A SYSTEMATIC REVIEW ON THE HEMOLYTIC EFFECT OF BISPHENOL-A ON HUMAN ERYTHROCYTES (*IN-VITRO*)

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Abstract

Bisphenol A (BPA) is a high-production volume industrial chemical, and human exposure to BPA is essentially ubiquitous with the increased use of BPA-associated products. Though the ubiquitous nature of BPA exposure has resulted in circulating levels of BPA, as reported in numerous biomonitoring studies, a limited number of studies have been carried out to investigate the impact of BPA on human red blood cells. Yet the findings remain ambiguous. Thus, this study aimed to systematically review the published literature on the hemolytic activity of BPA on human erythrocytes. A systematic review of published literature was conducted following the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) approach. A comprehensive search of the literature was undertaken using Google Scholar, PubMed and Research Gate for studies published from 2015 to September 2023. The keywords "human erythrocytes", "Bisphenol-A", "in vitro", and "hemolysis" were included in the search. The search identified a total of 933 articles (PubMed = 3, research gate=99, and Google Scholar = 831). After following the exclusion and inclusion criteria, four full papers were entitled to review. In these four studies, they have incubated isolated human red blood cells with varying concentrations for different durations. BPA showed a dose-dependent and time-dependent hemolytic activity in-vitro on human erythrocytes. Reasons for BPA-induced hemolysis in erythrocytes involve the generation of reactive oxygen species. As there are contradictory observations, meta-analysis is recommended. However, no comprehensive investigations have been carried out to evaluate the impact of BPA on human red blood cells under physiological concentrations so far. Consequently, it is recommended that further research in this area be undertaken to provide a more robust understanding of the physiological implications of BPA exposure on red blood cell function.

Keywords: Bisphenol-A, In-vitro, Hemolysis, Human erythrocytes

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Introduction:

Bisphenol A (BPA) is a widely used chemical in manufacturing epoxy resins, polycarbonate plastics and thermal receipts worldwide (Legeay & Faure, 2017). BPA is widely used to produce plastic food and beverage containers, water bottles, and other consumer goods. Epoxy resins, which are used as a coating for the interior of metal items such as food cans, bottle caps, and water supply lines, also contain BPA. Flame retardants, commonly used in various industries to enhance fire safety, often contain notable quantities of BPA. Dental sealants designed to prevent decay also include BPA as an essential component. In addition, plastic baby toys can be another source of exposure to this chemical compound. Furthermore, electrical appliances, essential in modern households, and various automobile parts, integral to the automotive industry, are known to incorporate significant levels of BPA, underlining the ubiquity of this substance in our daily lives. Biedermann et al.,2010; Monneret, 2017). According to the 'Coherent market insights' report, the BPA market was approximately 5.5 million tons in 2021, and a Compound Annual Growth Rate (CAGR) of 3.48% has been forecasted until 2032.

BPA exposure is essentially ubiquitous with the increased use of BPA-associated products (Geens et al., 2012). The primary source of BPA exposure is believed to be dietary and plastic bottles, food and beverage cans are discussed widely under dietary BPA exposure (Carwile et al., 2009; Geens et al., 2010; Mercea.,2009; Vandenberg et al., 2007). Dermal BPA exposure, which is many times higher than dietary exposure, has been experimented with thermal cash receipts (Natalie von Goetz et al., 2017). Routine occupational exposure to BPA is inevitable for employees in BPA-utilizing industries (Calafat et al., 2005). Various demographic and lifestyle elements have been linked to BPA exposure in the general population, such as gender, age, income, education, smoking, and other socioeconomic factors (Calafat et al., 2008; Nelson et al., 2012).

BPA ranks among the extensively researched endocrine-disrupting chemicals (EDCs), non-natural chemicals disrupting normal hormone function. (Monneret, 2017). Studies have linked BPA exposure with increased risk of cardiovascular diseases, high blood pressure and coronary artery disease (Bae et al., 2012; Lang et al.,2008; Melzer et al., 2010; Shankar et al., 2012). BPA has also been linked to metabolic disorders such as obesity, insulin resistance, and type 2 diabetes. BPA exposure has been shown to affect adipose tissue differentiation, liver function, and insulin signalling, contributing to metabolic dysfunction (Carwile & Michels, 2011; Lang et al., 2008; Rubin & Soto, 2009; Shankar & Teppala, 2011; Silver et al., 2011; Trasande et al., 2012; Vom Saal et al., 2012; Wang et al., 2012).

BPA undergoes liver metabolism inside the body, producing metabolites excreted through urine or faeces with a brief half-life of 6 hours. (Knaak et al., 1966). Some BPA has been shown to accumulate in lipid reservoirs, indicating a moderate potential for bioaccumulation (Christensen et al., 2012). A portion of absorbed BPA may be stored in the body and slowly released into the bloodstream over time (Fernandez et al., 2007). Shekhar et al. (2017) and Hiroi et al. (2004) have shown that blood BPA concentrations in individuals are around 20 ng/mL, even without intentional exposures.

Erythrocytes, also known as red blood cells, play a pivotal role within the circulatory system as they represent a significant category of cells that are consistently and widely exposed to the presence of Bisphenol A (BPA) circulating throughout the body. Xenobiotics, such as bisphenols, have the potential to interfere with the integrity of blood cell membranes, increasing the hemolysis potential and impairing physiological functioning (Burgos-Aceves et al., 2021). Hemolysis refers to the breakdown of red blood cells and the release of their contents into the surrounding environment, resulting in cell death (Ishiguro et al.,2020). Hence, any disruption in red blood cell function can have far-reaching consequences for the individual's overall health.

In vitro, hemolysis assays involve incubating red blood cells with the agent of interest and measuring the release of hemoglobin into the surrounding solution. This can be quantified using spectrophotometry or other methods. Many studies have been carried out to investigate the effects of bisphenols on animal blood cells. However, the number of studies on human red blood cells is limited, and the findings remain inconclusive. Therefore, this study aimed to systematically review the available literature to deduce the exact effect of BPA on red blood cell hemolysis.

In a systematic review, existing research studies are set to previously defined study criteria and sorted further by analyzing their content thoroughly. In the sorting process, the validity and suitability of the research question are highly assessed. The further systematic review assesses the methodological quality of the studies included, ensuring a rigorous and objective evaluation of the research conducted in this field. Finally, a qualitatively synthesized conclusion is extracted using the previously set inclusion and exclusion criteria. Further, this study will help to identify and analyze the potential mechanisms underlying the hemolytic effect of bisphenols on red blood cells, focusing on the biological processes involved and evaluating the dose-response and time-response relationships contributing to an understanding of this complex issue.

Methodology:

Search Strategy.

A systematic review of published studies on the effect of BPA on human red blood cell hemolysis was undertaken in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) approach. PRISMA analysis has four sequential steps: identification, screening, eligibility, and inclusion. For the "Identification" process, a comprehensive search was conducted using PubMed (US National Library of Medicine, USA), ResearchGate, and Google Scholar for peer-reviewed articles published from 2015 to 2023. The keywords were “human erythrocytes”, “Bisphenol-A”, “in-vitro", and "hemolysis”. Then, articles were screened by removing duplicates. Suitable articles were selected by reading abstracts. Articles initially chosen underwent further examination through full-text reading, and those meeting the exclusion criteria were carefully excluded. Most qualitatively suitable and eligible articles were included for analysis.

Studies published only in English were exclusively considered for the results, with the deliberate exclusion of conference proceedings and commentaries. This approach ensured that the investigation remained focused within the designated scope, allowing for a thorough examination of the chosen parameters. The papers obtained from the database search using the specified criteria were pooled, and duplicate entries were eliminated. Subsequently, the articles were first assessed by reviewing their titles and then by examining their abstracts. Studies that did not meet the inclusion criteria were excluded during the initial screening phases. The remaining articles underwent a final screening by reading their full texts, and those that did not meet the inclusion criteria were subsequently excluded.

Inclusion/ Exclusion Criteria.

The following inclusion criteria were applied when selecting articles:

(a) Studies conducted on human erythrocytes, (b) only in-vitro studies, (c) Treatment with BPA, (d) Studies on hemolysis.

The following exclusion criteria were applied in removing the articles:

(a) Duplicate articles, (b) Studies with other BPA analogous, (c) Studies on non-human erythrocytes, (d) Articles published in languages other than English, (e) Systematic reviews, literature reviews and conference proceedings. (f) only *in-vivo* studies (g) Errors with experimental

design and results presentation (no replicates, no average or standard errors of mean) (f) Studies with other blood components.

Results and discussion:

The literature search resulted in many articles in the databases as follows: PubMed (n=3), Research Gate (n =99) and Google Scholar (n = 831). Following the exclusions, only four articles were incorporated into the current review. Fig.1 illustrates the search strategy recruited for article selection. This systematic review aimed at existing scientific data on the hemolysis effect of BPA on human erythrocytes (*in-vitro*). All four studies included in this study have investigated the hemolysis activity of BPA on human erythrocytes and have calculated the percentage of hemolysis following *in vitro* assays (Katerina et al., 2022; Maćczak et al., 2015; Olchowik-Grabarek et al., 2018; Vaidya et al., 2019).

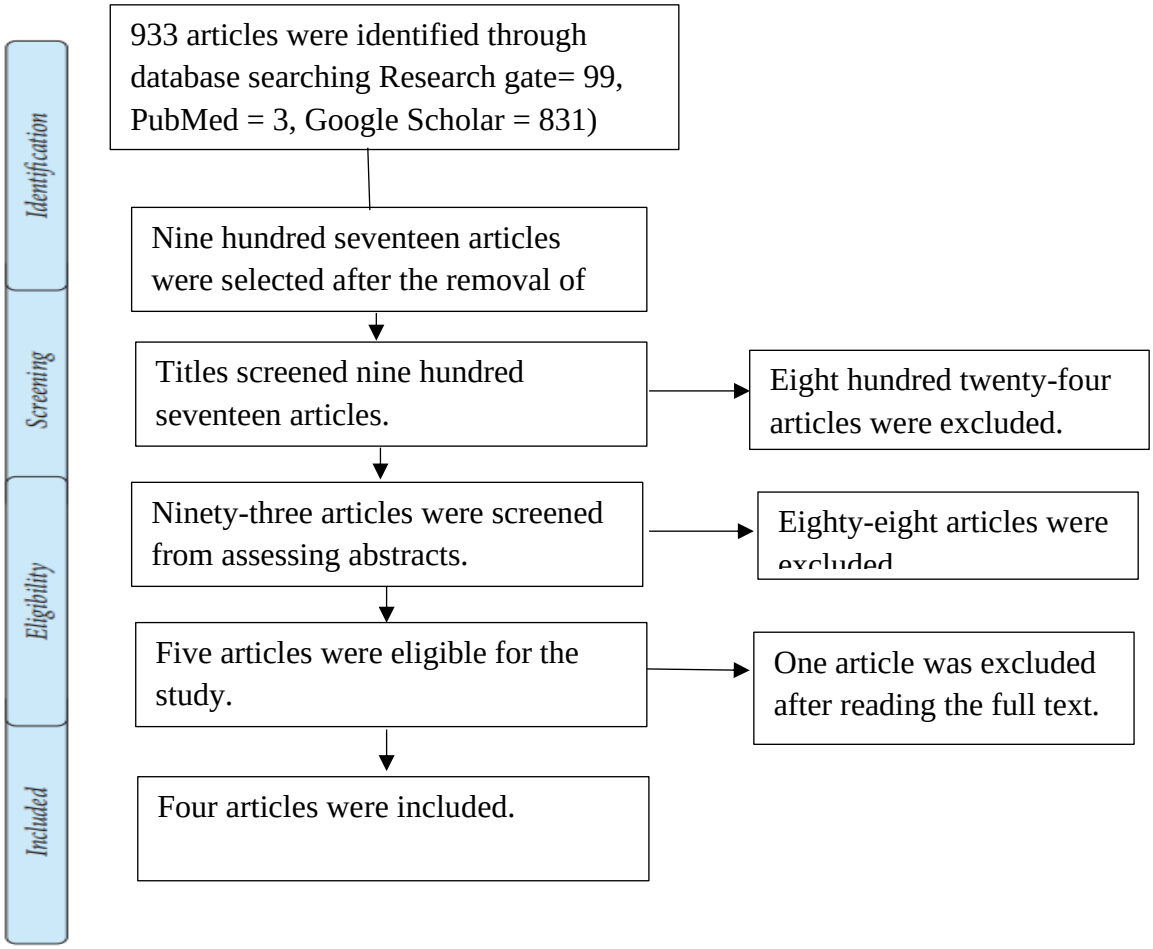

Figure 1: Flow diagram explaining the search strategy, inclusion and exclusion criteria used for the systematic review of scientific literature.

Table1: Summary of studies on *in-vitro* exposure to BPA on human red blood cells.

Research paper	Incubation time(hours)	Concentrations (µg/mL)	Significance of per cent hemolysis
Maćczak et al., 2015	1 hour	10	No significant hemolysis (P> 0.05)
		50	No significant hemolysis (P> 0.05)
		100	No significant hemolysis (P> 0.05)
		250	No significant hemolysis (P> 0.05)
		500	Significant hemolysis (P< 0.05)
	4 hours	10	No significant hemolysis (P> 0.05)
		50	No significant hemolysis (P> 0.05)
		100	No significant hemolysis (P> 0.05)
		250	Significant hemolysis (P< 0.05)
		500	Significant hemolysis (P< 0.05)
	24 hours	10	Significant hemolysis (P< 0.05)
		50	Significant hemolysis (P< 0.05)
		100	Significant hemolysis (P< 0.05)
		250	Significant hemolysis (P< 0.05)
		500	Significant hemolysis (P< 0.05)
Vaidya et al., 2019	4 hours	10	Significant hemolysis (P< 0.05)
		40	Significant hemolysis (P< 0.05, P< 0.01 and P< 0.001)
		80	Significant hemolysis (P< 0.05, P< 0.01 and P< 0.001)
		120	Significant hemolysis (P< 0.05, P< 0.01 and P< 0.001)
		160	Significant hemolysis (P< 0.05, P< 0.01 and P< 0.001)
		200	Significant hemolysis (P< 0.05, P< 0.01 and P< 0.001)
Katerina et al., 2022	1 hour	5	No significant hemolysis (P> 0.05)
		10	Significant hemolysis (P< 0.05)
		20	Significant hemolysis (P< 0.05)
		40	Significant hemolysis (P< 0.05)
		100	Significant hemolysis (P< 0.05)
		200	Significant hemolysis (P< 0.05)
	4 hours	5	Significant hemolysis (P< 0.05)
		10	Significant hemolysis (P< 0.05)
		20	Significant hemolysis (P< 0.05)
		40	Significant hemolysis (P< 0.05)
		100	Significant hemolysis (P< 0.05)
		200	Significant hemolysis (P< 0.05)
	24 hours	5	Significant hemolysis (P< 0.05)
		10	Significant hemolysis (P< 0.05)

		20	Significant hemolysis (P< 0.05)
		40	Significant hemolysis (P< 0.05)
		100	Significant hemolysis (P< 0.05)
		200	Significant hemolysis (P< 0.05)
Olchowik-Grabarek et al., 2018	24 hours	200	Significant hemolysis (P< 0.05)

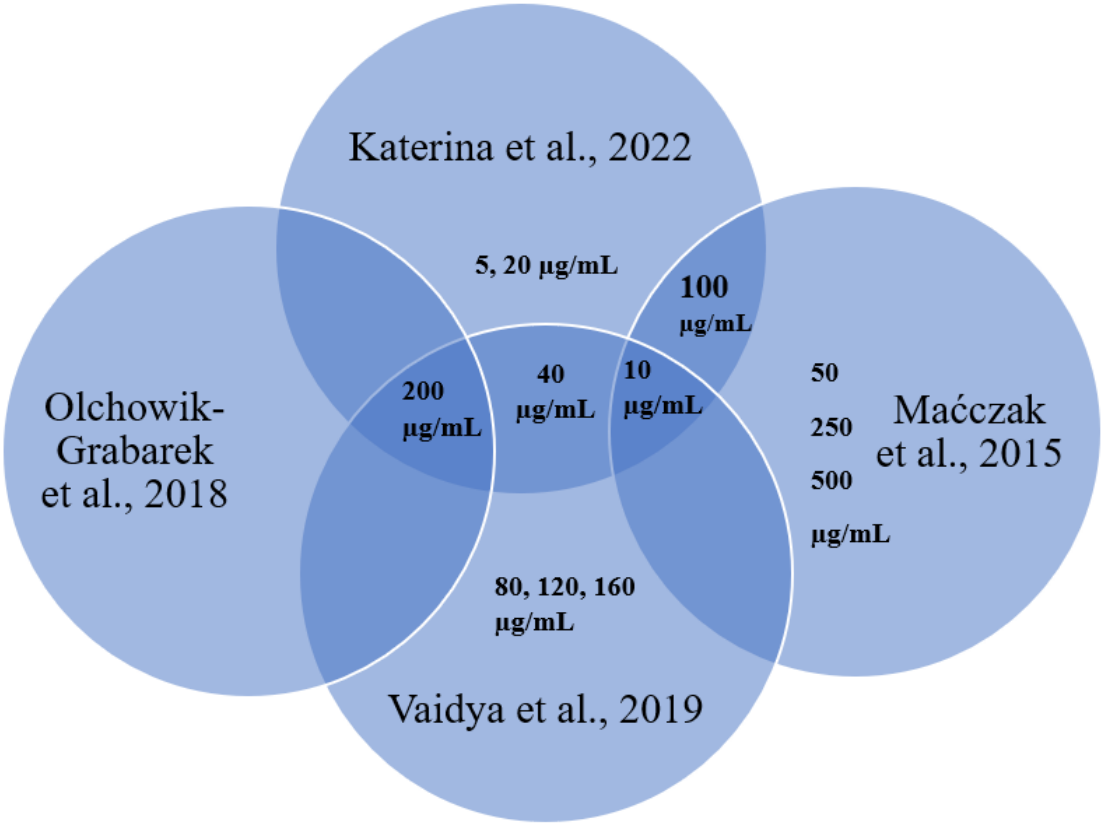

Figure 2: Venn diagrams indicating the BPA concentrations (µg/mL) used for *in-vitro* assays.

As shown in Table 1, Maćczak et al., 2015 has incubated isolated erythrocytes with 10 µg/mL,50 µg/mL, 100µg/mL, 250µg/mL and 500 µg/mL of BPA for time durations of 1 hour, 4 hours and 24 hours at 37 ^{0}C. They have shown a statistically significant increase in hemolysis when human red blood cells were incubated for 1 hour with 500 µg/mL BPA (P< 0.05). 250 µg/mL and 500 µg/mL BPA have significantly increased hemolysis with 4-hour exposure. All tested BPA concentrations have resulted in significant hemolysis after 24 hours of exposure. Here, the negative control has given 0% of hemolysis and has been used in calculating the percentage of hemolysis in other treatments.

Vaidya et al., 2019 has incubated isolated erythrocytes with 10 µg/mL,40 µg/mL, 80µg/mL, 120 µg/mL, 160 µg/mL and 200 µg/mL of BPA for a time duration of 4 hours at 37 ^{0}C. Vaidya and colleagues have performed the statistical analysis under 5%, 10% and 1% confidence intervals. 10 µg/mL of BPA showed significant hemolysis at $p < 0.05$. All the other tested BPA concentrations have shown a significant hemolysis at $p<0.001$.

Katerina et al., 2022 has incubated erythrocytes with 5 µg/mL,10 µg/mL, 20µg/mL, 40 µg/mL, 100 µg/mL and 200 µg/mL of BPA for time durations of 1 hour, 4 hours and 24 hours at 37 ^{0}C. Here, the comparison has been done with the positive control in which complete hemolysis occurred. After 1 hour incubation, 10 µg/mL, 20µg/mL, 40 µg/mL, 100 µg/mL and 200 µg/mL of BPA have shown a significant hemolysis. After 4 and 24 hours of incubation, all six BPA treatments have shown significant hemolysis.

Olchowik-Grabarek et al., 2018 has incubated isolated erythrocytes with 200 µg/mL of BPA for 24 hours at 37 ^{0}C and observed a significant percentage of hemolysis at $p< 0.001$.

Both Maćczak et al., 2015 and Katerina et al., 2022 have investigated the hemolysis effect of 10 µg/mL and 100µg/mL of BPA after 1 and 4 hours of incubation (Fig.2). However only Maćczak et al., 2015 has reported statistically insignificant levels of hemolysis after 10 µg/mL of BPA for 1 hour.
One hour of incubation with 100 µg/mL BPA has resulted in statistically insignificant hemolysis in Maćczak et al., 2015. However, Katerina et al., 2022 showed a significant percentage of hemolysis, leading to a discrepancy in results. After 4-hour incubation with 10 µg/mL and 100 µg/mL of BPA, Maćczak et al., 2015 have shown no significant percentage of hemolysis. However, Katerina et al., 2022 have shown a significant percentage of hemolysis under both concentrations.

Four hours of incubation with 200 µg/mL BPA, Vaidya et al., 2019 have shown a significant percentage of hemolysis even at $P< 0.001$. Nevertheless, in Katerina et al., 2022 hemolysis has been presented only at $P< 0.05$ when compared with negative control.

Maćczak et al., 2015, Katerina et al., 2022 and Olchowik-Grabarek et al., 2018 investigated hemolysis after 24-hour incubation (Fig.2). 10 µg/mL, 100µg/mL were the common concentrations in Maćczak et al., 2015 and Katerina et al., 2022 and 200 µg/mL is the common concentration in Katerina et al., 2022 and Olchowik-Grabarek et al., 2018. After 24-hour incubation with 10 µg/mL BPA, both Maćczak et al., 2015 and Katerina et al., 2022 have observed a significant percentage of hemolysis at $P< 0.05$.

After 24-hour incubation with 100 µg/mL BPA, both Maćczak et al., 2015 and Katerina et al., 2022 have shown a significant percentage of hemolysis at $P< 0.05$ compared to negative control. A similar experiment by Olchowik-Grabarek et al., 2018 with 200 µg/mL reported a significant percentage of hemolysis at $P< 0.05$ compared to negative control.

The discrepancies in observations may arise from variations in the experimental setup, including but not limited to differences in the choice of solvents, the source of red blood cells, or other methodological factors that can potentially influence the outcomes and results of the experiments. Maćczak and colleagues have used ringer buffer, and the other studies have used the phosphate buffered saline to dissolve BPA and to prepare red blood cell suspension. Only Vaidya and colleges have obtained freshly drawn blood, while others have used stored blood. The evident conclusion arises from the research findings that BPA exhibits toxicity towards human red blood cells, leading to the induction of hemolysis. This observed phenomenon underscores the significance of further exploration into the intricate mechanisms and potential implications of BPA-induced hemolytic effects on human red blood cells. According to the literature, this hemolytic effect of red blood cells occurred mainly due to the generation of reactive oxygen species due to the BPA exposure.

Furthermore, alterations associated with hemolysis serve as indicative markers elucidating changes in red blood cell viability. This observation underscores the importance of investigating the broader

spectrum of modifications and implications accompanying hemolysis, thereby contributing to a comprehensive understanding of the dynamic processes affecting red blood cell integrity. It can be observed that hemolysis intensifies in a discernible manner, demonstrating a proportional escalation with the concurrent increase in both the concentration of BPA and the duration of incubation.

Conclusions and Recommendations

Based on the published literature, it can be concluded that BPA exhibits a hemolytic effect on human red blood cells, and the hemolysis appears to be dose- and time-dependent. The escalation in hemolysis is directly associated with a subsequent reduction in red blood cell viability, leading to a compromise in their physiological functionality. The potential mechanism underlying BPA-induced hemolysis implicates the generation of reactive oxygen species. This identified pathway underscores the significance of a more detailed investigation to elucidate the intricacies surrounding how BPA may trigger the production of reactive oxygen species, contributing to the observed hemolytic effects on erythrocytes. Heterogeneity observed between different studies can be further analyzed via a forest plot of published literature.

A meta-analysis to scrutinize the absolute effect of BPA is also recommended. Most importantly, all the studies have used supra-physiological concentrations of BPA. Therefore, comprehensive studies under physiological concentrations of BPA are recommended to obtain a more robust understanding of the implications of circulating levels of BPA on human red blood cells.

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