Supplementary material

Search strategies used in OvidSP MEDLINE, OvidSP PubMed, OvidSP EMBASE, Global Health, Scopus, ISI Web of Science, GreenFILE, and AGRIS

Ovid MEDLINE
1990 to February Week 4 2021

1	nitrate*.kf,tw.	53889
2	nitrite*.kf,tw.	30929
3	no3.kf,tw.	11635
4	no3-n.kf,tw.	2401
5	no2.kf,tw.	11362
6	no2-n.kf,tw.	770
7	nitroso.kf,tw.	7475
8	nitrogen.kf,tw.	155149
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	229550
10	"river*1".kf,tw.	52951
11	(well adj water*1).kf,tw.	1952
12	(drinking adj water).kf,tw.	45362
13	drinkingwater.kf,tw.	3
14	groundwater.kf,tw.	16843
15	(fresh adj water).kf,tw.	5293
16	freshwater.kf,tw.	31614
17	(ground adj water).kf,tw.	2809
18	"aquifer*".kf,tw.	6374
19	(bottled adj water*1).kf,tw.	982
20	lake*.kf,tw.	32746
21	(surface adj water*1).kf,tw.	16878
22	(public adj water*1).kf,tw.	893
23	(water adj suppl*3).kf,tw.	12029
24	(water adj (pollutant*1 or pollution)).kf,tw.	4049
25	"fertili#er*1".kf,tw.	12324
26	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	195887
27	9 and 26	17145
28	limit 27 to humans	1823
29	limit 28 to yr="1990 -2021"	1610

PubMed
01/01/1990 – 28/02/2021
(nitrate OR nitrates OR nitrite OR nitrites OR no3 OR no3-n OR no2 OR no2-n OR nitrogen OR nitroso) AND (river OR rivers OR lake OR lake* OR "well water" OR "well waters" OR "drinking water" OR "drinkingwater" OR "ground

water" OR "groundwater" OR "fresh water" OR freshwater OR aquifer OR "bottled water" OR "surface water" OR "public water" OR "water supply" OR "water supplies" OR "water pollutant*" OR "water pollution" OR fertiliser OR fertilizer)
Limit to Humans

2,712 documents

Ovid EMBASE
1990 to March Week 1 2021

1	nitrate*.kw,tw.	85356
2	nitrite*.kw,tw.	43535
3	no3.kw,tw.	25045
4	no3-n.kw,tw.	4185
5	no2.kw,tw.	24294
6	no2-n.kw,tw.	1254
7	nitroso.kw,tw.	9590
8	nitrogen.kw,tw.	243695
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	365792
10	"river*1".kw,tw.	80590
11	(well adj water*1).kw,tw.	3079
12	(drinking adj water).kw,tw.	70214
13	drinkingwater.kw,tw.	85
14	groundwater.kw,tw.	26794
15	(ground adj water).kw,tw.	5892
16	(fresh adj water).kw,tw.	8536
17	freshwater.kw,tw.	41664
18	lake*.kw,tw.	50412
19	"aquifer*".kw,tw.	9887
20	(bottled adj water*1).kw,tw.	1392
21	(surface adj water*1).kw,tw.	25477
22	(public adj water*1).kw,tw.	1354
23	(water adj suppl*3).kw,tw.	16601
24	(water adj (pollutant*1 or pollution)).kw,tw.	7492
25	"fertili#er*1".kw,tw.	20089
26	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	297076
27	9 and 26	27345
28	limit 27 to humans	2286
29	limit 28 to yr="1990 - 2021"	2103

Web of Science

# 35	1,329	#34 NOT #33 Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 34	2,377	#32 AND #20 Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 33	4,941,874	#31 OR #30 OR #29 OR #28 OR #27 Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 32	9,647,719	#26 OR #25 OR #24 OR #23 OR #22 OR #21 Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 31	1,551,551	TS=("animal" OR "animals" OR "fish" OR "insects" OR "invertebrates" OR "crustaceans") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 30	160,570	TS=("monkey" OR "monkeys" OR "primate" OR "primates") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 29	834,598	TS=("dog" OR "dogs" OR "cat" OR "cats" OR "canine" OR "feline" OR "horse" OR "horses " OR "equine" OR "cattle" OR "bovine" OR "cow" OR "cows" OR "bull" OR "bulls") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 28	500,059	TS=("goat" OR "goats" OR "sheep" OR "ovine" OR "lambs" OR "lamb" OR "pig" OR "pigs" OR "swine" OR "piglet" OR "piglets" OR "porcine") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 27	2,966,470	TS=("rat" OR "rats" OR "mouse" OR "mice" OR "murine" OR "rodent" OR "rodents" OR "rabbit" OR "rabbits") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 26	6,549,139	TS=("participant" OR "participants" OR "patient" OR "patients") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 25	1,368,857	TS=("adult" OR "adults") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 24	563,155	TS=("pregnant" OR "pregnancy" OR "pregnancies" OR "mother" OR "mothers") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 23	1,933,130	TS=("woman" OR "women" OR "female" OR "females") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 22	1,666,854	TS=("man" OR "men" OR "male" OR "males") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 21	1,395,955	TS=("infant" OR "infants" OR "child" OR "children") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 20	99,214	#19 AND #7 Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 19	822,106	#18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 18	65,903	TS=("fertili?er" OR "fertil?ers") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 17	12,547	TS=("water pollutant" OR "water pollutants" OR "water pollution") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 16	30,345	TS=("water supply" OR "water supplies") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 15	1,517	TS=("public water" OR "public waters") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 14	72,112	TS=("surface water" OR "surface waters") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 13	1,873	TS=("bottled water" OR "bottled waters") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021

# 12	49,574	TS=("aquifer" OR "aquifers") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 11	117,626	TS=("ground water" OR "groundwater") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 10	84,054	TS=("drinking water" OR "drinkingwater") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 9	141,051	TS=("well water" or "well waters" OR "freshwater" OR "fresh water") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 8	456,465	TS=("river" OR "rivers" OR "lake" OR "lakes") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 7	840,097	#6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 6	625,377	TS="nitrogen" Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 5	10,029	TS="nitroso" Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 4	50,546	TS=("NO2" OR "NO2-N") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 3	76,553	TS=("NO3" OR "NO3-N") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 2	53,275	TS=("nitrite" OR "nitrites") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021
# 1	176,939	TS=("nitrate" OR "nitrates") Indexes=SCI-EXPANDED, ESCI Timespan=1990-2021

Global Health
1990 to March Week 1 2021

1	nitrate*.ab,ti,sh.	18606
2	nitrite*.ab,ti,sh.	10345
3	no3.ab,ti,sh.	4398
4	no3-n.ab,ti,sh.	1058
5	no2.ab,ti,sh.	5128
6	no2-n.ab,ti,sh.	336
7	nitroso.ab,ti,sh.	1073
8	nitrogen.ab,ti,sh.	49616
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	73225
10	"river*1".ab,ti,sh.	33474
11	(well adj water*1).ab,ti,sh.	2303
12	(drinking adj water).ab,ti,sh.	39459
13	drinkingwater.ab,ti,sh.	13
14	groundwater.ab,ti,sh.	14092
15	(ground adj water).ab,ti,sh.	2459
16	(fresh adj water).ab,ti,sh.	4402

17	freshwater.ab,ti,sh.	9182
18	"aquifer*".ab,ti,sh.	3667
19	(bottled adj water*1).ab,ti,sh.	1170
20	lake*.ab,ti,sh.	29186
21	(surface adj water*1).ab,ti,sh.	9281
22	(public adj water*1).ab,ti,sh.	1147
23	(water adj suppl*3).ab,ti,sh.	16045
24	(water adj (pollutant*1 or pollution)).ab,ti,sh.	5109
25	"fertili#er*1".ab,ti,sh.	8680
26	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	132722
27	9 and 26	10580
28	(infant*1 or child or children).ab,ti.	429231
29	(m#n or male*1).ab,ti.	603232
30	(wom#n or female*1).ab,ti.	517816
31	(pregnant or pregnanc*3 or mother*1).ab,ti.	173935
32	adult*1.ab,ti.	305772
33	(participant*1 or patient*s or subject*1).ab,ti.	1086605
34	28 or 29 or 30 or 31 or 32 or 33	2021132
35	27 and 34	1460
36	limit 35 to yr="1990 - 2021"	1092

Scopus
1990 – Feb 2021

((TITLE-ABS-KEY (nitrate)) OR (TITLE-ABS-KEY (nitrite)) OR (TITLE-ABS-KEY (no3 OR no3-n)) OR (TITLE-ABS-KEY (no2 OR no2-n)) OR (TITLE-ABS-KEY (nitrogen)) OR (TITLE-ABS-KEY (nitroso))) AND ((TITLE-ABS-KEY (river)) OR (TITLE-ABS-KEY (lake)) OR (TITLE-ABS-KEY ("well water" OR "well waters")) OR (TITLE-ABS-KEY ("drinking water" OR "drinkingwater")) OR (TITLE-ABS-KEY ("ground water" OR "groundwater")) OR (TITLE-ABS-KEY ("fresh water")) OR (TITLE-ABS-KEY (freshwater)) OR (TITLE-ABS-KEY (aquifer)) OR (TITLE-ABS-KEY ("bottled water")) OR (TITLE-ABS-KEY ("surface water")) OR (TITLE-ABS-KEY ("public water")) OR (TITLE-ABS-KEY ("water supply" OR "water supplies")) OR (TITLE-ABS-KEY ("water pollutant" OR "water pollution")) OR (TITLE-ABS-KEY (fertili?er))) AND ((TITLE-ABS-KEY (infant OR child OR children)) OR (TITLE-ABS-KEY (m?n OR male)) OR (TITLE-ABS-KEY (wom?n OR female)) OR (TITLE-ABS-KEY (pregnant OR pregnancy OR pregnancies OR mother)) OR (TITLE-ABS-KEY (adult)) OR (TITLE-ABS-KEY (participant OR patient OR subject))) AND NOT ((TITLE-ABS-KEY (rat OR mouse OR mice OR murine OR rodent OR rabbit)) OR (TITLE-ABS-KEY (goat OR sheep OR ovine OR lamb OR pig OR swine OR piglet OR porcine)) OR (TITLE-ABS-KEY (dog OR cat OR canine OR feline OR horse OR equine OR cattle OR bovine OR cow OR bull)) OR (TITLE-ABS-KEY (monkey OR primate)) OR (TITLE-ABS-KEY (animal OR insect OR invertebrate OR fish OR crustacean)))

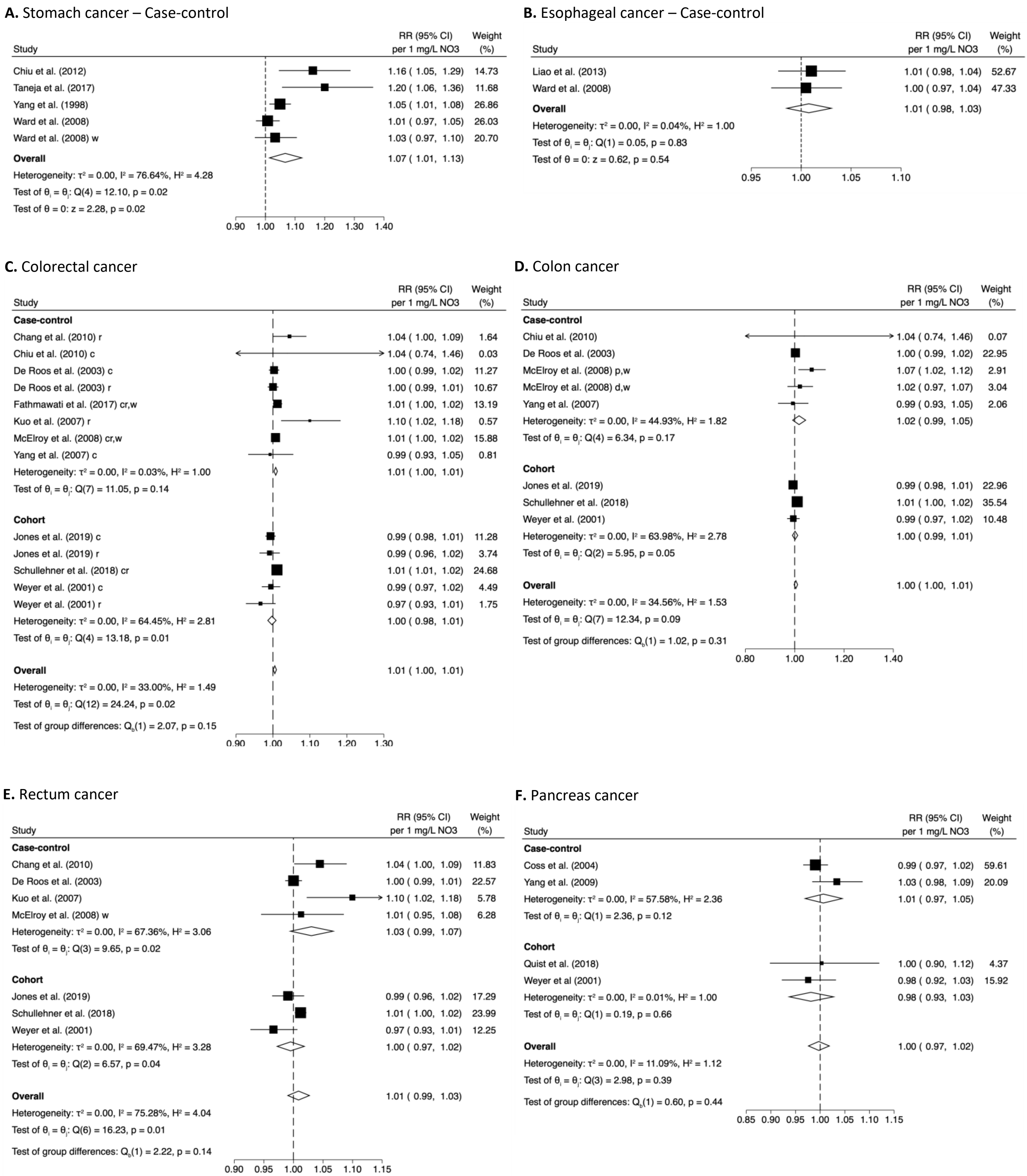
5,743 documents

GreenFILE
1990-Feb 2021

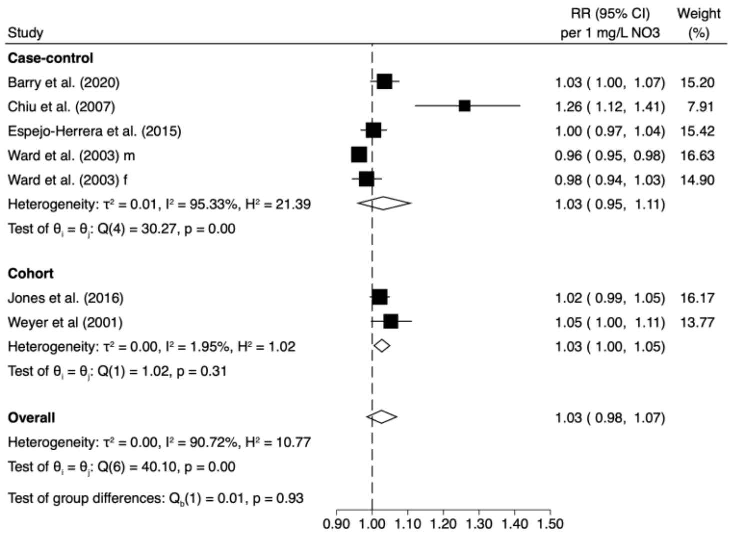
#	Query	Results
S26	S5 AND S24 AND S25	1,387
S25	S18 OR S19 OR S20 OR S21 OR S22 OR S23	108,413
S24	S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	169,826
S23	participant participants patient patients subject subjects	25,984
S22	adult adults	17,419
S21	pregnant pregnancy pregnancies mother mothers	12,557
S20	wom?n female females	20,652
S19	m?n male males	44,685
S18	infant infants child children	19,072
S17	fertili?er*	24,001
S16	"water pollutant" "water pollutants" " water pollution"	32,840
S15	"water supply" "water supplies"	20,500
S14	"public water" "public waters"	443
S13	"surface water" "surface waters"	12,901
S12	"bottled water"	1,097
S11	aquifer freshwater "fresh water"	30,452
S10	"ground water" groundwater	19,476
S9	"drinking water" drinkingwater	12,661
S8	"well water" "well waters"	688
S7	lake lakes	31,0292
S6	river rivers	52,753
S5	S1 OR S2 OR S3 OR S4	49,847
S4	nitrogen	38,834
S3	nitroso	161
S2	NO3 NO2 NO3-N NO2-N	6,871
S1	nitrate nitrates nitrite nitrites	15,382

AGRIS
(nitrate OR nitrates OR nitrite OR nitrites OR no3 OR no3-n OR no2 OR no2-n OR nitrogen OR nitroso) AND (river OR rivers OR lake OR lake* OR "well water" OR "well waters" OR "drinking water" OR "drinkingwater" OR "ground water" OR "groundwater" OR "fresh water" OR freshwater OR aquifer OR "bottled water" OR "surface water" OR "public water" OR "water supply" OR "water supplies" OR "water pollutant*" OR "water pollution" OR fertiliser OR fertilizer) AND (infant OR infants OR child OR children OR man OR men OR male OR male OR woman OR women OR female OR females OR pregnant OR pregnancy OR pregnancies OR mother OR mothers OR adult OR adults OR participant OR participants OR patient OR patients OR subject OR subjects)

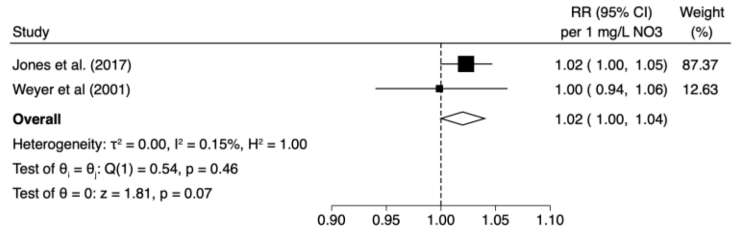
551 hits after 1990


A. Stomach cancer – Case-control
Study
RR (95% CI) per 1 mg/L NO3
Weight (%)
Chiu et al. (2012) 1.16 (1.05, 1.29) 14.73
Taneja et al. (2017) 1.20 (1.06, 1.36) 11.68
Yang et al. (1998) 1.05 (1.01, 1.08) 26.86
Ward et al. (2008) 1.01 (0.97, 1.05) 26.03
Ward et al. (2008) w 1.03 (0.97, 1.10) 20.70
Overall 1.07 (1.01, 1.13)
Heterogeneity: τ^2 = 0.00, I^2 = 76.64%, H^2 = 4.28
Test of $\theta_i = \theta_j$: Q(4) = 12.10, p = 0.02
Test of θ = 0: z = 2.28, p = 0.02
0.90 1.00 1.10 1.20 1.30 1.40
B. Esophageal cancer – Case-control
Study
RR (95% CI) per 1 mg/L NO3
Weight (%)
Liao et al. (2013) 1.01 (0.98, 1.04) 52.67
Ward et al. (2008) 1.00 (0.97, 1.04) 47.33
Overall 1.01 (0.98, 1.03)
Heterogeneity: τ^2 = 0.00, I^2 = 0.04%, H^2 = 1.00
Test of $\theta_i = \theta_j$: Q(1) = 0.05, p = 0.83
Test of θ = 0: z = 0.62, p = 0.54
0.95 1.00 1.05 1.10
C. Colorectal cancer
Study
RR (95% CI) per 1 mg/L NO3
Weight (%)
Case-control
Chang et al. (2010) r 1.04 (1.00, 1.09) 1.64
Chiu et al. (2010) c 1.04 (0.74, 1.46) 0.03
De Roos et al. (2003) c 1.00 (0.99, 1.02) 11.27
De Roos et al. (2003) r 1.00 (0.99, 1.01) 10.67
Fathmawati et al. (2017) cr,w 1.01 (1.00, 1.02) 13.19
Kuo et al. (2007) r 1.10 (1.02, 1.18) 0.57
McElroy et al. (2008) cr,w 1.01 (1.00, 1.02) 15.88
Yang et al. (2007) c 0.99 (0.93, 1.05) 0.81
Heterogeneity: τ^2 = 0.00, I^2 = 0.03%, H^2 = 1.00 1.01 (1.00, 1.01)
Test of $\theta_i = \theta_j$: Q(7) = 11.05, p = 0.14
Cohort
Jones et al. (2019) c 0.99 (0.98, 1.01) 11.28
Jones et al. (2019) r 0.99 (0.96, 1.02) 3.74
Schullehner et al. (2018) cr 1.01 (1.01, 1.02) 24.68
Weyer et al. (2001) c 0.99 (0.97, 1.02) 4.49
Weyer et al. (2001) r 0.97 (0.93, 1.01) 1.75
Heterogeneity: τ^2 = 0.00, I^2 = 64.45%, H^2 = 2.81 1.00 (0.98, 1.01)
Test of $\theta_i = \theta_j$: Q(4) = 13.18, p = 0.01
Overall 1.01 (1.00, 1.01)
Heterogeneity: τ^2 = 0.00, I^2 = 33.00%, H^2 = 1.49
Test of $\theta_i = \theta_j$: Q(12) = 24.24, p = 0.02
Test of group differences: $Q_b(1)$ = 2.07, p = 0.15
0.90 1.00 1.10 1.20 1.30
D. Colon cancer
Study
RR (95% CI) per 1 mg/L NO3
Weight (%)
Case-control
Chiu et al. (2010) 1.04 (0.74, 1.46) 0.07
De Roos et al. (2003) 1.00 (0.99, 1.02) 22.95
McElroy et al. (2008) p,w 1.07 (1.02, 1.12) 2.91
McElroy et al. (2008) d,w 1.02 (0.97, 1.07) 3.04
Yang et al. (2007) 0.99 (0.93, 1.05) 2.06
Heterogeneity: τ^2 = 0.00, I^2 = 44.93%, H^2 = 1.82 1.02 (0.99, 1.05)
Test of $\theta_i = \theta_j$: Q(4) = 6.34, p = 0.17
Cohort
Jones et al. (2019) 0.99 (0.98, 1.01) 22.96
Schullehner et al. (2018) 1.01 (1.00, 1.02) 35.54
Weyer et al. (2001) 0.99 (0.97, 1.02) 10.48
Heterogeneity: τ^2 = 0.00, I^2 = 63.98%, H^2 = 2.78 1.00 (0.99, 1.01)
Test of $\theta_i = \theta_j$: Q(2) = 5.95, p = 0.05
Overall 1.00 (1.00, 1.01)
Heterogeneity: τ^2 = 0.00, I^2 = 34.56%, H^2 = 1.53
Test of $\theta_i = \theta_j$: Q(7) = 12.34, p = 0.09
Test of group differences: $Q_b(1)$ = 1.02, p = 0.31
0.80 1.00 1.20 1.40
E. Rectum cancer
Study
RR (95% CI) per 1 mg/L NO3
Weight (%)
Case-control
Chang et al. (2010) 1.04 (1.00, 1.09) 11.83
De Roos et al. (2003) 1.00 (0.99, 1.01) 22.57
Kuo et al. (2007) 1.10 (1.02, 1.18) 5.78
McElroy et al. (2008) w 1.01 (0.95, 1.08) 6.28
Heterogeneity: τ^2 = 0.00, I^2 = 67.36%, H^2 = 3.06 1.03 (0.99, 1.07)
Test of $\theta_i = \theta_j$: Q(3) = 9.65, p = 0.02
Cohort
Jones et al. (2019) 0.99 (0.96, 1.02) 17.29
Schullehner et al. (2018) 1.01 (1.00, 1.02) 23.99
Weyer et al. (2001) 0.97 (0.93, 1.01) 12.25
Heterogeneity: τ^2 = 0.00, I^2 = 69.47%, H^2 = 3.28 1.00 (0.97, 1.02)
Test of $\theta_i = \theta_j$: Q(2) = 6.57, p = 0.04
Overall 1.01 (0.99, 1.03)
Heterogeneity: τ^2 = 0.00, I^2 = 75.28%, H^2 = 4.04
Test of $\theta_i = \theta_j$: Q(6) = 16.23, p = 0.01
Test of group differences: $Q_b(1)$ = 2.22, p = 0.14
0.90 0.95 1.00 1.05 1.10 1.15
F. Pancreas cancer
Study
RR (95% CI) per 1 mg/L NO3
Weight (%)
Case-control
Coss et al. (2004) 0.99 (0.97, 1.02) 59.61
Yang et al. (2009) 1.03 (0.98, 1.09) 20.09
Heterogeneity: τ^2 = 0.00, I^2 = 57.58%, H^2 = 2.36 1.01 (0.97, 1.05)
Test of $\theta_i = \theta_j$: Q(1) = 2.36, p = 0.12
Cohort
Quist et al. (2018) 1.00 (0.90, 1.12) 4.37
Weyer et al (2001) 0.98 (0.92, 1.03) 15.92
Heterogeneity: τ^2 = 0.00, I^2 = 0.01%, H^2 = 1.00 0.98 (0.93, 1.03)
Test of $\theta_i = \theta_j$: Q(1) = 0.19, p = 0.66
Overall 1.00 (0.97, 1.02)
Heterogeneity: τ^2 = 0.00, I^2 = 11.09%, H^2 = 1.12
Test of $\theta_i = \theta_j$: Q(3) = 2.98, p = 0.39
Test of group differences: $Q_b(1)$ = 0.60, p = 0.44
0.85 0.90 0.95 1.00 1.05 1.10 1.15

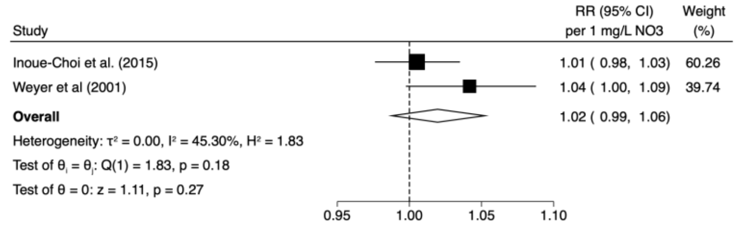
G. Bladder cancer



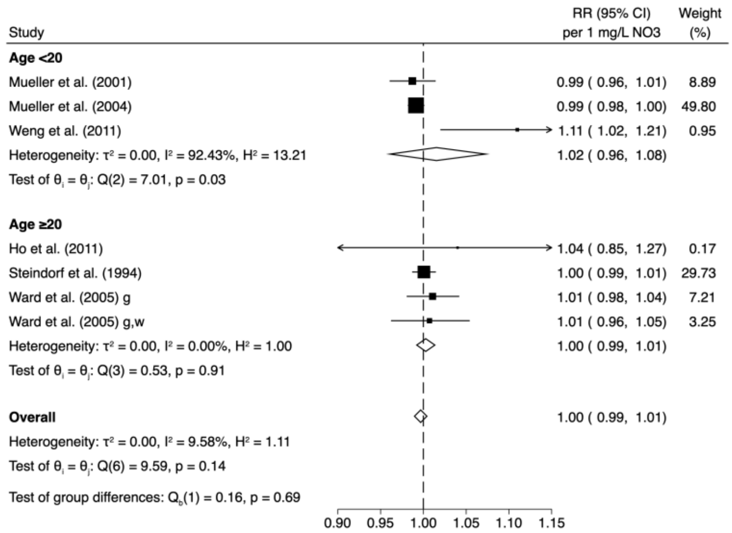
H. Kidney cancer – Cohort



I. Ovary cancer – Cohort



J. Brain cancer – Case-control



K. Non-Hodgkin lymphoma – Case-control

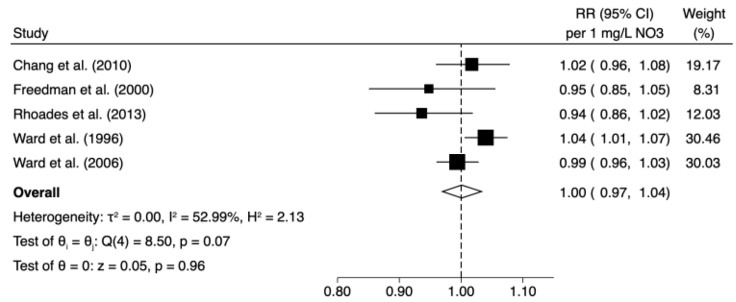


Fig. 1S. Pooled risk ratios of nitrate in drinking water and specific types of cancer (A to K). Meta-analyses stratified by study design are shown for colorectal, pancreas, and bladder cancers. The point estimate (black squares), statistical weight (area of each square), and 95% confidence interval for each study (horizontal line) are shown. Overall summary estimates are displayed (diamonds). Estimates are shown per 1 mg/L increase of nitrate.
Abbr.: c=colon, cr=colorectal, d=distal, f=female, g=glioma, m=male, p=proximal, r=rectum, w=well water.

Table 1S. Quality scores of included cohort studies.

Reference	Q1 Did the study address a clearly focused issue?	Q2 Was the cohort recruited in an acceptable way?	Q3 Was the water source clearly stated?	Q4 Was the exposure accurately measured to minimise bias?	Q5 Was the outcome accurately measured to minimise bias?	Q6* Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Q7 Have the authors identified or discussed potential confounders that could have improved or explained the results obtained?	Q8 Was the follow up of subjects complete enough?	Q9 Are the assumptions/ limitations stated?	%	quality <50% = low 50- 70% = medium >70%= high
Inoue-Choi 2015	1	1	1	1	1	0	1	1	1	88.9	High
Jones 2016	1	1	1	1	1	1	1	1	1	100.0	High
Jones 2017	1	1	1	1	1	1	1	1	1	100.0	High
Jones, 2019	1	1	1	1	1	1	1	1	1	100.0	High
Quist 2018	1	1	1	1	1	1	1	1	1	100.0	High
Schullehner 2018	1	1	1	1	1	1	1	1	1	100.0	High
Van Loon 1998	1	1	1	1	1	1	1	1	0	88.9	High
Van Loon 1997	1	1	0	0	1	1	0	1	0	55.6	medium
Volkmer 2005	1	1	1	0	0	0	1	1	0	55.6	medium
Ward 2010	1	1	1	1	1	1	1	1	1	100.0	high
Weyer 2001	1	1	1	1	1	1	1	1	1	100.0	high
Zeegers 2006	1	1	1	1	1	0	1	1	1	88.9	high

* The minimum set of confounders to be evaluated at least in the initial steps of the analyses if not in the final model were age, sex and socio-economic status, or place of residency as a proxy of the latter.

Table 2S. Quality scores of included case-control studies.

Reference	Q1 Did the study address a clearly focused issue?	Q2 Did the authors use an appropriate method to answer their question?	Q3 Were the cases recruited in an acceptable way?	Q4 Were the controls selected in an acceptable way?	Q5 Was the water source clearly stated?	Q6 Was the exposure accurately measured to minimise bias?	Q7* Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Q8 Have the authors identified or discussed potential confounders that could have improved or explained the results obtained?	Q9 Are the assumptions/ limitations stated?	%	quality <50% = low 50- 70% = medium >70%= high
Barry 2020	1	1	1	1	1	1	1	1	1	100.0	high
Boeing 1993	1	1	1	1	1	0	0	0	1	66.7	medium
Brody 2006	1	1	1	1	1	1	0	1	1	88.9	high
Chang 2010a	1	1	1	1	1	1	1	1	1	100.0	high
Chang 2010b	1	1	1	1	1	1	1	1	1	100.0	high
Chiu 2012	1	1	1	1	1	1	1	1	1	100.0	high

Chiu 2011	1	1	1	1	1	1	1	1	1	100.0	high
Chiu, 2010	1	1	1	1	1	1	1	1	1	100.0	high
Chiu 2007	1	1	1	1	1	1	1	1	1	100.0	high
Coss 2004	1	1	1	1	1	0	0	1	1	77.8	high
De Roos 2003	1	1	1	1	1	1	1	1	1	100.0	high
Espejo-Herrera 2015	1	1	1	1	1	1	1	1	1	100.0	high
Espejo-Herrera 2016a	1	1	1	1	1	1	1	1	1	100.0	high
Espejo-Herrera 2016b	1	1	1	1	1	1	1	1	1	100.0	high
Fathmawati 2017	1	1	1	1	1	1	1	0	0	77.8	high
Freedman 2000	1	1	1	1	1	1	1	0	1	88.9	high
Ho 2011	1	1	1	1	1	1	1	1	1	100.0	high
Infante-Rivard 2001	1	1	1	1	1	1	1	0	1	88.9	high
Kuo 2007	1	1	1	1	1	1	1	1	1	100.0	high
Liao 2013	1	1	1	1	1	1	1	1	1	100.0	high
McElroy 2008	1	1	1	1	1	1	1	1	1	100.0	high
Mueller 2001	1	1	1	1	1	0	1	1	1	88.9	high
Mueller 2004	1	1	1	1	1	0	1	1	1	88.9	high
Rademacher 1992	1	1	1	1	1	1	1	0	1	88.9	high
Rhoades 2013	1	1	1	1	1	1	1	1	1	100.0	high
Steinforf 1994	1	1	1	1	1	1	1	1	1	100.0	high
Taneja 2017	1	1	1	1	1	1	1	0	1	88.9	high
Ward 2003	1	1	1	1	1	1	1	1	1	100.0	high
Ward 2006	1	1	1	1	1	1	1	1	1	100.0	high
Ward 2008	1	1	1	1	1	1	1	1	1	100.0	high
Ward 2005	1	1	1	1	1	1	1	1	1	100.0	high
Ward 1996	1	1	1	1	1	1	1	1	1	100.0	high
Ward 2007	1	1	1	1	1	1	1	1	1	100.0	high
Weng 2011	1	1	1	1	1	1	1	1	1	100.0	high
Yang 2009	1	1	1	1	1	1	1	1	1	100.0	high
Yang 1998	1	1	1	1	1	1	1	1	0	88.9	high
Yang 1997	1	1	1	1	1	1	1	1	0	88.9	high
Yang 2007	1	1	1	1	1	1	1	1	1	100.0	high

* The minimum set of confounders to be evaluated at least in the initial steps of the analyses if not in the final model were age, sex and socio-economic status, or place of residency as a proxy of the latter.

Table 3S. Quality scores of included cross-sectional studies.

Reference	Q1 Did the study address a clearly focused issue?	Q2 Were the partecipants recruited in an acceptable way?	Q3 Was the water source clearly stated?	Q4 Was the exposure accurately measured to minimise bias?	Q5 Was the outcome accurately measured to minimise bias?	Q6* Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Q7 Have the authors identified or discussed potential confounders that could have improved or explained the results obtained?	Q8 Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Q9 Are the assumptions/ limitations stated?	%	quality <50% = low 50- 70% = medium >70%= high
Leclerc 1991	1	1	1	1	1	0	1	1	1	88.9	high
Morales-Suárez-Varela 1995	1	1	1	1	1	0	1	1	1	88.9	high

* The minimum set of confounders to be evaluated at least in the initial steps of the analyses if not in the final model were age, sex and socio-economic status, or place of residency as a proxy of the latter.

Table 4S. Quality scores of included ecologic studies.

Reference	Q1 Did the study address a clearly focused issue?	Q2 Is the studied population clearly defined?	Q3 Was the water source clearly stated?	Q4 Is the source of information reliable?	Q5 Was the exposure accurately measured to minimise bias?	Q6 Was the outcome accurately measured to minimise bias?	Q7* Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	Q8 Have the authors identified or discussed potential confounders that could have improved or explained the results obtained?	Q9 Are the assumptions/ limitations stated?	%	quality <50% = low 50- 70% = medium >70%= high
Barrett 1998	1	1	1	1	1	1	1	0	1	88.9	high
Cocco 2003	1	1	1	1	1	1	1	1	1	100.0	high
Gulis 2002	1	1	1	1	1	1	0	1	1	88.9	high
Law 1999	1	1	1	1	1	1	1	0	1	87.5	high
Sandor 2001	1	1	0	1	0	1	0	1	1	75.0	high
Thorpe 2005	1	1	1	1	1	1	0	1	1	88.9	high
Van Leeuwen 1999	1	1	1	1	1	1	1	0	1	88.9	high
Zhang 2012	1	1	1	1	1	1	0	1	1	88.9	high

* The minimum set of confounders to be evaluated at least in the initial steps of the analyses if not in the final model were age, sex and socio-economic status, or place of residency as a proxy of the latter.

Table 5S. Nitrate concentrations and relative risks by quantiles.

<table>
<tr><th>Type of cancer</th><th>Reference</th><th>NO3 concentration (mg/L)</th><th>Findings (95% CI). NO3 concentrations as mg/L</th></tr>
<tr><td>Gastric cancer</td><td>Barrett, 1998</td><td>Range= 1.5-40.1
Median= 8.1 (IQR=2.7-18.5)</td><td>NO3 Relative Risk
2.4 1.00
5.0 0.99 (0.92-1.08)
13.7 0.91 (0.84-0.98)
29.8 0.96 (0.89-1.05)
p=0.08 (unordered categorical)</td></tr>
<tr><td></td><td>Chiu, 2012</td><td>Not reported</td><td>NO3 OR
< 1.68 1.00
≥ 1.68 1.16 (1.05-1.29)</td></tr>
<tr><td></td><td>Gulis, 2002</td><td>Not reported</td><td>NO3 SIR
All Men Women
0-10 0.96 (0.71-1.30) | 1.08 (0.73-1.59) | 0.81 (0.48-1.34)
10.1-20 0.87 (0.59-1.12) | 0.81 (0.97-2.87) | 0.94 (0.67-1.33)
>20 1.08 (0.87-1.35) | 0.96 (0.70-1.30) | 1.24 (0.91-1.70)
p trend=0.012 | p trend=0.18 | p trend=0.10</td></tr>
<tr><td></td><td>Morales-Suárez-Varela, 1995</td><td>Not reported</td><td>Men Relative Risk
Age NO3-> 25-50 >50
<55 0.93 (0.50-1.75) 1.57 (0.75-3.30)
55-75 0.88 (0.64-1.23) 1.91 (1.36-2.67)
>75 0.67 (0.37-1.22) 1.13 (0.56-2.27)
Women
Age NO3-> 25-50 >50
<55 0.79 (0.32-1.91) 1.67 (0.17-2.67)
55-75 1.11 (0.74-1.66) 1.81 (1.15-2.87)
>75 0.92 (0.57-1.49) 1.42 (0.81-2.51)</td></tr>
<tr><td></td><td>Rademacher, 1992</td><td>Public water supply
mean NO3=4.20, SD=4.86
Private wells: mean=10.66, SD=16.81</td><td>NO3 OR
>2.21 0.92 (0.75-1.12)
>11.06 0.97 (0.74–1.35)
>22.11 0.86 (0.69–1.08)
>44.23 1.50 (0.12-18.25)
Private wells 1.09 (0.82-1.47)</td></tr>
<tr><td></td><td>Sandor, 2001</td><td>5% 2.05
Median 72.00
95% 290.70</td><td>Log-transformed nitrate levels
b=5.48x10^-2, 95% CI=(1.11–9.85)x10^-2, p=0.014</td></tr>
<tr><td></td><td>Taneja, 2017</td><td>Not reported</td><td>NO3 OR
≤45 1.00 (0.98–1.01)
>45 1.10 (0.99–1.15)
Adjusted OR=1.20 (1.04–1.34)</td></tr>
<tr><td></td><td>Van Leeuwen, 1999</td><td>NO3 range= 0.05-7.79
Average= 2 - Median=1.52</td><td>Variable: Ln(NO3) mg/L
Men: Regression parameter= -0.136, 95% CI=-0.151, -0.122
Women: similar, but not shown.</td></tr>
</table>

	Van Loon, 1997	NO3 daily intake: median 4 mg (95th percentile 19 mg).	Higher vs. lower quintile RR=1.02 (0.62-1.68), p trend = 0.89 (other quintiles not shown)
	van Loon, 1998	Mean NO3 ingested per day ± SD (mg/day) Subcohort = 5.8 ± 6.5 Cases = 6.1 ± 7.2	Nitrate ingested (mean, mg/day) Rate ratio Q I (0.02) 1 Q II (1.65) 0.93 (0.62-1.39) Q III (3.85) 0.87 (0.58-1.31) Q IV (6.91) 0.83 (0.55-1.24) Q V (16.5) 0.88 (0.59-1.32) p trend = 0.73 (0.39)
	Ward, 2008	Public water supply: range <2.21-53.07 Private wells: range <2.21-296.32	NO3 OR (Public water supply) | NO3 OR (Private wells) < 10.79 1.0 | <2.21 1.0 10.84-11.37 2.1 (1.0-4.4) | 2.21 – 19.9 4.7 (0.5-41) 11.41-19.11 1.2 (0.5-2.6) | >19.9 5.1 (0.5-52) >19.11 1.2 (0.5-2.7) p trend = 0.946
	Yang, 1997	Cases: mean=1.99, SD=1.90 Controls: mean=1.95, SD=1.95	NO3 (Median) OR ≤0.97 (0.18) 1.0 1.02-1.95 (1.64) 0.95 (0.87–1.03) ≥1.99 (2.96) 1.02 (0.93-1.11) p trend = 0.44
	Yang, 1998	Cases: mean=1.99, SD=1.90 Controls: mean=1.95, SD=1.95	NO3 (Median) OR ≤0.97 (0.18) 1.0 1.02-1.95 (1.64) 1.10 (1.00–1.20) ≥1.99 (2.96) 1.14 (1.04-1.25)
Esophageal cancer	Barrett, 1998	Range=1.5-40.1, Median=8.1 (IQR=2.7-18.5)	NO3 Relative Risk 2.4 1.00 5.0 1.01 (0.93-1.09) 13.7 1.01 (0.94-1.09) 29.8 1.06 (0.98-1.14)
	Liao, 2013	Not reported	NO3 (Median) OR < 1.68 (0.22) 1.0 1.73-2.88 (2.26) 1.00 (0.88–1.13) ≥ 2.92 (5.13) 1.05 (0.91–1.19) p for trend =0.79
	Ward, 2008	Public water supply: range <2.21-53.07 Private wells: range <2.21-296.32	NO3 OR (Public water supply) | NO3 OR (Private wells) < 10.79 1.0 | <2.21 1.0 10.84-11.37 2.1 (1.0-4.6) | Intermediate levels not reported 11.41-19.11 1.0 (0.5-2.7) | > 19.9 0.5 (0.1-2.9) >19.11 1.2 (0.6-2.7) p trend = 0.519
	Zhang, 2012	NO3 Well 35.74±19.42 River 24.72±10.58 Cistern 20.12±11.50	NO3 OR=46.29 (3.16-667.39), p=0.01

Colorectal cancer	Chang, 2010a	Not reported	NO3 OR rectum < 1.68 1.00 ≥ 1.68 1.15 (1.01-1.32)
	Chiu, 2010	Not reported	NO3 (Median) OR colon < 1.68 (0.25) 1.0 1.73-2.52 (1.93) 1.02 (0.90–1.15) ≥ 2.65 (4.41) 1.16 (1.04–1.30) p for trend=0.001
	Chiu, 2011	Not reported	NO3 (Median) OR colon < 1.68 (0.25) 1.0 1.73-2.52 (1.95) 1.02 (0.90–1.15) ≥ 2.65 (4.42) 1.16 (1.04–1.30)
	De Roos, 2003	Not reported	NO3 OR OR Colon Rectum ≤4.42 1.0 | 1.0 >4.42 to ≤13.27 1.0 (0.8-1.3) | 0.8 (0.6-1.1) >13.27 to ≤22.11 0.7 (0.4-1.1) | 0.7 (0.5-1.2) >22.11 1.2 (0.8-1.7) | 1.2 (0.8-1.8)
	Espejo-Herrera, 2016	Not reported	NO3 ingested (mg/day) OR OR Colorectal All Men Women ≤5 1.0 | 1.0 | 1.0 >5-10 1.17 (0.98-1.38) | 1.16 (0.94-1.44) | 1.20 (0.90-1.58) >10 1.49 (1.24-1.38) |1.50 (1.21-1.87) | 1.41 (1.04-1.91) Colon All Men Women ≤5 1.0 | 1.0 | 1.0 >5-10 1.28 (1.06-1.55) | 1.26 (0.99-1.61) | 1.33 (0.97-1.80) >10 1.52 (1.24-1.86) |1.51 (1.17-1.94) | 1.46 (1.04-2.05) Rectum All Men Women ≤5 1.0 | 1.0 | 1.0 >5-10 0.93 (0.70-1.23) | 0.94 (0.68-1.28) | 0.87 (0.52-1.45) >10 1.62 (1.23-2.14) |1.55 (1.16-2.08) | 1.49 (0.89-2.48)
	Fathmawati, 2017	Not reported	NO3 OR colorectal ≤50 1.00 >50 2.820 (1.075–7.395)
	Gulis, 2002	Not reported	NO3 SIR colorectal All Men Women 0-10 0.71 (0.57-0.88) | 0.77 (0.57-1.03) | 0.64 (0.46-0.89) 10.1-20 1.05 (0.92-1.20) | 0.99 (0.82-1.19) | 1.11 (0.93-1.34) >20 1.18 (1.04-1.34) | 1.07 (0.89-1.29) | 1.29 (1.08-1.55) p trend <0.001 | p trend=0.051 | p trend <0.001
	Jones, 2019	Not reported	NO3 OR Colon Rectum <1.59 1.0 | 1.0 1.63-3.54 1.13 (0.88-1.45) | 0.48 (0.28-0.84) 3.58-5.97 1.32 (1.03-1.69) | 0.86 (0.53-1.38)

			6.01-15.52 0.98 (0.76-1.27) | 0.94 (0.60-1.48) >15.52 0.97 (0.75-1.26) | 0.64 (0.38-1.07)
	Kuo, 2007	Cases: mean=2.03, SD=1.99 Controls: mean=1.90, SD=2.03	NO3 (median) OR rectum ≤ 0.49 (0.00) 1.0 0.84-1.99 (1.68) 1.22 (0.98–1.52) 2.12-12.61 (3.18) 1.36 (1.08–1.70)
	McElroy, 2008	Not reported	NO3 OR Colon Rectum Proximal colon Distal colon <2.21 1.0 | 1.0 |1.0 | 1.0 2.21-8.40 1.39 (1.02–1.89) | 1.29 (0.73-2.31) | 1.35 (0.81-2.26) | 1.58 (1.03-2.40) 8.85-26.09 1.32 (0.99–1.76) | 1.19 (0.69-2.06) | 1.36 (0.85-2.17) | 1.38 (0.92-2.06) 26.54-43.74 1.28 (0.88-1.88) | 1.11 (0.52-2.36) | 1.34 (0.73-2.47) | 1.43 (0.85-2.41) ≥44.22 1.57 (0.97-2.52) | 1.26 (0.47-3.43) | 2.76 (1.42-5.38) | 1.23 (0.59-2.56)
	Morales-Suárez-Varela, 1995.	Not reported	Men Relative Risk colon Age NO3-> 25-50 >50 <55 1.30 (0.47-3.58) 0 55-75 0.98 (0.58-1.66) 0.66 (0.25-1.75) >75 0.65 (0.24-1.75) 1.13 (0.36-3.53) Women Age NO3-> 25-50 >50 <55 0.24 (0.04-1.49) 1.05 (0.40-2.25) 55-75 1.19 (0.74-1.90) 1.15 (0.57-2.31) >75 0.32 (0.11-0.95) 0.94 (0.35-2.52))
	Schullehner, 2018	Lowest decile <0.69 Highest decile ≥16.75	Highest vs. lowest decile (no other levels provided) Colorectal: HR=1.14 (1.06-1.23) | Colon: HR=1.14 (1.04-1.26) | Rectum: HR=1.13 (1.00-1.27)
	Weyer, 2001	Not reported	Public water supply NO3 Colon Rectum Relative Risk < 1.59 1 | 1 1.59-4.42 1.54 (1.09-2.17) | 0.72 (0.42-1.26) 4.46-10.88 1.58 (1.13-2.23) | 0.98 (0.59-1.63) >10.88 1.01 (0.70-1.48) | 0.50 (0.27-0.93) Private wells Colon cancer RR= 1.14 (0.80-1.62) | Rectum cancer RR= 0.65 (0.37-1.12)
	Yang, 2007	Cases: mean=1.90, SD=1.95 Controls: mean=1.95, SD=1.95	NO3 (Median) OR colon < 0.97 (0) 1.0 1.02-1.99 (1.68) 0.98 (0.84–1.14) 2.12-12.69 (3.27) 0.98 (0.83-1.16) p trend =0.22
Gastrointestinal and urinary cancer	Leclerc, 1991	Median NO3= 26 mg/L	Men | Women Age NO3-> <45 >45 | NO3-> <45 >45 35-44 1 1.14 (0.71-1.81) | - - 45-54 1 0.89 (0.68-1.16) | 1 1.07 (0.68-1.67) 55-64 1 0.77 (0.65-0.92) | 1 0.83 (0.62-1.07) 65-74 1 1.05 (0.92-1.21) | 1 0.89 (0.74-1.07) age-standardised 1 0.94 (0.87-1.02) | 1 0.88 (0.77-1.02)

<table>
<tr><td>Other digestive tract cancers</td><td>Gulis, 2002</td><td>Not reported</td><td>NO3 SIR All digestive organs
All Men Women
0-10 0.78 (0.67-0.92) | 0.83 (0.68-1.03) | 0.73 (0.57-0.92)
10.1-20 1.0 (0.90-1.10) | 0.96 (0.84-1.11) | 1.04 (0.90-1.20)
>20 1.13 (1.03-1.25) | 1.06 (0.92-1.21) | 1.28 (1.12-1.47)
p trend <0.001 | p trend=0.051 | p trend <0.001</td></tr>
<tr><td></td><td>Weyer, 2001</td><td>Not reported</td><td>Public water supply
NO3 Relative Risk other digestive tract
< 1.59 1
1.59-4.42 1.31 (0.55-3.11)
4.46-10.88 1.55 (0.67-3.58)
>10.88 1.70 (0.74-3.88)
Private wells: RR= 1.69 (0.75-3.82)</td></tr>
<tr><td>Pancreatic cancer</td><td>Coss, 2004</td><td>Median= 5.75 (IQR 2.65– 12.38)</td><td>NO3 OR
< 2.65 1.0
2.65-7.55 1.2 (0.79-1.8)
7.55-12.38 0.54 (0.33-0.89)
>12.38 0.99 (0.64-1.5)</td></tr>
<tr><td></td><td>Quist, 2018</td><td>Not reported</td><td>NO3 HR
<2.08 1.0
2.08-4.78 1.40 (0.88-2.24)
4.82-13.14 1.51 (0.96-2.37)
13.18-25.16 1.14 (0.67-1.93)
>25.16 1.18 (0.52-2.67), p trend = 0.97
Continuous variables analysis HR=1.07 (0.92, 1.25)
Private wells HR=0.92 (0.56, 1.52) compared to first quartile of public supply</td></tr>
<tr><td></td><td>Yang, 2009</td><td>Cases: mean=1.95, SD=1.95
Controls: mean=1.90, SD=1.99</td><td>NO3 (Median) OR
< 0..80 (0) 1.0
0.84-1.99 (1.68) 1.03 (0.90–1.18)
2.12-12.65 (3.72) 1.10 (0.96-1.27)
p trend = 0.08</td></tr>
<tr><td></td><td>Weyer, 2001</td><td>Not reported</td><td>Public water supply
NO3 Relative Risk
< 1.59 1
1.59-4.42 0.84 (0.41-1.76)
4.46-10.88 1.25 (0.64-2.43)
>10.88 0.52 (0.22-1.22)
Private wells: RR= 0.66 (0.31-1.41)</td></tr>
<tr><td>Bladder cancer</td><td>Barry, 2020</td><td>Modelled Median among controls = 14.59</td><td>NO3 in water OR | Average daily NO3 ingested (mg)
≤0.93 1.00 | ≤1.33 1.00
>0.93-1.64 0.81 (0.61-1.1) | >1.33-2.74 1.1 (0.87-1.5)
>1.64-3.01 0.89 (0.68-1.2) | >2.74-5.71 1.1 (0.86-1.5)
>3.01-9.16 1.0 (0.79-1.4) | >5.71-20.30 1.5 (1.1-1.9)
>9.16 1.5 (0.97-2.3) | >20.30 1.4 (0.89-2.2)
P trend = 0.01 | P trend = 0.06</td></tr>
</table>

	Chiu, 2007	Not reported	NO3 (Median) OR < 0..80 (0) 1.0 0.84-1.99 (1.68) 1.76 (1.28-2.42) 2.12-12.65 (3.41) 1.96 (1.41-2.72) p trend <0.001
	Espejo-Herrera, 2015	Not reported	NO3 in water OR | Ingested through water (mg/day) ≤ 5 mg/L 1 | ≤4 1 >5 <10 mg/L 1.12 (0.65–1.94) | >4-8 0.74 (0.47-1.16) ≥10 mg/L 1.04 (0.60–1.81) | >8 0.65 (0.41-1.02)
	Jones, 2016	Not reported	NO3 HR <2.08 1.0 2.08-4.73 1.16 (0.70-1.92) 4.78-13.14 0.98 (0.59-1.64) >13.14 1.48 (0.92-2.40) p trend = 0.11 Continuous variables analysis: HR=1.12 (0.95-1.32)
	Morales-Suárez-Varela, 1995	Not reported	Men Relative Risk Age NO3-> 25-50 >50 <55 0.83 (0.20-3.41) 0 55-75 0.85 (0.52-1.37) 1.4 (0.8-2.48) >75 0.69 (0.31-1.54) 0.53 (0.14-2.07)
	Ward, 2003	Not reported	Men | Women NO3 OR | <2.65 1.0 | <2.96 1.0 2.65- <6.19 0.9 (0.6-1.2) | 2.96- <5.22 0.7 (0.4-1.2) 6.19-<13.67 0.8 (0.6-1.1) | 5.22-<10.97 0.6 (0.3-1.1) ≥13.67 0.5 (0.4-0.8) | ≥10.97 0.8 (0.4-1.3)
	Weyer, 2001	Not reported	Public water supply NO3 Relative Risk < 1.59 1 1.59-4.42 1.65 (0.65-4.19) 4.46-10.88 1.00 (0.35-2.85) >10.88 2.43 (1.01-5.88) Private wells: RR= 1.01 (0.83-1.22)
	Zeegers, 2006	Daily intake mg/day Cases: 5.3±6.2 Subcohort: 4.9±6.2	Range (median) Relative Risk 0–0.9 (0.5) 1.00 0.9–2.4 (1.4) 0.84 (0.64-1.11) 2.4–4.4 (3.4) 1.11 (0.86-1.44) 4.4–7.7 (5.6) 1.08 (0.84-1.40) 7.7–92.7 (10.6) 1.06 (0.82-1.38) p trend = 0.24 Increment per 10mg/day RR=1.09 (0.96–1.24)
Kidney cancer	Jones, 2017	Not reported	NO3 HR <2.08 1.0 2.08-4.73 0.98 (0.58-1.7)

			4.78-13.14 1.3 (0.81-2.1) 13.14-22.11 0.76 (0.41-1.4) >22.11 2.3 (1.2-4.3) p trend = 0.33 Continuous variables analysis: HR=1.3 (0.96-1.3)
	Volkmer, 2005	Mean NO3 Group A: 60 Group B: 10	Male RR=0.61 (0.28–1.33) Female RR=2.96 (0.66–13.18) Total RR=0.87 (0.34–2.22)
	Ward, 2007	Not reported	NO3 OR <2.74 1.0 2.74 - <5.62 0.88 (0.56-1.38) 5.62 - ≤12.3 0.83 (0.53-1.30) >12.3 0.89 (0.57-1.39)
	Weyer, 2001	Not reported	Public water supply NO3 Relative Risk < 1.59 1 1.59-4.42 1.32 (0.54-3.18) 4.46-10.88 1.26 (0.52-3.04) >10.88 1.06 (0.42-2.68) Private wells: RR= 1.07 (0.45-2.57)
Brain cancer	Barrett, 1998	Range= 1.5-40.1 Median= 8.1 (IQR=2.7-18.5)	NO3 Relative Risk 2.4 1.00 5.0 1.14 (1.04-1.26) 13.7 1.13 (1.03-1.25) 29.8 1.18 (1.08-1.30)
	Boeing, 1993	NO3, measured but not reported.	NO3 ≥50 mg/L Glioma RR = 0.1 (95% CI 0.0-1.0) | Meningioma RR = 0.2 (95%CI 0.0-1.2) (current NO3 levels were higher for controls than cases)
	Ho, 2011	Not reported	NO3 OR <1.68 1.0 ≥1.68 1.04 (0.85-1.27)
	Mueller, 2001	Not reported	NO3 OR None 1.0 10 0.4 (0.1–1.0) 25 0.6 (0.2–2.4) 50-100 1.4 (0.1-15) Any measured 0.6 (0.3-1.1)
	Mueller, 2004	Not reported	NO3 OR None 1.0 10 - <25 0.7 (0.5–1.1) 25 - <50 0.5 (0.3–1.0) 50+ 0.8 (0.4-1.5)
	Steindorf, 1994	case group: mean=15.98 (SD 15.61) control group: mean=16.16 (SD 15.72) range=0 - 97.8	NO3 Relative Risk 0–2.0 1.00 >2.0–11.3 0.99 (0.60-1.63)

			>11.3-25.2 1.12 (0.69-1.83) >25.2 1.00 (0.61-1.64)
	Thorpe, 2005	Max level of NO3 detected=31.5	Crude OR for exposure to all detectable concentrations of NO3 OR=1.23 (0.86–1.75)
	Ward, 2005	Public water: range 0-53.07 Controls: Median=11.41, IQR=10.53-19.11 Private wells: range 2.21-296.32 Controls: Median=10.17, IQR=0.88-32.73	NO3 OR <10.53 1.0 10.53-11.37 1.4 (0.7-2.7) 11.41-19.11 1.2 (0.6-2.3) >19.11 1.3 (0.7-2.6) Well water (≥44.2 vs <44.2 mg/ml): OR=1.2 (0.4-4.1)
	Weng, 2011	Cases: mean=2.03, SD=2.08 controls: mean=1.90, SD=2.08	NO3 OR ≤1.37 1.0 > 1.37 mg/L 1.40 (1.07–1.84)
Non-Hodgkin lymphoma	Chang, 2010b	Not reported	NO3 (median) OR ≤0.80 (0.00) 1.00 0.84-1.99 (1.68) 1.02 (0.87-1.20) 2.12-12.65 (3.41) 1.05 (0.89-1.24) p trend = 0.39
	Cocco, 2003	4.57 (SE=0.35; median=3.27) in 1993	NO3 OR Total | Men | Women ≤2.0 1.00 | 1.00 | 1.00 2.01-3.0 1.13 (0.87-1.47) | 1.29 (0.87-1.92) | 1.02 (0.71-1.45) 3.01-4.0 1.21 (0.91-1.61) | 1.70 (1.13-2.56) | 0.86 (0.56-1.30) 4.01-5.0 1.15 (0.88-1.49) | 1.42 (0.96-2.10) | 0.95 (0.66-1.37) 5.01-7.0 1.01 (0.76-1.33) | 1.46 (0.99-2.16) | 0.69 (0.46-1.03) 7.01-10.0 1.40 (0.99-1.99) | 1.98 (1.23-3.20) | 0.98 (0.57-1.66 10.01-15.0 1.0 (0.74-1.36) | 1.45 (0.95-2.22) | 0.69 (0.44-1.07) 15.01-26.64 1.32 (0.88-1.97) | 1.64 (0.92-2.91) | 1.10 (0.63-1.93)
	Freedman, 2000	NO3 level range: 0.4-31.8 Median in the highest tertile: 10.6	NO3 OR ≤2.21 1.0 >2.21 - ≤6.63 1.4 (0.7–2.5) >6.63 0.3 (0.1–0.9)
	Gulis, 2002	Not reported	NO3 SIR All Men Women 0-10 0.36 (0.11-1.11) | 0.25 (0.03-1.79) | 0.45 (0.11-1.80) 10.1-20 1.26 (0.82-1.93) | 1.66 (0.97-2.87) | 0.90 (0.45-1.81) >20 1.22 (0.76-1.96) | 1.09 (0.52-2.28) | 1.35 (0.72-2.50) p trend<0.021 | p trend=0.17 | p trend=0.13
	Law, 1999	Mean=11.86 - Range=1.48-40.01	1984-1988 | 1989-1993 NO3 IRR <3.24 1.00 | 1.00 3.24–14.85 1.170 (1.01-1.35) | 1.069 (0.92, 1.25) >14.85 1.210 (1.04-1.41) | 0.917 (0.78, 1.08)

	Rhoades, 2013	Not reported	NO3 OR ≤8.85 1.0 >8.85 0.6 (0.3-1.1)
	Thorpe, 2005	Max level of NO3 detected=31.5	Crude OR for exposure to all detectable concentrations of NO3 OR=1.41 (0.74–2.68)
	Ward, 1996	Public water median=8.0, IQR=7.5-16.8 Private wells median=11.9, IQR=3.1-29.2	NO3 OR Total | Men | Women <7.08 1.0 | 1.0 | 1.0 7.08 - <8.85 1.4 (0.8-2.5) | 1.7 (0.7-4.0) | 1.3 (0.6-2.7) 8.85 - <17.69 1.5 (0.7-3.0) | 1.4 (0.5-4.3) | 1.6 (0.6-4.0) ≥17.69 2.0 (1.1-3.6) | 1.9 (0.7-4.9) | 2.1 (1.0-4.4) p trend=0.03 | p trend=0.3 | p trend=0.04 Private wells: 44.2 vs <4.42 mg/l: OR=1.5 (0.6-3.8) Intake (mg/day) Total <11.06 1.0 11.06-17.25 1.5 (0.7-3.0) 17.69-27.42 1.6 (0.8-3.2) ≥27.86 1.9 (1.0-3.9) p trend=0.07
	Ward, 2006	Cases: median=6.19, IQR=3.1-12.83 controls: median=6.19, IQR=2.53-12.83	Public supplies | Public supplies and private wells NO3 OR <2.79 1.0 | 1.0 2.79-6.01 1.3 (0.7-2.4) | 0.9 (0.5-1.7) 6.06-12.78 1.0 (0.5-1.9) | 0.8 (0.4-1.4) ≥12.83 1.2 (0.6-2.2) | 0.9 (0.5-1.6)
	Weyer, 2001	Not reported	Public water supply NO3 Relative Risk < 1.59 1 1.59-4.42 0.91 (0.52-1.57) 4.46-10.88 0.87 (0.50-1.51) >10.88 0.71 (0.39-1.28) Private wells: RR= 0.88 (0.52-1.47)
Breast cancer	Brody, 2006	Not reported	Average annual NO3 excess concentration OR 0 - < 1.33 1.0 1.33 - < 2.65 1.0 (0.7 – 1.3) 2.65 - < 3.98 0.9 (0.6 – 1.2) 3.98 - < 5.31 0.9 (0.6 – 1.2) ≥ 5.31 0.9 (0.5 – 1.7)
	Espejo-Herrera, 2016	Not reported	NO3 ingested OR (mg/day) All Postmenopausal Premenopausal <2.3 1.0 | 1.0 | 1.0 ≥2.3-4.0 0.98 (0.79, 1.23) | 1.09 (0.84, 1.41) | 1.31 (0.83, 2.06) >4.0-8.8 1.01 (0.80, 1.28) |1.07 (0.81, 1.42) | 1.03 (0.64, 1.66) >8.8 1.08 (0.82, 1.43) |1.29 (0.92, 1.81) | 1.14 (0.67, 1.94) p trend=0.64 | p trend=0.20 | p trend=0.04

	Weyer, 2001	Not reported	Public water supply NO3 Relative Risk < 1.59 1 1.59-4.42 1.02 (0.84-1.25) 4.46-10.88 0.95 (0.77-1.17) >10.88 1.00 (0.82-1.23) Private wells: RR= 1.01 (0.83-1.22)
Leukemia	Infante-Rivard, 2001	95th percentile=1.99 mg/L	>95th percentile vs ≤95th percentile Prenatal: OR=0.68 (0.27-1.70) Postnatal: OR=0.59 (0.23-1.55)
	Thorpe, 2005	Max level of NO3 detected=31.5	Crude OR for exposure to all detectable concentrations of NO3 OR=1.81 (1.35–2.42)
	Weyer, 2001	Not reported	Public water supply NO3 Relative Risk < 1.59 1 1.59-4.42 0.83 (0.46-1.49) 4.46-10.88 0.38 (0.18-0.81) >10.88 0.92 (0.52-1.63) Private wells: RR= 0.82 (0.47-1.43)
Cancers to the reproductive organs	Inoue-Choi, 2015	Public water: median= 4.78 (range 0.04-112.07)	Ovarian cancer NO3 HR 0.04-2.09 1.0 2.09-4.78 1.36 (0.80-2.34) 4.82-13.14 1.55 (0.92-2.59) 13.18-112.07 2.14 (1.30-3.54) p trend = 0.002 Private wells (comparison with lower public water quartile): HR=1.53 (0.93 – 2.54)
	Morales-Suárez-Varela, 1995.	Not reported	Men Relative Risk Age NO3-> 25-50 >50 <55 0 3.07 (0.45-21.17) 55-75 1.19 (0.82-1.71) 1.86 (1.20-2.88) >75 1.15 (0.79-1.68) 1.80 (1.15-2.82)
	Volkmer, 2005	Mean NO3 Group A: 60 Group B: 10	Prostate cancer: RR=1.06 (0.76–1.48) Penis cancer: RR=0.66 (0.14–2.88) Testis cancer: RR=0.43 (0.21–0.90)
	Weyer, 2001	Not reported	Public water supply NO3 Ovarian Uterine Relative Risk < 1.59 1 | 1 1.59-4.42 1.52 (0.73-3.15) | 0.90 (0.58-1.39) 4.46-10.88 1.94 (0.96-3.90) | 1.01 (0.66-1.54) >10.88 2.03 (1.01-4.07) | 0.65 (0.40-1.06) Private wells Ovarian RR= 1.55 (0.77-3.13) , Uterine RR= 1.09 (0.74-1.61)
Other types of cancer	Gulis, 2002	Not reported	NO3 SIR All cancers All Men Women

			0-10 0.88 (0.82-0.95) | 0.90 (0.81-0.99) | 0.87 (0.72-1.96) 10.1-20 1.07 (1.03-1.13) | 1.08 (1.02-1.16) | 1.07 (1.00-1.13) >20 1.03 (0.97-1.08) | 0.94 (0.88-1.02) | 1.38 (1.28-1.47) p trend <0.001 | p trend <0.001 | p trend <0.001
	Thorpe, 2005	Max level of NO3 detected=31.5	Bone cancer Crude OR for exposure to all detectable concentrations of NO3 OR=1.28 (0.63–2.59)
	Volkmer, 2005	Mean NO3 Group A: 60 Group B: 10	Male RR=2.26 (1.34-3.79) Female RR=1.52 (0.78-2.96) Total RR=1.98 (1.10-3.54)
	Ward, 2010	Not reported	Thyroid NO3 RR <1.59 1.0 1.59-4.42 0.50 (0.13-2.01) 4.47-10.88 1.17 (0.37-3.66) >10.88 2.18 (0.83-5.76) P trend = 0.02 Private wells (comparison with lowest public water quartile): RR= 1.13 (0.83-3.66)
	Weyer, 2001	Not reported	Public water supply NO3 Lung and bronchus Melanoma Relative Risk < 1.59 1 | 1 1.59-4.42 1.00 (0.68-1.48) | 0.95 (0.48-1.89) 4.46-10.88 1.49 (1.04-2.14) | 0.98 (0.49-1.94) >10.88 0.83 (0.55-1.26) | 0.81 (0.40-1.64) Private wells Lung and bronchus RR= 0.97 (0.86-1.09), Melanoma RR= 1.01 (0.90-1.17)

Table 6S. Nitrite concentrations and relative risks by quantiles.

Type of cancer	Reference	Study design and population	Study location and years	Exposure	Findings (95% CI)
Glioma Meningioma	Boeing, 1993	Case-control 115 gliomas, 81 meningiomas 418 controls	Germany (Rhein-Neckar-Odenwald) 1987-1988	Drinking water NO2 traces seldom found.	Glioma RR = 0.96 (95% CI 0.1-8.3) Meningioma RR = 3.7 (95%CI 0.8-16.6)
Brain	Mueller, 2001	Case-control 119 cases - 191 controls (<20 years old)	USA (Washington State and California) 1 Jan 1984-31 Dec 1990 (WA) 1 Jan 1984-31 Dec 1991 (CA)	Public water supply Wells	NO2 level (mg/L) OR None 1.0 1 4.7 (1.1–23) 5 undefined 10 undefined Any measured 8.8 (2.1-46)
Brain	Mueller, 2004	Case-control 283 cases - 537 controls (children)	USA (CA, WA), France, Italy, Spain, Israel, Canada (Winnipeg), Australia 1976-1994	Public water supply Wells	NO2 level (mg/L) OR None 1.0 1 - <5 0.6 (0.4-1.1) 5+ 0.8 (0.4-1.9)
Esophageal	Zhang, 2012	Ecological 661 adults with cancer 54,055 non-cancer subjects	China (Shexian county) January to December 2010	Average NO2 concentrations (mg/L) Well 0.03±0.16 River 0.03±0.10 Cistern 0.13±0.16	OR=0.29 (0.05-1.68)

combined->																
Cancer type (no. of studies) ->	**Bladder (7)**	**Brain (9)**	**Breast (3)**	**Colorectal (12)**	**Esophagus (2)**	**Stomach (8)**	**Kidney (3)**	**Leukemia (2)**	**NHL (6)**	**Pancreas (4)**	**Thyroid (1)**	**Reproductive organs (3)**	**Lungs and bronchus (1)**	**Melanoma (1)**	**All cancers (1)**	**Total n (%)**
Confounder																
Age	7	7	3	12	1	6	3	2	4	4	1	3	1	1	1	56 (18.9)
Sex	5	7	1	9	1	6	2	1	2	3		3	1	1	1	43 (14.5)
Nutritional vars (vitamins, energy intake, protein intake)	3		2	4		1	2	2	2	2	1	4	2	2	2	29 (9.8)
Smoking	6	1	1	4		4	2	1	1	3		2	1	1	1	28 (9.5)
BMI, waist/hip ratio	2		2	4		1	4	2	2	2		5	2	2	2	30 (10.1)
Residence	2	3		5	1	2			1	1	1					16 (5.4)
Food (eg meat)	3		1	1			1	1	1	1		2	1	1	1	14 (4.7)
Socioeconomic status	3		2	2		3		1	2							13 (4.4)
Physical activity	1		1	2			1	1	1	1		2	1	1	1	13 (4.4)
Family history cancer			2	3		2			1			1				9 (3.0)
Marital status		1		4	1	1										7 (2.4)
Medications (NSAIDs, estrogen, oral contraceptives)	1		1	3								1				6 (2.0)
Other health data (eg urinary infections, gastric ulcers, previous cancer, diabetes)	1		1	2								1				5 (1.7)
Study location (eg state, town size, center)	1	1	1				1									4 (1.4)
Alcohol	1			2		1										4 (1.4)
Pregnancy characteristics (age at 1st birth, live births)			2									2				4 (1.4)
Study/interview period	1			1												2 (0.7)
Duration chlorinated water use	1			1												2 (0.7)
Diagnosis year		1	1													2 (0.7)
Age menopause			1									1				2 (0.7)
Use refrigerator/freezer						2										2 (0.7)
Ethnicity	1															1 (0.3)
Respondent type (eg self, sibling, spouse)		1														1 (0.3)
Diagnosis age			1													1 (0.3)
Age menarche												1				1 (0.3)
Vital status			1													1 (0.3)

Fig. 2S. Heat map of the number of models that included a given confounder (y axis) for a cancer type (x axis).