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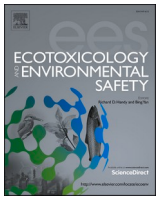

Oral reference dose (RfD) derivation for five bisphenol A alternatives integrating BMD and NOAEL/LOAEL approaches

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ABSTRACT

Bisphenols (BPs) are widely used in plastic manufacturing, food packaging, and other industrial applications, with bisphenol A (BPA) being one of the most extensively produced chemicals globally. However, due to its endocrine-disrupting properties, BPA has been linked to reproductive abnormalities, metabolic disorders, neurodevelopmental impairments, and other adverse health effects, leading to regulatory restrictions. These restrictions have resulted in increased usage of BPA alternatives and thus exposure to the alternatives, whose toxicity thresholds remain insufficiently characterized. To address this gap, this study derived reference doses (RfDs) for five BPA alternatives, i.e., bisphenol B (BPB), bisphenol P (BPP), bisphenol Z (BPZ), bisphenol AF (BPAF), and bisphenol AP (BPAP), by integrating epidemiological data and animal experiments. The RfDs were calculated using Benchmark Dose (BMD) modeling and no observed adverse effect level/lowest observed adverse effect level (NOAEL/LOAEL) approaches, combined with uncertainty analysis to quantify risk metrics. The results demonstrated that the BMD-derived RfDs for BPB, BPP, and BPZ were 1.05, 0.23, and 5.13 μg/kg-bw/day, respectively, while the NOAEL/LOAEL-based RfDs for BPAF and BPAP were 0.04 and 2.31 ng/kg-bw/day. By refining toxicity thresholds and risk assessment methodologies, this study not only highlights the potential health risks posed by BPs but also supports evidence-based policymaking to safeguard public health.

1. Introduction

Bisphenols (BPs) are extensively utilized in industrial applications, particularly in the production of polycarbonate plastics for beverage containers, epoxy resins for food can linings, and thermal receipt papers. As the most representative bisphenol, bisphenol A (BPA) has been one of the most extensively utilized industrial compounds in the world, with the global production of approximately 7 million metric tons in 2019 (İyİgÜndoĞdu et al., 2020) and over 1 million metric tons annually produced or imported within the European Economic Area (European Chemicals Agency (ECHA), 2023). It has been globally restricted for multiple health risks, including obesity (Liu et al., 2019a), cardiovascular disease (Zhang et al., 2020), and multiorgan toxicity affecting reproductive (Wang et al., 2024; Zhan et al., 2023), causing the widespread use of its structural analogues such as bisphenol B (BPB), bisphenol AF (BPAF), bisphenol P (BPP), bisphenol AP (BPAP), and bisphenol Z (BPZ). For example, the usage of BPAF reached up to 100-1000 metric tons according to the ECHA in 2023.

Growing environmental monitoring data indicate their detectable presence across multiple matrices including atmospheric (Vasiljevic and Harner, 2021), aquatic (Wang et al., 2025), and terrestrial systems (Xu et al., 2021), as well as in various organisms (Zhao et al., 2021). These

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chemicals finally can enter into human bodies, demonstrated by the detection of the chemicals in urine (Li et al., 2021; Liu et al., 2019b), breast milk (Deceuninck et al., 2015), and serum (Liu et al., 2017). Notably, these structural analogues exhibit comparable or even stronger effects than BPA (Table S1). For example, BPS and BPF demonstrate hormonal activity and endocrine-disrupting effects similar to those of BPA (Silva et al., 2019; Zhang et al., 2018), with BPS also impairing reproductive and nervous systems (Liu et al., 2021). BPB induces greater oxidative damage in neuronal cells than BPA (Pang et al., 2019). Ding et al. (2025) highlight the impact of BPZ on early embryonic development, whereas BPP has been associated with obesity (Zhang et al., 2023). Early exposure to BPAP adversely affects neural behavior in adult offspring (Wu et al., 2023a), and BPAF elevates the risk of uterine disorders (Wu et al., 2023b).

In non-carcinogenic health risk assessment, the oral reference dose (RfD) is a critical parameter. The U.S. Environmental Protection Agency (EPA) established an oral reference dose (RfD) for BPA at 0.05 mg/kg-bw/day as early as 1988 (USEPA, 1988), while the European Food Safety Authority (EFSA) set the tolerable daily intake (TDI) at 50 ng/kg-bw/day in 2006, further reducing to 0.2 ng/kg-bw/day in 2023 (EFSA Panel on Food Contact Materials, Enzymes and Processing Aids, 2023). Recently, the RfD values of 2.39, 0.37, and 8.09 ng/kg-bw/day for BPA, BPS, and BPF were established in our previous research (Cao et al., 2025). Although these five bisphenols (BPB, BPP, BPZ, BPAF, and BPAP) have been listed in Substances of Very High Concern (SVHC) for their endocrine-disrupting properties (Candidate List of SVHC, 2022), the RfDs remain unavailable. To address this gap, this study derives RfDs for these five analogues by integrating epidemiological and experimental data through benchmark dose (BMD) and no observed adverse effect level/lowest observed adverse effect level (NOAEL/LOAEL) approaches, thereby providing essential guidance for regulating bisphenol analogues and informing future research.

2. Materials and methods

2.1. Reference dose derivation

2.1.1. Reference dose calculation

The European Food Safety Authority (EFSA Scientific Committee, 2017) mandates the use of benchmark dose (BMD) and no observed adverse effect level (NOAEL)/lowest observed adverse effect level (LOAEL) methodologies for deriving human reference doses (RfD), with BMD being the preferred approach. For BMD modeling, rodent toxicological data was utilized due to insufficient human exposure-response data, with NOAEL/LOAEL values supplementing cases where dose-response modeling proved infeasible or where critical toxicity data gaps existed. The RfD calculation of the present study aligns with established toxicological protocols (Hughes et al., 2018; Barnes et al., 1988), wherein the point of departure (POD) - either BMD or NOAEL/LOAEL values from critical effect endpoints - is divided by composite uncertainty factors accounting for interspecies extrapolation, intraspecies variability, and data limitations, following the formula:

$$\mathrm{RfD} = \frac{\mathrm{POD}}{\mathrm{UF}} \tag{1}$$

where RfD (mg/kg-bw/day) is the reference dose; POD (mg/kg-bw/day) is the point of departure; and UF (dimensionless) is the uncertainty factor.

2.1.2. Benchmark Dose Software (BMDS) parameter settings

The BMDS used in the present study was developed by the United States Environmental Protection Agency (USEPA, 2012), for dose-response analysis. Dose-response modeling was performed using BMDS, with a benchmark response (BMR) of 10 % (default value) established as the harmful effect threshold. For continuous endpoints, the benchmark dose-response factor (BMRF) was defined as one standard deviation increment (default value = 1). The BMD was derived at the specified BMR, with the benchmark dose lower limit (BMDL) representing the one-sided 95 % confidence interval of the BMD by default. Model selection followed the Akaike Information Criterion (AIC), prioritizing the model with the lowest AIC value to optimize goodness-of-fit and ensure accurate representation of dose-response relationships.

2.1.3. Uncertainty factor

The uncertainty factor (UF) incorporates five critical components, and it is calculated through the following formula:

$$\mathrm{UF} = \mathrm{UF_L} \times \mathrm{UF_S} \times \mathrm{UF_A} \times \mathrm{UF_H} \times \mathrm{UF_D} \tag{2}$$

where $\mathrm{UF_L}$, $\mathrm{UF_S}$, $\mathrm{UF_A}$, and $\mathrm{UF_H}$ are LOAEL, subchronic, interspecies, and intraspecies uncertainty factors, respectively, and $\mathrm{UF_D}$ is the database deficiency factor. All the UFs are dimensionless parameters used in the calculations.

The values of uncertainty factors were based on the technical support document for deriving the non-cancer reference exposure level (OEHHA, 2008). When only the LOAEL is available instead of the NOAEL, $\mathrm{UF_L}$ ranging from 1 to 10 is applied to account for the gap between LOAEL and NOAEL, with 1 typically being the default value. If toxicity data comes from a subchronic rather than chronic study, $\mathrm{UF_S}$ is used, generally ranging from 1 to 10. A $\mathrm{UF_S}$ of 1 may be selected if the study duration exceeds 12 % of the estimated life, 3 if the duration is between 8 % and 12 %, and 10 if below 8 %. $\mathrm{UF_A}$ for animal-to-human extrapolation addresses interspecies differences, with a default value of 10 reflecting the assumption that humans are more sensitive than test animals, while $\mathrm{UF_A}$ is reduced to 1 for human studies or 3 when converting to a human equivalent dose. $\mathrm{UF_H}$ for human variability accounts for individual sensitivity differences, defaulting to 10 to cover 99 % of the population. Finally, $\mathrm{UF_D}$ for database deficiencies compensates for insufficient/missing data (e.g., reproductive or developmental toxicity studies), typically ranging from 1 to 10, with higher values assigned when more critical data gaps exist.

2.2. Data collection

2.2.1. Data identification and screening

Initially, we narrowed our focus to epidemiological studies. Articles reporting bisphenol concentrations in human urine (published before December 21, 2024) were identified through the Web of Science (WOS) database. Our search strategy employed Boolean operators: we used "OR" between bisphenol compounds (exposure domain) and reproductive health keywords (outcome domain), then connected these domains with "AND". The reproductive keywords included: 'semen', 'sperm', 'fertility', 'infertility', 'anogenital', and 'sexual development'. We restricted our search to English-language, peer-reviewed publications. However, since this approach yielded insufficient data to determine the point of departure (POD) for the target bisphenols, we expanded our search to include rodent studies assessing non-carcinogenic toxicity (not limited to reproductive effects). For this expanded search, we used bisphenol alternative names combined with the keyword 'toxicity'.

2.2.2. Eligibility criteria

The screening process initially involved title and abstract review to identify studies containing our target chemicals. We systematically excluded review articles, animal studies, *in vitro* experiments, methodological investigations, machine learning-related research, occupational exposure studies, meeting abstracts, and studies focusing exclusively on semen or blood analysis, along with awarded grants. For studies on the reproductive toxicity in human, animal studies should also be excluded. Full-text articles were then assessed for eligibility based on the following criteria: Further, the eligibility was assessed through a full-text

screening: (a) availability of original data in either the main text or supplementary materials, with each dataset containing at least three paired exposure-effect groups suitable for BMDS software analysis; (b) exclusion of studies reporting only mixed compound exposure data; (c) for epidemiological studies, requirement of general population subjects with urinary bisphenol measurements; (d) for animal studies, restriction to oral exposure pathways, with NOAEL/LOAEL values supplementing POD when BMD analysis was not applicable. Throughout this process, we maintained a data hierarchy prioritizing epidemiological BMD over animal experiment BMD, which in turn took precedence over animal experiment NOAEL/LOAEL values.

2.3. Data extraction and treatment

2.3.1. Data input for BMDS

For studies where the original data did not report mean exposure levels by group, we calculated median values using the following methods: when a range was provided, we derived the median as half the sum of the upper and lower limits; when only an upper exposure limit was available, we used half of this value as the median; when only a lower limit was present, we estimated the median as 1.5 times this value. These calculated medians were then used as dose group inputs for BMDS analysis. In cases where standard deviations were not reported but 95 % confidence intervals (95 % CI) were available, we estimated the standard deviation by dividing the sum of the upper and lower confidence limits by 3.92 (1.96 × 2). Our methods for estimating sample means and standard deviations from sample size, median, range, and/or interquartile range followed established protocols described by Luo et al. (2018) and Wan et al. (2014).

For BMDS analysis, either continuous or dichotomous variables were entered for model fitting. The animal study data processed through BMD methodology in original studies were directly utilized. Notably, when studies reported statistical significance, only datasets demonstrating significant differences were selected for BMDS fitting. This selection criterion ensured that included data exhibited either: (1) a statistically significant dose-response relationship (p-trend < 0.05), or (2) a clear biological dose-response trend. In cases where studies did not report significance testing, all available data were subjected to fitting procedures.

2.3.2. Human equivalent dose calculation

For rodent studies, dose conversion to human equivalent dose (HED, mg/kg-kw/day) was performed according to USEPA (2011) guidelines using the following formulas:

$$HED = POD \times DAF \tag{3}$$

$$DAF = \frac{BW_a^{\frac{1}{4}}}{BW_h^{\frac{1}{4}}} \tag{4}$$

where DAF (dimensionless) is the dosimetric adjustment factor; BW_a (kg) and BW_h

(kg) are animal and human weight, respectively; BW_a is 0.02 kg for mice and 0.2 kg for rats, and BW_h is 70 kg for adults (Sun et al., 2017).

3. Results and discussion

3.1. Literature search, screening, and data extraction

In this study, five BPA alternatives including BPB, BPP, BPZ, BPAF, and BPAP were selected as target compounds. Fig. 1 illustrates the article search process. Following screening, no suitable epidemiological data were identified, prompting a focus on animal toxicity experiments. After full-text review, three studies on BPB, one on BPP, and one on BPZ were deemed appropriate for BMDS analysis. Due to insufficient data for BMD modeling, BPAF and BPAP were instead evaluated using NOAEL/LOAEL values, with 18 and 1 study(s) included for POD determination, respectively.

3.2. Metabolism of BPs in organisms

The metabolism and distribution of these five alternatives remain

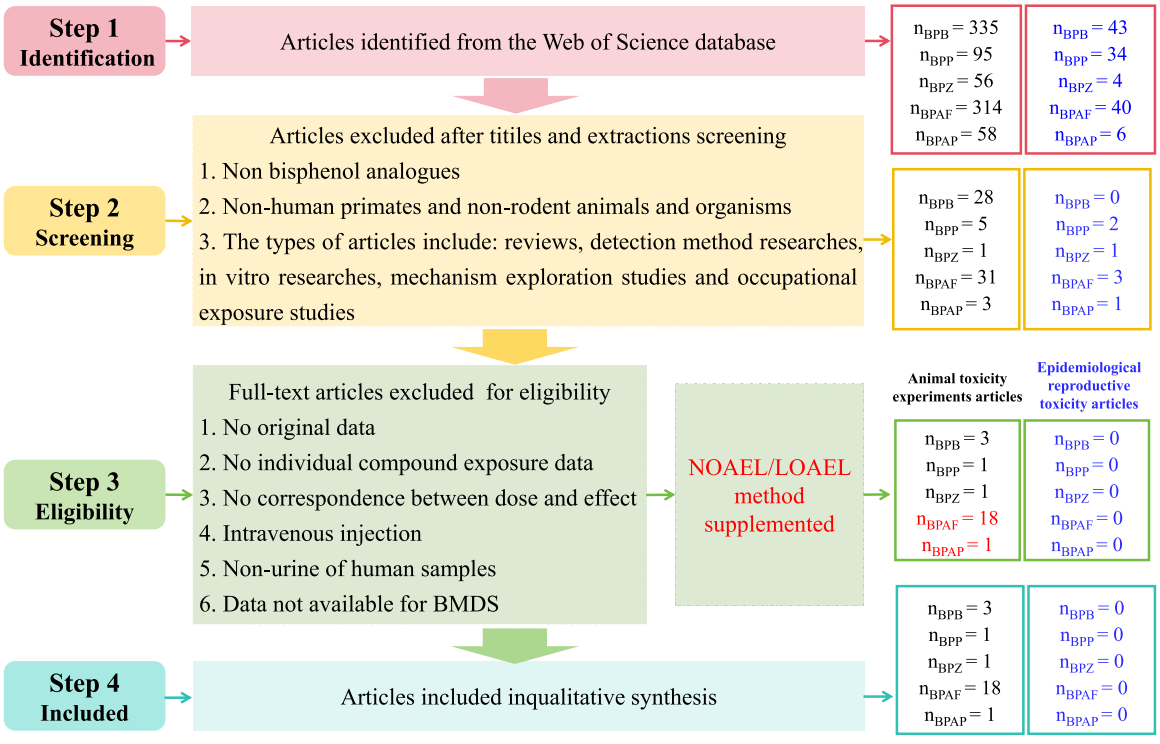

Fig. 1. Flow chart of the study selection process.

insufficiently characterized, underscoring the importance of including fecal sample analysis of bisphenol toxicity studies. Pharmacokinetic data reveal distinct excretion patterns of BPB: intravenous administration of BPB (6 μmol/kg BW) led to stabilized urinary excretion after 8 h (approximately 50 % recovery), reaching 55 ± 9.4 % by 24 h (Gely et al., 2023). Following oral administration, an increasing trend was observed after 10 h, culminating in a urinary excretion ratio of 40 ± 8.3 % after 24 h, demonstrating efficient gastrointestinal absorption (Gely et al., 2023). Notably, porcine studies of oral bisphenol mixtures demonstrated markedly lower urinary recovery of BPP (1.9 ± 0.8 % after 24 h), likely attributable to its high lipophilicity ($Log K_{OW} = 6.25$) which favors hepatic metabolism and fecal excretion (Gely et al., 2023). BPZ exhibited unique pharmacokinetics following oral administration (200 μmol/kg BW in pigs), with plasma concentrations peaking at 2 h and maintaining a plateau until 11 h, suggesting enterohepatic recirculation; urinary excretion reached 25 % by 11 h and 31 % by 24 h (Gely et al., 2023).

The predominant *in vivo* metabolite of BPAF is BPAF glucuronide (BPAF-G) (Skledar, et al., 2019). Cyclical fluctuations in BPAF blood concentrations were observed after 8 h in rats and mice following 7-day oral exposure (Waidyanatha et al., 2021), suggesting enterohepatic recirculation, a phenomenon also documented for BPZ, BPF, and BPS (Gely et al., 2023). Porcine toxicokinetic studies revealed 24-hour urinary recoveries of 32 ± 7.5 % for BPAF compared to just 12 ± 3.3 % for BPAP (Gely et al., 2023). The low BPAP recovery parallels the pharmacokinetics of BPP, likely reflecting extensive first-pass hepatic metabolism and fecal excretion due to its high molecular weight and poor intestinal absorption (Gely et al., 2023).

3.3. Hazard identification of BPs to animals

Bisphenols primarily exert endocrine-disrupting effects, subsequently leading to reproductive toxicity and neurotoxicity. *In vitro* studies have demonstrated BPB's endocrine-disrupting potential through its interactions with both the nuclear estrogen receptor ERα and the membrane receptor G protein-coupled estrogen receptor (GPER) (Boeckers et al., 2020). Serra et al. (2019) conducted a systematic evaluation of published *in vitro* and animal studies examining sex hormone-related parameters and reproductive dysfunction, providing comprehensive evidence for BPB's endocrine-disrupting properties. Experimental findings include BPB's impairment of spermatogenesis (Ullah et al., 2019a; 2019b), alteration of ovarian biochemical parameters in rats (Ijaz et al., 2020; Ullah et al., 2019b), and reduction of sperm quantity and quality in pubertal mice (Ikhlas and Ahmad, 2020). Furthermore, BPB exhibited stronger neurotoxic effects than both BPS and BPA in hippocampal cell lines, inducing apoptosis and inhibiting cell proliferation (Pang et al., 2019). Additional evidence confirming neurotoxicity of BPB has also been reported (Meng et al., 2023).

A study in mice has demonstrated that BPP can induce intestinal inflammation and barrier dysfunction via gut microbiota dysbiosis (Ma et al., 2023). Non-targeted metabolomics analyses further revealed that BPP disrupts hepatic metabolic pathways, resulting in lipid accumulation and subsequent obesity development (Zhang et al., 2023). While current research primarily investigates reproductive toxicity and endocrine-disrupting potential of BPZ, a recent in vitro murine study has identified its inhibitory effects on oocyte meiotic maturation (Ma et al., 2024). Mechanistically, BPZ was found to induce oxidative stress and DNA damage, consequently impairing spindle assembly and chromosome alignment, the effects consistent with those observed for BPA, BPF, BPB, and BPS exposures (Ding et al., 2022; Zhang et al., 2020) substantiated that BPZ exhibits BPA-like activities, including the induction of ERα/ERβ-mediated estrogenic responses and androgen receptor binding affinity.

Transcriptomic analyses demonstrated that BPAP exposure significantly dysregulated gene expression patterns, ultimately impairing hypothalamic development and inducing uterine/ovarian toxicity (Lv et al., 2023; Wu et al., 2023b; Yue et al., 2023). Cumulative evidence from reproductive toxicity studies confirms detrimental effects of BPAF on sexual organ development (Wu et al., 2019; Xue et al., 2023), with particularly pronounced impacts in male specimens (Gao et al., 2022). Preliminary investigations suggest that BPAP may exert antiestrogenic activity, as evidenced by its distinct uterine gene expression profile compared to 17β-estradiol (E2) (Xiao et al., 2018). Furthermore, a neurotoxicity study revealed that perinatal BPAP exposure leads to persistent neurobehavioral deficits in adulthood, correlating with sustained microglial hyperactivation in hippocampal regions (Wu et al., 2023a).

3.4. Hazard identification of BPs to human

Currently, research specifically investigating BPs in human populations remains limited, while epidemiological studies have primarily examined the reproductive and neurodevelopmental toxicity of environmental pollutants in humans. An *in vitro* study using human adipocytes has demonstrated that BPB disrupts normal metabolic processes similarly to BPA. Epidemiological investigations indicate that while BPB exposure does not appear to be a primary factor in unexplained recurrent miscarriage (URM) (Ao et al., 2021), elevated exposure levels may increase pregnancy-related anemia risk (Liang et al., 2022). Furthermore, neonatal telomere length shows significant association with BPS exposure, but not with BPB (Liang et al., 2023).

For BPP, two epidemiological studies have investigated the health effects of BPP exposure in female populations. While one study reported significantly higher BPP concentrations in case groups compared to controls, its effect size was notably smaller than those observed for BPAP, BPAF, and BPA in URM cases (Ao et al., 2021). Additionally, while thyroid effects have been a focus of BPP research due to its endocrine-disrupting potential, a comprehensive study found no significant association between BPP exposure and either thyroid function or volume in reproductive-aged women (Milczarek-Banach et al., 2020).

As for BPZ, epidemiological evidence indicates that it contributes significantly to the neurodevelopmental toxicity of bisphenol mixtures, with BPZ and BPA showing the strongest associations with neural tube defects (NTDs) (Zhu et al., 2023). Furthermore, BPZ has been identified as the primary driver of the positive correlation between bisphenol mixture exposure and polycystic ovary syndrome (PCOS) in reproductive-aged women (Zhan et al., 2023), highlighting its reproductive toxicity potential. Collectively, these findings establish BPZ as a critical risk component in bisphenol mixture exposures.

Unexplained recurrent miscarriage appears primarily associated with BPAP, BPAF, and BPA exposure, with advanced maternal age potentially exacerbating susceptibility to bisphenol-mediated effects (Ao et al., 2021). Also, emerging evidence links BPAF to neurodevelopmental impairments in infants (Xia et al., 2023), while separate prospective research has identified associations between prenatal exposure to BPAF-containing bisphenol mixtures and the 2D:4D, a parameter related to reproductive outcomes in children (Wang et al., 2021). These findings underscore the need for comprehensive epidemiological studies utilizing representative populations to better characterize the relationships between BPAP/BPAF exposure and adverse health outcomes.

3.5. Dose-response/effect correlation

Thirteen continuous-summarized datasets from three rat reproductive toxicity studies on BPB exposure were successfully imported into BMDS for analysis, with model fitting results presented in Table S2. Among male rat oral exposure datasets, only testicular Lipid Peroxidation (LPO) data (Ullah et al., 2018) yielded an optimal dose-response curve, producing a recommended BMDL of 28.29 mg/kg-bw/day based on AIC minimization principles. Analysis of three sperm DNA damage datasets (Ullah et al., 2019a) revealed that only the Tail DNA

percentage increase showed a statistically significant response, yielding a recommended BMDL of 4.10 mg/kg-bw/day. The Power model-fitted dose-response curve (Fig. 2D) demonstrated a positive correlation between Tail DNA percentage and administered dose, indicating dose-dependent DNA damage progression. Body weight data from Li et al. (2021) analysis produced a frequentist power model-derived BMDL of 7.81 mg/kg-bw/day, consistent with observed dose-dependent weight reduction. Epididymal mass analysis resulted in a higher BMDL of 110.10 mg/kg-bw/day using an Exponential Degree 3 model than the other fitting results. Applying conservative risk assessment principles, we established a point of departure (POD) of 0.95 mg/kg-bw/day as the HED, derived from the Tail DNA damage BMDL (4.10 mg/kg-bw/day) identified as the critical effect.

The BMDS analysis was performed on 23 continuous-summarized datasets from a comprehensive rat toxicity study examining multi-organ effects by BPP exposure (Table S3). The datasets encompassed organ mass measurements and oxidative stress parameters, with 12 meeting BMDS quality criteria for model recommendations. Calculated BMDL values ranged from 0.89 to 30.77 mg/kg-bw/day, with the lowest value (0.89 mg/kg-bw/day) derived from renal glutathione peroxidase (GSH-Px) activity, identified as the most sensitive endpoint. The optimal fit was achieved using a frequentist Polynomial degree-2 model (lowest AIC), with the dose-response curve (Fig. 3L) demonstrating significant dose-dependent suppression of renal GSH-Px activity by BPP. This pattern extended to all monitored antioxidant enzymes across organs, while thiobarbituric acid reactive substance (TBARS) concentrations showed inverse, dose-proportional increases. Histopathological analysis revealed dose-dependent necrotic changes in hepatic, cardiac, pulmonary, and glomerular tissues, with varying severity observed across organ systems (Sattar et al., 2024). The observed renal mass reduction was coincident with the adverse impact on both biochemical impairment and concomitant pulmonary damage, suggesting a dose-dependent deterioration. Based on conservative risk assessment principles, the POD was established at 0.89 mg/kg-bw/day (renal GSH-Px BMDL), with a corresponding human equivalent dose (HED) of 0.21 mg/kg-bw/day calculated for kidney protection.

Only one rodent study comparing the endocrine effects of BPZ and 2,2-bis(4-cyanatophenyl)propane (Yamasaki and Okuda, 2012) provided suitable data for BMDS analysis, with modeling results presented in Table S4. No epidemiologic studies met the inclusion criteria. Among 23 continuous BPZ datasets from this study, 14 yielded valid BMD estimates, with BMDL values ranging from 16.9 to 224 mg/kg-bw/day. The highest BMDL (224 mg/kg-bw/day) corresponded to hematocrit (HCT) reduction in male rats. While the Frequentist Polynomial Degree 3 Model identified a statistically significant dose-dependent decrease in HCT at higher exposures, the effect size was modest. The lowest BMDL (16.9 mg/kg-bw/day) was associated with cardiac mass reduction in male rats, showing a clear negative dose-response relationship. Notably, similar BMDL values were observed for decreased body weight and reduced mass of thymus, heart, and prostate (range: 16.9–22.4 mg/kg-bw/day), suggesting these organ mass changes likely reflect systemic weight loss rather than specific organ toxicity. Based on this consistent pattern, terminal body weight reduction was identified as the critical effect. The derived HED of 4.62 mg/kg-bw/day was calculated from the body weight BMDL of 19.97 mg/kg-bw/day, with the corresponding dose-response curve shown in Fig. 4N.

Due to insufficient toxicological data for BPAF and BPAP, NOAEL/LOAEL values were utilized as supplemental metrics. For BPAF, 18 studies examining neurotoxicity, immunotoxicity, and reproductive toxicity reported LOAELs spanning 0.5–200 mg/kg-bw/day, with the

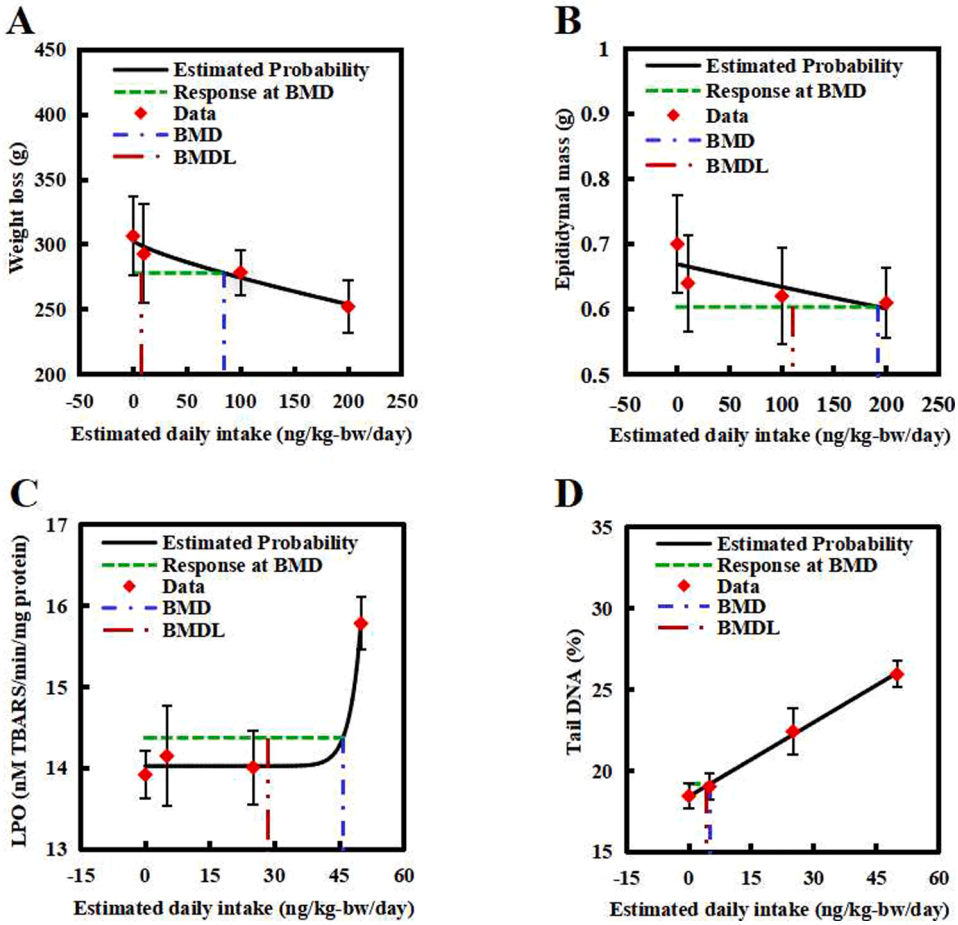

Fig. 2. BMDS builds the simulated dose-response/effect curves of BPB based on the rodent experiment studies.

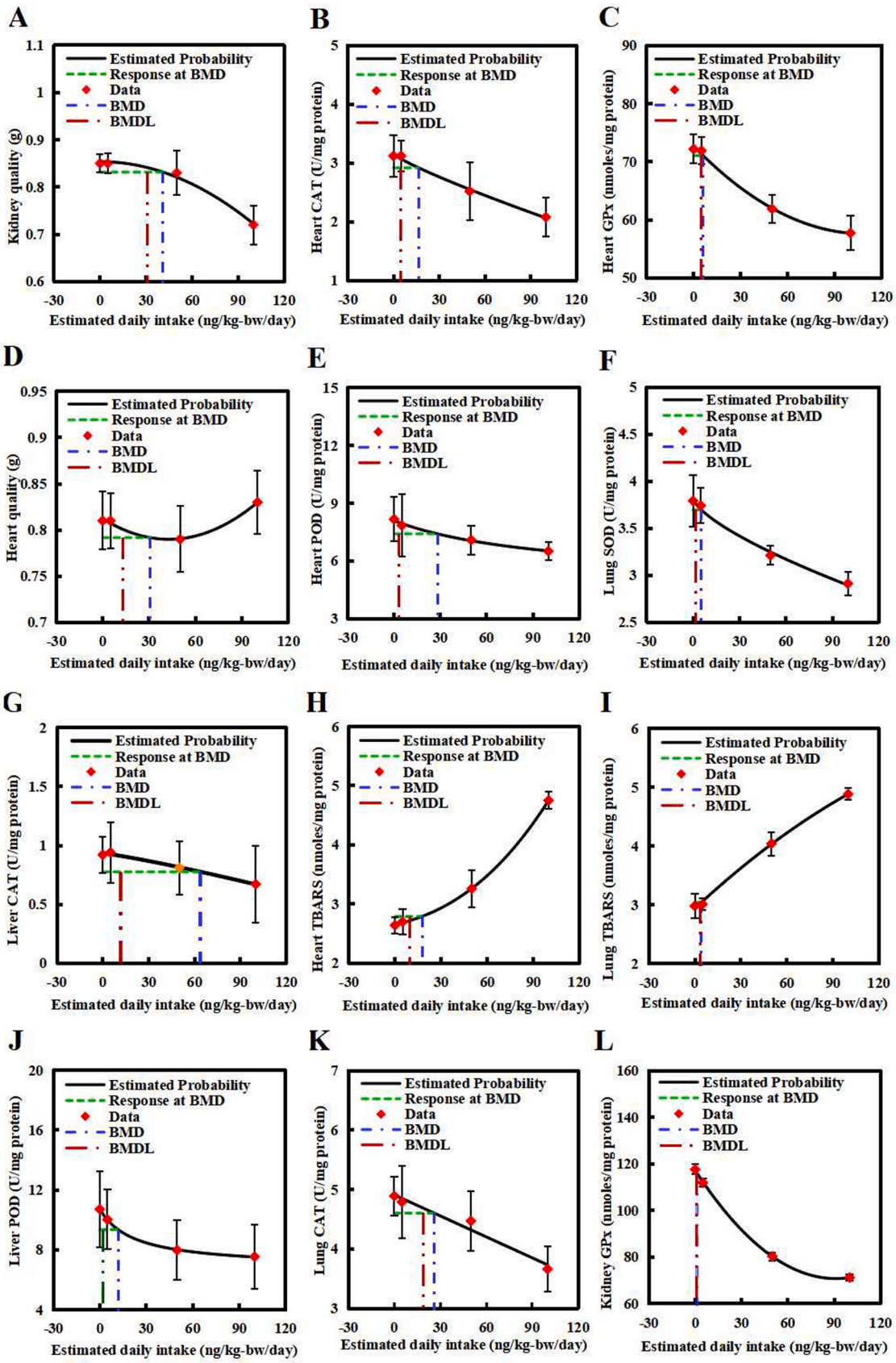

Fig. 3. BMDS builds the simulated dose-response/effect curves of BPP based on the rodent experiment studies.

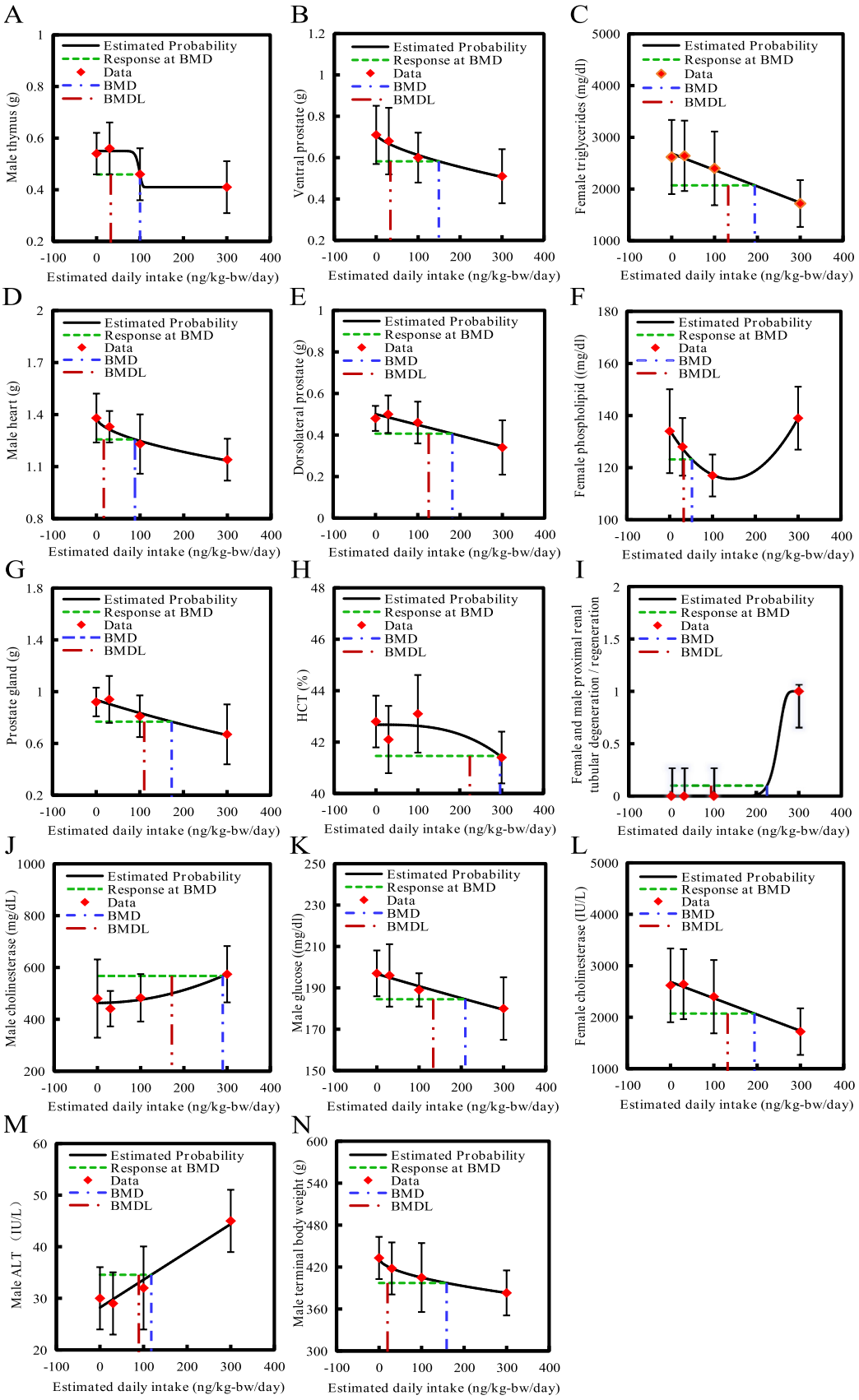

Fig. 4. BMDS builds the simulated dose-response/effect curves of BPZ based on the rodent experiment studies.

lowest LOAEL (0.5 μg/kg-bw/day) derived from a 28-day rat study demonstrating hepatic cytoplasmic vacuolization, testicular tubular necrosis, and epididymal histopathological alterations (Table S5). For BPAP, only one study evaluating anti-estrogenic activity via murine anti-uterotrophic assay in mice was identified, showing significant uterine weight reduction at 80 μg/kg-bw/day after 10-day exposure. The NOAEL/LOAEL analyses of BPAP in rodent experiment studies are shown in Table S6. Based on cumulative reproductive toxicity evidence, HEDs were calculated as 0.12 μg/kg-bw/day (converted from reproductive system LOAEL of BPAF) and 2.08 μg/kg-bw/day (derived from uterine mass reduction NOAEL of BPAP), representing the most sensitive endpoints for each compound.

3.6. Uncertainty factors

The application of UFs is detailed in Table 1, with all determinations based on the critical effects of bisphenols as aforementioned, and the selection criteria of UFs are shown in Table S7. For BPB, BPZ, BPP, and BPAP, a UF_L of 1 was assigned. Since the POD for BPAF was derived from a LOAEL, a factor of 10 was applied to account for the LOAEL uncertainty. An interspecies UF_A of 3 was implemented for all compounds to address extrapolation uncertainties from rodent models, particularly given the use of HEDs derived from animal data.

Current evidence indicates BPZ may induce NTDs through placental transfer and could contribute to maternal anemia or altered infant telomere length. Similarly, transplacental transfer of BPAP has been demonstrated, with potential associations to URM. Given the paucity of human exposure data and the need for protective measures, a maximum UF_H of 10 was uniformly applied to all five compounds to account for potential hypersensitivity in pregnant women and children.

It is critical to note that the RfD establishes toxicity thresholds for lifetime human exposure to exogenous compounds. Accordingly, a UF_S of 10 was assigned per the USEPA Technical Support Document (USEPA, 2011), as study durations represented less than 8 % of the estimated lifespan. While extensive toxicological database of BPAF (encompassing organ toxicity, reproductive/immune effects, and neurotoxicity) warranted a UF_D of 1, the more limited data available for BPB, BPZ, BPP, and BPAP justified application of a UF_D of 3 for these compounds.

3.7. Derived oral RfD values of the bisphenols

The derived RfDs presented in Table 1 span three orders of magnitude from 0.04 to 5.13 μg/kg-bw/day for the chemicals, reflecting variations in critical toxicity endpoints, data sources, and methodological approaches. These RfDs were calculated from animal-derived HEDs, introducing substantial uncertainty in extrapolation to human exposures.

Specifically, the RfD for BPB was calculated as 1.05 μg/kg-bw/day, derived from a reproductive toxicity HED of 0.95 mg/kg-bw/day, based on increased Tail DNA percentage in male Sprague-Dawley rats following 28-day exposure (composite UF = 900). For BPP, the RfD was established at 0.23 μg/kg-bw/day, derived from an organ toxicity HED of 0.21 mg/kg-bw/day, corresponding to decreased renal glutathione peroxidase (GSH-Px) activity in female Wistar rats after 28-day exposure with a composite UF of 900. In the present study, BPZ showed the highest RfD (5.13 μg/kg-bw/day), calculated from an endocrine-mediated HED of 4.62 mg/kg-bw/day associated with body weight reduction in rats following 28-day exposure with a composite UF of 900. The RfD for BPAF was determined to be 0.04 ng/kg-bw/day, calculated from an HED of 0.12 μg/kg-bw/day derived from rodent studies. Histopathological examination of rats exposed to 0.5 μg/kg-bw/day for 28 days revealed hepatic cytoplasmic vacuolization, testicular tubular necrosis, and epididymal abnormalities, with these findings used to establish a composite UF of 3000 for BPAF. Finally, for BPAP, the RfD of 2.31 ng/kg-bw/day was derived from an HED of 2.08 μg/kg-bw/day, based on significant uterine mass reduction observed in mice following 10-day exposure with a composite UF of 900.

While current toxicity data remain limited, preliminary RfD values have been established for the bisphenols. Nevertheless, additional studies are required to substantiate and refine these RfD estimates. Future research directions should prioritize expansion of human biomonitoring data, investigation of broader health endpoints, and development of alternative assessment methodologies.

3.8. Strengthens and limitations

This study establishes a scientific benchmark for the safe management of bisphenols while highlighting the critical need for data integration and methodological innovation in assessing emerging pollutants, offering a framework for future research. However, several limitations warrant consideration. The derived RfDs for BPB, BPP, and BPZ were approximately three orders of magnitude higher than those for BPAF and BPAP, primarily due to variations in toxicological endpoint sensitivity, data sources, and methodological approaches. Crucially, RfDs should not be interpreted as direct measures of "absolute toxicity", as individual substances may target distinct biological pathways and exhibit differential metabolic kinetics. These values remain endpoint- and exposure route-specific. The present analysis indicates that BPAF and BPAP merit heightened regulatory scrutiny.

Additionally, a key limitation arose during data collection: the paucity of epidemiological studies necessitated heavy reliance on animal-derived data for RfD calculations, substantially increasing uncertainty factors (UF=900–3000). To reduce such uncertainty, future studies should prioritize: (1) incorporation of diverse epidemiological evidence encompassing broader adverse outcomes, and (2) refinement of RfDs through more robust experimental datasets. These advances would enable more precise determination of exposure thresholds. While these findings advance our understanding, considerable additional investigation is warranted.

4. Conclusion

This study presents a systematic integration of epidemiological and toxicological data, employing a quantitative risk assessment framework based on five categories of UFs to derive RfDs for five bisphenols. The assessment identifies reproductive toxicity (impaired spermatogenesis, DNA damage) and organ toxicity (renal oxidative stress, uterine atrophy) as critical endpoints, demonstrating bisphenols' distinct capacity to disrupt endocrine and metabolic pathways. The RfD values were calculated as 1.05, 0.23, and 5.13 μg/kg-bw/day for BPB, BPP, and BPZ, and 0.04 and 2.31 ng/kg-bw/day for BPAF and BPAP, respectively. While the current derivation primarily relies on animal studies, these established RfDs provide crucial interim benchmarks for risk assessment. This work not only advances the scientific basis for bisphenol

Table 1
Uncertainty analysis and RfD calculation results of BPs.

Chemical	POD	UF_L	UF_A	UF_H	UF_S	UF_D	U_F	RfD
BPB	$BMDL_{HED}$= 0.95 mg/kg-bw/day	1	3	10	10	3	900	1.05 μg/kg-bw/day
BPP	$BMDL_{HED}$ = 0.21 mg/kg-bw/day	1	3	10	10	3	900	0.23 μg/kg-bw/day
BPZ	$BMDL_{HED}$ = 4.62 mg/kg-bw/day	1	3	10	10	3	900	5.13 μg/kg-bw/day
BPAF	$LOAEL_{HED}$ = 0.12 μg/kg-bw/day	10	3	10	10	1	3000	0.04 ng/kg-bw/day
BPAP	$NOAEL_{HED}$ = 2.08 μg/kg-bw/day	1	3	10	10	3	900	2.31 ng/kg-bw/day

regulation but also highlights key challenges in assessing emerging contaminants - particularly the need for innovative approaches to address data gaps and the complex interplay of exposure sources in modern environments.

CRediT authorship contribution statement

Chaoyang Long: Writing – review & editing. **Yingxin Yu:** Writing – review & editing. **Yanpeng Gao:** Methodology. **Jing Cao:** Methodology, Data curation. **Wenhua Ma:** Writing – original draft, Methodology, Data curation. **Yan Xia:** Writing – original draft, Methodology, Data curation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2025.118911.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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