NEFROLOGIA. 2024;xxx(xx):xxx–xxx

nefrología
Revista de la Sociedad Española de Nefrología
www.revistanefrologia.com

Editorial

Bisphenol A in renal insufficiency: how long will it be used? Is it time to avoid it?

Bisfenol A en la insuficiencia renal: ¿hasta cuando se podrá usar? ¿Es la hora de evitarlo?

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Introduction

Recent legislative changes and recommendations by European Union (EU) experts aim to eradicate bisphenol A (BPA) (2,2-bis-[4-hydroxyphenyl]-propane) in Spain. It has been banned in all food packaging[1] and the maximum recommended dose has been reduced by a factor of 20,000.[2] Six years ago, we published an editorial in this journal warning nephrologists about the importance of this endocrine disruptor in patients with renal failure, especially those on dialysis.[3] Legislators have again forgotten renal patients, and in this review, we intend to alert nephrologists to the danger of ignoring exogenous BPA in this population and provide the most recent data.

In addition to the increase in chronic diseases and most particularly chronic kidney disease (CKD), there has been a widespread increase in exposure to endocrine disruptors such as BPA, a recognized xenoestrogen.[4] It is used in the manufacture of polycarbonate plastics and epoxy resins widely used in the production of food packaging, bottles, including the inner lining of cans, as well as medical and surgical instruments, among many other uses. It is alarming that a chemically synthesized molecule is present in the urine of almost the entire population of developed countries.[5] In Spain, Cutanda et al.[6] found BPA in 97% of the sample population.

It is well established that BPA can leach or migrate, favoring human exposure. The main routes of exposure are oral, dermal and through medical-surgical equipment.[4,7] After ingestion, BPA is conjugated in the liver with glucuronic acid where it loses its estrogenic activity and is excreted into the intestine. The BPA that reaches the intestine has a behavior very similar to the p-cresol generated by the intestinal microbiota.[8] It is extremely important to know that both BPA and its metabolites are excreted in the urine.[9] Patients with CKD have higher levels of BPA than the general population,[10] and a negative correlation has been observed between increased serum BPA and the estimated glomerular filtration rate (Modification of Diet in Renal Disease [MDRD]).[11]

DOI of original article:
https://doi.org/10.1016/j.nefro.2023.10.003.
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In the last two decades, numerous studies have associated BPA with reproductive, hepatic, respiratory, thyroid, cognitive and behavioral alterations. It has also been linked to obesity, diabetes, cancer and even alterations in embryonic development.[4,7,8,11] From a nephrological point of view, more recent experimental studies have shown that BPA is able to induce podocytopathy with proteinuria and hypertension in a manner analogous to diabetic nephropathy.[12–15] These experimental findings are supported by epidemiological studies in New York, Shanghai and Seoul, which report that human exposure to BPA is associated with increased urinary protein excretion and hypertension (as reviewed by Bosch et al.[5]). More recent meta-analysis studies support the existence of a significant association between blood BPA and the risk of developing CKD and between urinary BPA excretion and a decrease in renal function.[4,11]

Bisphenol A in chronic kidney disease

One of the most relevant implications of BPA in the context of population health is kidney disease; however publications in this regard are scarce. BPA is known to be an endocrine disruptor, the focus of research on BPA has historically been on diseases related to the reproductive system; however, in 2017 Mas et al. hypothesized that BPA could be a uremic toxin.[3]

In 2015, the European Food Safety Authority (EFSA) established a safety limit of BPA based on its renal effects, guided by reports by Tyl et al., who determined the no-observed-adverse-effect level (NOAEL) in the kidney.[16] Starting from a dose of 50 mg/kg/day, EFSA calculated the benchmark dose, referring to the minimum amount of BPA that causes a mild adverse effect in mouse kidneys, such as a 10% alteration in mean organ weight. After extrapolation to human doses and applying an uncertainty factor, EFSA established as safe a dose of 4μ g/kg/day, which was widely adopted by the scientific community.

Moreno et al.[15] use the murine renal NOAEL as a reference to apply a lower oral dose, observing analogies to those seen in diabetic kidney disease.

The existence of cohort studies has made it possible to identify statistical relationships between renal function parameters and BPA. The meta-analysis by Moreno et al.[11] showed a relationship between BPA in blood and the risk of developing kidney damage.

Basic research models have clarified the need to include patients with CKD among those with special vulnerability to BPA exposure. In the final stages of CKD, in addition to the decrease in urinary elimination of BPA, there is a need for dialysis treatment. It is important to note that hemodialyzers contains polymers capable of releasing endocrine disruptors such as BPA itself. During hemodialysis this class of phenolic compounds can reach the blood system directly, bypassing the detoxification mechanisms of the oral or dermal routes.

It is plausible that a large proportion of the global population exceeds the EFSA proposed limits of 0.2 ng/kg. An average adult of 66.5 kg could have a daily intake 13.3 ng BPA. According to Völkel et al.,[17] this would imply a urinary concentration of approximately 9.5 pg/mL.

There is evidence that BPA exposure is increased in dialysis patients. Bosch et al. and others[7,18] show that the composition of dialysis membranes can quantitatively affect BPA exposure levels, increasing by one or two orders of magnitude with respect to the average exposure in the world population. The average values can vary from 1 to 2 ng/mL in the general population, to values above 10 ng/mL in patients undergoing hemodiafiltration, reaching over 100 ng/mL in the case of conventional dialysis.[4]

BPA exposure of renal patients may come from multiple sources. It is already found in the tap water used to prepare dialysis water and the purification system used is not able to completely remove it.[19] Along with dialysis water, measurable amounts of BPA have been described in dialysis concentrates and bicarbonate cartridges[20] as well as in prefilters and connecting tubing. However, the main source of BPA exposure in those on dialysis comes directly from dialysis membranes. Despite the stability of these polymers, leaching of BPA has been demonstrated, passing directly into the fluids with which it interacts.[21–23]

In the last decade, clinical evidence of this increase has accumulated both in conventional hemodialysis and, to a lesser extent, in hemodiafiltration, with indirect observations by means of the difference in serum concentrations of this xenobiotic after the hemodialysis session in multiple conditions.[7,10,18,23]

BPA has demonstrated a cytotoxic potency far superior to p-cresol, a protein-bound toxin with high clinical impact that clinicians seek to remove with sophisticated hemodialysis techniques.[24]

All this confirms that, although there are multiple sources of BPA in CKD patients, leaching of BPA from the dialysis membrane is the leading source of this compound in their blood, with the implications discussed above.

New legislation on Bisphenol A

In 2015 EFSA established a temporary tolerable daily intake (t-TDI) for BPA and highlighted the importance of having data on the toxicological effects of BPA. BPA can migrate from plastic food packaging and its presence in food may pose a risk to humans.[16] In 2017, the European Chemicals Agency (ECHA) confirmed that BPA is a substance with endocrine-disrupting properties and likely serious effects on human health.

On April 19, 2023 EFSA has published a re-evaluation of the risk of the presence of BPA in which it concludes that dietary exposure to BPA is a health concern for consumers of all age groups by identifying potentially harmful effects of BPA on the immune system.[25] As mentioned above, the new re-evaluation establishes a tolerable daily intake (TDI) of 0.2 ng/kg/day, replacing the previous TDI of 4μ g/kg/day, which is 20,000 times lower. Taking into consideration the newly established TDI, EFSA concludes that, at both average and extreme exposure to BPA, the recommended TDI is exceeded by two to three orders of magnitude in all age groups and that BPA is a health concern. Finally, EFSA notes that it is time for the European Commission and the Member States to take appropriate risk management measures to minimize the exposure of the EU population to BPA.

In 2011 the EU banned the use of BPA in the manufacture of baby bottles (https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:026:0011:0014:ES:PDF),[26] and it later also banned BPA in food packaging for children up to three years of age. But the need to restrict BPA has also been recommended by the EU in materials used in medicine, including dialysis materials. The *Scientific Committee on Emerging and Newly Identified Health Risks* (SCENIHR) in 2016[27] recommended replacing BPA in medical devices, especially in newborns, in intensive care units, in children undergoing prolonged medical procedures and in dialysis patients. In Spain, BPA in packaging has been banned since January 2023, when the packaging law came into force (https://www.boe.es/eli/es/l/2022/04/08/7/con).[28]

Conclusion

Renal patients present additional factors that significantly increase their BPA levels, among which are, in addition to the oral route itself, the decrease or loss of renal function and the use of BPA-containing medical material.[4,7]

Regarding exposure levels, it is important to keep in mind that not all effects of endocrine disruptors such as BPA are dose-dependent. Indeed, researchers have observed that BPA may present a non-monotonic effect, such that they can have effects at concentrations lower than the TDI similarly to that observed with certain hormonal stimuli. Recent studies indicate that the response to BPA is tissue-dependent, so while BPA induces hypertension in a dose-dependent manner,[14] it promotes podocytopathy in a non-monotonic manner.[12]

A recent systematic review showed exposure levels considered acceptable under the previous EFSA assumptions; however, this has changed substantially with the new EFSA update, which identified populations with high levels of exposure, including patients with occupational exposure, hospital patients and particularly patients with CKD.[4] Current scientific data provide sufficient evidence to consider patients with CKD as a priority group in which BPA exposure should be reduced by changing the composition of medical materials.[4,11]

The recent recommendations of the expert committees of the EU, and the prohibition of BPA in packaging in our country, have left renal patients, who have decreased urinary elimination of BPA and much higher serum BPA levels, without specific recommendations. We nephrologists must watch over the health of patients with renal insufficiency and warn legislators of their enormous and unjustifiable mistake. Legislation so far has only addressed people with normal renal function, neglecting those more susceptible to BPA. As stated in the 2015 EU recommendation, we should evaluate eliminating BPA in all dialytic medical material.

Financing

This work has not received any funding.

Conflict of interest

The authors declare that they have no conflicts of interest. Emilio Gonzalez-Parra has received research grants from Nipro corporation.

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