Exhibit N

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Exposure-based assessment and economic valuation of adverse birth outcomes and cancer risk due to nitrate in United States drinking water.

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ABSTRACT

Background: Nitrate ingestion from drinking water has been associated with an increased risk of adverse birth outcomes as well as elevated risk of colorectal cancer and several other cancers. Yet, to date, no studies have attempted to quantify the health and economic impacts due to nitrate in drinking water in the United States.
Methods: This study presents a first-of-its-kind comprehensive assessment of nitrate exposure from drinking water for the entire United States population. This exposure assessment serves as the basis for our analysis of the annual nitrate-attributable disease cases in the United States and the associated economic losses due to medical costs and lost productivity. Additionally, through a meta-analysis of studies on drinking water nitrate and colorectal cancer, we examine the exposure-response relationship for nitrate and cancer risk.
Results: On the basis of national nitrate occurrence data and relative risk ratios reported in the epidemiology literature, we calculated that annually, 2939 cases of very low birth weight, 1725 cases of very preterm birth, and 41 cases of neural tube defects could be related to nitrate exposure from drinking water. For cancer risk, combining nitrate-specific risk estimates for colorectal, ovarian, thyroid, kidney, and bladder cancers results in a range of 2300 to 12,594 annual nitrate-attributable cancer cases (mean: 6537 estimated cases). For medical expenditures alone, this burden of cancer corresponds to an annual economic cost of 250 million to 1.5 billion U.S. dollars, together with a potential 1.3 to 6.5 billion dollar impact due to lost productivity. With the meta-analysis of eight studies of drinking water nitrate and colorectal cancer, we observed a statistically significant positive association for nitrate exposure and colorectal cancer risk and calculated a one-in-one million cancer risk level of 0.14 mg/L nitrate in drinking water.
Conclusion: Health and economic analyses presented here suggest that lowering exposure to nitrate in drinking water could bring economic benefits by alleviating the impacts of nitrate-associated diseases.

1. Introduction

A large body of epidemiological research has found an elevated risk of cancer, adverse birth outcomes and other health impacts associated with the presence of nitrate in drinking water (Ward et al., 2018). These effects are often observed at drinking water nitrate concentrations significantly lower than the levels associated with methemoglobinemia, or blue-baby syndrome, a life-threatening condition that can kill an infant through oxygen deprivation. The U.S. drinking water standard for nitrate of 10 mg/L nitrate (as nitrogen) was first set in 1962 in order to protect against methemoglobinemia. The Canadian legal limit for nitrate in drinking water is equivalent to the U.S. standard, and the European standard is comparable, allowing up to 50 mg/L of nitrate as nitrate (corresponding to 11.3 mg/L nitrate as nitrogen).

For decades, methemoglobinemia was considered to be the primary health concern due to nitrate ingestion from water. This viewpoint is reflected in recent regulatory risk assessments published by government agencies, for example Health Canada (2013) and California Office of Environmental Health Hazard Assessment (OEHHA 2018a). Yet, the epidemiological evidence linking nitrate in drinking water with human health harms raises questions about whether the nitrate limit of 10 mg/L protects the general population against adverse health outcomes.

Recent epidemiological studies with large study populations conducted in Spain and Italy (Espejo-Herrera et al., 2016) and in Denmark (Schullehner et al., 2018) reported statistically significant increases in colorectal cancer risk associated with nitrate in drinking water at levels of 0.7–2 mg/L. Amongst these studies, the highest risk was observed for men with high red meat intake and highest exposure to nitrate from

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List of abbreviations

DALY	Disability-Adjusted Life Year
HR	Hazard Ratio
OEHHA	California Office of Environmental Health Hazard Assessment
OR	Odds Ratio
RR	Relative Risk
VOLY	Value of a Life Year
USGS	United States Geological Survey
U.S. EPA	U.S. Environmental Protection Agency
YLD	Years Lost due to Disability
YLL	Years of Life Lost

drinking water (Espejo-Herrera et al., 2016). These European publications corroborate the results from an earlier study conducted in Iowa, a region of the United States with a history of elevated nitrate in drinking water, where elevated colorectal cancer risk was observed for drinking water nitrate levels above 5 mg/L, for individuals with above median meat consumption and below median Vitamin C intake (De Roos et al., 2003). Additionally, statistically significant increases in the risk of ovarian, thyroid, kidney and bladder cancers associated with exposure to nitrate have been reported in studies of an Iowa cohort of women 55–69 years old (Inoue-Choi et al., 2015; Jones et al., 2017; Jones et al., 2016; Ward et al., 2010).

Notably, not all epidemiological studies report elevated risk for colorectal cancer and nitrate exposure, and some publications report null findings. For example, studies of a female-only cohort in Iowa observed no association between drinking water nitrate and colorectal cancer risk alone or when risk factors such as red meat intake and antioxidant intake levels were also considered (Jones et al., 2019; Weyer et al., 2001).

Cancer development upon nitrate ingestion is a complex process likely mediated by the endogenous formation of N-nitroso compounds, which are potent mutagens and carcinogens. In the body, nitrate can be reduced to nitrite and further metabolized to yield nitrosating agents capable of reacting with dietary amines to form such compounds. The World Health Organization's International Agency for Research on Cancer classified ingested nitrate as probably carcinogenic to humans, specifically when nitrate is ingested under conditions that promote endogenous nitrosation (IARC, 2010). Dietary consumption of nitrate-preserved meats and red meat in general contributes to nitrosation and has been associated with greater cancer risk. In contrast, intake of nitrate in the presence of compounds that inhibit endogenous nitrosation, such as Vitamin C and E, may prevent or reduce the formation of N-nitroso compounds (Khatri et al., 2017). There is some evidence that endogenous formation of N-nitroso compounds occurs upon ingestion of nitrate from drinking water, as documented by the urinary excretion of N-nitroso compounds (Mirvish et al., 1992; van Maanen et al., 1996).

In addition to cancer risk, exposure to drinking water nitrate during pregnancy has been associated with an elevated risk of adverse birth outcomes such as neural tube birth defects or other birth defects (Brender et al., 2013). Mother's exposure during pregnancy has been also associated with small for gestational age at birth (Migeot et al., 2013) as well as very preterm birth and very low birth weight (Stayner et al., 2017a). Potential mechanism(s) underlying these reproductive and developmental effects remain to be elucidated. While N-nitroso compound formation following nitrate ingestion exhibits developmental toxicity in animal studies, epidemiological data suggest that a different mechanism of nitrate toxicity might be involved in adverse birth outcomes (Brender et al., 2013). Additional pathways of nitrate toxicity could include inhibition of iodine uptake into the thyroid and changes in the thyroid function (Cao et al., 2010; Horton et al., 2015; Tonacchera et al., 2004) as well as interference with steroidogenesis (Edwards et al., 2018; Hamlin et al., 2016; Poulsen et al., 2018).

In light of the epidemiological data suggesting potential health harms at current levels of nitrate in drinking water, a population-wide assessment of nitrate-attributable health and economic impacts for the United States is both timely and practical. The present study utilizes nitrate occurrence data for public water systems in all 50 U.S. states to estimate the annual number of nitrate-associated adverse pregnancy outcomes, cancer cases and associated economic costs for the U.S. population as a whole. Additionally, we carried out a meta-analysis of studies on nitrate and colorectal cancer and determined nitrate's carcinogenic potency, also called the cancer slope factor, using established risk assessment methodologies (U.S. EPA, 1992). Together, these data form a solid platform for developing risk-based health benchmarks and drinking water standards that would protect human health from nitrate-attributable adverse effects.

2. Methods

2.1. Exposure assessment for nitrate in community water systems in the United States

This study is based on a national-level dataset for nitrate occurrence in public water systems in the United States for 2010–2017. The dataset is posted in an open access database available at https://www.ewg.org/tapwater/, which, to our knowledge, represents the most comprehensive, freely searchable source of tap water contaminant occurrence data for the U.S. Within the database, and throughout this paper, all nitrate concentrations in drinking water are expressed for nitrate as nitrogen, which is the standard metric in the United States for reporting drinking water nitrate concentrations. For the purposes of exposure assessment in this analysis, we calculated the arithmetic mean for all nitrate test results available for each individual public water system for 2010–2017, and this calculated value was assigned as the exposure level for this system. Test results reported as “non-detects” were assigned a value of zero and included in the overall data array for the calculation of averages. This approach is conservative and exerts a downward effect of the overall exposure estimates because, at least in some states, the detection limit of nitrate for purposes of reporting is higher than what is achievable with the analytical capabilities of the most sensitive test methods.

Population statistics for community water systems were obtained from the U.S. EPA Envirofacts database (https://www3.epa.gov/enviro/facts/sdwis/search.html), and supplemented with data available from state drinking water programs. These population numbers represent an estimate, and the specific number of customers and residents served by an individual water system may differ. Analyzing the population statistics in our dataset we found that for 38 out of 50 states, the overall population data for residents served by community water systems were within 10% of what was expected based on the 2017 Census data. For 8 states in our dataset, the calculated population was within 20% of expected, while for remaining 4 states (Alaska, Alabama, Massachusetts, and Mississippi), the population calculated from the U.S. EPA Envirofacts data diverged by more than 20% from the population expected from the census data. Based on this analysis, we applied a state-specific population adjustment factor where needed, to bring our estimates for the total population served by community water systems in each state in concordance with the 2017 census data.

2.2. Exposure assessment for nitrate in private water wells in the United States

To assess nitrate exposure for private well users, we developed an

extrapolation model that incorporates nitrate testing data for groundwater-based community and non-community systems that serve up to 50 people. Non-community systems are defined by the U.S. EPA as "a public water system that regularly supplies water to at least 25 of the same people at least six months per year" or a system that "provides water in a place such as a gas station or campground where people do not remain for long periods of time". Over 95% of non-community water systems are groundwater systems (U.S. EPA, 2018b), and over 90% of very small community systems use groundwater (National Research Council, 1997).

Our approach incorporates information on the number of people who use private water wells in each state (Kenny et al., 2009; U.S. EPA, 2011). For this analysis, we treated the nitrate concentrations in the non-community water systems and the smallest community water systems as a proxy for nitrate levels in private wells. Private water wells are likely to have the same depth or be shallower compared to public water systems and would likely have same or worse nitrate concentration profiles as what is found in the very small community or non-community water systems. Thus, our modeling approach represents a conservative scenario with respect to private well users' exposure to nitrate.

We analyzed the state-level profiles of nitrate occurrence in 2010–2017 in non-community and community water systems serving less than 50 people, and determined the state-level percentage of those systems that provide water with average nitrate concentrations exceeding a defined nitrate concentration level. For the purposes of this analysis, the nitrate occurrence distribution in the above dataset was considered equivalent to the nitrate occurrence distribution in the private wells in the same state.

To validate this approach, we utilized data from the U.S. EPA analysis of state-specific U.S. Geological Survey data on the percentage of area groundwater contaminated with nitrate above 5 mg/L (U.S. EPA, 2011). We compared these EPA estimates with our modeled estimates of the percentage of private well users in each state relying on water with more than 5 mg/L nitrate (Supplementary Table 1). These two metrics are distinct yet related, as one reflects the area of groundwater impacted by nitrate, and the other reflects a possible number of private well users impacted. In a correlation analysis, for 31 states that constitute 91% of the overall U.S. population served by private wells, the median of the absolute difference between the two metrics approaches zero, indicating overall concordance between the two datasets.

2.3. Calculation of nitrate-attributable cases of disease

In order to calculate the nitrate-attributable cases of diseases or health conditions, namely cancer and adverse reproductive outcomes, we adapted, with modifications, a published methodology for calculation of nitrate-attributable colorectal cancer cases in Europe (van Grinsven et al., 2010). The calculations formula incorporates relative risk from epidemiological studies, size of the population exposed to nitrate concentration above a specific cut-off level, and the current annual incidence proportions of a specific disease or health condition, available from the Centers for Disease Control and Prevention (U.S. Cancer Statistics, 2017). We first calculated baseline incidence proportion, referred to as Inc_B in the following equation:

$$Inc_B = \text{Disease Cases} / ((PoP_E * R_E) + (Pop_U * R_U)$$

where.

Inc_B = baseline incidence proportion in the unexposed population.
Disease Cases = National disease incidence proportion * total U.S. population.
Pop_E = exposed population (estimated number of people from public water systems and private wells drinking water with nitrate above a specified concentration).
Pop_U = unexposed population (total population minus Pop_E).
R_E = relative risk of the exposed population (odds ratio for a disease or a health condition in exposed population from epidemiological literature).
R_U = relative risk of the unexposed population (value = 1).

We than calculated the nitrate attributable cases using the following equation:

$$\text{Nitrate Attributable Cases} = Pop_E * \Delta R * Inc_B$$

where,

$\Delta R = R_E - R_U$ or the increased risk in the exposed population

To identify relevant epidemiological literature for cancer risk estimates and nitrate exposure levels, we queried the Pubmed database with a search term "drinking water nitrate and cancer", or a combination of such terms. An assumption of this methodology is the causal link between exposure to nitrate in drinking water and cancer development, therefore only studies indicating positive findings were used in our analysis of nitrate-attributable cancer cases. Five different risk scenarios for colorectal cancer were selected, based on reported nitrate exposure and significant increases in odds ratios or hazard ratios in studies by De Roos et al. (2003), Espejo-Herrera et al. (2016), and Schullehner et al. (2018). These studies were chosen because they had strong study designs incorporating large sample sizes, improved exposure assessment and control of factors influencing endogenous nitrosation. Of the three studies, Schullehner et al. (2018) presents a nation-wide assessment of colorectal cancer risk in Denmark coupled with reliable individually linked exposure data. For the assessment of other types of cancer risk related to nitrate, we used a kidney cancer risk scenario from Ward et al. (2007) for a cohort that included both men and women and reported similar risk estimates as Jones et al. (2017). For bladder cancer risk (Jones et al., 2016), ovarian cancer risk (Inoue-Choi et al., 2015), and thyroid cancer risk (Ward et al., 2010), risk estimates come from a well-defined cohort of over 20 thousand women 55–69 years old in Iowa who were enrolled in 1986 in the National Cancer Institute's Iowa Women's Health Study (National Cancer Institute, 2018).

For all studies analyzed here, odds ratios were interpreted as relative risk values since cancer is a rare event (Cochrane Collaboration, 2011). Risk estimates were used for exposure groups that found a significant increased risk relative to the lowest exposure group. Concentration cut-off levels were determined as the lower limit of the exposure group indicating an increased risk and are expressed as mg/L nitrate-nitrogen. Three studies reported elevated cancer risk from nitrate in drinking water relative to meat consumption. De Roos et al. (2003) classified this study population as above median meat consumers, while Espejo-Herrera et al. (2016) and Ward et al. (2007) further specified high red meat consumption. For these scenarios, we used increased relative risk values for R_E. Increased relative risk values were calculated using the following equation:

RE = OR above median meat/red meat consumer + nitrate /
OR above median meat/red meat consumer (no nitrate)

This approach accounts for the slight increased risk of cancer associated with red meat or meat consumption and no nitrate exposure and was used in the van Grinsven study (2010) and confirmed through personal communication with the author.

In some scenarios, we incorporated a population adjustment factor whereby the exposed population was adjusted to accurately reflect the characteristics of the at-risk population from our selected studies. Above median meat/red meat consumers were considered 50% of the total U.S. population. For scenarios applicable to women 55–69 years of age, we defined this group as 9% of the total U.S. population according to the 2017 U.S. census report. Women 55–69 years of age with no history of bilateral oophorectomy were considered 7% of the total U.S. population given that approximately 20% of women in this age range in

the United States have had bilateral oophorectomy surgery (Howe 1984).

A similar approach was employed for calculating nitrate-attributable cases of adverse birth outcomes, whereby we assessed the estimated numbers for nitrate-related neural tube defects, incidence of very low birth weight and very preterm births. Three thousand pregnancies in the U.S. each year are affected by neural tube defects (Oakeshott et al., 2010). Anencephaly and spina bifida account for approximately 80% of all neural tube defects based on incidence reported by the Centers for Disease Control and Prevention, and spina bifida is twice as common as anencephaly. Attributable cases were calculated based on national incidence proportions. For neural tube defects and very low birth weight outcomes, data was obtained from the 2016 Centers for Disease Control and Prevention National Health Statistics. For very preterm birth, data was obtained from 2014 to 2015 March of Dimes Perinatal Data Center (2019).

2.4. Assessment of economic costs for nitrate-attributable adverse birth outcomes

For all economic analyses presented here, costs are expressed in 2014 U.S. dollars. As recommended by Dunn et al. (2018), medical costs were indexed using the Bureau of Economic Analysis' Personal Consumption Expenditures health price index, while indirect economic losses were updated using the general Personal Consumption Expenditures price index (U.S. Department of Labor Bureau of Labor and Statistics, 2017). Full analysis of the direct and indirect economic costs for all nitrate-related adverse birth outcomes is beyond the scope of this manuscript and deserves its own investigation. In our analysis we incorporated the costs of hospitalization for medical concerns for three outcomes studied here (neural tube defects, very pre-term birth and very low birth weight) reported in the research literature. Due to uncertainty about potential overlap between the occurrence and registration of low birth weight and preterm birth, we did not aggregate the total costs for these birth outcomes but presented them separately.

For the very low birth weight, lost economic productivity was estimated based on the loss of IQ points (indirect costs) according to recently published methodology (Malits et al., 2018). Following this approach, low birth weight was considered to incur a 4.98-point loss in IQ, as defined through a meta-analysis of the impact of low birth weight on intelligence in adolescence and early adulthood (Kormos et al., 2014). Very low birth weight is a more severe health outcome compared to low birth weight, and thus out approach of assigning this IQ loss value to very low birth weight cases is conservative. Following the U.S. EPA economic analysis, each IQ point loss was valued at $11,745 – $15,883 in 2014 dollars (U.S. EPA, 2015a). Overall indirect economic cost is calculated by multiplying the number of nitrate-attributable very low weight births by the 4.98 IQ point loss per case and the cost of each IQ point loss (Malits et al., 2018).

2.5. Assessment of direct medical costs due to nitrate-attributable cancer cases

For cancer-related medical costs, we obtained annualized mean net costs of care per patient published by the National Cancer Institute, based on research by Mariotto et al. (2011), converted to 2014 U.S. dollars. We estimated the total costs per cancer case with the following formula:

$$\text{Total cost per case} = \text{Initial cost} + \text{Continuing Costs each Year} + \text{Cost for the Last Year of Life}$$

For calculation of continuing costs per year, annual continuing cost was multiplied by the median years lived with disease (Supplementary Table S2), minus 2 years, which represent the first year when the diagnosis is made and the last year of life. For the last year of life, National Cancer Institute gives two cost estimates, one for death due to cancer and another due to death from causes other than cancer (Mariotto et al., 2011). Here we average these two estimates to obtain a single average cost for the last year of life for specific cancers. Supplementary Table S2 lists calculated cost of medical care per cancer case for colorectal, ovarian, kidney and bladder cancer. We did not carry out cost of medical care calculations for thyroid cancer because the National Cancer Institute study did not include this type of cancer (Mariotto et al., 2011).

2.6. Assessment of economic losses due to nitrate-attributable cancer cases

For the indirect economic loss assessment, we used the World Health Organization metric for Disability-Adjusted Life Years (DALY), together with the Value of Life Year (VOLY) approach where the Value of Life Year is derived from research literature (World Health Organization, 2018; Desaigues et al., 2011; van Grinsven et al., 2010). This calculation incorporates two variables measuring the impact of a disease, namely the years of life lost (YLL) and the number of years lost due to disability (YLD) and is calculated as follows:

YLD = Years lived with disease * Disease-specific disability weight.

YLL = Average life expectancy for the population - median age at death for the disease.

DALY = Number of nitrate-attributable cases * (YLL + YLD).

Indirect Economic Loss = Total DALY * Value of Life Year (VOLY).

All parameters used in these calculations are listed in Supplementary Table S2. Median ages at diagnosis and death for specific cancers were obtained from the website of the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER). Years lived with disease (YLD) were calculated as the difference in years between the median age at death and the median age at diagnosis for the disease, multiplied by the disability weight for a specific cancer. Here, we used cancer site-specific disability weights for the diagnosis and primary therapy phase of the cancer: colorectal cancer (0.43), ovarian cancer (0.43), thyroid cancer (0.27), kidney cancer (0.27), bladder cancer (0.27), as described in Soerjomaataram et al. (2012).

There is a broad range of estimates in the research literature for the Value of Life Year that usually fall within one to three times the per capita GDP of a given country (Marseille et al., 2015). Similar to a recently published study of economic loss due to diseases attributable to environmental exposure (Grandjean and Bellanger 2017), we used a Value of Life Year derived from a nine-country European assessment (Desaigues et al., 2011). The Value of Life Year estimate of 40,000 euro recommended by Desaigues et al. (2011) was converted to 2014 U.S. dollars using the 2010 euro to USD conversion rate and adjusting for inflation between 2010 and 2014, resulting in a value of $57,757.

2.7. Meta-analysis of studies of colorectal cancer and nitrate

The U.S. National Library of Medicine Pubmed database was queried to identify academic literature using the search term "drinking water nitrate and colorectal cancer", or a combination of such terms. To be included in the dose-response analysis, studies needed to be of case-control or cohort study design, with risk values for colon or colorectal cancer reported as odds ratio (OR), relative risk (RR) or hazard ratio (HR). Studies on rectal cancer only were excluded due to a less robust dataset for this cancer site. Since colorectal cancer is a rare event (prevalent in less than 10% of the study population), OR were treated as RR for simplicity (Cochrane Collaboration, 2011). Additionally, studies had to report at least two levels of nitrate exposure quantified in mg/L, or mg/day (with estimations of water consumption), or mmol/L. Lastly, same study cases and controls could not be present in more than one study.

Data extracted from each study (Table 4) included dose estimates for each exposure group and the corresponding OR, RR or HR from the

Table 1
Estimated annual nitrate-attributable cases of adverse birth outcomes.

Data Imported from Peer-reviewed Literature				Calculated Outcomes			
Analysis ID and birth Outcome	Study author and publication year	Nitrate cut-off level (mg/L)	Risk in exposed Population	Estimated nitrate exposed births [a]	Number of annual attributable cases due to nitrate exposure from community water systems [b]	Number of annual attributable cases due to nitrate exposure from private wells [b]	Percent of annual adverse birth outcomes due to drinking water nitrate [c]
1 – Neural Tube Defect	Brender et al., 2013	4.5	1.43	126,575	32	9	1.4%
2 – Very low birth weight	Stayner 2017b	1	1.17	1,108,703	2592	347	5.3%
3 – Very preterm birth	Stayner 2017b	1	1.08	1,108,703	1522	204	2.7%

[a] The number of at-risk births is the percentage of total 2016 births that is equivalent to the same percentage of people exposed to the nitrate cut-off level relative the total U.S. population.
[b] Attributable cases were calculated based on national incidence proportions. For neural tube defects and very low birth weight outcomes, data was obtained from the 2016 Centers for Disease Control and Prevent National Health Statistics. For very preterm birth, data was obtained from 2014 to 2015 statistics from the March of Dimes Perinatal Data Center (https://www.marchofdimes.org/peristats/Peristats.aspx).
[c] Nitrate attributable cancer cases divided by total cases for each birth outcome based on 2014–2016 incidence statistics. Neural tube defects: 3000 cases; Very low birth weight: 55,242 cases; Very preterm birth: 63,134 cases.

analysis accounting for the most covariables as well as the number of cases and controls or person years. Mean/median values were used when provided in the study or directly provided to us by the author (Schullehner, personal communication). When mean/median values were not available, midpoint values were calculated. For the highest exposure groups where there was no upper concentration limit, dose estimates were calculated as the value plus the width of the previous interval. All values used for exposure/dose estimates are expressed as mg/L nitrate-nitrogen. To achieve this, several conversions were required for studies based on populations in Europe and Asia. For European studies reporting drinking water values as mg/L nitrate, values were multiplied by 0.2259. In the case of Espejo-Herrera et al. (2016), values reported as mg/day nitrate-N were first divided by the average water consumption rate of cases (1.4 L/day) and then converted to nitrate. Chiu et al. (2010) reported values as mmol/L nitrate-N, which were converted into mg/L concentrations.

All statistical analyses were performed in STATA (version 14, STATA, 2018). Generalized least squares regression analysis was used to generate study-specific slopes representing the estimated increase in log risk ratio per mg/L increase in nitrate concentration and standard errors for these slopes. Study-specific slopes and their standard errors were then incorporated into meta-analysis using a random effects model to derive a weighted pooled slope estimate with 95% confidence intervals based on the DerSimonian and Laird method (1986). A random effects model was used instead of a fixed effects model in order to account for both within-study variation and inter-study variation.

Study heterogeneity was assessed using the I^2 test and the heterogeneity chi-squared test for significance, whereby a p-value less than 0.1 considered to be significant (Higgins et al., 2003). I^2 values from 0 to 40%, 30–60%, 50–90% and greater than 75% are interpreted to represent low, moderate, substantial and considerable study heterogeneity, respectively (Deeks et al., 2011). To identify the source of heterogeneity, we conducted additional analysis by grouping studies based on similar covariables following methodology from Camargo et al. (2011). We also conducted sensitivity analysis by omitting single studies from the pooled estimates and examining the I^2 values and p-values for the meta-analysis of the remaining seven studies.

2.8. Analysis of risk-based benchmark values for nitrate protective of human health

We derived a cancer-based drinking water guideline for nitrate following established methodologies for the calculation of drinking water concentrations corresponding to a particular cancer risk level (U.S. EPA, 1992). Here we follow the California Office of Environmental Health Hazard formula (OEHHA, 2004) whereby:

$$C = R / CSF * BR * WCA$$

where.

C = drinking water concentration corresponding to a specified cancer risk level.

R = cancer risk level; in this study we use one-in-one-million or 10^{-6} risk level.

CSF = cancer slope factor.

BR = background cancer rate.

WCA = water consumption adjustment factor between populations.

Here, cancer slope factor is the pooled slope estimate for colorectal cancer, as calculated by meta-analysis; and the background cancer rate was the average annual U.S.-wide incidence of colorectal from 2011 to 2015 published by the Centers for Disease Control and Prevention, which is 39.4 cases per 100,000 people. A water consumption adjustment factor was used to account for differences in the amount of water consumed by the different populations in the included studies since differences in water consumption could lead to differences in internal dose. The water consumption adjustment factor was calculated by taking the inverse of the combined average minimum and maximum

Table 2
Estimated annual nitrate-attributable cases of colorectal, ovarian, thyroid, kidney and bladder cancers.

Data Imported from Peer-reviewed Literature					Calculated Outcomes			
Analysis ID and cancer type	Study author and publication year	Nitrate-N cut-off (mg/L) [a]	Cancer risk in exposed population	Additional risk factors and population adjustment (% of total U.S. Population) [b]	At-risk population [c]	Number of annual attributable cases due to nitrate exposure from community water systems [d]	Number of annual attributable cases due to nitrate exposure from private wells [d]	% of Total annual cancer cases attributable to nitrate exposure, rounded [e]
A - Colorectal	Espejo-Herrera et al., 2016	1.7	1.49	None (100%)	59,144,818	9054	1325	8.2%
B - Colorectal	Espejo-Herrera et al., 2016	0.7	1.3	Above median red meat consumers (50%)	55,479,150	5447	729	4.9%
C - Colorectal	Schullehner et al., 2018	0.9	1.11	None (100%)	96,442,751	3529	478	3.2%
D - Colorectal	Schullehner et al., 2018	2	1.15	None (100%)	46,871,865	2310	374	2.1%
E - Colorectal	De Roos et al., 2003	5	1.8	Above median meat consumers (50%)	3,989,662	939	294	1.0%
F - Ovarian	Inoue-Choi et al., 2015	3	2.03	Women 55–69 years of age with no history of bilateral oophorectomy (7%)	1,935,539	486	94	3.2%
G - Ovarian	Inoue-Choi et al., 2015	5	1.6	Women 55–69 years of age with no history of bilateral oophorectomy (7%)	600,570	84	26	0.6%
H - Thyroid	Ward et al., 2010	2.5	2.18	Women 55–69 years of age (9%)	3,066,241	880	167	2.2%
I – Thyroid	Ward et al., 2010	5	2.59	Women 55–69 years of age (9%)	750,712	281	88	0.8%
J – Kidney	Ward et al., 2007	5	1.7	Above median red meat consumers (50%)	3,989,662	346	108	0.9%
K – Bladder	Jones et al., 2016	5	1.61	Women 55–69 years of age (9%)	750,712	102	32	0.2%

[a] Nitrate concentration cut-offs were rounded to no more than one decimal place.
[b] Population adjustment factors reflect the additional risk factors or population characteristics, such as above median meat or red meat consumption, age and gender, and medical history as defined in the original epidemiological studies.
[c] At-risk population represents the size of the specified sub-population that is exposed to a given nitrate concentration.
[d] Attributable cancer cases were calculated based on age-adjusted annual cancer incidence from 2011 to 2015 obtained from the Centers for Disease Control and Prevention U.S. Cancer Statistics. For ovarian, thyroid and bladder cancers attributable cases were calculated on the basis of annual incidence from 2011 to 2015 for females 50 + years of age.
[e] Nitrate-attributed cancer cases divided by total expected cancer cases, rounded to one decimal place.

Table 3
Disability-adjusted life years (DALYs) and economic costs associated with estimated annual nitrate-attributable cancer cases.

Analysis ID and cancer type	Total nitrate attributable cases for community water systems and private wells [a]	Total years of life with disease [b]	Total years lost due to disability [b]	Total years of life lost [b]	Total DALYs[b]	Estimated indirect Economic Loss due to Lost Productivity, in 2014 U.S. dollars (billions)[c]	Combined medical costs of cancer treatment in 2014 U.S. dollars (billions) [d]
A - Colorectal	10,379	62,275	26,778	58,123	84,901	$4.90	$1.33
B - Colorectal	6176	37,053	15,933	34,583	50,516	$2.92	$0.79
C - Colorectal	4007	24,041	10,338	22,439	32,776	$1.89	$0.51
D - Colorectal	2684	16,104	6925	15,031	21,956	$1.27	$0.34
E - Colorectal	1233	7396	3180	6903	10,083	$0.58	$0.16
F - Ovarian	580	4062	1747	6441	8188	$0.47	$0.11
G - Ovarian	110	773	332	1226	1558	$0.09	$0.02
H - Thyroid	1047	23,026	6217	8478	14,695	$0.85	N/A
I – Thyroid	369	8113	2191	2987	5178	$0.30	N/A
J – Kidney	454	3179	858	3451	4310	$0.25	$0.06
K – Bladder	134	938	253	281	535	$0.03	$0.01

[a] Values from Table 2, combining the estimated cancer cases for private well users and for community water systems.
[b] Values in these columns refer to total years of life with disease, years lost due to disability, years of life lost and DALYs for all cases attributed to nitrate in each analysis. Calculations for cancer specific disability-adjusted life years are listed in Supplementary Table S2.
[c] Economic Loss = VOLY * Total DALYs where VOLY = $57,757.
[d] Economic loss due to medical costs of cancer treatment calculated on the basis of annualized mean net costs of care per patient published by the National Cancer Institute. As listed in Supplementary Table 2, medical costs per case of colorectal cancer are $127,890; per case of ovarian cancer are $196,452; per case of kidney cancer are $128,921; per case of bladder cancer are $92,127. No medical costs for thyroid cancer were listed by the National Cancer Institute study (Mariotto et al., 2011), indicated as N/A for "Not Available".

reported water consumption values (L/day) for each study included in our meta-analysis (Supplementary Table S4). This combined average value was 2.13 L/day. Where specific values for water consumption could not be identified, a value of 2 L/day was assumed, as common practice for U.S. EPA drinking water standards (U.S. EPA, 2018a).

3. Results

3.1. Annual nitrate-attributable disease cases

A unique and powerful feature of this analysis is our ability to calculate exposure information for the portion of the U.S. population, by state, that likely ingest nitrate above specified concentrations in drinking water. As expected, the population exposed negatively correlates with nitrate levels in the water supply, where a greater number of people are exposed to lower levels of nitrate and vice versa, with the exception of those with non-detectable levels (Fig. 1). From 2010 to 2017, approximately 81 million people served by community water systems in the U.S. had a mean drinking water nitrate level of 1 mg/L and above, while 6 million people had a mean level of 5 mg/L or more nitrate in their drinking water (Fig. 1). Similar calculations were conducted for nitrate exposure levels for private well users, and nitrate-attributable cases of disease were analyzed separately for private well and community water system users (Tables 1 and 2).

To assess the health risks associated with short-term exposure to drinking water nitrate during pregnancy, we calculated the number of nitrate-attributable adverse pregnancy outcomes. Such adverse outcomes affect a relatively small percent of the overall pregnancies. Centers for Disease Control and Prevention statistics show that approximately 0.07% of births have neural tube defects, while 1.4–1.6% of births are associated with very low birth weight or very preterm deliveries. Based on risk estimates reported in epidemiological studies on drinking water nitrate exposure and pregnancy outcomes (Brender et al., 2013; Stayner 2017b), we calculated that annually 2939 very low birth weight births, 1725 very preterm births, and 41 births with neural tube defects could be attributable to nitrate exposure (Table 1). Nitrate-attributable cases of neural tube defects, very low birth weight and very preterm birth account for 1.4, 5.3 and 2.7 percent of total annual cases of these adverse reproductive outcomes in the U.S.

Combining the exposed population and cancer case estimates for community water systems and private well users yields an estimated range of annual national nitrate-attributable colorectal cancer cases between 1233 and 10,379 cases, corresponding to between 1 percent and 8 percent of all annual U.S. colorectal cancer cases (Table 2). The lowest number of nitrate-attributable cancer cases was derived from a scenario based on findings from De Roos et al. (2003) (Scenario E) while the highest number of nitrate-attributable cancer cases was derived from the Espejo-Herrera et al. (2016) general population scenario (Scenario A). Previous published literature has estimated the number of nitrate attributable colorectal cancer cases in the European Union as approximately 4 percent of the annual incidence (van Grinsven et al., 2010), which is comparable to the range determined in our study.

This analysis was repeated for ovarian, thyroid, kidney and bladder cancer yielding an additional 110–580 ovarian, 369–1047 thyroid, 454 kidney and 134 bladder cancer cases respectively (Table 2). These additional cases represent approximately 0.6–3 percent of the annual US ovarian cancer cases, 0.8 to 2 percent of the thyroid cancer cases, 0.9 percent of the kidney cancer cases and just 0.2 percent of the annual bladder cancer cases. Adding estimated ovarian, thyroid, kidney and bladder cancers to the total colorectal cancer cases results in a modest increase in the total estimate for annual nitrate-attributable cancer cases, ranging from 2300 to 12,594, where 54–82% of cases correspond to colorectal cancer.

3.2. Medical costs and lost productivity costs due to nitrate-attributable diseases

Here we followed the examples of other studies by separately considering the direct and indirect costs of illness (U.S. EPA, 2010). For an economic assessment of costs related to neural tube defects, we relied on the lifetime direct costs for spina bifida of $577,000 to 791,900 per case (2014 U.S. dollars), as published by the National Center on Birth Defects and Developmental Disabilities, a part of the U.S. Centers for Disease Control and Prevention (Grosse et al., 2016). For 41 annual nitrate-attributable cases of neural tube defects, this cost per case corresponds to an economic impact of $24–32 million.

For premature births, we applied a value of $51,600 (in 2005 dollars) as reported by the Institute of Medicine (2007), corresponding to $67,022 in 2014 dollars, which translates to a medical cost of 116 million dollars for the 1725 annual nitrate-attributable cases of very preterm birth. Notably, there might be potential overlap between very preterm births and very low birth weight cases and additional epidemiological research is needed to better define these relative risks of nitrate-associated adverse birth outcomes. Further, following recently

Table 4
Number of cases and controls, estimated dose and relative risk values extracted from studies included in the meta-analysis.

Study	Cases	Controls	Exposure groups (mg/L)	Estimated dose (mg/L)	Relative risk	95% Confidence Interval lower limit	95% Confidence Interval upper limit
Case-Control Studies							
De Roos et al., (2003) [a b]	172	566	≤1	0.5	1		
Table 2	116	380	>1 ≤ 3	2	1.02	0.8	1.3
	27	124	>3 ≤ 5	4	0.7	0.4	1.1
	61	174	>5	7	1.2	0.8	1.7
Espejo-Herrera et al.,	778	1899	≤0.81	0.40	1		
(2016) [a c d]	447	803	>0.81–1.61	1.21	1.7	0.98	1.38
Table 2	644	828	>1.61	2.42	1.49	1.24	1.78
Chiu et al., (2010) [e f]	1921	2052	<0.38	0.06	1		
Table 3	730	732	0.39–0.57	0.43	1.02	0.9	1.15
	1056	923	>0.60	0.99	1.16	1.04	1.3
Yang et al., (2007) [f]	775	746	≤0.22	0.00	1		
Table 2	758	749	0.23–0.45	0.38	0.98	0.84	1.14
	701	739	0.48–2.86	0.74	0.98	0.83	1.16
Fathmawati et al., (2017)	56	67	≤11.3	5.65	1		
[a c]	19	8	>11.3	22.59	2.82	1.075	7.395
Table 2							
McElroy et al., (2008) [a g]	147	549	<0.5	0.25	1		
	104	274	0.5–1.9	1.20	1.39	1.02	1.89
	137	361	2.0–5.9	3.95	1.32	0.99	1.76
	57	159	6.0–9.9	7.95	1.28	0.88	1.88
	33	86	≥10.0	13.90	1.57	0.97	2.52
	Cases	**Person-years**	**Exposure Groups (mg/L**	**Estimated Dose (mg/L)**	**Risk Ratio**	**95% Confidence Interval Lower Limit**	**95% Confidence Interval Upper Limit**
Cohort Studies							
Weyer et al., (2001) [h i]	58	48,438	<0.36	0.20	1.00		
	86	48,163	0.36–1.00	0.70	1.53	1.09	2.16
	92	47,821	1.01–2.46	1.91	1.54	1.08	2.19
	64	48,011	>2.46	5.59	0.98	0.66	1.46
Schullehner et al., (2018)	788	4,071,980	<0.29	0.16	1.00		
[c j]	517	3,917,230	0.29–0.53	0.42	1.08	0.96	1.21
	478	4,169,923	0.53–0.87	0.66	0.97	0.87	1.09
	777	5,146,393	0.87–2.09	1.24	1.09	0.98	1.2
	1140	5,520,772	≥2.09	3.63	1.14	1.04	1.24

[a] Dose estimated as calculated midpoint.
[b] OR for second exposure group was originally 1 but changed to 1.02 by log-transforming the upper and lower confidence limits and exponentiating the midpoint of the two log-transformed confidence limits.
[c] Nitrate values were multiplied by 0.2259 to convert Nitrate-NO_3 to Nitrate-N.
[d] Converted mg/day to mg/L by dividing by average water consumption of cases (1.4 L/day).
[e] Exposure values were originally measured in mmol/L and converted into mg/L (multiplied by 14.0067).
[f] Dose estimated as median reported in the study.
[g] Case and control numbers are an approximation based on total sample size and percentages reported for each exposure group.
[h] Dose estimated as mean reported in the study.
[i] 25,736 women in the at-risk cohort.
[j] Dose estimated as median based on data received through personal communication with the authors.

published methodology (Malits et al., 2018), we estimated indirect costs due to lost productivity caused by IQ loss associated with low birth weight to be 172 million to 232 million dollars, at $11,745 – $15,883 (2014 dollars) per IQ point loss, for 2939 annual nitrate-attributable very low birth weight cases. Other economic costs, such as parental lost work days are not accounted for in this analysis, and the overall costs of nitrate-attributable adverse birth outcomes are likely to be greater than what is estimated here.

For economic valuation of nitrate-attributable cancer cases, we first estimated hospitalization and medical treatment costs, which are the direct cost of medical resources to treat disease that can be ascertained from national health care cost statistics. Next, we estimated economic losses due to disability and premature death of patients with nitrate-attributable cancer, which represent harder to define indirect costs. Our analysis does not include society-level non-medical costs associated with the illness, such as the loss of work time and productivity as well as the loss of leisure time for family members of patients with the disease, due to difficulties in estimating such economic impacts.

Based on the National Cancer Institute data for the cost of treatment, we calculated that a range of 250 million to 1.5 billion dollars of medical costs in 2014 dollars could be due to the nitrate-attributable cancer cases (Table 3). For the indirect economic costs, we used the Disability-Adjusted Life Years methodology, combined with the Value of Life Year approach. For all cancers combined, nitrate-attributable loss of years of life due to disability and premature death corresponds to the estimated range of 21,663 to 112,628 annual nitrate-attributable DALYs (Table 3). Using a published estimate of $57,757 (in 2014 dollars) for the Value of Life Year (Desaigues et al., 2011), this translates to 1.3 billion to 6.5 billion dollars in annual indirect economic losses.

3.3. Meta-analysis of colorectal cancer studies

Based on the risk estimates reported in epidemiological studies and potential number of nitrate-attributable cases calculated here, we concluded that colorectal cancers pose the greatest risk linked to exposure to nitrate in drinking water relative to other cancer sites, and thus presents an area where a meta-analysis would be warranted to define the exposure-response relationship.

In total, nineteen studies were returned based on our search query in Pubmed, of which 12 were relevant to our study question and eight

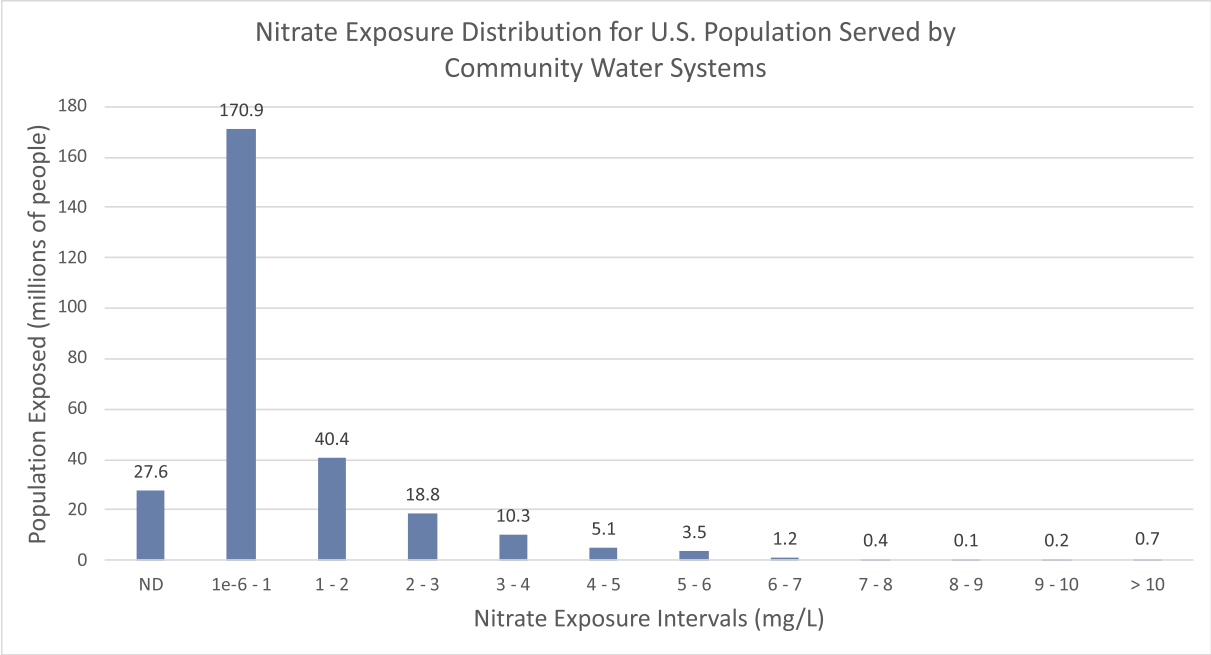

Fig. 1. U.S. population distribution for exposure to nitrate in drinking water at specific concentration ranges. Data from 2010 to 2017 for community water systems for all 50 states. The lower range of the nitrate exposure intervals represents the lowest average calculated. ND = non-detect. Source of data: Environmental Working Group Tap Water Database (https://www.ewg.org/tapwater/).

met our inclusion criteria (Supplementary Table 3). Of the studies not included, Morales-Suarez-Varela et al. (1995) and Gulis et al. (2002) were both ecological studies while Chang et al. (2010) included the same study population controls used in another publication already included in the meta-analysis (Chiu et al., 2010). Kuo et al. (2007) only assessed rectal cancer risks yet observed a significant increase in rectal cancer mortality for those exposed to a 0.72 mg/L median level of nitrate.

Findings of these studies were similar to others included in the meta-analysis, where the majority found positive associations between nitrate exposure in drinking water and colorectal cancer. Gulis et al. (2002) observed a positive trend for increased colorectal cancer in women exposed from low to high nitrate levels. Chang et al. (2010) found an increased risk of rectal cancer mortality at low concentrations of nitrate in drinking water (> 0.38 mg/L). Morales-Suarez-Varela et al. (1995) found no association between nitrate in drinking water and colon cancer mortality but did observe a statistically significant increase in risk of death from gastric cancer. Of the remaining eight studies, six were case-control studies resulting in a total of 8739 colorectal cancer cases and 12,219 controls, and two were cohort studies resulting in 4000 colorectal cancer cases over 1,758,862 person-years included in the meta-analysis.

Results of the generalized least squares regression analysis yielded positive study specific slopes for six studies, while negative study specific slopes were observed for the other two (Table 5). A study by Weyer et al. (2001) observed an increased risk in the second and third exposure groups, but a decreased risk in the highest exposure group, resulting in an overall negative slope. Overall, the dose response analysis of all studies (Fig. 2) yielded a statistically significant positive linear association between nitrate in drinking water and increased colorectal cancer risk, RR = 1.04 (95% CI 1.01-1.07) and a significant pooled linear slope estimate of 0.04 per mg/L increase (95% CI 0.009-0.072) (Table 5).

We observed substantial heterogeneity in our analysis (I^2 = 69.1%, p = 0.0002). Within the meta-analysis framework, heterogeneity can come from inconsistencies of study findings as well as study quality and study characteristics such as design and sample size (i.e. case control or cohort), geographic region (United States vs. Europe vs. Asia), and other variables explored in Table S5 and the literature (Camargo et al., 2011). Given the substantial amount of heterogeneity in the pooled estimate, an assessment was done to identify the source of heterogeneity among the studies by grouping studies based on certain

Table 5
Study specific dose-response slope estimates from general least squares regression and pooled slope estimate from meta-analysis of colorectal cancer risk and drinking water nitrate.

Study	Regression slope	Regression slope 95% Confidence Interval lower limit	Regression slope 95% Confidence Interval upper limit	Standard error
Case-Control Studies				
De Roos et al. (2003)	0.014	−0.034	0.062	0.025
Espejo-Herrera et al. (2016)	0.161	0.089	0.233	0.037
Chiu et al. (2010)	0.144	0.03	0.258	0.058
Yang et al. (2007)	−0.029	−0.256	0.198	0.116
Fathmawati et al. (2017)	0.046	0.003	0.09	0.022
McElroy et al. (2008)	0.026	−0.004	0.055	0.015
Cohort Studies				
Weyer et al. (2001)	−0.43	−0.108	0.021	0.033
Schullehner et al. (2018)	0.034	0.014	0.053	0.010
Pooled				
All studies	0.04	0.009	0.072	

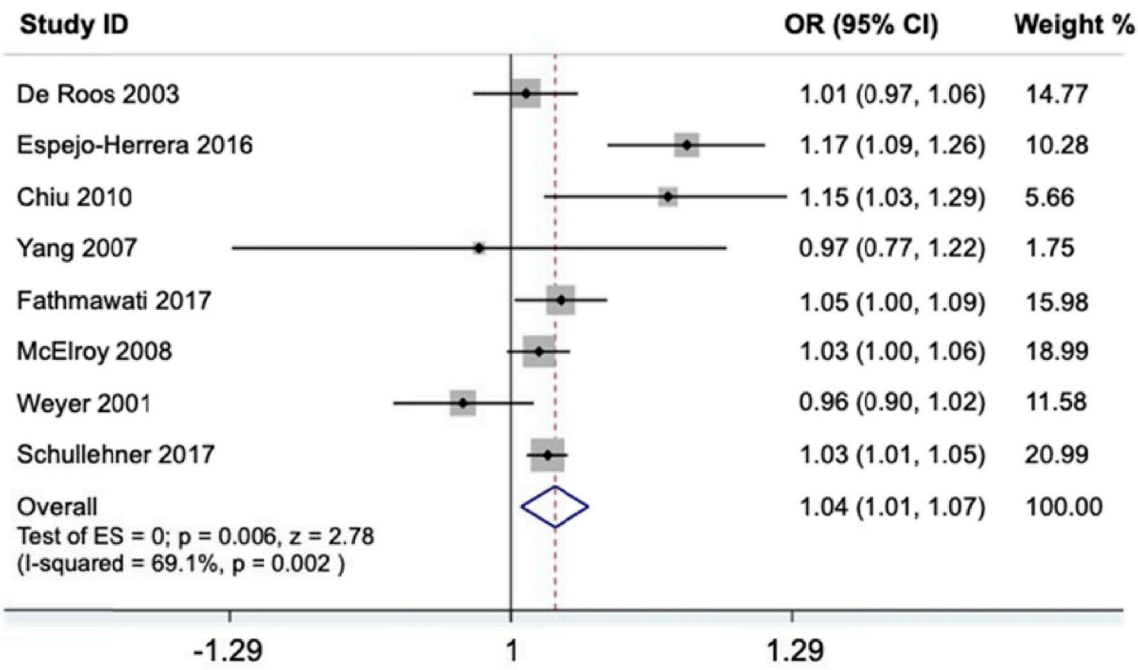

Fig. 2. Odds ratio (OR), 95% confidence intervals (95% CI), study weight within the overall meta-analysis and overall risk estimate based on studies of nitrate exposure from drinking water and colorectal cancer risk. ORs were obtained by exponentiating the study-specific slope estimates from generalized least squared regression to obtain log risk ratio estimates per mg/L increase in nitrate.

covariables as well as omitting single studies from the analysis (Supplementary Table S5 and S6).

Calculated pooled slopes from other study combinations based on covariables did not clearly identify a meaningful study covariable for which to attribute heterogeneity. There was some indication that for studies which did not account for dietary factors, a reduced slope estimate as well as reduced heterogeneity was observed. Additionally, these calculated slopes for analyses typically including more than two studies were within the 95% confidence intervals of the analysis including all eight selected studies (Supplementary Table S5).

After omitting single studies and rerunning the meta-analysis, one study in particular, Espejo-Herrera et al. (2016), was identified as the major source of statistical heterogeneity in the pooled analysis. Removing Espejo-Herrera from the pooled assessment reduced the heterogeneity (I^2 value) to 41.7%, which was no longer significant ($p = 0.113$). Given that Espejo-Herrera observed the greatest positive linear dose response for nitrate and colorectal cancer risk, the pooled slope estimate from the remaining seven studies was slightly reduced relative to the eight study meta-analysis, 0.027, yet remained statistically significant (Supplementary Table S6; Test of effect size = 0, $p = 0.019$). Espejo-Herrera used a strong study design that included exposure assessment from public water supplies, private wells and bottled water; accounted for factors that influence endogenous nitrosation; and pooled data from two European cohorts, increasing sample size. Given the high quality of this study, its inclusion is important to the calculation of the pooled slope. For the purposes of using this information to calculate a range of drinking water health benchmarks, it was determined that while removing Espejo-Herrera from the meta-analysis, statistically improves the heterogeneity, such an analysis would not accurately reflect the strength of evidence within the epidemiological literature and a more relevant analysis was not gained by omission of this study in an effort to reduce overall heterogeneity.

3.4. Risk-based drinking water benchmarks for nitrate

Based on the estimated nitrate-attributable colorectal cancer cases and colorectal cancer meta-analysis, we calculated an array of drinking water benchmarks corresponding to an annual one-in-one-million cancer risk (Table 6). First, we used our estimated nitrate-attributable cancer cases (Table 2), expressed as additional cases per million people at a given nitrate concentration to linearly extrapolate a concentration corresponding to one additional case of nitrate-attributable cancer per million people. This approach results in values that range from 0.04 to 1.3 mg/L. Similar to the nitrate attributable colorectal cancer cases, the lower range is derived from Espejo-Herrera et al. (2016) while the upper range is derived from De Roos et al. (2003). Second, using the cancer slope factor of 0.04 per mg/L increase in nitrate corresponding to pooled slope estimate from the meta-analysis, and following the equation outlined in section 2.8, results in a drinking water nitrate concentration of 0.14 mg/L (95% CI 0.08-0.63 mg/L) as the central estimate for annual one-in-one-million cancer risk level.

4. Discussion

Epidemiological data suggest that nitrate impacts on human health may occur at nitrate concentrations present in drinking water in the United States today. Among health impacts observed in epidemiological studies of nitrate in drinking water, colorectal cancer shows the strongest association, based on long-term studies with large numbers of study participants. National Cancer Institute statistics show that colorectal cancer is the fourth most prevalent cancer in the United States, with over 1.3 million people living with colorectal cancer in 2015 and 140,250 new cases estimated for 2018 (SEER, 2018). Recent trends suggest that both incidence and mortality due to colorectal cancer are decreasing slightly, with 2.4% and 2.6% decrease over the last decade, respectively (SEER, 2018). Yet, given the numbers of people affected by colorectal cancer, it remains imperative to continue research into risk factors for this disease and measures that can be taken to address them. Smoking, physical inactivity, high dietary intake of red meat and consumption of processed, nitrate-preserved meats are some of the known risk factors for colorectal cancer. Detection of additional risk factors and identification of measures to eliminate such risk would help decrease the health and economic impacts of colorectal cancer on society.

Through a combination of targeted study review and meta-analysis,

Table 6
Nitrate concentrations corresponding to one-in-one-million annual colorectal cancer risk derived from nitrate-attributable cancer case analysis and from meta-analysis.

Source of risk estimate	Nitrate cut-off concentration used in nitrate-attributable cancer case analysis (mg/L, Table 2)	Estimated nitrate- attributable cases per million at cut-off concentration [a]	Extrapolated concentration for annual one-in-one-million cancer risk [b]	Meta-analysis derived one-in-one-million cancer risk (95% Confidence Intervals) [c]
Nitrate-Attributable Cancer Case Analysis				
Espejo-Herrera et al., 2016 - A	1.7	30.70	0.06	
Espejo-Herrera et al., 2016 - B	0.7	18.51	0.04	
Schullehner et al., 2018 - C	0.9	11.94	0.08	
Schullehner et al., 2018 - D	2	7.71	0.26	
De Roos et al., 2003 - E	5	3.86	1.29	
Meta-Analysis				0.14 (0.08–0.63)

[a] Attributable cases per million was obtained by dividing the estimated number of nitrate-attributable cases by the total U.S. population from 2017 census estimates (325,719,178 people).
[b] Concentration corresponding to annual one-in-one-million cancer risk was obtained by dividing the nitrate concentration for a specified scenario (values in column 2) by the estimated number of attributable cases per million people in the U.S. population (values in column 3).
[c] Concentration corresponding to annual one-in-one million cancer risk obtained using the cancer slope factor derived from a meta-analysis of colorectal cancer risk and nitrate in drinking water and the equation listed in Methods section 2.8.

we developed a risk estimate of drinking water nitrate-attributable colorectal cancer in the United States. Our data suggest that exposure to nitrate in drinking water could account for 1–8% of total colorectal cancer cases, which translates into 1233–10,379 cancer cases annually. Of these cases, 12–24% are due to nitrate exposure for private well users, especially for people whose well water has 5 mg/L or more nitrate.

Given that our study focused on nitrate occurrence data in drinking water for 2010–2017 and that cancer is a disease with long latency, the findings presented in this study are most relevant for future cancer prevention efforts. Additionally, our analysis includes some uncertainty around the exact number and exposure information for people served by community water systems and private wells. However, we note that the impact of the population adjustment factor used here to account for this uncertainty is smaller than the variability observed in the range of reported risk estimates for nitrate-attributable diseases, and thus unlikely to influence significantly the disease case estimates presented here. Additional limitations in our estimation of nitrate-attributable disease cases and associated economic costs come from the assumption of causality necessary to perform such an analysis. Published studies have suggested that the lower limits of the health costs and exposure attributable cases may be zero (van Grinsven et al., 2010; U.S. EPA, 2005).

Exposure to drinking water contaminants has been described as a risk factor for other cancers such as exposure to drinking water disinfection byproducts and bladder cancer. In fact, using the risk estimate and slope calculated based on meta-analysis by Villanueva et al. (2003), the U.S. EPA (2005) estimated the annual number disinfection byproduct-attributable bladder cancer cases as 8899 (95% CI 4830-15,376). This estimated number of cancer cases is comparable to the number of nitrate-attributable colorectal cancer cases we present here. Of note, disinfection byproduct-attributable bladder cancer cases represent a greater percentage of the population-attributable fraction for this cancer site, approximately 16%, than nitrate-attributable colorectal cancer cases, 1–8%. This could be due to the steeper cancer slope factor for disinfection byproducts, 0.006 per μg/L increase compared to our calculated cancer slope factor for nitrate of 0.00004 per μg/L increase when expressed in the same units.

The latest research has produced strengthened epidemiological evidence for the risk of colorectal cancer at nitrate levels below the regulatory standard of 10 mg/L of nitrate as nitrogen. Even a small increase in risk, as suggested by our meta-analysis, can lead to large population-attributable risk and a large number of disease cases that could be avoided if these exposures were prevented (Rose, 2001). Additionally, our economic analysis suggests that this attributable risk to a large population also comes at large economic costs, initially felt by individuals and families as direct medical costs, and eventually translating into overall economic loss for the society because of loss of work time and productivity. The medical impacts for cancer treatment are particularly significant for the United States because patients in the U.S. may personally bear all or a large portion of these medical costs because of the lack of health insurance or limited coverage under existing insurance plans.

Current estimates for the annual prevalence cost of colorectal cancer in the United States is $14.1 billion (Yabroff et al., 2012). Based on our estimates that 1 to 8 percent of colorectal cancer cases could be attributed to nitrate exposure, expected medical costs would be $141 million to $1.1 billion, which is also reflected by the estimated medical costs presented in this study of $157 million to $1.3 billion. Given the increasingly aging population and the advancement of medical treatments, the annual costs of cancer are expected to grow 27 to 39 percent between 2010 and 2020 (Mariotto et al., 2011), highlighting the need for prevention strategies geared towards reducing the cancer burden.

For the calculation of indirect economic costs, we used a combination of the Disability-Adjusted Life Years approach together with the Value of Life Year (VOLY) valuation. Here we used a VOLY value of

$57,757 in 2014 US dollars, based on recent research literature (Desaigues et al., 2011; Grandjean and Bellanger, 2017; van Grinsven et al., 2010). It is possible that the VOLY value derived from these studies is underestimated. For example, an alternative VOLY value developed by the Institute for Clinical and Economic Review (2017) defined the value of one Quality-Adjusted Life Year between $100,000 and $150,000 with the median value of $125,000 was considered for use in this analysis. Additionally, in an assessment of economic loss due to cancer deaths in the United States, Yabroff et al. (2008) used a VOLY of $150,000. If either of these values were used, our calculated nitrate attributable economic losses would be up to approximately $12.8 billion (not adjusted for inflation). While such economic analyses produce only approximate estimates, the overall data presented form a solid foundation for the argument that existing levels of nitrate in U.S. drinking water may drive negative health and economic impacts on society and that lowering nitrate exposure from drinking water would protect public health.

For additional point of comparison, we note that U.S. EPA uses a different methodology for calculating the costs of environmental pollution, namely the "Value of Statistical Life" approach. A broad spread of estimates for the Value of Statistical Life ranging from $1 million to $10 million (2000 dollars) is reported in the literature (Viscusi and Aldy, 2003). In recent reports, U.S. EPA has recommended using a Value of Statistical Life of $7.9 million (in 2008 dollars) (U.S. EPA, 2010), while in a 2015 regulatory impact assessment, a value of $10 million was used (U.S. EPA, 2015b). There are scientific uncertainties around applying the Value of Statistical Life approach for the calculations of indirect economic loss due to cancer, since not every cancer case results in mortality. For the 2300 to 12,594 annual nitrate-attributable cancer cases calculated here, a Value of Statistical Life of $1 million translates into $2.3-$12.6 billion in indirect economic losses due to nitrate pollution of drinking water, while the Value of Statistical Life of $10 million would result in 10 times greater amount in indirect economic losses.

For the purposes of cost-benefit analysis, the estimates for the range of direct and indirect costs due to nitrate in drinking water can be compared with the costs of removing nitrate from drinking water. Based on the published methodology for estimating nitrate treatment costs per 1000 gallons of water treated (Jensen et al., 2012), a study published online by Environmental Working Group estimated that if all U.S. communities with drinking water nitrate concentrations at or above 5 mg/L, which lacked nitrate treatment as of 2014–2015, added ion exchange systems for nitrate removal, the total extra cost would range from about $102 million a year to almost $765 million a year (Weir Schechinger and Cox, 2018). If each of these communities without nitrate treatment opted for a reverse osmosis water treatment system instead, the added cost could be as high as $1.47 billion a year. These costs are particularly significant for small rural communities where water systems often lack funds for capital improvement. According to the same analysis, as much as $666 a year per person is added to the cost of providing drinking water in a very small community, while a reverse osmosis system could add as much as $2776 a year (Weir Schechinger and Cox, 2018).

Studies by the U.S. Geological Survey have pointed out a rising trend in nitrate concentrations in groundwater, particularly in the agricultural areas (Pennino et al., 2017; Rupert, 2008), and the number of nitrate-attributable disease may grow in future years. Every year, nitrogen-based fertilizer is spread in farming areas, and a significant portion of that nitrogen ends up as nitrate in surface water and ground water supplies that communities small and large depend on as a source of their drinking water. Nitrate contamination present in the ground water would likely stay there for years or decades, and the exposures identified in this study would likely continue or become more severe if nitrate removal technologies are not utilized.

Finally, our study has used two approaches to calculate a risk-based drinking water benchmark for nitrate. First, based on nitrate-attributable cancer cases from three studies, we calculated an array of cancer-based drinking water benchmarks for nitrate that range from 0.04 to 1.3 mg/L (Table 6). For a statistically valid central estimate of the one-in-one-million risk level, we used the cancer slop estimate for nitrate derived from a meta-analysis, to yield of value of 0.14 mg/L (95% CI: 0.08–0.63 mg/L). These benchmarks are based on annual background rates of colorectal cancer and therefore correspond to annual one-in-one-million cancer risk. Our heterogeneity analysis indicated that removing Espejo-Herrera from the pooled analysis would reduce the study heterogeneity. Using the pooled slope estimate and 95% confidence intervals from the seven study meta-analysis would still produce drinking water guideline values within this range.

In practice, regulatory agencies have considered a lifetime one-in-one-million risk (OEHHA 2018b) as the *de minimus* risk acceptable for general public exposure to cancer-causing chemicals. At lifetime risk level of one-in-one-million implies that not more than one person in a population of one million people drinking the water with the specified contaminant concentration daily for 70 years would be expected to develop cancer as a result of exposure to that chemical. Different government agencies use different risk frameworks and the choice of a specific risk level may depend on the specific policy context. For example, 10^{-6} risk level is used by the state of California for the development of public health goals for cancer-causing drinking water contaminants (OEHHA 2018b), while the state of Minnesota uses a 10^{-5} risk level for setting the water benchmarks for cancer-causing contaminants (Minnesota Administrative Rules Part 4717.7840).

Questions remain about the appropriate translation of the annual cancer risk benchmark into a lifetime benchmark. If the cancer risk were linear throughout the range of possible exposure concentrations and duration of exposures, then one could calculate the lifetime cancer risk benchmark by dividing the annual cancer risk benchmark by factor of 70, the length of life used in regulatory risk assessments or by using a lifetime background cancer rate, expressed as the number of cancer deaths divided by the number of total deaths. Future studies of the dose-response relationship for nitrate may help clarify whether such an approach can be used for deriving lifetime cancer risk benchmark for nitrate. As typical for epidemiological studies, data presented and analyzed here are suggestive but not conclusive for establishing causality and defining the dose-response function. To address this uncertainty, we present the calculations from the meta-analysis in the context of an array of estimates calculated based on relative risk reported by individual, high-quality epidemiological studies coupled with real nitrate exposure data that reinforces our confidence in the final assessment.

Another approach for derivation of drinking water benchmarks for nitrate can come from the consideration of non-cancer effects of nitrate exposure, specifically the effects on the developing fetus (Stayner, 2017b). These risks apply to nitrate exposure during pregnancy, which is a relatively short period of exposure and a window of greater vulnerability. Such epidemiological studies likely have greater reliability for the derivation of human-health protective water benchmarks, because they eliminate uncertainties due to interspecies extrapolation from laboratory animals to humans. On the other hand, uncertainty factors, sometimes also considered safety factors, may be appropriate for the assessment that involves LOAEL (Lowest Observed Adverse Effect Level) to NOAEL (No Observed Adverse Effect Level) extrapolation, where U.S. EPA-defined default uncertainty factor is 10 (U.S. EPA, 2002). Additionally, in some circumstances a children's health protection factor of 10 may also be warranted, to account for children's greater susceptibility to toxic chemicals (National Research Council, 1993). Applying a single uncertainty/safety factor of 10 to the two departure points for nitrate's developmental effects, 1 mg/L from Stayner et al. (2017a) and 4.5 mg/L from Brender et al. (2013), results in drinking water benchmarks of 0.1–0.45 mg/L, respectively. These values are consistent with health benchmarks developed on the basis of annual cancer risk due to nitrate.

Two key uncertainties remain, namely, the shape of the dose-response curve and the concentration of the nitrate in the water where no adverse effects would be observed. These can only be addressed by future toxicology and epidemiology studies. The topics of threshold effects and the shape of dose-response curve for environmental contaminants have been hotly debated in the risk assessment literature for decades (National Research Council 2009; Zeise et al., 1987). However, these uncertainties do not preclude the need to search for pragmatic solutions to water quality problems and nitrate pollution of water supplies that are faced by communities today.

Availability of data and materials

The U.S. nitrate occurrence dataset analyzed in this study is posted in an open access database available at https://www.ewg.org/tapwater/.

Declarations of interest

None.

Authors' contributions

All authors have made substantial contributions to conception and design of this research, analysis and interpretation of data, and manuscript preparation.

Submission declaration

This work is original, has not been previously published and is not under consideration for publication elsewhere.

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Ethics approval and consent to participate

Not applicable.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2019.04.009.

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