

## Short Update on Bisphenol A Exposure and Type 2 Diabetes: Focus on Workers

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### Abstract

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders. The interference of Bisphenol A (BPA) with different cellular communication routes involved in glucose homeostasis and the onset of insulin resistance is now documented. A bibliographic collection was made using the PubMed and Scopus database, focused on BPA exposure for humans, both in daily life and in occupational settings. A comparison between exposure levels of BPA in the general population and in specific workplaces showed possible higher BPA exposure in workers. Even with some controversies about the role of BPA in the onset of T2DM, the aim of this study is shedding light on the potential risk of diabetes in workers exposed to BPA and provide helpful information for occupational physicians in directing their health checks.

**Keywords:** Bisphenol A; BPA; Diabetes; Workers, Workplaces, Metabolic disease

### Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent metabolic disorders, characterized by impaired metabolism of carbohydrates, lipids and proteins [1,2]. The prevalence of diabetes worldwide has grown from about 108 million adults (4.7% of population) in 1980 [3] to 463 million (9.3%) in 2019 [4] and it is estimated that it will rise to 700 million by 2045 [4]. Diabetes leads to hyperglycemia, which results from defective insulin secretion, insulin resistance or a combination of both [5]. The etiology of this type of diabetes involves different factors, with a clear genetic background but also linked to possible environmental chemical exposure [6,7].

Bisphenol A (BPA) is the basic monomer of polycarbonate plastics and epoxy resins. It is used for food preservation in coating materials of cans and jar caps [8,9]. Other products containing BPA are dental materials and thermal paper for cash registers.

BPA has estrogenic properties [10], may affect pancreatic  $\beta$ -cell function and/or insulin action [11,12]. Moreover, at the hepatic level BPA can lead to glucose production,

glycogen synthesis reduction and damage insulin signals [13].

Routes for BPA exposure are: food consumption, like meat products (17-602ng/g), fish (5-109 ng/g), fruits and vegetables (9-76 ng/g), beverages (1-18ng/g), infant formula (0.1-13 ng/g); dust coming from laminate flooring, paints, electronic equipment (0.8-10 $\mu$ g/g), thermal paper (54.0-79.0 ng/cm<sup>2</sup>), dental material, mostly in the form of BPA-glycidyl methacrylate (0.013-30 mg) and plastic (0.2-26 ppb) [14].

The possible occupational BPA exposure can occur in industrial settings (in the petrochemical synthesis of the products; in the production of polycarbonate plastics; in the production of epoxy-based products; in the production of plastic coatings) as well as in activities in which these products are used for specific purposes (e.g., the application of epoxy resins as surface insulation, or epoxy paints) [15].

Handling thermal papers is a major occupational source of BPA exposure. Studies on cashiers [16], who routinely handle this type of receipts, have shown higher urine BPA level in workers in comparison with the general population.

Due to the risk for human health linked with BPA exposure, European legislation has adopted some preventive measures: it banned the use of this chemical in baby bottles and many limitations are present for the use of BPA in plastic for food contact [17]. Indeed, BPA levels in thermal paper has been strongly reduced by law from January 1<sup>st</sup> 2020.

The aim of this study is shedding light on the potential risk of diabetes in workers exposed to BPA and provide helpful information for the occupational physicians in directing their health checks.

### Materials and Methods

A bibliographic collection was made using the PubMed and Scopus databases, with these search items: “BPA and diabetes” “BPA and workers” “BPA and occupational exposure”; surveys prior to 2015 and articles not available as full text in English, Spanish or Italian were excluded from the study.

Reviews of scientific literature were excluded as well. Epidemiological surveys on adult men and women were taken into consideration for this update.

The article selection diagram is shown in Figure 1.

### Results

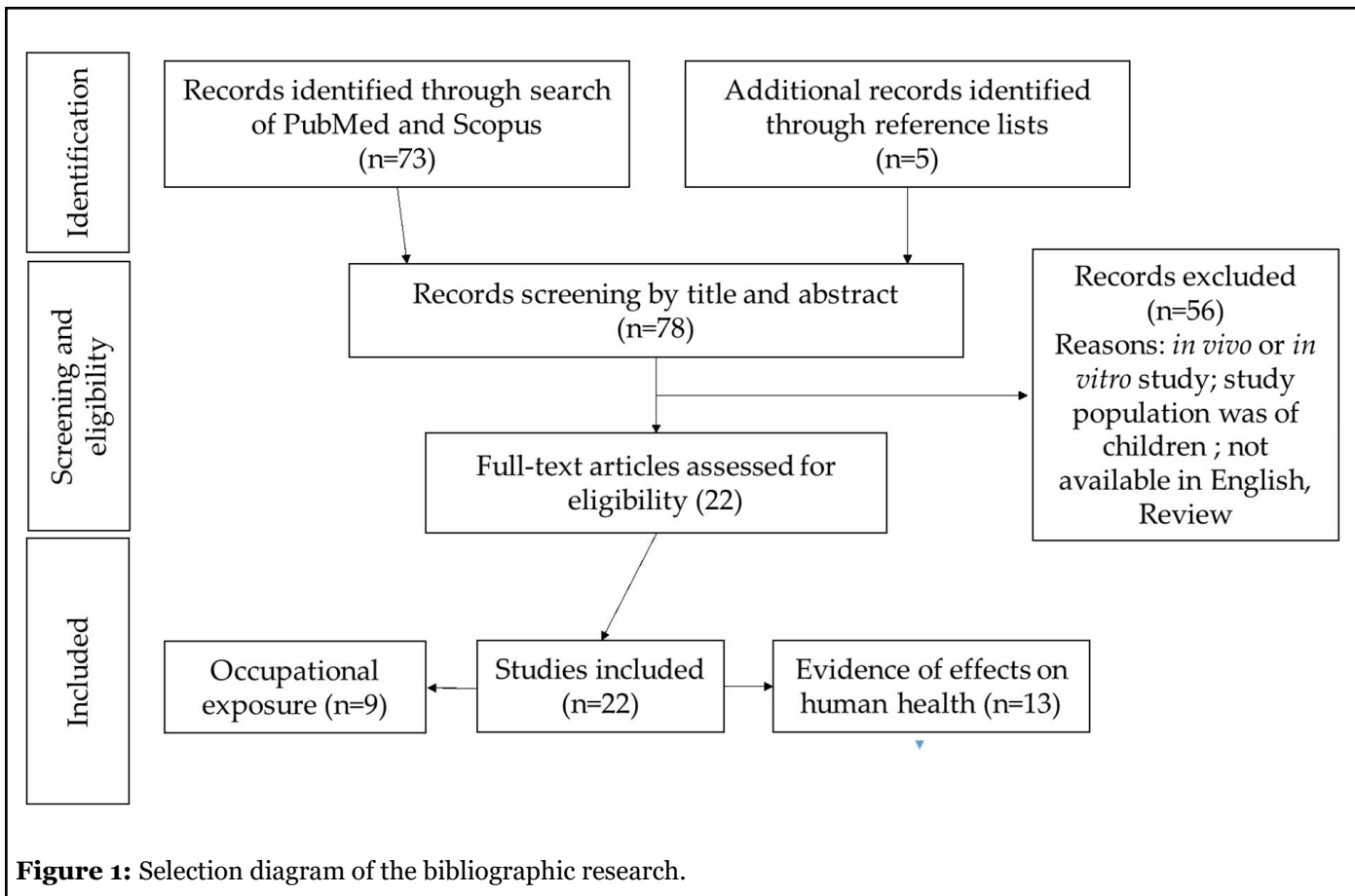
#### Studies on the population

The interference of BPA with different cellular communication routes involved in the glucose homeostasis and the onset of insulin resistance has been presented in literature and this involved the BPA exposure with T2DM [18].

A brief illustration about published studies is provided in Table 1.

#### The workplace: epidemiological and exposure data

While in the literature, in the last decade, numerous researches were published about BPA exposure and metabolic disease, mainly to characterize the possible risks for the general population; in workplaces the attention has been focused on the level of exposure more than to the possible target organ/system. Studies regarding adverse effects were mainly focused on the ability of BPA to act as an endocrine disruptor, particularly for male or female reproductive functions; while, at the moment, only one article has focused on metabolic disease [32].



**Figure 1:** Selection diagram of the bibliographic research.

Study type	No. of subjects	Geographic area of study	BPA mean levels	Results	Ref.
Case/ control	54/47	Saudi Arabia	3.9 vs 1.3 <sup>a</sup>	Urinary level of BPA is associated with increased risk of T2DM	19
Cross sectional	400 (247 with diabetes/153 without diabetes)	Pakistan	2.10 vs 1.86 <sup>a</sup>	BPA exposure is a risk factor of T2DM	20
Cross sectional	8498	USA	3.7 <sup>a</sup>	No correlation between urinary concentration of BPA and diabetes	21
Longitudinal	775/201 with diabetes after 9 years follow up	France	1.75 <sup>ax</sup>	Positive association between BPA exposure and the incidence of T2DM	22
Case control	70/334	Mexico	6.60/4.80 <sup>c</sup>	Association between urinary BPA level and diabetes (OR=1.85, 95% CI 1.04-3.38)	23
Longitudinal	2336 with follow up for 4 years	China	0.93 <sup>ab</sup>	No significant association between urinary BPA and glucose metabolic markers in men. In women higher OR values were identified (OR=1.37, 95% CI 1.10-1.72 for hyperglycaemia and OR=1.30, 95% CI 1.02-1.65 for $\beta$ -cell dysfunction)	24
Case control	251/251	China	0.599 vs 0.726 <sup>bc</sup>	No significant differences in BPA concentration between cases and controls	25
Cross sectional	350 (only women)	USA	1.3 <sup>ab</sup>	No association between BPA and glucose levels	26
Cross sectional	296	Korea	1.38 <sup>c</sup>	Positive association between urinary BPA levels and insuline resistance.	27
Cross sectional	240	Thailand	1.1 <sup>d</sup>	No association between BPA and T2DM, but a positive association with impaired glucose tolerance	28
Cross sectional	4320	Canada	1.21 <sup>ab</sup>	Urinary BPA levels were positively associated with adverse glucose homeostasis in men	29
Cross sectional	2581	Thailandia	0.34 <sup>d</sup>	Serum BPA was positively associated with T2DM	30
Longitudinal	3510/232 with diabetes after 5 years follow up	China	1.3 vs 1.6 <sup>e</sup>	No significant difference in serum BPA concentration between patients and controls	31

<sup>a</sup>  $\mu\text{g/L}$ , unadjusted urinary BPA; <sup>b</sup> median; <sup>c</sup>  $\mu\text{g/g}$ , urinary BPA adjusted for creatinine; <sup>d</sup>  $\mu\text{g/L}$ , serum BPA; <sup>e</sup>  $\mu\text{mol/L}$ , serum BPA; <sup>x</sup> urinary BPA glucuronide, 50<sup>th</sup> percentile

**Table 1:** Description of clinical studies on association between BPA and T2DM.

The possibility of dermal exposure related to contact with thermal papers (e.g., for a cashier) is an aspect of interest that should require additional considerations, with respect to the possible exposure routes [33]. Indeed, the Risk Assessment Committee of the European Chemical Agency

released a scientific opinion alerting that occupational BPA exposure for dermal contact via thermal paper might not be adequately controlled so the European Commission restricted the BPA level in this type of paper from January 2020 [34].

Study type	Focus	No. of subjects	Population type	Geographic area of study	BPA mean levels	Results	Ref.
Cross sectional	Exposure/hormones	592	Male workers in industry	China	685.9 <sup>cd</sup>	Association between urinary BPA and prolactina, estradiol, elevated sex hormone binding globulin level.	35
Cross sectional	Exposure/thyroid hormones	90	Workers of plastic industry	Egypt	15.6 <sup>ad</sup>	No correlation between BPA levels and thyroid hormones concentration	36
Cross sectional	Biological monitoring	29	Workers in waste incinerator	Spain	0.58 <sup>e</sup> / 0.86 <sup>a</sup>	All workers had shown BPA exposure	37
Case/control	Exposure/hormones	106/250	Female workers in epoxy resin production vs not exposed	China	22.2 <sup>bc</sup> / 0.9 <sup>bc</sup>	Urinary BPA levels were positive associated to serum prolactin and progesterone concentration.	38
Case-control	Exposure/hormones	110/113	Petrolchemical factory workers and not	Korea	0.628 <sup>e</sup> / 0.457 <sup>e</sup>	Serum BADGE* produced hormonal alterations but no difference between cases and controls.	39
Case/control	Exposure/hormones	281/278	Workers exposed to BPA vs not exposed	China	18.75 <sup>e</sup> / 3.37 <sup>e</sup>	Increased serum BPA level was associated with decreased mean serum androstenedione level and increased serum SHBG level.	40
Case/control	Exposure/hormones	62/62	PCOS women, working as market seller vs healthy women	Iran	0.48 <sup>e</sup> / 0.16 <sup>e</sup>	In cases, BPA level was higher than controls, together with higher levels of triglyceride, cholesterol, TSH and LH:FSH ratio.	41
Case/control	Biological monitoring	90/44	Cashiers exposed vs not exposed	France	6.76 <sup>c</sup> / 2.89 <sup>c</sup>	Cashiers handling daily thermal paper receipts had significant higher urinary BPA concentration	33
Longitudinal	Exposure/metabolic syndrome (MS)	1227/200 with MS after a follow up of 4 years	Male workers	China	3.89 <sup>bc</sup>	Exposure to BPA may increase the risk of MS, urinary BPA levels are positively associated to higher incidence, particularly for smokers	32

<sup>a</sup> µg/L; <sup>b</sup>geometric mean; <sup>c</sup>µg/g, urinary BPA adjusted for creatinine; <sup>d</sup>median; <sup>e</sup>µg/L, serum BPA; ; <sup>e</sup>µg/L, serum; BPA diglycidyl ether- BADGE (BPA precursor *in vivo*)

**Table 2:** Description of studies on workers with occupational BPA exposure.

A description of what emerged in the workplace is provided in Table 2.

## Discussion

Looking at the overall recent data on the general population, some controversy persists about the association of BPA exposure and incidence of T2DM. Indeed four of the seven cross sectional studies suggest a possible positive association with a useful sample dimension (4,320, 2,581, 400 and 296 subjects) [20,27,29,30], while the other articles express doubts about this conclusion. However, different types of bias should be considered: in the National Health and Nutrition Examination Survey NHANES study, on 8,498 subjects [21], cases of diabetes were self-reported and the authors do not distinguish between type 1 and type 2 diabetes; Bellavia et al. [26] used a specific sample, only pregnant women, and this poses problems for an extrapolation of data regarding a different population; the survey carried out by Chailurkit et al. [27] on 240 subjects, analysed serum BPA using an ELISA method, a comparison of accuracy between ELISA and HPLC/MS/MS methods shows very remarkable differences that should be taken into consideration. Furthermore cross-sectional study characteristics severely restrict the possibility to extrapolate elements of causality, this type of study only leads to formulate hypothesis.

Nevertheless, the case/control studies do not clarify the doubt. Two papers confirm the positive association, even if in one case [19] the sample dimension is too low (54 cases and 47 controls) for a robust result, the work of Murphy et al. [23] seems to be more consistent in this respect, but the third paper [25] with a useful number of subject does not confirm the starting hypothesis.

Finally, the longitudinal surveys, which by an epidemiological standpoint represent the golden study, confirm the correlation between BPA and T2DM, with a follow up of 9 years [22], while a shorter follow up (4/5 years) showed a partial confirmation, only for the female population [24] or no evidence [31].

Some methodological limitations make the conclusions of lesser impact; for example an influencing factor can be the choice to characterize the magnitude of exposure to BPA with urinary BPA concentration, on a spot urine sample, without proceeding with a standardization regarding the grams of urinary creatinine; this implies a very limited interpretation of the datum [42].

The studies carried out in the workplaces showed a detectable BPA exposure in every situation, sometimes at considerable higher level than the general population [35,36,38]. Attention was primarily given to the detectable concentration of BPA and then to the possible interaction

between BPA and hormones. Evidences emerged about a positive correlation between BPA and sexual hormones, while data about thyroid hormones seems to be less clear.

The only published prospective study [32] about occupational exposure to BPA and metabolic problems confirms the positive correlation between this chemical and the metabolic syndrome (a cluster of cardio-metabolic risk factors like obesity and insulin resistance that pose a major threat for future diabetes and cardiovascular disease).

## Conclusion

The onset of diabetes sees in the genetic predisposition and environmental factors clear elements of promotion, nevertheless other factors play a role [43], because the former may not fully clarify the increase in this type of pathology over the last century [44].

Exploratory studies on volunteers confirmed the association between BPA and glucose metabolism. 8 men and 3 women were orally administered a BPA dose (50 µg/Kg body weight, considered safe by US regulators) and an alteration of glucose-stimulated insulin response was found [45]. Moreover, a second study enrolled 11 subjects, in a double-blinded survey with placebo and orally administered BPA: evidence emerged of immediate effects on glucose, insulin and C-peptide concentration in the subgroup exposed to BPA [46]. A meta-analysis [47] carried out to clarify the role of BPA in T2DM, involved data from about 41,320 subjects: biological levels of BPA, both in urine and in serum, were collected and showed a positive correlation with T2DM risk (OR 1.28, 95% CI 1.14-1.44).

Starting from these literature evidences, even if some uncertainties persist, it is appropriate to consider BPA as possibly involved in the interference of glucose metabolism and therefore in the onset of T2DM.

The present short review of recent studies shows, although with some controversies, an association between BPA and T2DM, even if some methodological problems should be considered. For example, the use of standardized measurement units (i.e., for the micrograms of urinary creatinine in the case of urine). Often the use of simple concentration as micrograms/liter does not permit a correct evaluation of exposure and a comparability of data.

Overall, the improvement of prospective studies to highlight the predictability of data and their statistical force is desirable [48].

A comparison among biological BPA levels in workers and in the general population has led to a concern: often in workplaces there is a higher exposure than that of the general population. Considering that even at low doses



some evidence emerged of interference between BPA and glucose metabolism, the possibility of onset of diabetes in workers, with higher and documented exposure levels, could be greater. Even if the interest of researchers in workplaces was directed to a different target, data from literature, based on the general adult population, call for the definition of new epidemiological investigations to assess the role of BPA in diabetes, to further direct the activities of occupational doctors.

The role of occupational exposure to BPA in the etiology of diabetes is a possibility that the occupational doctor must consider in his or her working activity, in order to protect the workers' health.

## Conflict of Interest

The authors declare no conflict of interest.

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## Author Contributions

Conceptualization, methodology, writing—original draft preparation L. Caporossi; resources, B. Papaleo; data curation L. Caporossi; editing, supervision, M. De Rosa and B. Papaleo. All authors have read and agreed to the published version of the manuscript.

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