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Critical Analysis of Human Exposure to Bisphenol A and Its Novel Implications on Renal, Cardiovascular and Hypertensive Diseases

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Abstract

Bisphenol A (BPA), an endocrine disruptor involved in synthesizing numerous types of plastics, is detected in almost the entire population's urine. The present work aims to estimate daily exposure to BPA by systematically reviewing all articles with original data related to urinary BPA concentration. This approach is based on human pharmacokinetic models, which have shown that 100% of BPA (free and metabolized form) is eliminated only in a few hours through urine. Several extensive population studies and experimental data have recently proven a significant association between urinary excretion of BPA and albuminuria, associated with renal damage. Our team's previous work has shown that low-dose BPA can promote a cytotoxic effect on renal mouse podocytes. Moreover, BPA administration in mice promotes kidney damage and hypertension. Furthermore, preliminary studies in human renal cells in culture (podocytes) strongly suggest that BPA might also promote kidney damage. Overall, the present review analyzed BPA exposure data from mammalian cell studies, experimental animal models, and several human populations. Studying principal cohorts calculated the exposures to BPA globally, showing a high BPA exposure suggesting the need to decrease BPA exposure more effectively, emphasizing groups with higher sensitivity as kidney disease patients.

Keywords: bisphenol A, systematic review, human, urine, estimated daily intake

1. Introduction: brief historical overview

Bisphenol A is the perfect example of the double edge of industrial development. On the one hand, thanks to BPA, we have countless plastic objects with excellent physical properties at low prices; on the other hand, increasing exposure to this kind of xenobiotic compounds could be a severe health risk to the general population.

BPA is a phenolic compound widely distributed due to its multiple uses as an additive and plasticizer in plastic polymers' manufacture [1]. This compound can be found in various everyday items, such as food containers, toys, dental supplies, electronic devices, and even clothing [2–6].

The BPA problem presents a particular and curious situation: BPA is a compound whose properties as an estrogen modulator were already determined 84 years ago by medical researchers at the University of London [7], but its use increased substantially last decades. The discoverer's idea was to commercialize a compound that could treat female pathologies. Finally, they succeeded with Diethylstilbestrol, a substance with much greater potency than BPA, and was introduced in the 1940s [8].

It took about 50 years since the Russian chemist Dianin synthesized it in 1891 [9, 10] until the BPA began to be used in the industrial manufacturing of epoxy resins. Still, due to its incredible versatility, BPA quickly achieved great importance in the American industry. In the mid-1970s, the BPA was considered a part, directly or indirectly, of all major US industries [8]. In parallel, Schnell's contributions in 1956 demonstrated BPA's potential role in producing polycarbonates [11, 12]. Due to its unique combination of physical properties, this type of compound has had a significant impact on the world industry, as have epoxy resins. Today they are still used in numerous applications, such as in the automotive or LED sector [12]. In fact, there is a tendency to increase its consumption in the coming years, as can be seen in the Asian market, where there has been a substantial increase in the demand for polycarbonates in the last ten years [13]. It is expected to continue growing in the years to come, as observed in the American market [14].

2. Novel role of BPA in renal, cardiovascular and hypertensive diseases; latest discoveries

2.1 BPA in the renal system

BPA is a compound widely studied for its estrogenic properties within the field of fertility and sexual organs. However, other organs, such as the kidney and liver, may have the highest exposure ranges. In the kidney's case, BPA concentration has been positively correlated with a greater predisposition to kidney pathologies [15–17] or clinical signs associated with kidney diseases, such as increased albuminuria or decreased glomerular filtration rate [18–21].

Our group has worked on BPA's possible action on the renal system in recent years, using different cell and animal models. The first steps were carried out on a renal cell line of immortalized mouse podocytes. It was possible to observe how the chronic treatment of BPA exerts a cytotoxic effect on the cells. The administration of 10 and 100 nM doses for nine days exerted loss of cell viability and increased apoptosis (as assessed by MTT and TUNEL, respectively). These effects were accompanied by an increase in the synthesis of molecules classically involved in the pathogenesis of glomerulosclerosis, such as the cyclin-dependent kinase inhibitor p27kip1, the TGF- β system, and collagen IV. Furthermore, in these cells, BPA reduced the synthesis of nephrin and podocin, proteins of the filtration slits involved in proteinuria and podocyte survival mechanisms. As would be expected from these in vitro results, the kidneys of animals treated with BPA developed hypertrophy, hyperfiltration, and proteinuria. Along with the increased renal expression of p27kip1, TGF- β , and collagen IV, mesangial expansion and a decrease in the number of podocytes due to apoptosis were also seen. Electron microscopy showed hypertrophy of podocytes and pedicles. It should be noted that even when animals treated with BPA did not develop hyperglycaemia, their kidneys showed

structural and functional changes similar to those that occur in the initial stages of diabetic nephropathy (DN) (**Figure 1**) [22, 23].

Secondly, the possible effects of BPA on an immortalized human podocyte cell line were explored. We observed that BPA promotes a novel type of podocytopathy characterized by an impairment of cell adhesion by altering adhesion and cytoskeleton proteins' expression.

By using transcriptomics, proteomics, western-blot, and immunocytochemistry, it was possible to determine that BPA at low doses promotes a reduction in the expression of numerous structural or adhesion proteins, such as tubulin, vimentin, podocin, cofilin-1, vinculin, E-cadherin, nephrin, and VCAM-1, as well as an increase in the expression of proteins that negatively participate in adhesion mechanisms, such as Tenascin-C [24].

Since podocytes do not replicate in adults, the resulting podocytopenia after the urinary loss of podocytes might promote glomerulosclerosis. Collectively all available data suggest that BPA could participate in the pathogenesis and progression of renal diseases. It is essential to mention that these experimental results are supported by epidemiological studies conducted in the populations of New York [25], Shanghai [19],

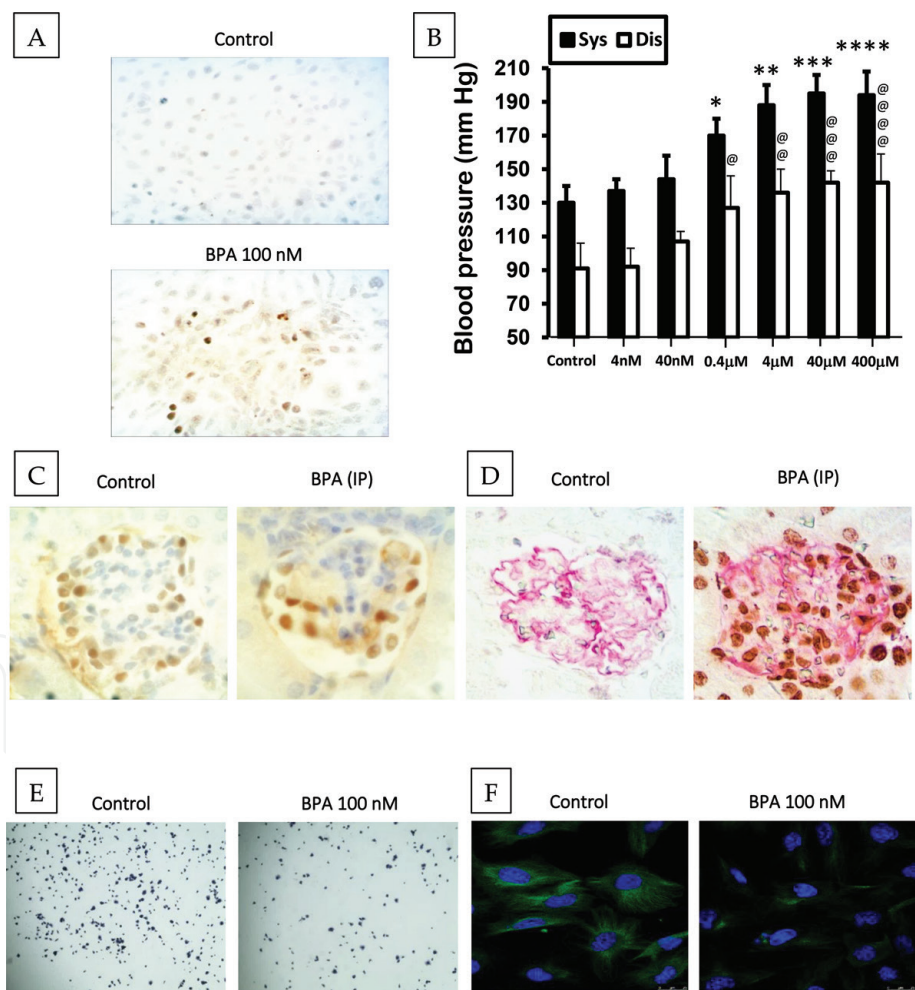


Figure 1. Notable evidence from cell and animal models. A) TUNEL technique performed in mouse podocytes. Note the significant increase in the number of apoptotic cells in the cells treated with BPA. B) Hypertensive effect of BPA administered to animals in drinking water. C) Reduction in the number of glomerular podocytes (labelled with WT-1) of the mice treated with intraperitoneal (IP) BPA. D) Increased number of apoptotic kidney cells (TUNEL) of mice treated with IP BPA. E) Adhesion assay in human podocytes. A reduction of up to 50% was observed in cells treated with BPA. F) Podocin immunocytochemistry in human podocytes. A significant loss of labelling is evidenced in cells treated with BPA. * or @ means p -value $< 0,05$; ** or @@ means $p < 0,01$; *** or @@@ means $p < 0,001$; **** or @@@@ means $p < 0,0001$. Figure made with our own results published in the *Journal of Cellular Physiology* [22], *FASEB Journal* [27] and *Scientific Reports* [24].

and Seoul [26], which describe an association between human exposure to BPA and an increase in proteinuria and hypertension.

2.2 BPA in the cardiovascular system

Further studies demonstrated that animals treated with BPA developed arterial hypertension and endothelial dysfunction in a dose-dependent manner (**Figure 1**). Microarray analysis of gene expression in murine endothelial cells treated with BPA demonstrated the activation of genes involved in vascular regulation, such as angiotensin II and calcium-calmodulin kinase II (CaMKII). This event was subsequently observed *in vivo* as well. The activation is responsible for the endothelial dysfunction and hypertension induced by BPA, given that CaMKII activation promotes the enzymatic uncoupling of endothelial nitric oxide synthase. This phenomenon leads to oxygen free radicals' production instead of nitric oxide, a primary vasodilator, and endothelial protector. Moreover, this increased production of oxygen free radicals indicates that BPA, and inducing hypertension, could participate in vascular damage mechanisms and atherosclerotic lesions' progression [23, 27]. Besides, recent data demonstrated the cardiotoxic effect of BPA by a mechanism that involved activation of the RIP 3-CaMKII necroptotic pathway leading to endothelial cell death. Decreased endothelial barrier function and weakening of the coronary vascular wall in the setting of hypertension may cause ventricular hemorrhages, cardiac and lung congestion, which ultimately led to heart failure [28].

3. BPA exposure in the general population. Identification of groups with higher exposure

3.1 Pharmacokinetics of BPA

The heterogeneous distribution of BPA results in the ability to enter the body in multiple ways. The main entry route is considered oral, through the ingestion of food or beverages containing BPA [29, 30]. However, there are other routes like inhalation (air or dust) [31–34], dermal (cosmetics, thermal tickets) [35–37], and it has even been hypothesized with the ocular [38] and sublingual routes [35, 39]. It is estimated that between 85 and 100% of the BPA ingested can be absorbed through the intestine. Thanks to its capacity to cross biological barriers, it has been observed that BPA has the potential to distribute itself through any fluid and biological tissue, even crossing the transplacental or blood–brain barrier [29, 40, 41]. In the case of the dermal route, it has been determined that the ability of BPA to enter the body is lower, with percentages less than 10% [42, 43]. For its part, the sublingual route (of great importance in the elements used in dentistry) seems that it could become more efficient than the intestinal entry [39].

BPA's metabolism is marked by phase II reactions, biochemical mechanisms capable of modifying its structure to facilitate its excretion [44]. BPA is metabolized towards glucuronidation or sulfonation in the intestine and the liver [41, 45, 46], but the metabolic capacity can be seriously reduced in diseases such as obesity or diabetes [47]. Glucuronidation is the majority reaction, mediated by uridine diphosphate glucuronosyltransferase (UGT) [44, 48]. It has also been suggested that a part of the BPA that reaches the intestine could be degraded to p-cresol by the intestinal microbiota, thus generating uremic toxins [49]. Another possible route studied has been hydroxylation to catechol, followed by a transformation to o-quinone. This route, like the previous one, can generate toxicity associated with oxidative stress [50].

Pharmacokinetic studies in rodents have determined that BPA is excreted in urine and feces [29, 51, 52]. It has been observed that BPA is excreted exclusively through the urine in non-human primates and humans [41, 53, 54]. This phenomenon makes it much easier to make a rough estimate of the degree of exposure by BPA's urinary quantification. The inter-species differences observed are attributed to a possible higher enterohepatic recirculation in rodents [29, 51, 52]. However, there is evidence that contradicts this hypothesis [55].

3.2 Calculation of BPA exposure in the general population

As mentioned above, thanks to pharmacokinetic studies in humans [41, 53, 54], it is accepted that 100% of BPA is eliminated via the urinary tract, which can be used to determine the degree of daily exposure to this compound quickly. For this reason, we proceed to evaluate the question of the degree of global exposure through a systematic review of principal cohorts in the world. To estimate human exposure to BPA, we first collected data published by one of the world's largest cohorts: the National Health and Nutrition Examination Survey (NHANES). NHANES is a survey research program conducted by the US National Center for Health Statistics (NCHS), with more than 72,000 patients studied between 2003 and 2016 [56].

After extracting all the data and unifying them, 18,244 urinary BPA concentrations were obtained. A non-parametric distribution was obtained after performing

Continent	N	Population group (cohort / city)	GM
America	18,244	General population [Own study*]	1.77
Asia	6,003	General Population (KoNEHS) [57]	1.13
America	5,476	General Population (CHMS) [58]	1.6
Asia	3,455	General Population (Shanghai) [19]	0.82
Asia	2,535	Pregnant (Wuhan) [59]	0.9
America	2,477	General Population (Ex-R study) [60]	1.96
America	2,318	General Population (HOPE) [61]	2.52
Asia	2,044	General Population (KRIEFS) [62]	1.83
Europe	1,996	Pregnant (SELMA) [63]	1.53
America	1,933	Pregnant (MIREC) [64]	0.9
America	1,868	Pregnant (PROTECT) [65]	2.02
Europe	1,764	Pregnant (Elfe) [66]	0.69
Asia	1,625	General Population (KEEP) [67]	0.71
America	1,543	Pregnant (LifeCodes) [68]	1.18
Europe	1,396	Pregnant (Generation R) [69]	1.68
Europe	1,146	General Population (DESIR) [70]	1.78
Europe	1,084	Pregnant (HELIX) [71]	3.38
Oceania	420	General Population (Brisbane) [72]	2.61
Africa	210	General Population (Giza) [73]	0.68

Note that two results have been included with a reduced sample size to include Oceania and Africa. Meaning of abbreviations: K, kids; A, adults; GM, geometric mean (or corrected median).
**Own study corresponds with NHANES 2003 – 2016 cohort.*

Table 1.
Representative data from the main cohorts in the world.

the normality tests, for which the geometric mean (GM) was calculated, obtaining a result of 1.77 ng/ml. A systematic review of urinary BPA was then carried out to select from among all the publications with the most representative cohorts from each continent and the largest number of people. Using the keywords: Bisphenol AND (urine OR urinary) in the reference search engines Pubmed and Web of Science, a total of 999 and 2,025 results were obtained, respectively. Once the duplicates were eliminated, a total of 2,414 publications remained. After screening by title/abstract, a total of 756 publications were selected. Finally, after reading in-depth, 447 articles were selected whose pages describe urinary concentrations of BPA in some population groups, either general or specific, such as patients with various pathologies, pregnant women, the elderly, or workers subjected to occupational exposure. All data from the 447 academic articles were collected and analyzed carefully. According to the country, population group, and sample size, the primary world cohorts were selected from all of them, obtaining 16 cohorts whose sample sizes exceed 1000 individuals from America, Asia, and Europe (**Table 1**). A result of Oceania and another from Australia was also included due to representability. All of them expressed the concentration of BPA in ng/ml except one of them, which expressed it in µg per gram of creatinine (µg/g creat.) [71]. Therefore, it was modified by calculating the average creatinine concentration in adults using the NHANES cohort's data and the other two major cohorts, KoNEHS and CHMS [74, 75].

We consider that in the study of urinary BPA, where the results follow non-parametric distributions, the values that should be analyzed would correspond to the GM or the median. To determine if both values can be unified, they were examined using linear regression, observing that they were always in the same range, and the variation between them was relatively small. The equation of a line was $Y = 0.9855 * X$, and $R^2 = 0.9919$. For this reason, the decision was reached to

Country	N	Population	GM	Units	nM
Iran	132	Gen.Pop. [76]	232.6	ng/ml	1,018.88
China	74	Oc.Exp. [77]	199.13	µg/g creat.	872.27
China	72	Oc.Exp. [78]	158.41	µg/g creat.	693.9
USA	525	Oc.Exp. [79]	107	ng/ml	468.7
Country	N	Population	Median	Units	nM
China	72	Oc.Exp. [78]	238.78	µg/g creat.	1,045.95
China	74	Oc.Exp. [77]	180.59	µg/g creat.	791.06
USA	525	Oc.Exp. [79]	108	ng/ml	473.08
China	198	Oc.Exp. [80]	84.6	µg/g creat.	370.58
Country	N	Population	P95	Units	nM
China	74	Oc.Exp. [77]	23,979.51	µg/g creat.	105,039.69
USA	112	Pregnant [81]	250.06	ng/ml	1,095.36
France	254	Pregnant [82]	115.4	ng/ml	505.5
Belgium	72	ICU patients [83]	113.7	ng/ml	498.05
Country	N	Population	MAX	Units	nM
China	74	Oc.Exp. [77]	264,219.38	µg/g creat.	1,157,384.82
USA	525	Oc.Exp. [79]	32,900	ng/ml	144,114.94
China	28	Oc.Exp. [84]	1,934.85	ng/ml	8,475.4
France	390	Oc.Exp. [85]	1,915	ng/ml	8,388.45

Meaning of abbreviations: Gen.Pop., General population; Oc.Exp., Occupational Exposure.

Table 2.
Higher urinary BPA values determined according to the geometric mean (GM), median, 95th percentile (P95), or maximum value (MAX).

use the GM, preferably, but if it was not recorded, use the median corrected with the equation obtained.

Next, the urinary BPA was averaged, considering each cohort's sample size, obtaining a final result of **1.55 ng/ml** (with a sample size of 57,537 individuals). Once the average concentration determined in the general population's urine has been established, the next step will be carried out on the highest values found in the systematic review to determine interest groups to study BPA exposure.

As reflected in **Table 2**, it is clear that workers subjected to occupational exposure are the ones who are likely to find a more significant entry of BPA into their bodies. The highest values observed, both of the median and the maximum value (MAX), correspond entirely to people subjected to occupational exposure, such as workers in the plastics industry. The highest GM value stands out, as it corresponds to the general Iranian population. An in-depth study would be necessary to be able to discern the problem that underlies this study area. Interestingly, unusually high 95th percentile values can also be seen in pregnant women and intensive care patients. It is likely that consumable medical supplies, such as catheters or hemodialyzers, could increase BPA exposure due to their plastic composition. Bearing this in mind, and in keeping with the discoveries described in basic research, the study and analysis of BPA exposure in patients undergoing hemodialysis is crucial.

4. Systematic review of BPA exposure in hemodialysis patients

After describing the latest advances in the BPA-kidney paradigm investigation, the need to include kidney patients as a group of special vulnerability to exposure to BPA is evident. Thereof, there is a point of convergence in the final stages within the different pathologies or stages: the need for dialysis due to the kidney's reduced functionality. Interestingly, there is evidence that the use of surgical medical equipment can increase exposure to compounds such as BPA due to the composition of its materials. Therefore, we will analyze the urinary concentration of BPA in patients undergoing hemodialysis procedures to estimate the daily exposure to which they are subjected. The systematic review methodology was used again, using the keywords: bisphenol AND (dialysis OR hemodialyzer OR hemodiafiltration OR hemodialysis OR dialyzer).

Thirty-eight results were obtained in Pubmed and 50 in Web of Science. After eliminating duplicates, a total of 66 documents were obtained. Once the first screening by title/abstract was done to look for BPA concentrations in patients undergoing hemodialysis, a total of 20 publications were accepted. After carefully studying the text, ten publications were selected¹. Of these, only 1 quantifies the urinary BPA concentration in dialysis patients [87] and 9 in serum [15, 86–94].

The publication by Schöringhumer et al., which quantifies urinary BPA, obtains concentrations between 0.4 and 2.6 ng/ml within the same range as the general population [87], equivalent to 1.75–11.39 nM. In general terms, low exposure would be considered. Still, considering the in vitro model results and the patient's pathology, it could pose an added risk for kidney disease evolution. In the case of publications that study BPA in serum, some show values similar to those observed in the general population's urine. Among them, we can find the publications of Kanno et al. (5.3 ± 0.3 ng/ml), Murakami et al. (values between 1.48 ± 1.41 and 6.62 ± 3.09), Sajiki et al. (values between 0.179 ± 0.263 and 0.642 ± 1.443), Shen et al. (1.01) or Turgut et al. (5.57 ± 1.2) [88, 90, 92–94]. Higher values have the publications of Quiroga et al. (high flux hemodialysis: 7.5 ± 3.5 ; online hemodiafiltration: 6.7 ± 2.5)

¹ Those publications without relevant data, reviews, and conference communications were discarded.

and Krieter et al. (10 ± 6.6) [15, 91]. Finally, Bosch-Panadero et al. and Mas et al. describe serum BPA values in patients undergoing conventional dialysis that range from 52.73 ± 60.6 to 163.03 ± 155.84 . Also, they quantify serum BPA concentrations in patients undergoing online hemodiafiltration from 8.79 ± 7.97 to 23.42 ± 20.38) [86, 89]. These high values would be equivalent to 230.98–714.14 nM in the case of conventional dialysis and 38.50–102.59 nM in online hemodiafiltration.

5. Systematic review of occupational exposure to BPA

The alarming data described in the previous pages denote the need to study occupational exposure. To this end, we proceeded to use two academic reference search engines, Pubmed and Web of Science, using the following keywords: Bisphenol AND (workers OR occupational exposure OR exposure workplace), obtaining a total of 658 publications (once repeated results were eliminated). Of all of them, 25 publications were adapted to the search. Only publications with urinary BPA (or blood) concentrations were selected in workers with high exposure or themselves before and after their work shift. Of the 25 studies selected for their affinity with the topic of interest, we can distinguish three subgroups: In the first (G1)², BPA concentrations can be observed well above the average, and with significant differences between the study groups. In the second group (G2)³, there are concentrations higher than the mean in a range closer to it, while in the third group (G3), the range of concentrations is within the range of values of the general population.

5.1 G1: extremely high BPA concentrations

From a quantitative perspective, within G1, the most interesting publication is Liu et al. [95]. It compares BPA concentrations in people with potential occupational exposure versus controls, obtaining substantially different values. The median values (interquartile range, IR) between exposed workers vs. controls are 685.9 (43.7–3671.8) vs. 4.2 (0–15.9) $\mu\text{g/g creat.}$ Other equally interesting values are Tian et al. [78] and Song et al. [77]. Firstly, they determine geometric mean (GM) values (standard deviation, SD) between exposed subjects vs. control of 158.41 (17.92) vs. 0.84 (6.53) $\mu\text{g/g creat.}$, reaching in the second publication, the values of 199.13 (19.65) vs. 0.77 (6.33) $\mu\text{g/g creat.}$ Song et al.'s publication determine the highest maximum urinary BPA concentration, reaching the value of 264,219.38 $\mu\text{g/g creat.}$, (264.22 mg/g creat.).

The next publications to consider are two by Hines et al. [79, 96], where they study exposure to BPA in different factories before and after the work shift. In them, essential differences can be appreciated, showing, to cite an example of each article, a GM (SD) in pre-shift vs. post-shift of 6.2 (4.3) vs. 130 (10) $\mu\text{g/sample}$ or 26.6 (5.74) vs. 178 (6.2) $\mu\text{g/g creat.}$ These groups show arithmetic mean (SD) values of 15 (22) vs. 2300 (5800) $\mu\text{g/sample}$ and 115 (252) vs. 812 (2330) $\mu\text{g/g creat.}$ The maximum BPA value is also very striking, reaching 32,900 ng/ml. We will continue with the study of publications with high BPA values, Xiao et al. [97], and the two publications by Li et al. [98, 99]. They show differences between exposed workers vs. control, showing medians of 101.94 vs. 0 ng/ml of serum in the first case and

² All those publications with geometric means or medians greater than 50 (ng/ml, $\mu\text{g/g creat.}$, $\mu\text{g/urine sample}$, or ng/ml of plasma) have been selected.

³ We have selected those publications with values of geometric means/medians lower than 50 and higher than 8 (at least four times above the global mean).

57.9 vs. 1.2 and 53.7 vs. 1.2 $\mu\text{g/g}$ in the other two. Finally, it is important to mention the works of He et al. [80] and Wang et al. [84]. In the first, they find pre-shift vs. post-shift differences of 84.6 vs. 111 $\mu\text{g/g creat.}$ (median) and 4630 vs. 5400 $\mu\text{g/g creat.}$ (AM). In the second publication, they quantify urinary BPA concentrations in workers of an epoxy resin factory, with a GM (SD) of 55.73 (5.48) and a maximum value of 1934.85 ng/ml.

5.2 G2: elevated BPA concentrations

Within G2, where the concentrations are not so high, articles such as those by Li et al. [100] or Miao et al. [101, 102]. In them, differences between exposed vs. control are determined, observing medians (IR) of 38.7 (6.3–354.3) vs. 1.4 (0.0–17.9) $\mu\text{g/g creat.}$ in the first case, AM (SD) of 36.23 (7.69) vs. 1.38 (6.89) $\mu\text{g/g creat.}$ in the second, and GM (95% confidence interval, CI) of 22.2 (12.4–39.8) vs. 0.9 (0.7–1.1) $\mu\text{g/g creat.}$ in the latter. The same pattern can be observed in the work of Ndaw et al. [85], where higher values are observed in cashiers exposed to thermal tickets vs. controls, determining a GM (SD) of 8.58 (2.83) vs. 3.52 (2.35). For their part, Zhuang et al. [103] carried out a slightly different approach since they determined differences between workers of an epoxy resin company with a working time greater than five years versus those in the company for less than five years. The median values observed reflected a significant increase in workers with a longer working time (27.18 vs. 9.73 ng/ml serum). Finally, the work of Heinälä et al. [104] is also included in this group, where the pre-shift vs. post-shift urinary concentration is studied, quantitatively highlighting the GM of the heat-sensitive paper producing company, 18.7 vs. 39.4 ng/ml, or from the liquid paint producer, 4.6 vs. 10.3 ng/ml of urine.

5.3 G3: “normal” range but with significant differences

The third group, G3, despite being in the range that we have determined as general, corresponding to the majority of the population, also presents interesting differences. Among them, the works of Zhou et al. [105] and Kouidhi et al. [106] stand out. Their comparison between exposed subjects vs. controls found values corresponding to the median of 3.198 vs. 0.276 ng/ml serum in the first and 3.81 vs. 0.73 ng/ml urine in the second. The same study line is the oldest academic article of the review, published by Hanaoka et al. in 2002 [107]. They determined very few differences between workers in the bisphenol diglycidyl ether (BADGE) industry vs. controls, with medians of 1.06 vs. 0.52 $\mu\text{mol/mol creat.}$ Similarly, He et al. [108] determine few differences between exposed workers and their families, determining a GM of 1.41 ng/ml in exposed men, compared to 0.58 in their women or 0.78 in their children under 20 years of age. Waldman et al. [109] and González et al. [110] also show low GM values. The first measures BPA's urinary concentrations in firefighters, engineers, captains, or battalion commanders, determining a GM of 1.58 ng/ml. In the second, they determine BPA's concentration in workers of an incinerator of hazardous waste, determining a GM of 0.68 in men and 1.2 ng/ml in women. Thayer et al. [111] and Lee et al. [36] carried out two publications focusing on cashiers exposed to thermal tickets. The first determines GM (SD) in pre-shift vs. post-shift cashiers of 1.89 (3.63) vs. 2.76 (3.53) $\mu\text{g/g creat.}$, being 1.25 (1.79) in controls that do not work as cashiers. The second publication finds subtle differences only in those cashiers who do not wear gloves, observing GM values pre- vs. post-shift of 0.4 vs. 0.9 ng/ml in cashiers without gloves, and 0.44 vs. 0.49 ng/ml in tellers with gloves. Finally, it remains to mention the work of Hehn et al. [112], in which analyzing the data from the American health program NHANES according to

the possible potential exposure. They determine GM values in women with probable vs. unlikely exposure of 5.45 vs. 2.16 ng/ml, thus as of 2.85 vs. 2.59 ng/ml in men’s case.

6. Tolerable daily intake (TDI); calculations and extrapolations

Tolerable Daily Intake (TDI) is “the maximum amount of a contaminant which can be eaten every day over a whole lifetime without incurring appreciable risk to health” [113]. Currently, the European Food Safety Authority (EFSA) estimates it at 4 µg/kg BW/day [31]. The TDI calculated by EFSA is based on the studies of Tyl et al. [114], in which the concentration limit at which no adverse effects were observed, NOEL or NOAEL, was determined. They used concentrations from 0.03 to 50 and 600 mg/kg BW/day (0.018–3500 ppm) in mice of different generations. They only observed renal effects (increase in organ weight) at the highest dose (600 mg/kg BW/day), thereby determining the NOEL at the next lower dose they used, which corresponds to 50 mg/kg BW/day. Thus, based on the renal NOEL/NOAEL and due to the presumption of limitations in the use of the parameter, the EFSA calculates the equivalent “Benchmark dose” (BMD). The equivalent concentration, in which it is estimated that there is an alteration in kidney weight in 10% of the treated animals, is 9 mg/kg. After applying a correction factor to estimate the equivalent dose in humans, a concentration of about 600 µg/kg is obtained. Finally, an uncertainty factor of 150 is applied to obtain the final result of 4 µg/kg BW/day [31].

To determine if the population is exposed to a high or low BPA concentration, the estimated daily intake (EDI) must finally be calculated. Exposure levels are expressed as a mass (nanograms or micrograms) per kg of weight per day. For this reason, it is necessary to multiply the urinary concentration of BPA in ng/ml by the average volume of urine (in ml) excreted per day and divide this number by the average weight measured in kilograms (reference values extracted from academic literature [115]). When taking the average value between adult men and women, a value of 1400 ml per day is obtained. The publication itself also shows the reference values for body weight, expressed in kg. When taking the same average as that applied to the urinary volume, adults’ average weight would correspond to a value of 66.5 kg. In this way, as reflected in Table 3, the main EDIs were calculated.

Statistical parameter	Population	Value (ng/ml)	µg/kg BW/day
GM	General population [own work]	1.55	0.03
AM	Conventional dialysis [86]	52.73 to 155.84	1.11 – 3.28
AM	Online hemodiafiltration [86]	8.79 to 23.42	0.19 – 0.49
Median	Occupational Exposure [78]	243.08	5.12
MAX	Occupational Exposure [77]	268,975.33	5.662.64
P95	Pregnant woman [81]	250.06	5.26
P95	ICU patients [83]	113.7	2.39

Note that the maximum occupational exposure value reaches 5.66 mg/kg BW/day (1000 times higher than TDI). Abbreviations: GM, geometric mean; AM, arithmetic mean; MAX, maximum value; P95, 95th percentile.

Table 3.
Most relevant values in the systematic review.

7. Discussion

In the first place, an interesting element to consider resides in the pharmacokinetics models since they add modifications to BPA in order to determine it efficiently and without contamination by HPLC. After the first model made by Volkel et al. [41], where they used d(16)-bisphenol A, successive authors have emulated this methodology in order to accurately measure the pharmacokinetics of administered BPA [54, 55, 116–119]. However, deuterium modification of drugs is used today to reduce toxicity by redirecting metabolic pathways [120]. Perhaps the possibility that not all BPA is excreted in urine should be reconsidered with this in mind. We know that mice excrete BPA in feces; however, there are no publications in the literature that quantify BPA in human feces, although the presence of microplastics in them has recently been demonstrated [121].

Secondly, since it is described that BPA is a hydrophobic molecule, but with slight aqueous solubility and with the capacity to cross all types of biological tissues [29, 41, 122], it is possible their bioaccumulation in the organism. To do this, Richard W. Stahlhut's team determined BPA concentrations as a function of fasting time. Surprisingly, BPA levels did not decrease rapidly with fasting time, suggesting that there may be non-food exposure or bioaccumulation in body tissues [123].

Thirdly, another critical element is the possible non-monotonic effects of BPA on various organs and tissues [124–126]. This non-monotonicity can significantly affect at low concentrations, below the current TDI, in the same way that it has been shown to happen with certain hormonal stimuli. In her review, Vanderberg [124] determined that non-monotonic dose–response curves (NMDRCs) are typical in the literature related to BPA, occurring in greater than 20% of all experiments and at least one endpoint in more than 30% of all studies examined [124]. Going a little deeper into the non-monotonic effects works such as that of Angle et al. demonstrate the existence of multimodal dose–response curves [127]. Recent data suggest that the non-monotonic effect of BPA could depend upon the target tissue. In our studies in mice, we observed that while BPA induces hypertension in a dose-dependent manner, it affects renal podocytes in a classical non-monotonic response curve [22, 23, 27]. In multimodal curves, increases and decreases are observed, and variations in the maximum response depending on the type of tissue [127] may further complicate the correct assessment of BPA's presumed safety concentrations currently found in the population.

Throughout this chapter, an average urinary BPA value for the general population has been determined using a systematic methodology to serve as a reference. Similarly, the analysis of the different statistical parameters shown in the publications determined population groups of special interest, such as workers with occupational exposure, pregnant women, or intensive care patients. With the latest discoveries in the BPA-nephro-vascular system paradigm, all this provides a sufficient basis to place kidney patients in the critical spotlight. The systematic review has determined relatively high BPA plasma values in patients undergoing hemodialysis, which could be a potentiating element for its worsening. In this way, the need to modify the materials used in specific treatments to reduce exposure to this endocrine disruptor is determined, thus avoiding some patients' possible deterioration. Similarly, the high values of urinary BPA in various publications related to occupational exposure show the need to improve personal protective equipment and working conditions in specific sectors related to the manufacture or recycling of plastics, since concentrations should not be detected urinary levels high enough to reach the micromolar or even nanomolar range. Although we have indeed normalized the existence of endocrine disruptors in the general

population's urine, which is a worrying fact, we should ensure that they are at the lowest possible threshold.

EFSA determines that the TDI is at four $\mu\text{g}/\text{kg BW}/\text{day}$, which is justified with experimental animal models. However, as in vitro experiments have shown, BPA can exert very different actions in murine and human cells, although with similar consequences, converging on the possibility of kidney damage. It remains to be determined whether it would be necessary to review the coherence of the calculations and extrapolations, taking into account the observed inter-species differences.

8. Conclusions

- Novel data suggest that human exposure to bisphenol A is associated with renal, cardiovascular, and hypertensive diseases.
- The inter-species differences observed in the basic research models show interesting evidence to rethink the institutions' calculations that determine the TDI.
- The use of modified molecules in the pharmacokinetic models and the absence of studies in feces (and the presence of microplastics) suggest the possibility that not all BPA is excreted in the urine, which would mean that the concentrations described would be below the actual exposure.
- The development of the systematic review using the premise of pharmacokinetic studies shows a relatively low general exposure, but with population groups of interest, such as workers with occupational exposure and patients from the hospital environment.
- The data obtained and the novelties in basic research provide sufficient evidence to consider the patient with kidney disease as one of the priority groups in which their exposure should be reduced, possibly by modifying the medical material's composition.

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