

## Drinking water – disinfection by-products: summary of epidemiologic evidence

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### 1. Overall summary

This section summarizes epidemiologic evidence cited in the tables below and will be updated as new evidence becomes available. I would appreciate feedback on any errors or omissions. [don.wigle@sympatico.ca](mailto:don.wigle@sympatico.ca)

Health effect	Level of evidence <sup>a</sup>	Comments
Early fetal deaths (spontaneous abortions)	Limited	A population-based case-control study in North Carolina found an association between early fetal deaths and drinking water THM levels when analyzed as a continuous variable but not with THM tertiles; this study found no association with THM dose based on water facility THM levels and self-reported tap water consumption (Savitz et al. 1995). An expert panel review (Mills et al. 1998) observed that the 3 available epidemiologic studies of fetal death provided inadequate evidence for an association between early or late fetal death and drinking water THMs; the panel also noted toxicologic evidence that high exposure to haloacetonitriles caused fetal death in rats. A large California cohort study of pregnant women found associations between early fetal death and tap compared to bottled water consumption and with THM dose based on tap water consumption and THM levels; analysis of specific THMs indicated that bromodichloromethane (BDCM) accounted for the association with THMs (Swan et al. 1998, Waller et al. 1998). The latter study found no association between early fetal death and showering or swimming (Waller et al. 1998). Recent reviews concluded that there is limited and fairly consistent evidence for an association between early fetal deaths and drinking water disinfection by-products (Nieuwenhuijsen et al. 2000, Graves et al. 2001, Bove et al. 2002). The two former reviews noted toxicologic evidence that high maternal DBP exposures caused fetal toxicity including fetal resorptions and reduced fetal weight and survival in experimental animals; DBPs tested and found to cause such toxicity included chloroform, BDCM, haloacetonitriles and haloacetic acids (Nieuwenhuijsen et al. 2000, Graves et al. 2001).
Late fetal deaths (stillbirths)	Limited	A small case-control study nested within a pregnancy cohort in Boston found a borderline association between late fetal deaths and maternal residences supplied by chlorinated compared to chloraminated surface water (Aschengrau et al 1993). An expert panel review (Mills et al. 1998) observed that the 3 available epidemiologic studies of fetal death provided inadequate evidence for an association between early or late fetal death and drinking water THMs; the panel also noted toxicologic evidence that high exposure to haloacetonitriles caused fetal death in rats. A large retrospective cohort study in Nova Scotia (Canada) showed that late fetal deaths were associated with drinking water THM levels; this relationship was stronger among the subset of late fetal deaths caused by asphyxia (mainly abruptio placenta) (Dodds et al. 1999, King et al. 2000). The latter study found that the association between late fetal deaths and

		<p>THMs was mainly related to BDCM (chloroform and BDCM comprised most of the total THM content) (King et al. 2000). Recent reviews concluded that there is limited and fairly consistent evidence for an association between late fetal deaths and drinking water disinfection by-products (Nieuwenhuijsen et al. 2000, Graves et al. 2001, Bove et al. 2002). The two former reviews noted toxicologic evidence that high maternal DBP exposures caused fetal toxicity including fetal resorptions and reduced fetal weight and survival in experimental animals; DBPs tested and found to cause such toxicity included chloroform, BDCM, haloacetonitriles and haloacetic acids (Nieuwenhuijsen et al. 2000, Graves et al. 2001). A recent case-control study showed that late fetal deaths in Nova Scotia and Ontario (Canada) were associated with drinking water chloroform, BDCM and total THM levels and with estimated total THM intake from tap water at home or work and from showering and bathing (Dodds et al. 2004). A retrospective cohort study in England found borderline increased risks of late fetal deaths among women living in regions with THM levels above 30 µg/dL during their third trimester (Toledano et al 2005).</p>
<p>Low birth weight (any gestation length)</p>	<p>Inadequate</p>	<p>Population-based case-control studies in Iowa and North Carolina found no association between low birth weight and drinking water chloroform or BDCM levels (Kramer et al. 1992) or THM levels (Savitz et al. 1995). A small retrospective cohort study of two communities in Italy found a non-significant association between low birth weight and chlorine-dioxide-treated surface water versus unchlorinated ground water (Kanitz et al. 1996). An expert panel review (Mills et al. 1998) observed that the 4 available epidemiologic studies of low birth weight provided limited evidence for an association with drinking water THMs. A retrospective cohort study in Denver found an association between low birth weight and THMs (Gallagher et al. 1998). A large retrospective cohort study in Nova Scotia (Canada) found no association between low birth weight and THMs (Dodds et al. 1999). A retrospective cohort study in Sweden found that low birth weight was associated with maternal residence in communities that used sodium hypochlorite compared to women in communities using unchlorinated water; there was no association with use of chlorine dioxide (Kallen and Robert 2000). A very large retrospective cohort study in Norway found no association between low birth weight and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to unchlorinated water with low levels of DBP precursors (Jaakkola et al. 2001). Two recent reviews concluded that there is inadequate evidence for an association between low birth weight at any gestation length and THMs (Graves et al. 2001, Bove et al. 2002). Two reviews noted toxicologic evidence that high-dose gestational exposure to several individual DBPs can cause fetal growth retardation in experimental animals (Nieuwenhuijsen et al. 2000, Graves et al. 2001). A retrospective cohort study in Taiwan found that preterm birth but not low birth weight was associated with maternal residence in municipalities served by chlorinated water (Yang 2004). A retrospective cohort study in England found borderline increased risks of low birth weight among women living in regions with THM levels above 30 µg/dL during their third trimester (Toledano et al 2005).</p>

<p>Small for gestational age (or variants including term low birth weight and intrauterine growth retardation)</p>	<p>Limited</p>	<p>Population-based case-control studies in Iowa and New Jersey found dose-response relationships between intrauterine growth retardation (IUGR) and drinking water chloroform and BDCM levels (Kramer et al. 1992) or between small for gestational age (SGA) and average gestational THM levels (Bove et al. 1995). The latter study also found an inverse dose-response relationship between birth weight at term (as a continuous variable) and average gestational THM levels (Bove et al. 1995). An ecologic study of 189 communities in Iowa found a borderline association between IUGR and drinking water chloroform analyzed as a continuous variable (Munger et al. 1997). An expert panel review (Mills et al. 1998) observed that the 2 available epidemiologic studies of SGA both showed an association with drinking water THMs. A retrospective cohort study in Denver found a relatively strong association between term low birth weight and THMs (Gallagher et al. 1998). However, a much larger retrospective cohort study in Nova Scotia (Canada) found only a weak association of borderline statistical significance between SGA and THMs (Dodds et al. 1999). A retrospective cohort study in Sweden found that a borderline association between SGA and maternal residence in communities that used sodium hypochlorite compared to women in communities using unchlorinated water; there was no association with use of chlorine dioxide (Kallen and Robert 2000). A retrospective cohort study in Taiwan found that term low birth weight was not associated with maternal residence in communities that used chlorinated water compared to women in communities using unchlorinated water (Yang et al. 2000). A very large retrospective cohort study in Norway found no association between SGA and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to unchlorinated water with low levels of DBP precursors (Jaakkola et al. 2001). Two recent reviews concluded that there is limited evidence for an association between IUGR or SGA and THMs (Graves et al. 2001, Bove et al. 2002). The ALSPAC birth cohort study found no association between birth weight adjusted for gestation length and prenatal maternal swimming intensity before gestation week 18-20 (Nieuwenhuijsen et al. 2002). A retrospective cohort study in Massachusetts found associations between SGA and average drinking water supply levels of THMs, MX and mutagenic activity but not HAAs during the 3<sup>rd</sup> trimester in the town of maternal residence (Wright et al 2004).</p>
<p>Preterm birth</p>	<p>Inadequate</p>	<p>Population-based case-control studies in Iowa and North Carolina found no association between preterm birth and drinking water chloroform or BDCM levels (Kramer et al. 1992) or THM levels (Savitz et al. 1995). A small retrospective cohort study of two communities in Italy found a non-significant association between preterm birth and chlorine-dioxide-treated surface water versus unchlorinated ground water (Kanitz et al. 1996). An expert panel review (Mills et al. 1998) observed that the 4 available epidemiologic studies of preterm birth provided inadequate evidence for an association with drinking water THMs. A retrospective cohort study in Denver and a much larger one in Nova Scotia (Canada) found no associations between preterm birth and THMs (Gallagher et al. 1998, Dodds et al. 1999). A retrospective cohort study in Sweden found that preterm birth was associated with maternal residence in communities that used sodium hypochlorite compared to women in communities using unchlorinated</p>

		<p>water; there was no association with use of chlorine dioxide (Kallen and Robert 2000). A retrospective cohort study in Taiwan found that preterm birth was associated with maternal residence in communities that used chlorinated water compared to women in communities using unchlorinated water (Yang et al. 2000). A very large retrospective cohort study in Norway found no association between preterm birth and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to unchlorinated water with low levels of DBP precursors (Jaakkola et al. 2001). Two recent reviews concluded that there is inadequate evidence for an association between preterm birth and THMs (Graves et al. 2001, Bove et al. 2002). A retrospective cohort study in Massachusetts found that preterm birth was <i>inversely</i> associated with THM levels and was not associated with MX, mutagenic activity or HAA levels during the 3<sup>rd</sup> trimester in the town of maternal residence (Wright et al 2004). A retrospective cohort study in Taiwan found that preterm birth was associated with maternal residence in municipalities served by chlorinated water (Yang 2004).</p>
Total birth defects	(Inadequate)	<p>A large case-control study in Boston found a non-significant association between total birth defects and maternal residence in communities using chlorinated surface versus chloraminated surface water (Aschengrau et al. 1993). A retrospective cohort study in Norway found no association between total birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A meta-analysis of 3 epidemiologic studies found a modest association between any birth defect and THM exposure indices (Hwang and Jaakkola 2003).</p>
CNS birth defects	Limited	<p>A retrospective cohort study found dose-response relationships between NTDs or total CNS birth defects and average 1<sup>st</sup> trimester drinking water THM levels (Bove et al. 1995). A large population-based case-control study in New York State found no association between CNS birth defects and drinking water THM levels exceeding 100 µg/L (Marshall et al. 1997). A retrospective cohort study in Nova Scotia (Canada) found no association between NTDs and periconceptual drinking water THM levels (Dodds et al. 1999). A retrospective cohort study in Norway found no association between NTDs and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A population-based case-control study in New Jersey found borderline associations between NTDs and indices of early postconceptual DBP exposure including surface versus ground water supply and THM or residual chlorine levels in water samples from the water treatment facility or residential taps (the latter associations were stronger when limited to subjects with known residences at conception); NTDs were not associated with tap water haloacetic acid or haloacetonitrile levels (Klotz and Pyrch 1999). Importantly, the latter study found that the association between NTDs and drinking water THM levels was limited to the subgroup of women who did not use vitamin supplements before conception. A retrospective cohort study in Sweden found no association between spina bifida and maternal residence in communities using</p>

		<p>water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A review of toxicologic and epidemiologic studies concluded that THMs <i>per se</i> do not appear to cause birth defects in experimental animals but halogenated acetic acids cause neural tube, craniofacial and cardiac defects; the potential teratogenicity of many other DBPs has not been evaluated (Nieuwenhuijsen et al. 2000). Another review concluded that there is inadequate toxicologic evidence that DBPs cause CNS birth defects in experimental animals and limited/inconsistent epidemiologic evidence for an association between such defects and DBPs in humans (Graves et al. 2001). A retrospective cohort study in Nova Scotia (Canada) found that NTDs were associated with periconceptual community drinking water BDCM levels but not with chloroform levels (Dodds and King 2001). A review of the epidemiologic literature by Bove et al. (2002) concluded that there was limited evidence for an association between NTDs and THM levels. A large Norwegian retrospective cohort study found no association between NTDs and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors (Hwang et al. 2002). A report of two population-based case-control studies of NTDs in California showed no association with periconceptual drinking water THM levels in one study and a borderline association, without a monotonic dose-response relationship, in the other study; neither study found an association with drinking water BDCM levels (Shaw et al. 2003). A meta-analysis of 4 epidemiologic studies found a modest association between NTDs and THM exposure indices (Hwang and Jaakkola 2003).</p>
Orofacial birth defects	(Inadequate)	<p>A retrospective cohort study found no association between oral clefts and 1<sup>st</sup> trimester drinking water THM levels (Bove et al. 1995). A retrospective cohort study in Nova Scotia (Canada) found no association between orofacial clefts and average 1<sup>st</sup> trimester drinking water THM levels (Dodds et al. 1999). A retrospective cohort study in Norway found no association between oral cleft birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A retrospective cohort study in Sweden found no association between orofacial clefts and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A review of toxicologic and epidemiologic studies concluded that THMs <i>per se</i> do not appear to cause birth defects in experimental animals but halogenated acetic acids cause neural tube, craniofacial and cardiac defects; the potential teratogenicity of many other DBPs has not been evaluated (Nieuwenhuijsen et al. 2000). Another review noted that chloroform caused cleft palate defects in mice and inadequate epidemiologic evidence for an association between such defects and DBPs in humans (Graves et al. 2001). A retrospective cohort study in Nova Scotia (Canada) found that a modest non-significant association between orofacial cleft defects and periconceptual community drinking water chloroform levels above 100 µg/L but no dose-response relationship (Dodds and King 2001). A review of</p>

		<p>the epidemiologic literature by Bove et al. (2002) concluded that there was limited evidence for an association between oral cleft defects and THM levels. A large Norwegian retrospective cohort study found modest non-significant associations between isolated cleft lip and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors; there was not a monotonic dose-response relationship (Hwang et al. 2002). A case-control study in California found an association between isolated cleft lip/palate and periconceptual drinking water THM levels but no dose-response relationship (Shaw et al. 2003). A meta-analysis of 3 epidemiologic studies found no association between oral cleft defects and THM exposure indices (Hwang and Jaakkola 2003).</p>
Cardiac birth defects	Inadequate	<p>A retrospective cohort study found no association between cardiac birth defects and 1<sup>st</sup> trimester drinking water THM levels (Bove et al. 1995). An expert panel review (Mills et al. 1998) noted toxicologic evidence that dichloroacetic acid and trichloroacetonitrile caused ventricular septal and other soft tissue birth defects in experimental animals. Retrospective cohort studies in New Jersey Bove et al. 1995) and Canada (Dodds et al. 1999) found no association between major cardiac birth defects and 1<sup>st</sup> trimester drinking water THM levels. A retrospective cohort study in Norway found no association between major cardiac birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A retrospective cohort study in Sweden found no association between cardiac birth defects and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A review of toxicologic and epidemiologic studies concluded that THMs <i>per se</i> do not appear to cause birth defects in experimental animals but halogenated acetic acids cause neural tube, craniofacial and cardiac defects; the potential teratogenicity of many other DBPs has not been evaluated (Nieuwenhuijsen et al. 2000). A review noted toxicologic evidence that haloacetic acids and haloacetonitriles caused cardiac defects in experimental animals and inadequate epidemiologic evidence for an association between such defects and DBPs in humans (Graves et al. 2001). A retrospective cohort study in Nova Scotia (Canada) found that no association between cardiovascular birth defects and periconceptual community drinking water BDCM or chloroform levels (Dodds and King 2001). A Swedish retrospective cohort study, however, did find a modest association between major cardiac birth defects and community drinking water THM levels and use of chlorine dioxide for disinfection (Dodds and King 2001). A review of the epidemiologic literature by Bove et al. (2002) concluded that there was inadequate evidence for an association between cardiac birth defects and THM levels. A large Norwegian retrospective cohort study found an association between ventricular septal cardiac defects and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors (Hwang et al. 2002). A case-control study in California found an association</p>

		between conotruncal cardiac defects and periconceptual drinking water THM levels but no dose-response relationship (Shaw et al. 2003). A meta-analysis of 3 epidemiologic studies found no association between major cardiac birth defects and THM exposure indices (Hwang and Jaakkola 2003).
Respiratory birth defects	Inadequate	A large case-control study in Boston found a moderately strong association between respiratory birth defects and maternal residence in communities using chlorinated surface versus chloraminated surface water (Aschengrau et al. 1993). A retrospective cohort study in Norway found no association between respiratory tract birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A review concluded that there was inadequate epidemiologic evidence for an association between such respiratory birth defects and DBPs in humans (Graves et al. 2001). A large Norwegian retrospective cohort study found an association between respiratory birth defects and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors (Hwang et al. 2002). A meta-analysis of 2 epidemiologic studies found a modest non-significant association between respiratory birth defects and THM exposure indices (Hwang and Jaakkola 2003).
Genitourinary tract birth defects	Limited	A large case-control study in Boston found a moderately strong association between urinary tract birth defects and maternal residence in communities using chlorinated surface versus chloraminated surface water (Aschengrau et al. 1993). A retrospective cohort study in Norway found an association between urinary tract birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A retrospective cohort study in Sweden found no association between hypospadias or kidney malformations and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A review noted toxicologic evidence that haloacetonitriles caused urogenital defects in experimental animals and limited epidemiologic evidence for an association between such defects and DBPs in humans (Graves et al. 2001). A review of the epidemiologic literature by Bove et al. (2002) concluded that there was limited evidence for an association between urinary tract birth defects and THM levels. A large Norwegian retrospective cohort study found a modest, non-significant association between obstructive urinary tract birth defects and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors (Hwang et al. 2002).
Musculoskeletal birth defects	(Inadequate)	A large population-based case-control study in New York State found no association between musculoskeletal birth defects and drinking water THM levels exceeding 100 µg/L (Marshall et al. 1997).

Chromosome abnormalities	(Inadequate)	A retrospective cohort study in Sweden found no association between chromosome abnormalities and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A retrospective cohort study in Nova Scotia (Canada) found that an association between chromosomal abnormalities and periconceptual community drinking water chloroform levels but accompanied by a non-monotonic dose-response relationship; there was no association with drinking water BDCM levels (Dodds and King 2001).
Childhood cancer	(Inadequate)	A Swedish retrospective cohort study found a borderline association between childhood cancer and maternal prenatal residence in communities using chlorine dioxide but not those using sodium hypochlorite for disinfection, compared to those living in communities using unchlorinated water (Kallen and Robert 2000). A large population-based case-control study of acute lymphatic leukemia (ALL) in Quebec found no association with prenatal or childhood drinking water THM exposure indices including time-weighted average or cumulative exposure (Infante-Rivard et al. 2001). The latter study did find a non-significant association between ALL and cumulative childhood but not prenatal drinking water chloroform exposure. A subsequent case-only analysis of the Quebec study showed borderline or significant but imprecise associations between the subsets of GSTT1-null and CYP2E1*5 ALL cases and prenatal or postnatal THM exposure indices (Infante-Rivard et al. 2002).

<sup>a</sup> Sufficient evidence = based on peer-reviewed reports of expert groups or authoritative reviews that concluded that a causal relationship existed; limited evidence = relationships for which several epidemiologic studies, including at least one case-control or cohort study, showed fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders; inadequate evidence = relationships for which epidemiologic studies were limited in number and quality (e.g., small studies, ecologic studies, limited control of potential confounders), had inconsistent results, or showed little or no evidence of exposure-risk relationships. Levels in parentheses are the author's interpretation of available evidence; other levels are based on expert group reviews.

## 2. Fetal deaths

Reference, location	Design	Exposure	Results	Association <sup>1</sup>	DR <sup>2</sup>	Covariates
(Aschengrau et al. 1993), Boston	Case-control study nested within cohort of 14,130 women enrolled at delivery with gestation at least 20 wk, 1977-1980; included 1,039 birth defects, 77 stillbirths, 1,177 controls	Assessed drinking water quality in 155 communities where women lived during pregnancy	Borderline association between stillbirths and chlorinated surface water (odds ratio, chlorinated vs chloraminated surface water)	2.6 (0.9-7.5)		Maternal race, age, hospital insurance coverage, previous infant with birth defect, alcohol, water source
(Savitz et al. 1995), North Carolina	Population-based case-control study, 261 spontaneous abortions, 237 matched controls, 1988-1991	Self-reported exposure information including drinking water source and daily consumption; THM data for relevant water treatment facility (5 facilities served the population at risk) during quarter closest to gestation wk 4	Spontaneous abortions not associated with THM tertiles (odds ratios for 60-81 and >81 vs <60 µg/L)[note high THM level of referent category] but were associated with THM analyzed as a continuous variable (odds ratio per THM increment of 1 µg/L)	tertiles 2&3 1.0 (0.5-2.0) 1.2 (0.6-2.4)	+	Controls were term normal weight infants matched on DOB, race, hospital; adjusted as necessary for maternal age, race, education, marital status, poverty level, smoking, alcohol, employment, nausea
			Spontaneous abortions not associated with THM dose tertiles (odds ratios for 140-275 and >275 vs <140)	tertiles 2&3 1.0 (0.6-1.9) 0.6 (0.3-1.2)		

<sup>1</sup> Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

<sup>2</sup> 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

			$\mu\text{g.glasses.day}^{-1}$ ) or with THM dose analyzed as a continuous variable (odds ratio per 250 unit change)	continuous 1.0 (0.7-1.2)	
(Mills et al. 1998), Canada	Expert panel review of toxicologic and epidemiologic evidence of health risks of DBPs; included epidemiologic studies of adverse pregnancy outcomes published during 1992-1996	Fetal deaths	<i>Animals</i> – haloacetonitriles caused fetal death in rats <i>Humans</i> – the only study of early fetal deaths (spontaneous abortions) found no association with THM levels >80 $\mu\text{g/L}$ ; one of two studies of late fetal deaths (stillbirths) found a borderline association with chlorinated surface water and the other found no association with THM levels >80 $\mu\text{g/L}$		
(Swan et al. 1998), California	Cohort study, 5,342 women interviewed during 1 <sup>st</sup> trimester at first prenatal visit (1990-1991), 3 regions served by Kaiser Permanente facilities; identified 499 spontaneous abortions (gestation wk <20) that occurred post-interview	Self-reported information including tap and bottled water ingestion since last menstrual period, use of water filters, showering;	Spontaneous abortions inversely associated with 1 <sup>st</sup> trimester bottled water ingestion (odds ratios for $\geq 6$ vs 0 glasses/day); stronger association for $\geq 6$ bottled + 0 tap water vs 0 bottled water + $\geq 6$ tap water glasses/day	0.6 (0.4-1.0) 0.2 (0.1-0.5)	Maternal age, race, weight, gestational age at interview, showering, prior spontaneous abortion
			Spontaneous abortions associated with 1 <sup>st</sup> trimester tap water consumption (odds ratio, $\geq 6$ tap + 0 bottled vs 0 tap + $\geq 6$ bottled glasses/day)	3.5 (1.4-8.6)	As above
(Waller et al.	Cohort study 5144	Obtained quarterly THM data for	Spontaneous abortions	2.0 (1.1-3.6)	Gestational age at

1998), California	women from the above cohort (Swan et al. 1998)	78 of the 85 water treatment facilities serving the residences of cohort members; subjects lived in 3 regions included I – mixture of surface and ground water, II – surface water only, III – ground water only; assessed THM level during 1 <sup>st</sup> trimester and used self-reported data on tap water consumption, water filter use, showering	associated with tap water THM intake (odds ratio for $\geq 5$ glasses/day and THM $\geq 75$ $\mu\text{g/L}$ vs $< 5$ glasses/day and THM $< 75$ $\mu\text{g/L}$ )		interview, maternal age, smoking, previous pregnancy loss, race, employment during pregnancy
			Spontaneous abortions associated with BDCM but not other specific THMs (odds ratio for $\geq 5$ glasses/day and BDCM $\geq 18$ $\mu\text{g/L}$ vs $< 5$ glasses/day and BDCM $< 18$ $\mu\text{g/L}$ )	3.0 (1.4-6.6)	As above
			Spontaneous abortion was not associated with daily time spent showering in a model that included ingested THMs (odds ratio, $\geq 15$ vs $< 15$ min/day)	1.0 (0.8-1.3)	As above
			Spontaneous abortions not associated with swimming (rates for women who swam 2+ times/wk vs whole group)	7.7 vs 9.7%	
(Dodds et al. 1999), Nova Scotia, Canada	Retrospective cohort study, 50,755 singleton births in province during 1988-1995 (all births with birth weights $\geq 500$ g); restricted to women	Used data on quarterly THM levels in municipalities with chlorinated surface water sources, 1987-1995; used regression analysis to estimate THM levels by year, month and water	Stillbirths associated with THM levels during pregnancy (odds ratios for 50-75, 75-99 and $\geq 100$ vs $< 50$ $\mu\text{g/L}$ )	1.3 (0.9-1.8) 1.3 (0.8-2.0) 1.7 (1.1-2.5)	+

	who resided at the time of their delivery in municipalities with $\geq 90\%$ of households served by a public supply using a surface water source; 197 stillbirths	treatment facility; avg chloroform and total THM levels were 64 and 71 $\mu\text{g/L}$				
(King et al. 2000), Nova Scotia, Canada	Retrospective cohort study, 49,756 singleton births in province during 1988-1995 (all births with birth weights $\geq 500$ g); restricted to women who resided at the time of their delivery in municipalities with $\geq 90\%$ of households served by a public supply using a surface water source; 214 stillbirths	THM levels in municipalities with chlorinated surface water sources; avg chloroform and total THM levels were 64 and 71 $\mu\text{g/L}$	Stillbirths associated with total THM levels (odds ratios for 50-74, 75-99 and $\geq 100$ vs $< 50$ $\mu\text{g/L}$ )	1.3 (0.9-1.9) 1.3 (0.8-2.0) 1.7 (1.1-2.5)	+	Maternal age, smoking
			Stillbirths associated with BDCM levels (odds ratios for 5-9, 10-19 and $\geq 20$ vs $< 5$ $\mu\text{g/L}$ )	1.1 (0.8-3.2) 1.4 (0.9-2.3) 2.0 (1.2-3.5)	+	As above
			Stillbirths from asphyxia (mainly abruptio placenta) were associated with total THM levels (odds ratios for 50-74, 75-99 and $\geq 100$ vs $< 50$ $\mu\text{g/L}$ )	2.7 (1.2-6.1) 2.5 (1.0-6.5) 4.6 (1.9-11)	+	As above
(Nieuwenhuijsen et al. 2000), UK	Review of toxicologic and epidemiologic		<i>Animals</i> – at high doses, several DBPs cause fetal			

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	literature on adverse pregnancy outcomes and DBPs; included 10 epidemiologic studies published during 1993-1999		toxicity including resorptions and reduced weight and survival; there has been little toxicologic evaluation of effects of many other DBPs on fetal growth	
			<i>Humans</i> – limited evidence for associations between spontaneous abortions and stillbirths and DBPs	
(Graves et al. 2001), USA	Review of epidemiologic (1989-2000) and toxicologic (1974-2001) literature on developmental and reproductive effects of disinfection by-products	Early fetal deaths (spontaneous abortions)	<i>Animals</i> – fetal resorption observed in rodents highly exposed to 3 THMs, 2 haloacetic acids and 2 haloacetonitriles; decreased litter size observed at high doses of 2 THMs and 3 chlorophenols; other embryotoxic effects observed at high doses of chloroform, BDCM and 3 haloacetonitriles <i>Humans</i> – all 3 studies found associations with DBP exposure indices; 1 of these studies found an association with surface vs ground but not with chlorinated vs unchlorinated surface water, another found an irregular dose-response relationship and the third was a cohort study that found a dose-response relationship	Limited

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		Late fetal deaths (stillbirths)	<i>Animals</i> – observed in rodents highly exposed to 3 THMs or chloral hydrate <i>Humans</i> – all 3 studies found borderline or significant associations with DBPs; 1 study found a moderately strong association between stillbirths from asphyxia and THMs	Limited	
(Bove et al. 2002), USA	Review of literature on adverse pregnancy outcomes and drinking water contaminants; included 19 reports of 16 studies published during 1989-2001; assessed risk of early (3 studies) and late fetal deaths (3 studies)	Assessed pregnancy outcomes in relation to tap water THM levels and water source/chlorination; most studies did not assess maternal tap water consumption; only one study used distribution system parameters to assess within-municipality THM variability	Early fetal deaths – the best study (a cohort study in California by Waller et al. 1998) found an association between spontaneous abortion and THM levels, especially for BDCM; two other studies (Savitz et al. 1995, Aschengrau et al. 1989) provided little evidence of an association with THM levels or chlorinated vs chloraminated surface water  Late fetal deaths – 2 of the 3 studies found associations with THMs or chlorinated vs chloraminated surface water		Virtually all studies found little or no effect of adjustment for potential confounders
(Dodds et al. 2004), Nova Scotia and eastern Ontario, Canada	Population-based case-control study, 112 late fetal deaths, 398 live birth controls, 1999-2001; assessed underlying cause of	Mother-reported tap and bottled water consumption, use of water filters, showering and bathing duration; sampled tap water 1 year after 1 <sup>st</sup> trimester (to control for seasonal THM variation);	Late fetal deaths associated with tap water total THM level (odds ratios for 1-49, 50-79 and $\geq 80$ vs 0 $\mu\text{g/L}$ ); similar associations with drinking water chloroform	1.6 (0.9-2.8) 1.3 (0.7-2.4) 2.2 (1.1-4.4)	+ Age, province, household income

stillbirths (birth defects, immaturity, intrauterine asphyxia, infections)	THM level for private wells assumed to be zero; reduced ingested tap water THM by 50% if activated charcoal filters used; estimated total exposure from water consumption at home and work, showering and bathing	and BDCM levels (data not shown here)		
		Late fetal deaths associated with total THM exposure quintile (odds ratios for increasing quintiles vs nil exposure); similar associations with total chloroform and BDCM exposure quintiles (data not shown here)	1.5 (0.8-3.2) 1.3 (0.6-2.8) 1.9 (0.9-4.0) 1.6 (0.8-3.4) 2.4 (1.2-4.6)	+ As above
		Late fetal deaths associated with tap water consumption and tap water THM level (odds ratio for 5+ glasses/day of cold tap water with 50+ µg/L vs ≤1 glass/day with tap water containing 0 µg/L)	4.0 (1.4-11)	As above
		Late fetal deaths associated with showering and tap water THM level (odds ratio for showering over 13 min/day with tap water containing 50+ µg/L vs showering <10 min/day with tap water containing 0 µg/L)	2.6 (1.1-5.8)	As above
		Similar associations between cause-specific fetal deaths and THM levels (odds ratios	asphyxia-deaths 2.3 (0.5-9.9)	As above

			for THMs $\geq 80$ vs 0 $\mu\text{g/L}$ (only 3 and 7 highly exposed case mothers in the two subgroups shown)	unexplained deaths 1.7 (0.7-4.5)	
(Toledano et al. 2005), England	Retrospective cohort study, births and stillbirths in north and midlands of England, 1992-1998	Drinking water THM levels from household tap water surveys conducted on average 5-11 times per year in study regions; categorized avg drinking water THM levels during 3 <sup>rd</sup> trimester: <30, 30-59 and $\geq 60$ $\mu\text{g/dL}$	Borderline increased risks of late fetal deaths among women living in regions with higher tap water THM levels during the 3 <sup>rd</sup> trimester; odds ratios, 30-59 and $\geq 60$ vs <30 $\mu\text{g/dL}$	1.06 (0.99-1.15) 1.11 (1.00-1.23)	Maternal age, SES

### Fetal deaths: summary

#### *Early fetal deaths (spontaneous abortions)*

A population-based case-control study in North Carolina found an association between early fetal deaths and drinking water THM levels when analyzed as a continuous variable but not with THM tertiles; this study found no association with THM dose based on water facility THM levels and self-reported tap water consumption (Savitz et al. 1995). An expert panel review (Mills et al. 1998) observed that the 3 available epidemiologic studies of fetal death provided inadequate evidence for an association between early or late fetal death and drinking water THMs; the panel also noted toxicologic evidence that high exposure to haloacetonitriles caused fetal death in rats. A large California cohort study of pregnant women found associations between early fetal death and tap compared to bottled water consumption and with THM dose based on tap water consumption and THM levels; analysis of specific THMs indicated that bromodichloromethane (BDCM) accounted for the association with THMs (Swan et al. 1998, Waller et al. 1998). The latter study found no association between early fetal death and showering or swimming (Waller et al. 1998). Recent reviews concluded that there is limited and fairly consistent evidence for an association between early fetal deaths and drinking water disinfection by-products (Nieuwenhuijsen et al. 2000, Graves et al. 2001, Bove et al. 2002). The two former reviews noted toxicologic evidence that high maternal DBP exposures caused fetal toxicity including fetal resorptions and reduced fetal weight and survival in experimental animals; DBPs tested and found to cause such toxicity included chloroform, BDCM, haloacetonitriles and haloacetic acids (Nieuwenhuijsen et al. 2000, Graves et al. 2001).

#### *Late fetal deaths (stillbirths)*

A small case-control study nested within a pregnancy cohort in Boston found a borderline association between late fetal deaths and maternal residences supplied by chlorinated compared to chloraminated surface water (Aschengrau et al. 1993). An expert panel review (Mills et al. 1998) observed that the 3 available epidemiologic studies of fetal death provided inadequate evidence for an association between early or late fetal death and drinking water THMs; the panel also noted toxicologic evidence that high exposure to haloacetonitriles caused fetal death in rats. A large retrospective cohort study in Nova Scotia (Canada) showed that late fetal deaths were associated with drinking water THM levels; this relationship was stronger among the subset of late fetal deaths caused by asphyxia (mainly abruptio placentae) (Dodds et al. 1999, King et al. 2000). The latter study found that the association between late fetal deaths and THMs was mainly related to BDCM (chloroform and BDCM comprised most of the total THM content) (King et al. 2000). Recent reviews concluded that there is limited and fairly consistent evidence for an association between late fetal deaths and drinking water disinfection by-products (Nieuwenhuijsen et al. 2000, Graves et al.

2001, Bove et al. 2002). The two former reviews noted toxicologic evidence that high maternal DBP exposures caused fetal toxicity including fetal resorptions and reduced fetal weight and survival in experimental animals; DBPs tested and found to cause such toxicity included chloroform, BDCM, haloacetonitriles and haloacetic acids (Nieuwenhuijsen et al. 2000, Graves et al. 2001). A recent case-control study showed that late fetal deaths in Nova Scotia and Ontario (Canada) were associated with drinking water chloroform, BDCM and total THM levels and with estimated total THM intake from tap water at home or work and from showering and bathing (Dodds et al. 2004). A retrospective cohort study in England found borderline increased risks of late fetal deaths among women living in regions with THM levels above 30 µg/dL during their third trimester (Toledano et al 2005).

### 3. Low birth weight, intrauterine growth retardation (IUGR) and preterm birth

Reference, location	Design	Exposure	Results	Association <sup>3</sup>	Covariates
(Kramer et al. 1992), Iowa	Population-based case-control study, 159 cases low birth weight (<2500 g) and 795 controls; 342 preterm infants (<37 wk) and 1,710 controls; 187 IUGR (<5 <sup>th</sup> percentile weight for gestation length) cases and 935 controls; based on Iowa birth certificates for 1989-1990	Residents of 151 towns dependent on a single source of drinking water; assessed water source and THM levels during a 1987 municipal water survey; only 13% of towns had chloroform levels $\geq 10 \mu\text{g/L}$	Low birth weight (any gestation length) not associated with drinking water chloroform (odds ratios for 1-9 and $\geq 10 \mu\text{g/L}$ vs non-detectable levels)	1.1 (0.7-1.6) 1.3 (0.8-2.2)	Marital status, maternal age, smoking, parity, education, prenatal care
			Low birth weight (any gestation length) not associated with drinking water BDCM (odds ratios for 1-9 and $\geq 10 \mu\text{g/L}$ vs non-detectable levels)	1.0 (0.5-1.9) 1.0 (0.7-1.9)	As above
			IUGR associated with drinking water chloroform (odds ratios for 1-9 and $\geq 10 \mu\text{g/L}$ vs non-detectable levels); association seen for both shallow and deep wells, tending to rule out confounding from unmeasured pesticides	1.3 (0.9-1.8) 1.8 (1.1-2.9)	As above
			IUGR associated with	1.2 (0.8-1.7)	As above

<sup>3</sup> Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

			drinking water BDCM (odds ratios for 1-9 and $\geq 10 \mu\text{g/L}$ vs non-detectable levels)	1.7 (0.9-2.9)	
			Preterm birth not associated with drinking water chloroform (odds ratios for chloroform 1-9 and $\geq 10 \mu\text{g/L}$ vs non-detectable levels)	1.1 (0.8-1.4) 1.1 (0.7-1.6)	As above
			Preterm birth not associated with drinking water BDCM (odds ratios for 1-9 and $\geq 10 \mu\text{g/L}$ vs non-detectable levels)	1.1 (0.9-1.5) 1.0 (0.6-1.5)	As above
(Savitz et al. 1995), North Carolina	Population-based case-control study, 412 preterm infants (<37 wk), 296 low birth weight infants (<2500 g), 543 matched controls, 1988-1991	Self-reported exposure information including drinking water source and daily consumption; THM data for relevant water treatment facility (5 facilities served the population at risk) during quarter closest to gestation wk 28	Preterm birth not associated with THM tertiles (odds ratios for 63.4-82.7 and >82.7 vs <63.4 $\mu\text{g/L}$ )[note high THM level of referent category] or with THM analyzed as a continuous variable (odds ratio per THM increment of 1 $\mu\text{g/L}$ )	tertiles 2&3 1.2 (0.8-1.8) 0.9 (0.6-1.5)  continuous 0.8 (0.6-1.2)	Controls were term normal weight infants matched on DOB, race, hospital; adjusted as necessary for maternal age, race, hospital, education, marital status, poverty level, smoking, alcohol, employment
			Preterm birth not associated with THM dose tertiles (odds ratios for 170-330.8 and >330.8 vs <170 $\mu\text{g.glasses.day}^{-1}$ ) or THM dose analyzed as a continuous variable	tertiles 2&3 1.2 (0.8-1.7) 0.9 (0.6-1.3)  continuous 0.9 (0.8-1.1)	As above

			(odds ratio per 250 unit change)		
			Low birth weight (any gestation length) not associated with THM tertiles (odds ratios for 63.4-82.7 and >82.7 vs <63.4 µg/L)[note high THM level of referent category] or with THM analyzed as a continuous variable (odds ratio per THM increment of 1 µg/L)	tertiles 2&3 1.5 (1.0-2.3) 1.3 (0.8-2.1)  continuous 0.9 (0.6-1.4)	As above
			Low birth weight (any gestation length) not associated with THM dose tertiles (odds ratios for 170-330.8 and >330.8 vs <170 µg.glasses.day <sup>-1</sup> ) or THM dose analyzed as a continuous variable (odds ratio per 250 unit change)	tertiles 2&3 1.0 (0.6-1.5) 0.8 (0.5-1.3)  continuous 1.0 (0.8-1.2)	As above
(Bove et al. 1995), New Jersey	Retrospective cohort study, 80,938 live births, 594 fetal deaths among residents of 75 towns, 1985-1988; live births included 1853 term low birth weight, 4082 small for gestational age and 7167 preterm infants	75 towns served by 49 public water systems; used data on quarterly THM to estimate monthly levels; assessed avg levels during 1 <sup>st</sup> trimester for birth defect and fetal death outcomes and throughout pregnancy for fetal growth outcomes	Association between small for gestational age (<5 <sup>th</sup> percentile weight for race, sex, gestational age) and avg THM during pregnancy (odds ratios for 21-40, 41-60, 61-80, 81-100 and >100 vs ≤20 µg/L; 99% confidence intervals)	1.0 (0.8-1.2) 1.3 (1.2-1.5) 1.1 (1.0-1.3) 1.2 (1.0-1.5) 1.5 (1.0-2.1)  p-trend<0.05	Maternal age, race, education, primiparity, previous pregnancy loss, infant sex, prenatal care

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			Term birth weight inversely associated with avg THM level during pregnancy when analyzed as a continuous variable ( $\beta$ coefficient $\pm$ SE (g), referent level = 3438 g)	-0.65 $\pm$ 0.07	As above
(Kanitz et al. 1996), Italy	Hospital-based retrospective cohort study, 676 pregnancies (1988-1989), 548 from city with two chlorinated surface water treatment facilities, 128 from city using unchlorinated ground water; information from hospital records on maternal smoking and other factors	Ecologic exposure index based on residence in two cities with different water disinfection methods; THM levels were 1-3 $\mu$ g/L in water treated with chlorine dioxide and 8-16 $\mu$ g/L in water treated with sodium hypochlorite	Non-significant association between preterm birth and chlorine dioxide treated water (odds ratios for surface water treated with chlorine dioxide or sodium hypochlorite vs unchlorinated ground water)	1.8 (0.7-4.7) 1.1 (0.3-3.7)	Maternal education, income, age, smoking, infant sex
			Borderline association between low birth weight (any gestation length) and chlorinated water (odds ratios for surface water treated with chlorine dioxide or sodium hypochlorite vs unchlorinated ground water)	5.9 (0.8-15) 6.0 (0.6-13)	
			Head circumference inversely associated with residence in area using water disinfected with chlorinated water (odds ratios for surface water	2.2 (1.4-3.9) 3.5 (2.1-8.5)	

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(Munger et al. 1997), Iowa	Ecologic study, 189 communities with surface, ground or mixed water supplies, including 13 communities with known triazine herbicide drinking water contamination; birth record data on birth weight, gestation length and prenatal smoking	Water supplies tested for 35 pesticides and 35 volatile organic contaminants including disinfection by-products; mother's exposure based on water quality for municipality of residence at time of delivery	treated with chlorine dioxide or sodium hypochlorite vs unchlorinated ground water)	Borderline association between IUGR and drinking water chloroform level	$\beta = 0.18$ ( $p = 0.06$ )	Aggregate census data on % of women in labour force, prenatal care index, median income, maternal education
(Mills et al. 1998), Canada	Expert panel review of toxicologic and epidemiologic evidence of health risks of DBPs; included epidemiologic studies of adverse pregnancy outcomes published during 1992-1996	Preterm birth	Among 4 epidemiologic studies of preterm birth, one found a borderline association with use of chlorine dioxide and no association with use of sodium hypochlorite for water disinfection; the other 3 studies found no association with THM levels	Among 4 studies of low birth weight (any gestation length), one found an association with THM levels and the others found borderline associations with THM levels or chlorine dioxide		
		Birth weight				

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			use		
			The two studies of small for gestational age both found associations with THM levels		
(Gallagher et al. 1998), Denver, Colorado	Retrospective cohort study, 1244 live births during 1990-1993 among women living in 28 census blocks served by either of 2 municipal water supplies near Denver; 68 preterm births, 29 term low birth weight infants	Modeled quarterly THM data at 4 different points in distribution systems during 1990-1993; assessed THM levels in distribution system near census blocks where mothers resided at time of delivery	Low birth weight (any gestation length) associated with THM levels above 60 µg/L (odds ratios for 21-40, 41-60 and ≥61 vs ≤20 µg/L)	1.0 (0.6-1.8) 0.8 (0.3-1.7) 2.1 (1.0-4.8)	
			Term low birth weight associated with THM levels above 60 µg/L (odds ratios for 21-40, 41-60 and ≥61 vs ≤20 µg/L)	1.3 (0.5-3.3) 1.2 (0.4-4.0) 5.9 (2.0-17)	Prenatal care, maternal education
			Preterm delivery not associated with THM levels above 60 µg/L (odds ratios for 21-40, 41-60 and ≥61 vs ≤20 µg/L)	1.0 (0.6-1.7) 0.7 (0.3-1.6) 1.0 (0.3-2.8)	Prenatal care
(Dodds et al. 1999), Nova Scotia, Canada	Retrospective cohort study, 50,755 singleton births in province during 1988-1995 (all births with birth weights ≥500 g); restricted to women who resided at the time of their delivery in municipalities with ≥90% of	Used data on quarterly THM levels in municipalities with chlorinated surface water sources, 1987-1995; used regression analysis to estimate THM levels by year, month and water treatment facility; avg chloroform and total THM levels	Borderline weak association between small for gestational age and THM levels during last 3 mos of pregnancy (odds ratios for 50-75, 75-99 and ≥100 vs <50 µg/L)	1.04 (0.97-1.11) 1.01 (0.92-1.11) 1.08 (0.99-1.18)	

	households served by a public supply using a surface water source; 4,673 small for gestational age (<10 <sup>th</sup> percentile for gestation week and sex), 2392 low birth weight (<2500 g) and 2689 preterm (<37 wk) infants	were 64 and 71 µg/L		
			No association between low birth weight (not adjusted for gestation length) and THM levels during last 3 mos of pregnancy (odds ratios for 50-75, 75-99 and ≥100 vs <50 µg/L)	1.07 (0.97-1.19) 1.11 (0.97-1.26) 1.04 (0.92-1.18)
			No association between preterm birth and THM levels during last 3 mos of pregnancy (odds ratios for 50-75, 75-99 and ≥100 vs <50 µg/L)	0.96 (0.88-1.06) 0.99 (0.88-1.12) 0.97 (0.87-1.09)
(Nieuwenhuijsen et al. 2000), UK	Review of toxicologic and epidemiologic literature on adverse pregnancy outcomes and DBPs; included 10 epidemiologic studies published during 1993-1999		<i>Animals</i> – at high doses, several DBPs cause fetal toxicity including resorptions and reduced weight and survival; there has been little toxicologic evaluation of effects of many other DBPs on fetal growth	
			<i>Humans</i> – inadequate evidence for association	Income

			between preterm birth and DBPs			
(Kallen and Robert 2000), Sweden	Retrospective cohort study, 3 groups of women who lived in areas with different drinking water disinfection practices; 114,484 births during 1985-1994 including 5,615 birth defects	Disinfection methods included none, chlorine dioxide only and sodium hypochlorite only	Preterm birth associated with sodium hypochlorite but not chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	1.09 (1.01-1.17)	Year of birth, maternal age, parity, education, smoking	
			Low birth weight associated with sodium hypochlorite but not chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	0.96 (0.88-1.04)		
			Borderline association between small for gestational age and sodium hypochlorite but not with chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	1.15 (1.05-1.26)		As above
			Borderline association between small for gestational age and sodium hypochlorite but not with chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	0.93 (0.84-1.03)		
(Yang et al. 2000), Taiwan	Retrospective cohort study, 10,007 singleton live births among residents of 14 municipalities in which $\geq 90\%$ of persons were served by a chlorinated water system and 8,018 live		Preterm birth associated with residence in municipalities using chlorinated water (relative risk, referent = women in municipalities using unchlorinated water)	1.07 (0.96-1.19)	As above	
				0.95 (0.84-1.07)		
			Preterm birth associated with residence in municipalities using chlorinated water (relative risk, referent = women in municipalities using unchlorinated water)	1.34 (1.15-1.56)	Municipalities matched for urbanization and had similar population density, % blue collar workers, % white collar workers;	

	births among residents of 14 municipalities in which <5% of population was served by a chlorinated water system; 719 preterm infants, 456 term low birth weight infants			adjusted for maternal age, education, marital status, infant sex
			Term low birth weight not associated with residence in municipalities using chlorinated water (relative risk, referent = women in municipalities using unchlorinated water)	0.90 (0.75-1.09) As above
(Graves et al. 2001), USA	Review of epidemiologic (1989-2000) and toxicologic (1974-2001) literature on developmental and reproductive effects of disinfection by-products	Low birth weight (<2500g, not adjusted for gestation length) – inadequate evidence for an association with DBPs	<i>Animals</i> – at very high levels of chloroform and usually associated with maternal toxicity <i>Humans</i> – 1 of 5 studies found an association with THMs (1 other study found strong associations of borderline statistical significance); 2 studies of very low birth weight (<1500 g) found no association with THMs	
		Preterm delivery – inadequate evidence for an association with DBPs	<i>Humans</i> – 1 of 7 studies found an association with THMs	
		IUGR or small for gestational age – limited evidence for an association with DBPs	<i>Animals</i> – at very high levels of chloroform and usually associated with maternal toxicity	

			Humans – all 3 studies found an association with THMs		
		Term low birth weight (<2500g, 37+ wk) – inadequate evidence for an association with DBPs	Humans – 1 of 3 studies found an association		
(Jaakkola et al. 2001), Norway	Retrospective cohort study, Norway 1993-1995, 123,747 infants with known gestational age and known municipal drinking water characteristics; 6,249 infants with birth weight <2500 g, 7,786 preterm births	DBP exposure estimated from raw water humic acid content (based on water colour) and chlorination method for supply to mother's residence during pregnancy; 233 chlorinated and 1,084 unchlorinated water supplies; assessed low and high colour chlorinated water supplies with unchlorinated low colour water supplies as referent	Low birth weight not associated with DBP exposure (odds ratios for chlorinated low and high colour vs unchlorinated low colour water supplies)	1.0 (0.9-1.1) 1.0 (0.9-1.1)	Maternal age, parity, child's place of birth, urban/rural, population density, industrial profile of community where mother lived during pregnancy
			Small for gestational age not associated with DBP exposure (odds ratios for chlorinated low and high colour vs unchlorinated low colour water supplies)	1.0 (0.9-1.1) 1.0 (0.9-1.1)	
			Preterm birth not associated with DBP exposure (odds ratios for chlorinated low and high colour vs unchlorinated low colour water supplies)	1.0 (0.9-1.0) 0.9 (0.8-1.0)	
(Bove et al. 2002), USA	Review of literature on adverse pregnancy	Assessed pregnancy outcomes in relation to tap water THM levels	3 studies provided moderate evidence of an		Virtually all studies found little or no effect

	outcomes and drinking water contaminants; included 19 reports of 16 studies published during 1989-2001; assessed small for gestational age (8 studies), preterm birth (9 studies)	and water source/chlorination; most studies did not assess maternal tap water consumption; only one study used distribution system parameters to assess within-municipality THM variability	association between narrowly defined small for gestational age (5 <sup>th</sup> percentile of weight by gestation wk or low birth weight at term); strongest association was found in the only study that assessed intra-municipality THM variability (Gallagher et al. 1998)  Broadly defined small for gestational age (10 <sup>th</sup> percentile of weight by gestation wk or low birth weight at any gestation length) weakly associated with THM levels  Preterm birth not associated with THM levels		of adjustment for potential confounders
(Nieuwenhuijsen et al. 2002), UK	ALSPAC birth cohort study, 11,462 pregnant women	Self-reported exposure information including swimming collected at about gestation wk 18-20; 31% swam up to 1 hr/wk and 10% swam longer (after conception)	Birth weight adjusted for gestation length not associated with swimming intensity (birth weight difference, ≤1 and 2+ vs 0 hr/wk)	7.8 g (-10 to 26)  17 g (-11 to 45)	Gestation length, maternal age, parity, education, ethnicity, housing tenure, drug use, smoking, alcohol
(Wright et al. 2004), Massachusetts	Retrospective cohort study, births during 1995-1998, towns with population >10,000; assessed gestation length and birth weight	Quarterly THM and HAA levels in drinking water supplies of 109 towns; MX and mutagenic activity levels for 34 towns; assigned average town-specific	SGA associated with 3 <sup>rd</sup> trimester average THM, MX and mutagenic activity but not HAA levels; odds ratios, 50 <sup>th</sup> -	THMs 1.06 (1.02-1.10) 1.13 (1.07-1.20)  HAAs	Median household income, prenatal care, maternal race, age, education, smoking, parity, previous infant

		DBP levels during 3 <sup>rd</sup> trimester to each woman	90 <sup>th</sup> and >90 <sup>th</sup> vs <50 <sup>th</sup> percentile	0.90 (0.81-1.01) 0.97 (0.77-1.23)  MX 0.97 (0.86-1.09) 1.14 (0.95-1.37)  Mutagenic activity 0.98 (0.87-1.11) 1.25 (1.04-1.51)	weighing >4000g, previous preterm delivery, maternal medical history
			Preterm birth <i>inversely</i> associated with 3 <sup>rd</sup> trimester average THM levels and not associated with MX, mutagenic activity or HAA levels; odds ratios, 50 <sup>th</sup> -90 <sup>th</sup> and >90 <sup>th</sup> vs <50 <sup>th</sup> percentile	THMs 0.95 (0.91-0.99) 0.88 (0.81-0.94)  HAAs 0.95 (0.83-1.10) 1.03 (0.77-1.39)  MX 1.03 (0.89-1.19) 0.87 (0.66-1.14)  Mutagenic activity 1.09 (0.94-1.27) 0.79 (0.59-1.05)	As above plus infant sex
(Yang 2004), Taiwan	Retrospective cohort study, births in 310 municipalities, 1994-1996	Municipality categorized as using chlorinated water if at least 95% of population served by chlorinated water; if <5% of population served by chlorinated water the municipality was categorized as unchlorinated; no DBP measurement data	Preterm birth but not low birth weight was associated with maternal residence in municipalities served by chlorinated water	Preterm birth 1.4 (1.2-1.6)  Low birth wt 1.1 (0.9-1.2)	Maternal age, marital status, education, infant sex, urban residence

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(Toledano et al. 2005), England	Retrospective cohort study, births and stillbirths in north and midlands of England, 1992-1998	Drinking water THM levels from household tap water surveys conducted on average 5-11 times per year in study regions; categorized avg drinking water THM levels during 3 <sup>rd</sup> trimester: <30, 30-59 and ≥60 µg/dL	Borderline increased risks of low birth weight (not adjusted for gestation length) among women living in regions with higher tap water THM levels during the 3 <sup>rd</sup> trimester; odds ratios, 30-59 and ≥60 vs <30 µg/dL	1.05 (0.96-1.15) 1.09 (0.93-1.27)	Maternal age, SES, study year
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### **Low birth weight, intrauterine growth retardation (IUGR) and preterm birth: summary**

#### *Low birth weight (any gestation length)*

Population-based case-control studies in Iowa and North Carolina found no association between low birth weight and drinking water chloroform or BDCM levels (Kramer et al. 1992) or THM levels (Savitz et al. 1995). A small retrospective cohort study of two communities in Italy found a non-significant association between low birth weight and chlorine-dioxide-treated surface water versus unchlorinated ground water (Kanitz et al. 1996). An expert panel review (Mills et al. 1998) observed that the 4 available epidemiologic studies of low birth weight provided limited evidence for an association with drinking water THMs. A retrospective cohort study in Denver found an association between low birth weight and THMs (Gallagher et al. 1998). A large retrospective cohort study in Nova Scotia (Canada) found no association between low birth weight and THMs (Dodds et al. 1999). A retrospective cohort study in Sweden found that low birth weight was associated with maternal residence in communities that used sodium hypochlorite compared to women in communities using unchlorinated water; there was no association with use of chlorine dioxide (Kallen and Robert 2000). A very large retrospective cohort study in Norway found no association between low birth weight and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to unchlorinated water with low levels of DBP precursors (Jaakkola et al. 2001). Two recent reviews concluded that there is inadequate evidence for an association between low birth weight at any gestation length and THMs (Graves et al. 2001, Bove et al. 2002). Two reviews noted toxicologic evidence that high-dose gestational exposure to several individual DBPs can cause fetal growth retardation in experimental animals (Nieuwenhuijsen et al. 2000, Graves et al. 2001). A retrospective cohort study in Taiwan found that preterm birth but not low birth weight was associated with maternal residence in municipalities served by chlorinated water (Yang 2004). A retrospective cohort study in England found borderline increased risks of low birth weight among women living in regions with THM levels above 30 µg/dL during their third trimester (Toledano et al 2005).

#### *Small for gestational age (or variants including term low birth weight and intrauterine growth retardation)*

Population-based case-control studies in Iowa and New Jersey found dose-response relationships between intrauterine growth retardation (IUGR) and drinking water chloroform and BDCM levels (Kramer et al. 1992) or between small for gestational age (SGA) and average gestational THM levels (Bove et al. 1995). The latter study also found an inverse dose-response relationship between birth weight at term (as a continuous variable) and average gestational THM levels (Bove et al. 1995). An ecologic study of 189 communities in Iowa found a borderline association between IUGR and drinking water chloroform analyzed as a continuous variable (Munger et al. 1997). An expert panel review (Mills et al. 1998) observed that the 2 available epidemiologic studies of SGA both showed an association with drinking water THMs. A retrospective cohort study in Denver found a relatively strong association between term low birth weight and THMs (Gallagher et al. 1998). However, a much larger retrospective cohort study in Nova Scotia (Canada) found only a weak association of borderline statistical

significance between SGA and THMs (Dodds et al. 1999). A retrospective cohort study in Sweden found that a borderline association between SGA and maternal residence in communities that used sodium hypochlorite compared to women in communities using unchlorinated water; there was no association with use of chlorine dioxide (Kallen and Robert 2000). A retrospective cohort study in Taiwan found that term low birth weight was not associated with maternal residence in communities that used chlorinated water compared to women in communities using unchlorinated water (Yang et al. 2000). A very large retrospective cohort study in Norway found no association between SGA and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to unchlorinated water with low levels of DBP precursors (Jaakkola et al. 2001). Two recent reviews concluded that there is limited evidence for an association between IUGR or SGA and THMs (Graves et al. 2001, Bove et al. 2002). The ALSPAC birth cohort study found no association between birth weight adjusted for gestation length and prenatal maternal swimming intensity before gestation week 18-20 (Nieuwenhuijsen et al. 2002). A retrospective cohort study in Massachusetts found associations between SGA and average drinking water supply levels of THMs, MX and mutagenic activity but not HAAs during the 3<sup>rd</sup> trimester in the town of maternal residence (Wright et al 2004).

#### *Preterm birth*

Population-based case-control studies in Iowa and North Carolina found no association between preterm birth and drinking water chloroform or BDCM levels (Kramer et al. 1992) or THM levels (Savitz et al. 1995). A small retrospective cohort study of two communities in Italy found a non-significant association between preterm birth and chlorine-dioxide-treated surface water versus unchlorinated ground water (Kanitz et al. 1996). An expert panel review (Mills et al. 1998) observed that the 4 available epidemiologic studies of preterm birth provided inadequate evidence for an association with drinking water THMs. A retrospective cohort study in Denver and a much larger one in Nova Scotia (Canada) found no associations between preterm birth and THMs (Gallagher et al. 1998, Dodds et al. 1999). A retrospective cohort study in Sweden found that preterm birth was associated with maternal residence in communities that used sodium hypochlorite compared to women in communities using unchlorinated water; there was no association with use of chlorine dioxide (Kallen and Robert 2000). A retrospective cohort study in Taiwan found that preterm birth was associated with maternal residence in communities that used chlorinated water compared to women in communities using unchlorinated water (Yang et al. 2000). A very large retrospective cohort study in Norway found no association between preterm birth and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to unchlorinated water with low levels of DBP precursors (Jaakkola et al. 2001). Two recent reviews concluded that there is inadequate evidence for an association between preterm birth and THMs (Graves et al. 2001, Bove et al. 2002). A retrospective cohort study in Massachusetts found that preterm birth was *inversely* associated with THM levels and was not associated with MX, mutagenic activity or HAA levels during the 3<sup>rd</sup> trimester in the town of maternal residence (Wright et al 2004). A retrospective cohort study in Taiwan found that preterm birth was associated with maternal residence in municipalities served by chlorinated water (Yang 2004).

**4. Birth defects**

Reference, location	Design	Exposure	Results	Association <sup>4</sup>	DR <sup>5</sup>	Covariates
(Aschengrau et al. 1993), Boston	Case-control study nested within cohort of 14,130 women enrolled at delivery, 1977-1980; included 1,039 birth defects, 77 stillbirths, 1,177 controls	Assessed drinking water quality in 155 communities where women lived during pregnancy	Borderline association between major birth defects and chlorinated surface water (odds ratio, chlorinated vs chloraminated surface water)	1.5 (0.7-2.1)		Maternal race, age, hospital insurance coverage, previous infant with birth defect, alcohol, water source
			Respiratory birth defects associated with chlorinated surface water (odds ratio, chlorinated vs chloraminated surface water)	3.2 (1.1-9.5)		As above
			Urinary tract birth defects associated with chlorinated surface water (odds ratio, chlorinated vs chloraminated surface water)	4.1 (1.2-14)		As above
(Bove et al. 1995), New Jersey	Retrospective cohort study, 80,938 live births, 594 fetal deaths among residents of	75 towns served by 49 public water systems; used data on quarterly THM to estimate	Association between CNS birth defects and avg 1 <sup>st</sup> trimester THM levels (odds	1.0 (0.4-2.4) 1.3 (0.7-2.5) 1.3 (0.6-2.7)	+	Maternal age, race, education, primiparity,

<sup>4</sup> Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

<sup>5</sup> 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

	75 towns, 1985-1988; live births included 118 CNS, 56 NTD, 83 oral cleft and 346 cardiac birth defects (the latter included 108 major cardiac defects of which 87 were VSDs)	monthly levels; assessed avg levels during 1 <sup>st</sup> trimester for birth defect and fetal death outcomes and throughout pregnancy for fetal growth outcomes	ratios for 21-40, 41-60, 61-80 and >80 vs ≤20 µg/L; 99% confidence intervals)	2.6 (1.1-5.6) p-trend<0.05	previous pregnancy loss, infant sex, prenatal care
			Association between NTDs and avg 1 <sup>st</sup> trimester THM levels (odds ratios for 21-40, 41-60, 61-80 and >80 vs ≤20 µg/L; 99% confidence intervals)	1.8 (0.5-5.9) 1.8 (0.6-5.0) 1.4 (0.4-4.5) 3.0 (0.8-9.8) p-trend<0.05	+ As above
			No association between oral clefts and avg 1 <sup>st</sup> trimester THM levels (odds ratios for 21-40, 41-60, 61-80, 81-100 and >100 vs ≤20 µg/L; 99% confidence intervals)	1.0 (0.4-2.5) 0.7 (0.3-1.5) 0.9 (0.3-2.0) 1.3 (0.3-3.8) 3.2 (0.6-10) p-trend>0.05	As above
			No association between major cardiac defects and avg 1 <sup>st</sup> trimester THM levels (odds ratios for 21-40, 41-60, 61-80 and >80 vs ≤20 µg/L; 99% confidence intervals)	1.3 (0.6-3.0) 1.5 (0.8-2.9) 0.8 (0.3-2.0) 1.8 (0.7-4.4) p-trend>0.05	As above
(Marshall et al. 1997), New York State	Population-based case-control study, 473 CNS and 3,305 musculoskeletal birth defects, 12,436 normal births, 1983-1986	Defined exposure based on residence at delivery within 1 mile of hazardous waste sites; assessed potential for exposure via air, water or soil/dust to toxicants from 643 hazardous waste sites;	CNS and musculoskeletal birth defects not associated with THMs (odds ratios, ≥100 vs <100 µg/L)	CNS 0.9 (0.5-1.5) musculoskeletal 0.8 (0.6-1.0)	Adjusted as necessary for maternal age, race, education, population density, parity, delayed prenatal care,

		included data on industrial air emissions and drinking water THM levels $\geq 100 \mu\text{g/L}$		infant sex
(Mills et al. 1998), Canada	Expert panel review of toxicologic and epidemiologic evidence of health risks of DBPs; included epidemiologic studies of adverse pregnancy outcomes published during 1992-1996	Birth defects	<p><i>Animals</i> – dichloroacetic acid, dichloroacetonitrile and trichloroacetonitrile caused soft tissue defects including ventricular septal cardiac defects in rats; dibromoacetic and dichloroacetic acids caused testicular degeneration in rats and dogs</p> <p><i>Humans</i> – among 2 studies, one found no association between total birth defects and use of chlorinated surface water and the other found associations between NTDs, oral cleft, cardiac and total birth defects and THM levels</p>	
(Dodds et al. 1999), Nova Scotia, Canada	Retrospective cohort study, 50,755 singleton births in province during 1988-1995 (all births with birth weights $\geq 500$ g); restricted to women who resided at the time of their delivery in municipalities with $\geq 90\%$ of households served by a public supply using a surface water source; 77 NTDs, 82 orofacial cleft and 430 major cardiac birth	Used data on quarterly THM levels in municipalities with chlorinated surface water sources, 1987-1995; used regression analysis to estimate THM levels by year, month and water treatment facility; avg chloroform and total THM levels were 64 and 71 $\mu\text{g/L}$	NTDs not associated with THM levels during month before and after conception (odds ratios for 50-75, 75-99 and $\geq 100$ vs $< 50 \mu\text{g/L}$ )	0.7 (0.4-1.2) 0.4 (0.2-1.0) 1.2 (0.7-2.1)

			defects; 96 infants with chromosomal abnormalities			
				Orofacial cleft defects not associated with THM levels during first 2 mos of pregnancy (odds ratios for 50-75, 75-99 and $\geq 100$ vs $< 50 \mu\text{g/L}$ )	0.8 (0.5-1.3) 0.8 (0.4-1.6) 1.0 (0.6-1.9)	
				Major cardiac defects not associated with THM levels during first 2 mos of pregnancy (odds ratios for 50-75, 75-99 and $\geq 100$ vs $< 50 \mu\text{g/L}$ )	1.0 (0.8-1.2) 1.0 (0.7-1.3) 0.8 (0.6-1.0)	
				Chromosomal abnormalities not associated with THM levels during 3 mos before conception (odds ratios for 50-75, 75-99 and $\geq 100$ vs $< 50 \mu\text{g/L}$ )	1.2 (0.7-2.0) 1.8 (1.0-3.3) 1.4 (0.7-2.6)	
(Magnus et al. 1999), Norway	Retrospective cohort study, 141,077 births in Norway among women living in municipalities with known chlorination and raw water colour status; 1993-1995, 2,608 infants had birth defects reported after examination during first postnatal week by a physician (usually a pediatrician)	Assessed municipal drinking water color and chlorination practice (certain dark surface waters are high in dissolved organic carbon and generate high levels of DBPs when chlorinated)		Total birth defects weakly associated with DBP indicator (odds ratio for chlorinated low and high colour vs unchlorinated low colour water supplies)	1.0 (0.9-1.1) 1.1 (1.0-1.3)	Maternal age, parity, place of birth, population density, industrial profile, urbanization
				Urinary tract defects associated with DBP	2.0 (1.1-3.6)	

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			indicator (odds ratio for chlorinated high colour vs unchlorinated low colour water supplies)		
			Neural tube, major cardiac, respiratory and oral cleft defects not associated with DBP indicator (respective odds ratios for chlorinated high colour vs unchlorinated low colour water supplies)	1.3 (0.6-2.6) 1.1 (0.8-1.5) 1.1 (0.5-2.2) 0.9 (0.6-1.4)	
(Klotz and Pyrch 1999), New Jersey	Population-based case-control study, 112 neural tube birth defect (NTD) cases, 248 matched controls; maternal interview data for 82 cases and 165 controls, tap water samples for 90 cases and 181 controls	Assessed THM exposure during 1 <sup>st</sup> month after conception; data for community water supplies and tap water samples collected about 4 mos after the expected date of delivery (i.e., about 1 yr from conception – to control for effect of seasonal THM changes)	Borderline association between NTDs and surface vs ground water source; association slightly stronger when limited to subjects with known residence at conception and isolated NTDs (respective odds ratios)	all subjects 1.5 (0.9-2.5)  subgroup 1.7 (0.9-3.2)	Matched for date of birth and birth order but not geographic location
			Borderline association between NTDs and municipal water supply THM levels; association formally significant when limited to subjects with known residence at conception and isolated NTDs (respective odds ratios for 5-39 and $\geq 40$ vs $< 5$ $\mu\text{g/L}$ )	all subjects 0.6 (0.3-1.2) 1.6 (0.9-2.7)  subgroup 0.9 (0.4-1.9) 2.1 (1.1-4.0)	As above
			Borderline association	all subjects	As above

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between NTDs and municipal water supply total chlorine residual levels; association slightly stronger when limited to subjects with known residence at conception and isolated NTDs (respective odds ratios for $\geq 0.5$ vs $< 0.5$ mg/L)	1.5 (0.8-2.7) subgroup 1.7 (0.9-3.1)		
Borderline association between NTDs and <i>tap</i> water supply THM levels; association slightly stronger when limited to subjects with known residence at conception and isolated NTDs (respective odds ratios for 5-39 and $\geq 40$ vs $< 5$ $\mu\text{g/L}$ )	all subjects 1.3 (0.7-2.6) 1.7 (0.9-3.8) subgroup 1.3 (0.7-3.1) 1.9 (1.0-4.0)	(+)	As above plus adjusted for late onset of prenatal care (after 1 <sup>st</sup> trimester); odds ratios changed by $< 10\%$ when adjusted for other potential confounders
NTDs not associated with <i>tap</i> water haloacetonitrile levels (respective odds ratios for 0.5-2.9 and $\geq 3$ vs $< 0.5$ $\mu\text{g/L}$ )	1.3 (0.6-2.8) 1.3 (0.6-2.5)		As above plus adjusted for maternal age, ethnicity, education
NTDs not associated with tap water haloacetic acid levels (respective odds ratios for 3-34 and $\geq 35$ vs $< 3$ $\mu\text{g/L}$ )	0.9 (0.4-2.0) 1.2 (0.5-2.6)		As above
Association between NTDs and THM levels limited to subjects who did not use	no vitamins 2.6 (1.2-6.0)		Little change in odds ratios after adjustment for

			vitamin supplements during 3 mos before conception (respective odds ratios for $\geq 40$ vs $< 5$ $\mu\text{g/L}$ )	vitamins 0.5 (0.1-1.7)	race, ethnicity, late onset of prenatal care, maternal education
(Nieuwenhuijsen et al. 2000), UK	Review of toxicologic and epidemiologic literature on adverse pregnancy outcomes and DBPs		<i>Animals</i> – THMs do not appear to cause birth defects in animals; halogenated acetic acids cause neural tube, craniofacial and cardiac defects; there has been little toxicologic evaluation of effects of many DBPs on specific birth defects  <i>Humans</i> – limited evidence for associations between birth defects and DBPs		
(Kallen and Robert 2000), Sweden	Retrospective cohort study, 3 groups of women who lived in areas with different drinking water disinfection practices; 114,484 births during 1985-1994 including 5,615 birth defects	Disinfection methods included none, chlorine dioxide only and sodium hypochlorite only	Spina bifida not associated with sodium hypochlorite or chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities) Cardiac defects not associated with sodium hypochlorite or chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	1.4 (0.7-1.4) 1.0 (0.5-2.1)  1.1 (0.9-1.3) 0.9 (0.7-1.1)	Year of birth, maternal age  As above
			Facial clefts not associated with sodium hypochlorite or	1.1 (0.8-1.6) 0.9 (0.6-1.3)	As above

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			chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)		
			Hypospadias not associated with sodium hypochlorite or chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	1.1 (0.6-2.0) 1.2 (0.6-2.3)	As above
			Severe kidney malformations not associated with sodium hypochlorite or chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	1.4 (0.7-3.0) 0.9 (0.3-2.3)	As above
			Chromosomal abnormalities not associated with sodium hypochlorite or chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	0.8 (0.5-1.3) 0.7 (0.4-1.2)	As above
(Graves et al. 2001), USA	Review of epidemiologic (1989-2000) and toxicologic (1974-2001) literature on developmental and reproductive effects of disinfection by-products	CNS birth defects	<i>Animals</i> – no evidence of CNS defects in animal studies <i>Humans</i> – 2 of 5 studies found an association with DBPs; one of these studies	Limited	

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	showed that the association was limited to the subgroup of women who did not take prenatal vitamin supplements, 3 studies found no association	
Oral cleft birth defects	<p><i>Animals</i> – one study found cleft palate defects in mice prenatally exposed to high amounts of chloroform by inhalation</p> <p><i>Humans</i> – 1 of 3 studies found a non-significant association between oral cleft defects and DBPs</p>	Inadequate
Cardiac birth defects	<p><i>Animals</i> – several studies found cardiac defects in rodents prenatally exposed to haloacetic acids or haloacetoneitriles</p> <p><i>Humans</i> – 1 of 4 studies found a borderline association between major cardiac defects and DBPs</p>	Inadequate
Respiratory birth defects	1 of 2 epidemiologic studies found an association with DBPs	Inadequate
Urinary tract birth defects	<p><i>Animals</i> – urogenital birth defects observed in rodents prenatally exposed to dichloroacetoneitriles or trichloroacetoneitriles</p> <p><i>Humans</i> – both of 2 studies</p>	Limited

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(Dodds and King 2001), Nova Scotia, Canada	Retrospective cohort study, 1988-1995, 48,929 births with known gestation length; 77 neural tube defects, 430 cardiovascular and 82 cleft defects, 96 chromosomal abnormalities	Chloroform and BDCM (BDCM) levels in municipal water supply for region where mother lived during month before and after conception for NTDs, first 2 mos of pregnancy for cardiac and cleft defects and 3 mos before conception for chromosomal abnormalities	found associations between urinary tract defects and DBPs			
			Neural tube defects associated with drinking water BDCM levels (odds ratios for 5-9, 10-19 and $\geq 20$ vs $< 5$ $\mu\text{g/L}$ )	1.4 (0.8-2.3)	+	Maternal age, income
				0.6 (0.2-1.5)		
				2.5 (1.2-5.1)		
			Neural tube defects not associated with drinking water chloroform levels (odds ratios for 50-74, 75-99 and $\geq 100$ vs $< 50$ $\mu\text{g/L}$ )	0.7 (0.4-1.2)		As above
	0.7 (0.3-1.5)					
	1.2 (0.7-2.3)					
	Cardiovascular birth defects not associated with drinking water chloroform levels (odds ratios for 50-74, 75-99 and $\geq 100$ vs $< 50$ $\mu\text{g/L}$ ); inversely associated with BDCM levels	1.0 (0.8-1.3)		As above		
		1.0 (0.8-1.4)				
		0.7 (0.5-1.0)				
	Cleft defects not associated with drinking water chloroform levels (odds ratios for 50-74, 75-99 and $\geq 100$ vs $< 50$ $\mu\text{g/L}$ ); no association with BDCM levels	1.2 (0.7-2.0)		Maternal age		
		0.9 (0.4-2.0)				
		1.5 (0.8-2.8)				
	Association between	1.3 (0.8-2.2)		Maternal age,		

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			chromosomal abnormalities and drinking water	1.9 (1.1-3.3) 1.4 (0.8-2.8)	income
			chloroform levels but no dose-response relationship (odds ratios for 50-74, 75-99 and $\geq 100$ vs $< 50$ $\mu\text{g/L}$ ); no association with BDCM levels		
(Elliott et al. 2001), UK	Ecologic study, birth defects and low birth weight, UK 1982-1997	Maternal residence within 2 km of any of 9,565 landfill sites operational during 1982-1997; included 774 hazardous waste sites	Birth defects associated with maternal residence near hazardous waste sites	1.07 (1.04-1.09)	Low income
			Cardiovascular birth defects associated with maternal residence near hazardous waste sites	1.11 (1.03-1.21)	Low income
			Hypospadias associated with maternal residence near hazardous waste sites	1.11 (1.03-1.21)	Low income
			Borderline association between neural tube birth defects and maternal residence near hazardous waste sites	1.07 (0.95-1.20)	Low income
			Stillbirths not associated with maternal residence near hazardous waste sites	0.99 (0.95-1.03)	Low income
			Low birth weight associated with maternal residence near hazardous waste sites	1.05 (1.04-1.06)	Low income

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(Cedergren et al. 2002), Sweden	Retrospective cohort study, 753 major cardiac birth defects among infants of 58,669 mothers at residences using municipal water supplies, 1982-1996	Drinking water quality data for the 80 municipal water supplies in the study region (one county); chlorination practices 1983-1994, THM levels during 1994-1995 survey	Major cardiac birth defects associated with use of chlorine dioxide and hypochlorite but not with use of hypochlorite alone (respective odds ratios relative to no chlorination)	1.6 (1.0-2.6) 0.9 (0.6-1.2)	Maternal age, parity, education
			Major cardiac birth defects associated with total THM levels (odds ratio for >10 vs ≤10 µg/L)	1.3 (1.1-1.6)	As above plus first trimester maternal smoking
(Bove et al. 2002), USA	Review of literature on adverse pregnancy outcomes and drinking water contaminants; included 19 reports of 16 studies published during 1989-2001; assessed risk of birth defects (7 studies)	Assessed pregnancy outcomes in relation to tap water THM levels and water source/chlorination; most studies did not assess maternal tap water consumption; only one study used distribution system parameters to assess within-municipality THM variability	Limited evidence for associations between neural tube, oral cleft and urinary tract birth defects and THM levels		Virtually all studies found little or no effect of adjustment for potential confounders
			Inadequate evidence for association between cardiac birth defects and THM levels		
(Hwang et al. 2002), Norway	Retrospective cohort study, Norway, 1993-1998, 184,676 infants in municipalities served by water supplies treated with one documented chlorination method; 5,764 birth defects	DBP exposure estimated from raw water humic acid content (based on water colour) and chlorination method for supply to mother's residence during pregnancy; 233 chlorinated and 1,084 unchlorinated water supplies; assessed low, medium and	Neural tube birth defects not associated with DBP exposure (odds ratios for chlorinated low, medium and high colour vs unchlorinated/low colour water supplies)	1.6 (0.8-3.2) 1.2 (0.6-2.4) 0.7 (0.2-2.0)	Maternal age, parity, urban/rural, population density, municipality mother lived in during pregnancy

			high colour chlorinated water supplies with unchlorinated low colour water supplies as referent		
			Ventricular septal cardiac birth defects associated with DBP exposure (odds ratios for chlorinated low, medium and high colour vs unchlorinated/ low colour water supplies)	0.9 (0.5-1.5) 1.6 (1.0-2.6) 1.8 (1.1-3.1)	
			Respiratory birth defects associated with DBP exposure (odds ratios for chlorinated low, medium and high colour vs unchlorinated/low colour water supplies)	1.0 (0.5-2.1) 1.9 (1.0-3.6) 2.0 (0.9-4.3)	
			Borderline association between isolated cleft lip and DBP exposure (odds ratios for chlorinated low, medium and high colour vs unchlorinated/ low colour water supplies)	0.9 (0.3-2.9) 2.1 (0.8-5.1) 2.0 (0.6-6.5)	
			Obstructive urinary tract birth defects associated with DBP exposure (odds ratios for chlorinated low, medium and high colour vs unchlorinated/ low colour water supplies)	1.0 (0.4-2.8) 1.9 (0.8-4.4) 2.0 (0.7-6.0)	
(Shaw et al.	Two population-based case-	Self-reported residential	Study 1 – neural tube	0.5 (0.3-1.0)	Maternal BMI,

2003), California	control studies: 1 – 538 neural tube birth defect cases, 539 healthy live birth controls among cohort of California births during 1989-1991; 2 – 265 neural tube birth defect cases, 409 orofacial cleft cases, 207 conotruncal cardiac birth defect cases, 481 live birth controls, California, 1987-1988	history, daily tap water intake during periconceptual period; characteristics of municipal water supply including chlorination, individual and total THM levels	defects not associated with drinking water supply total THM levels (odds ratios for 1-24, 25-49, 50-74 and $\geq 75$ vs 0 ppb)	0.7 (0.5-1.2)	education, race/ethnicity, periconceptual vitamin use	
				0.4 (0.2-0.7)		
				0.6 (0.3-1.5)		
			Study 2 – neural tube defects not associated with drinking water supply total THM levels (odds ratios for 1-24, 25-49 and 50-74 vs 0 ppb)	2.2 (0.9-5.9)		As above
				0.9 (0.5-1.5)		
				1.8 (0.9-3.7)		
	Neural tube defects not associated with BDCM levels in either study (odds ratio for $\geq 4.2$ vs $< 4.2$ ppb in study 1 and $\geq 9.6$ vs $< 9.6$ ppb in study 2)	study 1 0.7 (0.5-1.0)	As above			
		study 2 1.1 (0.7-1.8)				
	Study 2 – isolated cleft lip/palate not associated with drinking water supply total THM levels (odds ratios for 1-24, 25-49 and 50-74 vs 0 ppb)	2.6 (0.9-7.6)	As above			
		0.9 (0.5-1.6)				
		1.9 (0.8-4.5)				
	Study 2 – conotruncal cardiac defects not associated with drinking water supply total THM	3.1 (1.2-8.2)	As above			
		0.9 (0.5-1.5)				
		1.5 (0.7-3.5)				

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(Hwang and Jaakkola 2003), USA, Taiwan, UK, Finland	Meta-analysis of 3 retrospective cohort and 2 case-control studies of birth defects and chlorination disinfection by-products, 1993-1999; included studies with individuals as unit of observation and adequate exposure assessment, outcome definition and control of potential confounders	Studies included Aschengrau et al 1993, Bove et al. 1995, Dodds et al. 1999, Magnus et al. 1999 and Klotz and Pynch 1999; exposure based on water source and chlorination practice or on measured THM levels	levels (odds ratios for 1-24, 25-49 and 50-74 vs 0 ppb)	
			Any birth defect associated with exposure to chlorination by-products (summary odds ratio, 3 studies)	1.25 (1.11-1.40)
			Neural tube birth defects associated with exposure to chlorination by-products (summary odds ratio, 4 studies)	1.5 (1.1-2.1)
			Major cardiac defects not associated with exposure to chlorination by-products (summary odds ratio, 3 studies)	1.0 (0.8-1.2)
			Borderline association between respiratory birth defects and exposure to chlorination by-products (summary odds ratio, 2 studies)	1.5 (0.8-2.7)
Oral clefts not associated with exposure to chlorination by-products	1.1 (0.8-1.5)			

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(summary odds ratio, 3 studies)

Urinary tract birth defects associated with exposure to chlorination by-products (summary odds ratio, 2 studies) 2.3 (1.3-3.9)

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### **Birth defects: summary**

#### *Total birth defects*

A large case-control study in Boston found a non-significant association between total birth defects and maternal residence in communities using chlorinated surface versus chloraminated surface water (Aschengrau et al. 1993). A retrospective cohort study in Norway found no association between total birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A meta-analysis of 3 epidemiologic studies found a modest association between any birth defect and THM exposure indices (Hwang and Jaakkola 2003).

#### *CNS birth defects*

A retrospective cohort study found dose-response relationships between NTDs or total CNS birth defects and average 1<sup>st</sup> trimester drinking water THM levels (Bove et al. 1995). A large population-based case-control study in New York State found no association between CNS birth defects and drinking water THM levels exceeding 100 µg/L (Marshall et al. 1997). A retrospective cohort study in Nova Scotia (Canada) found no association between NTDs and periconceptual drinking water THM levels (Dodds et al. 1999). A retrospective cohort study in Norway found no association between NTDs and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A population-based case-control study in New Jersey found borderline associations between NTDs and indices of early postconceptual DBP exposure including surface versus ground water supply and THM or residual chlorine levels in water samples from the water treatment facility or residential taps (the latter associations were stronger when limited to subjects with known residences at conception); NTDs were not associated with tap water haloacetic acid or haloacetonitrile levels (Klotz and Pynch 1999). Importantly, the latter study found that the association between NTDs and drinking water THM levels was limited to the subgroup of women who did not use vitamin supplements before conception. A retrospective cohort study in Sweden found no association between spina bifida and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A review of toxicologic and epidemiologic studies concluded that THMs *per se* do not appear to cause birth defects in experimental animals but halogenated acetic acids cause neural tube, craniofacial and cardiac defects; the potential teratogenicity of many other DBPs has not been evaluated (Nieuwenhuijsen et al. 2000). Another review concluded that there is inadequate toxicologic evidence that DBPs cause CNS birth defects in experimental animals and limited/inconsistent epidemiologic evidence for an association between such defects and DBPs in humans (Graves et al. 2001). A retrospective cohort study in Nova Scotia (Canada) found that NTDs were associated with periconceptual community drinking water BDCM levels but not with chloroform levels (Dodds and King 2001). A review of the epidemiologic literature by Bove et al. (2002) concluded that there was limited evidence for an association between NTDs and THM levels. A large Norwegian retrospective cohort study found no association between NTDs and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to

those living in communities using unchlorinated water with low levels of DBP precursors (Hwang et al. 2002). A report of two population-based case-control studies of NTDs in California showed no association with periconceptual drinking water THM levels in one study and a borderline association, without a monotonic dose-response relationship, in the other study; neither study found an association with drinking water BDCM levels (Shaw et al. 2003). A meta-analysis of 4 epidemiologic studies found a modest association between NTDs and THM exposure indices (Hwang and Jaakkola 2003).

#### *Orofacial birth defects*

A retrospective cohort study found no association between oral clefts and 1<sup>st</sup> trimester drinking water THM levels (Bove et al. 1995). A retrospective cohort study in Nova Scotia (Canada) found no association between orofacial clefts and average 1<sup>st</sup> trimester drinking water THM levels (Dodds et al. 1999). A retrospective cohort study in Norway found no association between oral cleft birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A retrospective cohort study in Sweden found no association between orofacial clefts and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A review of toxicologic and epidemiologic studies concluded that THMs *per se* do not appear to cause birth defects in experimental animals but halogenated acetic acids cause neural tube, craniofacial and cardiac defects; the potential teratogenicity of many other DBPs has not been evaluated (Nieuwenhuijsen et al. 2000). Another review noted that chloroform caused cleft palate defects in mice and inadequate epidemiologic evidence for an association between such defects and DBPs in humans (Graves et al. 2001). A retrospective cohort study in Nova Scotia (Canada) found that a modest non-significant association between orofacial cleft defects and periconceptual community drinking water chloroform levels above 100 µg/L but no dose-response relationship (Dodds and King 2001). A review of the epidemiologic literature by Bove et al. (2002) concluded that there was limited evidence for an association between oral cleft defects and THM levels. A large Norwegian retrospective cohort study found modest non-significant associations between isolated cleft lip and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors; there was not a monotonic dose-response relationship (Hwang et al. 2002). A case-control study in California found an association between isolated cleft lip/palate and periconceptual drinking water THM levels but no dose-response relationship (Shaw et al. 2003). A meta-analysis of 3 epidemiologic studies found no association between oral cleft defects and THM exposure indices (Hwang and Jaakkola 2003).

#### *Cardiac birth defects*

A retrospective cohort study found no association between cardiac birth defects and 1<sup>st</sup> trimester drinking water THM levels (Bove et al. 1995). An expert panel review (Mills et al. 1998) noted toxicologic evidence that dichloroacetic acid and trichloroacetonitrile caused ventricular septal and other soft tissue birth defects in experimental animals. Retrospective cohort studies in New Jersey Bove et al. 1995) and Canada (Dodds et al. 1999) found no association between major cardiac birth defects and 1<sup>st</sup> trimester drinking water THM levels. A retrospective cohort study in Norway found no association between major cardiac birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A retrospective cohort study in Sweden found no association between cardiac birth defects and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A review of toxicologic and epidemiologic studies concluded that THMs *per se* do not appear to cause birth defects in experimental animals but halogenated acetic acids cause neural tube, craniofacial and cardiac defects; the potential teratogenicity of many other DBPs has not been evaluated (Nieuwenhuijsen et al. 2000). A review noted toxicologic evidence that haloacetic acids and haloacetonitriles caused cardiac defects in experimental animals and inadequate epidemiologic evidence for an association between such defects and DBPs in humans (Graves et al. 2001). A retrospective cohort study in Nova Scotia (Canada) found that no association between cardiovascular birth defects and

periconceptual community drinking water BDCM or chloroform levels (Dodds and King 2001). A Swedish retrospective cohort study, however, did find a modest association between major cardiac birth defects and community drinking water THM levels and use of chlorine dioxide for disinfection (Dodds and King 2001). A review of the epidemiologic literature by Bove et al. (2002) concluded that there was inadequate evidence for an association between cardiac birth defects and THM levels. A large Norwegian retrospective cohort study found an association between ventricular septal cardiac defects and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors (Hwang et al. 2002). A case-control study in California found an association between conotruncal cardiac defects and periconceptual drinking water THM levels but no dose-response relationship (Shaw et al. 2003). A meta-analysis of 3 epidemiologic studies found no association between major cardiac birth defects and THM exposure indices (Hwang and Jaakkola 2003).

#### *Respiratory birth defects*

A large case-control study in Boston found a moderately strong association between respiratory birth defects and maternal residence in communities using chlorinated surface versus chloraminated surface water (Aschengrau et al. 1993). A retrospective cohort study in Norway found no association between respiratory tract birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A review concluded that there was inadequate epidemiologic evidence for an association between such respiratory birth defects and DBPs in humans (Graves et al. 2001). A large Norwegian retrospective cohort study found an association between respiratory birth defects and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors (Hwang et al. 2002). A meta-analysis of 2 epidemiologic studies found a modest non-significant association between respiratory birth defects and THM exposure indices (Hwang and Jaakkola 2003).

#### *Genitourinary tract birth defects*

A large case-control study in Boston found a moderately strong association between urinary tract birth defects and maternal residence in communities using chlorinated surface versus chloraminated surface water (Aschengrau et al. 1993). A retrospective cohort study in Norway found an association between urinary tract birth defects and maternal residence in communities using chlorinated surface waters with high levels of DBP precursors compared to those living in communities using unchlorinated water with low levels of DBP precursors (Magnus et al. 1999). A retrospective cohort study in Sweden found no association between hypospadias or kidney malformations and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A review noted toxicologic evidence that haloacetonitriles caused urogenital defects in experimental animals and limited epidemiologic evidence for an association between such defects and DBPs in humans (Graves et al. 2001). A review of the epidemiologic literature by Bove et al. (2002) concluded that there was limited evidence for an association between urinary tract birth defects and THM levels. A large Norwegian retrospective cohort study found a modest, non-significant association between obstructive urinary tract birth defects and maternal residence in communities with chlorinated drinking water with high levels of DBP precursors, compared to those living in communities using unchlorinated water with low levels of DBP precursors (Hwang et al. 2002).

#### *Musculoskeletal birth defects*

A large population-based case-control study in New York State found no association between musculoskeletal birth defects and drinking water THM levels exceeding 100 µg/L (Marshall et al. 1997).

#### *Chromosome abnormalities*

A retrospective cohort study in Sweden found no association between chromosome abnormalities and maternal residence in communities using water chlorinated with sodium hypochlorite or chlorine dioxide, compared to those living in communities using unchlorinated drinking water (Kallen and Robert 2000). A retrospective cohort study in Nova Scotia (Canada) found that an association between chromosomal abnormalities and periconceptual community drinking water chloroform levels but accompanied by a non-monotonic dose-response relationship; there was no association with drinking water BDCM levels (Dodds and King 2001).

### 5. Childhood cancer

Reference, location	Design	Exposure	Results	Association <sup>6</sup>	DR <sup>7</sup>	Covariates
(Kallen and Robert 2000), Sweden	Retrospective cohort study, 3 groups of women who lived in areas with different drinking water disinfection practices; 72 cases childhood cancer up to end of 1994	Disinfection methods included none, chlorine dioxide only and sodium hypochlorite only	Non-significant associations between childhood cancer and sodium hypochlorite and chlorine dioxide use (respective relative risks, referent = women in unchlorinated municipalities)	1.6 (0.7-3.8) 1.5 (0.9-2.8)		Year of birth
(Infante-Rivard et al. 2001), Montreal	Population-based case-control study, 491 acute lymphatic leukemia cases, 491 matched controls, age < 10 yr, 1980-1993; assessed prenatal and childhood exposure to THMs	Child's residential history from conception to present, parent-reported drinking water source, water quality data for THMs, 1970-1993, 1995-1996 tap water survey (227 homes)	ALL not associated with avg drinking water THM during prenatal or postnatal period (respective odds ratios, >12.9-44 and >44 vs ≤12.9µg/L)	prenatal 1.2 (0.8-1.8) 1.1 (0.7-1.8)		Matched for age, sex, region; adjusted for maternal age, education
			ALL not associated with cumulated drinking water THM (µg.day.L <sup>-1</sup> ) during prenatal or postnatal period (respective odds ratios, >25-75 <sup>th</sup> and >75 <sup>th</sup> vs <25 <sup>th</sup> percentile of µg.day.L <sup>-1</sup> )	prenatal 1.1 (0.8-1.7) 1.2 (0.7-1.8)		As above
			Borderline association between postnatal but not prenatal cumulative chloroform exposure (odds ratio, >95 <sup>th</sup> vs ≤95 <sup>th</sup> )	prenatal 0.7 (0.4-1.5)		As above
				postnatal 1.1 (0.8-1.5) 1.1 (0.7-1.7)		

<sup>6</sup> Entries in this column include odds ratios, relative risks and certain other statistical measures of association as published in original epidemiologic studies; an entry of '+' means the measure of association was not an odds ratio or relative risk and was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

<sup>7</sup> 'DR' refers to a dose-response relationship in an epidemiologic study; an entry of '+' means the measure of dose-response relationship used in the citation was statistically significant at the 0.05 level; an entry of '(+)' means the association was almost statistically significant.

			percentile of $\mu\text{g}\cdot\text{day}\cdot\text{L}^{-1}$ )	1.6 (0.8-3.2)
(Infante-Rivard et al. 2002), Montreal	Case-only study, 170 of the 491 ALL cases included above (Infante-Rivard et al. 2001), age 0-9 yr; measured polymorphisms in the <i>GSTT1</i> and <i>CYP2E1</i> genes	Assessed avg prenatal and postnatal THM levels	GSTT1-null ALL cases associated with avg postnatal but not prenatal THM levels (odds ratios, THM >110 vs $\leq$ 110 $\mu\text{g}/\text{L}$ )	prenatal 2.4 (0.4-13) postnatal 9.1 (1.4-58)
			GSTT1-null ALL cases not associated with cumulative prenatal or postnatal THM levels (odds ratio, >95 <sup>th</sup> vs $\leq$ 95 <sup>th</sup> percentile of $\mu\text{g}\cdot\text{day}\cdot\text{L}^{-1}$ )	prenatal 2.4 (0.4-13) postnatal 2.5 (0.6-10)
			Imprecise associations between CYP2E1*5 ALL cases and avg prenatal and postnatal THM levels (odds ratios, >44 vs $\leq$ 12.9 $\mu\text{g}/\text{L}$ )	prenatal 9.8 (1.1-86) postnatal 4.1 (0.8-22)
			Imprecise associations between CYP2E1*5 ALL cases and cumulative prenatal and postnatal THM levels (odds ratio, >75 <sup>th</sup> vs $\leq$ 25 <sup>th</sup> percentile of $\mu\text{g}\cdot\text{day}\cdot\text{L}^{-1}$ )	prenatal 8.0 (0.9-73) postnatal 6.0 (0.7-54)

#### Childhood cancer: summary

A Swedish retrospective cohort study found a borderline association between childhood cancer and maternal prenatal residence in communities using chlorine dioxide but not those using sodium hypochlorite for disinfection, compared to those living in communities using unchlorinated water (Kallen and Robert 2000). A large population-based case-control study of acute lymphatic leukemia (ALL) in Quebec found no association with prenatal or childhood drinking water THM exposure indices including time-weighted average or cumulative exposure (Infante-Rivard et al. 2001). The latter study did find a non-significant association between ALL and cumulative childhood but not prenatal drinking water chloroform exposure. A subsequent case-only analysis of the Quebec study showed borderline or significant but imprecise associations between the subsets of GSTT1-null and CYP2E1\*5 ALL cases and prenatal or postnatal THM exposure indices (Infante-Rivard et al. 2002).

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