OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Proposition 65

Reconsideration of a Chemical Listed under Proposition 65 as Known to Cause Reproductive Toxicity

Chemical Listed via the Labor Code Mechanism:

Chloroform

August 2016

Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
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Acronyms and abbreviations

adj	adjusted
ass	association
BCAA	bromochloroacetic acid
BD	birth defects
BDCAA	bromodichloroacetic acid
BDCM	bromodichloromethane - $CHCl_2Br$
BrTHM	total brominated trihalomethanes (BDCM+DBCM+TBM)
btwn	between
BW	birth weight
CHL	chloroform (trichloromethane) - $CHCl_3$
conc	concentration
DBAA	dibromoacetic acid
DBCAA	dibromochloroacetic acid
DBCM	dibromochloromethane - $CHClBr_2$
DBP	disinfection by-product
DCAA	dichloroacetic acid
d	day
diff	difference
dist	distribution
e.g.	for example
exp	exposure
freq	frequency
GA	gestational age
GSTM1	glutathione S-transferase Mu 1
GSTT1	glutathione S-transferase theta-1
HAA	haloacetic acid
HAA5	sum of 5 HAAs = MCAA + DCAA + TCAA + MBAA + DBAA
HAA9	9 species of HAA - MCAA, DCAA, TCAA, MBAA, DBAA, TBAA, BCAA, DBCAA, BDCAA
HR	hazard ratio
incl	included
info	information
IQR	interquartile range
LBW	low birth weight
LGA	large for gestation age
MBAA	monobromoacetic acid
MCAA	monochloroacetic acid
MX	halogenated furanone
N	population size
n	sample size
NTD	neural tube defect
OR	odds ratio
PTB	preterm birth (preterm delivery)
RR	relative risk

SAB	spontaneous abortion
SB	still birth
SGA	small for gestational age – also referred to as intrauterine growth restriction (IGR, IUGR), fetal growth restriction (FGR)
STD	sexually transmitted diseases
suppl	supplement
TBAA	tribromoacetic acid
TBM	bromoform (tribromoform) - $CHBr_3$
TCAA	trichloroacetic acid
THM	trihalomethane
TTHM	total trihalomethanes (sum of the 4 THM = CHL + BDCM + DBCM + TBM)
VLBW	very low birth weight
w/	with
w/in	within

Background

Proposition 65[1] requires the State of California to publish a list of chemicals known to cause cancer or reproductive toxicity. This list must be updated at least once a year. Reproductive toxicity includes developmental toxicity, and female and male reproductive toxicity. Chemicals added to the list as known to cause reproductive toxicity affect one or more of these endpoints.

Chloroform was added to the list as known to cause reproductive toxicity in 2009 because it was identified by reference as such in the California Labor Code. Proposition 65 thus required its inclusion on the list, as discussed in greater detail below. There are three additional ways for a chemical to be added to the Proposition 65 list:

1. The Developmental and Reproductive Toxicant Identification Committee (DARTIC) finds that the chemical has been clearly shown to cause reproductive toxicity.
2. An organization designated as an "authoritative body" by the DARTIC has identified it as causing reproductive toxicity[2].
3. An agency of the state or federal government requires that it be labeled or identified as causing reproductive toxicity.

Reason for Reconsideration of Listing

Because of changes in federal regulations, chloroform no longer meets the criteria for inclusion on the list on the basis of the Labor Code mechanism. Following the process for the first of the three listing mechanisms cited above, OEHHA is presenting chloroform to the DARTIC for a decision as to whether it has been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity. If the Committee makes that determination, the chemical will remain on the list.

Chloroform was added to the list on the basis of a Threshold Limit Value (TLV) developed by the American Conference of Governmental Industrial Hygienists (ACGIH)

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986: Health and Safety Code section 25249.5 *et seq.,* passed by voter initiative.

[2] Title 27, California Code of Regulations, section 25306(l). The authoritative bodies are: U.S. Environmental Protection Agency, U.S. Food and Drug Administration, National Institute for Occupational Safety and Health, National Toxicology Program solely as to final reports of the National Toxicology Program's Center for Evaluation of Risks to Human Reproduction, and International Agency for Research on Cancer solely as to transplacental carcinogenicity.

that was based in part on developmental toxicity. The TLV provided a basis for listing via the Labor Code at the time because:

- Proposition 65 provides that the list of chemicals known to the state to cause reproductive toxicity "shall include at a minimum those substances identified by reference in Labor Code Section 6382(b)(1) and those substances identified additionally by reference in Labor Code Section 6382(d)[3]".

- California Labor Code Section 6382(d) further provides that "…any substance within the scope of the federal Hazard Communication Standard (29 C.F.R. Section 1910.1200) is a hazardous substance subject to this chapter".

- Until 2012, the federal Hazard Communication Standard (HCS) incorporated TLVs as a definitive source for establishing that a chemical is hazardous.

In March 2012, the federal Occupational Safety and Health Administration amended the HCS to remove reference to ACGIH TLVs as a mandatory basis for establishing that chemicals are hazardous. Consequently, a TLV based on reproductive or developmental toxicity no longer provides the basis for listing a chemical as known to the state to cause reproductive toxicity under Proposition 65.

Reconsideration Procedure

Chloroform is being brought to the DARTIC because it does not meet the criteria for inclusion on the list by any of the other listing mechanisms contained in the statute.

The Office of Environmental Health Hazard Assessment (OEHHA) has, through a contract with the Sheldon Margen Public Health Library at the University of California, Berkeley, conducted literature searches to identify studies that potentially provide information on the reproductive toxicity of chloroform. The searches covered the three major reproductive toxicity endpoints, namely developmental toxicity and male and female reproductive toxicity. The databases searched and parameters used in these searches are described in Appendix D.

The results of these searches were reviewed by OEHHA staff and all studies that provided data on reproductive toxicity were identified. The design parameters and results of these studies on male reproductive, female reproductive and developmental toxicity are summarized in tables as described below. The complete study reports for

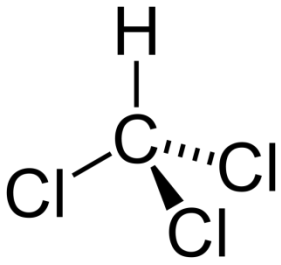
[3] Health and Safety Code section 25249.8(a)

chloroform have been provided to the DARTIC and are available to the public upon request.

For completeness, the original ACGIH document that specifically supported development of the chloroform TLV has also been provided to the DARTIC in electronic form. This document was not used in the process that resulted in the 2009 listing of chloroform under Proposition 65. Rather, the inclusion of the chloroform TLV based in part on a reproductive toxicity endpoint in the document, “Threshold Limit Values for Chemical Substances and Physical Agents in the Environment, American Conference of Governmental Industrial Hygienists (ACGIH)” (latest edition) resulted in the listing. The relevant entry from that document also has been provided in electronic form to the committee. In addition, chloroform was previously considered for listing by the DARTIC in 2004 and again in 2005 after additional information and analysis of data were provided at the DARTIC’s request. Chloroform was not identified by the DARTIC at that time as causing reproductive toxicity. The hazard identification materials provided to the DARTIC in 2004 and 2005 are also being provided to the current Committee members (see Attachment 1 and Appendix C, respectively).

1. Introduction

1.1. Compound identification, physical properties and uses



Chloroform (1,1,1-Trichloromethane)
Molecular Formula: $CHCl_3$, CAS Number 67-66-3

Chloroform (CHL) is a colorless liquid with a pleasant odor. Its physical properties are as follows (NIOSH Pocket Guide to Chemical Hazards http://www.cdc.gov/niosh/npg/npgd0127.html):

Molecular Weight 119.4	**Boiling Point** 143°F	**Freezing Point** -82°F	**Solubility** (77°F): 0.5%
Vapor Pressure 160 mmHg	**Ionization Potential** 11.42 eV	**Specific Gravity** 1.48	

1.2. Use and exposure information

The major use of chloroform is in production of chlorodifluoromethane, in turn a major precursor of tetrafluoroethylene. It is a common laboratory solvent and reagent, a byproduct of chlorine water disinfection, and was formerly used as a surgical anesthetic.

2. Human Studies of Reproductive and Developmental Toxicity of Chloroform

2.1. Notes on Exposure Assessment in Epidemiologic Studies of Chloroform

Information on exposures to chloroform is discussed in Sections B.2 and C.4.1 of the 2004 OEHHA Hazard Identification Document, "Evidence on the Developmental and Reproductive Toxicity of Chloroform" (Attachment 1). Additional more recent relevant exposure information is briefly summarized here.

In 2002, U.S. EPA lowered the total trihalomethane drinking water standard from 0.10 mg/L to 0.08 mg/L for large surface water systems and in 2004 for smaller systems ("Stage 1 and Stage 2 Disinfectants and Disinfection Byproducts Rules", available at https://www.epa.gov/dwreginfo/stage-1-and-stage-2-disinfectants-and-disinfection-byproducts-rules). Analysis of the National Health and Nutrition Examination Survey (NHANES) data showed a significant decline (76%) in blood chloroform levels between 1999-2004; however, a similar decrease was not seen in the other trihalomethanes levels (LaKind et al., 2010; Riederer et al., 2014).

Well-controlled exposure studies have identified many factors that affect blood chloroform levels in humans, including showering and bathing, washing dishes by hand, and ingestion of hot beverages made with tap water, etc., with showering and bathing shown to be a strong if not the strongest predictor of blood chloroform levels (Lynberg et al., 2001; Nuckols et al., 2005; Backer et al., 2008). Additionally, genetic participants with GSTT1-null (inactive enzyme) have been shown to have higher post-shower blood chloroform concentrations than GSTT1-positive participants (Backer et al., 2008). GSTT1-1 is polymorphic in humans, with approximately 20-25% of Caucasian and 50% of Asians having a homozygous deletion of this gene, resulting in the null genotype (Landi et al., 1999).

Recent studies have used blood chloroform levels as measures of exposure. Although blood chloroform decreases within a relatively short timeframe (minutes to hours), a steady-state concentration is thought to exist due to frequency of exposure throughout the day, from activities such as showering and bathing, and slow partitioning out of adipose tissue (Blount et al., 2011).

Few epidemiologic studies have measured chloroform at the tap water in each participant's residence. Chloroform levels can change with distance from the municipal water treatment plant. With an increased amount of organic matter in the system, chloroform levels will likely increase by the time the water is delivered to a residence at increasing distance from the treatment plant. The amount of organic matter can vary depending on season. Therefore, relying on chloroform measurements taken at the treatment plant would likely introduce exposure misclassification. However, this misclassification should be non-differential in that the probability of being misclassified should not differ across groups of study participants.

Products containing triclosan have been shown to react with free chlorine in drinking water to increase the formation of chloroform (Rule et al. 2005). Fiss et al. (2007) found that reactions between triclosan in household consumer products (such as anti-microbial soaps) and free chlorine at the tap leads to exposure to reaction products such as chloroform, chlorinated phenols and chlorinated phenoxy-phenols. In model simulations for formation of chloroform from tap water (at the maximum contaminant level of 80 µg/L for trihalomethanes) and triclosan-containing products, Fiss et al. (2007) calculated that exposure from inhalation and dermal routes could lead to exposures of 6.8–28 mg/year, or an increase in an individual's overall exposure by 15-40%. Since the use of many triclosan-containing products is widespread, this could conceivably lead to considerable misclassification of exposure.

Imprecise exposure assessment resulting in non-differential misclassification of exposure would likely bias the estimate of any association of risk towards the null (i.e., to not detecting an effect even if one were present).

2.2. Notes on the Tables and Figures Presenting Human Studies of Reproductive Outcomes

The tables and figures in this document include almost all the studies presented in the 2004 HID, as well as studies published from 2004 into 2015. Two studies in the 2004 HID which are not included here are Tylleskar-Jensen (1967), a case study of eclampsia published in Danish and cited in Reprotext 2004 but not translated by OEHHA, and a study of semen quality (Fenster et al., 2003) that presented results for total trihalomethanes only, in which chloroform was not the dominant trihalomethane in the water.

Three studies in which chloroform was not included in the statistical analysis assessing risk of exposure were included in these tables. In the studies of Lewis et al. (2006, 2007) chloroform accounted for ~90 percent of total trihalomethane concentration but the statistical analysis was conducted only for total trihalomethane concentration. In the study by Patelarou et al. (2011), a very well-conducted study, chloroform concentrations were very low and thus were not included in the statistical analysis. Hence, this study does not appear in Tables 3a, 3b or A3a.

To facilitate consideration of this complex data set, the tables and figures for the human studies of reproductive outcomes are presented in order of increasing detail. Thus, Table 1 is a list of the studies and outcomes, organized by the measure of exposure, which provides a high level overview of the scope of the dataset.

Table 2 provides more detailed information of each study concerning study design and exposure, organized chronologically. This table, however, is still intended as an overall reference for the dataset.

Figures 1-9 are forest plots of specific reproductive outcomes organized by outcome and by measure of exposure:

Figure 1 – Preterm birth by water concentration;
Figure 2 – Preterm birth by estimated internal dose;
Figure 3 – Small for gestational age by water concentration;
Figure 4 – Small for gestational age by estimated internal dose;
Figure 5 – Low birth weight and very low birth weight by water concentration;
Figure 6 – Low birth weight and very low birth weight by change in water concentration;
Figure 7 – Low birth weight and VLBW by estimated internal dose;
Figure 8 – Birth weight by water concentration;
Figure 9 – Birth weight by estimated internal dose.

The studies in each figure are organized by increasing chloroform exposure based on the lowest value for each study's highest exposure category.

Table 3a provides a detailed summary of each of the studies examining preterm birth, small for gestational age, low birth weight or birth weight, ordered chronologically. Similarly, Table 4a provides summaries for the studies of spontaneous abortion, stillbirth, birth defects, fertility and menstrual cycle function, with Table 5a providing the summaries for studies of sperm quality.

Tables 3b, 4b, and 5b provide the findings of associations between chloroform exposure levels and risk estimates for the studies in Tables 3a, 4a, and 5a. These tables are organized by increasing water chloroform concentration exposure, based on the lowest value for each study's highest exposure category. If the study did not present risk estimates for water chloroform concentration, then ranking was based on the next most relevant measure (e.g., integrated uptake values). Companion tables presented in Appendix A as Tables A3c, A4c and A5c correspond to Tables 3c, 4c and 5c,with the addition of the risk estimates for other trihalomethanes, in addition to those for chloroform.

Additionally, Table B1 in Appendix B presents measured concentrations for chloroform exposures as well as those for total trihalomethanes, bromodichloromethane, and dibromochloromethane.

The complete list of Tables included in Appendices presenting information from these human studies is as follows:

Appendix A:
Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Studies that examined uptake of chloroform (or other trihalomethanes) through various routes of exposure used different terminology to represent estimated internal dose (e.g. internal uptake, total integrated uptake, etc.). In most of the figures and tables presented in this HID, for ease of reading and comparison across studies, this document generally used the term “estimated internal dose” to indicate uptake. The exception is the detailed summary tables (Tables 3a, 4a, and 5a) in which the terms used in the studies were retained in order for the reader to more easily read the table in conjunction with the study publications.

Unless otherwise noted, low birth weight was defined as birth weight less than 2,500 grams, small for gestational age was the lowest 10^{th} centile of birth weight for each gestational week, and preterm birth was <37 weeks gestation.

The sample sizes are presented using the abbreviation N for the initial study population and n for the resulting sample population after any exclusion or loss to follow-up, etc. All odds ratios and risk ratios where the confidence interval does not include 1, or analyses where the p value is < 0.05 are shown in bold.

All results are presented as adjusted for covariates/confounders unless otherwise noted.

Under the column “Covariates/Confounders” (Tables 3a, 4a, and 5a) the variables adjusted for in the analysis are noted. Other variables considered but not adjusted for in the models are noted at the bottom of that column.

In most studies, covariates were retained in the models if they were statistically significant or if they changed the effect estimate (odds ratio or β-coefficient) by greater than 10%. If a study used different criteria for the inclusion of covariates it was noted in the table.

Most studies assessed maternal residence from birth records and did not account for maternal residential mobility during pregnancy. Therefore, it is only noted in the comments section of the detailed summary tables (Tables 3a, 4a, and 5a) when a study did take this into account.

Some studies collected information concerning exposure to trihalomethanes at work. However, few studies that collected this information quantified it and included it in the statistical analysis. Therefore, as with residential mobility, work exposure is only noted in the comments section of the detailed summary tables when the study did take this exposure into account.

None of the studies adjusted for multiple comparisons.

Unless otherwise noted, estimated internal dose (including total uptakes, etc.) incorporated estimated uptake from ingestion, inhalation and dermal exposure.

Findings for other disinfection by-products were only presented if results were statistically significant. However, significant associations for total trihalomethanes were not routinely presented in the tables since in almost all the studies chloroform accounted for the majority of the total trihalomethane concentration and the results were similar.

The studies were reviewed for their disclosure statements with respect to any declared conflict of interest. Almost all the studies included a statement in which the authors declared “no conflict of interest or “no competing interests” and/or “no competing financial interests”. One of the older studies (Dahl et al., 1999) and the study by Zhou et al. (2010) translated from Chinese did not include such a statement.

The following groups of studies, noted by different symbols, were conducted using the same participants or a subset of the same participants. These symbols are used throughout the tables to indicate these related studies.

* Botton et al., 2015; Villanueva et al., 2011, Patelarou et al., 2011
  Botton et al. used a subset of the participants from a mother-child cohort study in Spain (Infancia y Medio Ambiente (INMA)) (Villanueva et al.).
  Although Botton et al. also included participants from another cohort in Greece (RHEA) (Patelarou et al., 2011), the chloroform levels for the Greek cohort were mostly undetectable and thus were excluded from the analyses.

† Hoffman et al., 2008; Savitz et al., 2005
Hoffman et al. included a subset of the cohort enrolled in Savitz et al. Savitz et al., 2006 is a peer-reviewed article with a subset of findings published in Savitz et al., 2005, thus this HID only cites the more complete 2005 publication.

‡ Lewis et al., 2007; Lewis et al., 2006
These study populations were from the same database of vital records and were almost exactly the same participants.

* * King et al., 2000; Dodds and King, 2001
These study populations were from the same population-based perinatal database. The same environmental monitoring data was used by both studies for exposure assessment.

† † Zeng et al., 2014; Zeng et al., 2013
Zeng et al., 2013 used a subset of study participants included in Zeng et al., 2014.

‡ ‡ Grazuleviciene et al., 2013; Danileviciute et al., 2012; Grazuleviciene et al., 2011
Each study used different subsets of subjects from the same prospective cohort (Kaunas HiWATE).

Table 1. Reproductive Outcomes Assessed in Human Studies of Chloroform (CHL) Exposure, Grouped by Exposure Measure.

Studies Grouped by Exposure Measure[1]	Outcome (number of studies by any exposure measure)								
	PTB (9)	SGA (15)	LBW (9)	BW (10)	SAB (3)	SB (4)	BD (3)	Sperm Quality (4)	Other (3)
Water Concentration									
Iszatt et al. 2014			X (and VLBW)			X			
Iszatt et al. 2013								X	
Rivera-Nuñez and Wright 2013	X	X		X					
Summerhayes et al. 2012		X		X					
Patelarou et al. 2011*	X	X	X						
Zhou et al. 2010				X					
Hoffman et al. 2008 †		X		X					
Lewis et al. 2007 ‡	X								
Lewis et al. 2006 ‡			X						
Hinckley et al. 2005	X	X	X						
Porter et al. 2005		X							
Toledano et al. 2005			X (and VLBW)			X			
Dodds et al. 2004						X			
Infante-Rivard 2004		X							
Wright et al. 2004	X	X		X					
Windham et al. 2003									X (Menstrual cycle function)
Dodds and King 2001 * *							X		
King et al. 2000 * *						X			
Waller et al. 1998					X				
Kramer et al. 1992	X	X	X						

Abbreviations: BD - birth defects; BW - birth weight; CHL - chloroform; LBW - low birth weight; PTB - preterm birth; SAB - spontaneous abortion; SB - stillbirth; SGA - small for gestational age; VLBW - very low birth weight.

[1] Studies with the same symbol (e.g., *) are drawn from the same population or cohort. See "Introductory notes for tables" for an explanation of the relationship of study populations among the studies marked with a given symbol.

Table 1. Reproductive Outcomes Assessed in Human Studies of Chloroform (CHL) Exposure, Grouped by Exposure Measure (cont'd).

Studies Grouped by Exposure Measure	Outcome								
	PTB	SGA	LBW	BW	SAB	SB	BD	Sperm Quality	Other
Estimated Internal Dose[2]									
Botton et al. 2015* [3]									X (Postnatal weight gain)
Smith et al. 2015				X					
Zeng et al. 2014 † † [3,4]								X	
Grazuleviciene et al. 2013 ‡ ‡							X		
Costet et al. 2012 [3,5]	X	X							
Danileviciute et al. 2012 ‡ ‡		X	X						
Levallois et al. 2012 [3,5]		X							
Grazuleviciene et al. 2011 ‡ ‡		X	X	X					
Iszatt et al. 2011[3,5]							X		
Villanueva et al. 2011*	X	X	X	X					
Savitz et al. 2005 † [3,5]	X	X		X	X				
Blood Level									
Zeng et al. 2013 † †								X	
Air Samples									
Chang et al. 2001								X	
Questionnaire re: Occupational Exposure									
Wennborg et al. 2000				X	X				
Dahl et al. 1999									X (Fertility)

[2] Generally these studies estimated the internal dose of CHL as the sum of uptakes from the dermal, inhalation, and ingestion routes of exposure.
[3] Results for individual routes of exposure were also reported.
[4] Zeng et al. (2014) did not report total dose; only results for routes of exposure through ingestion and showering/bathing were reported.
[5] Risks were also calculated for CHL concentration in water.

Table 2. Summary of Selected Study Design Elements and Measured or Estimated Chloroform (CHL) Levels in Human Reproductive Studies.

Study					*Exposure*		
Author Year of Study	***Design***	***Location***	***Outcomes/ Sample Size***	***Timing***	***Assessment***	***CHL Level[1]***	***Other DBPs Measured and Analyzed [2]***
Botton et al.* 2015	Prospective cohort	Spain (3 locations)	Postnatal weight growth Total n = 2,216	Entire pregnancy	Monitoring data	Median (µg/L): Gipuzkoa = ~12, Sabadell = ~20, Valencia = ~0	TTHM BrTHM
					Estimated internal dose	Range (µg/d): Gipuzkoa = ~0-0.05, Sabadell = ~0-1.4, Valencia = ~0-2.1	
Smith et al. 2015	Prospective cohort	England	BW n = 7,438	Each trimester Entire pregnancy	Monitoring data	Time-weighted average conc: Mean (SD) (µg/L) = 37.8 (3.8)	THMs[3] HAAs BrTHM
					Estimated internal dose	Mean (SD) (µg/d) = 1.61 (1.46)	
Iszatt et al. 2014	Retrospective cohort Intervention - enhanced coagulation water treatment (EC)	England	Total live births n = 429,599 LBW n = 27,664 VLBW n = 4,209 SB n = 2,279	Entire pregnancy	Monitoring data	Mean (SD) (µg/L): Before EC = 38.6 (4.2) After EC = 19.4 (1.0)	TTHM BDCM DBCM
Zeng et al. † † 2014	Prospective cohort	China	Sperm parameters n = 324	Time of semen sample relative to days of abstinence	Monitoring data	Mean (µg/L) =13.71	TTHM BrTHM
					Estimated internal dose	Ingestion: IQR (µg/d) = 0.005–0.019 Showering/bathing: IQR (µg/d) = 0.064–0.246	
Grazuleviciene et al. ‡ ‡ 2013	Prospective cohort	Lithuania	Birth Defects Heart n = 57 Musculo-skeletal n = 37 Urogenital n = 23 Total n = 3,074	1st, 2nd, and 3rd month 1st trimester	Monitoring data	Mean (SD) (µg/L): all sites = 7.8 (10.2) 3 plants = 0.9 (1.0) 1 plant = 17.7 (9.0)	THMs TTHM HAAs [4] MX [4]
					Estimated internal dose	Range (µg/d) = 0.001–2.109	

Abbreviations: BDCM - bromodichloromethane; BrTHM - total brominated trihalomethanes; BW - birth weight; CHL - chloroform; conc - concentration; d – day; DBCM - dibromochloromethane; DBP - disinfection by-products; EC - enhanced coagulation; exp - exposure; HAA - haloacetic acid; IQR - interquartile range; IUGR - intrauterine growth restriction; L – liter; LBW - low birth weight; NTD - neural tube defect; PTB - preterm birth; SB - stillbirth; SD - standard deviation; SGA - small for gestational age; MX - halogenated furanone (trichloromethane); TBM - bromoform; TCAA - trichloroacetic acid; THMs - trihalomethanes; TTHM - total trihalomethanes (sum of CHL, BDCM, DBCM, and TBM); VLBW - very low birth weight.
Total n - number of individuals included in the final analysis.

* Studies with the same symbol (e.g. *) are drawn from the same population or cohort. See “Introductory notes for tables” for an explanation of the relationship between studies.

[1] CHL level measured in monitored water samples unless otherwise noted.
[2] Other DBPs which were included in the statistical analysis unless otherwise noted.
[3] In every instance where THMs appears in this table, statistical analyses were conducted on each of the THMs separately.
[4] Measured concentration occurred only at very low levels, and was therefore not included in the statistical analysis.

Table 2. Summary of Selected Study Design Elements and Measured or Estimated Chloroform (CHL) Levels in Human Reproductive Studies (cont'd).

Study					*Exposure*		
Author Year of Study	***Design***	***Location***	***Outcomes/ Sample Size***	***Timing***	***Assessment***	***CHL Level[1]***	***Other DBPs Measured and Analyzed [2]***
Iszatt et al. 2013	Case-control	England	Sperm concentration and motility cases n = 642 controls n = 926	Sampled 3–5 days after abstinence	Monitoring data	Mean (SD) (µg/L): cases = 25.9 (19.0) controls = 27.3 (19.1)	TTHM BrTHM
Rivera-Nuñez and Wright 2013	Retrospective cohort (semi-ecologic)	Massachusetts	SGA n = 68,409 BW n = 651,512 PTB n = 37,136 Total n = 672,120	Each trimester	Monitoring data	Mean (µg/L) = 30.6	THMs TTHM BrTHM HAAs
Zeng et al. † † 2013	Cross-sectional	China	Sperm parameters Serum testosterone n = 401	Time of semen sample relative to days of abstinence	Blood conc	Mean (µg/L) = 0.057 Median = 0.050	THMs TTHM BrTHM
Costet et al. 2012	Prospective cohort	France	SGA n = 171 PTB n = 105 Total n = 3,226	Each trimester	Monitoring data	Mean (SD) (µg/L) = 9.3 (7.0)	THMs TTHM Urinary TCAA
					Estimated internal dose	IQR (µg/d) = <0.068–<0.237	
Danileviciute et al.‡ ‡ 2012	Nested case-control	Lithuania	SGA n = 96 LBW n = 59 Total n = 682	Each trimester Entire pregnancy	Monitoring data	Mean (SD) (µg/L): all sites = 7.8 (10.2) 3 plants = 0.9 (1.0) 1 plant = 17.7 (9.0)	THMs TTHM HAAs [4] MX [4]
					Estimated internal dose Assessed GSTT1 and GSTM1 genotype	Median (µg/d) = 0.1424 Range = 0.0013–2.13	
Levallois et al. 2012	Population-based case-control	Quebec City	SGA cases n = 571 controls n = 1,925	Each trimester	Monitoring data	Mean (SD) (µg/L): cases = 43.3 (40.7) controls = 41.1 (39.2)	THMs TTHM BrTHM HAAs
					Estimated internal dose	IQR (µg/d) = <42.24–169.81	
Summerhayes et al. 2012	Retrospective cohort	Australia	SGA n = 31,813 BW n = 314,982 Total n = 314,982	Each trimester Entire pregnancy	Monitoring data	Mean (SD) (µg/L) = 33.6 (16.0) Median = 30.9 Range = 3.4–121.5	TTHM BDCM DBCM BrTHM HAAs [5]

[5] Not included in the statistical analysis.

Table 2. Summary of Selected Study Design Elements and Measured or Estimated Chloroform (CHL) Levels in Human Reproductive Studies (cont'd).

Study				*Exposure*		
Author Year of Study	***Design***	***Location***	***Outcomes/ Sample Size***	***Timing***	***Assessment***	***CHL Level[1]***	***Other DBPs Measured and Analyzed [2]***
Grazuleviciene et al. ‡ ‡ 2011	Prospective cohort	Lithuania	SGA n = 270 LBW n = 156 BW n = 3,341 Total n = 3,341	Each trimester Entire pregnancy	Monitoring data	Mean (SD) (µg/L): all sites = 7.8 (10.2) 3 plants = 0.9 (1.0) 1 plant = 17.7 (9.0)	THMs TTHM HAAs [4] MX [4]
					Estimated internal dose	Range (µg/d): 0.0013–2.13	
Izsatt et al. 2011	Case-control	England	Birth Defect - Hypospadias cases n = 354 controls n = 336	1st trimester	Monitoring data	Median (µg/L) = 2.9 Range = 0.0–90	THMs TTHM BrTHM
					Estimated internal dose	IQR (µg/d) = 0–101	
Patelarou et al.* [6] 2011	Prospective cohort	Greece	SGA n = 73 LBW n = 76 PTB n = 156 Total n = 1,359	Each trimester Entire pregnancy	Sampling of tap water in selected sites	Mean (SD) (µg/L) = 0.15 (0.15)	THMs BrTHM
Villanueva et al.* 2011	Prospective cohort	Spain (5 locations)	SGA n = 220 BW n = 2,074 LBW n = 95 PTB n = 77	Each trimester Entire pregnancy	Monitoring data and sampling of tap water from geographically representative areas	THM levels and percentiles were reported graphically	BrTHM
					Estimated internal dose	Median appeared to be under 0.5 µg/d	
Zhou et al. 2010	Retrospective cohort	China	BW n = 1,385	Each trimester 1st & 2nd trimester Entire pregnancy	Monitoring data	Range (µg/L) of mean values = 6.0–51.2	BrTHM HAAs
Hoffman et al. † 2008	Prospective cohort	US (3 locations)	SGA n = 113 BW n = 1,854 Total n = 1,958	Each trimester	Sampling of tap water from geographically representative locations - weekly and intensive short-term sampling	Mean (SD) (µg/L) = 46.7 (13.3) at chlorinated sites 13.7 (3.3) at brominated sites	THMs TTHM HAAs
Lewis et al. ‡ 2007	Population-based case-control	Massachusetts	PTB n = 2,813 Total n = 37,498	1st & 2nd trimester 4 weeks before birth Entire pregnancy	Monitoring data - weekly	TTHM (µg/L): Interquartile range = 59 Min, max of range = 28–87 CHL fraction of TTHM = 83–93%	TTHM
Lewis et al. ‡ 2006	Retrospective cohort	Massachusetts	LBW n = 780 Total n = 36,529	Each trimester Entire pregnancy	Monitoring data - weekly	TTHM (µg/L): IQR = 59 Min, max of range = 28–87 CHL fraction of TTHM = 83–93%	TTHM

[6] No separate statistical analysis was conducted for CHL as the measured concentrations were very low. Statistical analysis was conducted only for BrTHM.

Table 2. Summary of Selected Study Design Elements and Measured or Estimated Chloroform (CHL) Levels in Human Reproductive Studies (cont'd).

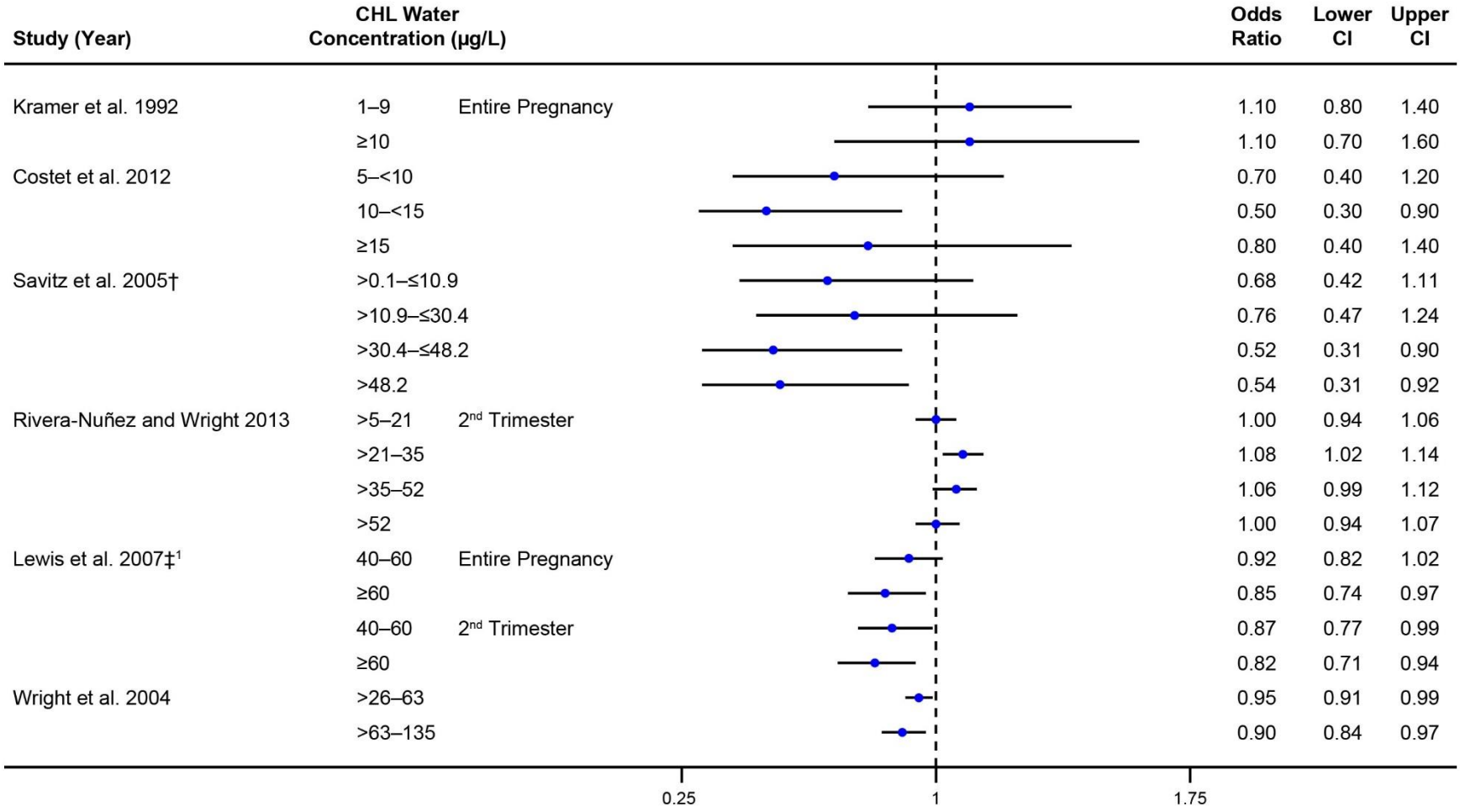
Study					*Exposure*		
Author Year of Study	***Design***	***Location***	***Outcomes/ Sample Size***	***Timing***	***Assessment***	***CHL Level[1]***	***Other DBPs Measured and Analyzed [2]***
Hinckley et al. 2005	Retrospective cohort	Arizona	IUGR n = 4,396 LBW n = 1,010 PTB n = 4,008 Very PTB n = 564 Total n = 48,119	Various time windows within the 3rd trimester	Monitoring data	Mean not reported CHL categories (µg/L) = <10, 10–16, ≥16	THMs TTHM HAAs
Porter et al. 2005	Retrospective cohort	Maryland	SGA n = 1,114 Total n = 15,315	Each trimester Entire pregnancy	Monitoring data	Mean (µg/L) (95% CI): all sites = 34.1 (32.5, 35.7)	THMs TTHM HAAs
Savitz et al. † 2005	Prospective cohort	US (3 locations)	Total n = 2,409 SGA n = 102 BW n = 1,738 PTB n = 196 SAB n = 258 Total n = 1,934	Early pregnancy (up to week 20)	Sampling of tap water from geographically representative locations – weekly and intensive short-term sampling	Mean (µg/L) = - 45.6 at chlorinated sites - Below minimum reporting level at brominated sites - 11.9 at low DBP site	THMs TTHM BrTHM HAAs
					Estimated internal dose	Range (week 27-birth) (µg/d) = 0–>1.3 (in the highest quartile)	
Toledano et al. 2005	Retrospective cohort	United Kingdom	LBW n = 60,641 Very LBW n = 9,167 SB n = 4,852 Total n = 920,571	3rd trimester (93 days before birth)	Monitoring data	Mean levels not reported CHL tertiles (µg/L) = <20, 20–40, >40	TTHM BDCM BrTHM
Dodds et al.[7] 2004	Population-based case-control	Nova Scotia and Ontario	SB cases n = 112 controls n = 398 Total n = 510	1st & early 2nd trimester	Residential tap water sampled for each subject	Mean levels not reported CHL categories (µg/L) = 0, 1–49, 50–79, >80	TTHM BDCM
Infante-Rivard 2004	Case-control	Montreal	SGA cases n = 458 controls n = 426 Total n = 884	Entire pregnancy	Monitoring data Assessed CYP2E1 and MTHFR C677Tgenotype	Mean (SD) (µg/L): cases = 11.84 (11.84) controls = 11.58 (16.31)	THMs TTHM
Wright et al. 2004	Retrospective cohort	Massachusetts	SGA n = 17,359 BW n = 3,463 PTB n = 11,580 Total n = 187,731	3rd trimester	Monitoring data	Median (µg/L) = 26 Range 0–135	THMs TTHM BDCM HAAs MX
Windham et al. 2003	Prospective cohort	California	Menstrual cycle function n = 403	90 day window	Monitoring data	Mean not reported CHL categories (µg/L) = 1st quartile, 2nd–3rd quartile, 4th quartile (≥17)	THMs TTHM BDCM DBCM TBM

[7] Daily exposure from ingestion, inhalation and absorption were also estimated but no values were presented.

Table 2. Summary of Selected Study Design Elements and Measured or Estimated Chloroform (CHL) Levels in Human Reproductive Studies (cont'd).

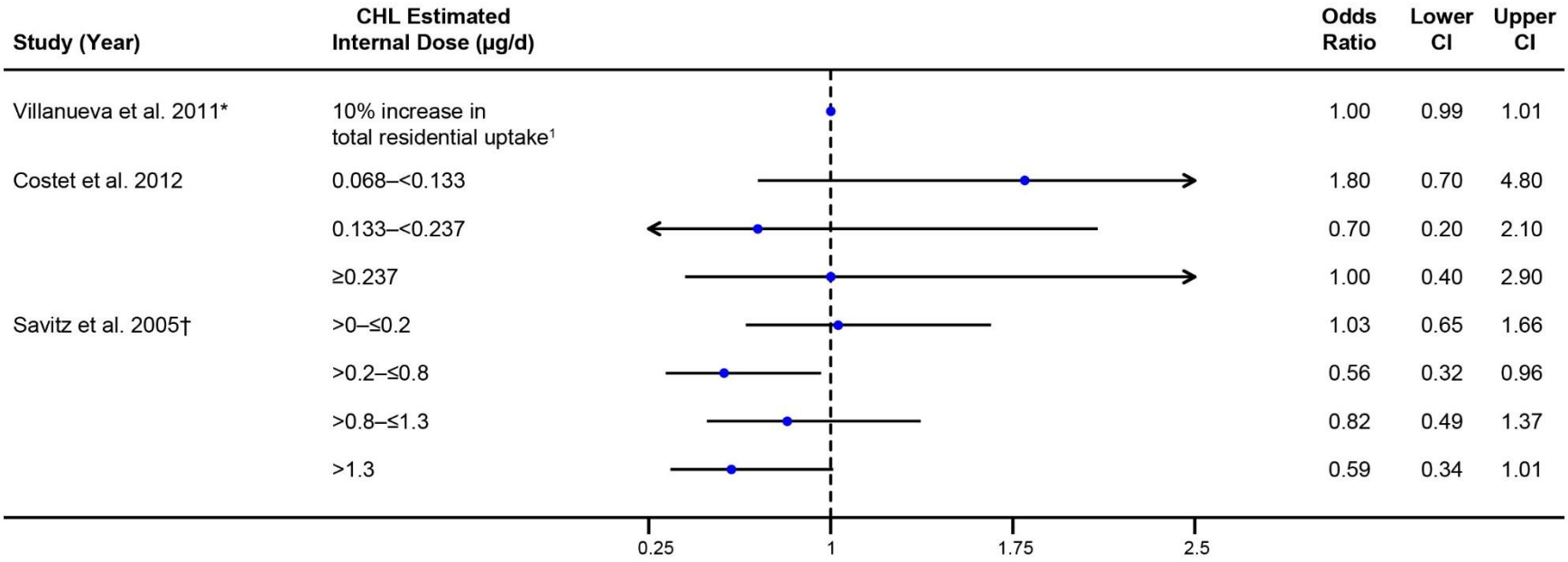
Study				*Exposure*			
Author Year of Study	***Design***	***Location***	***Outcomes/ Sample Size***	***Timing***	***Assessment***	***CHL Level[1]***	***Other DBPs Measured and Analyzed [2]***
							BrTHM
Chang et al. 2001	Case report	Taiwan	Sperm Parameters n = 1	Sampled 4 days after abstinence	Reconstructed scenario of air exposure using passive and active sampling	Air samples = 8.5 ppm active sample 4.6 ppm passive sample	
Dodds and King * * 2001	Retrospective cohort	Nova Scotia	Birth Defects NTD n = 77 Cleft n = 82 Cardiovascular n = 430 Chromosomal abnormalities n = 96 Total n = 49,842	1 -3 months prior to pregnancy and 1 month after conception (time frames were specific to the birth defect	Monitoring data	Mean (µg/L) = 64.1	BDCM DCBM [4] TBM [4]
King et al. * * 2000	Retrospective cohort	Nova Scotia	SB n = 214 Total n = 49,756	Entire pregnancy	Monitoring data	Mean (µg/L) = 64.1	TTHM BDCM DCBM [4] TBM [4]
Wennborg et al. 2000	Retrospective cohort (BW) Case control (SAB)	Sweden	BW n = 654 SAB n = 73 Total n = 869 (number of pregnancies)	Pre-pregnancy	Interview questionnaire: work history with exp to CHL	No CHL levels measured	
Dahl et al. 1999	Retrospective cohort	Norway	Fertility measured as time to pregnancy n = 1408 pregnancies	6 months pre-pregnancy	Interview questionnaire: work performed w/ dental restorative materials and chemicals (number per week)	75% reported use of CHL-based materials	
Waller et al. 1998	Prospective cohort	California	SAB n = 499 Total n = 5,144	1st trimester	Monitoring data Ingestion data	CHL reported as categories (µg/L): 0–3 = 13.6% 4–16 = 30.1% ≥17 = 17.6%	THMs TTHM
Kramer et al. 1992	Population-based case-control	Iowa	SGA cases n = 187 controls n = 935 LBW cases n = 159 controls n = 795 PTB cases n = 342 controls n = 1,710	At time of birth	Monitoring data	Mean (SD) (µg/L) = 12.5 (38.7) Median = 1 Range = 0–350	THMs Total organic halides

Figure 1. Preterm Birth (PTB). Forest plot of the association between chloroform (CHL) exposure [water concentration] and PTB. Confidence intervals (95%) are denoted by "CI." Studies are ordered based on the lowest value of each study's highest exposure category. Results represent third trimester exposure unless otherwise noted.



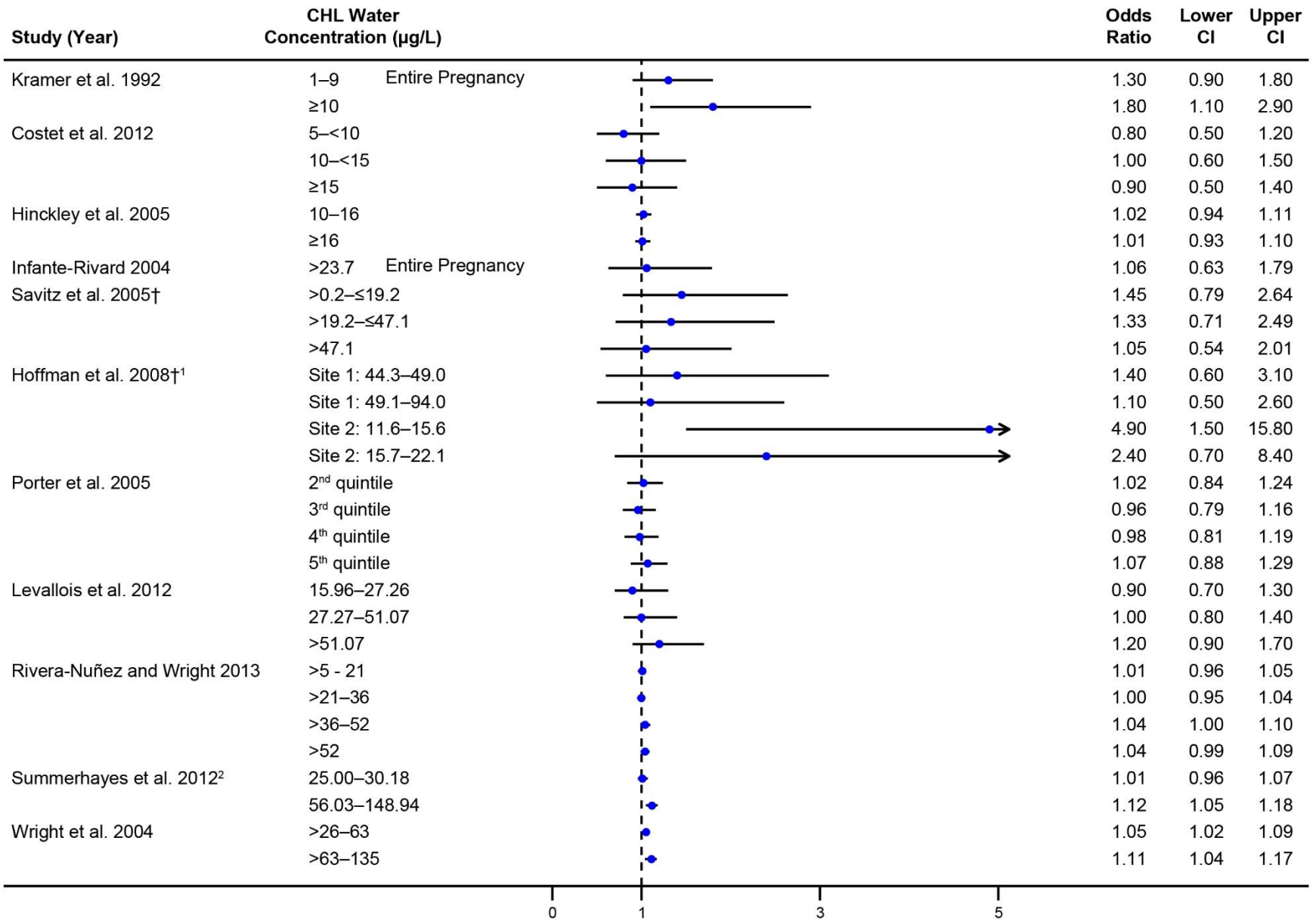
[1] Lewis et al. 2007 measured total trihalomethanes (TTHM), of which CHL constituted ~90%. Risk estimate is a hazard ratio.

Figure 2. Preterm Birth (PTB). Forest plot of the association between chloroform (CHL) exposure [estimated internal dose] and PTB. Confidence intervals (95%) are denoted by "CI." Studies are ordered based on the lowest value of each study's highest exposure category. Results represent third trimester exposure.



[1] β-coefficients from the regression model were multiplied by the logarithm of 1.1 to derive an effect estimate for a 10% increase in exposure.

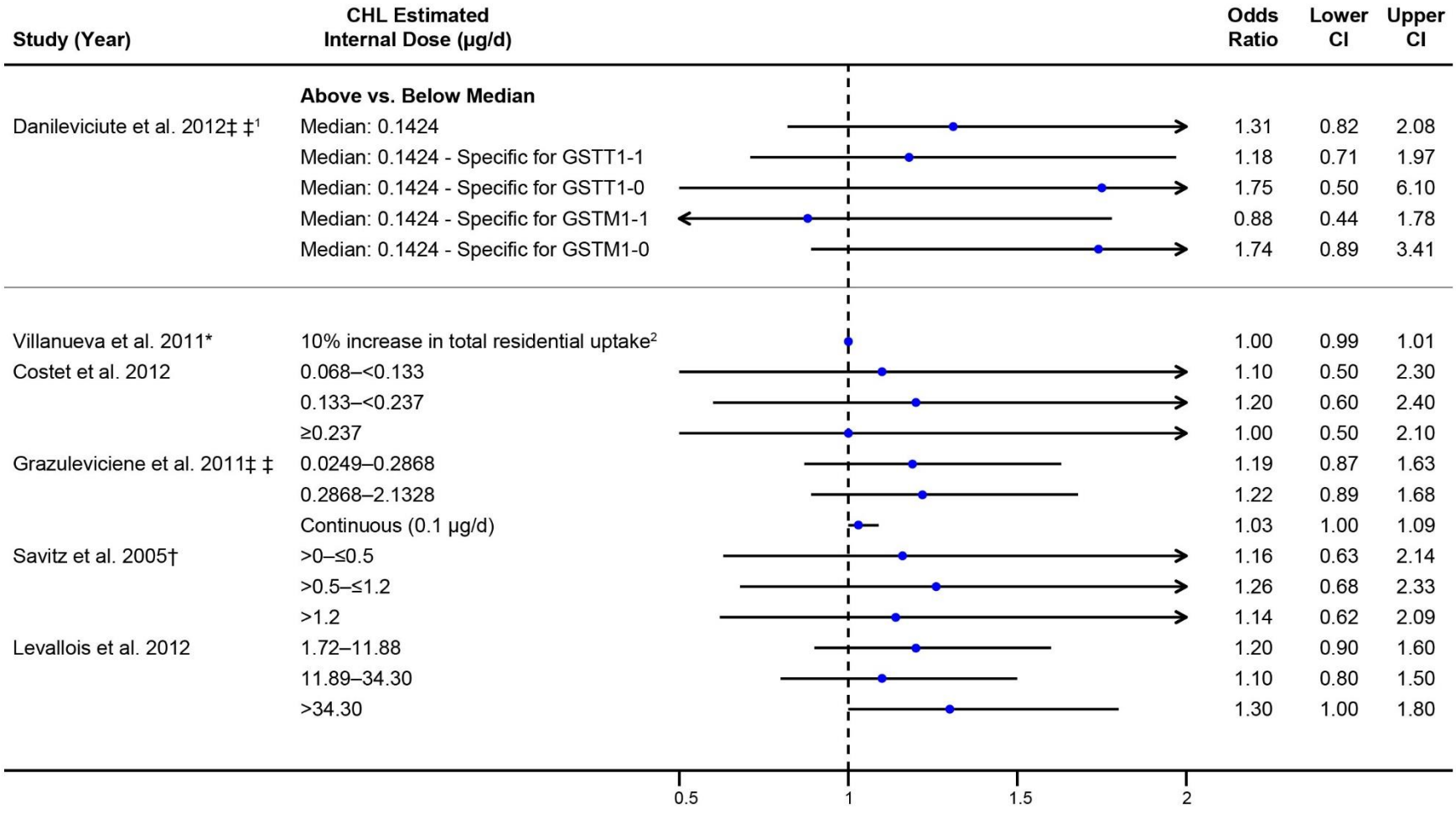
Figure 3. Small for Gestational Age (SGA). Forest plot of the association between chloroform (CHL) exposure [water concentration] and SGA. Confidence intervals (95%) are denoted by "CI." Studies are ordered based on the lowest value of each study's highest exposure category. Results represent third trimester exposure unless otherwise noted.



[1] Hoffman et al. 2008 analyzed CHL exposure at two sites. Site 1 consisted predominantly of chlorinated disinfection by-products (DBPs). Site 2 consisted predominantly of brominated DBPs.

[2] Summerhayes et al. 2012 reported risk estimates as relative risks. Water concentration values represent 5th and 10th decile exposure values.

Figure 4. Small for Gestational Age (SGA). Forest plot of the association between chloroform (CHL) exposure [estimated internal dose] and SGA. Confidence intervals (95%) are denoted by "CI." Studies are ordered based on the lowest value of each study's highest exposure category. Results represent third trimester exposure.

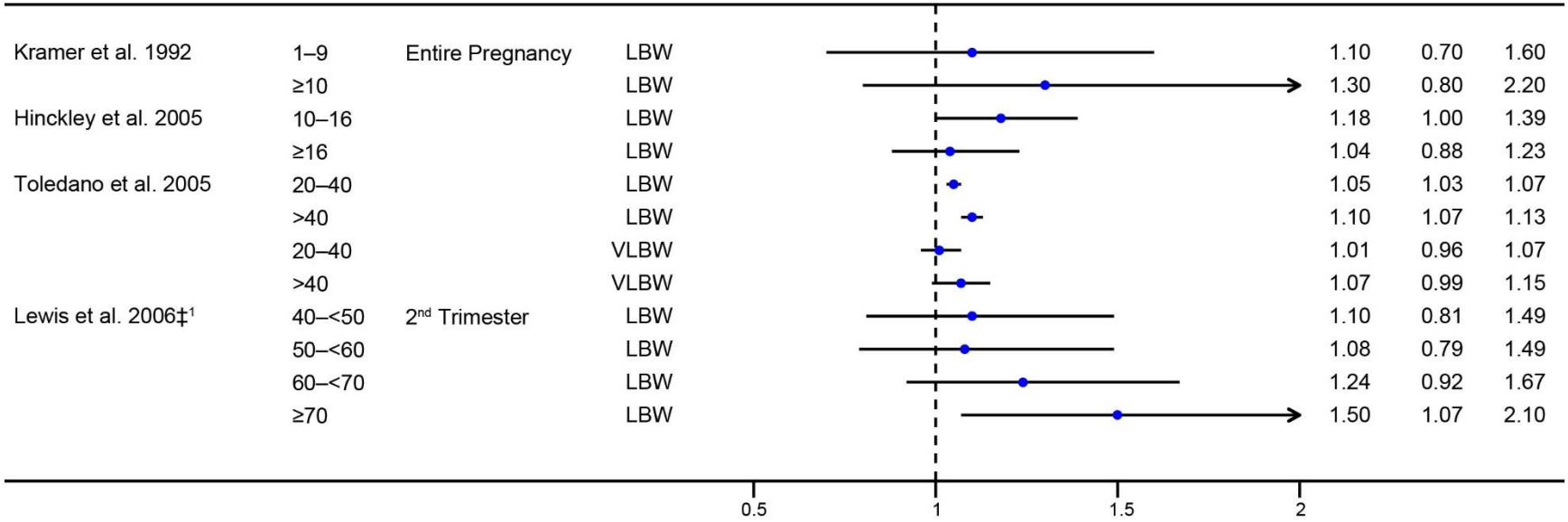


[1] Danileviciute et al. 2012 examined the polymorphisms of glutathione S-transferase (GST), GSTT1 and GSTM1. "GSTT1-1" represents the presence of gene activity and "GSTT1-0" represents the absence of gene activity. Similarly, "GSTM1-1" represents the presence of gene activity and "GSTM1-0" represents the absence of gene activity.

[2] β-coefficients from the regression model were multiplied by the logarithm of 1.1 to derive an effect estimate for a 10% increase in exposure.

Figure 5. Low Birth Weight (LBW) and Very Low Birth Weight (VLBW). Forest plot of the association between chloroform (CHL) exposure [water concentration] and LBW and VLBW. Confidence intervals (95%) are denoted by "CI." Studies are ordered based on the lowest value of each study's highest exposure category. Results represent third trimester exposure unless otherwise noted.

Study (Year)	CHL Water Concentration (µg/L)		Outcome	Odds Ratio	Lower CI	Upper CI
Kramer et al. 1992	1–9	Entire Pregnancy	LBW	1.10	0.70	1.60
	≥10		LBW	1.30	0.80	2.20
Hinckley et al. 2005	10–16		LBW	1.18	1.00	1.39
	≥16		LBW	1.04	0.88	1.23
Toledano et al. 2005	20–40		LBW	1.05	1.03	1.07
	>40		LBW	1.10	1.07	1.13
	20–40		VLBW	1.01	0.96	1.07
	>40		VLBW	1.07	0.99	1.15
Lewis et al. 2006‡[1]	40–<50	2nd Trimester	LBW	1.10	0.81	1.49
	50–<60		LBW	1.08	0.79	1.49
	60–<70		LBW	1.24	0.92	1.67
	≥70		LBW	1.50	1.07	2.10



[1] Lewis et al. 2006 measured total trihalomethanes (TTHM), of which CHL constituted ~90%. This study also examined third trimester exposure; for which the odds ratios were not significant.

Figure 6. Low Birth Weight (LBW) and Very Low Birth Weight (VLBW). Forest plot of the association between the change in chloroform (CHL) exposure [water concentration] and LBW and VLBW. Confidence intervals (95%) are denoted by "CI." Rate change is the percent change calculated as the exponential of the regression coefficient (e.g. rate ratio of after/before) minus 1 and multiplied by100. The timeframe for exposure is the entire pregnancy.

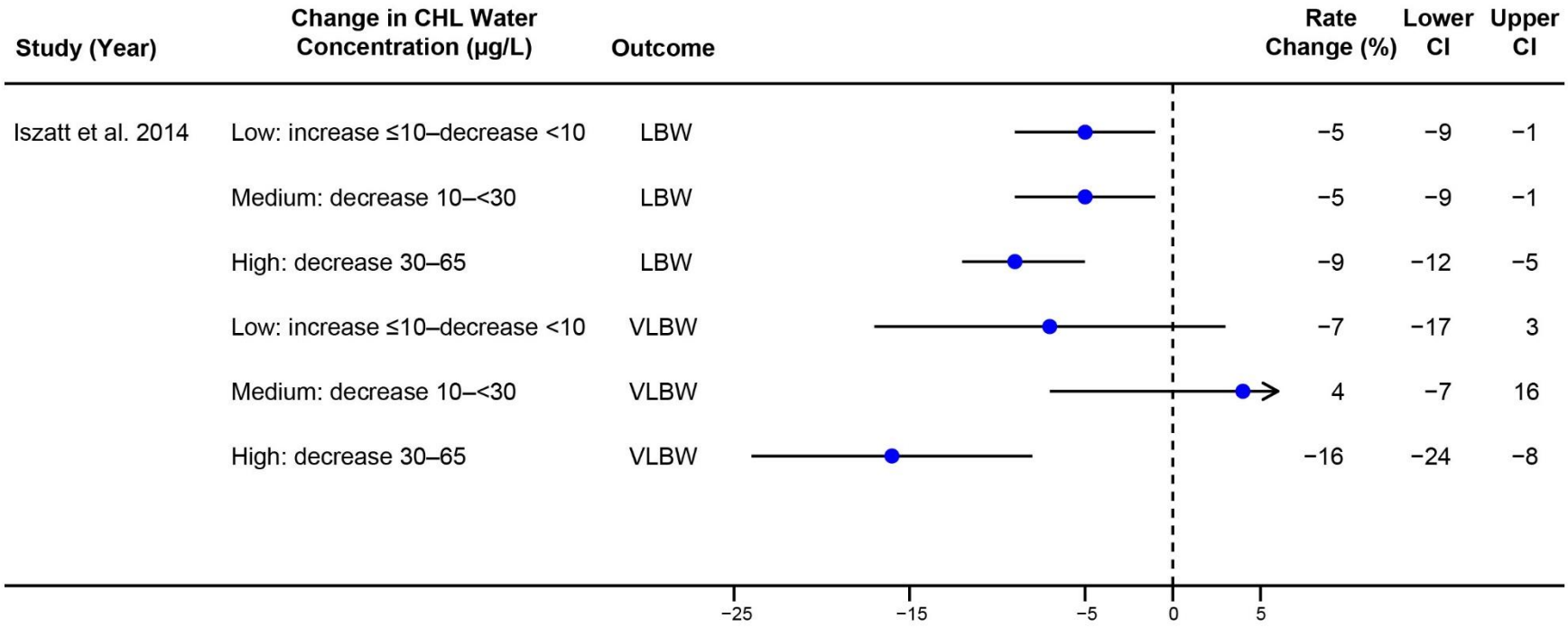
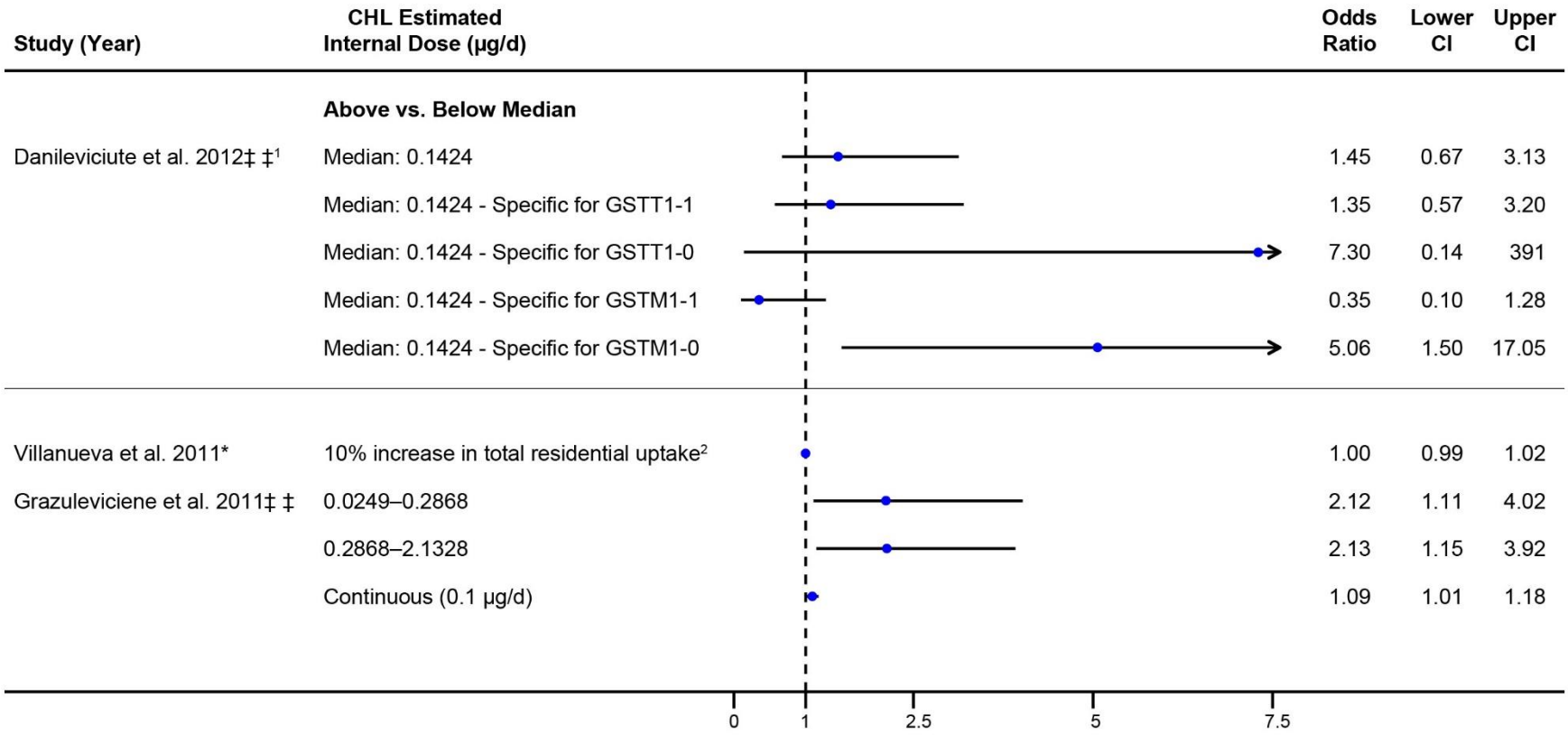


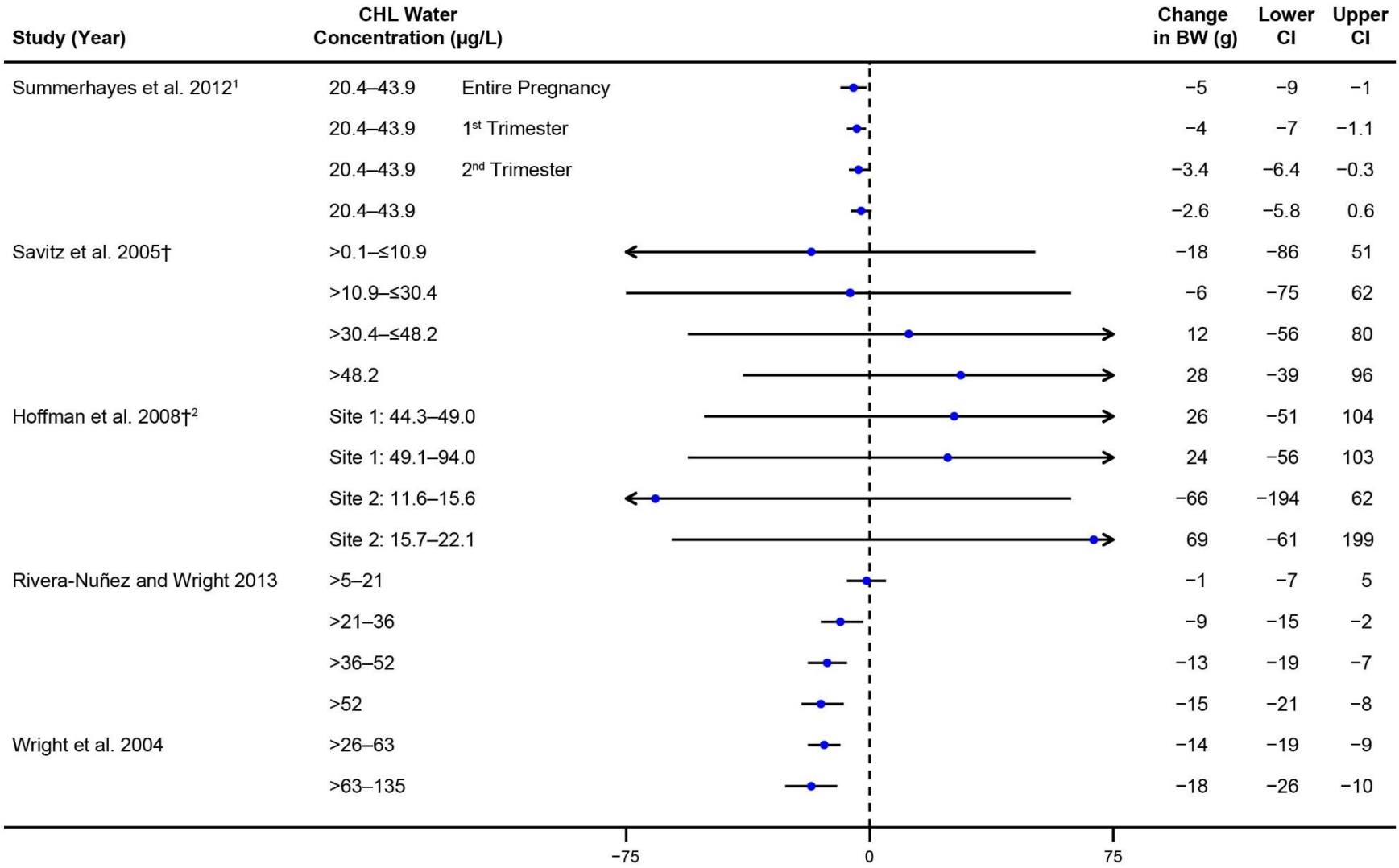
Figure 7. Low Birth Weight (LBW). Forest plot of the association between chloroform (CHL) exposure [estimated internal dose] and LBW. Confidence intervals (95%) are denoted by "CI." Studies are ordered based on the lowest value of each study's highest exposure category. Results represent third trimester exposure.



[1] Danileviciute et al. 2012 examined the polymorphisms of glutathione S-transferase (GST), GSTT1 and GSTM1. "GSTT1-1" represents the presence of gene activity and "GSTT1-0" represents the absence of gene activity. Similarly, "GSTM1-1" represents the presence of gene activity and "GSTM1-0" represents the absence of gene activity.

[2] β-coefficients from the regression model were multiplied by the logarithm of 1.1 to derive an effect estimate for a 10% increase in exposure.

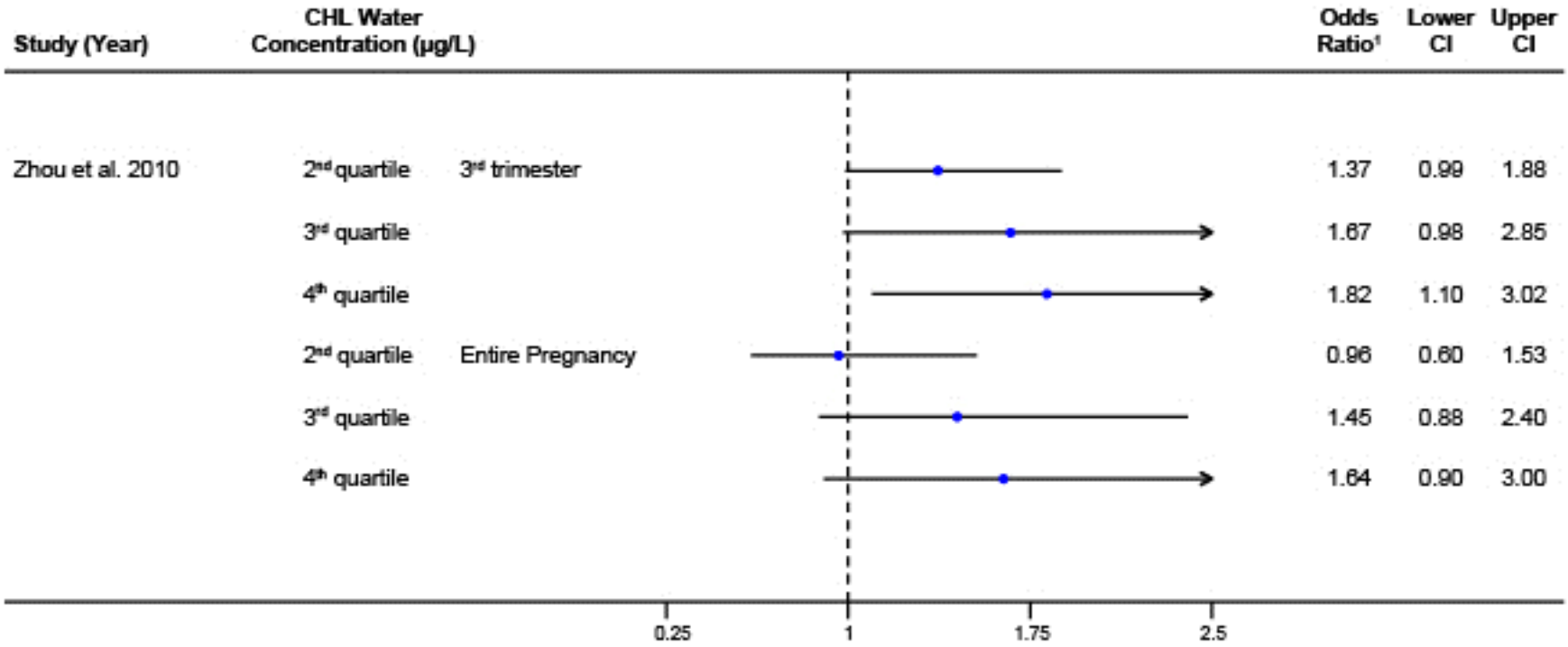
Figure 8. Birth Weight (BW). Forest plot of the association between chloroform (CHL) exposure [water concentration] and BW. Confidence intervals (95%) are denoted by "CI." Studies are ordered based on the lowest value of each study's highest exposure category. Results represent third trimester exposure unless otherwise noted.



[1] Summerhayes et al. 2012. Water concentration values represent inter-quartile range increase in exposure during the entire pregnancy. Exposure level values for other timeframes of exposure did not vary from these values by more than ~2 µg/L.

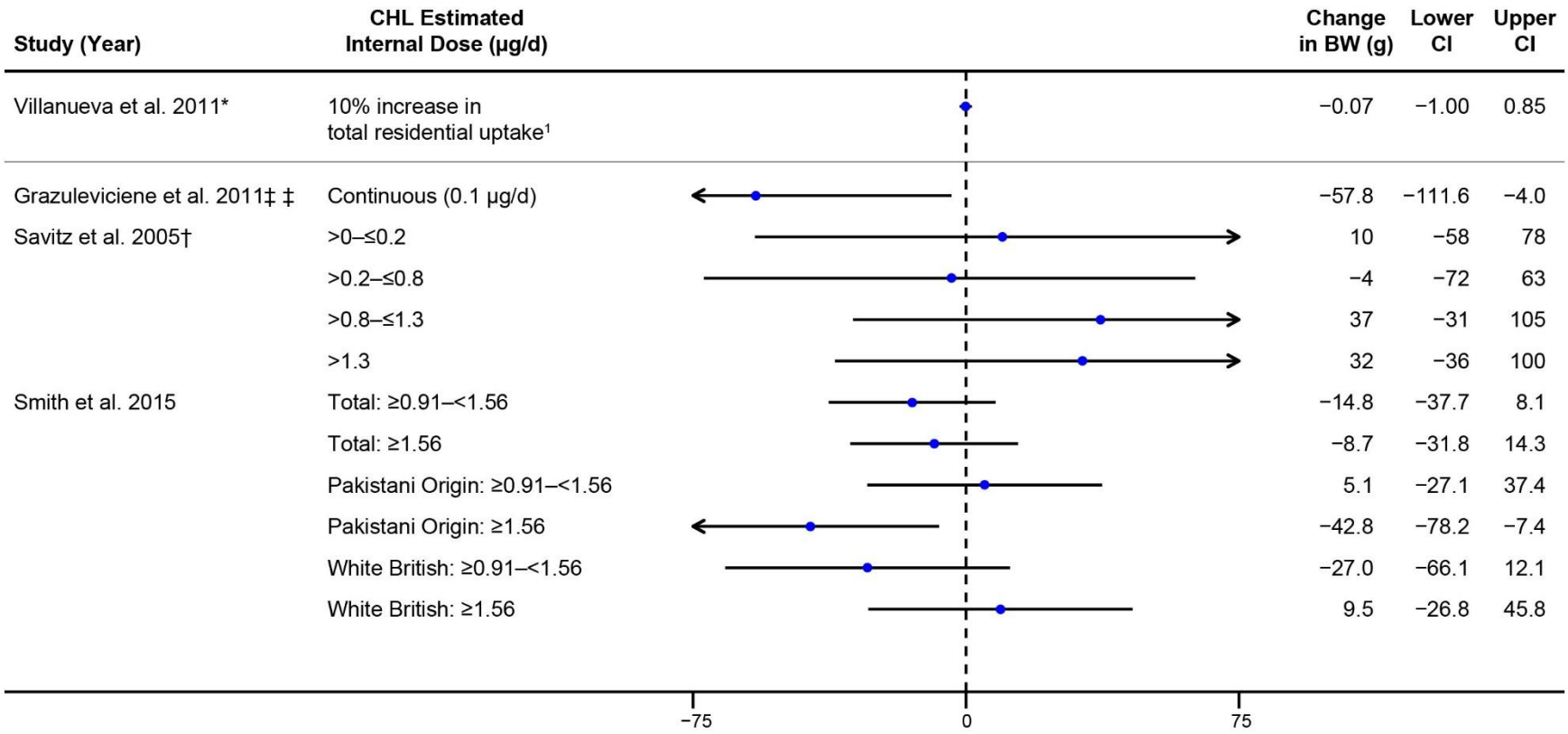
[2] Hoffman et al. 2008 analyzed CHL exposure at two sites. Site 1 consisted predominantly of chlorinated disinfection by-products (DBPs). Site 2 consisted predominantly of brominated DBPs.

Figure 8. Birth Weight (BW). Forest plot of the association between chloroform (CHL) exposure [water concentration] and BW (cont'd). Confidence intervals (95%) are denoted by "CI."



[1] Above versus below the median.

Figure 9. Birth Weight (BW). Forest plot of the association between chloroform (CHL) exposure [estimated internal dose] and BW. Confidence intervals (95%) are denoted by "CI." Studies are ordered based on the lowest value of each study's highest exposure category. Results represent third trimester exposure.



[1] The β-coefficient (g) from the regression model was multiplied by the logarithm of 1.1 to derive an effect estimate for a 10% increase in exposure.

Table 3a. Detailed Summaries for Human Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Botton et al.* 2015 Spain (3 study sites) and Greece	Prospective cohort (from 2 mother-child cohort studies Hospital recruitment at week 10–13 of pregnancy 2003–2008 n = 2,216 term births (mother-child pairs) Valencia 2003–2005 n = 594 Sabadell 2004–2006 n = 473 Gipuzkoa 2006–2008 n = 407 Crete 2007–2008 n = 742	Postnatal weight growth 4 measures of weight between delivery and 1 year of age	<u>Water Sampling:</u> Residential THM conc were collected through sampling campaigns of tap water, and from selected public buildings for all study areas and regulatory monitoring data in Sabadell cohort Number of THM samples: Gipuzkoa = 421 Sabadell = 198 Valencia = 162 Crete = 72 Data collected almost every month in Gipuzkoa and Sabadell, 3 time points in Valencia, and 4 time points in Crete <u>Exposure Measure:</u> THM conc were determined at residence for all months of pregnancy Interviews and questionnaires were collected at different time points for the different locations ranging from <12 weeks gestation to the 3rd trimester Information included: water type (municipal/bottled/private well); home and away from home water use; cooking water use; filter use (assumed 90% reduction in THM);	All the following CHL values were approximated from a figure in the publication CHL water conc (µg/L): Median = Gipuzkoa ~12 Sabedell ~20 Valencia ~0 Range = Gipuzkoa ~0–20 Sabadell ~0–40 Valencia ~0–50 Crete - CHL levels were mostly undetected and excluded from CHL analysis Total integrated CHL uptake through all routes (µg/d): Range = Gipuzkoa ~0–0.5 Sabadell ~0–1.4 Valencia ~0–2.1	Beta coefficients (95% CI) of postnatal weight gain (0–6 months) for an entire pregnancy IQR increase of total integrated CHL uptake (µg/d): - through all routes for all sites = -9.30 (-87.3, 68.7) - through ingestion for all sites = -40.3 (-122, 41) - through ingestion for specific sites - Gipuzkoa = 9.63 (-174, 193) Sabadell = **-151 (-288, -15)** Valencia = 36.7 (-87, 160)	Models adj for: Cohort Maternal age Gender Gestational age Parity Maternal pre-pregnancy weight Paternal weight Paternal height Maternal education Maternal smoking during pregnancy Other covariates considered: Breastfeeding Respiratory infection before 6 months Bathing and showering in the first months of life Formula water type	THM conc in the woman's residence during pregnancy ranged from median value of 1 µg/L in Crete to 117 µg/L in Sabadell Exp data included extensive detailed water use collected prospectively (e.g. water source, filter use, exp at work, showering/bathing, swimming, etc.) Data came from a large cohort study providing wide variability in exp Examined residential mobility - only 5% of mothers reported a change in residence during pregnancy (between week 12 and week 32) Excluded population was not significantly different from the final population in terms of exp, outcome, and potential confounders Percent of women remaining after exclusion for missing data was Gipuzkoa (67%), Sabadell (76%), Valencia (75%) Tap water consumption varied across sites, but overall few women consumed tap water during pregnancy Data collection differed for all study sites There was a lack of information on postnatal THM exp; however, excluding infants

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			frequency and duration of showering and bathing; swimming pool use; and water-based fluid consumption Residential THM conc and uptake through ingestion, showering, and bathing during the whole pregnancy were calculated Estimated THM blood conc was determined using the product of residential THM conc, daily personal water use and uptake factors				consuming formula with tap water, or adjusting for bathing/showering only marginally changed the results seen for Sabadell Other DBP analyzed: TTHM and BrTHM Beta coefficients (95% CI) of postnatal weight gain (0–6 months) for an IQR increase of THM and BrTHM ingestion in Sabadell (µg/d): BrTHM = **-146 (-280, -12.3)** Results were similar for TTHMs and BrTHM

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Smith et al. 2015 England	Prospective birth cohort 2007–2010 N = 11,928 Singleton births BW n = 7,438 term births (after exclusions including: PTB (531); missing data, including water use data (2,100); THM levels (98); covariate data)	BW	<u>Water Sampling:</u> Routine monitoring of THM (2006–2011) Sampling occurred 9 times per year on average, for each of the 8 water supply zones <u>Exposure Measure:</u> Average individual and total THM conc were estimated by trimester as a time-weighted mean of the months for that trimester Baseline questionnaire on water consumption and activities completed via interview with study administrator included: - typical daily consumption of tap water, bottled water, tea, coffee, etc. at home, work/study or elsewhere - water filtering at home and work - time spent showering, bathing and swimming	Time-weighted average CHL water conc (µg/L): Mean (SD) for the entire pregnancy = 37.8 (3.8) Total integrated CHL uptake (µg/d): Mean (SD) for the entire pregnancy: = 1.61 (1.46) Tertiles of total integrated CHL uptake (µg/d) for the entire pregnancy: 1) <0.91 2) ≥ 0.91–<1.56 3) ≥1.56	Mean difference in term BW (g) (95% CI) for total integrated CHL uptake for the entire pregnancy (µg/d) (Supplemental material Table S4): Total population: 1) referent 2) -16.3 (-39, 6.5) 3) -20.9 (-44.6, 2,8) Pakistani origin: 1) referent 2) 10.3 (-21.2, 41.9) **3) -48.3 (-84.6, -12.1)** p-value for trend = **0.025** White British: 1) referent 2) -13.3 (-52.9, 26.3) 3) 9.0 (-23.5, 46.5) p-value for interaction = **0.011** Mean difference in term BW (g) (95% CI) for total integrated CHL uptake during the 3rd trimester (µg/d):	Models adj for: Caffeine intake Education Fasting and post load glucose Ethnicity Smoking Parity Age Body Mass Index (BMI) Index of Multiple Deprivation Gestational age at delivery Infant sex	Integrated uptake for CHL accounted for 86% of the integrated TTHM uptake Compared to White British women, women of Pakistani-origin drink less water from all sources combined, spend less time bathing but more time showering, and very few went swimming (2% Pakistani-origin vs 14% White British) Longer bathing duration was associated with BW reductions for Pakistani-origin, but not White British Cold tap water consumption was associated with increased BW for Pakistani-origin infants only Exp data included extensive detailed water use collected prospectively (e.g. water source; filter use, exp at work, showering/bathing, swimming, etc.) Other DBP analyzed include: TTHM, BrTHM, BDCM, HAA3 (BDCAA, TCAA, and DCAA), BDCAA, DBP7(sum of TTHM and BDCAA, TCAA, and DCAA) TBM was not modeled individually as it had many data points below the limit of detection (LOD) HAA samples were collected quarterly from the 8 water supply zones from 2007 to

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
					Total population: 1) referent 2) -14.8 (-37.7, 8.1) 3)-8.7 (-31.8, 14.3) Pakistani origin: 1) referent 2) 5.1 (-27.1, 37.4) 3) **-42.8 (-78.2, -7.4)** p-value for trend = **0.035** p-value for interaction = **0.023** White British: 1) referent 2) -27.0 (-66.1, 12.1) 3) 9.5 (-26.8, 45.8)		2010 Only 3 HAAs had sufficient detectable data points (DCAA, TCAA, BDCAA) There was no evidence of an association between BW and ingestion of HAAs alone, or combined with THMs and HAAs, via drinking water consumption OR (95% CI) by tertile of total integrated BrTHM uptake (µg/d): <u>Entire pregnancy</u> Pakistani origin 1) referent 2) -6.5 (-38.0, 25.0) 3) **-56.4 (-93.1, -19.6)** <u>1st trimester</u> Total population 1) referent 2) **-24.5 (-47.3, -1.7)** 3) -21.6 (-45.7, 2.5) Pakistani origin 1) referent 2) -19.1 (-50.5, 12.3) 3) **-51.7 (-88.8, -14.5)** <u>2nd trimester</u> Pakistani origin 1) referent 2) 0.4 (-31.3, 32.1) 3) **-56.3 (-92.7, -19.9)** <u>3rd trimester</u> Pakistani origin 1) referent 2) -7.5 (-39.0, 24.1)

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
							3) **-52.8 (-89.3, -16.3)** OR (95% CI) by tertile of total integrated BDCM uptake (µg/d): <u>Entire pregnancy</u> Pakistani origin 1) referent 2) -11.5 (-43.3, 20.2) 3) **-49.8 (-86.3, -13.4)** <u>1st trimester</u> Pakistani origin 1) referent 2) -8.6 (-40.6, 23.4) 3) **-44.1 (-80.5, -7.7)** <u>2nd trimester</u> Pakistani origin 1) referent 2) 6.5 (-25.8, 38.8) 3) **-60.8 (-96.5, -25.1)** <u>3rd trimester</u> Pakistani origin 1) referent 2) -1.2 (-33.2, 30.9) 3) **-48.7 (-84.8, -12.5)**

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Iszatt et al. 2014 England	Retrospective cohort Birth and SB records Two sample periods: 2000–2002 and 2005–2007 Intervention component - enhanced coagulation water treatment (EC) (a process that improves removal of DBP precursors, reducing DBP formation potential) EC was introduced to 4 water treatment works (88 of 258 water zones) in 2003–2004 N= 472,526 (live births) LBW n = 27,664 VLBW n = 4,209 BW (≥2,500 g)	LBW (<2,500g) Very LBW (<1500 g) (SB outcomes reported in Table 4a)	<u>Water Sampling:</u> Routine THM monitoring of public water supply: - at geographically random samples - a minimum of 4 times per year Two time periods for water sampling: 3-year period before and 3-year period after EC intervention <u>Exposure Measure:</u> Postcode of maternal residence at birth was linked to water zone boundary in use during the year of birth Births in the first 6 weeks of the year were linked to the water zone boundary of the preceding year Water zone boundary information was linked to THM conc A water zone is a supply area with approximately uniform water quality, with a population ≤100,000 Two exp metrics were constructed for each water zone – 1) EC identified treatment status 2) conc change for THMs	CHL water conc (µg/L): Mean (SD) = Before (2000–2002) 38.6 (4.2) After (2005–2007) 19.4 (1.0) CHL distribution change (µg/L): Mean (SD) = Overall -19.2 (17.6) No EC -14.0 (17.4) EC -29.2 (13.2) Categories for changes in CHL water conc (based on TTHMs) (µg/L): 1) Low increase–increases ≤10 to decreases <10 2) Medium decrease–decreases 10 to <30 3) High decrease–decreases 30 to 65	Percent change (95% CI) for rates before and after EC (calculated as the exponential of the regression coefficient (i.e., rate ratio of after/before) minus 1 and multiplied by 100) (for the entire pregnancy)): <u>LBW</u> 1) **-5 (-9, -1)** 2) **-5 (-9, -1)** 3) **-9 (-12, -5)** <u>VLBW *</u> 1) -7 (-17, 3) 2) 4 (-7, 16) 3) **-16 (-24, -8)** *significant interaction between before/after EC and CHL change p = **0.02**	Unadjusted rates presented, as infant sex, parity, and maternal age were found not to affect the rates	TTHM change was strongly correlated with CHL change (*r* = 0.99) The background mean TTHM conc decrease was 15.1 µg/L in non-EC water zones; with a statistically significant greater mean decrease of 30.5 µg/L in EC water zones Overall statistically significant reduction in conc of TTHM, CHL, BrTHM, DBCM Change in average CHL accounted for 94% of the change in TTHM after EC (calculated from Table 1 in the publication) Of the BrTHM, the mean change in conc with EC was only significant for BDCM (borderline p = 0.05) Statistically significant difference between categories of change in TTHM conc in EC and non-EC water zones No information on individual water use or water consumption pattern changes Other DBP analyzed: TTHM, BrTHM, BDCM, DBCM, TBM Statistically significant changes were observed for some of the BDCM and DBCM conc, although there were no significant interactions between before/after and changes in conc (Supplemental material

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
	n = 401,040						Data 4 and 5) <u>LBW</u> Percent change (95% CI) for rates before and after EC: BDCM 1) -3 (-8, 2) 2) **-8 (-12, -5)** 3) **-7 (-11, -4)** DBCM 1) **-7 (-10, -3)** 2) **-9 (-14, -5)** 3) **-5 (-9, -1)** <u>VLBW</u> Percent change (95% CI) for rates before and after EC: BDCM 1) -12 (-22, 0) 2) **-10 (-18, -1)** 3) -3 (-12, 8) DBCM 1) **-9 (-17, -1)** 2) **-13 (-23, -1)** 3) -2 (-12, 9)

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Rivera-Nuñez and Wright 2013 Massachusetts	"Retrospective cohort study with a semi-ecologic study design" Birth certificate data 1996–2004 n = 672,120 (live singleton births) PTB n = 37,136 (5.7%) SGA n = 68,409 (11.1%) BW n = 477,101	PTB SGA BW	<u>Water Sampling:</u> 276 public water systems (PWS) Quarterly town DBP averages were calculated from all available monitoring data collected 1995–2004 Towns with annual THM measurements were assigned the same conc for each quarter Residents of towns using private wells and towns that did not disinfect were assigned DBP exp of 0 (births n = 72,180) (Supplemental material) <u>Exposure Measure:</u> Town level exp for 1st, 2nd, and 3rd trimester Residential zip code at birth was linked to PWS To estimate 3rd trimester exp for infants born in the 2nd or 3rd month of a quarter, DBP quarterly values for the town of residence were used Births in the 1st month of a quarter were given DBP levels of the previous quarter (Supplemental material; Wright and Rivera-Nuñez, 2011) 2nd trimester levels were based on the quarter prior to that used for the 3rd trimester value	CHL water conc (µg/L): 2nd trimester Mean = 30.1, Median = 27.0 Range = 0–265.9 3rd trimester Mean = 30.6 Median = 27.4 Range = 0–265.9 Quintiles of CHL water exp (µg/L) 3rd trimester: 1) ≤5 2) >5–21 3) >21–36 4) >36–52 5) >52 1st and 2nd trimester (for PTB analyses): 1) ≤5 2) >5–21 3) >21–35 4) >35–52 5) >52	<u>PTB</u> OR (95% CI) by quintile of 2nd trimester CHL exp: 1) referent 2) 1.00 (0.94, 1.06) 3) **1.08 (1.02, 1.14)** 4) 1.06 (0.99, 1.12) 5) 1.00 (0.94, 1.07) Associations for PTB and 1st trimester CHL exp were comparable to those shown above (Supplemental material Table 3) <u>SGA</u> OR (95% CI) by quintile of 3rd trimester CHL exp: 1) referent 2) 1.01 (0.96, 1.05) 3) 1.00 (0.95, 1.04) 4) 1.04 (1.00, 1.10) 5) 1.04 (0.99, 1.09) Associations for 2nd trimester exp were comparable to those shown above (Supplemental material Table 2) <u>BW</u> Change (g) (95% CI) by quintile of 3rd trimester CHL exp: 1) referent 2) -1 (-7, 5) 3) **-9 (-15, -2)** 4) **-13 (-19, -7)** 5) **-15 (-21, -8)**	Models adj for: Maternal age Race/ethnicity (except in SGA models) Education Prenatal care source of payment ZIP code Median household income Marital status Water source Disinfection TTHM/HAA5 conc Other covariates considered: Smoking Parity Prenatal care adequacy (Kotelchuck Index) Maternal medical and reproductive health factors (e.g. hydramnios preeclampsia pregnancy weight gain) Season	Study is an extension of Wright et al., 2004 which included births in 1995–1998 The correlation between CHL and TTHM conc was high (r = 0.97) Mean CHL was 80.3% of 2nd and 3rd trimester mean TTHM levels (30.1/37.5 and 30.6/38.1 µg/L respectively; Table 2) Potential misclassification where annual DBP measurements were assigned the same conc for each quarter in towns where only annual measurements were made Other DBP analyzed: THM4, BDCM, BrTHM, HAAs, DBP9 (sum of TCM, BDCM, DBCM, TBM, TCAA, DCAA, MBAA, MCAA, and DBAA) After adjustment for HAA5 (sum of TCAA, DCAA, MBAA, MCAA, DBAA) and other covariates: - BrTHM was associated with reduced BW (mean BrTHM conc was ~1/5 of mean CHL conc) - CHL was no longer associated with a decreased BW - CHL association with PTB was stronger Sensitivity analyses using unexposed as the referent showed a statistically significant decrease in adj BW associated with TTHM exp

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			Quarter measurements were an average across all sampling locations Births before 29 weeks were not assigned a 3rd trimester value				(including adjustment for HAA5), as well as a statistically significant increased risk of PTB (Supplemental material Table 6) <u>SGA</u> OR (95% CI) by quintile of 3rd trimester BrTHM exp: 1) referent 2) 1.00 (0.97, 1.04) 3) **1.06 (1.02, 1.10)** 4) **1.08 (1.04, 1.12)** 5) 1.05 (1.00, 1.09) OR (95% CI) by quintile of 3rd trimester BDCM exp: 1) referent 2) 1.04 (1.00, 1.08) 3) **1.08 (1.03, 1.12)** 4) **1.09 (1.04, 1.14)** 5) **1.09 (1.04, 1.13)** <u>BW</u> Change (g) (95% CI) by quintile of 3rd trimester BrTHM exp: 1) referent 2) **-10 (-16, -4)** 3) **-17 (-21, -8)** 4) **-19 (-26, -14)** 5) **-13 (-22, -10)** Change (g) (95% CI) by quintile of 3rd trimester BDCM exp: 1) referent 2) **-11 (-17, -5)** 3) **-14 (-21, -8)** 4) **-20 (-26, -14)** 5) **-16 (-22, -10)**

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
					Change (g) (95% CI) by quintile of 3rd trimester DBP9 exp: 1) referent 2) **-39 (-62, -18)** 3) **-42 (-64, -19)** 4) **-45 (-68, -22)** 5) **-39 (-62, -16)**		Significant findings were observed for some HAAs

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Costet et al. 2012 France	Prospective birth cohort Medical records 2002–2006 N = 3,421 n = 3,226 (live singleton births) PTB n = 105 SGA n = 171	PTB SGA (as Fetal Growth Restriction*) * defined as BW <5th percentile of the cohort's expected BW distribution	<u>Water Sampling:</u> THM conc taken from database of water distribution networks Routine monitoring of THMs began in 2004 Sampling frequency based on population size 258 of 369 networks recorded at least 1 THM measurement in 2002–2006 2,847 women had THM measurements: - 68.1% had at least 1 annual measurement - 41.1% had at least 2 annual measurements - 19.1% had monthly measurements Hierarchical models were used to impute missing monthly levels Separate models used for each water source (groundwater, surface, mixed) <u>Exposure Measure</u>: Average THM levels were estimated by trimester as a time weighted mean of the months for that trimester Self-administered questionnaires: Taken in early pregnancy	CHL water conc (µg/L): Mean (SD) All sites = 9.3 (7.0) Quartiles of CHL water conc (µg/L): 1) <5 2) 5–<10 3) 10–<15 4) ≥15 Quartiles of total integrated CHL uptake (µg/d): 1) <0.068 2) 0.068–<0.133 3) 0.133–<0.237 4) ≥0.237	<u>PTB</u> OR (95% CI) by quartile of 3rd trimester CHL water conc (µg/L): 1) referent 2) 0.7 (0.4, 1.2) 3) **0.5 (0.3, 0.9)** 4) 0.8 (0.4, 1.4) OR (95% CI) by quartile of 3rd trimester total integrated CHL uptake (µg/d): 1) referent 2) 1.8 (0.7, 4.8) 3) 0.7 (0.2, 2.1) 4) 1.0 (0.4, 2.9) <u>SGA</u> OR (95% CI) by quartile of 3rd trimester CHL water conc (µg/L): 1) referent 2) 0.8 (0.5, 1.2) 3) 1.0 (0.6, 1.5) 4) 0.9 (0.5, 1.4) OR (95% CI) by quartile of 3rd trimester total integrated CHL uptake (µg/d): 1) referent 2) 1.1 (0.5, 2.3) 3) 1.2 (0.6, 2.4) 4) 1.0 (0.5, 2.1)	Models adj for: Parity Marital status Diabetes before and during pregnancy Hypertension before or during pregnancy Tobacco use Alcohol consumption Other covariates considered: Obstetric history Educational level Dietary habits	Average composition of TTHMs (%): CHL - 22 BDCM - 25 DBCM - 33 TBM - 20 Estimated participation rate = 80% 99.4% were followed through the end of pregnancy CHL conc (µg/L): mean (SD) and % of water distribution networks in: ground water 3.8 (3.2), 19.3; surface water 12.5 (6.5), 47.9; mixed water 8.0 (6.8), 32.8 Exp data included extensive detailed water use collected prospectively (e.g. bottled water, hot beverages, showering /bathing, swimming, etc.) Ingestion levels were only measured at the beginning of pregnancy; however, sensitivity analysis simulating a 25% increase in tap water consumption between the 1st and 2nd trimester did not significantly affect the results Info on showering, bathing, and swimming was only available for 1,505 subjects at 2 year follow-up No information on exp at work was included; however, 82% of mothers reported drinking bottled water at work

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			Daily water intake, percent of bottled water Total integrated uptake: exp estimated using inhalation, ingestion, dermal absorption (including showering/bathing, swimming) Coefficient factor of 0.3 used for hot beverages Length and frequency of shower/bath/swimming collected at 2 year follow-up				A large proportion of women had only 1 annual THM measurement Other DBP analyzed: BDCM, TBM, DBCM, TTHM <u>SGA</u> OR (95% CI) by quartile of 1st trimester total integrated DBCM uptake (µg/d): 1) referent 2) 1.7 (0.8, 3.7) 3) **2.4 (1.1, 5.1)** 4) 1.3 (0.6, 3.0)

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Danileviciute et al. ‡ ‡ 2012 Lithuania	Nested case-control Prenatal clinics in Kaunas (Lithuania) HiWATE* study 2007–2009 N = 682 (pregnant women) SGA n = 96 LBW n = 59 in term newborns *Health Impacts of Long-term Exposure to Disinfection By-products in Drinking Water in Europe	SGA LBW	<u>Water Sampling:</u> 4 treatment plants: all groundwater sources, each sampled at 3 distances from each plant (near the plant, at 5 and ≥10 km), 4 times/year for 3 years (85 samples in total) Mean quarterly conc was calculated for each plant <u>Exposure Measure</u>: Used geocoded maternal address at birth to determine CHL exp conc Average level was calculated for entire pregnancy and each trimester Internal dose (uptake): (inhalation, ingestion and dermal absorption) was calculated from algorithms using interview data (collected prospectively for most of the women - ~76%, 24% within the 1st month of delivery) on trimester-specific water consump-tion including: - size and number of glasses of tap water per day (including cold and boiled water), use of bottled water at home, at work,other - number and average length of showers and baths, swimming pool visits	CHL water conc (µg/L): Mean (SD) as reported in Grazuleviciene et al. 2011: All sites = 7.8 (10.2) 3 plants with low THM levels = 0.9 (1.0) 1 plant with high THM levels = 17.7 (9.0) Average total CHL daily uptake (µg/d): Median = 0.1424 Range = 0.0013–2.13	ORs (95% CI) for 3rd trimester CHL above vs below the median internal dose (µg/d): <u>SGA</u> 1.31 (0.82, 2.08) <u>LBW</u> 1.45 (0.67, 3.13) Maternal Polymorphisms: <u>SGA</u> *Specific for GSTM1-1* 0.88 (0.44, 1.78) *Specific for GSTM1-0* 1.74 (0.89, 3.41) *Specific for GSTT1-1* 1.18 (0.71, 1.97) *Specific for GSTT1-0* 1.75 (0.50, 6.10) <u>LBW</u> *Specific for GSTM1-1* 0.35 (0.10, 1.28) *Specific for GSTM1-0* **5.06 (1.50, 17.05)** *Specific for GSTT1-1* 1.35 (0.57, 3.20) *Specific for GSTT1-0* 7.30 (0.14, 391) (ORs *specific for GSTM1-0* were also significant for the entire pregnancy) GSTM1 gene interaction was significant for the entire pregnancy and each specific trimester: <u>3rd trimester interaction</u>: **15.86 (2.75, 91.40)**	Models adj for: <u>SGA</u> Parity Marital status Maternal education Maternal smoking BMI Birth year <u>LBW</u> Gestational age[2] Marital status Maternal education BMI Blood pressure Maternal and paternal smoking Alcohol consumption Ethnic group Pregnancy history Infant gender Birth year	Individual THMs were highly correlated (r = 0.91–0.99) CHL accounted for ~80% of the TTHMs Exp data included extensive detailed water use collected prospectively (included filter use, exp at work, hot beverages, showering/ bathing, swimming, etc.) Considered genotype for 2 relevant genes Accounted for residential mobility by restricting analysis to women who did not change residence during pregnancy Small sample size Low prevalence of GSTT1-0 genotype = 16.4% Prevalence of GSTM1-0 = 48.7% Authors report results are preliminary and require confirmation in a larger sample with greater contrast in THM conc and internal doses Halogenated DBPs (9 HAAs, 2 haloketones, chloropricrin, chloral hydrate and MX) were measured but not included in the analysis since they were present only in low or sub µg/L, if detected at all Other DBP analyzed include: TTHM, BDCM, DBCM

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Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			Estimated uptake factors were used for ingestion (including heated water), inhalation and dermal exp Glutathione S-transferase mu 1 (GSTM1) and glutathione S-transferase theta 1 (GSTT1)-null genotypes were identified by multiplex polymerase chair reaction (PCR) (null genotypes = GSTM1-0 and GSTT1-0)				<u>SGA</u> OR (95% CI) for 1st trimester DBCM above vs below the median internal dose (µg/d): **2.19 (1.20, 3.99)** OR (95% CI) for 3rd trimester DBCM above vs. below the median internal dose (µg/d): *Specific for GSTT1-1* **1.89 (1.01, 3.54)** *Specific for GSTT1-0* 1.04 (0.31, 3.53) <u>LBW</u> ORs (95% CI) for BDCM above vs below the median internal uptake (µg/d): *Specific for GSTM1 gene* <u>Entire pregnancy interaction:</u> **5.16 (1.01, 26.52)** <u>3rd trimester interaction:</u> **5.29 (1.03, 27.15)**

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Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Levallois et al. 2012 Quebec City, Canada	Population based case-control Birth certificate database 2006–2008 cases n = 571 (singleton births - 111 of which were LBW) controls n = 1925	SGA (births ≥37 weeks, sex-specific 10th percentile as per Canadian standards of BW for gestational age)	<u>Water Sampling:</u> 16 water systems: 9 surface water sources, 7 groundwater sources Sampled 46 sites monthly for 4 THMs and 9 HAAs in the 9 surface water systems, and 7 sites in the 7 groundwater systems Systems were divided into subsystems with at least 1 sampling site in each subsystem Considered spatial and temporal factors in estimation of tap water exp (using closest sampling site in the subsystem and sampled closest to specific trimester being studied) <u>Exposure Measure:</u> Internal dose: - ingestion, inhalation, and dermal absorption, calculated from interview info including: - volume and # of glasses of tap water per day, hot and cold beverages, bottled water - water handling (filtering, boiling, storage in fridge) -frequency and duration of showering and bathing)	CHL water conc (µg/L): Mean (SD): cases = 43.3 (40.7) controls = 41.1 (39.2) Quartiles of CHL water conc (µg/L): 1) <15.96 2) 15.96–27.26 3) 27.27–51.07 4) >51.07 Quartiles of CHL uptake (µg/d): Ingestion: 1) 1.72 2) .72–11.88 3) 1.89–34.30 4) 34.30 Total Pathway: 1) 42.24 2) 2.24–80.21 3) 0.22–169.81 4) 169.81	OR (95% CI) by quartile of 3rd trimester CHL water conc (µg/L): 1) referent 2) 0.9 (0.7, 1.3) 3) 1.0 (0.8, 1.4) 4) 1.2 (0.9, 1.7) OR (95% CI) by quartile of 3rd trimester integrated CHL uptake by route of exp (µg/d): Ingestion: 1) referent 2) 1.2 (0.9, 1.6) 3) 1.1 (0.8, 1.5) 4) 1.3 (1.0, 1.8) p-trend = 0.10 Total Pathway: 1) referent 2) 0.9 (0.7, 1.2) 3) 1.0 (0.7, 1.3) 4) 1.0 (0.8, 1.4) p-trend = 0.67 Results for quartiles of CHL inhalation/dermal exp were reported but had no significant results	Models adj for: Maternal age Calendar week Highest education level obtained Annual household income Pre-pregnancy BMI Parity History of LBW Maternal smoking during pregnancy Passive smoking at home Coffee consumption Alcohol consumption History of chronic disease Preeclampsia Other covariates considered: Maternal ethnicity Working status Marital Status Medical problem during pregnancy Risky occupational exp	CHL was highly correlated with TTHM (r = 0.99) Using multiple routes of exp assessment and modeling did not result in higher ORs as compared with exp using water conc High participation rate (cases = 91%, controls = 93%) Exp data included extensive detailed water use (e.g. hot beverages, bottled water, filter use, showering/bathing, etc.) Extensive monthly sampling scheme allowing consideration of spatial and temporal variability Validation study (n = 115) was conducted for spatial assignment of THM values to a residence Authors reported no significant difference was found between measurements of TTHMs or HAA9 in the participants' tap water and estimated values using the study's sampling strategy Pharmacokinetic models were used in exp assessment Interviews were conducted a median of ~ 9 weeks after birth Other DBP analyzed: BDCM, BrTHM, TTHM, DCAA, TCAA, THAA Significant findings were observed for some HAAs

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Summerhayes et al. 2012 New South Wales, Australia	Retrospective cohort Birth records linked to birth defects registry 1998–2004 N = 362,013 (live singleton births) n = 314,982 (excluded infants with BD, SB, multiple births, data, gestational age <22 or > 43 weeks, births with a BW >5 SDs of the average for gestational age, or with missing BW or gestational age data, etc.) SGA n = 31,813	SGA BW	<u>Water sampling:</u> Sydney/Illawarra water utility has a 3-level hierarchical structure with 14 delivery systems containing 33 distribution systems and 180 water supply zones Monthly THM monitoring rotated through 3–6 sites in each distribution system on a 3–6 month cycle THM exp was assigned at the distribution system level THM data were averaged w/in each zone (68% of values were missing), then across zones w/in a distribution system (13% of values were missing) for a distribution/month THM conc During the study period, 5,341 THM observations were available <u>Exposure measure:</u> Maternal residence at time of delivery was geocoded and mapped to distribution systems	CHL water conc (µg/L): Mean (SD) = 33.6 (16.0) Median = 30.9 Range = 3.4–121.5 (Supplemental material) Analyzed by each trimester and entire pregnancy	<u>SGA</u> RR (95% CI) for an IQR increase in 3rd trimester CHL exp in water (25 µg/L): **1.04 (1.02, 1.06)** Similar associations were reported for the entire pregnancy RR (95% CI) for the 5th and 10th deciles of CHL water exp in the 3rd trimester (µg/L): 5th decile = 1.01 (0.96, 1.07) 10th decile = **1.12 (1.05, 1.18)** Larger associations were seen for SGA <3rd percentile <u>Interaction between THMs and smoking</u> In stratified analysis the association between SGA and 3rd trimester exp increased slightly in nonsmokers and was protective in smokers <u>BW</u> (Supplemental material) Linear regression model of change in mean BW (g) (95% CI) with an IQR increase in CHL exp for entire pregnancy (25 µg/L): **-5.0 g (-8.6, -1.4)**	Models adj for: Maternal age Indigenous status Maternal country of birth Infant's gender Smoking anytime during pregnancy Parity Hypertension Maternal diabetes Preeclampsia Gestational diabetes Antenatal visit Year of birth Season of birth Area-based measure of mother's socioeconomic status (SES)	68% of zone/month values were missing CHL was correlated with BDCM (r = 0.90) DBCM (r = 0.27) Calculation of distribution-system-level exp used average w/in zones (68% of zone/month were missing), then average across zones, etc. THM exp was higher in women living in areas supplied by chlorinated water vs chloraminated water (86% of women) The association between CHL and SGA was larger for nonsmokers Large sample size A two-pollutant model was examined with DBCM (as a dichotomous variable due to the small range of exp conc) and found that the effects of CHL on SGA were independent of DBCM Sensitivity analyses were conducted to test robustness of the results (including influence of disinfection type and potential threshold effects) for the association between THMs and SGA Possible misclassification of SES, assigned using an area-based measure at the census level (approximately 80–200

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							households) Higher proportions of SGA births were seen in mothers from lower SES (13.2%) Other DBP analyzed, include: TTHM, BDCM, DBCM Significant association observed for BDCM and SGA A significant increase in mean BW (g) was seen with an IQR increase in DBCM for the entire pregnancy (2 µg/L): **4 (2, 5)** RR (95% CI) for the 5th and 10th deciles of BDCM water exp in the 3rd trimester (µg/L): 5th decile = 1.04 (0.99, 1.09) 10th decile = **1.10 (1.04, 1.16)**

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Grazuleviciene et al. ‡ ‡ 2011 Lithuania	Prospective cohort All pregnant women in Kaunas city 2007–2009 N = 5,405 n = 3,341 (excluded multiple pregnancies, invalid data for THM exp, newborn >4,500 g, etc.) SGA n = 270 LBW n = 156 term births	SGA LBW BW	<u>Water Sampling:</u> 4 treatment plants: all groundwater sources, each sampled at 3 distances from each plant (near the plant, at 5 and ≥10 km), 4 times/year for 3 years (85 samples in total) Mean quarterly conc was calculated for each plant <u>Exposure Measure</u>: Used geocoded maternal address at birth to determine CHL exp conc Average level was calculated for entire pregnancy and each trimester Internal dose (uptake): (inhalation, ingestion and dermal absorption) was calculated from algorithms using interview data (collected prospectively for most of the women - ~76%, 24% within the 1st month of delivery) on trimester-specific water consumption including: - size and number of glasses of tap water per day (including cold and boiled water), use of bottled water at home, at work, other - number and average length of showers, baths, swimming pool visits	CHL water conc (µg/L) Mean (SD): All sites = 7.8 (10.2) At 3 plants with low THM levels = 0.9 (1.0) At 1 plant with high THM levels = 17.7 (9.0) Internal dose for CHL (µg/d): Range = 0.0013–2.1328 Tertiles: 1) 0.0013–0.0249 2) 0.0249–0.2868 3) 0.2868–2.1328	OR (95% CI) by tertile of 3rd trimester total integrated CHL uptake: <u>SGA</u> 1) Referent 2) 1.19 (0.87, 1.63) 3) 1.22 (0.89, 1.68) Continuous (0.1 µg/d) 1.04 (1.00, 1.09) <u>LBW</u> 1) Referent 2) **2.12 (1.11, 4.02)** 3) **2.13 (1.15, 3.92)** Continuous (0.1 µg/d): **1.09 (1.01, 1.18)** Similar findings were seen for each trimester and the entire pregnancy Change in BW (g) (95%CI) for every 1 µg/d increase in total integrated CHL uptake for the 3rd trimester: **-57.8 (-111.6, -4.0)** This was also significant for the 1st trimester and the entire pregnancy	Models adj for: <u>SGA</u> Previous preterm delivery Maternal education Marital status Smoking Alcohol consumption BMI Maternal age Parity Birth year <u>LBW</u> Gestational age* (squared) Marital status Maternal education Chronic diseases BMI Blood pressure Smoking Alcohol consumption Previous preterm delivery Infant gender Birth year * Gestational age was determined by ultrasound	CHL accounted for ~80% of the TTHM Individual THM conc were highly correlated (r = 0.91–0.99) Participation rate = 79% Median gestational age at interview = 8 weeks Exp data included extensive detailed water use collected prospectively (included filter use, exp at work, hot beverages, showering/ bathing, swimming, etc.) Dose response association with significant effect measures Outcomes also stratified by gender and maternal ethnicity 54.9% of the subjects received water from the plant with highest THM levels Questionnaire and birth certificate data were compared for participants and non-participants Accounted for residential mobility by restricting analysis to women who did not change residence during pregnancy Collected questionnaire info repeatedly on 10% of subjects finding no sign difference in water use habits or other covariates

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			Estimated uptake factors were used for ingestion (including heated water), inhalation and dermal exp				Incorporated individual water use info in estimating personal exp and internal dose Low spatial variability of THM levels in all treatment plants Other DBP analyzed: BDCM, DBCM, TTHM Significant association between 3rd trimester DBCM exp and LBW <u>LBW</u> OR (95% CI) by tertile of 3rd trimester total integrated DBCM uptake (µg/d): 1) referent 2) **2.44 (1.05, 5.70)** 3) **2.42 (1.03, 5.66)**

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Patelarou et al. * 2011 Greece	Prospective cohort "Rhea" cohort 2007–2008 N = 1,760 n = 1,359 (pregnant women after excluding multiple births, SB, women with incomplete questionnaire data, etc.) PTB n = 156 SGA n = 73 LBW n = 76	PTB SGA LBW	<u>Water Sampling</u>: 18 sampling points (2 points randomly selected from each of 6 urban water zones and 1 point in 6 rural areas) Home tap water was also sampled 4 times (72 samples in total) <u>Exposure Measure</u>: Women assigned a water supply zone by reported address at time of interview Exp level per month based on individual levels of TTHM and BrTHM modeled using generalized additive models of water plant zone and spline of the month of sampling Face-to-face, computer-aided questionnaire, collected prospectively, per trimester: - drinking water source; tap/bottled/spring water at home and other places - average daily consumption - average frequency and duration for showering and bathing - swimming pool attendance - type of water used to cook - use of filter both for drinking and cooking water	CHL water conc (µg/L): Mean (SD): All sampling sites = 0.15 (0.15) Urban = 0.14 (0.11) Rural = 0.17 (0.20)	Exp calculations were limited to the use of 3 brominated THMs because CHL levels were very low; therefore, no results were reported for CHL No association was seen between residential and total uptake exp with reproductive outcomes for either trimester or average total pregnancy	Models adjusted for: Maternal age at delivery Maternal education Smoking Marital status Greek ethnicity Parity Infant sex Gestational age was included in linear regression models with infant size metrics (weight, length, head circumference)	Brominated THMs accounted for >80% of TTHM Very low levels of CHL and other THMs Particpation rate = ~91% Estimated exp through multiple routes Exp data included extensive water use collected prospectively (e.g. filter use, exp at home and work, bottled water use, showering/bathing, swimming, dishwashing, etc.) Main water source was ground water Sampled tap water from individual homes over time Assessed temporal variation-THM conc did not differ over 3 years Assessed spatial variation – THM conc differed significantly by water supply zones and by season Prospective study with follow-up data after birth Other DBP analyzed: levels of specific THMs were too low to analyze individually

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			- usual method of dishwashing (by hand/dishwashing machine/both) - use of gloves for dishwashing by hand - frequency and duration of dishwashing per day Fluid consumption was assessed from interviews - during the 3rd month of pregnancy - during the 2nd trimester (food frequency questionnaire) - during the 3rd trimester - questions on average daily consumption Internal dose: - exp through ingestion, dermal, and inhalation by sum of residential THM conc and self-reported water use from interview				

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Villanueva et al. * 2011 Spain (5 areas)	Prospective cohort 2000–2008 Hospital data N = 5,621 n = 2,074 live births PTB - 3.7% SGA - 10.6% LBW - 4.6%	PTB SGA LBW BW	<u>Water Sampling:</u> THM levels were sampled from locations determined to be geographically representative of study areas THM conc were determined from sampling campaigns of tap water and regulatory monitoring data Number of samples varied between areas (128–421) Samples were collected to represent the period between the minimum and maximum conception dates of study subjects for each area Swimming pools were sampled in the municipalities that accounted for ≥70% of each cohort <u>Exposure Measure:</u> THM conc was assigned to the distribution system of each woman's residence Interview at 32 weeks - water use during pregnancy including: - sources of drinking water inside and outside the home - use of a home water filter	Not reported for overall cohort, but graphically represented for each area by different uses (e.g. ingestion, showering/bathing) Figure 1 in the article indicates median and 75th percentile of total residential uptake of CHL (ingestion + showering/bathing) were well below 1 µg/d for each area Area median THM levels ranged from 5.9 (Valencia) to 114.7 µg/L (Sabadell, of which >30% was CHL [estimates based on Figure 1])	No significant associations between any THM and PTB, SGA, LBW or BW Effect estimates for a 10% increase in 3rd trimester total integrated CHL uptake (µg/d): <u>PTB</u> OR (95% CI) = 1.00 (0.99, 1.01) <u>SGA</u> OR (95% CI) = 1.00 (0.99, 1.01) <u>LBW</u> OR (95% CI) = 1.00 (0.99, 1.02) <u>BW</u> β-coefficient (g) (95% CI) = -0.07 (-1.00, 0.85) Results varied by area but none were significant	Models adj for: <u>PTB</u> SGA covariates Sex BW <u>SGA</u> Parity Maternal height and weight Weight gain Smoking during pregnancy Cohort <u>BW and LBW</u> SGA covariates, Sex Weeks of gestation (linear and quadratic) Various area specific results were adj for some of the following variables: Maternal education Marital status Paternal weight Social class Season of conception Temporal and geographic variation Variables also considered: Maternal age Country of origin (Supplemental	Residential ingestion uptake was very low (11% of total uptake) with most uptake resulting from showering/bathing In Granada, 132 women's water use during pregnancy was collected retrospectively, 6–8 years after delivery (final number of women included in the analysis = 84) Exp data included extensive detailed water use collected prospectively (e.g. sources of drinking water, filter use, exp at work, showering/bathing, swimming, etc.) Women who changed residence between weeks 12 and 32 were excluded from the analyses (5% overall) to minimize exp misclassification Analyses included models that adj simultaneously for all trimesters with no significant results Misclassification was likely higher for estimated exp from swimming pools as a reduced number of samples were measured from selected pools and were taken a few years after the pregnancies Included extensive questionnaire data on water consumption, however, calculated consumption seems fairly low

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			- changes in water ingestion in pregnancy - frequency and duration of showering, bathing, and swimming pool use (indoor, outdoor, winter, summer) - tap water ingestion was also ascertained at 12 weeks Integrated Uptake: 12- and 32-week tap water intakes were averaged to compute ingested THMs Estimated daily THM blood conc determined by the product of residential THM levels, daily personal use and uptake factors			material)	Participation rate was 45%–98% Other DBP analyzed: BrTHM (BDCM, DBCM, and TBM were measured but not included separately in the analysis)

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Zhou et al. 2010 China	Retrospective cohort Birth records 2008–2009 N =1,385 (Women living in a water supply area of a single large scale water plant, and their term singleton infants)	BW	<u>Water sampling:</u> DBP conc were measured monthly for 1 ½ years at 3 sampling sites - 1, 4, and 8 km away - from a single water supply company CHL conc for each month was calculated as the average value of the 3 sampling sites <u>Exposure measure:</u> Individual exp was the average DBP conc of each month multiplied by days of pregnancy divided by total days of pregnancy	CHL water conc (µg/L) Range of mean values (SD) = 6.0 (2.5)–51.2 (36.1) highest levels occurred during the summer Each trimester, 1st + 2nd trimester, and the entire pregnancy were analyzed Quartiles of average daily CHL exp: 1) P_{1}–P_{25} 2) P_{26}–P_{50} 3) P_{51}–P_{75} 4) P_{76}–P_{100} Actual values for quartiles were not presented; however, the study reported CHL exp ranged from 6.53–41.98 (µg/L) BW exp was categorized as above/below the median	OR (95% CI) by quartile of CHL exp during the 3rd trimester: 1) referent 2) 1.37 (0.99, 1.88) 3) 1.67 (0.98, 2.85) 4) **1.82 (1.10, 3.02)** OR (95% CI) by quartile of CHL exp during the entire pregnancy: 1) referent 2) 0.96 (0.60, 1.53) 3) 1.45 (0.88, 2.40) 4)1.64 (0.90, 3.00) Other significant findings included OR (95% CI): - CHL exp during the 1st trimester in the 2nd quartile: **1.74 (1.10, 2.77)** - CHL exp during the 1st and 2nd trimester in the 3rd quartile: **1.62 (1.05, 2.50)**	Models adj for: Total gestation days Gender Mother's age Gravidity Education # of prenatal examinations Birth season Other covariates considered: Occupation Prenatal residence Postpartum residence Time of last menstrual period Parity Illness during pregnancy Term-infant gender Body weight Body length Presence or absence of malformations	Article was translated from Chinese Accounted for residential mobility by limiting participants to those who lived in the area during pregnancy Small sample size Other DBP analyzed include: DBCM, BDCM, TBM, BrTHM, DCAA, TCAA OR (95% CI) by quartile of BrTHM exp during the 3rd trimester: 1) referent 2) 1.40 (0.99, 1.98) 3) 1.21 (0.81, 1.81) 4) **1.51 (1.05, 2.17)** Significant findings were observed for some HAAs

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Hoffman et al.† 2008 US (3 communities)	Prospective cohort Community outreach and prenatal clinics 2000–2004 N = 2,766 (singleton births) n = 1,958 (excluded pregnancies: incomplete interview data; lost to follow up that ended in a loss; <25 or >42 weeks gestation, etc.) <u>SGA</u> n = 113 <u>BW</u> n = 1,854 (term birth) Additional analyses were reported in Savitz et al. 2005	SGA BW	<u>Water sampling</u> 3 sites represented: 1- moderate chlorinated DBPs (CHL was the dominant species) 2- moderate brominated DBPs 3- low levels of all DBPs Sites 1 and 2 used chloramination rather than free chlorine for termination disinfection Water samples collected weekly from sites 1 and 2, and biweekly from site 3 at a representative location within the distribution system DBP conc below the minimum reporting level for each analytic method were set to 0 <u>Exposure measure:</u> 2 exp metrics were considered for TTHM: 1) Estimated residential tap water conc 2) Estimated integrated uptake for TTHMs: - tap water conc combined with detailed exp information collected at baseline by phone interview (at 16 weeks gestation and at follow-up between 20–25 weeks) - ingestion, showering, and bathing were included	CHL water conc (µg/L) Mean (SD) in 2nd trimester, by site: 1) 46.7 (13.3) 2) 13.7 (3.3) 3) < reporting limit Tertiles of residential CHL exp (µg/L) in 3rd trimester, by site: Site 1 1) 19.9–44.2 2) 44.3–49.0 3) 49.1–94.0 Site 2 1) 6.4–11.5 2) 11.6–15.6 3) 15.7–22.1	ORs (95% CI) by tertile of the 3rd trimester average residential CHL exp by site: <u>SGA</u> Site 1 Maximum likelihood (ML) models (Supplemental material): 1) referent 2) 1.4 (0.6, 3.1) 3) 1.1 (0.5, 2.6) Bayesian models: 1) referent 2) 1.9 (0.5, 8.1) 3) 1.7 (0.4, 7.1) Site 2 ML models: 1) referent 2) **4.9 (1.5, 15.8)** 3) 2.4 (0.7, 8.4) Bayesian models: 1) referent 2) 4.2 (0.6, 33.7) 3) 3.6 (0.5, 30.1) <u>BW</u> Site 1 ML models: 1) referent 2) 26 (-51, 104) 3) 24 (-56, 103) Bayesian models: 1) referent 2) 58 (-51, 165) 3) 49 (-62, 156)	Models adj for: <u>ML models</u> Maternal age (site 1 only) Race/ethnicity Income (site 1 only) Education (site 1 only) Employment status (site 1 only) Marital status Pre-pregnancy BMI (site 1 only) Parity Caffeine intake <u>Bayesian models</u> Other DBP species Maternal age, Race/ethnicity Income Education Employment status Marital status Pre-pregnancy BMI Parity Caffeine intake	CHL and BDCM were highly correlated at the brominated site (r = 0.9) CHL conc in the 1st tertile at site 1 was similar to or greater than the 3rd tertile conc at site 2 SGA proportion was higher at the brominated site and mean BW was higher at the chlorinated site Water sampling was done at multiple areas in the distribution system and confirmed to be uniform throughout Used weekly or biweekly samples so temporal variability is more likely to be represented Use of chloramination results in minimal additional DBP formation within the distribution system (sites 1 and 2) thus minimizing spatial variability Exp data included detailed water use collected prospectively (included sources of drinking water, filter use, exp at work, showering/bathing, etc.); however, estimates were only presented for TTHM Bayesian models were used to allow for simultaneous modeling of highly correlated exp such as other DBPs Authors state that estimates of personal exp did not show stronger associations than residential conc

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					Site 2 ML models: 1) referent 2) -66 (-194, 62) 3) 69 (-61, 199) Bayesian models: 1) referent 2) 64 (-146, 278) 3) 70 (-146, 294) "Estimates of personal exp to individual DBP species were also examined, and results were similar to those for residential concentrations (results not shown)"		Small sample size Research was supported by the American Water Works Association Research Foundation and US EPA Other DBP analyzed include: BDCM, DBCM, TTHM, and CAA, DCAA, TCAA, BCAA, BDCAA, DBCAA, BAA, DBAA, TBAA, and HAA5 A significant association was seen between 3rd trimester average residential TTHM exp ≥80 vs < 80 and SGA: RR (95% CI) = **2.0 (1.1, 3.6)** Significant findings were observed for some HAAs

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Lewis et al. ‡ 2007 Massachusetts	Population-based case-control Birth certificate data 1999–2001 N = 39,593 (singleton births) n = 37,498 (births: excluding births <35 or >45 weeks gestation; <500 or >5000 g; missing information; etc.) <u>PTB</u> n = 2,813	PTB	<u>Water Sampling:</u> Abstracted THM data from Massachusetts Department of Environmental Protection 2003 records for 27 communities receiving water from a single supplier (894 samples) Weekly TTHM monitoring data from 4 sites based on maternal residence at birth applied to 24 out of 27 communities <u>Exposure Measure:</u> Exp measures averaged over 1 week to 1 month TTHM exp consisted of: - maternal residence - gestational age - environmental sample per gestational period (each trimester and 4, 2, 1 weeks before birth) Calculated trimester specific and pregnancy average exp	TTHM water conc (µg/L): Interquartile range= 59 Min–max of range = 28–87 CHL fraction of TTHM = 83–93% Tertiles of TTHM exp (µg/L): 1) <40 2) 40–60 3) <u>≥</u>60	HR (95% CI) by tertile of entire pregnancy TTHM exp: 1) referent 2) 0.92 (0.82, 1.02) 3) **0.85 (0.74, 0.97)** per 10 µg/L: **0.95 (0.92, 0.99)** HR (95% CI) by tertile of 2nd trimester TTHM exp: 1) referent 2) **0.87 (0.77, 0.99)** 3) **0.82 (0.71, 0.94)** Per 10 µg/L: **0.95 (0.92, 0.99)** During the last 4 weeks before birth for women with a government source of payment for prenatal care 1) referent 2) 1.07 (0.85, 1.34) 3) **1.39 (1.06, 1.81)** Per 10µg/L: 1.03 (0.96, 1.11) High exp in 2nd trimester was associated with PTB when stratified by race (African American: HR (95% CI) = **0.62 (0.46, 0.84)**.	Models adj for: Infant sex Marital status Kessner Index (prenatal care adequacy) Maternal age Maternal race/ethnicity Maternal education Parity Birth interval Maternal smoking Previous PTB or SGA child Prenatal care source of payment Conception season Birth season Community per capita income Previous diseases Previous trimester TTHM exp	CHL contributed 83–93% (average = 89%) of TTHM monthly averages CHL was measured; however, effects of exp were only analyzed for TTHM Exp measures were based on weekly THM samples Controls were matched to cases by gestational age Collected data on multiple covariates Study was able to examine exp over time Multiple exp time intervals were used for assessments Very large and diverse study population

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Lewis et al. ‡ 2006 Massachusetts	Population-based case-control Birth certificate data 1999–2001 N = 40,514 (singleton births) n = 36,529 (excluding births <32 or >45 weeks gestation; <500 or >5000 g; missing information; etc.) LBW n = 780	LBW (defined as term LBW - <2500 g and >36 weeks gestation)	<u>Water Sampling</u> Abstracted data from Massachusetts Department of Environmental Protection records for 27 communities from a single supplier (894 samples) 3 communities conducted their own chloramination, 24 received chloramination from a single facility Weekly average of 4 sampling sites that captured nearly all individual site values was used for the single average for the 24 communities supplied by the same facility <u>Exposure Measure:</u> Exp measures were averaged over 1 week to 1 month TTHM exp estimates were based on: - maternal residence at birth - gestational age - environmental sampling data Exp estimates were calculated for each trimester and pregnancy average	TTHM water conc (µg/L): Interquartile range= 59 Min, max of range = 28–87 CHL fraction of TTHM = 83–93% Quintiles of 2nd trimester TTHM exp (µg/L): 1) <40 2) 40–<50 3) 50–<60 4) 60–<70 5) ≥70	OR (95% CI) by quintile of 2nd trimester TTHM exp: 1) referent 2) 1.10 (0.81, 1.49) 3) 1.08 (0.79, 1.49) 4) 1.24 (0.92, 1.67) 5) **1.50 (1.07, 2.10)** Per 10 µg/L increase: 1.08 (1.00, 1.17) OR (95% CI) by quintile and race of 2nd trimester TTHM exp: <u>Caucasian:</u> 1) referent 2) 1.11 (0.69, 1.78) 3) 1.10 (0.67, 1.79) 4) 1.22 (0.76, 1.97) 5) 1.37 (0.80, 2.36) Per 10 µg/L increase: 1.06 (0.95, 1.20) <u>Non-Caucasian:</u> 1) referent 2) 1.08 (0.73, 1.61) 3) 1.09 (0.72, 1.66) 4) 1.27 (0.86, 1.87) 5) **1.60 (1.03, 2.47)**	Models adj for: Gestational age Infant sex Marital status Kessner Index Maternal age race/ethnicity education Parity Maternal smoking Prenatal care source of payment Conception season Birth season Per capita income Previous preterm or SGA infant Previous trimester TTHM exp Maternal disease factors (anemia cardiac disease diabetes hydramnios chronic hypertension pregnancy-related hypertension Rh sensitivity sickle cell anemia uterine bleeding) Other covariates considered:	CHL contributed to 83–93% of (average = 89%) TTHM monthly average Seasonal variation with peaks in May–Aug Exp measures were based on weekly THM samples Unique conditions of water system for exp classification that may reduce non-differential misclassification Multiple exp time intervals were used for assessments Study was able to examine exp over time Did not distinguish between various pathways of exp

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
					Per 10 µg/L increase: 1.10 (1.00, 1.22)	Interval since the previous live birth Previous infant who weighed >4000g Previous SGA infant	

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Hinckley et al. 2005 Arizona	Retrospective cohort Birth records 1998–2002 N = 48,119 (live births and fetal deaths) <u>SGA</u> n = 4,346 (exclusions: because values for the lowest 10th percentile were not available for extreme gestational ages, births <23 weeks gestation were excluded; for Native American births <29 weeks were excluded) <u>PTB</u> n = 4,008 <u>Very PTB</u> n = 564 <u>LBW</u> n = 1010	PTB Very PTB (<32 weeks) SGA (as intrauterine growth retardation (IUGR*) LBW (at <u>></u> 37 weeks) *term or preterm babies that fell below the published value for the lowest 10th percentile of birth weight by race, ethnicity, and gestation age	<u>Water Sampling:</u> Data from 3 community water treatment facilities were used to calculate 3rd trimester exp Total and individual THMs were measured quarterly for each facility, and monthly at some facilities for certain years Other DBP measurements were also taken at varying frequencies, depending on the facility DBPs were measured at 2–4 locations within the distribution system of each facility Procedures were used to impute missing exp data <u>Exposure Measure:</u> Subjects were matched to a water treatment facility by zip code of mother's residence at birth	Mean CHL water conc was not reported Tertiles of CHL exp (µg/L): 1) <10 2) 10–16 3) ≥16	<u>PTB and Very PTB</u> Authors reported that no associations were observed; no ORs were presented <u>SGA</u> OR (95% CI) by tertile for 3rd trimester CHL exp: 1) referent 2) 1.02 (0.94, 1.11) 3) 1.01 (0.93, 1.10) Continuous - 1.00 (1.00, 1.01) <u>LBW</u> OR (95% CI) by tertile for 3rd trimester CHL exp: 1) referent 2) 1.18 (1.00, 1.39) 3) 1.04 (0.88, 1.23) Continuous - 1.00 (1.00, 1.01)	Models adj for: <u>SGA</u> Parity Education Smoking Kessner index <u>LBW</u> Maternal age Race Ethnicity Education Parity Smoking Kessner index	Large sample size By comparing subjects within the same community with respect to exp levels, may have reduced potential residual confounding Considered multiple time periods of exp The community studied was selected in order to minimize misclassification due to spatial variability within the distribution systems Large temporal variability and low spatial variability for DBPs within water distribution systems Other DBP analyzed: BDCM, DBCM, TTHM, HAA5, DBAA, DCAA, TCAA Significant findings were observed for some HAAs

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Porter et al. 2005 Maryland	Retrospective cohort Birth certificate data 1998–2002 N = 18,087 (singleton births) n = 15,315 (restricted to African American, Caucasian, and Hispanic American infants; excluded infants born <25 or >42 weeks gestation) <u>SGA</u> n = 1,114	SGA (as IUGR*) * defined as affecting an infant whose birth weight was below the 10th percentile for gestational age (adjusted for sex and race) using standards from the US Census data"	<u>Water Sampling:</u> Monthly conc of TTHM and individual THMs (including CHL) at 4 sampling points in study obtained from the water utility company for 1997–2002 Sampling points represented varying distances from the water treatment facility <u>Exposure Measure:</u> Women whose residences were in zip codes corresponding to the water utility's point measurements were included in the analysis. Measurements were averaged biweekly TTHM levels based on estimated gestational period TTHM measurements from 1997 were used for infants born in the 1st 3 quarters of 1998	CHL water conc (µg/L): Mean (95% CI) = 34.1 (32.5, 35.7) Quintiles of CHL exp (µg/L): (specific quintile ranges not mentioned)	OR (95% CI) by quintile of CHL exp for the entire pregnancy: 1) Referent 2) **1.24 (1.02, 1.50)** 3) 1.08 (0.88, 1.32) 4) 1.12 (0.92, 1.36) 5) 1.04 (0.85, 1.27) OR (95% CI) by quintile of 3rd trimester CHL exp: 1) Referent 2) 1.02 (0.84, 1.24) 3) 0.96 (0.79, 1.16) 4) 0.98 (0.81, 1.19) 5) 1.07 (0.88, 1.29)	Models adj for: Marital status Mother's age Kessner index Tobacco use Other covariates considered: Maternal weight gain Child's race/ethnicity Alcohol use Mother's residence	TTHM values fluctuated by season, summer months were higher Other DBP analyzed: BDCM, DBCM, TBM, TTHM, BAA, CAA, DBAA, DCAA, CAA, TCAA, HAA5 Significant findings were observed for some HAAs

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Savitz et al. † 2005 US (3 locations)	Prospective cohort Prenatal clinics and community outreach 2000–2004 N = 2,766 (women) n = 1,934 (excluding multiple gestations, missing data, etc.) PTB n = 196 SGA n = 102 BW n = 1,738	PTB SGA BW (SAB outcome reported in Table 4a)	<u>Water Sampling</u>: 3 sites represented: 1) moderate chlorinated DBP (CHL was the dominant species); 2) moderate brominated DBP 3) low levels of all DBP Sites 1 and 3 used chloramination rather than free chlorine for terminal disinfection For each site, water samples were measured weekly at a location that reflected DBP conc throughout the system <u>Exposure Measure</u>: Tap water exp was the average weekly sample values over time of pregnancy Daily exp, collected prospectively: Ingestion - residential tap water conc water x consumption (number and cup size per day of tap, filtered, hot, and cold water) x uptake factors Total integrated exp - Including ingestion, inhalation and dermal absorption (water conc x duration x uptake factors) [inhalation and dermal from showering and	CHL water conc (µg/L) by site: Mean (range) = 1) 45.6 (14.7–124) 2) below minimium reporting level (maximum 2.4) 3) 11.9 (3.0–52.7) <u>SGA</u> Quartiles of 3rd trimester CHL water conc (µg/L): 1) >0.0–≤0.2 2) >0.2–≤19.2 3) >19.2–≤47.1 4) >47.1 Quartiles of 3rd trimester total integrated CHL exp (µg/d): 1) 0 2) >0–≤0.5 3) >0.5–≤1.2 4) >1.2 <u>PTB/ BW</u> Quintiles of 3rd trimester CHL water conc (µg/L): 1) ≥0.0–≤0.1 2) >0.1–≤10.9 3) >10.9–≤30.4 4) >30.4–≤48.2 5) >48.2	<u>SGA</u> OR (95% CI) by quartile of 3rd trimester CHL water conc (µg/L): 1) referent 2) 1.45 (0.79, 2.64) 3) 1.33 (0.71, 2.49) 4) 1.05 (0.54, 2.01) OR (95% CI) by quartile of 3rd trimester total integrated CHL exp (µg/d): 1) referent 2) 1.16 (0.63, 2.14) 3) 1.26 (0.68, 2.33) 4) 1.14 (0.62, 2.09) <u>PTB</u> OR (95% CI) by quintile of 3rd trimester CHL water conc (µg/L): 1) referent 2) 0.68 (0.42, 1.11) 3) 0.76 (0.47, 1.24) 4) **0.52 (0.31, 0.90)** 5) **0.54 (0.31, 0.92)**	Model adj for: <u>SGA</u> Maternal race (black) Education Smoking BMI Live birth history <u>PTB</u> Maternal caffeine consumption Income BMI Live birth history Other covariates considered: Maternal age Age at mother's interview Parity Infant gender Employment Ethnicity Marital status Diabetes Previous alcohol intake Vitamin use Study site Season <u>BW (Term)</u> Maternal race (black) Gestational age (included both as gestational age and gestational age squared) Maternal caffeine	CHL was dominant THM species at chlorinated DBP site (range = 20–120 µg/L) with the highest levels in summer Sites were chosen for their use of chloramination for terminal disinfection as it results in minimal additional DBP formation within the distribution system Extensive water sampling was done, including at multiple areas in the distribution system and confirmed to be uniform throughout Exp data included extensive detailed water use collected mostly prospectively (e.g. water source; filter use, exp at work, showering/bathing, etc.) A biomarker study was conducted on a small sample of women; however, a simple linear relationship between CHL water conc and blood levels was not evident Authors note that site characteristics (e.g. demographic) or the recruitment methods across the sites may have led to biases in the estimated effects of DBP Multiple comparisons Research was supported by the American Water Works Association Research Foundation and US EPA

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			bathing] Estimated DBP levels for hot, cold, unfiltered, and filtered water were adjusted based on empirical laboratory experiments	Quintiles of 3rd trimester total integrated CHL exp (µg/d): 1) 0 2) >0–≤0.2 3) >0.2–≤0.8 4) >0.8–≤1.3 5) >1.3	OR (95% CI) by quintile of 3rd trimester total integrated CHL exp (µg/d): 1) referent 2) 1.03 (0.65, 1.66) 3) **0.56 (0.32, 0.96)** 4) 0.82 (0.49, 1.37) 5) 0.59 (0.34, 1.01) <u>BW</u> Mean change (95% CI) by quintile of 3rd trimester CHL water conc (µg/L): 1) referent 2) -18 (-86, 51) 3) -6 (-75, 62) 4) 12 (-56, 80) 5) 28 (-39, 96) Mean change (95% CI) by quintile of 3rd trimester total integrated CHL exp (µg/d): 1) referent 2) 10 (-58, 78) 3) -4 (-72, 63) 4) 37 (-31, 105) 5) 32 (-36, 100)	consumption Education Income Smoking BMI Employment Diabetes status Live birth history	Other DBP analyzed: THM4, BDCM, HAA9, BrTHM, HAA5, BrHAA, TOX <u>SGA</u> OR (95% CI) by quartile of 1st trimester BDCM water exp (µg/L): 1) referent 2) **0.51 (0.26, 0.99)** 3) 0.89 (0.50, 1.59) 4) 1.04 (0.60, 1.8) Significant elevated ORs were observed for TTHM above and below 80 µg/L at all sites, with the highest OR observed for site 1 – **2.45 (1.09, 5.50)** (Supplemental table 8.15) Significant findings were observed for some HAAs <u>PTB</u> OR (95%CI) by quintile of 1st trimester BDCM water exp (µg/L): 1) referent 2) 0.78 (0.48, 1.26) 3) 0.78 (0.47, 1.28) 4) **0.58 (0.34, 0.96)** 5) 0.73 (0.45, 1.21) OR (95% CI) by quintile of 3rd trimester BDCM water exp (µg/L): 1) referent 2) 0.63 (0.38, 1.04) 3) **0.47 (0.27, 0.83)** 4) 0.69 (0.41, 1.15)

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
							5) 0.96 (0.60, 1.54) OR (95% CI) by quintile of 1st trimester BrTHM water exp (µg/L): 1) referent 2) 0.90 (0.56, 1.45) 3) 0.69 (0.41, 1.16) 4) **0.48 (0.27, 0.84)** 5) 1.01 (0.63, 1.62) OR (95% CI) by quintile of 3rd trimester BrTHM water exp (µg/L): 1) referent 2) **0.58 (0.35, 0.97)** 3) **0.45 (0.25, 0.78)** 4) **0.51 (0.29, 0.88)** 5) 1.03 (0.65, 1.63) OR (95% CI) by quintile of 1st trimester BrTHM total integrated exp (µg/d): 1) referent 2) 0.84 (0.51, 1.38) 3) **0.49 (0.27, 0.86)** 4) 0.81 (0.49, 1.34) 5) 0.92 (0.56, 1.51)

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Toledano et al. 2005 United Kingdom (3 study sites)	Retrospective cohort Birth and stillbirth records 1992–1998 (years varied by water utility) N = 969,304 n = 920,571 (excluding births that could not be assigned water zones, etc.) <u>LBW</u> n = 60,641 <u>VLBW</u> n = 9,167	LBW Very LBW (SB outcome reported in Table 4a)	<u>Water sampling:</u> Samples from 3 water companies (analyzed for CHL and other DBPs) Regulations required ≥ 4 samples/year (more frequent samples were required if the standard of 100 µg/L TTHM was breached, only 1 sample/year was required if TTHM conc <50 µg/L) Mean number of samples/year: Northumbrian 4.5 United Utilities 11.2 Severn Trent 6.3 <u>Exposure Measure:</u> Individual postal code records extracted from birth registries and linked to water zone Individual THM conc were modeled, taking into account seasonal variation and THM profiles associated with particular water sources, to obtain more robust estimates of mean TTHM in each zone Modeled quarterly TTHM estimates were weighted (based on the proportion of the pregnancy trimester in each quarterly period) and the weighted average THM conc for last 93 days	CHL water conc mean (SD), range (µg/L) not stated CHL exp categories (µg/L): 1) Low <20 2) Med 20–40 3) High >40	ORs (95% CI) by categories of 3rd trimester CHL exp, for all water utilities combined (µg/L) (Supplemental material Table 4.12): <u>LBW</u> 1) Referent 2) **1.05 (1.03, 1.07)** 3) **1.10 (1.07, 1.13)** <u>VLBW</u> 1) Referent 2) 1.01 (0.96, 1.07) 3) 1.07 (0.99, 1.15)	Models adj for: <u>LBW</u> Maternal age Sex of infant Year of study Carstairs quintile (Carstairs index is a measure of socioeconomic deprivation at the level of the enumeration district, which has a population=400 on average) <u>VLBW</u> Maternal age Carstairs quintile Year of study Interaction parameters with all covariates were tested in final models	Large sample size Hierarchical links built into the model so exp was estimated with comparable precision across zones and quarters Possibility of high exp misclassification due to weighted averages No data on gestation age If CHL affects gestation length, this relationship could either contribute to or obscure the observed relationship between CHL and BW Other DBP analyzed: TTHM, BDCM, BrTHM Authors reported conc of BDCM and BrTHM did not show any association with LBW or VLBW (data not shown)

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			before birth were categorized into 3 levels				

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Infante-Rivard 2004 Montreal	Case-Control University-based medical center 1998–2000 N = 985 (singleton births >24 weeks gestation) n = 884 cases n = 458 controls n = 426	SGA* *(Defined as IUGR in the study - BW below 10th percentile matched for gestational age, race, and sex)	<u>Water Samples</u> THM conc from regulatory data collected by municipalities 189 distribution systems Average daily measures <u>Exposure measure:</u> TTHM exp according to place of residence Individual THM exp as average level from treatment plant averaged over pregnancy period Cumulative index was the cumulative level over the pregnancy period (sum of conc x duration in days at specific level) Average level at tap multiplied by # of glasses of tap water per day averaged over the pregnancy (1 version included a weight of 0.9 for filter use or refrigeration) Face to face interview: (within 2 days of delivery) - maternal residence - drinking water source - use and type of domestic water filter - # of glasses of water (average/d) at home and elsewhere - usual way of	CHL water conc (µg/L): Mean (SD): cases = 11.84 (18.19) controls = 11.58 (16.31) 90 percentile cutoff (23.7 µg/L) for average CHL conc for the entire pregnancy: 1) ≤ 90th percentile 2) > 90th percentile Gene-environment interaction: 90th percentile CHL levels + categories for mother and newborn variants of *CYP2E*1 and *MTHFR C677T:* 1) wild type 2) 1 or 2 variant alleles	OR (95% CI) of entire pregnancy CHL water conc: 1) Referent 2) 1.06 (0.63, 1.79) No increased risks were observed using other exp indices for drinking water or showering (data not shown) ORs (95% CI) for relation to entire pregnancy CHL water conc according to newborn and maternal polymorphisms – <u>Newborn</u>: *CYP2E1*5(G1259C)* 1) 0.99(0.57, 1.74) 2) 5.62(0.82, 38.39) *MTHFR* C677T 1) 1.78 (0.82, 3.87) 2) 0.83 (0.38, 1.54) <u>Mother</u>: *CYP2E1*5(G1259C)* 1) 0.88 (0.50, 1.54) 2) 4.40 (0.73, 26.42) *MTHFR* C677T 1) 1.00 (0.46, 2.18)	Models adj for: Gestational age Sex Race Pregnancy weight gain Prepregnancy BMI 3rd trimester smoking Primiparity Preeclampsia History of IUGR Other covariates considered: Parity Preeclampsia history Smoking in pregnancy	Controls born at the same hospital were matched to cases on gestational week, sex and race Substantial number of women drank bottled water Controls reported higher use of domestic water filters Genetic data included Accounted for residential mobility Exp data included detailed water use (e.g. water source, filter use, refrigeration, showering, bottled water use, etc.) Extensive control for confounding Small sample size in exposed category using 90th percentile Limited water contaminant measures of distribution systems, no specific location within distribution system when multiple locations within system were sampled Other DBP analyzed: BDCM, DBCM, TBM, TTHM

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			consuming water from tap - # and duration of showers/week		2) 1.12 (0.56, 2.32) The author reported statistical heterogeneity in the risk of SGA between newborn carriers and noncarriers of the CYP2E1 variant for exp to average levels of CHL (data not shown)		

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Kramer et al. 1992 Iowa	Population-based case-control Birth certificate data 1989–1990 All live singleton infants born to non-Hispanic white women 19 years of age or older from towns with 1,000–5,000 inhabitants that derived all their public drinking water from a single source PTB cases n = 342 controls n = 1,710 IUGR* (excluding births ≤22 weeks or ≥46 weeks gestation) cases n = 187 controls n = 935 LBW cases n = 159 controls n = 795	Population based case-control PTB SGA* LBW *defined as weighing less than the 5th percentile for gestational age, based on California standards for non-Hispanic whites	<u>Water Sampling:</u> Water samples taken from a 1987 municipal water survey Water samples based on towns that had single source for drinking water defined by surface water supply from a single intake or ground water supply of one or more wells of a single aquifer <u>Exposure measure:</u> Exp based on maternal residence at birth Births were from 1989 and 1990 while water samples were from 1987 data (birth data from 1989 and 1990 were used as smoking questions were included on birth certificates only after 1987)	CHL water conc (µg/L): Mean (SD) = 12.5 (38.7) Median = 1 Range = 0–350 Categories of CHL exp (µg/L) (percent of water supplies): 1) Undetectable (45.7) 2) Low: 1–9 (41.7) 3) High: ≥ 10 (12.6)	OR (95% CI) by categories of entire pregnancy water CHL conc: <u>PTB:</u> 1) referent 2)1.1 (0.8, 1.4) 3)1.1 (0.7, 1.6) <u>SGA:</u> 1) referent 2)1.3 (0.9, 1.8) 3)**1.8 (1.1, 2.9)** <u>LBW:</u> 1) referent 2)1.1 (0.7, 1.6) 3)1.3 (0.8, 2.2)	Models adj for: Maternal age Number of previous children Marital status Education Prenatal care Maternal smoking Stratified analysis by water source to control for effects of pesticides in drinking water	CHL conc ≥10 µg/L tended to be found in towns in the extreme northern and southern sections of the state, but undetectable conc and conc between 1 and 9 µg/L were widely scattered throughout Iowa CHL conc were reported as high as 350 µg/L as cities with <10,000 inhabitants did not have to conform to the TTHM standard of 100 µg/L When analysis was restricted to chlorinated water only, the highest level of CHL exp (≥10 µg/L) had an OR (95% CI) of **1.8 (1.03, 3.0)** When stratified by type of water source to control for pesticides in drinking water, SGA analysis of CHL ≥10 µg/L still had an elevated OR in water from shallow and deep wells As the 1987 survey was conducted during a drought, the TTHM levels in 1989 and 1990 would be expected to be higher due to the higher conc of organic material Authors attempted to control for unmeasured factors, such as lifestyle differences, through restriction to towns with 1,000–5,000 inhabitants Gestational age was determined from the mother's last menstrual period as reported on the birth certificate

Table 3a. Detailed Summaries for Epidemiologic Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) (cont'd).

Study/ Location	*Study Design/ Sample sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
	*for the purposes of this assessment IUGR will be considered as SGA						Cases were not mutually exclusive THM exp levels were based on a one-time 1987 municipal water survey Total organic halides were measured in 62% of water supplies OR (95% CI) for SGA for exp to the highest levels of total organic halides (≥100 µg/L) = 1.8 (0.9,3.4) 90.6% of those exposed to CHL ≥10 µg/L were also exposed to total organic halides ≥100 µg/L Other DBP analyzed: BDCM, DBCM, TBM

Table 3b. Associations between Chloroform (CHL) Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
Danileviciute et al. ‡ ‡ 2012 Lithuania	<u>Estimated internal dose (µg/d)</u> CHL ≥0.1424 (median level)	<0.1424		<u>Entire pregnancy</u> 1.31 (0.82, 20.9) GSTM1-1 0.84 (0.42, 1.68) GSTM1-0 1.78 (0.90, 3.50) GSTT1-1 1.30 (0.78, 2.17) GSTT1-0 0.99 (0.28,3.58) <u>3rd trimester</u> 1.31 (0.82, 2.08) GSTM1-1 0.88 (0.44, 1.78) GSTM1-0 1.74 (0.89, 3.41) GSTT1-1 1.18 (0.71, 1.97) GSTT1-0 1.75 (0.50, 6.10)	<u>Entire pregnancy</u> 1.24 (0.57, 2.68) GSTM1-1 0.34 (0.09, 1.22) GSTM1-0 **4.08 (1.20, 13.9)** Test for interaction: **12.88 (2.27, 73.2)** GSTT1-1 1.9 (0.5, 2.82) GSTT1-0 7.48 (0.13, 409) <u>3rd trimester</u> 1.45 (0.67, 3.13) GSTM1-1 0.35 (0.10, 1.28) GSTM1-0 **5.06 (1.50,17.05)** Test for interaction: **15.86 (2.75,91.40)** GSTT1-1 1.35 (0.57, 3.20) GSTT1-0 7.30 (0.14, 391)	
Botton et al.* 2015 Spain (3 study sites) and Greece	<u>Estimated internal dose (µg/d)</u> <u>All sites:</u> CHL IQR inc <u>Ingestion (µg/d)</u> <u>All sites:</u> CHL IQR inc					<u>Entire pregnancy Postnatal weight gain</u> -9.30 (-87.3, 68.7) -40.3 (-122, 41)

Abbreviations: BDCM - bromodichloromethane; BrTHM - total brominated trihalomethanes; BW - birth weight; CHL - chloroform; CI - confidence interval; conc - concentration; DBCM - dibromochloromethane; dec - decrease; FGR - fetal growth restriction; inc - increase; LBW - low birth weight; med - medium; PTB - preterm birth; SGA - small for gestational age; TCAA – trichloroacetic acid; TTHM - total trihalomethanes; VLBW - very low birth weight.

Table 3b. Associations between Chloroform (CHL) Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	By site: Gipuzkoa CHL IQR inc Sabadell CHL IQR inc Valencia CHL IQR inc					9.63 (-174, 193) **-151 (-288, -15)** 36.7 (-87, 160)
Grazuleviciene et al. 2011 ‡ ‡ Lithuania	Estimated internal dose (µg/d) 0.0249–0.2868 0.2868–2.1328 Continuous (per 0.1 µg/d increase)	0.0013–0.0249		3rd trimester 1.19 (0.87, 1.63) 1.22 (0.89, 1.68) 1.04 (1.00, 1.09)	3rd trimester **2.12 (1.11, 4.02)** **2.13 (1.15, 3.92)** **1.09 (1.01, 1.18)**	3rd trimester Change in BW in grams, of infants below 3,500 g, for every 1 µg/d increase in internal dose: **-57.8 (-111.6, -4.0)**
Smith et al. 2015 England	Estimated internal dose (µg/d) CHL ≥0.91–<1.56 ≥1.56	<0.91				Entire pregnancy Total population: -16.3 (-39.0, 6.5) -20.9 (-44.6, 2.8) Pakistani origin: 10.3 (-21.2, 41.9) **- 48.3 (-84.6, -12.1)** White British: -13.3 (-52.9, 26.3) 9.0 (-23.5, 46.5) 3rd trimester Total population: -14.8 (-37.7, 8.1) -8.7 (-31.8, 14.3) Pakistani origin: 5.1 (-27.1, 37.4) **-42.8 (-78.2, -7.4)** White British: -27.0 (-66.1, 12.1) 9.5 (-26.8, 45.8)
Kramer et al. 1992 Iowa	Water conc (µg/L) CHL 1–9 ≥10	ND <1	Entire pregnancy 1.1 (0.8, 1.4) 1.1 (0.7, 1.6)	Entire pregnancy 1.3 (0.9, 1.8) **1.8 (1.1, 2.9)**	Entire pregnancy 1.1 (0.7, 1.6) 1.3 (0.8, 2.2)	

Table 3b. Associations between Chloroform (CHL) Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
Costet et al. 2012 France	Water conc (µg/L) CHL 5–<10 10–<15 ≥15 Estimated internal dose (µg/d) CHL 0.068–<0.133 0.133–<0.237 ≥0.237 Nested TCAA Study Estimated internal dose via ingestion (µg/d) CHL 0.001–<0.006 0.006–<0.015 ≥0.015	< 5 < 0.068 0–0.001	3rd trimester 0.7 (0.4,1.2) **0.5 (0.3,0.9)** 0.8 (0.4,1.4) 1.8 (0.7, 4.8) 0.7 (0.2, 2.1) 1.0 (0.4, 2.9) 0.7 (0.3, 1.5) 0.8 (0.4, 1.8) 1.2 (0.6, 2.5)	3rd trimester (as FGR) 0.8 (0.5, 1.2) 1.0 (0.6, 1.5) 0.9 (0.5, 1.4) 1.1 (0.5, 2.3) 1.2 (0.6, 2.4) 1.0 (0.5, 2.1) 1.0 (0.6, 1.7) 0.8 (0.4, 1.5) 1.2 (0.7, 2.2)		
Hinckley et al. 2005 Arizona	Water conc (µg/L) CHL 10–16 ≥16	<10	No OR were presented Authors reported no associations were observed	3rd trimester 1.02 (0.94, 1.11) 1.01 (0.93, 1.10)	3rd trimester 1.18 (1.00, 1.39) 1.04 (0.88, 1.23)	
Infante-Rivard 2004 Montréal, Canada 1) Wild type 2) 1 or 2 variant alleles	Water conc (µg/L) CHL >23.7 Gene-environment interaction: 90th percentile CHL conc + categories for mother and newborn variants of CYP2E1 and MTHFR C677T: Newborn CYP2E1*5 CHL >23.7 MTHFR CHL >23.7 Maternal CYP2E1*5 CHL >23.7	≤23.7 ≤23.7 ≤23.7 ≤23.7	 1) 0.99 (0.57, 1.74) 2) 5.62 (0.82, 38.39) 1) 1.78 (0.82, 3.87) 2) 0.83 (0.38, 1.54) 1) 0.88 (0.50, 1.54) 2) 4.40 (0.73, 26.42)	Entire pregnancy 1.06 (0.63, 1.79)		

Table 3b. Associations between Chloroform (CHL) Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	MTHFR CHL >23.7	≤23.7	1) 1.00 (0.46, 2.18) 2) 1.12 (0.56, 2.32)			
Porter et al. 2005 Maryland	<u>Water conc (µg/L)</u> CHL (Mean = 34.1) 2nd quintile 3rd quintile 4th quintile 5th quintile	1st quintile		<u>Entire pregnancy</u> **1.24 (1.02, 1.50)** 1.08 (0.88, 1.32) 1.12 (0.92, 1.36) 1.04 (0.85, 1.27) <u>3rd trimester</u> 1.02 (0.84, 1.24) 0.96 (0.79, 1.16) 0.98 (0.81, 1.19) 1.07 (0.88, 1.29)		
Toledano et al. 2005 United Kingdom (3 study sites)	<u>Water conc (µg/L)</u> <u>LBW</u> CHL 20–40 >40 <u>VLBW</u> CHL 20–40 >40	<20 <20			<u>3rd trimester</u> **1.05 (1.03, 1.07)** **1.10 (1.07, 1.13)** 1.01 (0.96, 1.07) 1.07 (0.99, 1.15)	
Savitz et al. † 2005 US (3 study sites)	<u>Water conc (µg/L)</u> CHL >0.1–≤10.9 >10.9–≤30.4 >30.4–≤48.2 >48.2 <u>Estimated internal dose (µg/d)</u> CHL >0-≤0.2 >0.2-≤0.8 >0.8-≤1.3 >1.3	≥0-≤0.1 0	<u>3rd trimester</u> 0.68 (0.42, 1.11) 0.76 (0.47, 1.24) **0.52 (0.31, 0.90)** **0.54 (0.31, 0.92)** 1.03 (0.65, 1.66) **0.56 (0.32, 0.96)** 0.82 (0.49, 1.37) 0.59 (0.34, 1.01)	Used quartiles <u>3rd trimester</u> 1.45 (0.79, 2.64) 1.33 (0.71, 2.49) 1.05 (0.54, 2.01) <u>Used quartiles</u> 1.16 (0.63, 2.14) 1.26 (0.68, 2.33) 1.14 (0.62, 2.09)		<u>3rd trimester</u> -18 (-86, 51) -6 (-75, 62) 12 (-56, 80) 28 (-39, 96) 10 (-58, 78) -4 (-72, 63) 37 (-31, 105) 32 (-36, 100)
Hoffman et al. † 2008 3 US communities	<u>Site 1 (chlorinated) water conc (µg/L)</u> CHL 44.3–49.0 49.1–94.0	19.9–44.2		<u>Bayesian models 3rd trimester</u> 1.9 (0.5, 8.1) 1.7 (0.4, 7.1)		<u>Bayesian models 3rd trimester</u> 58 (-51, 165) 49 (-62, 156)

Table 3b. Associations between Chloroform (CHL) Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	Site 2 (brominated) water conc (µg/L) CHL 11.6–15.6 15.7–22.1	 6.4–11.5		 4.2 (0.6, 33.7) 3.6 (0.5, 30.1)		 64 (-146, 278) 70 (-146, 294)
Levallois et al. 2012 Quebec City, Canada	Water conc (µg/L) CHL 15.96–27.26 27.27–51.07 >51.07 Estimated internal dose via total pathway (µg/d) CHL 42.24–80.21 80.22–169.81 >169.81	 <15.96 <42.24		3rd trimester 0.9 (0.7, 1.3) 1.0 (0.8, 1.4) 1.2 (0.9, 1.7) 0.9 (0.7, 1.2) 1.0 (0.7, 1.3) 1.0 (0.8, 1.4)		
Rivera-Nuñez and Wright 2013 Massachusetts	Water conc (µg/L) CHL >5–21 >21–36 >36–52 >52	 ≤5	2nd trimester 1.00 (0.94, 1.06) **1.08 (1.02, 1.14)** 1.06 (0.99, 1.12) 1.00 (0.94, 1.07)	3rd trimester 1.01 (0.96, 1.05) 1.00 (0.95, 1.04) 1.04 (1.00, 1.10) 1.04 (0.99, 1.09)		3rd trimester -1 (-7, 5) **-9 (-15, -2)** **-13 (-19, -7)** **-15 (-21, -8)**
Summerhayes et al. 2012 New South Wales, Australia	Water conc (µg/L) CHL IQR increase (25 µg/L) 5th decile 25.00–30.18 10th decile 56.03–147.94	 1st decile 1.68–13.71		Relative Risk 3rd trimester **1.04 (1.02, 1.06)** 1.01 (0.96, 1.07) **1.12 (1.05, 1.18)**		 Entire pregnancy **-5.0 (-8.6, -1.4)**
Lewis et al. ‡ 2007 Massachusetts	Water conc (µg/L) TTHM (CHL = 83–93%) 40–<60 ≥60 Continuous (per 10 µg/L increase)	 <40	Hazard Ratios 2nd trimester **0.87 (0.77, 0.99)** **0.82 (0.71, 0.94)** **0.95 (0.92, 0.99)** Pregnancy average 0.92 (0.82, 1.02) **0.85 (0.74, 0.97)** **0.95 (0.91, 0.99)**			

Table 3b. Associations between Chloroform (CHL) Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
			4 weeks before birth[1] 1.07 (0.85, 1.34) **1.39 (1.06, 1.81)** 1.03 (0.96, 1.11)			
Wright et al. 2004 Massachusetts	Water conc (µg/L) CHL >26–63 >63–135	0–26	3rd trimester **0.95 (0.91, 0.99)** **0.90 (0.84, 0.97)**	3rd trimester **1.05 (1.02, 1.09)** **1.11 (1.04, 1.17)**		3rd trimester **-14 (-19, -9)** **-18 (-26, -10)**
Lewis et al. ‡ 2006 Massachusetts	Water conc (µg/L) TTHM (CHL = 83–93%) 40–<50 50–<60 60–<70 ≥70 Per 10 µg/L increase	≤40			2nd trimester 1.10 (0.81, 1.49) 1.08 (0.79, 1.49) 1.24 (0.92, 1.67) **1.50 (1.07, 2.10)** 1.08 (1.00, 1.17) Caucasian 1.11 (0.69, 1.78) 1.10 (0.67, 1.79) 1.22 (0.76, 1.97) 1.37 (0.80, 2.36) 1.06 (0.95, 1.20) Non-Caucasian 1.08 (0.73, 1.61) 1.09 (0.72, 1.66) 1.27 (0.86, 1.87) **1.60 (1.03, 2.47)** 1.10 (1.00, 1.22)	
Villanueva et al.* 2011 Spain (5 areas)	Total residential water conc (µg/L) CHL 10% increase		3rd trimester 1.00 (0.99, 1.01)	3rd trimester 1.00 (0.99, 1.01)	3rd trimester 1.00 (0.99, 1.02)	3rd trimester -0.07 (-1.00, 0.85)

[1] Hazard ratios for prenatal care paid for by government or Healthy Start.

Table 3b. Associations between Chloroform (CHL) Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
Iszatt et al. 2014 England	Water conc (µg/L) LBW CHL 1) Low inc: ≤10 to dec <10 2) Med dec: 10–<30 3) High dec: 30–65 VLBW CHL				Entire pregnancy LBW[2] **1) -5 (-9, -1)** **2) -5 (-9, -1)** **3) -9 (-12, -5)** VLBW -7 (-17, 3) 4 (-7, 16) **-16 (-24, -8)**	
Zhou et al. 2010 China	Water conc (µg/L) CHL 2nd quartile 3rd quartile 4th quartile	1st quartile				Odds Ratio Entire pregnancy 0.96 (0.60, 1.53) 1.45 (0.88, 2.40) 1.64 (0.90, 3.00) 1st trimester **1.74 (1.10, 2.77)** 0.90 (0.47, 1.74) 0.89 (0.44, 1.77) 3rd trimester 1.37 (0.99, 1.88) 1.67 (0.98, 2.85) **1.82 (1.10, 3.02)** 1st and 2nd trimester 1.10 (0.71, 1.68) **1.62 (1.05, 2.50)** 0.93 (0.54, 1.60)
Wennborg et al. 2000 Sweden	Women working in a laboratory with CHL n = 66	Women working in non-laboratory departments				Entire pregnancy 27 (-136, 190)

[2] Reported as rate change, which is the percent change calculated as the exponential of the regression coefficient (e.g. rate ratio of after/before) minus 1 and multiplied by 100.

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Reproductive Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function.

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Iszatt et al. 2014 England	Retrospective cohort Birth and SB records Two sample periods - 2000–2002 and 2005–2007 Intervention component - enhanced coagulation water treatment (EC; a process that improves removal of DBP precursors, reducing DBP formation potential) was introduced to 4 water treatment works (88 of 258 water zones) in 2003–2004 N = 472,526 (live births) n = 429,599 (live births) SB n = 2,279	SB (LBW and VLBW outcomes reported in Table 3a)	<u>Water Sampling:</u> Routine monitoring of public water supply: - at geographically random samples - a minimum of 4 times per year Two time periods for water sampling: 3-year period before and 3-year period after EC intervention <u>Exposure Measure:</u> Postcode of maternal residence at birth was linked to water zone boundary in use during the year of birth Births in the first 6 weeks of the year were linked to the water zone boundary of the preceding year Water zone boundary information was linked to THM conc A water zone is a supply area with approximately uniform water quality, with a population ≤100,000 Two exp metrics were constructed for each water zone: EC identified treatment status conc change for THMs	CHL water conc (µg/L): Mean (SD) = Before (2000–2002) 38.6 (4.2) After (2005–2007) 19.4 (1.0) CHL distribution change (µg/L): Mean (SD) = Overall: -19.2 (17.6) No EC: -14.0 (17.4) EC: -29.2 (13.2) Categories for changes in CHL levels (based on TTHMs (µg/L): 1) Low increases/ decreases– decrease <10 to increase ≤10 2) Medium Decreases - 10 to <30 3) High decreases - 30 to 65 Exposure metric included annual average THM data covering the entire pregnancy	Percent change (95% CI) for rates before and after EC (calculated as the exponential of the regression coefficient (i.e., rate ratio of after/before) minus 1 and multiplied by 100): 1) 5 (-9, 20) 2) 2 (-13, 20) 3) -4 (-16, 8)	Unadjusted rates were presented because infant sex, parity, and maternal age were found not to affect the rates Other covariates considered: Multiple birth Ethnicity (area-level Census data) Analysis included an interaction term to estimate the difference in rates before and after the intervention and across the exp categories Analysis was included to determine possible influence of income on birth outcome rates using variable for income deprivation score at water zone level	TTHMs were strongly correlated with CHL (r=0.99) Change in average CHL accounted for 94% of the change in TTHM after EC (calculated from Table 1 of the paper) Background mean TTHM conc decrease of 15.1 µg/L in non-EC water zones and statistically significant greater mean decrease of 30.5 µg/L in EC water zones Due to the intervention design of the study, it was assumed that few social class factors changed over time, thus decreasing the possibility of residual confounding Overall statistically significant reduction in conc of TTHMs, CHL, BrTHM and BDCM Only 6% of EC water zones received 100% EC water No information on individual water use Other DBPs analyzed: TTHMs, BDCM, DBCM, TBM, BrTHM

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Grazuleviciene et al. ‡ ‡ 2013 Lithuania	Prospective cohort All pregnant women in Kaunas (2nd largest city in Lithuania) 2007–2009 N = 3341 (pregnant women) n = 3,074 <u>BD:</u> Heart: n = 57 Musculo-skeletal: n = 37 Urogenital: n = 23	BD From registry - based data, diagnosed after a live birth and before discharge from hospital: Heart Musculo-skeletal Urogenital	<u>Water Sampling:</u> 4 treatment plants: all groundwater sources, each sampled at 3 distances from each plant (near the plant, at 5 and ≥10 km), 4 times/year for 3 years (85 samples in total) Mean quarterly conc was calculated for each plant <u>Exposure Measure</u>: Geocoded maternal address at birth was used to determine CHL exp conc Average conc was calculated for 1st, 2nd, and 3rd months, each trimester, and entire pregnancy Internal dose (total integrated uptake): (inhalation, ingestion & dermal absorption) was calculated from algorithms using interview data, on trimester-specific water consumption including: - size and number of glasses of tap water per day (including cold and boiled water), use of bottled water at home, at work, other - number and average length of showers and baths, swimming pool visits	CHL water conc (µg/L) Mean (SD): At 3 plants with low THM levels = 0.9 (1.0) At 1 plant with high THM levels = 17.7 (9.0) (54.9% of subjects) Internal dose for 1st trimester CHL exp: Range (µg/d): 0.001–2.109 Tertiles (µg/d): 1) 0.001–0.026 2) 0.026–0.288 3) 0.288–2.109	OR by tertiles of 1st trimester internal CHL exp (µg/d): Heart: 1) referent 2) 1.05 (0.53, 2.08) 3) 1.37 (0.72, 2.63) P-trend: 0.245 Continuous (1 µg/d): 1.97 (0.90, 4.35) Musculoskeletal: 1) referent 2) 0.61 (0.29, 1.32) 3) 0.51 (0.22, 1.14) P-trend: 0.111 Continuous (1 µg/d): 0.43 (0.11,1.71) Urogenital: 1) referent 2) 2.21 (0.67, 7.23) 3) 2.50 (0.78, 8.06) P-trend: 0.118 Continuous (1 µg/d):	Models adj for: Heart anomalies: Age BMI Chronic disease Alcohol consumption Fetus number Musculoskeletal anomalies: BMI Fetus number Previous Premature birth Infant sex Urogenital anomalies: Age BMI Chronic disease Previous premature birth Infant sex Other covariates considered: Ethnicity Education Parity Smoking "among others"	Individual THMs were highly correlated (r = 0.91–0.99) Most women were interviewed during the 3rd trimester (76%); 24% within the 1st month after delivery Collected information on water filter use (yes/ no), however, no adjustment was included in the internal dose calculation based on use No significant difference was seen in filter use habits Accounted for residential mobility by restricting study to women who did not change residence during pregnancy Questionnaire information was collected repeatedly on 10% of subjects Exp data included extensive detailed water use collected prospectively (e.g. filter use, exp at work, showering and bathing, swimming) SB or pregnancy terminations due to congenital anomalies diagnosed prenatally were excluded from the sample Low spatial and temporal variability between the low and high sites Other measured DBPs did not vary across plants and were at low or sub µg/L levels (including TBM,

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			Estimated uptake factors were used for ingestion (including heated water), inhalation and dermal exp		2.22 (0.69, 7.17)		5 haloacetonitriles, 2 haloketones, chloropicrin, chloral hydrate, halogenated furanone) Thus, only TTHMs and 3 individual THMs (CHL, BDCM, DBCM) were evaluated BDCM was associated with heart anomalies OR (95% CI) = **2.16 (1.05, 4.46**) in the 1st month of pregnancy, with a significant dose-response relationship p = **0.02** Significant associations were also seen for a continuous measure for the 1st 3 months and the 1st trimester Some significant associations were also seen for DBCM and heart anomalies (for a continuous measure), and musculoskeletal anomalies (for a categorical measure)

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Iszatt et al. 2011 England	Case-control Surgeon recruited male children born in 1997–2002 2000–2003 N = 191,438 male births n = 731 invited case mothers cases n = 354 controls n = 336	Hypo-spadias	<u>Water Sampling:</u> 6 water companies provided THM data for 140 water zones Monitoring data for 1997 was unavailable - 1998 data was used for infants born in 1997 as spatial variation was greater than temporal variation <u>Exposure Measure:</u> Participants' water zones were geocoded using postal codes then linked to their residential water zone and to the THM conc estimates Annual average THM levels were estimated from quarterly modeled data Computer assisted telephone interviews 2000–2003 THM ingestion = amount of cold water consumed at home during 1st trimester x THM conc Activities = duration of dishwashing, bathing, showering, & swimming x THM conc Total uptake: Estimates from ingestion & water use activities	CHL water conc (µg /L): Median = 2.9 Quartiles of CHL water conc (µg/L): 1) 0.0–0.9 2) 1.0–2.9 3) 3.0–6.9 4) 7.0–90 Quartiles of CHL ingestion at home (µg/d): 1) 0.0 2) >0.0–1.4 3) 1.5–4.2 4) 4.3–65.0 Quartiles of CHL total uptake (µg/d): 1) 0–1.37 2)1.38–4.78 3) 4.79–13.98 4)13.99–101	OR (95% CI) for exp to CHL in water (µg/L): 1) referent 2) 1.17 (0.67, 2.03) 3) 0.99 (0.57, 1.69) 4) 0.84 (0.49, 1.46) OR (95% CI) for CHL ingestion at home (µg/d): 1) referent 2) 1.26 (0.79, 2.01) 3) 1.12 (0.70, 1.79) 4) 1.36 (0.84, 2.22) OR (95% CI) for CHL total uptake (µg/d): 1) referent 2) 0.93 (0.56, 1.53) 3) 0.86 (0.52, 1.42) 4) 0.74 (0.45, 1.21) (from Supplemental material Table 9) Significant dose response association with OR (95% CI) presented for highest exp category: Cold tap water consumption at home **1.17 (1.07, 2.76)** p-trend = **0.01** Total water consumption **1.70 (1.09, 2.67)** p-trend = **0.02**	Models adj for: Family income Low birth weight Folate supplement use Maternal smoking weeks 6–18 Maternal occupational exp to phthalates Swimming Other covariates considered: Family history of hypospadias History of previous stillbirth Gestational diabetes High intake of cold tap water or bottled water	CHL was not the predominant THM THM data were available for 354 of the 468 case mothers and 336 of the 485 control mothers Used a stochastic model based on Bayesian hierarchical mixture distributions to estimate the mean conc for TTHM, CHL, BDCM, DBCM by quarter for each water zone Estimated type of water source (e.g. ground, surface, etc.) for water zones used in the model Exp data included detailed water use (e.g. exp at work, activities such as dishwashing, and swimming) Monitoring data for 1997 was unavailable Long interval between the end of the pregnancy and the interview (2½–6 yrs) No information on paternal exp previously associated with hypospadias, e.g. pesticides Participation rates of eligible mothers were 64% of cases, 33% of controls Sample size was decreased due to lack of valid postal codes, or lack of THM data for 271 participants

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			were multiplied by modeled uptake factors		Bottled water **1.64 (1.09, 2.48)** p-trend = **0.05** Total fluid consumption **1.55 (1.01, 2.39)** p-trend = 0.07		Other DBPs analyzed include: TTHMs, BDCM, DBCM, TBM, BrTHM BDCM ingestion at home OR (95% CI) (highest exp category 6–50µg/d): **1.65 (1.02, 2.69)** P for trend = 0.13

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Savitz et al. † 2005 US (3 study sites)	Prospective cohort Prenatal clinics and community outreach 2000–2004 N = 3,132 (pregnant women or women planning to become pregnant) n = 2,409 (excluding women >12 weeks gestation, multiple pregnancies, moved out of area, etc.) SAB n = 258	SAB (pregnancy loss up to 20 weeks gestation) (LBW, SGA, BW, PTB outcomes were reported in Table 3a)	<u>Water Sampling</u>: 3 sites represented: 1) moderate chlorinated DBPs (CHL was the dominant species) 2) moderate brominated DBPs 3) low DBP levels Sites 1 & 2 used chloramination rather than free CHL for termination disinfection For each site, water samples were measured weekly at a location that reflected DBP conc throughout the system <u>Exposure Measurement</u>: Tap water exp was the average weekly sample values over time of pregnancy Daily exp: Ingestion - residential tap water conc x consumption (number and cup size per day of tap, filtered, hot, and cold water) x uptake factors Total integrated exp - including ingestion, inhalation and dermal absorption (water conc x duration x uptake factors) [inhalation and dermal from showering and bathing]	CHL water conc by site for periconceptional period (µg/L): Mean = 1) 47.9 2) 12.4 3) 0.2 All sites = 23.9 Quintiles of CHL water conc (µg/L)): 1) ≥0.0–≤0.6 2) >0.06–≤8.6 3) >8.6–≤30.27 4) >30.27–≤48.71 5) >48.71 Quintiles of CHL total integrated exp (µg/d): 1) 0 2) >0.0–≤0.24 3) >0.24–≤0.78 4) >0.78–≤1.4 5) >1.4 The above exp categories were for the time period 9 weeks after the last menstrual period to 20 weeks after the last menstrual period	OR (95% CI) of CHL water conc, including all three locations (µg/L): 0.9 (0.6, 1.4) OR of CHL water conc (µg/L): 1) referent 2) 0.82 (0.51, 1.34) **3)1.66 (1.06, 2.61)** 4) 0.89 (0.55, 1.45) 5) 0.95 (0.58, 1.54) OR of CHL total integrated exp (µg/d): 1) referent 2) 0.88 (0.54, 1.42) 3) 1.15 (071, 1.86) 4) 1.09 (0.68, 1.76) 5) 1.14 (0.72, 1.81)	Models adj for: Maternal age Black race Hispanic ethnicity Education Marital status Alcohol use Age at menarche Vitamin use Other covariates considered: Ethnicity Income Study site Season Cigarette smoking Alcohol intake Caffeine consumption BMI Employment Diabetes History of spontaneous abortion Previous induced abortion Vitamin use	CHL was dominate THM species at chlorinated DBP site (20–120 µg/L) 81 pregnancy losses occurred before the initial interview Exp data included extensive detailed water use collected mostly prospectively (e.g. filter use, hot or cold water use; exp at work; and showering/bathing) Authors note that site characteristics (e.g., demographics) or the recruitment methods across the sites could possibly have led to biases in the estimated effects of DBPs Research was supported by the American Water Works Association Research Foundation and U.S. EPA No karyotyping of normal or abnormal fetal losses Initial interviews were conducted after pregnancy loss in 31.4% of the women Numerous comparisons were across various exposure periods using various estimates of exposure A biomarker study was conducted by site, and by season for Site 1: - No clear linear relationship was seen between tap water conc and blood

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			Estimated DBP levels for hot, cold, unfiltered, and filtered water were adjusted based on empirical laboratory experiments				levels for CHL or for any of the other THMs - Baseline THM levels in blood differed across sites; however, not nearly to the extent expected Other DBPs analyzed include: THM4, BDCM, HAA9, total organic halide Sporadic indications of increased risk of SAB associated with higher exp to DBPs were most notable for ingested total organic halide in the upper quintile: OR (95% CI) = 1.5 (1.0, 2.2) Although this study explicitly included categorization of exp for comparability with results of Waller et al. 1998, the findings of this study were not supportive of those results

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Toledano et al. 2005 United Kingdom (3 water regions)	Retrospective cohort Birth and stillbirth records 1992–1998 (years varied by water utility) N = 969,304 n = 920,571* (excluding births that could not be assigned water zones, etc.) <u>SB</u> n = 4,852 *n - from descriptive table (Table 1 of the paper)	SB (LBW and VLBW outcomes were reported in Table 3a)	<u>Water sampling:</u> Samples from 3 water companies Regulations required ≥4 samples/year, unless TTHM conc was <50 µg/L, in which case only 1 sample/year was required More frequent samples were required if the standard of 100 µg/L TTHM was breached Mean number of samples/year: Northumbrian = 4.5 United Utilities = 11.2 Severn Trent = 6.3 <u>Exposure Measurement:</u> Individual postal code records were extracted from birth registries and linked to water zone Individual THM conc were modeled, taking into account seasonal variation and THM profiles associated with particular water sources, to obtain more robust estimates of mean TTHM in each zone Modeled quarterly TTHM estimates were weighted (based on the proportion of the trimester in each quarterly period) and the weighted average THM conc for last 93 days	CHL water conc (µg/L): Mean - not stated CHL exp categories*: 1) Low <20 2) Med 20–40 3) High>40 *Personal correspondence (2/10/14)	ORs (CI) for CHL, for all water utilities combined (Supplemental material Table 4.12): 1) Referent 2) **1.11 (1.03, 1.19)** 3) **1.12 (1.02, 1.23)**	Models adj for: Maternal age Castairs quintile (Carstairs index is a measure of socioeconomic deprivation at the level of the enumeration district, which has a population=400 on average) Other covariates considered: Sex Interaction parameters with all covariates were tested in final models	Large sample size Hierarchical links built into the model so exp are estimated with comparable precision across zones and quarters "…[C]hloroform showed a similar pattern of risk for stillbirths and low and very low birth weight to that of TTHM, for the overall summary estimates across the three regions and in each individual region" Possibility of high exp misclassification due to weighted averages Other DBPs analyzed: TTHMs, BDCM, BrTHM No association was found with BDCM or BrTHM

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			before births were categorized into 3 levels				

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Dodds et al. 2004 Nova Scotia and Eastern Ontario, Canada	Population based case-control study Population-based perinatal databases 1999–2001 N = 777 n = 510 cases n = 112 controls n = 398	SB (fetus >500g at delivery)	<u>Water Sampling:</u> Residential samples from each subject's tap were taken 1 year later to coincide with 15 weeks gestation <u>Exposure Measure:</u> Telephone interview: - conducted >6 months after delivery - questions asked about water behaviors at ~ 3–4 months gestation including: - consumption of tap water beverages; - bottle water consumption; - water use at work; - water filters usage; - length of time bathing/showing Total daily THM exp: - integrated THM levels from residential tap water x estimates of daily exp from reported water use through ingestion, showering, and bathing (1 L ingested water = 5 min shower and 15 min bath)	CHL water conc (µg/L): Mean - not stated Max = 315 (Mean TTHM levels in residential samples with a chlorinated water supply: cases = 57 µg/L controls = 55 µg/L Max TTHM = 318 µg/L) Categories of CHL residential levels (µg/L): 1) 0 2) 1–49 3) 50–79 4) >80 Quintiles of total CHL exp (µg/L) (based on exp distribution of controls): 1) no exp 2) Quintile 1 (low) 3) Quintile 2 4) Quintile 3 5) Quintile 4 6) Quintile 5	OR (95%CI) for CHL residential levels (µg/L): 1) referent 2) **1.8 (1.1, 3.0)** 3) 0.9 (0.5, 1.9) 4) 2.2 (1.0, 4.8) OR for total CHL exp (µg/L): 1) referent 2) 1.8 (0.9, 3.7) 3) 1.3 (0.6, 3.0) 4) **2.3 (1.1, 4.7)** 5) 1.3 (0.6, 2.8) 6) 2.0 (1.0, 4.0)	Models adj for: Age Province of residence Household income Other covariates considered: Pregnancy history Index pregnancy information Maternal education Occupation Smoking during pregnancy Pesticide exp	70% cases and 62% controls had a chlorinated household water supply Joint analysis was conducted with number of cups of tap water consumed and THM level (categorical) Water conc was determined by sampling each subject's residential tap water Accounted for residential mobility Women were eligible to participate if they lived in the study area for first 5+ months of pregnancy, delivered in the study area, and were residents in study area at time of recruitment Exp data included detailed water use (e.g. filter use and exp at work) Adj THM exp estimates for use of filter, bottled water and boiled drinks Water sampling was not done at time of exp, due to retrospective nature of study design; water was collected 1 year later, so misclassification is possible. Subject response rates, with interviews completed, were 68% for controls and 60% for cases Referent categories for analyses contained subjects

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
							who had a private well, therefore, risk may be observing effect of private versus public water supply Other DBPs analyzed include: TTHMs and BDCM OR (95% CI) for risk of SB with THM exp: - 5+ cold tap water-based drinks and residential TTHM 1–49 (µg/L) = **2.4 (1.1, 1.9)** THM ≥50 (µg/L) **= 4.0 (1.4, 11)** (adj for showering/bathing did not alter these results) significant effects were also seen for the joint effects of minutes showering/bathing and TTHM exp

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Windham et al. 2003 California	Prospective cohort Women's Reproductive Health Study May 1990–June 1991 N = 1,092 eligible women n = 403 (after 89 dropped out and 61 became ineligible due to moving, early pregnancy, or starting birth control pills)	Menstrual cycle function (measured as: -menstrual cycle length -follicular phase length; -luteal phase length -menses length)	<u>Water sampling:</u> Collected quarterly THM measurements from 10 water utility companies. Calculated utility-wide averages (i.e., average of all measurements taken by a utility company) <u>Exposure measure:</u> Participants' addresses were geocoded, and assigned the appropriate water utility company in the county Participants completed a detailed baseline interview by telephone about water consumption and frequency and duration of showers per week Participants filled out a daily diary Participants were assigned a 90 day exp time period for each cycle (Estimated ingestion uptake for TTHM but not for CHL)	CHL water conc (µg/L): Mean - not reported CHL exp categories (µg/L): 1) 1st quartile 2) 2nd–3rd quartile 3) 4th quartile (≥17)	Differences (day) (95% CI) for CHL exp categories: <u>Menstrual cycle length</u> 1) referent 2) -0.43 (-0.99, 0.13) 3) -0.30 (-1.0, 0.40) <u>Follicular phase length</u> 1) referent 2) -0.42 (-0.96, 0.12) 3) -0.13 (-0.82, 0.56) OR (95% CI) for risk of having a short luteal phase at the highest CHL quartile level: 2.2 (1.0, 4.7)	Models adj for: Income Age Pregnancy history BMI Caffeine consumption Alcohol consumption Race Smoking Other covariates considered: Demographics Reproductive history Lifestyle factors (i.e., smoking, alcohol consumption, caffeine consumption, and exercise)	Participation rate was about 40% of the eligible population Considered participant mobility by calculating utility measures for each address lived in and using a weighted average Menstrual function parameters were based on biologic measures rather than self-reporting Other DBPs analyzed include: TTHMs, BDCM, DBCM, TBM and BrTHM Monotonic decrease in follicular phase length was observed for TTHM (µg/L):exp: >40-60 -0.39 (-0.98, 0.20) >60 **-0.94 (-1.6, -0.24)** Similar findings were observed for mean cycle length Significant findings were also observed for BDCM, DBCM, TBM, and BrTHM analyzed by quartile of exp OR (95% CI) for risk of having a long follicular phase at the highest conc of BrTHM: **0.26 (0.12, 0.60)** Similar findings were reported for individual brominated compounds

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Dodds and King * * 2001 Nova Scotia	Retrospective cohort Perinatal database 1988–1995 Singleton births N = 49,842 n = 48,845 (excluded births with unknown gestational age, and women with missing values for adjustment factors) NTD n = 77 Cardiovascular n = 430 Cleft n = 82 Chromosomal n = 96	<u>BD</u> Neural tube defects (NTD) Cardio-vascular anomalies Cleft defects Chromo-somal abnormalities	<u>Water sampling:</u> Routine monitoring of THMs at water facilities Samples taken at irregular intervals 4 times/year from 3 locations within the distribution systems of each facility <u>Exposure measure:</u> Individual levels were determined by TTHM values of the water facility that serves the area of maternal residence at birth NTD: average CHL conc in the facility from 1 month prior to conception to 1 month after conception Cardiac and cleft defects: average CHL conc in the facility during the 1st 2 months of preg Chromosomal: average CHL conc in the facility 3 months before pregnancy	CHL water conc (µg/L): Mean (SD) = 64.1 Categories of CHL conc (µg/L): 1) <50 2) 50–74 3) 75–99 4) ≥100 <u>Timing of exp</u> See previous column (Exposure measure)	RR for CHL exp: <u>NTD</u> 1) referent 2) 0.7 (0.4, 1.2) 3) 0.7 (0.3, 1.5) 4) 1.2 (0.7, 2.3) <u>Cardiovascular</u> 1) referent 2) 1.0 (0.8, 1.3) 3) 1.0 (0.8, 1.4) 4) 0.7 (0.5, 1.0) <u>Cleft</u> 1) referent 2) 1.2 (0.7, 2.0) 3) 0.9 (0.4, 2.0) 4) 1.5 (0.8, 2.8) <u>Chromosomal</u> 1) referent 2) 1.3 (0.8, 2.2) **3) 1.9 (1.1, 3.3)** 4) 1.4 (0.8, 2.8)	Models adj for: Maternal age Income level (not for cleft defects) Other covariates considered: Parity Maternal smoking Neighborhood family income	CHL accounted for 90% of TTHMs and they were highly correlated (r = 0.98) CHL and BDCM were not highly correlated (r = 0.26) The study incorporated therapeutic pregnancy terminations for antenatally diagnosed congenital abnormalities Confounders limited to those found in the database No information on ingestion, dermal, or inhalation exp or uptake No information on work water consumption was included Other DBPs analyzed include: BDCM Less than half subjects living in areas with high BDCM also had high CHL conc (>20 µg/L and >100 µg/L respectively) Excess risk was seen at BCDM conc ≥20 µg/L for NTD compared to conc <5 µg/L: RR (95% CI) = **2.5 (1.2, 5.1)** Decreased risk was seen at BCDM conc ≥20 ug/L for NTD compared to conc <5 µg/L: RR (95% CI) = **0.3 (0.2, 0.7)**

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
King et al. * * 2000 Nova Scotia	Retrospective cohort Perinatal database 1988–1995 N = 49,756 (singleton births) SB n = 214	SB	<u>Water sampling:</u> Water samples taken from the Nova Scotia Dept. of the Environment records THMs measured by each facility on average 4 samples per year Monthly estimates predicted by regression analysis <u>Exposure Measure:</u> Mother's residence at time of delivery was linked to the geographic area served by each water facility Individual estimates were averaged predicted values of THMs for the months covering the duration of the mother's pregnancy	CHL water conc (µg/L): Mean = 64.1 Average exp for 95% of women in referent category = 25–49 µg/L Quartiles of CHL exp (µg/L): 1) <50 2) 50–74 3) 75–99 4) ≥100	RR (95% CI) by quartile of CHL exp (µg/L): 1) referent 2) 1.2 (0.85,1.68) 3) 1.35 (0.87, 2.08) **4) 1.56 (1.04, 2.34)** Continuous (per 10 µg/L): 1.04 (1.00, 1.09) In a model with continuous representation of CHL and BDCM (per 10 µg/L) entered simultaneously (data reported but not shown): RR (95% CI) for CHL = 1.03 (0.98, 1.07)	Models adj for: Smoking Maternal age Other covariates considered: Parity Infant sex Neighborhood family income	TTHM and CHL were highly correlated (r = 0.98) CHL and BDCM (r = 0.26) Data restricted to municipalities with >90% households served by public water facilities, reducing probability that subjects in these areas did not use public water supply Individual water behaviors were not taken into account Data restricted to surface water only Other DBPs analyzed include: TTHMs, BDCM, DBCM, TBM A significant association was observed for BDCM and SB in the highest versus lowest exp category (≥ 20 versus < 5 µg/L): RR (95% CI) = **1.98 (1.23, 3.49)**

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Wennborg et al. 2000 Sweden	Retrospective cohort Population based case-control Case-control analysis Medical records, Swedish Employee Board 1990–1994 N = 1052 women n = 697 women (856 pregnancies included mothers who had worked up to the time of conception, excluded women who had become pregnant before employment, twin pregnancies, etc.) SAB: cases n = 73 controls n = 783	SAB (defined as case-control and fetal deaths up to gestational age of 20 weeks) (information about SAB was self-reported) (BW outcome included in detailed summary Table 3a)	<u>Water Sampling:</u> No water sample <u>Exposure Measure:</u> Interview Questionnaire: - laboratory work - period and time worked - exp to individual solvents (one of which was CHL) Exp information collected for time period before, and up to conception	Number of women who reported working in a lab with CHL: yes = 86 no = 770 Work in a lab with CHL: 1) No 2) Yes	OR of work with CHL 1) referent 2) 2.3 (0.9, 5.9)	Models adj for: Maternal age Previous miscarriage Other covariates considered: High blood pressure Other chronic diseases Gynecological Diseases Sexually transmitted infectious diseases Smoking Father's laboratory work at time of conception Presence of small children in the home Previous spontaneous abortions Consecutive pregnancy number	Specific substances in the labs were not measured, just reported use High proportion of non-respondents (27%) Other laboratory exp (e.g. solvents, bacteria) Relied on self-report of SAB No karyotyping of normal or abnormal fetal losses

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Dahl et al. 1999 Norway	Retrospective cohort Female dental surgeons in the Norwegian Dental Association N = 1320 Female high school teachers N = 1084 n = 1408 pregnancies of 1008 women (834 of 558 dental surgeons, and 574 of 450 high school teachers)	Fertility ("measured as time to pregnancy defined as months of unprotected intercourse required to become pregnant")	<u>Water Sampling:</u> Not applicable <u>Exposure Measure:</u> Number of root fillings with CHL-based root canal sealing material for dental surgeons Responses to open questions about chemical use and frequency of exp for high school teachers Occupational history was restricted to 6 months prior to pregnancy	Categories of CHL-containing root canal sealer (number of fillings per week): 1) 0 2) <1 3) 1–2 4) 3–5 5) >5	Percent of women exposed: 1) 26.7 2) 51.0 3) 15.0 4) 6.7 5) 0.5 Fecundability ratio (CI) of placing CHL-based fillings (Referent = female high school teachers) 1.06 (0.95, 1.10)	Models adj for: Maternal age Smoking habits Medical history Indicating reduced fertility	Response rates were dental surgeons = 65% high school teachers = 70% CHL-based sealing material usage was reported in about 75% of the pregnancies Retrospective time-to-pregnancy is suitable for occupational fertility problems No quantification of CHL was reported Possibility of recall bias of exp with longer wait time to pregnancy

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Waller et al. 1998 California (3 facilities)	Prospective cohort Birth records of a managed health care program (Kaiser) 1989–1991 N = 7,881 pregnant women n = 5,144 pregnancies	SAB (loss at ≤ 20 weeks gestation)	<u>Water Sampling:</u> Monitoring data was obtained from 78 of 85 utilities (serving 96% of the cohort) TTHM distribution system quarterly measurements and annual water quality reports from the utilities were used 3 sites were represented: 1) primarily mixed water source 2) primarily surface water 3) primarily ground water Tap water consumption at 8 weeks was based on telephone interview <u>Exposure Measure:</u> Residential drinking water utility was determined by the subject's address Estimated TTHM levels for each subject were averages of all distributions taken by their utility within the 1st trimester, or average measurements taken within 30 days of the 1st trimester Telephone interview: daily cold tap water intake at 8 weeks gestation, and total tap water intake (cold plus hot)	CHL water conc (µg/L): Mean (SD) None stated Category of 1st trimester CHL in tap water (µg/L): 1) 0–3 2) 4–16 3) <u>></u>17 Categories for personal exp to CHL: 1) high: <u>></u> 5 glasses/day cold tap water and 1st trimester CHL level of <u>></u>17 µg/L 2) low: <5 glasses/day of cold tap water and CHL level of <17 µg/L	Percent SAB by category of 1st trimester CHL tap water levels (µg/L): 1) 8.1% 2) 10.7% 3) 9.5% p-value = 0.15 OR (95% CI) for SAB with high personal CHL exp (category 1): 0.9 (0.5, 1.6)	Models adj for: Gestational age at interview Maternal age at interview Cigarette smoking History of pregnancy loss Maternal race Employment during pregnancy	Mean total TTHM conc was 46.5 µg/L Exp data included detailed water use (e.g. filter use, and exp at work) Data were collected on hot versus cold tap water usage No data were collected on other routes of exp (e.g. bathing, washing) Other DBPs analyzed: TBM, BDCM, DBCM Significant associations were observed between SAB and high personal exp to TTHMs and BDCM for all regions OR (95% CI) = **2.0 (1.2, 3.5)** In a logistic regression model for all regions, adj for all 4 individual THMs simultaneously, the OR (95% CI) for high personal exp to BDCM was significant = **3.0 (1.4, 6.6)** However, the degree to which the THMs were correlated was not reported, and no analysis for multicollinearity was mentioned

Table 4a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Developmental Outcomes: Spontaneous Abortion (SAB), Stillbirth (SB), Birth Defects (BD), Fertility and Menstrual Cycle Function (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			Personal exp: TTHM level and cold tap water consumption				

Table 4b. Associations between Chloroform (CHL) Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects and Fertility in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
Grazuleviciene et al. ‡ ‡ 2013 Lithuania	Estimate internal dose (µg/d) CHL 0.026–0.288 0.288–2.109 Continuous (per 1 µg/d increase)	0.001–0.026			1st trimester exposure Heart anomalies 1.05 (0.53, 2.08) 1.37 (0.72, 2.63) 1.97 (0.90, 4.35) Musculoskeletal anomalies 0.61 (0.29, 1.32) 0.51 (0.22, 1.14) 0.43 (0.11, 1.71) Urogenital anomalies 2.21 (0.67, 7.23) 2.50 (0.78, 8.06) 2.22 (0.69, 7.17)	
Iszatt et al. 2011 England	Water conc (µg/L) CHL 1.0–2.9 3.0–6.9 7–90 Estimated internal dose (µg/d) CHL 1.38–4.78 4.79–13.98 13.99–101	0.0–0.9			Entire pregnancy exposure 1.17 (0.67, 2.03) 0.99 (0.57, 1.69) 0.84 (0.49, 1.46) 0.93 (0.56, 1.53) 0.86 (0.52, 1.42) 0.74 (0.45, 1.21)	
Waller et al. 1998 California (3 facilities)	Water conc (µg/L) CHL ≥17 and 5 glasses/d	<17 and <5 glasses/d	1st trimester exposure 0.9 (0.5, 1.6)			
Windham et al. 2003 California	Water conc (µg/L) CHL 2nd–3rd quartile 4th quartile (≥17)	1st quartile				Difference in menstrual cycle length -0.43 (-0.99, 0.13) -0.30 (-1.0, 0.40) Difference in follicular phase length -0.42 (-0.96, 0.12) -0.13 (-0.82, 0.56)

Abbreviations: CHL - chloroform; CI - confidence interval; conc - concentration; d – day; dec - decrease; inc - increase; L – liter; LMP - last menstrual period; med - medium; NTD - neural tube defects; SAB - spontaneous abortion.

Table 4b. Associations between Chloroform (CHL) Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects and Fertility in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
Toledano et al. 2005 United Kingdom (3 water regions)	Water conc (µg/L) CHL 20–40 >40	<20		3rd trimester exposure **1.11 (1.03, 1.19)** **1.12 (1.02, 1.23)**		
Savitz et al. † 2005 US (3 study sites)	Water conc (µg/L) CHL >0.06–≤8.6 >8.6–≤30.27 >30.27–≤48.71 >48.71 Estimated internal dose (µg/d) CHL >0–≤0.24 >0.24–≤0.78 >0.78–≤1.4 >1.4	 ≥0–≤0.06 0	9 weeks after last menstrual period (LMP) to 20 weeks after LMP 0.82 (0.51, 1.34) **1.66 (1.06, 2.61)** 0.89 (0.55, 1.45) 0.95 (0.58, 1.54) 0.88 (0.54,1.42) 1.15 (0.71,1.86) 1.09 (0.68,1.76) 1.14 (0.72,1.81)			
Iszatt et al. 2014 England	Water conc (µg/L) Low inc ≤10 to dec <10 Med dec 10–<30 High dec 30–65			Entire pregnancy exposure -5 (-9, 20)[1] 2 (-13, 20) -4 (-16, 8)		
Dodds et al. 2004 Nova Scotia and Eastern Ontario, Canada	Water conc (µg/L) CHL 1–49 50–79 >80 Total exposure (µg/L) CHL Quintile 1 Quintile 2 Quintile 3 Quintile 4 Quintile 5	 0 No exposure		1st + early 2nd trimester exposure **1.8 (1.1, 3.0)** 0.9 (0.5, 1.9) 2.2 (1.0, 4.8) 1.8 (0.9, 3.7) 1.3 (0.6, 3.0) **2.3 (1.1, 4.7)** 1.3 (0.6, 2.8) 2.0 (1.0, 4.0)		

[1] Reported a rate change, which is the percent change calculated as the exponential of the regression coefficient (e.g. rate ratio of after/before) minus 1 and multiplied by 100.

Table 4b. Associations between Chloroform (CHL) Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects and Fertility in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
King et al. * * 2000 Nova Scotia	Water conc (µg/L) CHL 50–74 75–99 ≥100 Continuous (per 10 µg/L increase)	<50		Entire pregnancy exposure 1.20 (0.85, 1.68) 1.35 (0.87, 2.08) **1.56 (1.04, 2.34)** 1.04 (1.00, 1.09)		
Dodds and King* * 2001 Nova Scotia	Water conc (µg/L) CHL 50–74 75–99 ≥100	<50			NTD - 1 month before conception to 1 month after 0.7 (0.4, 1.2) 0.7 (0.3, 1.5) 1.2 (0.7, 2.3) Cardiovascular anomalies 1st 2 months of pregnancy 1.0 (0.8, 1.3) 1.0 (0.8, 1.4) 0.7 (0.5, 1.0) Cleft defects 1st 2 months of pregnancy 1.2 (0.7, 2.0) 0.9 (0.4, 2.0) 1.5 (0.8, 2.8) Chromosomal abnormalities 3 months before pregnancy 1.3 (0.8, 2.2) **1.9 (1.1, 3.3)** 1.4 (0.8, 2.8)	
Wennborg et al. 2000 Sweden	Women working in a laboratory with CHL n = 86	Women with no laboratory work exposure n = 770	2.3 (0.9, 5.9)			

Table 4b. Associations between Chloroform (CHL) Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects and Fertility in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
Dahl et al. 1999 Norway	Placement of CHL based root fillings by female dental surgeons	High School teachers				Fecundability Ratio (95% CI) 1.06 (0.95, 1.10)

Table 5a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Male Reproductive Outcomes.

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Zeng et al.† † 2014 China	Prospective cohort Men who presented to an infertility clinic for semen examination 2011–2012 N = 351 n = 324 (including fertile and sub-fertile men)	Sperm parameters: conc, count, motility Sperm motion parameters: straight line velocity (VSL), curvilinear velocity (VCL), linearity (LIN)	<u>Water sampling</u>: One water treatment plant supplied water Monthly samples were collected at 3 sites (0.1 km, 4 km, and 8 km from the plant) THM conc in tap water measured within 90 days preceding semen collection <u>Exposure Measurement:</u> Subjects' home tap water THM levels estimated by averaging monthly THM conc from the 3 sampling sites for 90 days preceding semen sample collection Interviewed to quantify last 3 months' routine water-use activities: - tap water consumption at home and work (including number and size of glasses) - personal hygiene - bathing/ showering - swimming in chlorinated pools THM uptake: - models created using self- reported routine water use, THM conc in tap water, and uptake factors - a 30% factor was applied to boiled tap water consumption to reflect reduced THM conc	CHL water conc (µg/L): Mean = 13.71 Range = 2.68–29.90 LOD = 0.2 CHL estimated uptake by quartile (µg/d): Ingestion 1) <0.005 2) 0.005–0.011 3) 0.011–0.019 4) ≥ 0.019 Showering/bathing 1) <0.064 2) 0.064–0.126 3) 0.126–0.246 4) ≥0.246	Regression coefficients (95% CI) by quartile of CHL uptake through ingestion or showering/bathing: <u>Semen quality</u> <u>Ingestion:</u> (natural log transformation was applied to sperm conc and count) Sperm conc: 1) referent 2) -0.19 (-0.43, 0.05) 3) -0.25 (-0.51, 0.00) 4) **-0.28 (-0.53, -0.02)** **p-trend = 0.03** **Continuous = -0.15 (-0.25, -0.04)** Sperm count: 1) referent 2) -0.15 (-0.40, 0.10) 3) **-0.34 (-0.61, -0.07)** 4) -0.22 (-0.49, 0.05) **p-trend = 0.05** **Continuous = -0.12 (-0.24, -0.01)** Sperm motility: 1) referent 2) -4.66 (-9.93, 0.60) 3) -3.19 (-8.80, 2.41) 4) -4.13 (-9.73, 1.47) p-trend = 0.25 Continuous = -1.75 (-4.17, 0.16) Significant inverse associations were also reported for continuous measures of CHL uptake via ingestion and decreased sperm conc (β (95% CI) = **-0.15 (-0.25,**	Models adj for: Age Smoking status (current and former vs. never smoker) Alcohol use Education level Abstinence time Other covariates considered: BMI Income Occupational exp	CHL was the dominant species in the water distribution network Spatial variability of average DBP levels among the 3 sites was relatively low (18-month average CHL levels = ~14, 12 and 16 µg/L at the 3 sampling sites) Temporal variability was "high", with a range of ~3–30 µg/L for monthly CHL levels Extensive exp assessment (although no mention of filter use) Lack of specific information for smoking and alcohol use Other DBPs analyzed: BrTHMs Significant trends were reported for BrTHM uptake: - via ingestion and decreasing sperm conc; increasing VSL and VCL - via showering/bathing and increasing VCL Continuous measures of BrTHM uptake via ingestion was significantly associated with decreasing sperm conc: (β (95% CI)= **-0.13 (-0.24, -0.02)**

Table 5a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Male Reproductive Outcomes (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
			- bottled water was given a null THM level Exp from swimming in chlorinated pools was not included in analyses because few (4.0%) had swum in the past 3 months		**-0.04)**) and sperm count (β (95% CI) = **-0.12 (-0.24, -0.01)**) <u>Showering/bathing:</u> No significant associations were observed with any semen quality measures <u>Sperm motion Ingestion:</u> VSL: 1) referent 2) -0.25 (-1.85, 1.35) 3) 0.38 (-1.32, 2.08) 4) **1.77 (0.07, 3.47)** **p-trend = 0.03** VCL: 1) referent 2) -1.08 (-3.64, 1.48) 3) -0.28 (-3.00, 2.45) 4) **2.74 (0.01, 5.46)** **p-trend = 0.03** LIN: 1) referent 2) 1.22 (-1.07, 3.52) 3) 1.67 (-0.77, 4.12) 4) 0.00 (-2.44, 2.44) p-trend = 0.94 <u>Showering/bathing:</u> VSL: 1) referent 2) -0.30 (-2.04, 1.43) 3) 0.17 (-1.34, 1.69) 4) 1.38 (-1.31, 3.07) p-trend = 0.12 VCL: 1) referent 2) -0.13 (-2.92, 2.67) 3) 1.90 (-0.54, 4.35)		

Table 5a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Male Reproductive Outcomes (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
					4) 2.32 (-0.40, 5.04) **p-trend = 0.04** LIN: 1) referent 2) -0.74 (-3.22, 1.73) 3) **-2.28 (-4.44, -0.11)** 4) -0.17 (-2.58, 2.24) p-trend = 0.42		

Table 5a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Male Reproductive Outcomes (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Iszatt et al. 2013 England and Wales	Case-Referent study (from Chemicals and Pregnancy Study, Chaps-UK) Infertility clinic recruitment (13 clinics in 9 urban centers) 1999–2002 N = 2249 Cases had low motile sperm conc (MSC) n = 642 Controls n = 926	Semen quality (percent motile sperm was defined as % moving forward at ≥ 5 µm/s) (low MSC was defined relative to days of abstinence)	<u>Water sampling:</u> Routinely collected THM measurements, typically 1 per quarter per water zone - for all water zones covered by 10 water companies in 6 water regions (1,568 water zones) THM data were modeled using Bayesian models to obtain more robust quarterly water zone-specific estimates of the mean conc of each THM <u>Exposure Measurement:</u> Participants' postcode of residence was mapped to the corresponding water zone Participant exp was the sum of weighted quarterly estimates during the 90 days prior to semen sample collection	CHL water conc (µg/L): Mean (SD) cases = 25.9 (19.0) controls = 27.3 (19.1) Interquartile range (µg/L) = 12–38	OR for <u>Low MSC</u>, per 10 µg/L increase CHL: 1.00 (0.92, 1.09) OR per inter-quartile increase for MSC as a continuous variable, sperm conc, and % motile sperm: no significant relationship was found for any of these outcomes (results only presented in graphic form)	Models adj for: Surgery to testes Regular alcohol consumption Occupational exp to glycol ether Abstinence (for models of sperm conc, % motile sperm, and MSC) Other covariates considered: Age Ethnicity Social class Regular smoking Wearing restrictive underwear Previous conception by the male Manual work Season of semen sampling	TTHM and CHL were highly correlated (r = 0.95) 75% of men from the original Chaps-UK study were eligible for the investigation due to availability of water company data Analysis of quarterly THM data from the water companies showed greater variance between than within water zones A 74-day exp window was investigated, but no material difference was observed Used multi-level modeling and sensitivity analysis No data were collected on: - inhalation or dermal exp - personal water use - workplace (though majority of participants were employed (93.6% of cases, 96.2% of controls)) Other DBPs analyzed: TTHMs; BrTHMs (variations in TBM, DBCM, and BDCM conc were too small for analysis except as a sum)

Table 5a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Male Reproductive Outcomes (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Zeng et al. † † 2013 China	Cross-sectional infertility clinic recruitment 2011–2012 N = 467 (men) n = 401	Sperm parameters Serum total testosterone	<u>Water sampling:</u> No water sampling was conducted <u>Exposure measurement:</u> Interviews included questions about routine water use: - daily boiled tap water consumption - time showering or bathing - swimming in a chlorinated pool in the previous 3 months THM in blood samples: - samples were collected in the morning prior to any major water-use activity	CHL blood conc (ng/L): Mean = 57.68 Median = 50.17 Min = <LOD (1.95) Max = 202.09 Tertiles of CHL blood conc (ng/L): 1) <35.87 2) 35.87–66.35 3) >66.35	Multivariate regression coefficients (β) for CHL tertiles: (natural log transformation was applied to sperm conc and count) <u>Sperm conc (million/mL)</u> 1) 0 (referent) 2) -0.04 (-0.12, 0.04) 3) -0.08 (-0.16, 0.01) p (trend) = 0.07 <u>Sperm count (millions)</u> 1) 0 (referent) 2) -0.02 (-0.11, 0.08) 3) -0.07 (-0.16, 0.03) p (trend) = 0.19 <u>Sperm motility (%)</u> 1) 0 (referent) 2) 2.19 (-2.27, 6.64) 3) 1.35 (-3.13, 5.82) p (trend) = 0.55 <u>Curvilinear velocity (µm/s)</u> 1) 0 (referent) 2) 1.03 (-1.28, 3.34) 3) 2.15 (-0.17, 4.47) p (trend) = 0.07 <u>Straight-line velocity (µm/s)</u> 1) 0 (referent) 2) 0.89 (-0.59, 2.38) 3) **1.95 (0.46, 3.44)** **p (trend) = 0.01** <u>Linearity (%)</u> 1) 0 (referent) 2) 1.13 (-0.86, 3.12) 3) 1.19 (-0.80, 3.19) p (trend) = 0.24	Covariates were entered into the multivariable model if their *p*-value < 0.2 Models adj for: Age BMI Sexual abstinence time Alcohol use Smoking Other covariates considered: Race Education Income Occupational exp Medical Characteristics	CHL accounted for >90% of ΣTHMs All results for ΣTHMs were very similar to those of CHL The suggestive positive dose–response relationship between CHL and curvilinear velocity, and significant dose–response relationship between CHL and straight-line velocity were contrary to expectations A single blood sample was used to assess exp but intra-individual variability is not known Taking blood samples before any major water use might have missed important routine exp and reduced variability in exp assessments between individuals Sperm parameters not included in the statistical analysis due to high interdependence include: morphology; beat cross frequency; average path velocity; amplitude of lateral head displacement; straightness Other DBPs analyzed: THMs; TTHMs; BrTHMs BDCM was significantly associated with decreased sperm count in the 2nd tertile but there was no dose

Table 5a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Male Reproductive Outcomes (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
					Serum total testosterone 1) 0 (referent) 2) 0.92 (-35.25, 37.09) 3) -9.83 (-46.14, 26.47) p (trend) = 0.59		response (β=-**0.13** million **(-0.22, -0.03)**, p = **0.01**) DBCM was significantly associated with linearity in the 2nd tertile (**-4.74% (-8.07, -1.42**)) but there was no dose-response relationship There was a suggestive dose-response relationship between DBCM and reduced serum total testosterone

Table 5a. Detailed Summaries of Human Studies of Chloroform (CHL) Exposure and Male Reproductive Outcomes (cont'd).

Study/ Location	*Study Design/ Sample Sizes*	*Outcomes of Interest*	*Exposure Measurement Methods*	*Exposure Dosages*	*Results*	*Covariates/ Confounders*	*Comments*
Chang et al. 2001 Taiwan	Case study N = 1 (the subject was a laboratory worker who presented for infertility after the ventilation system in his workplace had shut down for 8 months ("exposure"))	Infertility Astheno-spermia (reduced sperm motility)	Exp scenario was reconstructed based on laboratory records and subject's description of work habits and conditions Field study: active air sampling using collection tubes and passive air sampling using badges Authors also conducted an experiment to determine evaporation rate of solvents and estimate conc in air Interview to determine exp time Semen analysis was conducted ~1 year prior to exp (during a complete fertility screening test) and 3 times after exp ended	Active air samples of CHL (ppm) = 8.5 Passive air samples of CHL (ppm) = 4.6 Authors also estimated CHL conc of 4.5 ppm based on evaporation CHL estimated at 450 ppm for 2 hours at the beginning of the workday (6 times/week) due to overnight accumulation and lack of ventilation	Semen parameters had been normal at fertility screening ~1 year prior to exp (May 1996) with 92% normal morphology and 95% motile at a normal speed at 30 min after ejaculation Exp occurred from August 1996 to April 1997 In samples following exp the proportions of motile sperm were as follows: July = 26% August = 11% October = 40% During the post-exp period: - sperm counts increased from 68.6 to 90.6 million/mL - white blood counts decreased from 15–20/high power field (HPF) to 1–2/HPF - path velocity (µm/sec) increased from 35 to 50	Use of drugs, alcohol, tobacco; and history of surgery had not changed Subject was also exposed to "considerable amounts" of tetrahydrofuran and isooctane to prepare for analysis of petrochemical products Authors state these chemicals have not been linked with male reproductive hazards No reported exp to extreme heat or radiation Anti-sperm antibody was negative Hormone levels, semen volume, sperm count, and morphology were normal Diagnoses of necrospermia, seminal tract infection, protein-carboxyl methylase deficiency, and axonemal defect were excluded	Possible underestimation of the evaporation of CHL due to no stirring, wiping, or other operations in simulation experiment Possible misclassification from the inability to completely reconstruct the exp setting due to ethical considerations Authors note that CHL has been associated with abnormal sperm morphology, which could affect motility; however, the authors reported that the semen analysis after exp showed normal morphology Morphology was left blank in Table 1

Table 5b. Associations between Chloroform (CHL) Exposure and Sperm Parameters in Human Studies.

Study/ Location	Exposure Level	Reference Level	β-coefficients (95% CI)			
			Sperm Concentration[1] (million/mL)	Sperm Count[1] (million)	Sperm Motility (%) & Motile Sperm Concentration (MSC)	Sperm Motion[2]
Zeng et al. † † 2014 China	<u>Estimated internal dose by ingestion (µg/d)</u> CHL 0.005–0.011 0.011–0.019 ≥0.019 P for trend Continuous[3] <u>Estimated internal dose by showering/bathing</u> CHL 0.64–0.126 0.126–0.246 ≥0.246 P for trend Continuous[3]	 <0.005 <0.064	 -0.19 (-0.43, 0.05) -0.25 (-0.51, 0.00) **-0.28 (-0.53, -0.02)** **0.03** **-0.15 (-0.25, -0.04)** 0.10 (-0.16, 0.36) -0.07 (-0.30, 0.15) -0.04 (-0.29, 0.21) 0.13 -0.05 (-0.15, 0.05)	 -0.15 (-0.40, 0.10) **-0.34 (-0.61, -0.07)** -0.22 (-0.49, 0.05) **0.05** **-0.12 (-0.24, -0.01)** 0.00 (-0.28, 0.28) 0.07 (-0.17, 0.32) 0.04 (-0.23, 0.31) 0.74 0.01 (-0.10, 0.11)	 Sperm motility (%) -4.66 (-9.93, 0.60) -3.19 (-8.80, 2.41) -4.13 (-9.73, 1.47) 0.25 -1.75 (-4.17, 0.66) -0.86 (-6.58, 4.86) -2.57 (-7.57, 2.43) 0.26 (-5.30, 5.83) 0.41 -0.44 (-2.61, 1.74)	<u>Ingestion</u> <u>VSL</u> 0.25 (-1.85, 1.35) 0.38 (-1.32, 2.08) **1.77 (0.07, 3.47)** **0.03** <u>VCL</u> -1.08 (-3.64, 1.48) -0.28 (-3.00, 2.45) **2.74 (0.01, 5.46)** **0.03** <u>LIN</u> There were no significant findings <u>Showering/Bathing</u> <u>Straight-line velocity</u> There were no significant findings <u>Curvilinear velocity</u> -0.13 (-2.92, 2.67) 1.90 (-0.54, 4.35) 2.32 (-0.40, 5.04) **0.04**

Abbreviations: CHL - chloroform; CI - confidence interval; conc - concentration; L – liter; LIN- linearity; MSC - motile sperm concentration; VCL - curvilinear velocity; VSL - straight-line velocity.

[1] Natural log transformation was applied.

[2] Units of measurement for sperm motion parameters were straight-line velocity = µm/s, curvilinear velocity = µm/s, linearity = %, path velocity = µm/sec.

[3] Continuous - quartiles of uptake (µg/day).

Table 5b. Associations between Chloroform (CHL) Exposure and Sperm Parameters in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	β-coefficients (95% CI)			
			Sperm Concentration[1] (million/mL)	Sperm Count[1] (million)	Sperm Motility (%) & Motile Sperm Concentration (MSC)	Sperm Motion[2]
						Linearity -0.74 (-3.22, 1.73) **-2.28 (-4.44, -0.11)** -0.17 (-2.58, 2.24) 0.42
Iszatt et al. 2013 England and Wales	Water conc (µg/L) Upper quartile Mean: Cases = 25.9 Controls = 27.3	Lower quartile (12)	No significant relationship was observed for the effect of CHL on sperm conc (results presented graphically)	Not assessed	Low MSC per 10 µg/L increase in CHL: Odds ratio = 1.00 (0.92, 1.09) No significant relationship was observed for the effect of CHL on change in percent motile sperm	Not assessed
Zeng et al. † † 2013 China	Blood conc (ng/L) 35.87–66.35 >66.35 P for trend	<35.87	-0.04 (-0.12, 0.04) -0.08 (-0.16, 0.01) 0.07	-0.02 (-0.11, 0.08) -0.07 (-0.16, 0.03) 0.19	2.19 (-2.27, 6.64) 1.35 (-3.13, 5.82) 0.55	Curvilinear velocity 1.03 (-1.28, 3.34) 2.15 (-0.17, 4.47) 0.07 Straight-line velocity 0.89 (-0.59, 2.38) **1.95 (0.46, 3.44)** **0.01** Linearity 1.13 (-0.86, 3.12) 1.19 (-0.80, 3.19) 0.24

Table 5b. Associations between Chloroform (CHL) Exposure and Sperm Parameters in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	β-coefficients (95% CI)			
			Sperm Concentration[1] (million/mL)	Sperm Count[1] (million)	Sperm Motility (%) & Motile Sperm Concentration (MSC)	Sperm Motion[2]
Chang et al. 2001 Taiwan	Active air samples of CHL = 8.5 ppm Passive air samples of CHL = 4.6 ppm Estimated air CHL for 2 hours at the beginning of the workday = 450 ppm	---	Not assessed	Authors state that sperm count was normal ~1 year prior to exposure. During the post-exposure period: sperm counts were as follows (by time since end of exposure): ≈ 3 months: 68.6 ≈ 4 months: 73.8 ≈ 6 months: 90.6	Semen parameters at screening ~1 year prior to exposure had been normal, with 95% motile at a normal speed at 30 min after ejaculation During the post-exposure period: the percentage of motile sperm were as follows (by time since end of exposure): ≈ 3 months: 26% ≈ 4 months: 11% ≈ 6 months: 40%	<u>Path velocity</u> ≈ 3 months: 35 ≈ 4 months: 40 ≈ 6 months: 50

3. Animal Studies of Reproductive and Developmental Toxicity of Chloroform

Table 6. Studies of Developmental Toxicity of Chloroform in the Rat, Inhalation Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Maternal Toxicity+	Developmental Toxicity+	
Schwetz et al., 1974	"Reagent grade" chloroform, Burdick & Jackson Lab, Inc. Sample assayed: purity 99.30%	Sprague-Dawley rats 8-77 females/group	Inhalation teratology study Food and water withheld during exposure; ad lib at night	7 hr/day; GD 6-15	0, 30, 100, 300 ppm Plus feed-restricted, "starved" control (3.7 g food, daily, GD 6-16)	Standard teratology evaluation SGPT* activity determined in pregnant and non-pregnant rats	↓ feed consumption 100 & 300 ppm; only on GD 6-7 for 30 ppm ↓ BW on GD 13 at 30, 100, & 300 ppm; on GD 21 at 100 & 300 ppm ↓absolute liver weight at 300 ppm; ↑ relative liver weight at 100 & 300 ppm	300 ppm: ↓ pregnancy rate (3/20) ↓ litter size ↑ resorptions Altered sex ratio (M:F; 34:66) ↓ fetal weight & crown-rump length (CRL) 100 ppm: ↑ gross anomalies 30 ppm: ↑ skeletal anomalies ↓ CRL	No effect on SGPT in any group Starved controls: ↓ fetal growth measures, but no effect on viability
US EPA, 1978	"Analytical grade" chloroform, Mallinckrodt, purity not specified	Sprague-Dawley rats 10 females/group	Inhalation teratology study	1 hr/day; GD 7-14	0; 4.6 mg/l (950 ppm = 110 mg/kg); 10.9 mg/l (2200 ppm = 260 mg/kg); 20.1 mg/l (4100 ppm = 480 mg/kg); plus feed-restricted control	Standard teratology evaluation	All: ↓ food consumption during days of treatment. 20.1 mg/l: All slept through exposure 1 death; ↓ BW^ 10.9 mg/l: Some slept through exposure	Feed-restricted controls: ↑ embryotoxicity ↓ fetal wt ↓caudal ossification centers 20.1 mg/l: ↑ embryotoxicity ↓ fetal wt	Feed-restricted controls appear to have been matched to food consumption by the high concentration group.

Table 6. Studies of Developmental Toxicity of Chloroform in the Rat, Inhalation Route (cont'd).

Baeder & Hoffman, 1988	Chloroform, source and purity not specified, measured by infrared gas analyzer	Wistar rats 20-21 females/group	Inhalation teratology study	7 hr/day; GD 7-16	0, 30, 100, 300 ppm	Standard teratology evaluation	All concentrations: ↓ feed consumption (GD 14-17 & 17-21) ↑ BW on GD 0 ↓ BW GD 17 ↓ heart wt GD 21 100 & 300 ppm only: ↓ BW GD 21	All concentrations: ↑ total (early) resorbed litters (no statistical evaluation) ↓CRL 300 ppm: ↓fetal weight	
Garcia-Estrada et al., 1990	Chloroform, source and purity not specified	Sprague-Dawley rats 3 females/group.	Inhalation developmental toxicity study Mated, sperm in vaginal smear= gestation day (GD) 1	Inhalation (two 10-minute periods/day) GD 17 to GD 21	Controls: No exposure Treated: Cotton impregnated with the chemical, placed inside of hermetic exposure chamber. No concentration provided. Authors reported that the chamber was saturated with chloroform	Pup body weight (BW), body length, cranial size and diameter at birth, 24, 48 and 72h of age. Random selection of 2 pups per litter for perfusion and histological analysis of the cerebellum (2 pups from each of 3 litters at 24, 48, and 72 hours)	Not evaluated	Decreased pup BW, body length and cranial diameter at all time points - Statistically significant ($p<0.01$) at some time points Decreased number of Purkinje cells at 24, 48, and 72 hours post-natally ($p\leq 0.01$) at all time points No abortions, resorptions or neonatal mortality were found	Spanish language publication
Baeder & Hoffman, 1991	"Reagent grade" chloroform, Merck, purity 99.0-99.4%	Wistar rats 22-25 females/group; 20 females/group evaluated	Inhalation teratology study	7 hr/day; GD 7-16	0, 3, 10, 30 ppm	Standard teratology evaluation	All concentrations, GD 7-14, and 30 ppm all times: ↓ feed consumption 10 & 30 ppm only: ↓ BW & wt gain	All concentrations: ↑ ossification variations/fetus (not per litter) 30 ppm: ↓ fetal weight & CRL	

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted in table; ^ no statistical analysis reported; * Serum glutamic-pyruvic transaminase

Table 7. Study of Developmental Toxicity of Chloroform in the Mouse, Inhalation Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Maternal Toxicity+	Developmental Toxicity+	
Murray et al., 1979	"spectral grade" chloroform, Mallinckrodt , purity not specified	CF-1 mice 34-40 females/group	Inhalation teratology study, varied days of exposure	7 hrs/day, GD 6-15, 1-7, or 8-15	0, 100 ppm	Standard teratology evaluation Maternal SGPT* activity determined on GD-16 following exposure on GD 6-15	GD 6-15: 1/35 maternal death ↑ SGPT activity GD 1-7 or 8-15: ↓ wt gain, GD 6-15 or 8-15: ↑ absolute & relative liver wt	GD 1-7: ↑resorptions (2 litters completely resorbed) GD 1-7 or 6-15: ↓pregnancy rate GD 1-7 or 8-15: ↓fetal BW & CRL ↑retarded ossification of sternebrae GD 8-15: ↑cleft palate GD 1-7, 6-15, & 8-15: ↑ delayed ossification of skull bones	Study also included in table on female reproductive effects below

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted in table; * Serum glutamic-pyruvic transaminase

Table 8. Studies of Developmental Toxicity of Chloroform in the Rat, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Maternal Toxicity+	Developmental Toxicity+	
Thompson et al., 1974	Chloroform, Mallinckrodt; purity not specified	Sprague-Dawley rats 6 females/group	Range-finding teratology study	Oral gavage, corn oil vehicle; dose divided 2X per day; GD 6-15	0, 79, 126, 300, 316, 501 mg/kg-day	Fetal viability, wt, sex; Histology on liver and kidney from 2 dams per group on GD 20	> 126 mg/kg-day: ↓ feed consumption and wt gain 316 & 501 mg/kg-day: 1 and 4 maternal deaths, respectively	501 mg/kg-day: No live fetuses from 2 surviving dams 316 mg/kg-day: ↑ resorptions ↓ litter size and fetal wt	Data described in text only; no tables. No statistics
	As above	Sprague-Dawley rats 25 females/group	Teratology study	As above	0, 20, 50, 126 mg/kg-day	Standard teratology evaluation; Histology on liver, kidney, and heart from 2 dams per group on GD 15	126 mg/kg-day: Clinical symptoms ↓ feed consumption 126 & 50 mg/kg-day: ↓wt gain Fatty changes in livers	126 mg/kg-day: ↑ implantations ↓fetal wt ↑ bilateral extra lumbar ribs (fetal incidence, not litter)	
Ruddick et al., 1983	Chloroform, Caledon Laboratories, purity 99%	Sprague-Dawley rats 15 females/group	Teratology study	Oral gavage, corn oil vehicle,1X daily; GD 6-15	0, 100, 200, 400 mg/kg-day	Standard teratology evaluation. Maternal hematology, marrow cytology, serum & liver biochemistry, organ histology	All doses: ↓ wt gain ↑ liver wt (relative) ↓hemoglobin & hematocrit ↓ sorbitol dehydrogenase 400 mg/kg-day: ↑ kidney wt (relative) ↓red blood cell counts 200 & 400 mg/kg-day: ↑ inorganic phosphorus & cholesterol	400 mg/kg-day: ↓ fetal wt ↑ aberrant sternebrae (8/8 surviving litters affected, no statistics) ↑ runts (8/8 surviving litters affected, no statistics)	At 400 mg/kg-day 4 dams died before term, and 3 were not pregnant. No details provided, but stated as not due to treatment.

Lim et al., 2004	Chloroform, source and purity not specified	Wistar rats Nulliparous 200–250 g 4 females/group	Effect of *in utero* and lactational exposure to chloroform on birth wt and postnatal indicators of type 2 diabetes On postnatal day (PND) 1, litters were evaluated and then culled to 3 males each. N=3/litter; 4 litters/group	Chloroform administered in drinking water from 2 wk prior to mating until parturition (*in utero* exposure only) or until weaning (*in utero* + lactational exposure)	0, 75 µg/L	Litter size, sex ratio, birth wt, postnatal growth. Fasting glucose concentration: on PND 1, and at 4 and 26 weeks of age. Oral glucose tolerance test at 4 and 26 weeks of age. Pancreas β-cell area.	Not evaluated	At PND 1, pups of dams exposed to chloroform had significantly higher serum glucose levels and lower insulin levels; not due to β-cell depletion in the neonatal pancreas. No change in glucose homeostasis in response to a glucose challenge at 4 or 26 weeks of age. No effect on birth wt; however, with chloroform *in utero* only exposure offspring had significantly lower body wts at weaning (PND 21), but not at 26 weeks of age. With chloroform *in utero* + lactational exposure, reduced postnatal growth continued through 26 weeks. No effect on litter size or sex ratio at birth.	Animals exposed to chloroform during fetal and neonatal development did not exhibit persistent metabolic changes associated with the onset of type 2 diabetes. However, these animals did exhibit impaired postnatal growth, indicating some alteration in offspring physiology.

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 9. Study of Developmental Toxicity of Chloroform in the Mouse, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Maternal Toxicity	Developmental Toxicity+	
Burkhalter & Balster, 1979; Balster & Borzelleca, 1982	"Nanograde purity" chloroform, Mallinckrodt	Albino ICR mice Males and females treated prior to mating Housed 3 female:1 male for mating 5 females/group	Behavioral teratology study Liveborn litters culled to 8 pups	Daily by gavage, 3 weeks prior to mating, through mating (up to 21 days), gestation and lactation, directly to weaned pups Emulphor vehicle (polyoxyethylated vegetable oil and saline)	0, 31.1 mg/kg-day	Righting reflex, Forelimb placing, Forepaw grasp, Rooting reflex, Cliff drop aversion, Auditory startle, Bar holding ability, Eye opening, Motor performance and learning measures	Not discussed	↓postnatal wt gain (not statistically significant) ↓ scores for forelimb placement on PND 5 & 7	

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 10. Study of Developmental Toxicity of Chloroform in the Rabbit, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Maternal Toxicity+	Developmental Toxicity+	
Thompson et al., 1974	Chloroform, Mallinckrodt; purity not specified	Dutch-belted rabbits 5 females/group	Range-finding teratology study	GD 6-18, split dose 2X/day by gavage	0, 25, 63, 100, 159, 251, 398 mg/kg-day	C-section on GD 29 Fetal viability, weight, CRL, sex Histology on does' heart, liver, kidney	> 100 mg/kg-day: 100% maternal death 100 mg/kg-day: 3/5 does died 63 mg/kg-day: Anorexia, weight loss 25 mg/kg-day: Mild diarrhea and anorexia	100 mg/kg-day: No viable conceptuses 63 mg/kg-day: 2/4 not pregnant ↓ fetal viability	Data described in text, no tables No statistics
	As above	Dutch-belted rabbits 15 females/group	Teratology study	GD 6-16, single dose 1X/day by gavage	0, 20, 35, 50 mg/kg-day	C-section on GD 29, fetuses incubated 24 hrs Standard teratology evaluation	50 mg/kg-day: 4/15 maternal deaths ↓ BW gains	All doses, and controls: Aborted litters (1-4/15, no statistics or apparent dose response) 20 & 50 mg/kg-day: ↓ fetal wt 20 & 35 mg/kg-day: ↑ fetal incidence of incompletely ossified skull bones	Rat experiments described in table above

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 11. Study of Developmental Toxicity of Chloroform in Zebrafish, *in vitro*.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Maternal Toxicity+	Developmental Toxicity+	
Teixidó et al., 2015	Chloroform, Sigma-Aldrich, purity not specified	Zebrafish embryos, 4 hours post fertilization (hpf)	*In vitro* whole embryo culture 30 embryos/concentration; 10 embryos/concentration X 3 independent spawning events (n=3)	72 hours exposure in buffered embryo medium	0, 0.14, 0.31, 0.63, 1.26 mM in buffered embryo medium	Mortality checked at 8, 28, 52, 76 hpf LC_{50} at end of test EC_{50} (fraction of abnormal embryos) Teratogenic index (TI) = LC_{50}/EC_{50} "Fingerprint endpoint" = concentration-response + $\geq$ 50% of malformed embryos showing index malformation Hatching success Minimum concentration to inhibit growth (MCIG) = significant ↓ tail length Comet assay	Not relevant	EC_{20} = 0.7 mM (84.7 mg/L) EC_{50} = 0.85 mM (100.3 mg/L) LC_{50} = 2.1 mM (286.5 mg/L) TI = 2.5 MCIG = 1.26 mM Fingerprint endpoints = eyes, heart, tail (78.4%, 75.7%, 78.4%, respectively) ↓ hatching success at 76 hpf: 0.63, 1.26 mM ↓ motility of unhatched embryos after dechorionation on 76 hpf Comet assay: EC_{50} produced significant DNA damage compared to solvent control group	

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 12. Studies of Female Reproductive Toxicity of Chloroform in Rats, Inhalation Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity+	Reproductive Toxicity+	
Schwetz et al., 1974	"Reagent grade" chloroform, Burdick & Jackson Lab, Inc. Sample assayed: purity 99.30%	Sprague-Dawley rats 8-77 females/group	Inhalation teratology study Food and water withheld during exposure; ad lib at night	7 hr/day; GD 6-15	0, 30, 100, 300 ppm plus feed-restricted, "starved" control (3.7 g food, daily, GD 6-16)	Standard teratology evaluation SGPT* activity determined in pregnant and non-pregnant rats	↓ feed consumption 100 & 300 ppm; only on GD 6-7 for 30 ppm ↓ BW on GD 13 at 30, 100, & 300 ppm; on GD 21 at 100 & 300 ppm ↑ absolute liver wt at 300 ppm; ↓ relative liver wt at 100 & 300 ppm	300 ppm: ↓ pregnancy rate (3/20) ↓ litter size ↑ resorptions	No effect on SGPT in any group Starved controls: ↓ fetal body measures, but no effect on viability
Baeder & Hoffman, 1988	Chloroform, source and purity not specified, measured by infrared gas analyzer	Wistar rats 20-21 females/group	Inhalation teratology study	7 hr/day; GD 7-16	0, 30, 100, 300 ppm	Standard teratology evaluation	All concentrations: ↓ feed consumption (GD 14-17 & 17-21) ↑ BW on GD 0 ↓ BW GD 17 ↓ heart wt GD 21 100 & 300 ppm only: ↓ BW GD 21	↑ in completely resorbed litters at all concentrations of chloroform	
Baeder & Hoffman, 1991	"Reagent grade" chloroform, Merck; purity 99.0-99.4%	Wistar rats 22-25 females/group; 20 pregnant females/group evaluated	Inhalation teratology study	7 hr/day; GD 7-16	0, 3, 10, 30 ppm	Standard teratology evaluation	All concentrations, GD 7-14, and 30 ppm all times: ↓ feed consumption 10 & 30 ppm only: ↓ BW & wt gain (no stats)	1 lost litter at 30 ppm (not statistically significant) No effect on litter size or resorption frequency	

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 13. Study of Female Reproductive Toxicity of Chloroform in Mice, Inhalation Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity+	Reproductive Toxicity+	
Murray et al., 1979	"Spectral grade" chloroform, Mallinckrodt, purity not specified	CF-1 mice 34-40 females/group	Inhalation teratology study, varied days of exposure	7 hrs/day, GD 6-15, 1-7, or 8-15	0, 100 ppm	Standard teratology evaluation Maternal SGPT* activity determined on GD-16 following exposure on GD 6-15	GD 6-15: 1/35 maternal death ↑ SGPT activity GD 1-7 or 8-15: ↓ wt gain, GD 6-15 or 8-15: ↑ absolute & relative liver wt	GD 1-7: ↑resorptions (2 litters completely resorbed) GD 1-7 or 6-15: ↓pregnancy rate	Study also described in table on developmental effects above

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted in table ; * Serum glutamic-pyruvic transaminase;

Table 14. Studies of Female Reproductive Toxicity of Chloroform in Rats, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity+	Reproductive Toxicity+	
Thompson et al., 1974	Chloroform, Mallinckrodt, purity not specified	Sprague-Dawley rats 6 females/group	Range-finding oral teratology study	Oral gavage, dose divided 2X per day; GD 6-15 corn oil vehicle	0, 79, 126, 300, 316, 501 mg/kg-day	Fetal viability, wt, sex; Histology on liver and kidney from 2 dams/group on GD 20	> 126 mg/kg-day: ↓ feed consumption and wt gain 316 & 501 mg/kg-day: Maternal deaths	501 mg/kg-day: No live fetuses from 2 surviving dams 316 mg/kg-day: ↑ resorptions ↓ litter size	Data described in text only; no tables No statistics
	As above	Sprague-Dawley rats 25 females/group	Oral teratology study	As above	0, 20, 50, 126 mg/kg-day	Standard teratology evaluation; Histology on liver, kidney, and heart from 2 dams/group on GD 15	126 mg/kg-day: Clinical symptoms ↓ feed consumption 126 & 50 mg/kg-day: ↓wt gain Fatty changes in livers	126 mg/kg-day: ↑ implantations	
Ruddick et al., 1983	Chloroform, Caledon Laboratories purity 99%	Sprague-Dawley rats 15 females/group	Oral teratology study	Oral gavage, 1X daily; GD 6-15 corn oil vehicle	0, 100, 200, 400 mg/kg-day	Standard teratology evaluation. Maternal hematology, marrow cytology, serum & liver biochemistry, organ histology	All doses: ↓ wt gain ↑ liver wt (relative) ↓hemoglobin & hematocrit ↓ sorbitol dehydrogenase 400 mg/kg-day: ↑ kidney wt (relative) ↓red blood cell counts 200 & 400 mg/kg-day: ↑ inorganic phosphorus & cholesterol	No effect on live litter size or resorption frequency	

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 15. Studies of Female Reproductive Toxicity of Chloroform in Mice, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity+	Reproductive Toxicity+	
Chapin et al., 1977 NTP, 1988	Chloroform, Aldrich Chemical Co., purity >99%	VAF Crl:CD-1 (ICR)BR mice 20 male and female pairs/group; 40 control pairs	Continuous breeding study. P0: all dose groups evaluated F1: control & high dose only	Oral, gavage, P0 dosed daily for 1 week prior to, 14 weeks during, & 3 weeks after co-habitation. Final F1 litters treated after weaning corn oil vehicle	0, 6.6, 15.9, 41.2 mg/kg-day	P0: Clinical signs, bw, water consumption, fertility and litter data. F1: body and organ wt	41.2 mg/kg-day, P0: ↓Maternal wt at delivery of 4th litter 41.2 mg/kg-day, F1 females: ↑ absolute & adjusted liver wt Minimal to moderate hepatocellular degeneration	41.2 mg/kg-day, F1: ↑ fertility index ↑ female pups/litter ↑ female + male pups/litter	All P0 groups delivered 4 litters Study also described in table on male effects below
US EPA, 1980	"Pesticide quality" chloroform, Matheson Coleman Bell, distilled by test lab to remove diethyl carbonate impurity	B6C3F1 mice 30 females /group; 40 controls	90-day subacute toxicity study	90-day drinking water study Fresh solutions prepared 2X/week	0, 20, 40, 60, 90, 180, 270 mg/kg-day 2 control groups: ad lib, and water consumption matched to high-dose group	Daily observations Weekly BW Days 0, 30, 60, & 90; 10 rats/group sacrificed for pathology and biochemistry	Deaths at 60, 90, 270 mg/kg-day Effects on BW at ≥ 60 mg/kg-day during first three weeks (no clear dose response) Fatty liver ↑ at 270 mg/kg-day, at each of the 3 sacrifice time-points; also ↑ for water-matched controls at final sacrifice		No pathological changes noted for any group at any time in mammary, ovaries, or uterus

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 16. Study of Female Reproductive Toxicity of Chloroform in Rabbits, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity+	Reproductive Toxicity+	
Thompson et al., 1974	Chloroform, Mallinckrodt, purity not specified	Dutch-belted rabbits 5 females/group	Range-finding oral teratology study	GD 6-18, split dose 2X/day by gavage	0, 25, 63, 100, 159, 251, 398 mg/kg-day	Fetal viability, weight, CRL, sex Histology on does' heart, liver, kidney	159, 251, 398 mg/kg-day: 100% maternal death 100 mg/kg-day: 3/5 maternal deaths 63 mg/kg-day: Anorexia, weight loss 25 mg/kg-day: Mild diarrhea and anorexia	100 mg/kg-day: No viable conceptuses 63 mg/kg-day: 2/4 not pregnant ↓ fetal viability	Data from range-finding study described in text, no tables; no statistical analysis
	As above	Dutch-belted rabbits 15 females/group	Oral teratology study	GD 6-16, single dose 1X/day by gavage	0, 20, 35, 50 mg/kg-day	C-section on GD 29, fetuses incubated 24 hrs Standard teratology evaluation	50 mg/kg-day: 4/15 maternal deaths ↓ BW gains (data not provided, but stated to be significant)	All doses, and controls: Aborted litters (1-4/15, no statistics or apparent dose response)	

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 17. Study of Female Reproductive Toxicity of Chloroform in Beagle Dogs, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Heywood et al., 1979	Chloroform, source and purity not specified	Beagle dogs Dosed, untreated controls, and controls given alternate toothpaste: 8 dogs/sex/group Vehicle toothpaste controls: 16 dogs/sex/group	7.5 year chronic study Treatment ceased at week 376; all animals sacrificed at week 395-399	Doses mixed into toothpaste and given in capsules	0, 15, 30 mg/kg-day; 6 days/wk	Clinical symptoms, food and water consumption, clinical exams, biochemistry terminal histopathology	At end of treatment: Dose-related ↑biochemical indicators of liver damage; appeared reversible during recovery phase, at least in some dogs Significance levels varying among dose and week of measurement from $p < 0.05$-0.001)	No treatment-related changes in ovaries or uteri "Nodular hyperplasia of mammary gland" in 3 females at 15 mg/kg-day, in 5 vehicle controls, and 1 untreated control No statistical analysis	Preliminary study included in paper not reported here as no reproductive endpoints assessed

Table 18. Study of Male Reproductive Toxicity of Chloroform in Mice, Inhalation Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Land et al., 1981	Chloroform, Fischer Scientific, purity not specified Delivered to inhalation cages in air	Mice Males, 15 controls, (10) 9 "survivors" in each dose group	Sperm morphology study Sacrifice at 28 days following 1st day of exposure	Inhalation, 4 hr/day, 5 consecutive days	0, 0.04, 0.08% in air	Epididymal sperm morphology	Not discussed Appears that 1 animal in each dose group died	0.04 & 0.08%: ↑ frequency of abnormal sperm morphology ($p < 0.01$)	Normal mouse spermatogenesis cycle 35-36 days; 28 day evaluation mid-cycle

Table 19. Study of Male Reproductive Toxicity of Chloroform in Rats, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity+	Reproductive Toxicity+	
US EPA, 1980	"pesticide quality" chloroform, Matheson Coleman Bell, distilled by test lab to remove diethyl carbonate impurity	Osborne-Mendel rats 30 males/group; 40 controls Additional controls paired for water-consumption	Subacute toxicity study	90-day drinking water study Fresh solutions prepared 2X/week	0, 20, 38, 57, 81, 160 mg/kg-day 2 control groups: ad lib, and water consumption matched to high-dose group	Daily observations Weekly BW Days 0, 30, 60, & 90; 10 rats/group sacrificed for pathology and biochemistry	160 mg/kg-day, all days: ↓ BW, also seen in water-matched controls 81 mg/kg-day: ↓ BW for 1st week of treatment	160 mg/kg-day, day 30 sacrifice: One case each of testicular hyperplasia and interstitial cell hyperplasia (not clear if single animal)	NS reduction in water consumption with chloroform Mouse portion of study discussed in table on female effects above

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 20. Study of Male Reproductive Toxicity of Chloroform in Mice, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity+	Reproductive Toxicity+	
Chapin et al., 1997; NTP, 1988	Chloroform, Aldrich Chemical Co., purity >99%	VAF Crl:CD-1 (ICR)BR mice 20 male and female pairs/group; 40 control pairs	Continuous breeding study. P0: all dose groups evaluated F1: control & high dose only	Oral, gavage, P0 dosed daily for 1 week prior to, 14 weeks during, & 3 weeks after co-habitation. Final F1 litters treated after weaning corn oil vehicle	0, 6.6, 15.9, 41.2 mg/kg-day	P0: Clinical signs, BW, water consumption, fertility and litter data. F1: Sperm data, body and organ weights	41.2 mg/kg-day, P0: ↓Maternal wt at delivery of 4th litter 41.2 mg/kg-day, F1 females: ↑ absolute & adjusted liver wt Minimal to moderate hepatocellular degeneration	41.2 mg/kg-day, P0: ↑ fertility index ↑ female pups/litter ↑ female + male pups/litter F1: ↑ Absolute right epididymal wt Minimal to mild degeneration of epididymal ductal epithelium.	All P0 groups delivered 4 litters Study also described in table on female effects above

+ All effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

Table 21. Study of Male Reproductive Toxicity of Chloroform in Beagle Dogs, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Heywood et al., 1979	Chloroform, source and purity not specified	Beagle dogs Dosed, untreated controls, and controls given alternate toothpaste: 8 dogs/sex/group Vehicle toothpaste controls: 16 dogs/sex/group	7.5 year chronic study Treatment ceased at week 376; all animals sacrificed at week 395-399	Doses mixed into toothpaste and given in capsules	0, 15, 30 mg/kg-day; 6 days/wk	Clinical symptoms, food and water consumption, clinical exams, biochemistry terminal histo-pathology	At end of treatment: Dose-related ↑biochemical indicators of liver damage; appeared reversible during recovery phase, at least in some dogs Significance levels varying among dose and week of measurement from $p < 0.05$-0.001)	"Ectopic testes with inhibition of spermatogenesis" in 2 dogs at 30 mg/kg-day, 1 dog at 15 mg/kg-day, and 1 untreated control No statistical analysis reported	Preliminary study included in paper not reported here as no reproductive endpoints assessed

Figure 10. Schematic of Protocol for Multigeneration Reproductive Toxicity Study with Satellite Components Used by Borzelleca and Carchman, 1982.

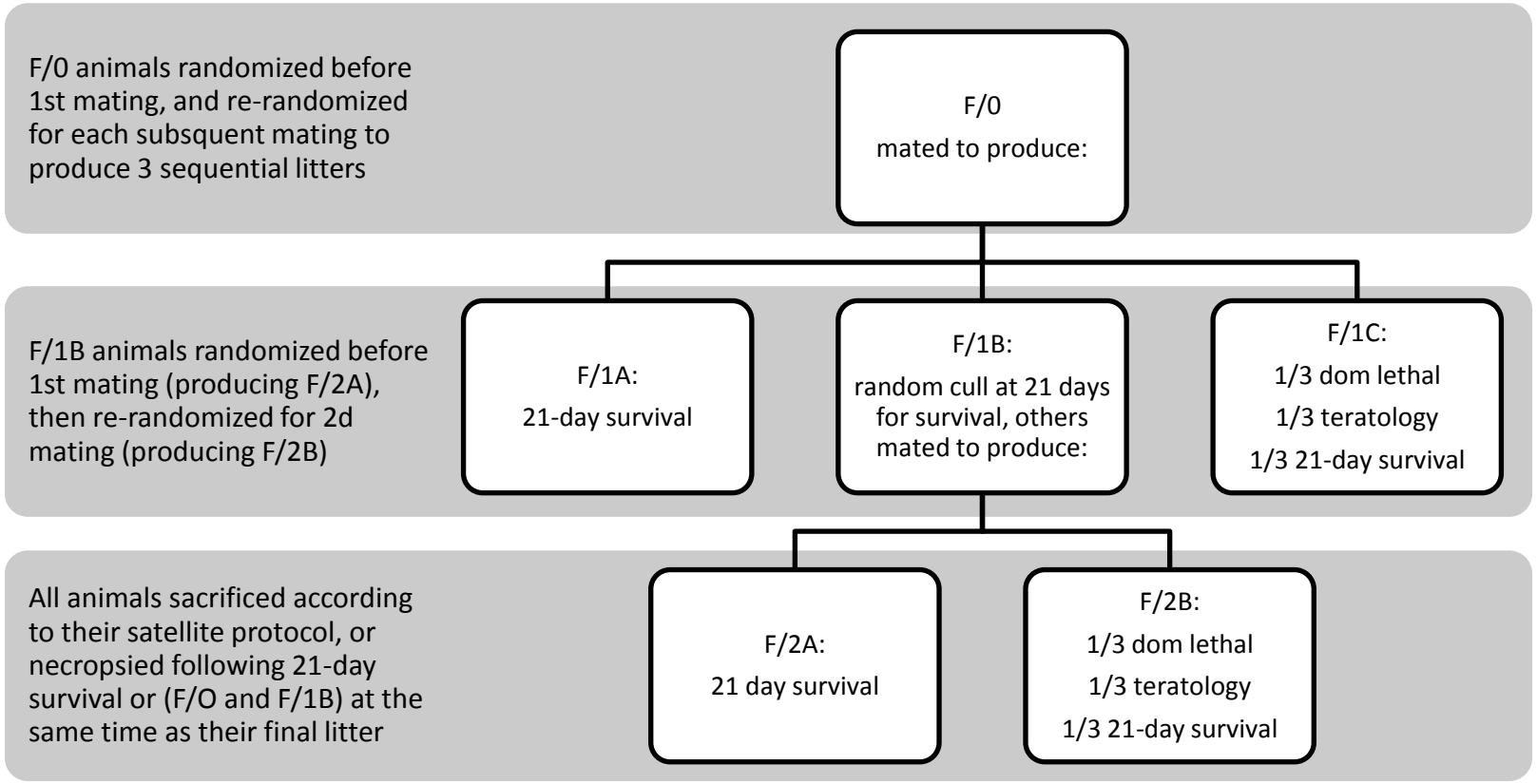

Table 22. Study of Multigeneration Reproductive Toxicity of Chloroform in Mice, Oral Route.

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Maternal/Systemic Toxicity+	Developmental/Reproductive Toxicity+	
Borzelleca and Carchman, 1982	Chloroform, Fischer Scientific, purity 99%	ICR Swiss mice (obtained at 7 weeks of age and then quarantined for 2 weeks) Co-habited for 1 week at a ratio of 1 male to 3 females N=10 males/ group N=30 females/ group	See figure 1 for diagram. Multi-generation reproductive toxicity study; with satellite studies. Parental matings produced 3 F1 litters; F1b matings produced 2 F2 litters. F/1C and F/2B litters were divided between dominant lethal, teratology, and 21-day survival studies.	Drinking water, continuous exposure Vehicle: emulphor (poly-ethoxylated vegetable oil):water (1:1000)	0.0 (distilled, deionized water and vehicle control groups), 0.1, 1.0, 5.0 mg/ml	No methods description included, endpoints assessed can only be inferred from reported results	↓ Body weight gain (both sexes) in F/0 and F/1B generations exposed to 5.0 mg/ml, and F/1B females exposed to 1.0 mg/ml ↓ 21-day survival: F/0 males and females, 5.0 mg/ml F/1B males, all doses F/1B females, 5.0 mg/ml Enlarged livers, 5.0 mg/ml, F/0 and F/1B "almost all animals" Final necropsies found liver pathology "characteristic of chlorinated hydrocarbon toxicity"	↓ gestation index* at 5.0 mg/ml: F/1A, F/1C, F/2A; but not for F/1B or F/2B. ↓ mating index** at 0.1 mg/ml, F/1C; and at 5.0 mg/ml for F/1A, F/1B, and F/2A; but not F/1C or F/2B. ↓ litter size at 5.0 mg/ml for F/1A, F/1B, F/1C, F/2A, and F/2B (as reported in table 13 of the study). ↓ viability Index# (PND 4) at 1.0 mg/ml F/1B; and at 5.0 mg/ml in F/1A, F/1B, and F/2A litters. ↓ lactation index## at 1.0 mg/ml in F/1A litters; and at 5.0 mg/ml in F/1A and F/2A litters .	Document is an unpublished study, provided to US EPA by the Medical College of Virginia. Some tables cite to an "in press" reference – no evidence could be found that the paper was ever published

Table 22. Study of Multigeneration Reproductive Toxicity of Chloroform in Mice, Oral Route (cont'd).

	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/Sex/Age) N (Control/ Treated)	Study Design	Exposure (Route/Period / Frequency/ Vehicle)	Doses/ Concen-trations		Maternal/Systemic Toxicity+	Developmental/Reproductive Toxicity+	
			Dominant lethal satellite	As above	As above	As above	As above	No significant dominant lethal effects	
Borzelleca and Carchman, 1982 (continued)			Teratology satellite	As above	As above	As above	As above	From tables 20 – 22: No significant effects of treatment noted on number of litters, number of implantations per dam, live fetuses per litter, percent of implants resorbed, or sex ratio in F/1C or F/2B generations. No evidence for an effect of treatment on external, internal, or skeletal abnormalities from F/1C or F/2B generations -- skeletal abnormality not assessed for F/2B.	Fetuses do not appear to have been weighed in the teratology component of the protocol.
			21-Day survival satellite	As above	As above	As above	Decreased 21-day survival in exposed males and females from F/0 and F/1B; lowest effective concentration = 0.1 mg/ml		

*gestation index = N females delivering live young/N pregnant females X 100

**mating index = N pairs mating/N pairs cohabited X 100# viability index = N live offspring per litter on PND4/N live offspring per litter at birth X 100

lactation index = N live offspring per litter at weaning (PND21)/N live offspring born (adjusted for culling if necessary) X 100

+ AII effects listed significantly differ from controls at $p < 0.05$ level unless otherwise noted

4. Summary

Preterm Birth

Eight epidemiologic studies specifically examined the risk of preterm birth associated with chloroform exposure. Five of these studies found no significant association (Kramer et al. 1992; Hinckley et al. 2005; Villanueva et al. 2011; Costet et al. 2012; Rivera-Nuñez and Wright 2013). One study did not analyze the risk from exposure to chloroform specifically (Patelarou et al. 2011), but reported no increased risk with exposure to total trihalomethanes. Interestingly, three studies (Wright et al. 2004; Savitz et al. 2005; Lewis et al. 2007) observed a significant, fairly consistent, inverse risk of preterm birth associated with chloroform exposure (i.e., a protective effect). It is not clear what mechanism may be responsible for this association, if it is real; however, Savitz et al. (2005) postulated that perhaps some selective loss leaves a heartier group of surviving fetuses who are less prone to be adversely affected by chemical exposures.

No effects of chloroform on gestation length were reported in experimental studies in animals.

Small for Gestational Age

A large number of epidemiologic studies examined the risk of small for gestational age associated with exposure to chloroform. Ten studies observed no increased risk or no statistically significant increased risk with chloroform exposure (Hinckley et al. 2005; Porter et al. 2005; Savitz et al. 2005; Hoffman et al. 2008; Grazuleviciene et al. 2011; Villanueva et al. 2011; Costet et al. 2012; Danileviciute et al. 2012; Levallois et al. 2012; Rivera-Nuñez and Wright, 2013). In three studies increased risk of small for gestational age was reported in a dose-dependent manner (Kramer et al. 1992; Wright et al. 2004; Summerhayes et al. 2012). One other study assessed the association between chloroform exposure and small for gestational age (as intrauterine growth restriction) and included consideration of a gene-environment interaction (Infante-Rivard, 2004). This case-control study examined two genetic polymorphisms, one in the *CYP2E1* gene (G1259C), and another in the 5,10-methylenetetrahydrofolate reductase (*MTHFR*) gene (C677T). The results showed an increased odds ratio with certain polymorphisms; however, these were not statistically significant. The Developmental and Reproductive Toxicant (DART) Identification Committee reviewed these data in 2004 and asked that OEHHA request Dr. Infante-Rivard to reanalyze the data using a less conservative cutoff. The results of the analysis were not statistically significant. Dr. Infante-Rivard did not agree with the use of this cutoff as she believed the cutoff should be based on where effects are likely. The chloroform levels in this study were not high and the sample size was small (see Appendix C: Re-analysis of Data from Two Chloroform

Epidemiological Studies: Wennborg et al. (2000) and Infante-Rivard (2004)). In the study by Patelarou et al. (2011), the risk from exposure to chloroform was not specifically analyzed.

As described below under “Low Birth Weight”, experimental studies in several species of laboratory animals reported adverse effects of maternal chloroform exposure on fetal weight. Crown-rump length was also reduced in rats (Schwetz et al. 1974; Baeder and Hoffman 1988, 1991; Garcia-Estrada et al. 1990) and mice (Murray et al. 1979) exposed by inhalation.

Low Birth Weight

There are a number of well-conducted epidemiologic studies with extensive exposure assessment that examined the risk for low birth weight in association with chloroform exposure. Statistically significant increased risks were observed in studies by Toledano et al. (2005), Lewis et al. (2006), Iszatt et al. (2014), Danileviciute et al. (2012), and Grazuleviciene et al. (2011). The findings of particular interest are from a nested case-control study (Danileviciute et al., 2012), which was part of the European Commission Health Impacts of long-term Exposure to Disinfection By-products in Drinking Water in Europe (HiWATE) study. This study included extensive exposure assessment as well as analysis of the maternal genetic polymorphisms for two metabolic genes and disinfection by-product-related gene-environment interactions. A large statistically-significant increased risk of low birth weight was observed in chloroform-exposed women, assessed as estimated internal dose, who had the GSTM1-0 (glutathione-S-transferase M1 null) genotype but not in those with the GSTM1-1 (glutathione-S-transferase M1) genotype. These associations were more pronounced when interactions between genotype and chloroform exposure were examined.

Reduced fetal weights were also reported in experimental animal studies in rats following maternal exposure to chloroform by the inhalation (Schwetz et al. 1974; US EPA 1978; Baeder and Hoffman 1988, 1991) and oral (Thompson et al. 1974; Ruddick et al. 1983) routes of exposure, as well as in mice exposed by inhalation (Murray et al. 1979) and rabbits exposed orally (Thompson et al. 1974).

Birth Weight

The association between chloroform exposure and birth weight was examined in ten epidemiologic studies. Four of the studies reported no significant association (Wennborg et al. 2000; Savitz et al. 2005; Hoffman et al. 2008; Villanueva et al. 2011). Six of the studies observed statistically significant decrements in birth weight with chloroform exposure (Wright et al. 2004; Zhou et al. 2010; Grazuleviciene et al. 2011; Summerhayes et al. 2012; Rivera-Nuñez and Wright 2013; Smith et al. 2015) with most of these showing evidence of a dose-response relationship. Of note is the study by

Smith et al. (2015), which reported no significant findings when examining the total study population. However, a significant dose-dependent decrement in birth weight was associated with chloroform exposure, assessed as estimated internal dose, in infants of Pakistani origin in comparison to those of white British origin.

Spontaneous Abortion

Three epidemiologic studies were identified that examined the risk of spontaneous abortion in relation to chloroform exposure; one reported an elevated risk estimate. In the retrospective cohort study by Wennborg et al. an elevated risk of spontaneous abortion (OR = 2.3 (95% CI, 0.9, 5.9) was associated with working in a laboratory with chloroform, which was assessed through a questionnaire. The Developmental and Reproductive Toxicant (DART) Identification Committee reviewed these data in 2004 and asked that OEHHA request Dr. Wennborg to reanalyze the data excluding previous spontaneous abortions. In the re-analysis the resulting odds ratio did not change substantially; however, with the narrower 95% CI this association was now statistically significant (OR = 2.1 (95% CI, 1.1, 4.0)). (see Appendix C: Re-analysis of Data from Two Chloroform Epidemiological Studies: Wennborg et al. (2000) and Infante-Rivard (2004)).

Reported effects of chloroform in experimental studies in animals on indices of fetal viability resulting from exposure by the inhalation route included decreased litter size in rats (Schwetz et al. 1974; Baeder and Hoffman 1988) and increased resorptions in rats (Schwetz et al. 1974) and mice (Murray et al. 1979). Exposure by the oral route resulted in increased resorptions in rats and decreased fetal viability in rabbits (Thompson et al. 1974). One study in rats exposed orally reported no effect on live litter size or resorption frequency (Ruddick et al. 1983).

Stillbirth

Four epidemiologic studies examined stillbirths in association with chloroform water concentration. In an intervention study (Iszatt et al., 2014), changes in water treatment methods by the utilities company resulted in increases or decreases in water chloroform concentration, however, no significant changes in stillbirth rates were observed in association with changes in chloroform concentration. Three studies observed an increased risk of stillbirth with chloroform exposure, although in two studies the estimates were not consistently statistically significant (Dodds et al. 2004; King et al., (2000). The results of Toledano et al. (2005) showed a small but statistically significant increased risk of stillbirth.

Birth Defects

Of the three epidemiologic studies that examined the risk of birth defects with exposure to chloroform (Dodd and King, 2001; Iszatt et al., 2011; Grazuleviciene et al., 2011), only one reported an association, that being with chromosomal abnormalities (Dodd and King, 2001). This study is notable in that it was one of the few studies in this dataset to sample the participants' tap water.

In experimental studies of chloroform conducted in animals, an increase in gross and skeletal anomalies in rats (Schwetz et al. 1974) and an increased incidence of cleft palate in mice (Murray et al. 1979) exposed by inhalation were reported. Effects on ossification and skeletal development were reported in studies of several species including rats (US EPA 1978; Baeder and Hoffman 1991; Thompson et al. 1974; Ruddick et al. 1983), mice (Murray et al. 1979) and rabbits (Thompson et al. 1974). Some of the effects may be indicative of general developmental delay, rather than frank malformations.

Postnatal Weight Gain

One prospective cohort study examined postnatal weight gain in infants born in 3 study sites (Botton et al., 2015). The results showed a statistically significant decrease in postnatal weight gain with chloroform exposure as estimated internal dose through ingestion in the community with the highest chloroform water concentrations.

In experimental studies of chloroform conducted in animals, pup body weight was reduced in rats exposed via maternal inhalation exposure during gestation (Garcia-Estrada et al. 1990), as was weight at weaning in rats exposed only during gestation (Lim et al. 2004).

Fertility

An occupational retrospective cohort study conducted by Dahl et al. (1999) examined fertility in female dental surgeons. Chloroform exposure was assessed using a questionnaire concerning the number of root fillings with chloroform-based root canal sealing material placed per week. No association was observed for time to pregnancy.

One experimental study in mice exposed to chloroform by inhalation reported reduced pregnancy rate (Murray et al. 1979), while another study in mice exposed orally reported an increased fertility index associated with exposure (Chapin et al. 1977; NTP 1988).

Menstrual Cycle Function

In a prospective study of menstrual cycle length, (Windham et al., 2003), no significant association was evident for chloroform exposure and cycle length.

Sperm Quality

Four studies examined associations between chloroform exposure in men and sperm quality, with two studies reporting significant decreases in sperm quality, one study reporting a suggestive dose-response association, and another study observing no association.

In the human case study by Chang et al. (2001), investigators reconstructed the exposure situation created by a ventilation system shut down lasting months. Significantly reduced sperm motility was reported following chloroform exposure as compared to the normal baseline measures taken before exposure. After exposure stopped sperm motility improved.

Two related studies include a cross-sectional study (Zeng et al, 2013) and a prospective cohort study (Zeng et al., 2014), which examined a number of different indices of sperm quality including various measures of sperm motion. Zeng et al. (2013) reported a suggestive dose response association between blood chloroform concentration and decreased sperm concentration. An unexpected reverse association was also observed where increases in blood chloroform concentration resulted in increased straight-line velocity. Zeng et al. (2014) reported statistically significant associations including significant trends between chloroform exposure (measured as estimated internal dose via ingestion) and decreased sperm concentration as well as some suggestive associations with sperm concentration.

An experimental study of sperm morphology in mice exposed to chloroform by inhalation reported an increased incidence of abnormal sperm morphology (Land et al. 1981). Studies of chloroform in rats (US EPA 1980), mice (Chapin et al. 1977; NTP 1988) and dogs (Heywood et al. 1979) reported low incidences of testicular and epididymal abnormalities.

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Appendix A. Tables of Associations between Chloroform and Other Disinfection By-Products Exposure and Reproductive Outcomes in Human Studies.

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
Danileviciute et al. ‡ ‡ 2012 Lithuania	Estimated internal dose (µg/d) CHL ≥0.1424 (median level)	<0.1424		Entire pregnancy 1.31 (0.82, 20.9) GSTM1-1 0.84 (0.42, 1.68) GSTM1-0 1.78 (0.90, 3.50) GSTT1-1 1.30 (0.78, 2.17) GSTT1-0 0.99 (0.28,3.58) 3rd trimester 1.31 (0.82, 2.08) GSTM1-1 0.88 (0.44, 1.78) GSTM1-0 1.74 (0.89, 3.41) GSTT1-1 1.18 (0.71, 1.97) GSTT1-0 1.75 (0.50, 6.10)	Entire pregnancy 1.24 (0.57, 2.68) GSTM1-1 0.34 (0.09, 1.22) GSTM1-0 **4.08 (1.20, 13.9)** Test for interaction: **12.88 (2.27, 73.2)** GSTT1-1 1.9 (0.5, 2.82) GSTT1-0 7.48 (0.13, 409) 3rd trimester 1.45 (0.67, 3.13) GSTM1-1 0.35 (0.10, 1.28) GSTM1-0 **5.06 (1.50,17.05)** Test for interaction: **15.86 (2.75,91.40)** GSTT1-1 1.35 (0.57, 3.20) GSTT1-0 7.30 (0.14, 391)	
	BDCM ≥0.0280	<0.0280		3rd trimester 1.31 (0.82, 2.09) GSTM1-1 1.05 (0.52, 2.10) GSTM1-0	3rd trimester 1.26 (0.58, 2.72) GSTM1-1 0.55 (0.16, 1.89) GSTM1-0	

Abbreviations: BDCM - bromodichloromethane; BrTHM - total brominated trihalomethanes; BW - birth weight; CHL - chloroform; CI - confidence interval; conc - concentration; DBCM - dibromochloromethane; dec - decrease; FGR - fetal growth restriction; inc - increase; LBW - low birth weight; med - medium; PTB - preterm birth; SGA - small for gestational age; TCAA – trichloroacetic acid; TTHM - total trihalomethanes; VLBW - very low birth weight.

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
				1.43 (0.73, 2.81) GSTT1-1 1.29 (0.77, 2.15) GSTT1-0 1.03 (0.29, 3.69) <u>3rd trimester</u> 1.68 (0.97, 2.89) GSTM1-1 1.63 (0.73, 3.64) GSTM1-0 1.55 (0.72, 3.36) GSTT1-1 **1.89 (1.01, 3.54)** GSTT1-0 1.04 (0.31, 3.53)	2.74 (0.88, 8.51) Test for interaction: **5.29 (1.03, 27.15)** GSTT1-1 1.36 (0.58, 3.22) GSTT1-0 0.89 (0.05, 15.9) <u>3rd trimester</u> 1.54 (0.65, 3.63) GSTM1-1 1.36 (0.36, 5.11) GSTM1-0 1.78 (0.55, 5.75) GSTT1-1 1.41 (0.54, 3.70) GSTT1-0 0.54 (0.02, 12.51)	
	DBCM ≥0.0026	<0.0026				
Botton et al.* 2015 Spain (3 study sites) and Greece	<u>Estimated internal dose (µg/d)</u> <u>All sites:</u> CHL IQR inc BrTHM IQR inc <u>Ingestion (µg/d)</u> <u>All sites:</u> CHL IQR inc BrTHM IQR inc <u>By site:</u> <u>Gipuzkoa</u> CHL IQR inc BrTHM IQR inc <u>Sabadell</u> CHL IQR inc					<u>Entire pregnancy Postnatal weight gain</u> -9.30 (-87.3, 68.7) -17.2 (-63.4, 29.1) -40.3 (-122, 41) -45.6 (-118, 26.5) 9.63 (-174, 193) 18.0 (-181, 217) **-151 (-288, -15)**

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	BrTHM IQR inc					**-146 (-280, -12.3)**
	Valencia CHL IQR inc					36.7 (-87, 160)
	BrTHM IQR inc					36.7 (-79.9, 153)
Grazuleviciene et al. 2011 ‡ ‡ Lithuania	Estimated internal dose (µg/d) 0.0249–0.2868 0.2868–2.1328 Continuous (per 0.1 µg/d increase)	 0.0013–0.0249		3rd trimester 1.19 (0.87, 1.63) 1.22 (0.89, 1.68) 1.04 (1.00, 1.09)	3rd trimester **2.12 (1.11, 4.02)** **2.13 (1.15, 3.92)** **1.09 (1.01, 1.18)**	3rd trimester Change in BW in grams, of infants below 3,500 g, for every 1 µg/d increase in internal dose: **-57.8 (-111.6, -4.0)**
	BDCM 0.0124–0.0501 0.0501–0.3359 Continuous (per 0.01 µg/d increase)	 0.0001–0.0124		 1.37 (1.00, 1.88) 1.25 (0.91, 1.73) 1.20 (0.90, 1.62)	 1.64 (0.89, 3.02) 1.80 (1.00, 3.26) 1.04 (1.00, 1.10)	 -25.7 (-57.2, 5.8)
	DBCM 0–0.0039 0.0039–0.0644 Continuous (per 0.01 µg/d increase)	 0		 1.76 (0.56, 1.03) 0.85 (0.63, 1.15) 1.06 (0.92, 1.22)	 **2.44 (1.05, 5.70)** **2.42 (1.03, 5.66)** 1.23 (0.93, 1.61)	 -45.9 (-207.6, 114.8)
Smith et al. 2015 England	Estimated internal dose (µg/d) CHL ≥0.91–<1.56 ≥1.56	 <0.91				Entire pregnancy Total population: -16.3 (-39.0, 6.5) -20.9 (-44.6, 2.8) Pakistani origin: 10.3 (-21.2, 41.9) **- 48.3 (-84.6, -12.1)** White British: -13.3 (-52.9, 26.3) 9.0 (-23.5, 46.5) 3rd trimester Total population: -14.8 (-37.7, 8.1) -8.7 (-31.8, 14.3)

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	BDCM ≥0.12–<0.21 ≥0.21	<0.12				Pakistani origin: 5.1 (-27.1, 37.4) **-42.8 (-78.2, -7.4)** White British: -27.0 (-66.1, 12.1) 9.5 (-26.8, 45.8) Entire pregnancy Total population: -11.1 (-33.9, 11.8) -17.9 (-41.5, 5.7) Pakistani origin: -11.5 (-43.3, 20.2) **- 49.8 (-86.3, -13.4)** White British: 8.2 (-31.6, 48.1) 10.9 (-26.4, 48.2) 3rd trimester Total population: -9.9 (-32.9, 13.0) -10.2 (-33.4, 13.0) Pakistani origin: -1.2 (-33.2, 30.9) **-48.7 (-84.8, -12.5)** White British: -4.2 (-43.8, 35.5) 15.2 (-21.1, 51.6)
Kramer et al. 1992 Iowa	Water conc (µg/L) CHL 1–9 ≥10 BDCM 1–9 ≥10 DBCM 1–3 ≥4 TBM ≥1	 ND <1 ND <1 ND <1 ND <1	Entire pregnancy 1.1 (0.8, 1.4) 1.1 (0.7, 1.6) 1.1 (0.9, 1.5) 1.0 (0.6, 1.5) 1.1 (0.7, 1.4) no cases 1.1 (0.8, 1.4)	Entire pregnancy 1.3 (0.9, 1.8) **1.8 (1.1, 2.9)** 1.2 (0.8, 1.7) 1.7 (0.9, 2.9) 1.0 (0.7, 1.5) 0.9 (0.1, 8.6) 1.1 (0.7, 1.6)	Entire pregnancy 1.1 (0.7, 1.6) 1.3 (0.8, 2.2) 1.0 (0.5, 1.9) 1.0 (0.7, 1.5) 0.7 (0.5, 1.1) 0.8 (0.4, 1.4) 0.9 (0.6, 1.5)	

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
Costet et al. 2012 France	Water conc (µg/L)		3rd trimester	3rd trimester (as FGR)		
	CHL 5–<10	< 5	0.7 (0.4,1.2)	0.8 (0.5, 1.2)		
	10–<15		**0.5 (0.3,0.9)**	1.0 (0.6, 1.5)		
	≥15		0.8 (0.4,1.4)	0.9 (0.5, 1.4)		
	BDCM 9–<13	<9	1.1 (0.7, 2.0)	0.8 (0.5, 1.2)		
	13–<16		0.7 (0.4, 1.3)	0.9 (0.6, 1.4)		
	≥16		0.8 (0.4, 1.5)	1.0 (0.6, 1.6)		
	DBCM 13–<15	<13	1.0 (0.6, 1.8)	1.0 (0.6, 1.6)		
	15–<18		1.3 (0.7, 2.5)	1.3 (0.8, 2.1)		
	≥18		0.8 (0.4,1.5)	1.2 (0.8, 1.9)		
	TBM 5–<7.5	< 5	0.7 (0.4, 1.3)	1.4 (0.8, 2.2)		
	7.5–<10		1.0 (0.5, 2.0)	1.3 (0.8, 2.3)		
	≥10		1.1 (0.6, 2.0)	1.4 (0.8, 2.3)		
	Estimated internal dose (µg/d)					
	CHL 0.068–<0.133	< 0.068	1.8 (0.7, 4.8)	1.1 (0.5, 2.3)		
	0.133–<0.237		0.7 (0.2, 2.1)	1.2 (0.6, 2.4)		
	≥0.237		1.0 (0.4, 2.9)	1.0 (0.5, 2.1)		
	BDCM 0.083–<0.141	<0.083	0.6 (0.2, 1.6)	1.5 (0.7, 3.2)		
	0.141–<0.226		0.9 (0.4, 2.2)	1.5 (0.7, 3.1)		
	≥0.226		0.7 (0.3, 1.8)	1.6 (0.8, 3.4)		
	DBCM 0.118–<0.188	<0.118	0.7 (0.2, 1.9)	1.6 (0.7, 3.6)		
	0.188–<0.267		0.9 (0.3, 2.4)	1.7 (0.8, 3.8)		
	≥0.267		0.8 (0.3, 2.2)	1.9 (0.9, 4.1)		
	TBM 0.057–<0.113	<0.057	0.5 (0.2, 1.3)	1.1 (0.6, 2.2)		
	0.113–<0.205		1.2 (0.5, 3.0)	0.9 (0.4, 1.9)		
	≥0.205		0.8 (0.2, 2.6)	1.8 (0.8, 3.9)		
	Nested TCAA Study Estimated internal dose via ingestion (µg/d)					
	CHL					
	0.001–<0.006	0–0.001	0.7 (0.3, 1.5)	1.0 (0.6, 1.7)		
	0.006–<0.015		0.8 (0.4, 1.8)	0.8 (0.4, 1.5)		
	≥0.015		1.2 (0.6, 2.5)	1.2 (0.7, 2.2)		

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	BDCM 0.0005–<0.0016 0.0016–<0.004 ≥0.004 DBCM 0.0008–<0.0023 0.0023–<0.267 ≥0.0052 TBM 0.0003–<0.0013 0.0013–<0.0034 ≥.0.0034	 0–0.0005 0–0.0008 0–0.0003	 0.8 (0.3, 1.5) 1.0 (0.5, 1.9) 1.5 (0.7, 2.8) 0.7 (0.3, 1.5) 1.2 (0.6, 2.3) 1.5 (0.7, 2.9) 0.9 (0.5, 1.8) 1.1 (0.5, 2.2) 1.3 (0.6, 2.7)	 1.3 (0.7, 2.2) 1.1 (0.6, 2.0) 1.3 (0.7, 2.3) 1.4 (0.8, 2.4) 1.2 (0.7, 2.2) 1.4 (0.8, 2.5) 1.4 (0.8, 2.4) 1.4 (0.8, 2.6) 1.1 (0.6, 2.2)		
Hinckley et al. 2005 Arizona	Water conc (µg/L) CHL 10–16 ≥16 BDCM 13–18 ≥18 DBCM 12–16 ≥16	 <10 <13 <12	No OR were presented Authors reported no associations were observed	3rd trimester 1.02 (0.94, 1.11) 1.01 (0.93, 1.10) 0.93 (0.85, 1.01) 1.03 (0.95, 1.12) 0.96 (0.89, 1.05) 1.01 (0.94, 1.10)	3rd trimester 1.18 (1.00, 1.39) 1.04 (0.88, 1.23) 1.05 (0.89, 1.24) 1.04 (0.88, 1.23) 1.00 (0.84, 1.18) 1.05 (0.89, 1.24)	
Infante-Rivard 2004 Montréal, Canada	Water conc (µg/L) CHL >23.7 TTHM >29.4 BDCM >6.3 DBCM >3.9 TBM >1.22 Gene-environment interaction: 90th percentile CHL (or TTHM) conc + categories for mother and newborn variants of CYP2E1 and MTHFR C677T: 3) Wild type 4) 1 or 2 variant alleles	 ≤23.7 ≤29.4 ≤6.3 ≤3.9 ≤1.22		Entire pregnancy 1.06 (0.63, 1.79) 0.97 (0.57, 1.62) 0.84 (0.50, 1.43) 0.62 (0.27, 1.44) 2.44 (0.19, 31.10)		

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	Newborn CYP2E1*5 CHL >23.7 MTHFR CHL >23.7 Maternal CYP2E1*5 CHL >23.7 MTHFR CHL >23.7 Newborn CYP2E1*5 TTHM >29.4 MTHFR TTHM >29.4 Maternal CYP2E1*5 TTHM >29.4 MTHFR TTHM >29.4	 ≤23.7 ≤23.7 ≤23.7 ≤23.7 ≤29.4 ≤29.4 ≤29.4 ≤29.4		 3) 0.99 (0.57, 1.74) 4) 5.62 (0.82, 38.39) 3) 1.78 (0.82, 3.87) 4) 0.83 (0.38, 1.54) 3) 0.88 (0.50, 1.54) 4) 4.40 (0.73, 26.42) 3) 1.00 (0.46, 2.18) 4) 1.12 (0.56, 2.32) 1) 0.82 (0.47, 1.45) 2) **13.20 (1.19, 146.72)** 1) 1.63 (0.72, 3.71) 2) 0.76 (0.38, 1.54) 1) 0.83 (0.48, 1.44) 2) 6.54 (0.59, 71.45) 1) 0.98 (0.46, 2.10) 2) 0.94 (0.47, 1.89)		
Porter et al. 2005 Maryland	Water conc (µg/L) CHL (Mean = 34.1) 2nd quintile 3rd quintile 4th quintile 5th quintile BDCM (Mean = 13.4)	1st quintile		Entire pregnancy **1.24 (1.02, 1.50)** 1.08 (0.88, 1.32) 1.12 (0.92, 1.36) 1.04 (0.85, 1.27) 3rd trimester 1.02 (0.84, 1.24) 0.96 (0.79, 1.16) 0.98 (0.81, 1.19) 1.07 (0.88, 1.29) Entire pregnancy 1.05 (0.87, 1.27) 0.96 (0.79, 1.17) 1.07 (0.89, 1.30) 0.97 (0.80, 1.18)		

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	DBCM (Mean = 4.35)			3rd trimester 0.92 (0.76, 1.12) 1.04 (0.86, 1.25) 0.92 (0.76, 1.12) 0.98 (0.81, 1.19) Entire pregnancy 0.98 (0.81, 1.19) 0.91 (0.75, 1.11) 0.92 (0.75, 1.11) 0.96 (0.79, 1.17)		
	TBM (Mean = 0.29)			3rd trimester 0.95 (0.79, 1.15) 0.84 (0.69, 1.02) 0.92 (0.76, 1.12) 0.90 (0.74, 1.09) Entire pregnancy **1.32 (1.08, 1.60)** 1.21 (0.99, 1.48) 1.10 (0.90, 1.35) 1.16 (0.94, 1.41) 3rd trimester 1.14 (0.94, 1.38) 1.00 (0.82, 1.23) 1.20 (0.99, 1.46) 1.01 (0.83, 1.23)		
Toledano et al. 2005 United Kingdom (3 study sites)	Water conc (µg/L) LBW CHL 20–40 >40 BDCM 6–12 >12 VLBW CHL 20–40 >40 BDCM 6–12 >12	 <20 <6 <20 <6			3rd trimester **1.05 (1.03, 1.07)** **1.10 (1.07, 1.13)** 1.02 (0.99, 1.04) 0.99 (0.97, 1.05) 1.01 (0.96, 1.07) 1.07 (0.99, 1.15) 1.01 (0.95, 1.07) 0.98 (0.92, 1.04)	

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
Savitz et al. † 2005 US (3 study sites)	Water conc (µg/L)			Used quartiles		
			3rd trimester	3rd trimester		3rd trimester
	CHL >0.1–≤10.9	≥0-≤0.1	0.68 (0.42, 1.11)	1.45 (0.79, 2.64)		-18 (-86, 51)
	>10.9–≤30.4		0.76 (0.47, 1.24)	1.33 (0.71, 2.49)		-6 (-75, 62)
	>30.4–≤48.2		**0.52 (0.31, 0.90)**	1.05 (0.54, 2.01)		12 (-56, 80)
	>48.2		**0.54 (0.31, 0.92)**			28 (-39, 96)
	BrTHM >3.4–≤12.7	≥0.0-≤3.4	**0.58 (0.35,0.97)**	0.86 (0.45, 1.66)		12 (-55, 79)
	>12.7–≤17.1		**0.45 (0.25, 0.78)**	1.03 (0.54, 1.97)		51 (-17, 119)
	>17.1-≤32.5		**0.51 (0.29, 0.88)**	1.58 (0.88, 2.83)		29 (-40, 97)
	>32.5		1.03 (0.65, 1.63)			-54 (-126, 17)
	BDCM >1.1-≤10.8	≥0.0-≤1.1	0.63 (0.38, 1.04)	1.06 (0.55, 2.02)		-15 (-82, 52)
	>10.8-≤13.2		**0.47 (0.27, 0.83)**	1.07 (0.56, 2.07)		42 (-26, 110)
	>13.2-≤19.7		0.69 (0.41, 1.15)	1.63 (0.90, 2.96)		-10 (-78, 58)
	>19.7		0.96 (0.60, 1.54)			-21 (-91, 49)
	Estimated internal dose (µg/d)			Used quartiles		
	CHL >0-≤0.2	0	1.03 (0.65, 1.66)	1.16 (0.63, 2.14)		10 (-58, 78)
	>0.2-≤0.8		**0.56 (0.32, 0.96)**	1.26 (0.68, 2.33)		-4 (-72, 63)
	>0.8-≤1.3		0.82 (0.49, 1.37)	1.14 (0.62, 2.09)		37 (-31, 105)
	>1.3		0.59 (0.34, 1.01)			32 (-36, 100)
	BrTHM >0.1-≤0.2	≥0.0-≤0.1	0.78 (0.47, 1.28)	1.02 (0.54, 1.95)		-20 (-87, 47)
	>0.2-≤0.3		0.60 (0.35, 1.04)	0.89 (0.45, 1.75)		-4 (-72, 63)
	>0.3-≤0.7		0.68 (0.40, 1.15)	1.65 (0.93, 2.94)		-31 (-99, 37)
	>0.7		0.76 (0.46, 1.26)			-31 (-101, 39
	BDCM >0-≤0.1	0	0.77 (0.47, 1.26)	1.15 (0.62, 2.14)		-27 (-95, 41)
	>0.1-≤0.3		0.65 (0.38, 1.11)	1.05 (0.54, 2.02)		20 (-48, 87)
	>0.3-≤0.4		0.60 (0.35, 1.03)	1.35 (0.75, 2.43)		-20 (-88, 47)
	>0.4		0.76 (0.46, 1.26)			-20 (-89, 50)
Hoffman et al. † 2008 3 US communities	Site 1 (chlorinated) water conc (µg/L)			Bayesian models		Bayesian models 3rd trimester
				3rd trimester		
	CHL 44.3–49.0	19.9–44.2		1.9 (0.5, 8.1)		58 (-51, 165)
	49.1–94.0			1.7 (0.4, 7.1)		49 (-62, 156)
	BDCM 11.9–14.1	8.2–11.8		1.4 (0.6, 3.2)		-8 (-84, 64)
	14.2–28.5			1.5 (0.6, 3.7)		-28 (-126, 51)

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	DBCM 3.3–4.4 4.5–9.1	1.1–3.2		1.3 (0.6, 2.9) 1.9 (0.8, 5.3)		0 (-73, 77) -16 (-102, 67)
	Site 2 (brominated) water conc (µg/L) CHL 11.6–15.6 15.7–22.1	6.4–11.5		4.2 (0.6, 33.7) 3.6 (0.5, 30.1)		64 (-146, 278) 70 (-146, 294)
	BDCM 20.2–22.9 23–29.2	15.8–20.1		0.8 (0.3, 1.9) 0.9 (0.4, 2.4)		90 (-15, 191) 73 (-50, 176)
	DBCM 19.4–26 26.1–38.7	15.2–19.3		0.7 (0.3, 1.6) 0.7 (0.2, 1.7)		**105 (7, 215)** 100 (-15, 224)
Levallois et al. 2012 Quebec City, Canada	Water conc (µg/L) CHL 15.96–27.26 27.27–51.07 >51.07	<15.96		3rd trimester 0.9 (0.7, 1.3) 1.0 (0.8, 1.4) 1.2 (0.9, 1.7)		
	BrTHM 3.12–5.00 5.01–9.02 >9.02	<3.12		1.0 (0.7, 1.3) 0.9 (0.6, 1.2) 0.9 (0.7, 1.2)		
	Estimated internal dose via total pathway (µg/d) CHL 42.24–80.21 80.22–169.81 >169.81	<42.24		0.9 (0.7, 1.2) 1.0 (0.7, 1.3) 1.0 (0.8, 1.4)		
	BrTHM 7.55–14.62 14.63–26.08 >26.08	<7.55		0.9 (0.7, 1.3) 0.9 (0.7, 1.3) 0.8 (0.6, 1.1)		
Rivera-Nuñez and Wright 2013 Massachusetts	Water conc (µg/L) CHL >5–21 >21–36 >36–52 >52	≤5	2nd trimester 1.00 (0.94, 1.06) **1.08 (1.02, 1.14)** 1.06 (0.99, 1.12) 1.00 (0.94, 1.07)	3rd trimester 1.01 (0.96, 1.05) 1.00 (0.95, 1.04) 1.04 (1.00, 1.10) 1.04 (0.99, 1.09)		3rd trimester -1 (-7, 5) **-9 (-15, -2)** **-13 (-19, -7)** **-15 (-21, -8)**
	BDCM >1–4 >4–6 >6–10 >10	≤1	0.96 (0.91, 1.01) 0.99 (0.94, 1.04) **0.90 (0.86, 0.95)** **0.93 (0.88, 0.98)**	1.04 (1.00, 1.08) **1.08 (1.03, 1.12)** **1.09 (1.04, 1.14)** **1.09 (1.04, 1.13)**		**-11 (-17, -5)** **-14 (-21, -8)** **-20 (-26, -14)** **-16 (-22, -10)**

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	BrTHM >2–5 >5–8 >8–13 >13	≤2	0.97 (0.92, 1.01) 0.96 (0.91, 1.01) **0.89 (0.85, 0.94)** **0.92 (0.88, 0.97)**	1.00 (0.97, 1.04) **1.06 (1.02, 1.10)** **1.08 (1.04, 1.12)** 1.05 (1.00, 1.09)		**-10 (-16, -4)** **-17 (-23, -11)** **-19 (-25, -13)** **-13 (-19, -7)**
Summerhayes et al. 2012 New South Wales, Australia	Water conc (µg/L) CHL IQR increase (25 µg/L) 5th decile 25.00–30.18 10th decile 56.03–147.94 BDCM 13.17–14.43 21.96–52.55	 1st decile 1.68–13.71 2.95–9.78		Relative Risk 3rd trimester **1.04 (1.02, 1.06)** 1.01 (0.96, 1.07) **1.12 (1.05, 1.18)** 1.04 (0.99, 1.09) **1.10 (1.04, 1.16)**		Entire pregnancy **-5.0 (-8.6, -1.4)**
Lewis et al. ‡ 2007 Massachusetts	Water conc (µg/L) TTHM (CHL = 83–93%) 40–<60 ≥60 Continuous (per 10 µg/L increase)	 <40	Hazard Ratios 2nd trimester **0.87 (0.77, 0.99)** **0.82 (0.71, 0.94)** **0.95 (0.92, 0.99)** Pregnancy average 0.92 (0.82, 1.02) **0.85 (0.74, 0.97)** **0.95 (0.91, 0.99)** 4 weeks before birth[1] 1.07 (0.85, 1.34) **1.39 (1.06, 1.81)** 1.03 (0.96, 1.11)			
Wright et al. 2004 Massachusetts	Water conc (µg/L) CHL >26–63 >63–135 BDCM >5–13 >13–46	 0–26 0–5	3rd trimester **0.95 (0.91, 0.99)** **0.90 (0.84, 0.97)** **0.89 (0.85, 0.93)** **0.92 (0.85, 0.99)**	3rd trimester **1.05 (1.02, 1.09)** **1.11 (1.04, 1.17)** **1.1 (1.07, 1.14)** **1.15 (1.08, 1.22)**		3rd trimester **-14 (-19, -9)** **-18 (-26, -10)** **-12 (-17, -8)** **-12 (-20, -3)**

[1] Hazard ratios for prenatal care paid for by government or Healthy Start.

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
Lewis et al. ‡ 2006 Massachusetts	Water conc (µg/L) TTHM (CHL = 83–93%) 40–<50 50–<60 60–<70 ≥70 Per 10 µg/L increase	≤40			2nd trimester 1.10 (0.81, 1.49) 1.08 (0.79, 1.49) 1.24 (0.92, 1.67) **1.50 (1.07, 2.10)** 1.08 (1.00, 1.17) Caucasian 1.11 (0.69, 1.78) 1.10 (0.67, 1.79) 1.22 (0.76, 1.97) 1.37 (0.80, 2.36) 1.06 (0.95, 1.20) Non-Caucasian 1.08 (0.73, 1.61) 1.09 (0.72, 1.66) 1.27 (0.86, 1.87) **1.60 (1.03, 2.47)** 1.10 (1.00, 1.22)	
Villanueva et al.* 2011 Spain (5 areas)	Total residential water conc (µg/L) CHL 10% increase BrTHM 10% increase		3rd trimester 1.00 (0.99, 1.01) 1.01 (0.98, 1.03)	3rd trimester 1.00 (0.99, 1.01) 1.00 (0.99, 1.02)	3rd trimester 1.00 (0.99, 1.02) 1.01 (0.98, 1.03)	3rd trimester -0.07 (-1.00, 0.85) 0.36 (-1.19, 1.92)
Iszatt et al. 2014 England	Water conc (µg/L) LBW CHL 1) Low inc: ≤10 to dec <10 2) Med dec: 10–<30 3) High dec: 30–65 BDCM 1) Low inc: ≤10 to dec <10				Entire pregnancy LBW[2] **1) -5 (-9, -1)** **2) -5 (-9, -1)** **3) -9 (-12, -5)** -3 (-8, 2)	

[2] Reported as rate change, which is the percent change calculated as the exponential of the regression coefficient (e.g. rate ratio of after/before) minus 1 and multiplied by 100.

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	2) Med dec: 10–<30 3) High dec: 30–65 DBCM 1) Low inc: ≤10 to dec <10 2) Med dec: 10–<30 3) High dec: 30–65 <u>VLBW</u> CHL BDCM DBCM				**-8 (-12, -5)** **-7 (-11, -4)** **-7 (-10, -3)** **-9 (-14, -5)** **-5 (-9, -1)** <u>VLBW</u> -7 (-17, 3) 4 (-7, 16) **-16 (-24, -8)** -12 (-22, 0) **-10 (-18, -1)** -3 (-12, 8) **-9 (-17, -1)** **-13 (-23, -1)** -2 (-12, 9)	
Zhou et al. 2010 China	<u>Water conc (µg/L)</u> CHL 2nd quartile 3rd quartile 4th quartile	1st quartile				<u>Odds Ratio</u> <u>Entire pregnancy</u> 0.96 (0.60, 1.53) 1.45 (0.88, 2.40) 1.64 (0.90, 3.00) <u>1st trimester</u> **1.74 (1.10, 2.77)** 0.90 (0.47, 1.74) 0.89 (0.44, 1.77) <u>3rd trimester</u> 1.37 (0.99, 1.88) 1.67 (0.98, 2.85) **1.82 (1.10, 3.02)** <u>1st and 2nd trimester</u> 1.10 (0.71, 1.68) **1.62 (1.05, 2.50)** 0.93 (0.54, 1.60)

Table A3c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Preterm Birth (PTB), Small for Gestational Age (SGA), Low Birth Weight (LBW), and Birth Weight (BW) in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			BW (g) (95% CI)
			PTB	SGA	LBW	
	BrTHM 2nd quartile 3rd quartile 4th quartile	1st quartile				Entire pregnancy 1.03 (0.65, 1.66) 1.58 (0.95, 2.63) 1.06 (0.57, 1.96) 3rd trimester 1.40 (0.99, 1.98) 1.21 (0.81, 1.81) **1.51 (1.05, 2.17)**
Wennborg et al. 2000 Sweden	Women working in a laboratory with CHL n = 66	Women working in non-laboratory departments				Entire pregnancy 27 (-136, 190)

Table A4c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects, Fertility and Menstrual Cycle Function in Human Studies.

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
Grazuleviciene et al. ‡ ‡ 2013 Lithuania	Estimated internal dose (µg/d) CHL 0.026–0.288 0.288–2.109 Continuous (per 1 µg/d increase) BDCM 0.013–0.051 0.051–0.436 Continuous (0.1 µg/d) DBCM 0.002–0.006 0.006–0.093 Continuous (0.01 µg/d)	 0.001–0.026 0.000–0.013 0.000–0.002			1st trimester exposure Heart anomalies 1.05 (0.53, 2.08) 1.37 (0.72, 2.63) 1.97 (0.90, 4.35) 1.74 (0.85, 3.54) 1.82 (0.89, 3.69) **1.70 (1.09, 2.66)** 0.73 (0.36, 1.48) 1.35 (0.73, 2.51) **1.25 (1.01, 1.54)** Musculoskeletal anomalies 0.61 (0.29, 1.32) 0.51 (0.22, 1.14) 0.43 (0.11, 1.71) 1.18 (0.51, 2.71) 1.29 (0.57, 2.92) 0.97 (0.46, 2.06) 0.95 (0.42, 2.18) 1.16 (0.52, 2.57) 1.20 (0.91, 1.58) Urogenital anomalies 2.21 (0.67, 7.23) 2.50 (0.78, 8.06) 2.22 (0.69, 7.17) 1.65 (0.48, 5.67) 2.87 (0.92, 8.99) 1.57 (0.74, 3.37) 0.92 (0.29, 2.87) 1.79 (0.65, 4.90) 1.17 (0.80, 1.72)	

Abbreviations: BDCM - bromodichloromethane; BrTHM – total brominated trihalomethanes; CHL - chloroform; CI - confidence interval; conc - concentration; d - day; DBCM - dibromochloromethane; d – day; dec - decrease;inc - increase; L – liter; LMP - last menstrual period; med - medium; NTD - neural tube defects; SAB - spontaneous abortion; TBM - bromoform.

Table A4c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects, Fertility and Menstrual Cycle Function in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
Iszatt et al. 2011 England	Water conc (µg/L) CHL 1.0–2.9 3.0–6.9 7–90 BrTHM 11–18 19–24 25–70 BDCM 1.1–5.0 6–9 10–23 DBCM 4–7 8–10 11–34 TBM 2.5–3.9 4.0–6.9 7–27 Estimated internal dose (µg/d) CHL 1.38–4.78 4.79–13.98 13.99–101 BrTHM 1.674–3.204 3.205–6.24 6.25–48 BDCM 0.314–1.057 1.058–2.275 2.276–24 DBCM 0.454–0.96 0.97–2.13 2.14–19 TBM 0.481–0.894 0.895–1.901 1.902–13	 0.0–0.9 0–10 0.0–1.0 0–3 0.0–2.4 0–1.37 0–1.673 0–0.313 0–0.453 0–0.480			Entire pregnancy exposure 1.17 (0.67, 2.03) 0.99 (0.57, 1.69) 0.84 (0.49, 1.46) 1.02 (0.63, 1.65) 0.82 (0.51, 1.34) 1.06 (0.66, 1.71) 1.15 (0.71, 1.88) 0.83 (0.51, 1.35) 1.05 (0.65, 1.68) 1.00 (0.61, 1.64) 0.91 (0.56, 1.47) 0.92 (0.57, 1.49) 0.94 (0.56, 1.58) 0.88 (0.54, 1.45) 1.06 (0.66, 1.69) 0.93 (0.56, 1.53) 0.86 (0.52, 1.42) 0.74 (0.45, 1.21) 1.54 (0.94, 2.55) 0.70 (0.42, 1.17) 1.04 (0.63, 1.72) 1.21 (0.79, 1.87) 1.13 (0.73, 1.74) 1.20 (0.78, 1.85) 0.93 (0.56, 1.54) 0.70 (0.42, 1.16) 0.90 (0.54, 1.47) 1.06 (0.64,1.76) 0.87 (0.52, 1.46) 0.92 (0.55, 1.56)	

Table A4c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects, Fertility and Menstrual Cycle Function in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
Waller et al. 1998 California (3 facilities)	Water conc (µg/L) CHL ≥17 and 5 glasses/d BDCM ≥18 and 5 glasses/d DBCM ≥31 and 5 glasses/d TBM ≥16 and 5 glasses/d	 <17 and <5 glasses/d <18 and <5 glasses/d <31 and <5 glasses/d <16 and <5 glasses/d	1st trimester exposure 0.9 (0.5, 1.6) **2.0 (1.2, 3.5)** 1.3 (0.7, 2.4) 1.0 (0.5, 2.0)			
Windham et al. 2003 California	Water conc (µg/L) CHL 2nd–3rd quartile 4th quartile (≥17) BrTHM 2nd–3rd quartile 4th quartile (≥45)	 1st quartile 1st quartile				Difference in menstrual cycle length -0.43 (-0.99, 0.13) -0.30 (-1.0, 0.40) Difference in folicular phase length -0.42 (-0.96, 0.12) -0.13 (-0.82, 0.56) Difference in menstrual cycle length **-0.72 (-1.4, -0.04)** **-1.2 (-2.0, -0.40)** Difference in folicular phase length -0.66 (-1.3, 0.02) **-1.1 (-1.9, -0.29)**
Toledano et al. 2005 United Kingdom (3 water regions)	Water conc (µg/L) CHL 20–40 >40 BDCM 6–12 >12	 <20 <6		3rd trimester exposure **1.11 (1.03, 1.19)** **1.12 (1.02, 1.23)** 0.96 (0.88, 1.04) 0.99 (0.91, 1.07)		

Table A4c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects, Fertility and Menstrual Cycle Function in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
Savitz et al. † 2005 US (3 study sites)	Water conc (µg/L) CHL >0.06–≤8.6 >8.6–≤30.27 >30.27–≤48.71 >48.71 BrTHM >3.13–≤12.3 >12.3–≤17.83 >17.83–≤32.26 >32.26 Estimated internal dose (µg/d) CHL >0–≤0.24 >0.24–≤0.78 >0.78–≤1.4 >1.4 BrTHM >0.08–≤0.2 >0.2–≤0.38 >0.38–≤0.82 >0.82	 ≥0–≤0.06 ≥0–≤3.13 0 ≥0–≤0.8	9 weeks after last menstrual period (LMP) to 20 weeks after LMP 0.82 (0.51, 1.34) **1.66 (1.06, 2.61)** 0.89 (0.55, 1.45) 0.95 (0.58, 1.54) 0.92 (0.57, 1.47) 0.96 (0.58, 1.59) 1.1 (0.68, 1.76) 1.54 (0.96, 2.46) 0.88 (0.54,1.42) 1.15 (0.71,1.86) 1.09 (0.68,1.76) 1.14 (0.72,1.81) 0.79 (0.47, 1.33) 0.94 (0.57, 1.56) 1.34 (0.84, 2.14) 1.48 (0.9, 2.44)			
Iszatt et al. 2014 England	Water conc (µg/L) Low inc ≤10 to dec <10 Med dec 10–<30 High dec 30–65			Entire pregnancy exposure -5 (-9, 20)[1] 2 (-13, 20) -4 (-16, 8)		
Dodds et al. 2004 Nova Scotia and Eastern Ontario, Canada	Water conc (µg/L) CHL 1–49 50–79 >80 Total exposure (µg/L) CHL Quintile 1 Quintile 2 Quintile 3	 0 No exposure		1st + early 2nd trimester exposure **1.8 (1.1, 3.0)** 0.9 (0.5, 1.9) 2.2 (1.0, 4.8) 1.8 (0.9, 3.7) 1.3 (0.6, 3.0) **2.3 (1.1, 4.7)**		

[1] Reported a rate change, which is the percent change calculated as the exponential of the regression coefficient (e.g. rate ratio of after/before) minus 1 and multiplied by 100.

Table A4c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects, Fertility and Menstrual Cycle Function in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
	Quintile 4 Quintile 5 BDCM 1–4 5–9 ≥10	 0		1.3 (0.6, 2.8) 2.0 (1.0, 4.0) 1.7 (1.0, 3.0) 0.9 (0.5, 1.9) 2.2 (1.0, 4.9)		
King et al. * * 2000 Nova Scotia	<u>Water conc (µg/L)</u> CHL 50–74 75–99 ≥100 Continuous (per 10 µg/L increase) BDCM 5–9 10–19 ≥20	 <50 <5		<u>Entire pregnancy exposure</u> 1.20 (0.85, 1.68) 1.35 (0.87, 2.08) **1.56 (1.04, 2.34)** 1.04 (1.00, 1.09) 1.07 (0.77, 3.19) 1.44 (0.90, 2.27) **1.98 (1.23, 3.49)**		
Dodds and King * * 2001 Nova Scotia	<u>Water conc (µg/L)</u> CHL 50–74 75–99 ≥100 BDCM 5–9 10–19 ≥20	 <50 <5			<u>NTD - 1 month before conception to 1 month after</u> 0.7 (0.4, 1.2) 0.7 (0.3, 1.5) 1.2 (0.7, 2.3) 1.4 (0.8, 2.3) 0.6 (0.2, 1.5) **2.5 (1.2, 5.1)** <u>Cardiovascular anomalies 1st 2 months of pregnancy</u> 1.0 (0.8, 1.3) 1.0 (0.8, 1.4) 0.7 (0.5, 1.0) 1.0 (0.8, 1.2) 0.7 (0.5, 1.0) **0.3 (0.2, 0.7)** <u>Cleft defects 1st 2 months of pregnancy</u> 1.2 (0.7, 2.0) 0.9 (0.4, 2.0) 1.5 (0.8, 2.8)	

Table A4c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Spontaneous Abortion (SAB), Stillbirth, Birth Defects, Fertility and Menstrual Cycle Function in Human Studies (cont'd).

Study/ Location	Exposure Level	Reference Level	Odds Ratio (95% CI)			
			SAB	Stillbirth	Birth Defects	Fertility
					0.7 (0.4, 1.2) 1.1 (0.6, 2.1) 0.6 (0.2, 1.9) <u>Chromosomal abnormalities 3 months before pregnancy</u> 1.3 (0.8, 2.2) **1.9 (1.1, 3.3)** 1.4 (0.8, 2.8) 1.0 (0.6, 1.5) 0.7 (0.4, 1.6) 0.9 (0.4, 2.3)	
Wennborg et al. 2000 Sweden	Women working in a laboratory with CHL n = 86	Women with no laboratory work exposure n = 770	2.3 (0.9, 5.9)			
Dahl et al. 1999 Norway	Placement of CHL based root canal fillings by female dental surgeons	High School teachers				Fecundability Ratio (95% CI) 1.06 (0.95, 1.10)

Table A5c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Sperm Parameters in Human Studies.

Study/ Location			β-coefficients (95% CI)			
	Exposure Level	Reference Level	Sperm Concentration[1] (million/mL)	Sperm Count[1] (million)	Sperm Motility (%) & Motile Sperm Concentration (MSC)	Sperm Motion[2]
Zeng et al. † † 2014 China	<u>Estimated internal dose by ingestion (µg/d)</u>					<u>Ingestion</u> <u>Straight-line velocity (VSL)</u>
					<u>Sperm motility (%)</u>	<u>CHL</u>
	CHL 0.005–0.011	< 0.005	-0.19 (-0.43, 0.05)	-0.15 (-0.40, 0.10)	-4.66 (-9.93, 0.60)	-0.25 (-1.85, 1.35)
	0.011–0.019		-0.25 (-0.51, 0.00)	**-0.34 (-0.61, -0.07)**	-3.19 (-8.80, 2.41)	0.38 (-1.32, 2.08)
	≥0.019		**-0.28 (-0.53, -0.02)**	-0.22 (-0.49, 0.05)	-4.13 (-9.73, 1.47)	**1.77 (0.07, 3.47)**
	P for trend		**0.03**	**0.05**	0.25	**0.03**
	Continuous[3]		**-0.15 (-0.25, -0.04)**	**-0.12 (-0.24, -0.01)**	-1.75 (-4.17, 0.66)	
						<u>BrTHM</u>
	BrTHM 0.001–0.002	<0.001	**-0.23 (-0.44, -0.01)**	**-0.31 (-0.54, -0.09)**	-4.23 (-8.86, 0.41)	-0.25 (-1.65, 1.15)
	0.002–0.003		-0.16 (-0.42, 0.11)	-0.26 (-0.53, 0.02)	0.72 (-5.06, 6.50)	**2.18 (0.44, 3.93)**
	≥0.003		**-0.26 (-0.52, -0.01)**	-0.21 (-0.48, 0.06)	-3.76 (-9.39, 1.88)	**1.76 (0.06, 3.46)**
	P for trend		**0.05**	0.09	0.40	**0.01**
	Continuous[3]		**-0.13 (-0.24, -0.02)**	-0.11 (-0.23, 0.01)	-1.59 (-4.02, 0.84)	
	<u>Estimated internal dose by showering/bathing</u>					<u>Curvilinear velocity (VCL)</u>
						<u>CHL</u>
	CHL 0.064–0.126	<0.064	0.10 (-0.16, 0.36)	0.00 (-0.28, 0.28)	-0.86 (-6.58, 4.86)	-1.08 (-3.64, 1.48)
	0.126–0.246		-0.07 (-0.30, 0.15)	0.07 (-0.17, 0.32)	-2.57 (-7.57, 2.43)	-0.28 (-3.00, 2.45)
	≥0.246		-0.04 (-0.29, 0.21)	0.04 (-0.23, 0.31)	0.26 (-5.30, 5.83)	**2.74 (0.01, 5.46)**
	P for trend		0.13	0.74	0.41	**0.03**
	Continuous[3]		-0.05 (-0.15, 0.05)	0.01 (-0.10, 0.11)	-0.44 (-2.61, 1.74)	
						<u>BrTHM</u>
	BrTHM 0.036–0.069	<0.036	0.09 (-0.15, 0.34)	0.21 (-0.05, 0.46)	1.66 (-3.69, 7.01)	-0.94 (-3.19, 1.31)
	0.069–0.120		-0.14 (-0.40, 0.11)	0.07 (-0.20, 0.34)	-2.37 (-7.95, 3.22)	**3.21 (0.40, 6.02)**
	≥0.120		-0.10 (-0.34, 0.14)	0.01 (-0.24, 0.26)	-1.79 (-7.00, 3.43)	2.53 (-0.21, 5.27)
	P for trend		0.17	0.79	0.28	**0.01**
	Continuous[3]		-0.30 (-0.13, 0.07)	0.01 (-0.09, 0.12)	-0.29 (-2.44, 1.86)	

Abbreviations: BDCM - bromodichloromethane; BrTHM - total brominated trihalomethanes; CHL - chloroform; CI - confidence interval; d – day; conc - concentration; DBCM - dibromochloromethane; L – liter; LIN - linearity; MSC - motile sperm concentration; VCL - curvilinear velocity; VSL - straight-line velocity.

[1] Natural log transformation was applied.

[2] Units of measurement for sperm motion parameters were straight-line velocity = µm/s, curvilinear velocity = µm/s, linearity = %, path velocity = µm/sec.

[3] Continuous - quartiles of uptake (µg/day).

Table A5c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Sperm Parameters in Human Studies (cont'd).

Study/ Location			β-coefficients (95% CI)			
	Exposure Level	Reference Level	Sperm Concentration[1] (million/mL)	Sperm Count[1] (million)	Sperm Motility (%) & Motile Sperm Concentration (MSC)	Sperm Motion[2]
						Linearity (LIN) There were no significant findings for any of the DBPs Showering/Bathing Straight-line velocity (VSL) There were no significant findings Curvilinear velocity (VCL) CHL -0.13 (-2.92, 2.67) 1.90 (-0.54, 4.35) 2.32 (-0.40, 5.04) **0.04** BrTHM 0.65 (-1.95, 3.25) -0.01 (-2.73, 2.70) **3.23 (0.70, 5.77)** **0.02** Linearity (LIN) CHL -0.74 (-3.22, 1.73) **-2.28 (-4.44, -0.11)** -0.17 (-2.58, 2.24) 0.42 BrTHM -1.79 (-4.12, 0.54) -0.70 (-3.13, 1.74) -1.75 (-4.02, 0.52) 0.25

Table A5c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Sperm Parameters in Human Studies (cont'd).

Study/Location			β-coefficients (95% CI)			
	Exposure Level	Reference Level	Sperm Concentration[4] (million/mL)	Sperm Count[1] (million)	Sperm Motility (%) & Motile Sperm Concentration (MSC)	Sperm Motion
Iszatt et al. 2013 England and Wales	Water conc (µg/L) CHL Upper quartile Mean: Cases = 25.9 Controls = 27.3 BrTHM Mean: Cases = 13.1 Controls= 13.2	Lower quartile (12)	No significant relationship was observed for the effect of CHL on sperm conc (results presented graphically) No significant relationship was observed for the effect of BrTHM on sperm conc (results presented graphically)	Not assessed	Low MSC per 10 µg/L increase in CHL: Odds ratio = 1.00 (0.92, 1.09) No significant relationship was observed for the effect of CHL on change in percent motile sperm Low MSC per 10 µg/L increase in BrTHM: 0.93 (0.58, 1.49) No significant relationship was observed for the effect of BrTHM on change in percent motile sperm	Not assessed

[4] Natural log transformation was applied.

Table A5c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Sperm Parameters in Human Studies (cont'd).

Study/ Location			β-coefficients (95% CI)			
	Exposure Level	Reference Level	Sperm Concentration[1] (million/mL)	Sperm Count[1] (million)	Sperm Motility (%) & Motile Sperm Concentration (MSC)	Sperm Motion[2]
Zeng et al. † † 2013 China	<u>Blood conc (ng/L)</u> CHL 35.87–66.35 >66.35 P for trend BDCM 1.02–2.35 >2.35 P for trend DBCM 0.68–1.00 >1.00 P for trend BrTHM 3.03–4.71 >4.71 P for trend	 < 35.87 < 1.02 < 0.68 <3.03	 -0.04 (-0.12, 0.04) -0.08 (-0.16, 0.01) 0.07 -0.07 (-0.15, 0.02) -0.02, (-0.10, 0.06) 0.61 -0.07 (-0.21, 0.07) -0.10 (-0.25, 0.06) 0.13 -0.03 (-0.11, 0.05) -0.01 (-0.09, 0.08) 0.83	 -0.02 (-0.11, 0.08) -0.07 (-0.16, 0.03) 0.19 **-0.13 (-0.22, -0.03)** -0.04 (-0.13, 0.06) 0.44 -0.06 (-0.23, 0.10) -0.11 (-0.29, 0.06) 0.14 -0.04 (-0.14, 0.06) -0.02 (-0.12, 0.08) 0.67	 2.19 (-2.27, 6.64) 1.35 (-3.13, 5.82) 0.55 -0.16 (-4.62, 4.30) -0.70 (-5.16, 3.76) 0.76 -1.92 (-9.43, 5.58) -4.24 (-12.37, 3.89) 0.26 1.95 (-2.48, 6.38) -0.07 (-4.59, 4.45) 0.97	<u>Curvilinear velocity</u> <u>CHL</u> 1.03 (-1.28, 3.34) 2.15 (-0.17, 4.47) 0.07 <u>Straight-line velocity</u> <u>CHL</u> 0.89 (-0.59, 2.38) **1.95 (0.46, 3.44)** **0.01** <u>Linearity</u> <u>CHL</u> 1.13 (-0.86, 3.12) 1.19 (-0.80, 3.19) 0.24 <u>DBCM</u> **-4.74 (-8.07, -1.42)** 0.03 (-3.57, 3.63) 0.23 There were no other significant findings for any other DBPs

Table A5c. Associations between Chloroform (CHL) and Other Disinfection By-Products Exposure and Sperm Parameters in Human Studies (cont'd).

Study/ Location			β-coefficients (95% CI)			
	Exposure Level	Reference Level	Sperm Concentration[1] (million/mL)	Sperm Count[1] (million)	Sperm Motility (%) & Motile Sperm Concentration (MSC)	Sperm Motion[2]
Chang et al. 2001 Taiwan	Active air samples of CHL = 8.5 ppm Passive air samples of CHL = 4.6 ppm Estimated air CHL for 2 hours at the beginning of the workday = 450 ppm		Not assessed	Authors state that sperm count was normal ~1 year prior to exposure. During the post-exposure period: sperm counts were as follows (by time since end of exposure): ≈ 3 months: 68.6 ≈ 4 months: 73.8 ≈ 6 months: 90.6	Semen parameters at screening ~1 year prior to exposure had been normal, with 95% motile at a normal speed at 30 min after ejaculation During the post-exposure period: the percentage of motile sperm were as follows (by time since end of exposure): ≈ 3 months: 26% ≈ 4 months: 11% ≈ 6 months: 40%	<u>Path velocity</u> ≈ 3 months: 35 ≈ 4 months: 40 ≈ 6 months: 50

Appendix B. Tables of Exposure Measures, Uptake Factors Used In Estimating Internal Dose, and Windows of Exposure in Human Studies.

Table B1. Exposure Measures for Chloroform (CHL), Total Trihalomethane (TTHM), Bromodichloromethane (BDCM), and Dibromochloromethane (DBCM) in Human Studies of Reproductive Outcomes: (A) Water Concentration, (B) Water Concentration and Estimated Internal Dose.

A.

Study	CHL Concentration (µg/L)	TTHM Concentration (µg/L)	BDCM Concentration (µg/L)	DBCM Concentration (µg/L)
Iszatt et al. 2014	Mean[1] (SD): Before EC (2000–2002) **38.6** (4.2) After EC (2005–2007) **19.4** (1.0)	Mean (SD): Before EC (2000–2002) **49.3** (5.2) After EC (2005–2007) **28.9** (1.4)	Mean (SD): Before EC (2000–2002) **7.5** (0.8) After EC (2005–2007) **6.3** (0.4)	Mean (SD): Before EC (2000–2002) **2.5** (0.1) After EC (2005–2007) **2.4** (0.2)
Iszatt et al. 2013	Mean (SD): Cases: **25.9** (19.0) Controls: **27.3** (19.1) Range of means across 9 sites: 3.2–51.6	Mean (SD): Cases: **39.1** (19.5) Controls: **40.6** (20.0) Range of means across 9 sites: 12.2–61.0	Not reported	Not reported
Rivera-Nuñez and Wright 2013	Mean in 3rd trimester: **30.6** Median: 27.4 Range: 0–265.9	Mean in 3rd trimester ***38.1*** ***Median: 36.2*** Range: 0–273.5	Mean in 3rd trimester **6.1** Median: 5.3 Range: 0–49.5	Not reported
Summerhayes et al. 2012	Mean (SD) for entire pregnancy: **33.6** (16.0) Median: 30.9 Range: 3.4–121.5	Mean (SD) for entire pregnancy: **57.7** (20.5) Median: 55.5 Range: 23.2–154.9	Mean for entire pregnancy (SD): **15.8** (4.5) Median: 15.3 Range: 5.7–33.8	Mean for entire pregnancy (SD): **6.3** (2.2) Median: 5.9 Range: 0.7–25.6
Patelarou et al.* 2011	Mean (SD) for all sites across all years: **0.15** (0.15)	Mean (SD) for all sites across all years: **3.71** (5.75) Range across sites: 0.004–26.0	Mean (SD) for all sites across all years: **0.19** (0.36)	Mean (SD) for all sites across all years: **0.55** (1.12)
Zhou et al. 2010	Mean: not reported Range of monthly means: 5.99–51.19	Not reported	Not reported	Not reported
Hoffman et al.†[2] 2008	Mean (SD): Site 1 **46.7** (13.3) Site 2 **13.7** (3.3)	Mean (SD): Site 1 **66.4** (15.8) Site 2 **63.6** (11.8)	Mean (SD): Site 1 **15.1** (4.4) Site 2 **21.1** (2.9)	Mean (SD): Site 1 **4.4** (2.1) Site 2 **23.1** (6.5)

Abbreviations: BDCM - bromodichloromethane; d - day; CHL - chloroform; DBCM - dibromochloromethane; DBPs - disinfection by-products; EC - enhanced coagulation; IQR - interquartile range; L – liter; Max - maximum; Min - minimum; ND - not detectable; SD - standard deviation; THM - trihalomethane; TTHM - total trihalomethane.

[1] Mean values for DBPs are presented in **bold**.

[2] Hoffman et al. 2008 measured DBPs at two sites. Site 1 consisted predominantly of chlorinated DBPs. Site 2 consisted predominantly of brominated DBPs.

Table B1. Exposure Measures for Chloroform (CHL), Total Trihalomethane (TTHM), Bromodichloromethane (BDCM), and Dibromochloromethane (DBCM) in Human Studies of Reproductive Outcomes: (A) Water Concentration, (B) Water Concentration and Estimated Internal Dose (cont'd).

Study	CHL Concentration (µg/L)	TTHM Concentration (µg/L)	BDCM Concentration (µg/L)	DBCM Concentration (µg/L)
Lewis et al.‡ 2007	Same as for Lewis et al. 2006	Same as for Lewis et al. 2006	Same as for Lewis et al. 2006	Same as for Lewis et al. 2006
Lewis et al.‡ 2006	CHL on average: 89% of TTHM (min/max of monthly means ~25/~77)	Interquartile range (IQR) of monthly means: 59 (min 28, max 87)	Range: Not Detectable (ND) to 9 75th percentile = 6.1	ND to <1
Hinckley et al. 2005	Mean: not reported Tertiles: <10, 10–16, ≥16	Range of yearly means from 1998–2002: 43.4–56.9	Mean: not reported Tertiles: <13, 13–18, ≥18	Mean: not reported Tertiles: <12, 12–16, ≥16
Porter et al. 2005	Mean (95% CI): **34.1** (32.5, 35.7)	Mean (95% CI): **53.7** (49.3, 56.0)	Mean (95% CI): **13.4** (12.8, 14.1)	Mean (95% CI): **4.35** (4.01, 4.68)
Toledano et al. 2005	Mean: not reported Exposure categories: <20, 20–40, >40	Mean (5th, 95th percentiles) by site: Northumbrian: **56.6** (27.0, 81.1) United: **52.0** (19.0, 81.1) Severn Trent: **35.8** (2.8, 72.5)	Mean: not reported Exposure categories: <6, 6–12, >12	Levels were often below detection limit and too low for meaningful analysis
Dodds et al. 2004	Mean: not reported Quartiles: 0, 1–49, 50–79, >80 Max: 315	Mean[3]: Cases: **57** Controls: **55** Max: 318	Mean: not reported Quartiles: 0, 1–4, 5–9, ≥10 Max: 21	Not reported
Infante-Rivard 2004	Tap Mean (SD): Cases: **11.84** (18.19) Controls: **11.58** (16.31)	Tap Mean (SD): Cases: **18.74** (19.76) Controls: **18.26** (18.89)	Tap Mean (SD): Cases: **4.34** (2.94) Controls: **4.24** (3.42)	Tap Mean (SD): Cases: **2.21** (1.95) Controls: **2.08** (2.30)
Wright et al. 2004	Mean (SD): **31.0** (23.6) 10th & 90th percentile: 4, 63 Max: 135	Mean (SD): **38.2** (27.0) 10th & 90th percentile: 8, 74 Max: 163	Mean (SD): **5.7** (5.1) 10th & 90th percentile: 1, 12 Max: 46	Not reported
Windham et al. 2003	Mean: not reported Categories: 1st quartile, 2nd–3rd quartile, 4th quartile (≥17)	Mean: not reported Tertiles: 0–40, >40–60, >60	Mean: not reported Categories: 1st quartile, 2nd–3rd quartile, 4th quartile (≥16)	Mean: not reported Categories: 1st quartile, 2nd–3rd quartile, 4th quartile (≥20)
Dodds and King* * 2001	Quartiles: <50, 50–74, 75–99, ≥100	Not reported	Quartiles: <5, 5–9,10–19, ≥20	Occurred at very low levels, and thus, not analyzed

[3] In residential water among subjects with chlorinated water supply.

Table B1. Exposure Measures for Chloroform (CHL), Total Trihalomethane (TTHM), Bromodichloromethane (BDCM), and Dibromochloromethane (DBCM) in Human Studies of Reproductive Outcomes: (A) Water Concentration, (B) Water Concentration and Estimated Internal Dose (cont'd).

Study	CHL Concentration (µg/L)	TTHM Concentration (µg/L)	BDCM Concentration (µg/L)	DBCM Concentration (µg/L)
King et al.* * 2000	Mean: **64.1**	Mean: **71.3**	Mean: **6.9**	Not reported
Waller et al. 1998	"high" exposure defined as ≥17 CHL [upper quartile] +≥5 glasses/d	"high" exposure defined as ≥75 TTHM +≥5 glasses/d	"high" exposure defined as ≥18 BDCM [upper quartile] +≥5 glasses/d	"high" exposure defined as ≥31 DBCM [upper quartile] +≥5 glasses/d
Kramer et al. 1992	Mean (SD): **12.5** (38.7) Median:1 Range: 0–350	Not reported	Mean: not reported <u>Tertiles:</u> Non-detectable, 1–9, ≥10	Mean: not reported <u>Tertiles:</u> Non-detectable, 1–3, ≥4

B.

Study	CHL		TTHM		BDCM		DBCM	
	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)
Botton et al.* 2015	Median by site[4]: Gipuzkoa ~12 Sabadell ~20 Valencia ~0 Crete Not reported	Median by site[4]: Gipuzkoa ~0.1 Sabadell ~0.2 Valencia ~0 Crete Not reported	Median by site[4]: Gipuzkoa ~20 Sabadell ~120 Valencia ~5 Crete ~0	Median (IQR) by site: Gipuzkoa ~0.22 (0.14–0.32) Sabadell ~1.6 (1.1–2.1) Valencia ~0.1 (0.05–1.1) Crete ~0.021 (0.0077–0.071)	Not reported	Not reported	Not reported	Not reported
Smith et al. 2015	Mean (SD): **37.8** (3.8)	Mean (SD): **1.61** (1.46)	Mean (SD): **45.6** (4.0)	Mean (SD): **1.86** (1.66)	Mean (SD): **6.6** (0.6)	Mean (SD): **0.20** (0.16)	Mean (SD): **0.9** (0.2)	Mean (SD): **0.03** (0.03)
Zeng et al.† † 2014	Mean: **13.71** Range: 2.68–29.90	Quartiles: <0.005 0.005–0.011 0.011–0.019 ≥0.019	Mean: **21.39** Range: 6.38–40.36	Quartiles: <0.006 0.006–0.012 0.012–0.021 ≥0.021	Not reported	Not reported	Not reported	Not reported

[4] Values were approximated from a figure in the publication.

Table B1. Exposure Measures for Chloroform (CHL), Total Trihalomethane (TTHM), Bromodichloromethane (BDCM), and Dibromochloromethane (DBCM) in Human Studies of Reproductive Outcomes: (A) Water Concentration, (B) Water Concentration and Estimated Internal Dose (cont'd).

Study	CHL		TTHM		BDCM		DBCM	
	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)
Grazuleviciene et al.‡ ‡ 2013	Mean (SD): in 3 sites with low THM level - **0.9** (1.0) in 1 site with high THM level - **17.7** (9.0)	Median: 0.1424 Range: 0.001–2.109 Tertiles: 0.001–0.026 0.026–0.288 0.288–2.109	Mean (SD): **1.3** (1.2) **21.9** (10.9)	Range: 0.003–2.448 Tertiles: 0.031–0.040 0.040–0.356 0.356–2.448	Mean (SD): **0.3** (0.5) **3.6** (2.1)	Range: 0.000–0.436 Tertiles: 0–0.013 0.013–0.051 0.051–0.436	Mean (SD): **0.1** (0.2) **0.5** (0.6)	Range: 0–0.093 Tertiles: 0–0.002 0.002–0.006 0.006–0.093
Costet et al. 2012	Mean (SD) for all sites: **9.3** (7.0)	Quartiles: <0.068 0.068–<0.133 0.133–<0.237 ≥0.237	Mean (SD) for all sites: **41.6** (16.1)	Quartiles: <0.351 0.351–<0.578 0.578–<0.940 ≥0.940	Mean (SD) for all sites: **10.4** (5.4)	Quartiles: <0.083 0.083–<0.141 0.141–<0.226 ≥0.226	Mean (SD) for all sites: **13.8** (5.5)	Quartiles: <0.118 0.118–<0.188 0.188–<0.267 ≥0.267
Danileviciute et al.‡ ‡ 2012	Mean (SD) for all sites: **7.8** (10.2) In 3 sites with low THM level - **0.9** (1.0) In 1 site with high THM level - **17.7** (9.0) Range: 0.9–17.7	Median: 0.1424 Range: 0.0013–2.1328	Mean (SD) for all sites: **9.8** (12.4) **1.3** (1.2) **21.9** (10.9) Range: 1.3–21.9	Median: 0.1733 Range: 0.0025–2.4040	Mean (SD) for all sites: **1.7** (2.2) **0.3** (0.5) **3.6** (2.1) Range: 0.3–3.6	Median: 0.0280 Range: 0.0001–0.34	Mean (SD) for all sites: **0.3** (0.5) **0.1** (0.2) **0.5** (0.6) Range: 0.1–0.5	Median: 0.0026 Range: 0–0.064

Table B1. Exposure Measures for Chloroform (CHL), Total Trihalomethane (TTHM), Bromodichloromethane (BDCM), and Dibromochloromethane (DBCM) in Human Studies of Reproductive Outcomes: (A) Water Concentration, (B) Water Concentration and Estimated Internal Dose (cont'd).

Study	CHL		TTHM		BDCM		DBCM	
	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)
Levallois et al. 2012	Mean (SD): Cases: **43.3** (40.7) Controls: **41.1** (39.2)	Quartiles: <42.24 42.24–80.21 80.22–169.81 >169.81	Mean (SD): Cases: **49.3** (39.8) Controls: **47.2** (38.3)	Quartiles: <58.02 58.02–102.44 102.45–195.73 >195.73	Mean (SD): Cases: **4.7** (3.1) Controls: **4.7** (2.9)	Not reported	Mean (SD): Cases: **1.3** (1.4) Controls: **1.3** (1.4)	Not reported
Grazuleviciene et al.‡ ‡ 2011	Mean (SD) for all sites: **7.8** (10.2) In 3 sites with low THM level - **0.9** (1.0) In 1 site with high THM level - **17.7** (9.0) Range: 0.9–17.7	Range: 0.0013–2.1328	Mean (SD) for all sites: **9.8** (12.4) **1.3** (1.2) **21.9** (10.9) Range: 1.3–21.9	Range: 0.0025–2.4040	Mean (SD) for all sites: **1.7** (2.2) **0.3** (0.5) **3.6** (2.1) Range: 0.3–3.6	Range: 0.0001–0.34	Mean (SD) for all sites: **0.3** (0.5) **0.1** (0.2) **0.5** (0.6) Range: 0.1–0.5	Range: 0–0.064
Iszatt et al. 2011	Median: 2.9 Range: 0.0–90 Quartiles: 0.0–0.9 1.0–2.9 3.0–6.9 7–90	Range: 0–65 Quartiles: 0.0 >0.0–1.4 1.5–4.2 4.3–65.0	Median: 23 Range: 0–105 Quartiles: 0–11 12–23 24–36 37–105	Range: 0–190 Quartiles: 0.0 >0.0–8.4 8.5–21.0 22–190	Median: 5.0 Range: 0.0–23 Quartiles: 0.0–1.0 1.1–5.0 6–9 10–23	Range: 0–50 Quartiles: 0.0 >0.0–1.0 2–5 6–50	Median:7 Range: 0–34 Quartiles: 0–3 4–7 8–10 11–34	Range: 0–85 Quartiles: 0.0 >0.0–2.4 2.5–7.1 7.2–85.0

Table B1. Exposure Measures for Chloroform (CHL), Total Trihalomethane (TTHM), Bromodichloromethane (BDCM), and Dibromochloromethane (DBCM) in Human Studies of Reproductive Outcomes: (A) Water Concentration, (B) Water Concentration and Estimated Internal Dose (cont'd).

Study	CHL		TTHM		BDCM		DBCM	
	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)	Concentration (µg/L)	Estimated Internal Dose (µg/d)
Villanueva et al.* 2011	Mean: not reported Median by sites[5]: Asturias ~26 Gipuzkoa ~9 Sabadell ~20.4 Valencia 0.65 Granada ~4.7	Mean: not reported Median total residential uptake by sites[5]: Asturias ~0.3 Gipuzkoa ~0.1 Sabadell ~0.2 Valencia ~0 Granada ~0	Mean: not reported Median by sites[5]: Asturias ~ 40 Gipuzkoa ~20 Sabadell ~120 Valencia ~5 Granada ~10	Not reported	Mean: not reported Median by sites[5]: Asturias ~8 Gipuzkoa ~6 Sabadell ~12 Valencia ~1.1 Granada ~2.5	Not reported	Mean: not reported Median by sites[5]: Asturias ~4 Gipuzkoa ~4.4 Sabadell ~24 Valencia ~2 Granada ~2	Not reported
Savitz et al.† 2005	Mean: **23.93** Range of means between sites: 0.24–47.90	Mean: **25.77**	Mean: **42.62** Range of means between sites: 3.29–67.11	Mean: **44.69**	Mean: **10.72** Range of means between sites: 1.04–20.31	Mean: **11.0**	Not reported	Not reported

[5] Values approximated from figures.

Table B2. Uptake Factors and Percent Reductions Used in Calculations of Estimated Internal Dose in Human Studies of Chloroform (CHL) Exposure.

Study	CHL Uptake Factors				CHL Reduction	
	Ingestion	Showering	Bathing	Swimming	Filter Use/ Bottled Water	Thermal Treatment
Botton et al.* 2015	0.00490196	0.001563091	0.001320755	Considered[1]	90%/ 100%	Not considered
Smith et al. 2015	0.00490196	0.001563091	0.001320755	0.002541407	90%/ Considered but not included	92%
Zeng et al. †† 2014	0.00490196	0.001536261	0.001320755	Considered but not included[2]	Not considered/ 100%	Boiled tap water 30% coefficient factor
Grazuleviciene et al. ‡‡ 2013	0.00490196	0.001536	0.001321	Considered but not included[3]	Considered but not included[4]/ Not clear	Heating 85–100%[5]
Costet et al. 2012	0.00490196	0.001563091	0.001320755	0.002541407	Not considered/ Considered but not included	Hot beverages 0.3 correction factor
Danilevicute et al. ‡‡ 2012	0.00490196	0.001536261	0.001320755	Considered but not included[3]	Not considered/ 100%	Heated water 85–100%[5]
Levallois et al. 2012	Multiplied volume ingested from various sources (i.e., hot and cold beverages) x estimated conc in the ingested water	Based on toxicokinetic model by Haddad et al. (2006)	Based on toxicokinetic model by Haddad et al. (2006)	Considered but not included	86.8%/ 100%	Boiling 81.6% Hot tap water --------[6] Refrigeration 13%

Abbreviations: CHL - chloroform; conc - concentration; exp – exposure; L - liter; min - minute; THM - trihalomethane

[1] Personal attendance at indoor and outdoor pools was multiplied by the area THM average, then added together.
[2] Number of study participants who swam in chlorinated pools was very low (4.0%), therefore swimming was not included in the estimated internal dose estimates.
[3] The percentage of participants who attended swimming pools was low (~7%), and it appears that this factor was not included in estimating internal dose.
[4] The study reported there was no difference in the proportion of women who did and did not use water filters.
[5] The study cited two references for the reduction in CHL due to heating water. These references are Savitz et al. 2006, which reported a 100% reduction, and Whitaker et al. 2003, which reported an 85% reduction. It is not clear which was used for the CHL estimates.
[6] Used 160% increase in CHL for hot tap water.

Table B2. Uptake Factors and Percent Reductions Used in Calculations of Estimated Internal Dose in Human Studies of Chloroform (CHL) Exposure (cont'd).

Study	CHL Uptake Factors				CHL Reduction	
	Ingestion	Showering	Bathing	Swimming	Filter Use/ Bottled Water	Thermal Treatment
Grazuleviciene et al. ‡ ‡ 2011	0.00490196	0.001536261	0.001320755	Considered but not included[3]	Considered but not included[4]/ 100%	Heated water 85–100%[5]
Iszatt et al. 2011	0.00490196	0.001506877	0.000994222	0.002541407[7] Dishwashing 0.000745	Not considered/ Assumed negligible THM exp	Not considered
Villanueva et al.* 2011	0.00490196	0.00153626	0.00132075	0.00254141	Home filter 90%/ Considered[8]	Not considered
Savitz et al. † 2005	0.00490	0.001536261	0.001320755	Not considered	Faucet filter 100% Pitcher filter 41% Bottled Water 100%	Kettle boiling 100% Microwave boiling 18%
Dodds et al. 2004	Defined as total liters of water consumed	Assumed 5 min shower was equivalent to 1 L of ingested water	Assumed 15 min bath was equivalent to 1 L of ingested water	Not considered	Carbon filter 50%/ 100%	Boiled hot water drinks 70%

[7] Swimming was included as a confounder, but was not used in estimating internal dose.
[8] Because logarithm of zero values in tap water ingestion from bottled water consumers led to invalid transformed variables, these were imputed arbitrarily using half the area-specific lowest value for ingestion.

Table B3. Windows of Exposure Assessed in Human Studies of Chloroform Exposure and Reproductive Outcomes.

Study	Exposure Windows (trimester)[1]								
	PTB	SGA	LBW	VLBW	BW	SAB	SB	BD	Other
Botton et al.* 2015									Postnatal weight gain at 6 months Entire pregnancy
Smith et al. 2015					1st, 2nd, **3rd** **Entire pregnancy**				
Iszatt et al. 2014			Entire pregnancy	Entire pregnancy			Entire pregnancy		
Grazuleviciene et al.‡ ‡ 2013								**1st** 1st month 2nd month 3rd month	
Rivera-Nuñez and Wright 2013	1st, **2nd**	1st, 2nd, **3rd**			1st, 2nd, **3rd**				
Costet et al. 2012	1st, 2nd, **3rd**	1st, 2nd, **3rd**							
Danileviciute et al.‡ ‡ 2012		1st, 2nd, **3rd** **Entire pregnancy**	1st, 2nd, **3rd** **Entire pregnancy**						
Levallois et al. 2012		3rd							
Summerhayes et al. 2012		1st, 2nd, **3rd** Entire Pregnancy			**1st, 2nd, 3rd** **Entire pregnancy**				
Grazuleviciene et al.‡ ‡ 2011		1st, 2nd, **3rd** Entire pregnancy	1st, 2nd, **3rd** Entire pregnancy		1st, 2nd, **3rd** Entire pregnancy				

Abbreviations: BD - birth defects; BW - birth weight; LBW - low birth weight; LMP - last menstrual period; NTD - neural tube defects; PTB - preterm birth; SAB - spontaneous abortion; SB - still birth; SGA - small for gestational age; VLBW - very low birth weight.

[1] For studies that examined more than one window of exposure, the window(s) for which risk estimates are presented in other tables and figures are indicated in **bold**.

Table B3. Windows of Exposure Assessed in Human Studies of Chloroform Exposure and Reproductive Outcomes (con't).

Study	Exposure Windows (trimester)[1]								
	PTB	SGA	LBW	VLBW	BW	SAB	SB	BD	Other
Iszatt et al. 2011								1st	
Villanueva et al.* 2011	1st, 2nd, **3rd** Entire pregnancy	1st, 2nd, **3rd** Entire pregnancy	1st, 2nd, **3rd** Entire pregnancy		1st, 2nd, **3rd** Entire pregnancy				
Zhou et al. 2010					**1st**, 2nd, **3rd**, **1st + 2nd** **Entire pregnancy**				
Hoffman et al.† 2008		3rd			3rd				
Lewis et al.‡ 2007	1st, **2nd** **Entire pregnancy** **4 weeks before birth** 4-week risk sets								
Lewis et al.‡ 2006			1st**, 2nd**, 3rd **Entire pregnancy**						
Hinckley et al. 2005	<37 weeks gestation	3rd	3rd						
Porter et al. 2005		1st, 2nd, **3rd** **Entire pregnancy**							

Table B3. Windows of Exposure Assessed in Human Studies of Chloroform Exposure and Reproductive Outcomes (con't).

Study	Exposure Windows (trimester)[1]								
	PTB	SGA	LBW	VLBW	BW	SAB	SB	BD	Other
Savitz et al.† 2005	1st, 2nd, **3rd**	1st, 2nd, **3rd**			1st, 2nd, **3rd**	**9 weeks after last menstrual period (LMP) to 20 weeks after LMP** 4 weeks prior to LMP to 3 weeks after LMP 4 weeks after LMP to 8 weeks after LMP			
Toledano et al. 2005			3rd	3rd			3rd		
Dodds et al. 2004							1st + early 2nd trimester		
Infante-Rivard 2004		Entire pregnancy							
Wright et al. 2004	3rd	3rd			3rd				
Windham et al. 2003									<u>Menstrual cycle function</u> 90 day exposure windows
Dodds and King** 2001								<u>NTD</u> 1 month before conception to 1 month after <u>Cardiovascular anomalies</u>	

Table B3. Windows of Exposure Assessed in Human Studies of Chloroform Exposure and Reproductive Outcomes (con't).

Study	Exposure Windows (trimester)[1]								
	PTB	SGA	LBW	VLBW	BW	SAB	SB	BD	Other
								1st 2 months of pregnancy <u>Cleft defects</u> 1st 2 months of pregnancy <u>Chromosomal abnormalities</u> 3 months before pregnancy	
King et al.** 2000							Entire pregnancy		
Wennborg et al. 2000					Entire pregnancy	Entire pregnancy			
Dahl et al. 1999									Fecundability ratio 6 months prior to pregnancy
Waller et al. 1998						1st			
Kramer et al. 1992	Entire pregnancy	Entire pregnancy	Entire pregnancy						

Appendix C. OEHHA (2005) Re-analysis of Data from Two Chloroform Epidemiological Studies: Wennborg et al. (2000) and Infante-Rivard (2004).

On November 4, 2004 the Developmental and Reproductive Toxicant (DART) Identification Committee, the State's qualified experts for reproductive toxicity for Proposition 65, met to consider whether chloroform had been clearly shown through scientifically valid testing according to generally accepted principles to cause reproductive toxicity. The committee voted not to list this chemical as known to cause reproductive toxicity under Proposition 65 for the either developmental, male reproductive or female reproductive toxicity endpoints. However, the Committee did request that the Office of Environmental Health Hazard Assessment (OEHHA) try to obtain additional information regarding re-analyses of findings from two epidemiologic studies, one by Wennborg et al. (2000), and the other by Infante-Rivard (2004). OEHHA contacted the primary authors of these articles and, after discussion of the issues raised by the DART Committee, the authors have provided OEHHA with the results of the requested re-analyses. Below is a description of the specific requests made of the authors and the results from their re-analyses.

Re-analysis from Dr. Wennborg:

As summarized in the draft Hazard Identification Document on Chloroform (OEHHA, 2004: pages 13-14), Dr. Wennborg and coauthors conducted an occupational study of women, which examined exposure to chloroform in association with pregnancy outcomes. The study reported a weak association between women working with chloroform during the time before conception and the occurrence of spontaneous abortion (SAB) (odds ratio = 2.3; 95% confidence interval 0.9 – 5.9). The regression analysis resulting in this finding included adjustment for mother's age and previous SAB. However, as discussed at the DART Committee meeting, it was not clear from the study whether the previous SABs occurred before or during the time when the women were exposed to chloroform. If the women were exposed to chloroform and/or other chemicals at the time the previous SAB occurred, including this variable in the regression analysis could have resulted in over control, which would have biased the results. Therefore, following the direction of the DART Committee, OEHHA requested that Dr. Wennborg either: 1) verify that the SABs occurred before exposure to the chloroform, or 2) rerun the statistical analyses of the data omitting the previous SABs.

Dr. Wennborg responded that previous SABs included SABs that were "previous" in relation to the pregnancy in question. Thus these did include SABs that occurred while the women were occupationally exposed to chemicals. Therefore, she reran the analysis excluding the previous SABs, and reported the following results. The odds ratio was 2.1, with 95% confidence interval 1.1 – 4.0. Thus the odds ratio was about the same (2.1 vs. 2.3), but the 95% confidence interval was smaller (1.1 – 4.0 vs. 0.9 – 5.9), and now statistically significant. Dr. Wennborg noted that the analysis in 2000 was performed with STATA 6.0, and the new analysis with STATA 8.0. STATA is a statistical data analysis program similar to programs such as SAS.

Re-analysis from Dr. Infante-Rivard:

As summarized in the draft Hazard Identification Document on Chloroform (OEHHA, 2004: pages 20-22), Dr. Infante-Rivard conducted a case-control study that examined the association between exposure to chloroform and fetal growth. The study also tested for gene-environment interactions to determine whether effects of chloroform exposure were modified by newborn and genetic variants. In analyzing the effect of exposure to trihalomethanes (THMs) and chloroform, Dr. Infante-Rivard used the 90th percentile as a cutoff, thus considering the top 10th percentile of individuals as exposed. The author concluded that the findings suggest exposure to THMs at the highest levels can affect fetal growth but only in genetically susceptible newborns. The results are not statistically significant for chloroform. However, as discussed at the DART committee meeting, the size of the sample of women in the exposed group was small when the 90th percentile cutoff was used. This may have limited the power of the study to detect an effect, if one were present. Therefore, following the direction of the DART committee, OEHHA requested that Dr. Infante-Rivard reanalyze the data using a less conservative cutoff. Table 1 below shows the results of the analysis conducted using the 90th percentile cutoff, as reported in the study, as well as the reanalysis using the 75th percentile cutoff. These results using the 75th percentile were not statistically significant for either THMs or chloroform.

Dr. Infante-Rivard pointed out that she disagreed with choosing a 75th percentile cutoff since she believed one should choose the cutoff based on where effects are likely. The levels of chloroform exposure in this study were considerably lower, even at the 90th percentile, than those in studies that had reported a statistically significant effect.

Table 1. Adjusted ORs (95% CIs) for exposure to THMs (chloroform and total THMs) in drinking water measured as average level at the tap, according to newborn and maternal polymorphisms in the CYP2E1 and MTHFR genes.

	OR (95% CI) Using a 90th percentile cutoff		OR (95% CI) Using a 75th percentile cutoff	
Gene	Chloroform	Total THMs	Chloroform	Total THMs
Newborns				
*CYP2E1*5* (G1259C)				
Wild type	0.99 (0.57-1.74)	0.82 (0.47-1.45)	0.92 (0.67-1.28)	0.74 (0.68-1.31)
1 or 2 variant alleles	5.62 (0.82-38.39)	13.20 (1.19-146.72)*	1.86 (0.63-5.08)	1.32 (0.68-5.98)
MTHFR C677T				
Wild type	1.78 (0.82-3.87)	1.63 (0.72-3.71)	--	--
1 or 2 variant alleles	0.83 (0.38-1.54)	0.76 (0.38-1.54)	--	--
Mothers				
*CYP2E1*5* (G1259C)				
Wild type	0.88 (0.50-1.54)	0.83 (0.48-1.44)	0.94 (0.68-1.38)	0.92 (0.66-1.28)
1 or 2 variant alleles	4.40 (0.73-26.42)	6.54 (0.59-71.45)	1.38 (0.54-3.52)	1.38 (0.54-3.53)
MTHFR C677T				
Wild type	1.00 (0.46-2.18)	0.98 (0.46-2.10)	--	--
1 or 2 variant alleles	1.12 (0.56-2.32)	0.94 (0.47-1.89)	--	--

* Chi-square (1degree of freedom) for effect modification = 4.87; p = 0.027.
Adapted from Infante-Rivard (2004).

Appendix D. Parameters for Literature Searches on the Reproductive Toxicity of Chloroform.

General searches of the scientific literature on the reproductive and developmental toxicity of chloroform were conducted under contract by the University of California at Berkeley (Charleen Kubota, M.L.I.S.). The goal was to identify peer-reviewed open source and proprietary journal articles, print and digital books, reports and gray literature that potentially reported relevant toxicological and epidemiological information on the reproductive and developmental toxicity of the chemical, chloroform. The search sought to identify all literature relevant to the assessment of evidence on male reproductive, female reproductive and developmental neurotoxicity.

Search Process

ChemSpider was searched first to gather chemical names, synonyms, CAS registry numbers, MeSH and Chemical Abstracts Service headings for chlorpyrifos before searching bibliographic databases. The MeSH database was used to identify relevant subject headings for reproductive and developmental toxicology endpoints. MeSH (Medical Subject Headings) terms at the top of hierarchical lists of subject headings are automatically “exploded” in a search to retrieve citations with more specific MeSH terms. For example, the heading “Congenital Abnormalities” includes numerous specific conditions such as spina bifida and congenital heart defects. The broad subject heading “Pregnancy Complications” encompasses multiple conditions or pathological processes associated with pregnancy. Spontaneous abortion and many fetal diseases are listed under this term.

Relevant MeSH subject terms were entered into the PubMed Search Builder to execute a PubMed search.

(“*chloroform*” [Mesh] OR 67-66-3 [RN]) AND ("Congenital Abnormalities"[Mesh] OR "Pregnancy Complications"[Mesh] OR "Reproductive Physiological Phenomena"[Mesh] OR "Embryonic and Fetal Development"[MeSH] OR "Receptors, Androgen"[Mesh] OR "Receptors, Estrogen"[Mesh] OR “Endocrine System”[MeSH] OR “Thyroxine”[MeSH])

Additional databases listed below were then searched. Research strategies were tailored according to search features unique to each database. BIOSIS Previews, for example, was searched by entering chloroform and refining the search by applying these facets: toxicology, neural coordination, nervous system, development, behavior, reproduction, population studies, reproductive system, pediatrics, obstetrics and psychiatry. Hand searching of reference lists from relevant articles, book chapters and other sources was done to find articles that were not retrieved through database searches.

Databases

The researcher utilized some or all of the following databases/ search platforms/database vendors:

BIOSIS Previews® (Thomson-Reuters™, Inc.) 1926 - present

CABI: CAB Abstracts® (Thomson-Reuters™, Inc.) 1910 - present

ChemSpider (Royal Society of Chemistry)

MeSH (Medical Subject Headings) (National Library of Medicine)

Developmental and Reproductive Toxicology Database (DART/ETIC) (National Library of Medicine) early 1900s – present

MeSH (Medical Subject Headings) (National Library of Medicine)

EMBASE® (Elsevier) 2012 - present

Environmental Sciences and Pollution Management (Proquest) 1967 - present

PubMed (National Library of Medicine) 1950 - present

National Technical Research Library (NTRL v3.0) (National Technical Information Service) 1900s - present

ReproRisk® System: **REPROTEXT®** Reproductive Hazard Reference**, REPROTOX®** Reproductive Hazard Information, **Shepard's Catalog of Teratogenic Agents**, **TERIS Teratogen Information System (RightAnswer® Knowledge Solutions OnSite™ Applications) date coverage varies**

Scifinder®: CAS (Chemical Abstracts Service) 1907 - present

TOXLINE (National Library of Medicine TOXNET) 1840s - present

Web of Science™ (Thomson-Reuters™, Inc.) 1900 – present

Attachment 1: OEHHA (2004) Evidence of Developmental and Reproductive Toxicity of Chloroform.