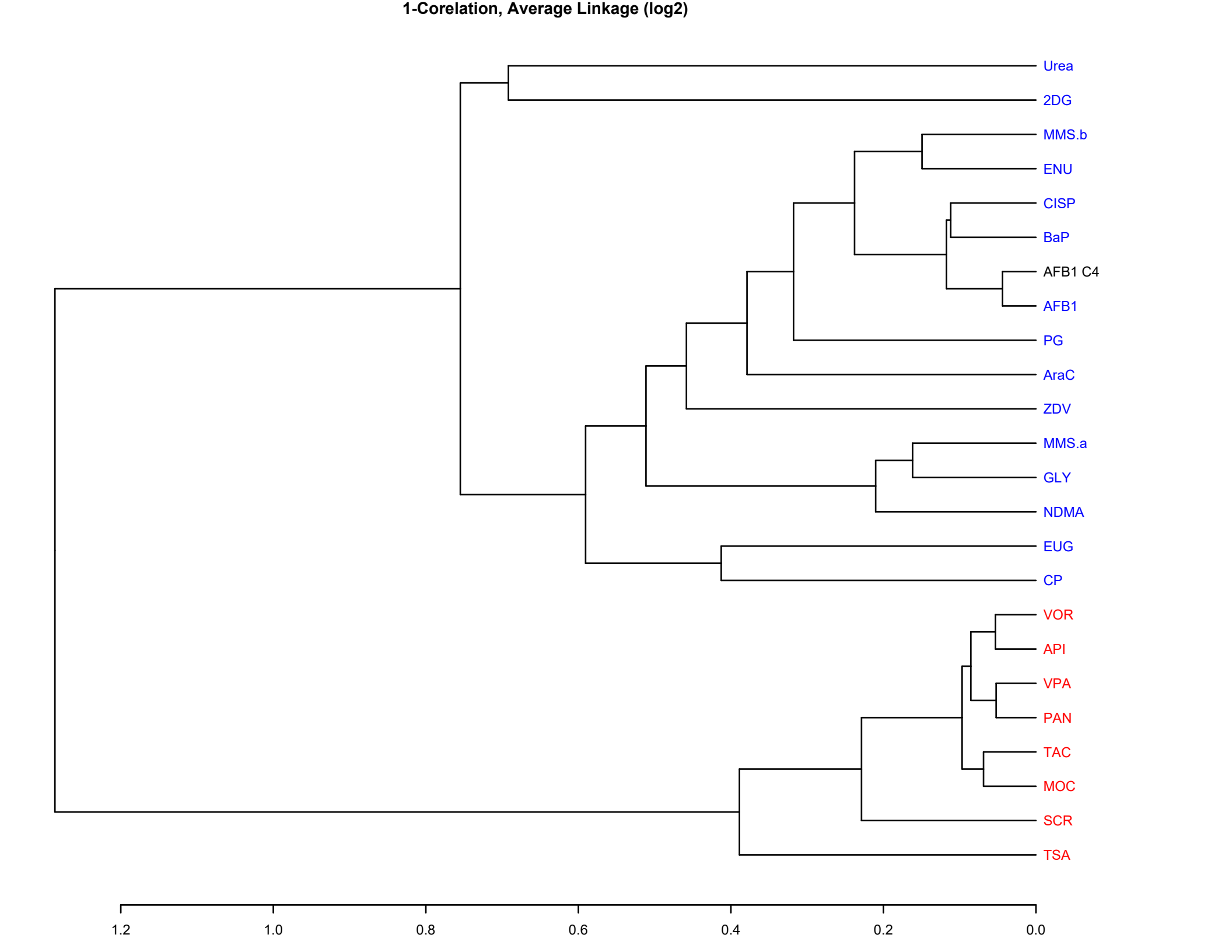

1-Corelation, Average Linkage (log2)
2DG C4
2DG
Urea
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3J:
Aflatoxin B1 (AFB1) Concentrations 1-5 (C1-C5)

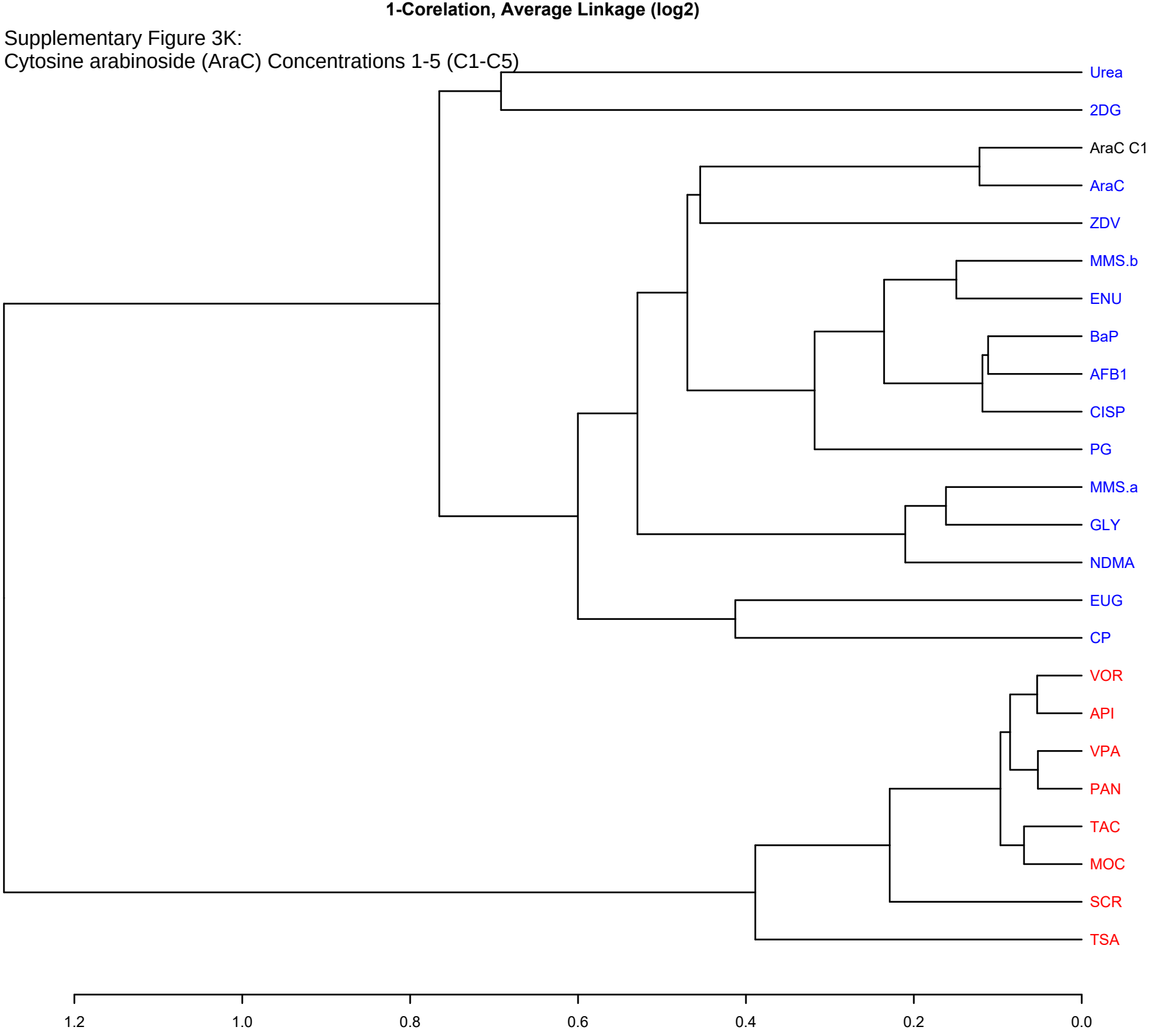


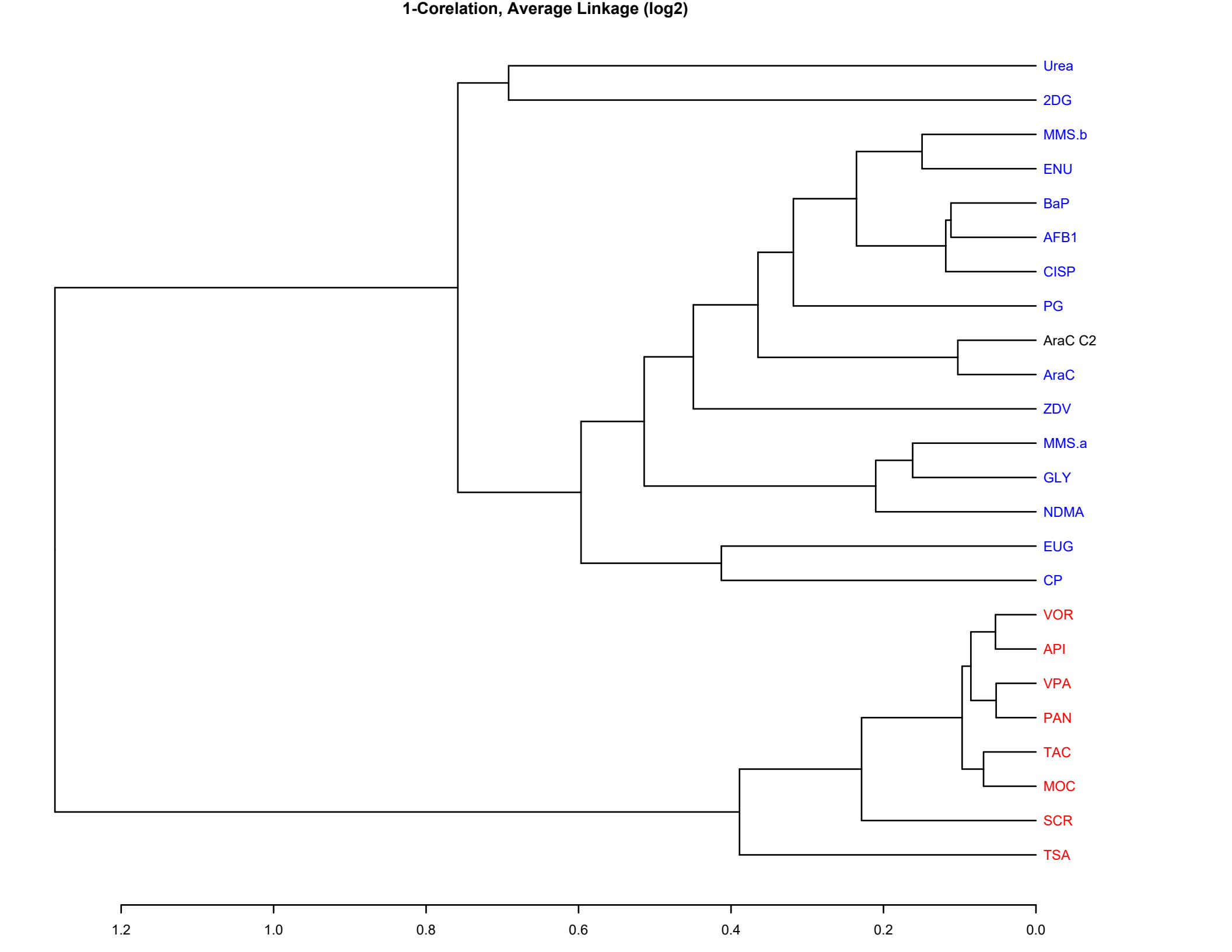

1-Corelation, Average Linkage (log2)
Urea
2DG
ZDV
AraC
BaP
AFB1
CISP
AFB1 C2
MMS.b
ENU
PG
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

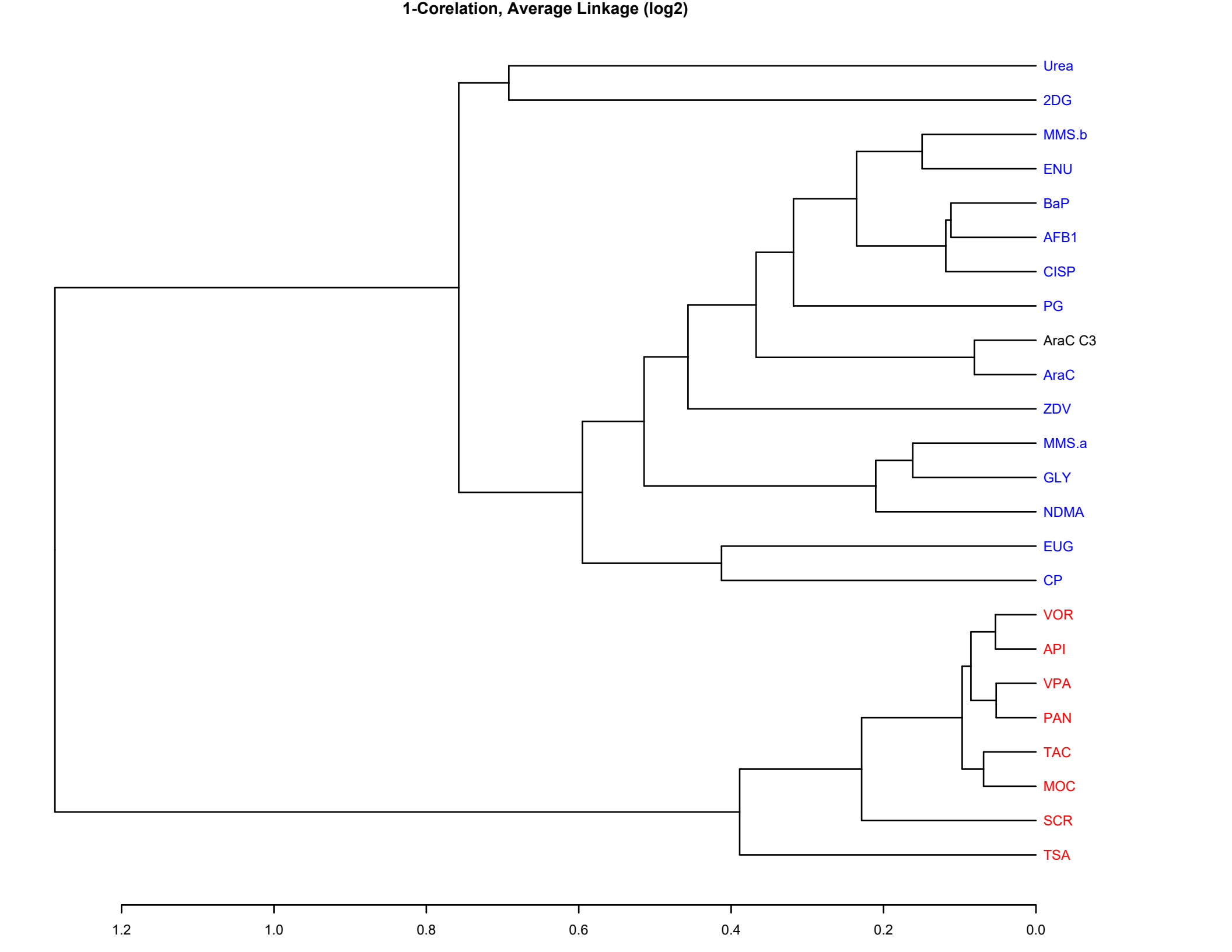

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
CISP
BaP
AFB1 C3
AFB1
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

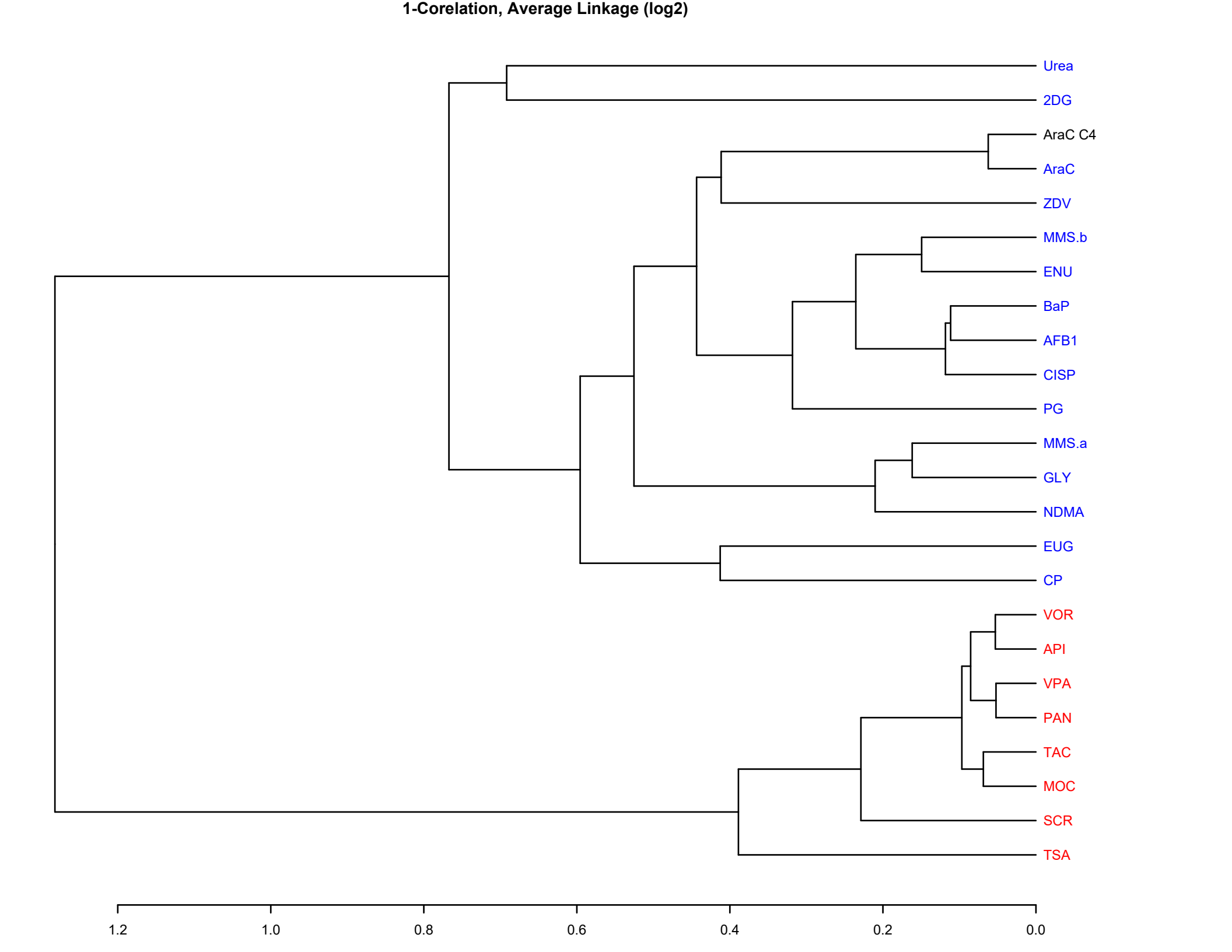

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
CISP
BaP
AFB1 C4
AFB1
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3K:
Cytosine arabinoside (AraC) Concentrations 1-5 (C1-C5)

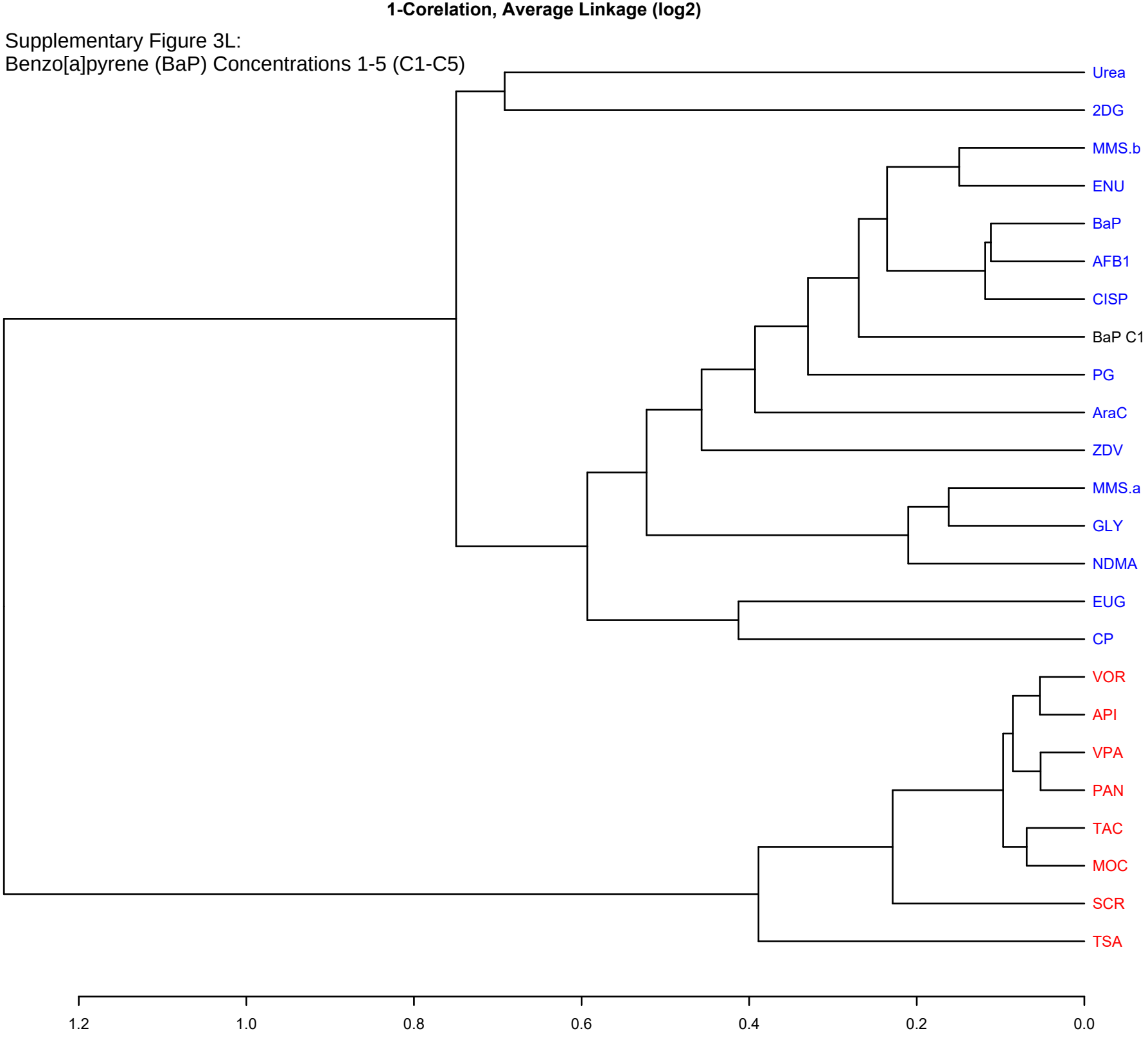


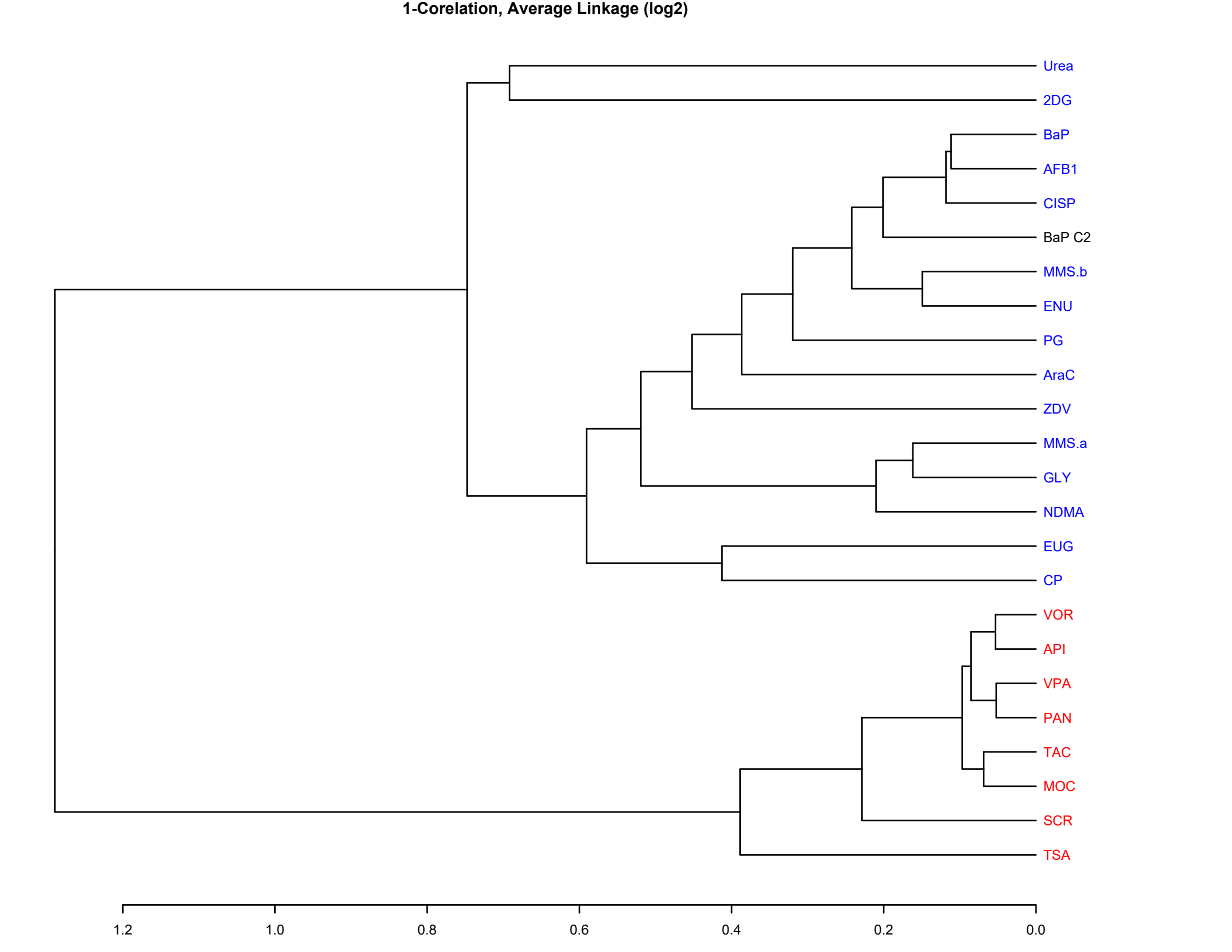

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC C2
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

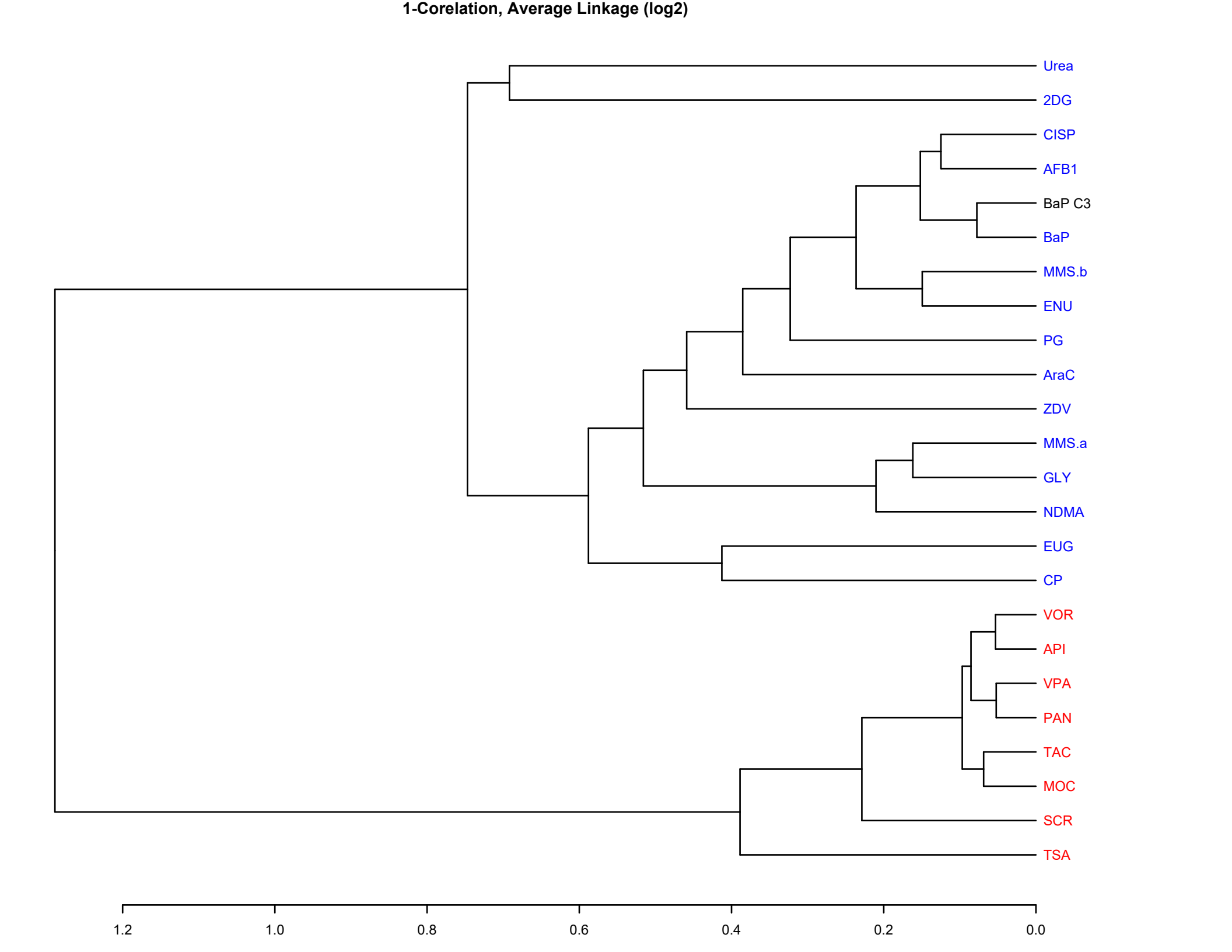

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC C3
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

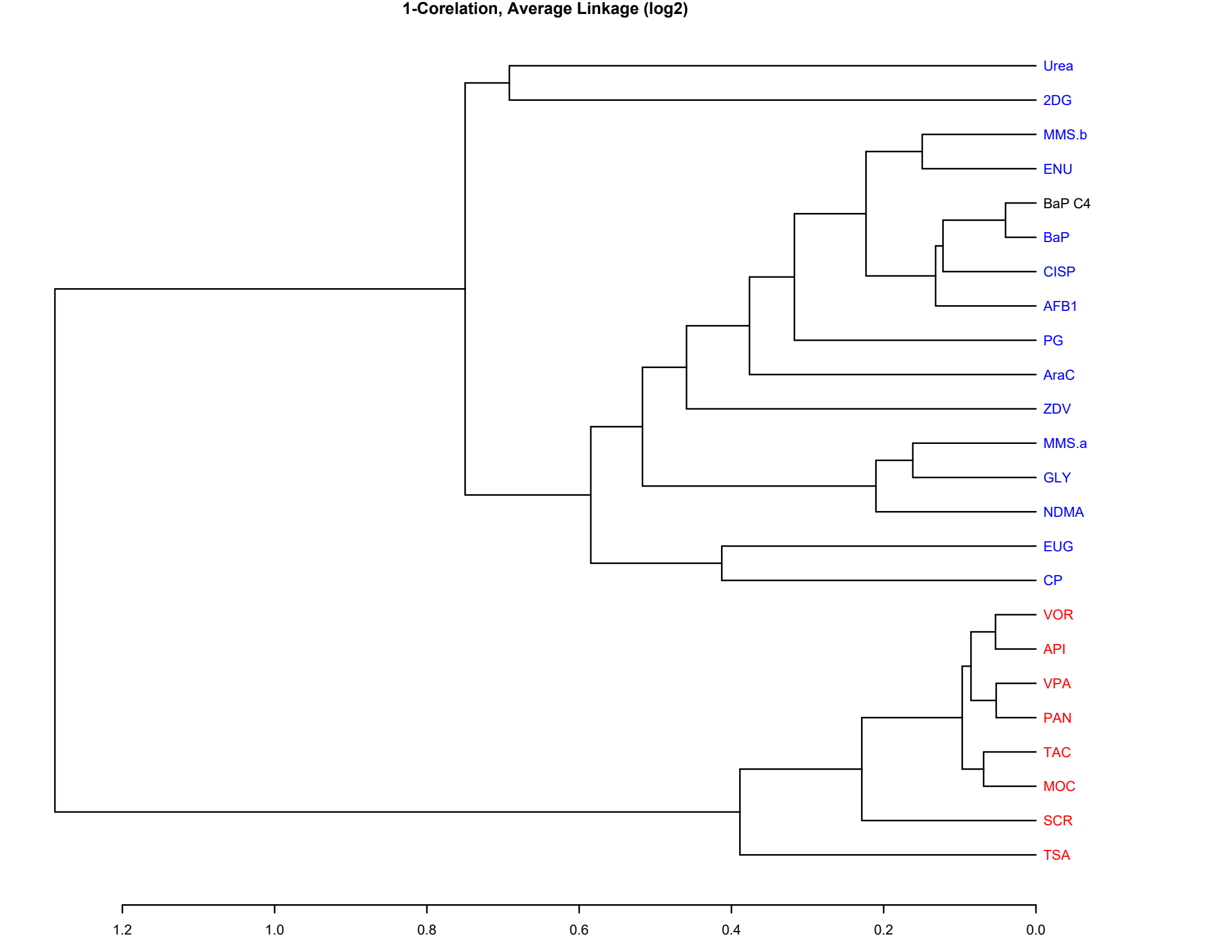

1-Corelation, Average Linkage (log2)
Urea
2DG
AraC C4
AraC
ZDV
MMS.b
ENU
BaP
AFB1
CISP
PG
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3L:
Benzo[a]pyrene (BaP) Concentrations 1-5 (C1-C5)



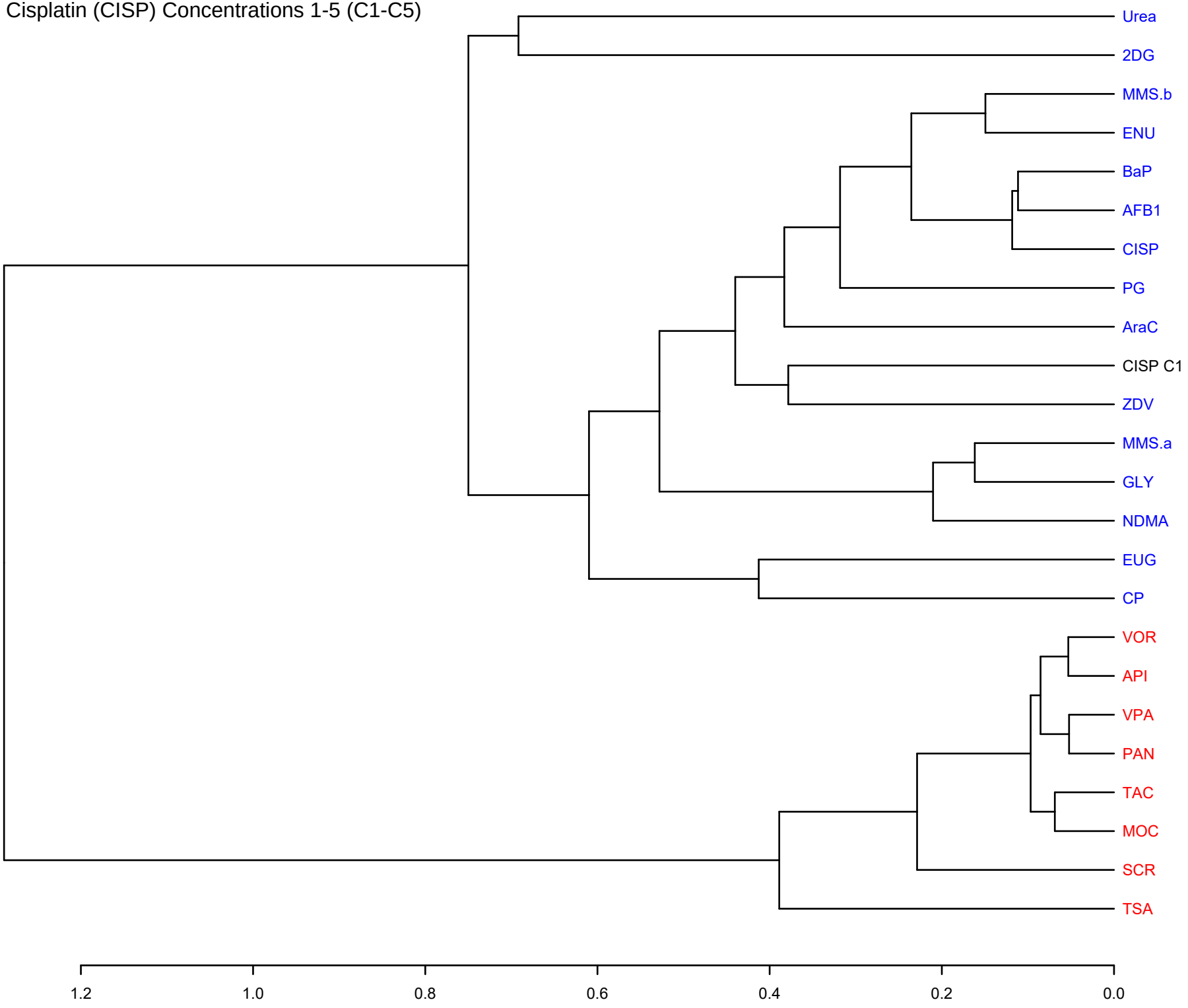

1-Corelation, Average Linkage (log2)
Urea
2DG
BaP
AFB1
CISP
BaP C2
MMS.b
ENU
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

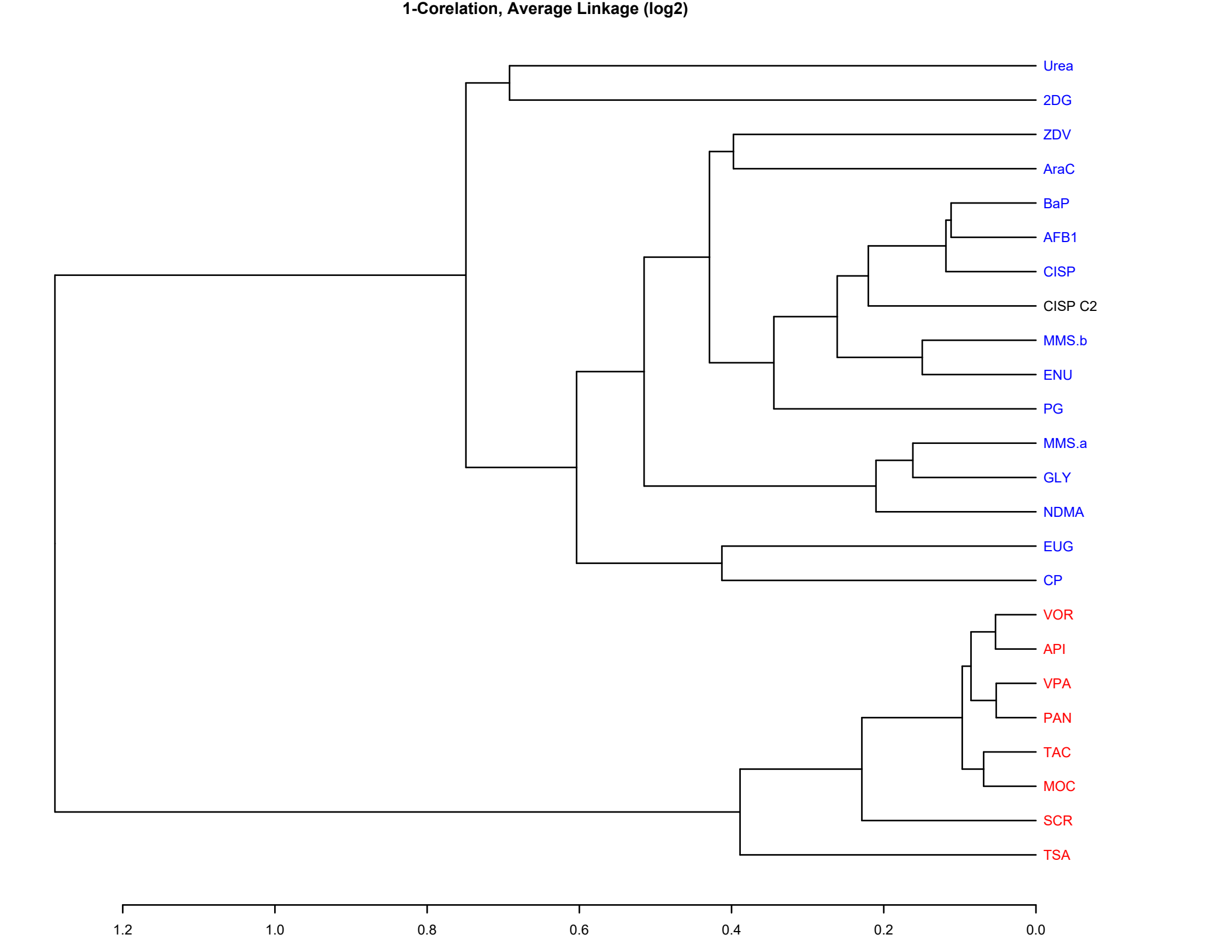

1-Corelation, Average Linkage (log2)
Urea
2DG
CISP
AFB1
BaP C3
BaP
MMS.b
ENU
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

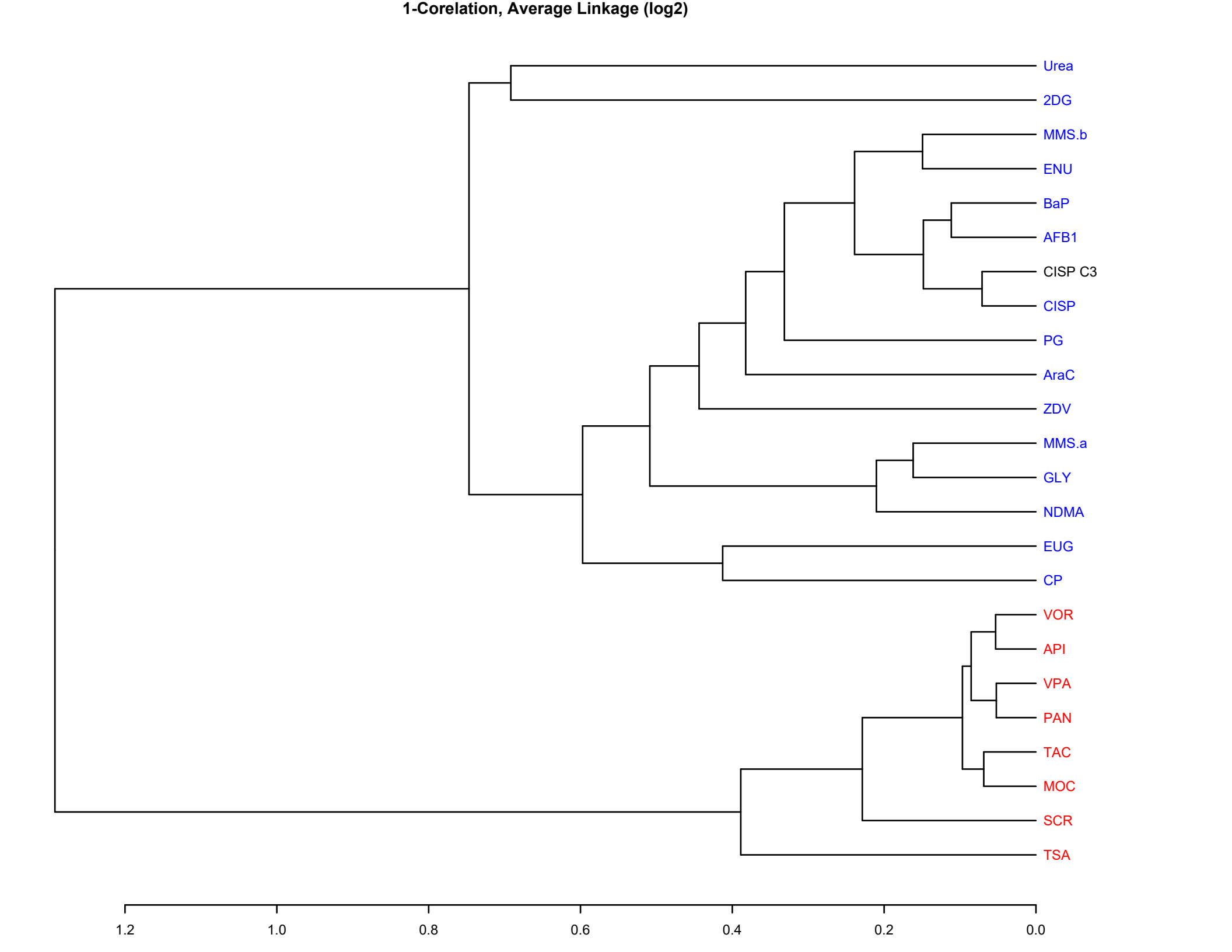

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP C4
BaP
CISP
AFB1
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

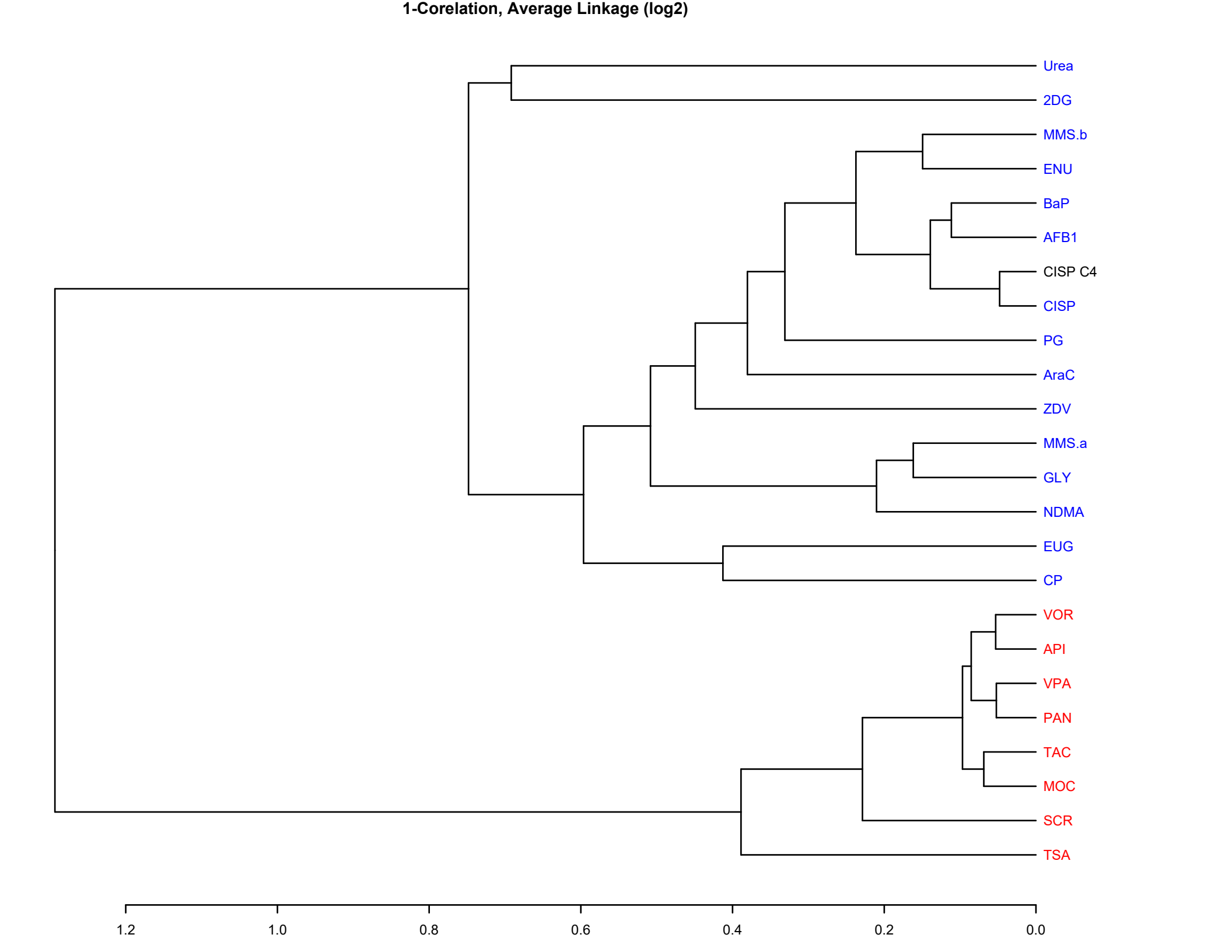
1-Corelation, Average Linkage (log2)

Supplementary Figure 3M:
Cisplatin (CISP) Concentrations 1-5 (C1-C5)

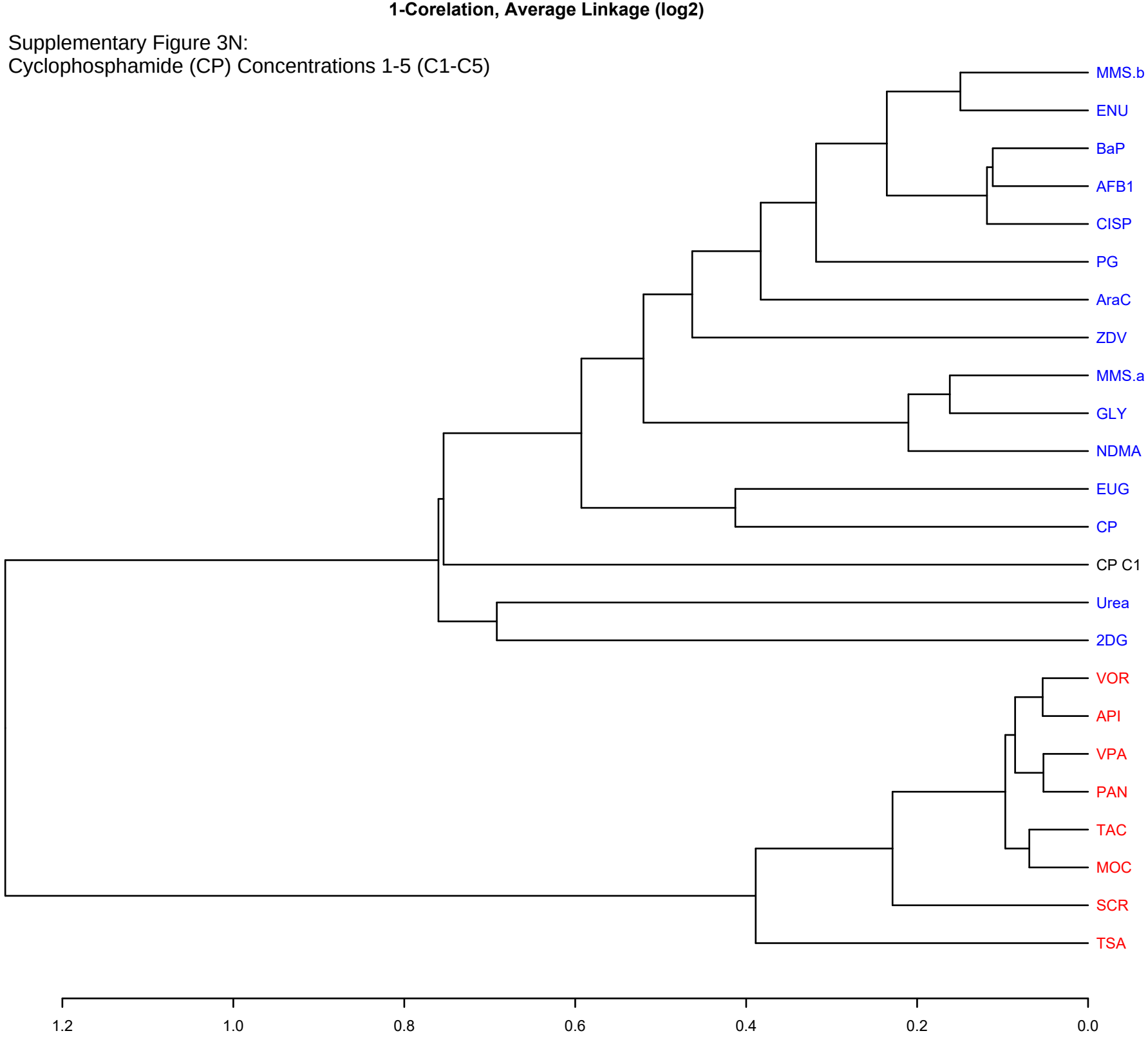


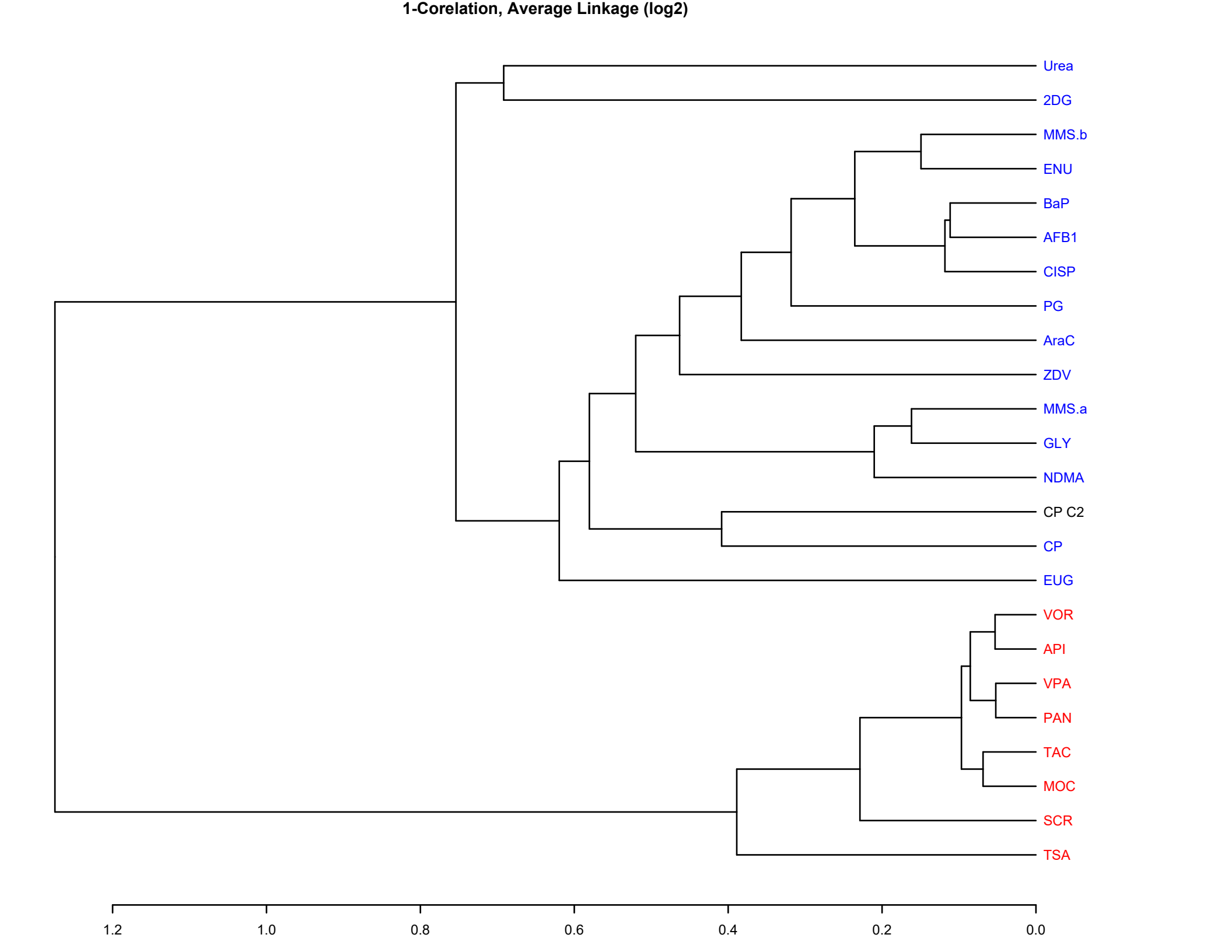

1-Corelation, Average Linkage (log2)
Urea
2DG
ZDV
AraC
BaP
AFB1
CISP
CISP C2
MMS.b
ENU
PG
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

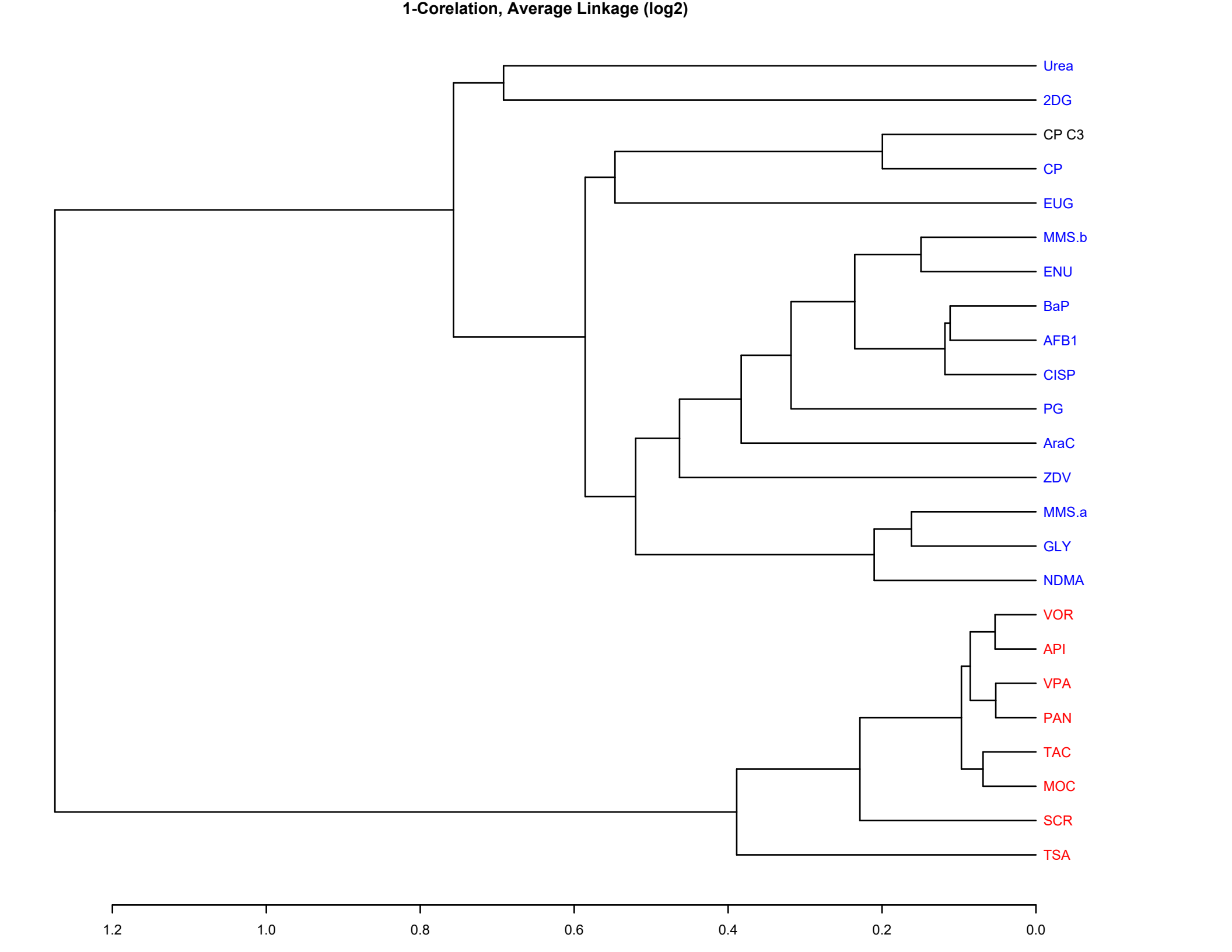

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP C3
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

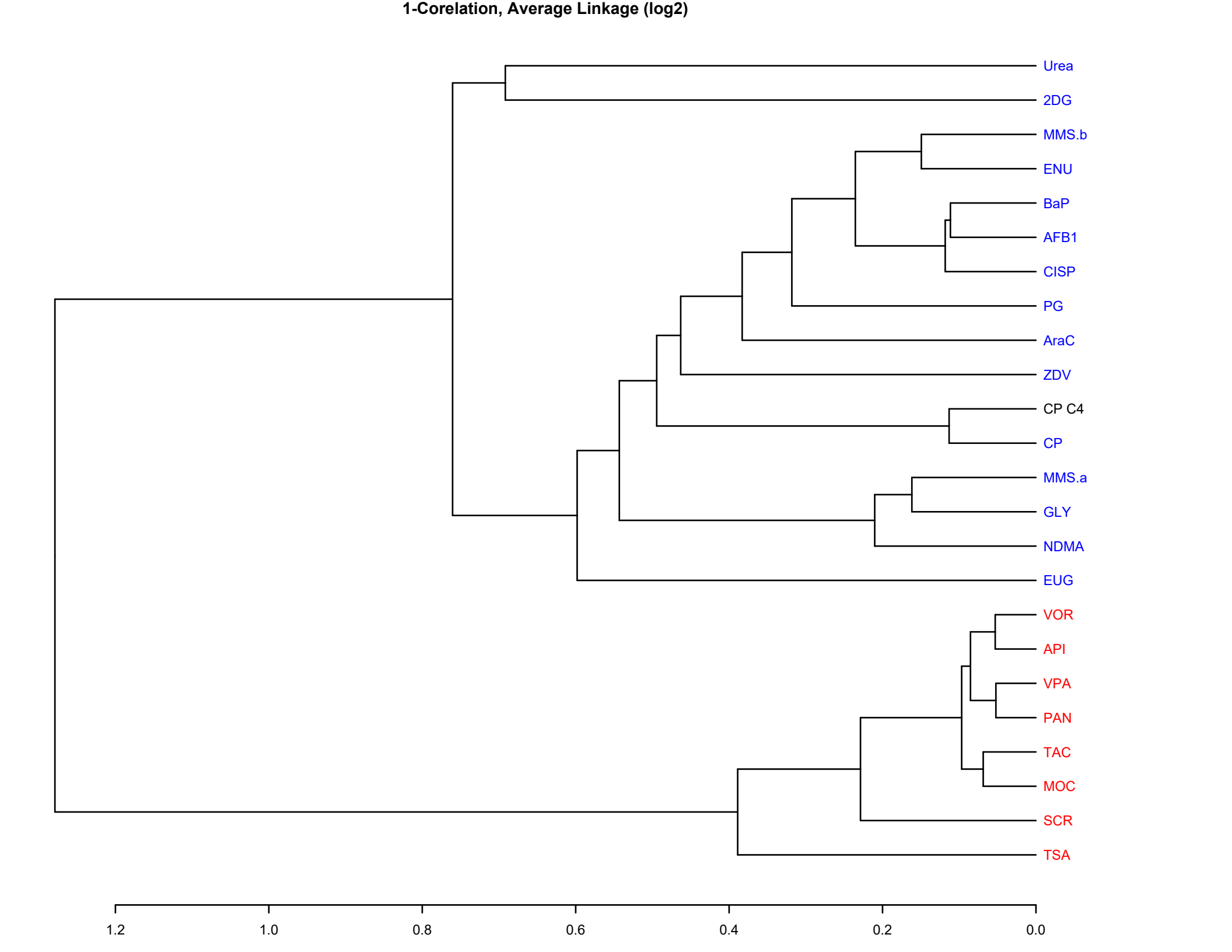

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP C4
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3N:
Cyclophosphamide (CP) Concentrations 1-5 (C1-C5)

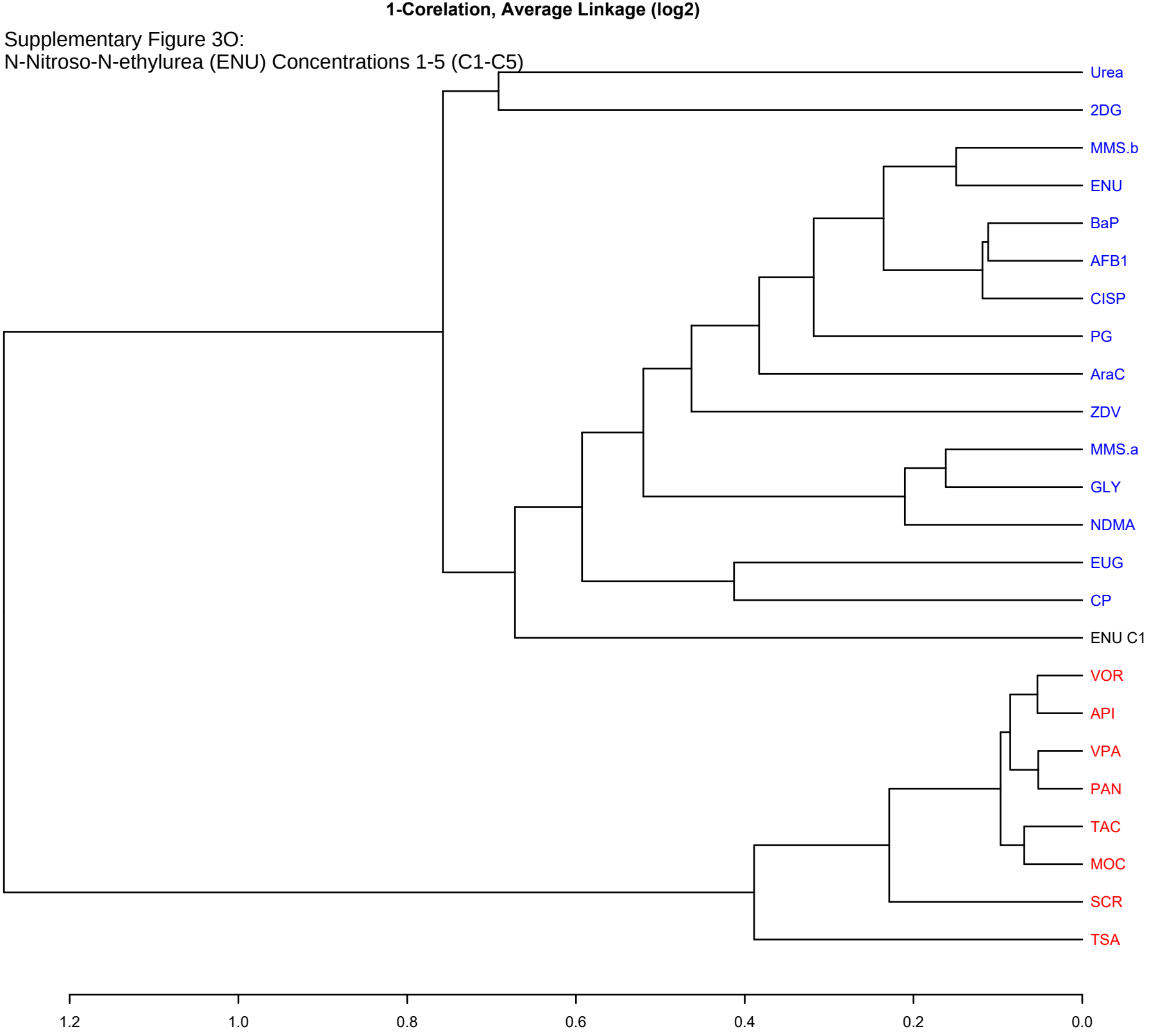


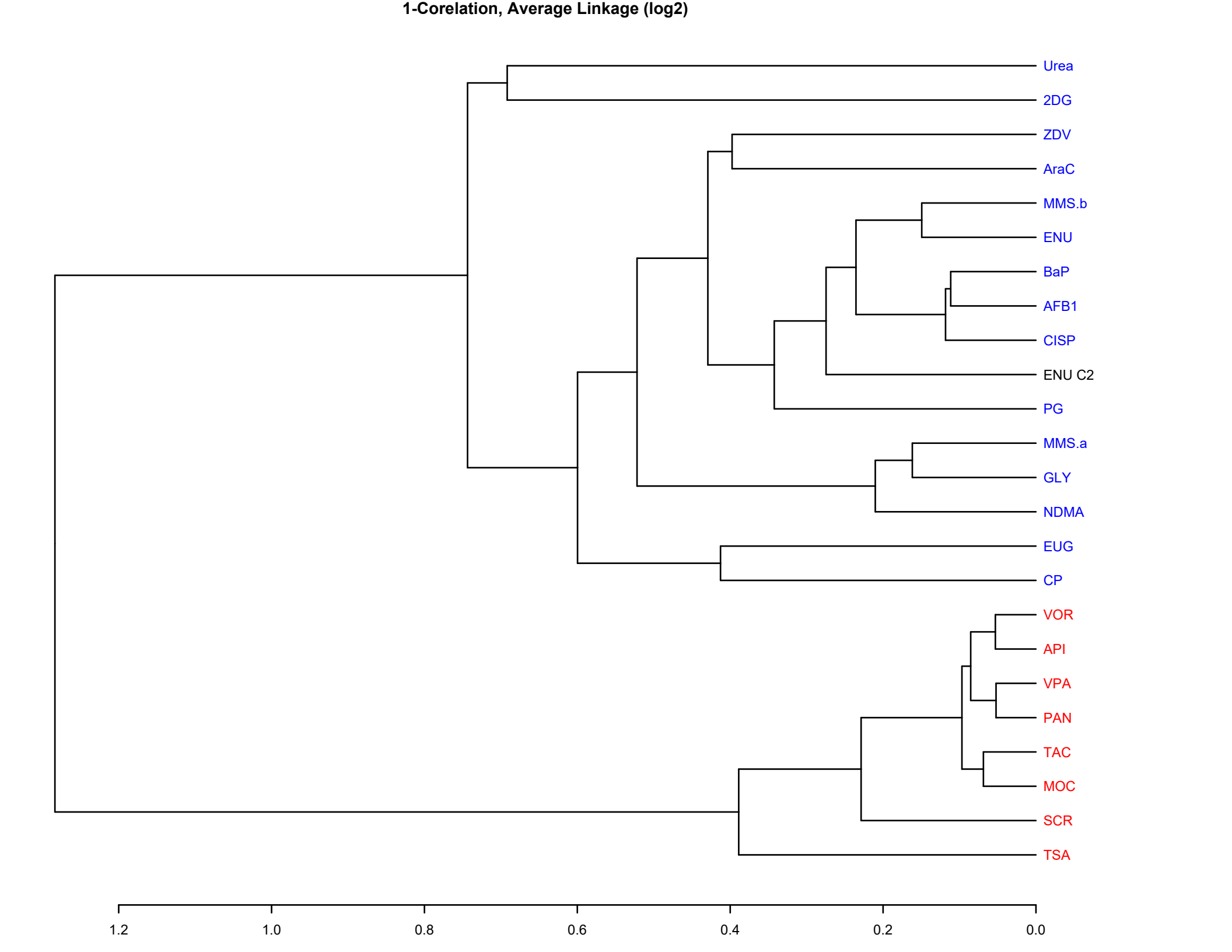

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
CP C2
CP
EUG
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

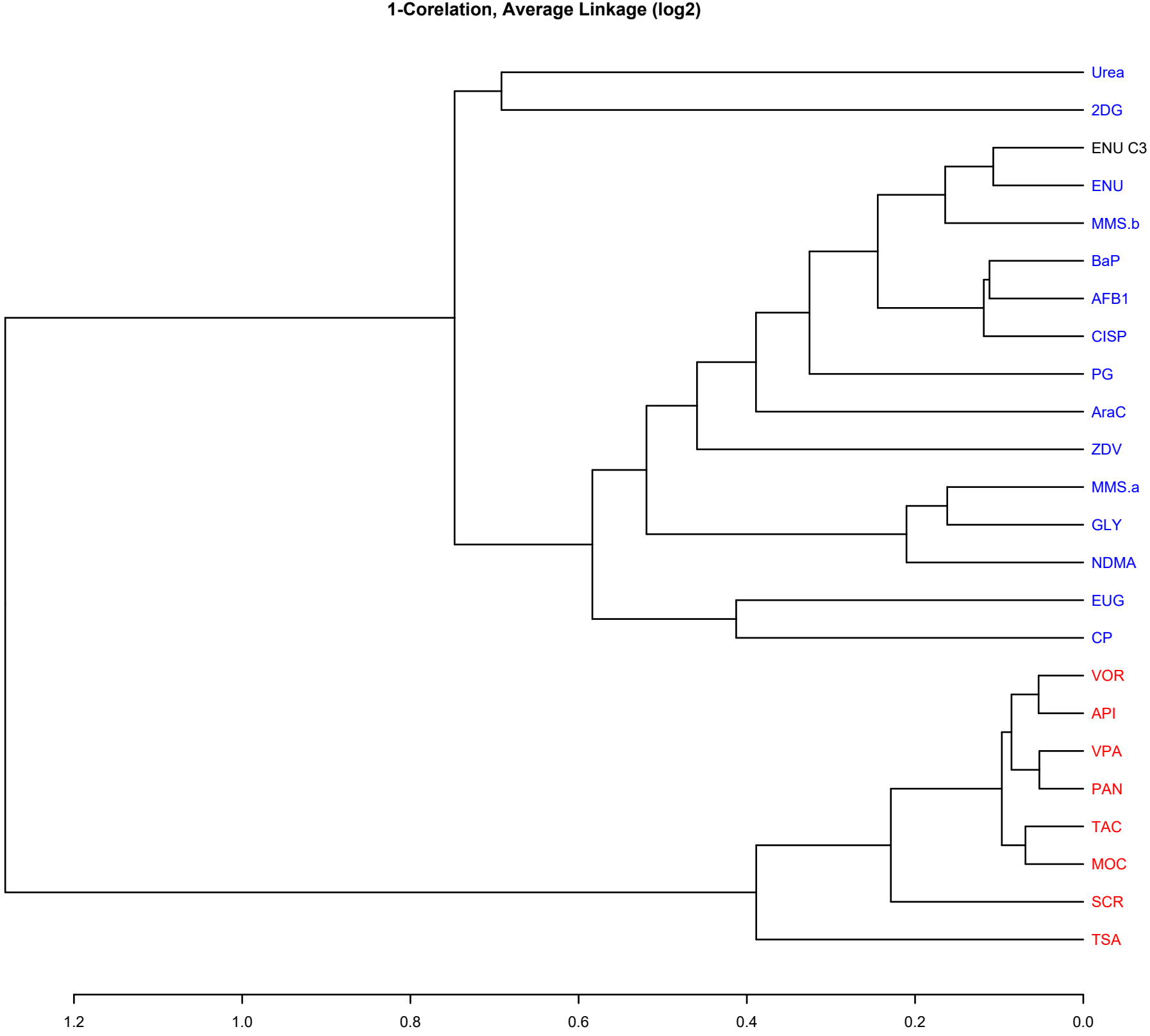

1-Corelation, Average Linkage (log2)
Urea
2DG
CP C3
CP
EUG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0


1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
CP C4
CP
MMS.a
GLY
NDMA
EUG
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

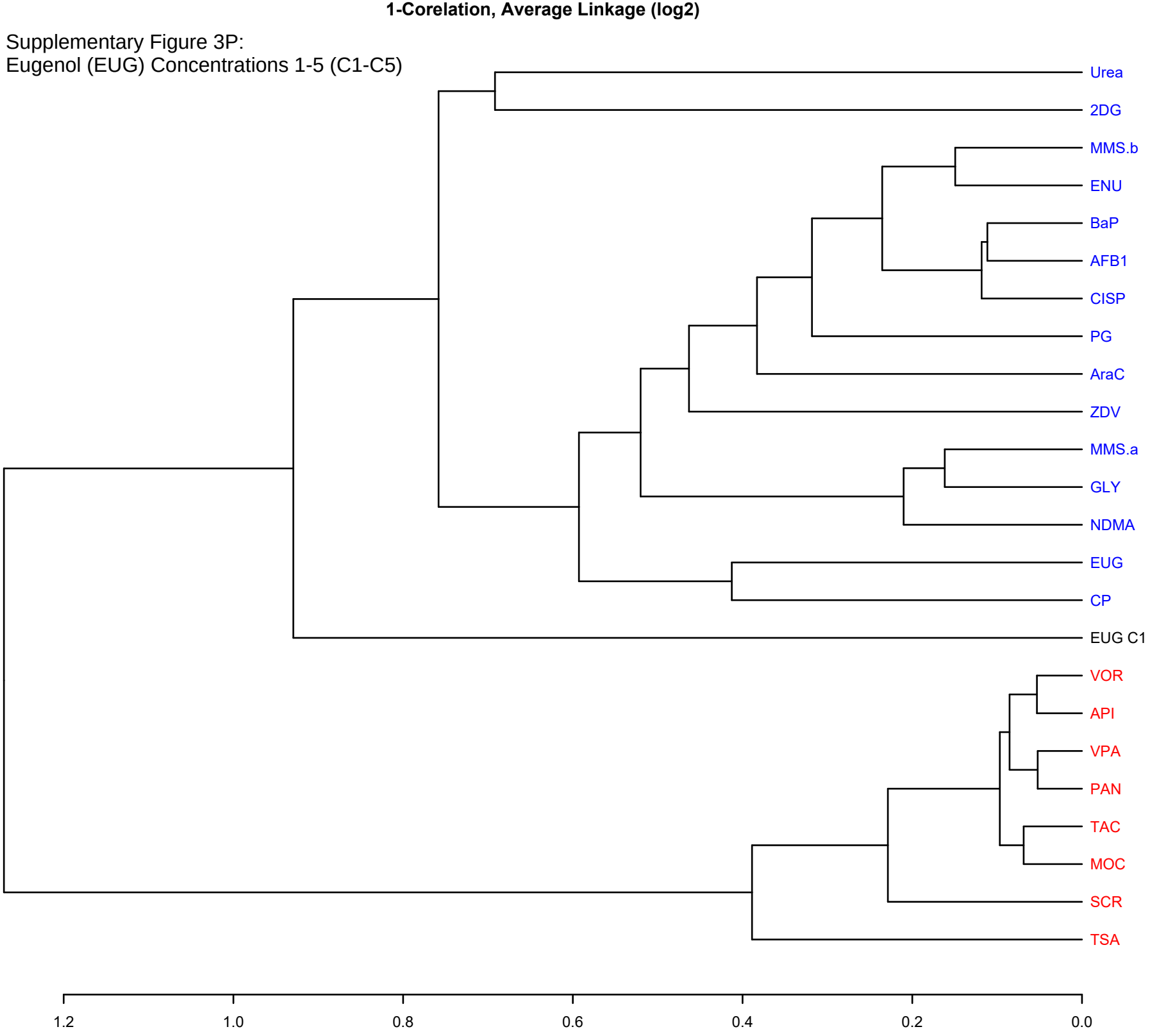
Supplementary Figure 3O:
N-Nitroso-N-ethylurea (ENU) Concentrations 1-5 (C1-C5)

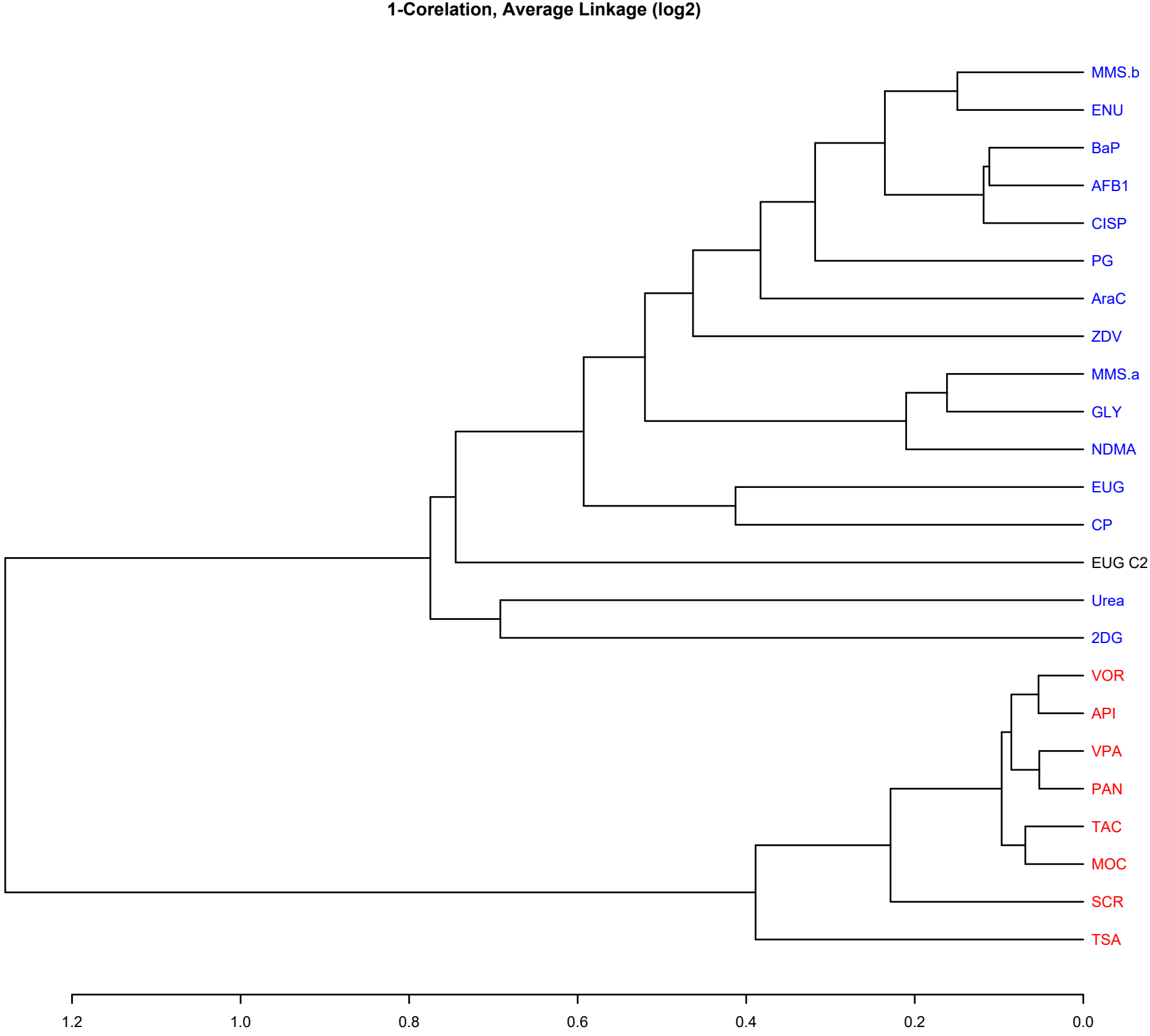


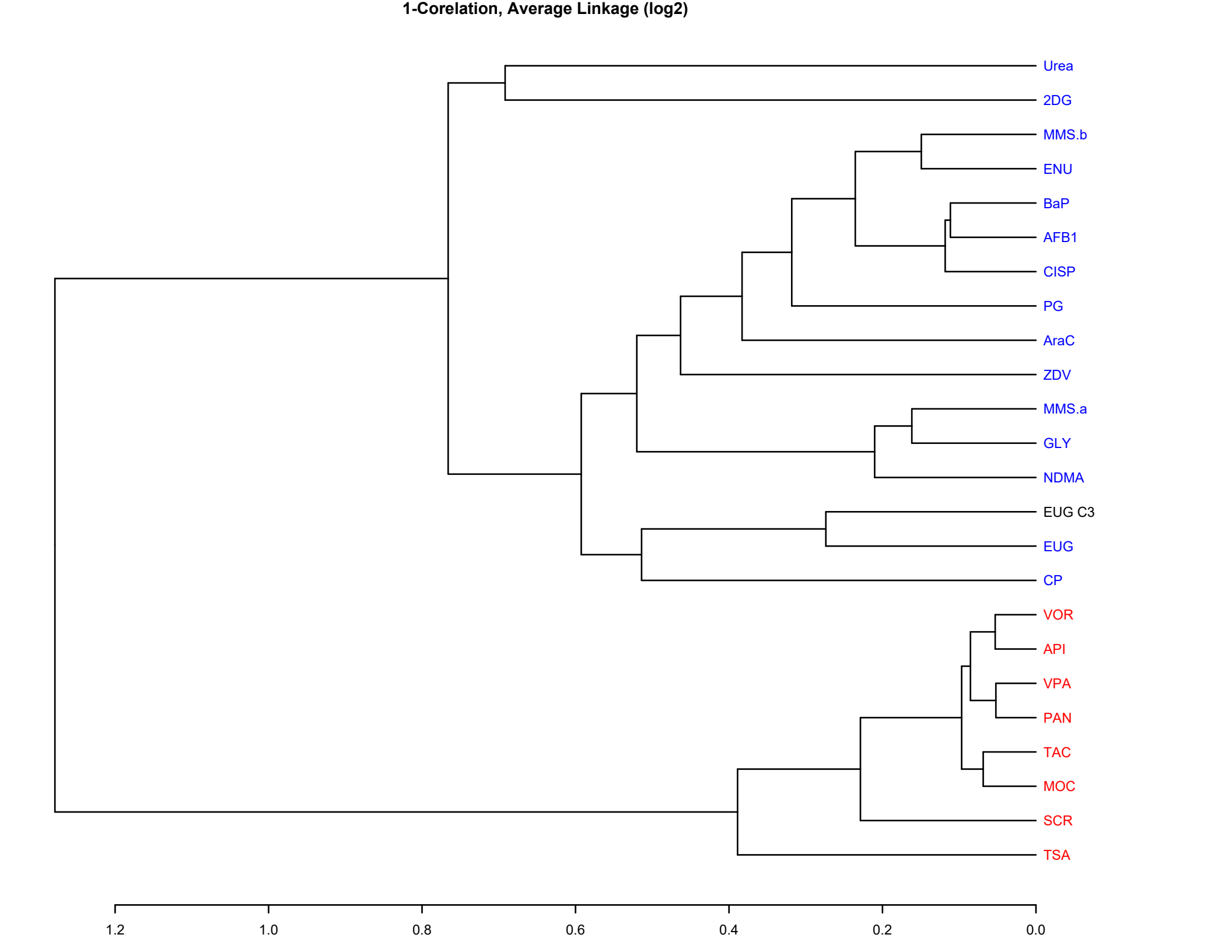

1-Corelation, Average Linkage (log2)
Urea
2DG
ZDV
AraC
MMS.b
ENU
BaP
AFB1
CISP
ENU C2
PG
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0


1-Corelation, Average Linkage (log2)
Urea
2DG
ENU C3
ENU
MMS.b
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

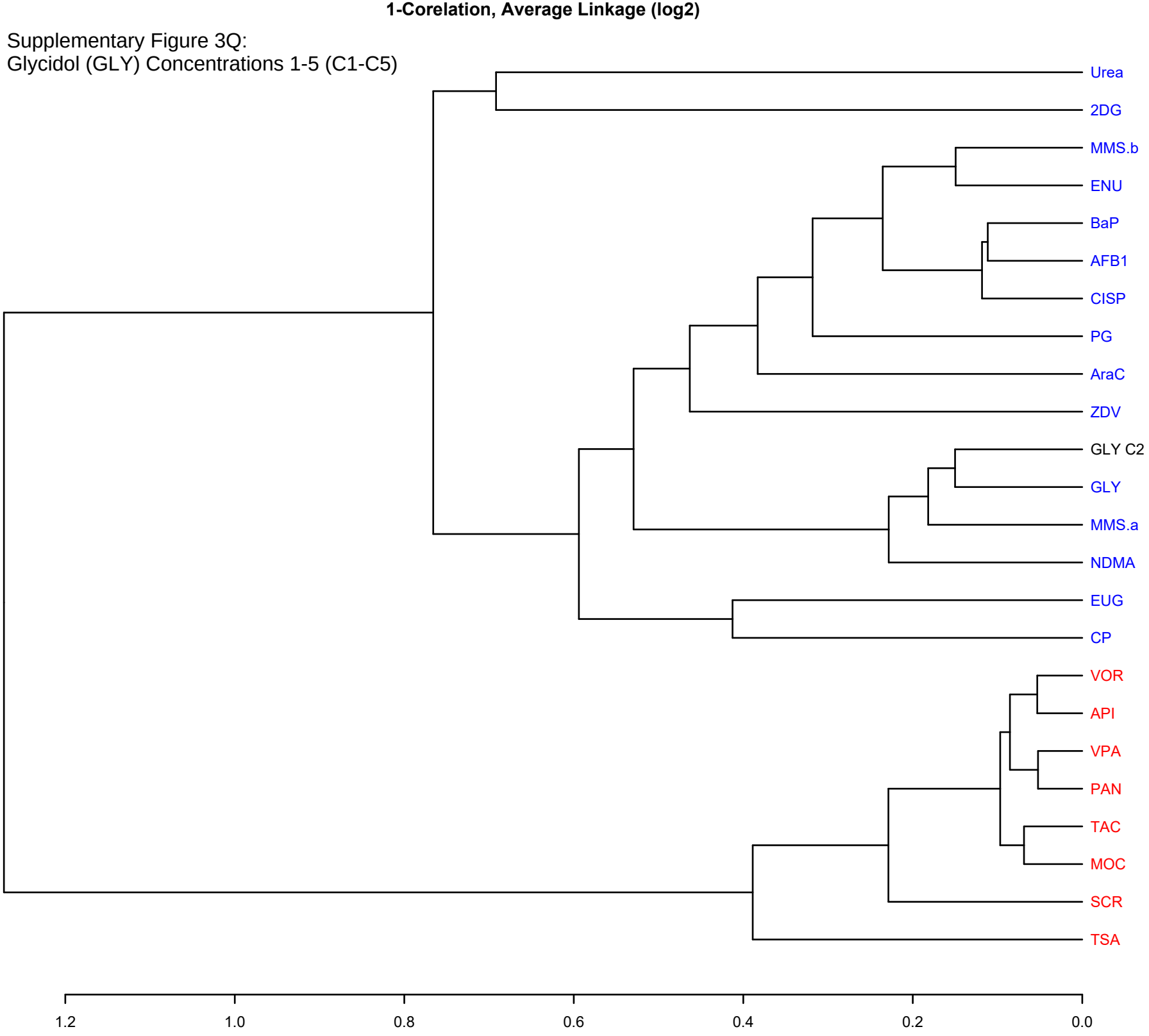
Supplementary Figure 3P:
Eugenol (EUG) Concentrations 1-5 (C1-C5)

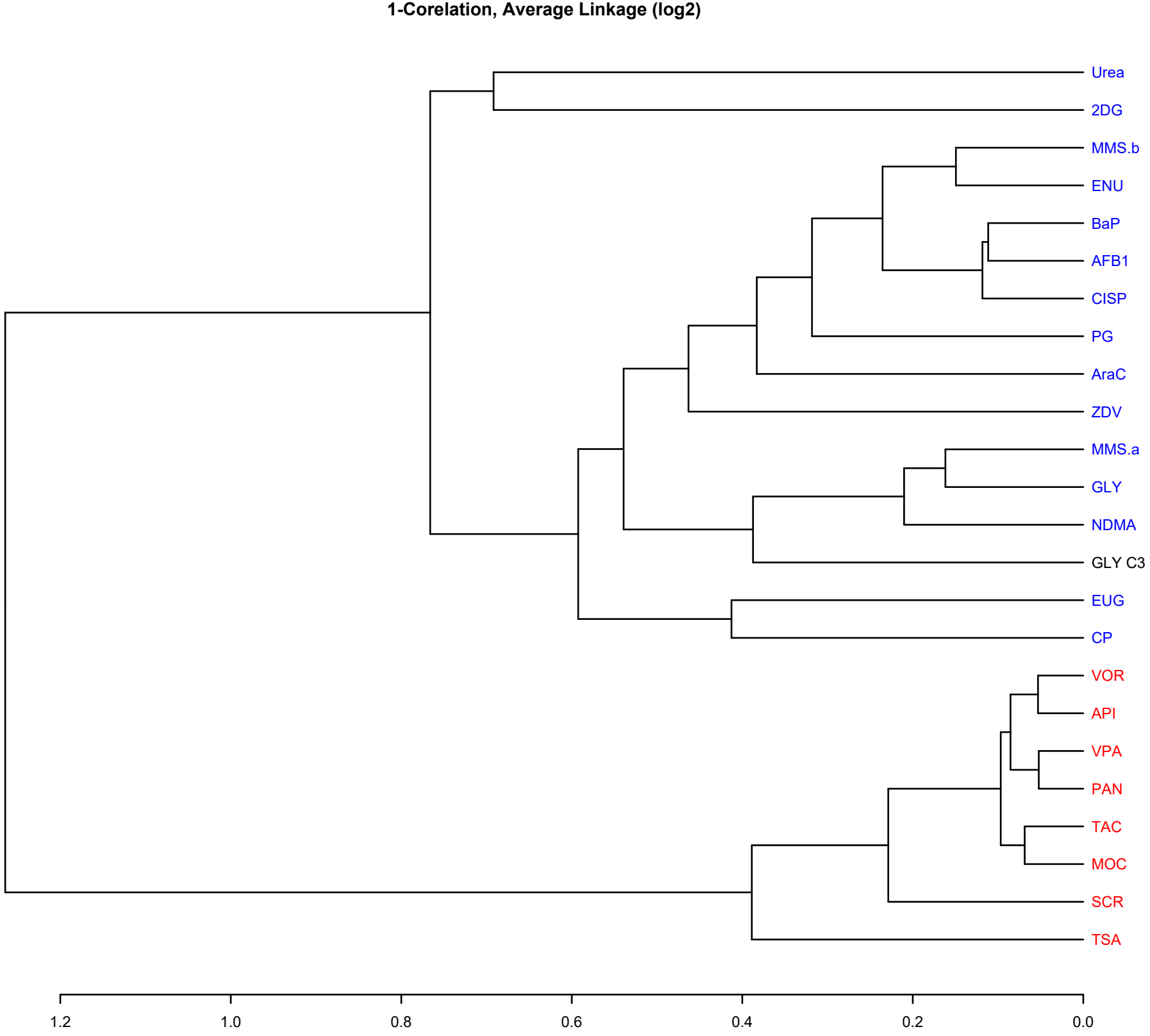


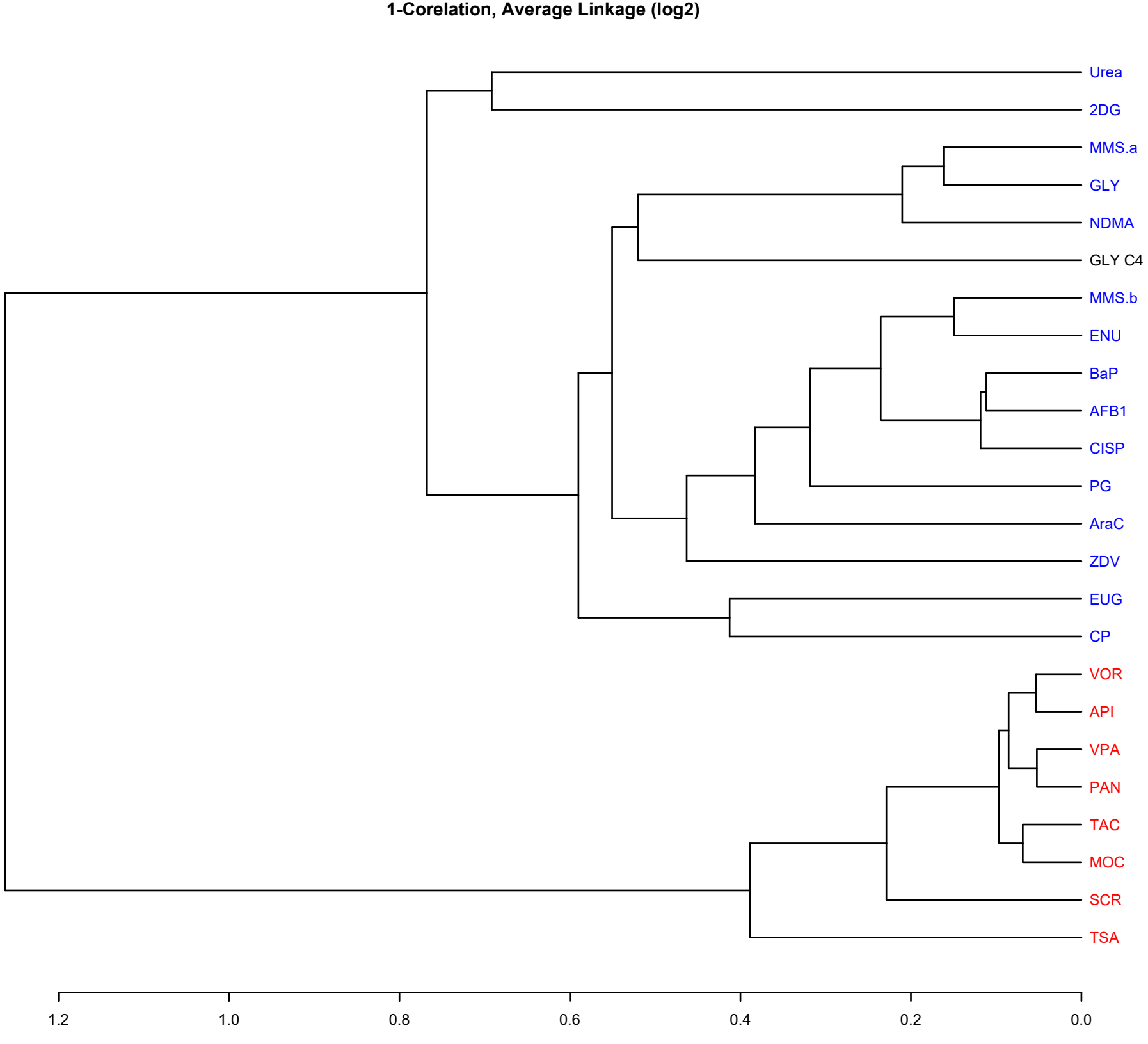

1-Corelation, Average Linkage (log2)
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
EUG C2
Urea
2DG
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

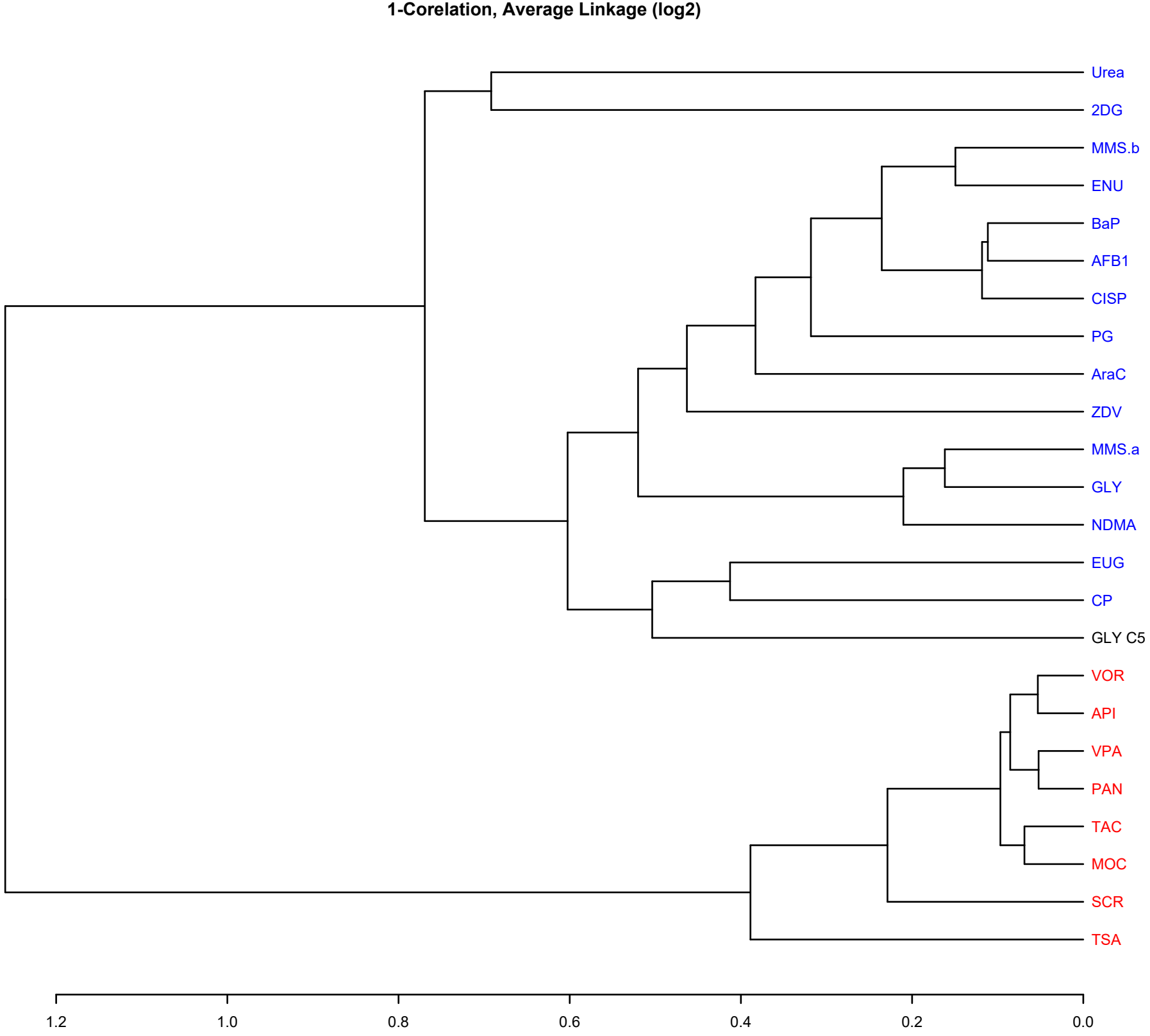

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG C3
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3Q:
Glycidol (GLY) Concentrations 1-5 (C1-C5)

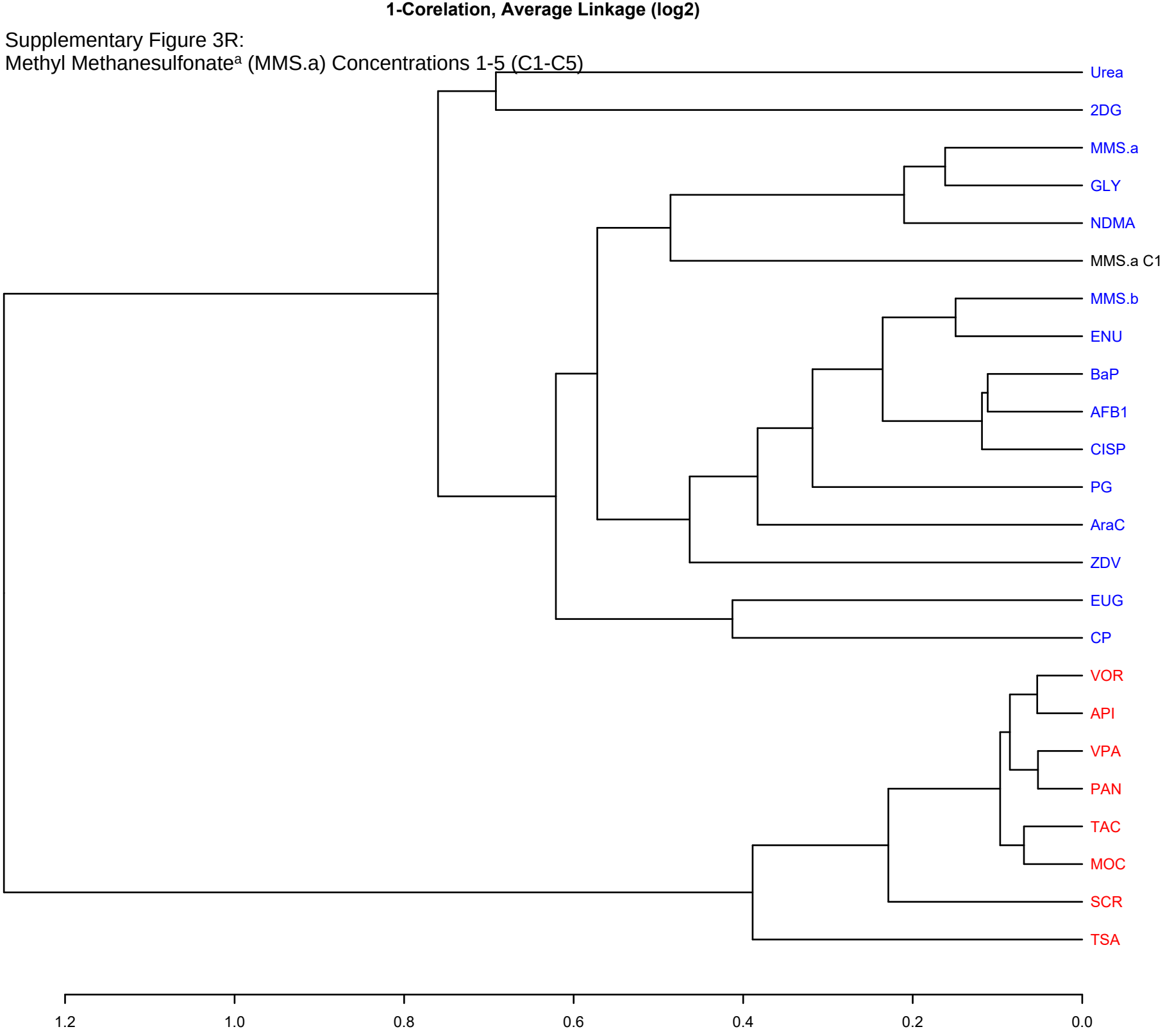


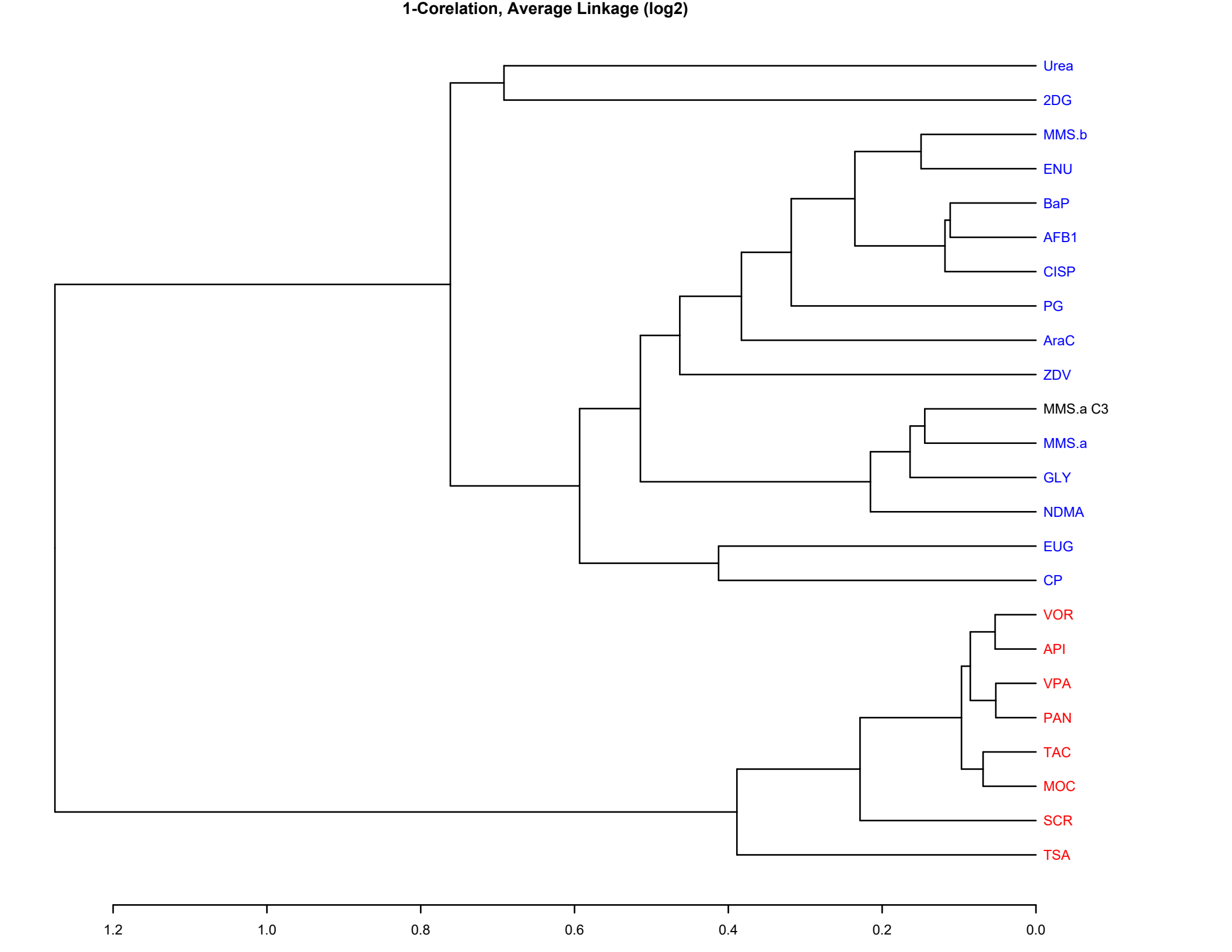

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
GLY C3
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

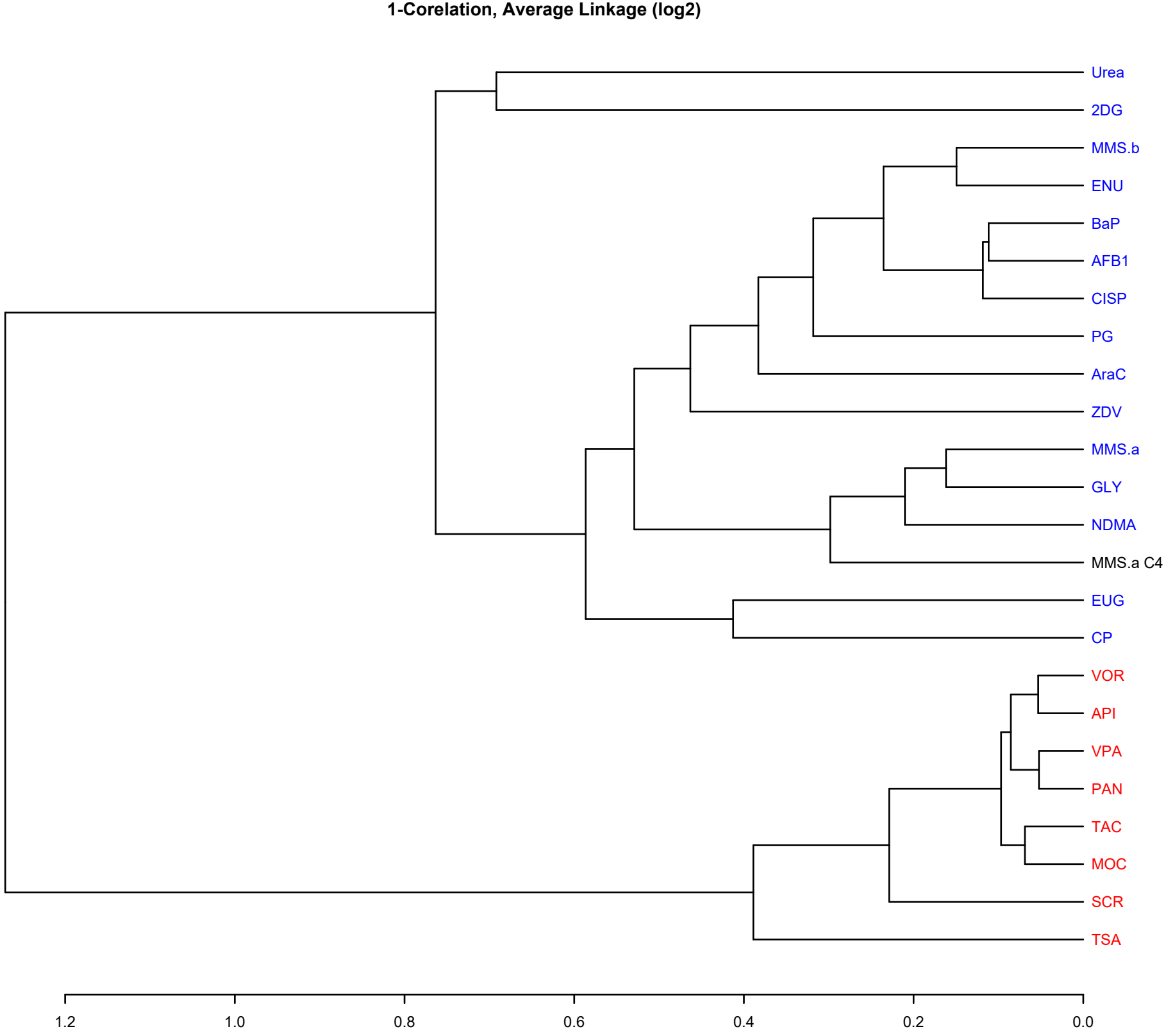

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.a
GLY
NDMA
GLY C4
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

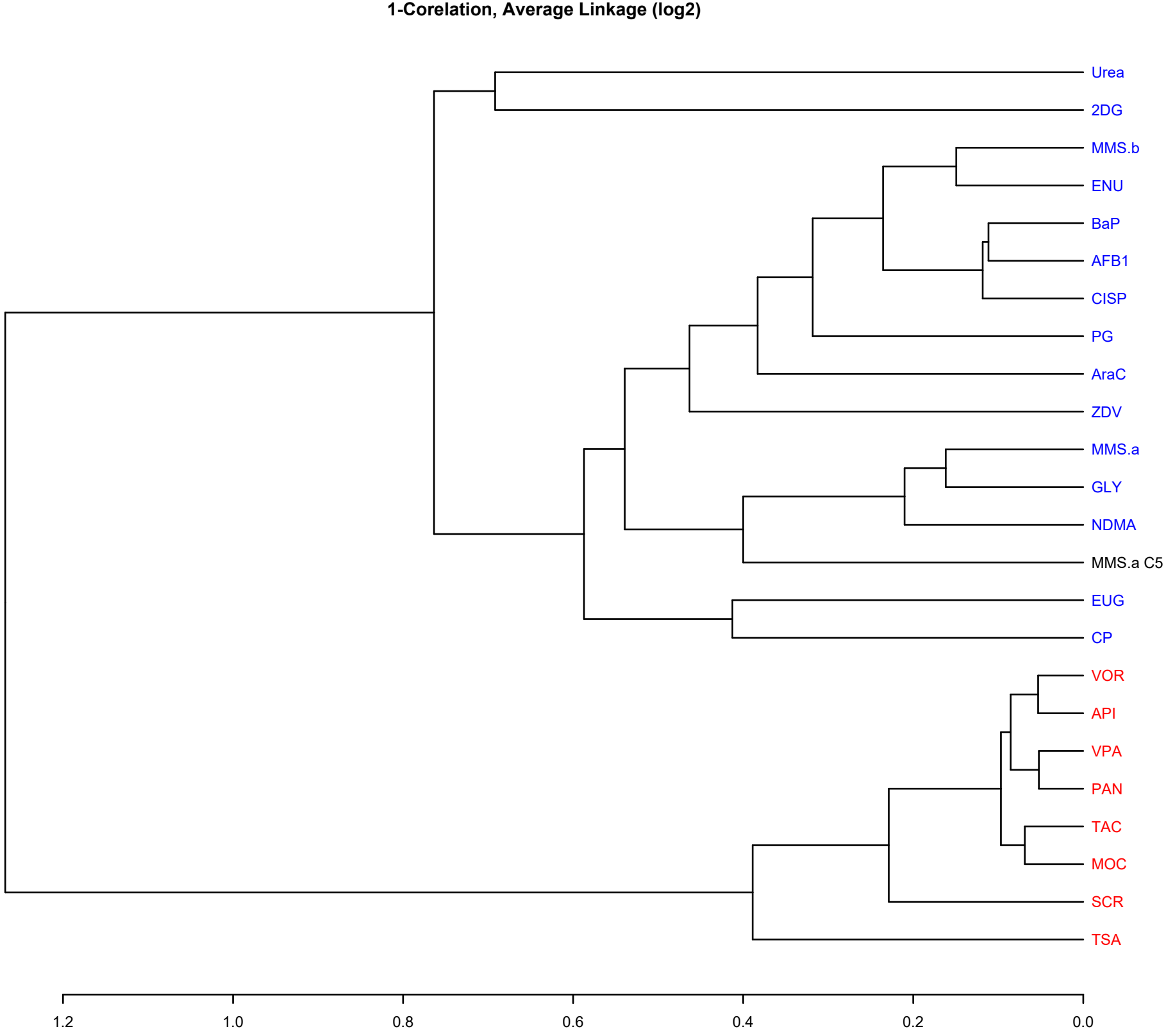

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
GLY C5
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3R:
Methyl Methanesulfonate[a] (MMS.a) Concentrations 1-5 (C1-C5)

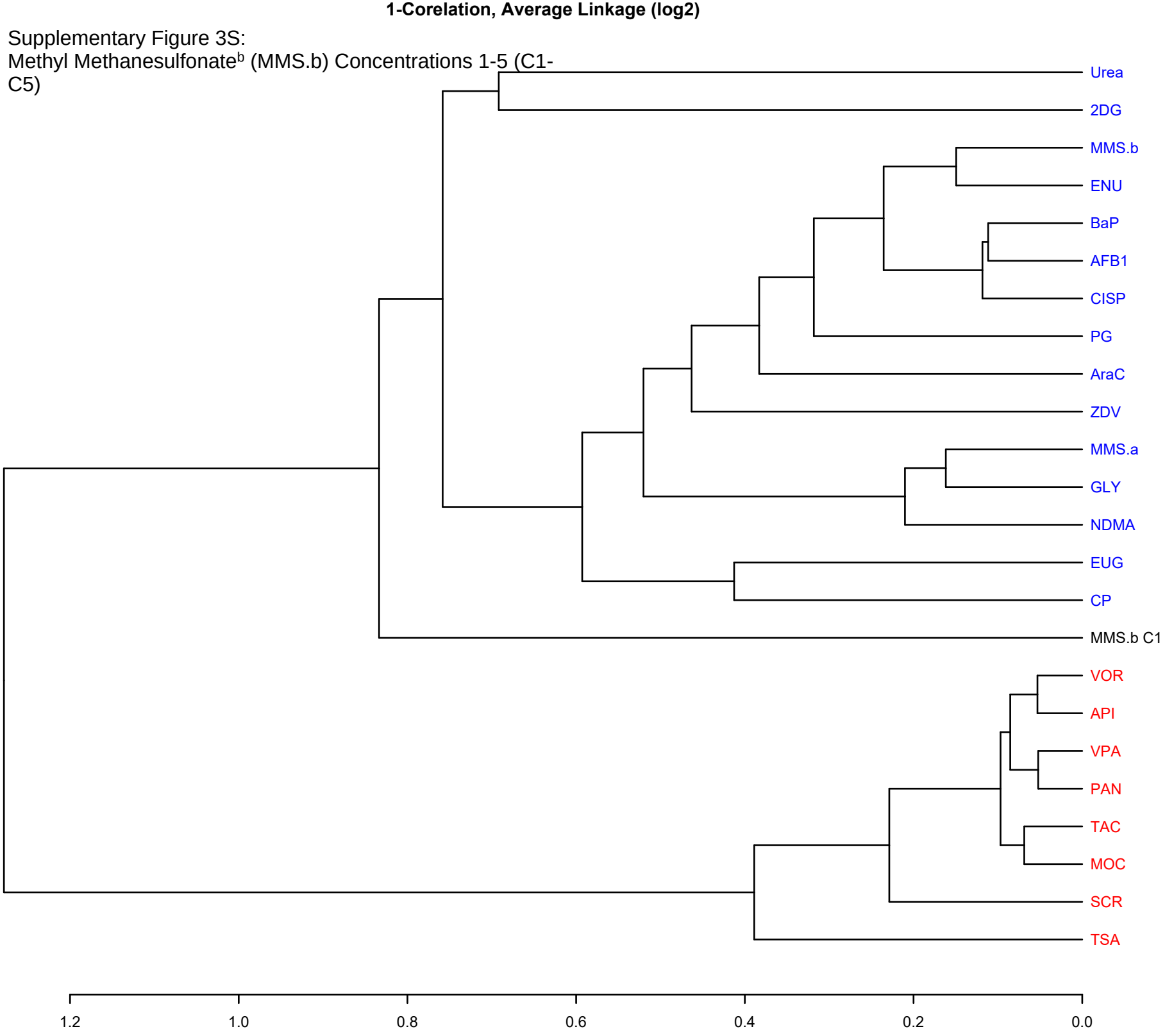


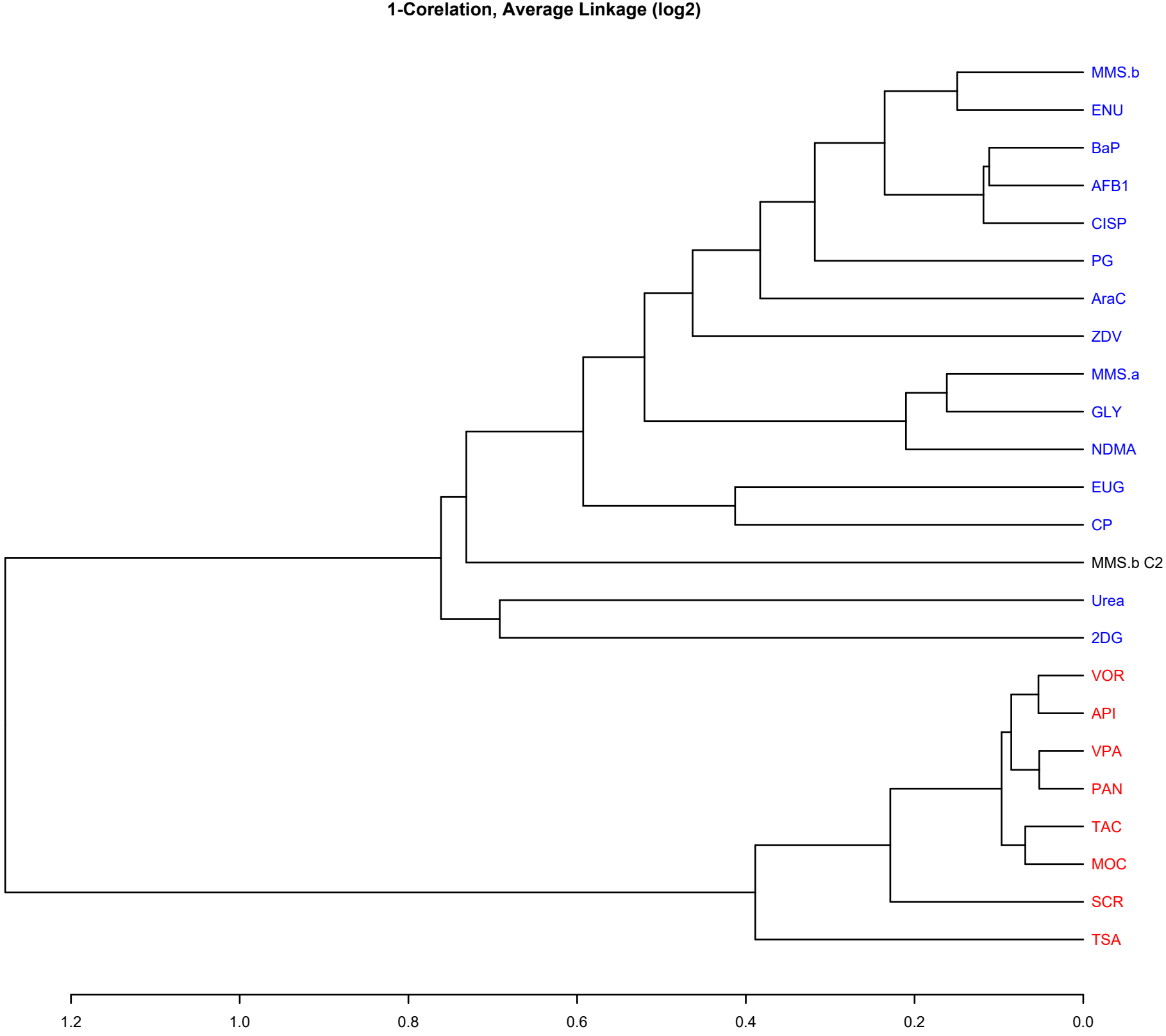

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a C3
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

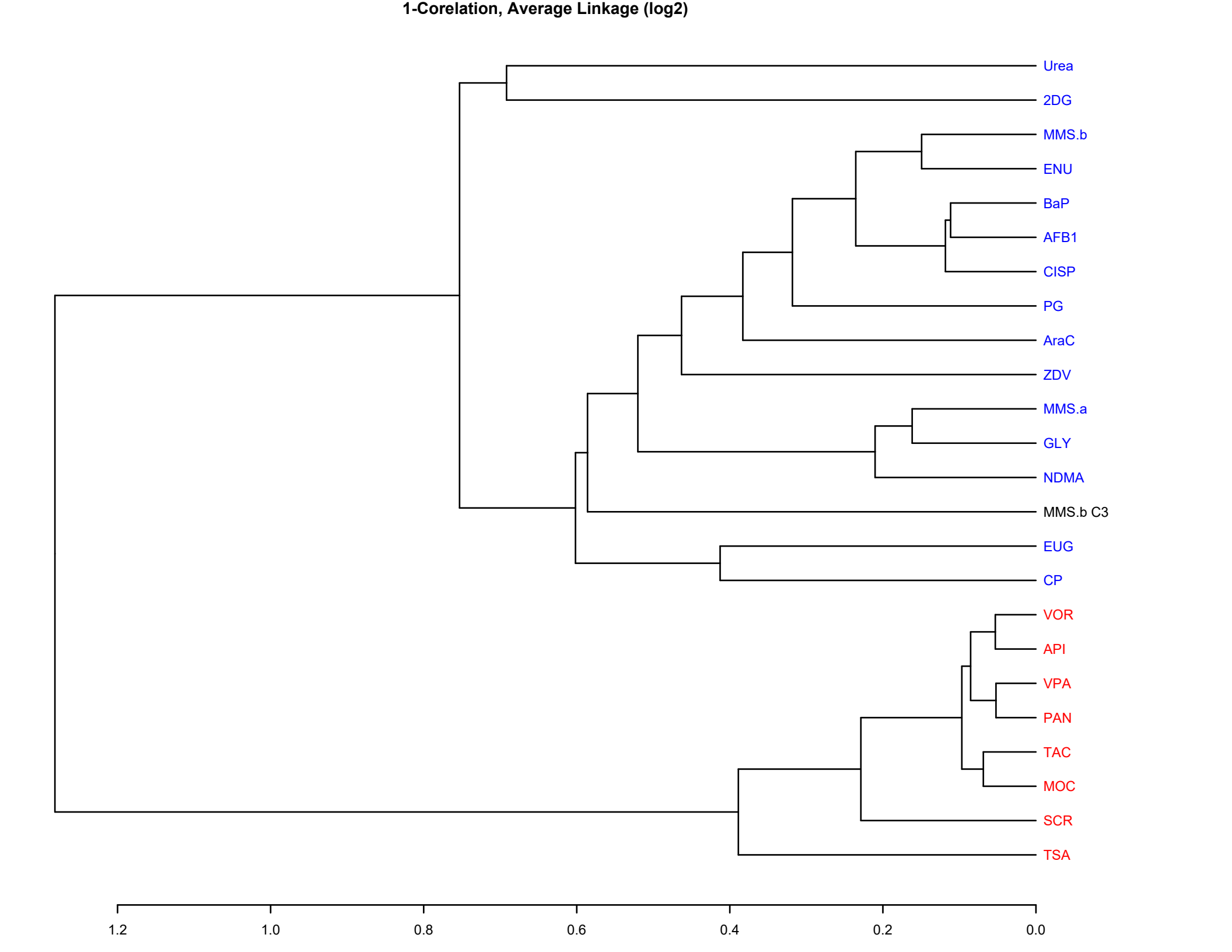

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
MMS.a C4
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

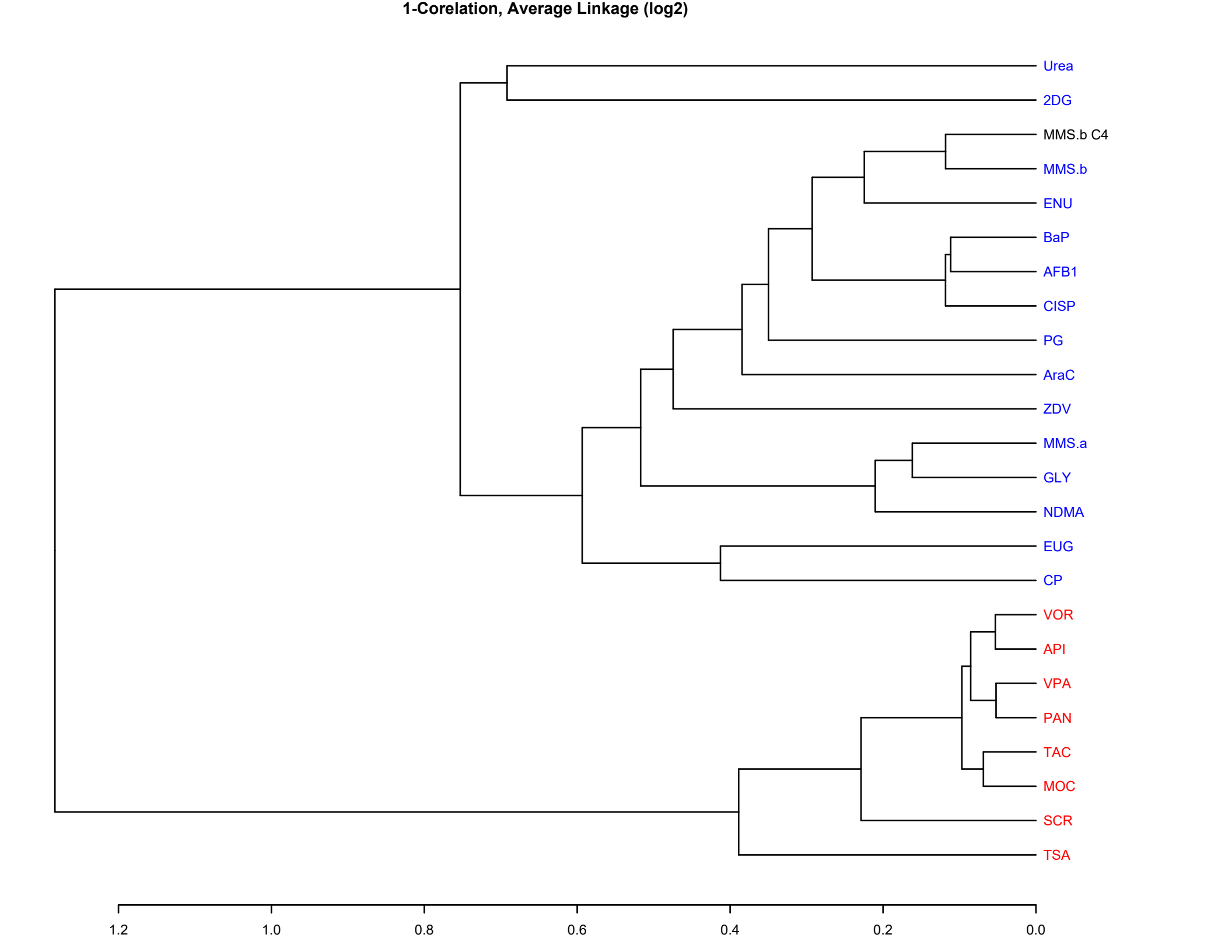

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
MMS.a C5
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3S:
Methyl Methanesulfonate[b] (MMS.b) Concentrations 1-5 (C1-C5)

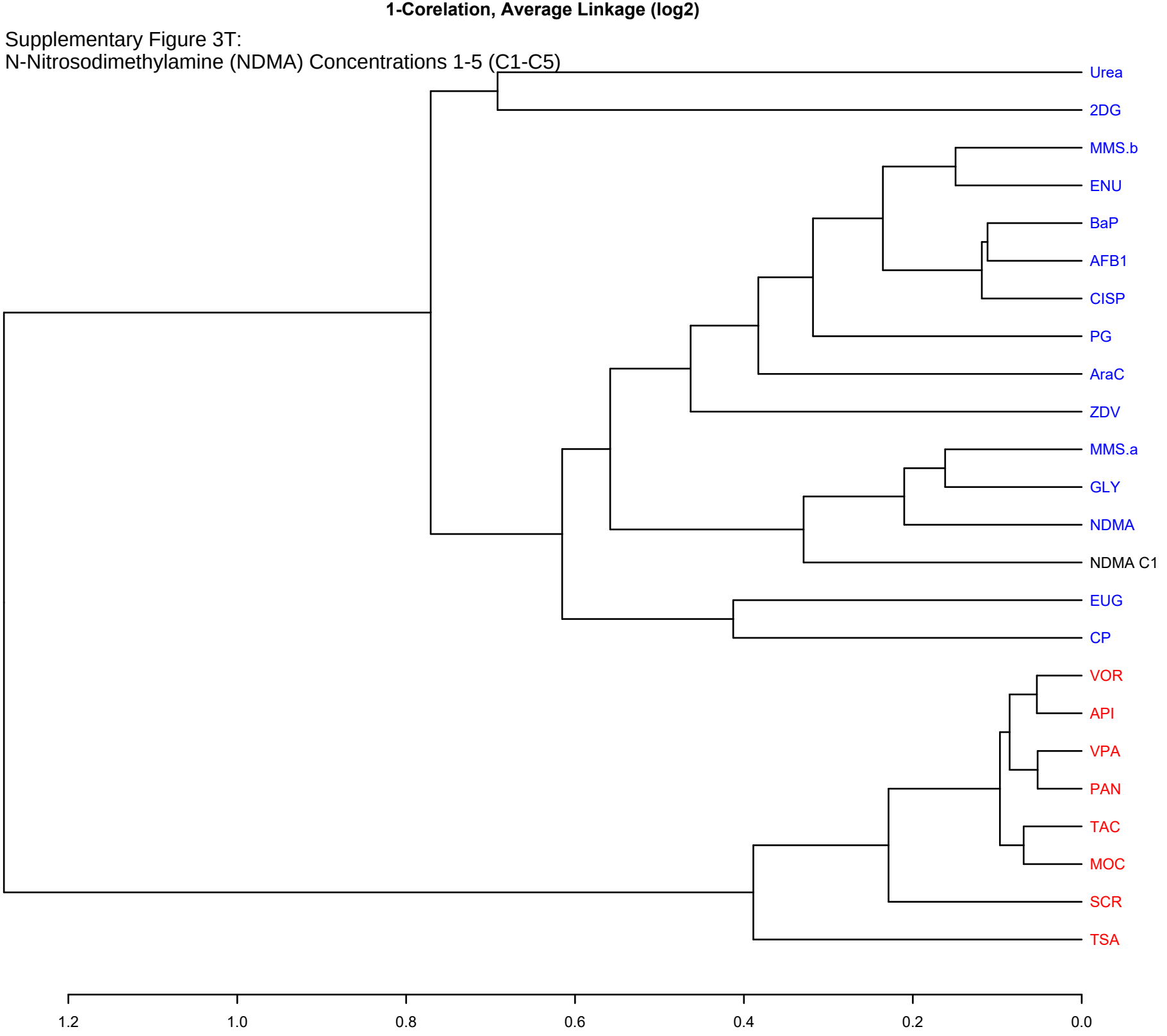


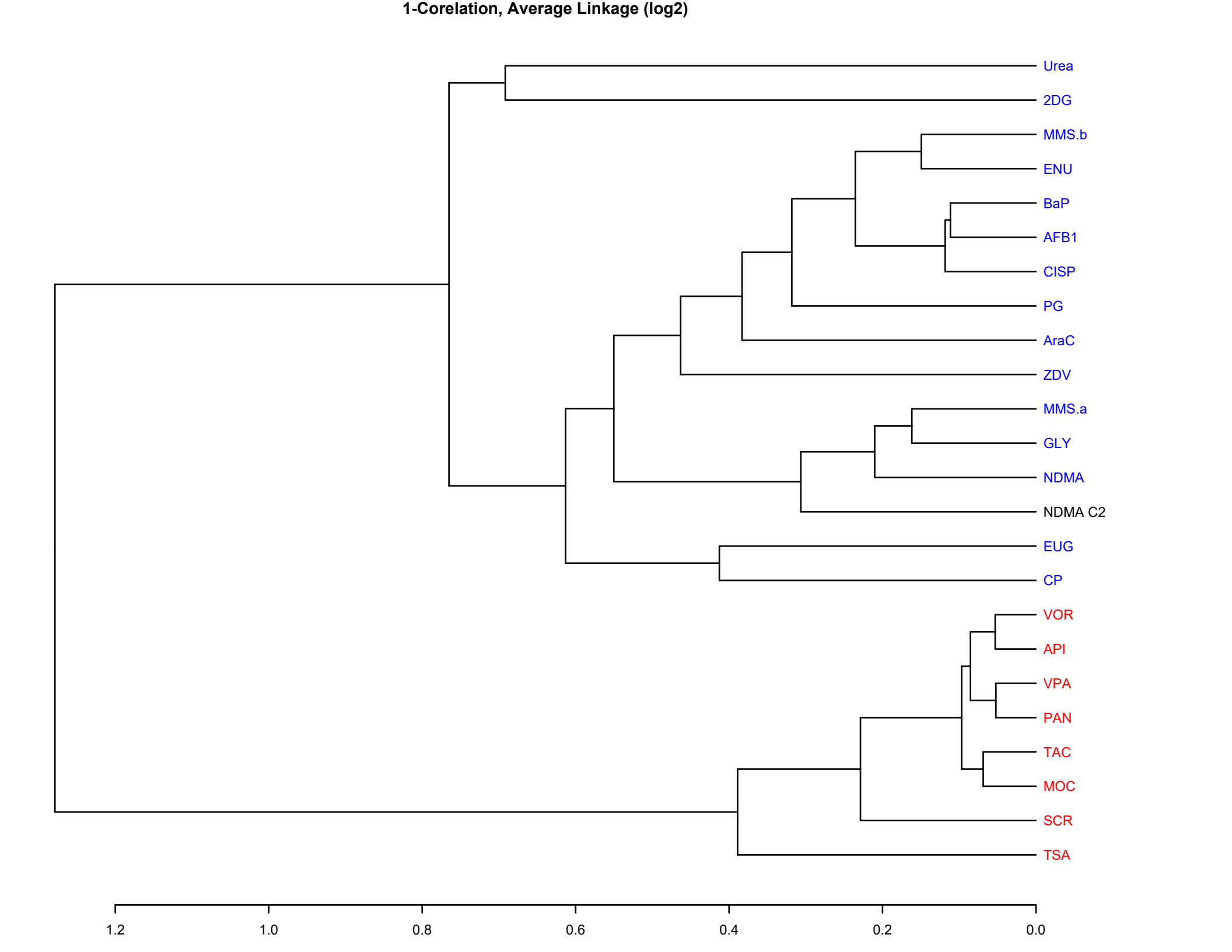

1-Corelation, Average Linkage (log2)
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
MMS.b C2
Urea
2DG
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

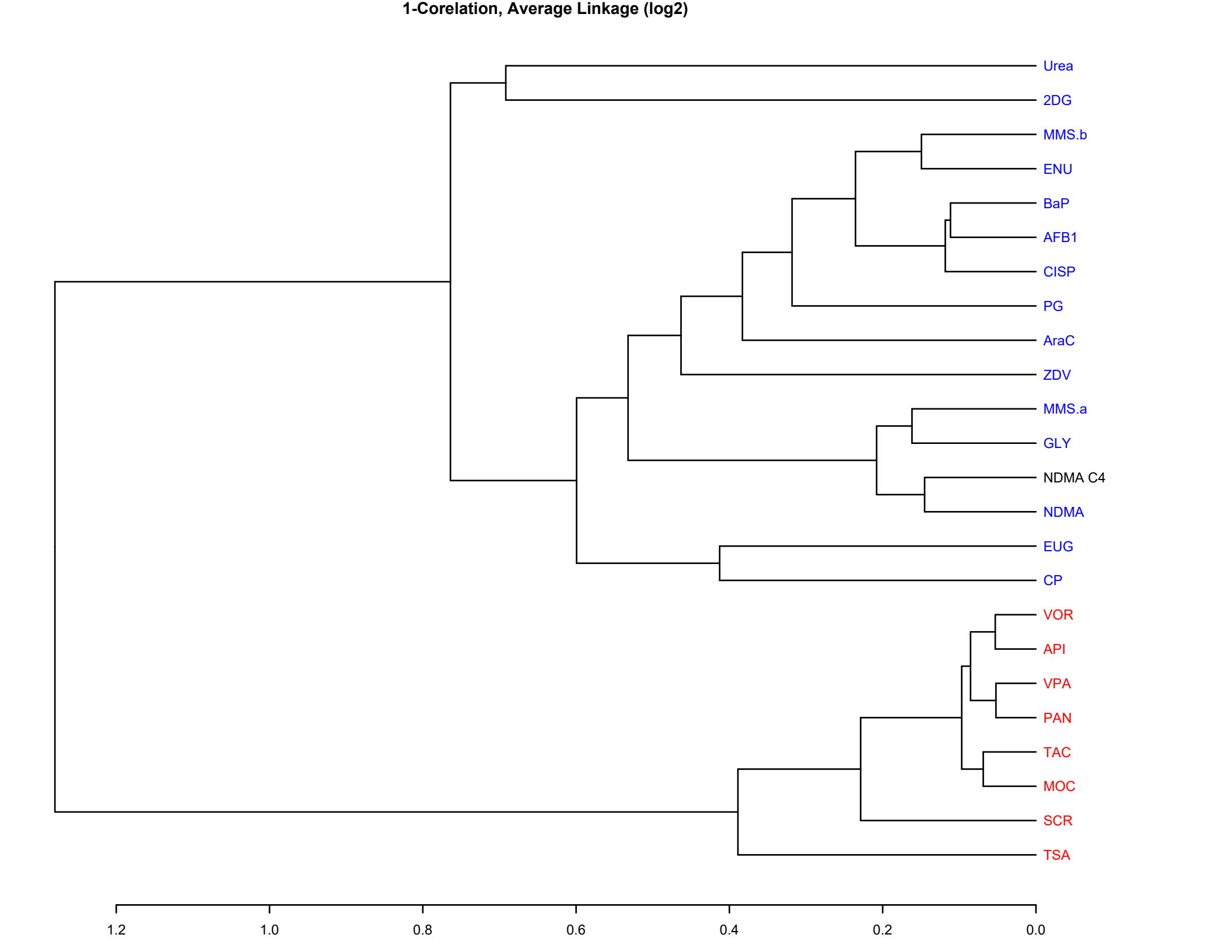

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
MMS.b C3
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

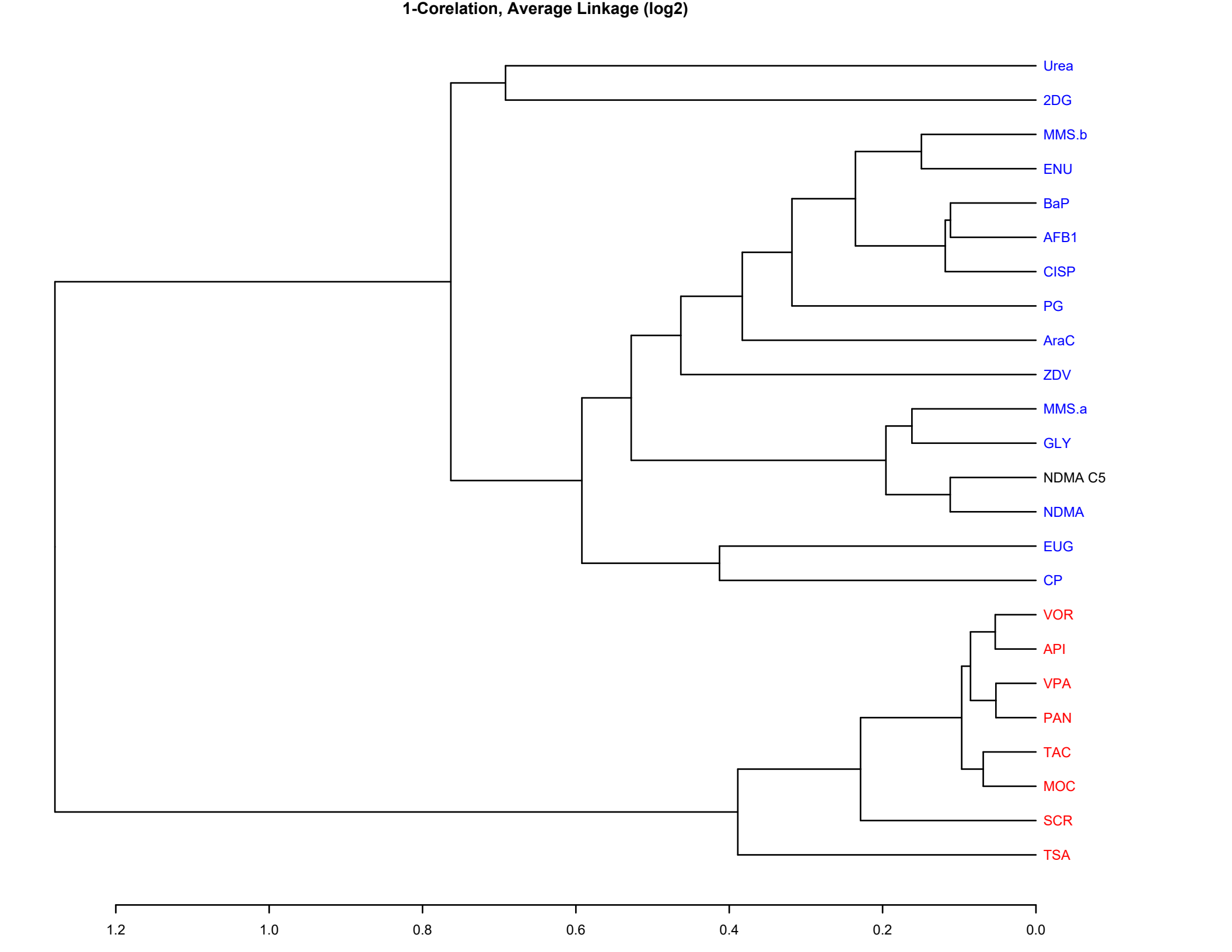

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b C4
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3T:
N-Nitrosodimethylamine (NDMA) Concentrations 1-5 (C1-C5)

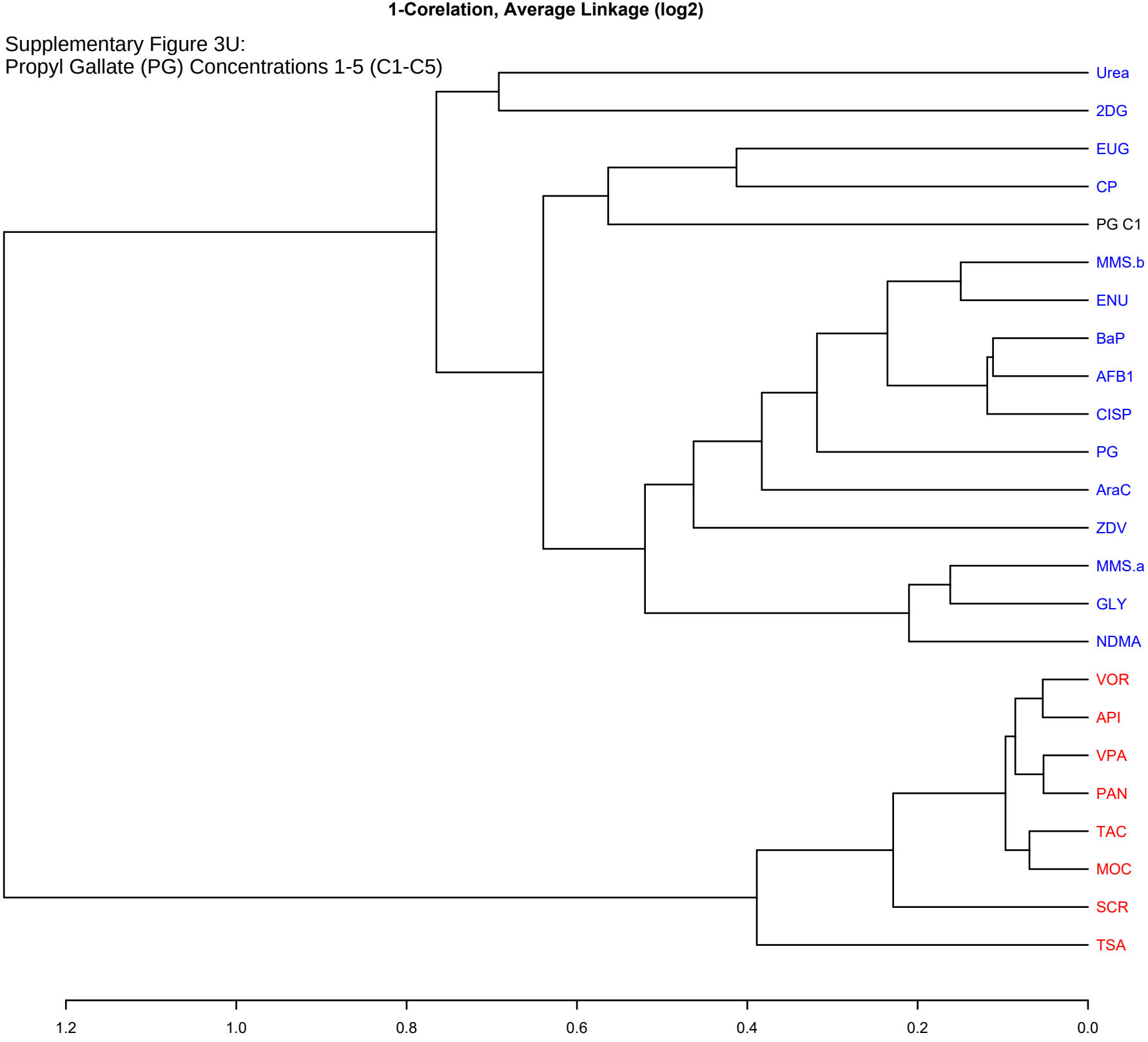


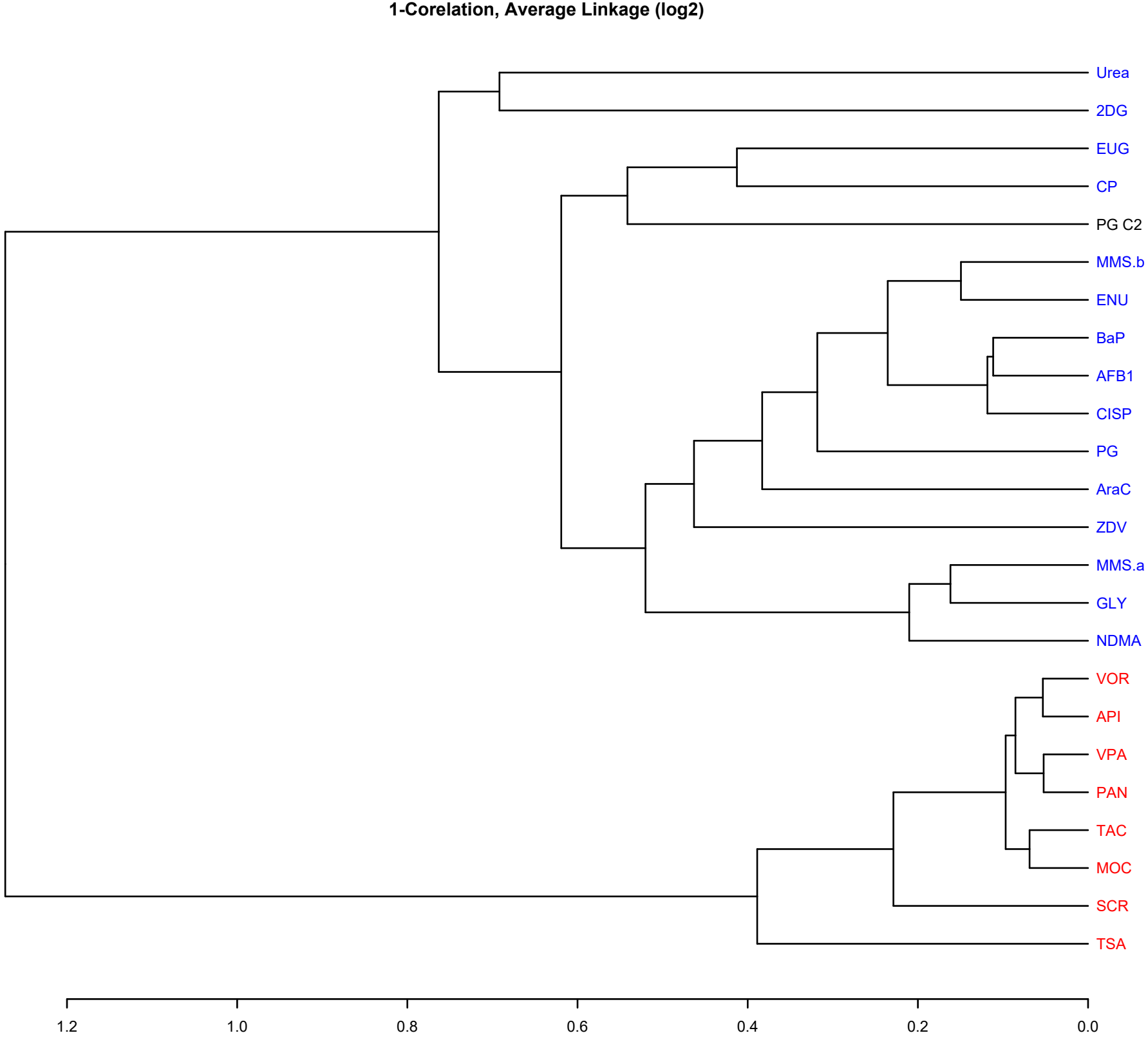

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
NDMA C2
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

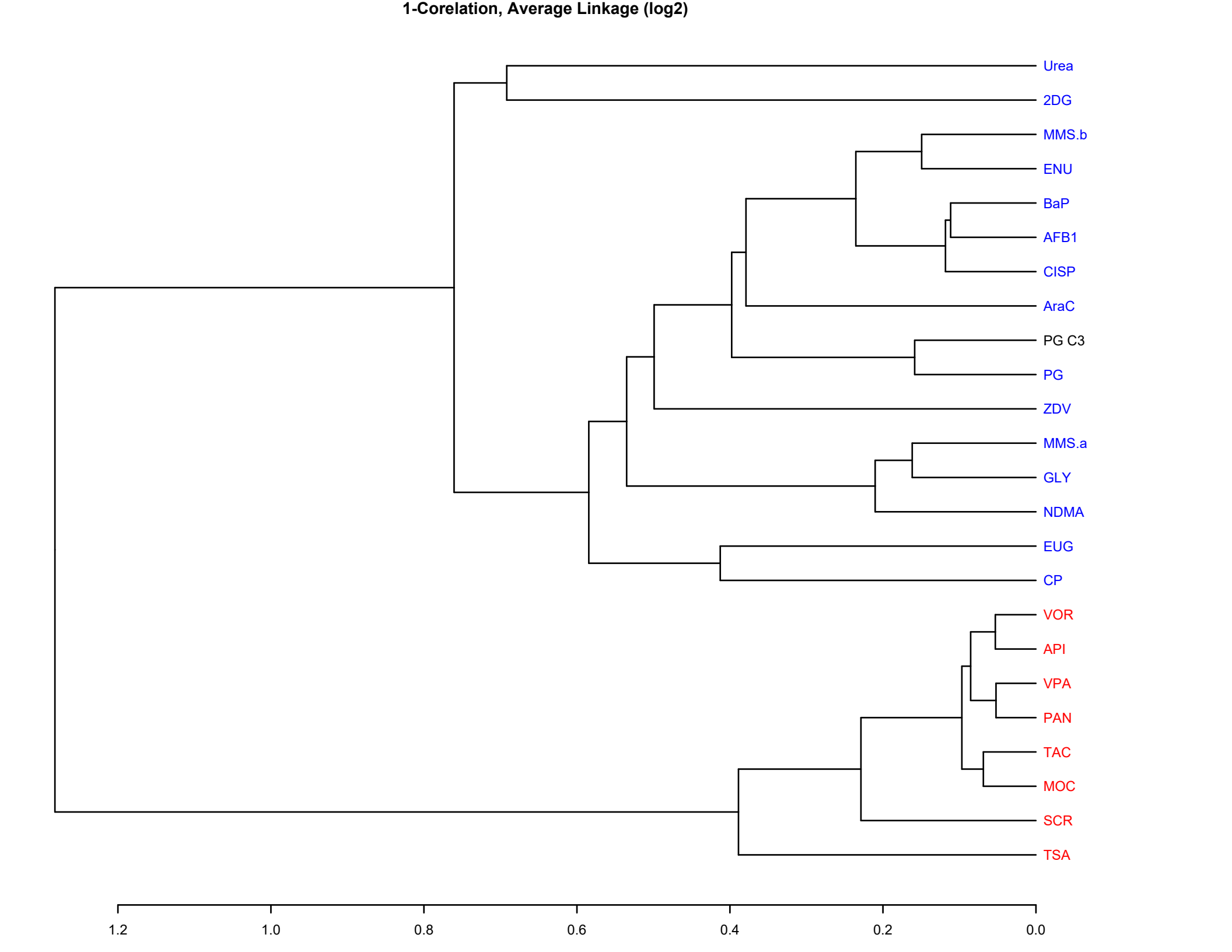

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA C4
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0


1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA C5
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3U:
Propyl Gallate (PG) Concentrations 1-5 (C1-C5)

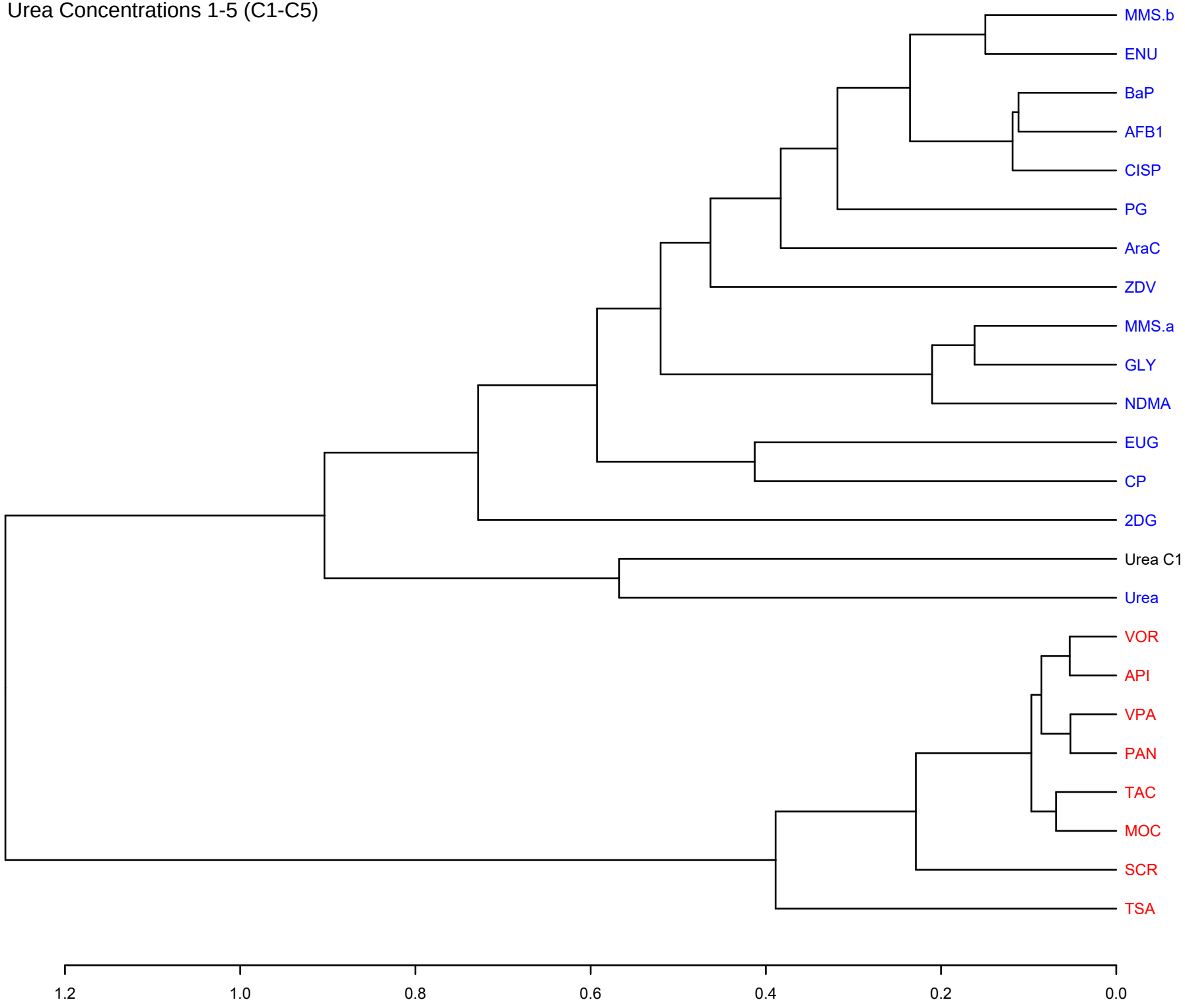


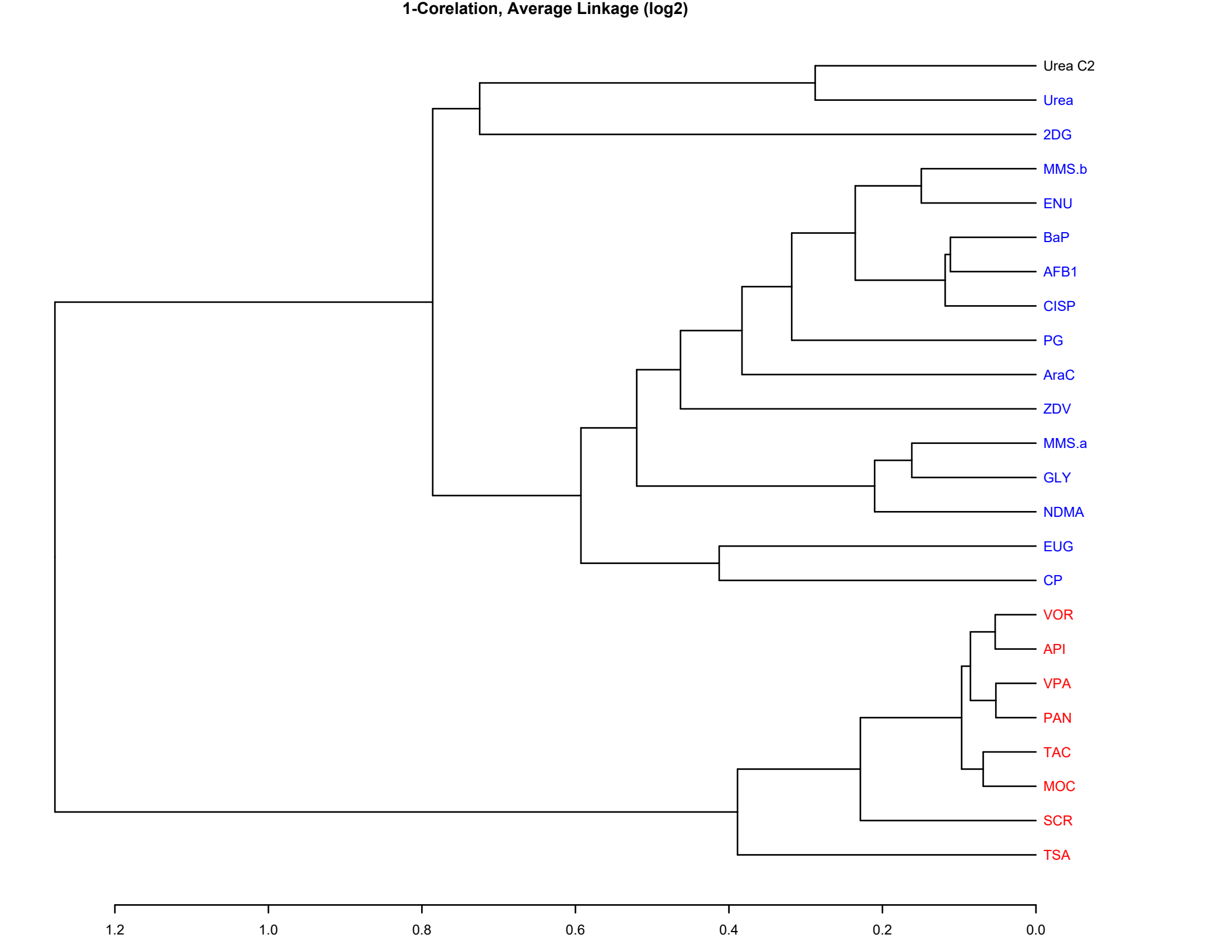

1-Corelation, Average Linkage (log2)
Urea
2DG
EUG
CP
PG C2
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

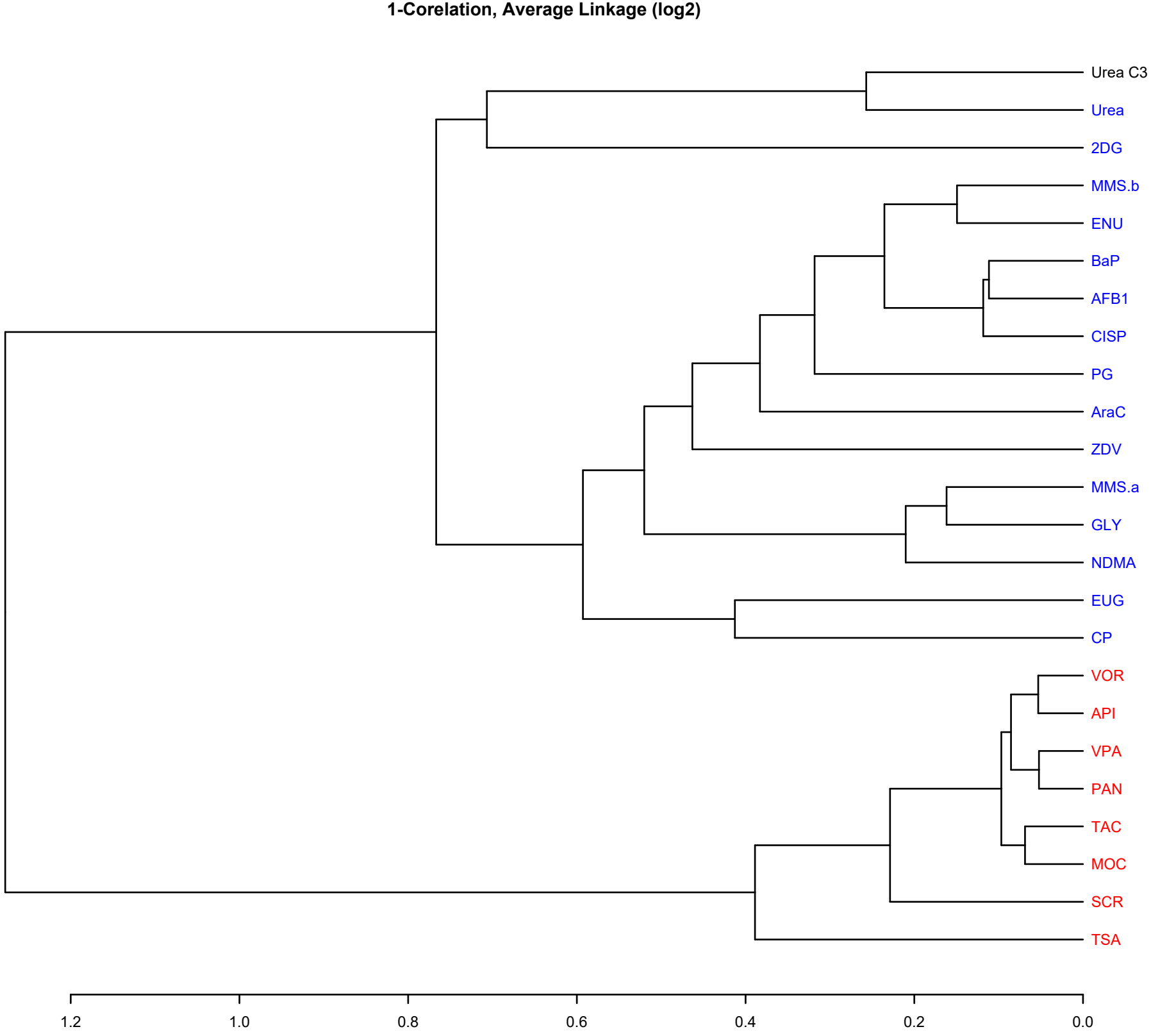

1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
AraC
PG C3
PG
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

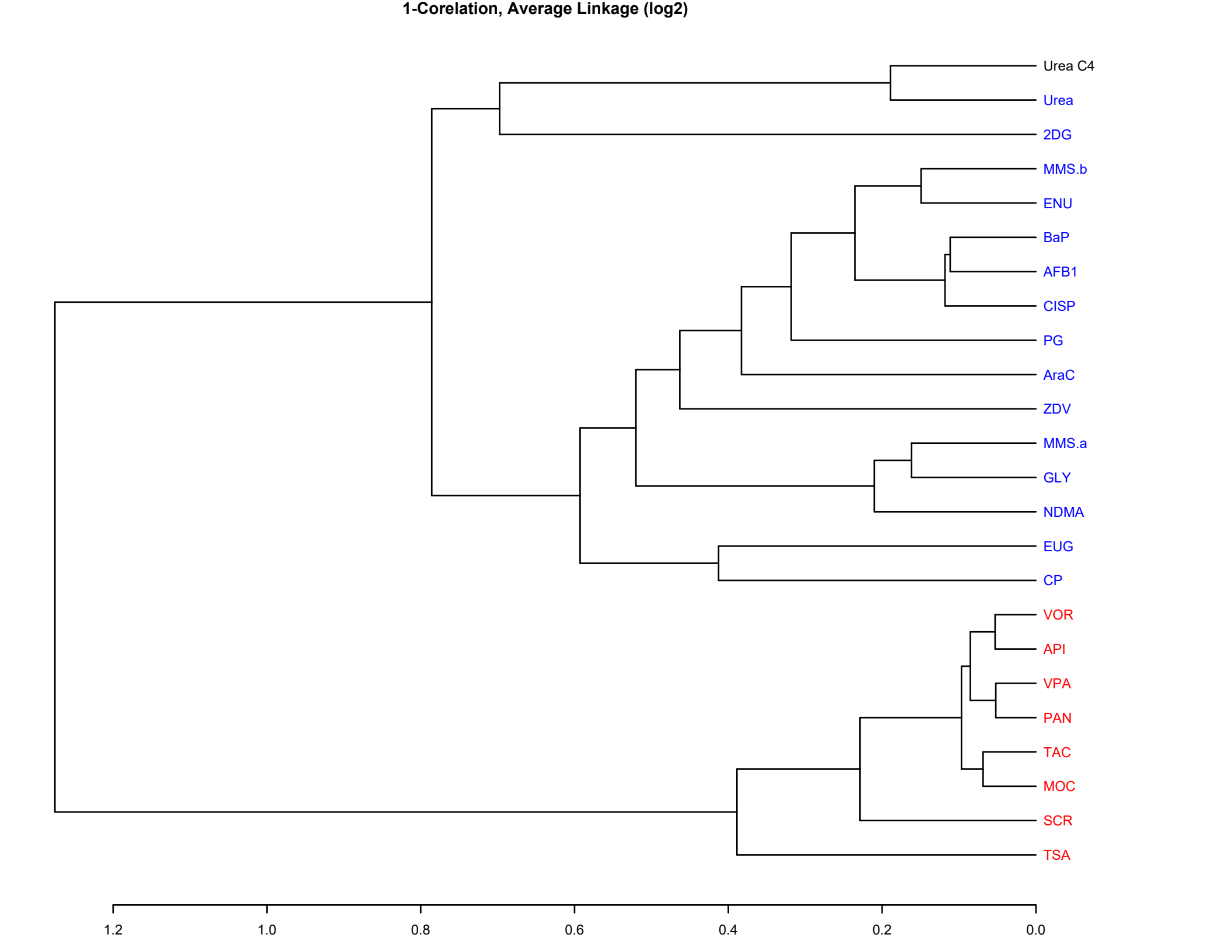
1-Corelation, Average Linkage (log2)

Supplementary Figure 3V:
Urea Concentrations 1-5 (C1-C5)

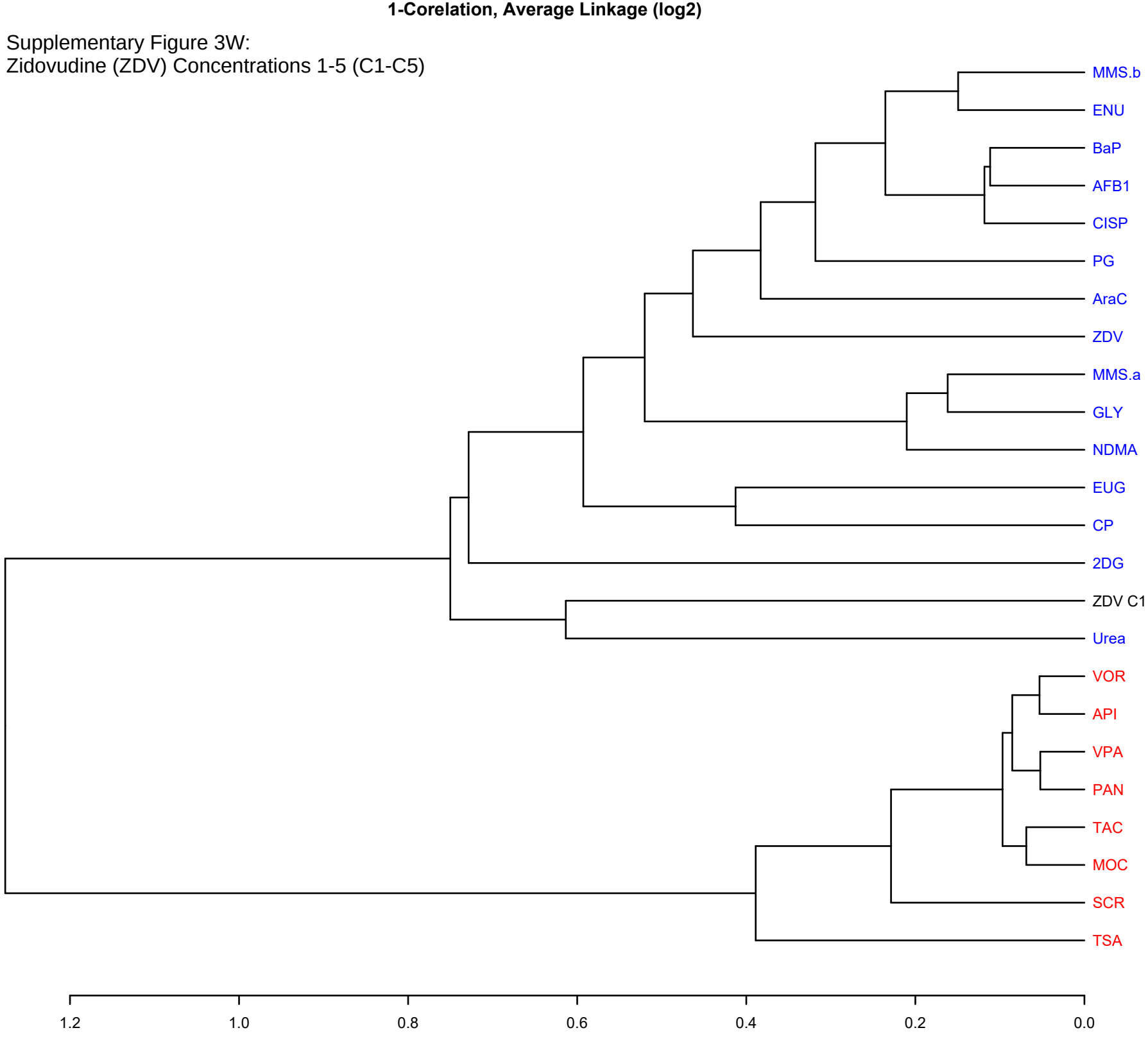


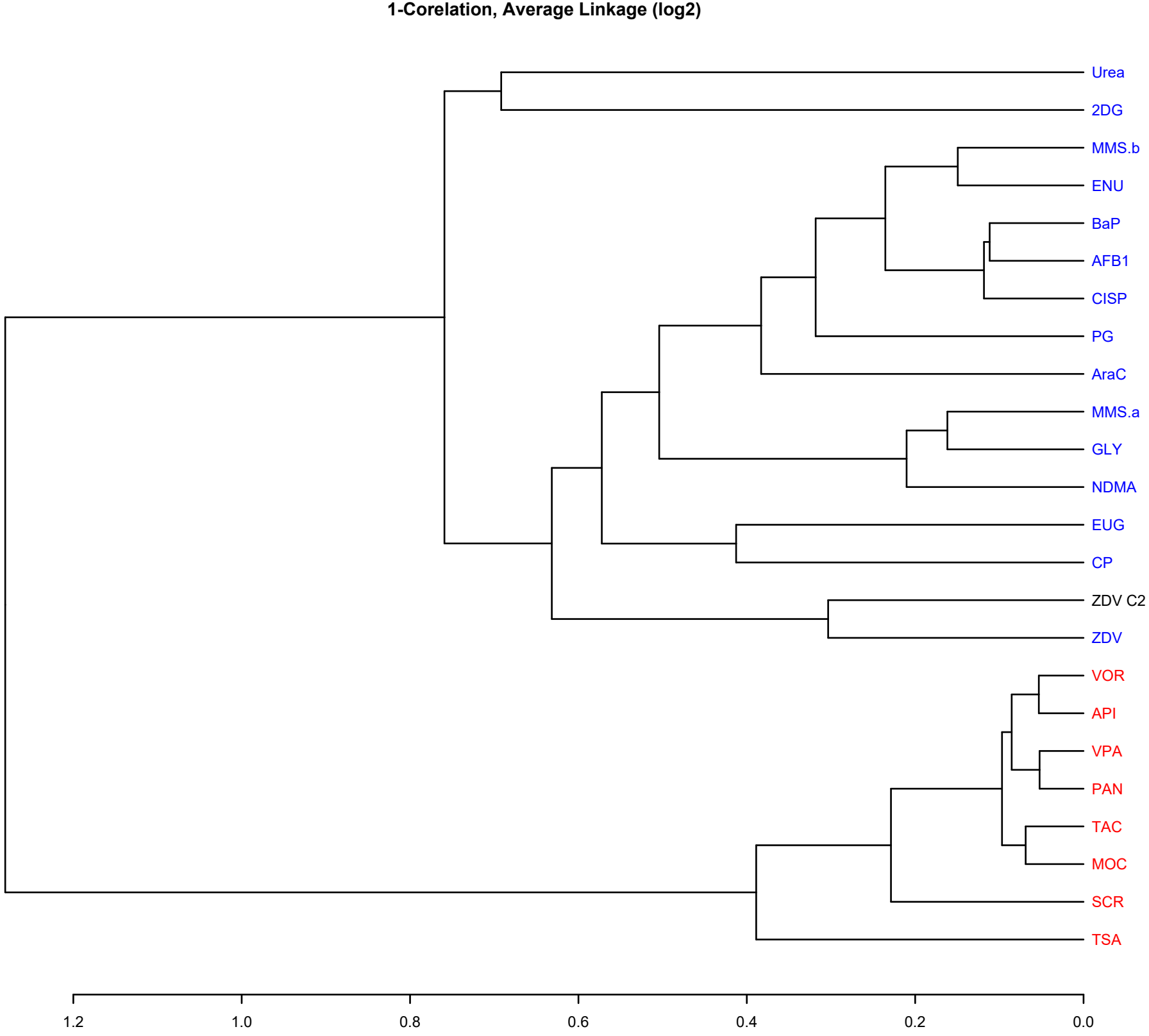

1-Corelation, Average Linkage (log2)
Urea C2
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

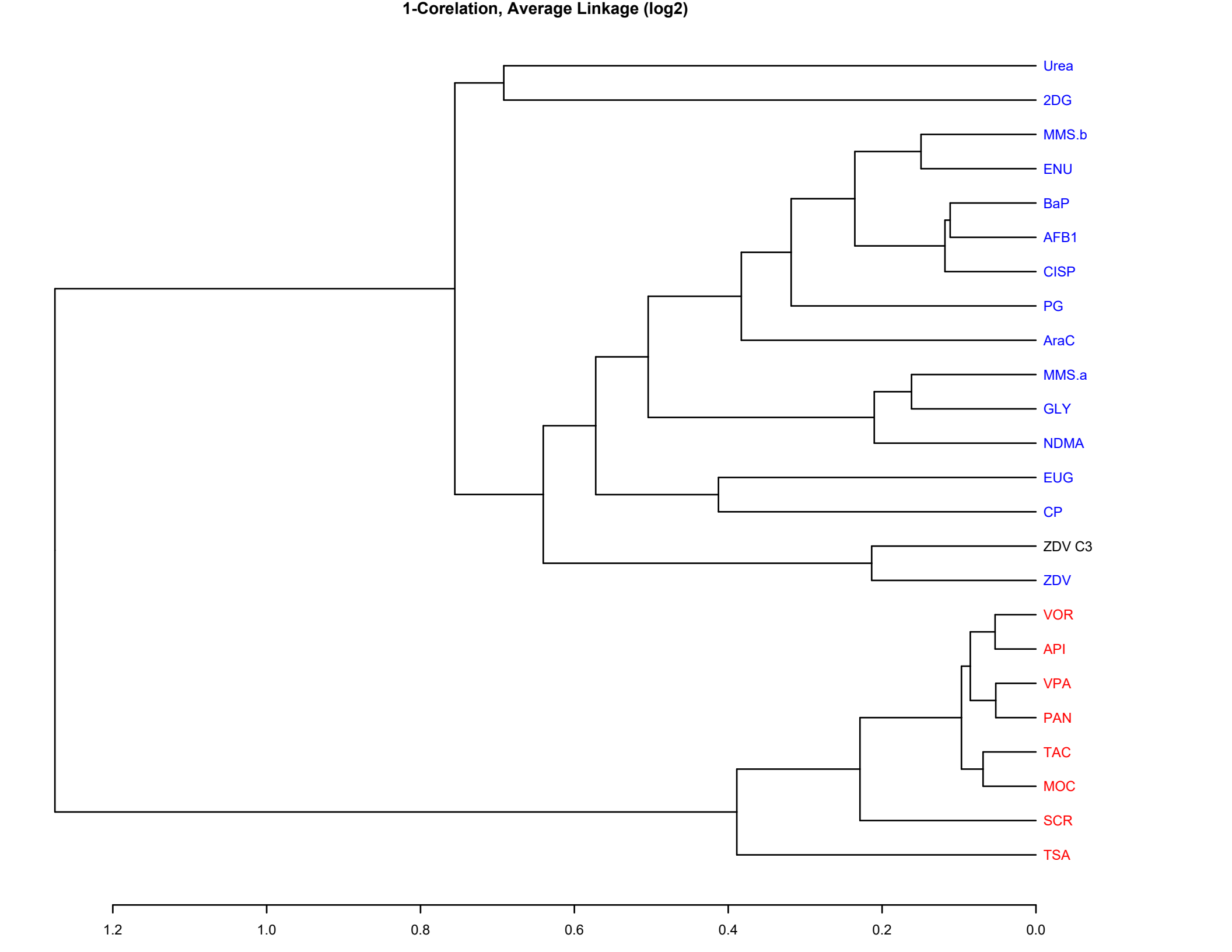

1-Corelation, Average Linkage (log2)
Urea C3
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

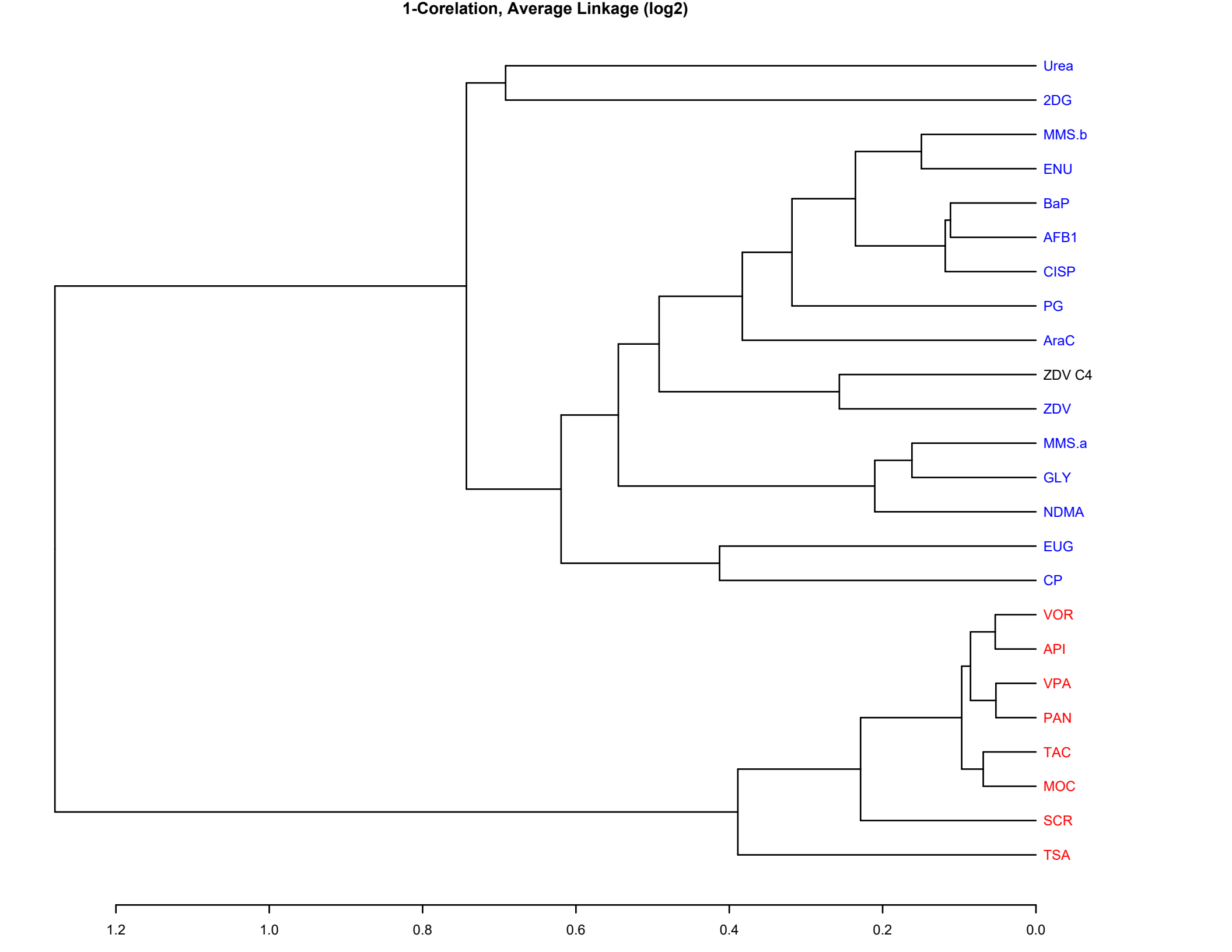

1-Corelation, Average Linkage (log2)
Urea C4
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0

Supplementary Figure 3W:
Zidovudine (ZDV) Concentrations 1-5 (C1-C5)




1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
MMS.a
GLY
NDMA
EUG
CP
ZDV C2
ZDV
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0


1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
MMS.a
GLY
NDMA
EUG
CP
ZDV C3
ZDV
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0


1-Corelation, Average Linkage (log2)
Urea
2DG
MMS.b
ENU
BaP
AFB1
CISP
PG
AraC
ZDV C4
ZDV
MMS.a
GLY
NDMA
EUG
CP
VOR
API
VPA
PAN
TAC
MOC
SCR
TSA
1.2
1.0
0.8
0.6
0.4
0.2
0.0