Chloroform: Reproductive and Developmental Toxicity

Developmental and Reproductive Toxicant Identification Committee Meeting
October 27, 2016

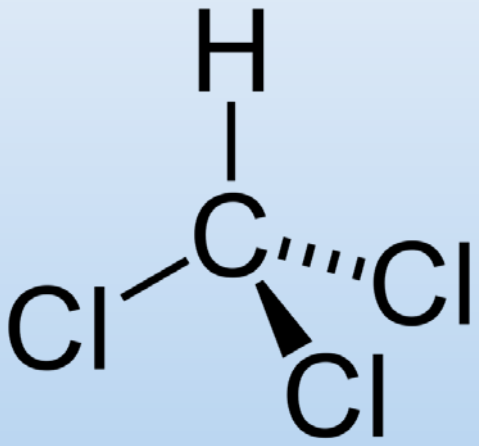
Reproductive and Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

2016 Chloroform Hazard Identification Materials

- Reconsideration of a Chemical Listed under Proposition 65 as Known to Cause Reproductive Toxicity. Chemical Listed under the Labor Code Mechanism: Chloroform (OEHHA August 2016)
  - Cited studies
    - Attachment 1: Evidence on the Developmental and Reproductive Toxicity of Chloroform (OEHHA August 2004)
    - Appendix C: Supplemental Analyses (OEHHA August 2005)

Background

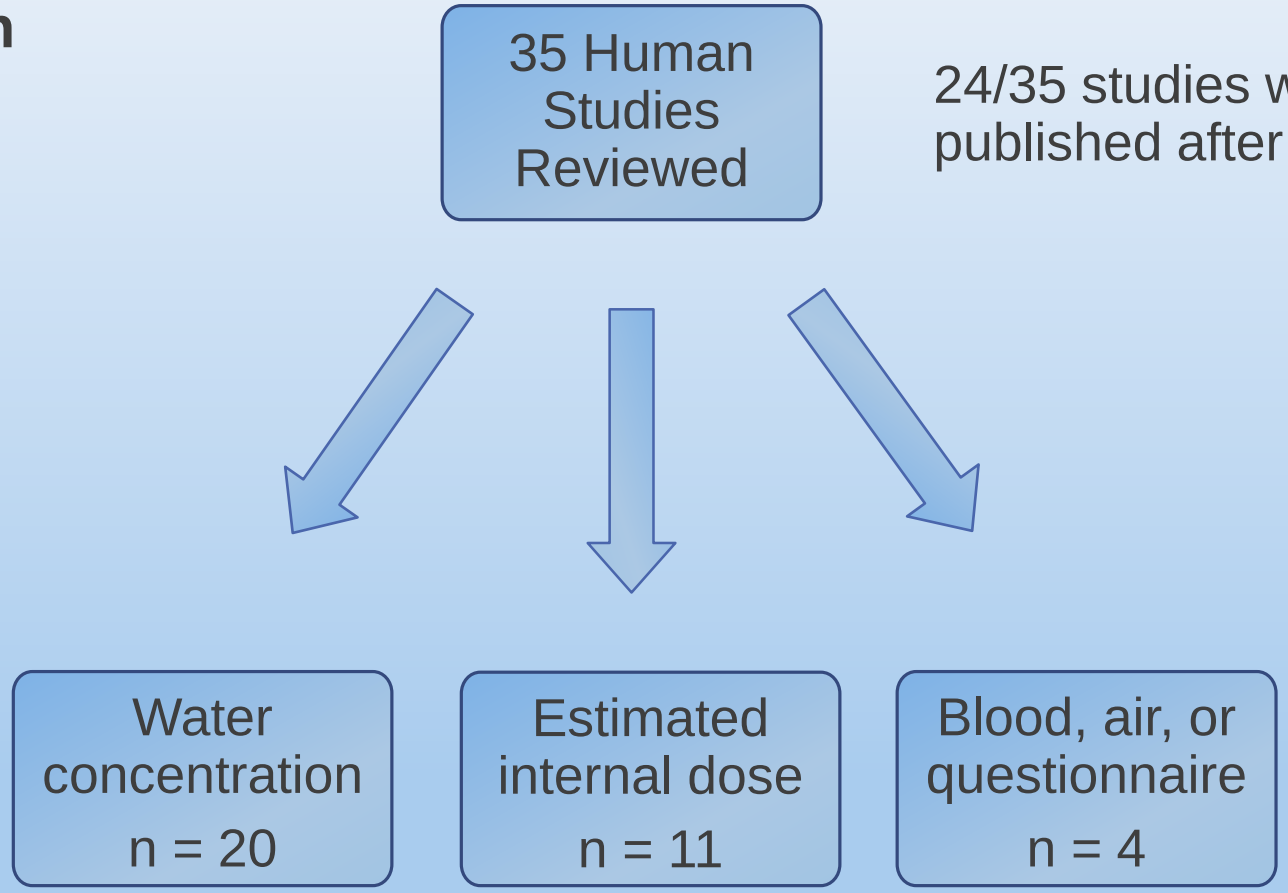
- Tetrahedral polar compound
- Uses – solvent
- By-product of water disinfection using chlorine
  - most abundant trihalomethane in most water treatment systems
  - formed when residual chlorine reacts with organic matter



Human Studies Reviewed

Complex data set of human studies including:

- Different study designs
- Different windows of exposure
- Different measures of exposure
- Different routes of exposure



24/35 studies were published after 2004

Exposure to CHL as a Disinfection By-Product

Levels vary depending on:

- Water source (groundwater, surface water)
- pH
- Temperature
- Residual chlorine levels
- Organic matter (humic and fulvic acid)
- Residence time

Exposure to CHL as a Disinfection By-Product (cont'd)

Potential sources of exposure

- Ingestion of tap water
- Showering and bathing
- Swimming
- Dishwashing by hand

Exposure Assessment

Showering and bathing

- Contribute to large fraction of uptake via inhalation and dermal absorption

Dishwashing

- Can also be a significant source of exposure if using triclosan-containing soaps
  - Use of triclosan-containing soaps can increase an individual's overall CHL exposure by 15-40%

Potential Misclassification of Exposure in Human Studies

- CHL concentrations measured at water treatment plant
  - differences in temporal and spatial CHL formation
  - very few studies measured CHL in tap water at the residence
- Individual variability in water use practices
  - amount of water ingested, use of filters, time spent showering or bathing, water temperature
- Use of maternal residence at birth
- Lack of estimates of workplace exposure

Most misclassification likely to be non-differential

Covariates and Other Factors in Human Studies

- Gene-environment interactions
  - variation in polymorphisms (e.g., CYP2E1, GSTT1, GSTM1)

- Co-occurrence of other trihalomethanes, haloacetic acids
  - additional information on other trihalomethanes provided (Appendices A & B)

Reproductive Outcomes Assessed

Preterm birth (PTB) n = 9	Small for gestational age (SGA) n = 15	Low birth weight (LBW) Very low birth weight (VLBW) n = 9	Birth weight (BW) n = 10
Spontaneous abortion (SAB), Stillbirth (SB), Birth defects (BD) n = 10	Postnatal weight gain n = 1	Menstrual function, Fertility n = 2	Sperm quality n = 4

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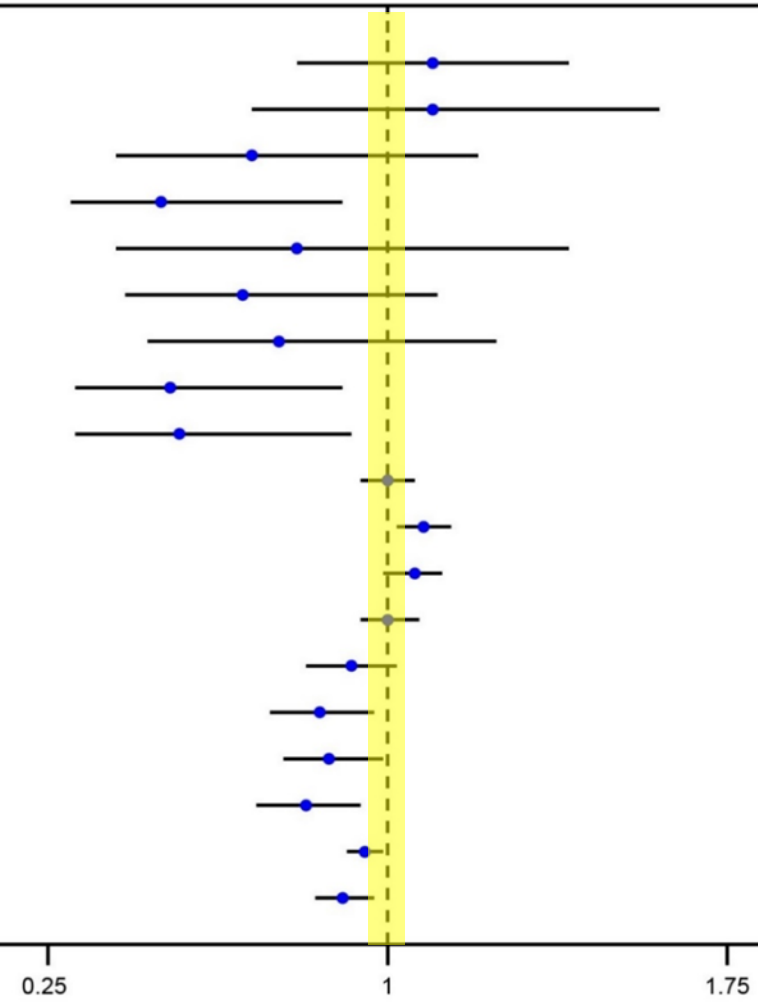
Forest plot of the association between CHL exposure [water concentration] and PTB

Study (Year)	CHL Water Concentration (µg/L)		Odds Ratio	Lower CI	Upper CI
Kramer et al. 1992	1–9	Entire Pregnancy	1.10	0.80	1.40
	≥10		1.10	0.70	1.60
Costet et al. 2012	5–<10		0.70	0.40	1.20
	10–<15		0.50	0.30	0.90
	≥15		0.80	0.40	1.40
Savitz et al. 2005†	>0.1–≤10.9		0.68	0.42	1.11
	>10.9–≤30.4		0.76	0.47	1.24
	>30.4–≤48.2		0.52	0.31	0.90
	>48.2		0.54	0.31	0.92
Rivera-Nuñez and Wright 2013	>5–21	2nd Trimester	1.00	0.94	1.06
	>21–35		1.08	1.02	1.14
	>35–52		1.06	0.99	1.12
	>52		1.00	0.94	1.07
Lewis et al. 2007‡	40–60	Entire Pregnancy	0.92	0.82	1.02
	≥60		0.85	0.74	0.97
	40–60	2nd Trimester	0.87	0.77	0.99
	≥60		0.82	0.71	0.94
Wright et al. 2004	>26–63		0.95	0.91	0.99
	>63–135		0.90	0.84	0.97



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	10–<15		0.50	0.30	0.90
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	>10.9–≤30.4		0.76	0.47	1.24
	>30.4–≤48.2		0.52	0.31	0.90
	>48.2		0.54	0.31	0.92
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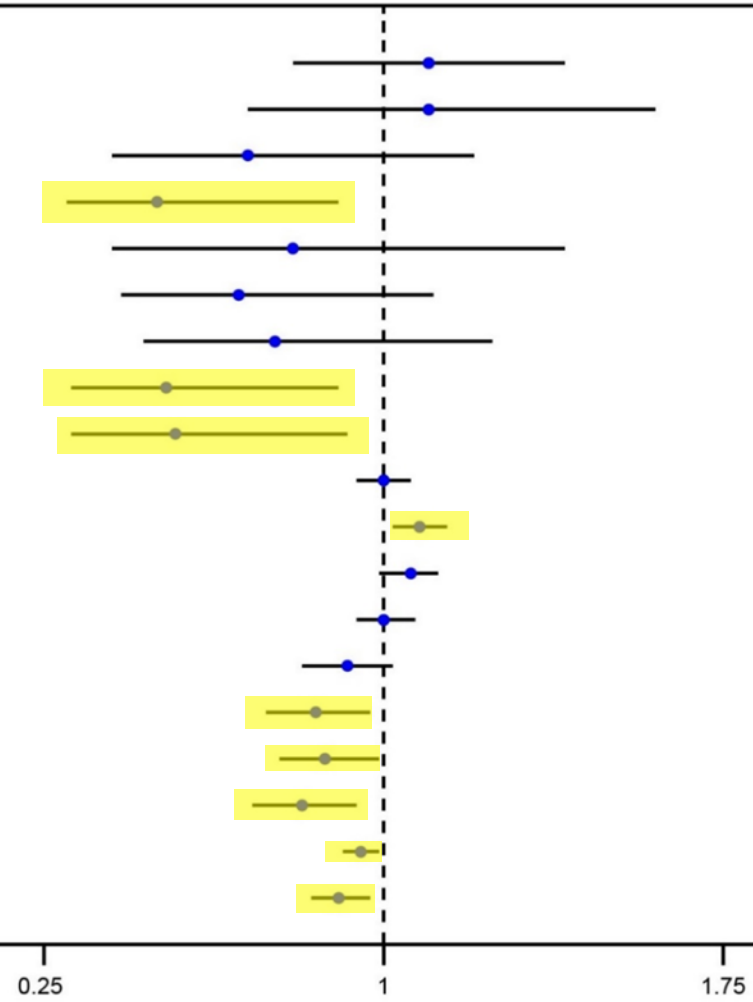
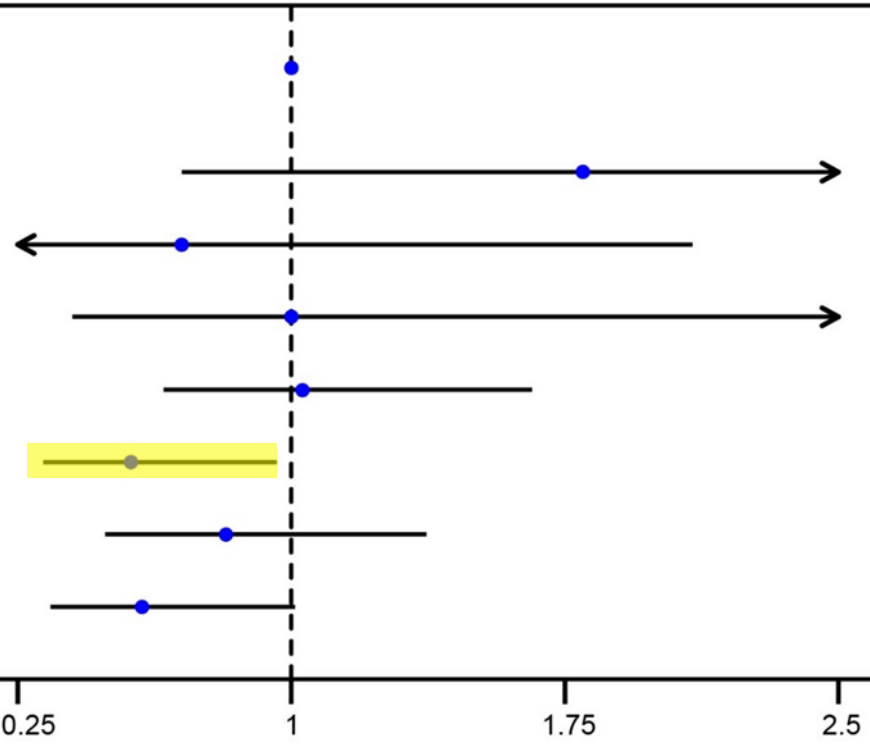


CHL exposure as estimated internal dose and PTB

Study (Year)	CHL Estimated Internal Dose (µg/d)	Odds Ratio	Lower CI	Upper CI
Villanueva et al. 2011*	10% increase in total residential uptake	1.00	0.99	1.01
Costet et al. 2012	0.068–<0.133	1.80	0.70	4.80
	0.133–<0.237	0.70	0.20	2.10
	≥0.237	1.00	0.40	2.90
Savitz et al. 2005†	>0–≤0.2	1.03	0.65	1.66
	>0.2–≤0.8	0.56	0.32	0.96
	>0.8–≤1.3	0.82	0.49	1.37
	>1.3	0.59	0.34	1.01



Reproductive Outcomes Assessed

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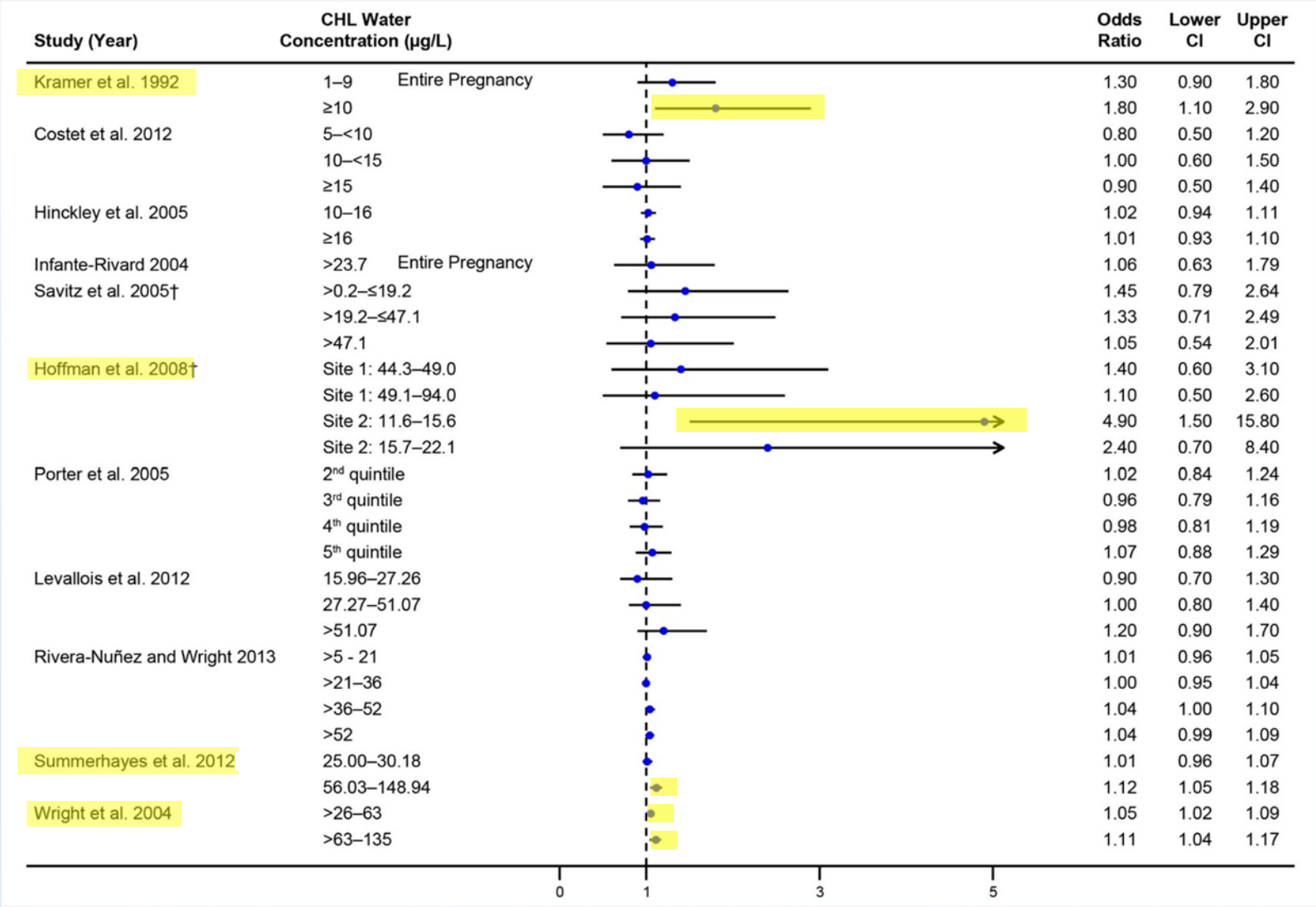
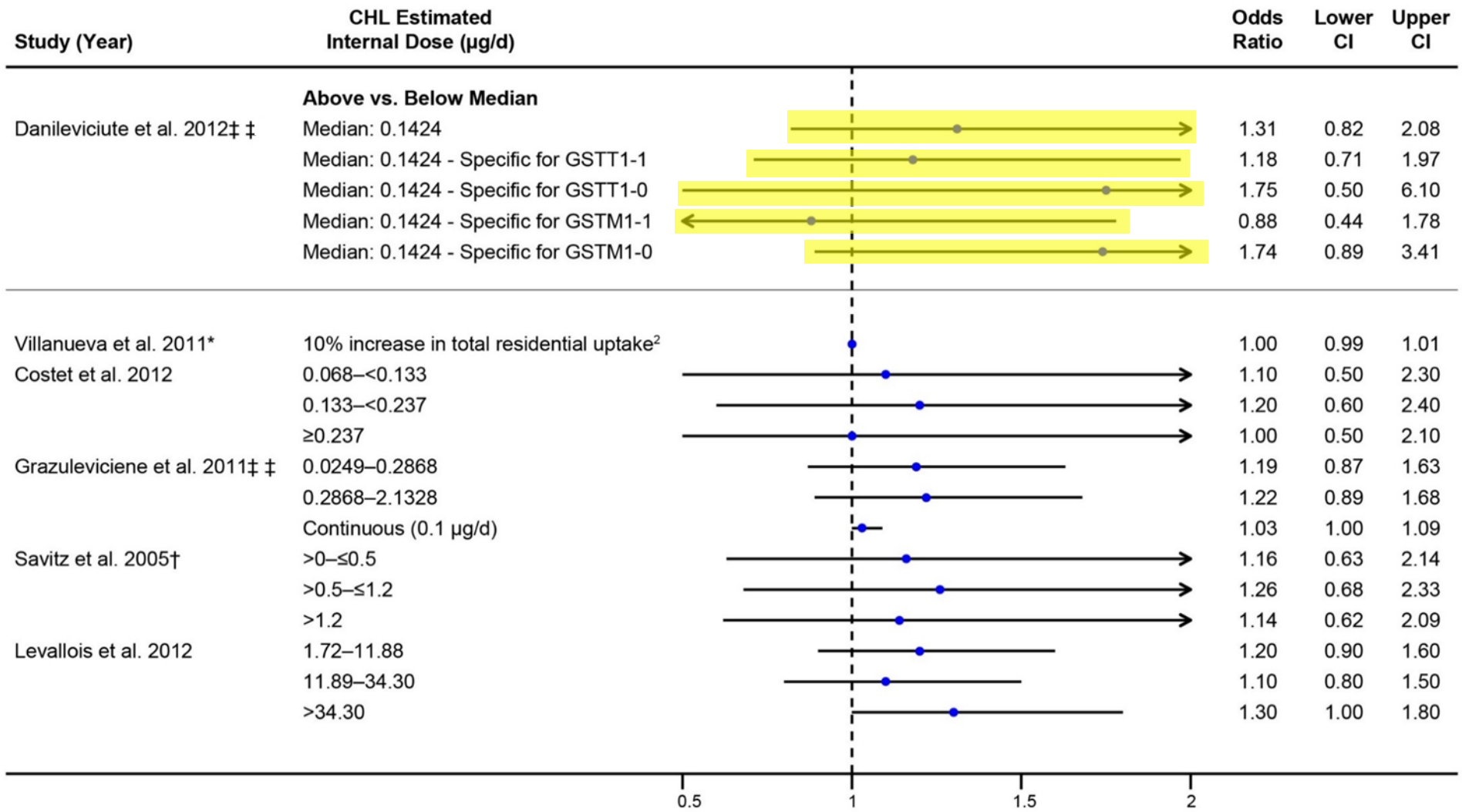
CHL exposure as water concentration and SGA



CHL exposure as estimated internal dose and SGA



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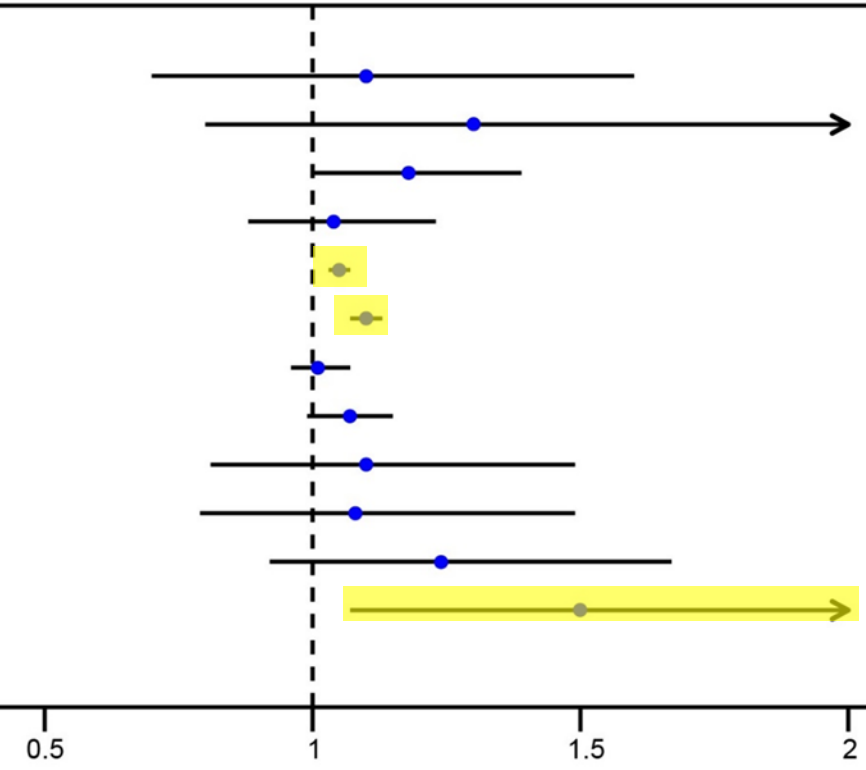
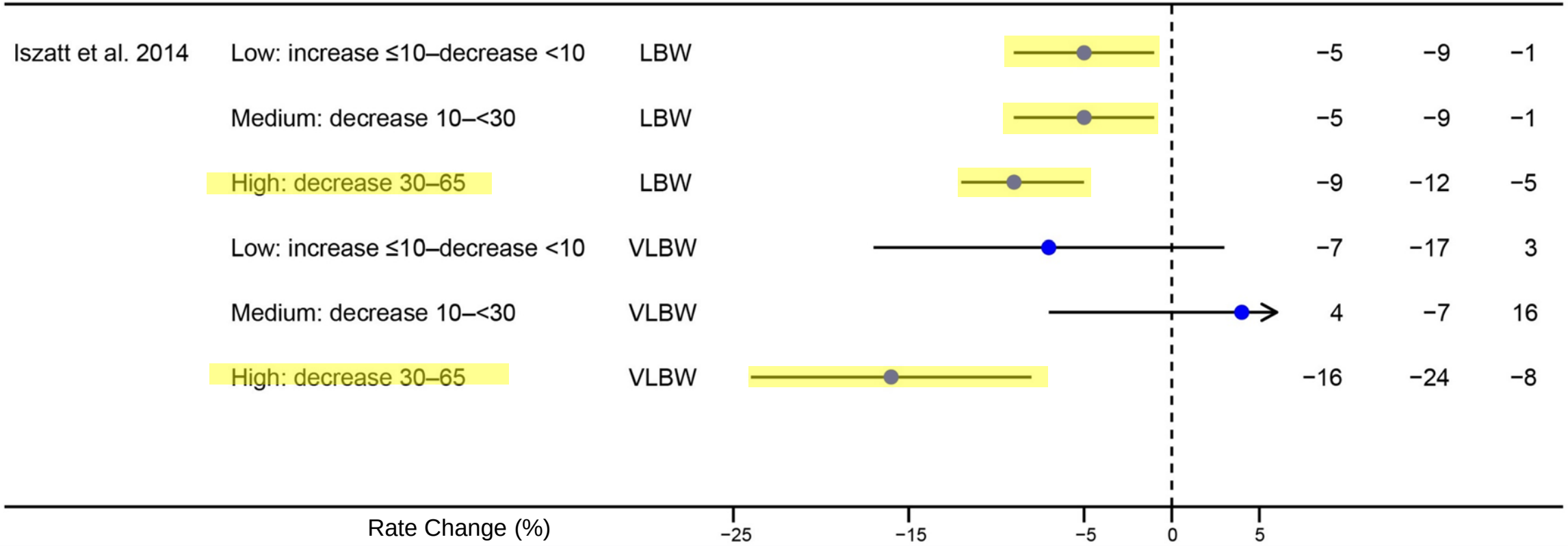
CHL exposure as water concentration and LBW and VLBW

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‡	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



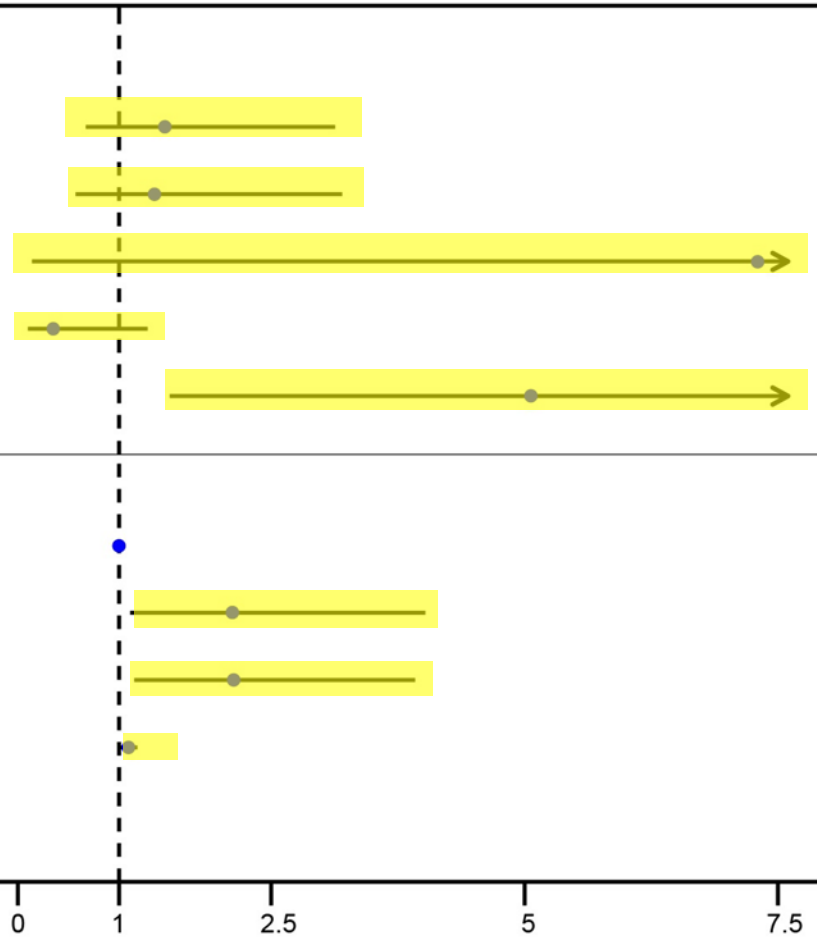
Change in water concentration of CHL and Change in Rates of LBW and VLBW

Study (Year)	Change in CHL Water Concentration (µg/L)	Outcome	Rate Change (%)	Lower CI	Upper CI
Iszatt et al. 2014	Low: increase ≤10–decrease <10	LBW	−5	−9	−1
	Medium: decrease 10–<30	LBW	−5	−9	−1
	High: decrease 30–65	LBW	−9	−12	−5
	Low: increase ≤10–decrease <10	VLBW	−7	−17	3
	Medium: decrease 10–<30	VLBW	4	−7	16
	High: decrease 30–65	VLBW	−16	−24	−8



CHL exposure as estimated internal dose and LBW

Study (Year)	CHL Estimated Internal Dose (µg/d)	Odds Ratio	Lower CI	Upper CI
	Above vs. Below Median			
Danileviciute et al. 2012‡ ‡	Median: 0.1424	1.45	0.67	3.13
	Median: 0.1424 - Specific for GSTT1-1	1.35	0.57	3.20
	Median: 0.1424 - Specific for GSTT1-0	7.30	0.14	391
	Median: 0.1424 - Specific for GSTM1-1	0.35	0.10	1.28
	Median: 0.1424 - Specific for GSTM1-0	5.06	1.50	17.05
Villanueva et al. 2011*	10% increase in total residential uptake	1.00	0.99	1.02
Grazuleviciene et al. 2011‡ ‡	0.0249–0.2868	2.12	1.11	4.02
	0.2868–2.1328	2.13	1.15	3.92
	Continuous (0.1 µg/d)	1.09	1.01	1.18



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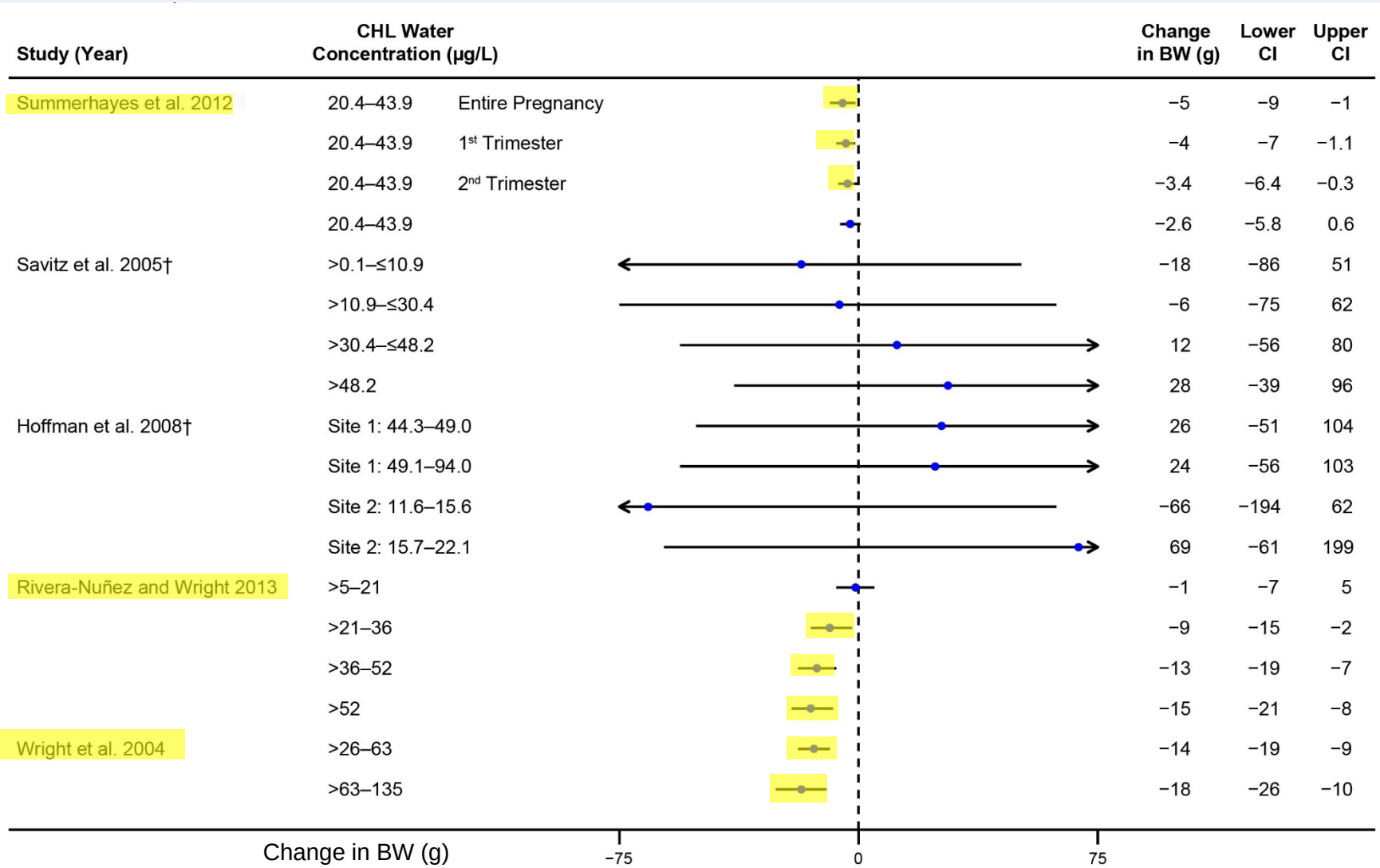
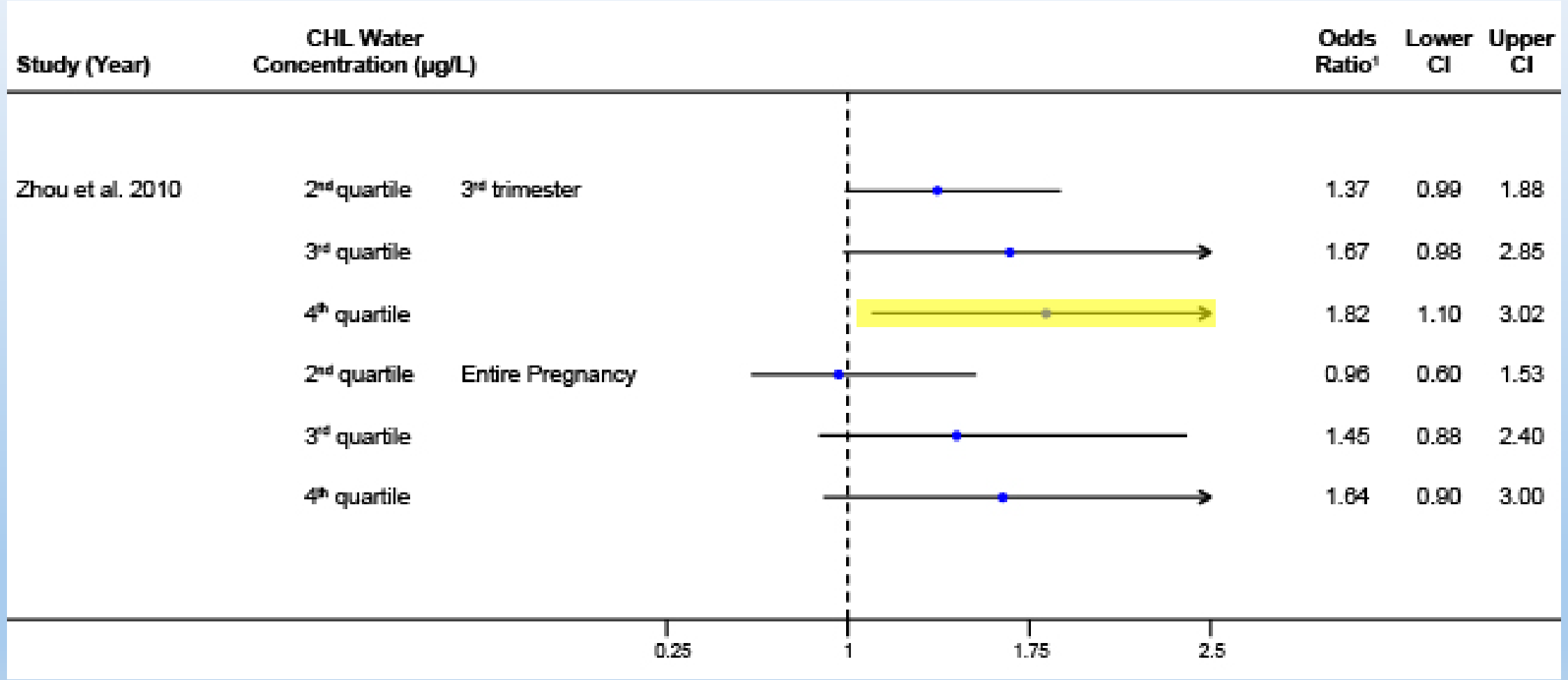
CHL exposure as water concentration and BW

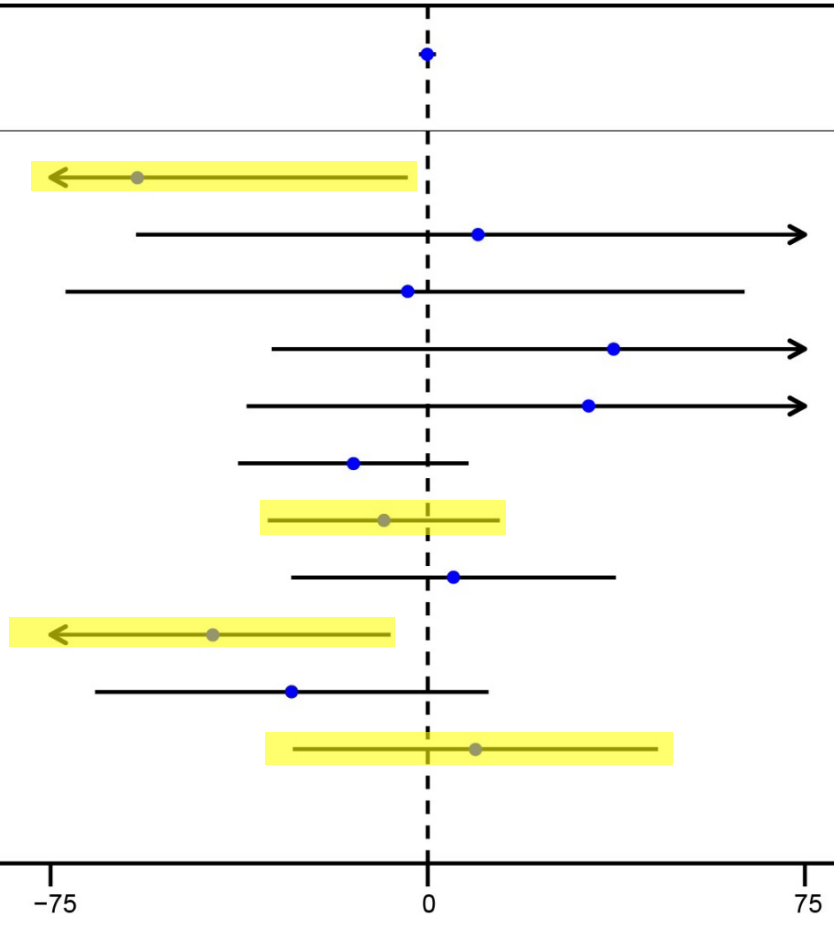


CHL exposure as water concentration and BW (cont'd)



CHL exposure as estimated internal dose and BW

Study (Year)	CHL Estimated Internal Dose (µg/d)	Change in BW (g)	Lower CI	Upper CI
Villanueva et al. 2011*	10% increase in total residential uptake	−0.07	−1.00	0.85
Grazuleviciene et al. 2011‡ ‡	Continuous (0.1 µg/d)	−57.8	−111.6	−4.0
Savitz et al. 2005†	>0–≤0.2	10	−58	78
	>0.2–≤0.8	−4	−72	63
	>0.8–≤1.3	37	−31	105
	>1.3	32	−36	100
Smith et al. 2015	Total: ≥0.91–<1.56	−14.8	−37.7	8.1
	Total: ≥1.56	−8.7	−31.8	14.3
	Pakistani Origin: ≥0.91–<1.56	5.1	−27.1	37.4
	Pakistani Origin: ≥1.56	−42.8	−78.2	−7.4
	White British: ≥0.91–<1.56	−27.0	−66.1	12.1
	White British: ≥1.56	9.5	−26.8	45.8



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Summary of SAB, SB, and BD studies

SAB (n = 3)

- None of the studies showed significant increased risk (Waller et al.1998; Wennborg et al. 2000; Savitz et al. 2005)
  - Reanalysis of Wennborg et al. 2000
    - data yielded a significant increased odds ratio associated with working in a lab using chloroform (OR = 2.1 (95% CI 1.1, 4.0))

SB (n = 4)

- 3 studies observed increased risk (King et al. 2000; Dodds et al. 2004; Toledano et al. 2005)
  - Toledano et al. 2005 observed a small but significant increased risk (OR = 1.12 (95% CI 1.02,1.23)
- 1 study with changes in water treatment methods observed no significant change in rates (Iszatt et al. 2014)

BD (n = 3)

- 2 studies reported no significant findings (Iszatt et al. 2011; Grazuleviciene et al. 2013)
- 1 study (Dodds and King, 2001) reported an association with chromosomal abnormalities (OR = 1.9 (95% CI 1.1, 3.3)
  - sampled participants' tap water

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Summary of Postnatal Weight Gain

- Botton et al. 2015
  - CHL exposure as estimated internal dose
  - significant decrease (-151 g) over 6 months in the community with highest CHL water concentration for exposure through ingestion

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Summary of Menstrual Cycle Function and Fertility

Menstrual cycle function

- no significant association between CHL exposure and cycle length (Windham et al. 2003)

Fertility

- no association was observed for time to pregnancy (Dahl et al. 1999)

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Associations between CHL Exposure and Sperm Parameters

Study	Exposure	Sperm concentration (million/ml)	Sperm count (million)	Sperm motility (%) and motile sperm concentration	Sperm Motion
Zeng et al. 2014 † †	Ingestion (µg/d) 0.019	-0.28 (-0.53, -0.02)	-12 (-0.24, -0.01)	No significant findings	Increasing straight-line and curvilinear velocity
Iszatt et al. 2013	Water conc (µg/L)	No significant findings	–	No significant findings	–
Zeng et al. 2013 † †	Blood conc (ng/L) >66.35	No significant findings	No significant findings	No significant findings	Straight line velocity 1.95 (0.46, 3.44) P for trend = 0.01
Chang et al. 2001 (Case report)	Air samples Active = 8.5 ppm Passive = 450 ppm	–	Time since end of exposure		Path velocity
			≈ 3 months 68.6	26%	35
			≈ 4 months 73.8	11%	40
			≈ 6 months 90.6	40%	50