EUROPEAN URAEMIC TOXIN WORK GROUP

SUMMARY OF ACTIVITIES

(2000-2008)
EUROPEAN UREMIC TOXIN WORK GROUP (EUTox)

- A Argiles (F)
- U Baurmeister (G)
- J Beige (G)
- P Brouckaert (B)
- P Brunet (F)
- G Cohen (A)
- PP De Deyn (B)
- T Drüke (F)
- D Fliser (G)
- S Herget-Rosenthal (G)
- W Hörl (A)
- J Jankowski (G)
- A Jörres (G)
- ZA Massy (F)
- H Mischak (G)
- A Perna (I)
- M Rodriguez (Sp)
- G Spasovski (Mac)
- B Stegmayr (Sw)
- P Stenvinkel (Sw)
- P Thornalley (UK)
- R Vanholder (B)
- C Wanner (G)
- A Wiecek (P)
- W Zidek (G)

- Amgen
- Bayer HealthCare
- Baxter Healthcare
- F. Hoffman – La Roche
- Fresenius Medical Care
- Gambro
- Genzyme
- Membrana
- Nipro
- Shire
MEMBERS OF THE EUTox GROUP
ACADEMIC INSTITUTES

1. Production and preparation of the molecules

Argiles (France); Brunet (France); Cohen/Hörl (Austria); Drüeke (France); Jörres (Germany); Jankowski (Germany); Massy (France); Rodriguez (Spain); Thornalley (UK); Vanholder (Belgium)
2. Study patho-physiologic mechanisms and elements

Argiles (France); Brunet (France); De Deyn (Belgium); Drüeke (France); Fliser (Germany); Herget-Rosenthal (Germany); Hörl (Austria); Jankowski (Germany); Jörres (Germany); Massy (France); Perna (Italy); Rodriguez (Spain); Stenvinkel (Sweden); Thornalley (UK); Vanholder (Belgium); Wiecek (Poland)
3. Clinical evaluation

Argiles (France); Brunet (France); Drüeke (France); Fliser (Germany); Herget-Rosenthal (Germany); Hörl (Austria); Jörres (Germany); Massy (France); Perna (Italy); Rodriguez (Spain); Spasovski (Macedonia); Stegmayr (Sweden); Stenvinkel (Sweden); Vanholder (Belgium); Wanner (Germany); Wiecek (Poland)
ACADEMIC INSTITUTES

4. Genomics/proteomics

Argiles (France); Brouckaert (Belgium); Fliser (Germany); Jankowski (Germany); Massy (France); Mischak (Germany); Perna (Italy); Rodriguez (Spain); Stenvinkel (Sweden); Wiecek (Poland)
MEETINGS EUTox GROUP

🔹 2000
  - Lausanne, Switzerland

🔹 2001
  - Paris, France
  - Cologne, Germany
  - Gent, Belgium

🔹 2002
  - Montpellier, France
  - Vicenza, Italy
  - Würzburg, Germany
  - Gent, Belgium

🔹 2003
  - Cordoba, Spain
  - Vienna, Austria
  - Aachen, Germany
  - Niedernberg, Germany
MEETINGS EUTox GROUP

◆ 2004
  – Marseille, France
  – Berlin, Germany
  – Vienna, Austria

◆ 2005
  – Skopje, Macedonia
  – Potsdam, Germany
  – Brussels, Belgium

◆ 2006
  – Potsdam, Germany
  – Marseille, France
  – Naples, Italy

◆ 2007
  – Krakow, Poland
  – Essen, Germany
  – Dresden/Leipzig, Germany

◆ 2008
  – Sevilla, Spain
MEETINGS EUTox GROUP

- Symposium: “Uremic toxins and cardiovascular disease”
- October 3-5, 2008
- Amiens France

Organization:
» Z Massy, President
» R Vanholder, Chairman EUTox
Vanholder et al.
Uremic toxicity: present state of the art
*Int J Artif Org, 24, 695-725, 2001*

Vanholder et al.
Uraemic toxins and cardiovascular disease
*Nephrol Dial Transplant, 18, 463-466, 2003*

Vanholder et al.
New insights in uremic toxins
*Kidney Int, 63 (Suppl 84), S6-S10, 2003*
UREMIC TOXINS WITH VASCULAR IMPACT

**Polymorphnuclear Neutrophils**
- Advanced glycation products
- Advanced oxidation protein products
- Angiogenin (DIP I)
- Complement factor D (DIP II)
- Cytokines
- Ig Light chains
- Leptin

**Endothelial Cells**
- Advanced glycation products
- Advanced oxidation protein products
- β2-microglobulin
- Cytokines
- Homocysteine
- Leptin
- Oxalic Acid
- Oxidized LDL

**Monophages/Macrophages**
- Advanced glycation products
- Advanced oxidation protein products
- AGE-β2-microglobulin
- β2-microglobulin
- Cytokines
- Homocysteine
- Leptin

**Smooth muscle cells**
- β2-microglobulin
- Homocysteine

**Neutrophils**
- Monocytes
- Platelets
- Cytokines
- Leptin

**Platelets**
- Cytokines
- Leptin

Vanholder et al, IJAO, 24, 695-725, 2001
Vanholder et al.

Uremic toxicity: present state of the art
*Int J Artif Org, 24, 695-725, 2001*

Vanholder et al.

Uraemic toxins and cardiovascular disease
*Nephrol Dial Transplant, 18, 463-466, 2003*

Vanholder et al.

New insights in uremic toxins
*Kidney Int, 63 (Suppl 84), S6-S10, 2003*
Vanholder et al.
Review on uremic toxins: classification, concentration and interindividual variability
*Kidney Int, 63, 1934-1943, 2003*

Vanholder et al.
Chronic kidney disease as cause of cardiovascular morbidity and mortality
*NDT, 20, 1048-1056, 2005*

Vanholder et al.
The European artificial organ scene
*Artif Organs, 29, 498-506, 2005*
UREMIC SOLUTES LISTED

Small water soluble compounds (<500D): 1-Methyladenosine, 1-Methylguanosine, 1-Methylinosine, ADMA, γ-Keto-guanidinovaleric acid, α-N-acetylarginine, Arab(in)itol, Argininic acid, Benzylalcohol, β-guanidinopropionic acid, Creatine, Creatinine, Cytidine, Dimethylglycine, Erythritol, γ-guanidinobutyric acid, Guanidine, Guanidinoacetic acid, Guanidonosuccinic acid, Hypoxanthine, Mannitol, Methylguanidine, Myoinositol, N4-acetylcystidine, N6-methyladenosine, Orotic acid, Orotidine, Oxalate, Phenylacetylglutamine, Pseudouridine, SDMA, Sorbitol, Taurocyamine, Threitol, Thymine, Uracil, Urea, Uric acid, Uridine, Xanthine, Xanthosine

Protein-bound molecules: 2-Methoxyresorcinol, 3-deoxyglucosone, CMPF, Dimethylguanosine, Fructoselysine, Glyoxal, Hippuric acid, Homocysteine, Hydroquinone, Indole-3-acetic acid, Indoxyl sulfate, Interleukin 1β, Interleukin 6, Kinurenine, Kynurenic acid, Leptin, Melatonin, Methyleneoxal, N-(carboxymethyl)lysine, P-cresol, Pentosidine, Phenol, Phenylacetic acid, Phenylethylamine, P-OHhippuric acid, Putrescine, Quinolinic acid, Retinol binding protein, S-nitrosothiol, Spermidine, Spermine, Thiocyanate, Tumor Necrosis Factor α

Middle molecules (>500D): Adrenomedullin, Atrial natriuretic peptide, β2-microglobulin, β-endorphin, Cholecystokinin, Clara cell protein, Complement factor D, Cystatin C, Degranulation inhibiting protein I, Delta-sleep inducing peptide, Endothelin (ng/L), Ghrelin, Hyaluronic acid, Interleukin 1β, Interleukin 6, Interleukin-18, κ-lg light chain, λ-lg light chain, Leptin, MC-SF, Methionine-enkephalin, Neuropeptide Y, Orexin A, Parathyroid hormone, Retinol binding protein, Tumor Necrosis Factor α

Vanholder et al, KI, 63, 1934-1943, 2003
Vanholder et al.  
Chronic kidney disease as cause of cardiovascular morbidity and mortality  
*NDT, 20, 1048-1056, 2005*

Vanholder et al.  
The European artificial organ scene  
*Artif Organs, 29, 498-506, 2005*

Meert et al.  
Inconsistency of reported uremic toxin concentrations  
*Artif Organs, 31, 600-611, 2007*
Vanholder et al.
Review on uremic solutes II – Variability in reported concentrations: causes and consequences
*NDT, 2007, in press*

Cohen et al.
Review on uremic solutes III – Recommendations for handling uraemic retention solutes in vitro: towards a standardised approach for research on uraemia
*NDT, 2007, in press*
European Uremic Toxin (EUTox) Work Group of the ESAO

Purpose

Knowing is not enough, we must apply
Willing is not enough, we must do

- Goethe -

The European Society of Artificial Organs (ESAO) decided to install a Work Group in several areas of progress in the field of Artificial Organs, such as Artificial Liver, Heart Support, Artificial Kidney and Adequacy, Tissue Engineering, Education and Uremic Toxins.

Starting in October 1999, the European Uremic Toxins (EUTox) Work Group was launched by those of its members (R. Vanholder, B.G. Stegmayr and U. Baumsteiner). In September 2000, at the occasion of the 21st ESAO meeting in Louvain, the Work Group convened for its first meeting.

In 2002, the Work Group was composed of 15 European Research Institutes involving biochemists and clinicians working in uremic toxicity. Apart from these members from academia, 7 scientists from leading industries in this area (Amgen, Baxter Healthcare, Fresenius Medical Care, Centocor, Genzyme, Medtronic, and Roche) are involved. All members have been involved based on their previous accomplishments and their current research and development activities in uremic toxicity and its therapies.

One of the first projects EUTox accomplished was to write a "Know Review" about the main topic of interest of each member. This has been followed by a number of projects such as the publication of a list of uremic toxins with their threshold concentrations for in vitro research, the development of a complete toxicology and its therapies.

In June 2002, the group submitted an "Expression of Interest to the EU's 6th Framework in response to call ECHP 2000 and is continuously applying for research grants.

A "Severus statement and review publications were generated by the group as well as 11 scientific papers were published in which at least two member groups of EUTox jointly contributed. An "Uremic Toxins DATABASE was established.

R. Vanholder (Chairman)
U. Baumsteiner (Co-Chairman)

www.EUTox.info
UREMIC TOXINS DATABASE OF EUTox GROUP
www.EUTox.info
59 JOINT PUBLICATIONS

◆ 2002
  – Clin Chem
  – Circulation
◆ 2004
  – JASN (2)
◆ 2005
  – JASN (3)
  – Nat Med
  – Hypertension
  – Circulation
◆ 2006
  – Proteomics
◆ 2007
  – JASN
  – Proteomics
  – Arterioscler Thromb Vasc Biol
◆ 2008
  – JASN
CURRENT RESEARCH ACTIVITIES OF THE EUTOX GROUP

Investigation of effects of uremic toxins on:

- Endothelial cell function
- Thrombocyte aggregation
- NADPH oxidase activity, leukocyte free radical production
- Vascular smooth muscle cell reactivity
- Tubular cells
- Fibroblasts
AIMS FUTURE RESEARCH

1. *In vitro* studies
   Identification of uremic toxins responsible for vascular damage (effect on the 4 major cell systems involved: endothelium, leukocytes, thrombocytes, smooth muscle cells)

2. *In vivo* studies
   Identification of mechanisms leading to vascular damage in CKD
AIMS FUTURE RESEARCH
MORE EMPHASIS ON:

1. **Proteomics**
2. **Genomics**
3. **Metabolomics**