Drinking water disinfection by-products exposure and health effects on pregnancy outcomes: a systematic review

Funanani Mashau, Esper Jacobeth Ncube and Kuku Voyi

ABSTRACT

Epidemiological studies have found that maternal exposure to disinfection by-products (DBPs) may lead to adverse pregnancy outcomes although the findings tend to be inconsistent. The objective of this study was to systematically review the evidence in associated with drinking water DBP exposure in relation to adverse pregnancy outcomes. Peer-reviewed articles were identified using electronic databases searched for studies published in the English language. Studies selected for review were evaluated for exposure assessment, confounders, and analyses risks of bias in the selection, outcomes assessment, and attrition. A comprehensive search and screening yielded a total of 32 studies, of which 12 (38%) reported a statistical association between maternal exposure to DBPs and adverse pregnancy outcomes. A maternal exposure to trihalomethanes (THMs) shows an increased risk of small for gestational age (SGA) and slightly increased risk of pregnancy loss. Risks of bias were low among the studies included in the review. Evidence on association relating to adverse pregnancy outcomes to DBP exposure is still less significant. There is a need for future robust research in this field, with the use of urinary trichloroacetic acid (TCAA) biomarkers as a direct exposure assessment method for this field.

Key words | adverse pregnancy outcomes, disinfection by-product exposure, drinking water

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INTRODUCTION

The use of disinfectants as a drinking water treatment step in developing countries has led to an effective decrease of waterborne diseases (World Health Organization (WHO) 2011). Since then, chlorine and other related compounds are being used globally because of successes and milestones in public health protection. It has been known for more than 20 years that chlorination of surface water produces chloroform and other toxic compounds that are health risks (Rook 1974). More than 600 DBPs have been identified to date (Richardson *et al.* 2007; Nieuwenhuijsen *et al.* 2009a). The most commonly studied DBPs are THMs and haloacetic acids (HAAs) as they occur in higher concentrations in tap water compared to others.

The health effects of drinking water DBPs on adverse pregnancy outcomes have been previously reviewed; however, the conclusions of these reviews varied widely, from indicating association to suggesting no association of DBPs on pregnancy outcomes (Bove *et al.* 2002; Hwang & Jaakkola 2003; Nieuwenhuijsen *et al.* 2009b, 2010; Grellier *et al.* 2010). In addition, previous reviews published on this subject did not assess the risk of bias among the articles studied.

The aim of this study was to systematically review the evidence on the risks of spontaneous abortion (miscarriage), preterm or premature birth (PTB), low birth weight (LBW) and SGA associated with exposure to different drinking water DBPs.

doi: 10.2166/wh.2018.167

METHODOLOGY

The current study followed Preferred Reporting Items for Systematic Reviews and Metal-Analyses (PRISMA) guidelines and guidance of observational studies in epidemiology criteria (Moher *et al.* 2009). The study received ethical approval from the Faculty of Health Sciences, University of Pretoria (reference no. 115/2016).

Study question

The pertinent object of this study was to evaluate the evidence/literature on risk of spontaneous abortion (miscarriage), premature birth, LBW and SGA among women exposed to different drinking water DBPs during pregnancy.

Inclusion and exclusion criteria for this review

Observational studies that measure the association of drinking water DBPs and maternal exposure and adverse pregnancy outcomes were included in this review. Published studies in peer-reviewed journals from 1986 to 2016 formed part of the investigation. We limited ourselves to articles published in English with females as participants, and articles conducted in communities or populations. Studies with information on (1) THMs, (2) HAAs, (3) haloacetonitriles (HAs), (4) haloketones (HANs), (5) bromate and (6) chlorate as selected drinking water DBPs were included. The studies, which provide rational information on the method of measuring the maternal exposure to DBPs and their effects on selected adverse pregnancy outcomes, were considered for inclusion in the review. Studies with less than 30 participants, and summarized publications and studies using chlorination and monochloramination in other matrices or contexts other than drinking water disinfection, were excluded from this review.

Types of studies

Peer-reviewed observational studies, retrospective or prospective cohort studies, case-control studies, and cross-sectional studies were included in the review.

Type of participants

In this review, we included studies identifying pregnant women exposed to various drinking water DBPs during the time of pregnancy (at any stage of gestation).

Exposure assessment

Data regarding maternal exposure to drinking water DBPs obtained via three sources were eligible for inclusion: (1) measurement of participants' urine TCAA levels as a biomarker; (2) measuring DBPs from drinking water source (i.e., residential tap water); and (3) linking data obtained from municipal or national monitoring database on water quality measurements, resulting in an estimated value for women's exposure during time of pregnancy.

Outcomes assessment

We included any studies that reported data on four of the following outcomes: (1) pregnancy loss or spontaneous abortion (miscarriage); (2) premature/preterm birth or premature delivery (PTB or PTD), defined as gestational age of less than 37 weeks; (3) LBW, defined as birth weight of less than 2.5 kg; and (4) SGA, defined as birth weight below the 10th percentile for gestational age.

Search strategy

Searches were performed using PubMed, Medline and Google scholar electronic databases using the terms and key words and a combination of the key words. Additional data were extracted from grey literature, which include but are not limited to World Health Organization, ProQuest dissertations as well as theses, databases and conference proceedings. Water industry bodies, such as the South African Water Research Commission (WRC), were also used to search for data. The phrases and key words used were based on the terminology commonly used in this subject, including: 'drinking water disinfection by-products', 'chlorination of water', 'monochloramination of water', 'chlorination disinfection by-products', 'chloramination disinfection by-products', 'exposure to disinfection by-products', 'disinfection by-products health effects', 'haloacetonitriles',

'haloketones', 'trihalomethanes', 'haloacetic acids', 'bromate', 'chlorate', 'birth outcomes', 'adverse pregnancy outcomes', 'gestational age', 'premature birth or preterm birth', and 'birth weight' (Table 1). The searched articles were screened from their titles and abstracts to select the eligible studies.

Methods of review

Data extraction

Two reviewers independently evaluated each of the full texts of eligible studies and any disagreement was resolved via discussion, with the help of a third reviewer. Data extracted from each were piloted on to the data collection form without modifying its origin. Lists of confounders were also collected before being adjusted for analysis in the studies. The included articles were then assessed for quality.

Risk assessment of bias among included studies

The tool to assess the quality was adopted from Shah & Zao (2009) (Table 2) with the scale from none to high bias. The table includes the following characteristics: selection, exposure assessment, outcome assessment, confounding factor, analytical and attrition bias.

Data synthesis

A systematic review of these was made rather than performing meta-analyses, as heterogeneities were recognized in previous reviews. We did not assess statistical heterogeneity and publication bias, as the meta-analyses were not performed. However, studies were assessed for methodological differences and data were reported.

RESULTS

Description of studies

Search results and the number of studies are summarized in Figure 1, along with the reasons for excluding the studies from this review. Detailed characteristics of all included studies are reported in Table 1.

Quality assessment of included studies

Risks of bias assessment of the included studies were studied. Of the 32 studies included, 26 (81%) had an overall low risk of bias, whereas six (19%) had an overall moderate risk of bias. In exposure assessment, moderate risks of bias were assigned to the studies due to indirect use of exposure methods employed. Most studies had no risk of bias for outcome assessment, confounder adjustments and participant selection (see Table 3 for details).

Outcomes

Adverse pregnancy outcomes according to various drinking water DBPs were assessed. Studies included in the review reported various drinking water DBPs; however, the majority of studies reported on THMs followed by HAAs, or both. The results below are classified according to individual DBPs. The details of level of exposure, time of exposure and birth outcomes are reported in Tables 2–6.

Trihalomethanes

Twenty-nine studies reported data on adverse pregnancy outcomes following THM exposure (Table 2). Studies reported on various levels of exposure, ranging from 0 to 108.8 μg/L. Sixteen studies investigated the association between THM exposure and SGA, and 13 studies reported on either PTB, PTD or LBW and pregnancy loss, or all three. Ten studies reported on exposure to THMs during the third trimester, 13 studies during the entire pregnancy, five studies on both first trimester and entire pregnancy, or second trimester and third trimester, or only the second trimester's maternal exposure. One study reported on first, second and third trimesters and entire pregnancy) THM exposure. Nine studies reported on evidence of association between maternal THM exposure and adverse pregnancy outcomes (Dodds *et al.* 1999; Aggazzotti *et al.* 2004; Maclehose *et al.* 2008; Grazuleviciene *et al.* 2011; Levallois *et al.* 2012;

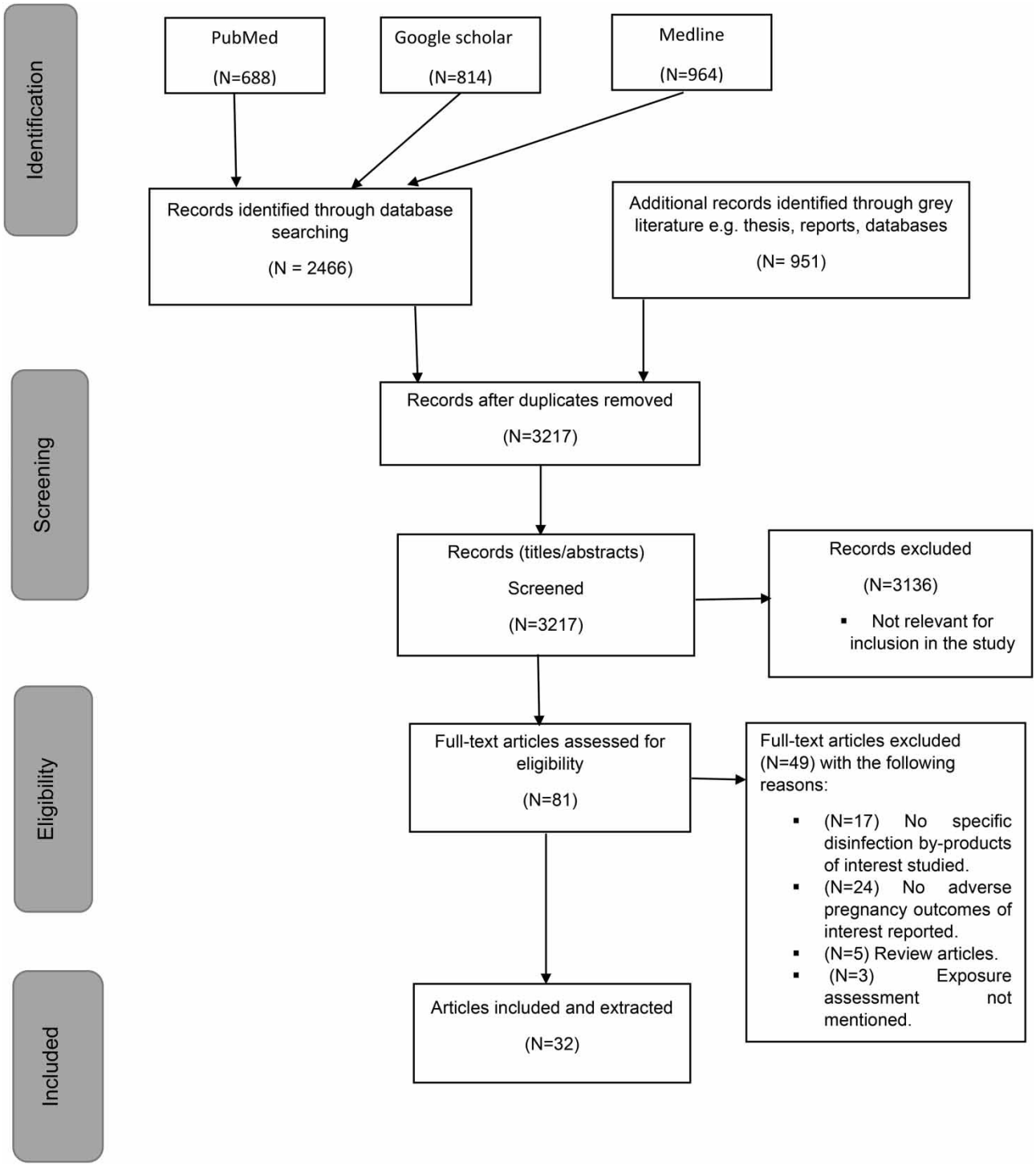

Figure 1 | Flow diagram of search, screening and study selection.

Rivera-Núñez & Wright 2013; Kumar *et al.* 2014; Iszatt *et al.* 2014; Cao *et al.* 2016). These studies were conducted in countries including the USA, UK, Canada, China, Italy and Europe. Twenty studies reported no association between THM exposure and adverse pregnancy outcomes (see Table 2).

Table 1 | Characteristics of included studies

Author (year)	Study details	Exposure measurement details	DBPs studied	Outcome studied	Outcome assessment details
Aggazzotti *et al.* (2004)	1999–2000; case-control study in Italy; $n = 1,194$	Collection of water and questionnaire on mother's personal habits	THM, chlorite and chlorate	Preterm birth (PTB) and small for gestational age (SGA)	Interviews and medical records
Botton *et al.* (2015)	2003–2008; prospective cohort study in Gipuzkoa, Sabedell, Valencia, Spain. 2007–2008; cohort study in Crete (Greece RHEA study); $n = 2,216$	Interviews at recruitment. Collection of water sample in the tap covering the study areas and data abstracted from monitoring program	THM	Birth weight (BW)	Medical records and log books
Bove *et al.* (1995)	1985–1988; cross-sectional study; $n = 80,938$ live births and $n =$ 598 fetal deaths	Water quality data obtained from monitoring program run by companies	THM	SGA, low birth weight (LBW), PTB, BW	Birth databases and medical records
Cao *et al.* (2016)	2011–2013; prospective cohort in Wuhan and Xiagan, Hubei, China; $n = 1,184$	Questionnaires used	TTMs	BW, birth length (BL) and SGA	Clinical birth records
Costet *et al.* (2011)	2002–2006; PELAGIE cohort in France; $n = 3,421$	National database was used to estimate individual exposure to THMs together with measuring the maternal urinary TCAA exposure	THMs and HAAs	Fetal growth restrictions (FGR), PTB	Midwives, paediatricians and medical records
Danileviciute *et al.* (2012)	2007–2009; nested–control study part of Kaunas (Lithuania) cohort in Europe; $n = 682$	Water-use questionnaire and residential exposure index were used. Blood samples were also used to measure the internal dose of individual exposure	THMs, HAAs, HANs, HAs, chloropicrin and choral hydrate	LBW, SGA	Medical records
Dodds *et al.* (1999)	1988–1995; retrospective cohorts study in Canada; $n = 93,295$	Water quality data obtained from monitoring program	TTHM	LBW, SGA	Medical records and database
Gallagher *et al.* (1998)	1990–1993; retrospective cohort study in Colorado, USA; $n =$ 1,893	Data obtained from monitoring program	TTHM	LBW, SGA and preterm delivery (PTD)	Medical records and database
Grazuleviciene *et al.* (2011)	2007–2009; prospective cohort study in Kaunas (Lithuania); $n =$ 4,161	Questionnaire was used to interview the participants on water use activities	THMs	LBW, SGA and BW	Medical records
Hinckley *et al.* (2005)	1998–2003; retrospective cohort study in Arizona, USA; $n =$ 48,119	Water quality data obtained from monitoring program	THMs and HAAs	LBW, PTB	Vital records and birth records
Hoffman *et al.* (2008a)	2000–2004; prospective cohort study in USA; $n = 2,039$	Water samples collected in each site. Interviews conducted from the participants	TTHM and HAAs	PTB	Medical records, vital records and self-reports

(*continued*)

Table 1 | continued

Author (year)	Study details	Exposure measurement details	DBPs studied	Outcome studied	Outcome assessment details
Hoffman *et al.* (2008b)	2000–2004; US communities cohort study; $n = 2,766$	Water samples were collected at a respective location in the distribution system. Self-reporting information on water-use was also collected	TTHMs, HAAs and TOX	SGA	Medical records
Horton *et al.* (2011)	2000–2004; US community cohort study consisting of two sites: chlorinated DBP site ($n = 27,062$); brominated DBP site ($n = 3,946$)	Weekly collections of water samples from representative location sites (i.e., chlorinated–brominated containing DBP) were used	TTHMs, HAAs and TOX	SGA, PTB	Birth records
Ileka-Priouzeau *et al.* (2015)	2006–2008; Quebec, Canada, case-control study; cases ($n = 330$), controls ($n = 1,100$)	Water samples were measured for HANs and HAs combined with the previous data on THMs and HAAs	HANs, HAs, THMs and HAAs	SGA	Birth certificates and medical records
Iszatt *et al.* (2014)	2000–2005 and 2005–2007; Case-control study in UK; $n = 472,526$ live births and $n = 2,631$ stillbirths	National water quality data base was used to assign the individual exposure	THMs	LBW	Birth records
Kogevinas *et al.* (2016)	2002–2010; prospective cohort studies in France Greece, Lithuania, Spain and UK; $n =$ 14,0005	Water samples collected and additional data from regulatory monitoring program. Questionnaire administered to the participants	THM	SGA, LBW, PTB	Birth records
Kumar *et al.* (2014)	1998–2003; cross-sectional study in New York state; $n = 1,528,681$ singleton live births	Exposure data obtained from public water system of maternal residence at the time of birth	TTHMs	LBW, SGA, PTB	Birth certificate records
Levallois *et al.* (2012)	2006–2008; Quebec, Canada, case-control study; cases ($n = 571$), controls ($n = 1,925$)	Chlorination by-products concentrations were measured in the tap water at the participant's residence	THMs and HAAs	SGA	Birth certificates and medical records
Lewis *et al.* (2006)	1999–2001; retrospective cohort study in Massachusetts; $n =$ 40,514 records of singletons birth	Water sampling for total THMs were used to estimate the exposure on maternal residence at birth and gestational age	THMs	LBW	Registry of vital records
Lewis *et al.* (2007)	1999–2001; retrospective cohort study in Massachusetts; $n =$ 39,593 records of singletons birth	Water sampling for total THMs were used to estimate the exposure on maternal residence at birth and gestational age	TTHMs	PTB	Birth certificates
Maclehose *et al.* (2008)	2000–2004; prospective cohort study in USA; $n = 2,506$	Sampling of water at respective points. Questionnaires were administered to the participants	THMs, HAAs, TOX	Pregnancy loss	Medical records

Patelarou *et al.* (2011)	2007–2008; prospective cohort study in Crete ('Rhea' study), Greece; $n = 1,359$	Questionnaires administered. Tap water samples were also collected in representative mothers' homes for DBP analysis	THMs	SGA, LBW, PTB	Interview after birth
Rivera-Nunez & Wright (2013)	1996–2004; retrospective cohort study in Massachusetts; $n =$ 12,394 live infants	Public water systems used and participants assigned the exposure together with collection of water samples in area	THMs and HAAs	BW, SGA, PTD	Birth certificates
Savitz *et al.* (1995)	1988–1991; case-control study in central North Carolina. Miscarriage: case 418 and controls 341; LBW 464; preterm delivery 586; controls 782	Water quality data obtained from regulatory monitoring program. Telephone interviews and person to person questionnaire were conducted with the participants	THM	Miscarriage, PTD, LBW	Medical records
Savitz *et al.* (2006)	2000–2004; prospective cohort study in three US locations; $n =$ 2,409 women	Water samples were analysed from three US locations, one referred to chlorinated DBP site, one to brominated DBP site and on to low DBP site	THM, HAA and TOX	Spontaneous abortion	Medical records
Summerhayes *et al.* (2012)	1998–2004; retrospective cohort study in New South Wales, Australia; $n = 314,982$ births	THM data were obtained from the water supply database where participants resided	THM	SGA	Midwives' data collection records
Toledano *et al.* (2005)	1992–1998; retrospective cohort study in UK; $n = 1$ million	Collection of water samples for quality	TTHM	LBW	National birth registers and health statistics in UK
Villanueva *et al.* (2011)	2000–2008; prospective cohort in Spain; $n = 2,074$	Interviews were conducted with the participants. THMs were ascertained based on sampling campaigns program and additional water quality data were obtained from local authorities and water companies	THM	SGA, LBW, PTD	Birth outcomes recorded by trained midwives at delivery
Waller *et al.* (1998)	1989–1991; prospective cohort study (Pregnancy Outcome Study) in California; $n = 5,144$	Water quality data were obtained from water utilities. Questionnaires were conducted with the participants	THM	Spontaneous abortion	Hospital discharge, medical records, birth registry and follow-up interviews
Wright *et al.* (2004)	1995–1998; retrospective cohort study in Boston, Massachusetts, USA; $n = 282,645$	Water quality data were abstracted from department of environmental protection records. Water samples were also collected for analysis	TTHM and HAAs	SGA, BW, PTD	Birth certificates

(*continued*)

Table 1 | continued

Author (year)	Study details	Exposure measurement details	DBPs studied	Outcome studied	Outcome assessment details
Yang (2004)	2000–2002; retrospective cohort study in Taiwan; $n = 90,848$	Water samples were collected for water quality and other water quality data obtained from authorities (EPA). Participant habits' data were obtained from registration books	TTHMs	LBW, SGA, PTD	Registration of births and vital records
Yang *et al.* (2007)	2000–2002; cross-sectional study in Taiwan; $n = 90,848$ women residing in 65 municipalities	Maternal exposure was assigned with the previous data of TTHM concentration for the municipality of residence at birth	THM	LBW, SGA, PTD	Birth registry
Zhou *et al.* (2012)	2008–2009; cross-sectional study in Wuhan, China; $n = 398$	Face-to-face interviews were conducted. Urine samples were also collected from the participants	HAA (TCAA)	BW	Birth records

TTHMs, total trihalomethanes; THM, trihalomethanes; HAA, haloacetic acids; TCCA, trichloroacetoc acid; TOX, total organic halide; PTB, preterm birth; SGA, small for gestational age; BW, birth weight; LBW, low birth weight; BL, birth length; FGR, fetal growth restrictions.

Haloacetic acids

The exposure to HAAs and adverse pregnancy outcomes was explored in 12 studies (Table 3). The levels of exposure to HAAs ranged from 0.1 to 75.9 μg/L among the studies. Five studies reported on exposure to HAAs and SGA, four studies reported on exposure to HAAs and PTB/PTD, and five studies on either LBW, BW or BWT. Two studies reported on exposure to HAAs and pregnancy loss. Hoffman *et al.* (2008b), Hinckley *et al.* (2005), Wright *et al.* (2004) and Zhou *et al.* (2012) reported exposure to HAAs during the third trimester; six studies reported on exposure during the entire pregnancy (Savitz *et al.* 2006; Maclehose *et al.* 2008; Costet *et al.* 2011; Grazuleviciene *et al.* 2011; Horton *et al.* 2011; Danileviciute *et al.* 2012); Hoffman *et al.* (2008a) reported on the first trimester and entire pregnancy; and Rivera-Nunez & Wright (2013) reported on the second and third trimesters. Eight studies were conducted in the USA, two in Europe, one in China and one in France. A slightly positive association between adverse pregnancy outcomes and high level of HAA exposure was reported among the studies (see Table 3).

Haloacetaldehydes (HAs)

Two studies (Danileviciute *et al.* 2012; Ileka-Priouzeau *et al.* 2015) reported on adverse pregnancy outcomes following HA exposure (Table 4). The levels of exposure to HAs ranged from 1.0 to 9.00 μg/L. Both articles studied HA exposure and SGA or LBW, or both. Studies were conducted in Europe and Canada, respectively. No association between HA exposure and SGA or LBW was reported.

Haloacetonitriles (HANs)

Three studies (Aggazzotti *et al.* 2004; Danileviciute *et al.* 2012; Ileka-Priouzeau *et al.* 2015) reported on pregnancy outcomes following chloropicrin and chloral hydrate exposure (Table 5). The levels of exposure were ≥200 μg/L for chlorate or chlorite concentrations. Two studies reported on exposure to HANs during the entire pregnancy and one during the third trimester. Studies reported on SGA and PTD, SGA and LBW, and SGA, respectively. Studies were conducted in Italy, Europe and Canada. None of the studies reported an association.

Table 2 | Exposure to THMs and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Aggazzotti *et al.* (2004)	10 μg/L to 30 μg/L	Third trimester	PTD, SGA	OR = 1.38; (95% Cl: 0.92–2.07) for term SGA. OR = 0.84; (95% Cl: 0.59–1.19) for preterm birth
Bove *et al.* (1995)	>100 ppb	First trimester; entire pregnancy	LBW, SGA, PTB	OR = 1.42; (50% Cl: 1.22–1.65) for LBW. OR = 1.50; (50% Cl: 1.36–1.65) for PTB. Mean decrease in BW 70.4 g (50% Cl: −58.2 to −82.6)
Cao *et al.* (2016)	5.3 to 52.3 ng/L	Third trimester	BW, SGA	Mean birth weight decrease (−60.9 g; 95% CI: –116.2–5.6). OR = 2.25; (95% CI: 1.01–5.03) for SGA
Danileviciute *et al.* (2012)	1.3 to 21.9 μg/L	Entire pregnancy	LBW, SGA	OR = 4.37; (95% CI: 1.36–14.08) for LBW. OR = 5.06; (95% CI: 1.50–17.05) for SGA
Dodds *et al.* (1999)	0–49 μg/L, 50–74 μg/L, 75–99 μg/L and ≥100 μg/L	Third trimester	LBW, SGA, PTB	RR = 1.8; (95% Cl: 0.99–1.18) for SGA. RR = 1.04; (95% Cl:0.92–1.18) for LBW. RR = 0.97; (95% Cl: 0.87–1.09) for PTB. RR = 0.89; (95% Cl: 0.64– 1.23) for VLBW
Gallagher *et al.* (1998)	Low (0–49 ppb) and high (≥50 ppb)	Third trimester	LBW, PTD, term LBW	OR = 1.5; (95% Cl: 0.8–3.0) for LBW. OR = 2.6; (95% Cl: 1.1–6.1) for term LBW. OR = 0.9; (95% Cl: 0.4–2.0) for PTD
Grazuleviciene *et al.* (2011)	1.3 to 21.9 μg/L	Entire pregnancy	LBW, SGA	AOR = 2.17; (95% CI: 1.19–3.98) for LBW AOR = 1.19; (95% CI: 0.87–1.163) for SGA
Hinckley *et al.* (2005)	≥53 μg/L for TTHMs	Third trimester	Term LBW	OR = 1.11; (95% Cl: 0.94–1.31)
Hoffman *et al.* (2008a)	33.1–55.0, 55.1–66.3, 66.4–74.8 and 74.9–108.8 μg/L	First trimester; entire pregnancy	PTB	OR range from 0.5 to 1.25 with 95% Cl ranging (0.3–0.8) and (0.96–1.64), respectively
Hoffman *et al.* (2008b)	<80 μg/L and ≥80 μg/L	Third trimester	SGA	RR = 2.0; (95% CI: 1.1–3.6)
Horton *et al.* (2011)	60.7 to 75.9 μg/L (chlorinated site); 58.9 to 67.4 μg/L (brominated site)	Entire pregnancy	SGA, PTB	AOR = 1.02; (95% CI: 0.91–1.15) for SGA and AOR = 0.93; (95% CI: 0.84–1.04) for PTB in chlorinated site. AOR = 0.81; (95% CI: 0.53–1.24) for SGA and AOR = 1.16; (95% CI: 0.77–1.74) for PTB in brominated site
Iszatt *et al.* (2014)	27.6 to 55.2 μg/L	Entire pregnancy	Still birth, LBW	Decrease in chloroform from 30 to 65 μg/L shows percentage decrease in LBW by −9% (−12, –5) and very LBW −16% (9–24, –8) rates
Kogevinas *et al.* (2016)	≥10 μg/L	Entire pregnancy	SGA, LBW, PTB	OR = 10 μg/L = 1.02; (95% Cl: 0.95–1.10) for LBW, OR = 0.99; (95% Cl: 0.94–1.03) for SGA and OR = 0.98; (95% Cl: 0.9–1.05) for PTB
Kumar *et al.* (2014)	0 to 40 μg/L	Entire pregnancy	LBW, SGA, PTB	OR = 1.14; (95% CI: 1.08–1.21) for LBW; OR = 1.14; (95% CI: 1.08–1.20) for PTB and OR = 1.10; (95% CI 1.04–1.16) for SGA
Levallois *et al.* (2012)	>80 μg/L and <80 μg/L	Third trimester	SGA	AOR = 1.5; (95% Cl: 1.1–1.9)

(*continued*)

Table 2 | continued

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Lewis *et al.* (2006)	≥70 μg/L	Second trimester	LBW	OR = 1.50; (95% CI: 1.07–2.10)
Lewis *et al.* (2007)	≥60 μg/L	Third trimester	PTB	HR = 1.13; (95% CI: 0.95–1.35)
Maclehose *et al.* (2008)	3.7 to 67.3 μg/L	Entire pregnancy	Pregnancy loss	AOR = 1.2; (95% Cl :1.0–1.4)
Patelarou *et al.* (2011)	0.39 to 8.74 μg/L	Entire pregnancy	SGA, LBW, PTB	OR = 0.7; (95% CI 0.4–1.4) for LBW. OR = 1.1; (95% CI 0.6–2.2) for SGA. OR = 0.8; (95% CI 0.5–1.3) for PTD
Rivera-Nunez & Wright (2013)	37.5 to 38.1 μg/L	Second and third trimester	BWT, SGA, PTD	AOR = 1.02; (95% CI 0.97–1.07) for SGA. AOR = −17; (95% CI: −24 to −11) for BWT. AOR = 1.02; (95% CI: 0.96–1.08) for PTD
Savitz *et al.* (1995)	≥40.8 ppb	Entire pregnancy	Miscarriage, PTD, LBW	AOR = 2.8; (95% Cl: 1.1–2.7) for miscarriage. AOR = 1.2; (95% Cl: 0.8–1.7) for preterm birth. AOR = 1.3; (95% Cl: 0.8–2.1) for LBW
Savitz *et al.* (2006)	≥75 μg/L	Entire pregnancy	Pregnancy loss	OR = 1.1; (95% CI: 0.7–1.7)
Summerhayes *et al.* (2012)	≥0.3 μg/L	Third trimester	SGA	RR = 1.04; (95% CI:1.02–1.06)
Toledano *et al.* (2005)	<30 μg/L, 30–59 μg/L, ≥60 μg/L	Entire pregnancy	LBW	OR = 1.09; (95% Cl: 0.93–1.27) for LBW and OR = 1.05; (95% CI: 0.82–1.34) for VLBW
Villanueva *et al.* (2011)	5.9 μg/L to 114.7 μg/L	First, second, third trimester and the entire pregnancy	SGA, LBW, PTB	OR = 1.005; (95% CI: 0.97–1.032) for PTB. OR = 1.003; (95% CI: 0.990–1.017) for SGA. Birth weight was reduced 0.45 g; (95% CI: −1.36 to 0.45) for total residential chloroform uptake and increased 0.16 g; (95% CI: −1.38 to 1.70) for total brominated THM uptake
Waller *et al.* (1998)	≥120 μg/L	First trimester	Spontaneous abortion	AOR = 1.8; (95% CI: 1.1–3.0)
Wright *et al.* (2004)	>40 μg/L	Third trimester	SGA, BW, PTD	OR = 1.25; (95% CI:1.04–1.51) for SGA and mean birth weight −27 g; (95% CI: −54 to −1)
Yang (2004)	0–4.93 mg/L, 4.93–13.11 mg/L, >13.11 mg/L	Entire pregnancy	LBW, SGA, PTD	ORs in medium versus low and high versus low exposure categories were 0.98; (95% CI :0.90–1.08) and 1.03; (95% CI: 0.94–1.13). respectively. for term LBW; 1.02; (95% CI: 0.93–1.13) and 1.09; (95% CI: 0.99–1.19), respectively. for PTD; they were 0.99; (95% CI: 0.94–1.05) and 0.99; (95% CI: 0.94–1.04), respectively. for SGA
Yang *et al.* (2007)	4.93 to 13.11 μg/L	Entire pregnancy	SGA, LBW, PTD	AOR = 1.00; (95% CI: 0.91–1.10) for LBW. AOR = 1.08; (95% CI: 0.98–1.18) for PTD. AOR = 0.96; (95% CI: 0.91–1.02) for SGA

SGA, small for gestational age; PTB, premature or preterm birth; PTD, premature or preterm delivery; LBW, low birth weight; BWT, mean birth weight; BW, birth weight; HR, hazard ratio; RR, relative risk; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval.

Table 3 | Exposure to HAAs and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Costet *et al.* (2011)	7.4 μg/L	Entire pregnancy	PTB	AOR = 0.8; (95% CI: 0.3–2.6)
Danileviciute *et al.* (2012)	0.1 to 0.5 μg/L	Entire pregnancy	LBW, SGA	Not mentioned
Grazuleviciene *et al.* (2011)	0.1 to 0.5 μg/L	Entire pregnancy	LBW, SGA	Not mentioned
Hoffman *et al.* (2008b)	21.2 to 5.9 μg/L	Third trimester	SGA	RR = 1.3; (95% CI: 0.7–2.4)
Horton *et al.* (2011)	58.9 to 75.9 μg/L	Entire pregnancy	SGA, PTB	Not mentioned
Rivera-Nunez & Wright (2013)	20.0 to 20.1 μg/L	Second and third trimester	BWT, SGA, PTD	AOR = 1.10; (95% CI: 0.94–1.29)
Savitz *et al.* (2006)	45.2 to 45.9 μg/L	Entire pregnancy	Pregnancy loss	Not mentioned
Hinckley *et al.* (2005)	≥19 μg/L	Third trimester	Term LBW	
Hoffman *et al.* (2008a)	17.9–22.0, 22.1–31.5, 31.6–40.4 and 40.5–52.8 μg/L	First trimester; entire pregnancy	PTB	OR = 0.5 and 1.1; 95% Cl: (0.3– 0.8) and (0.8–1.7), respectively
Maclehose *et al.* (2008)	1.7 to 12.3 μg/L	Entire pregnancy	Pregnancy loss	OR = 1.2; (95% Cl: 1.0–1.4)
Wright *et al.* (2004)	≤58 μg/L	Third trimester		OR = −0.9 days; (95% CI: −1.7 to −0.1) for SGA. OR = 1.48; 95% CI, 0.84–2.61). for PTD
Zhou *et al.* (2012)	0.9 μg/g Cr to 123.3 μg/g Cr and 2 μg/L to 57.7 μg/L, respectively	Third trimester	BW	AOR = 20.6 g; (95% CI: −84.1, 125.3)

SGA, small for gestational age; PTB, premature or preterm birth; PTD, premature or preterm delivery; LBW, low birth weight; BWT, mean birth weight; BW, birth weight; HR, hazard ratio; RR, relative risk; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval.

Table 4 | Exposure to HAs and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Danileviciute *et al.* (2012)	1.0 μg/L	Entire pregnancy	LBW and SGA	Not mentioned
Ileka-Priouzeau *et al.* (2015)	8.78 to 9.00 μg/L	Third trimester	SGA	OR = 1.4; (95% CI: 0.9–2.1)

SGA, small for gestational age; LBW, low birth weight; OR, odds ratio; CI, confidence interval.

Table 5 | Exposure to HANs (chloropicrin and chloral hydrate) and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Aggazzotti *et al.* (2004)	Chlorites = 216.5 μg/L; chlorates = 76.5 μg/L	Entire pregnancy	PTD, SGA	AOR = 1.38; (95% CI: 0.92–2.07)
Danileviciute *et al.* (2012)	<1.0 μg/L	Entire pregnancy	LBW, SGA	Not mentioned
Ileka-Priouzeau *et al.* (2015)	1.80–1.86 μg/L	Third trimester	SGA	OR = 1.1; (95% CI 0.7–1.6)

SGA, small for gestational age; LBW, low birth weight; PTD, premature or preterm delivery; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval.

Table 6 | Exposure to TOX and adverse pregnancy outcomes

Author (year)	Level of exposure	Time of exposure	Birth outcomes	Results (statistical)
Hoffman *et al.* (2008b)	≤173.8 μg/L	Third trimester	SGA	RR = 1.3; (95% CI: 0.7–2.3)
Horton *et al.* (2011)	170.8 to 186.1 μg/L	Entire pregnancy	SGA and PTB	AOR = 1.01; (95% CI: 0.90–1.13) for SGA. AOR = 0.96; (95% CI: 0.87–1.05) for PTB
Savitz *et al.* (2006)	173.7 to 182.3 μg/L	Entire pregnancy	Pregnancy loss	AOR = 1.2; (95% CI: 0.8–1.8)
Maclehose *et al.* (2008)	18.7 to 178.8 μg/L	Entire pregnancy	Pregnancy loss	AOR = 1.5; (95% CI:1.2–1.8)

SGA, small for gestational age; PTB, premature or preterm birth; AOR, adjusted odds ratio; RR, relative risk; CI, confidence interval.

Total organic halide (TOX)

Four studies (Savitz *et al.* 2006; Hoffman *et al.* 2008b; Maclehose *et al.* 2008; Horton *et al.* 2011) reported data on TOX and pregnancy outcomes (Table 6). The levels of exposure to TOX ranged from 18.7 to 186 μg/L. Three studies were conducted during the entire pregnancy and one during the third trimester. The adverse pregnancy outcomes reported were either pregnancy loss, SGA or PTB. A slightly positive association between pregnancy loss with an increased TOX exposure was reported (see Table 6).

DISCUSSION

We used a systematic review of 32 studies to assess the associations between exposure to drinking water DBPs and adverse pregnancy outcomes. We identified various DBPs on adverse pregnancy outcomes of spontaneous abortion (miscarriage), preterm or premature birth, LBW and SGA. Various DBPs found in drinking water include THMs, HAAs, HAs, HANs and TOX.

In this review, 38% of the studies included in the review reported on evidence of association between maternal exposure to drinking water DBPs and adverse pregnancy outcomes. This was consistent with the findings from Grellier *et al.*'s (2010) review, where 40% of studies included were statistically associated with birth outcomes. THMs were associated with SGA and slightly with LBW or pregnancy loss. Higher concentrations of HAA and TOX exposures were slightly associated with SGA and pregnancy loss, respectively. The evidence of any association between other drinking water DBPs (HAs, HANs) and adverse pregnancy outcomes is still inconclusive. The examination of drinking water DBPs and adverse pregnancy outcomes or birth outcomes is still a challenge in most epidemiological studies.

Our reviewed articles demonstrated different exposure assessment methods used, of which 31% of the studies used exposure data obtained from national or local databases housed by water utilities/industries, 34% used water sampling campaigns to measure the DBP concentrations in residential areas, and 22% used both water sampling campaigns and national or local databases from water utilities/industries to assign the exposure to the participants with some instances relying on questionnaires for personal habits. The indirect approach of measuring exposure assessments is still the most commonly applied methodology because it is less costly.

Recently, other methods of measuring exposure in epidemiological studies have been explored. For instance, the use of blood samples to measure the internal exposure was reported by Danileviciute *et al.* (2012) in this review. Blood THMs decrease within minutes to hours after exposure; however, slower partitioning out of adipose tissue and the relatively high (e.g., daily) frequency of exposure events such as showering/bathing are thought to produce steady-state blood concentrations. Costet *et al.* (2011) and Zhou *et al.* (2012) also explored the use of urine samples to measure the TCAA levels. TCAA is one of the major HAAs and is used as a biomarker because it is stable, unmetabolized in urine and is not readily degraded through the collection and storage processes (Smith *et al.* 2013). The eradication half-life of TCAA is between 2 and 6 days, which provides enough information on urinary concentration (Savitz 2012). Both studies showed positive evidence of using a biomarker for exposure assessment.

In this review, included studies were carried out in well-developed countries. The effects of exposure on adverse pregnancy outcomes can vary according to the country in which the study is being conducted, as the regulatory standards differ. Countries in the European Union, the USA, the UK, Australia, China and others (e.g., Canada) have set standards which benchmark against the WHO drinking water quality guidelines of 2011. For instance, the EU set the drinking water quality standard for total THMs to 100 μg/L (WHO 2011). The USA set a regulatory standard for THMs to 80 μg/L and 60 μg/L for five HAAs, 10 μg/L for bromate and 1,000 μg/L for chlorite (USEPA 2011). Canada set a limit of 80 μg/L for THMs with provisional maximum acceptable concentrations of 100 μg/L level of THMs according to the 2003 guidelines for Canadian drinking water quality (Rodriguez *et al.* 2004).

A previous review by Bove *et al.* (2002) found moderate association between THM exposure and birth outcomes (SGA and spontaneous abortions). Their results correlate with the findings from the review conducted by Grellier *et al.* (2010), where SGA was associated with exposure to total THMs; of nine studies included in Grellier *et al.*'s (2010) review, none found statistically significant association of DBPs with preterm birth (Kramer *et al.* 1992; Savitz *et al.* 1995; Gallagher *et al.* 1998; Dodds *et al.* 1999; Wright *et al.* 2003, 2004; Lewis *et al.* 2007; Yang *et al.* 2007; Hoffman *et al.* 2008a). Our results have both similarities and differences compared with the previous reviews. However, none of the previous reviews have used the PRISMA guidelines. In addition, impact based on individual drinking water DBPs was not observed from previous reviews.

This review has demonstrated several strengths. To our knowledge, it is the first review to assess associations of adverse pregnancy outcomes using PRISMA guidelines. The method of reviewing also assesses the maternal exposure to individual drinking water DBPs. Risk assessment of biases in the included studies and analyses of exposure-outcome measurement also gives strength to this review. However, it also has its limitations. We did not retrieve the raw data for studies included in the review. We also limited our search strategies to English language publications so there may be a low possibility of obtaining different results in non-English language articles.

Health determinant factors that contribute to adverse pregnancy outcomes should be considered when interpreting the results. Therefore, our data in most studies included in the review were extracted after adjusting the confounders. Another limitation, as in other reviews, is that the adverse pregnancy outcomes' definitions are not the same across the studies. These limitations are important to bear in mind when considering the conclusions of this review. The purpose of this article was to assess associations or risks, not to disprove or prove causality.

CONCLUSION

Mothers' exposures to common (THMs, HAAs) drinking water DBPs are associated with adverse pregnancy outcomes. In addition, the concentration levels of DBPs studied varied between studies. Most studies are being conducted in developed countries where the set standards are well established and regulated. Evidence of any association between other drinking water DBPs (HAs, HANs) and adverse pregnancy outcomes is still inconclusive. However, the absence of association results does not demonstrate the absence of health effects on pregnancy outcomes. Likewise, a statistical significance does not always suggest clinical importance. Difficulty in measuring exposure, inappropriate time of measurement and interaction between drinking water DBPs may have resulted in absence of association in most studies. The use of urinary TCCA biomarkers as a direct exposure assessment method is deemed to be the future in this field.

Implications for practice

Health impact associated with DBPs is a global issue for public health perspectives. The findings of this review underline the need for action to be taken in the reduction of exposure to DBPs, especially during pregnancy. The association of THMs and pregnancy outcomes indicates that exposure to high THM concentration during pregnancy is harmful to the foetus. The association of other health determinants factors and birth outcomes are important, as indicated in other studies. National, regional and local water industry efforts are needed to reduce the production of DBPs in drinking water. Even though common DBPs are regulated internationally, exposure to them can vary according to individual actions, such as water activity habits (especially during pregnancy) as many pregnant women tend to consume more water than normal.

Implications for research

Future studies need to focus on the underlying biological mechanisms to understand the impact of individual contaminants as well as the interactions between them. Previous studies have underlined the key areas where research is needed to improve the understanding of the association between DBPs in drinking water and adverse pregnancy outcomes (Villanueva *et al.* 2015). These include the use of cohort study design with the use of biomarkers and understanding the biological mechanism of action between DBP exposure and adverse pregnancy outcomes. Studies with large sample sizes are needed to achieve sufficient statistical power (Villanueva *et al.* 2014) and a better understanding of the pathways by which DBPs or contaminants cause birth outcomes (Ferguson *et al.* 2013). Developing countries must also form part of this assessment in this field in order to add to the existing knowledge.

ACKNOWLEDGEMENTS

The authors would like to thank Mrs Groebler, Librarian, for her assistance in searching and retrieving some of the articles. This study was sponsored by the South African National Research Foundation (NRF) Grant (SFH150625121049). The NRF did not play any role in the analyses, writing of the report, interpretation of data or decision to submit the manuscript. The views expressed in this article are those of the authors and do not reflect the views of the NRF. No conflict of interest is declared.

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First received 9 August 2017; accepted in revised form 16 January 2018. Available online 19 February 2018