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CKJ REVIEW

A history of uraemic toxicity and of the European Uraemic Toxin Work Group (EUTox)

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ABSTRACT

The uraemic syndrome is a complex clinical picture developing in the advanced stages of chronic kidney disease, resulting in a myriad of complications and a high early mortality. This picture is to a significant extent defined by retention of metabolites and peptides that with a preserved kidney function are excreted or degraded by the kidneys. In as far as those solutes have a negative biological/biochemical impact, they are called uraemic toxins. Here, we describe the historical evolution of the scientific knowledge about uraemic toxins and the role played in this process by the European Uraemic Toxin Work Group (EUTox) during the last two decades. The earliest knowledge about a uraemic toxin goes back to the early 17th century when the existence of what would later be named as urea was recognized. It took about two further centuries to better define the role of urea and its link to kidney failure, and one more century to identify the relevance of post-translational modifications caused by urea such as carbamoylation. The knowledge progressively extended, especially from 1980 on, by the identification of more and more toxins and their adverse biological/biochemical impact. Progress of knowledge was paralleled and impacted by evolution of dialysis strategies. The last two decades, when insights grew exponentially, coincide with the foundation and activity of EUTox. In the final section, we summarize the role and accomplishments of EUTox and the part it is likely to play in future action, which should be organized around focus points like biomarker and potential target identification, intestinal generation, toxicity mechanisms and their correction, kidney and extracorporeal removal, patient-oriented outcomes and toxin characteristics in acute kidney injury and transplantation.

Keywords: cardiovascular, dialysis, haemodialysis, history, uraemic toxins

INTRODUCTION

Proper metabolism implies the generation of waste products that must be removed from the body to avoid accumulation and biological malfunction. Together with the liver and lungs, the kidneys are the main organs for waste removal. Normal kidneys filter ~170 L of plasma water daily, of which ultimately only 2 L is excreted. The remaining water is reabsorbed together with most essential compounds. The 2 L that is excreted contains all waste products that should be removed from the body.

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When function is lost, either acutely [acute kidney injury (AKI)] or chronically [chronic kidney disease (CKD)], the metabolites that in normal circumstances are excreted or degraded by the kidneys, are retained. This condition is commonly named as uraemia after urea, the retention product with the highest concentration [1]. The solutes that accumulate are labelled uraemic retention products. If these have an adverse biological or biochemical impact, they are called uraemic toxins, and can in principle affect every bodily function [2]. The sum of these problems is called the 'uraemic syndrome'. Because of the broad functional impact, kidney failure has correctly been defined as a systemic disease [3], whereby kidney dysfunction affects various organs, while these failing organs in their turn also impact kidney functioning, like in the cardio-renal syndrome [4].

The study of the uraemic syndrome and its causes and consequences has engendered a whole science dedicated to unravelling a myriad of complex mechanisms linked to a broad spectrum of retention solutes. The intention of the present review is to describe the evolution over time of this knowledge and its impact on medical and therapeutic reasoning in nephrology and related specialties. As dialysis remains as of today one of the main interventions to remove uraemic toxins and to preserve life in end-stage kidney disease (ESKD), the knowledge about dialysis techniques and uraemia are strongly intertwined. Therefore, in this publication, we will review both.

In the last sections, we will describe the role of the European Uraemic Toxin Work Group (EUTox), a work group of the European Society for Artificial Organs (ESAO) and an endorsed work group of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), which has been closely involved in the evolutions in this field over the last 20 years.

In our description, we will follow the usual classification of uraemic toxins (Supplementary Table S1), based on their removal by classical haemodialysis, currently still the most frequently applied extracorporeal treatment strategy of uraemia: small water-soluble compounds, protein-bound compounds and the larger 'middle molecules', which in fact refers to small peptides and proteins that under normal conditions cross the glomerular basement membrane. It should be noted, however, that other methods to reduce uraemic toxin concentration like preserving residual kidney function and reducing intestinal generation are currently emerging and will gain importance in future [5, 6], so that uraemic toxin classification might take also these strategic interventions into account next to dialysis.

In spite of their vital importance, we will not discuss non-organic retention solutes (e.g. potassium, phosphate or water).

THE EARLY DAYS OF URAEMIC TOXIN HISTORY (THE BIRTH AND RISE OF BIOCHEMISTRY) (1600–1960)

It may be no surprise that the first uraemic retention solute to be detected was urea, as it is the retention compound with by far the highest plasma concentration in uraemia. However, more surprisingly, its discovery goes back to the 17th century [7–9], and is attributed to Jan-Baptist Van Helmont (1580–1644), who lived in Brussels which at that time was part of Spain. Van Helmont has by some been quoted as 'the last alchemist and the first biochemist'.

He detected 'a salt in urine that never occurs outside the body, bred in the course of digestion from a substance not a salt' which 'differed from sea salt that is also present in the urine' and 'remained unchanged in its course through the body and on purification of urine'. After that, the knowledge about urea and its role in kidney pathology progressed stepwise [7, 8] (Supplementary Table S2) until in the 19th century Dumas and Prévost in Geneva observed that urea was retained in nephrectomized dogs, after which the German physician von Frerichs proposed the term 'uraemia'. Von Frerichs was an interesting person because in his theoretical concept of kidney failure, he diverged from the great theorist of kidney disease at that time, Richard Bright. Whereas Bright's view was essentially anatomical, whereby he concentrated on the kidneys as the central place where it all happened, von Frerichs proposed a humoral view, which implies that what occurred in the kidneys was reflected by changes throughout the organism, a concept complementary to that of Bright's and quite conforming with our current view of uraemia.

It took substantially more time before other uraemic retention products came into focus. One of the first to be identified was creatinine [10], like urea a small water-soluble compound, allowing the determination of creatinine clearance as a proxy of glomerular filtration rate [11, 12].

The introduction of more refined analytical methods such as chromatography and later mass-spectrometry simplified the detection of protein-bound solutes like indoxyl sulphate (first named indican) and phenolic compounds [13]. However, at the time of the first descriptions, to the best of our knowledge, no data on their biological or biochemical impact were available.

Babb and Scribner developed the middle molecule hypothesis in 1965, suggesting that in uraemia retention of solutes with a molecular weight 500 Da caused polyneuropathy [14]. Those molecules were difficult to remove by the haemodialysis strategies available at that time (relatively short sessions with low surface and small pore dialysers) but were more easily removed by peritoneal dialysis, during which less neuropathy was observed. When Babb and Scribner formulated their hypothesis, no middle molecules were known, although later research would identify a large number of retention solutes conforming to their definition [15, 16] (Supplementary Table S3).

THE EARLY DAYS OF DIALYSIS (1854–1960)

Early (unsuccessful) attempts to remove impurities from the organism or the blood go back to ancient Greece and the Middle Ages. The principle of dialysis as such was at first formulated by the Scottish scientist Thomas Graham in the 19th century, who described the phenomenon of purification of solutions through a semi-permeable membrane when the membrane was surrounded by a liquid in which the concentration of the solute was lower than inside the membrane [17]. The phenomenon described was diffusion, which is the principal physical law ruling removal with most current dialysis methods until now.

The first to apply this principle for blood purification *in vivo* were Abel and Turner in Baltimore, USA, who demonstrated in 1913 the removal of salicylate from the blood of dogs [18]. The first application in humans is attributed to Georg Haas in Giessen, Germany [19] who had been upset by the observation of soldiers dying from AKI in the first World War without possibility to save them. He managed to wake two patients from their uraemic coma using a primitive dialysis device but it was a technical impossibility to continue this treatment long enough and he discontinued his experiments after receiving a lack of support from the German scientific community.

Although some further attempts to refine dialysis treatment occurred across the world, the first series of dialysis treatments

that ultimately would prove to be life-saving was performed in Kampen, the Netherlands, in 1942, by the Dutch physician Willem Kolff [20]. Kolff too was frustrated by patients dying from kidney failure without possibilities to treat them. The introduction of cellophane as a membrane and heparin as anticoagulant [20] enabled him to save the life of a first patient, Sofia Schafstadt, in 1945. As he could not find sufficient support in the Netherlands for his work, Kolff subsequently migrated to Cleveland, Ohio, USA. Of note, in those early days, dialysis was mainly applied for AKI, because of the difficulties in accomplishing repeated access to the vascular bed, and the short-term chances for recovery of kidney function.

The first large-scale application of dialysis occurred during the Korean war (1950–53) when Paul Teschan (Nashville, Tennessee, USA), a military doctor in the US army, applied dialysis to treat soldiers suffering from AKI. The mortality of war victims with AKI, which before had been as high as 80–90%, suddenly decreased to 53% [21]. This development was made possible partially by the involvement of Travenol [22], a subsidiary of Baxter International launched in 1949. This was the first step towards industrial involvement in haemodialysis.

Still, it remained difficult to gain access to the vascular bed, excluding most CKD patients from treatment. Introduction of the Scribner shunt for the first time allowed repeated connection to the bloodstream via an external plastic cannula connecting an artery and a vein [23], while shortly thereafter the Cimino-Brescia fistula allowed connection of the arterial and venous vascular bed using autologous vessel material, decreasing clotting and infection risk and enabling easy access by needle puncture of the venous bed while the latter was enlarged by the direct inflow of arterial blood [24].

Peritoneal dialysis followed a similar evolution and development. Several reports appeared between the two World Wars and after World War II of treatments, mainly in AKI patients [25], that were often only partially successful due to complications. These were mostly related to the insufficient barrier against infection provided by the access systems to the peritoneal cavity, which was only solved in 1968 by the development of a sustainable access system by Tenckhoff and Schechter [26], which enabled maintenance peritoneal dialysis treatment in CKD.

URAEMIC TOXIN RESEARCH AT THE END OF THE 20TH CENTURY (1960–2000)

From then on, the histories of uraemic toxicity and dialysis run to a large extent in parallel, as innovations in one field influenced the other, thanks to more refined analytical techniques, understanding of biological pathways and immunology, as well as changes in membrane technology and polymer chemistry and insights in flow and transport mechanisms. This phase cannot be described without making tribute to pioneers such as Friedman [27], Massry [28] and Teschan [29] in the USA; Bergström [30], Funck-Brentano [31] and Ringoir [32] in Europe; and Niwa [33] in Japan.

Since the start of modern haemodialysis, the material from which the applied membranes were constructed was cellulose, based on a natural product derived from cotton linters, containing small pores [34]. The first synthetic dialysis membrane resulting from polymer chemistry was AN69, characterized by larger pores and thus a higher ultrafiltration capacity. When patients who had been subjected to (in almost all cases cellulosic membrane) dialysis for longer periods started developing cystic lesions in bones and tendons [35], those appeared to be linked to the tissue deposition of amyloid, containing β_2-microglobulin as one of its main components [36]. Consequently, β_2-microglobulin became one of the first middle molecules to be identified. AN69 and other large-pore membranes had a higher capacity to remove β_2-microglobulin than classical cellulosic membranes [37] and it was suggested that patients exclusively treated with AN69 had a lower prevalence of dialysis amyloidosis [38]. The complement activation and inflammatory reactions observed with cellulosic membranes were largely attenuated with synthetic membranes [39], and synthetic large-pore membranes (the so-called high-flux dialysers) in a haemodialysis or haemo(dia)filtration setting became progressively more popular.

Parathyroid hormone was another middle molecule that was recognized in that early phase. In a series of elegant animal experiments, Massry *et al.* demonstrated that experimental animals with kidney failure in which the parathyroid glands had been kept intact showed a large array of biological defects that were attenuated after parathyroidectomy [40, 41].

Finally, also more data emerged on the protein-bound uraemic retention solutes. Although described as uraemic solutes much earlier by European analytical chemists [13], attention to their toxicity was to the best of our knowledge to a large extent the work of Japanese researchers [33].

Also, the knowledge on the clinical impact of uraemic toxicity was growing. Ginn *et al.* started an extended study on neurologic dysfunction in uraemia [42] and Lindner *et al.* were the first describing accelerated vascular damage in kidney disease [43], more than two decades before the analysis by Foley *et al.* which is generally considered the eye-opener on this issue [44].

THE ROLE OF EUTox (1999–2020)

Thus, by the end of last century, the knowledge on individual uraemic toxins, their physico-chemical characteristics, their biological and clinical impact and their removal, grew prolifically (Figure 1), but research was often not well harmonized, without much collaboration. In this context of growing knowledge but also need for more coordination and integration, the EUTox was founded.

At the end of last century, the ESAO (https://www.esao.org) decided to create Work Groups for all main artificial organs it represented, and thus the plan was conceived to do this also for artificial kidney. B. Stegmayr (University of Umeå, Sweden), U. Baurmeister (Enka/Membrana, Wuppertal, Germany) and R.V. (Ghent University, Belgium) were commissioned to propose a work plan.

At a meeting in 1999, this group proposed to join several European scientists who were involved in uraemic toxicity research into a not-for-profit collaborative network. It was thought that there were enough different research groups involved in the field with diverse interests to inspire collaborative investigations triggering faster progress, a broadening of the scope and more cohesion in the targeted results.

As some industries, especially dialysis companies, also included research units in this field, industry became part of the Work Group from the very beginning and actively participated in the research projects.

The first meeting took place in Lausanne in September 2000, during the 27th Annual Meeting of ESAO, to be followed from January 2001 on by thrice- or twice-yearly meetings (EUTox website; www.uremic-toxins.org). During those meetings, the aims and strategies of the Group were defined, which are still applicable today [45] (Table 1). They essentially focus on

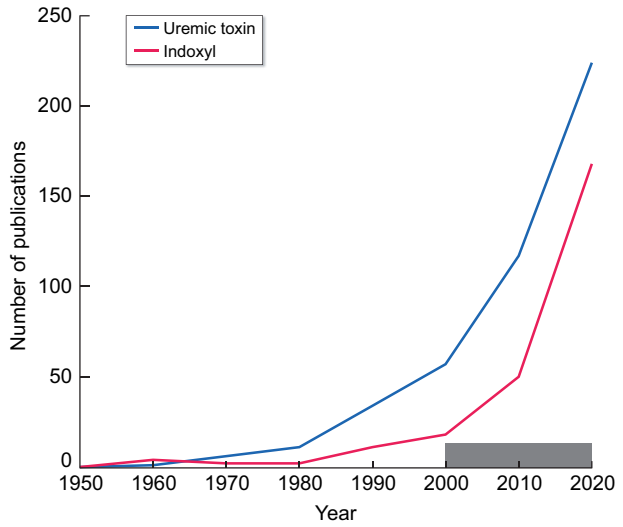

FIGURE 1: Number of yearly publications from 1950 onwards, with 10-year intervals. An Endnote search was done with either 'uremic toxin' (blue line—as illustration of the general interest in the topic) or 'indoxyl' (red line—representing indoxyl sulphate, as illustration of a specific frequently studied uraemic toxin) as keywords and the number of retrieved publications for that specific year was counted. For 2020, references retrieved per 30 November 2020 were multiplied by 12/11. In the period 1950–70, there was very little activity. From 1980 onwards, there was a progressive increase in publication number, starting first with the more general topic 'uremic toxin' and somewhat later for the more specific 'indoxyl' (as a surrogate for indoxyl sulphate). With regards to this timeline, EUTox became operational in 2000. The rectangle points to the period over which EUTox has been (and still is) active.

Table 1. Aims and strategies of EUTox

A: Aims

- The identification of yet unknown uraemic toxins
- The identification of biomarkers allowing the early detection of the disease
- The identification of therapeutic targets
- The characterization of known uraemic toxins and their biological/biochemical impact
- The development of new therapeutic approaches for the treatment of CKD
- The improvement of existing therapeutic strategies
- Focus on curative treatment but also on prevention
- Unravelling of the reasons for the extremely high burden of cardiovascular disease in uraemia

B: Strategies

- Description of pathophysiologic processes
- Focus on inflammation and cardiovascular damage
- Classification of known uraemic toxins
- Publication of original data with reference to EUTox involvement
- Promotion of common research projects
- Sharing of ideas
- Mutual problem solving
- Stimulation of young coworkers to present their data
- Creation of a web-based platform devoted to uraemic toxins and their concentration
- Advocacy to include sessions on uraemic toxins at nephrology meetings
- Presentation of EUTox data at international and national conferences
- CME courses/seminars
- Congresses with focus in uraemic toxins

FIGURE 2: EUTox logo.

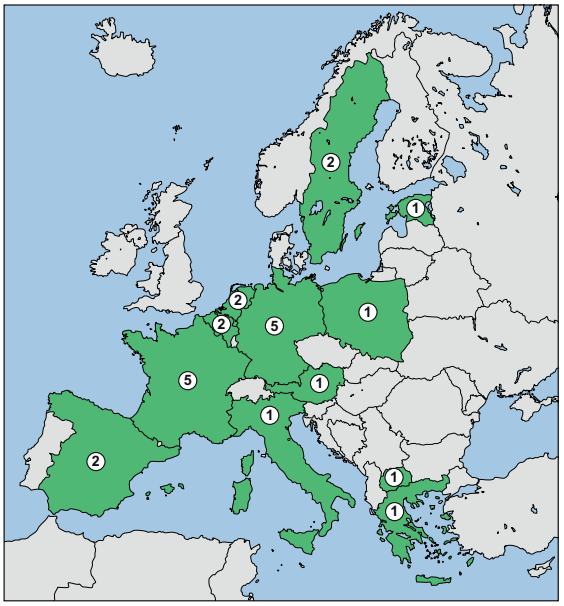

FIGURE 3: Country distribution of EUTox members (green). Participating countries are: Austria, Belgium, Estonia, France, Germany, Greece, Italy, the Netherlands, North Macedonia, Poland, Spain and Sweden. Number of members for each country mentioned inside the circles.

identification and pathophysiologic characterization of uraemic toxins, the detection of biomarkers and therapeutic targets, as well as the development of preventive and therapeutic interventions. Strategies to increase visibility of EUTox include publications, presentations, web-based tools and stimulating collaborative research among groups with specific attention to involving junior researchers.

The acronym EUTox was introduced in 2002, to be followed soon by the logo (Figure 2). Next to its status as Work Group of ESAO, later during its existence, EUTox has also been endorsed by the ERA-EDTA since 2009.

For the time being, the group is composed of 24 academic research units representing 12 countries (Figure 3; Supplementary Table S4).

ACCOMPLISHMENTS OF EUTox

Over the 20 years of the existence of EUTox, its members met over 50 times and published almost 3000 publications, of which >300 (±15 years) were collaborative papers (involving two or more EUTox members). Thirty-five students successfully defended a doctoral thesis on uraemic toxicity. At least seven European and large national research grants were acquired [45], covering topics such as the gut–kidney axis, cardio-renal syndrome, treatment of AKI, cardiovascular disease in CKD and pathophysiology of CKD. Two of the EUTox review publications on uraemic toxins and their concentration [1, 46] also were the basis for constructing an interactive uraemic toxin database [47]. This prolific activity coincided with a real boost in uraemic

Table 2. EUTox publications in high impact journals[a]

IF[b]	References	Title	Journal
60.4	Ortiz *et al.* [48]	Epidemiology, contributors to and clinical trials of mortality risk in chronic kidney failure	*Lancet*
31.1	Jankowski *et al.* [49]	Uridine adenosine tetraphosphate: a novel endothelium-derived vasoconstrictive factor	*Nat Med*
25.3	Vanholder *et al.* [51]	Clinical management of the uraemic syndrome in CKD	*Lancet Diab Endocrinol*
25.3	Tofte *et al.* [52]	Early detection of diabetic kidney disease by urinary proteomics and subsequent intervention with spironolactone to delay progression (PRIORITY): a prospective observational study and embedded randomized placebo-controlled trial	*Lancet Diab Endocrinol*
23.6	Salem *et al.* [53]	Identification of the 'vasoconstriction inhibiting factor' a potent endogenous cofactor of angiotensin II acting on the AT2 receptor	*Circulation*
23.6	Phan *et al.* [54]	Sevelamer prevents uraemia-enhanced atherosclerosis progression in apolipoprotein E deficient (apoE$^{-/-}$) mice	*Circulation*
23.6	Drüeke *et al.* [55]	Iron therapy, advanced oxidation protein products and carotid artery intima–media thickness in ESKD	*Circulation*
22.7	Speer *et al.* [50]	Carbamylated low-density lipoprotein induces endothelial dysfunction	*Eur Heart J*
20.7	Zoccali *et al.* [3]	The systemic nature of CKD	*Nat Rev Nephrol*
20.7	Mischak *et al.* [56]	Proteomic biomarkers in kidney disease: issues in development and implementation	*Nat Rev Nephrol*
20.5	Zewinger *et al.* [57]	Apolipoprotein C3 induces inflammation and organ damage by alternative inflammasome activation	*Nat Immunol*
16.3	Mischak *et al.* [58]	Recommendations for biomarker identification and qualification in clinical proteomics	*Scii Transl Med*

[a]Involving at least two EUTox members; publications not dealing with the uraemic syndrome or uraemic toxins are not included; [b]IF: impact factor for 2019 extracted from Web of Science—Journal Citation Reports on 1 December 2020. The cited papers were published in journals with IF >15.

toxin research in Europe, but also in the USA, Asia and more recently Latin America (Figure 1).

The publications [3, 48–58] in journals with an impact factor >15 are summarized in Table 2. In addition, also the most cited papers (Table 3) are expounded [1, 46, 48, 58–66]. These publications are representative for the entire EUTox activity, i.e. reviews describing uraemic toxin concentration, the clinical picture of uraemia and the mechanisms at play, original studies identifying novel toxins and/or describing biological/biochemical effects of newly defined or known toxins, effects of therapeutic interventions on uraemic toxins, and studies and recommendations on use of biomarkers of CKD and its progression. A synopsis of the publications reaching the highest scores in Tables 2 and 3 can be found as Supplementary Material.

EUTox has organized several meetings on the link between uraemic toxins and cardiovascular damage, in Amiens, Groningen, Oxford and Marseille, taken part on a regular basis with specifically devoted sessions during the annual ESAO and ERA-EDTA congresses, and organized a large number of continuous medical education (CME) events around Europe, in conjunction with the regular group meetings.

THE FUTURE OF URAEMIC TOXIN RESEARCH AND OF EUTox

There has been not much progress in the therapeutic approaches to CKD and in the concept of dialysis treatment until the turn of the last century, but over the last few years a number of novel initiatives are prone to generate progress in kidney treatment, such as the development of more advanced dialysis systems to improve the removal of protein-bound uraemic toxins, or the application of binding competitors such as ibuprofen, folates and charcoal sorbents.

Another promising strategy is to increase the free fractions of hydrophobic uraemic toxins at the expense of the protein-bound fraction. Separation rates of hydrophobic toxins can be increased by enhancing the ionic strength of absorber systems [67], by enhancing plasma ionic strength [68] or by applying high-frequency electric fields [69].

After 20 years of advocacy action by the American Society of Nephrology, the US Congress approved a financial injection of more than $2 billion to stimulate kidney research [70] and in July 2019, President Trump signed an executive order to reform the US ESKD treatment industry leading to new payment models and favouring more sustainable kidney replacement options, especially transplantation (TP) and home dialysis strategies [71]. In addition, the Kidney Health Initiative, a public–private partnership aimed at stimulating innovative approaches optimizing drugs and devices to improve the future of kidney patients [72, 73], also supported the development by several collaborative groups of a wearable artificial kidney [74].

In Europe, the European Kidney Health Alliance (EKHA) has been acting at several levels to create more awareness of kidney disease [75], especially by informing the European Commission and from there top to bottom the Member States of the European Union (EU). EKHA is an alliance of all major European stakeholders in kidney disease, thus not only physicians and scientists, but also nurses, technicians, kidney foundations and kidney patients. The actions of EKHA include the development

Table 3. Most cited EUTox publications[a]

No. of citations[b]	First author	Title	Journal
957	Vanholder *et al.* [1]	Review on uraemic toxins: classification, concentration and interindividual variability	*Kidney Int*
488	Barreto *et al.* [59]	Serum indoxyl sulphate is associated with vascular disease and mortality in CKD patients	*Clin J Am Soc Nephrol*
444	Vanholder *et al.* [60]	CKD as cause of cardiovascular morbidity and mortality	*Nephrol Dial Transplant*
429	Duranton *et al.* [46]	Normal and pathologic concentrations of uraemic toxins	*J Am Soc Nephrol*
309	Dou *et al.* [61]	The uraemic solutes *p*-cresol and indoxyl sulphate inhibit endothelial proliferation and wound repair	*Kidney Int*
268	Good *et al.* [62]	Naturally occurring human urinary peptides for use in diagnosis of CKD	*Mol Cell Proteomics*
262	Liabeuf *et al.* [63]	Free *p*-cresylsulphate is a predictor of mortality in patients at different stages of CKD	*Nephrol Dial Transplant*
250	Fliser *et al.* [64]	A European Renal Best Practice position statement on the Kidney Disease: Improving Global Outcomes clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy	*Nephrol Dial Transplant*
243	Spasovski *et al.* [65]	Clinical practice guideline on diagnosis and treatment of hyponatraemia	*Eur J Endocrinol*
210	Mischak *et al.* [56]	Recommendations for biomarker identification and qualification in clinical proteomics	*Sci Transl Med*
182	Ortiz *et al.* [48]	Epidemiology, contributors to and clinical trials of mortality risk in chronic kidney failure	*Lancet*
190	Vanholder *et al.* [66]	A bench to bedside view of uraemic toxins	*J Am Soc Med*

[a]Involving at least two EUTox members; publications not dealing with the uraemic syndrome or uraemic toxins are not included; [b]No. of citations: number of citations as extracted from Web of Science on 1 December 2020.

in 2015 of 'Recommendations for Sustainable Kidney Care' [76]; the creation of a supportive group of Members of European Parliament; and yearly Kidney Fora in the European Parliament, bringing together several stakeholders and focusing on themes like prevention, patient choice of treatment and TP. In addition, a number of publications on societal and advocacy issues related to kidney disease were issued [77–83], as well as a Joint Statement informing the EU and its Member States on approaches to increase organ donation and TP [84]. EKHA also is part of and currently chairs European Chronic Disease Alliance [85], a platform of 11 chronic disease associations, representing the whole spectrum of non-communicable diseases. In the Netherlands, the Dutch Kidney Foundation supports several major research networks on kidney disease [86], has created the 'Beating Kidney Disease' initiative with the intention to streamline kidney research in the Netherlands in the coming years [87], finances the development of a portable artificial kidney [88] and partnered in the initiation of research on the bioartificial kidney [89].

EUTox will play a significant role in this process aimed at lifting the approach to kidney disease to a higher level (Figure 4). Next to continuing existing efforts advancing insight in the biological and clinical impact of uraemic toxins and in the characteristics of uraemic retention and removal, EUTox can offer innovative support by characterizing: (i) biomarkers linked to uraemia, especially those identifying fast progression of CKD, and, linked to that, prevention of development and progression of kidney disease [52, 90]; (ii) mechanisms of generation of uraemic toxins by the intestine and ways to influence this process at the site of origin [91]; (iii) action modes of uraemic toxins especially in cardiovascular disease, potentially disclosing routes to block these pharmacologically [49]; (iv) mechanisms of removal by the kidneys of uraemic toxins especially by tubular cells that may lead to projects related to regenerative medicine and bioartificial kidney [92, 93]; (v) novel extracorporeal removal strategies, which might include, but should not be limited to, adsorption [94] or approaches to decrease solute protein binding [95]; (vi) the role of uraemic toxins in uraemia-related patient-oriented outcomes, such as itching, fatigue or cognitive dysfunction, which might make use of big data analysis [96]; (vii) the role of uraemic toxin retention in transplant recipients [97] or AKI [98], allowing the identification of the mechanisms influencing concentrations in those conditions; and (viii) development of real-time monitoring methods for extracorporeal uraemic toxin removal [99–101]. The EUTox work group also remains available to offer support in any other initiative designed to improve outcomes and life quality of kidney patients.

Finally, the EUTox model could serve as an example for other platforms for collaborative research and action that join groups with common interests and allows variable subgroups to team up depending on the topic of interest and expertise. For example, the ERA-EDTA is currently creating a European network on AKI with the intention to make it function in a way similar to the EUTox concept [102]. Likewise, a similar approach was followed when developing the Aachen-Maastricht Institute for Cardiorenal Research (AMICARE), whereby the Aachen (Germany) and Maastricht Universities (the Netherlands) combine their cardio-renal research units in a separate building, integrating basic scientists, clinicians and manufacturers to develop new therapeutic options for cardiovascular disease in CKD. Also the collaboration between the universities of Utrecht and Twente (the Netherlands) on creating bioartificial kidney devices, dwells upon the same principle [103].

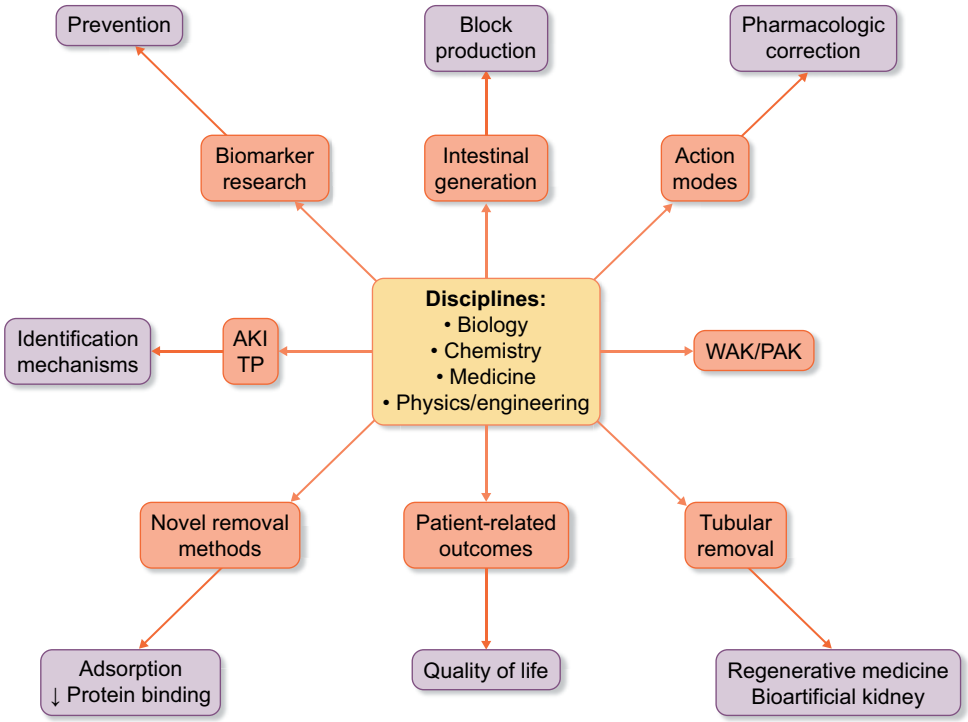

FIGURE 4: Flowchart summarizing the potential role of EUTox in future kidney research in Europe. Starting from the basic disciplines in of EUTox (yellow), a number of major research fields can be identified (salmon). The resulting benefits or improvements vis-à-vis the current situation are shaded purple. AKI: acute kidney injury; TP: transplantation; WAK: wearable artificial kidney; PAK: portable artificial kidney.

CONCLUSIONS

Scientific knowledge on uraemic toxins and uraemic toxicity has a long history. Especially in the last two decades, understanding grew exponentially, a process to which EUTox contributed significantly. Currently, many worldwide initiatives are boosting research efforts on kidney disease and its therapies, including the search for more sustainable treatment of ESKD. EUTox, with its long-standing knowhow in studying mechanisms and therapeutic approaches of uraemia, offers an ideal network to partner in these.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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CONFLICT OF INTEREST STATEMENT

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