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### **Supplemental Material**

#### **Drinking Water Disinfection by-Products and Congenital Malformations: A Nationwide Register-Based Prospective Study**

Melle Säve-Söderbergh, Jonas Toljander, Carolina Donat-Vargas, and Agneta Åkesson

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**Table S2.** Associations between total trihalomethanes (TTHM) in municipal drinking water during the 1<sup>st</sup> trimester of pregnancy and major congenital malformations, expressed as odds ratios (OR) and 95% confidence interval (CI), and using <5 µg TTHM/l as reference.

Table S1 Prevalence of major and minor malformations (prevalence >1.5 cases/10,000 births) by chlorination treatment (no chlorination, hypochlorite or chloramine) and exposure to total trihalomethanes (TTHM) in drinking water during the 1<sup>st</sup> trimester of pregnancy. The study included a total of 623,468 children born during 2005-2015 to mothers living in large urban areas (>10,000 inhabitants) in Sweden.

Malformations	No chlorination n (%)	Hypochlorite			Chloramine		
		<5 µg TTHM/L n (%)	5-15 µg TTHM/L n (%)	>15 µg TTHM/L n (%)	<5 µg TTHM/L n (%)	5-15 µg TTHM/L n (%)	>15 µg TTHM/L n (%)
n	65,154	30,883	54,144	48,044	188,428	18,934	40,135
<b>All malformations</b>	1,373 (2.1)	680 (2.2)	1,094 (2.0)	936 (1.9)	3,992 (2.1)	416 (2.2)	1,042 (2.6)
<b>Nervous system</b>	37 (0.06)	22 (0.07)	30 (0.06)	20 (0.04)	78 (0.04)	9 (0.05)	36 (0.09)
Neural Tube Defects	17 (0.03)	6 (0.02)	11 (0.02)	9 (0.02)	15 (0.008)	4 (0.02)	8 (0.02)
<b>Eye</b>	12 (0.02)	8 (0.03)	28 (0.05)	10 (0.02)	37 (0.02)	4 (0.02)	10 (0.01)
<b>Ear, face and neck</b>	15 (0.02)	8 (0.03)	17 (0.03)	18 (0.04)	58 (0.03)	10 (0.05)	18 (0.04)
<b>Congenital Heart Defects</b>	586 (0.9)	262 (0.8)	453 (0.8)	372 (0.8)	1355 (0.7)	139 (0.7)	345 (0.9)
Severe congenital heart defects	103 (0.2)	33 (0.1)	87 (0.2)	66 (0.1)	204 (0.1)	29 (0.2)	61 (0.2)
Transposition of great vessels	21 (0.03)	3 (0.01)	12 (0.02)	12 (0.02)	36 (0.02)	6 (0.03)	12 (0.03)
Ventricular septal defect	312 (0.5)	151 (0.5)	258 (0.5)	214 (0.4)	740 (0.4)	67 (0.4)	198 (0.5)
Atrial septal defect	147 (0.2)	35 (0.1)	81 (0.1)	69 (0.1)	150 (0.08)	28 (0.1)	88 (0.2)
Atrioventricular septal Defect	19 (0.03)	4 (0.01)	16 (0.03)	11 (0.02)	42 (0.02)	6 (0.03)	13 (0.03)
Tetralogy of Fallot	15 (0.02)	5 (0.02)	12 (0.02)	13 (0.03)	36 (0.02)	2 (0.01)	8 (0.02)
Pulmonary valve stenosis	21 (0.03)	7 (0.02)	15 (0.03)	9 (0.02)	44 (0.02)	3 (0.02)	17 (0.04)
Coarctation of aorta	16 (0.02)	6 (0.02)	19 (0.04)	12 (0.02)	32 (0.02)	6 (0.03)	15 (0.04)
Patent ductus arteriosus as only in full-term infants	67 (0.1)	28 (0.1)	38 (0.07)	34 (0.07)	103 (0.06)	18 (0.01)	43 (0.1)
<b>Respiratory</b>	9 (0.01)	6 (0.02)	10 (0.02)	6 (0.01)	39 (0.02)	5 (0.03)	6 (0.01)
<b>Oro-facial clefts</b>	107 (0.2)	44 (0.1)	87 (0.2)	64 (0.1)	247 (0.1)	27 (0.1)	51 (0.1)
Cleft lip with or without cleft palate	66 (0.1)	26 (0.08)	54 (0.1)	31 (0.06)	151 (0.08)	15 (0.08)	31 (0.08)
Cleft palate	42 (0.06)	18 (0.06)	54 (0.06)	34 (0.07)	97 (0.05)	11 (0.06)	20 (0.05)
<b>Digestive system</b>	87 (0.1)	37 (0.1)	70 (0.1)	77 (0.2)	202 (0.1)	14 (0.07)	54 (0.1)
Oesophageal atresia with or without trachea- oesophageal fistula	18 (0.03)	9 (0.03)	10 (0.02)	14 (0.03)	38 (0.02)	2 (0.01)	9 (0.02)
Ano-rectal atresia and stenosis	20 (0.03)	7 (0.02)	18 (0.03)	17 (0.04)	47 (0.02)	1 (0.005)	8 (0.02)
Diaphragmatic hernia	11 (0.02)	6 (0.02)	9 (0.02)	9 (0.02)	27 (0.01)	2 (0.01)	8 (0.02)
<b>Abdominal wall defects</b>	19 (0.03)	10 (0.03)	13 (0.02)	13 (0.03)	28 (0.01)	1 (0.005)	7 (0.02)
<b>Urinary</b>	101 (0.2)	63 (0.2)	72 (0.1)	62 (0.1)	668 (0.4)	66 (0.3)	128 (0.3)
Congenital hydronephrosis	71 (0.1)	43 (0.1)	46 (0.08)	42 (0.08)	562 (0.3)	60 (0.3)	89 (0.2)
<b>Genital</b>	161 (0.2)	97 (0.3)	167 (0.3)	145 (0.3)	544 (0.3)	63 (0.3)	178 (0.4)
Hypospadias	150 (0.2)	94 (0.3)	154 (0.3)	134 (0.3)	510 (0.3)	60 (0.3)	164 (0.4)
<b>Limbs</b>	274 (0.4)	146 (0.5)	230 (0.4)	184 (0.4)	864 (0.5)	91 (0.5)	232 (0.6)
Limb reduction defects	15 (0.02)	11 (0.04)	21 (0.04)	13 (0.03)	48 (0.03)	13 (0.07)	8 (0.02)
Club foot – talipes equinovarus	64 (0.1)	43 (0.1)	58 (0.1)	46 (0.1)	172 (0.09)	16 (0.08)	50 (0.1)
Hip dislocation and /or dysplasia	51 (0.08)	14 (0.05)	33 (0.06)	46 (0.1)	153 (0.08)	16 (0.08)	66 (0.2)
Polydactyly	71 (0.1)	33 (0.1)	54 (0.1)	45 (0.09)	220 (0.1)	19 (0.1)	57 (0.1)
Syndactyly	40 (0.06)	28 (0.09)	33 (0.06)	24 (0.05)	158 (0.08)	20 (0.1)	36 (0.09)
<b>Chromosomal</b>	88 (0.1)	39 (0.1)	61 (0.1)	68 (0.1)	245 (0.1)	24 (0.1)	49 (0.1)
Down syndrome	68 (0.1)	29 (0.09)	49 (0.09)	57 (0.1)	190 (0.1)	19 (0.1)	33 (0.08)

Table S2 Associations between total trihalomethanes (TTHM) in municipal drinking water during the 1<sup>st</sup> trimester of pregnancy and major congenital malformations, expressed as odds ratios (OR) and 95% confidence interval (CI), and using <5 µg TTHM/l as reference.

Congenital malformations	Chlorination treatment		<5 µg TTHM/l OR (95% CI)	5-15 µg TTHM/l OR (95% CI)	>15 µg TTHM/l OR (95% CI)	p-trend
Nervous system	Hypochlorite	Cases (n)	22	30	20	
		Non-cases (n)	30,861	54,114	48,024	
		Multivariable adjusted	1.00 (ref)	0.81 (0.44-1.50)	0.56 (0.28-1.11)	0.1
	Chloramine	Cases (n)	78	9	36	
		Non-cases (n)	188,350	18,925	40,099	
		Multivariable adjusted	1.00 (ref)	0.81 (0.34-1.90)	1.99 (1.29-3.08)	0.02
Heart Defects	Hypochlorite	Cases (n)	2,218	1,185	723	
		Non-cases (n)	287,697	177,997	88,494	
		Multivariable adjusted	1.00 (ref)	1.02 (0.86-1.20)	0.94 (0.79-1.12)	0.5
	Chloramine	Cases (n)	1,355	139	345	
		Non-cases (n)	187,073	18,795	39,790	
		Multivariable adjusted	1.00 (ref)	0.98 (0.80-1.20)	1.24 (1.09-1.41)	0.001
Oro-facial clefts	Hypochlorite	Cases (n)	44	87	64	
		Non-cases (n)	30,839	54,057	47,980	
		Multivariable adjusted	1.00 (ref)	1.08 (0.73-1.58)	0.99 (0.66-1.48)	0.9
	Chloramine	Cases (n)	247	27	51	
		Non-cases (n)	188,181	18,907	40,084	
		Multivariable adjusted	1.00 (ref)	1.13 (0.74-1.73)	0.93 (0.67-1.29)	0.6
Digestive system	Hypochlorite	Cases (n)	37	70	77	
		Non-cases (n)	30,846	54,074	47,967	
		Multivariable adjusted	1.00 (ref)	1.01 (0.64-1.58)	1.34 (0.87-2.08)	0.2
	Chloramine	Cases (n)	202	14	54	
		Non-cases (n)	188,226	18,920	40,081	
		Multivariable adjusted	1.00 (ref)	0.63 (0.34-1.16)	1.26 (0.91-1.76)	0.2
Urinary	Hypochlorite	Cases (n)	63	72	62	
		Non-cases (n)	30,820	54,072	47,982	
		Multivariable adjusted	1.00 (ref)	0.64 (0.44-0.92)	0.65 (0.45-0.94)	0.02
	Chloramine	Cases (n)	668	66	128	
		Non-cases (n)	187,760	18,868	40,007	
		Multivariable adjusted	1.00 (ref)	1.06 (0.80-1.40)	0.89 (0.72-1.09)	0.3
Genital	Hypochlorite	Cases (n)	97	167	145	
		Non-cases (n)	30,786	53,977	47,899	
		Multivariable adjusted	1.00 (ref)	0.96 (0.74-1.25)	0.91 (0.69-1.19)	0.5
	Chloramine	Cases (n)	544	63	178	
		Non-cases (n)	187,884	18,871	39,957	
		Multivariable adjusted	1.00 (ref)	1.21 (0.92-1.60)	1.50 (1.24-1.81)	<0.001
Limbs	Hypochlorite	Cases (n)	146	230	194	
		Non-cases (n)	30,737	53,914	47,850	
		Multivariable adjusted	1.00 (ref)	0.89 (0.71-1.11)	0.87 (0.70-1.10)	0.2
	Chloramine	Cases (n)	864	91	232	
		Non-cases (n)	187,564	18,843	39,903	
		Multivariable adjusted	1.00 (ref)	0.96 (0.75-1.23)	1.27 (1.08-1.49)	0.004

Chromosomal	Hypochlorite	Cases (n)	39	61	68	
		Non-cases (n)	30,844	54,083	47,976	
		Multivariable adjusted	1.00 (ref)	0.94 (0.60-1.47)	1.15 (0.74-1.79)	0.6
	Chloramine	Cases (n)	245	24	49	
		Non-cases (n)	188,183	18,910	40,086	
		Multivariable adjusted	1.00 (ref)	0.80 (0.48-1.33)	1.09 (0.79-1.50)	0.6

Models multivariable-adjusted for the following factors: maternal age, BMI (body mass index), diabetes, any use of teratogenic drugs, parity, smoking at registration to the antenatal care, highest attained education and household income using inverse probability weighting.