Science of the Total Environment 985 (2025) 179693

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Exposure to disinfection by-products and risk of birth defects: A systematic review and dose-response meta-analysis

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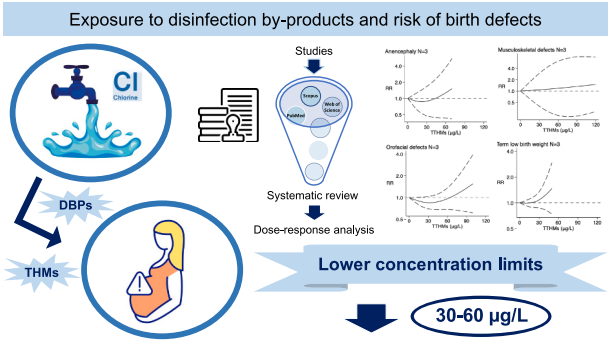
HIGHLIGHTS

- Exposure to trihalomethanes (THMs) and birth outcomes is controversial.
- High THM exposure increases risk of most growth-related birth outcomes and some birth defects.
- Dose-response analysis indicates nonlinear association with higher risks above 30–60 μg THMs/L.
- Current THM limits of 80 (US) and 100 (EU) μg/L may not be safe to protect vulnerable populations, such as pregnant women.

GRAPHICAL ABSTRACT



ARTICLE INFO

Editor: Lidia Minguez Alarcon

Keywords:
Birth defects
Disinfection by-products
Dose-response
Public health
Trihalomethanes

ABSTRACT

The disinfection of drinking water has been a major public health achievement, significantly reducing waterborne diseases. However, there are also some drawbacks in this practice, particularly the fact that chlorinated disinfectants can generate disinfection by-products (DBPs) which in turn have been associated with adverse health effects, including birth defects. The extent to which such adverse reproductive effect may occur following chlorinated water consumption, and the possible threshold of exposure involved, are however not entirely clear. This systematic review and dose-response meta-analysis aimed to evaluate the association between DBP exposure and the risk of congenital anomalies, with a focus on exposure thresholds. We conducted systematic search in Scopus, PubMed, and Web of Science up to March 18, 2025, to retrieve the observational studies assessing DBP exposure and reporting congenital anomalies and birth-related outcomes. We performed a dose-response meta-analysis to assess exposure thresholds. A total of 31 studies met the inclusion criteria. The meta-analysis comparing the highest versus the lowest exposure levels found a positive association between trihalomethanes

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https://doi.org/10.1016/j.scitotenv.2025.179693
Received 1 April 2025; Received in revised form 12 May 2025; Accepted 15 May 2025
Available online 28 May 2025

(THMs) and prevalence at birth of cardiovascular, musculoskeletal, neural tube, urinary tract defects, as well as most growth-related birth outcomes. The dose-response analysis revealed a nonlinear association, with increased risks for anencephaly, musculoskeletal, and orofacial defects at THM levels exceeding 60 μg/L, and for term low birth weight at levels above 30 μg/L. A plateau effect was observed for urinary tract defects at 30 μg/L, while low birth weight and small-for-gestational-age infants showed a nearly linear association with DBP exposure. These findings suggest that high THM exposure, particularly above certain thresholds, increase the risk of growth and urinary tract defects, findings that are also supported by biological plausibility. Given existing regulatory limits (80–100 μg/L in US and EU), our results indicate the need for stricter standards to protect vulnerable populations such as pregnant women.

1. Introduction

The widespread adoption of water disinfection practices represents one of the most important public health achievements of the modern era (World Health Organization, 2022). The disinfection of drinking water, first implemented in the early 20th century, has resulted in a significant improvements, reducing the incidence of waterborne diseases such as cholera, typhoid fever, and dysentery (Cutler and Miller, 2005; World Health Organization, 2023). This pivotal advancement increased life expectancy and enhanced the overall quality of life by ensuring millions of people worldwide have access to safe and clean drinking water (Centers for Disease Control and Prevention (CDC), 2024b).

However, disinfection of drinking water with chlorinated substances has some drawbacks, particularly the occurrence of disinfection by-products (DBPs), an undesirable group of compounds formed during the water treatment process. In fact, disinfectants such as chlorine, chloramine, and ozone react in water with naturally occurring organic and inorganic compounds, leading to various volatile and non-volatile DBPs (Environmental Protection Agency, 2025; Nieuwenhuijsen et al., 2009a). The predominant group of volatile DBPs is known as trihalomethanes (THMs). This group includes chloroform (CHLF), bromodichloromethane (BDCM), dibromochloromethane (DBCM), and bromoform (BRF). Among the non-volatile DBPs, haloacetic acids (HAAs) are the most prevalent, often measured as the sum of five (HAA5) or nine (HAA9) specific acids (Richardson et al., 2007; United Nations Environment Programme (UNEP) and International Labour Organization (ILO), 2000).

The occurrence and distribution of DBPs vary seasonally and geographically and depend on several characteristics, including the type and dose of the disinfectant used, and in particular the water source, content of organic precursors, temperature, and pH. For instance, surface waters typically lead to higher DBP formation compared to groundwaters, given the higher organic content of the former. Temperature influences the reaction rates, with higher temperatures generally accelerating the formation of DBPs. Additionally, pH levels can shift the chemical equilibrium, affecting the types and concentrations of DBPs produced (Nieuwenhuijsen et al., 2000; United Nations Environment Programme (UNEP) and International Labour Organization (ILO), 2000).

Long-term exposure to DBPs has been related to an increased risk of cancer (bladder and rectal cancer in particular) and of adverse reproductive and developmental effects, thus representing a significant concern in water treatment (Evlampidou et al., 2020; Helte et al., 2025; Kalita et al., 2024; Morris et al., 1992; National Cancer Institute, 2025; Villanueva et al., 2017). Regulatory agencies have therefore set limits on their concentrations to ensure the safety of drinking water (Dettori et al., 2022). Among the possible health risks associated with DBPs, their impact on reproductive health and adverse developmental outcomes, particularly birth defects, gained particular attention (Bove et al., 1995; European Commission, 2024; Jauniaux et al., 2024), given the widespread distribution of chlorinated drinking water and the relatively high prevalence of this endpoint. In fact, congenital anomalies affect approximately 1 in 33–50 infants born annually (Centers for Disease Control and Prevention (CDC), 2024). Understanding their etiological factors is crucial for public health interventions and regulatory policies, in order to reduce their occurrence (Roberts and Hoberman, 2023).

A few systematic reviews of DBPs and adverse reproductive outcomes have been published, encompassing both animal and human studies (Mashau et al., 2018; Nieuwenhuijsen et al., 2009b; Summerhayes et al., 2021). However, none has thoroughly analyzed the effects of overall DBPs and their specific compounds using a dose-response approach and trying to identify possible thresholds of exposure. We therefore aimed at elucidating the association between DBP exposure and the risk of birth defects, with emphasis on the dose-response relation across the entire range of exposure.

2. Methods

We conducted this review following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines, after registering it in the PROSPERO database (no. CRD42024590034) (Page et al., 2021). PRISMA checklist is reported in Supplementary Appendix A1.

2.1. Literature search and study selection

We defined the inclusion criteria according to the Population, Exposure, Comparator, Outcomes, and Study design (PECOS) statement: "What is the dose-response relation between exposure to disinfection by-products through drinking water and risk of overall and specific birth defects in observational studies?" (Morgan et al., 2018). Then, we performed online literature searches in Scopus, PubMed, and Web Of Science databases through March 18, 2025, using keywords "disinfection by-products" and "birth defects" and "trihalomethanes" and "birth defects" with no language restrictions. When necessary, we also contacted the authors of the included studies to request additional information for data analysis. Details about the search strategies are reported in Supplementary Table S1.

Using Rayyan QCRI online application, we merged records from the three databases and removed duplicates. Two authors (GD and TF) conducted independent screening of titles and abstracts, with the help of a third author (MV) to solve controversies. We retrieved the full text of the remaining records and assessed them for inclusion. Two authors (GD and TF) independently performed a full-text assessment and in case of disagreement, we sought two other co-authors (AZ and MV) to facilitate resolution. We considered a study eligible for inclusion if: (i) exposure to DBPs was assessed through measurements in drinking water; (ii) the outcome of interest was prevalence at birth of any type of birth defects; (iii) it was an observational study (case-control, cross-sectional or cohort study); (iv) risk estimates were provided by computing odds ratio (OR), hazard ratio (HR), or rate/risk ratio (RR) of the outcome along with their corresponding 95 % confidence interval (CI). Furthermore, we conducted a comprehensive review of the reference lists of the included studies and other relevant reviews to identify additional relevant studies using also backward and forward citation retrieval techniques (EUnetHTA JA3WP6B2–2 Authoring Team, 2019).

2.2. Risk of bias assessment

We evaluated the quality of included studies using the Risk of Bias for Non-randomized Studies of Exposures (ROBINS-E) tool (Morgan et al., 2019). We considered seven domains, including: (i) bias due to confounding; (ii) bias in selecting participants in the study; (iii) bias in exposure classification; (iv) bias due to departures from intended exposures; (v) bias due to missing data; (vi) bias in outcome measurement; (vii) bias in the selection of reported results (Morgan et al., 2019). In Supplementary Table S2, we present criteria for risk of bias evaluation performed by two authors (GD and TF). In the event of a discrepancy, we consulted a third author (MV) to reach a final decision. We classified a study as having a moderate or high risk of bias if it was deemed moderate or high risk, respectively, in $\geq$1 domain.

2.3. Data analysis

We synthesized the evidence through both qualitative and quantitative approaches. In the qualitative approach, the inclusion criteria were configured through PECOS criteria. In the quantitative synthesis, we assessed the risk of congenital anomalies at increasing levels of DBP exposure. We compared risk between the highest versus the lowest exposure categories using forest-plots within a restricted maximum likelihood random-effects model, provided that at least three studies were available for each DBP group and outcome.

We also conduct a dose-response meta-analysis through the one-stage approach (Crippa et al., 2019; Orsini, 2021), whenever possible given data availability. In particular, we employed the mean or median value of each exposure category, if available. When only the range of the category was reported, we used its midpoint. When mean or median values were missing for the highest and/or the lowest exposure categories, we set a value 20 % higher or lower than the closest cut-point (Iamandii et al., 2024; Veneri et al., 2023). We used a restricted cubic spline model with knots at three fixed points (10th, 50th, and 90th percentiles) of DBP exposure (Crippa et al., 2019) within a restricted maximum likelihood random-effects model. The reference for the dose-response meta-analysis was set to 0, with no a priori assumptions regarding the shape of the association.

We assessed the heterogeneity of studies using the graphical overlay of study-specific curves showing the influence of variation across studies (Murad et al., 2023; Orsini et al., 2022). Finally, we assessed the presence and influence of publication bias using funnel plots with Egger's test (Egger et al., 1997; Lin et al., 2020) and trim-and-fill analysis (Duval and Tweedie, 2000) when at least five studies are available for each outcome. We conducted all analyses using 'meta', 'mkspline', and 'drmeta' routines of Stata software (v18.0, Stata Corp., College Station, TX, 2023).

3. Results

A flowchart illustrating the literature search, screening, and selection process is presented in Fig. 1, providing a visual summary of the methodology. The initial search identified a total of 742 records. After removing duplicates, 632 studies remained for further screening. We reviewed titles and abstracts, resulting in the selection of 47 articles for a more detailed evaluation. During this phase, we excluded 16 articles due to insufficient or unsuitable data, incorrect outcome or exposure, or lack of a dose-response effect. Ultimately, 31 articles met the inclusion criteria, comprising 12 cohort studies, 5 cross-sectional studies, and 14 case-control studies (Aggazzotti et al., 2004; Bove et al., 1995;

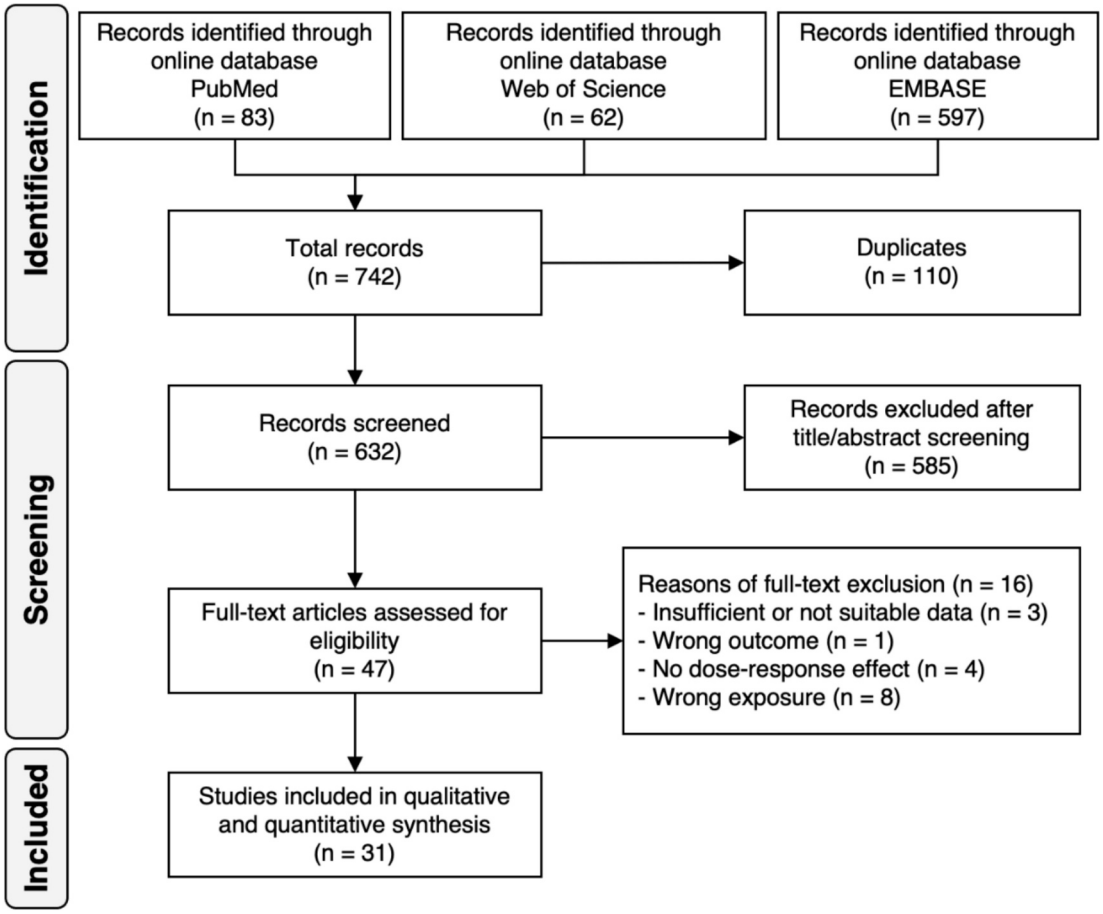

Fig. 1. Flow-chart of systematic literature search.

Cedergren et al., 2002; Chisholm et al., 2008; Dodds et al., 1999; Dodds and King, 2001; Gallagher et al., 1998; Grazuleviciene et al., 2013; Hinckley et al., 2005; Hwang et al., 2008; Iszatt et al., 2011; Jensen et al., 2023; Kaufman et al., 2018, 2020; Kaufman et al., 2024; Klotz and Pyrch, 1999; Kramer et al., 1992; Kumar et al., 2014; Luben et al., 2008; Nieuwenhuijsen et al., 2008; Righi et al., 2012; Save-Soderbergh et al., 2021; Save-Soderbergh et al., 2020; Shaw et al., 2003; Toledano et al., 2005; Weyer et al., 2018; Wright et al., 2017; Wright et al., 2003; Wright et al., 2004; Yang et al., 2007; Zaganjor et al., 2020).

Detailed characteristics of the selected articles, including study design, population, outcomes, and exposures, are summarized in Table 1. The included articles were published between 1992 and 2023, with studies conducted in Europe (n = 10), Oceania (n = 1), North America (n = 18), and Asia (n = 2). Collectively, these studies investigated 56 birth defects, which we grouped into 12 categories, as detailed in Supplementary Table S3. Specifically, identified "abdominal wall defects", "cardiovascular defects", "chromosomal defects", "digestive system defects", "growth defects", "integument congenital defects", "musculoskeletal defects", "nervous system defects", "neural tube defect", "orofacial defects", "respiratory system defects", and "urogenital defects". Overall, 14 studies focused on growth defects, 12 on orofacial and cardiovascular defects, 9 on neural tube defects, 7 on urogenital defects, 5 on chromosomal defects, 4 on musculoskeletal defects, and 3 each on abdominal wall, digestive system, nervous system, and respiratory system defects. Additionally, one study examined congenital integumentary defects.

Risk of bias of the included studies is presented Supplementary Table S4. Six studies were judged at high risk of bias due to lack of adequate control of confounding factors. Specifically, three studies reported crude risk estimates, while three studies did not include any adjustment factors among education/socioeconomic status, age or smoking habits. As regards all other domains, the included studies were considered al low risk of bias except for bias in departure from intended exposure that was considered at low risk in 10 studies, and at moderate risk in 22 studies due to lack of reporting of exposure levels across the increasing categories, precluding the inclusion of these studies in the dose-response analysis.

Results of the meta-analysis analysis comparing the highest versus the lowest exposure category is reported in Supplementary Fig. S1-S8. We detected a positive association for cardiovascular defects (RR = 1.08, 95 % CI 0.90–1-30) (Supplemental Fig. S1), all growth defects except very low birth weight (Supplemental Fig. S3), namely low birth weight (RR = 1.06, 95 % CI 0.99–1.15), small for gestational age (RR = 1.07, 95 % CI 1.01–1.15), and term low birth weight (RR = 1.64, 95 % CI 0.62–4.37), musculoskeletal defects (RR = 1.41, 0.71–2.81) (Supplemental Fig. S4), neural tube defects (RR = 1.23, 95 % CI 0.90–1.69) (Supplemental Fig. S5), and urinary tract defects (RR = 1.25, 95 % CI 0.95–0.65) (Supplemental Fig. S8).

Funnel plot analysis of publication bias was feasible for five outcomes, generally showing some amount of small-study effects (Supplementary Fig. S9). The trim-and-fill analysis (Supplementary Fig. S10) showed that that risk of cardiovascular defects and neural tube defects decreased after addition of two studies in each analysis (observed+imputed RR = 1.02, 95 % CI 0.85–1.22 and RR = 1.12, 95 % CI 1.0.84–1.49, respectively), while lower to null effect was noted for other outcomes, namely low birth weight (observed+imputed RR = 1.06, 0.99, 1.13), small for gestational age (observed+imputed RR = 1.06, 95 % CI 0.98–1.15), and urinary tract defects (observed+imputed RR = 1.16, 95 % CI 0.89–1.49).

The curve of non-linear dose-response associations between DBP exposure and reproductive outcomes is shown in Fig. 2. For most of the outcomes, we did find a positive association over the entire range of exposure; for anencephaly, musculoskeletal defects, and orofacial defects little increase in risk can be noted for exposure above 60 μg/L, and for term low birth weight above 30 μg/L. The only small inverse association can be noted for cleft lip with or without cleft palate at high (60 μg/L) exposure. Moreover, there was a positive and almost linear association for low birth weight and small for gestational age, while the risk of urinary tract defects increased till a plateau at 30 μg/L, above which it flattened. Sensitivity analysis for study-specific curves (Supplementary Fig. S11), showed large heterogeneity for most of the outcomes that did not demonstrate any clear association with THMs exposure. Conversely, lower heterogeneity can be noted for small for gestational age and term low birth weight, and especially for orofacial defects and urinary tract defects and orofacial defects showing very low variation from the overall estimate.

4. Discussion

Results of this systematic review and dose-response meta-analysis suggest an association between exposure to THMs and increased risk of some birth defects, though not always with a linear pattern, and give an indication for some specific threshold effects.

The meta-analysis comparing the highest versus the lowest exposure levels revealed a positive association with cardiovascular defects, most growth defects, and musculoskeletal, neural tube, and urinary tract defects. However, previous research on this topic has produced mixed findings, with some studies failing to identify positive associations or reporting inconsistent effects (Grellier et al., 2010; Hwang and Jaakkola, 2003; Nieuwenhuijsen et al., 2009b; Summerhayes et al., 2021). Furthermore, the limited number of studies available for each specific defect underscores the need for cautious interpretation of these findings. Finally, forest plot analysis has major limitations, being a comparison of different and highly heterogeneous categories of exposure across studies, and not allowing to identify the possible exposure thresholds above which an excess risk starts to occur.

Conversely, the results of our key analysis, the dose-response one across the entire range of DBP exposure, clearly highlight a nonlinear relation between THM exposure and several adverse outcomes, and show the overall pattern of association between various exposure type and reproductive endpoints, provided that there were enough data to shape that relation. Notably, an increased risk for anencephaly, musculoskeletal, and orofacial defects emerged at exposure levels exceeding 60 μg/L, while term low birth weight showed a risk increase above 30 μg/L. These threshold effects suggest that higher THM concentrations may be particularly concerning for specific birth defects. In contrast, low birth weight and small for gestational age exhibited a more linear association, reinforcing concerns about the impact of THM exposure on fetal growth even at low doses.

The plateau effect observed for urinary tract defects above 30 μg/L suggests a risk saturation at high exposure levels, possibly reflecting physiological adaptation or underlying exposure-response mechanisms. The unexpected inverse association observed for cleft lip with or without cleft palate at high exposure levels warrants further investigation to determine whether it represents a true biological effect, or is influenced by residual confounding.

Several toxicological studies reported findings similar to epidemiological studies, especially retardation of growth rate and urinary tract defects (Graves et al., 2001). A few mechanisms underlying this possible association have been suggested, including genotoxicity, oxidative stress, alteration of levels of some hormones, and metabolism of some vitamins (Nieuwenhuijsen et al., 2009a), thus providing biological plausibility for the epidemiologic findings. One potential explanation for the overall study findings related to congenital anomalies is the mutagenic and cytotoxic potential of DBPs, including THMs. Some of these compounds have been shown to induce DNA damage, double strain DNA breaks or interfere with cellular signaling pathways, which could contribute to developmental abnormalities (Kargalioglu et al., 2002; Lan et al., 2018; Potter et al., 1996; Shi et al., 2024). In addition, recent evidence indicates that DBPs may act as endocrine disrupting chemicals (Colman et al., 2011; Gonsioroski et al., 2020), explaining the increased risk of cardiovascular and neural tube defects, and growth defects (e.g.

Table 1
Characteristics of the included studies.

Reference	Year	Population	Region	Design	Outcome	Exposure	RoB
Aggazzotti et al. (2004)	1999–2000	239/955	Italy	Case-control	growth defects	other DBPs	M
Bove et al. (1995)	1985–1988	80,938	New Jersey, US	Cross-sectional	cardiovascular defects growth defects nervous system defects neural tube defects orofacial defects	TTHMs	H
Cedergren et al. (2002)	1982–1996	597/48926 753/58669	Sweden	Case-control	cardiovascular defects	TTHMs other DBPs	M
Chisholm et al. (2008)	2000–2004	20,870 (1097 cases)	Australia	Cohort	cardiovascular defects digestive system defects integument congenital defects musculoskeletal defects nervous system defects respiratory system defects c	TTHMs	L
Dodds et al. (1999)	1988–1995	NR	Nova Scotia, Canada	Cohort	cardiovascular defects chromosomal defects growth defects neural tube defects orofacial defects	TTHMs	M
Dodds and King (2001)	1988–1995	NR	Nova Scotia, Canada	Cohort	cardiovascular defects chromosomal defects neural tube defects orofacial defects	TTHMs	M
Gallagher et al. (1998)	1990–1993	1244 (72 cases) (29 cases)	Denver, US	Cohort	growth defects	TTHMs	M
Grazuleviciene et al. (2013)	2007–2011	NR	Lithuania	Cohort	cardiovascular defects musculoskeletal defects urogenital defects	TTHMs	L/H
Hinckley et al. (2005)	1998–2002	48,119 (1010 cases)	Arizona, US	Cohort	growth defects	TTHMs HAAs	M
Hwang et al. (2008)	2001–2003	396,049 (2148 cases)	Taiwan	Cross-sectional	cardiovascular defects chromosomal defects neural tube defects orofacial defects urogenital defects	TTHMs	H
Iszatt et al. (2011)	1997–1998	289/292	United Kingdom	Case-control	orofacial defects	TTHMs	M
Jensen et al. (2023)	1991–2015	1,078,892 (110,439 cases)	Denmark	Cohort study	growth defects	other DBPs	H
Kaufman et al. (2018)	2000–2004	366/3660	Massachusetts, US	Case-control	orofacial defects	TTHMs HAAs other DBPs	M
Kaufman et al. (2020)	2000–2004	187/1870	Massachusetts, US	Case-control	abdominal wall defects musculoskeletal defects	TTHMs HAAs other DBPs	L
Kaufman et al. (2024)	2000–2004	210/2100	Massachusetts, US	Case-control	urogenital defects	TTHMs HAAs other DBPs	M
Klotz and Pyrch (1999)	1993–1994	112/248	New Jersey, US	Case-control	neural tube defects	TTHMs	H
Kramer et al. (1992)	1989–1990	NR	Iowa, US	Case-control	growth defects	TTHMs	M
Kumar et al. (2014)	1998–2003	728,613 (47,264 cases) (71,909 cases)	New York, US	Cross-sectional	growth defects	TTHMs	M
Luben et al. (2008)	1998–2002	320/614	Arkansas, US	Case-control	orofacial defects	TTHMs HAAs	M
Nieuwenhuijsen et al. (2008)	1993–2001	2,605,226	United Kingdom	Cohort	abdominal wall defects cardiovascular defects neural tube defects orofacial defects respiratory system defects urogenital defects	TTHMs	L
Righi et al. (2012)	2002–2005	1150/4984	Emilia-Romagna, Italy	Case-control	abdominal wall defects cardiovascular defects chromosomal defects digestive system defects neural tube defects orofacial defects respiratory system defects urogenital defects	TTHMs other DBPs	M
Save-Soderbergh et al. (2020)	2005–2015	552,372 (10,887 cases)	Sweden	Cohort	growth defects	TTHMs	L
Save-Soderbergh et al. (2021)	2005–2015	623,468	Sweden	Cohort	cardiovascular defects chromosomal defects	TTHMs	L

(*continued on next page*)

Table 1 (*continued*)

Reference	Year	Population	Region	Design	Outcome	Exposure	RoB
					digestive system defects musculoskeletal defects nervous system defects orofacial defects urogenital defects		
Shaw et al. (2003)	1989–1991	NR	California, US	Case-control	neural tube defects cardiovascular defects neural tube defects orofacial defects	TTHMs	M
Toledano et al. (2005)	1993–1998	20,624 412,973 486,974	United Kingdom	Cohort	growth defects	TTHMs	L
Weyer et al. (2018)	2000–2005	NR	United States	Case-control	orofacial defects	TTHMs HAAs	H
Wright et al. (2003)	1990	56,513 (1325 cases) (5310 cases)	Massachusetts; US	Cross-sectional	growth defects	TTHMs	M
Wright et al. (2004)	1995–1998	194,827 (17,359 cases)	Massachusetts, US	Cross-sectional	growth defects	TTHMs HAAs	M
Wright et al. (2017)	2000–2005	904/9040	Massachusetts, US	Case-control	cardiovascular defects	TTHMs HAAs other DBPs	L
Yang et al. (2007)	2000–2002	90,848	Taiwan	Cohort	growth defects	TTHMs	M
Zaganjor et al. (2020)	2000–2005	330/917	United States, US	Case-control	growth defects	TTHMs HAAs	L

Abbreviations: H: high risk; M: moderate risk; L: low risk; TTHMs: total trihalomethanes (THMs); HAAs: haloacetic acids; DBPs: disinfection by-products.

low birth weight, SGA, etc.). Specifically, toxicologic studies suggested that some THMs could affect the synthesis and/or secretion of placental syncytiotrophoblast-derived chorionic gonadotropin (Chen et al., 2003) and lower testosterone levels (Potter et al., 1996).

The observed threshold effects may reflect dose-dependent mechanisms in which lower exposures are effectively managed by cellular repair systems, while higher exposures overwhelm these defenses, leading to adverse outcomes.

These findings are particularly significant given the heterogeneity of regulatory standards across different regions, and may have implication for public health policy. The European Union sets a maximum allowable concentration of 100 μg/L, while the United States enforces a threshold of 80 μg/L (European Union, 2025; US Environmental Protection Agency, n.d.). Our results suggest that these limits could be inadequate to fully protect pregnant women, and should be possibly lowered to enhance public health protection. However, single countries have adopted more stringent and adequate limits, such as the 30 μg/L standard in Italy, which is associated with minimal or none effects on birth defects (Gazzetta Ufficiale della Repubblica Italiana, n.d.-a; Gazzetta Ufficiale della Repubblica Italiana, n.d.-b). Our findings highlight the need for stricter international standards in this field, though further research on this topic is clearly warranted.

Some limitations of this analysis should be acknowledged. First, variations in study design, exposure assessment methods, and confounding adjustments may have been a source of heterogeneity, thus explaining some discrepancies among studies. In addition, the limited studies for several outcomes precluded the implementation of stratified analyses, especially by country and subtypes of defects. Similarly, the analysis restricted to studies with low or intermediate risk of bias could not be conducted due to the limitation of sample size for each outcome.

In addition, given the observational nature of the design of the studies, residual confounding could not be entirely excluded. Nonetheless, we extracted the most adjusted estimates for each study, and only three studies reported crude estimates with no adjustment for possible confounding factors.

The predominance of studies from North America and Europe underscores the need for further research in underrepresented regions, particularly in low- and middle-income countries, where DBP exposure levels and health effects may differ due to interactions with genetic factors (Bonou et al., 2017; Infante-Rivard, 2004), lifestyles (Gomersall et al., 2024), or other environmental exposures (Felisbino et al., 2024; Feretti et al., 2020; Gaughan et al., 2023; Gomersall et al., 2024; Nie et al., 2024; Vinceti et al., 2009; Vinceti et al., 2016; Vinceti et al., 2025).

Nevertheless, to the best of our knowledge, this is the first dose-response analysis investigating the relation between DBP exposure and adverse birth outcomes. The use of a dose-response approach allows for a more precise evaluation of the exposure-outcome relation and of its pattern in the intermediate amount of exposure, offering valuable insights into potential threshold effects. Furthermore, the inclusion of 31 studies covering a wide range of birth defects enhances the robustness and generalizability of our findings.

In conclusion, our findings suggest that high levels of exposure to THMs may be associated with an increased risk of several birth defects, and that such increase may occur only above a certain threshold of exposure. In particular taking into account evidence from both toxicological and epidemiologic studies, the stronger evidence of the detrimental THMs exposure was found for most of the growth defects (namely low birth weight, term low birth weight, and small for gestational age), and urinary tract defects, especially when THMs are above 30 μg/L.

These results highlight the importance of continued monitoring and of updating DBP standards in drinking water, to minimize potential health risks especially for vulnerable populations such as pregnant women and developing fetuses, and to pool new, well-conducted studies as soon as they become available.

CRediT authorship contribution statement

Giovanna Deiana: Resources, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing, Writing – original draft. **Tommaso Filippini:** Resources, Investigation, Formal analysis, Data curation, Conceptualization, Writing – review & editing. **Marco Dettori:** Investigation, Writing – review & editing. **Marco Vinceti:** Methodology, Investigation, Conceptualization, Writing – review & editing. **Antonio Azara:** Methodology, Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial

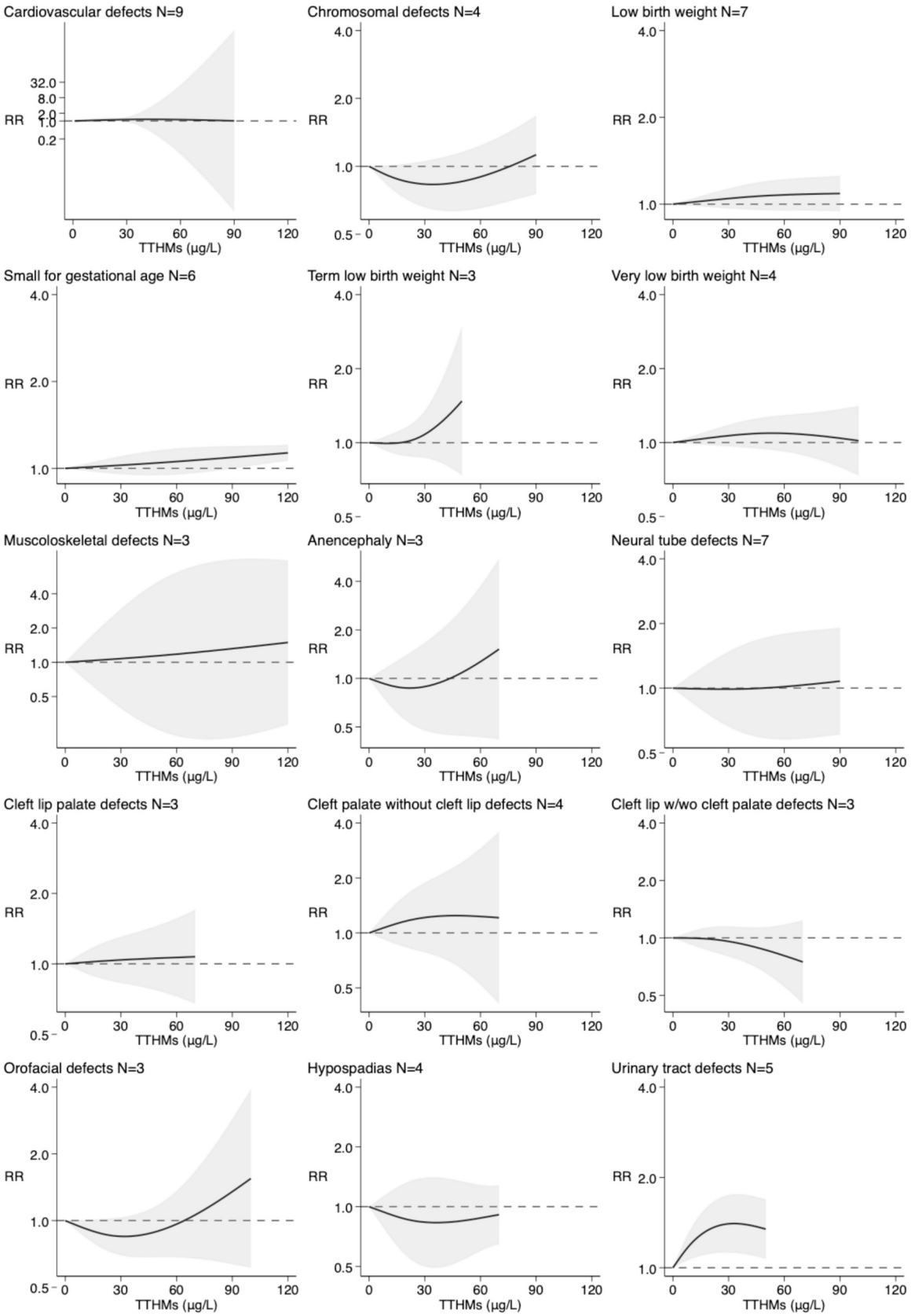

Fig. 2. Dose-response meta-analysis of risk of birth defects according to increasing exposure to total trihalomethanes (TTHMs). Spline curve (black solid line) with 95 % confidence limits (grey area). The curves are designed using restricted cubic spline method using 3 knots at fixed cutpoints (10th, 50th, and 90th percentiles) and considering null exposure as reference. The long dash line represents the null effect, RR = 1. RR: risk ratio.

interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2025.179693.

Data availability

Data will be made available on request.

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