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Bisphenol A in Chronic Kidney Disease

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Abstract

Several types of medical devices are produced using polycarbonate (PC) polymer. Unfortunately, these medical devices produced using PC could contain and release Bisphenol A (BPA) residual in routinely use. Published evidence on BPA in dialysis or Chronic Kidney patients (CKD) is scarce and limited to the observation of increased blood BPA levels. Increased serum BPA with decreasing renal function was observed in a smaller study of 32 CKD patients, suggesting that BPA may accumulate. Recently a crossover study evaluated the impact of the choice of dialyzer (BPA-free versus BPA-containing) on serum and intracellular BPA levels and on inflammation and oxidative stress markers. Currently, BPA is still considered, from regulatory agencies, safe enough in the general population, despite several red flags, as it is readily excreted in the urine. However, patients in End Stage Renal Disease (ESRD) are unable to excrete BPA in their urine, leading to BPA accumulation. Repeated loading of BPA during hemodialysis with BPA-containing membranes may aggravate the problem due to migration of BPA from dialyzers to the blood of patients. In contrast, some recent studies on the chronic use of BPA-free dialyzers, results in decreased BPA levels.

Keywords: BPA, chronic kidney disease, hemodialysis

1. Introduction

Bisphenol A, normally abbreviated as BPA, is an organic compound with two vicinal phenolic group. It is also known as 2,2-bis-(4-hydroxyphenyl) propane. BPA is a high-volume industrial chemical used in the production of epoxy resins and polycarbonate (PC) plastics.

The chemical synthesis and industrial conversion of BPA in PC and epoxy resin are shown in **Figure 1**.

Many food and drink containers are manufactured with PC plastics. On the other side, epoxy resins are normally used as inner liners in food and drink containers; polycarbonate plastics may be encountered in many products, especially in food and drink containers, while epoxy resins are frequently used as inner liners of metallic food and drink recipients with the aim to prevent corrosion. Some thermal paper used in cash registers or similar devices could be a source of BPA. Additionally, BPAs have been used in polyvinylchloride (PVC) industries and metal foundries for cast and molding production.

BPA was synthesized for the first time by the Russian chemist A.P. Dianin in 1891, and in the early 1930s, the British biochemist E.C. Dodds tested BPA as an artificial estrogen but found it less effective than estradiol [1].

Dodds eventually developed a structurally similar compound, diethylstilbestrol (DES), which was used as a synthetic estrogen drug [2] in women and in animals until it was banned in 1971 due to its risk of causing cancer. Actually, bisphenol A is used primarily to make plastics, and BPA is contained in products that have been in commercial use since 1957. BPA-based plastic is clear and tough and is made into a variety of common consumer goods, such as water bottles, sports equipment, CDs, and DVDs. Epoxy resins containing BPA are used to line water pipes, as coatings on the inside of many food and beverage cans and in making thermal paper such as that used in sale receipts. In 2015, an estimated 5.4 million tonnes of BPA chemical were produced for manufacturing polycarbonate plastic, making it one of the highest volume of chemicals produced worldwide.

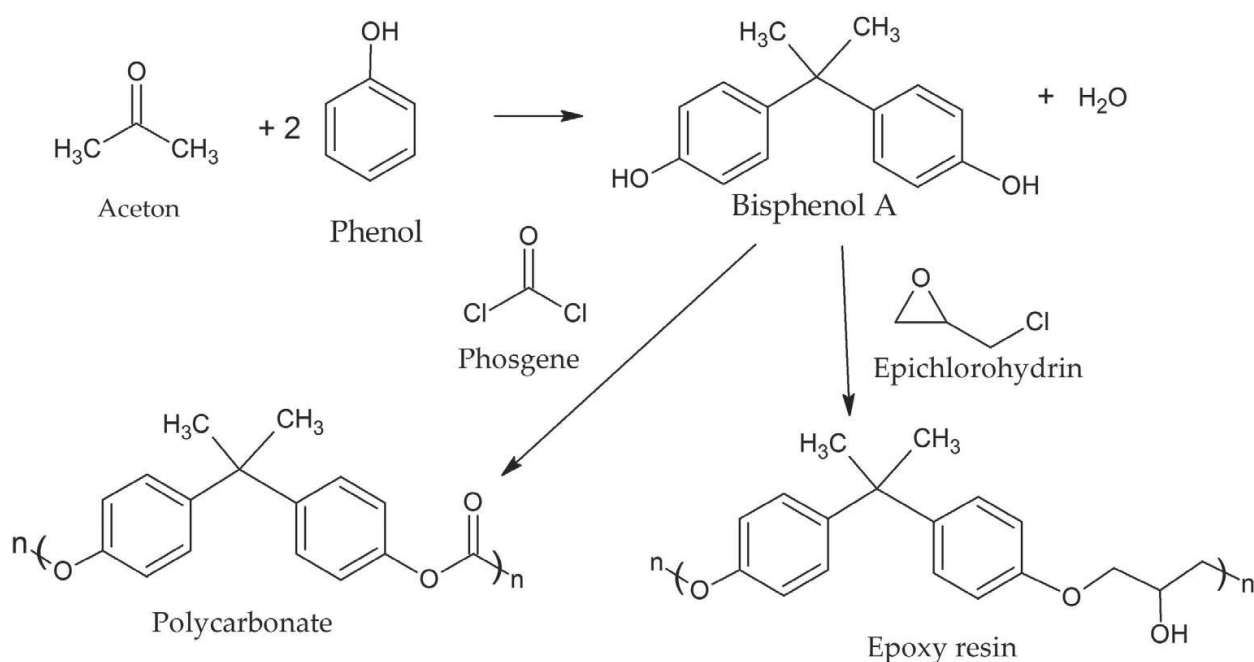


Figure 1. Bisphenol A as a commodity chemical and essential component of two classes of polymers.

2. Human exposure to BPA

The human population is primarily exposed to BPA through the diet. Other possible sources of bisphenol A exposure are air, dust, water, and skin contact with thermal paper. From this point of view, most of 50% of BPA exposure account from food and beverages packed and distributed in boxes, bottles, or cans containing BPA. The remaining 50% is coming from thermal paper, or paper in general, in contact with skin. Monomers of BPA are released from slow decay of polymers in contact with food and liquids. BPA release could be accelerated by heating, contact with alkaline or acidic substances, repeated use and exposure to microwaves. In **Table 1**, an overview of typical concentration in food and non-food BPA-containing materials is shown.

BPA may be absorbed in the gastrointestinal tract after ingesting products packed in plastic containers. Like intestinal phenols, BPA is conjugated by glucuronic acid in bowel and liver and excreted in urine as BPA-glucuronide [3].

Levels, normally less than 1 µg/L, measured in human biological fluids indicate a recent exposure to the molecule because of its rapid conjugation and elimination by the liver and gastrointestinal tract in a few hours. Kinetics in vivo study support this hypothesis of rapid plasma clearance of BPA metabolites.

Measured concentrations of BPA in human blood, urine, and other tissues indicated that the majority of the population (91–99%) has detectable levels of BPA-conjugates in their urine, confirming that exposure is widespread in the human population.

Type of food product	Typical BPA concentration
Canned food	30–50 µg/kg
Noncanned food	0–10 µg/kg
Canned drinks and dairy products	0.5–5 µg/kg
Noncanned drinks and dairy products	0–1 µg/kg
Initial breast milk	3 µg/L
Mature breast milk	1.5 µg/L
Cosmetics	31 µg/kg product
Thermal paper	0.8–3.2 µg/100 g
Indoor air	0.5–5.3 ng/m ³
Dust	117–20,000 µg/kg
Toys/rattles (mouthed)	0.14 µg/kg product
Pacifiers (mouthed)	0.28–0.36 µg/product

Source: European Food Safety Authority.

Table 1. Overview of BPA typical concentration in food and nonfood BPA-containing materials.

The largest scale studies with a consistently high number of enrolled participants ($n = 2517$ and 5476 individuals) spread over a broad range of age were carried out in the USA and Canada, respectively [4–6].

In these studies, the highest BPA levels detected in urine were 3.6 ng/mL for the US and 1.30 ng/mL for the Canadian ones in a subgroup of population within the age group of 6 and 11 years. On the contrary, the adult population had lower BPA urine concentration: 2.6 and 1.16 ng/mL, respectively. Zhang et al. show the same results in a recent study conducted on the Asian population [7].

Mose et al. [8] studied the BPA trans-placental transfer rate in human placentas in ex vivo experiments. Results led the authors to conclude that free BPA can cross the placenta by passive diffusion with a trans-placental transfer rate of 1 (e.g., the concentration in the fetal blood was equal to the concentration in the blood of the mother), as previously demonstrated by Balakrishnan et al. [9].

3. Bisphenol A and human health

Searching in the literature an increasing number of studies are found containing data coming from epidemiological studies on the association between BPA exposure and healthy outcomes. Unfortunately, this number is still limited, and results are coming from cross-sectional trials that limit their interpretability for pathology with long latency periods like cardiovascular diseases or diabetes. An example of number of publication per year, found in PubMed, is shown in **Figure 2**.

Six cross-sectional analyses of data from the US National Health and Nutrition Examination Survey (NHANES) reported associations of BPA exposure with self-reported diagnosis of pre-existing cardiovascular disease, hypertension, obesity, diabetes, and liver-enzyme abnormalities [10–15]. Two other studies in the US [16] and China [17] reported an association between BPA exposure and coronary disease at the time of diagnosis and obesity and insulin resistance, respectively. In addition, a study found associations between urine BPA and immune function and allergy [18]. These cross-sectional analyses have the same weaknesses that limit their interpretation. One of the major limitations of these studies could be assigned to the problem relating to sampling procedure (single spot urine) reflecting only recent BPA exposure and not on a long period (months or years) much more useful to assess the exposure effect on cardiovascular disease and diabetes pathologies.

Progressive exposure to BPA can affect adiposity, glucose or insulin regulation, lipid profiles or other end-points relating to diabetes or metabolic syndrome [19–27].

Finally, BPA could have a negative effect on the heart: stimulating estrogen concentration and modifying free calcium concentration control inside heart cells in women. Provoking an increase of Ca^{2+} release from sarcoplasmic reticulum that could cause arrhythmias that in some case could degenerate into infarction [28].

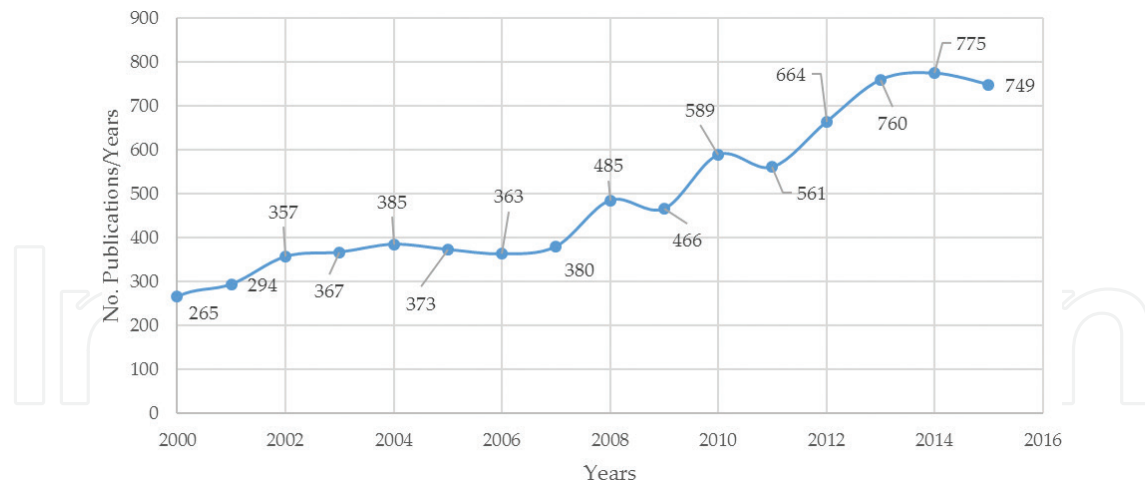


Figure 2. Number of publication on BPA (2000–2015). Source: PubMed.

4. Bisphenol A in hemodialyzers

Several types of medical devices are produced using polycarbonate (PC) polymer. Industries utilize PC for its toughness and stability, optical clarity, and resistance to heat and electricity. Unfortunately, these medical devices produced using PC could contain and release BPA residual in routine use. Additional source of BPA is coming from other materials such as dental supplies manufactured using bisphenol derivatives like bisphenol A glycidyl methacrylate (Bis-GMA) and bisphenol A dimethacrylate (Bis-DMA). Bisphenol A is also used in the production of inks and adhesives, as well as in polysulphone (PS) membranes widely used in hemodialyzer production.

Recently, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) published an opinion of the safety of bisphenol A use in medical devices [29].

In their report, the SCENIHR described the risk assessment of exposure to BPA via medical devices that are manufactured with materials that potentially leach BPA. This include oral (via dental material), subcutaneous, and intravenous (e.g., during hemodialysis) routes of exposure.

This group evaluated the different scenarios of exposition considering the type of materials used, frequency and duration of a single treatment as well as the information relating to BPA leaching, generating an accurate report on short- and long-term toxicological exposure.

As a conclusion, the SCENIHR group reports a possible existence of adverse events risk of BPA when this is directly available in the blood, and in a particular case, for neonates in intensive care units, infants undergoing prolonged medical procedures, and for dialysis patients. Although the use of medical device should be considered together with the benefit for the patient, a BPA-free device should be taken into consideration if available. What they also suggest is to consider the possibility of replacing BPA in medical device products against their efficiency in the treatment, as well as the toxicological profile of the alternative materials.

Several studies have reported the leaching of BPA from hemodialyzers. Haishima et al. [30] studied the amount of BPA released from different hemodialyzers composed of a combination of polycarbonate housing and cellulose acetate hollow-fibers, polycarbonate housing and polysulfone fibers, and polystyrene and polysulfone. Water and bovine serum were circulated at room temperature in the four different devices tested. The bovine serum was used as a stimulant for human blood circulating into hollow fibers during hemodialysis.

BPA recovered ranged from 3.78 to 141.8 ng/module using water circulation and from 140.7 to 2090 ng/module when bovine serum was used. The highest values of BPA released corresponded to hemodialyzers consisting of PC housing and PS.

Murakami et al. [31] reported a BPA concentration of 8.33 and 12.25 ng extracted from 10 mg of polysulfone and polyester polymer alloy (PEPA) hollow fibers. The fibers, taken from individual dialyzers, were crushed and dissolved in hexane.

Fink [32] investigated BPA leaching from five different types of dialyzers and polyvinylchloride blood tubing. All the dialyzers were composed of either polycarbonate or polysulfone: polycarbonate housing and polysulfone-polyvinylpyrrolidone (PVP) blend membranes, PC housing and polyamide-polysulfone blend membrane, and polypropylene housing, polysulfone-PVP blend membrane. Different surface area range was investigated (from 1.3 to 1.8 m²). Dialysis was simulated using two different eluents: reverse osmotic water and 17.2% ethanol [32].

In agreement with the study of Haishima et al., the highest levels were measured when 17.2% ethanol was used, ranging from 54.8 to 4299 ng/dialyzer. Using osmotic water as eluent, the BPA levels measured span from 6.4 to 71.3 ng/dialyzer.

Additional factors influence the BPA released from dialyzers, like the type of dialyzer, surface area, and duration of dialysis session. Generally, large amount of BPA is released in long dialysis sessions or in dialyzer with high surface area.

The contribution of the PVC tubing to total BPA content in the eluates was negligible, and the levels found were below the limit of quantification.

Krieter et al. [33] also reported release of BPA from three different high and low flux dialyzers with different surface area (from 1.3 to 1.7 m²) and with polycarbonate housing. BPA-free sterile water was circulated through the blood and dialysate compartments at 37°C, and BPA was measured by ELISA method. The amount of BPA eluted was significantly different between dialyzers evaluated, with average levels from 140.8 ± 38.7 to 6.2 ± 2.5 ng/dialyzer. These results are in the range with those reported in other studies when using water as eluent. The highest BPA levels were eluted from the low-flux dialyzer with polysulfone membrane, and the lowest from the dialyzer with polyethersulfone (PES) membrane. A summary of data available from the literature is presented in **Table 2**.

Table 2 summarizes the levels of BPA released by dialyzers and measured in different fluids.

Reference	Sample	Type of fluid (units)	BPA concentration
Haishima et al. [30]	PC housing/PS fibers	Water (A)	(A): 31.0/141.8
		Bovine serum (B) (ng/module)	(B): 1010/2090
	PC housing/CA fiber	(A): 34.1 (B): 196.1	
Murakami et al. [31]	Polystyrene housing/PS fiber		(A): 3.78 (B): 140.7
	(A) PS fiber (B) PEPA fiber	Extraction with hexane (ng/mg fiber)	(A): 8.33 (B): 12.55
Fink [32]	Dialyzers with PS or PC (1.3–1.8 m ²)	(A) Osmotic water (B) 17.2 % EtOH (ng/dialyzer)	(A): 6.4–71.3 (B): 54.8–4299
Krieter et al. [33]	1.3 PS HF fiber (PC housing)	Water recirculation (400 ml), 3 h, 250 ml/min; 37°C (ng/dialyzer)	48.1 ± 7.7
	1.3 PS LF fiber (PC housing)		140.8 ± 38.7
	1.7 PES HF fiber (PC housing)		6.2 ± 2.5

Table 2. Levels of BPA released by dialyzers and measured in different fluids reported in the literature.

5. BPA in chronic kidney disease

The large number of molecules that accumulate in chronic kidney disease (CKD) are responsible for the uremic symptoms and contribute to increasing comorbidities and mortality in patients undergoing extracorporeal blood purification.

Removal of uremic toxins then is accompanied by an improvement in the clinical situation. They have been classified from the EuTox in differ groups according to their size and molecular weight [34]. A first group of molecules, around 350 toxins, is composed of small uremic toxins with molecular weight below 500 Da. Another group is characterized by medium-size toxins with molecular weight between 500 and 5000 Da. A new, and important, group or uremic toxins are represented by molecules with high affinity for proteins (protein-bound uremic toxins), which hamper their clearance.

One of the best characterized class of protein-bound toxins is phenols and indoles, a metabolite of protein catabolism by intestinal bacteria that have been related to renal failure progression and vascular damage in CKD. Proteins and peptides coming from diet are degraded by proteases and peptidases to simple amino acids. Some part of those amino acids reach the colon and are degraded by intestinal bacteria. This degradation generates potentially toxic metabolites such as ammonium, amines, thiols, phenols, and indoles.

Bisphenol A contains phenolic rings with structural similarity to phenols. While the origin of the toxins differs, the metabolism and side effects of BPA may have common characteristics

with phenols of intestinal origin. BPA is eliminated by the kidney, and increased blood levels have been observed in CKD. Like intestinal phenols, after glucuronization in the liver, BPA is rapidly eliminated by the kidneys with a half-life in blood of less than 2 hours after oral ingestion that generally results in low blood levels. On the contrary, patients with impaired renal function could have BPA accumulation due to the less urinary excretion.

The National Health and Nutrition Examination Survey 2003–2006 (NHANES III) observed in 2573 patients a decrease of urinary excretion of BPA with renal function impairment [35]. The meaning of these data is uncertain: low urinary BPA excretion may reflect low exposure to BPA (which would be desirable) or retention of BPA by kidney disease (which would not be desirable).

By contrast, increased serum BPA with decreasing renal function and higher levels in hemodialysis was observed in different studies, suggesting that BPA may accumulate in CKD [31–33].

Additionally, the fractions of protein-bound and free plasma BPA in the maintenance of dialysis patients are 74 ± 5 and $26 \pm 5\%$, respectively [33]. Moreover, a tissue/blood partition coefficient of 1.4 for nonadipose tissues and 3.3 for fat tissues further compromises the dialyzability of BPA [36], implying a concentration gradient highly in favor of driving BPA from dialysate to patient's blood.

Besides the other environmental sources, patients with end-stage renal disease on hemodialysis are repeatedly exposed to BPA from components of the dialyzer, more specifically polycarbonate housings and some dialysis membranes, resulting in a higher BPA blood levels of ESRD patients than healthy subjects.

BPA is found in the housing (polycarbonate) and membranes of some commonly used dialyzers; in **Table 3**, a summary of BPA contents in different dialyzers available on the market is provided.

Dialyzer BPA content is variable and depends on the manufacturer. All housings made with polycarbonate contain BPA (as a starting material), while the BPA contents in the fibers are variable. Generally, polysulfone membrane contains BPA in different amounts depending on the dialyzer surface. Other membranes such as polyethersulfone, polyarylethersulfone, polyamide, and polymethyl methacrylate are “naturally” BPA free.

The amount of BPA released depends on the experimental conditions and is higher in dialyzers perfused with blood than when perfused with saline. This difference has been attributed to the effect of blood hydrophobic components such as lipids or lipoproteins to extract BPA from the medical devices. An additional source of uncertainty on the quantitative determination of BPA is the analytical method used for determination. The most sensitive analytical method is represented by HPLC coupled with mass spectroscopy. Recently, simple ELISA methods are available on the market for BPA determination in biological fluids.

BPA may leach into aqueous solutions due to hydrolysis of the ester bonds in BPA-based polymers. With respect to the clinical situation, blood and water may differ in their ability to leach BPA. However, Krieter et al. [33] showed that considerable amounts of BPA were eluted from dialyzers with polysulfone membranes in 180 min of simulating (*in vitro*) dialysis conditions

Company	Model name	BPA content		Company	Model name	BPA content	
		Fiber	Housing			Fiber	Housing
ALLMED	Polypure	Yes	Yes	FRESENIUS	Optiflux	Yes	Yes
ASAHI KASEI	Rexeed	Yes	No	FRESENIUS	F S	Yes	Yes
ASAHI KASEI	Leocceed	Yes	No	FRESENIUS	F HPS	Yes	Yes
ASAHI KASEI	APS	Yes	No	FRESENIUS	F	Yes	Yes
ASAHI KASEI	ViE	Yes	No	GAMBRO	Polyflux Revaclear	No	Yes
BAIN	BNoH	No	Yes	GAMBRO	Polyflux	No	Yes
BAXTER	Xenium XPH	No	Yes	GAMBRO	Evodial	No	Yes
BAXTER	Xenium	No	Yes	KAWASUMI	RENAK PS	Yes	Yes
BAXTER	Xenium PLUS	No	No	MEDICA	Smartflux	No	Yes
BAXTER	Exeltra	No	Yes	NIKKISO	FDY	No	Yes
BAXTER	Dicea	No	Yes	NIKKISO	FDX	No	Yes
BBRAUN	Xevonta	Yes	Yes	NIPRO	Solacea	No	No
BBRAUN	Diacap	Yes	Yes	NIPRO	Elisio	No	No
BELLCO	Phylther	No	Yes	NIPRO	Pureflex	No	No
BELLCO	Phylther UP	No	No	NIPRO	Sureflux	No	No
BELLCO	BLS	No	Yes	SERUMWERK	VITAPES	No	Yes
BELLCO	BLS UP	No	No	TORAY	TS	Yes	Yes
FRESENIUS	FX cordiax	Yes	No	TORAY	CS	Yes	No
FRESENIUS	FX	Yes	No	TORAY	Filtryzer	No	No

Table 3. Summary of BPA contents in different dialyzers available on the market.

with sterile water at body temperature. Previous studies had already shown that different polysulfone membranes leach varying amounts of BPA [31–37]. Obviously, this is also true for polysulfone membranes from the same manufacturer, indicating variations in different polysulfone lots or different extraction processes during fiber spinning. Additionally, a different amount of BPA is eluted from low-flux polysulfone membranes compared with high-flux polysulfone membranes. This difference, higher in HF membranes, may be attributed to a higher polymer content; usually less permeable low-flux membranes have a tighter wall structure compared with high-flux membranes. Since BPA is not a starting material of polyethersulfone membranes, the very small amounts of BPA eluted from this dialyzer most likely originate, in some cases, from the polycarbonate housing. Moreover, Krieter in his study also found that no differences in BPA levels were determined between the blood and dialysate compartments. This was because the unbound BPA can easily pass the dialysis membrane and equilibrate during recirculation. In vitro experiment suggests that dialyzers differing in elutable BPA used during chronic hemodialysis would have an impact on plasma BPA levels.

Recently, Bosch-Panadero et al. [38] performed a cross-over study to evaluate the impact of the dialyzer choice (BPA-free versus BPA-containing) on serum and intracellular BPA levels and on inflammation and oxidative stress markers in a group of 69 prevalent patients on hemodialysis.

The main finding of this study was that the choice of dialyzer in terms of BPA content impacts on acute (after a single dialysis session) and chronic (after 3 months of continuous use of the same type of dialyzer) changes in serum BPA levels. This reinforces the hypothesis of Krieter et al. that dialyzer BPA content may contribute to BPA burden in patients on hemodialysis.

The expression of oxidative stress markers was significantly higher after 3 months of hemodialysis with BPA-containing membranes with respect to BPA-free dialyzers. Three months of hemodialysis with BPA-containing membranes increased significantly circulating C-reactive protein (CRP) and IL-6 with respect to BPA-free dialyzers. These patients are more sensitive to BPA accumulation and potential toxicity due to the loss of the physiologic BPA excretion mechanisms in urine. In this same work, authors indicated that the serum BPA levels were 35-fold higher in patients on hemodialysis than in healthy controls confirming that serum BPA levels increased with decreasing renal function and are highest in individuals on hemodialysis.

A particular group of hemodialysis patients are those with diabetes. Recently, in a cross-over study, values of serum BPA have been measured in a group of 47 patients in which 12 had diabetes [39]. All patients were treated with low-flux polysulfone dialyzers.

In this study, postdialysis serum levels of BPA were significantly higher than predialysis levels. Additionally, diabetic patients showed higher predialytic BPA levels compared with those without diabetes. This difference disappeared for postdialysis measurement.

Unfortunately, no association was found between serum BPA levels and age, body mass index, dialytic vintage, blood pressure, and other medical parameters, probably due to the small number of subject investigated.

Up to now, we analyzed the dialyzer contribution to BPA in the blood of hemodialyzed patients, but recently, Bacle et al. [40] evaluated the potential exposure to BPA via the entire process of

hemodialysis treatment, from production of purified water to dialysate and dialyzers. In their work, they could confirm that no BPA leaching is observed from bloodlines, confirming the information provided by the European PVC manufacturers who no longer use BPA in polyvinylchloride (PVC) production. At the same time, no leaching was observed from rinsing bags (0.9% sodium chloride), but larger amounts of BPA were found in dialyzers based on polysulfone and polycarbonate, as described by other authors and confirming the hypothesis that the dialyzers used during hemodialysis treatment may expose patients to a significant amount of BPA.

Concerning the water purification process, BPA has been detected in over 90% of collected samples, with significant amounts of BPA found after each step of the water treatment process. This suggests that none of the different processes applied in water purification is able to totally remove BPA. An additional source of BPA contamination already found in water of BPA could come from dialysis machine and dialysate cartridges, slightly increasing the BPA content in the dialysate.

In **Table 4**, a summary of selected study cited with the number of patients evaluated as well as BPA concentration in the serum samples is reported. Up to now, information provided by scientific literature on specific hemodialyzed population is scarce. Nevertheless, all studies reported showed an increase of BPA serum concentration in patients treated with BPA-containing dialyzers.

Reference	Number of patients	Type of study	Type of dialyzer (time of observation)	BPA concentration (ng/mL)
Turgut et al. [39]	47	Cross-over	PS (single session)	From 4.06 ± 0.73 to 5.57 ± 1.2
Bosch-Panadero et al. [38]	69	Cross over	PS (3 month)	From 48.8 ± 6.8 to 69.1 ± 10.1
			PN (3 month)	From 70.6 ± 8.4 to 47.1 ± 7.5
Krieter et al. [33]	18	Prospective	LF PS (4 weeks)	From 12.0 ± 6.0 to 10.52
			HF PS (4 weeks)	From 9.1 ± 4.5 to 8.72
			HF PES (4 weeks)	From 10.0 ± 4.9 to 8.45
Murakami et al. [31]	15	Cross-over	PS (3 month)	From 4.83 ± 1.94 to 6.62 ± 3.09
			Ce (1 month)	From 2.07 ± 2.10 to 1.48 ± 1.41
			PS (1 month)	From 3.78 ± 2.57 to 4.27 ± 2.98

Ce, cellulose; PS, polysulfone; PN, polynephron; PES, polyethersulfone; HF, high flux; LF, low flux.

Table 4. Levels of BPA measured in serum samples reported in the literature.

6. Conclusion

BPA is an estrogenic endocrine disruptor molecule with phenolic structure, used in the synthesis of polycarbonate plastics and epoxy resins. Exposition in the human population occurs mainly through the diet, in particular from food and beverages.

BPA could migrate into food from food and beverage containers with internal epoxy resin coatings and from products made of polycarbonate plastic such as tableware, food containers, and water bottles. BPA exposure results from either the release of unpolymerized monomers or the slow decay of polymer bonds in polycarbonate, leading to monomer release into foods and liquids. Starting from this information, data analysis coming from several large studies in various countries shows that the majority of the population examined have detectable levels of BPA conjugates in the urine. Indeed, in view of the rapid conjugation and elimination half-time of BPA, these levels reflect the exposure of the past hours just before the sample collection.

On the contrary, in patients with limited or absent kidney function, BPA may accumulate in the serum. The BPA accumulation in these subjects accounts from diet and medical device containing BPA, that is, extracted from the device by hydrophobic components present in the blood. Repeated loading of BPA during hemodialysis with BPA-containing membranes may aggravate the problem due to migration of BPA from dialyzers to the blood of patients and its inefficient removal due to the high protein-bound fraction of plasma BPA.

Some recent studies on the chronic use of BPA-free dialyzers indicate decrease of BPA serum levels in dialyzed patients reflecting a potential beneficial effect on inflammation and oxidative stress.

Furthermore, additional BPA contamination sources come from water and medical devices used to produce the dialysate fluid involved in hemodialysis treatment.

It is also advised that attention should be taken to avoid BPA cross contamination during medical devices production, with particular consideration to hemodialyzers. The possibility to replace BPA in these products should be assessed as well as the toxicological profile of the alternative materials. This issue could be a criterion for the purchase of medical devices commonly used in hemodialysis.

In conclusion, patients on hemodialysis have higher levels of serum and intracellular BPA with respect to healthy controls and the choice of dialysis membrane impacts on these levels. Dialyzers with BPA-containing membranes increase serum BPA levels. Studies indicate an increase of BPA serum concentration after a single dialysis session, confirming that hemodialysis does not compensate lack of urine BPA excretion.

Use of BPA-containing dialysis membranes further adds to the BPA burden of patients on hemodialysis. In contrast, it would be advisable the chronic use of BPA-free dialyzers to decrease BPA serum levels and related clinical effects.

Conflict of interest

The authors are full employees of Bellco (part of Medtronic) company. A company that produces and commercializes medical devices.

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