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Review article

Endocrine disruptors in dialysis therapies: A literature review

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ABSTRACT

Endocrine disrupting chemicals (EDCs) were defined as “an exogenous substance or mixture that alters function (s) of the endocrine system and consequently causes adverse health effects”. These compounds are mainly eliminated by the renal route. However, patients with end-stage kidney disease treated by dialysis (ESKDD) can no longer eliminate these EDCs efficiently. Furthermore, EDCs exposure could occur *via* leaching from medical devices used in dialysis therapy. As a result, ESKDD patients are overexposed to EDCs. The aims of this study were to summarize EDCs exposure of ESKDD patients and to evaluate the factors at the origin of this exposure. To handle these objectives, we performed a literature review. An electronic search on PubMed, Embase and Web of science databases was performed. Twenty-six studies were finally included. The EDCs reported in these studies were Bisphenol A (BPA), Bisphenol S (BPS), Bisphenol B (BPB), Nonylphenol, Di(2-ethylhexyl) phthalate (DEHP), Di-n-butyl phthalate (DBP), and Butylbenzyl phthalate (BBP). Regarding the environment of dialysis patients, BPA, BPB, BPS, DEHP, DBP and nonylphenol have been found. Environmental exposure affects EDCs blood levels in ESKDD patients who are overexposed to BPA, BPS, BPB and DEHP. For ESKDD patients, dialyzers with housing in polycarbonate and fibers in polysulfone seem to overexpose them to BPA. Regarding dialysis therapy, peritoneal dialysis seems to decrease patient exposure *vs* hemodialysis therapy, and hemodiafiltration therapy seems to reduce this exposure *vs* hemodialysis therapy. Regarding DEHP, levels tend to increase during dialysis and when DEHP plasticizer is used in PVC devices. Finally, in the European Union a regulation on medical devices was adopted on 5 April 2017 and has been applied recently. This regulation will regulate EDCs in medical devices and thereby contribute to reconsideration of their conceptions and, finally, to reduction of ESKDD patients' exposure.

Abbreviations: BBP, Butylbenzyl phthalate; BPA, Bisphenol A; BPB, Bisphenol B; BPS, Bisphenol S; BSA, Bovine serum albumin; CE, Cellulose; CKD, Chronic kidney disease; DBP, Di-n-butyl phthalate; DEHP, Di(2-ethylhexyl) phthalate; DEHT, Bis(2-ethylhexyl) terephthalate; DEP, Diethyl phthalate; DINP, Di-isononylphthalate; EDCs, Endocrine disrupting chemicals; ELISA, Enzyme-linked immunosorbent assay; ESKDD, End stage kidney disease treated by dialysis; GC-MS, Gas chromatography couples to mass spectrometer; GFR, Glomerular filtration rate; HD, Hemodialysis therapy; HDF, Online hemodiafiltration therapy; HM, Housing material; HPLC, High performance liquid chromatography; HPLC-UV, High performance liquid chromatography couples to ultra-violet spectroscopy; NMR, Nuclear magnetic resonance; MeSH, Medical Subject Headings; MF, Membrane fibers; NA, Not available; ND, Undetected; NS, Not significant; PA, Polyamide; PBS, Phosphate-buffered saline; PC, Polycarbonate; PD, Peritoneal dialysis; PES, Polyethersulfone; PP, Polypropylene; PS, Polysulfone; PST, Polystyrene; PVC, Polyvinyl chloride; PVP, Polyvinylpyrrolidone; TEHTM, Tri-(2-ethylhexyl) trimellitate; TOTM, Trioctyltrimellitate; UHPLC, Ultra-high performance liquid chromatography; UHPLC-MS/MS, Ultra-high performance liquid chromatography couples to mass spectrometer; WHO, World Health Organization.

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1. Introduction

Chronic kidney disease (CKD) is defined as a “condition in which the kidneys are damaged and cannot filter blood as well as they should” (Centers for Disease Control and Prevention, 2022). The glomerular filtration rate (GFR) calculated as the sum of fluid filtered by all the functioning nephrons per unit of time is the most widely used indicator of kidney function. The biological diagnosis of CKD is defined by international guidelines as abnormalities of kidney structure or function, present for more than 3 months and with implications for health. Criteria of CKD can be markers of kidney damage like albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, history of kidney transplantation or $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$, or both (Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

In 2017, the global prevalence of CKD was estimated at 9.1 % with 697.5 million people affected, one-third living in either China or Vietnam (GBD Chronic Kidney Disease Collaboration, 2020). Face to severe decreased renal function ($\text{GFR} < 5 \text{ mL/min/1.73 m}^2$) or subjective symptoms of uraemia, patients can be transplanted or can be initiated dialysis. In 2017, approximately 286,000 patients were end stage kidney disease treated by dialysis (ESKDD), corresponding to prevalence of 0.041 % (GBD Chronic Kidney Disease Collaboration, 2020). Conventional hemodialysis, online hemodiafiltration and peritoneal dialysis (PD) are renal replacement therapies mostly used to artificially remove from patients an excess of water, solutes, and toxins.

The two main causes of CKD are diabetes and hypertension (Webster et al., 2017). Indeed diabetes affects 537 million people worldwide, corresponding to prevalence of 10.5 %, and accounts for 30 to 50 % of all CKD cases (Sun et al., 2022; Webster et al., 2017). In 2019, hypertension affected 1.28 billion adults aged 30–79 years worldwide and was a demonstrated risk factor for CKD (NCD Risk Factor Collaboration (NCD-RisC), 2021). However, glomerulonephritis and other causes like analgesic abuse, herbal mediations, pesticides, unregulated food additives and environmental pollution like endocrine disrupting chemicals (EDCs) can lead to CKD (Jha et al., 2013). Intrauterine exposure to environmental factors such as EDCs is likely to have health consequences not only on fetal development (prematurity, nervous system disturbance), but also for the fetus' future life with for instance reduced kidney function and hypertension. This is supporting by the Developmental Origins Hypothesis of Health and Diseases (DOHaD) theory (Hsu and Tain, 2021). Two longitudinal studies by Hu et al. concluded that elevated blood concentrations of Bisphenol A (BPA), a recognized EDC, could be a predisposing factor to kidney damage for patients with diabetes or hypertension (Hu et al., 2015, Hu et al., 2016). Regarding phthalates, Di(2-ethylhexyl) phthalate (DEHP) and Di-n-butyl phthalate (DBP) exposure has been associated with metabolic effects such as diabetes and thereby contribute to CKD (Radke et al., 2019).

EDCs were defined in 2002 by the World Health Organization (WHO) as “an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny” (World Health Organization, 2002). Currently, about one thousand chemical compounds with endocrine-disrupting activity have been reported such as plasticizers (bisphenols, phthalates), antibacterial and antifungal agents (parabens) and pesticides. EDCs have multiples biological activities with estrogenic, anti-estrogenic, androgenic or anti-androgenic effects but also thyroid disruption and can therefore increase or inhibit normal endocrine function and lead to effects on human health (Schug et al., 2016; Kahn et al., 2020). Recently, regarding BPA, the European Food Safety Authority highlighted the human dietary exposure and identified harmful effects on the immune system (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids (CEP) et al., 2023). Due to their ubiquitous properties, organisms can be exposed by multiple routes like ingestion, inhalation, or dermal contact.

Patients with CKD can be exposed to these pollutants due to their pathophysiology (decreased renal function and elimination of these EDCs in urine) and due to medical devices composed of EDCs and used for ESKDD patients' therapy (dialyzers...). A recent meta-analysis summarized the effects of BPA exposure on kidney diseases (Moreno-Gómez-Toledano et al., 2021). However, to our knowledge, no previous study has reviewed EDCs involved in ESKDD patients' exposure, especially during dialysis therapy.

Therefore, our main objective was to fulfil a state-of-the art of the literature with a literature review to summarize EDCs exposure of ESKDD patients and to evaluate factors and medical device components at the origin of this exposure according to dialysis therapy and to the materials used. The present study investigates the monitoring of EDCs involved in ESKDD patients' exposure in several environmental matrices (medical devices, dialysate, effluents...) or biological matrices (blood, urine).

2. Materials and methods

2.1. Search strategy

An electronic search on PubMed, Embase and Web of science databases was performed to screen studies. PubMed was selected for controlled vocabulary and standardized indexation with Medical Subject Headings (MeSH) and for coverage of multiple disciplines of biomedical literature. Embase was selected for Emtree indexation (Elsevier's authoritative life science thesaurus) and for coverage of medical databases including all journals available in Medline and others. Finally, Web of science was selected to perform research in a multidisciplinary database. We created for each database a specific research equation. Boolean operators “AND” and “OR” were used. Regarding EDCs, we selected key words according to the list of recognized EDCs provided by the European Chemicals Agency (ECHA) or substances from list I of the European Union endocrine disruptor lists (National Authorities in Belgium, Denmark, France, the Netherlands, Spain and Sweden, 2022). The key words selected were: “endocrine disruptors”, “Phenol”, “DEHP”, “nonylphenol”, “formaldehyde”, “paraben”, “benzene”, “1,2,4-triazole”, “methylene”, “BHP”, “isophorone”, “cresol”, “bisphenol”, “chloralose”, “carbon disulfide”, “azole”, “cyanamide”, “dapsone”, “diuron”, “formic acid”, “melamine”, “methyl salicylate”, “peracetic acid”, “sodium fluoride”, “sodium perchlorate”, “sulphur dioxide”, “tributyl citrate”, “triclosan”, “dichloromethane”, “thiram”, “tributyl”, “triphenyl phosphate”, “dioxin”, “polycyclic aromatic hydrocarbon”, “Plasticizers”, “Preservatives, Pharmaceutical”, “Food Preservatives”, “Pesticides”, “Flame Retardants”, “Cosmetics”. Key words selected concerning dialysis were: “dialysis”, “hemodialysis”, “hemofiltration”, “hemodiafiltration”, “biofiltration”, “renal dialysis”, “renal replacement therapy”, “convection”. The three research equations in PubMed, Web of science and Embase were performed the 06/29/2022 and no geographic filter or population criteria was used. To ensure that no studies were missed, the references of retrieved articles were analysed. Search in the “grey” literature for additional articles was not conducted. This electronic research was fulfilled according to the PRISMA reporting guidelines to improve the quality, value, and transparent reporting of this literature review (Page et al., 2021). Search equations are available in the Supplemental Material.

2.2. Inclusion and exclusion criteria

Inclusion criteria were defined as follows: original research published, regarding patients' EDCs exposure from dialysis treatment or patients' EDCs exposure due to the release of EDCs from dialysis equipment, or environmental studies on EDCs release from dialysis equipment into dialysis liquids.

Exclusion criteria were defined as follows: research focused on validation method only, research not focused on dialysis equipment, research focused on uraemia substances, research focused on allergenic

molecules, research with unavailable full text, non-English language research, repeated publications, letters, editorials, comments, reviews, meta-analysis, and animal studies.

2.3. Selection and data extraction

First, duplicated literatures, retracted literatures and non-English literatures were excluded according to the exclusion criteria. Then, two authors of this work (GC and JG) independently checked the relevance of literatures to exclude unqualified literature by reading titles. Then, these authors checked the relevance of selected literatures by reading Title and Abstract. Finally, the last selection of articles was done by reading full text. A third author (S-AT) judged the literature in case of questions or disagreement between the first two authors.

Regarding data extraction, two authors (GC and JG) independently collected information coming from each included literature before pooling these data. Information collected included titles, authors, years of publication, EDCs studied, matrix studied, EDCs levels and potential effects of EDCs exposure.

3. Results and Discussion

3.1. Study selections

A total of 5244 studies were screened from three electronic databases. After screening and evaluation, we finally enrolled twenty-six studies. The screening flow chart is described in Fig. 1 and all the literature data are exhibited in Table 1.

The EDCs investigated in the studies were BPA, Bisphenol S (BPS), Bisphenol B (BPB), Nonylphenol, DEHP, DBP, and Butylbenzyl phthalate (BBP).

In our research, ten studies regarding EDCs in the environment of dialysis patients have been reported. The occurrence of EDCs in the medical devices used for ESKDD patients will be detailed in the following section.

3.2. Endocrine disrupting chemicals in medical devices

Medical devices are composed of complex materials to respond to the requirements of ESKDD patients' management. Several studies have highlighted the detection of EDCs in these devices.

Regarding tubing used in dialysis procedure, DEHP and DBP were assessed in flexible and rigid tubing. DEHP levels for flexible and rigid tubing were 79.3 ± 8.7 to 163 ± 21 and 17.8 ± 2.0 to 23.7 ± 1.9 mg/g of devices, respectively and DBP levels for flexible and rigid tubing were from undetected (ND) to 0.024 ± 0.005 and from undetected to 0.055 ± 0.009 mg/g of devices, respectively. The concentrations of DEHP found were at least five times higher in flexible tubing than in rigid tubing (Veiga et al., 2012). This result was expected since plasticizers are added to make Polyvinyl chloride (PVC) more flexible.

Regarding dialyzers, EDCs extraction was performed from housing materials (HM) and membrane fibers (MF). Elution of BPA from HM in polycarbonate (PC) with methanol were 296 and 345 ng/housing (Haishima et al., 2001). Regarding MF, elution of BPA from polysulfone (PS) and polyester-polymeralloy with hexane and dimethylsulfoxide were 83.1 ± 5.1 and 122.5 ± 6.1 ng, respectively. BPA was detected in other MF of poly-methylmethacrylate, cellulose triacetate and cellulose (CE) in lower concentrations with 0.08 ± 0.01 , 0.08 ± 0.01 and 0.16 ± 0.2 ng (Murakami et al., 2007). Another study focused on BPA, BPB, and BPS contents in fibers of dialyzers with dimethyl sulfoxide and acetonitrile extraction from three dialyzer fibers (PS, Polyamide (PA) and Polyethersulfone (PES) fibers). Both PS and PA fibers contain BPA (20.86 ± 1.18 and 18.70 ± 2.88 ng/mg, respectively) but, on the contrary, PES was BPA-free. Membranes were all composed of BPB (0.30 ± 0.10 , 0.27 ± 0.08 and 2.04 ± 0.40 ng/mg, respectively). The membrane in PES was the only one with BPS contents (0.01 ± 0.01 ng/mg) (Shen

et al., 2019). Finally, regarding MF, one study evaluated DEHP, DBP and BBP in dialyzer fibers in CE and PS. Extraction was fulfilled with hexane. Concentrations reported for DEHP and DBP in CE fibers were 11.3 ± 2.3 and 0.109 ± 0.021 mg/g, respectively (other phthalates were not detected), whereas concentrations reported for DEHP, DBP and BBP in PS fibers were 4.75 ± 0.71 , 0.022 ± 0.010 , and 0.088 ± 0.017 mg/g, respectively. While PS fibers contain DEHP and 2 other phthalates, total amounts of phthalates in CE fibers were more than double compared to PS fibers (Veiga et al., 2012).

One study evaluated BPA extraction from two complete dialyzers (one with a HM in PC and the other with polypropylene (PP), and both with MF in PS and Polyvinylpyrrolidone (PVP)). BPA levels were $18,700 \pm 5,600$ ng/dialyzer and ND, for both, respectively (Badding et al., 2020).

Finally, two studies evaluated DEHP extraction from materials used in PD. The concentrations of DEHP in dialysis bags were assessed. DEHP levels from the packaging materials ranged from 23.02 ± 1.24 to 324.98 ± 14.17 mg/g in the first study and was assessed at 115 ± 23 mg/g in the second study (Kostic et al., 2016; Veiga et al., 2012).

Thus, EDCs were detected in all medical devices evaluated in hemodialysis therapy (HD) or PD. Regarding tubing, extracted EDCs levels were higher in flexible tubing due to plasticizer. However, flexibility is required to perform dialysis session. Regarding dialyzers, HM and MF are composed of EDCs. Levels reported were related to the materials used. Indeed, for instance, a total of 6 EDCs were detected in PS fibers. Thus, manufacturers need to identify the fabrication processes at the origin of this EDCs contribution and to identify alternatives to reduce their presence.

3.3. Endocrine disrupting chemicals in dialysis fluids

EDCs in medical devices according to various process could be released into dialysis fluids and simulated blood compartment. All reports regarding release of EDCs into dialysis fluids are detailed in Fig. 2.

EDCs were found throughout the dialysis process from tap water to dialysate regarding HD and Online hemodiafiltration therapy (HDF) (Bacle et al., 2016, 2019; Veiga et al., 2012). EDCs were also found in dialysate used in PD (Kostic et al., 2016; Mettang et al., 1996a; Nässberger et al., 1987; Sugimura et al., 2001).

BPA was found in tap water used to produce dialysis water (Bacle et al., 2016). Water purification process in dialysis unit was not able to remove BPA from water.

In clinical practice, dialyzers are rinsed before treatment of ESKDD patients. EDCs have been assessed in these rinsing solutions, from several dialyzers, in two studies. The first one focused on five dialyzers (Filtrizer BK-2.1F, Meditor® composed of HM in Polystyrene and MF in Poly(methylmethacrylate); Evodial 2.2, R & D Hospal® composed of HM in PC and MF in acrylonitrile and sodium methallyl sulfonate copolymer; ViE-211, AsahiKASEI® composed of HM in PC and MF in PS; Polyflux 21L, Gambro® composed of HM in PC and MF in polyarylethersulfone, PVP and PA blend and ELISIO-M 210 M, Nipro Europe® composed of HM in PP and MF in PES). Concentrations reported were 96.1 ± 162.7 , 268.0 ± 296.3 , 550.2 ± 317.0 , 721.0 ± 297.4 and 360.0 ± 301.0 ng/dialyzer, respectively (Bacle et al., 2016). The second one, focused on four dialyzers (TS-2.1SL, Toray® composed of HM in PC and MF in PS; Polyflux 210H, AsahiKASEI® composed of HM in PC and MF in polyarylethersulfone, PVP and polyamide blend; Vie-21A, Nipro® composed of HM in PC and MF in PS; and Elisio-21H, Gambro® composed of HM in PP and MF in PES) used for online hemodiafiltration. Concentrations reported were 365.9 ± 266.1 , 299.0 ± 129.7 , 440.4 ± 188.3 , and 111.7 ± 48.4 ng/dialyzer, respectively (Bacle et al., 2019). The levels reported in rinsing solutions were significant and higher than 100 ng/dialyzer, except for one dialyzer. The same result was observed regarding rinsing solutions from ultrafilter used to produce replacement fluid in HDF therapy. Indeed, BPA releases were evaluated for four hours during a stimulate dialysis session, and levels were decreasing from $1033.0 \pm$

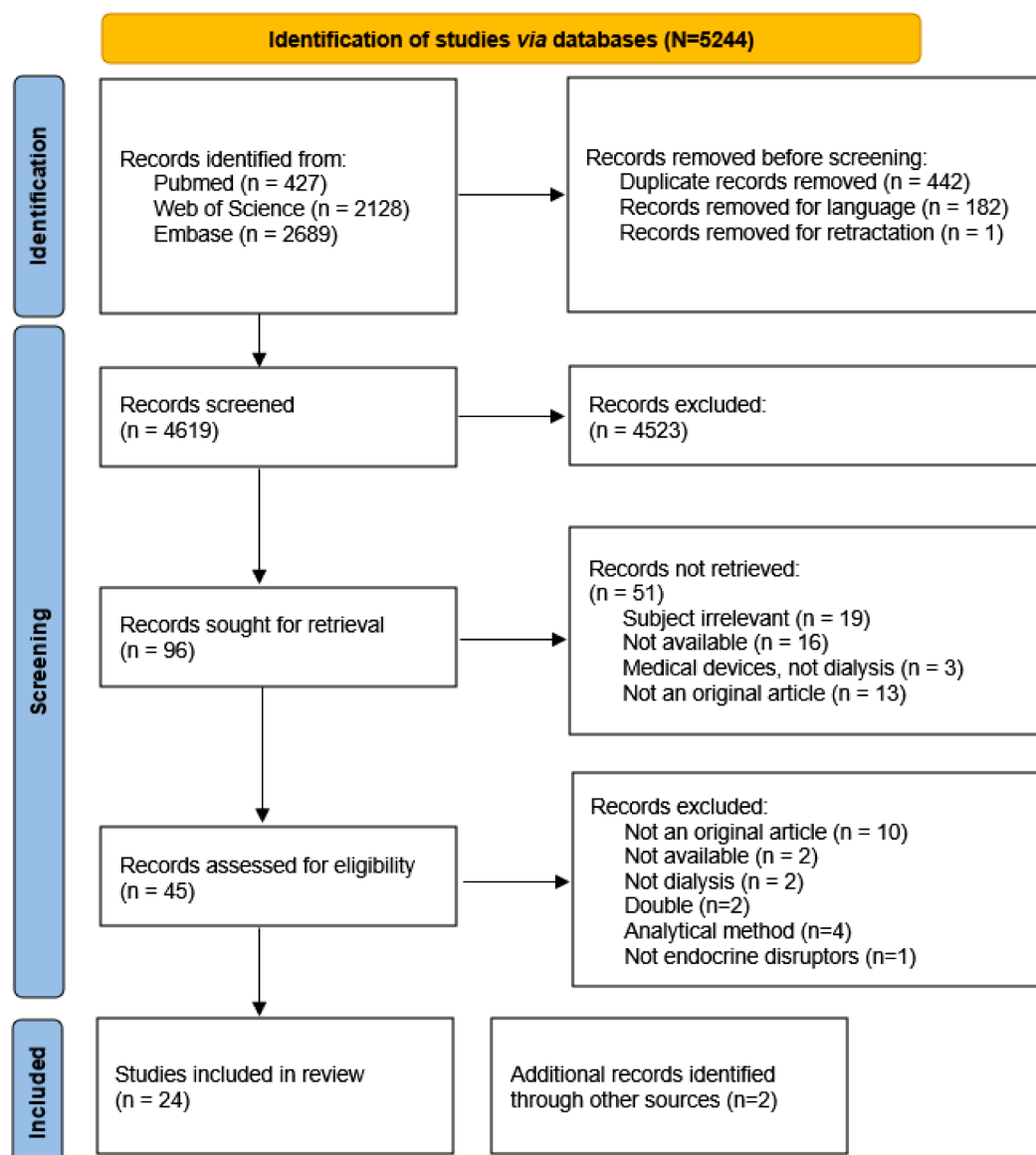


Fig. 1. Flow diagram from the study selection process.

400.8 (T0h) to 265.0 ± 136.0 ng/L (T4h) (Bacle et al., 2019). Thus, rinsing dialyzers and ultrafilters before starting the patient's dialysis session is an essential precaution to reduce ESKDD patients' exposure.

One study evaluated BPA, BPB, and BPS releasing with circulation of phosphate-buffered saline (PBS) containing 40 g/L BSA from three ground dialyzer fibers only (PS, PA, and PES fibers). Both PS and PA fibers release BPA (10.31 ± 5.80 and 15.38 ± 2.85 ng/mL, respectively) but, on the contrary, PES did not release BPA. No membranes release BPB. The membrane in PES was the only one which release BPS (0.09 ± 0.01 ng/mL) (Shen et al., 2019).

Six studies have reported BPA levels eluted from complete dialyzers with the circulation of a simulating blood compartment. All reports regarding elution of BPA in simulating blood compartment and reported concentrations from several dialyzers are detailed in Table 2. The results are presented according to the composition of HM and MF. As a result, we grouped several dialyzers with the same membrane and housing composition together in the same column.

The studies have mainly focused on dialyzers composed of PC housing and PS fibers. One study reported the impact of HM on BPA levels with dialyzers composed of the same fibers but different HM. PC housing seems to release more BPA than PP housing (Badding et al.,

2020). This result was also reported in most of the studies, except for two dialyzers composed of PC housing and PES fibers and for PC housing and polyarylethersulfone (Bacle et al., 2016, Bacle et al., 2019). This result is in accordance with PC composition. Indeed, PC is unanimously recognized as being composed of BPA used as chemical building blocks (Endocrine society, International Pollutants Elimination Network, 2020). MF in poly(methylmethacrylate), acrylonitrile and sodium methallyl sulfonate copolymer, polyarylethersulfone, PVP, PA blend and PES seem to release less BPA than PS fibers (Bacle et al., 2016, 2019; Krieter et al., 2013). In all of these environmental studies, the solvent differences used to identify the presence of EDCs released by dialyzers could influence these results. To better compare studies, it would be necessary to standardize the solvents used.

Regarding the tubes connecting the dialyzer to blood and to dialysate compartment, no significant BPA release was found (Bacle et al., 2016, Bacle et al., 2019). This result is in accordance with the data provided by the European PVC manufacturers who no longer use BPA in their PVC products (SCENIHR - Scientific Committee on Emerging and Newly Identified Health Risks, 2015; Testai et al., 2016).

Several studies have evaluated patient BPA exposure estimates resulting from hemodialysis sessions. One study focused on dialyzer and

Table 1
Characteristics of the twenty-six studies included in the review.

Reference, country	Type of study	Endocrine disruptor	Studied samples	Number of samples	Analytical method
Bacle et al., 2016 (France)	Environmental study	BPA	/ Dialysis water Dialysate Rinsing dialyzer solution Simulating blood (water) Simulating dialysate (water)	Total samples N = 159 n = 72 n = 42 n = 15 n = 15 n = 15	UHPLC-MS/MS
Bacle et al., 2019 (France)	Environmental study	BPA	/ Dialysis water Ultrapure water Ultrapure dialysate Replacement fluid Dialysis concentrates Ultrafilters Rinsing dialyzer solution Simulating blood (water) Simulating dialysate (water)	Total samples N = 246 n = 42 n = 6 n = 30 n = 30 n = 24 n = 6 n = 36 n = 36 n = 36	UHPLC-MS/MS
Badding et al., 2020 (USA)	Environmental study	BPA	Simulating dialysate (95 % ethanol in 0.9 % saline (vol/vol) and 17.2 % ethanol in 0.9 % saline (vol/vol))	n = 6	UHPLC time of flight MS
Bosch-Panadero et al., 2015 (Spain)	Interventional study, crossover study	BPA	Blood Blood mononuclear cells	n = 69 patients treated by HD n = 10 healthy volunteers	ELISA
Christensson et al., 1991 (Sweden)	Interventional study, crossover study	DEHP	Blood	n = 11 patients treated by HD	HPLC-UV
Dine et al., 2000 (France)	Noninterventional study	DEHP	Blood	n = 11 patients treated by HD	HPLC-UV
Faouzi et al., 1998 (France)	Noninterventional study	DEHP	Blood	n = 21 patients treated by HD n = 5 healthy volunteers	HPLC-UV
Fernandes et al., 2018 (Brazil)	Noninterventional study	DEHP	Blood	n = 5 patients treated by HD n = 3 healthy volunteers	HPLC-UV
Haishima et al., 2001 (Japan)	Environmental study	BPA	Water Bovine serum	n = 4 hemodialyzers	HPLC, GC-MS, LC-MS and NMR spectroscopy
Kambia et al., 2001 (France)	Interventional study, crossover study	DEHP	Blood	n = 20 patients treated by HD	HPLC-UV
Kanno et al., 2007 (Japan)	Noninterventional study	BPA	Blood	n = 88 patients (45 patients treated by HD, and 43 patients treated by peritoneal dialysis therapy (PD)) n = 12 healthy controls	ELISA
Kostic et al., 2016 (Serbia)	Environmental study	DEHP	Dialysis bag (hexane) Tubing from dialysis set (hexane) Infusion bottle (hexane) Tubing from infusion set (hexane) Peritoneal dialysis solution Physiological saline solution Ringer's solution	n = 3 n = 3 n = 3 n = 3 n = 6 n = 6	GC-MS
Krieter et al., 2013 (Germany)	Environmental study, / / Noninterventional study	BPA	Simulating blood (water) Simulating dialysate (water) Blood	n = 6 n = 18 dialyzer / / n = 152 patients + 18 patients treated by HD n = 24 healthy controls	ELISA

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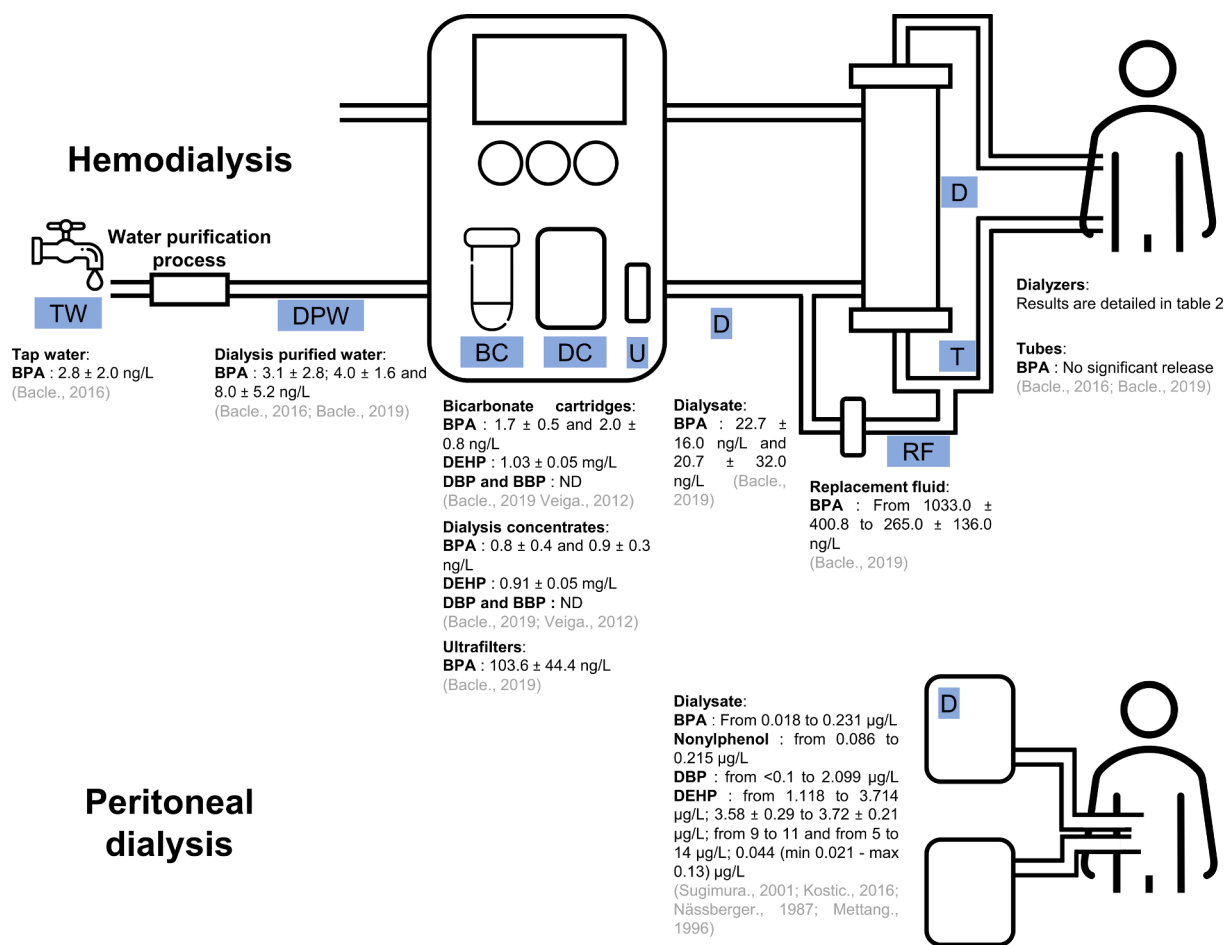


Fig. 2. Endocrine disruptors in dialysis fluids. Legend: ND: undetected.

estimated patient exposure to 26 ng/kg b.w./day (Badding et al., 2020). Regarding all the materials, water contamination and dialysis concentrate cartridges, this exposure could reach 140 ng/kg b.w./day in HD and HDF, respectively (Bacle et al., 2016; Bacle et al., 2019). Regarding other EDCs, exposure estimates of DEHP from one PD were evaluated to 30 μg (Kostic et al., 2016).

These data highlight the presence of several EDCs in the environment of the dialysis patient: dialysis water, dialysate used in HD and PD and substitution fluid. Dialyzers with HM in PC and MF in PS seem to overexpose ESKDD patients to BPA. Regarding MF in PS, BPA, and phthalates like DBP, BBP and DEHP have been quantified. On the contrary, fibers in CE release less BPA but more DEHP. The presence of EDCs in dialysis fluids could lead to internal exposure of ESKDD patients. Indeed, EDCs released in dialysate by bicarbonate cartridges, dialysis concentrates and ultrafilters and EDCs in dialysis purified water could lead to overexpose ESKDD patients. Furthermore, EDCs in replacement fluid used in HDF, dialysate used in PD, simulated blood compartments from dialyzers used in HD or HDF and tubing used in HD, HDF and PD will be directly available and responsible of systemic exposure of ESKDD patients. These theoretical and systemic exposure will be involved in ESKDD patients' exposure and will be detailed in the following section.

3.4. Endocrine disrupting chemicals assessed in dialysis patients

ESKDD patients are exposed to EDCs during dialysis sessions. This exposure is related to several criteria.

3.4.1. Endocrine disrupting chemicals assessed according to patient's profile

During the progress of kidney disease, patients' exposure to EDCs increases. Indeed, several studies highlighted an overexposure of ESKDD patient's vs healthy controls regarding BPA (Bosch-Panadero et al., 2016; Kanno et al., 2007; Krieter et al., 2013; Mas et al., 2021, 2018; Shen et al., 2019), and BPS (Mas et al., 2021; Shen et al., 2019). Regarding DEHP, one study highlighted overexposure of ESKDD patients, and, at the opposite, another one did not (Faouzi et al., 1999; Mettang et al., 1996a). Regarding BPA and BPS, levels increased as renal function deteriorated (Krieter et al., 2013; Murakami et al., 2007; Shen et al., 2019). Indeed, BPA and BPS levels were negatively associated with GFR (Krieter et al., 2013; Shen et al., 2019) and BPA was positively associated with serum creatinine (Murakami et al., 2007). Regarding BPB, no correlation was identified (Shen et al., 2019).

Regarding diabetes, ESKDD diabetic patients were overexposed in pre-dialysis samples with 4.4 ± 0.6 vs. 3.9 ± 0.7 ng/mL in ESKDD non-diabetic patients (Turgut et al., 2016).

Other studies including clinical data did not show any common differences in exposure according to these data (Bosch-Panadero et al., 2016; Mas et al., 2018; Mettang et al., 2000; Quiroga et al., 2017; Shen et al., 2019). To date, only the study previously described found a relationship between dialysis, EDCs exposure and health effects, with a positive correlation between diabetes and pre-dialysis BPA levels (Turgut et al., 2016). However, this study does not explain this correlation which could be due to other factors that dialysis therapy. An editorial recommends performing longer follow-up of ESKDD patients to explore if EDCs like BPA may have negative effects on this population, especially on cardiovascular risk, blood pressure increase and monocyte

Table 2
Levels of Bisphenol A (BPA) eluted from several dialyzers in simulated blood compartment (ng/dialyzer).

	Solvent	HM: PST MF: Poly (methylmethacrylate)	HM: PC MF: Acrylonitrile and sodium methallyl sulfonate copolymer	HM: PC MF: PS	HM: PC MF: PS, PVP	HM: PP MF: PS, PVP	HM: PC MF: Polarylethersulfone, PVP, PA blend	HM: PC MF: PES	HM: PP MF: PES	HM: PC MF: acetate cellulose	HM: PST MF: PS	HM: PC MF: PA
Bacle et al., 2016 (France)	Water	0.7 ± 0.6	23.6 ± 26.0	174.9 ± 95.0			5.3 ± 4.3		8.7 ± 19.8			
Bacle et al., 2019 (France)	Water			0.6 ± 0.5 38.5 ± 41.7			1.4 ± 0.2		3.7 ± 0.5			
Badding et al., 2020 (USA)	17.2 % ethanol				3,700 ± 400	ND						
Haishima et al., 2001 (Japan)	Water			141.8 31.0						34.1	3.78	
	Bovine serum			2,090 1,010						196.1	140.7	
Krieter et al., 2013 (Germany)	Water			140.8 ± 38.7 48.1 ± 7.7				6.2 ± 2.5				
Shen et al., 2019 (China)	40 g/L BSA			515.5 ± 290				ND				769 ± 142.5

Legend: BPA: Bisphenol A; BSA: Bovine serum albumin; HM: Housing material; MF: Membrane fibers; ND: Undetected; PA: Polyamide; PC: Polycarbonate; PES: Polyethersulfone; PP: Polypropylene; PS: Polysulfone; PST: Polystyrene; PVP: Polyvinylpyrrolidone.

Filtryzer BK-2.1F® (Meditor, Tokyo, Japan): HM in PST and MF in Poly (methylmethacrylate); **Evodial (Dialycard) 2.2® (R & D Hospital, Meyzieu, France):** HM in PC and MF: in Acrylonitrile and sodium methallyl sulfonate copolymer; **ViE-21® (AsahiKASEI, Tokyo, Japan):** HM in PC and MF in PS; **Polyflux® 21L (Gambro, Colombes, France):** HM in PC and MF in Polarylethersulfone, PVP and polyamide blend; **Elisio 21 M® (Nipro Europe St. Beauzire, France):** HM in PP and MF in PES; **TS-2.1SL (Toray, Tokyo, Japan):** HM in PC MF in PS; **Elisio 21H® (Nipro Europe St. Beauzire, France):** HM in PP and MF in PES; **Polyflux® 210H (Gambro, Colombes, France):** HM in PC and MF in Polarylethersulfone, PVP and polyamide blend; **Optiflux F250® (Fresenius Medical Care, Waltham, USA):** HM in PC and MF in PS and PVP; **FX CorDiax 120® (Fresenius Medical Care, Waltham, USA):** HM in PC and MF in PS and PVP; **Pureflux 170H® (Nipro Europe St. Beauzire, France):** HM in PC and MF in PES; **F 60 S® (Fresenius Medical Care, Waltham, USA):** HM in PC and MF in PS; **F 6 HPS® (Fresenius Medical Care, Waltham, USA):** HM in PC and MF in PS.

cytotoxicity (Neri, 2016). Regarding phthalates, no study has found a relationship between dialysis exposure and health effects. Further studies are needed to demonstrate a relationship between exposure to EDCs throughout the dialysis therapy and health effects. However, due to the ESKDD patients' profile with multiple comorbidities, it is difficult to associate EDCs exposure with a health effect. As a result, we should not wait for these studies to be available before implementing policies to reduce exposure to ESKDD patients.

3.4.2. Endocrine disrupting chemicals assessed according to dialysis modalities

Regarding dialysis modalities, two studies compared the BPA exposure from HD and HDF in ESKDD patients. In the first, ESKDD patients were treated for 3 weeks with HD, followed by 3 weeks with HDF and finally another 3 weeks with HD. BPA samples were filled during the last session of each period and BPA levels decreased significantly during HDF (Quiroga et al., 2017). The second compared BPA pre dialysis in ESKDD patients treated for 6 months with HD or HDF. Patients treated by HD were overexposed compared to HDF (98.96 ± 120.75 vs 12.12 ± 15.9 ng/mL) regardless of the type of dialyzer used (PS or PN fibers) (Mas et al., 2018). As a result, HDF seems to prevent BPA exposure of ESKDD patients. However, regarding the first study, BPA levels decreased during HDF therapy but HD and HDF levels at the end of each period were similar (Quiroga et al., 2017). Regarding the second one, ESKDD patients exposure to BPA treated by HDF was compared to previous results coming from a prior study (Bosch-Panadero et al., 2016). Thus, these results shall need to be confirmed with further studies. No data were available regarding other EDCs according to these dialysis modalities.

Two studies compared the role of HD and PD on ESKDD patients' exposure. In the first, serum BPA levels were higher in patients treated by HD (5.3 ± 0.3 ng/mL) vs PD (3.08 ± 0.2 ng/mL) (Kanno et al., 2007). The same observation was fulfilled with BPA in one study but also with BPB and BPS. Indeed, BPA levels were higher in patients treated by HD with 1.01 ($1.01, 8.65$ ng/mL) vs PD 1.01 ($1.01, 1.01$ ng/mL), BPB levels were higher in patients treated with HD with 7.66 ($5.24, 9.77$ ng/mL) vs PD (data not available) and BPS levels were higher in patients treated with HD with 23.73 ($23.73, 23.73$ ng/mL) vs PD (data not available) (Shen et al., 2019).

Finally, regarding DEHP, PD vs HD seems to decrease patient exposure, however, further studies are still needed to confirm these results (Nässberger et al., 1987).

3.4.3. Endocrine disrupting chemicals assessed according to medical devices

Several studies have evaluated the impact of a dialysis session and/or its conditions on the bisphenol's pre and post dialysis levels found. Table 3 summarize the available data regarding bisphenols levels according to the dialyzer used for a single dialysis session (bisphenols pre and post dialysis).

The main dialyzers investigated were composed of PS and PN fibers. All studies included patients treated with a dialyzer in PS fibers. Some studies highlighted the role of the dialyzer composition on BPA levels in blood patients. Indeed dialyzer fibers in PS seem to overexpose ESKDD patients to BPA (Bosch-Panadero et al., 2016; Murakami et al., 2007; Turgut et al., 2016). At the opposite, 3 studies did not highlight this overexposure (Krieter et al., 2013; Mas et al., 2021, Mas et al., 2018). Overexposure to BPA with PS dialyzers was also evaluated in one study with assessment in pre-post dialysis samples on the day when the type of dialyzer was changed. This study detected a significant decrease of BPA levels when patients were switched from PS to PN dialyzer from 23.42 ± 20.88 to 6.44 ± 10.77 ng/mL whereas switch from PN to PS did not impact levels (8.97 ± 7.88 vs. 8.43 ± 6.99) (Mas et al., 2018).

Chronic exposure was also evaluated in five literatures (Bosch-Panadero et al., 2016; Krieter et al., 2013; Mas et al., 2021, 2018; Murakami et al., 2007). Again, dialyzer with fibers in PS seemed to overexpose ESKDD patients to BPA vs fibers in PN. Indeed, patients were treated

with PS fibers then switch to PN fibers and levels reported in pre-dialysis samples were 70.6 ± 8.4 vs. 47.1 ± 7.5 ng/mL; 23.42 ± 20.88 vs. 8.98 ± 7.88 ng/mL and 4.83 ± 1.94 vs. 3.78 ± 2.57 ng/mL, for 3 studies (Bosch-Panadero et al., 2016; Mas et al., 2018; Murakami et al., 2007).

Regarding DEHP exposure, several studies have evaluated the impact of a dialysis session and/or its conditions on the DEHP pre-post levels found. Table 4 summarizes the available data regarding DEHP levels reported in the literature according to the dialyzer used for a single dialysis session.

DEHP levels tend to increase during a dialysis session with dialyzers composed of PS, PES and Polyacrylonitrile (Dine et al., 2000; Faouzi et al., 1999; Fernandes et al., 2018; Mettang et al., 1996b). However, no data were available regarding the composition of the tubing except for two of them (Christensson et al., 1991; Kambia et al., 2001). They evaluated DEHP exposure according to the materials used in tubing for a single HD session without data on dialyzer fibers. In the first, DEHP level decreased after one day, one month and 6 months of treatment with tubing composed of Tri-(2-ethylhexyl) trimellitate (TEHTM) plasticizer (Christensson et al., 1991). The same result was observed with DEHP decreased when using TOTM-DEHP plasticizer vs DEHP plasticizer (122.95 ± 33.94 vs 41.80 ± 4.47 mg) (Kambia et al., 2001).

For PD, DEHP exposure occurs with peritoneal dialysis solutions and bags composed of PVC plastics with 0.09 ± 0.065 mg/L and 0.079 (min 0.032 –max 0.21) vs. 0.134 (min 0.027 –max 0.48) for DEHP pre-post PD (Mettang et al., 1999, Mettang et al., 1996a). One study evaluated chronic exposure from PD with collection of blood before, and 42 days after switching from a plasticizer containing PVC to the polyolefine plasticizer-free. DEHP levels seems to decrease (0.097 ± 0.076 vs. 0.069 ± 0.046 µg/mL), but no significant relation was observed (Mettang et al., 2000). Thus, regarding HD and PD, DEHP levels tend to increase between pre and post dialysis samples regardless of materials composition. However, materials with alternative plasticizer of DEHP seem to decrease ESKDD patients' exposure like for tubing. Due to the lack of data and to the date of some studies, these results shall need to be confirmed with further studies.

Our study highlights the multiple exposures of patients to EDCs like bisphenols (BPA, BPS and BPB) and plasticizers like DEHP, DBP and BBP. Indeed, adult patients undergoing dialysis therapy have the highest exposure level to BPA and DEHP, due to the chronic nature of the treatment (SCENIHR - Scientific Committee on Emerging and Newly Identified Health Risks, 2015; Testai et al., 2016; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2016). All these results lead to multiple and repeated exposure of ESKDD patients. It also leads to a combined toxicity named mixture or cocktail effects (Gaudriault et al., 2017; Kortenkamp, 2007). Cocktail effects are described as synergistic toxicity when several EDCs are simultaneously present at their target place. Exposure to EDCs can lead to reproductive disorders, metabolic syndromes such as type 2 diabetes, obesity and cardiovascular diseases such as angina, heart attack and hypertension (Rochester, 2013; Chen et al., 2016; Hu et al., 2019; Eales et al., 2022). Combine effects of BPA and DBP lead to up-regulated gonadotrophin-releasing hormone receptor, progesterone receptor and androgen receptors expression levels in rats with synergistic or additive effect (Zhang et al., 2013). A recent review summarizes the combined toxicity of EDCs reported in literature (Hamid et al., 2021). It has an important impact not only on fertility in young people, but also on the development of chronic diseases that can affect elderly patients. Hence, ESKDD patients are a vulnerable population regarding EDCs.

3.5. Strategies to reduces endocrine disrupting chemical exposure

Regarding the literature, a recent commentary suggested some solutions to decrease BPA exposure of CKD patients: BPA-free dialyzers or HDF instead of HD (Quiroga, 2021). Furthermore, our review has highlighted the importance of rinsing medical devices before connecting them to patients (dialyzers, dialysis machines, ultrafilters, etc.) (Bacle

Table 3

Levels of Bisphenols in blood compartment from patients undergoing dialysis therapy according to dialyzers used (ng/mL).

	Patients and study design	Dialysis modalities	Bisphenols levels in pre vs post dialysis blood samples according to the dialyzer fibers used (ng/mL)			
			PS	PN	PES	CE
Bosch-Panadero et al., 2015 (Spain)	Group A: 28 patients treated with PS fibers, 3 months with PN fibers and 3 months with PS fibers Group B: 41 patients treated with PN fibers, 3 months with PS fibers and 3 months with PN fibers	HD	BPA levels 46.3 ± 8.5 vs 78.4 ± 11.0 ng/mL (p < 0.05)	BPA levels NA (NS)		
Krieter et al., 2013 (Germany)	Group A: 18 patients treated with PS fibers twice 4 weeks Group B: 18 patients treated with PES fibers 4 weeks	HD	BPA levels NA (NS)		BPA levels NA (NS)	
Mas et al., 2018 (Spain)	Group A: 31 patients treated with PN fibers 6 months and with PS 3 months fibers Group B: 29 patients treated with PS fibers 6 months and with PN fibers 3 months	HDF	BPA levels 11.14 ± 15.98 vs 11.86 ± 10.41 (NS)	BPA levels 11.42 ± 12.88 vs 7.83 ± 10.98 (NS)		
Mas et al., 2021 (Spain)	Group A: 9 patients treated with triacetate fibers, with PS fibers, with triacetate fibers and with PN fibers each one for 1 week Group B: 5 patients treated with triacetate fibers, with PN fibers, with triacetate fibers and with PS fibers each one for 1 week	HDF	BPA levels 13.17 ± 14.81 vs 15.83 ± 19.25 (NS)	BPA levels 11.51 ± 13.55 vs 12.42 ± 11.10 (NS)		
Murakami et al., 2007 (Japan)	15 patients treated 3 months with PS fibers, 1 month with CE fibers and 1 month with PS fibers	HD	BPA levels 4.83 ± 1.94 vs 6.62 ± 3.09 (p < 0.05) 3.78 ± 2.57 vs 4.27 ± 2.98 (p < 0.05)			BPA levels 2.01 ± 2.10 vs 1.48 ± 1.41 (NS)
Turgut et al., 2016 (Turkey)	47 patients treated with PS fibers	HD	BPA levels 4.06 ± 0.73 vs 5.57 ± 1.20 (p < 0.0001)			

Legend: BPA: Bisphenol A; BPS: Bisphenol S; CE: Cellulose; HD: Hemodialysis therapy; HDF: Online hemodiafiltration therapy; NA: Not available; NS: Not significant; PES: Polyethersulfone; PN: polynephron; PS: Polysulfone.

Table 4

Levels of Di(2-ethylhexyl) phthalate (DEHP) in blood compartments from patients undergoing dialysis therapy according to materials used (µg/mL).

	Patients and study design	Dialysis modalities	DEHP levels in pre vs post dialysis blood samples according to the materials used (µg/mL)					
			Tubing			Fibers		
			DEHP plasticizer	TEHTM plasticizer	TOTM-DEHP plasticizer	Polyacrylonitrile	PES	PS
Christensson et al., 1991 (Sweden)	11 Patients switched from tubing containing DEHP to tubing containing TEHTM for 6 months	HD	0.10 (<0.05 – 0.11) vs 0.70 (0.30 – 1.6)	<0.05 (<0.05–0.11) vs <0.05 (<0.05 – 0.18) ND vs ND ND vs 0.065 (<0.05 – 0.11)				
Kambia et al., 2001 (France)	Group A: 10 patients treated with DEHP tubing for 1 session Group B: 10 patients treated with TEHTM tubing for 1 session	HD	NA		NA			
Dine et al., 2000 (France)	11 patients treated with polyacrylonitrile fibers for 1 session	HD				0.47 ± 0.16 vs 1.99 ± 0.83 (calculated from data)		
Faouzi et al., 1999 (France)	21 patients treated with polyacrylonitrile fibers for 1 session	HD				0.43 ± 0.19 vs NA		
Fernandes et al., 2018 (Brazil)	5 patients treated with PES fibers for 1 session	HD					0.21 ± 0.23 vs 0.34 ± 0.30 (calculated from data)	
Mettang et al., 1996b (Germany)	21 patients treated with PS fibers for 1 session	HD						NA (p < 0.05)

Legend: DEHP: Di(2-ethylhexyl) phthalate; HD: Hemodialysis therapy; NA: Not available; ND: Undetected; PES: polyethersulfone; PS: Polysulfone; TEHTM: Tri-(2-ethylhexyl) trimellitate-Di(2-ethylhexyl) phthalate; TOTM: Tri(2-ethylhexyl) trimellitate; TOTM: Trioctyltrimellitate.

et al., 2016, Bacle et al., 2019). The prevention of dialysis patient exposure must simultaneously consider exposure to all EDCs. On this subject, our study underlined the presence of BPA analogues such as low levels of BPS in a BPA-free dialyzer (Shen et al., 2019). Similarly, dialyzers in PS were identified in our study as releasing more BPA, but on the contrary they would decrease the release of DEHP (Veiga et al., 2012). Further studies are still required regarding the presence and release of all EDCs within the different medical devices. Moreover, medical device manufacturers need to identify the fabrication processes at the origin of this EDCs contribution and identify alternatives to reduce their presence. In parallel, the international non-governmental organization Health Care Without Harm (HCWH) has published a guide for replacement of hazardous chemicals like BPA and phthalates in medical devices (Health Care Without Harm, 2014). The French National Institute for Industrial Environment and Risks has created a website with various families of molecules that are alternatives to EDCs like bisphenols or phthalates, or alternatives to materials that require bisphenols or phthalates, by illustrating them with accurate examples of substitution and with concrete practices or experiences in supply chains (INERIS - French National Institute for Industrial Environment and Risks, 2022). Finally, in the European Union a regulation on medical devices was adopted on 5 April 2017 and has been applied recently. This regulation specifies that medical devices shall contain only the carcinogenic, mutagenic, or toxic to reproduction ('CMR'), of category 1A or 1B substances and substances having endocrine-disrupting properties in a concentration that is above 0.1 % weight by weight (w/w) (Regulation (EU) (2017)/745 of the European Parliament and of the Council of 5 April (2017) on medical devices, 2020). This regulation will contribute to reconsider the conception of medical devices and, ultimately, to reduced ESKDD patients' exposure.

3.6. Limitations and perspectives

Our work has some limitations. Our study only focuses on recognized and under assessment EDCs, even though dialysis patients are also exposed to other suspected EDCs like Bisphenol F (another analogues of BPA), Dimethyl phthalate and diethyl phthalate (DEP) (plasticizer belonging to the phthalates), and chlorinated derivatives of BPA (ClxBPA) (Bacle et al., 2019; Shen et al., 2019; Veiga et al., 2012). ClxBPAs formation results from a reaction between chlorine and BPA in drinking water from water treatment plants (Dupuis et al., 2012). ClxBPAs have estrogenic activity up to 38 times higher than BPA and have been detected in water, ultrapure water, dialysate and the replacement fluid used in dialysis therapy (Fukazawa et al., 2002; Bacle et al., 2019). Regarding phthalates, the literature is quite old and is almost exclusively centred on DEHP. However, patients are not only exposed to DEHP. In fact, manufacturers were forced to find alternatives of DEHP like TEHTM, Di-isononylphthalate (DINP), Trioctyltrimellitate (TOTM) or Bis(2-ethylhexyl) terephthalate (DEHT) to maintain the elasticity of PVC when the European directive classified DEHP as a product with a toxicity risk (Bernard et al., 2014). Furthermore, the French National Agency for the Safety of Medicines and Health Products (ANSM) checked PVC medical devices advertised as DEHP-free and found the presence of DEHP in 41 out of 61 samples (more than 67 % of cases) (ANSM - Agence nationale de sécurité du médicament et des produits de santé, 2016). It is consequently important to conduct further studies on ESKDD patients' exposure to phthalates.

In this review, studies quantified EDCs in the environment and in the blood of ESKDD patients. For ESKDD patients who perform dialysis sessions very frequently, blood sampling does not add a sample to patient's management. For this type of patient, blood matrix is required to assess acute exposure during a single dialysis session. However, blood matrix is not optimal to assess long-time exposure to EDCs with short half-life like bisphenols and phthalates (Martín et al., 2016). To investigate chronic exposure (over 1 month) to a dialysis machine, for

instance, the detection of EDCs could be conducted in the hair. Recently, several analytical methods have been developed and would enable this type of study to be envisaged in future research (Robin et al., 2022; Hsu et al., 2022).

4. Conclusion

In conclusion we have successfully carried out a literature review of the literature regarding ESKDD patients' exposure to EDCs during dialysis sessions. With this review, we have demonstrated multiple exposure of ESKDD patients during dialysis, recommended measures to reduce this exposure and provided guidance for future research.

CRedit authorship contribution statement

Guillaume Cambien: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Antoine Dupuis:** Conceptualization, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft. **Jérémy Guihenneuc:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft. **Marc Bauwens:** Conceptualization, Validation, Writing – original draft. **Mohamed Belmouaz:** Conceptualization, Validation, Writing – original draft. **Sarah Ayraud-Thevenot:** Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

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