Drinking Water Nitrates and Public Health: A Literature Review

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Background: In Oregon's Southern Willamette Valley a Groundwater Management Area was created due to high concentrations of groundwater nitrate. Nitrate is a widespread drinking water contaminant and associated health risks have been studied world-wide. A synthesis of current research was needed to enable accurate communication of potential health effects to the residents of the groundwater management area.

Methods: An epidemiological literature review was conducted for the illnesses most frequently associated with nitrate in drinking water: methemoglobinemia, cancer, type 1 childhood diabetes, and adverse reproductive outcomes. Emerging disease associations were also evaluated.

Results: There is no consensus on the association between nitrates in drinking water and adverse health outcomes. Results are mixed and a definitive conclusion could not be reached with studies finding nitrates to have positive, negative, or no correlation to disease incidence.

Conclusions: The nature of epidemiological research makes conducting high-quality studies difficult. The absence of long-term data on individual exposure, the latency of cancer onset, and the use of gross annual nitrate values hampers the reliable estimation of health risk. Attempts to quantify nitrate exposure should include inputs from well water, endogenous nitrosation, and dietary intake, and integrate the role metabolic inhibitors, genetic precursors, and subpopulation vulnerabilities. The complex environmental and physiological interactions of nitrate must be further examined to untangle the effects co-contaminants and the role of disease cofactors.

While the potential health effects of nitrates have been documented, the ambiguous results of this review will complicate risk communication. Care will need to be taken when communicating to reflect the current state of research.

Disease	Author (Year)	# of Subjects	Study Design	Study Location	Summary of Findings
Methemoglobinemia	Knobeloch, *et al.* (2000)	2	Case series	Wisconsin	Positive association
	Gupta, *et al.* (2001)	88	Cross-sectional	Rajasthan, India	Positive association with acute recurrent diarrhea
	Gupta, *et al.* (2000)	178	Cross-sectional	Rajasthan, India	Positive association with cytochrome b5 reductase activity; possible adaptation to compensate for methemoglobinemia
	Comly (1945)	2	Case series	Iowa	Established initial causal link with drinking water nitrate levels; suggested bacterial involvement
	Walton (1951)	278	Literature review	USA	Basis for nitrate maximum contaminant level standard
	Avery (1999)	-	Literature review	-	Nitrate an exacerbating factor but may not be the cause
	Fewtrell (2004)	-	Literature review	-	Single association in question; no exposure-response relationship
	L'hirondel & L'hirondel (2002)	-	Literature review	-	Methemoglobinemia caused by some other factor associated with polluted wells; nitrate link does not fit observations
Reproductive Outcomes	Aschengrau, *et al.* (1989)	286	Case-control	Massachusetts	Negative association with spontaneous abortions
	Arbuckle, *et al.* (1988)	130	Case-control	New Brunswick, Canada	Positive association with central nervous system birth defects for well water; negative association with municipal water supplies, both non-significant
	Croen, *et al.* (2001)	538	Case-control	California	Positive association with risk for anencephaly when nitrate above maximum contaminant level and for groundwater drinkers below maximum contaminant level
	Brender, *et al.* (2004)	43	Case-control	Texas	Positive association with neural tube defects; nitrate increases adverse effects of nitrosatiable drugs
	Bukowski, *et al.* (2001)	210; 336	Case-control	Prince Edward Island, Canada	Positive association with growth restrictions and prematurity; significant dose-response trend
	Cedergren, *et al.* (2002)	753	Cohort	Sweden	Non-significant positive association with cardiac defects
Diabetes	Virtanen, *et al.* (1994)	471	Case-control	Finland	No association with drinking water nitrate; positive association with dietary nitrite
	Casu, *et al.* (2000)	1,975	Case-control	Sardinia, Italy	No association
	van Maanen, *et al.* (2000)	1,064	Case-control	Netherlands	No association when nitrate <25 mg/L; non-significant positive association when nitrate >25 mg/L
	Zhao, *et al.* (2001)	517	Case-control	Devon and Cornwall, England	No association
	Moltchanova, *et al.* (2004)	3,564	Case-control	Finland	No association; non-significant positive trend
	Kostraba, *et al.* (1992)	1,280	Case-control	Colorado	Positive association when nitrate below maximum contaminant level
	Parslow, *et al.* (1997)	1,797	Case-control	Yorkshire, England	Positive association
Other	Eskiocak, *et al.* (2005)	-	Animal	Turkey	Nitrate impairs thyroid function
	Ogur, *et al.* (2005)	-	Animal	Turkey	Nitrate impairs liver function; causes changes in histology
	Xu, *et al.* (1992)	92	Cross-sectional	China	Positive association with gastric histology changes
	Gupta, *et al.* (2000)	88	Cross-sectional	Rajasthan, India	Positive association with acute recurrent respiratory infection
	Kleinjans, *et al.* (1991)	75	Cohort	Netherlands	Non-significant negative association with genotoxic events indicative of cancer risk
Cancer multiple sites	Barrett, *et al.* (1998)	3,441; 15,544; 5,399	Case-control	Yorkshire, England	Positive association with brain cancer; no association with stomach or esophageal cancer
	Gulius, *et al.* (2002)	19,854	Case-control	Trnava District, Slovakia	Positive association with non-Hodgkin's lymphoma and colorectal cancer; no association with kidney or bladder cancer
	Weyer, *et al.* (2001)	21,977	Cohort	Iowa	Positive association with bladder and ovarian cancer; negative association with uterine and rectal cancer; no association with total cancer incidence, leukemia, non-Hodgkin's lymphoma, melanoma, lung, colon, kidney, or breast cancer
	Ward, *et al.* (2004)	180,181	Case-control	Iowa	No association with non-Hodgkin's lymphoma; no overall association with adult brain cancer
esophageal	Zhang, *et al.* (2003)	unknown	Case-control	China	Positive association
gastric	Rademacher, *et al.* (1992)	1,161	Case-control	Wisconsin	No association
	Yang, *et al.* (1997)	6,766	Case-control	Taiwan	No association
	van Loon, *et al.* (1998)	282	Cohort	Netherlands	No association
	Van Leeuwen, *et al.* (1999)	unknown	Cohort	Ontario, Canada	Negative association with stomach cancer
	Yang, *et al.* (1998)	6,766	Case-control	Taiwan	Positive association
	Sandor, *et al.* (2001)	108,000	Case-control	Hungary	Positive association especially at high exposure levels
pancreatic	Coss, *et al.* (2004)	189	Case-control	Iowa	No association
bladder	Ward, *et al.* (2003)	808	Case-control	Iowa	No association
	Volkmer, *et al.* (2005)	57,253; 10,037	Cohort	Germany	Positive association with urothelial cancer; no association with penile, rectal, or prostate cancer
colorectal	De Roos, *et al.* (2003)	685; 655	Case-control	Iowa	No association
non-Hodgkin's lymphoma	Law, *et al.* (1999)	-	Cohort	Yorkshire, England	No association
	Cocco, *et al.* (2003)	703,000	Cohort	Sardinia, Italy	No association
	Ward, *et al.* (1996)	156	Case-control	Nebraska	Positive association
	Freedman, *et al.* (2000)	73	Case-control	Minnesota	No association
leukemia	Infante-Rivard, *et al.* (2001)	491	Case-control	Quebec, Canada	Negative pre- and post-natal association
childhood brain tumor	Mueller, *et al.* (2001)	540	Case-control	USA West Coast	No association