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Perspective

The silent threat and countermeasures: Navigating the mixture risk of endocrine-disrupting chemicals on pregnancy loss in China

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ABSTRACT

Currently, many countries and regions worldwide face the challenge of declining population growth due to persistently low rates of female reproduction. Since 2017, China's birth rate has hit historic lows and continued to decline, with the death rate now equaling the birth rate. Concerns have emerged regarding the potential impact of environmental contaminants on reproductive health, including pregnancy loss. Endocrine-disrupting chemicals (EDCs) like phthalate esters (PAEs), bisphenol A (BPA), triclosan (TCS), and perfluoroalkyl substances (PFASs) have raised attention due to their adverse effects on biological systems. While China's 14th Five-Year Plan (2021–2025) for national economic and social development included the treatment of emerging pollutants, including EDCs, there are currently no national appraisal standards or regulatory frameworks for EDCs and their mixtures. Addressing the risk of EDC mixtures is an urgent matter that needs consideration from China's perspective in the near future. In this Perspective, we delve into the link between EDC mixture exposure and pregnancy loss in China. Our focus areas include establishing a comprehensive national plan targeting reproductive-aged women across diverse urban and rural areas, understanding common EDC combinations in women and their surrounding environment, exploring the relationship between EDCs and pregnancy loss via epidemiology, and reconsidering the safety of EDCs, particularly in mixtures and low-dose scenarios. We envision that this study could aid in creating preventive strategies and interventions to alleviate potential risks induced by EDC exposure during pregnancy in China.

1. Introduction

The reliance on synthetic chemicals has resulted in unintended consequences for both human health and the environment. Among these concerns, the adverse effects of endocrine-disrupting chemicals (EDCs) have emerged as a significant threat to biological systems worldwide. EDCs encompass a wide range of chemicals, including phthalate esters (PAEs), bisphenol A (BPA), triclosan (TCS), and perfluoroalkyl substances (PFASs) (Table 1). These compounds have been found in environmental matrixes, wildlife, and humans worldwide [1,2]. EDCs might increase the risk of adverse outcomes in pregnant women and children by disrupting hormone-mediated processes that are critical for growth and development during gestation, infancy, and childhood [3]. Given the potential risks posed by EDCs, efforts have been made globally, including initiatives in the Stockholm Convention and the implementation of REACH (Registration, Evaluation, Authorization and Restriction of Chemicals) Regulation, to regulate the use and minimize the exposure to EDCs to protect human health and the ecosystems. However, regulatory frameworks and toxicological testing protocols have primarily been designed to assess the risks associated with a single EDC in isolation. This approach overlooks the complex reality of real-world exposure scenarios, where humans and ecosystems are exposed to mixtures of these chemicals [4]. Recent research revealed an association between early prenatal exposure to a mixture of EDCs (PAEs, BPA, TCS, and PFASs) and language delay in offspring [5]. It is crucial to track complex chemical mixtures in a changing environment [6].

Several countries, including China, are grappling with a persistent issue of declining populations due to decreasing birth rates [7]. Since

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2017, China's birth rate has hit historic lows and continued to decline, with the death rate now equaling the birth rate (Fig. 1) [8]. This demographic trend poses one of the most significant challenges for China in the years ahead. In addition to socioeconomic and personal reasons, other factors, such as infertility and pregnancy loss, also contribute to the population decrease. There is growing evidence suggesting that chemical pollutants, particularly EDCs, play a role in pregnancy loss [9]. Recent studies have shown a positive association between EDC mixtures and the risk of early miscarriage and recurrent spontaneous abortion in China, with EDCs being detected in urine samples [10,11]. In 2015, the European Union Commission's Horizon 2020 program funded a four-year project named EDC-MixRisk, which focused on evaluating the effects of EDC mixtures on children and developing risk assessment methods [12]. Although the treatment of emerging pollutants, including EDCs, was included in China's 14th Five-Year Plan (2021–2025) for national economic and social development and long-range objectives through 2035, there are no appraisal standards or regulatory frameworks on EDCs and their mixtures from a national perspective. Addressing the risk of EDC mixtures is thus an urgent matter that needs to be considered from China's perspective in the near future. Several key aspects are discussed below.

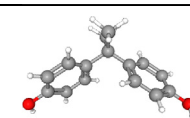
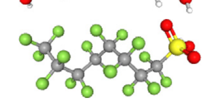
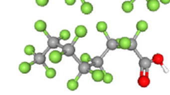
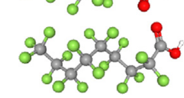
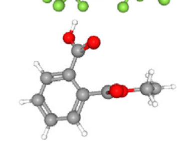
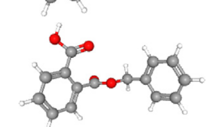
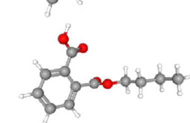
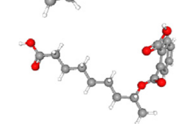
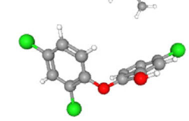
2. Develop a thorough plan for EDC management with a focus on reproductive-aged women

It is paramount to create a comprehensive strategic plan, evaluation framework, and management system focusing on EDCs from a national perspective, with a special emphasis on women of reproductive age in both rural and urban areas across various regions and demographic groups in China. While some scientific studies have reported on the distribution and levels of EDCs in women, including pregnant women, the size of the investigated population remains limited. To ensure accurate and reliable assessments, it is imperative to expand the sample size to represent a broader population. Furthermore, current pregnancy loss studies lack clear criteria for selecting case and control groups. For instance, in a study investigating the effects of PAE exposure on the risk of early miscarriage, women seeking medical services due to miscarriage were categorized as the case group, while women planning to terminate unintended pregnancies were assigned to the control group [10]. In another case–control study examining the association between PAE metabolites and pregnancy loss, women who experienced clinical pregnancy loss were considered the case group, while healthy pregnant women served as the controls [13]. Therefore, to accurately evaluate the EDC mixture risk on pregnancy loss in China, it is essential to establish explicit and appropriate criteria for selecting both the cases and controls.

3. Optimal EDC mixture design: Integrating targeted and nontargeted analysis as well as statistical techniques

Understanding and assessing the mixture effects of EDCs requires acknowledging the frequent combinations of EDCs found in women of reproductive age and the environment. Tracking complex chemical mixtures in a changing environment is crucial but presents a great challenge [6]. Fig. 2 illustrates that individuals from China and 25 other countries have been simultaneously exposed to multiple types of EDCs, such as PAEs, BPA, TCS, and PFAS, in the past decade. Targeted analysis

Table 1
Selected physicochemical characteristics of the prevalent EDCs.

EDC	Abbr.	CAS	M.W.	Log K_{OW}	Structure
Bisphenol A	BPA	80-05-7	228.29	3.32	
Perfluorooctane sulfonate	PFOS	1763-23-1	500.13	4.49	
Perfluorooctanoic acid	PFOA	335-67-1	414.07	4.81	
Perfluorononanoic acid	PFNA	375-95-1	464.08	5.48	
Monoethyl phthalate	MEHP	2306-33-4	194.18	1.86	
Monobenzyl phthalate	MBzP	2528-16-7	256.25	3.07	
Monobutyl phthalate	MBP	131-70-4	222.24	2.84	
Mono-carboxy-isooctyl phthalate	MCiOP	898544-09-7	322.4	3.99	
Triclosan	TCS	3380-34-5	289.5	4.66	

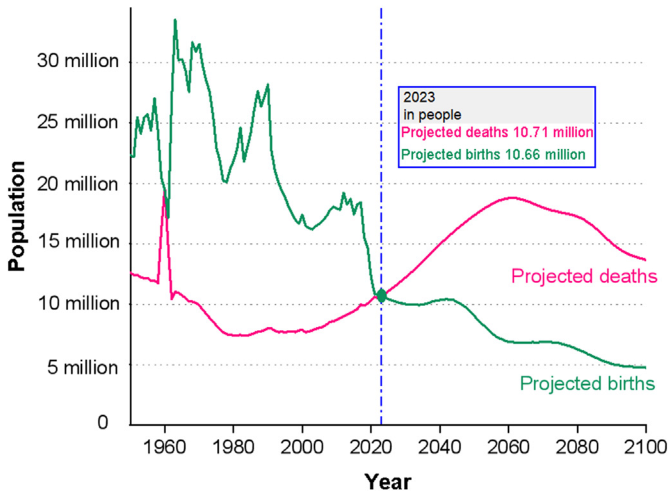


Fig. 1. Data from https://ourworldindata.org/grapher/births-and-deaths-projected-to-2100?country=~CHN. Source: United Nations, World Population Prospects (2022) – processed by Our World in Data.

focuses on identifying and quantifying specific chemicals within a mixture, but it does not fully encompass the broader range of chemical diversity present in the samples. An integrated approach that combines targeted analysis and nontargeted analysis provides a more holistic view of the EDC mixture composition and can uncover novel compounds, transformation products, or chemical combinations that may contribute to the overall mixture effects. Traditional toxicological testing approaches are often inadequate for assessing mixtures due to the high number of possible combinations among the compounds. In this regard, multivariate statistical analysis can be used to detect patterns and correlations within intricate datasets, facilitating the uncovering of combinations of EDCs that commonly co-occur. For instance, Kapraun et al. [14] tackled this issue by introducing frequent itemset mining (FIM), a technique for identifying patterns and correlations within complex datasets, thereby enabling the identification of prevalent combinations of EDCs in humans. By applying FIM to biomonitoring data from the National Health and Nutrition Examination Survey (NHANES), they identified 90 chemical combinations comprising relatively few chemicals and occurring in at least 30% of the US population [14]. Nevertheless, accurately evaluating the EDC mixture risk continues to present significant challenges, primarily due to the fluctuating levels of EDCs in the environment and the body. Continuous efforts are needed to overcome these complexities and ensure effective assessment of EDC mixture risks.

4. Utilize epidemiology to study EDC mixtures and pregnancy loss

From an epidemiological perspective, the association between EDCs and their mixtures and pregnancy loss can be initially explored, which can reduce the need for *in vitro* or *in vivo* tests, thus minimizing animal use and resource requirements. A cohort study involving couples attempting pregnancy from the general population demonstrated a positive link between females' preconception concentrations of the polybrominated diphenyl ether 28 and cadmium, components of a mixture of 66 persistent EDCs, and incident human gonadrophin chorionic (hCG) pregnancy loss [15]. Given that pregnancy loss can occur at any stage until childbirth, a comprehensive examination of the link between EDCs and pregnancy loss risk throughout all three trimesters is imperative. To accurately evaluate the risk of pregnancy loss, efforts should be made to minimize residual confounding. Collecting comprehensive data on covariates, such as individual characteristics, behavioral factors, and socioeconomic factors, is essential. The combined impact of multiple EDCs, whether acting simultaneously or sequentially, often manifests at lower doses than experimental effect thresholds for single compounds, resulting in synergistic or additive effects that cannot be predicted based solely on the effects of individual chemicals [16]. Thus, in epidemiological studies focusing on EDC mixtures, the pivotal data analysis strategy involves robust statistical methods that can account for complex interactions and correlations among multiple chemicals, as well as potential confounding factors such as demographics, lifestyle factors, and co-exposures. Advanced techniques like machine learning algorithms and Bayesian approaches are often employed to disentangle the combined effects of EDC mixtures on health outcomes while controlling for

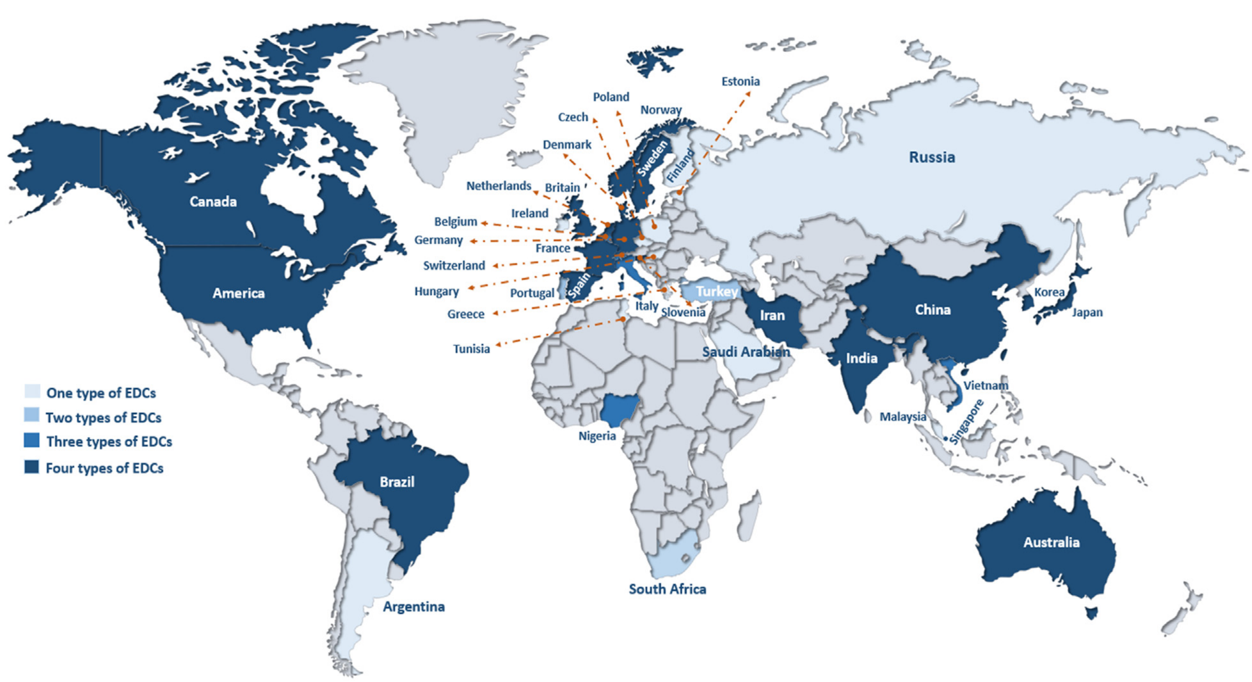


Fig. 2. Global distribution of mixtures of PAEs, BPA, TCS, and PFASs detected in humans. Data were from Web of Science ranging June 1st, 2013 to June 1st, 2023 using the keywords of "phthalates" and "human", "bisphenol A" and "human", "triclosan" and "human", and "perfluoroalkyl substance" and "human", respectively.

various covariates. Additionally, sensitivity analyses and validation techniques are crucial for assessing the robustness and generalizability of findings in such studies. Furthermore, after acknowledging the link between EDC mixtures and pregnancy loss through epidemiological studies, further research should focus on *in vitro* and *in vivo* testing of these EDC mixtures to better understand the underlying mechanisms. Drawing from existing research, we have formulated hypotheses regarding the mechanism of EDC-induced pregnancy loss. The fetal thyroid gland remains immature until mid-pregnancy (18–20 weeks), making the placental transfer of maternal thyroid hormones during early pregnancy critical [17]. Previous studies have indicated that pregnant women are exposed to these EDCs before conception, with pollutants such as PFASs exhibiting placental transport characteristics [18]. These pollutants may bind to placental thyroid hormone transporters, competing with thyroid hormones for binding sites, thereby impeding the transport of maternal thyroid hormones to the fetus during early pregnancy. This interference could impact the development of the thyroid–pituitary–hypothalamus axis, potentially leading to pregnancy loss. Further studies are required to identify the underlying mechanisms.

5. Low-dose mixture effects: Non-monotonic dose–response curve

The concept of low-dose effects challenges the prevailing notion that "the dose makes the poison" and highlights the need for reevaluating the safety of EDCs, particularly in mixture scenarios. Traditional toxicological studies have primarily focused on high-dose exposures, assuming that adverse effects follow a linear dose–response relationship. However, mounting evidence suggests that EDCs can exert significant effects at low doses, often below the thresholds established by traditional toxicological testing [19]. The non-monotonic nature of low-dose effects poses a challenge to traditional dose–response modeling [20]. Non-monotonic dose–response curves, known as J shape or inverted U shape, deviate from the traditional linear relationship, showing complex patterns where the response may increase, decrease, or reach a maximum at different dose ranges. This phenomenon is also referred to as hormesis, with stimulation at low doses and inhibition at high doses [21]. These non-linear relationships at environmentally relevant concentrations challenge traditional toxicological paradigms and further emphasize the importance of considering low-dose effects when assessing the mixture toxicity of EDCs.

6. Comparisons with existing plan and the future challenge

In China, specific laws addressing EDC mixture exposure in pregnancy loss are absent. However, the recently unveiled Action Plan for Emerging Pollutants effectively targets environmental and health risks, emphasizing comprehensive environmental risk management and strengthening institutional and technological support. This plan is crucial for alleviating the impact of EDCs on the environment and human health, especially for pregnant women and fetuses. Released by the State Council in September 2021, the "Outline for Women's Development in China (2021–2030)" and the "Outline for Children's Development in China (2021–2030)" provide overarching guidelines. To enhance maternal and child healthcare quality, the National Health Commission has devised the Implementation Plan for the 2021–2030 Outline for Women and Children Development in China. This plan, structured into five sections, emphasizes a people-centered approach and integrates traditional and modern medical practices. It outlines health-related goals, key tasks, and support measures, highlighting the importance of robust leadership and effective monitoring mechanisms in implementation. Overall, our study proposes specific measures aligning with both the Action Plan for the Control of Emerging Pollutants and the Implementation Plan for the 2021–2030 Outline for Women and Children Development in China, focusing on improving maternal and child health outcomes.

We recognize logistical challenges in developing a comprehensive plan for EDC management targeting reproductive-aged women, such as resource allocation and multi-stakeholder cooperation. We plan to address this by engaging relevant government agencies, healthcare providers, and community organizations to ensure comprehensive implementation. Additionally, overcoming difficulties in utilizing epidemiology for studying EDC mixtures and pregnancy loss entails prioritizing adherence to strict ethical guidelines, obtaining informed consent, and ensuring transparency in reporting findings. To protect participants' rights and privacy, specific methods will be implemented: 1) Informed Consent: Obtaining comprehensive informed consent from participants; 2) Confidentiality: Safeguarding personal information with unique identifiers and restricted access; 3) Data Security: Employing robust measures to protect participant data; 4) Ethical Compliance: Adhering to ethical guidelines and obtaining approval from regulatory bodies; and 5) Participant Right Assurance: Providing assurances of participants' rights throughout the study. Through interdisciplinary collaborations and rigorous methodologies, our goal is to advance the understanding of EDC mixture risks related to pregnancy loss while mitigating adverse effects on human health.

CRediT authorship contribution statement

Y.Q.X.: conceptualization, investigation, and writing; T.W., J.Y., and L.G.H.: writing and reviewing; C.Y.L.: conceptualization, reviewing and supervision.

Declaration of competing interests

The authors declare no competing financial interest.

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