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Eric Lindberg Attachment 1

Minnesota Center for
Environmental Advocacy

February 14, 2022

Mary H. Lynn
Cathy O'Dell
Minnesota Pollution Control Agency
520 Lafayette Road North
St. Paul, MN 55055-4194

Via OAH Comments Portal

RE: Request For Comments on Possible Amendments to Rules Governing Water Quality Standards – Use Classification 1, Minnesota Rules chapters 7050, 7052, 7053, and 7060, Revisor's ID Number R-04727
OAH Docket No. 5-9003-37887

Dear Ms. Lynn and Ms. O'Dell:

The Minnesota Center for Environmental Advocacy ("MCEA") is a nonprofit environmental advocacy organization with offices in St. Paul and Duluth. Since 1974, MCEA has defended Minnesota's natural resources, water, air and climate, and the health and welfare of Minnesotans. MCEA is driven by the principle that everyone has a right to a clean and healthy environment, and that decisions must be based on fact, science, and the law.

MCEA submits these comments in response to the Minnesota Pollution Control Agency ("MPCA") request for comments on proposed changes to water quality standards ("WQS") as referenced above.

1. MPCA should ensure that all groundwater is protected from degradation, including groundwater that is located on private property.

MCEA agrees with MPCA's proposal to "ensure the rule language clearly conveys that the standards apply to all groundwater." Consistent with this goal, MPCA should revise the rules to ensure that standards protecting groundwater from degradation are not applied at property boundaries, but instead apply to all groundwater. The rules should be clarified to specify that it is not acceptable for a regulated party to degrade groundwater or exceed water quality standards applicable to groundwater because it may be possible to deploy a remediation measure prior to reaching the property boundary that will reduce the level of contaminants in the groundwater. The MPCA should ensure that regulated parties employ measures (such as competent liners) that prevent groundwater pollution, not remediate groundwater pollution after it has happened.

2. MPCA should expand the Class 1 designation to connected surface waters.

Scientists studying the fate and transport of perfluorinated alkyl substances (PFAS) have demonstrated that these pollutants can flow freely from groundwater to surface water and back again. *See* Jennifer Geulfo, State Agencies Liaison, Brown SRP, Subsurface Fate and Transport of Poly- and Perfluoroalkyl Substances (PFAS) (May 23, 2016); Andrea K. Tokranov, Denis R.

LeBlanc, Heidi M. Pickard, Bridger J. Ruyle, Larry B. Barber, Robert B. Hull, Elsie M. Sunderland & Chad D. Vecitis, *Surface-water/Groundwater Boundaries Affect Seasonal PFAS Concentrations and PFAA Precursor Transformations*, 23 Env't Sci.: Processes & Impacts 1893 (2021).[1] Similarly, as MPCA has noted, nitrate has the potential to move freely from contaminated surface waters into groundwater and vice versa. As a result, MCEA strongly supports MPCA's adoption of a provision allowing the application of Class 1 standards where it can be shown that surface water has the potential to impact the quality of groundwater protected as Class 1 waters. Similarly, MPCA should have the authority to impose more stringent conditions on sources impacting groundwater if that groundwater has the potential to affect a surface water subject to more stringent standards. Minn. R. 7050.0210, subp. 13 already expresses this authority, insofar as it states that "The quality of any waters of the state receiving sewage, industrial waste, or other waste effluents shall be such that no violation of the standards of any waters of the state in any other class shall occur by reason of the discharge of the sewage, industrial waste, or other waste effluents."

MCEA also supports adoption of a rule that designates "sensitive areas" where surface conditions and surface waters are known to directly impact groundwater (for example, karst) to ensure that Class 1 standards are protected, but that rule must also allow for a process to identify areas that fit the criteria for a "sensitive area" outside the regions where the land surface/groundwater connection is known to be prevalent.

3. MPCA should update the scientific basis for the numeric Class 1 water quality standards.

MCEA supports MPCA's reassessment of the health-basis for the Class 1 water quality standards in coordination with the Minnesota Department of Health ("MDH"), but needs additional information to determine what the best method is for adding new standards to the rule.

MCEA supports combining the standards into a single set of standards without subclasses based on treatment. The availability of treatment should not be considered in setting standards and, as a result, subclasses based on treatment should be eliminated. The fact that water can be treated to achieve safe consumption levels is concern that should not be considered in either a narrative or a numeric standard intended to protect Class 1 waters. Similarly, the standards should not distinguish between health-based standards or standards based on other deleterious characteristics caused by pollutants, as discussed below in part 5.

In setting any new standards, MPCA and MDH should consider populations that are especially vulnerable due to traditional consumption patterns and ensure that any standards adopted recognize these populations, including tribal standards that have been adopted. MCEA also supports MPCA's consideration of climate-change induced changes to toxicological impacts when establishing standards.

[1] References cited in this comment letter are attached.

MPCA should use this rulemaking to update the water quality standards based on more recent research demonstrating that a higher level of protection must be maintained. The narrative standard in Minn. R. 7050.0221, subp. 6 should be more clearly identified as such. The following standards should be updated.

Nitrate

MPCA and MDH should reexamine the 10 mg/L standard for nitrate because scientific consensus is growing that a lower number would be more protective. A number of scientific studies demonstrate that nitrate levels lower than 10 mg/L are implicated in heightened risk for colorectal cancer, thyroid disease, and neural tube defects. *See* Sarah Porter & Anne Weir Schechinger, *Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate*, Env't Working Grp. (Jan. 14, 2020), https://www.ewg.org/interactive-maps/2020_nitrate_in_minnesota_drinking_water_from_groundwater_sources/; Jayne Richards, Tim Chambers, Simon Hales, Mike Joy, Tanja Radu, Alistair Woodward, Alistair Humphrey, Edward Randal & Michael G. Baker, *Nitrate Contamination in Drinking Water and Colorectal Cancer: Exposure Assessment and Estimated Health Burden in New Zealand*, 204 Env't Rsch., Mar. 2022, at 112322, 2; Mary H. Ward, Rena R. Jones, Jean D. Brender, Theo M. de Kok, Peter J. Weyer, Bernard T. Nolan, Cristina M. Villanueva & Simone G. van Breda, *Drinking Water Nitrate and Human Health: An Updated Review*, 15 Int'l J. Env't Rsch. & Pub. Health, Jul. 2018, at 1557. MDH itself has noted that "a growing body of literature indicates potential associations between nitrate/nitrite exposure and other health effects such as increased heart rate, nausea, headaches, and abdominal cramps." Minn. Dept. of Health, *Nitrate and Methemoglobinemia* 3 (2018). MDH also affirms that "[s]ome studies also suggest an increased risk of cancer, especially gastric cancer, associated with dietary nitrate/nitrite exposure, but there is not yet scientific consensus on this question." *Id.*

Sulfate

Although originally classified by U.S. Environmental Protection Agency ("EPA") as a secondary water quality standard needed for "such as taste, color, and odor," more recent research demonstrates that sulfate has health impacts, particularly diarrhea and other gastrointestinal related issues. Muhammad Tariq Bashir, Salmiaton Ali & Adnan Bashir, *Health Effects from Exposure to Sulphates and Chlorides in Drinking Water*, 6 Pak. J. Med. & Health Sci. 648, 651-52 (2012); Muhammad Mohsin, Samira Safdar, Faryal Asghar & Farrukh Jamal, *Assessment of Drinking Water Quality and its Impact on Residents' Health in Bahawalpur City*, 3 Int'l J. Human. & Soc. Sci. 114, 120 (2013); Patricio Moreno, Hal Aral & Angelica Vecchio-Sadus, Environmental Impact and Toxicology of Sulphate at EnviroMine 2009: First International Seminar on Environmental Issues in the Mining Industry 6 (2009). Based on this research, MPCA should establish a WQS that will ensure that vulnerable populations are protected.

Other Pollutants

Other contaminants are still a major concern for public health, both in short- and long-term exposure. Fluoride, for example, has a primary Maximum Contaminant Level ("MCL") at 4.0 mg/L set by the EPA (EPA, National Primary and National Secondary Drinking Water Regulations), but research by the American Cancer Society ("ACS") suggests that long term exposure to this contaminant may cause skeletal fluorosis, causing a secondary MCL standard to be set at 2.0 mg/L to help protect children. Am. Cancer Soc'y, *Water Fluoridation and Cancer Risk* 2-3 (2015). Manganese is another contaminant of concern due to its impacts on the nervous system, with higher risks for the elderly and infants. The World Health Organization ("WHO") recommends that manganese in drinking water be limited to 0.08 mg/L, and MDH has established a Health Risk Limit ("HRL") for manganese at 0.1 mg/L, indicating a need for reassessment of the guidance for this contaminant in drinking water, particularly in regards to sensitive populations such as infants. World Health Org., *Manganese in Drinking-Water* 14-15 (2011). Aluminum is another contaminant that has neurological impacts, with connections to Alzheimer's and dementia. The secondary MCL for aluminum is currently 2.0 mg/L, but recent studies have shown that aluminum can have harmful impacts to human health at 0.1 mg/L. Virginie Rondeau, Hélène Jacqmin-Gadda, Daniel Commenges, Catherine Helmer & Jean-François Dartigues, *Aluminum and Silica in Drinking Water and the Risk of Alzheimer's Disease or Cognitive Decline: Findings From 15-Year Follow-Up of the PAQUID Cohort*, 169 Am. J. Epidemiology 489, 489 (2009).

MCEA supports MPCA's proposal to add WQS for some emerging pollutants of concern, including per-and polyfluoroalkyl substances (PFAS), pesticides, *see* Muhammad Syafrudin, Risky Ayu Kristanti, Adhi Yuniarto, Tony Hadibarata, Jongtae Rhee, Wedad A. Al-onazi, Tahani Saad Algarni, Abdulhadi H. Almarri & Amal M. Al-Mohaimeed, *Pesticides in Drinking Water—A Review*, 18 Int'l J. Env't Rsch. & Pub. Health, Jan. 2021, at 468, pharmaceuticals, *see* World Health Org., *Pharmaceuticals in Drinking-Water* (2011), algal toxins, *see* Env't Protection Agency, *Algal Toxin Risk Assessment and Management Strategic Plan for Drinking Water* (2015), disinfection by-products, *see* Xing-Fang Li & William A. Mitch, *Drinking Water Disinfection Byproducts (DBPs) and Human Health Effects: Multidisciplinary Challenges and Opportunities*, 52 Env't Sci. & Tech. 1681 (2018), and/or additional industrial chemicals.

4. MPCA should not eliminate standards that were based on secondary MCLs.

MPCA claims that "[u]nder the federal Clean Water Act (CWA), WQS for the protection of domestic consumption should be solely based on human health considerations." (Class 1 Concepts, p. 2). The CWA does not limit state water quality standards intended to protect water for domestic consumption solely to a "health" basis. In fact, the CWA directs that such standards "shall be such as to protect the public health *or welfare*" and that "such standards shall be established taking into consideration their use *and value* for public water supplies…" 33 U.S.C. § 1313(c)(2)(A). Nothing in state law is to the contrary. *See* Minn. Stat. § 115.03. Indeed, numerous state laws express the policy that potable waters are deserving of the highest protection. *See, e.g.*, Minn. Stat. § 115.063; Minn. Stat. § 103H.001. Removing protections for

domestic consumption waters based on taste, color or odor will simply increase costs for those who consume those waters, or for public water treatment systems that must prepare waters for public consumption.

Conclusion:

MCEA supports amendments to the Class 1 standards provided those amendments serve to preserve and enhance the protections that currently exist for groundwater and surface waters used for domestic consumption. MPCA should not adopt any amendments that are directed toward reduction of costs for industry, and maintain protections that are consistent with current state policy to protect all sources of water for domestic consumption from degradation, even if that degradation is argued to be without health impacts. To the extent that any might argue that the current standards place an unreasonable cost burden on certain dischargers or users, MPCA should recognize that these costs should be dealt with through means other than removing regulatory standards that protect public health and welfare.

MCEA also notes (as it did in its Triennial Review comment (April 9, 2021)) that it appears that MPCA's ideas about what to address in this Class 1 rulemaking are still developing. As a result, MCEA encourages MPCA to continue to share the options that it is considering with stakeholder groups, so that interested parties can develop a better understanding of the choices as this rulemaking moves forward.

An index to the attached cited references follows.

Sincerely,

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Water Policy Associate

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References

Jennifer Geulfo, State Agencies Liaison, Brown SRP, Subsurface Fate and Transport of Poly- and Perfluoroalkyl Substances (PFAS) (May 23, 2016).

Andrea K. Tokranov, Denis R. LeBlanc, Heidi M. Pickard, Bridger J. Ruyle, Larry B. Barber, Robert B. Hull, Elsie M. Sunderland & Chad D. Vecitis, *Surface-water/Groundwater Boundaries Affect Seasonal PFAS Concentrations and PFAA Precursor Transformations,* 23 Env't Sci.: Processes & Impacts 1893 (2021).

Sarah Porter & Anne Weir Schechinger, *Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate,* Env't Working Grp. (Jan. 14, 2020), https://www.ewg.org/interactive-maps/2020_nitrate_in_minnesota_drinking_water_from_groundwater_sources/.

Jayne Richards, Tim Chambers, Simon Hales, Mike Joy, Tanja Radu, Alistair Woodward, Alistair Humphrey, Edward Randal & Michael G. Baker, *Nitrate Contamination in Drinking Water and Colorectal Cancer: Exposure Assessment and Estimated Health Burden in New Zealand*, 204 Env't Rsch., Mar. 2022, at 112322.

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World Health Org., *Pharmaceuticals in Drinking-Water* (2011).

Muhammad Syafrudin, Risky Ayu Kristanti, Adhi Yuniarto, Tony Hadibarata, Jongtae Rhee, Wedad A. Al-onazi, Tahani Saad Algarni, Abdulhadi H. Almarri & Amal M. Al-Mohaimeed,

Pesticides in Drinking Water—A Review, 18 Int'l J. Env't Rsch. & Pub. Health, Jan. 2021, at 468.

Env't Protection Agency, *Algal Toxin Risk Assessment and Management Strategic Plan for Drinking Water* (2015).

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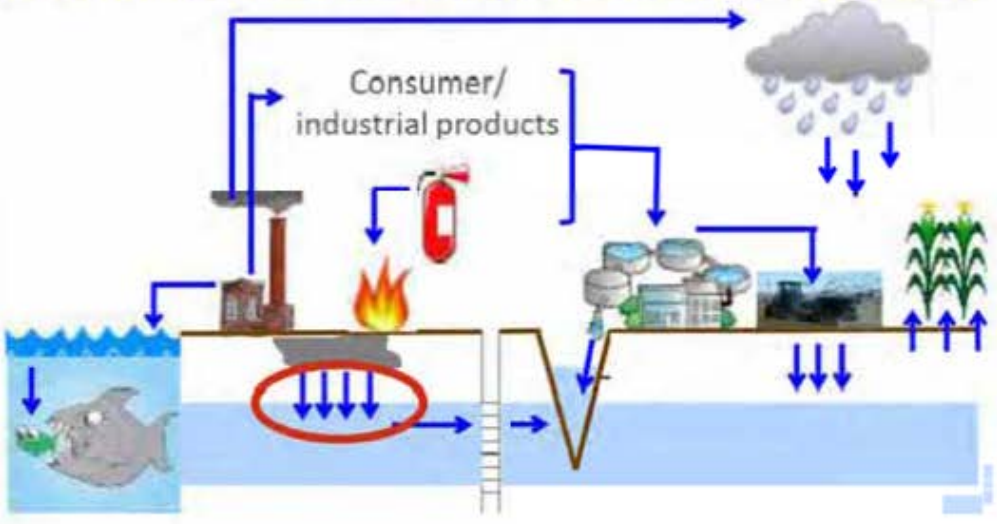
SUBSURFACE FATE AND TRANSPORT OF POLY- AND PERFLUOROALKYL SUBSTANCES (PFAS)

Jennifer Guelfo, PhD
State Agencies Liaison, Brown SRP
May 23, 2016


INTRODUCTION: ENVIRONMENTAL DISTRIBUTION



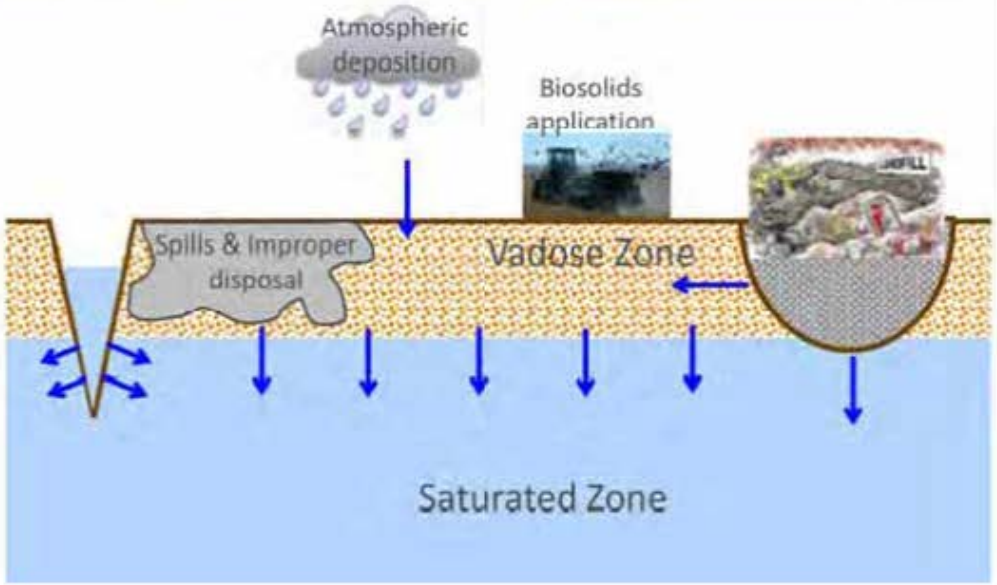
2

OVERVIEW

- Key sources and pathways
- Ideal subsurface transport
- Factors impacting ideal transport
- Conceptual model considerations

3

PFAS GROUNDWATER SOURCE/PATHWAY OVERVIEW



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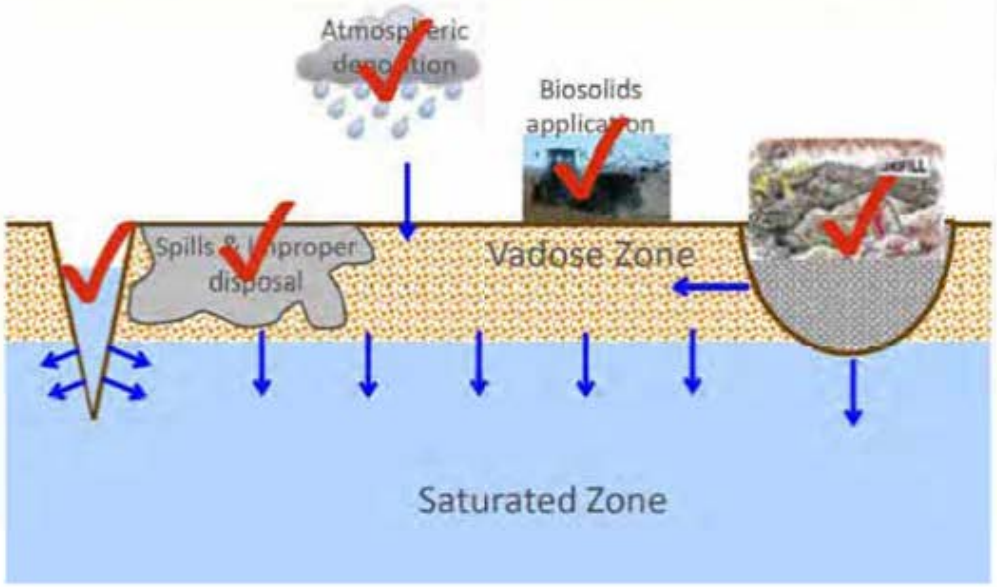
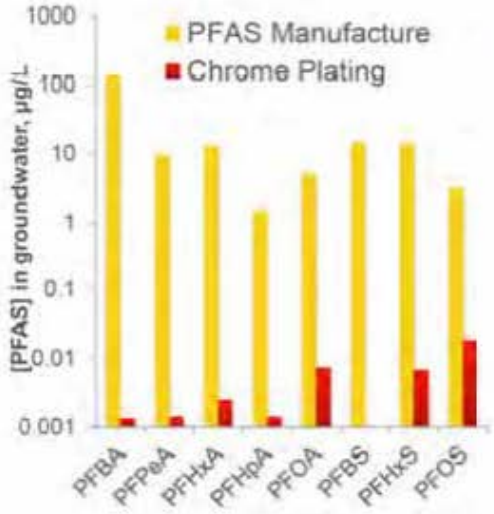


5

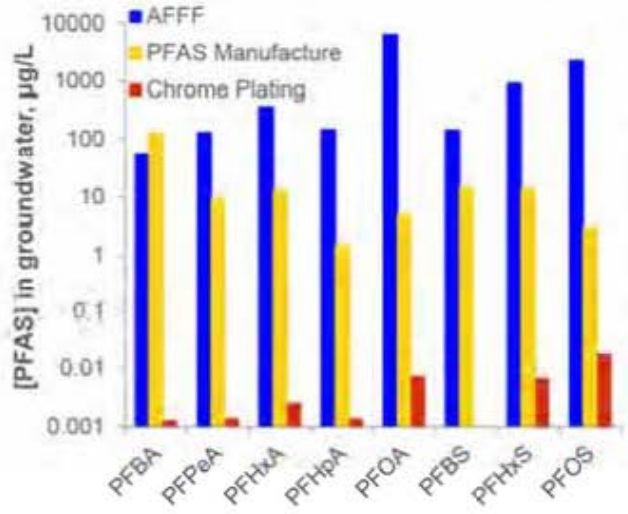
SOURCE/PATHWAY: SPILLS, 'IMPROPER' DISPOSAL[2,3]



- [PFAS] in groundwater 0.0013-126 µg/L
- Manufacturing max = 126 µg/L PFBA
- Plating max = 0.018 µg/L PFOS
- Data from other secondary industrial (e.g. textiles, paper)?

SOURCE/PATHWAY: SPILLS, 'IMPROPER' DISPOSAL[4-7]

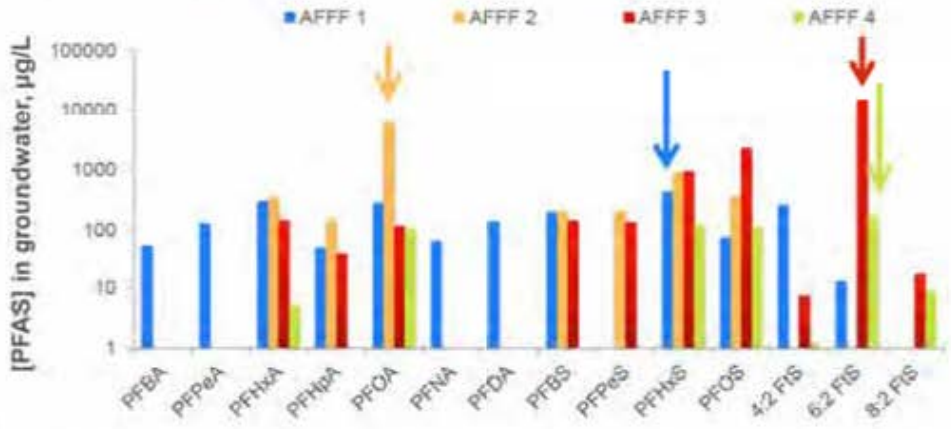
A closer look at AFFF groundwater impacts



- Most groundwater [PFAS] greater in AFFF vs. manufacture, plating

SOURCE/PATHWAY: SPILLS, 'IMPROPER' DISPOSAL[4-7]

A special look at AFFF groundwater impacts



- Max AFFF 1 = PFHxS, 462 µg/L
- Max AFFF 2 = PFOA, 6570 µg/L
- Max AFFF 3= 6:2 FtS, 14600 µg/L
- Max AFFF 4 = 6:2 FtS, 173 µg/L

SOURCE/PATHWAY: SPILLS, 'IMPROPER' DISPOSAL[4-7]

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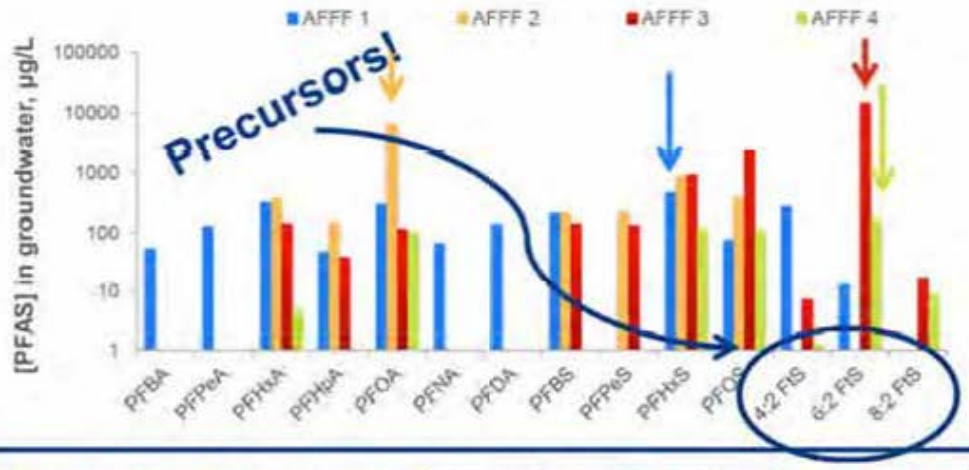

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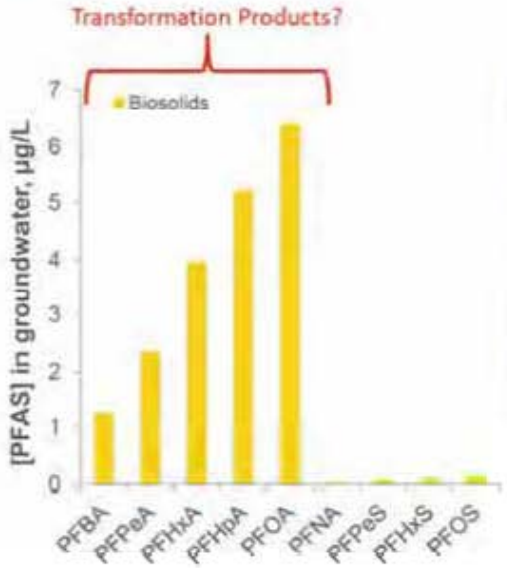
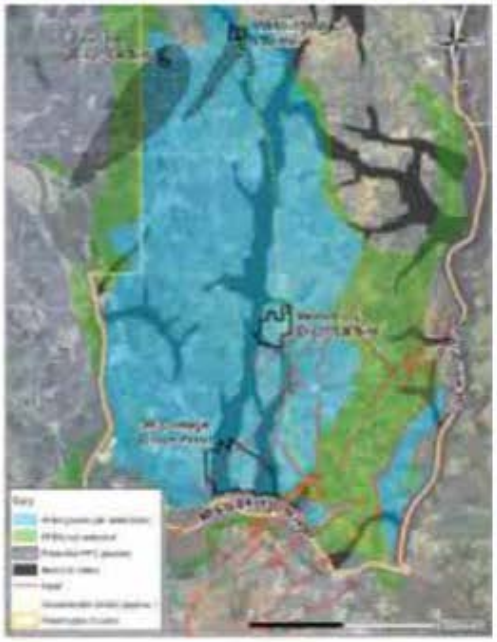
SOURCE/PATHWAY: BIOSOLIDS APPLICATION[8,9]



- WWTP received industrial effluent incl. ECF, telomer
- Present in municipal biosolids, potential to leach but…
- No documented impact to GW

SOURCE/PATHWAY: SURFACE WATER – GROUNDWATER[10]



- GW-SW interactions in MN aid in spread of PFBA plume
- ~100 square miles
- [PFAS] near GW-SW exchange:
  - PFBA: 0.29-3.4 µg/L
  - PFOA: 0.067-3 µg/L
  - PFOS: 0.058-3.3 µg/L

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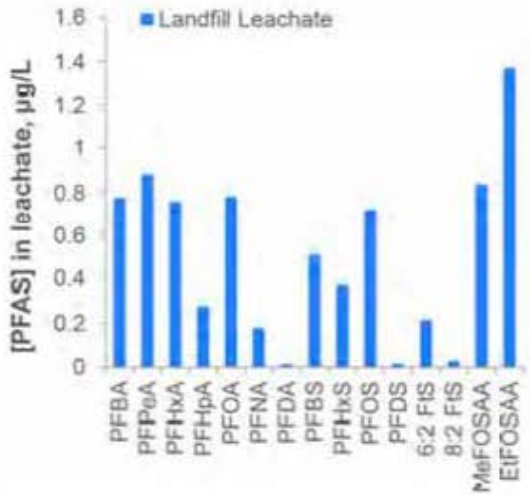
SOURCE/PATHWAY: LANDFILLS[11-14]

PFAS in municipal landfill **leachate**



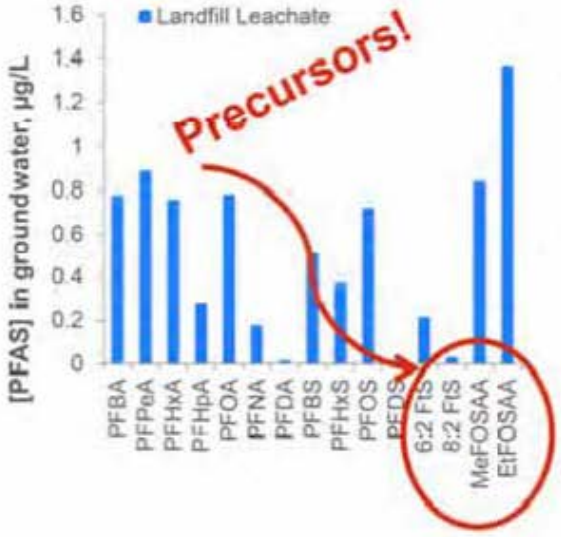
Additional landfill data:

- Near 3M in MN, **GW [PFAS]** near landfill:
  - PFOA = 65 µg/L
  - PFOS = 30 µg/L
- Near 3M in MN, landfill **leachate PFAS**:
  - PFHxA = 29 µg/L
  - PFOA = 82 µg/L
  - PFOS = 31 µg/L

12

SOURCE/PATHWAY: LANDFILLS[11-14]

PFAS in municipal landfill **leachate**



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SOURCE/PATHWAY: ATMOSPHERIC DEPOSITION[15-19]

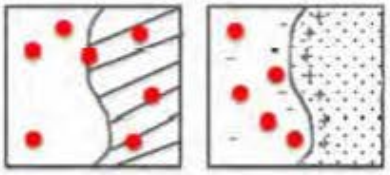
Media	Value	Units	Constituent	Reference
Rural air	0.000125	µg/m³	6:2 FTOH	Jahnke et al., 2007
Urban air	0.000275	µg/m³	8:2 FTOH	Jahnke et al., 2007
Manufacturing air	0.9	µg/m³	PFOA (only)	Davis et al., 2007
WWTP Air	12.29	µg/m³	6:2 FTOH	Ahrens et al., 2011
Landfill Air	17.38	µg/m³	8:2 FTOH	Ahrens et al., 2011
Urban Rain	0.042	µg/L	PFOA	Eschauzier et al., 2010
Urban Snow	0.0196	µg/L	PFOA	Kim and Kannan, 2007
GW from atm. dep.	78	µg/L	PFOA (only)	Davis et al., 2007

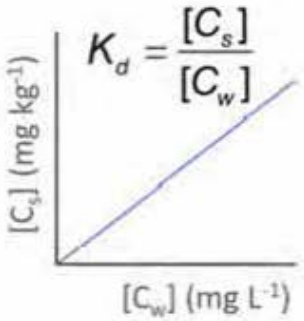
Considerations:

- Proximity to sources: manufacturing, WWTP, landfill
- How to separate atmospheric vs. other impacts at these sites?
- May contribute to background in soils, surface water

TRANSPORT: IDEAL

Sorption: accumulation of a chemical from a fluid phase into and/or onto a non-fluid phase





- Measured in laboratory (equilibrium) scenarios
- Isotherms not always linear, PFAS slightly nonlinear
- Primary process impacting perfluoroalkyl acids, once released

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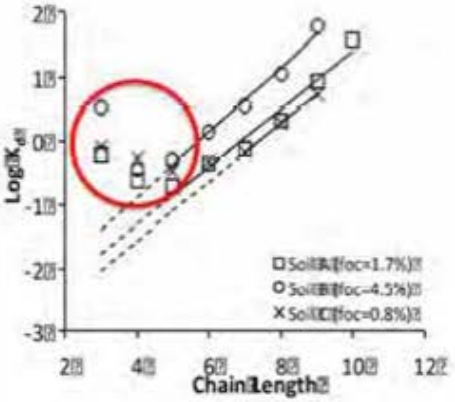
TRANSPORT: IDEAL[20-21]



Analyte Name	Tail Length[a]	Average Log K_{oc}	±	n[b]
PFBA	3	1.88	0.11	3
PFPeA	4	1.37	0.46	3
PFHxA	5	1.31	0.29	3
PFHpA	6	1.63	0.15	3
PFOA	7	1.89	0.02	3
PFNA	8	2.36	0.04	3
PFDA	9	2.96	0.15	3
PFUnA	10	3.56		1
PFBS	4	1.79	0.10	3
PFHxS	6	2.05	0.08	3
PFOS	8	2.80	0.08	3

- Primary impacts on sorption: f_{oc}, chain length (some exceptions)
- Other factors: functional group, pH, Ca^{2+}

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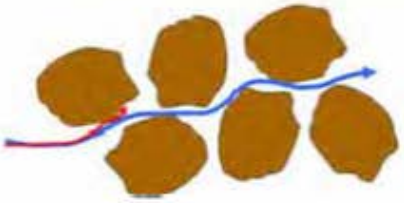
TRANSPORT: IDEAL



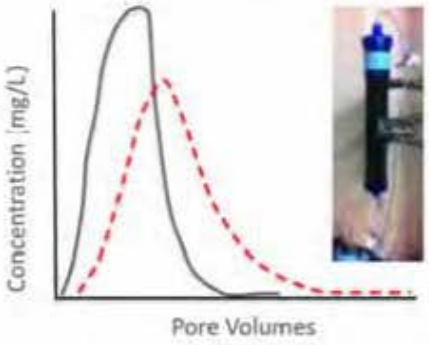
$$R\frac{fC}{ft} = D_L\frac{f^2D}{fx^2} - v_x\frac{fC}{fx}$$

sorption dispersion advection

Sorption and Retardation

- The velocity of water relative to velocity of contaminant
- Retardation factor (R):

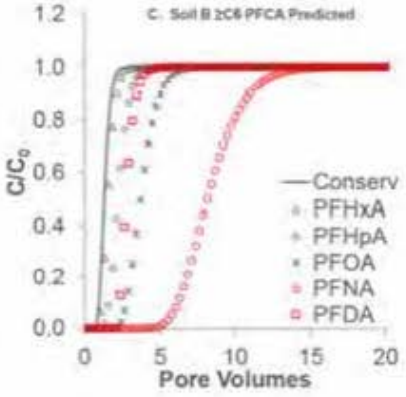
$$R = 1 + \frac{\rho_b}{\phi}K_f n C_w^{n-1}$$

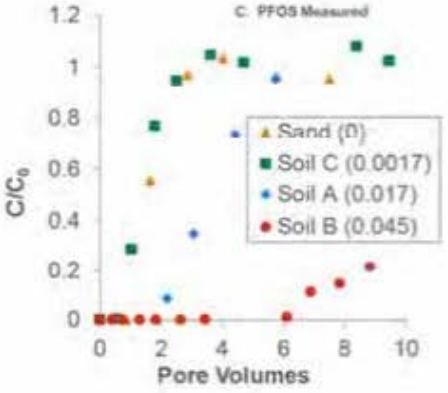


- ↑ R leads to ↓ transport

17

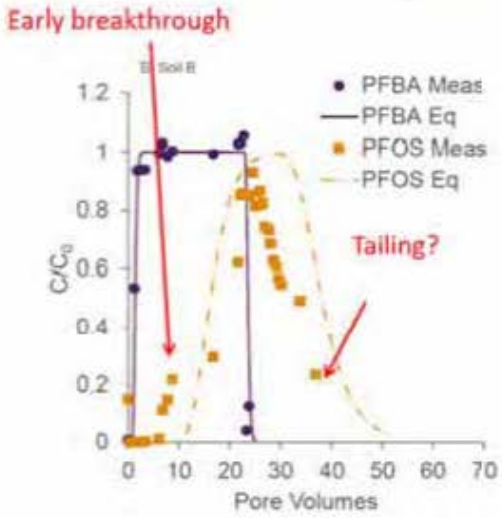
TRANSPORT: IDEAL In Prep





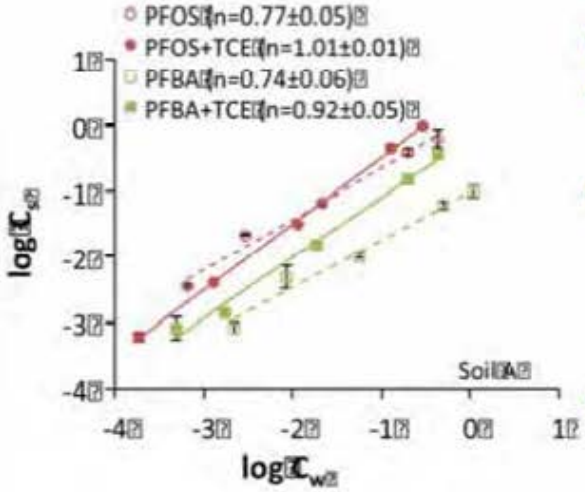
- Chain length dependent breakthrough
- Increased f_{oc} = slower transport

TRANSPORT: NON-IDEAL[In Prep]



- Short chain: equilibrium
- Long chain: Early breakthrough, tailing = rate-limited (kinetic) effects
- Most relevant for longer chains, higher f_{oc}
- Particularly pumping scenarios

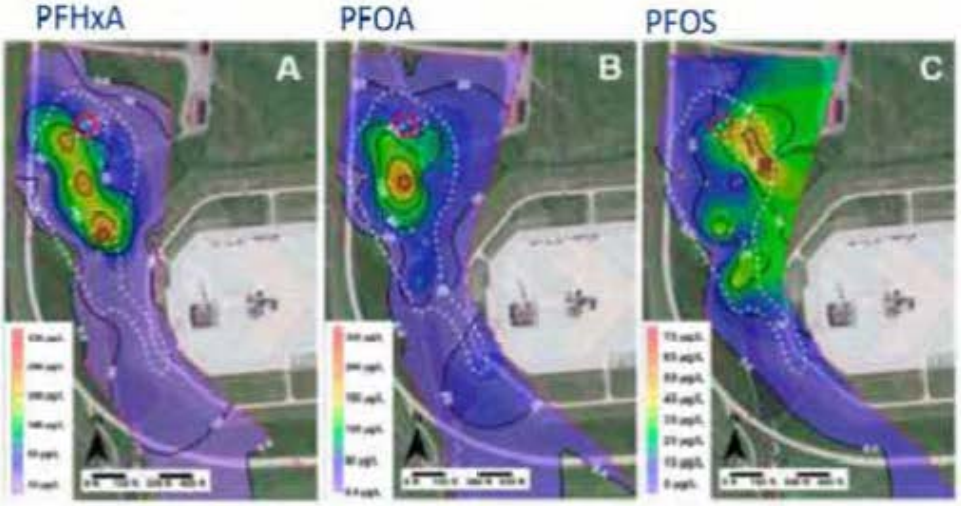
PATHWAY: NON-IDEAL TRANSPORT[21]



Co-Contaminant effects:

- Multiple PFAS – competitive sorption?
- AFFF sites
  - Other AFFF components
  - Hydrocarbon constituents
  - Chlorinated solvents
  - NAPL
- Other types of sites?

PATHWAY: NON-IDEAL TRANSPORT[4]

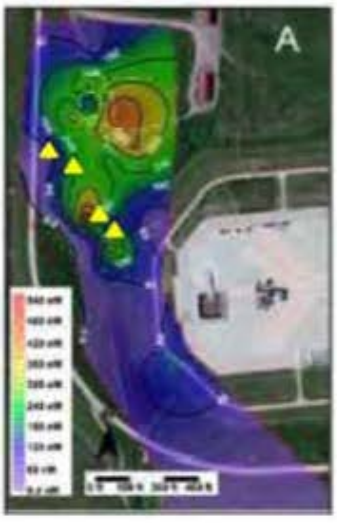


No evidence of differential transport.

21

TRANSPORT: NON-IDEAL[4]

Total Precursors in groundwater:



- Oxygen infusion wells
- [Precursor] elevated *outside* of oxygen infusion areas
- Elevated precursors = areas for potential [PFAA] ↑

22

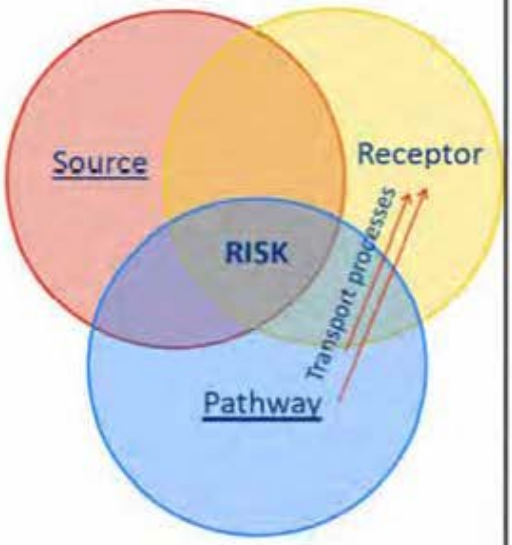
CONCEPTUAL MODEL CONSIDERATIONS

Source/Pathway:

- Max [PFAS] of mg/L (AFFF) to low µg/L (bisolids, GW-SW)
- Target PFAS vary by source
- PFOA/PFOS not always max
- Precursors indirect source of PFCAs/PFSAs

Transport:

- Non-ideal transport likely: kinetics, co-contaminants, transformation
- Plume lengths of miles possible



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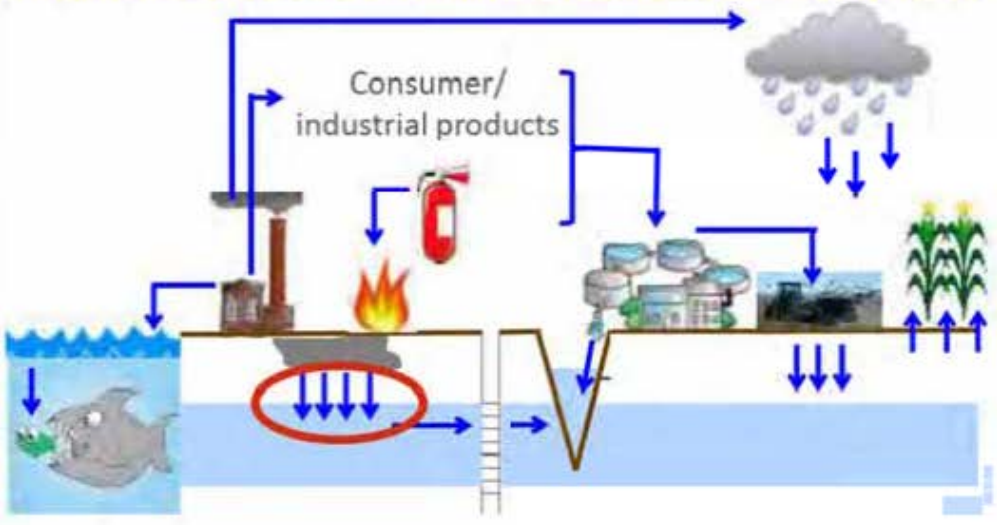
SUBSURFACE FATE AND TRANSPORT OF POLY- AND PERFLUOROALKYL SUBSTANCES (PFAS)

Jennifer Guelfo, PhD
State Agencies Liaison, Brown SRP
May 23, 2016


1

INTRODUCTION: ENVIRONMENTAL DISTRIBUTION



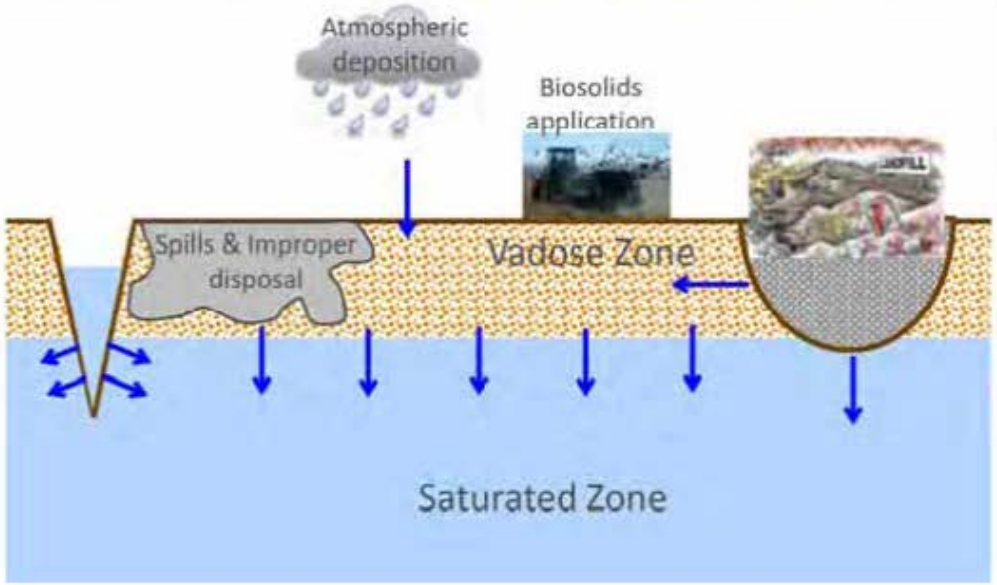
2

OVERVIEW

- Key sources and pathways
- Ideal subsurface transport
- Factors impacting ideal transport
- Conceptual model considerations

3

PFAS GROUNDWATER SOURCE/PATHWAY OVERVIEW



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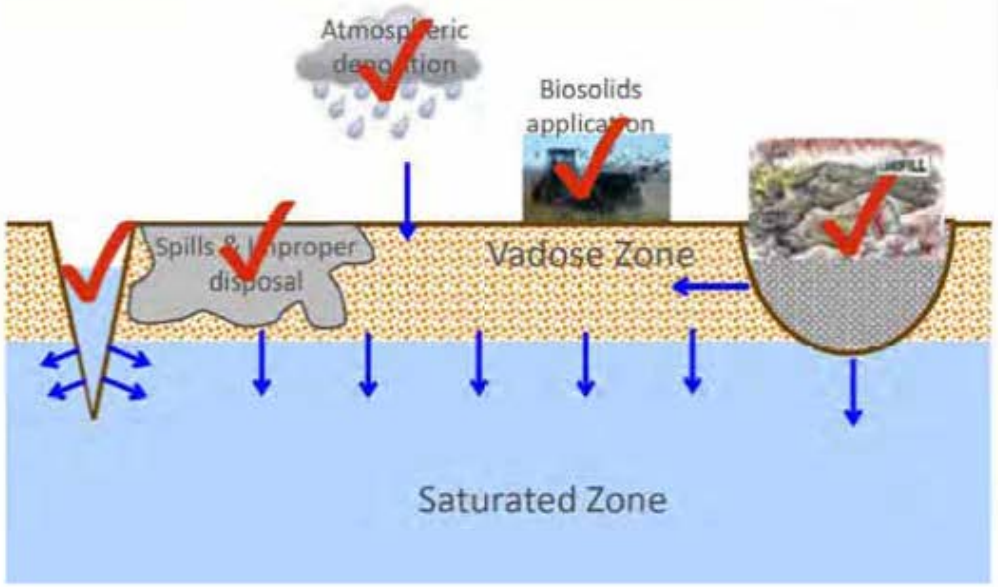

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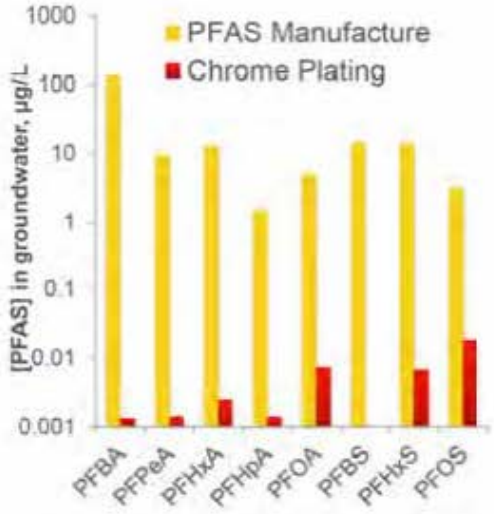
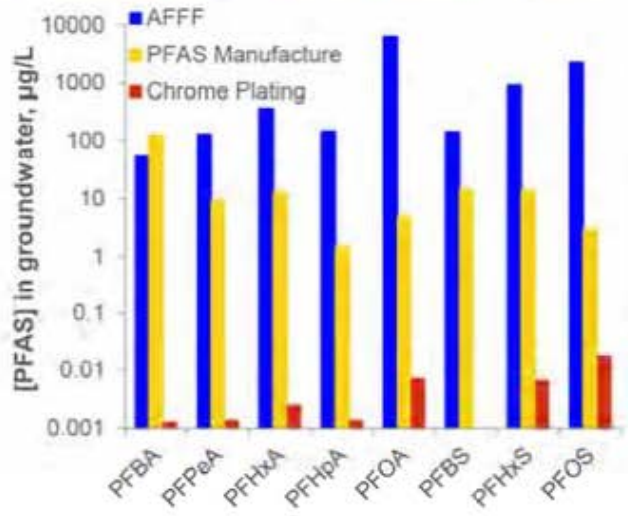
SOURCE/PATHWAY: SPILLS, 'IMPROPER' DISPOSAL[2,3]



- [PFAS] in groundwater 0.0013-126 µg/L
- Manufacturing max = 126 µg/L PFBA
- Plating max = 0.018 µg/L PFOS
- Data from other secondary industrial (e.g. textiles, paper)?

SOURCE/PATHWAY: SPILLS, 'IMPROPER' DISPOSAL[4-7]

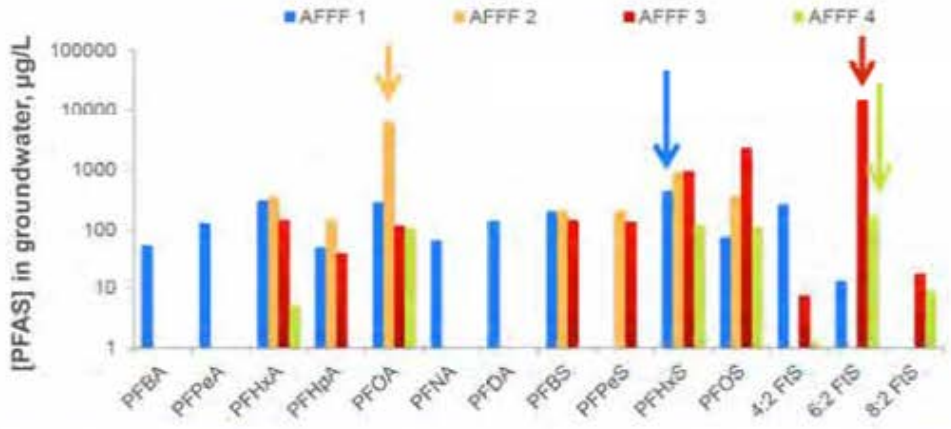
A closer look at AFFF groundwater impacts



- Most groundwater [PFAS] greater in AFFF vs. manufacture, plating

SOURCE/PATHWAY: SPILLS, 'IMPROPER' DISPOSAL[4-7]

A special look at AFFF groundwater impacts



- Max AFFF 1 = PFHxS, 462 µg/L
- Max AFFF 2 = PFOA, 6570 µg/L
- Max AFFF 3= 6:2 FtS, 14600 µg/L
- Max AFFF 4 = 6:2 FtS, 173 µg/L

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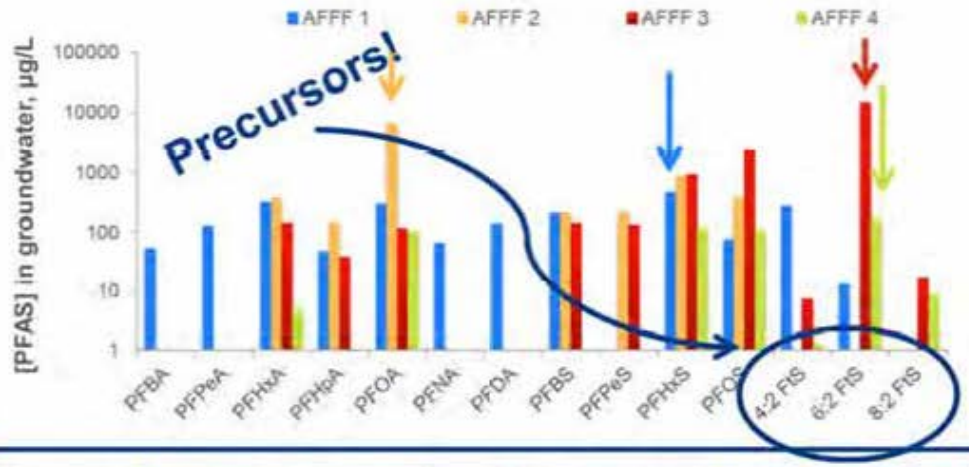

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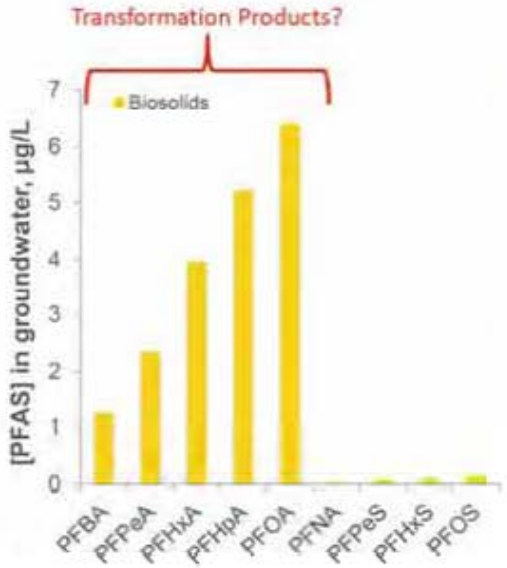
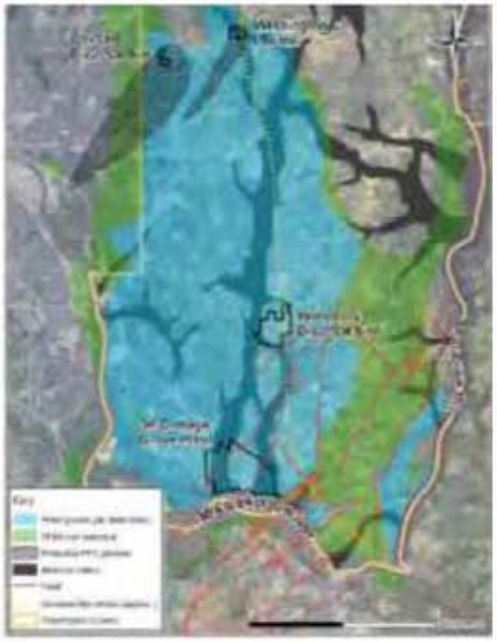
SOURCE/PATHWAY: BIOSOLIDS APPLICATION[8,9]



- WWTP received industrial effluent incl. ECF, telomer
- Present in municipal biosolids, potential to leach but…
- No documented impact to GW

SOURCE/PATHWAY: SURFACE WATER – GROUNDWATER[10]

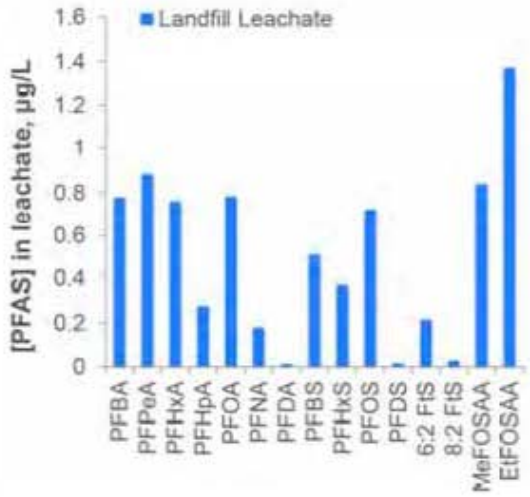


- GW-SW interactions in MN aid in spread of PFBA plume
- ~100 square miles
- [PFAS] near GW-SW exchange:
  - PFBA: 0.29-3.4 µg/L
  - PFOA: 0.067-3 µg/L
  - PFOS: 0.058-3.3 µg/L

11

SOURCE/PATHWAY: LANDFILLS[11-14]

PFAS in municipal landfill **leachate**



Additional landfill data:

- Near 3M in MN, **GW [PFAS]** near landfill:
  - PFOA = 65 µg/L
  - PFOS = 30 µg/L
- Near 3M in MN, landfill **leachate PFAS**:
  - PFHxA = 29 µg/L
  - PFOA = 82 µg/L
  - PFOS = 31 µg/L

12

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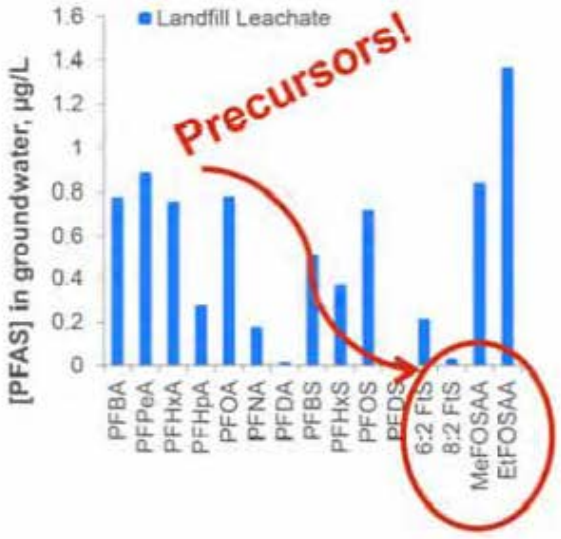

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13

SOURCE/PATHWAY: ATMOSPHERIC DEPOSITION[15-19]

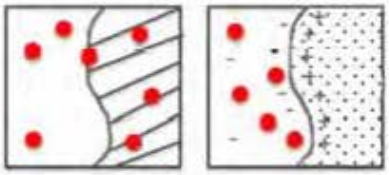
Media	Value	Units	Constituent	Reference
Rural air	0.000125	µg/m³	6:2 FTOH	Jahnke et al., 2007
Urban air	0.000275	µg/m³	8:2 FTOH	Jahnke et al., 2007
Manufacturing air	0.9	µg/m³	PFOA (only)	Davis et al., 2007
WWTP Air	12.29	µg/m³	6:2 FTOH	Ahrens et al., 2011
Landfill Air	17.38	µg/m³	8:2 FTOH	Ahrens et al., 2011
Urban Rain	0.042	µg/L	PFOA	Eschauzier et al., 2010
Urban Snow	0.0196	µg/L	PFOA	Kim and Kannan, 2007
GW from atm. dep.	78	µg/L	PFOA (only)	Davis et al., 2007

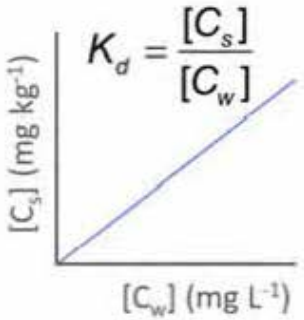
Considerations:

- Proximity to sources: manufacturing, WWTP, landfill
- How to separate atmospheric vs. other impacts at these sites?
- May contribute to background in soils, surface water

TRANSPORT: IDEAL

Sorption: accumulation of a chemical from a fluid phase into and/or onto a non-fluid phase

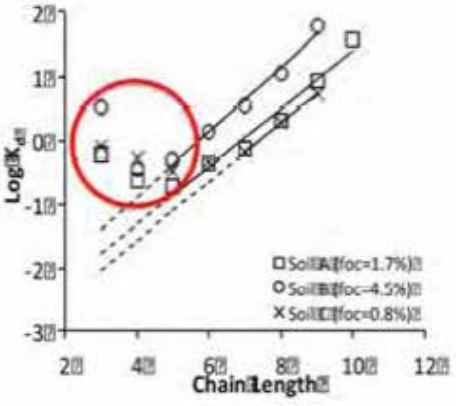




- Measured in laboratory (equilibrium) scenarios
- Isotherms not always linear, PFAS slightly nonlinear
- Primary process impacting perfluoroalkyl acids, once released

15

TRANSPORT: IDEAL[20-21]



Analyte Name	Tail Length[a]	Average Log K_{oc}	±	n[b]
PFBA	3	1.88	0.11	3
PFPeA	4	1.37	0.46	3
PFHxA	5	1.31	0.29	3
PFHpA	6	1.63	0.15	3
PFOA	7	1.89	0.02	3
PFNA	8	2.36	0.04	3
PFDA	9	2.96	0.15	3
PFUnA	10	3.56		1
PFBS	4	1.79	0.10	3
PFHxS	6	2.05	0.08	3
PFOS	8	2.80	0.08	3

- Primary impacts on sorption: f_{oc}, chain length (some exceptions)
- Other factors: functional group, pH, Ca^{2+}

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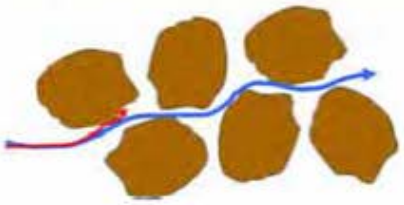
TRANSPORT: IDEAL



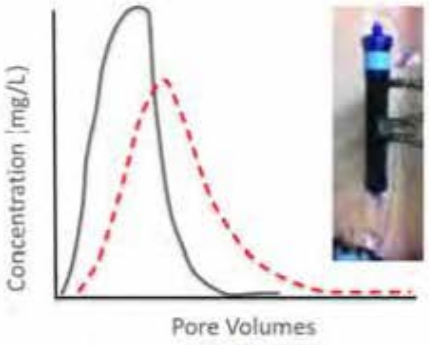
$$R\frac{fC}{ft} = D_L\frac{f^2D}{fx^2} - v_x\frac{fC}{fx}$$

sorption dispersion advection

Sorption and Retardation

- The velocity of water relative to velocity of contaminant
- Retardation factor (R):

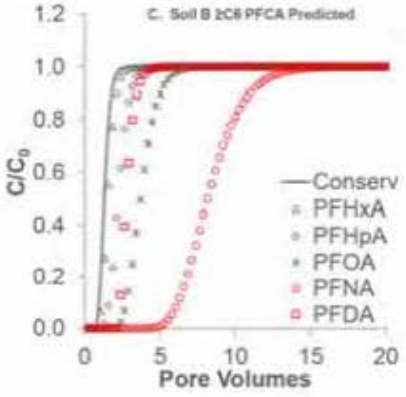
$$R = 1 + \frac{\rho_b}{\phi}K_f n C_w^{n-1}$$

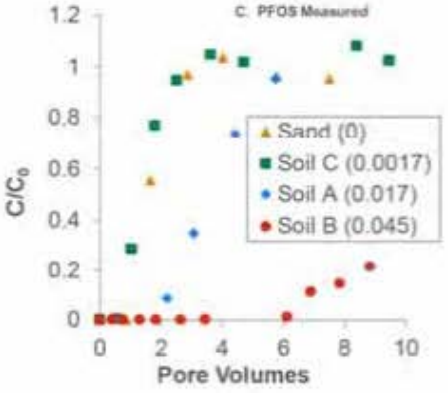


- ↑ R leads to ↓ transport

17

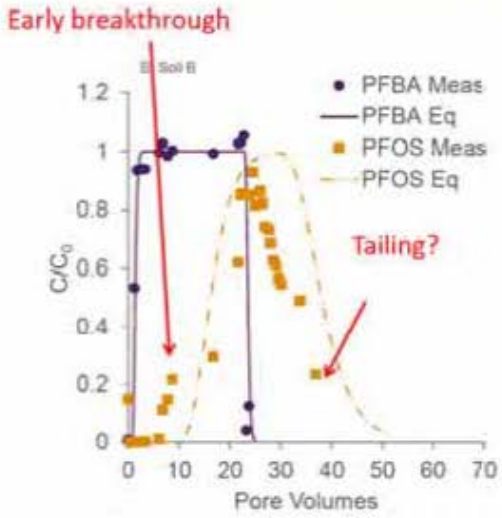
TRANSPORT: IDEAL In Prep





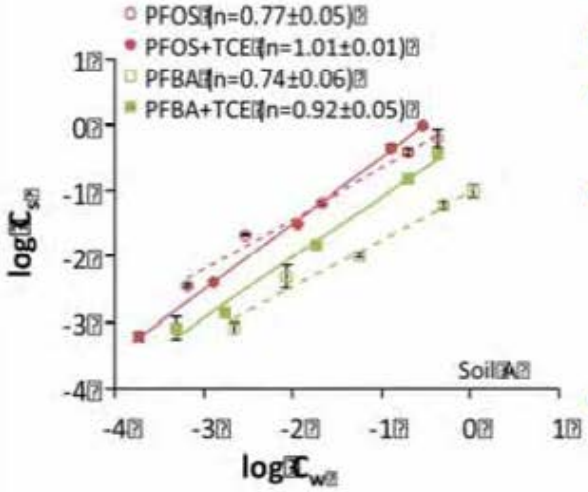
- Chain length dependent breakthrough
- Increased f_{oc} = slower transport

TRANSPORT: NON-IDEAL[In Prep]



- Short chain: equilibrium
- Long chain: Early breakthrough, tailing = rate-limited (kinetic) effects
- Most relevant for longer chains, higher f_{oc}
- Particularly pumping scenarios

PATHWAY: NON-IDEAL TRANSPORT[21]

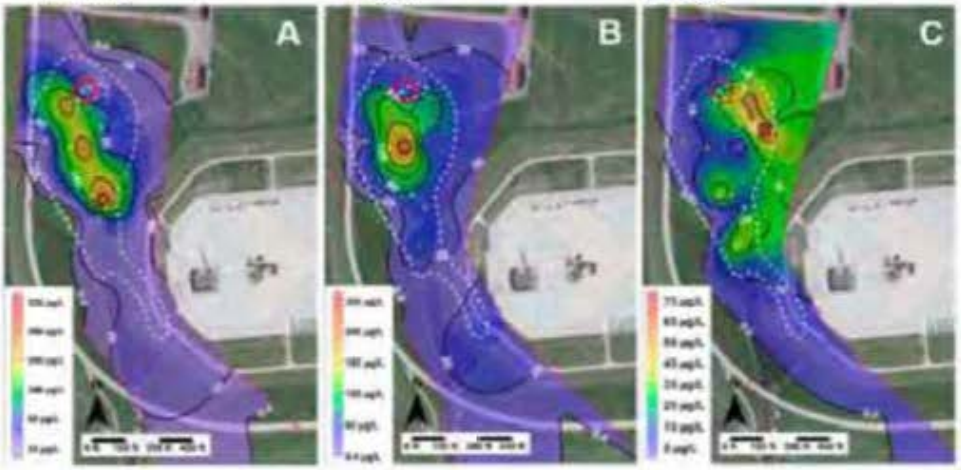


Co-Contaminant effects:

- Multiple PFAS – competitive sorption?
- AFFF sites
  - Other AFFF components
  - Hydrocarbon constituents
  - Chlorinated solvents
  - NAPL
- Other types of sites?

PATHWAY: NON-IDEAL TRANSPORT[4]

PFHxA PFOA PFOS

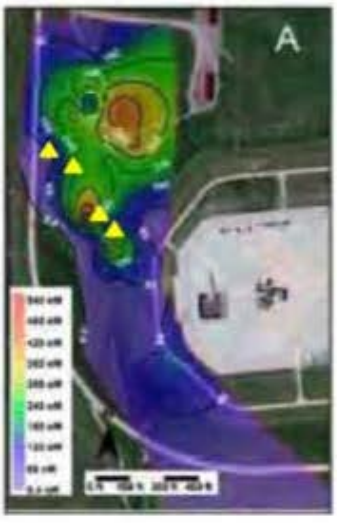


No evidence of differential transport.

21

TRANSPORT: NON-IDEAL[4]

Total Precursors in groundwater:



- Oxygen infusion wells
- [Precursor] elevated *outside* of oxygen infusion areas
- Elevated precursors = areas for potential [PFAA] ↑

22

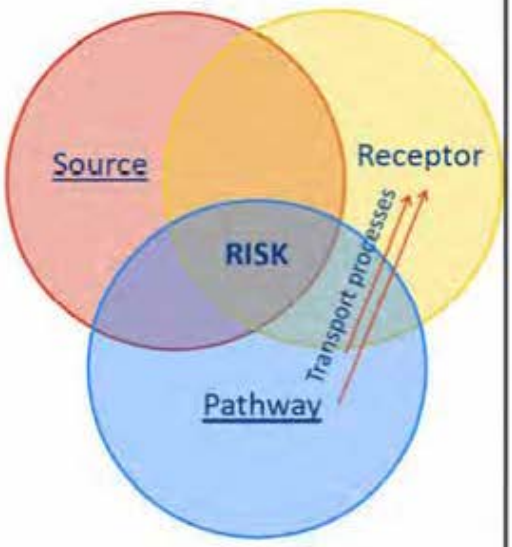
CONCEPTUAL MODEL CONSIDERATIONS

Source/Pathway:

- Max [PFAS] of mg/L (AFFF) to low µg/L (bisolids, GW-SW)
- Target PFAS vary by source
- PFOA/PFOS not always max
- Precursors indirect source of PFCAs/PFSAs

Transport:

- Non-ideal transport likely: kinetics, co-contaminants, transformation
- Plume lengths of miles possible



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Surface-water/groundwater boundaries affect seasonal PFAS concentrations and PFAA precursor transformations†

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Elevated concentrations of per- and polyfluoroalkyl substances (PFAS) in drinking-water supplies are a major concern for human health. It is therefore essential to understand factors that affect PFAS concentrations in surface water and groundwater and the transformation of perfluoroalkyl acid (PFAA) precursors that degrade into terminal compounds. Surface-water/groundwater exchange can occur along the flow path downgradient from PFAS point sources and biogeochemical conditions can change rapidly at these exchange boundaries. Here, we investigate the influence of surface-water/groundwater boundaries on PFAS transport and transformation. To do this, we conducted an extensive field-based analysis of PFAS concentrations in water and sediment from a flow-through lake fed by contaminated groundwater and its downgradient surface-water/groundwater boundary (defined as ≤100 cm below the lake bottom). PFAA precursors comprised 45 ± 4.6% of PFAS (PFAA precursors + 18 targeted PFAA) in the predominantly oxic lake impacted by a former fire-training area and historical wastewater discharges. In shallow porewater downgradient from the lake, this percentage decreased significantly to 25 ± 11%. PFAA precursor concentrations decreased by 85% between the lake and 84–100 cm below the lake bottom. PFAA concentrations increased significantly within the surface-water/groundwater boundary and in downgradient groundwater during the winter months despite lower stable concentrations in the lake water source. These results suggest that natural biogeochemical fluctuations associated with surface-water/groundwater boundaries may lead to PFAA precursor loss and seasonal variations in PFAA concentrations. Results of this work highlight the importance of dynamic biogeochemical conditions along the hydrological flow path from PFAS point sources to potentially affected drinking water supplies.

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Environmental significance

Groundwater contamination by per- and polyfluoroalkyl substances (PFAS) poses risks for drinking-water supplies across the United States. Surface-water/groundwater boundaries are frequently found along flow paths downgradient from point sources. Transport through these boundaries results in rapid changes in aqueous biogeochemistry, but the impact of these changes on PFAS transport and precursor transformation is poorly understood. We examined PFAS transport through surface-water/groundwater boundaries and discovered order-of-magnitude seasonal fluctuations in perfluoroalkyl acid (PFAA) concentrations and loss of ~85% of influent precursors. PFAA concentrations were significantly and inversely associated with temperature and nitrate concentrations. This work highlights the possibility of substantial spatial and temporal variability in PFAS concentrations originating in boundary regions of high biogeochemical reactivity.

Introduction

Human exposure to per- and polyfluoroalkyl substances (PFAS) has been linked to many health effects such as adverse effects on metabolism, endocrine disruption, and immunotoxicity.[1–3] Aqueous film-forming foams (AFFF) containing PFAS and used during fire emergencies and fire-training activities have contaminated water supplies across the United States of America (USA).[4–7] Processes such as sediment-water sorption and perfluoroalkyl acid (PFAA) precursor transformation

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(herein referred to as precursors) influence PFAS mobility and potential contamination of drinking-water supplies near PFAS source zones.[8] Thus, understanding processes that control PFAS transport and transformation is essential for developing strategies for protecting groundwater and surface-water supplies.

High PFAS concentrations and diverse precursors have been reported at AFFF-impacted sites.[9–11] Some precursors degrade in the environment into terminal PFAA known to be a concern for human health.[12] Biotransformation of precursors can also lead to the formation of persistent intermediate precursors,[13,14] with altered mobility and transformation rates compared to the primary compounds. Prior work has suggested PFAA precursor biotransformation rates are slower in anaerobic environments compared to oxic conditions, and that biotransformation under anaerobic and oxic conditions produces different end products.[14–16] However, impacts of redox gradients and enhanced biological activity, as found at surface-water/groundwater boundaries, on precursor transformation and transport are poorly understood.

Numerous laboratory studies have illustrated that PFAS sorption at the sediment-water interface affects mobility in groundwater.[17–19] The perfluorocarbon chain length (η_{pfc}), head group, and a variety of environmental properties (*e.g.*, sediment organic carbon content, mineral and grain coating composition, pH, aqueous calcium and humic acid concentration) have all been shown to influence PFAS partitioning in laboratory experiments.[17–21] However, it is not clear whether PFAS sorption in the field is affected by the gradients in redox and biological activity frequently observed across surface-water/groundwater boundaries. Experimental data on sorption of precursors is more limited due to difficulties in detecting and quantifying the diverse compounds that occur at AFFF-impacted sites, making new field-based observations especially useful.

Globally, lakes and rivers are commonly hydraulically connected to groundwater. PFAS-contaminated groundwater has been shown to contaminate surface waters, and *vice versa* in such systems.[22–24] For example, our prior work on Cape Cod, Massachusetts (MA), USA, characterized a contaminated groundwater plume that discharges to a groundwater-flow-through glacial kettle lake (Ashumet Pond).[6] Such glacial kettle lakes are common in northern latitudes and formed when blocks of glacial ice left behind by retreating ice sheets melted resulting in depressions (kettle holes) in the land surface that subsequently filled with water.[25,26] Upgradient from Ashumet Pond, we detected PFAS and precursors throughout a 1.2 km-long longitudinal transect of the suboxic groundwater plume, highlighting the mobility of precursors in groundwater at this site.[6] PFAS from the upgradient groundwater plume discharges to Ashumet Pond, and the PFAS-contaminated lake water then passes through a downgradient surface-water/groundwater boundary and recharges the downgradient aquifer. The surface-water/groundwater recharge boundary is a dynamic region of increased biological and chemical activity.[25,27–29]

Here we hypothesize that biogeochemical fluctuations such as oxygen content within the downgradient surface water/groundwater boundary layer (defined for this study as the top 100 cm of the lake-bottom sediments) affects PFAS transport and transformation on both daily and seasonal timescales. To test this hypothesis and determine if there are significant changes in PFAS and precursor concentrations across the surface-water/groundwater boundary, we sampled groundwater, surface water, and sediment downgradient from the PFAS groundwater plume, with a focus on Ashumet Pond, and measured changes in 23 targeted PFAS, inferred precursor concentrations from the total oxidizable precursor (TOP) assay, and extractable organofluorine (EOF). The results of this work are used to better understand how shifts in biogeochemical conditions along the hydrological flow path affect PFAS transport and precursor persistence.

Materials and methods

Site overview

This study was conducted on western Cape Cod, MA, USA (Fig. 1). We measured PFAS concentrations along the hydrological pathway of the contaminated groundwater plume as it discharges to Ashumet Pond, mixes with the lake water, and subsequently recharges back into downgradient groundwater (Fig. 1B and C), thereby passing through groundwater/surface-water discharge and surface-water/groundwater recharge boundaries. Exchange between groundwater and surface water occurs predominantly in the shallow, near-shore zones of lakes, and seepage velocity decreases with increasing distance from the shoreline.[30] At the study site, groundwater generally flows from northwest to southeast (average flow velocity ~0.4 m d^{-1} (ref. 31–33)) and is intersected by two kettle lakes (Ashumet Pond and Johns Pond) along the flow path. The term "lake" is used to describe Ashumet Pond herein because of its large volume and surface area. Ashumet Pond is the focus of this study, unless otherwise stated. Ashumet Pond is the first kettle lake along the hydrological flow path of groundwater contaminated by PFAS from a former fire training area (FTA) and former wastewater infiltration beds (Fig. 1A).[6] Regular AFFF use at the FTA ended in 1985, and one additional application occurred in 1997 due to a fire emergency.[6] The use of wastewater infiltration beds at the site was discontinued in 1995.[6]

This study focuses on the downwelling surface-water/groundwater recharge boundary rather than the upwelling boundary, because Ashumet Pond provides a spatially and temporally consistent source of PFAS concentrations to the downwelling groundwater. PFAS concentrations at the upwelling surface-water/groundwater boundary are highly influenced by location relative to the discharging groundwater contamination plume. This means that in the upwelling groundwater PFAS concentration fluctuations due to biogeochemical effects are not easily distinguishable from those due to the dynamic plume position.

Ashumet Pond is a mesotrophic groundwater-flow-through kettle lake with no permanent surface-water inflow or outflow.[34] It has an area of 0.82 km^2, an estimated hydraulic residence time of 1.6 years, and a maximum depth of 26 m.[34,35] The lake level varied by about 1.1 m during this study (Fig. S1†).[36] Residences with septic systems surround Ashumet Pond (Fig. 1A). The potential areal extent of recharged lake

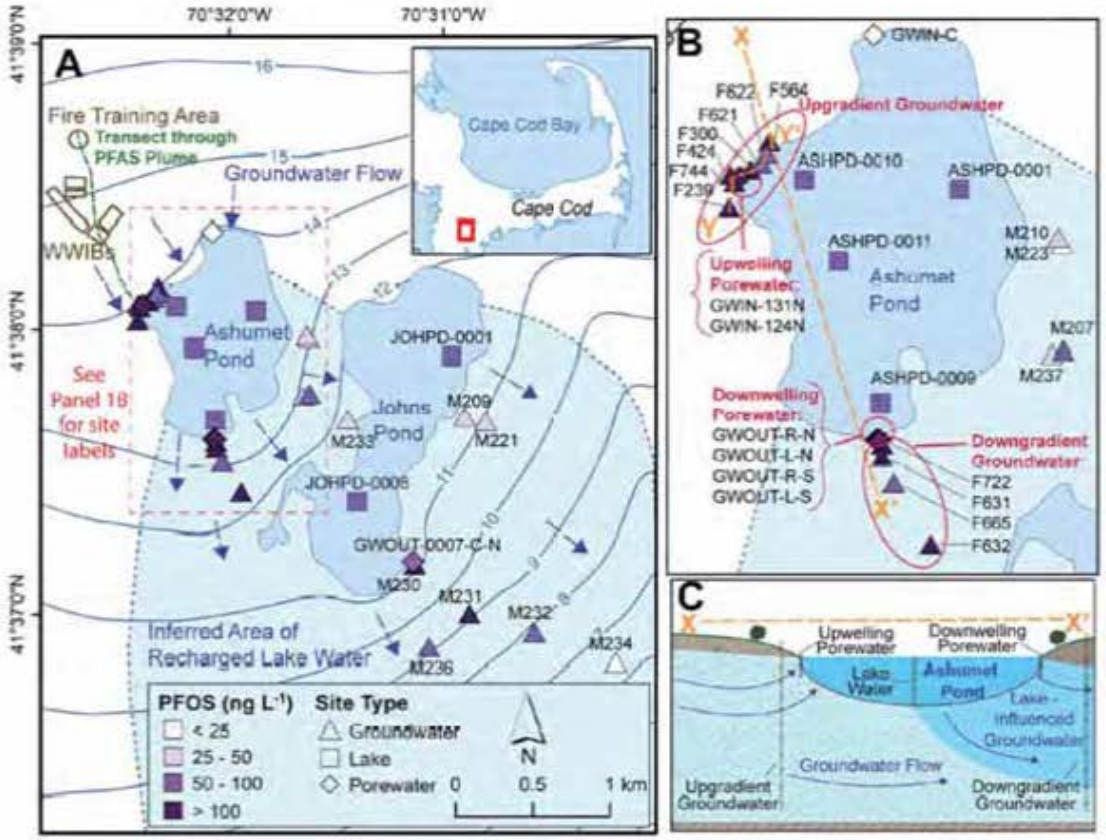

Fig. 1 Study sampling locations. (A) Map of locations sampled between 2016 and 2019. WWIBs denotes wastewater infiltration beds. Most sampling locations include multiple sampling depths. Blue arrows indicate groundwater flow directions. Contours show elevation of water table in m above sea level, referenced to the National Geodetic Vertical Datum of 1929 (NGVD 29).[38] The plume of per- and polyfluoroalkyl substances (PFAS)[8] primarily discharges to Ashumet Pond near the westernmost extent of the lake. The maximum aqueous perfluorooctane sulfonate (PFOS) concentration is shown for each location.[41] The locator map is from the U. S. Geological Survey National Hydrography Dataset, data refreshed April 2019.[66] (B) Enlarged view of Ashumet Pond and associated sampling sites. (C) Cross-sectional representation of Ashumet Pond (not to scale) along section line X–X' depicted in (B).

water from Ashumet Pond in the downgradient aquifer was determined using the groundwater-flow directions inferred from water-table maps prepared from field water-level measurements[37] and simulated flow paths from calibrated groundwater-flow models[38,39] (see "Inferred Area of Recharged Lake Water", Fig. 1A, blue shading). The ESI† contains additional site details.

Sampling overview

We collected 289 water samples and 13 deionized (DI) water equipment blanks) between 2016 and 2019 following U.S. Geological Survey (USGS) field protocols.[40] Ancillary data collected in the field during sampling included temperature, specific conductance, pH, dissolved oxygen (DO), and nitrate. Data are provided in the associated data release,[41] and additional details on sample collection are provided in the ESI.† Water samples were collected from depth profiles in Ashumet Pond and Johns Pond (Fig. 1) in September 2017 (n = 40 samples, 4 profiles) and November 2017 (n = 10, 1 profile).

Upgradient and downgradient groundwater. Upgradient groundwater samples were collected from a "fence" of well clusters and multilevel samplers (herein referred to as wells) that provides a cross section of the PFAS contamination plume approximately transverse to the direction of groundwater flow along the northwestern, upgradient shore of Ashumet Pond (section line Y–Y', Fig. 1B) in July/August 2016 (n = 75) to confirm the location of the PFAS contamination plume. Downgradient groundwater samples were collected in July 2017 (n = 39), September 2017 (n = 40), February 2018 (n = 24), and February 2019 (n = 18). Wells F722, F631, F665, and F632 create a transect with significant vertical resolution (40 sample ports)[41] along the flow path downgradient from the kettle lake. Water levels for these wells are presented in Table S1† and closely track the lake water level (Fig. S1†). Additional wells to the west of the Ashumet Pond and downgradient from Johns Pond were

included to investigate the width of the area impacted by PFAS-containing lake water.

Upwelling and downwelling lake-bottom porewater. Sediment porewater samples (Fig. 1) were collected in the surface-water/groundwater boundary layer between 15–100 cm below the bottom of Ashumet Pond and Johns Pond at near-shore sites where groundwater was upwelling (northwestern side of Ashumet Pond) or downwelling (southern and southeastern sides of Ashumet and Johns Ponds, respectively). The maximum water depth at these near-shore sites during the sampling events was 66 cm. Associated lake-water samples were also taken 20 cm above the lake bottom from both lakes. Upwelling porewater (GWIN; $n = 8$, water depth at sampling location = 39–48 cm) and associated lake-water samples ($n = 2$) were collected in September 2017 near the northwestern shore of Ashumet Pond where PFAS-contaminated groundwater from FTA and wastewater disposal sources was expected to discharge. Upwelling porewater samples were also collected in September 2017 in the northern section of Ashumet Pond (GWIN-C; $n = 2$, water depth at sampling location = 66 cm) where PFAS-free groundwater was expected to discharge to the lake, along with an associated lake-water sample ($n = 1$). Downwelling porewater (GWOUT) and associated lake-water samples were collected in September 2017 (porewater $n = 10$ and lake water $n = 2$, water depth at sampling location = 31–33 cm except for GWOUT-R-S, which was above the shoreline), February 2018 ($n = 2$ and $n = 1$, water depth at sampling location = 58–62 cm), and February 2019 ($n = 8$, $n = 2$, water depth at sampling location = 46–54 cm) in the southern section of Ashumet Pond immediately upgradient from wells F722, F631, F665, and F632. Downwelling porewater and associated lake water were collected from the southeastern section of Johns Pond in February 2019 (porewater $n = 4$ and lake water $n = 1$, water depth at sampling location = 44 cm). The water-surface elevation of Ashumet Pond varied over a range of 1.1 m at the field site during the study (Fig. S1†), but on the dates of sampling the water level only varied over a range of 0.5 m: ~13.5 m above mean sea level in September 2017, ~13.8 m above mean sea level in February 2018, and ~14.0 m above mean sea level in February 2019.

Sediment and soil samples. Sediment samples from the surface-water/groundwater boundary-layer ($n = 14$) were collected from 7 locations near the Ashumet Pond and Johns Pond shorelines at locations where porewater was sampled in September 2017 and February 2019 (Fig. 1). Sediment samples were collected by driving a 5 cm-diameter aluminum tube into the lake bottom. Sediment cores were subsampled from the 0–5 cm and 15–30 cm depth intervals. In February 2019, 1 beach sediment sample (~0–5 cm depth) was collected near the southeastern shore of Johns Pond, and 2 topsoil samples were collected near the southern shore of Ashumet Pond from 0–13 cm depth adjacent to wells F722 and F631 (Fig. 1B).

Chemicals and materials

Table S2† contains the full names and abbreviations for all PFAS compounds analyzed in this study. PFAS standards (24 native compounds and 19 isotopically labeled compounds, Table S2†) were obtained from Wellington Laboratories (Guelph, Canada). Other chemicals used in the analyses are listed in the ESI.†

PFAS extraction and analysis

Water samples were spiked with 40 μL of a 0.03 ng μL^{-1} internal standard solution before offline solid phase extraction (SPE) using Oasis® WAX cartridges (6 mL, 150 mg, 30 μm particle size, Waters, Milford, MA, USA) following established methods.[5,42,43] Oasis WAX SPE cartridges were preconditioned with 4 mL of 0.1% ammonium hydroxide in methanol, 4 mL of methanol, and 4 mL of DI water, and then the 20 mL sample was added to the cartridge and placed under vacuum to yield a flow rate of ~1 drop per second followed by a 4 mL DI water rinse before drying the cartridge under vacuum. The samples were eluted with 4 mL of methanol followed by 4 mL of 0.1% ammonium hydroxide in methanol, and the collected eluent was evaporated to dryness using an ultra-high-purity nitrogen gas stream, reconstituted in 0.75 mL of methanol, heated to 40 °C for 30 min, and vortexed. Finally, 0.75 mL of water was added, the sample was transferred to a polypropylene microcentrifuge tube and centrifuged at 13 000 rpm for 20 min, and the supernatant was transferred to a polypropylene autosampler vial for analysis. Samples were analyzed with an Agilent (Santa Clara, CA) 6460 triple quadrupole liquid chromatograph-tandem mass spectrometer (LC-MS/MS), as detailed in the ESI† and previously described.[5] 6:2 Fluorotelomer sulfonate (6:2 FtS) was removed from the reported results due to periodic blank contamination. Precursors that were quantified included 4:2 FtS, 8:2 FtS, *N*-methyl perfluorooctane sulfonamidoacetate (*N*-MeFOSAA), *N*-ethyl perfluorooctane sulfonamidoacetate (*N*-EtFOSAA), and perfluorooctane sulfonamide (FOSA). Further details including quality control, recovery, and precision results (Table S3) are presented in the ESI.†

TOP assay

The TOP assay[44,45] was applied to 79 water samples (8 upwelling porewater, 16 lake water, 5 lake water near shore above porewater locations, 12 downwelling porewater, and 38 downgradient groundwater) from July 2017 to February 2018. All lake-water and porewater samples subjected to the TOP assay were from Ashumet Pond. Oxidation was completed by combining a 20 mL water sample with 20 mL of an aqueous potassium persulfate sodium hydroxide solution. Samples were placed in a heated (85 °C) water bath overnight, cooled, neutralized with hydrochloric acid, and extracted with offline SPE. For method validation, groundwater and lake-water samples were spiked, in triplicate, with 3 ng of 6:2 FtS, 8:2 FtS, *N*-MeFOSAA, *N*-EtFOSAA, and FOSA. These precursor concentrations were all reduced by >95%, and the molar recovery calculated from the produced perfluoroalkyl carboxylates (PFCA) was between 93% and 104%, indicating near-quantitative recovery. Details are available in the ESI,† and recovery and precision results are presented in Table S4.†

The total concentration of oxidizable precursors (Σ precursors) for aqueous samples was inferred from the measured increases in PFCA with $\eta_{pfc} = 3$ to $\eta_{pfc} = 8$ produced by the TOP

assay using a previously developed Bayesian inference method that has been applied to both AFFF and AFFF-impacted freshwater[46,47] for all samples with measured increases in PFCA following the TOP assay. The model produces a distribution of inferred precursor concentrations using measurements of the PFCA produced upon oxidation and representative precursor yields from the literature, and their respective uncertainties.[47] This inference method provides a more realistic estimate of precursor concentrations than the analytically detected changes in individual PFCA concentrations because it accounts for method and instrumentation uncertainties as well as incomplete recovery due to potential losses during oxidation to fluoride and ultra-short chain length PFCA.[47] We report the median of inferred precursor concentrations. Details of the model and the criteria used to perform inference are provided in the ESI.†

Sediment PFAS and metals analysis

Sediment samples were extracted for PFAS analysis in triplicate with 0.1% ammonium hydroxide in methanol following previously developed methods.[5,41,48] Selected sediment sample extracts were subjected to the TOP assay to estimate sediment precursor concentrations. Separate aliquots of sediment were extracted with 0.5 M hydrochloric acid, and extractable metal concentrations, including aluminum, iron, and manganese, were measured by inductively coupled plasma mass spectrometry (ICP-MS). See ESI† for sediment extraction and analysis details, and Tables S5–S12† for results and quality assurance and quality control.

Extractable organofluorine (EOF)

EOF analysis was performed on a subset of samples from Ashumet Pond and downwelling groundwater following the procedure described in prior work.[46] Briefly, weak anion exchange cartridges (Oasis® WAX) were preconditioned and then loaded with sample. Then, 10 mL of 0.01% v/v ammonium hydroxide (ACS grade, BDH® VWR International, Radnor, PA) in deionized water was passed through the cartridges to remove inorganic fluorine and the sample was eluted with LC-MS grade methanol (Honeywell, Charlotte, NC) and 0.1% v/v ammonium hydroxide in methanol, evaporated to dryness, and finally reconstituted into 1.5 mL methanol. Extracts were split 50 : 50 between the LC-MS/MS and the combustion ion chromatograph (CIC) with a combustion unit from Analytik Jena (Jena, Germany) and a 920 Absorber Module and 930 Compact IC Flex ion chromatograph from Metrohm (Herisau, Switzerland). Isotopically labeled internal standards (MPFAC-24 ES, Wellington Laboratories, Guelph, Ontario, Canada) were added to the LC-MS/MS fraction after the extract was split. See ESI† for details and results (Table S13†).

Statistics

All statistical tests were performed in Python version 3.6 using scipy.stats or scikit_*posthocs*. We used nonparametric statistics for our analysis as data frequently failed Shapiro Wilk tests for normality ($p < 0.05$). The Mann–Whitney *U*-test (a nonparametric *t*-test) was used to evaluate significant differences between two populations. For comparisons of more than two populations of nonparametric data, the Kruskal–Wallis test with Dunn's *post hoc* test was used to identify groups that differed significantly.

Results and discussion

Homogenous PFAS concentrations in the groundwater-fed kettle lake

Our results showed the upgradient groundwater PFAS plume primarily discharges to Ashumet Pond (Fig. 1 and S2†). This was confirmed by elevated PFAS concentrations in upwelling porewater at sites GWIN-131N and GWIN-124N (Fig. 1B). These results are consistent with previously reported groundwater discharge patterns.[34,35,49–51]

In Ashumet Pond, mean PFAS concentrations were highest for perfluorohexane sulfonate (PFHxS) (74 ± 6.5 ng L^{-1}), perfluorooctane sulfonate (PFOS) (50 ± 4.1 ng L^{-1}), and perfluorooctanoate (PFOA) (29 ± 2.8 ng L^{-1}). No significant temporal differences in concentrations of the sum of 23 targeted PFAS (Σ_{23}PFAS) were observed between September and November 2017 (Mann–Whitney *U* test, $p > 0.05$), despite the collapse of the thermocline between the two sampling dates (Fig. S3†).[41] Non-parametric Kruskal–Wallis with *post hoc* Dunn's test performed on all vertical profile sampling stations and for all seasons in Ashumet Pond revealed Σ_{23}PFAS concentrations showed no significant spatial differences (Dunn's test, $p > 0.05$, Fig. S3†) except between two profiles in Ashumet Pond (ASHPD-0010 and ASHPD-0011, Dunn's test, $p < 0.05$). Inspection of the data reveals the median Σ_{23}PFAS is 200 ng L^{-1} for ASHPD-0010 and 230 ng L^{-1} for ASHPD-0011, which is a 14% difference and within analytical uncertainty. These data suggest PFAS concentrations were spatially and temporally consistent in Ashumet Pond.

Elevated PFAS concentrations in wells downgradient from both Ashumet and Johns Pond confirm that PFAS are present in groundwater in the inferred area of recharged lake water.[41] Mixing of the upgradient shallow groundwater PFAS plume (<30 m below land surface,[5] Fig. S2†) of limited lateral dimensions (<200 m wide) with a surface-water body creates a much wider zone (>3 km; Fig. 1A) of PFAS-contaminated groundwater upon recharge of lake water to the downgradient groundwater. This general hydrological dispersion mechanism has important implications for other PFAS-contaminated regions with significant groundwater/lake interactions. For example, when a groundwater plume of limited lateral and vertical dimensions enters a well-mixed surface-water body, the spatial extent of contamination will disperse to the extent of the surface-water body. Further, if the surface-water body discharges downgradient to groundwater (as is the case here) and/or river outlets, the PFAS contamination will be transported to the entire area that receives and transmits the discharging water. Although dilution of PFAS from a more concentrated groundwater contamination plume will occur upon interaction with a surface-water body, the spatial footprint of contamination of

PFAS has the potential to increase substantially, as observed here.

Precursor degradation within the surface-water/groundwater boundary layer

We hypothesized that precursors would biodegrade during transport through the biogeochemically active surface-water/groundwater boundary layer. Consistent with this hypothesis, the sum of total inferred precursors (Fig. 2, center) decreased by 85% and the inferred precursor mole fraction (Fig. 3) decreased by 59% between Ashumet Pond lake water sampled above the downwelling zone and samples taken 84–100 cm below the lake bottom ($n = 5$) (Fig. 2, center). In Ashumet Pond water ($n = 19$), the mole fraction of inferred precursors measured was statistically greater (non-parametric Kruskal–Wallis with *post hoc* Dunn's test) than in downwelling porewater ($n = 12$, $p < 0.05$) and downgradient groundwater ($n = 37$, $p < 0.05$) (Fig. 3). The presence of precursors in the downgradient groundwater indicates some precursors persist and are transported intact (or transformed to intermediate precursors) across the surface-water/groundwater boundary.

Both sorption and biotransformation could cause the observed reduction in precursors across the surface-water/groundwater boundary. Estimated sediment precursor concentrations (Table S7†) indicate only small increases in terminal PFAAs following the TOP assay compared to pre-TOP PFAA concentrations suggesting minimal precursor sorption. A statistically significant inverse correlation (Spearman, $r = -0.62$, $p < 0.05$) was observed between inferred precursor concentrations and nitrate in porewater downwelling from Ashumet Pond, suggesting the decrease in concentration is related to biotransformation. Nitrate concentrations increased below the lake bottom in the downwelling zone, reaching a maximum of 15 μM at 100 cm below the lake bottom in the September 2017 samples (temperature >20 °C, Fig. 2). This increase in nitrate is consistent with previous observations at

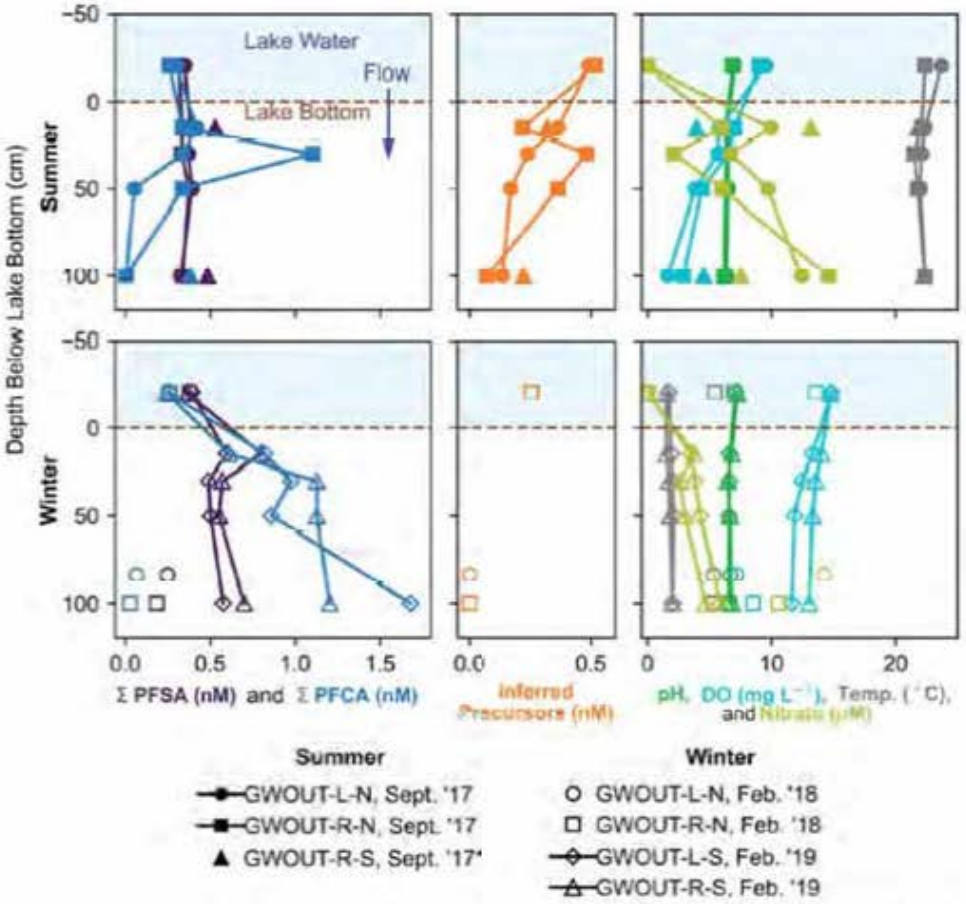

Fig. 2 Seasonal fluctuations in perfluoroalkyl acids (PFAA) at the surface-water/groundwater boundary. Vertical depth profiles of the sum of perfluoroalkyl sulfonates (PFSA), the sum of perfluoroalkyl carboxylates (PFCA), inferred precursors, pH, dissolved oxygen (DO), temperature, and nitrate at the surface-water/groundwater boundary at downwelling sites in September 2017, February 2018, and February 2019. *Site GWOUT-R-S sampled in September 2017 (see legend) was landward of the lake shore due to low water level in Ashumet Pond; the samples are from 15 and 100 cm below the water table, located 40 cm below the ground surface. See Fig. S4† for profiles of individual PFAA concentrations.

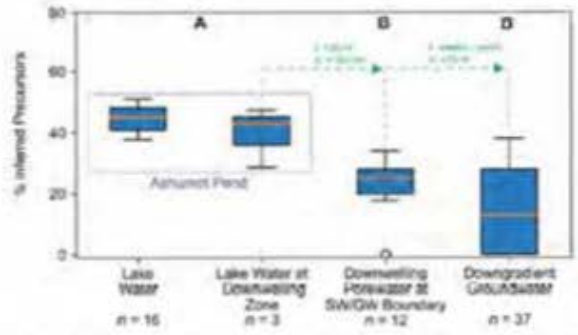

Fig. 3 Precursor fraction along the hydrological flow path. The inferred molar fraction of precursors out of the total molar mass of per- and polyfluoroalkyl substances (PFAS) (inferred precursors, perfluoroalkyl carboxylates (PFCA), and perfluoroalkyl sulfonates (PFSA)) along the hydrological flow path. The box encompasses the 1st and 3rd quartiles of the data and the orange line denotes the median. Whiskers represent the 3rd quartile plus 1.5 times the interquartile range (upper bound) or the 1st quartile minus 1.5 times the interquartile range (lower bound) and extend only to the highest (upper bound) or lowest (lower bound) data point within that range. Circles represent data outside of the whisker range. Common letters above each boxplot indicate no significant difference ($p < 0.05$) between group comparisons using the non-parametric Kruskal–Wallis test and *post hoc* Dunn's test for multiple comparisons. For statistical tests, the three lake-water samples from the second boxplot from the left were combined with the 16 lake-water samples. The travel time (t) and distance (d) from one sample type to the next is indicated in green. Porewater velocities at the downwelling sites at Ashumet Pond have been observed to range from 67 to 440 cm d^{-1}, assuming a porosity of 0.39,[28,32,34,47] which equates to a maximum transport time of 36 hours from the lake bottom to 100 cm below the lake bottom. SW/GW stands for surface-water/groundwater.

this field site and has been hypothesized to reflect biomineralization of organic nitrogen coupled to nitrification.[34] These results suggest an association between conditions that lead to increased nitrate concentrations and precursor loss. Prior work has shown that the surface-water/groundwater boundary is a zone of increased microbial activity relative to the overlying water column owing to the greater nutrient and microbial abundance in the sediments compared to lake water.[33,35] Nitrification is microbially driven and typically requires oxygen, ammonia, and redox gradients to proceed.[34,35] Nitrification dominates over denitrification in areas with short porewater residence times, as found at this site.[34] The production of nitrate (Fig. 2) indicates an active microbial community, which likely also facilitates biodegradation of PFAS precursor compounds during passage through the surface-water/groundwater boundary and would explain the inverse correlation between nitrate and inferred precursor concentrations.

Seasonal changes in PFAA concentrations at the surface-water/groundwater boundary

PFCA and perfluoroalkyl sulfonates (PFSA) concentrations in downwelling porewater (Fig. 2 and 4) and downgradient groundwater were significantly different (Mann–Whitney U test, $p < 0.05$) between seasons, with lower average concentrations in the summer (September) and higher average concentrations in the winter (February). These seasonal differences are supported by a strong inverse correlation (highest concentrations at low temperature) between temperature and the sum of PFCA concentrations (Spearman, $r = -0.50$, $p < 0.05$, $n = 102$) and the sum of PFSA concentrations (Spearman, $r = -0.38$, $p < 0.05$, $n = 102$) for all porewater and groundwater directly downgradient from Ashumet Pond (Fig. 4). Ashumet Pond is the source water for downwelling porewater and downgradient groundwater. Temporal trends in the porewater and groundwater are not linked to PFAA concentration changes in the source water because PFAA concentrations in Ashumet Pond water were consistent across all sampling dates (Fig. 4).

At the downwelling surface-water/groundwater boundary (GWOUT) of Ashumet Pond, the mean concentration in porewater increased from September (Σ_{23}PFAS = 270 ng L^{-1}, Σ_{11}PFCA = 110 ng L^{-1}, Σ_7PFSA = 160 ng L^{-1}) to February (Σ_{23}PFAS = 510 ng L^{-1}, Σ_{11}PFCA = 280 ng L^{-1}, Σ_7PFSA = 230 ng L^{-1}). Concentrations differed significantly between the September and February samples for Σ_{23}PFAS, Σ_{11}PFCA, and Σ_7PFSA (Mann–Whitney U test, $p < 0.05$). Porewater PFCA concentrations varied with depth over the 100 cm porewater profile. In September 2017, the lowest PFCA concentrations were observed in the deepest, 100 cm samples (Fig. 2, upper left), suggesting loss of aqueous PFCA with depth. In contrast, PFCA concentrations increased with increasing depth for the February 2019 samples (Fig. 2, lower left). This is a large (>3-fold) increase in aqueous PFCA concentrations, considering the shallow depth of the boundary-layer porewater samples (<100 cm below the lake bottom) and short hydraulic residence times (<36 h) relative to other regions along the hydrological flow path such as the upgradient groundwater and Ashumet Pond lake water. The two samples of downwelling porewater from February 2018 appeared to be more consistent with the trends seen in September 2017 samples (Fig. 2). However, the general water-quality parameters (high nitrate concentrations, an intermediate temperature of 5.3 °C, and intermediate DO concentrations, Fig. 2, lower right, circles and squares)[48] indicate the February 2018 porewater had not completely transitioned to wintertime conditions. In contrast, February 2019 conditions were indicative of a complete wintertime transition, with mean water temperatures of 1.8 °C and high DO concentrations (Fig. 2, lower right, diamonds and triangles).

Similar to the porewater at the surface-water/groundwater boundary, PFCA concentrations in F722, the first groundwater well downgradient from Ashumet Pond, were also significantly different than in the lake water at all sampling dates (Mann–Whitney, $p < 0.05$) and varied by an order of magnitude across sampling times. Specifically, well F722 displayed low PFCA concentrations (mean ± std. dev.: 27 ± 34 ng L^{-1}) in September 2017 and high concentrations in February 2018 (340 ± 200 ng L^{-1}) and February 2019 (230 ± 150 ng L^{-1}) (Fig. 4). PFSA concentrations followed similar, but less pronounced, trends than PFCA, with low September 2017 concentrations (130 ± 38 ng L^{-1}) and increased concentrations in February 2018 (170 ± 30 ng L^{-1}) and February 2019 (220 ± 100 ng L^{-1}) (Fig. 4). September 2017 PFCA and PFSA concentrations were

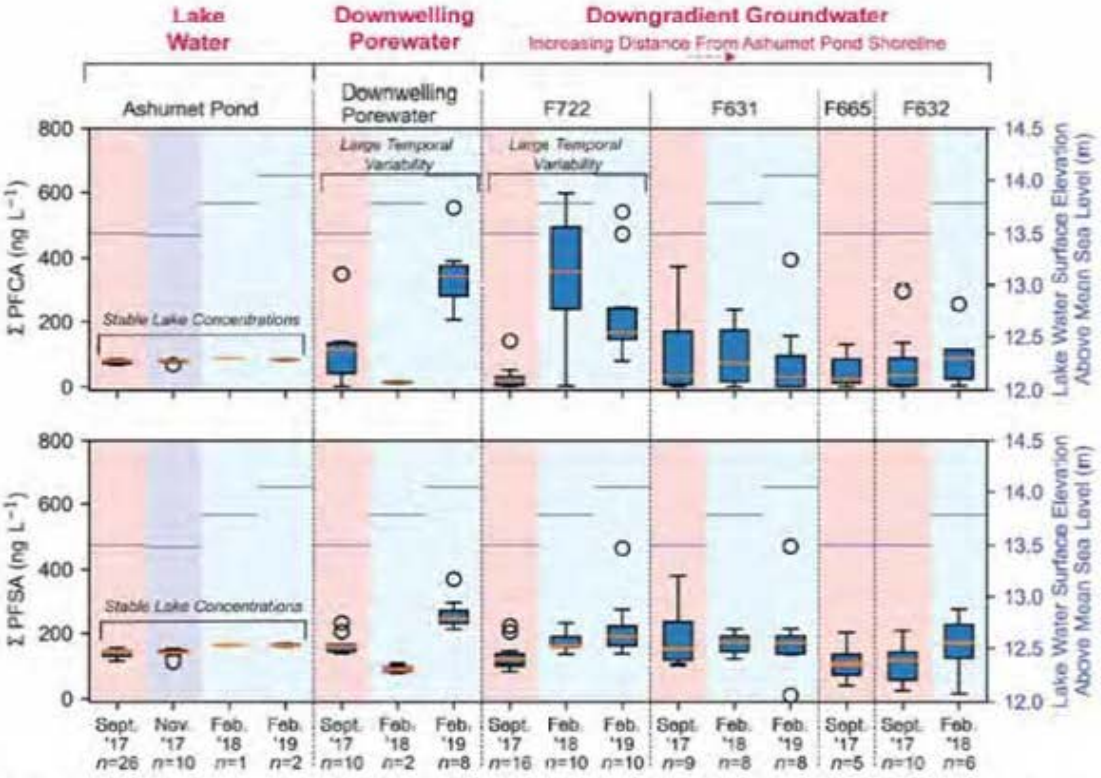

Fig. 4 Perfluoroalkyl acid (PFAA) concentrations along the hydrological flow path. The sum of measured concentrations of perfluoroalkyl carboxylates (PFCA) and perfluoroalkyl sulfonates (PFSA) along the hydrological flow path (from left to right). The box encompasses the 25th and 75th percentiles and the orange line represents the 50th percentile. Whiskers represent the 3rd quartile plus 1.5 times the interquartile range (upper bound) or the 1st quartile minus 1.5 times the interquartile range (lower bound). Circles represent outliers. Lake-water samples from February 2018 and 2019 were collected 20 cm above the lake bottom at the downwelling-porewater sampling locations. The mean lake water surface elevation above mean sea level (National Geodetic Vertical Datum of 1929) in Ashumet Pond[96] associated with each sampling event is shown on the right axis in blue. Downwelling-zone profiles can be found in Fig. 2.

statistically different from February 2018 and February 2019 concentrations at well F722 (Mann–Whitney, $p < 0.05$). PFCA and PFSA concentrations were not significantly different for February 2018 and February 2019 (Mann–Whitney, $p > 0.05$), supporting the seasonal pattern in concentrations. Similar trends are observed for both PFCA and PFSA when considering nanomolar units (Fig. S5†) and individual PFSA compounds (Fig. S6–S10†).

PFCA and PFSA concentrations in wells with increasing distance from Ashumet Pond (F631, F665, F632) were not statistically different (Mann–Whitney, $p > 0.05$) from those in Ashumet Pond except for PFSA concentrations in the February 2018 samples from well F631 and the September 2017 samples from well F632. PFAA concentrations in wells aligned along the hydrological flow path downgradient from Ashumet Pond were more variable than those sampled within the lake (Fig. 4). This reflects the observed variability in PFAA concentrations at the surface-water/groundwater boundary. Processes such as mixing, vertical layering of seasonal waters, and accumulation of groundwater recharge at the water table along the flow path likely dampen the signal of seasonal fluctuations in PFAA groundwater concentrations farther away from the lake.

Temporal changes in PFAA concentration cannot be explained by precursor transformations alone because the inferred total precursor concentration in Ashumet Pond water is less than the fluctuation in PFAA concentration. Increases in median PFAA (0.73 nM) concentrations in downwelling porewater between September and February exceeded the median estimate for the concentrations of all inferred precursors in Ashumet Pond samples (0.43 ± 0.09 nM). Additionally, biotransformation of precursors would be expected to be more rapid in summer when there is high biological activity due to increased temperatures.[57] This would lead to higher downgradient aqueous PFAA concentrations in summer, not in winter (as observed here). Temporal changes in EOF concentrations (Table S13†) further support the conclusion that temporal differences in PFAA are not driven by precursor transformation. Concentrations of EOF decrease by 73% from Ashumet Pond (32 ± 3.6 nM F) to MA-FSW 722-05BKT (8.7 nM F) in September 2017. Conversely, concentrations of EOF at MA-FSW 722-05BKT in February 2018 (60.7 nM F) and 2019

(34.2 nM F) are similar to or exceed concentrations in Ashumet Pond. EOF captures both terminal compounds and precursors, thus total EOF concentrations would not be expected to change temporally if transformation of precursors into PFAAs at the surface-water/groundwater boundary drove PFAA fluctuations.

Adsorption at the air–water interface cannot explain the observed temporal trends at the surface water/groundwater boundary either. For example, GWOUT-L-N was fully submerged throughout the sampling campaign, yet PFAA loss with depth was still observed in the summer. Also, temporal trends were strongest for PFCA, including short chain-length compounds like perfluoropentanoate (PFPeA) that would be expected to sorb less strongly at the air–water interface (Fig. S6–S10†).[38,39] While neither precursor transformation nor adsorption at the air–water interface can explain the observed seasonal trends, the reduction of porewater PFAA concentrations in summertime and increased porewater PFAA concentrations in wintertime indicates a reversible phenomenon. The strong inverse correlation between nitrate and the sum of PFCA concentrations (Spearman, $r = -0.55$, $p < 0.05$, $n = 102$) and sum of PFSA concentrations ($r = -0.28$, $p < 0.05$, $n = 102$) for all porewater and groundwater directly downgradient from Ashumet Pond suggests biological activity is driving the temporal variations, as further discussed in the following section.

The groundwater and porewater results indicate that: (1) the surface-water/groundwater boundary is the source of fluctuations in downgradient groundwater concentrations, (2) concentrations in downwelling porewater and nearby downgradient groundwater change temporally (seasonally), with lower concentrations in the summer (September) and higher concentrations in the winter (February), and (3) these temporal changes are not driven by precursor transformation or the air–water interface. There have been few studies investigating temporal trends of PFAS in groundwater or PFAS transport across surface-water/groundwater boundaries. Steele *et al.*[40] found no statistically significant temporal trend in groundwater data from a site in Alaska, but did find (weakly) statistically significant temporal trends for groundwater at Pease Air Force Base in New Hampshire. Our results indicate stronger seasonal trends, likely owing to the surface-water/groundwater boundary investigated in this work. Another study investigated transport of PFAS between groundwater and surface water, but was primarily focused on mass transfer rates.[24] The data presented here provide new information about the importance of the surface-water/groundwater boundary layer and its potential to drive temporal fluctuations in downgradient groundwater.

Elevated PFCA sediment/water K_d values at lake downwelling sites

To investigate the processes driving the PFAA (particularly PFCA) temporal variability, PFAS concentrations in sediment from the surface-water/groundwater boundary layer were analyzed at upwelling and downwelling sites on Ashumet Pond (Fig. S11–S13†). The sediment PFAS composition at the surface water/groundwater boundary at downwelling sites (GWOUT) was dominated by C4–C7 PFCA (21–76% of the total molar mass, $n = 8$), whereas at upwelling sites (GWIN) the sediment PFAS composition had only a small molar fraction of C4–C7 PFCA (0.80–3.2%, $n = 4$).

Field-derived sediment-water partition coefficients (K_d) were determined from porewater and solid-phase measurements (Fig. 1B, S12 and Table S8†). In the upwelling zone (GWIN), PFCA and PFSA homologues of equivalent perfluorocarbon chain length had similar K_d values, as expected, and varied by a factor of ≤5.3 within each sample (Fig. S12 and Table S8†). The samples from the upwelling zone also followed expected trends of increasing K_d values with increasing perfluorinated chain length (for $\eta_{pfc} > 5$, Fig. S12†). K_d values typically decreased with increasing sediment depth (Table S8†).

By contrast, in the downwelling zone (GWOUT), field-derived PFCA K_d values were larger than PFSA K_d values for homologues of equivalent η_{pfc} (for $\eta_{pfc} < 8$, Fig. S12†) and varied by up to a factor of 28 within each sample (Fig. S12 and Table S8†). Additionally, downwelling-zone PFCA K_d values were not always dependent on chain length, as observed for site GWOUT-R-N 15–30 cm (Sept. 2017), where PFCA K_d values had no chain-length dependence for $\eta_{pfc} \leq 8$ (Fig. S12†). K_d values typically decreased with depth (Table S8†) for $\eta_{pfc} > 6$ and increased with depth for $\eta_{pfc} \leq 6$. The high PFCA K_d values compared to PFSA K_d values was unexpected but is consistent with the temporal trends observed in porewater and downgradient groundwater that were particularly pronounced for PFCA.

Prior work, based primarily on laboratory studies, has shown perfluorocarbon chain length is a primary factor mediating sorption to sediments, with each additional perfluorinated carbon increasing the K_d by 0.50–0.60 log units.[5,17] Chain-length effects are less prominent for PFAA with $\eta_{pfc} < 5$.[61,62] PFSA are reported to adsorb more strongly (+0.23 log units) than PFCA with the same perfluorocarbon chain length due to headgroup (sulfonate *vs.* carboxylate) effects.[5,17] Sorption to solids has also been shown to increase with increasing sediment organic carbon content, iron and aluminum oxide grain coatings, and divalent cation concentrations.[17,19,63] However, these studies find that the trends observed for chain-length and headgroup are typically preserved. Our field-derived K_d results display important differences compared to the lab-based results. Specifically, chain-length dependent relationships are not always observed, and PFCA sorbed more strongly than PFSA in the downwelling surface-water/groundwater boundary examined during this field study.

There are important geochemical and hydrologic differences between the upgradient and downgradient sides of Ashumet Pond that may help explain the observed differences in PFAA sorption. Measured sediment concentrations of iron (Fe) and manganese (Mn) (Table S9†) were typically higher at the upwelling sites (Fe: 360 ± 440 μg g^{-1}; Mn: 968 ± 1000 μg g^{-1}) compared to downwelling sites (136 ± 45 μg g^{-1} for Fe and 32 ± 24 μg g^{-1} for Mn), where increased sorption for PFCA was observed. Total carbon in sediment near the downwelling site is higher (92 ± 1 μmol g^{-1}) than in the sediment near the upwelling sites (~43 μmol g^{-1}).[24] Higher sediment organic carbon would lead to higher expected K_d values at the downgradient site, as reported here (Fig. S12 and Table S8†), but PFAS

sorption by organic carbon is also expected to result in a larger K_d for PFSA than for PFCA, which contrasts with the field observations presented here.[17] Porewater velocity measurements indicate flow rates are typically higher in the downwelling zone compared to the upwelling zone (Table S14†). Higher flow rates favor non-equilibrium conditions. However, non-equilibrium conditions and/or sorption nonlinearity cannot explain the large PFCA K_d values and temporal aqueous PFAA trends, especially given the homogenous concentrations in the Ashumet Pond source water.

The field evidence suggests that PFAA are reversibly sequestered in summer (during times of high biogeochemical activity) and subsequently released in the winter (during times when biological activity is diminished).[52,57] Biologically mediated sorption (such as sorption to microbial biofilms or incorporation into lipid bilayers) would explain both the temporal trends in downgradient porewater and groundwater and also the strong PFCA K_d values observed in sediment. On the upgradient side of the lake, suboxic PFAS-containing groundwater containing recalcitrant dissolved organic carbon concentrations of 0.78–1.1 mgC L^{-1} discharges to the largely oxic lake water.[34,43] On the downgradient side of the lake, oxic lake water containing more labile and higher concentrations of dissolved organic carbon (~2 mgC L^{-1})[34,43] recharges the groundwater and stimulates microbial growth (*e.g.* the porewater DO concentrations progressively decrease with depth below the lake bottom in the summer (Fig. 2), indicating biological consumption). In winter, the porewater within 100 cm of the lake bottom remains oxygen-rich (Fig. 2), likely owing to a decrease in biological activity during the winter. Observed temporal fluctuations in aqueous PFCA and PFSA concentrations are associated with cyclical changes in biogeochemical conditions (DO, temperature, nitrate) in the downgradient porewater (Fig. 2 and 4). There is a statistically significant inverse correlation (Spearman, $r = -0.69$, $p < 0.05$) between PFCA and nitrate concentrations at well F722 for all available sample data, suggesting sorption may be related to biological processes. Sorption to bacteria, lipid bilayers, and proteins has been shown to be stronger for PFSA than PFCA with similar η_{pfc},[64,65] in contrast to observations presented here. However, it has also been reported that live Gram-negative bacteria may accumulate more PFAS (particularly PFOA) than dead bacteria.[64] This is consistent with high porewater and groundwater aqueous PFCA concentrations in winter, when the sediment is less biologically active and thus may sorb less PFCA mass and/or potentially release PFCA mass back to the aqueous phase as the local algal and microbial activity is reduced. Similarly, the increased porewater and groundwater aqueous PFCA concentrations in winter coincide with a general decrease in downwelling PFCA K_d values from September 2017 to February 2019 (Fig. S12†). The findings here suggest that typical oxic laboratory partitioning experiments using sterilized, dried sediments may not reflect partitioning in a natural environment where a range of dynamic processes and biogeochemical conditions occur, such as those found at the surface-water/groundwater recharge boundary.

Conclusion

This study investigated variability in PFAS concentrations between a surface-water body and the region where recharge of surface water to the downgradient groundwater occurs and disperses PFAS over an area that is much larger than the original upgradient groundwater plume. This work demonstrates that sorption and transformation mechanisms at the surface-water/groundwater boundary are important in reducing transport of precursors into downgradient groundwater. A fraction of the precursors persists in the downgradient groundwater, indicating a need for better accounting of their contribution to the total PFAS burden in the environment, even at locations distant (>km) from sites of direct AFFF application. PFAS concentrations in source water from Ashumet Pond were constant over time and space, but fluctuated significantly at the surface-water/groundwater boundary at the downgradient side of the lake, which can impact downgradient PFAS concentrations in groundwater that may be used as a drinking-water supply. The spatial and temporal variability in aqueous PFAS concentrations found at this site, where the hydrology is well known and the well-characterized source water has consistent PFAS concentrations, indicate that single space-time-point sampling is insufficient to fully characterize PFAS concentrations in groundwater and may neglect substantial temporal concentration fluctuations. The temporal variability in groundwater PFCA concentrations (and, to a lesser degree, PFSA concentrations) and large field-derived K_d values for PFCA suggest that there are processes that have not been accounted for and need to be examined further to allow for accurate modeling and prediction of PFAS fate, transport, and risk. The combined evidence of temporal trends and strong inverse correlations with nitrate suggests that future work should investigate biologically driven sorption mechanisms and whether rapid biotransformation of precursors affects field K_d values. Specifically, future studies should incorporate analysis of microbial community and abundance and investigate the interconnection between redox conditions, biological activity, and PFAS sorption.

Data availability

For U.S. Geological Survey data release see: http://doi.org/10.5066/P9HPBFRT.

Author contributions

Conceptualization, A. K. T. and D. R. L.; formal analysis, A. K. T.; funding acquisition, E. M. S. and C. D. V.; investigation, A. K. T., D. R. L., H. M. P., B. J. R., and R. B. H; methodology, A. K. T., D. R. L., and B. J. R.; resources, D. R. L., E. M. S., and C. D. V.; supervision, E. M. S., and C. D. V.; validation, A. K. T.; visualization, A. K. T.; writing – original draft, A. K. T., E. M. S., and C. D. V.; writing – review and editing, A. K. T., D. R. L., H. M. P., L. B. B., B. J. R., R. B. H., E. M. S., and C. D. V.

Conflicts of interest

There are no conflicts to declare.

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Tap Water for 500,000 Minnesotans Contaminated With Elevated Levels of Nitrate

By Sarah Porter, Senior GIS Analyst, and Anne Weir Schechinger, Senior Analyst of Economics

TUESDAY, JANUARY 14, 2020

Drinking water for an estimated half a million Minnesotans is drawn from groundwater contaminated with elevated levels of nitrate, a toxic pollutant that is linked to cancer and is especially dangerous for infants, according to an EWG analysis of federal and state test data.

About one in eight Minnesotans served by groundwater-based public water systems consume tap water that, in tests performed over the past 10 years, had at least one detection of nitrate at or above the level the state considers a marker of potentially worsening contamination. Tens of thousands more Minnesotans are drinking from private household wells with elevated nitrate.

Nitrate is a chemical component of fertilizer and manure that can run off of farm fields and seep into groundwater. Our analysis shows that nitrate contamination is far worse in parts of Minnesota where the types of soil and geology make it easier for nitrate in fertilizer and manure to get into groundwater.

To its credit, Minnesota is implementing a Groundwater Protection Rule to reduce nitrate in drinking water. The rule – three years in the making and administered by the Minnesota Department of Agriculture – is a welcome first step that must be implemented quickly and robustly. But EWG's analysis shows that even full implementation of the new rule may be too little, too late to protect Minnesotans – especially those drinking water from private household wells – from unsafe levels of nitrate.

Nitrate's Health Effects

Under the federal Clean Water Act, the legal limit for nitrate in drinking water is 10 milligrams per liter, or mg/L.[1] This limit was set, in 1962, to guard against so-called blue baby syndrome, a potentially fatal condition that starves infants of oxygen if they ingest too much nitrate.

But newer research indicates that drinking water with 5 mg/L or even lower is associated with higher risks of colorectal cancer and adverse birth outcomes, such as neural tube birth defects. And the Minnesota Department of Health says a level of 3 mg/L indicates that "human-made sources of nitrate have contaminated the water and the level could increase over time."

In June, EWG researchers released a peer-reviewed study that found nitrate pollution of U.S. drinking water at levels far below the legal limit may cause up to 12,594 cases of cancer a year. The article reviewed epidemiological studies of the health effects of nitrate-contaminated drinking water. Recent large-scale studies in Spain and Italy and in Denmark found statistically significant increases in colorectal cancer risk associated with nitrate in drinking water at levels of 0.7 to 2 mg/L.

In 2017, the Environmental Protection Agency began the work needed to review and revise the current legal limit for nitrate. But in April 2019, the agency announced it would no longer consider that re-evaluation a high priority. Drinking water with nitrate levels at or below 10 mg/L meets federal standards, but it is clear that protecting public health requires keeping the contamination level far below the legal limit.

Nitrate in Public Water Systems

Data from the U.S. Environmental Protection Agency show that 472,983 Minnesotans – more than the population of Minneapolis – are served by a total of 727 public water systems that were contaminated with at least 3 mg/L of nitrate. Almost 300,000 people drink from public systems contaminated at or above 5 mg/L, and more than 150,000 from public systems with at least 10 mg/L.

Table 1. Minnesota Public Water Systems With Elevated Levels of Nitrate, 2009-2018

	With at Least 1 test >= 3 mg/L		With at Least 1 test >= 5 mg/L		With at Least 1 test >= 10 mg/L	
System Type	Systems	People Served	Systems	People Served	Systems	People Served
Community	95	405,386	55	258,985	20	146,202
Non-community	632	67,597	358	38,251	104	8,448
All public ground water systems	727	472,983	413	297,236	124	154,650

Source: U.S. EPA Safe Drinking Water Information System, from tests by public water systems.

Many public systems have nitrate tests that are dangerously high. Twenty-two systems serving 4,178 people had nitrate tests at twice the legal limit or more, with two of those systems testing close to 50 mg/L – five times the legal limit.

Public water systems are either community or non-community systems. Community water systems mostly serve residents in cities and towns year-round. There are far more non-community systems, which serve sites like churches and schools with their own source of drinking water, but they serve much smaller populations and usually for only part of the year. Out of the 727 public systems that supply drinking water contaminated with nitrate at or above 3 mg/L, 95 are community systems and 632 are non-community systems.

Nitrate in Private Wells

Tests by the Minnesota Department of Health and Department of Agriculture in the past 10 years show that 7,657 Minnesota households drink from private wells with at least one test at or above 3 mg/L of nitrate. Even if those wells serve just three people each, it means almost 23,000 more Minnesotans are drinking water contaminated with nitrate at or above that level.

Table 2. Private Drinking Water Wells in Minnesota With Elevated Levels of Nitrate, 2009-2018

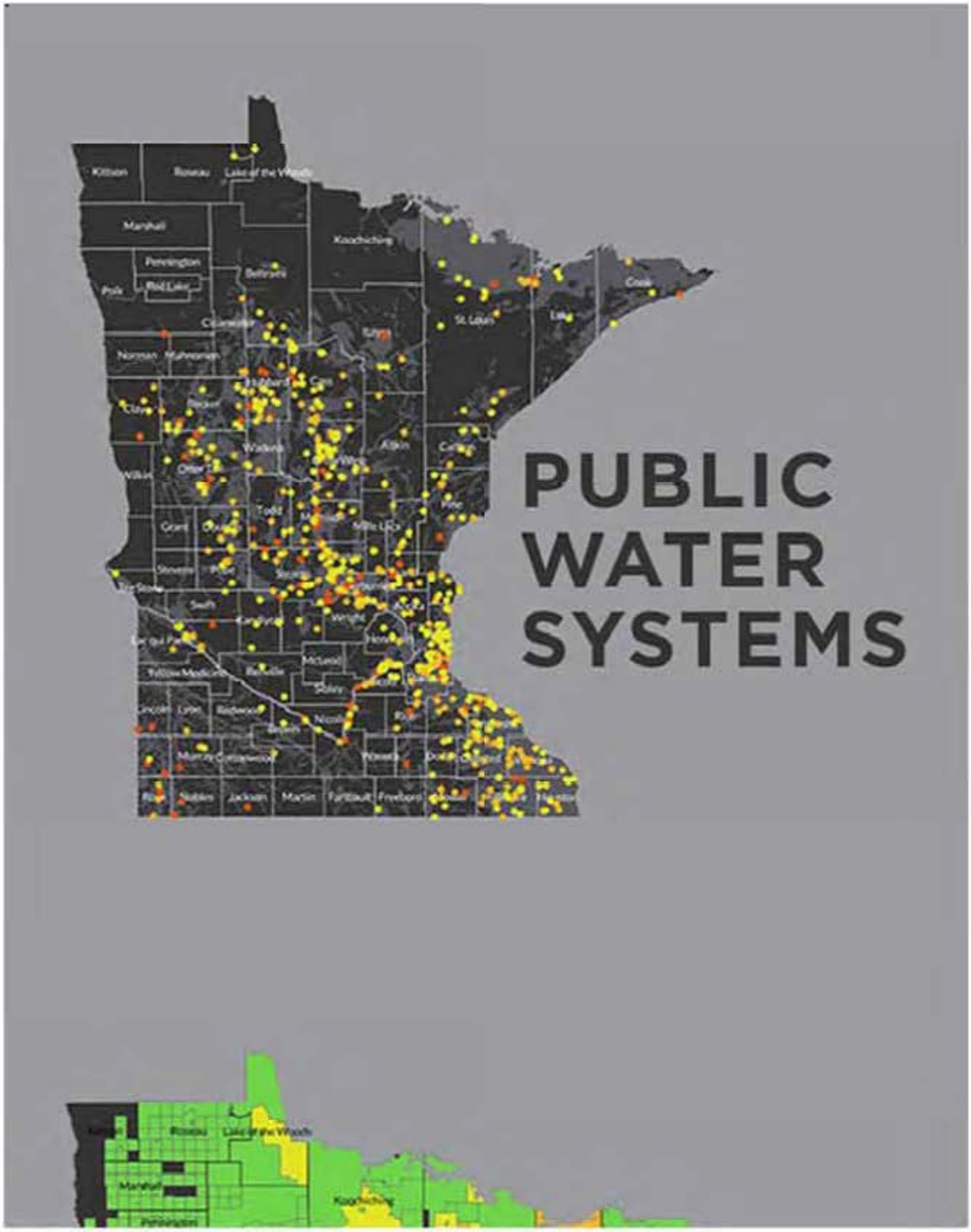
	At least 1 test at or above 3 mg/L	At least 1 test at or above 5 mg/L	At least 1 test at or above 10 mg/L
Households with Private wells	7,657	5,825	3,364

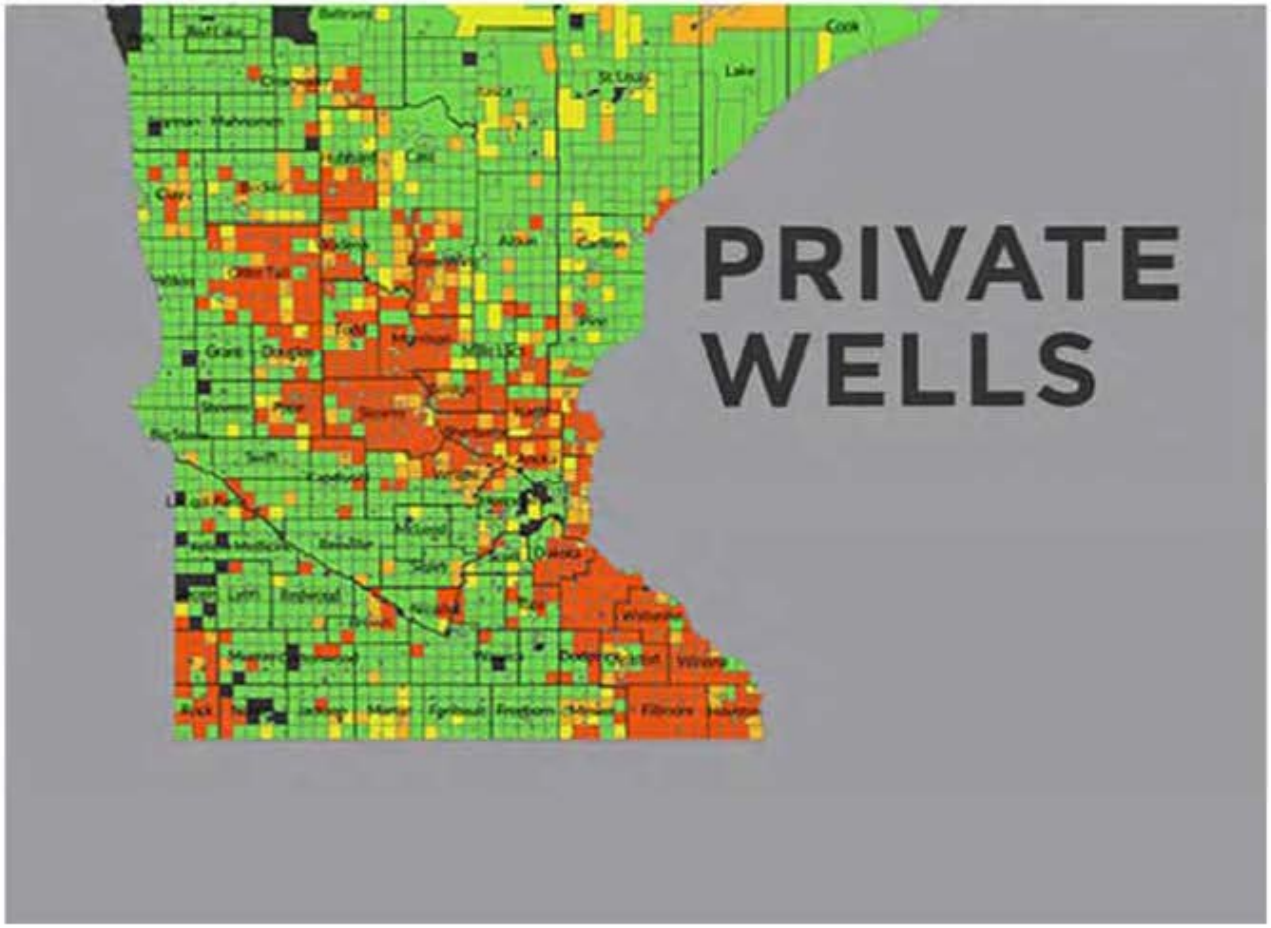
Sources: Minnesota Department of Health, Minnesota Department of Agriculture Township Testing Program and Central Sands and Southeast Minnesota Volunteer Nitrate Monitoring Networks.

Of the households that drink from private wells, almost 6,000 wells were contaminated at or above 5 mg/L, and more than 3,000 were contaminated at or above the federal legal limit of 10 mg/L. At least 164 households had private wells that tested at or above twice the legal limit, or 20 mg/L.

Mapping Nitrate Contamination

EWG's interactive maps show the locations and levels for nitrate in Minnesota's public water systems and private household wells.





The Minnesota Fertilizer Nitrogen Management Plan, released in 2015 and updated this year, found that the millions of pounds of fertilizers and manure applied to cropland each year are the leading sources of nitrate that can pollute drinking water. More importantly, the report found that without careful management, much of the nitrate remains after crops are harvested and can seep into drinking water.

EWG's maps confirm that nitrate contamination is far worse in regions of Minnesota where the types of soil and geology make it easier for nitrate in fertilizer and manure to get into groundwater. The area of highest vulnerability makes up almost one-fourth of the state and is home to 2.5 million acres of cropland and 6,287 livestock feedlots.

Almost 90 percent of public water systems with nitrate levels at or above 3 mg/L draw on groundwater in or very near areas considered highly vulnerable to nitrate contamination. About the

same percentage of private household wells also draws on groundwater in these highly vulnerable areas. If you live in one of these areas, you are very likely drinking nitrate-contaminated water.

Who Is Affected?

Nitrate contamination of drinking water is a largely rural issue. Eighty-five percent of public water systems with at least one test at or above 5 mg/L served people living in rural Minnesota. Fully 98 percent of townships where at least one test of domestic wells revealed nitrate contamination at or above 5 mg/L were located in rural areas.

About half of the communities and households affected by high nitrate levels are located in areas where household incomes fall below the state median. Of 413 public water systems with at least one test at or above 5 mg/L, 203 are located in U.S. Census block groups where household income is less than the state median. Of 617 townships with at least one private well detection at or above 5 mg/L, 299 are also in areas with household income below the state median.

Groundwater Protection Rule May Be Too Little, Too Late

Minnesota's Groundwater Protection Rule was finalized in June 2019 and will be implemented starting in 2020. The rule is a welcome first step, but it is likely to fall short. Here's why:

Most troubling is that the new rule is designed to prevent nitrate in community water systems from exceeding the EPA's legal limit of 10 mg/L – despite the growing evidence that the existing legal limit is not safe. The research cited earlier – that nitrate levels as low as less than 1 mg/L may increase the risk of colorectal cancer – means the target level should be set far lower.

The new rule bans the application of nitrogen fertilizer in the fall or on frozen soil in highly vulnerable areas. That will affect about 2.2 million acres of cropland and also applies to about 310,000 crop acres around public wells with high nitrate that are designated for protection. But a 2014 survey by the state agriculture department and USDA found that statewide, 61 percent of fields received more nitrogen fertilizer, and 71 percent more manure nitrogen, than recommended by the University of Minnesota. Even higher proportions of fields in highly vulnerable southeast Minnesota received more nitrogen than recommended. To ensure groundwater is safe to drink, state-of-the-art fertilizer and manure management practices are needed on far more fields in the highly vulnerable areas than is required by the new rule.

To improve the way farmers and landowners use and manage fertilizer and manure, the rule relies heavily on their voluntary participation. Mandatory best management practices can be enforced but only in areas to protect community water systems with contamination approaching the legal limit. Provisions in the rule could delay enforcement of mandatory measures for years. EWG has steadfastly supported voluntary programs, but they have proven to be too slow and poorly targeted to succeed at addressing the challenges Minnesota faces to make sure people have safe drinking water.

Analysis of the nitrate data shows that private wells are also likely contaminated with pesticides and bacteria. People on well water cannot rely on the monitoring and regulatory oversight their neighbors on public water enjoy. The health department directs public education and outreach initiatives to help private well owners but says that in the end, "private well users are responsible for making sure their water is safe for everyone in the household to drink." There must be far more frequent and systematic testing of private wells, for more contaminants, and more technical and financial assistance designed to help households make sure their water is safe.

Finally, the data show that nitrate contamination of Minnesota groundwater, the focus of this analysis, is a serious problem in highly vulnerable areas. If contamination of surface water were included in this analysis, the state's nitrate problem would appear even worse.

Reliance on treating drinking water so that it has safe levels of nitrate is an expensive and often ineffective way to protect people. It is more effective to prevent nitrate contamination of drinking water in the first place. What is needed is an aggressive policy and programmatic approach that strategically combines voluntary and mandatory approaches to cleaning up Minnesota's sources of drinking water.

To see more results of this study, click here.

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NOTES

1. One milligram per liter is equal to one part per million, or ppm, a measurement often used for reporting water contamination levels. A part per million is about four drops in a 55-gallon

barrel of water. The State of Minnesota measures nitrate contamination in milligrams per liter.

Methodology

Environmental Research

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Nitrate contamination in drinking water and colorectal cancer: Exposure assessment and estimated health burden in New Zealand

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Abstract

Background

Epidemiological evidence in multiple jurisdictions has shown an association between nitrate exposure in drinking water and an increased risk of colorectal cancer (CRC).

Objective

We aimed to review the extent of nitrate contamination in New Zealand drinking water and estimate the health and financial burden of nitrate-attributable CRC.

Methods

We collated data on nitrate concentrations in drinking water for an estimated 85% of the New Zealand population (~4 million people) who were on registered supplies. We estimated nitrate levels for the remaining population (~600,000 people) based on samples from 371 unregistered (private) supplies. We used the effective rate ratio from previous epidemiological studies to estimate CRC cases and deaths attributable to nitrate in drinking water.

Results

Three-quarters of New Zealanders are on water supplies with less than 1 mg/L NO_3-N. The population weighted average for nitrate exposure for people on registered supplies was 0.49 mg/L NO_3-N with 1.91% (95%CI 0.49, 3.30) of CRC cases attributable to nitrates. This correlates to 49.7 cases per year (95%CI 14.9, 101.5) at a cost of 21.3 million USD (95% 6.4, 43.5 million USD). When combining registered and unregistered supplies, we estimated 3.26% (95%CI 0.84, 5.57) of CRC cases were attributable to nitrates, resulting in 100 cases (95%CI 25.7, 171.3) and 41 deaths (95%CI 10.5, 69.7) at a cost of 43.2 million USD (95%CI 10.9, 73.4).

Conclusion

A substantial minority of New Zealanders are exposed to high or unknown levels of nitrates in their drinking water. Given the international epidemiological studies showing an association between cancer and nitrate ingestion from drinking water, this exposure may cause an important burden of preventable CRC cases, deaths, and economic costs. We consider there is sufficient evidence to justify a review of drinking water standards. Protecting public health adds to the strong environmental arguments to improve water management in New Zealand.

Introduction

Colorectal cancer (CRC) contributes almost 10% of global cancer incidence (Favoriti et al., 2016). There are major geographic variations in CRC burden worldwide, with high-income countries such as New Zealand (NZ) experiencing markedly higher CRC rates (35.3 age-standardised cases per 100,000) compared with low and middle-income (Bangladesh 3.8 cases per 100,000) (Bray et al., 2018). Māori (NZ's Indigenous population) experience lower rates of CRC than non-Māori, although this gap is reducing over time. Further, while experiencing fewer CRC registrations than non-Māori, Māori are more likely to die from CRC (Blakely et al., 2015).

An estimated 90% of CRCs are sporadic (non-hereditary), meaning they develop after birth due to a range of modifiable risk factors (Purcell et al., 2017). Common risk factors for CRC include obesity, alcohol consumption, physical inactivity, smoking, and red and processed meat consumption (Bray et al., 2018). Emerging epidemiological evidence has shown that high nitrate

concentrations in drinking water may also be a risk factor for CRC (Temkin et al., 2019; Ward et al., 2018).

An International Agency for Research on Cancer (IARC) assessment of studies up to 2006 reported that ingested nitrate under conditions that result in endogenous nitrosation is probably carcinogenic to humans (International Agency for Research on Cancer, 2010). Endogenous nitrosation is a process that involves the reactions between nitrosation agents (metabolised from nitrate) and nitrosatable compounds (eg amines or haeme) to form N-nitroso compounds (NOC). These NOC induce DNA-damaging metabolites, which could lead to cancerous lesions in cells (Gurjao et al., 2021; Zhu et al., 2014). Vitamin C is a known inhibitor of nitrosation so vegetables are a key moderator in this pathway. The role of Vitamin C may explain why vegetable consumption has a protective effect against CRC despite the majority of ingested nitrate coming from vegetables (Johnson et al., 2013). In contrast, water does not contain any NOC inhibiting features. A randomised-controlled trial with human participants showed water-based nitrate increased bio-makers of NOC formation in faeces (van Breda et al., 2019), which supports human feeding studies focusing on dietary nitrate consumption (Hughes et al., 2001; Rowland et al., 1991).

International guidelines for nitrate in drinking water are designed to prevent the acute risk of infantile methemoglobinemia, rather than the chronic risk of cancer (World Health Organization, 2017). Thus, the current WHO drinking water guidelines and NZ drinking water standards for nitrate are 11.3 mg/L nitrate-nitrogen (NO_3-N – referred to from here on simply as mg/L). However, subsequent well-designed studies have reported associations between nitrate contamination in drinking water and CRC (Espejo-Herrera et al., 2016; Schullehner et al., 2018; Ward et al., 2018).

Nitrate contamination of drinking water can come from agricultural activities, sanitation and from industrial processes (Almasri, 2007). The largest source of nitrate contamination in NZ waterways is from pastoral farming, specifically from intensive dairy farming (Morgenstern and Daughney, 2012). Nitrate leaching from urine patches is the largest source of nitrate contamination from pastoral farming (Parliamentary Commissioner for the Environment, 2013). There is relatively little nitrate leaching from fertilizer application unless the fertilizer application is poorly timed, such as a few days before a high rainfall event (Vogeler et al., 2015). Pre-agricultural, background nitrate levels in groundwater in NZ are estimated to have been 0.16 ± 0.08 mg/L (Morgenstern and Daughney, 2012). The latest survey of groundwater sites, but not necessarily drinking water, (n = 342) in NZ found 34% had concentrations above 3 mg/L (Ministry for the Environment & Stats NZ 2019) However, in NZ, no comprehensive national database for drinking water nitrate contamination exists.

Drinking water quality in NZ is regulated under the Health (Drinking Water) Amendment Act 2007 (2019) by the Ministry of Health (MoH). This Act requires suppliers of drinking water to more than 25 people to be included on the Register of NZ Drinking Water Suppli

there were 677 registered drinking water suppliers, serving approximately 4,095,200 people (ESR, 2020) or ~87% of the 2018 population (Statistics New Zealand, 2020). About 13% of the population (~603,500 people) (ESR, 2020) is not served by a registered drinking water supplier (Statistics New Zealand, 2020). These people are likely to be served by either very small networked supplies or are classified as self-supplied. For the purposes of our analyses we call these 'unregistered supplies.'

In New Zealand, the 'Priority 2 Chemical Determinand Identification Programme ran between 1995 and 2004 (ESR, 2019). If a determinand was found to be less than 50% of the Maximum Acceptable Value (MAV) ongoing monitoring was not deemed to be required, meaning any water supply reporting less than 5.7 mg/L was not required to conduct ongoing testing. As a result, in 2019, nitrate monitoring was only required on supplies that serviced 53,900 people or 1.1% of the NZ population (Ministry of Health, 2020).

The burden of CRC attributable to nitrate contaminated water has not been estimated in NZ. Temkin et al. (2019) estimated between one and eight percent of CRC cases in the US could be attributable to nitrate contamination in drinking water. A NZ study has estimated the CRC rates attributable to other known risk factors such as obesity (9%), alcohol (7%), physical inactivity (4%), smoking (3%), consumption of red meat (5%) and processed meat (3%) (Richardson et al., 2016). These estimates represent the population attributable fractions (PAF), the proportion of disease in the population that could be prevented if the modifiable risk factor (or exposure) was eliminated (Webb et al., 2017).

The aims for this present study are to:

1) Estimate the nature and extent of New Zealanders' exposure to nitrate in drinking water.
2) Estimate the number of colorectal cancers attributable to nitrate contamination of drinking water.
3) Estimate the potential health costs associated with excess nitrate concentrations in drinking water.

Section snippets

Nitrate contamination dataset

Data requests for current and historical nitrate data, supply characteristics and spatial files for supply boundaries were sent to the 66 District Councils in January 2020. Most District Councils treated the data request as an Official Information Act (OIA) Request under the Local Government Official Information and Meetings Act 1987, which requires the District Council to provide an

official response within 20-working days. Due to privacy restrictions, contact details for private non-District...

Nitrate database completeness by supply type

In total, we collated nitrate data on an estimated 85% of the NZ population (Table 1). The majority of the data come from large water suppliers (3.4 million, 73%) who supply more than 10,000 people, while supplies with less than 25 people service around 13% of the population. The data coverage increases with the size of the water supplier from 0.4% for under 25 people to 100% for suppliers serving greater than 10,000 people. It is likely people on unregistered supplies are the most at-risk of...

Discussion

The majority of people in NZ are on water supplies with low levels of nitrate contamination (less than 0.5 mg/L). In total, 410,292 people supplied by registered water suppliers (9%) had nitrate exposure greater than that observed by Schullehner et al. (2018) as a CRC risk (1 mg/L). However, there are a large proportion of people on unregistered supplies (600,000 or ~15%) who are at the greatest risk of exposure to nitrate in drinking water, and data were missing from an additional 130,000...

Conclusion

Most New Zealanders are exposed to relatively low levels of nitrate but some are exposed to high levels (eg 14% exposed to water supplies with more than 1 mg/L NO_3-N), and many take water from supplies that are not monitored for nitrate. Consequently, we estimate that about 3% of CRC cases in NZ may be attributed to nitrate contamination of drinking water. Recent epidemiological studies of the association between cancer and nitrate ingestion from drinking water reinforce the urgency to review...

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper....

Acknowledgments

This work would not have been possible without the significant contribution of the drinking water suppliers who provided nitrate data and supply information for their water supplies and the Regional Councils that provided nitrate data and information on the use of b...

domestic consumption. Thank you also to ESR, Environment Canterbury and the MoH for providing data and advice throughout the project. We also acknowledge those private water suppliers that provided data to the project. No...

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Review

Drinking Water Nitrate and Human Health: An Updated Review

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Abstract: Nitrate levels in our water resources have increased in many areas of the world largely due to applications of inorganic fertilizer and animal manure in agricultural areas. The regulatory limit for nitrate in public drinking water supplies was set to protect against infant methemoglobinemia, but other health effects were not considered. Risk of specific cancers and birth defects may be increased when nitrate is ingested under conditions that increase formation of *N*-nitroso compounds. We previously reviewed epidemiologic studies before 2005 of nitrate intake from drinking water and cancer, adverse reproductive outcomes and other health effects. Since that review, more than 30 epidemiologic studies have evaluated drinking water nitrate and these outcomes. The most common endpoints studied were colorectal cancer, bladder, and breast cancer (three studies each), and thyroid disease (four studies). Considering all studies, the strongest evidence for a relationship between drinking water nitrate ingestion and adverse health outcomes (besides methemoglobinemia) is for colorectal cancer, thyroid disease, and neural tube defects. Many studies observed increased risk with ingestion of water nitrate levels that were below regulatory limits. Future studies of these and other health outcomes should include improved exposure assessment and accurate characterization of individual factors that affect endogenous nitrosation.

Keywords: drinking water; nitrate; cancer; adverse reproductive outcomes; methemoglobinemia; thyroid disease; endogenous nitrosation; *N*-nitroso compounds

1. Introduction

Since the mid-1920s, humans have doubled the natural rate at which nitrogen is deposited onto land through the production and application of nitrogen fertilizers (inorganic and manure),

the combustion of fossil fuels, and replacement of natural vegetation with nitrogen-fixing crops such as soybeans [1,2]. The major anthropogenic source of nitrogen in the environment is nitrogen fertilizer, the application of which increased exponentially after the development of the Haber–Bosch process in the 1920s. Most synthetic fertilizer applications to agricultural land occurred after 1980 [3]. Since approximately half of all applied nitrogen drains from agricultural fields to contaminate surface and groundwater, nitrate concentrations in our water resources have also increased [1].

The maximum contaminant level (MCL) for nitrate in public drinking water supplies in the United States (U.S.) is 10 mg/L as nitrate-nitrogen (NO_3-N). This concentration is approximately equivalent to the World Health Organization (WHO) guideline of 50 mg/L as NO_3 or 11.3 mg/L NO_3-N (multiply NO_3 mg/L by 0.2258). The MCL was set to protect against infant methemoglobinemia; however other health effects including cancer and adverse reproductive outcomes were not considered [4]. Through endogenous nitrosation, nitrate is a precursor in the formation of *N*-nitroso compounds (NOC); most NOC are carcinogens and teratogens. Thus, exposure to NOC formed after ingestion of nitrate from drinking water and dietary sources may result in cancer, birth defects, or other adverse health effects. Nitrate is found in many foods, with the highest levels occurring in some green leafy and root vegetables [5,6]. Average daily intakes from food are in the range of 30–130 mg/day as NO_3 (7–29 mg/day NO_3-N) [5]. Because NOC formation is inhibited by ascorbic acid, polyphenols, and other compounds present at high levels in most vegetables, dietary nitrate intake may not result in substantial endogenous NOC formation [5,7].

Studies of health effects related to nitrate exposure from drinking water were previously reviewed through early 2004 [8]. Further, an International Agency for Research on Cancer (IARC) Working Group reviewed human, animal, and mechanistic studies of cancer through mid-2006 and concluded that ingested nitrate and nitrite, under conditions that result in endogenous nitrosation, are probably carcinogenic [5]. Here, our objective is to provide updated information on human exposure and to review mechanistic and health effects studies since 2004. We summarize how the additional studies contribute to the overall evidence for health effects and we discuss what future research may be most informative.

2. Drinking Water Nitrate Exposures in the United States and Europe

Approximately 45 million people in the U.S. (about 14% of the population) had self-supplied water at their residence in 2010 [9]. Almost all (98%) were private wells, which are not regulated by the U.S. Environmental Protection Agency (EPA). The rest of the population was served by public water supplies, which use groundwater, surface water, or both. The U.S. Geological Survey's National Water Quality Assessment (USGS-NAWQA) Project [10] sampled principal groundwater aquifers used as U.S. public and private drinking water supplies in 1988–2015. Nitrate levels in groundwater under agricultural land were about three times the national background level of 1 mg/L NO_3-N (Figure 1) [11]. The mixed land use category mostly had nitrate concentrations below background levels reflecting levels in deeper private and public water supply wells. Based on the NAWQA study, it was estimated that 2% of public-supply wells and 6% of private wells exceeded the MCL; whereas, in agricultural areas, 21% of private wells exceeded the MCL [10]. The USGS-NAWQA study also revealed significant decadal-scale changes in groundwater nitrate concentrations among wells sampled first in 1988–2000 and again in 2001–2010 for agricultural, urban, and mixed land uses [12]. More sampling networks had increases in median nitrate concentration than had decreases.

A study of U.S. public water supplies (PWS) using data from EPA's Safe Drinking Water Information System estimated that the percentage of PWS violating the MCL increased from 0.28 to 0.42% during 1994–2009; most increases were for small to medium PWS (<10,000 population served) using groundwater [13]. As a result of increasing nitrate levels, some PWS have incurred expensive upgrades to their treatment systems to comply with the regulatory level [14–16].

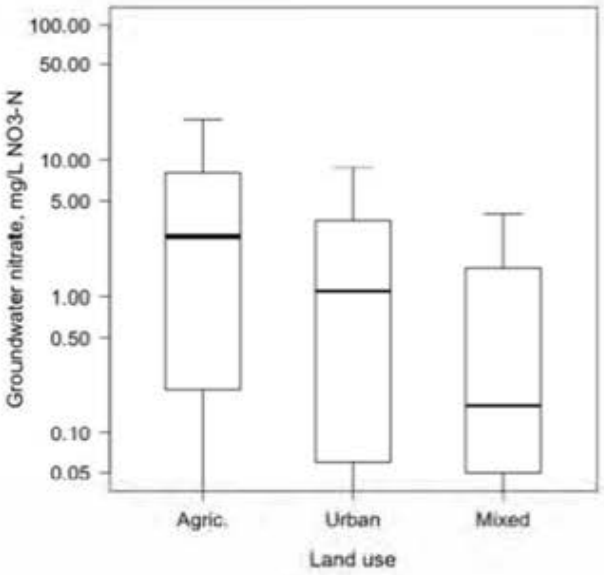

Figure 1. Boxplots of nitrate concentrations in shallow groundwater beneath agricultural and urban land uses, and at depths of private and public drinking water supplies beneath mixed land use. The number of sampled wells were 1573 (agricultural land), 1054 (urban), and 3417 (mixed). The agricultural and urban wells were sampled to assess land use effects, whereas the mixed category wells were sampled at depths of private and public supplies. Median depths of wells in the agricultural, urban, and mixed categories were 34, 32, and 200 feet, respectively. The height of the upper bar is 1.5 times the length of the box, and the lower bound was truncated at the nitrate detection limit of 0.05 mg/L NO_3-N.

In Europe, the Nitrates Directive was set in 1991 [17,18] to reduce or prevent nitrate pollution from agriculture. Areas most affected by nitrate pollution are designated as 'nitrate vulnerable zones' and are subject to mandatory Codes of Good Agricultural Practice [18]. The results of compliance with this directive have been reflected in the time trends of nitrate in some countries. For example, nitrate levels in groundwater in Denmark increased in 1950–1980 and decreased since the 1990s [19]. Average nitrate levels in groundwater in most other European countries have been stable at around 17.5 mg/L NO_3 (4 mg/L NO_3-N) across Europe over a 20-year period (1992–2012), with some differences between countries both in trends and concentrations. Average concentrations are lowest in Finland (around 1 mg/L NO_3 in 1992–2012) and highest in Malta (58.1 mg/L in 2000–2012) [20]. Average annual nitrate concentrations at river monitoring stations in Europe showed a steady decline from 2.7 NO_3-N in 1992 to 2.1 mg/L in 2012 [20], with the lowest average levels in Norway (0.2 mg/L NO_3-N in 2012) and highest in Greece (6.6 mg/L NO_3-N in 2012).

Levels in finished public drinking water have been published only for a few European countries. Trends of nitrate in drinking water supplies from 1976 to 2012 in Denmark showed a decline in public supplies but not in private wells [21]. In Spain, median concentrations were 3.5 mg/L NO_3 (range: 0.4–66.8) in 108 municipalities in 2012 [22], and 4.2 mg/L (range: <1–29) in 11 provinces in 2010 [23]. Levels in other countries included a median of 0.18 mg/L (range: <0.02–7.9) in Iceland in 2001–2012 [24], a mean of 16.1 mg/L (range: 0.05–296 mg/L) in Sicily, Italy in 2004–2005 [25] and a range from undetected to 63.3 mg/L in Deux-Sèvres, France in in 2005–2009 [26].

Nitrate levels in bottled water have been measured in a few areas of the EU and the U.S. and have been found to be below the MCL. In Sicily, the mean level was 15.2 mg/L NO_3(range: 1.2–31.8 mg/L) in 16 brands [25] and in Spain, the median level was 5.2 mg/L NO_3 (range: <1.0–29.0 mg/L) in 9 brands [23]. In the U.S., a survey of bottle water sold in 42 Iowa and 32 Texas communities found

varying but generally low nitrate levels. Nitrate concentrations ranged from below the limit of detection (0.1 mg/L NO_3-N) to 4.9 mg/L NO_3-N for U.S. domestic spring water purchased in Texas.

There are few published studies of nitrate concentrations in drinking water outside the U.S. and Europe. Nitrate concentrations in groundwater were reported for Morocco, Niger, Nigeria, Senegal, India-Pakistan, Japan, Lebanon, Philippines and Turkey with maximum levels in Senegal (median 42.9 mg/L NO_3-N) [5]. In India, nitrate in drinking water supplies is particularly high in rural areas, where average levels have been reported to be 45.7 mg/L NO_3 [27,28] and 66.6 mg/L NO_3 [28]; maximum levels in drinking water exceeded 100 mg/L NO_3 in several regions [27,29]. Extremely high levels of nitrate have been reported in The Gaza Strip, where nitrate reached concentrations of 500 mg/L NO_3 in some areas, and more than 50% of public-supply wells had nitrate concentrations above 45 mg/L NO_3 [30].

3. Exposure Assessment in Epidemiologic Studies

With the implementation of the Safe Drinking Water Act in 1974, more than 40 years of monitoring data for public water supplies in the U.S. provide a framework of measurements to support exposure assessments. Historical data for Europe are more limited, but a quadrennial nitrate reporting requirement was implemented as part of the EU Nitrates Directive [17,18]. In the U.S., the frequency of sampling for nitrate in community water systems is stipulated by their sources (ground versus surface waters) and whether concentrations are below the MCL, and historically, by the size of the population served and vulnerability to nitrate contamination. Therefore, the exposure assessment for study participants who report using a public drinking water source may be based on a variable number of measurements, raising concerns about exposure misclassification. In a study of bladder cancer risk in Iowa, associations were stronger in sensitivity analyses based on more comprehensive measurement data [31]. Other studies have restricted analyses to subgroups with more complete or recent measurements [32–35], with implications for study power and possible selection biases. Sampling frequency also limits the extent to which temporal variation in exposure can be represented within a study population, such as the monthly or trimester-based estimates of exposure most relevant for etiologic investigations of adverse reproductive outcomes. In Denmark, limited seasonal variation in nitrate monitoring data suggested these data would sufficiently capture temporal variation for long-term exposure estimates [36]. Studies have often combined regulatory measurements with questionnaire and ancillary data to better characterize individual variation in nitrate exposure, such as to capture changes in water supply characteristics over time or a participant's duration at a drinking water source [31,33,37,38]. Most case-control studies of drinking water nitrate and cancer obtained lifetime residence and drinking water source histories, whereas cohort studies typically have collected only the current water source. Many studies lacked information about study participants' water consumption, which may be an important determinant of exposure to drinking water contaminants [39].

Due to sparse measurement data, exposures for individuals served by private wells are more difficult to estimate than exposures for those on public water supplies. However, advances in geographic-based modeling efforts that incorporate available measurements, nitrogen inputs, aquifer characteristics, and other data hold promise for this purpose. These models include predictor variables describing land use, nitrogen inputs (fertilizer applications, animal feeding operations), soils, geology, climate, management practices, and other factors at the scale of interest. Nolan and Hitt [40] and Messier et al. [41] used nonlinear regression models with terms representing nitrogen inputs at the land surface, transport in soils and groundwater, and nitrate removal by processes such as denitrification, to predict groundwater nitrate concentration at the national scale and for North Carolina, respectively. Predictor variables in the models included N fertilizer and manure, agricultural or forested land use, soils, and, in Nolan and Hitt [40], water-use practices and major geology. Nolan and Hitt [40] reported a training R^2 values of 0.77 for a model of groundwater used mainly for private supplies and Messier, Kane, Bolich and Serre [41] reported a cross-validation testing R^2 value of 0.33 for a point-level

private well model. These and earlier regression approaches for groundwater nitrate [42–46] relied on predictor variables describing surficial soils and activities at the land surface, because conditions at depth in the aquifer typically are unknown. Redox conditions in the aquifer and the time since water entered the subsurface (i.e., groundwater age) are two of the most important factors affecting groundwater nitrate, but redox constituents typically are not analyzed, and age is difficult to measure. Even if a well has sufficient data to estimate these conditions, the data must be available for all wells in order to predict water quality in unsampled areas. In most of the above studies, well depth was used as a proxy for age and redox and set to average private or public-supply well depth for prediction.

Recent advances in groundwater nitrate exposure modeling have involved machine-learning methods such as random forest (RF) and boosted regression trees (BRT), along with improved characterization of aquifer conditions at the depth of the well screen (the perforated portion of the well where groundwater intake occurs). Tree-based models do not require data transformation, can fit nonlinear relations, and automatically incorporate interactions among predictors [47]. Wheeler et al. [48] used RF to estimate private well nitrate levels in Iowa. In addition to land use and soil variables, predictor variables included aquifer characteristics at the depth of the well screen, such as total thickness of fine-grained glacial deposits above the well screen, average and minimum thicknesses of glacial deposits near sampled wells, and horizontal and vertical hydraulic conductivities near the wells. Well depth, landscape features, nitrogen sources, and aquifer characteristics ranked highly in the final model, which explained 77% and 38% of the variation in training and hold-out nitrate data, respectively.

Ransom et al. [49] used BRT to predict nitrate concentration at the depths of private and public-supply wells for the Central Valley, California. The model used as input estimates of groundwater age at the depth of the well screen (from MODFLOW/MODPATH models) and depth-related reducing conditions in the groundwater. These estimates were generated by separate models and were available throughout the aquifer. Other MODFLOW-based predictor variables comprised depth to groundwater, and vertical water fluxes and the percent coarse material in the uppermost part of the aquifer where groundwater flow was simulated by MODFLOW. Redox variables were top-ranked in the final BRT model, which also included land use-based N leaching flux, precipitation, soil characteristics, and the MODFLOW-based variables described above. The final model retained 25 of an initial 145 predictor variables considered, had training and hold-out R^2 values of 0.83 and 0.44 respectively, and was used to produce a 3D visualization of nitrate in the aquifer. These studies show that modeling advances and improved characterization of aquifer conditions at depth are increasing our ability to predict nitrate exposure from drinking water supplied by private wells.

4. Nitrate Intake and Endogenous Formation of *N*-Nitroso Compounds

Drinking water nitrate is readily absorbed in the upper gastrointestinal tract and distributed in the human body. When it reaches the salivary glands, it is actively transported from blood into saliva and levels may be up to 20 times higher than in the plasma [50–53]. In the oral cavity 6–7% of the total nitrate can be reduced to nitrite, predominantly by nitrate-reducing bacteria [52,54,55]. The secreted nitrate as well as the nitrite generated in the oral cavity re-enter the gastrointestinal tract when swallowed.

Under acidic conditions in the stomach, nitrite can be protonated to nitrous acid (HNO_2), and subsequently yield dinitrogen trioxide (N_2O_3), nitric oxide (NO), and nitrogen dioxide (NO_2). Since the discovery of endogenous NO formation, it has become clear that NO is involved in a wide range of NO•mediated physiological effects. These comprise the regulation of blood pressure and blood flow by mediating vasodilation [56–58], the maintenance of blood vessel tonus [59], the inhibition of platelet adhesion and aggregation [60,61], modulation of mitochondrial function [62] and several other processes [63–66].

On the other hand, various nitrate and nitrite derived metabolites such as nitrous acid (HNO_2) are powerful nitrosating agents and known to drive the formation of NOC, which are

suggested to be the causal agents in many of the nitrate-associated adverse health outcomes. NOC comprise *N*-nitrosamines and *N*-nitrosamides, and may be formed when nitrosating agents encounter *N*-nitrosatable amino acids, which are also from dietary origin. The nitrosation process depends on the reaction mechanisms involved, on the concentration of the compounds involved, the pH of the reaction environment, and further modifying factors, including the presence of catalysts or inhibitors of *N*-nitrosation [66–69].

Endogenous nitrosation can also be inhibited, for instance by dietary compounds like vitamin C, which has the capacity to reduce HNO_2 to NO; and alpha-tocopherol or polyphenols, which can reduce nitrite to NO [54,70–72]. Inhibitory effects on nitrosation have also been described for dietary flavonoids such as quercetin, ferulic and caffeic acid, betel nut extracts, garlic, coffee, and green tea polyphenols [73,74]. Earlier studies showed that the intake of 250 mg or 1 g ascorbic acid per day substantially inhibited *N*-nitrosodimethylamine (NDMA) excretion in 25 women consuming a fish meal rich in amines (nitrosatable precursors) for seven days, in combination with drinking water containing nitrate at the acceptable daily intake (ADI) [75]. In addition, strawberries, garlic juice, and kale juice were shown to inhibit NDMA excretion in humans [76]. The effect of these fruits and vegetables is unlikely to be due solely to ascorbic acid. Using the *N*-nitrosoproline (NPRO) test, Helser et al. [77] found that ascorbic acid only inhibited nitrosamine formation by 24% compared with 41–63% following ingestion of juices (100 mL) made of green pepper, pineapple, strawberry or carrot containing an equal total amount of ascorbic acid.

The protective potential of such dietary inhibitors depends not only on the reaction rates of *N*-nitrosatable precursors and nitrosation inhibitors, but also on their biokinetics, since an effective inhibitor needs to follow gastrointestinal circulation kinetics similar to nitrate [78]. It has been argued that consumption of some vegetables with high nitrate content, can at least partially inhibit the formation of NOC [79–81]. This might apply for green leafy vegetables such as spinach and rocket salad, celery or kale [77] as well as other vegetables rich in both nitrate and natural nitrosation inhibitors. Preliminary data show that daily consumption of one bottle of beetroot juice containing 400 mg nitrate (the minimal amount advised for athletes to increase their sports performances) for one day and seven days by 29 young individuals results in an increased urinary excretion of apparent total nitroso compounds (ATNC), an effect that can only be partially inhibited by vitamin C supplements (1 g per day) [82].

Also, the amount of nitrosatable precursors is a key factor in the formation of NOC. Dietary intakes of red and processed meat are of particular importance [83–87] as increased consumption of red meat (600 vs. 60 g/day), but not white meat, was found to cause a three-fold increase in fecal NOC levels [85]. It was demonstrated that heme iron stimulated endogenous nitrosation [84], thereby providing a possible explanation for the differences in colon cancer risk between red and white meat consumption [88]. The link between meat consumption and colon cancer risk is even stronger for nitrite-preserved processed meat than for fresh meat leading an IARC review to conclude that processed meat is carcinogenic to humans [89].

In a human feeding study [90], the replacement of nitrite in processed meat products by natural antioxidants and the impact of drinking water nitrate ingestion is being evaluated in relation to fecal excretion of NOC, accounting for intakes of meat and dietary vitamin C. A pilot study demonstrated that fecal excretion of ATNC increased after participants switched from ingesting drinking water with low nitrate levels to drinking water with nitrate levels at the acceptable daily intake level of 3.7 mg/kg. The 20 volunteers were assigned to a group consuming either 3.75 g/kg body weight (maximum 300 g per day) red processed meat or fresh (unprocessed) white meat. Comparison of the two dietary groups showed that the most pronounced effect of drinking water nitrate was observed in the red processed meat group. No inhibitory effect of vitamin C intake on ATNC levels in feces was found (unpublished results).

5. Methemoglobinemia

The physiologic processes that can lead to methemoglobinemia in infants under six months of age have been described in detail previously [8,91]. Ingested nitrate is reduced to nitrite by bacteria in the mouth and in the infant stomach, which is less acidic than adults. Nitrite binds to hemoglobin to form methemoglobin, which interferes with the oxygen carrying capacity of the blood. Methemoglobinemia is a life-threatening condition that occurs when methemoglobin levels exceed about 10% [8,91]. Risk factors for infant methemoglobinemia include formula made with water containing high nitrate levels, foods and medications that have high nitrate levels [91,92], and enteric infections [93]. Methemoglobinemia related to high nitrate levels in drinking water used to make infant formula was first reported in 1945 [94]. The U.S. EPA limit of 10 mg/L NO_3-N was set as about one-half the level at which there were no observed cases [95]. The most recent U.S. cases related to nitrate in drinking water were reported by Knobeloch and colleagues in the late 1990s in Wisconsin [96] and were not described in our prior review. Nitrate concentrations in the private wells were about two-times the MCL and bacterial contamination was not a factor. They also summarize another U.S. case in 1999 related to nitrate contamination of a private well and six infant deaths attributed to methemoglobinemia in the U.S. between 1979–1999 only one of which was reported in the literature [96,97]. High incidence of infant methemoglobinemia in eastern Europe has also been described previously [98,99]. A 2002 WHO report on water and health [100] noted that there were 41 cases in Hungary annually, 2913 cases in Romania from 1985–1996 and 46 cases in Albania in 1996.

Results of several epidemiologic studies conducted before 2005 that examined the relationship between nitrate in drinking water and levels of methemoglobin or methemoglobinemia in infants have been described previously [8]. Briefly, nitrate levels >10 mg/L NO_3-N were usually associated with increased methemoglobin levels but clinical methemoglobinemia was not always present. Since our last review, a cross-sectional study conducted in Gaza found elevated methemoglobin levels in infants on supplemental feeding with formula made from well water in an area with the highest mean nitrate concentration of 195 mg/L NO_3 (range: 18–440) compared to an area with lower nitrate concentration (mean: 119 mg/L NO_3; range 18–244) [101]. A cross-sectional study in Morocco found a 22% increased risk of methemoglobinemia in infants in an area with drinking water nitrate >50 mg/L (>11 as NO_3-N) compared to infants in an area with nitrate levels <50 mg/L nitrate [102]. A retrospective cohort study in Iowa of persons (aged 1–60 years) consuming private well water with nitrate levels <10 mg/L NO_3-N found a positive relationship between methemoglobin levels in the blood and the amount of nitrate ingestion [103]. Among pregnant women in rural Minnesota with drinking water supplies that were mostly ≤3 mg/L NO_3-N, there was no relationship between water nitrate intake and women's methemoglobin levels around 36 weeks' gestation [104].

6. Adverse Pregnancy Outcomes

Maternal drinking water nitrate intake during pregnancy has been investigated as a risk factor for a range of pregnancy outcomes, including spontaneous abortion, fetal deaths, prematurity, intrauterine growth retardation, low birth weight, congenital malformations, and neonatal deaths. The relation between drinking water nitrate and congenital malformations in offspring has been the most extensively studied, most likely because of the availability of birth defect surveillance systems around the world.

Our earlier review focused on studies of drinking water nitrate and adverse pregnancy outcomes published before 2005 [8]. In that review, we cited several studies on the relation between maternal exposure to drinking water nitrate and spontaneous abortion including a cluster investigation that suggested a positive association [105] and a case-control study that found no association [106]. These studies were published over 20 years ago. In the present review, we were unable to identify any recently published studies on this outcome. In Table 1, we describe the findings of studies published since 2004 on the relation between drinking water nitrate and prematurity, low birthweight, and congenital malformations. We report results for nitrate in the units (mg/L NO_3 or NO_3-N) that

were reported in the publications. In a historic cohort study conducted in the Deux-Sèvres district (France), Migeot et al. [26] linked maternal addresses from birth records to community water system measurements of nitrate, atrazine, and other pesticides. Exposure to the second tertile of nitrate (14–27 mg/L NO_3) without detectable atrazine metabolites was associated with small-for-gestational age births (Odds Ratio (OR) 1.74, 95% CI 1.1, 2.8), but without a monotonic increase in risk with exposures. There was no association with nitrate among those with atrazine detected in their drinking water supplies. Within the same cohort, Albouy-Llaty and colleagues did not observe any association between higher water nitrate concentrations (with or without the presence of atrazine) and preterm birth [107].

Stayner and colleagues also investigated the relation between atrazine and nitrate in drinking water and rates of low birth weight and preterm birth in 46 counties in four Midwestern U.S. states that were required by EPA to measure nitrate and atrazine monthly due to prior atrazine MCL violations [108]. The investigators developed county-level population-weighted metrics of average monthly nitrate concentrations in public drinking water supplies. When analyses were restricted to counties with less than 20% private well usage (to reduce misclassification due to unknown nitrate levels), average nitrate concentrations during the pregnancy were associated with increased rates of very low birth weight (<1.5 kg Rate Ratio $(RR)_{per\ 1\ ppm}$ = 1.17, 95% CI 1.08, 1.25) and very preterm births (<32 weeks $RR_{per\ 1\ ppm}$ = 1.08, 95% CI 1.02, 1.15) but not with low birth weight or preterm birth overall.

In record-based prevalence study in Perth Australia, Joyce et al. mapped births to their water distribution zone and noted positive associations between increasing tertiles of nitrate levels and prevalence of term premature rupture of membranes (PROM) adjusted for smoking and socioeconomic status [109]. Nitrate concentrations were low; the upper tertile cut point was 0.350 mg/L and the maximum concentration was 1.80 mg/L NO_3-N. Preterm PROM was not associated with nitrate concentrations.

Among studies of drinking water nitrate and congenital malformations, few before 2005 included birth defects other than central nervous system defects [8]. More recently, Mattix et al. [110] noted higher rates of abdominal wall defects (AWD) in Indiana compared to U.S. rates for specific years during the period 1990–2002. They observed a positive correlation between monthly AWD rates and monthly atrazine concentrations in surface waters but no correlation with nitrate levels. Water quality data were obtained from the USGS-NAWQA project that monitors agricultural chemicals in streams and shallow groundwater that are mostly not used as drinking water sources. A case-control study of gastroschisis (one of the two major types of AWD), in Washington State [111] also used USGS-NAWQA measurements of nitrate and pesticides in surface water and determined the distance between maternal residences (zip code centroids) and the closest monitoring site with concentrations above the MCL for nitrate, nitrite, and atrazine. Gastrochisis was not associated with maternal proximity to surface water above the MCL for nitrate (>10 mg/L NO_3-N) or nitrite (>1 mg/L NO_2-N) but there was a positive relationship with proximity to sites with atrazine concentrations above the MCL. In a USA-wide study, Winchester et al. [112] linked the USGS-NAWQA monthly surface water nitrate and pesticide concentrations computed for the month of the last menstrual period with monthly rates of 22 types of birth defects in 1996–2002. Rates of birth defects among women who were estimated to have conceived during April through July were higher than rates among women conceiving in other months. In multivariable models that included nitrate, atrazine, and other pesticides, atrazine (but not nitrate or other pesticides) was associated with several types of anomalies. Nitrate was associated with birth defects in the category of "other congenital anomalies" (OR 1.18, 95% CI 1.14, 1.21); the authors did not specify what defects were included in this category. None of these three studies included local or regional data to support the assumption that surface water nitrate and pesticide concentrations correlated with drinking water exposures to these contaminants.

Using a more refined exposure assessment than the aforementioned studies, Holtby et al. [113] conducted a case-control study of congenital anomalies in an agricultural county in Nova Scotia,

Canada. They linked maternal addresses at delivery to municipal water supply median nitrate concentrations and used kriging of monthly measurements from a network of 140 private wells to estimate drinking water nitrate concentrations in private wells. They observed no associations between drinking water nitrate and all birth defects combined for conceptions during 1987–1997. However, the prevalence of all birth defects occurring during 1998–2006 was associated with drinking water nitrate concentrations of 1–5.56 mg/L NO_3-N (OR 2.44, 95% CI 1.05, 5.66) and ≥5.56 mg/L (OR 2.25, 95% CI 0.92, 5.52).

None of the studies of congenital anomalies accounted for maternal consumption of bottled water or the quantity of water consumed during the first trimester, the most critical period of organ/structural morphogenesis. Attempting to overcome some of these limitations, Brender, Weyer, and colleagues [38,114] conducted a population-based, case-control study in the states of Iowa and Texas where they: (1) linked maternal addresses during the first trimester to public water utilities and respective nitrate measurements; (2) estimated nitrate intake from bottled water based on a survey of products consumed and measurement of nitrate in the major products; (3) predicted drinking water nitrate from private wells through modeling (Texas only); and (4) estimated daily nitrate ingestion from women's drinking water sources and daily consumption of water. The study populations were participants of the U.S. National Birth Defects Prevention Study [115]. Compared to the lowest tertile of nitrate ingestion from drinking water (<0.91 mg/day NO_3), mothers of babies with spina bifida were twice as likely (95% CI 1.3, 3.2) to ingest ≥5 mg/day NO_3 from drinking water than control mothers. Mothers of babies with limb deficiencies, cleft palate, and cleft lip were, respectively, 1.8 (95% CI 1.1, 3.1), 1.9 (95% CI 1.2, 3.1), and 1.8 (95% CI 1.1, 3.1) times more likely to ingest ≥5.4 mg/day of water NO_3 than controls. Women were also classified by their nitrosatable drug exposure during the first trimester [116] and by their daily nitrate and nitrite intake based on a food frequency questionnaire [117]. Higher ingestion of drinking water nitrate did not strengthen associations between maternal nitrosatable drug exposure and birth defects in offspring [38]. However, a pattern was observed of stronger associations between nitrosatable drug exposure and selected birth defects for women in the upper two tertiles of total nitrite ingestion that included contributions from drinking water nitrate and dietary intakes of nitrate and nitrite compared to women in the lowest tertile. Higher intake of food nitrate/nitrite was found to also modify the associations of nitrosatable drug exposure and birth defects in this study [118,119] as well as in an earlier study of neural tube defects conducted in south Texas [120]. Multiplicative interactions were observed between higher food nitrate/nitrite and nitrosatable drug exposures for conotruncal heart, limb deficiency, and oral cleft defects [118].

In summary, five out of six studies, conducted since the 1980s of drinking water nitrate and central nervous system defects, found positive associations between higher drinking water nitrate exposure during pregnancy and neural tube defects or central nervous system defects combined [38,120–123]. The sixth study, which did not find a relationship, did not include measures of association, but compared average drinking water nitrate concentrations between mothers with and without neural tube defect-affected births, which were comparable [124].

Table 1. Studies of drinking water nitrate [a] and adverse pregnancy outcomes published January 2005–March 2018.

First Author, Year, Country	Study Design Regional Description	Years of Outcome Ascertainment	Exposure Description	Pregnancy Outcome	Summary of Findings
Albouy-Llaty, 2016 France [107]	Historic cohort study Deux-Sèvres	2005–2010	Measurements of atrazine metabolites and NO_3 in community water systems (263 municipalities) were linked to birth addresses	Preterm birth	No association for >26.99 mg/L vs. <14.13 mg/L NO_3 in community water systems with or without atrazine detections, adjusted for neighborhood deprivation
Brender, 2013 Weyer, 2014 USA [38]	Population-based case-control study Iowa and Texas	1997–2005	Maternal addresses during the first trimester linked to public water utility nitrate measurements; nitrate intake from bottled water estimated with survey and laboratory testing; nitrate from private wells predicted through modeling; nitrate ingestion (NO_3) estimated from reported water consumption	Congenital heart defects Limb deficiencies Neural tube defects Oral cleft defects	≥5 vs. <0.91 mg/day NO_3 from drinking water spina bifida OR = 2.0 (95% CI: 1.3, 3.2) ≥3.42 vs. <1.0 mg/day NO_3 from water: limb deficiencies OR = 1.8 (CI: 1.1, 3.1); cleft palate OR = 1.9 (CI: 1.2, 3.1) cleft lip OR = 1.8 (CI: 1.1, 3.1)
Holtby, 2014 Canada [113]	Population-based case-control study Kings County, Nova Scotia	1988–2006	Maternal addresses at delivery linked to municipal water supply median nitrate (NO_3-N) concentrations; nitrate in rural private wells estimated from historic sampling and kriging	Congenital malformations combined into one group	Conceptions in 1987–1997: no association with nitrate concentrations Conceptions in 1998–2006: 1–5.56 mg/L NO_3-N (vs. <1 mg/L) OR = 2.44 (CI: 1.05, 5.66); ≥5.56 mg/L OR = 2.25 (CI: 0.92, 5.52)
Joyce, 2008 Australia [109]	Record-based prevalence study Perth	2002–2004	Linked birth residences to 24 water distribution zones; computed average NO_3-N mg/L from historical measurements; independent sampling conducted for 6 zones as part of exposure validation; also evaluated trihalomethanes (THM)	Premature rupture of membranes at term (PROM) (37 weeks' gestation or later)	ORs for tertiles (vs. <0.125 mg/L NO_3-N): 0.125–0.350 mg/L OR = 1.23 (CI: 1.03, 1.52); >0.350 mg/L OR = 1.47 (CI: 1.20, 1.79) No association with THM levels
Mattix, 2007 USA [110]	Ecologic study Indiana	1990–2002	Monthly abdominal wall defect rates linked to monthly surface water nitrate and atrazine concentrations (USGS-NAWQA monitoring data [b])	Abdominal wall birth defects	No correlation observed between nitrate levels in surface water and monthly abdominal wall defects Positive correlation with atrazine levels

Table 1. *Cont.*

First Author, Year, Country	Study Design Regional Description	Years of Outcome Ascertainment	Exposure Description	Pregnancy Outcome	Summary of Findings
Migeot, 2013 France [26]	Historic cohort study Deux-Sèvres	2005–2009	Measurements of atrazine metabolites and NO_3 in community water systems (263 municipalities) were linked to birth addresses	Small-for-gestational age (SGA) births	ORs for tertiles (vs. <14.13 mg/L NO_3) in community water systems with no atrazine detections: 14–27 mg/L OR = 1.74 (CI: 1.10, 2.75); >27 mg/L OR = OR 1.51 (CI: 0.96, 2.4); no association with nitrate when atrazine was detected
Stayner, 2017 USA [108]	Ecologic study 46 counties in Indiana, Iowa, Missouri, and Ohio	2004–2008	Counties had one or more water utility in EPA's atrazine monitoring program; excluded counties with >20% of population on private wells and >300,000 population. Computed county-specific monthly weighted averages of NO_3-N in finished drinking water; exposure metric was average 9 months prior to birth	Preterm birth Low birth weight	Average nitrate not associated with low birth weight and preterm birth Very low birth weight: RR for 1 ppm increase in NO_3-N = 1.17 (CI: 1.08, 1.25); Very preterm birth RR for 1 ppm increase = 1.08 (CI: 1.02, 1.15)
Waller, 2010 USA [111]	Population-based case-control study Washington State	1987–2006	Calculated distance between maternal residence and closest stream monitoring site with concentrations >MCL for NO_3-N, NO_2-N, or atrazine in surface water (USGS-NAWQA data [b])	Gastroschisis	Gastroschisis was not associated with maternal residential proximity to surface water with elevated nitrate (>10 mg/L) or nitrite (>1 mg/L)
Winchester, 2009 USA [112]	Ecologic study USA-wide	1996–2002	Rates of combined and specific birth defects (computed by month of last menstrual period) linked to monthly surface water nitrate concentrations (USGS-NAWQA data [b]); also evaluated atrazine and other pesticides (combined)	Birth defects categorized into 22 groups	Birth defect category "other congenital anomalies": OR for continuous log nitrate = 1.15 (CI: 1.12, 1.18); adjusted for atrazine and other pesticides: OR = 1.18, CI: 1.14, 1.21); No association with other birth defects

Abbreviations: CI, 95% CI confidence interval; OR, odds ratio; RR, rate ratio; USGS-NAWQA, U. S. Geological Survey National Water Quality Assessment; [a] nitrate units are specified as reported in publications. NO_3 can be converted to NO_3-N by multiplying by 0.2258; [b] USGS-NAWQA data for 186 streams in 51 hydrological study areas; streams were not drinking water sources.

7. Cancer

Most early epidemiologic studies of cancer were ecologic studies of stomach cancer mortality that used exposure estimates concurrent with the time of death. Results were mixed, with some studies showing positive associations, many showing no association, and a few showing inverse associations. The results of ecologic studies through 1995 were reviewed by Cantor [125]. Our previous review included ecologic studies of the brain, esophagus, stomach, kidney, ovary, and non-Hodgkin lymphoma (NHL) published between 1999 and 2003 that were largely null [8]. We did not include ecologic studies or mortality case-control studies in this review due to the limitations of these study designs, especially their inability to assess individual-level exposure and dietary factors that influence the endogenous formation of NOC.

Since our review of drinking water nitrate and health in 2005 [8], eight case-control studies and eight analyses in three cohorts have evaluated historical nitrate levels in PWS in relation to several cancers. Nitrate levels were largely below 10 mg/L NO_3-N. Most of these studies evaluated potential confounders and factors affecting nitrosation. Table 2 shows the study designs and results of studies published from 2005 through 2018, including findings from periodic follow-ups of a cohort study of postmenopausal women in Iowa (USA) [31,37,126–129]. In the first analysis of drinking water nitrate in the Iowa cohort with follow-up through 1998, Weyer and colleagues [130] reported that ovarian and bladder cancers were positively associated with the long-term average PWS nitrate levels prior to enrollment (highest quartile average 1955–1988: >2.46 mg/L NO_3-N). They observed inverse associations for uterine and rectal cancer, but no associations with cancers of the breast, colon, rectum, pancreas, kidney, lung, melanoma, non-Hodgkin lymphoma (NHL), or leukemia. Analyses of PWS nitrate concentrations and cancers of the thyroid, breast, ovary, bladder, and kidney were published after additional follow-up of the cohort. The exposure assessment was improved by: (a) the computation of average nitrate levels and years of exposure at or above 5 mg/L NO_3-N, based on time in residence (vs. one long-term PWS average nitrate estimate used by Weyer and colleagues); and (b) by estimation of total trihalomethanes (TTHM) and dietary nitrite intake.

Thyroid cancer was evaluated for the first time after follow-up of the cohort through 2004. A total of 40 cases were identified [37]. Among women with >10 years on PWS with levels exceeding 5 mg/L NO_3-N for five years or more, thyroid cancer risk was 2.6 times higher than that of women whose supplies never exceeded 5 mg/L. With follow-up through 2010, the risk of ovarian cancer remained increased among women in the highest quartile of average nitrate in PWS [129]. Ovarian cancer risk among private well users was also elevated compared to the lowest PWS nitrate quartile. Associations were stronger when vitamin C intake was below median levels with a significant interaction for users of private wells. Overall, breast cancer risk was not associated with water nitrate levels with follow-up through 2008 [128]. Among women with folate intake $\geq$ 400 µg/day, risk was increased for those in the highest average nitrate quintile (Hazard Ratio (HR) = 1.40; 95% CI: = 1.05–1.87) and among private well users (HR = 1.38; 95% CI: = 1.05–1.82), compared to those with the lowest average nitrate quintile. There was no association with nitrate exposure among women with lower folate intake. With follow-up through 2010, there were 130 bladder cancer cases among women who had used PWS >10 years. Risk remained elevated among women with the highest average nitrate levels and was 1.6 times higher among women whose drinking water concentration exceeded 5 mg/L NO_3-N for at least four years [31]. Risk estimates were not changed by adjustment for TTHM, which are suspected bladder cancer risk factors. Smoking, but not vitamin C intake, modified the association with nitrate in water; increased risk was apparent only in current smokers (p-interaction <0.03). With follow-up through 2010, there were 125 kidney cancer cases among women using PWS; risk was increased among those in the 95th percentile of average nitrate (>5.0 mg/L NO_3-N) compared with the lowest quartile (HR = 2.2, 95% CI: 1.2–4.2) [127]. There was no positive trend with the average nitrate level and no increased risk for women using private wells, compared to those with low average nitrate in their public supply. An investigation of pancreatic cancer in the same population (follow-up through 2011)

found no association with average water nitrate levels in public supplies and no association among women on private wells [126].

In contrast to the positive findings for bladder cancer among the cohort of Iowa women, a cohort study of men and women aged 55–69 in the Netherlands with lower nitrate levels in PWS found no association between water nitrate ingestion (median in top quintile = 2.4 mg/day NO_3-N) and bladder cancer risk [131]. Dietary intake of vitamins C and E and history of cigarette smoking did not modify the association. A hospital-based case-control study of bladder cancer in multiple areas of Spain [33] assessed lifetime water sources and usual intake of tap water. Nitrate levels in PWS were low, with almost all average levels below 2 mg/L NO_3-N. Risk of bladder cancer was not associated with the nitrate level in drinking water or with estimated nitrate ingestion from drinking water, and there was no evidence of interaction with factors affecting endogenous nitrosation.

Several case-control studies conducted in the Midwestern U.S. obtained lifetime histories of drinking water sources and estimated exposure for PWS users. In contrast to findings of an increased risk of NHL associated with nitrate levels in Nebraska PWS in an earlier study [132], there was no association with similar concentrations in public water sources in a case-control study of NHL in Iowa [35]. A study of renal cell carcinoma in Iowa [34] found no association with the level of nitrate in PWS, including the number of years that levels exceeded 5 or 10 mg/L NO_3-N. However, higher nitrate levels in PWS increased risk among subgroups who reported above the median intake of red meat intake or below the median intake of vitamin C (p-interaction <0.05). A small case-control study of adenocarcinoma of the stomach and esophagus among men and women in Nebraska [133] estimated nitrate levels among long-term users of PWS and found no association between average nitrate levels and risk.

A case-control study of colorectal cancer among rural women in Wisconsin estimated nitrate levels in private wells using spatial interpolation of nitrate concentrations from a 1994 water quality survey and found increased risk of proximal colon cancer among women estimated to have nitrate levels >10 mg/L NO_3-N compared to levels < 0.5 mg/L. Risk of distal colon cancer and rectal cancer were not associated with nitrate levels [134]. Water nitrate ingestion from public supplies, bottled water, and private wells and springs over the adult lifetime was estimated in analyses that pooled case-control studies of colorectal cancer in Spain and Italy [135]. Risk of colorectal cancer was increased among those with >2.3 mg/day NO_3-N (vs. <1.1 mg/day). There were no interactions with red meat, vitamins C and E, and fiber except for a borderline interaction (p-interaction = 0.07) for rectum cancer with fiber intake. A small hospital-based case-control study in Indonesia found that drinking water nitrate levels above the WHO standard (>11.3 mg/L as NO_3-N) was associated with colorectal cancer [136]. A national registry-based cohort study in Denmark [32] evaluated average nitrate concentrations in PWS and private wells in relation to colorectal cancer incidence among those whose 35th birthday occurred during 1978–2011. The average nitrate level was computed over residential water supplies from age 20 to 35. Increased risks for colon and rectum cancer were observed in association with average nitrate levels ≥9.25 mg/L NO_3 (≥2.1 as NO_3-N) and ≥3.87 mg/L NO_3 (>0.87 as NO_3-N), respectively, with a significant positive trend. Because the study did not interview individuals, it could not evaluate individual-level risk factors that might influence endogenous nitrosation.

A case-control study of breast cancer in Cape Cod, Massachusetts (US) [137] estimated nitrate concentrations in PWS over approximately 20 years as an historical proxy for wastewater contamination and potential exposure to endocrine disruption compounds. Average exposures >1.2 mg/L NO_3-N (vs. <0.3 mg/L) were not associated with risk. A hospital-based case-control study in Spain found no association between water nitrate ingestion and pre- and post-menopausal breast cancers [138].

Table 2. Case-control and cohort studies of drinking water nitrate and cancer (January 2004–March 2018) by cancer site.

First Author (Year) Country	Study Design, Years Regional Description	Exposure Description	Cancer Sites Included	Summary of Drinking-Water Findings [a,b]	Evaluation of Effect Modification [c]
Zeegers, 2006 Netherlands [131]	Cohort Incidence, 1986–1995 204 municipal registries across the Netherlands	1986 nitrate level in 364 pumping stations, exposure data available for 871 cases, 4359 members of the subcohort	Bladder	Highest vs. lowest quintile intake from water (≥1.7 mg/day NO_3-N [median 2.4 mg/day] vs. <0.20) RR = 1.11 (CI: 0.87–1.41; *p*-trend = 0.14)	No interaction with vitamin C, E, smoking
Espejo-Herrera, 2015 Spain [33]	Hospital-based multi-center case-control Incidence, 1998–2001 Asturias, Alicante, Barcelona, Vallès-Bages, Tenerife provinces	Nitrate levels in PWS (1979–2010) and bottled water (measurements of brands with highest consumption based on a Spanish survey); analyses limited to those with ≥70% of residential history with nitrate estimate (531 cases, 556 controls)	Bladder	Highest vs. lowest quartile average level (age 18-interview) (≥2.26 vs. 1.13 mg/L NO_3-N) OR = 1.04 (CI: 0.60–1.81) Years >2.15 mg/L NO_3-N (75th percentile) (>20 vs. 0 years) OR = 1.41 (CI: 0.89–2.24)	No interaction with vitamin C, E, red meat, processed meat, average TTHM level
Jones, 2016 USA [31]	Population-based cohort of postmenopausal women ages 55–69 Incidence, 1986–2010 Iowa	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence with nitrate and trihalomethane estimates (20,945 women; 170 bladder cases); no measurements for private wells Adjusted for total trihalomethanes (TTHM)	Bladder	Highest vs. lowest quartile PWS average (≥2.98 vs. <0.47 mg/L NO_3-N) HR = 1.47 (CI: 0.91–2.38; *p*-trend = 0.11) Years >5 mg/L (≥4 years vs. 0) HR = 1.61 (CI: 1.05–2.47; *p*-trend = 0.03) Private well users (vs. <0.47 mg/L NO_3-N on PWS) HR = 1.53 (CI: 0.93–2.54)	Interaction with smoking (*p*-interaction = 0.03); HR = 3.67 (CI: 1.43–9.38) among current smokers/≥2.98 mg/L vs. non-smokers/<0.47 mg/L NO_3-N); No interaction with vitamin C, TTHM levels
Mueller, 2004 USA, Canada, France, Italy, Spain [139]	Pooled case-control studies Incidence among children <15 years (USA <20 years) 7 regions of 5 countries	Water source during pregnancy and first year of child's life (836 cases, 1485 controls); nitrate test strip measurements of nitrate and nitrite for pregnancy home (except Italy) (283 cases, 537 controls; excluding bottled water users: 207 cases, 400 controls)	Brain, childhood	Private well use versus PWS associated with increased risk in 2 regions and decreased risk in one; No association with nitrate levels in water supplies Astrocytomas (excludes bottled water users): ≥1.5 vs. <0.3 mg/L NO_2-N OR = 5.7 (CI: 1.2–27.2)	Not described
Brody, 2006 USA [137]	Case-control Incidence, 1988–1995 Cape Cod, Massachusetts	Nitrate levels in public water supplies (PWS) since 1972 was used as an indicator of wastewater contamination and potential mammary carcinogens and endocrine disrupting compounds; excluded women on private wells	Breast	Average ≥1.2 mg/L NO_3-N vs. <0.3 OR = 1.8, (CI: 0.6–5.0); summed annual NO_3-N ≥ 10 vs. 1–< 10 mg/L OR = 0.9, CI: 0.6–1.5); number of years >1 mg/L NO_3-N ≥8 vs. 0 years OR = 0.9 (CI: 0.5–1.5)	Not described

Table 2. *Cont.*

First Author (Year) Country	Study Design, Years Regional Description	Exposure Description	Cancer Sites Included	Summary of Drinking-Water Findings [a,b]	Evaluation of Effect Modification [c]
Inoue-Choi, 2012 USA [128]	Population-based cohort of postmenopausal women ages 55–69 Incidence, 1986–2008 Iowa	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence (20,147 women; 1751 breast cases); no measurements for private wells	Breast	Highest vs. lowest quintile PWS average (≥3.8 vs. ≤0.32 mg/L NO_3-N) HR = 1.14 (CI: 0.95–1.36; *p*-trend = 0.11); Private well (vs. ≤ 0.32 mg/L NO_3-N) HR = 1.14 (CI: 0.97–1.34); Private well (vs. ≤0.32 mg/L NO_3-N on PWS) HR = 1.38 (CI: 1.05–1.82); No association among those with low folate <400 µg/day	Interaction with folate for PWS (*p*-interaction = 0.06). Folate ≥400 µg/d: (≥3.8 vs. ≤0.32 mg/L NO_3-N) HR = 1.40 (CI: 1.05–1.87; *p*-trend = 0.04)
Espejo-Herrera, 2016 Spain [136]	Hospital-based multi-center case-control Incidence, 2008–2013 Spain (8 provinces)	Nitrate levels in PWS (2004–2010), bottled water measurements and private wells and springs (2013 measurements in 21 municipalities in León, Spain, the area with highest non-PWS use) Analyses include women with ≥70% of period from age 18 to 2 years before interview (1245 cases, 1520 controls)	Breast	Water nitrate intake based on average nitrate levels (age 18 to 2 years prior to interview) and water intake (L/day). Post-menopausal women: >2.0 vs. 0.5 mg/day NO_3-N OR = 1.32 (0.93–1.86); Premenopausal women: >1.4 vs. 0.4 mg/day NO_3-N OR = 1.14 (0.67–1.94)	No interaction with red meat, processed meat, vitamin C, E, smoking for pre- and post-menopausal women
McElroy, 2008 USA [134]	Population-based case-control, women Incidence, 1990–1992 and 1999–2001 Wisconsin	Limited to women in rural areas with no public water system (475 cases, 1447 controls); nitrate levels at residence (presumed to be private wells) estimated by kriging using data from a 1994 representative sample of 289 private wells	Colorectal	All colon cancers: Private wells ≥10.0 mg/L NO_3-N vs. <0.5 OR = 1.52 (CI: 0.95–2.44); Proximal colon cancer: OR = 2.91 (CI: 1.52–5.56)	Not described
Espejo-Herrera, 2016 Spain, Italy [135]	Multi-center case-control study Incidence, 2008–2013 Spain (9 provinces) and population-based controls; Italy (two provinces) and hospital-based controls	Nitrate levels in PWS (2004–2010) for 349 water supply zones, bottled water (measured brands with highest consumption), and private wells and springs (measurements in 2013 in 21 municipalities in León, Spain, the area with highest non-PWS use) Analyses include those with nitrate estimates for ≥70% of period 30 years before interview (1869 cases, 3530 controls)	Colorectal	Water nitrate intake based on average nitrate levels (estimated 30 to 2 years prior to interview) and water intake (L/day) Highest vs. lowest exposure quintiles (≥2.3 vs. <1.1 mg/day NO_3-N) OR = 1.49 (CI:1.24–1.78); Colon OR = 1.52 (CI: 1.24–1.86), Rectum OR = 1.62 (CI: 1.23–2.14)	Interaction with fiber for rectum (*p*-interaction = 0.07); >20 g/day fiber + >1.0 mg/L NO_3-N vs. <20 g/day + ≤1.0 mg/L HR = 0.72 (CI: 0.52–1.00). No interaction with red meat, vitamin C, E

Table 2. *Cont.*

First Author (Year) Country	Study Design, Years Regional Description	Exposure Description	Cancer Sites Included	Summary of Drinking-Water Findings [a,b]	Evaluation of Effect Modification [c]
Fathmawati, 2017 Indonesia [126]	Hospital-based case-control Incidence, 2014–2016 Indonesia (3 provinces)	Nitrate levels in well water collected during the raining season (Feb-March 2016) and classified based on >11.3 or ≤11.3 mg/L as NO_3-N and duration of exposure >10 and ≤10 years Analyses included participants who reported drinking well water (75 cases, 75 controls)	Colorectal	Water nitrate > WHO standard vs. below (> 11.3 vs. ≤11.3 mg/L NO_3-N) OR = 2.82 (CI: 1.08–7.40); > 10 years: 4.31 (CI: 11.32–14.10); ≤10 years: 1.41 (CI: 0.14–13.68)	Not described
Schullehner, 2018 Denmark [32]	Population-based record-linkage cohort of men and women ages 35 and older, 1978–2011 Denmark	Nitrate levels in PWS and private wells among 1,742,321 who met exposure assessment criteria (5944 colorectal cancer cases, including 3700 with colon and 2308 with rectal cancer)	Colorectal	Annual average nitrate exposure between ages 20–35 among those who lived ≥75% of study period at homes with a water sample within 1 year (61% of Danish population). Highest vs. lowest exposure quintile (≥2.1 vs. 0.16 mg/L NO_3-N); Colorectal: HR = 1.16 (CI: 1.08–1.25); colon: 1.15 (CI: 1.05–1.26); rectum: 1.17 (CI: 1.04–1.32)	No information on dietary intakes or smoking
Ward, 2007 USA [34]	Population-based case control Incidence, 1986–1989 Iowa	Nitrate levels in PWS among those with nitrate estimates for ≥70% of person-years ≥1960 (201 cases, 1244 controls)	Kidney (renal cell carcinomas)	Highest vs. lowest quartile PWS average (≥2.8 mg/L NO_3-N vs. <0.62) OR = 0.89 (CI 0.57–1.39); Years >5mg/L NO_3-N 11+ vs. 0 OR = 1.03 (CI: 0.66–1.60)	Interaction with red meat intake (p-interaction = 0.01); OR = 1.91 (CI 1.04–3.51) among 11+ years >5 mg/L NO_3-N and red meat ≥1.2 servings/day. Interaction with vitamin C showed similar pattern (p-interaction = 0.13)
Jones, 2017 USA [127]	Population-based cohort of postmenopausal women ages 55–69 Incidence, 1986–2010 Iowa	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence. PWS measurements for nitrate and TTHM; no measurements for private wells (20,945 women; 163 kidney cases)	Kidney	Nitrate and TTHM metrics computed for duration at water source (11+ years) 95th percentile vs. lowest quartile PWS average (≥5.00 vs. <0.47 mg/L NO_3-N) HR = 2.23 (CI: 1.19–4.17; p-trend = 0.35) Years >5 mg/L (≥4 years vs. 0) HR = 1.54 (CI: 0.97–2.44; p-trend = 0.09) Private well users (vs. <0.47 mg/L NO_3-N in PWS) HR = 0.96 (CI: 0.59–1.58)	No interaction with smoking, vitamin C
Ward, 2006 USA [35]	Population-based case-control Incidence, 1998–2000 Iowa	Nitrate levels in PWS among those with nitrate estimates for ≥70% of person-years ≥1960 (181 case, 142 controls); nitrate measurements for private well users at time of interviews (1998–2000; 54 cases, 44 controls)	Non-Hodgkin lymphoma	Private wells: >5.0 mg/L NO_3-N vs. ND OR = 0.8 (CI 0.2–2.5) PWS average: ≥2.9 mg/L NO_3-N vs. <0.63 OR = 1.2 (CI 0.6–2.2) Years ≥5mg/L NO3-N: 10+ vs. 0 OR = 1.4 (CI: 0.7–2.9)	No interaction with vitamin C, smoking

Table 2. *Cont.*

First Author (Year) Country	Study Design, Years Regional Description	Exposure Description	Cancer Sites Included	Summary of Drinking-Water Findings [a,b]	Evaluation of Effect Modification [c]
Inoue-Choi, 2015 USA [129]	Population-based cohort of postmenopausal women ages 55–69 Incidence, 1986–2010 Iowa	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence; PWS measurements for nitrate and TTHM; no measurements for private wells (17,216 women; 190 ovarian cases)	Ovary	Nitrate and TTHM metrics computed for reported duration at water source (11+ years) Highest vs. lowest quartile PWS average (≥2.98 mg/L vs. <0.47 mg/L NO_3-N) HR = 2.03 (CI = 1.22–3.38; *p*-trend = 0.003) Years >5 mg /L (≥4 years vs. 0) HR = 1.52 (CI: 1.00–2.31; *p*-trend = 0.05) Private well users (vs. <0.47 mg/L NO_3-N in PWS) HR = 1.53 (CI: 0.93–2.54)	No interaction with vitamin C, red meat intake, smoking for PWS nitrate Interaction with private well use and vitamin C intake (*p*-interaction = 0.01)
Quist, 2018 USA [126]	Population-based cohort of postmenopausal women ages 55–69 Incidence, 1986–2011 Iowa	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence; nitrate and TTHM estimates for PWS (20,945 women; 189 pancreas cases); no measurements for private wells Adjusted for TTHM (1955–1988), measured levels in 1980s, prior year levels estimated by expert)	Pancreas	Nitrate and TTHM metrics computed for reported duration at water source (11+ years) 95th percentile vs. lowest quartile PWS average (≥5.69 vs. <0.47 mg/L NO_3-N) HR = 1.16 (CI: 0.51–2.64; *p*-trend = 0.97) Years >5 mg /L (≥4 years vs. 0) HR = 0.90 (CI: 0.55–1.48; *p*-trend = 0.62) Private well users (vs. <0.47 mg/L NO_3-N) HR = 0.92 (CI: 0.55–1.52)	No interaction with smoking, vitamin C
Ward, 2008 USA [133]	Population-based case control Incidence, 1988–1993 Nebraska	Controls from prior study of lymphohematopoetic cases and controls interviewed in 1992–1994; Proxy interviews for 80%, 76%, 61% of stomach, esophagus, controls, respectively. Nitrate levels (1965–1985) in PWS for ≥70% of person-years (79 distal stomach, 84, esophagus, 321 controls); Private well users sampling at interview (15 stomach, 22 esophagus, 44 controls)	Stomach and esophagus (adenocarcinomas)	Highest vs. lowest quartile PWS average (>4.32 vs. <2.45 mg/L NO_3-N): stomach OR = 1.2 (CI 0.5–2.7); esophagus OR = 1.3 (CI: 0.6–3.1); Years >10 mg/L NO_3-N (9+ vs. 0): stomach OR = 1.1 (CI: 0.5–2.3); esophagus OR = 1.2 (CI: 0.6–2.7) Private well users (>4.5 mg/L NO_3-N vs. <0.5) stomach OR = 5.1 (CI: 0.5–52; 4 cases, 13 controls); esophagus OR = 0.5 (CI: 0.1–2.9; 8 cases; 13 controls)	No interaction with vitamin C, processed meat, or red meat for either cancer
Ward, 2010 USA [37]	Population-based cohort of postmenopausal women ages 55–69 Incidence, 1986–2004 Iowa	Nitrate levels in PWS (1955–1988) and private well use among women >10 years at enrollment residence (21,977 women; 40 thyroid cases); no measurements for private wells	Thyroid	Highest vs. lowest quartile PWS average (>2.46 vs. <0.36 mg/L NO_3-N) HR = 2.18 (CI: 0.83–5.76; *p*-trend = 0.02) Years >5 mg /L (≥5 years vs. 0) HR = 2.59 (CI: 1.09–6.19; *p*-trend = 0.04); Private well (vs. <0.36 mg/L NO_3-N on PWS) HR = 1.13 (CI: 0.83–3.66) Dietary nitrate intake quartiles positively associated with risk (*p*-trend = 0.05)	No interaction with smoking, vitamin C, body mass index, education, residence location (farm/rural vs. urban)

ND = not detected; PWS = public water supplies; [a] nitrate or nitrite levels presented in the publications as mg/L of the ion were converted to mg/L as NO_3-N or NO_2-N; [b] Odds ratios (OR) for case-control studies, incidence rate ratios (RR) and hazard ratios (HR) for cohort studies, and 95% confidence intervals (CI); [c] Factors evaluated are noted. Interaction refers to reported $p \leq 0.10$ from test of heterogeneity.

Animal studies demonstrate that in utero exposure to nitrosamides can cause brain tumors in the exposed offspring. Water nitrate and nitrite intake during pregnancy was estimated in a multi-center case-control study of childhood brain tumors in five countries based on the maternal residential water source [139]. Results for the California and Washington State sites were reported in our previous review [8,140]. Nitrate/nitrite levels in water supplies were measured using a nitrate test strip method in four countries including these U.S. sites; most of these measurements occurred many years after the pregnancy. Measured nitrate concentrations were not associated with risk of childhood brain tumors. However, higher nitrite levels (>1.5 mg/L NO_2-N) in the drinking water were associated with increased risk of astrocytomas.

8. Thyroid Disease

Animal studies demonstrate that ingestion of nitrate at high doses can competitively inhibit iodine uptake and induce hypertrophy of the thyroid gland [141]. An early study of women in the Netherlands consuming water with nitrate levels at or above the MCL, found increased prevalence of thyroid hypertrophy [142]. Since the last review, five studies have evaluated nitrate ingestion from drinking water (the Iowa cohort study also assessed diet) and prevalence of thyroid disease. A study of school-age children in Slovakia found increased prevalence of subclinical hypothyroidism among children in an area with high nitrate levels (51–274 mg/L NO_3) in water supplies compared with children ingesting water with nitrate ≤50 mg/L (11 mg/L NO_3-N). In Bulgarian villages with high nitrate levels (75 mg/L NO_3) and low nitrate levels (8 mg/L), clinical examinations of the thyroids of pregnant women and school children revealed an approximately four- and three-fold increased prevalence of goiter, respectively, in the high nitrate village [143,144]. The iodine status of the populations in both studies was adequate. Self-reported hypothyroidism and hyperthyroidism among a cohort of post-menopausal women in Iowa was not associated with average nitrate concentrations in PWS [37]. However, dietary nitrate, the predominant source of intake, was associated with increased prevalence of hypothyroidism but not hyperthyroidism. Modeled estimates of nitrate concentrations in private wells among a cohort of Old Order Amish in Pennsylvania (USA) were associated with increased prevalence of subclinical hypothyroidism as determined by thyroid stimulating hormone measurements, among women but not men [145].

9. Other Health Effects

Associations between nitrate in drinking water and other non-cancer health effects, including type 1 childhood diabetes (T1D), blood pressure, and acute respiratory tract infections in children were previously reviewed [8]. Since 2004, a small number of studies have contributed additional mixed evidence for these associations. Animal studies indicate that NOC may play a role in the pathology of T1D through damage to pancreatic beta cells [146]. A registry-based study in Finland [147] found a positive trend in T1D incidence with levels of nitrate in drinking water. In contrast, an ecological analysis in Italy showed an inverse correlation with water nitrate levels and T1D rates [148]. A small T1D case-control study in Canada with 57 cases showed no association between T1D and estimated intake of nitrate from drinking water (highest quartile >2.7 mg/day NO_3-N) [149]. Concentrations of nitrate in drinking water (median ~2.1 mg/L NO_3-N) were not associated with progression to T1D in a German nested case-control study of islet autoantibody-positive children, who may be at increased risk of the disease [150].

In a prospective, population-based cohort study in Wisconsin (USA), increased incidence of early and late age-related macular degeneration was positively associated with higher nitrate levels (≥5 mg/L vs. <5 mg/L NO_3-N) in rural private drinking water supplies [151]. The authors suggested several possible mechanisms, including methemoglobin-induced lipid peroxidation in the retina.

Potential benefits of nitrate ingestion include lowering of blood pressure due to production of nitric oxide in the acidic stomach and subsequent vasodilation, antithrombotic, and immunoregulatory effects [152]. Experimental studies in animals and controlled feeding studies in humans have

demonstrated mixed evidence of these effects and on other cardiovascular endpoints such as vascular hypertrophy, heart failure, and myocardial infarction (e.g., [152–154]). Ingested nitrite from diet has also been associated with increased blood flow in certain parts of the brain [155]. Epidemiologic studies of these effects are limited to estimation of dietary exposures or biomarkers that integrate exposures from nitrate from diet and drinking water. Recent findings in the Framingham Offspring Study suggested that plasma nitrate was associated with increased overall risk of death that attenuated when adjusted for glomerular function (HR: 1.16, 95% CI: 1.0–1.35) but no association was observed for incident cardiovascular disease [156]. No epidemiologic studies have specifically evaluated nitrate ingested from drinking water in relation to these outcomes. Another potential beneficial effect of nitrate is protection against bacterial infections via its reduction to nitrite by enteric bacteria. In an experimental inflammatory bowel disease mouse model, nitrite in drinking water was associated with both preventive and therapeutic effects [157]. However, there is limited epidemiologic evidence for a reduced risk of gastrointestinal disease in populations with high drinking water nitrate intake. One small, cross-sectional study in Iran found no association between nitrate levels in public water supplies with mean levels of ~5.6 mg/L NO_3-N and gastrointestinal disease [158].

10. Discussion

Since our last review of studies through 2004 [8], more than 30 epidemiologic studies have evaluated drinking water nitrate and risk of cancer, adverse reproductive outcomes, or thyroid disease. However, the number of studies of any one outcome was not large and there are still too few studies to allow firm conclusions about risk. The most common endpoints studied were colorectal cancer, bladder, and breast cancer (three studies each) and thyroid disease (four studies). Considering all studies to date, the strongest evidence for a relationship between drinking water nitrate ingestion and adverse health outcomes (besides methemoglobinemia) is for colorectal cancer, thyroid disease, and neural tube defects. Four of the five published studies of colorectal cancer found evidence of an increased risk of colorectal cancer or colon cancer associated with water nitrate levels that were mostly below the respective regulatory limits [32,134,135,159]. In one of the four positive studies [159], increased risk was only observed in subgroups likely to have increased nitrosation. Four of the five studies of thyroid disease found evidence for an increased prevalence of subclinical hypothyroidism with higher ingestion of drinking water nitrate among children, pregnant women, or women only [37,144,145,160]. Positive associations with drinking water nitrate were observed at nitrate concentrations close to or above the MCL. The fifth study, a cohort of post-menopausal women in Iowa, had lower drinking water nitrate exposure but observed a positive association with dietary nitrate [37]. To date, five of six studies of neural tube defects showed increased risk with exposure to drinking water nitrate below the MCL. Thus, the evidence continues to accumulate that higher nitrate intake during the pregnancy is a risk factor for this group of birth defects.

All but one of the 17 cancer studies conducted since 2004 were in the U.S. or Europe, the majority of which were investigations of nitrate in regulated public drinking water. Thyroid cancer was studied for the first time [37] with a positive finding that should be evaluated in future studies. Bladder cancer, a site for which other drinking water contaminants (arsenic, disinfection by-products [DBPs]) are established or suspected risk factors, was not associated with drinking water nitrate in three of the four studies. Most of the cancer studies since 2004 evaluated effect modification by factors known to influence endogenous nitrosation, although few observed evidence for these effects. Several studies of adverse reproductive outcomes since 2004 have indicated a positive association between maternal prenatal exposure to nitrate concentrations below the MCL and low birth weight and small for gestational age births. However, most studies did not account for co-exposure to other water contaminants, nor did they adjust for potential risk factors. The relation between drinking water nitrate and spontaneous abortion continues to be understudied. Few cases of methemoglobinemia, the health concern that lead to the regulation of nitrate in public water supplies, have been reported in the U.S. since the 1990s. However, as described by Knobeloch et al. [96], cases may be underreported

and only a small proportion of cases are thoroughly investigated and described in the literature. Based on published reports, [100] areas of the world of particular concern include several eastern European countries, Gaza, and Morocco, where high nitrate concentrations in water supplies have been linked to high levels of methemoglobin in children. Therefore, continued surveillance and education of physicians and parents will be important. Biological plausibility exists for relationships between nitrate ingestion from drinking water and a few other health outcomes including diabetes and beneficial effects on the cardiovascular system, but there have been only a limited number of epidemiologic studies.

Assessment of drinking water nitrate exposures in future studies should be improved by obtaining drinking water sources at home and at work, estimating the amount of water consumed from each source, and collecting information on water filtration systems that may impact exposure. These efforts are important for reducing misclassification of exposure. Since our last review, an additional decade of PWS monitoring data are available in the U.S. and European countries, which has allowed assessment of exposure over a substantial proportion of participants' lifetimes in recent studies. Future studies should estimate exposure to multiple water contaminants as has been done in recent cancer studies [31,33,127,129]. For instance, nitrate and atrazine frequently occur together in drinking water in agricultural areas [161] and animal studies have found this mixture to be teratogenic [162]. Regulatory monitoring data for pesticides in PWS has been available for over 20 years in the U.S.; therefore, it is now feasible to evaluate co-exposure to these contaminants. Additionally, water supplies in agricultural areas that rely on alluvial aquifers or surface water often have elevated levels of both DBPs and nitrate. Under this exposure scenario, there is the possibility of formation of the nitrogenated DBPs including the carcinogenic NDMA, especially if chloramination treatment is used for disinfection [163,164]. Studies of health effects in countries outside the U.S. and Europe are also needed.

A comprehensive assessment of nitrate and nitrite from drinking water and dietary sources as well as estimation of intakes of antioxidants and other inhibitors of endogenous nitrosation including dietary polyphenols and flavonoids is needed in future studies. Heme iron from red meat, which increases fecal NOC in human feeding studies, should also be assessed as a potential effect modifier of risk from nitrate ingestion. More research is needed on the potential interaction of nitrate ingestion and nitrosatable drugs (those with secondary and tertiary amines or amides). Evidence from several studies of birth defects [38,118–120] implicates nitrosatable drug intake during pregnancy as a risk factor for specific congenital anomalies especially in combination with nitrate. Drugs with nitrosatable groups include many over-the-counter and prescription drugs. Future studies with electronic medical records and record-linkage studies in countries like Denmark with national pharmacy data may provide opportunities for evaluation of these exposures.

Populations with the highest exposure to nitrate from their drinking water are those living in agricultural regions, especially those drinking water from shallow wells near nitrogen sources (e.g., crop fields, animal feeding operations). Estimating exposure for private well users is important because it allows assessment of risk over a greater range of nitrate exposures compared to studies focusing solely on populations using PWS. Future health studies should focus on these populations, many of which may have been exposed to elevated nitrate in drinking water from early childhood into adulthood. A major challenge in conducting studies in these regions is the high prevalence of private well use with limited nitrate measurement data for exposure assessment. Recent efforts to model nitrate concentrations in private wells have shown that it is feasible to develop predictive models where sufficient measurement data are available [41,48,49]. However, predictive models from one area are not likely to be directly translatable to other geographic regions with different aquifers, soils, and nitrogen inputs.

Controlled human feeding studies have demonstrated that endogenous nitrosation occurs after ingestion of drinking water with nitrate concentrations above the MCL of 10 mg/L NO_3-N (~44 mg/L as NO_3). However, the extent of NOC formation after ingestion of drinking water with nitrate

concentrations below the MCL has not been well characterized. Increased risks of specific cancers and central nervous system birth defects in study populations consuming nitrate below the MCL is indirect evidence that nitrate ingestion at these levels may be a risk factor under some conditions. However, confounding by other exposures or risk factors can be difficult to rule out in many studies. Controlled human studies to evaluate endogenous nitrosation at levels below the MCL are needed to understand interindividual variability and factors that affect endogenous nitrosation at drinking water nitrate levels below the MCL.

A key step in the endogenous formation of NOC is the reduction of nitrate, which has been transported from the bloodstream into the saliva, to nitrite by the nitrate-reducing bacteria that are located primarily in the crypts on the back of the tongue [165–167]. Tools for measuring bacterial DNA and characterizing the oral microbiome are now available and are currently being incorporated into epidemiologic studies [168,169]. Buccal cell samples that have been collected in epidemiologic studies can be used to characterize the oral microbiome and to determine the relative abundance of the nitrate-reducing bacteria. Studies are needed to characterize the stability of the nitrate-reducing capacity of the oral microbiome over time and to determine factors that may modify this capacity such as diet, oral hygiene, and periodontal disease. Interindividual variability in the oral nitrate-reducing bacteria may play an important role in modifying endogenous NOC formation. The quantification of an individual's nitrate-reducing bacteria in future epidemiologic studies is likely to improve our ability to classify participants by their intrinsic capacity for endogenous nitrosation.

In addition to characterizing the oral microbiome, future epidemiologic studies should incorporate biomarkers of NOC (e.g., urinary or fecal NOC), markers of genetic damage, and determine genetic variability in NOC metabolism. As many NOC require α-hydroxylation by CYP2E1 for bioactivation and for formation of DNA adducts, it is important to investigate the influence of polymorphisms in the gene encoding for this enzyme. Studies are also needed among populations with medical conditions that increase nitrosation such as patients with inflammatory bowel disease and periodontal disease [8]. Because NOC exposures induce characteristic gene expression profiles [170,171], further studies linking drinking water intake to NOC excretion and gene expression responses are relevant to our understanding of health risks associated with drinking water nitrate. The field of 'Exposome-research' [172,173] generates large numbers of genomics profiles in human population studies for which dietary exposures and biobank materials are also available. These studies provide opportunities to measure urinary levels of nitrate and NOC that could be associated with molecular markers of exposure and disease risk.

Nitrate concentrations in global water supplies are likely to increase in the future due to population growth, increases in nitrogen fertilizer use, and increasing intensity and concentration of animal agriculture. Even with increased inputs, mitigation of nitrate concentrations in water resources is possible through local, national, and global efforts. Examples of the latter are the International Nitrogen Initiative [174] and the EU Nitrates Directive [17,18], which aim to quantify human effects on the nitrogen cycle and to validate and promote methods for sustainable nitrogen management. Evidence for the effectiveness of these efforts, which include the identification of vulnerable areas, establishment of codes of good agricultural practices, and national monitoring and reporting are indicated by decreasing trends in groundwater nitrate concentrations in some European countries after the implementation of the EU Nitrates Directive [19]. However, the effect of this initiative was variable across the EU. In the U.S., nitrogen applications to crop fields are not regulated and efforts to reduce nitrogen runoff are voluntary. Although strategies such as appropriate timing of fertilizer applications, diversified crop rotations, planting of cover crops, and reduced tillage can be effective [175], concentrations in U.S. ground and surface water have continued to increase in most areas [10]. Climate change is expected to affect nitrogen in aquatic ecosystems and groundwater through alterations of the hydrological cycle [176]. Climatic factors that affect nitrate in groundwater include the amount, intensity, and timing of precipitation. Increasing rainfall intensity, especially in

the winter and spring, can lead to increases in nitrogen runoff from agricultural fields and leaching to groundwater.

11. Conclusions

In summary, most adverse health effects related to drinking water nitrate are likely due to a combination of high nitrate ingestion and factors that increase endogenous nitrosation. Some of the recent studies of cancer and some birth defects have been able to identify subgroups of the population likely to have greater potential for endogenous nitrosation. However, direct methods of assessing these individuals are needed. New methods for quantifying the nitrate-reducing bacteria in the oral microbiome and characterizing genetic variation in NOC metabolism hold promise for identifying high risk groups in epidemiologic studies.

To date, the number of well-designed studies of individual health outcomes is still too few to draw firm conclusions about risk from drinking water nitrate ingestion. Additional studies that incorporate improved exposure assessment for populations on PWS, measured or predicted exposure for private well users, quantification of nitrate-reducing bacteria, and estimates of dietary and other factors affecting nitrosation are needed. Studies of colorectal cancer, thyroid disease, and central nervous system birth defects, which show the most consistent associations with water nitrate ingestion, will be particularly useful for clarifying these risks. Future studies of other health effects with more limited evidence of increased risk are also needed including cancers of the thyroid, ovary, and kidney, and the adverse reproductive outcomes of spontaneous abortion, preterm birth, and small for gestational age births.

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DEPARTMENT OF HEALTH

Nitrate and Methemoglobinemia

Drinking water with high nitrate can cause a potentially fatal disorder called methemoglobinemia. Methemoglobinemia is a condition in which more than one percent of the hemoglobin in red blood cells take the form of methemoglobin. Hemoglobin carries oxygen in our blood, delivering it from the lungs to the rest of our body. Methemoglobin does not carry oxygen well and, when it replaces hemoglobin, it can cause a gray-blueness of the skin (cyanosis).

We have a lot of information about how excess nitrate in drinking water behaves in our bodies and leads to methemoglobinemia. Nitrate in water is almost completely absorbed into the blood. Our bodies convert a portion of that nitrate into nitrite. Nitrite reacts with blood to create methemoglobin. The more methemoglobin in the blood, the worse that blood is at carrying oxygen where it is needed. Along with these changes in blood chemistry, a person suffering methemoglobinemia may also experience elevated resting heart rate, weakness, nausea, and in severe cases, death.

Methemoglobinemia in Minnesota and Wisconsin

Research and case reports show that nitrate in well water above 10 milligrams per liter (mg/L) can cause methemoglobinemia in infants less than six months old. In 1945 the hypothesis that high levels of nitrate in well water caused methemoglobinemia was published.[1] Two years later, an infant near the town of Tyler became the first published case in Minnesota.[2] In the following three years, there were 146 cases voluntarily reported in Minnesota, including 14 deaths. In 1979 and 1980 there were two reported cases of methemoglobinemia in Minnesota. In both cases nitrate concentrations in the wells were over 50 mg/L. Once the source of water was changed in the homes, the methemoglobinemia resolved.[3]

Most Minnesota cases of methemoglobinemia in infants occurred in the southwestern part of the state, but cases have been reported from the southern border to as far north as Becker County. Some infants developed symptoms after fewer than two days, and other infants were fed formula prepared with well water for up to 60 days before symptoms appeared. It is suspected that many milder cases were resolved by changing the source of the infant's water and were never reported.[2] There were no methemoglobinemia cases reported in breast fed babies.

The most recognized symptom of methemoglobinemia is a gray-blue color to the lips that eventually spreads to the whole body. In some cases, the bluish color can be so subtle that it goes unnoticed.[2] This was the case when parents in Columbia County, WI brought their child in for immunizations in 1998. They noticed that their child had been "crabbier than normal" and had been vomiting after feeding since they moved to a new house served by a private drinking water well. Concerned that this may be a case of methemoglobinemia, a home nurse visited the family and took water samples. The concentration of nitrate in their well water was 22.9 mg/L. The doctor placed the baby on bottled water and the methemoglobinemia resolved.[4]

Other Cases of Methemoglobinemia

Nitrate in well water and methemoglobinemia are not unique to the Midwest. It occurs all over the country, as well as around the world. According to the Centers for Disease Control and Prevention, between 1979 and 1996 there were six infant deaths from methemoglobinemia in Texas, South Dakota, Louisiana, Virginia, and Colorado. Additionally, it is a common problem in Eastern Europe, where most methemoglobinemia cases are associated with contaminated water.[4]

Infants Are Especially Sensitive to Nitrate in Water

While adults can develop methemoglobinemia due to high levels of nitrate in drinking water, public health actions mainly focus on infants less than six months old because they are an especially sensitive population. Infants fed formula prepared with water high in nitrate are the most highly exposed population. They receive the highest dose of nitrate compared to all other age groups based on body weight.[5] In addition to their high exposure, infants have different body chemistries than adults. They convert more nitrate to nitrite, which leads to the creation of methemoglobin, and their bodies are less able to convert methemoglobin back into hemoglobin. This causes methemoglobin to build up in the body of an infant faster than it builds up in the body of an adult.

Scientific Support for 10 Milligrams per Liter

The evidence supporting the 10 mg/L US EPA Maximum Contaminant Level (MCL) for nitrate in drinking water and the Minnesota Health Risk Limit (HRL; which is the adopted MCL) is strong. Because exposure to nitrate and resulting illness has been observed in humans rather than just laboratory animals, values derived to protect people do not have to be adjusted to account for differences in animals and humans.

Additionally, the six Minnesota cases of methemoglobinemia in infants described by Rosenfield and Huston occurred in water with nitrate levels above 10 mg/L.[2] A nationwide survey performed by the American Public Health Association in 1949 showed this was a national trend. The survey collected details of 278 methemoglobinemia cases, of which 214 included information about drinking water sources. All 214 cases were associated with drinking water that had a concentration of nitrate above 10 mg/L.[6]

Factors That May Reduce Cases of Methemoglobinemia

Much of what is known about the health risks of nitrate is from reports, surveys, and other work done in the mid-1900s. Physicians and scientists quickly concluded that water with nitrate above 10 mg/L is potentially lethal to infants less than six months old. Since that time, there have been several changes that may have reduced the real or perceived number of methemoglobinemia cases in Minnesota.

- The high number of cases of methemoglobinemia in 1947-1949 lead to a familiarity with the illness in infants and how to treat it (switch water sources). There has been a gradual drop off in the number of cases voluntarily reported by physicians following this awareness. Additionally, new mothers are more aware of their water source and may opt to feed their babies formula reconstituted with bottled water.
- The condition may not be easily recognized by health care providers, particularly in mild cases with symptoms like irritability, lethargy, and/or a blue skin color that may fade and return.
- Methemoglobinemia is not a reportable illness in Minnesota and there is no mechanism in place for a provider to report cases to the state health department. This limits our ability to know how many infants are treated for this condition each year. In a recent review of hospital discharge data and emergency department records in Minnesota from 2000-2016, there were 10 cases of methemoglobinemia in infants greater than one day old and less than one year old. The majority of the case records lacked supporting information needed to definitively rule out nitrate in drinking water as a cause or contributor to the diagnosis.
- The 1974 MDH Well Code set a new standard for construction for all new wells in Minnesota. Requirements on casing materials, distances from contamination sources, and well construction

methods all help reduce nitrate and bacteria contamination. For example, Walton noted that in Iowa, water samples with nitrate concentrations over 10 mg/L occurred in 39.7 percent of dug wells, 21.5 percent of bored wells, and only 4.5 percent of drilled wells.[6]

- Baby formula ingredients have changed since the 1950s. Formulas now contain antioxidants such as Vitamin C that can turn nitrite into nitric oxide, a beneficial molecule, and block the formation of methemoglobinemia. This is also why vegetables, a source of high nitrate in the diet, have not likely resulted in cases of methemoglobinemia. Their high antioxidant content may be playing a role in converting the nitrite from nitrate to nitric oxide, reducing harmful effects of nitrate.

Emerging Health Risks for Adults from Nitrate in Water

In sum, the evidence remains compelling that high levels of nitrate in well water cause methemoglobinemia. While methemoglobinemia in infants may be less common today, it has not disappeared, and remains an important public health concern. Only recently has scientific evidence emerged to assess the health impacts of drinking water with high nitrate on adults. A growing body of literature indicates potential associations between nitrate/nitrite exposure and other health effects such as increased heart rate, nausea, headaches, and abdominal cramps. Some studies also suggest an increased risk of cancer, especially gastric cancer, associated with dietary nitrate/nitrite exposure,[7,8] but there is yet no scientific consensus on this question.

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ORIGINAL ARTICLE

Health Effects from Exposure to Sulphates and Chlorides in Drinking Water

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ABSTRACT

This study was designed keeping in view the negative and harmful effects of high levels of Sulphates and Chlorides present in drinking water sources after investigating Sulphate and Chloride contents. Sadiqabad, Rahim Yar Khan, Khanpur and Liaqatpur cities of district RYK, Punjab, Pakistan were investigated for the Sulphate and Chloride levels in different drinking water sources.53 and 23 percent of Sulphate and Chloride samples respectively were found having values greater than the guideline value obtained from the whole district of Rahim Yar Khan. Health Survey was conducted in the areas with higher contents of Sulphates and Chlorides .Almost 55 percent of population confirmed laxative effect and taste problem. Suggestions to prevent health effects were given.

Key words: Health effects, sulphates, chloride, drinking water

INTRODUCTION

In Pakistan, most of the population relies on shared water sources. Whether it is ground water, nearby river, ponds or even harvested rainwater, these water sources are usually shared by both humans and animals. Human uses include purposes such as bathing, washing, laundering, cooking and drinking. These uncontrolled varieties of human and animal use potentially alter the quality of natural source waters significantly. This calls for the need for effective management that warrants the maintenance of the fitness for use of water resources on a sustained basis, achieving a balance between usage and environmental protection.

Globally the subject of contaminant levels in drinking water has been a long contentious issue. However, in Pakistan and other developing nations where relevant institutional capacities are either non-existent or fragile, robust surveillance and early warning systems for chemical contaminants rarely exist. In cases where they do, the focus is on water access and not water quality bearing in mind the peculiarity of the location. Whereas water supply is seen as a national issue, pollution is mainly felt at, and dealt with, at the local level. National governments, with few exceptions, have little information on the relative importance of various types of pollution (agriculture, municipal, industrial, animal husbandry, aquaculture, etc.) and therefore have no notion of which is of greatest economic or public health significance (Abbaspour, 2007). Consequently, it is difficult to develop a strategic water quality management plan or to efficiently focus domestic and donor funds on priority issues as quality surveillance. Our study is one of the few independent reports that attempt to evaluate the concentrations of chlorides and sulphates in drinking water sources in Pakistan with an attempt to provide by surveys, epidemiological linkages to suggest potential health effects from exposure to elevated levels of the chemicals in drinking water.

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MATERIALS AND METHODS

Rahim Yar Khan District has an area of 11,880 square kilometers and comprises four Tehsils, which are Liaqatpur, Khanpur, Rahim Yar Khan, Sadiqabad with a total population of more than 4.73 million in 2011. The district Rahimyarkhan lies between 27.40' - 29.16' N latitudes and 60.45' - 70.01' E longitudes. The climate of the district is hot and dry in the summer and cold and dry in the winter.

Water samples were collected from different water sources (hand pumps, tube wells, canals and public water supply systems) from cities of Sadiqabad, Rahimyarkhan, Khanpur and Liaqatpur during the period of 2010-11. Water quality determinations of sulphate and chloride contents were carried out in chemistry laboratories of Sadiqabad College of Technology Sadiqabad, and Agriculture Department, Punjab Pakistan. Chloride was measured by silver nitrate titration using a chromate indicator, and a chloride ion-selective electrode. Sulphate ion was precipitated in a hydrochloric acid medium with barium chloride to form $BaSO_4$ crystals of uniform size. Light absorbance of the $BaSO_4$ suspension was then measured by nephelometery using a turbidimeter.

Sulphate concentration was extrapolated with the help of a prepared standard curve (15).

With collaborative assistance received from a local non-governmental organization (SAWACO), a health survey was conducted in areas with high values of chlorides and sulfates. Volunteers assisted in the administration of questionnaires among population in polluted areas in 1st quarter of 2012. Results were analyzed to identify any health concerns related to the elevated levels of chloride and sulfates in source waters available for residents each considered community.

RESULTS

A total of one hundred and fifty one samples were analyzed during the study. This consisted of hand pumps (n=88), tube wells (n=54), surface water (Canals) (n=06) and public water supply system (n=03). Out of the 151 samples analysed, 47% has sulphate levels within guideline limits while 53 percent of the samples had values above the limits. The number of samples with sulphate levels within and above guideline values is presented in Fig. 1. Curiously, as in Table 1, sulphate concentrations of a sample was as high as 7760 mg/L for samples collected from hand pumps. Altogether, 6.7%, 18.5% and 25.2% respectively had sulphate values within the range 250-300mg/L, 300-500mg/L and > 500 mg/L respectively. Out of 151 samples analysed, 77 percent had chloride levels within guideline value (Fig 2). For samples that exceeded the guideline values, chloride concentration was relatively low (23%) (Table 2). However, high chloride levels of up to 3190 mg/L were detected in samples from hand pumps. On the whole, 4.0%, 9.3% and 9.9% respectively had sulphate values within the range 250-300mg/L, 300-500mg/L and > 500 mg/L respectively.

Results from the health survey revealed that prolonged exposure to excessive levels of chlorides and sulphates may be attributable to health effects in the sampled population. In areas where consistently higher than guideline values were observed, residents complained of gastrointestinal tract problems such as diarrhea, nausea, inflammatory bowel disease. Almost fifty five percent among survey reported diarrheal symptoms and consequent dehydration. From an analysis of our survey questionnaires, chloride concentrations in excess of about 250 mg/Litre was associated with detectable taste in water. Consumers can, however, become accustomed to concentrations in excess of 250 mg/Litre. Individuals moving into areas with high Sulphate concentrations from areas with low Sulphate concentrations in drinking water complained about health effects such as gastroenteritis. Although it was not possible to screen out the possibility of gastroenteritis resulting from other sources, for example bacterial infection; tourists, hunters and students not normally resident in Rahimyarkhan were generally more affected. Questionnaire response also revealed that water distribution system in the urban area is either un-adequate or has reached its full development. Physical observation revealed that there is no public water supply system in rural area considered in the study neither was there any water treatment plant. Consequently, most of population resolve to the use of groundwater through electric pumps or hand pumps.

Fig.1: Samples (%) with sulphate levels within (-ve) and above (+ve) guideline values

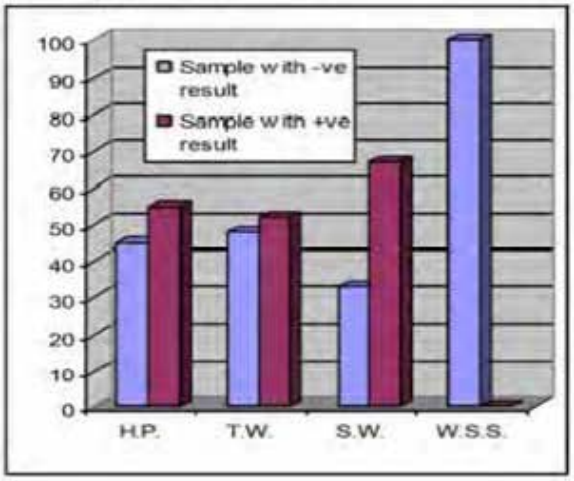

Fig. 2: Samples (%) with chloride levels within (-ve) and above (+ve) guideline values

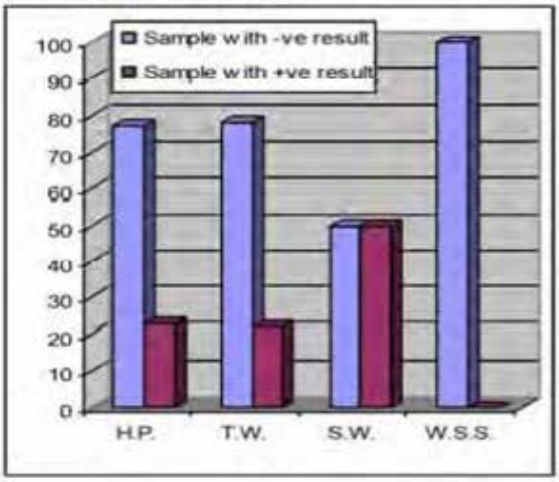

Table 1: Observed sulphate levels of different water samples

Sample source	Sulphate levels within guideline values	Sulphate levels higher than guideline values	Range (Mg/L)
HP	40(45.5%)	48(54.44%)	31.2-7760
TW	26(48.5%)	28(51.85%)	0-1990
SW	02 (33.33%)	04(66.67%)	180-413
WSS	03 (100%)	0	82.3-99.2

Table 2: Observed chloride levels of different water samples

Sample source	Sulphate levels within guideline values	Sulphate levels higher than guideline values	Range (Mg/L)
HP	68(77.27%)	20(22.73%)	14-3190
TW	42(77.78%)	12(22.22%)	18-780
SW	02 (50.00%)	03(50.00%)	35-56
WSS	03(100%)	0	148-405

DISCUSSION

Sulfates occur naturally in drinking water, usually as a combination of sulfur and oxygen. Some minerals present in soil also get dissolved and are ultimately released to groundwater as Sulfates. A number of health concerns regarding sulfate in drinking water have been raised because of reports that diarrhea may be associated with the ingestion of water containing high levels of sulfate. In the current study, high sulfate levels were observed especially in hand-pumps. In most developing countries, major settlements enjoy pipe borne water supply albeit erratic. In the rural communities, bore holes fitted with hand pumps serve as the main source of alternative 'potable' water. In an age where more and more emphases is suggested to be placed on the provision of hand pumps and wells for rural settlements, the results of this study thus gives cause for concern. High sulphate levels in drinking water as observed in the current study may be attributable to relatively shallow depth of wells attached to these pumps and the proximity to resources of pollution from human dwelling and animal yards. One striking observation in support of this assumption was the high sulphate levels from hand pumps on lands close to cattle feed lots and intensive agricultural sites in Punjab where chemical fertilizers were regularly applied.

There may be up to one percent sulfate present in gastric fluids. Normally, the body maintains a homeostasis between absorbed inorganic Sulphate, Sulphate compounds, and renal excretion; membrane transport and regulation contribute to this homeostasis. There have been a number of studies conducted to determine the toxicity of sulphate in humans. Chien et al. presented case reports of diarrhea in three infants exposed to water containing Sulphate (ranging from 630-1,150mg/L)[10]. However, there were other potential causes of the diarrhea in these infants like consuming infant formula with high osmolarity or the presence of microbial pathogens that were not thoroughly addressed by the investigators. Almost fifty five percent among survey reported diarrheal symptoms and consequent dehydration. These are mainly related to sulphate toxicity and due to these above mentioned effects patients having dehydration. Sulfates have a laxative effect that leads to dehydration especially infants are more prone to its effects. But with passage of time, people and young live stocks become acclimated to the sulfate and the symptoms disappear[9].

A survey conducted in North Dakota found a slight increase in the percentage of people (28%) who reported that their drinking water had a laxative effect when the drinking water contained 500 to 1,000 mg/L Sulphate compared to the percentage of people (21%) who reported a laxative effect from drinking water that contained <500 mg/L. Fifty one percent of people who consumed water with 1,000 to 1,500 mg/L reported a laxative effect. Arguably, the generally accepted concern is that which relates to greater risk from the laxative effects of sulfate when vulnerable populations experience an abrupt change from drinking water with low sulfate concentrations to drinking water with high sulfate concentrations. One such potentially sensitive population is infants receiving their first bottles containing tap water, either as water alone or as formula mixed with water. Another group of people who could potentially be adversely affected by water with high Sulphate concentrations are transient populations like tourists, hunters, and other temporary visitors who moves into areas with high Sulphate concentrations in the drinking water from areas with low Sulphate concentrations in drinking water[12].

It is suggested that most people may experience laxative effect when they drank water containing >1000 mg of Sulphate per litre[13,14]. However, like other ones, the current study may not be assertive about a statistically significant association between consumption of water with excessive sulphate levels and clinical syndromes experienced by the surveyed population. The science of sulphate levels in drinking water is itself rocked with inherent questions which still remain answered. Where reported studies suggest that a certain sulfate level would not be likely to cause adverse effects, existing data do not identify the level of sulfate in drinking water that would be unlikely to cause adverse human health effects.

Again with the assumption of acclimatization or adaptation to certain levels of sulphates in drinking water, findings on how long this takes is still yet to be published. Furthermore, in referring to the potential health effects of elevated sulfate levels in drinking water, one is quick to refer to vulnerable populations as being at risk, particularly infants. However, there are no dose-response studies to substantiate this partly because of the difficulty of locating a population of women feeding their infants formula mixed with unfiltered tap water containing high levels of sulfate. Consequently, it appears that there is not enough scientific evidence on which to base a regulation but a mere health advisory in places where drinking water has sulfate levels of >500mg/L, based solely on precautionary principle

Chlorides occur in surface and groundwater as a result of intrusion from both natural and anthropogenic sources, such as run-off containing road de-icing salts, the use of inorganic fertilizers, landfill leachates, septic tank effluents, animal feeds, industrial effluents, irrigation drainage, and seawater intrusion in coastal areas (DNHW, 1978). Available data reveal that the mean chloride concentration in several rivers in the United Kingdom is in the range 11–42mg/litre during 1974–81 (Brooker and Johnson, 1984). Also evidence of a general increase in chloride concentrations in groundwater and drinking-water has been found (WHO, 1978). In developed nations, aquifers prone to seawater intrusion have been found to contain chloride at concentrations ranging from 5 to 460 mg/litre (Phelan, 1987), whereas contaminated wells in developing nations such as the Philippines have been reported to have an average chloride concentration of 141 mg/litre (Morales, 1987). Chloride levels in unpolluted waters are often below 10 mg/litre and sometimes below 1mg/litre (WHO, 1996)

However, high chloride levels of up to 3190 mg/L were detected in samples from hand pumps in our current study. Chloride in surface water and groundwater from both natural and anthropogenic sources, such as extensive use of Potassium fertilizer in which Potassium Chloride is used during production, landfill leachates, septic tank effluent, animal feeds, industrial effluents, and irrigation drainage. High values of Chlorides may also be due to extensive use of Sodium Chloride in production of industrial chemicals such as Caustic Soda, Chlorine, Sodium Chlorite and Sodium hypochlorite. The chloride ion is highly mobile and is transported to nearby watershed and river basins.

Usually, chloride concentrations in excess of about 250 mg/Litre can give rise to detectable taste in water, but the threshold depends upon the associated cations, a typical example being Sodium. The presence of sodium in drinking water is of significant health concerns. Therefore, the US Environmental Protection Agency (EPA) now requires drinking water to be monitored for sodium and public water suppliers are directed to report local health authorities any concentration above 250 mg/L. Chlorides in drinking water usually create taste and odor problems at concentrations exceeding 250 mg/L. In New Hampshire from 1983 to 2003 the NHDOT replaced more than 424 private wells contaminated by road salt at a cost of $3.2 million. Several public water supply wells have also been abandoned due to contamination[1,2]. Although excessive intake of drinking-water containing sodium chloride at concentration above 250mg/L has been reported to produce hypertension[3], this effect is believed to be related to the sodium ion concentration. Consumers may become accustomed to concentrations in excess of 250mg/L.

In humans, 88% of chloride is extracellular and contributes to the osmotic activity of body fluids. A normal adult human body contains approximately 81.7g chloride. On the basis of a total obligatory loss of chloride of approximately 530mg/day, a dietary intake for adults of 9mg of chloride per kg of body weight has been recommended for children up to 18 years of age, a daily dietary intake of 45 mg of chloride should be sufficient[4]. A dose of 1 g of sodium chloride per kg of bodyweight was reported to have been lethal in a 9 week old child[7]. Chloride toxicity has not been observed in humans except in the special case of impaired sodium chloride metabolism, e.g. in congestive heart failure[8]. Healthy individuals can tolerate the intake of large quantities of chloride provided that associated intake of fresh water. Little is known about the effect of prolonged intake of large amounts of chloride in the diet. As in experimental animals, hypertension associated with sodium chloride intake appears to be related to the sodium rather than the chloride ion[4]. However, adverse effects related to high chloride concentration are increased number of polymorhonuclear leukocyte and disturbed blood cell counts in full blood count analysis.

CONCLUSION

On a conclusive note, the current study revealed that higher than guideline levels of consumers of sulfates and chlorides in available drinking water in Rahimyarkhan. Consumers can however, become accustomed to concentrations in excess of 250mg/Litre. Individuals moving into areas with high Sulphate concentrations from areas with low Sulphate concentrations in drinking water complained about health effects such as gastroenteritis. Although

it was not possible to screen out the possibility of gastroenteritis resulting from other sources, for example bacterial infection; tourists, hunters and students not normally resident in Rahim Yar Khan were generally more affected. It is thus suggested that efforts be made to provide at least one laboratory in each city working in collaboration with health officials in district hospitals.

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Assessment of Drinking Water Quality and its Impact on Residents Health in Bahawalpur City

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Assessment of Drinking Water Quality and its Impact on Residents Health in Bahawalpur City

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Abstract

Present study aimed to assess and compare the ground water quality with WHO standards and its related diseases in Bahawalpur city. Three sample areas Satellite town, Shahdrah and Islamic colony were chosen and two water samples have been taken from each area. Data collection based on the questionnaire and laboratory analysis of water samples. Certain physical and chemical parameters like total dissolved solids (TDS), electrical conductivity (EC), pH, hardness, alkalinity (Alk) etc. was examined to find out quality of ground water. Findings reveal that groundwater quality in Bahawalpur is deteriorating. Situation was much worse in Islamic colony where 48%, 55% and 41% residents have diluted, brackish and water with slight smell respectively. Laboratory analysis of water parameters also disclosed the fact of significant contamination in ground water. EC, TDS, hardness, pH etc. were considerably high from WHO permissible limits. Such poor quality of water reasoned severe waterborne diseases like diarrhea, cholera etc. In Islamic colony, about 36% residents have been facing serious diseases. To save local residents study suggests; regular monitoring of water quality should be practiced; more water filtration plants should be installed by local govt. to provide safe drinking water etc.

Key Words: Water quality parameters, Bahawalpur city, WHO standards, Waterborne diseases.

1. Introduction

Water is most vital liquid for maintaining the life on the earth. About 97% water is exists in oceans that is not suitable for drinking and only 3% is fresh water wherein 2.97% is comprised by glaciers and ice caps and remaining little portion of 0.3% is available as a surface and ground water for human use (Miller, 1997). Safe drinking water is a basic need for good health and it is also a basic right of humans. Fresh water is already a limiting resource in many parts of the world. In the next century, it will become even more limiting due to increased population, urbanization and climate change (Jackson et al., 2001). Unfortunately, in developing countries (i.e. Pakistan) the drinking quality of water is continuously being contaminated and hazardous for human use due to high growth of population, expansion in industries, throwing away of waste water and chemical effluents into canals and other water sources. According to recent estimates, the quantity of available water in developing regions of South Asia, Middle East and Africa is decreasing sharply while quality of water is deteriorating rapidly due to fast urbanization, deforestation, land degradation etc.

Therefore, many cities in Asia facing increase in organic and nutrient material in drinking water due to the discharge of untreated domestic and industrial waste water into these resources (Annachhatre, 2006). Situation is more aggravated in South Asia, where more than 0.5 million deaths of infants happened per year with additional health threats due to poor water quality and bad sanitation. For instance, in West Bengal (India) and some areas of Bangladesh, groundwater is contaminated with arsenic at levels as much as 70 times higher than the national drinking water standard of 0.05mg/l (UNEP, 1999). Worldwide, more people are dying from poor quality of water per year than from all forms of violence including war and it is estimated that about 26% of all deaths are outcome from contagious diseases caused by pathogenic bacteria (WHO, 2002; UNEP GEMS/ Water Programme, 2008). Lack of access to safe and clean water created waterborne diseases excessively by the residents of slums in India (Lal et al., 1996). Diarrhea, a waterborne disease is reported as the leading cause of death in infants and children in the country while every fifth citizen suffers from illness and disease caused by the polluted water (Khalown et al., 2006).

Although, the issue of drinking water quality has a rising concern in developed world but little debated in developing countries. Pakistan is ranked a water stress country with the availability of about 1,200 m^3 per capita that is rapidly declining. Moreover, the production of domestic and industrial wastewater is about 4 million acre feet (MAF) per year in Pakistan that is discharging directly into water bodies except a little amount of 3% that is brought under treatment. About 70 percent of the people in Pakistan rely on ground water for their household uses (Malik et al., 2010). Due to contamination and micro-biological impurities majority of the Pakistani citizens have inadequate access to safe drinking water with poor water supply lines and faulty drainage system (Farrukh et al., 2004). Resultantly, this caused many diseases among people (Tanwir et al., 2003). Particularly, biological diseases caused high child mortality rate of 128/ 1000 per year (UNICEF and Meta-Meta, 2009). It is estimated that, in Pakistan, 30% of all diseases and 40% of all deaths are caused by bad quality of water (Global Water Partnership, 2000). Therefore, various studies have been conducted to examine and evaluate the quality of drinking water in Pakistan. For instance, a study conducted by Pakistan Council of Research in Water Resources (PCRWR) in all four provinces of Pakistan conclude that majority of the taken samples of water found insecure for drinking purposes. High arsenic found in major industrial cities of Punjab due to industrial and chemical waste discharge, high iron concentration is found in Khyber Pakhtunkhwa (KPK) while high turbidity level is observed in Sindh (Soomro et al., 2011). In Islamabad, to determine microbiological quality, water and food items were collected from different schools and colleges. Results show that out of 30 water and 10 food samples, 20 water samples and 7 food samples were highly toxic and not safe for human use (Saddozai et al., 2009).

Similarly, during a study conducted in Pakistan's biggest city Karachi, out of hundreds of samples of water no one was found safe for drinking purposes (Ihsanullah, 2009). Another study conducted in district Kohat (KPK) analyzed 18 samples collected from different sites to test the physiochemical parameters i.e. pH, TDS, Alkalinity, Electrical conductivity etc. Results indicate that most of the samples were contaminated (Ahmad et al., 2012). Similarly a study conducted by Khan et al. (2012) in Kohat (KPK) indicates most of the samples taken from wells, tube wells, hand pumps, streams and tanks were contaminated particularly in Shakardrara, Lachi and Ara Khail storage and wells were highly polluted whereas tube well water found safe for human use. It is summarize in a study conducted in district Charsadda (KPK) that drinking water of the study areas was contaminated with SO_4, NO_3 and heavy metals such as Pb, Cd, Fe, Ni, Zn and coliform bacteria.

Therefore, majority of the inhabitants of study area have been facing various health issues. Improper disposal of solid waste, sewage water, and too much use of fertilizers were the main reasons of water contamination (Khan et al., 2012). In a study to determine the effects of polluted water used for irrigation on ground water quality and causing health problems in Jamber, district Qasur (Pakistan) results indicate that use of polluted water enhance the value of conductivity, total dissolved solids (TDS) and sodium absorption ratio etc. in ground water and exceeds the national standards (Ashraf et al., 2010). It is proved that there is a keen relationship between people income and literacy of mother to water quality and health issue. More literate mothers and high income groups have the ability to prevent waterborne diseases to their family (Kausar et al., 2009). A study to analyze physiochemical parameters of water before and after monsoon period in southern Lahore shows that before monsoon the contamination of water ranges from 50-65% that risen after monsoon and reach 75%. This is possibly because of leaking of water main and sewers main found close to each other (Haydar et al., 2009). Therefore, it is clear fact that a broad range of physiochemical parameters of drinking water in Pakistan are not to meet the standards for drinking water set by WHO and Pakistan (Malana et al., 2011; Farid et al., 2012).

Polluted drinking water causes many diseases as diarrhea, vomiting, gastroenteritis, dysentery, kidney problems etc. found in Thatta, Badin and Thar districts of southern Sindh, Pakistan (Memon et al., 2011). The ground water in Bahawalpur city is generally saline and brackish and not suitable for drinking purposes apart from areas lies close to canals and river Sutlej that is the main water body of the region. Majority of the inhabitants have complaints to Tehsil Municipal Administration (TMA) Bahawalpur city against the quality of water that was found colored and sediment with bacterial contamination. In addition, absence of the effective monitoring of ground water quality on regular basis being made the situation more serious. The planning and management for better water quality supply is not much efficient in Bahawalpur city (Anwar and Bureste, 2011). As a study conducted in Bahawalpur city by PCRWR indicates after treating 25 samples data, it is estimated that 24% samples were polluted with E.Coliform bactaria; 52% samples were found contaminated with Coliform bacterium: 76% possessed excess Arsenic (As) of more than 50 ppb (which is 5 times above than WHO set limits); 32% possessed excess level of Turbidity and Satellite town has extreme levels of Turbidity may be due to damaged strainer pipes; 60% samples have higher concentration of Calcium (Ca) (Govt. of Punjab & World Bank, 2006). About 75% water samples were influence by coliform bacteria in Bahawalpur city (Mehmood et al., 2012). Hence, the main objective of the study is to assess the ground water quality and its causing diseases in Bahawalpur city.

2. Study Area and Data Collection

Bahawalpur city is located in semi-arid region with dry and hot climate and less precipitation. It is lies between latitude 29°-22' and longitude 71°-37' approximately. In recent years, rapidly increasing population and economic and educational developments of the city brought a huge stress on natural resources including ground water, land use, farmland etc. Specifically, the quality of ground water is regularly being reported contaminated in many areas of the city by PCRWR etc. and highly threaten the health of the local inhabitants. Majority of the people have used electric pumps to extract water while few people used hand pumps.

In an order to assess the ground water quality and its related diseases, three sample areas were chosen namely Islamic colony, Satellite town and Shahdrah (Figure 1). Islamic colony is a typical slum area where majority of the residents have lower standard of life and poor housing conditions. Satellite town is a well planned scheme by government where middle and high class people are living and having all modern facilities. Standard of living is reasonably high to Islamic colony residents. In Shahdrah mix standard of living exists. People engaged in shop keeping, dairying and govt. jobs etc. Two water samples have been taken from each study area and got tested in PCRWR regional lab to find out the quality status of selected physical and chemical parameters of the water. The samples were collected from electric pumps the most common source of drinking water in Bahawalpur city. After it, the results of these parameters were compared and discussed with WHO standards. In addition, to discover the overall physical quality of water and main waterborne diseases in study areas, a field survey was conducted and data was gathered through questionnaire using random cluster sampling. Results were portrayed in graphs prepared in MS Excel. Maps of study areas were made using ArcView 3.2a software.

3. Water Quality of the Study Areas

Water quality is the physical, chemical, and biological characteristics of water in association to the set of standards. These parameters directly related to the safety of the drinking water to human use. Water quality parameters provide important information about the health of a water body. These parameters are used to find out the quality of water for drinking purpose. During field survey the following physical parameters were also investigated using questionnaire;

3.1 Color of the water

Water usually think a colorless liquid however it possesses some level of color. Colors in ground waters can originate from decomposition of organic matter and leakage through sewage. Figure 2 clears that in Shahdrah, 86% residents have clear water and very small numbers of residents have diluted and faint. Over all water quality was satisfactory in this area may be because of proximity to river Sutlej as compare to other areas. In Satellite town, 61% residents have clear water while the residents having faint and diluted water were less in number. The main reason for the change in water color was the over exploitation of water and lowing water table with passing time. In Islamic colony, 48% residents have clear water while 50% residents have diluted water. It was possibly due to suspended minerals and dead organic matter.

3.2 Taste of the Water

Various odors and tastes may be present in water. Taste is generally classified in three groups of sweet, medium and brackish. Taste in water can be traced to a number of factors including decaying organic matter, living organisms, iron, mixing industrial waste etc.

Figure 3 portrays that in Shahdrah, water condition is much better as compared to other areas. About 79% residents have sweet ground water and a small numbers have medium (16%) and brackish water (5%). Water is naturally of good quality and has sweet taste except some cases. Medium taste is because of the naturally occurring salts contents. In Satellite town, about 48% residents have accessed to sweet water while 32% and 20% residents having access to medium and brackish water respectively. Generally, quality of water is good except some patches. Major sources of changing ground water taste were observed as sewer leakage, over pumping of ground water, residential waste disposal etc. In Islamic colony water is brackish and bears a typical odor. About 55% residents have brackish water while 41% residents have accessed to sweet water. Bad taste and odor has natural origin. The poor residents of this slum area were forced to use toxic water because they were unable to afford mineral water etc.

3.3 Smell/ Odor of the Water

Smell in water in the present study was classified into three categories of slight smell, no smell, and fast smell. In Satellite town and Shahdrah water has no smell except few patches while in Islamic colony slight and fast smells were noted in water. It is analyzed that 70% residents in Satellite town have accessed to water without any smell while 20% residents have water with a slight smell (Figure 4). Smell in water may be due to the sewage leakage. In Shahdrah 84% residents have water without any smell while 14% have the problem of slight smell. In Islamic colony, 42% residents have water with no smell while a large number of residents (41%) have water with slight smell. The level of fast smell in this area is also higher as compare to other study areas.

4. Analysis of Physical and Chemical Parameters of Water

Both physical and chemical parameters of collected water samples have been tested from the regional laboratory of Pakistan Council of Research in Water Resources (PCRWR) in Bahawalpur city (Table 1.1). Important physical parameters that were tested included Total dissolved solids (TDS), Electrical conductivity (EC) and pH of water. While, important chemical parameters have been tested were Bicarbonates, chloride, sulfate, magnesium, calcium, hardness, sodium, potassium, alkalinity and nitrate. The results were then matched and discussed with WHO standards.

4.1 Total Dissolved Solids (TDS)

Water has the ability to dissolve a wide range of inorganic and some organic minerals or salts such as potassium, calcium, sodium, bicarbonates, chlorides, magnesium, sulfates etc. These minerals produced un-wanted taste and diluted color in appearance of water. There is no agreement have been developed on negative or positive effects of water that exceeds the WHO standard limit of 1,000 ppm. Total dissolved solids (TDS) in drinking water is originates many ways from sewage to urban industrial wastewater etc. Therefore, TDS test is considered a sign to determine the general quality of the water. Figure 5 clears that in Islamic colony these values were ranges from 290-595 ppm. In Satellite town TDS range is 406-694 ppm and in Shahdrah these values range from 401-429 ppm. Hence, these ranges were acceptable and concentration of TDS is not harmful.

4.2 Electrical Conductivity (EC)

Pure water is not a good conductor of electric current rather a good insulator. Increase in ions concentration enhances the electrical conductivity of water. Generally, the amount of dissolved solids in water determines the electrical conductivity. Electrical conductivity (EC) is actually measures the ionic process of a solution that enables it to transmit current.

According to WHO standards EC value should not exceeded 400 µS/cm. In study areas, EC value in Islamic colony was 290-595 µS/cm, 406-694 µS/cm in Satellite town and 401-429 µS/cm in Shahdrah (Figure 6). These results clearly indicate that water in study areas was considerably ionized and has the higher level of ionic concentration activity due to excessive dissolve solids. Thus, it is a fine conductor of electric current.

4.3 pH of water

The pH of pure water is refers to the measure of hydrogen ions concentration in water. It ranges from 0 to 14. In general, water with a pH of 7 is considered neutral while lower of it referred acidic and a pH greater than 7 known as basic. Normally, water pH ranges from 6 to 8.5. It is noticed that water with low pH is tend to be toxic and with high degree of pH it is turned into bitter taste. According to WHO standards pH of water should be 6.5 to 8.5. In Islamic colony, it is ranges from 7.2-7.35; in Satellite town pH was 7.4-7.5 and in Shahdrah pH values observed at 7.4-7.35 (Figure 7). Hence, in study areas the pH values were not exceeded the standard limit however these were falling in basic or alkaline range.

4.4 Bicarbonates (HCO_3)

Bicarbonates concentration in water relies on pH and is usually less than 500 mg/l in groundwater. It is the standard alkaline constituent found almost all surface and ground water bodies and therefore affects alkalinity and hardness of water. The weathering of rocks adds bicarbonate content in water. Mostly bicarbonates are soluble in water i.e. bicarbonate of magnesium and calcium etc. is the main causes of hardness of water. The hard water is not suitable for drinking purpose and causes the gastro diseases. The value of bicarbonates is not recommended by WHO however it is considered to be not more than 500 mg/l. Current study revealed the concentration of bicarbonates ranges from 225-320 mg/l in Islamic colony, 170-175 mg/l in Satellite town and 160 to 180 mg/l in Shahdrah and hence these were within the standard values (Figure 8).

4.5 Chloride (Cl)

Chloride is mainly obtained from the dissolution of salts of hydrochloric acid as table salt (NaCl), $NaCO_2$ and added through industrial waste, sewage, sea water etc. Surface water bodies often have low concentration of chlorides as compare to ground water. It has key importance for metabolism activity in human body and other main physiological processes. High chloride concentration damage metallic pipes and structure as well as harms growing plants. According to WHO standards concentration of chloride should not exceed 250 mg/l. In study areas the chloride value ranges from 16-66 mg/l in Islamic colony, 54-78 mg/l in Satellite town and from 51-88 mg/l in Shahdrah. Thus, all the samples have lower concentration of chloride (Figure 9).

4.6 Sulfate (SO_4)

Sulfate mainly derived from the dissolution of salts of sulfuric acid and abundantly found in almost all water bodies. High concentration of sulfate may be due to oxidation of pyrite and mine drainage etc. Sulfate concentration in natural water ranges from a few to a several hundred mg per liter but no major negative impact of sulfate on human health is reported. The WHO has established 250 mg/l as the highest desirable limit of sulfate in drinking water. In study areas, concentration of sulfate ranges from 33-106 mg/l in Islamic colony, 79-310 mg/l in Satellite town and 72-86 mg/l in Shahdrah (Figure 10). The results exhibit that concentration of sulfate in Satellite town was higher from standard limit and may harmful for human health.

4.7 Magnesium (Mg)

Magnesium is the 8th most abundant element on earth crust and natural constituent of water. It is an essential for proper functioning of living organisms and found in minerals like dolomite, magnesite etc. Human body contains about 25g of magnesium (60% in bones and 40% in muscles and tissues). According to WHO standards the permissible range of magnesium in water should be 150 mg/l. In study areas magnesium was ranges from 6-36 mg/l in Islamic colony, 36-56 mg/l in Satellite town and 58-84 mg/l in Shahdrah (Figure 11). The quantity of magnesium is significantly low in Islamic colony as compare to Satellite town and Shahdrah. Such a low concentration somewhat effects health of residents as it is essential for human body.

4.8 Calcium (Ca)

Calcium is 5th most abundant element on the earth crust and is very important for human cell physiology and bones. About 95% calcium in human body stored in bones and teeth. The high deficiency of calcium in humans may caused rickets, poor blood clotting, bones fracture etc. and the exceeding limit of calcium produced cardiovascular diseases. According to WHO (1996) standards its permissible range in drinking water is 75 mg/l whereas PSQCA (2002) established the limit of 200 mg/l. However, an adult requires 1,000 mg/ day to work properly. Despite others, the standards set by WHO were kept in consideration.

In study areas, results show that the concentration of calcium ranges from 26-40 mg/l in Islamic colony, 61-84 mg/l in Satellite town and 18-29 mg/l in Shahdrah (Figure 12). Calcium quantity in Satellite town was exceeded the limit by WHO and may harmful for local residents.

4.9 Hardness

Hard water is characterized with high mineral contents that are usually not harmful for humans. It is often measured as calcium carbonate ($CaCO_3$) because it consist mainly calcium and carbonates the most dissolved ions in hard water. According to World Health Organization (WHO) hardness of water should be 500 mg/l. In study areas, hardness ranges from 195-330 mg/l in Islamic colony, 190-310 mg/l in Satellite town and from 265-285 mg/l in Shahdrah (Figure 13). These results clear, that hardness of water is according to the WHO standards and it is not harmful for local inhabitants.

4.10 Sodium (Na)

Sodium is a silver white metallic element and found in less quantity in water. Proper quantity of sodium in human body prevents many fatal diseases like kidney damages, hypertension, headache etc. In most of the countries, majority of water supply bears less than 20 mg/l while in some countries the sodium quantity in water exceeded from 250 mg/l (WHO, 1984). According to WHO standards, concentration of sodium in drinking water is 200 mg/l. In study areas, finding shows that sodium concentration ranges from 36-93 mg/l in Islamic colony, 61-140 mg/l in Satellite town and 28-33 mg/l in Shahdrah (Figure 14). Sodium quantity in Shahdrah is quietly low which could be harmful for the health of local inhabitants.

4.11 Potassium (k)

Potassium is silver white alkali which is highly reactive with water. Potassium is necessary for living organism functioning hence found in all human and animal tissues particularly in plants cells. The total potassium amount in human body lies between 110 to 140 g. It is vital for human body functions like heart protection, regulation of blood pressure, protein dissolution, muscle contraction, nerve stimulus etc. Potassium is deficient in rare but may led to depression, muscle weakness, heart rhythm disorder etc. According to WHO standards the permissible limit of potassium is 12 mg/l. Results show that the concentration of potassium in study areas ranges from 5.2-7.5 mg/l in Islamic colony, 5.4-7.9 mg/l in Satellite town and 3.2-3.6 mg/l in Shahdrah (Figure 15). These results were meet the WHO standards and may become preventive from diseases associated from potassium extreme deficiency.

4.12 Alkalinity

Alkalinity is the presence of one or more ions in water including hydroxides, carbonates and bicarbonates. It can be defined as the capacity to neutralize acid. Moderate concentration of alkalinity is desirable in most water supplies to stable the corrosive effects of acidity. However, excessive quantities may cause a number of problems. The WHO standards tell the alkalinity only in terms of total dissolved solids (TDS) of 500 mg/l. In study areas, results show that alkalinity ranges from 181-289 mg/l in Islamic colony, 171-188 mg/l in Satellite town and 277-211 mg/l in Shahdrah (Figure 16). Thus, these values were under the permissible limit of WHO standards and may not caused health related problems.

4.13 Nitrate (NO_3)

Nitrate one of the most important diseases causing parameters of water quality particularly blue baby syndrome in infants. The sources of nitrate are nitrogen cycle, industrial waste, nitrogenous fertilizers etc. The WHO allows maximum permissible limit of nitrate in drinking water is 10 mg/l. In study areas, results clear that the concentration of nitrate ranges from 4.5-6.4 mg/l in Islamic colony, 3.4-3.5 mg/l in Satellite town and 3.2-3.6 mg/l in Shahdrah (Figure 17). These results indicate that the quantity of nitrate in study sites is acceptable instead Islamic colony where the range of nitrate is exceeding in water and posing threat on the health of inhabitants.

5. Diseases caused by Poor Water Quality

Unfortunately, the intensity of waterborne diseases in under developing countries is very high due to polluted drinking water and poor hygienic conditions. Resultantly, the rate of casualties particularly in infants is alarming. It is estimated that in Pakistan, about 230,000 infants (less than five year old) have been died each year due to waterborne diseases (DigiTex, 2013). The treatment facilities of water is almost absent in rural and suburban areas and water is being contaminated through sewage, fertilizers use, decayed and leached organic matter etc.

A wide variety of fatal diseases are associated with poor water quality i.e. diarrhea, cholera, typhoid etc. In study areas, many of these diseases were being occurred by the use of infected ground water.

Table 2 and Figure 18 have proved that in Islamic colony 16.1% residents were suffered from cholera, 7.2% in diarrhea, 6.3% in typhoid, 4.4% in jaundice and 2% people in kidney stone disease. This is mainly caused by the use of contaminated water and bad sanitation condition. In Satellite town, 12.6% inhabitants were suffered in diarrhea and little portion of inhabitants suffered in kidney stone, typhoid, cholera and jaundice. This is because of the better ground water quality and healthy life style of the inhabitants of Satellite town. In Shahdrah, 15.6% residents were suffered in diarrhea, 3.8% in typhoid, 1.6% in kidney stone and 1.1% inhabitants were in cholera. It is analyzed that in Islamic colony 36.0% residents were suffered from water born diseases because they were being used to bad quality water as they cannot afford bottled and filtered water while 64.0% residents have no water caused disease. In Satellite town 81.9% residents have no water born disease and less number of people (18.1%) was suffered from water caused diseases because people can afford filtered and bottled water. In Shahdrah, 77.9% residents have no water related disease because the quality of ground water is good as compare to other study areas. Whereas, remaining 22.1% have been face various waterborne diseases.

6. Conclusion

Groundwater quality in Bahawalpur is deteriorating like in other main cities of Pakistan. The situation is much aggravated in Islamic colony where ground water quality was highly toxic. Survey results depict that in Islamic colony 48% residents have diluted water, 55% residents have brackish water and 41% residents have water with slight smell. In Satellite town, 61% residents have clear water, 48% residents have access to sweet water and 70% residents have access to water without any smell. As compare to these, situation of ground water quality is much better in Shahdrah where 79% residents have sweet water and 84% have found no smell in water. The laboratory analysis of physical and chemical parameters of collected water samples disclosed the fact of significant contamination in ground water. The findings of these parameters either were exceed the permissible values established by WHO or going below the average limits. For instance, among physical parameters, Electrical conductivity (EC) of water samples was very high from permissible limit of 400 µS/cm. Total dissolved solids (TDS) and Hardness of ground water in Islamic colony and Satellite were also increasing and caused harmful diseases. Similarly, the pH values of water samples were above the neutral (> 7) limit and falls in basic (alkaline) range. The values of sulfate (SO_4) and calcium (Ca) in Satellite town were 310 mg/l and 84 mg/l which were above the permissible limits of 250 mg/l and 75 mg/l respectively causing health related problems.

In Islamic colony, chloride (Cl) recorded 16-66 mg/l which is quite below than WHO standard of 250 mg/l. Sodium quantity in Shahdrah was 28-33 mg/l which was also quietly lower from WHO standard limit of 200 mg/l and could be harmful for the health of local inhabitants. Other parameters also reflect significant variations to WHO standards. Due to this poor quality of water, the waterborne diseases like diarrhea, cholera, typhoid etc. were common in study areas particularly in Islamic colony about 36% residents have been facing serious diseases. While, the severity of waterborne diseases among the residents of Satellite town (18.1%) and Shahdrah (22.1%) was proportionally less as compare to the Islamic colony. Therefore, in order to rescue precious human lives from water related diseases current study suggests; regular monitoring of ground water quality should be practiced; District government should installed more water filtration plants to provide safe drinking water; Sewer drains should kept away from water supply drains to avoid waste water leaching in ground water; Sanitary conditions should be improved on urgent basis; The awareness campaign of waterborne diseases and importance of safe water for human health should be commenced by TMA etc.

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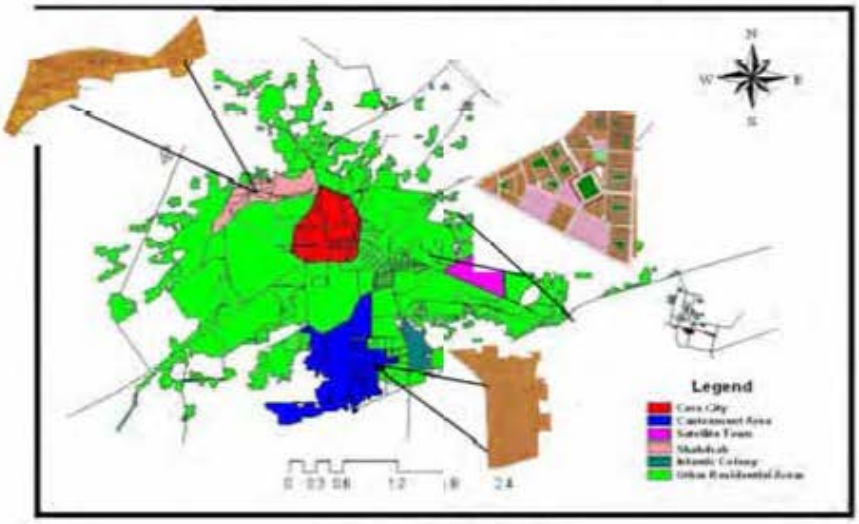
Table 1: Laboratory Analysis of Physical and Chemical Parameters of Study Areas and WHO Standards

Sample	Location	Parameters and Permissible Limit set by WHO												
		TDS (1000 ppm)	EC (400 µS/cm)	pH (6.5-8.5)	HCO_3 (500 mg/l)	Cl (250 mg/l)	SO_4 (250 mg/l)	Mg (150 mg/l)	Ca (75 mg/l)	Hardness (500 mg/l)	Na (200 mg/l)	K (12 mg/l)	Alk (500 mg/l)	NO_3 (10 mg/l)
1	Islamic Colony	290	467	7.2	225	16	33	36	26	195	36	7.5	181	4.5
2	Islamic Colony	595	930	7.3	320	66	106	66	40	330	93	5.2	289	6.4
3	Satellite Town	406	635	7.4	170	54	79	36	84	190	61	5.4	171	3.4
4	Satellite Town	694	1085	7.5	175	78	310	56	61	310	140	7.9	188	3.5
5	Shahdrah	401	627	7.4	180	51	72	58	29	265	33	5.5	277	3.6
6	Shahdrah	429	670	7.3	160	88	86	84	18	285	28	5.2	211	3.2

Source: Laboratory Analysis of Water Samples (2013)

Figure 1: Location of Study Areas in Bahawalpur City



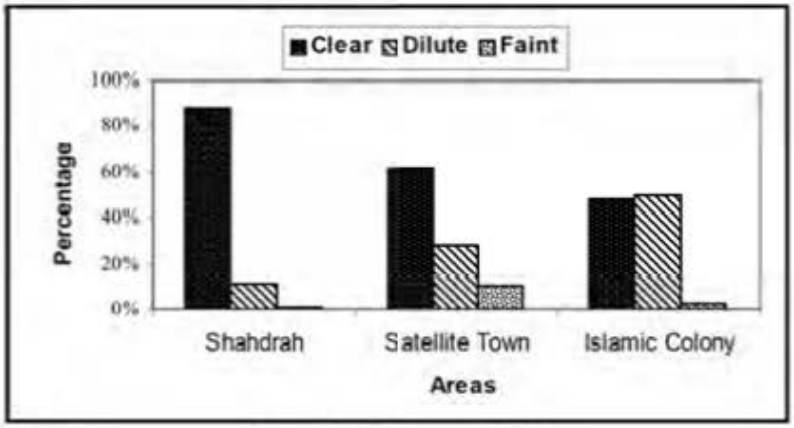
Source: Author (2013)

Table 2: Waterborne Diseases in Study Areas

Types of Diseases	Islamic Colony	Satellite Town	Shahdrah
Diarrhea	7.2%	12.4%	15.6%
Jaundice	4.4%	0.9%	0.0%
Typhoid	6.3%	1.6%	3.8%
Cholera	16.1%	0.9%	1.1%
Kidney stone	2.0%	2.3%	1.6%
No disease	64.0%	81.9%	77.9%
Total	100%	100%	100%

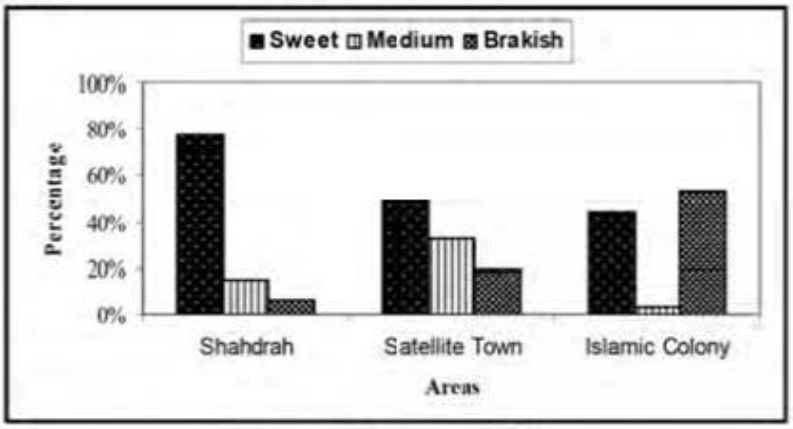
Source: Field Survey (2013)

Figure 2: Color of the water



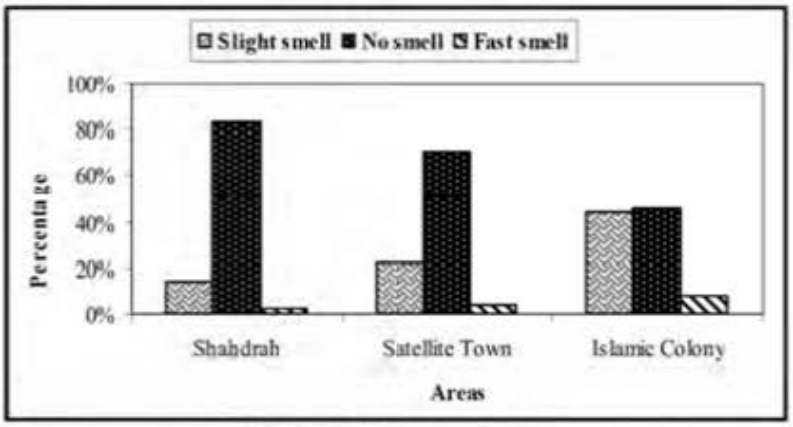
Source: Field Survey (2013)

Figure 3: Taste of water



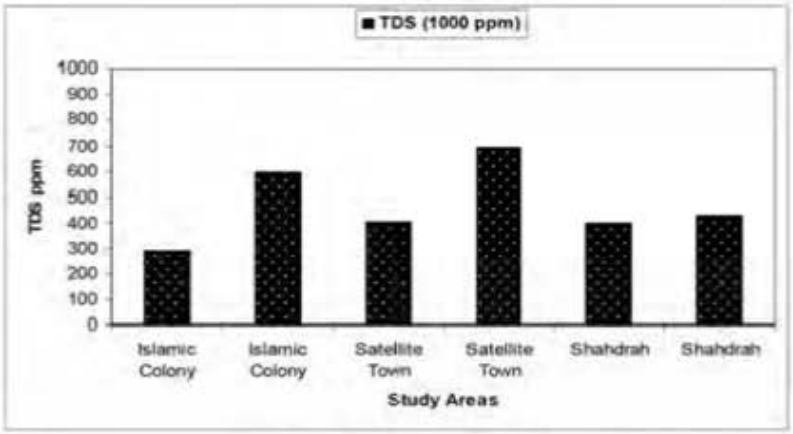
Source: Field Survey (2013)

Figure 4: Smell of water



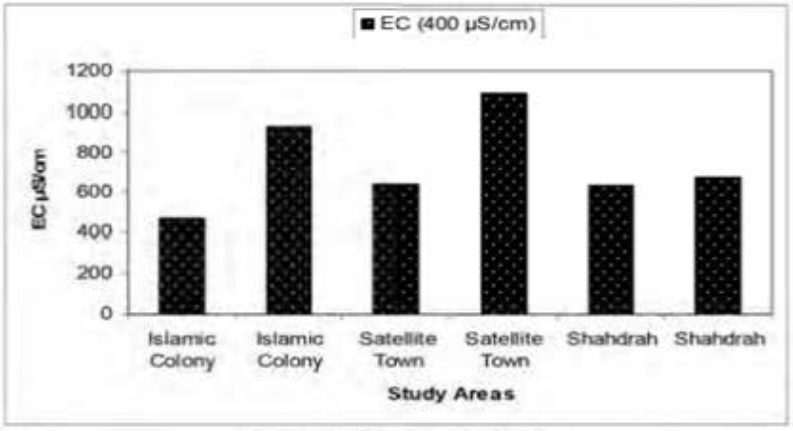
Source: Field Survey (2013)

Figure 5: Values of Total Dissolved Solids (TDS) in Study Areas



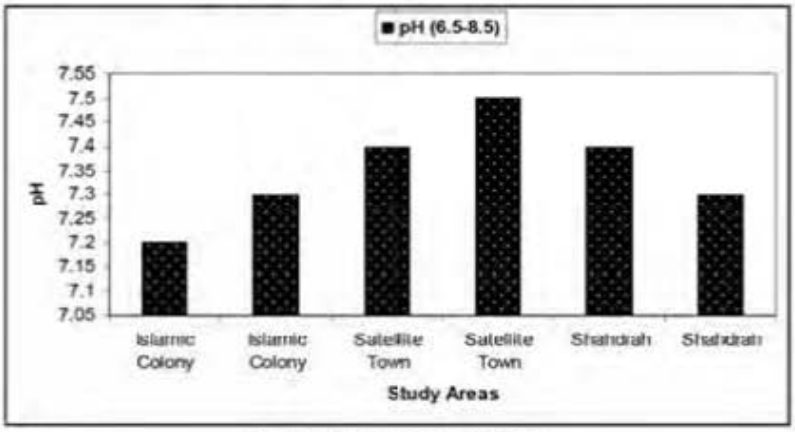
Source: Laboratory Analysis

Figure 6: Values of Electrical Conductivity (EC) in Study Areas



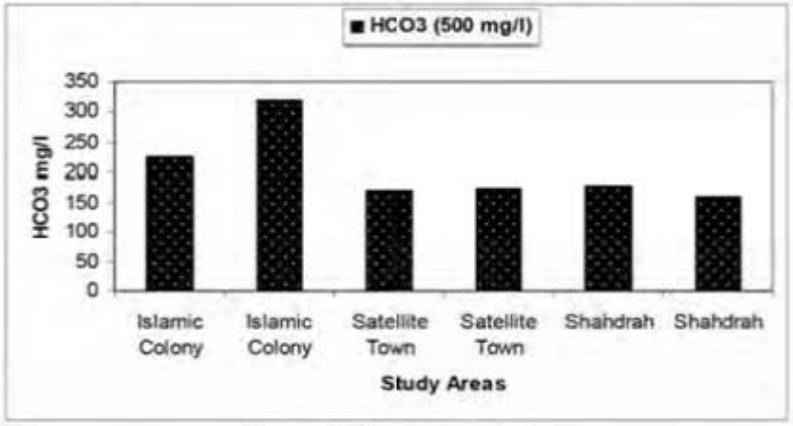
Source: Laboratory Analysis

Figure 7: Values of pH in Study Areas



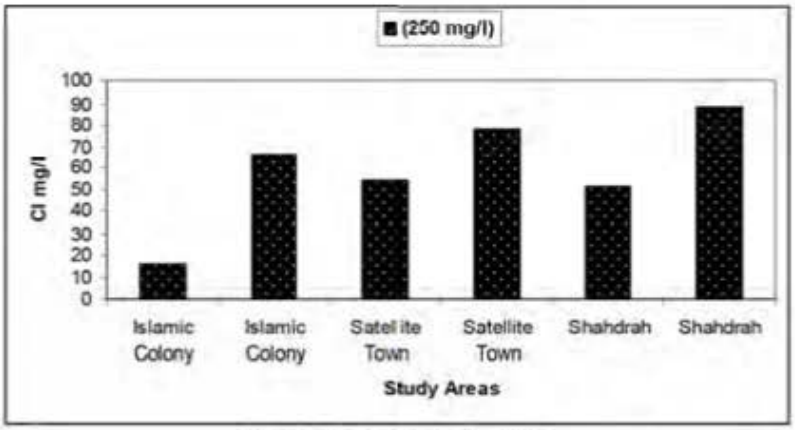
Source: Laboratory Analysis

Figure 8: Values of Bicarbonates (HCO_3) in Study Areas



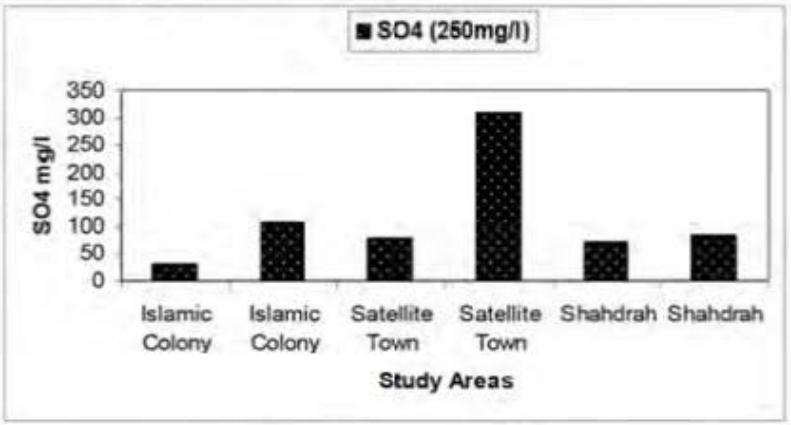
Source: Laboratory Analysis

Figure 9: Values of Chloride (Cl) in Study Areas



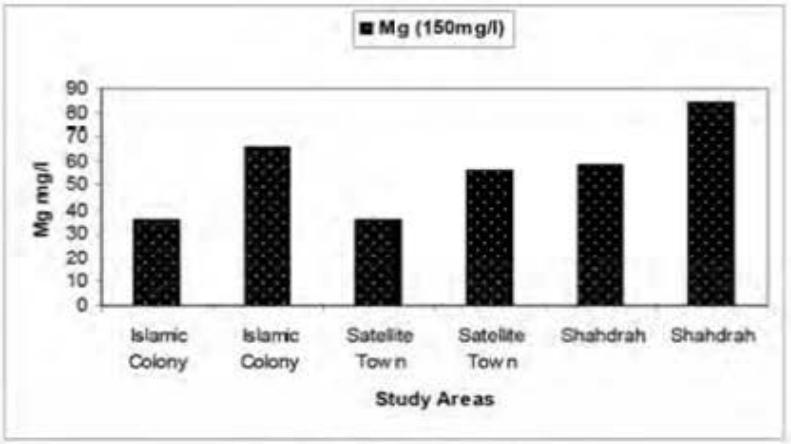
Source: Laboratory Analysis

Figure 10: Values of Sulfate (SO_4) in Study Areas



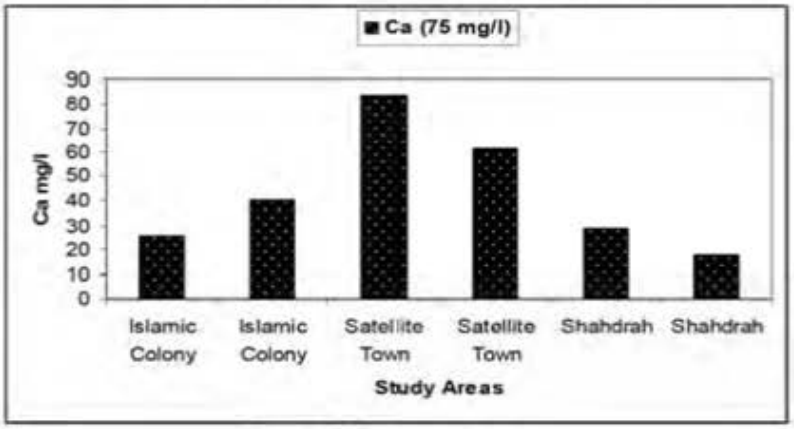
Source: Laboratory Analysis

Figure 11: Values of Magnesium (Mg) in Study Areas



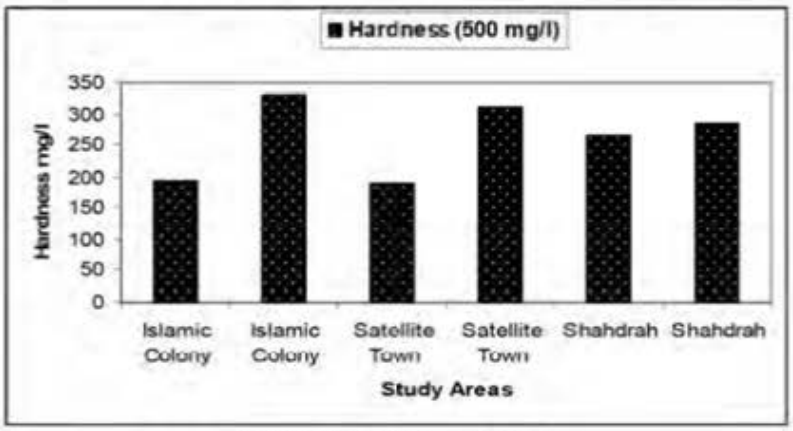
Source: Laboratory Analysis

Figure 12: Values of Calcium (Ca) in Study Areas



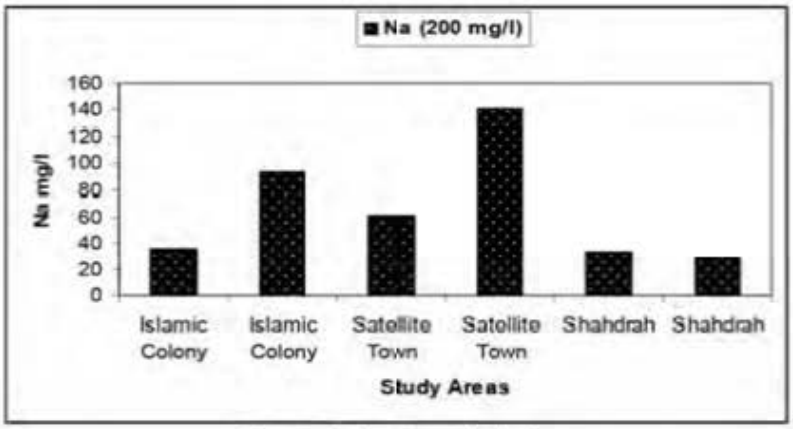
Source: Laboratory Analysis

Figure 13: Values of Hardness in Study Areas



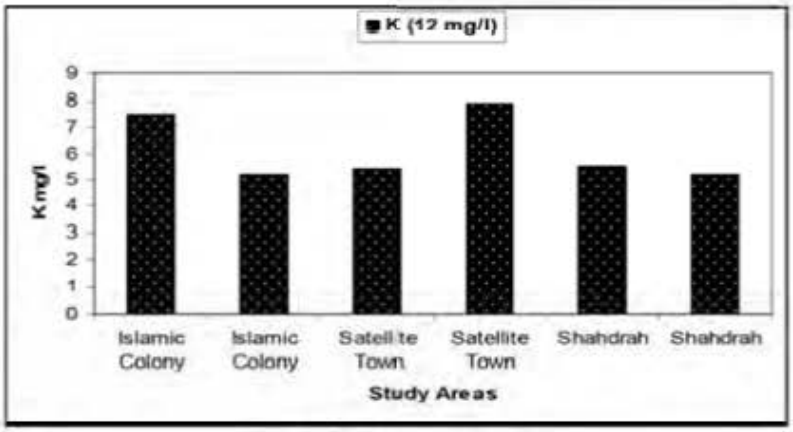
Source: Laboratory Analysis

Figure 14: Values of Sodium (Na) in Study Areas



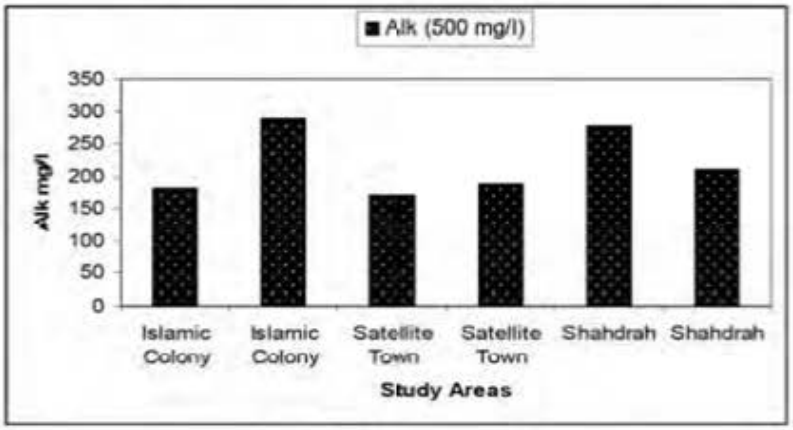
Source: Laboratory Analysis

Figure 15: Values of Potassium (K) in Study Areas



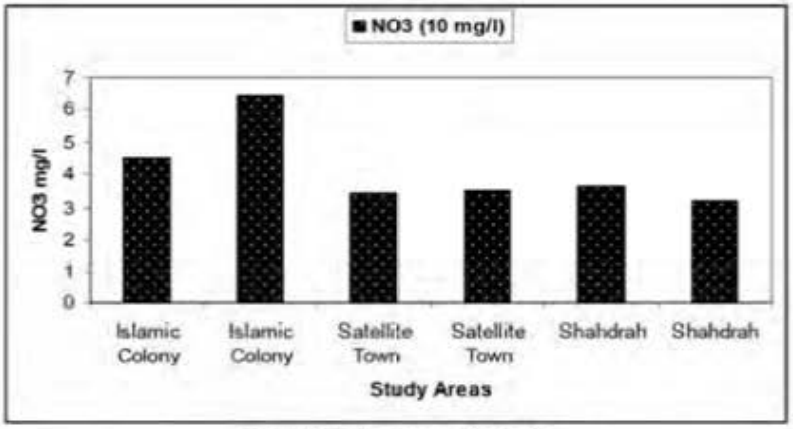
Source: Laboratory Analysis

Figure 16: Values of Alkalinity (Alk) in Study Areas



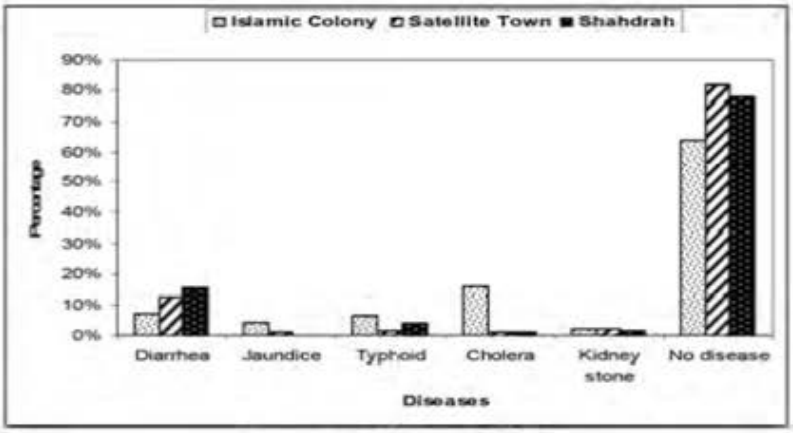
Source: Laboratory Analysis

Figure 17: Values of Nitrate (NO_3) in Study Areas



Source: Laboratory Analysis

Figure 18: Waterborne Diseases in Study Areas



Source: Field Survey (2013)

ENVIRONMENTAL IMPACT AND TOXICOLOGY OF SULPHATE

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ABSTRACT

Sulphate can be found in the environment as a result of atmospheric and terrestrial processes. Major natural contributors of sulphate to the environment are sulphur released from erosion of evaporite deposits and sulphide containing rocks and minerals as well as volcanoes. During this cycle sulphate is taken up by plants and microorganisms, and is later consumed by animals, thereby moving sulphur through the food chain. One third of the sulphur reaching the environment is anthropogenic, and it is generated from industrial activities such as mining and mineral processing, agriculture, paper and pulp, combustion of fossil fuels and refuse. The mineral processing industries emit sulphur to the environment in the form of sulphate, sulphuric acid, hydrogen sulphide and SOx gases. Sulphate in mine discharge waters is a major issue around the world where acidic tailings are periodically affected by drought and rain, and in mines where sulphuric acid is used to process the ore and mineral concentrates. Many Latin-American surface waters have been affected by mining activities with high sulphate concentrations well above recommended limits of 250-500 mg/L for drinking water and 500-1,000 mg/L for discharge into surface water bodies. Some of these water streams are used for irrigation, animal watering and human consumption. Sulphate levels in the Toro River, Chile, have shown maximum concentrations of 1,161 mg/L, attributed to acid mine drainage. Water samples collected from the Caren Creek draining the El Teniente mine tailings showed elevated levels (1,440 to 1,490 mg/L) of sulphate.

INTRODUCTION

High sulphate in surface waters as a result of industrial development is becoming more and more an issue around the world. Most countries in the world recommend a drinking water standard for sulphate between 250 and 500 mg/L [35]. This is often based on a taste and odour threshold as sulphates can contribute to an undesirable taste in water. In several places in Chile, sulphate discharge levels into surface water bodies is well above this limit. Some of these waters are used for irrigation, animal watering and human consumption. In agriculture, the use of irrigation waters containing high concentrations of sulphate could generate non-toxic stains in fruits and leaves of trees. It could also cause scaling of pipes and blockage of sprinklers when associated with iron and calcium.

There is currently no evidence of adverse health effects in animals or humans from chronic exposure to sulphate in drinking water, however, infants are more sensitive to sulphate. Groups within the general population may be at greater risk from the laxative effects of sulphate when they experience an abrupt change from drinking water with low sulphate concentrations to drinking water with high sulphate concentrations. Cattle have shown change in their metabolism due to high concentrations of sulphate in drinking water.

This paper discusses the extent of the sulphate problem in some Latin American countries and the impact of sulphate on the aqueous and terrestrial environments, and human and animal health.

SULPHATE IN THE ENVIRONMENT

Sulphate is present in the environment as part of the sulphur cycle [37]. The sulphur cycle contains both atmospheric and terrestrial processes. Within the terrestrial processes, the cycle begins with the erosion of sulphate (evaporites) and sulphide containing rocks and minerals. This is a process that releases the stored sulphur into the environment. The sulphur then comes into contact with air where it is converted into sulphate (SO_4^{2-}). The sulphate is taken up by plants and microorganisms and is converted into organosulphur compounds. Plants and animals consume the organic sulphur which moves the sulphur up through the food chain. As plants and organisms die, some of the sulphur is released back into the environment as sulphate. The breakdown of vegetation in swamps and tidal flats releases hydrogen sulphide (H_2S) gas into the environment. Hydrogen sulphide converts to sulphate in aqueous environments. The other major natural contributor to the sulphur budget in the environment is volcanoes. The fumarolic activity of volcanoes introduce SO_x (SO_2, SO_3) and hydrogen sulphide gases to the atmosphere. These gases eventually convert to sulphate ions in water and precipitate as alkali sulphate salts. On geological timescales, the precipitated sulphate salts may form evaporite deposits.

Various forms of sulphur-containing chemicals are commonly used in the production of fertilisers, fungicides, algae control and insecticides, as well as in the production of glass, paper and wood pulp industries, soap and detergent, in medicine, in hide-skin processing and water treatment [35]. One-third of all sulphur that reaches the atmosphere, including 90% of sulphur dioxide, stems from human activities. These include industries such as mining and mineral processing, agriculture, and paper and pulp. Sulphur enters the atmosphere primarily through the burning of fossil fuels, incineration of refuse, and the processing of minerals and metals. The burning of coal and petroleum by industry and power plants creates large amounts of toxic gases such as sulphur dioxide (SO_2) and sulphur trioxide (SO_3) which react with atmospheric water and oxygen to produce sulphuric acid (H_2SO_4) which lowers the pH of soils and raises sulphate levels of surface waters.

Sulphate is especially a problem where acidic soils and mine tailings are periodically affected by drought and rain, and in places where sulphuric acid is used to process the ore and mineral concentrates. Sulphate may enter surface and ground water from industrial sources as the discharge or disposal of sulphate-containing tailings, and seepage from acidic tailings ponds. Within the ocean, some sulphur cycles through marine flora and fauna, and moves up through the food chain. A large part of the sulphate in water combines with iron and manganese to form black ooze and wad which is responsible for the black colour of most marine sediments.

SOURCES OF MAN-MADE SULPHATE IN LATIN AMERICA

Figure 1 shows the location and altitude of some mines in Chile and Peru. To extract copper from oxidised ore, the lixiviation process is applied in the northern Chilean mines (Escondida, Gaby, Collahuasi) and Peruvian mines (Toquepala, Tintaya y Cerro Verde). Lixiviation or heap leaching is a hydrometallurgical procedure in which sulphuric acid and water are sprayed onto stockpiles of oxidised copper ore to leach copper sulphate ($CuSO_4$) which is later transported to the solvent extraction plant to obtain a high grade copper concentrate. Indiscriminant heap leaching of stockpiles of oxidised copper ores using sulphuric acid is claimed [27] to increase the likelihood of environmental contamination due to dusting, and leakage into the subterranean water supplies, therefore, causing damage to the surrounding fauna and flora.

Table 1 shows sulphur emissions from various smelters in Chile over a three-year period. In central Chile, three copper smelters produced 95% of the sulphur emissions in the area. Emissions from the Caletones smelter alone accounts for 0.4% of the world anthropogenic emissions of sulphur, causing environmental risks to the surrounding population and agriculture [26]. Other smelters that emit sulphur include Ventanas, Potrerillos (3rd District) and Chuquicamata (2nd District), the latter two being located in the northern part of Chile. These four smelters together contributed more than 935,000 tonnes of SO_2 atmospheric emissions between 2005 and 2007. Populated areas such as

Catemu, Puchuncavi (5th District) and Nos (Metropolitan District) were found to be the sources of acid rain in Chile, affecting the infrastructure and human health within its vicinity. The main problems associated with the acid rain were widespread corrosion of infrastructure, and diminishing of husbandry and agricultural activity in the region [14].

Table 1: SO_2 emissions from smelters in Chile [5]

Smelter	Thousand Tonnes of SO_2 per year		
	2005	2006	2007
Chuquicamata	57.51	75.73	78.19
Potrerillos	93.39	89.24	80.27
Ventanas	12.15	13.73	11.51
Caletones	115.80	152.74	155.10
Total	**278.85**	**331.44**	**325.07**

High sulphate in surface waters is an issue around the world and this is especially the case in Latin American countries like Chile. The World Health Organization states that the sulphate content of fresh water averages 20 mg/L, ranging from 0 to 630 mg/L in rivers, lakes range from 2 to 250 mg/L, and groundwater from 0 to 230 mg/L [35]. In the 4th District of Chile, the Choapa River showed a range of sulphate concentrations reaching up to 1,352 mg/L [7]. A slightly higher maximum concentration of sulphate was found in the Loa River, 2nd District of Chile, ranging from 20 to 2,293 mg/L [8]. Another industrial focus for the discharge of sulphate is the paper and pulp industry. In Valdivia, Chile, a major pulp and paper plant discharges 40 tonnes of aluminum sulphate every day into the Cruces River [30].

The increase in the sulphate concentrations and decrease in acidity in water bodies can be an indicator of the acid mine drainage problem. The Toro River located in the 4th District of Chile, is one of the runoffs of the Elqui River, a very important water body used as a source of potable water by 300,000 inhabitants and the agroindustry (crops, grapes for export, and vine production). Mining activities in the area date from the 19th century, and ended with the closure of the El Indio mine (gold, silver and copper). The Toro River is a direct receptor of acid drainage from El Indio where sulphate was measured at a maximum concentration of 1,161 mg/L [15]. There may be downstream problems associated with structural dam failure due to seismic activity in tailing dams, and contamination of water bodies with high concentrations of heavy metals, low pH and sulphates. For example, in Mexico, the inactive tailings of the Santa Barbara mine were found to contain sulphate concentrations of 2,133 mg/L [16].

In 2006, more than five million tonnes of copper was produced in Chile [22]. Chile generates an average of 28 tonnes of tailings for every tonne of copper concentrate produced [36]. Recently, the National Commission for the Environment in Chile approved a special regulation for sulphate discharges to the Caren Creek in the 6th District that allowed effluent concentration of 2,000 mg/L sulphate from tailings dams of the El Teniente mine [10]. This special regulation created controversy among the affected people in the area and nationwide. Nearly 46 million tonnes of tailings were generated by El Teniente during 2007, with seven programmed discharges during the year into the Caren Creek with a volume of over 51 million cubic metres released [4]. The discharge volume of El Teniente tailings accounted for more than 60% of the total discharges of CODELCO (Copper Corporation of Chile) mines in Chile. In 2006, seven significant accidental spills occurred in the Caren Creek with a total 10,938 m^3 of tailings released [3].

In this study, five water samples were collected from accessible locations of the Caren Creek (Fig. 2) in October 2008 by personnel from Universidad Diego Portales. The analysis of these samples for sulphate (SO_4^{2-}), iron (Fe), molybdenum (Mo), copper (Cu) and pH is shown in Table 2. Water composition is highly uniform along the track of water. The variation was within the analytical sensitivity levels and there was only negligible interference from other sources. Copper concentration was relatively low, but molybdenum concentrations ranged from 0.7 to 1 ppm, well above the levels

in normal surface waters. The measured sulphate concentrations were under the present acceptable level of 2,000 mg/L. The water of the Caren Creek is used for irrigation in Alhue (a small town located on the side of the creek). CODELCO has conducted studies over a decade using waters from the Caren Creek for alfalfa irrigation which showed that sulphate was not retained in the soil because it was leached easily [31].

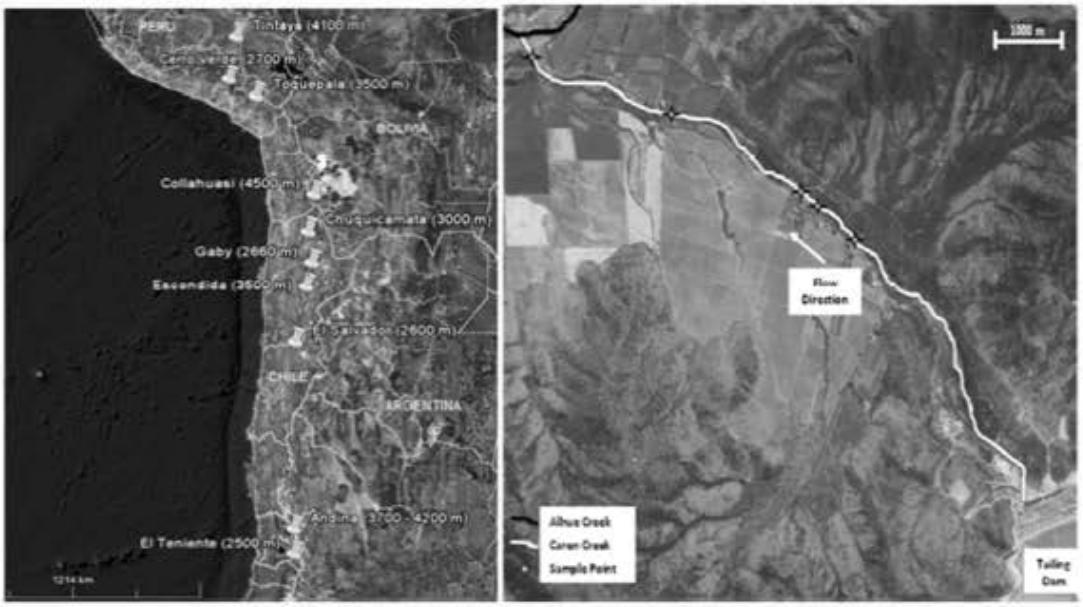

Figure 1 (left): Location and altitude of some copper mines in Chile and Peru. Source: Google Earth

Figure 2 (right): Caren Creek sample points. Source: Google Earth

Table 2: pH, Cu, Mo, Fe and SO_4^{2-} content in the Caren Creek

Parameters	Approximate Distance from Tailing Dam Wall (m)				
	3,367	3,661	3,761	5,178	6,687
pH	7.2	7.25	7.28	7.29	7.04
Cu (mg/L)	<0.08	<0.08	<0.08	<0.08	<0.08
Mo (mg/L)	0.86	0.9	0.73	0.81	1.02
Fe (mg/L)	0.22	0.21	0.21	0.23	0.35
Sulphate (mg/L)	1,469	1,462	1,475	1,491	1,441

ENVIRONMENTAL IMPACT

Impact on the Terrestrial Environment

Sulphur in the form of sulphate minerals is an essential nutritional element for plant growth and development. Like nitrogen, sulphur is a mobile nutrient that may move rapidly downward through the soil, especially through sandy surface layers. In humid regions such as North Carolina and the southeastern United States, most of the sulphur in the surface soil is associated with organic matter. Soluble sulphates seldom accumulate in the plough layer because they are leached into the subsoil. Most of this sulphate probably comes from past applications of fertilisers that contain sulphur. Sulphur often accumulates in the subsoil where soluble sulphates are absorbed by iron and aluminium oxides. Sulphur accumulation rises as subsoil acidity increases. If this accumulation occurs in the top 43-51 cm of soil, and if the roots grow into the subsoil, the plants can get an adequate amount of sulphate. Forest soils may have considerable capacity to adsorb sulphate ions from soil solution. Decreasing pH will have an increasing effect on sulphate adsorption to a maximum adsorption level

which occurs at around pH 4. Swedish forest soils were found to have pH 4.6-4.7 and sulphate concentrations of 100-400 mol/L [18].

The sulphur content of upland and wetland vegetation was examined in north central Minnesota (USA) [19]. The mean sulphur content varied between woody (0.1%) and non-woody (wetland) plants. Submerged plants contained 0.31% sulphur, floating-leaved plants contained 0.16% sulphur, and emergent life forms contained 0.23% sulphur. Sulphur content was estimated in fruits and vegetables such as apples, strawberries, cabbage, carrots, cucumbers and early potatoes from Lower Silesia, Poland [25]. Based on the analysis of 2,347 samples it was expected that with the present state of the natural environment, about 5.7% of the crops of fruits and vegetables cultivated in this region would show excessive levels of sulphur. The limits of sulphur concentration were only slightly exceeded in the samples studied which did not render the crops unfit for human consumption.

Sulphur oxides in ambient air are capable of causing harm to the environment and have been known to damage vegetation, soils, watercourses and building materials. Irrigation water containing high concentrations of sulphate could generate white non-toxic stains on the leaves and fruits of trees. High concentrations of sulphate could cause scaling of pipes and blockage of sprinklers if associated with iron and calcium [31]. They can produce pitting, crevice corrosion, dealloying, stress corrosion cracking, and stress-oriented hydrogen-induced cracking of metals and public works [20]. The physical scale over which the sulphur cycle influences corrosion varies with the environment. The complete sulphur cycle of oxidation and reduction reactions can take place in macro-environments, including sewers and polluted harbors, or within the micro-environment of biofilms [20]. Iron- and sulphur-oxidising bacteria of the genus Thiobacillus have been shown to be active geochemical agents in the oxidative weathering of sulphide minerals and production of acid drainage [39].

Impact on the Aquatic Environment

One of the adverse effects of sulphate in the environment is its conversion in a process known as bacterial sulphate reduction where sulphate-sulphur is converted to hydrogen sulphide:

$$SO_4^{2-} + 2CH_2O = H_2S + 2HCO_3^-$$

Hydrogen sulphide is a distasteful and highly toxic gas, and its release to the atmosphere is a problem. However, hydrogen sulphide re-oxidises by reacting with dissolved oxygen in overlying pore-water or with Fe(III) or Mn(IV) from within the sediment. Sulphate reduction is the most important pathway for mineralisation of marine sedimentary organic matter. Around 75% to 90% of sulphide produced is re-oxidised in this way. The smaller fraction of sulphide produced reacts with Fe(II) to form FeS and ultimately FeS_2 (pyrite).

Marine algae produce and accumulate high concentrations of sulphur compounds more than most terrestrial plants because they live in habitats that are characterised by limited nitrogen and abundant sulphur supply (such as underground volcanoes) [38]. The biogenic sulphur when come into contact with seawater converts to sulphate ions. Sulphur is also imported into cells where it is incorporated into organic sulphate (e.g., extracellular polysaccharides like agar) or is reduced to sulphide before being incorporated as the thiol group of cysteine. Sulphur-containing metabolites participate in a variety of cellular processes including disease resistance, tolerance to oxidation, heavy metals, water stress, and developmental signalling.

A studywas carried out of the biological effects of the detergent sodium dodecyl sulphate (SDS) on the intestine of the gilthead seabream, Sparus aurata L [28]. Sixty five giltheads weighing between 30-40 g were exposed to SDS concentrations of 5, 8.5, 10, and 15 mg/L until 50% of the fish in each treatment had died. After the animals had died, examinations showed that the effect of SDS on the intestinal epithelium depended upon concentration and exposure time, with a greater variation in those specimens subjected to higher concentrations and longer exposure times. The levels of proteins in

general and siderophil proteins decreased due to the observed development of the lesions and exposure to the toxin, SDS.

Impact on Humans and Animals

There is limited information on the inhalation and oral, chronic and subchronic toxicity, carcinogenity, and developmental and reproductive toxicity of sulphate in humans and animals [29]. While sulphur oxides in ambient air are capable of causing harm to human health and have been associated with the aggravation of asthma and chronic bronchitis, sulphate is one of the least toxic anions associated with many metabolites or foreign substances, increasing their water solubility and elimination properties [6]. No reference dose has been derived for sulphate. The sulphate ion is poorly absorbed from the human intestine [34], however, some absorption of the component ions of sulphate salts does occur [6]. Sulphate itself slowly penetrates mammalian cellular membranes and is rapidly eliminated through the kidneys [34]. Taste thresholds are 200-500 mg/L for sodium sulphate, 250-900 mg/L for calcium sulphate, 400-600 mg/L for magnesium sulphate, and 300-400 mg/L for the sulphate ion in water [29, 34].

The US EPA has found no evidence of adverse health effects in animals or humans from chronic exposure to sulphate in drinking water. People living in regions with high-sulphate drinking water appeared to show no adverse effect, whereas newcomers drinking that region's water may initially experience a laxative effect [17]. Infants are more sensitive to sulphate than healthy adults [2]. Infants aged 5 to 12 months old who were given formulas prepared with water containing 630 to 1,150 mg/L of sulphate, developed diarrhea shortly after they ingested the formula but the diarrhea stopped once the use of high sulphate water was terminated.

High concentrations of sulphate in cattle drinking water have been found to affect the cattle's metabolism by decreasing ruminal metabolic activity [5]. High concentrations of total salts and/or sulphates also decreased forage digestibility, and negatively affected consumption, health and cattle production.

According to a study by the Universidad Austral de Chile [30], the industrial discharge of aluminium sulphate to the Cruces River in Valdivia (Chile) caused the diminishing of 'luchecillo' (Egeria densa) the main source of food of the black neck swans, causing their death and migration from a natural sanctuary downflow from the plant. The excess sulphate in the river precipitated as calcium bicarbonate which depleted the carbon dioxide levels of the water needed for the photosynthesis process for the survival of 'luchecillo'.

In general, sulphate ion is not considered a respiratory irritant [1]. The amount of sulphate that could be transferred from the atmosphere through the pulmonary system to the gastrointestinal tract is very small compared to what could be ingested.

REGULATORY LIMITS

Sulphate is a substance that occurs naturally in drinking water. The WHO has not proposed a health standard for sulphate, however, most countries in the world recommend a drinking water standard for sulphate between 250 and 500 mg/L [35]. This is often based on a taste and odour threshold as sulphates can contribute to an undesirable taste in water. The US Public Health Service recommended that sulphate in drinking water should not exceed 250 mg/L, except when no more suitable supplies are or can be made available [29]. The US EPA has recommended a contamination concentration of 250 mg/L of sulphate for drinking water [32]. The European Standards for Drinking Water sulphate limit is set to 250 mg/L [21]. The Canadian guideline for the maximum acceptable concentration of sulphate in drinking water is 500 mg/L [13]. According to the Australian Drinking Water Guidelines [24], the taste threshold for sulphate is in the range 250-500 mg/L. Interestingly, in 2005 the Chilean government increased the sulphate limit in drinking water from 250 mg/L (according to the 1984

Drinking Water Code) to 500 mg/L [23]. The new maximum limit is still within the WHO recommendations.

The Water Corporation in Western Australia [33] has indicated an acceptance criteria for industrial waste discharged to Water Corporation sewers of 600 ppm (~600 mg/L) sulphate. There may be variations to this limit in individual permits to discharge industrial waste. In the Chilean code for underground water, the vulnerability of the underground aquifer is classified into three categories (high, medium and low) according to the velocity in which the contaminant may migrate into the saturated zone of the aquifer [9, 11, 12]. If the vulnerability is considered to be high, the sulphate concentration infiltrated must be less than the one in the natural aquifer. If found to be medium, the maximum concentration must be less than 250 mg/L, and if the vulnerability is considered to be low, the maximum sulphate concentration is 500 mg/L [9]. The maximum concentration to be discharge into surface water bodies or sea water should not be greater than 1,000 mg/L [11]. The maximum sewer discharge is set up in 1,000 mg/L [12].

CONCLUSION

Many Latin-American surface waters have been affected by mining activities with high sulphate concentrations well above WHO recommended levels. Some of these waters are used for irrigation, animal watering and human consumption. In agriculture, the use of irrigation waters containing high concentrations of sulphate could generate non-toxic stains in fruits and leaves of trees. It could also cause scaling of pipes and blockage of sprinklers when associated with iron and calcium.

Most countries in the world recommend a sulphate discharge limit to the environment not greater than 1,000 mg/L. In Chile, exemptions have been made to a copper mine (El Teniente, Codelco) accepting a maximum sulphate discharge concentration of 2,000 mg/L. Further research is required to establish the toxicity and carcinogenity of sulphate to humans and animals.

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Water Fluoridation and Cancer Risk

Many decades after fluoride was first added to drinking water in some parts of the United States, there is still controversy about the possible health effects of drinking water fluoridation. Many people have strong views either for or against water fluoridation. Their concerns are based on everything from legitimate scientific research, to freedom of choice issues, to government conspiracy theories.

This is a review of the possible link between water fluoridation and cancer. Other possible health effects of fluoridation (positive or negative) are not addressed here. This is not a position statement of the American Cancer Society.

What is fluoride?

Fluorides are compounds that combine the element fluorine with another substance, usually a metal. Examples include sodium fluoride, stannous fluoride, and fluoride monofluorophosphate (MFP fluoride).

Some fluorides occur naturally in soil, air, or water, although the levels of fluoride can vary widely. Just about all water has some fluoride. Fluoride is also found in plant and animal food sources.

Once inside the body, fluorides are absorbed into the blood through the digestive tract. They travel through blood and tend to collect in areas high in calcium, such as the bones and teeth.

How are people exposed to fluoride?

The major sources of fluoride for most people are water and other beverages, food, and fluoride-containing dental products (toothpastes, mouth rinses, etc.). Because dental

products are generally not swallowed (except, perhaps, by younger children), they cause less concern for possible health issues.

Fluoride in drinking water

Water fluoridation began in some parts of the United States in 1945, after scientists noted that people living in areas with higher water fluoride levels had fewer cavities. Starting in 1962, the United States Public Health Service (PHS) recommended that public water supplies contain fluoride to help prevent tooth decay.

Fluoride is now used in the public drinking water supplied to about 3 out of 4 Americans. The decision to add fluoride to drinking water is made at the state or local level. The types of fluoride added to different water systems include fluorosilicic acid, sodium fluorosilicate, and sodium fluoride.

Natural drinking water sources in the US also have some fluoride in them, although the levels are much higher in some places than in others.

How is fluoride in drinking water regulated?

Fluoride is not required in all drinking water sources in the United States, but the levels of fluoride in water are regulated by several government agencies.

Starting in 1962, the United States Public Health Service (PHS) recommended that public water supplies contain between 0.7 and 1.2 milligrams of fluoride per liter (mg/L) of drinking water to help prevent tooth decay. This recommendation was updated in 2015 to a fluoride level of 0.7 mg/L, The change was made in part to account for the fact that people now get more fluoride from other sources (such as toothpaste) than in the past. (Natural drinking water sources in the US have an average fluoride level of about 0.2 mg/L, although in some places it can be much higher.)

The US Environmental Protection Agency (EPA) has set a maximum amount of fluoride allowable in drinking water of 4.0 mg/L. Long-term exposure to levels higher than this can cause a condition called *skeletal fluorosis*, in which fluoride builds up in the bones. This can eventually result in joint stiffness and pain, and can also lead to weak bones or fractures in older adults.

The EPA has also set a secondary standard of no more than 2.0 mg/L to help protect children (under the age of 9) from *dental fluorosis*. In this condition, fluoride collects in developing teeth, preventing tooth enamel from forming normally. This can cause permanent staining or pitting of teeth. (The secondary standard is a guideline, as

opposed to an enforceable regulation, but public water systems must tell their customers if the fluoride level goes above it.)

States can set maximum fluoride levels in drinking water that are lower than the national 4.0 mg/L standard.

Bottled water standards are set by the US Food and Drug Administration (FDA). The fluoride levels allowed vary based on the annual average air temperature in the place where the water is sold.

For bottled water with no fluoride added, the maximum fluoride level allowed is 2.4 mg/L (in places with colder temperatures).

For water in which fluoride is added, the maximum allowed is 1.7 mg/L (in colder climates). However, if fluoride is added, the FDA recommends that manufacturers not go above 0.7 mg/L, which is in line with the PHS recommendation.

Does fluoride cause cancer?

People have raised questions about the safety and effectiveness of water fluoridation since it first began. Over the years, many studies have looked at the possible link between fluoride and cancer.

Some of the controversy about the possible link stems from a study of lab animals reported by the US National Toxicology Program (NTP) in 1990. The researchers found "equivocal" (uncertain) evidence of cancer-causing potential of fluoridated drinking water in male rats, based on a higher than expected number of cases of osteosarcoma[1] (a type of bone cancer). There was no evidence of cancer-causing potential in female rats or in male or female mice.

Most of the concern about cancer seems to be around osteosarcoma. One theory on how fluoridation might affect the risk of osteosarcoma is based on the fact that fluoride tends to collect in parts of bones where they are growing. These areas, known as *growth plates*, are where osteosarcomas typically develop. The theory is that fluoride might somehow cause the cells in the growth plate to grow faster, which might make them more likely to eventually become cancerous.

What have studies found?

More than 50 population-based studies have looked at the potential link between water fluoride levels and cancer. Most of these have not found a strong link to cancer. Just

about all of the studies have been retrospective (looking back in time). They have compared, for example, the rates of cancer in a community before and after water fluoridation, or compared cancer rates in communities with lower levels of fluoride in drinking water to those with higher levels (either naturally or due to fluoridation). Some factors are hard to control for in these types of studies (that is, the groups being compared may be different in ways other than just the drinking water), so the conclusions reached by any single study must be looked at with caution.

And there are other issues that make this topic hard to study. For example, if fluoridation is a risk factor, is the type of fluoride used important? Also, is there a specific level of fluoride above which the risk is increased, or a certain amount of time or an age range during which a person would need to be exposed?

Osteosarcoma is a rare cancer. Only about 400 cases are diagnosed in children and teens each year in the United States. This means it can be hard to gather enough cases to do large studies. Smaller studies can usually detect big differences in cancer rates between 2 groups, but they might not be able to detect small differences. If fluoride increased the risk only slightly, it might not be picked up by these types of studies.

Assessments by expert groups

Small studies by themselves might not provide the answers, but taken as a whole they tend to have more weight. Several systematic reviews over the past 25 years have looked at all of the studies published on this subject.

In its review published in 1987, the International Agency for Research on Cancer (IARC), part of the World Health Organization, labeled fluorides as "non-classifiable as to their carcinogenicity [ability to cause cancer] in humans." While they noted that the studies "have shown no consistent tendency for people living in areas with high concentrations of fluoride in the water to have higher cancer rates than those living in areas with low concentrations," they also noted that the evidence was inadequate to draw conclusions one way or the other.

In 1991, the US Public Health Service issued a report on the benefits and risks of fluoride. When looking at a possible link with cancer, they first reviewed the results of studies done with lab animals. They concluded that the few studies available "fail[ed] to establish an association between fluoride and cancer." They also looked at population-based studies, including a large study conducted by the National Cancer Institute. They concluded: "Optimal fluoridation of drinking water does not pose a detectable cancer risk to humans as evidenced by extensive human epidemiological data available to date, including the new studies prepared for this report."

The National Research Council (NRC), part of the National Academies, issued a report titled "Health Effects of Ingested Fluoride" in 1993. Its conclusion was that "the available laboratory data are insufficient to demonstrate a carcinogenic effect of fluoride in animals." They also concluded that "the weight of the evidence from the epidemiological [population-based] studies completed to date does not support the hypothesis of an association between fluoride exposure and increased cancer risk in humans." The report recommended that additional well-designed studies be done to look at the possible link to cancers, especially osteosarcomas.

In the United Kingdom, the National Health Service (NHS) Centre for Reviews and Dissemination, University of York, published a systematic review of water fluoridation in the year 2000. After searching through the medical literature, they included 26 studies in their analysis, all of which were considered to be of "low" to "moderate" quality. They concluded, "Overall, no clear association between water fluoridation and incidence or mortality of bone cancers, thyroid cancer, or all cancers was found." However, they also noted, "Given the level of interest surrounding the issue of public water fluoridation, it is surprising to find that little high quality research has been undertaken."

The National Research Council issued an update of its 1993 review in early 2006. While the review included some new data, the results of this report were essentially the same: "On the basis of the committee's collective consideration of data from humans, genotoxicity assays, and studies of mechanisms of actions in cell systems, the evidence on the potential of fluoride to initiate or promote cancers, particularly of the bone, is tentative and mixed."

The European Scientific Committee on Health and Environmental Risks (SCHER) reviewed the evidence on water fluoridation in 2010. It concluded that the evidence linking fluoride in water to osteosarcoma was "equivocal," and that therefore "fluoride cannot be classified as to its carcinogenicity."

In 2011, the state of California's Carcinogen Identification Committee (CIC) reviewed the evidence and concluded that "fluoride and its salts has not been clearly shown to cause cancer."

The general consensus among the reviews done to date is that there is no strong evidence of a link between water fluoridation and cancer. However, several of the reviews noted that further studies are needed to clarify the possible link.

More recent research

Several studies looking at a possible link between water fluoridation and cancer have been published in recent years.

A partial report of a study from the Harvard School of Public Health, published in 2006, found that exposure to higher levels of fluoride in drinking water was linked to a higher risk of osteosarcoma in boys but not in girls. However, researchers linked to the study noted that early results from a second part of the study did not appear to match those of the report. They therefore advised caution in interpreting the results.

The second part of the Harvard study, published in 2011, compared the fluoride levels in bones near tumors in people with osteosarcoma to the levels in people with other types of bone tumors. The researchers found no difference between the fluoride levels in the two groups.

More recent studies have compared the rates of osteosarcoma in areas with higher versus lower levels of fluoridation in Great Britain, Ireland, and the United States. These studies have not found an increased risk of osteosarcoma in areas of water fluoridation.

Can you reduce your fluoride exposure?

Even without fluoridation, the natural levels of fluoride in water in some places can be even higher than 4 mg/L. Community water systems in such areas are required to lower the fluoride level below the acceptable standard. But the levels in private water sources, such as wells, may still be higher.

For people concerned that they or their families may be exposed to too much fluoride, there are some steps you can take to reduce your exposure.

- **Know the level of fluoride in your drinking water.** If your drinking water comes from a public source, you can find out about the levels of fluoride in your drinking water by contacting your local community water system. People who get their drinking water from a private source such as a well can have the fluoride levels tested by a reputable laboratory. Each system is also required to provide its customers with an annual report on water quality known as a *Consumer Confidence Report*. This report lists the levels of certain chemicals and other substances in the water, including fluoride. You can also contact the EPA's Safe Drinking Water Hotline at 1-800-426-4791 for more general information about drinking water safety.
- **People who live in areas with high levels of fluoride in the water might consider using alternate sources of drinking water, such as bottled water.** Most bottled water has some fluoride, with natural spring waters tending to have the least. You can contact the bottler to find out about fluoride levels. There are also several methods to filter fluoride out of water, although these can be expensive.

The US Centers for Disease Control and Prevention (CDC) recommends that parents give children under the age of 6 only a pea-sized amount of toothpaste for brushing, and should do their best to make sure their children are not swallowing, as this can be a significant source of fluoride. Speak to your child's dentist before using fluoride toothpaste in children under 2 years of age. Low- and no-fluoride toothpastes and other dental products are also available.

Hyperlinks

1. www.cancer.org/cancer/osteosarcoma.html
2. http://www.cdc.gov/
3. http://www.cdc.gov/fluoridation/
4. https://www.epa.gov/
5. https://water.epa.gov/drink/
6. http://www.cancer.gov/
7. http://www.cancer.gov/about-cancer/causes-prevention/risk/myths/fluoridated-water-fact-sheet

Additional resources

Along with the American Cancer Society, other sources of information include:

Centers for Disease Control and Prevention (CDC) Toll-free number: 1-800-CDC-INFO (1-800-232-4636) Website: www.cdc.gov (http://www.cdc.gov/)[2]

Community water fluoridation page: www.cdc.gov/fluoridation (http://www.cdc.gov/fluoridation/)[3]

Environmental Protection Agency Toll-free number (Safe Drinking Water Hotline): 1-800-426-4791 Website: www.epa.gov (www.epa.gov/)[4]

Epa: Ground water & Drinking Water (water.epa.gov/drink/)[5]

National Cancer Institute Toll-free number: 1-800-4-CANCER (1-800-422-6237) Website: www.cancer.gov (http://www.cancer.gov/)[6]

Fluoridated water page (http://www.cancer.gov/about-cancer/causes-prevention/risk/myths/fluoridated-water-fact-sheet)[7]

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

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Manganese in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

Rev/1: Revisions indicated with a vertical line in the left margin.

Manganese in Drinking-water
Background document for development of WHO *Guidelines for Drinking-water Quality*

Preface

One of the primary goals of the World Health Organization (WHO) and its Member States is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose ... regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2006 and the second addendum to the third edition was published in 2008. The fourth edition will be published in 2011.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Japan, the United Kingdom and the United States of America (USA) prepared the documents for the fourth edition.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint FAO/WHO Meetings on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

Acknowledgements

The current version of Manganese in Drinking-water, Background document for development of WHO *Guidelines for Drinking-water Quality*, is a revision of the background document prepared for an earlier edition of the Guidelines by Dr J. Du, United States Environmental Protection Agency.

The work of the following working group coordinators was crucial in the development of this document and others contributing to the fourth edition:

Dr J. Cotruvo, J. Cotruvo & Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants* and *Pesticides*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
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Professor Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr A.V. Festo Ngowi, Muhimbili University of Health and Allied Sciences, United Republic of Tanzania (*Pesticides*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Expert Consultation for the fourth edition of the GDWQ, held in December 2011. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants at the meeting is gratefully acknowledged.

The WHO coordinators were Mr R. Bos and Mr B. Gordon, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr M. Zaim, Public Health and the Environment Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms P. Ward provided invaluable administrative support at the Expert Consultation and throughout the review and publication process. Ms M. Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comments are greatly appreciated.

Acronyms and abbreviations used in the text

IOM	Institute of Medicine (USA)
LD_{50}	median lethal dose
MMT	methylcyclopentadienyl manganese tricarbonyl
NOAEL	no-observed-adverse-effect level
TDI	tolerable daily intake
USA	United States of America

Table of contents

1. GENERAL DESCRIPTION

1.1 Identity

Compound	*Chemical Abstracts Service No.*	*Molecular formula*
Manganese	7439-96-5	Mn
Manganese(II) chloride	7773-01-5	$MnCl_2$
Manganese(II, III) oxide	1317-35-7	Mn_3O_4
Manganese dioxide	1313-13-9	MnO_2
Potassium permanganate	7722-64-7	$KMnO_4$
Manganese sulfate	7785-87-7	$MnSO_4$

Source: ATSDR (2000).

Manganese is one of the most abundant metals in Earth's crust, usually occurring with iron. It is a component of over 100 minerals but is not found naturally in its pure (elemental) form (ATSDR, 2000). Manganese is an element essential to the proper functioning of both humans and animals, as it is required for the functioning of many cellular enzymes (e.g. manganese superoxide dismutase, pyruvate carboxylase) and can serve to activate many others (e.g. kinases, decarboxylases, transferases, hydrolases) (IPCS, 2002). Manganese can exist in 11 oxidative states; the most environmentally and biologically important manganese compounds are those that contain Mn^{2+}, Mn^{4+} or Mn^{7+} (USEPA, 1994).

1.2 Physicochemical properties

The physical and chemical properties of different manganese compounds vary substantially. These characteristics in turn determine the environmental behaviour and fate, exposure potential and subsequent toxicological potential of each compound.

Property	*Mn*	*$MnCl_2$*	*Mn_3O_4*	*MnO_2*	*$KMnO_4$*	*$MnSO_4$*
Melting point (°C)	1244	650	1564	Loses oxygen at 535 °C	Decomposes at <240 °C	700
Boiling point (°C)	1962	1190	No data	No data	No data	Decomposes at 850 °C
Density (g/cm^3)	7.21–7.44	2.98	4.86	5.03	2.70	3.25
Water solubility (g/l)	Decom-poses	723 (25 °C)	Insoluble	Insoluble	63.8 (20 °C)	520 (5 °C) 700 (70 °C)

Source: ATSDR (2000)

1.3 Organoleptic properties

At concentrations exceeding 0.1 mg/l, the manganese ion imparts an undesirable taste to beverages and stains plumbing fixtures and laundry (Griffin, 1960). When manganese(II) compounds in solution undergo oxidation, manganese is precipitated,

resulting in encrustation problems. At concentrations as low as 0.02 mg/l, manganese can form coatings on water pipes that may later slough off as a black precipitate (Bean, 1974). A number of countries have set standards for manganese of 0.05 mg/l, above which problems with discoloration may occur.

1.4 Major uses

Manganese is used principally in the manufacture of iron and steel alloys and manganese compounds and as an ingredient in various products (IPCS, 1999; ATSDR, 2000). Manganese dioxide and other manganese compounds are used in products such as batteries, glass and fireworks. Potassium permanganate is used as an oxidant for cleaning, bleaching and disinfection purposes (ATSDR, 2000; HSDB, 2001). Manganese greensands are used in some locations for potable water treatment (ATSDR, 2000). An organic manganese compound, methylcyclopentadienyl manganese tricarbonyl (MMT), is used as an octane-enhancing agent in unleaded petrol in Canada, the United States of America (USA), Europe, Asia and South America (Lynam et al., 1999). Other manganese compounds are used in fertilizers, varnish and fungicides and as livestock feeding supplements (HSDB, 2001).

1.5 Environmental fate

Manganese compounds may be present in the atmosphere as suspended particulates resulting from industrial emissions, soil erosion, volcanic emissions and the burning of MMT-containing petrol (IPCS, 1999). In surface waters, manganese occurs in both dissolved and suspended forms, depending on such factors as pH, anions present and oxidation–reduction potential (ATSDR, 2000). Anaerobic groundwater often contains elevated levels of dissolved manganese. The divalent form (Mn^{2+}) predominates in most water at pH 4–7, but more highly oxidized forms may occur at higher pH values or result from microbial oxidation (ATSDR, 2000). Manganese can be adsorbed onto soil, the extent of adsorption depending on the organic content and cation exchange capacity of the soil. It can bioaccumulate in lower organisms (e.g. phytoplankton, algae, molluscs and some fish) but not in higher organisms; biomagnification in food-chains is not expected to be very significant (ATSDR, 2000).

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

Levels of manganese compounds in air vary widely depending on the proximity of point sources, such as ferroalloy production facilities, coke ovens and power plants. Average manganese levels in ambient air near industrial sources have been reported to range from 220 to 300 ng/m^3, whereas manganese levels in urban and rural areas without point sources have been reported to range from 10 to 70 ng/m^3 (Barceloux, 1999). Existing data indicate that little difference is found between manganese levels in ambient air in areas where MMT is used in the petrol and air levels in areas where MMT is not used (Lynam et al., 1999). The United States Environmental Protection Agency (USEPA, 1990) estimated the average annual background concentration of

manganese in urban areas to be 40 ng/m^3, based on measurements in 102 cities in the USA.

2.2 Water

Manganese occurs naturally in many surface water and groundwater sources and in soils that may erode into these waters. However, human activities are also responsible for much of the manganese contamination in water in some areas.

A survey of snow samples near an urban expressway in Montreal, Canada (where MMT is used in petrol), was unable to establish an association between automobile emissions and manganese concentrations in the snow (Loranger et al., 1996). Loranger et al. (1994) found ambient manganese concentrations to be significantly correlated with traffic density. Areas of intermediate and high traffic densities in Montreal had ambient manganese concentrations above the natural background level of 40 ng/m^3 (Loranger & Zayed, 1994; Loranger et al., 1994).

Ambient manganese concentrations in seawater have been reported to range from 0.4 to 10 µg/l (ATSDR, 2000), with an average of about 2 µg/l (Barceloux, 1999). Levels in fresh water typically range from 1 to 200 µg/l (Barceloux, 1999). ATSDR (2000) reported that a river water survey in the USA found dissolved manganese levels ranging from <11 to >51 µg/l. The United States Geological Survey's National Water Quality Assessment Program has gathered limited data since 1991 on representative study basins around the USA. These data indicate a median manganese level of 16 µg/l in surface waters, with 99th-percentile concentrations of 400–800 µg/l (Leahy & Thompson, 1994; USGS, 2001). Higher levels in aerobic waters are usually associated with industrial pollution.

The reducing conditions found in groundwater and some lakes and reservoirs favour high manganese levels; concentrations up to 1300 µg/l in neutral groundwater and 9600 µg/l in acidic groundwater have been reported (ATSDR, 2000). The National Water Quality Assessment Program data indicate that the 99th-percentile level of manganese in groundwater (5600 µg/l) is generally higher than that in surface waters, but the median level in groundwater (5 µg/l) is lower than that in surface water (USGS, 2001).

Overall, the detection frequency of manganese in groundwater in the USA is high (approximately 70% of sites) due to the ubiquity of manganese in soil and rock, but the levels detected in groundwater are generally below levels of public health concern (USEPA, 2002). Similarly, manganese is detected in about 97% of surface water sites (at levels far below those likely to cause health effects) and universally in sediments and tissues of aquatic biota (at levels that suggest that manganese does not bioaccumulate) (USEPA, 2002).

In the USA, the National Inorganic and Radionuclide Survey collected data from 989 community public water systems served by groundwater in 49 states between 1984 and 1986 and found that manganese was detected in 68% of the groundwater systems,

with a median concentration of 10 µg/l. Supplemental survey data from public water systems supplied by surface water in five states reported occurrence ranges similar to those of groundwater. In Germany, the drinking-water supplied to 90% of all households contained less than 20 µg of manganese per litre (Bundesgesundheitsamt, 1991).

2.3 Food

Manganese occurs naturally in many food sources, such as leafy vegetables, nuts, grains and animal products (IOM, 2002). Food is the most important source of manganese exposure in the general population (ATSDR, 2000; USEPA, 2002). Typical ranges of manganese concentrations in common foods are shown below:

Type of food	*Range of mean concentrations (mg/kg)*
Nuts and nut products	18.21–46.83
Grains and grain products	0.42–40.70
Legumes	2.24–6.73
Fruits	0.20–10.38
Fruit juices and drinks	0.05–11.47
Vegetables and vegetable products	0.42–6.64
Desserts	0.04–7.98
Infant foods	0.17–4.83
Meat, poultry, fish and eggs	0.10–3.99
Mixed dishes	0.69–2.98
Condiments, fats and sweeteners	0.04–1.45
Beverages (including tea)	0.00–2.09
Soups	0.19–0.65
Milk and milk products	0.02–0.49

Source: ATSDR (2000).

Heavy tea drinkers may have a higher manganese intake than the general population. An average cup of tea may contain 0.4–1.3 mg of manganese (ATSDR, 2000). In addition to dietary sources, approximately 12% of the adult population of the USA consumed manganese supplements in 1986 (Moss et al., 1989). The median intake of manganese in these dietary supplements was determined to be 2.4 mg/day, similar to the amount of the element consumed in the diet (based on information from the Third National Health and Nutrition Estimation Survey, held in 2001).

The hazard posed by overexposure to manganese must be weighed against the necessity for some minimum amount of manganese in the diet, because manganese is an essential nutrient, acting as a component of several enzymes and a participant in a number of important physiological processes. Freeland-Graves et al. (1987) suggested a range of 3.5–7 mg/day for adults based on a review of human studies. After

reviewing dietary surveys, Greger (1999) presented a range for average intakes from adult Western and vegetarian diets of 0.7–10.9 mg of manganese per day.

Infant formulas contain 50–300 µg of manganese per litre (Collipp et al., 1983), whereas human milk contains approximately 3.5–15 µg/l (USEPA, 1997; ATSDR, 2000). Assuming an intake of 742 ml of breast milk per day (USEPA, 1996), a breastfed infant would have an estimated daily manganese intake of 2.6–11.1 µg. An infant consuming the same volume of infant formula would have an estimated daily manganese intake of 37.1–223 µg. Assuming an average weight of 6 kg for an infant aged 6 months, the weight-adjusted average daily intake would range from 0.4 to 1.9 µg/kg of body weight per day for breastfed infants. The corresponding weight-adjusted intake for a formula-fed infant would be 6.2–37.2 µg/kg of body weight per day. Regarding the high manganese content of milk-based formula, the underexposure of infants to manganese appears less probable than their overexposure (Keen et al., 1986; Dörner et al., 1987; Davidsson et al., 1989a). Once solid foods are introduced, however, the contribution of manganese intake from milk becomes less significant.

In addition to manganese concentrations in food, an important consideration for determining human exposure to manganese in food is bioavailability. Several factors can influence the degree to which manganese in foods is absorbed upon ingestion. These include intake of dietary fibre, oxalic acids, tannins and phytic acids, which tend to decrease manganese absorption (Gibson, 1994; USEPA, 2002), as well as possibly sex-specific iron status (low iron can result in increased manganese absorption; Finley, 1999).

The Food and Nutrition Board of the Institute of Medicine (IOM, 2002) set adequate intake levels for manganese at 2.3 mg/day for men and 1.8 mg/day for women. Adequate intake levels for manganese were also set for other age groups; the values were 0.003 mg/day for infants from birth to 6 months, 0.6 mg/day for infants from 7 months to 1 year, 1.2 mg/day for children aged 1–3 years, 1.5–1.9 mg/day for children aged 4–13 years and 1.6–2.3 mg/day for adolescents and adults (IOM, 2002). The adequate intake for infants (newborn to 6 months) was set based on an average manganese concentration of 0.0035 mg/l in human milk and an average milk consumption of 0.78 litres/day. The manganese concentration in human milk varies. For example, manganese concentrations in human milk have been found to range from 0.003 to 0.01 mg/l (ATSDR, 2000) and from 0.007 to 0.015 mg/l (USEPA, 1997). Assuming an intake of 0.78 litres of milk per day and concentrations in human milk ranging from 0.003 to 0.015 mg/l, an infant (0–6 months) would ingest 0.002–0.012 mg of manganese per day from human milk, the upper limit of which is higher than the adequate intake set by IOM (2002) (i.e. 0.003 mg/day).

The IOM also set a tolerable upper intake level at 11 mg/day for adults, based on a recent review (Greger, 1999; IOM, 2002) that stated that the average manganese intake for adults eating typical Western and vegetarian diets in various surveys ranged from 0.7 to 10.9 mg of manganese per day. Davis & Greger (1992) reported that women given daily supplements of 15 mg of manganese (as an amino acid–chelated

manganese supplement) for 90 days experienced no adverse effects other than a significant increase in lymphocyte manganese-dependent superoxide dismutase, a biomarker that increases in direct relation to manganese exposure (Greger, 1998, 1999).

WHO (1973) reviewed several investigations of adult diets and reported that the average daily consumption of manganese ranged from 2.0 to 8.8 mg/day. Higher manganese intakes were associated with diets high in whole-grain cereals, nuts, green leafy vegetables and tea. From manganese balance studies, WHO (1973) concluded that 2–3 mg of manganese per day is adequate for adults and 8–9 mg/day is "perfectly safe."

Evaluations of standard diets from the USA, the United Kingdom and the Netherlands reveal average daily intakes of 2.3–8.8 mg of manganese per day. Depending on individual diets, however, a normal intake may be well over 10 mg of manganese per day (Schroeder et al., 1966), especially for vegetarian diets.

2.4 Estimated total exposure and relative contribution of drinking-water

The greatest exposure to manganese is usually from food. Adults consume between 0.7 and 10.9 mg/day in the diet (Greger, 1999), with even higher intakes reportedly being associated with some vegetarian diets (Schroeder et al., 1966; Freeland-Graves et al., 1987).

Manganese intake from drinking-water is normally substantially lower than intake from food. At the median drinking-water level of 10 µg/l determined in the National Inorganic and Radionuclide Survey described above, the intake of manganese would be 20 µg/day for an adult, assuming a daily water intake of 2 litres. Drinking mineral water regularly can add significantly to manganese intake (Dieter et al., 1992). Exposure to manganese from air is generally several orders of magnitude less than that from the diet, typically around 0.04 ng/day on average (USEPA, 1990), although this can vary substantially depending on proximity to a manganese source.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Absorption of manganese across the gastrointestinal tract is regulated by normal physiological processes to help maintain manganese homeostasis. A 7-week study in which seven adult male volunteers ingested high-fibre diets containing 12.0–17.7 mg of manganese per day (0.17–0.25 mg/kg of body weight per day) found that an average of 7.7% ± 6.3% of the manganese was absorbed during weeks 5–7, with no measurable net retention of manganese (Schwartz et al., 1986). Similarly, an average absorption of 8.4% ± 4.7% was observed in seven adults ingesting infant formula containing manganese (Sandström et al., 1986). Johnson et al. (1991) studied the absorption of radiolabelled manganese from various plant foods in adult men and women and reported that the absorption ranged from 1.4% to 5.5% and was significantly lower than the mean values of 7.8–10.2% from controls (manganese(II)

chloride dissolved in water). Manganese absorption may be higher in young animals and infants (Keen et al., 1986).

As mentioned above, several factors can influence the degree to which manganese in foods is absorbed upon ingestion. These include intake of dietary fibre, oxalic acids and phytic acids, which tend to decrease manganese absorption (Gibson, 1994; USEPA, 2002). The absorption of manganese is also closely linked to iron absorption; iron-deficient diets lead to an increased absorption of both iron and manganese (Thomson et al., 1971; Sandström et al., 1986; Finley, 1999). Absorption is also related inversely to the level of calcium in the diet (Schroeder et al., 1966; McDermott & Kies, 1987; Lutz et al., 1993). Certain constituents of tea, such as tannins, can result in reduced manganese absorption (Freeland-Graves & Llanes, 1994).

Some constituents of both infant formula and breast milk may also affect manganese bioavailability. Formula made from soy protein contains high levels of phytic acids and vegetable proteins, which probably decrease manganese bioavailability. Data from Keen et al. (1986) indicate that overall uptake of manganese from soy formula in rat pups was much greater than that from human milk or cow's milk, even though fractional manganese absorption was lowest in the soy formula, because formula contains much more manganese than human milk does. If the formula is also iron-fortified, manganese bioavailability may be further decreased, although studies on the inhibitory influences of iron have produced conflicting results (Freeland-Graves, 1994). Davidsson et al. (1989a) reported that the fractional absorption of manganese in adult humans given human milk (8.2%) was significantly higher than absorption from cow's milk (2.4%) and soy formula (0.7%). Manganese in infant formula is in the divalent state (Mn^{2+}), the absorption of which cannot be regulated by the lactoferrin receptors in the gut; breast milk manganese is in the trivalent form bound to lactoferrin, and its absorption is thus regulated (USEPA, 1997). Davidsson et al. (1989a) suggested that the lactoferrin in human milk as well as the higher calcium content in cow's milk contributed to the difference in absorption. Therefore, many factors probably control manganese absorption from infant formula, and firm conclusions are difficult to make in the absence of further data.

It should be noted that Davidsson et al. (1989a) performed their studies in adults; manganese body burden in infants may be influenced by the fact that the biliary excretion system, which is the primary route of manganese excretion, is not completely developed in human infants (Lönnerdal, 1994). Dörner et al. (1989) reported high retention of manganese in infants ingesting both human milk and cow's milk formulas. Studies in rats have demonstrated that young animals absorb significantly more manganese in the gut than do mature animals (Lönnerdal et al., 1987). Also, experimental animal studies have shown that manganese crosses the blood–brain barrier in neonates at a rate 4 times higher than that in adults (Mena, 1974). The relevance of these studies to humans is unknown, however, and few direct absorption data for manganese in human infants are available. Evidence exists, however, to indicate that infants are less well protected than adults against manganese overload. The manganese contents of erythrocytes in infants up to the age of 6 weeks

are higher by about 7–9% than those in adults (Hatano et al., 1985). Collipp et al. (1983) reported manganese levels in hair that increased significantly from birth (0.19 µg/g) to 6 weeks (0.865 µg/g) and 4 months (0.685 µg/g) of age in infants given formula, whereas infants given breast milk exhibited no significant increase (0.330 µg/g at 4 months). This study also reported that the average manganese level in hair in children exhibiting learning disabilities was significantly increased (0.434 µg/g) compared with that in children who exhibited normal learning ability (0.268 µg/g). It should be noted that the Collipp et al. (1983) study did not indicate that the increased manganese level in hair was from ingested manganese.

Manganese is present in all tissues of the body, the highest levels usually being found in the liver, kidney, pancreas and adrenals (Tipton & Cook, 1963; Sumino et al., 1975). It accumulates preferentially in certain regions of the brain in infants and young animals (Zlotkin & Buchanan, 1986; Kontur & Fechter, 1988).

Manganese is almost entirely excreted in the faeces, only a small proportion (0.1–2%) being eliminated in the urine (Davis & Greger, 1992). Faecal manganese is composed of unabsorbed dietary manganese plus manganese excreted in bile. In humans, elimination is biphasic, with half-lives of 13 and 37 days (Sandström et al., 1986; Davidsson et al., 1989b). Sweat, hair and the milk of lactating mothers also contribute to excretion (Roels et al., 1992).

Possible indicators of manganese exposure are the blood, with background levels ranging from 6.7 to 7.6 µg/ml (Roels et al., 1992; Mergler et al., 1994; Loranger & Zayed, 1995), and perhaps the hair (Fergusson et al., 1983; Chutsch & Krause, 1987). Manganese levels in blood do not provide data on long-term exposure. However, the blood platelet monoamine oxidase should be taken into consideration as an early biochemical indicator for adverse oxidative effects of manganese (Benedetti & Dostert, 1989; Humfrey et al., 1990).

4. EFFECTS ON LABORATORY ANIMALS AND IN VITRO TEST SYSTEMS

4.1 Acute exposure

ATSDR (2000) noted that the acute lethality of manganese in animals appears to vary depending on the chemical species and whether exposure is via gavage or dietary ingestion. Single-dose oral median lethal dose (LD_{50}) values in adult rats exposed by gavage ranged from 331 mg of manganese per kilogram of body weight per day (as manganese chloride) (Kostial et al., 1989) to 1082 mg of manganese per kilogram of body weight per day (as manganese acetate) (Smyth et al., 1969), whereas 14-day exposure of rats to 1300 mg of manganese per kilogram of body weight per day (as manganese sulfate) in feed resulted in no deaths (NTP, 1993).

4.2 Short-term exposure

The central nervous system is the chief target of manganese toxicity. Oral doses ranging from 1 to 150 mg/kg of body weight per day produced a number of

neurological effects in rats and mice, mainly involving alterations in neurotransmitter and enzyme levels in the brain. These changes were sometimes accompanied by clinical signs, such as incoordination and changes in activity level (ATSDR, 2000). Deskin et al. (1980) reported an increase in monoamine oxidase activity in the hypothalamus in rats intubated with a daily dose of 20 mg of manganese per kilogram of body weight per day from birth to 24 days of age. Gastric irritation in the form of patchy necrosis of the epithelium was observed in guinea-pigs administered 10 mg of manganese per kilogram of body weight per day via gavage for 30 days (Chandra & Imam, 1973); the method of administration might have contributed to the observed effects, however. Male mice fed high doses of manganese in food for 13 weeks exhibited mild hyperplasia and hyperkeratosis of the forestomach; no effects were seen in female mice or male and female rats (NTP, 1993).

4.3 Long-term exposure

Chronic ingestion of 1–2 mg of manganese per kilogram of body weight per day produced changes in appetite and reduction in haemoglobin synthesis in rabbits, pigs and cattle (Hurley & Keen, 1987). Transient effects on biogenic amine levels and activities of dopamine β-hydroxylase and monoamine oxidase in rat brain have been noted with long-term exposures to manganese (Lai et al., 1984; Eriksson et al., 1987; Subhash & Padmashree, 1990). An increase in physical activity level and a transient increase in dopaminergic function were observed in rats given 40 mg of manganese per kilogram of body weight per day for 65 weeks (Nachtman et al., 1986). Two-year oral exposures to extremely high doses (1800–2250 mg/kg of body weight per day as manganese(II) sulfate) in male and female mice resulted in hyperplasia, erosion and inflammation of the forestomach; no effects were seen in rats (NTP, 1993).

Neurotoxicity is a known effect of long-term exposure to inhaled manganese in humans and animals, but the potential for neurotoxicity resulting from oral exposure is less well characterized. Muscular weakness and lower limb rigidity were observed in four male rhesus monkeys given oral doses of 6.9 mg of manganese per kilogram of body weight per day (as manganese chloride) for 18 months (Gupta et al., 1980). Degenerated neurons in the substantia nigra were observed at autopsy.

4.4 Reproductive and developmental toxicity

The results of several studies in rats and mice indicate that the ingestion of manganese can delay reproductive maturation in male animals (ATSDR, 2000). Testosterone levels were reduced in male rats given an oral dose of 13 mg of manganese per kilogram of body weight per day for 100–224 days (Laskey et al., 1982), whereas delayed growth of the testes was observed in young rats ingesting 140 mg of manganese per kilogram of body weight per day for 90 days (Gray & Laskey, 1980). These effects do not appear to be severe enough to affect male reproductive function (ATSDR, 2000). Several studies that found effects on male reproductive organs, however, did not assess reproductive performance (IPCS, 1999).

The results of most studies indicate that oral exposure to manganese does not result in reproductive toxicity in the female rodent (e.g. rats and mice) and rabbit (ATSDR, 2000), although increased post-implantation loss was observed in female rats in at least one study (Szakmáry et al., 1995). Results from several developmental studies in rodents and rabbits are equivocal. Data from the majority of these studies indicate that manganese exposure during part or all of gestation results in increased manganese levels in the pups (Järvinen & Ahlström, 1975; Kontur & Fechter, 1988) but generally causes 1) no measurable effect (Grant et al., 1997), 2) transient effects such as weight decreases and hyperactivity (Pappas et al., 1997) or 3) self-correcting effects on skeletal and organ development (Szakmáry et al., 1995). Studies involving oral exposures to manganese in drinking-water or by gavage in neonatal pups have reported changes in brain neurochemistry but generally do not show effects on neurological development (ATSDR, 2000). The data from one recent study indicate that rodent pups administered 22 mg of manganese per kilogram of body weight per day in drinking-water from birth to weaning (21 days) resulted in changes in brain neurochemistry and evoked sensory response (Dorman et al., 2000).

4.5 Mutagenicity and related end-points

The genotoxic potential of manganese in humans is not known (IPCS, 1999). Laboratory evidence for the mutagenicity and genotoxicity of manganese is equivocal. In vitro bacterial gene mutation tests have yielded both positive and negative results, whereas in vitro tests with fungi and mammalian cells have been predominantly positive. In vivo rat studies have been negative, and in vivo mouse studies have been positive (ATSDR, 2000). Manganese chloride produced an increased frequency of mutations in *Salmonella typhimurium* strain TA1537, but negative results in other strains; manganese sulfate was reported to be both positive and negative in separate studies in *Salmonella* strain TA97, but negative in other strains (IPCS, 1999). Positive results were obtained with various manganese compounds in *Photobacterium fischeri* and *Escherichia coli*, as well as in *Saccharomyces cerevisiae*, mouse lymphoma cells and hamster embryo cells (ATSDR, 2000). Manganese sulfate and potassium permanganate have been shown to increase sperm head abnormalities in vivo and increased the number of chromosomal aberrations and micronuclei in rat bone marrow (ATSDR, 2000). In spite of these results, the genotoxic potential of manganese in humans is not known (IPCS, 1999).

4.6 Carcinogenicity

No studies are available on the potential carcinogenicity of manganese following inhalation or dermal exposure in humans or experimental animals (ATSDR, 2000). A 2-year oral study of manganese sulfate in rats and mice produced equivocal evidence of carcinogenicity (NTP, 1993). In rats fed manganese sulfate (30–331 mg of manganese per kilogram of body weight per day in males, 26–270 mg of manganese per kilogram of body weight per day in females), no treatment-related increases in tumour incidence were reported. In mice fed manganese sulfate (63–722 mg of manganese per kilogram of body weight per day in males, 77–905 mg of manganese per kilogram of body weight per day in females), the incidence of follicular cell

adenoma of the thyroid was increased slightly in high-dose animals compared with controls. These increases were not statistically significant, and the tumours were observed at the end of the study only. However, follicular cell adenoma of the thyroid appears with low frequency in historical control male mice of this strain. Thus, the significance of these results and their relevance to normal human exposure to manganese are questionable.

5. EFFECTS ON HUMANS

Manganese is an essential element for many living organisms, including humans. For example, some enzymes require manganese (e.g. manganese superoxide dismutase), and some are activated by the element (e.g. kinases, decarboxylases). Adverse health effects can be caused by inadequate intake or overexposure. Manganese deficiency in humans appears to be rare, because manganese is present in many common foods. Animals experimentally maintained on manganese-deficient diets exhibit impaired growth, skeletal abnormalities, reproductive deficits, ataxia of the newborn and defects in lipid and carbohydrate metabolism (USEPA, 1984; Hurley & Keen, 1987).

The neurological effects of inhaled manganese have been well documented in humans chronically exposed to elevated levels in the workplace (Canavan et al., 1934; Cook et al., 1974; Roels et al., 1999; ATSDR, 2000). The syndrome known as "manganism" is caused by exposure to very high levels of manganese dusts or fumes and is characterized by a "Parkinson-like syndrome", including weakness, anorexia, muscle pain, apathy, slow speech, monotonous tone of voice, emotionless "mask-like" facial expression and slow, clumsy movement of the limbs. In general, these effects are irreversible. Some motor functions may already be affected following chronic exposure to levels of manganese of ≤ 1 mg/m^3 (if the inhaled manganese is respirable), but individuals in these situations have not shown the overt, clinical symptoms of those exposed to much higher levels (Roels et al., 1992; Mergler et al., 1994).

From animal experiments, it is known that inhaled manganese (even the insoluble manganese dioxide) is transported in a retrograde direction from the olfactory epithelium to the striatum of the brain (Gianutsos et al., 1997; Roels et al., 1997). During its uptake through the olfactory nerve endings (Tjälve et al., 1996; Brenneman et al., 2000; Vitarella et al., 2000; Bench et al., 2001), it may damage the astrocytes (Henriksson & Tjälve, 2000). After peroral uptake, manganese, like all other metals, is filtered from the blood by the choroid plexus (Zheng et al., 1991; Ingersoll et al., 1995). The retrograde transport of manganese through the olfactory epithelium directly into certain regions of the central nervous system or the brain could explain why the safe dose is much lower following inhalation exposure than after oral ingestion (Wang et al., 1989).

By the oral route, manganese is often regarded as one of the least toxic elements, although there is some controversy as to whether the neurological effects observed with inhalation exposure also occur with oral exposure. Several case reports of oral exposure to high doses of manganese have described neurological impairment as an

effect, but the quantitative and qualitative details of exposure necessary to establish direct causation are lacking. An individual who took large mineral supplements over several years displayed symptoms of manganism (Banta & Markesbery, 1977). Another individual who ingested 1.8 mg of potassium permanganate per kilogram of body weight per day for 4 weeks developed symptoms similar to Parkinson disease 9 months later (Holzgraefe et al., 1986; Bleich et al., 1999).

An epidemiological study in Japan described adverse effects in humans consuming manganese dissolved in drinking-water, probably at a concentration close to 28 mg/l (Kawamura et al., 1941). The manganese was derived from 400 dry-cell batteries buried near a drinking-water well. Fifteen cases of poisoning were reported among 25 persons examined, with symptoms including lethargy, increased muscle tone, tremor and mental disturbances. The most severe effects were seen in elderly people; less severe effects were seen in younger people, and effects were absent in children aged 1–6 years. However, the level of exposure to manganese was poorly quantified, and the people were also exposed to high levels of zinc. The rapid onset and progression of the symptoms and the recovery of some patients prior to mitigation of the manganese-contaminated well water suggest that exposure to other chemicals may also have been a factor in the presentation of symptoms.

An epidemiological study was conducted in Greece to investigate the possible correlation between long-term (i.e. more than 10 years) manganese exposure from water and neurological effects in elderly people (Kondakis et al., 1989). The levels of manganese in the drinking-water of three different geographical areas were 3.6–14.6 µg/l in the control area and 81–253 µg/l and 1800–2300 µg/l in the test areas. The authors concluded that progressive increases in the manganese concentration in drinking-water are associated with a progressively higher prevalence of neurological signs of chronic manganese poisoning and higher manganese concentrations in the hair of older persons. However, no data were given on exposure from other sources such as food and dust, and little information was provided on nutritional status and other possible confounding variables.

The individuals examined in the Kondakis et al. (1989) study also had exposure to manganese in their diet. This was originally estimated to be 10–15 mg/day because of the high intake of vegetables (X.G. Kondakis, personal communication, 1990). This estimate was subsequently lowered to 5–6 mg/day (X.G. Kondakis, personal communication, 1993). Because of the uncertainty in the amount of manganese in the diet and the amount of water consumed, it is impossible to estimate the total oral intake of manganese in this study. These limitations preclude the use of this study to determine a quantitative dose–response relationship for the toxicity of manganese in humans.

Contrary to the above study, another long-term drinking-water study in a northern rural area of Germany (Vieregge et al., 1995) found no neurological effects of manganese at a level of at least 0.3 mg/l. No significant differences in neurological tests were found in older people (41 subjects older than 40 years with a mean age of 57.5 years) consuming well water containing at least 0.3 mg of manganese per litre

(0.3–2.16 mg/l) for 10–40 years. The control group (74 subjects, mean age 56.9 years) was exposed to water containing less than 0.05 mg of manganese per litre. Subjects of both groups were randomly selected and matched with respect to age, sex, nutritional habits and drug intake. However, like the Kondakis et al. (1989) study, this study lacks exposure data from other routes and sources, and the manganese concentration range in the water is very wide.

In one area of Japan, a manganese concentration of 0.75 mg/l in the drinking-water supply had no apparent adverse effects on the health of consumers (Suzuki, 1970). No signs of toxicity were observed in patients given 30 mg of manganese citrate (9 mg of manganese) per day for many months (Schroeder et al., 1966). The incidence of motor neuron disease in a small Japanese town was positively correlated with a significantly increased manganese concentration in local rice and a low magnesium concentration in the drinking-water (Iwami et al., 1994). The study did not provide good estimates of overall exposure to manganese in either the control population or the population with motor neuron disease; therefore, development of the disease could not be conclusively attributed to manganese exposure. The simultaneous exposure to manganese and the deficiency of other essential minerals were possibly the reasons for the enhanced incidence of neurotoxicological symptoms in Japan and in another population in Guam (Yoshida et al., 1988; Florence & Stauber, 1989). There was also some speculation on a link between mineral deficiency, enhanced oral manganese uptake and manganese-catalysed denaturation of copper-free prion protein to the pathogenic prion protein (Brown et al., 2000), which could contribute to the enhanced occurrence of some prion diseases in certain world regions (Purdey, 2000).

Adverse neurological effects (decreased performance in school and in neurobehavioural examinations of the World Health Organization core test battery) were reported in 11- to 13-year-old children who were exposed to excess manganese through ingestion of contaminated water and from wheat fertilized with sewage water (He et al., 1994; Zhang et al., 1995). The exposed and control groups were both from farming communities and were matched for age, sex, grade, family income level and parental education level. The average manganese concentration of the drinking-water of the exposed group was 0.241 mg/l compared with the control level of 0.04 mg/l. The total exposure data, including manganese exposure from food, water and air, exposure duration, the nutritional status of the children and other confounding factors were not well characterized. Therefore, it was not possible to establish a cause–effect link between ingestion of excess manganese and preclinical neurological effects in children. Oral uptake of environmental manganese together with a deficiency of other minerals was suggested as a possible contributory factor to explain the enhanced incidence of neurological symptoms in isolated populations on Guam and the Kii Peninsula in East Asia (Yoshida et al.. 1988; Florence & Stauber, 1989; Iwami et al., 1994).

6. PRACTICAL CONSIDERATIONS

6.1 Analytical methods

Sensitive methods exist for measuring total manganese in biological and environmental samples, although distinguishing between different oxidation states of manganese is not possible (IPCS, 1999). Atomic absorption spectroscopy is used for determining manganese concentrations in biological samples (e.g. urine, faeces and hair) at a detection limit as low as 1 µg/l for urine and 0.2 µg/g for hair. The technique has also been used to analyse manganese concentrations in water samples at levels as low as 0.01 µg/l (ATSDR, 2000). Inductively coupled argon–plasma optical emission spectrometry has also been used to measure manganese concentrations in biological fluids, water, waste products and air and has a detection limit of around 1–2 µg/l for liquids and 5 µg/m^3 for air (ATSDR, 2000). Colorimetric methods are also used in water analysis and have detection limits of about 10 µg/l (ISO, 1986).

6.2 Treatment methods and performance

Manganese concentrations in drinking-water are easily lowered using common treatment methods. Oxidation and filtration are usually adequate to achieve a manganese concentration of 0.05 mg/l in drinking-water.

7. CONCLUSION

Experimental animal data, especially rodent data, are not desirable for human risk assessment, because the physiological requirements for manganese vary among different species. Further, rodents are of limited value in assessing neurobehavioural effects, because the neurological effects (e.g. tremor, gait disorders) seen in primates are often preceded or accompanied by psychological symptoms (e.g. irritability, emotional lability), which are not apparent in rodents. The only primate study (Gupta et al., 1980) is of limited use in a quantitative risk assessment, because only one dose group was studied in a small number of animals, and information on the manganese content in the basal diet was not provided.

While several studies have determined average levels of manganese in various diets, no quantitative information is available to indicate toxic levels of manganese in the diet of humans. Because of the homeostatic control that humans maintain over manganese, manganese is generally not considered to be very toxic when ingested with the diet.

A review of typical Western and vegetarian diets found average adult manganese intakes ranging from 0.7 to 10.9 mg/day (Greger, 1999; IOM, 2002). The upper range manganese intake value of 11 mg/day from dietary studies is considered a no-observed-adverse effect level (NOAEL). It is not believed that this amount of manganese in the diet represents an overexposure to the element (IOM, 2002).

A health-based value can be calculated using this upper range value. A tolerable daily intake (TDI) of 0.06 mg/kg of body weight can be calculated by dividing the NOAEL of 11 mg/day by an uncertainty factor of 3 (to allow for the possible increased bioavailability of manganese from water) and an adult body weight of 60 kg. The guideline value of 0.4 mg/l is then derived from the TDI by assuming an allocation of 20% of the TDI to drinking-water and consumption of 2 litres of drinking-water per day by a 60 kg adult. However, as this health-based value is well above concentrations of manganese normally found in drinking-water, it is not considered necessary to derive a formal guideline value.

It should be noted that the presence of manganese in drinking-water will be objectionable to consumers if the manganese is deposited in water mains and causes water discoloration. Concentrations below 0.05 mg/l are usually acceptable to consumers, although this may vary with local circumstances.

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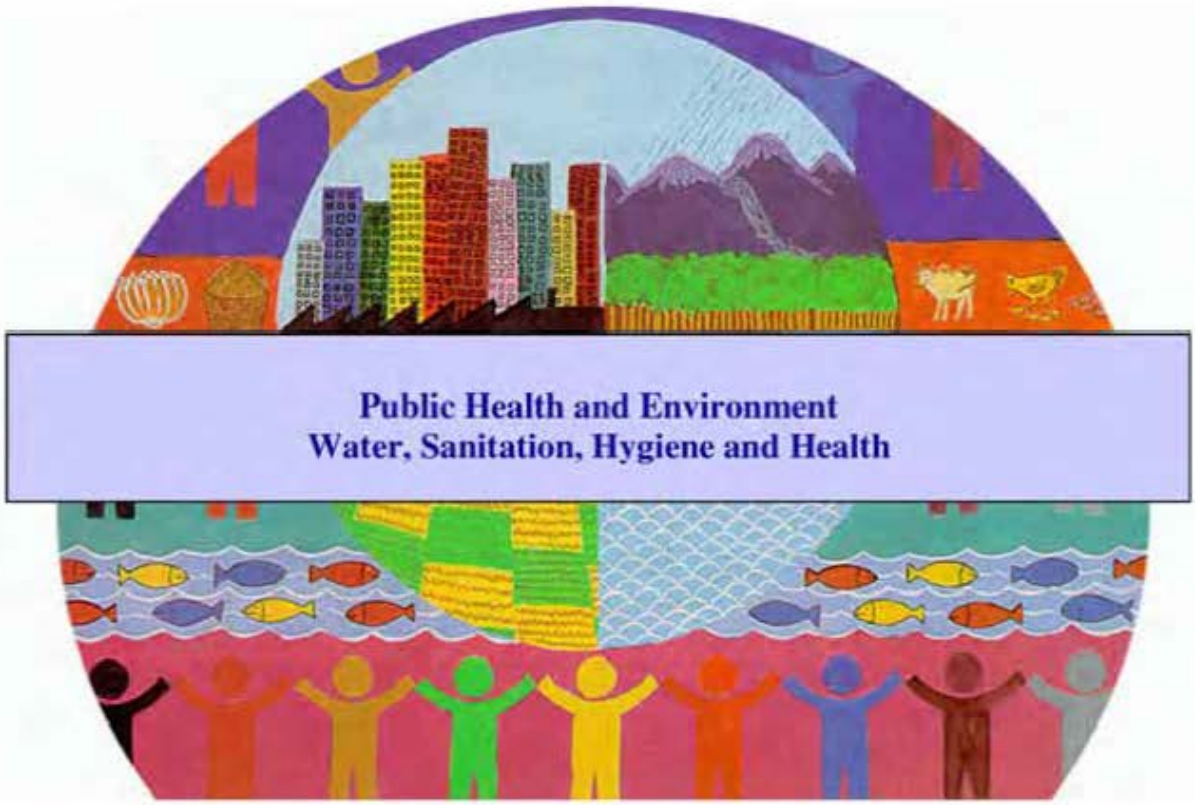

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Pharmaceuticals in Drinking-water

Contents

List of acronyms and abbreviations

ADI	acceptable daily intake
DWEL	drinking-water equivalent level
EDC	endocrine disrupting chemical
FAO	Food and Agriculture Organization of the United Nations
GAC	granular activated carbon
GC	gas chromatography
LC	liquid chromatography
LOAEL	lowest-observed-adverse-effect level
LOQ	limit of quantification
MF	microfiltration
MOE	margin of exposure
MS	mass spectrometry
MS/MS	tandem mass spectrometry
MTD	minimum therapeutic dose
nd	not detected
NF	nanofiltration
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
PAC	powdered activated carbon
PoD	point of departure
PUB	Public Utilities Board (Singapore)
RO	reverse osmosis
SF	sand filtration
TDI	tolerable daily intake
UF	ultrafiltration
USA	United States of America
USEPA	United States Environmental Protection Agency
UV	ultraviolet
WHO	World Health Organization
WSH	Water, Sanitation, Hygiene and Health unit (WHO)

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Executive summary

Background

In the last decade, traces of pharmaceuticals, typically at levels in the nanograms to low micrograms per litre range, have been reported in the water cycle, including surface waters, wastewater, groundwater and, to a lesser extent, drinking-water. Advances in analytical technology have been a key factor driving their increased detection. Their presence in water, even at these very low concentrations, has raised concerns among stakeholders, such as drinking-water regulators, governments, water suppliers and the public, regarding the potential risks to human health from exposure to traces of pharmaceuticals via drinking-water.

Following requests from several Member States for information regarding the potential health impacts of residual concentrations of pharmaceuticals in drinking-water, this issue was added to the work plan of the World Health Organization (WHO) Drinking-water Quality Committee in 2005. It was proposed that a working group of experts be assembled to undertake a rapid review of the state of the science of pharmaceuticals in drinking-water and develop guidance and recommendations in a report and fact sheet.

A WHO working group that comprised experts in toxicology, water chemistry, water quality and health, water treatment, pharmacology, and drinking-water regulation and policy was formed in 2009. Consultations were held in 2009 and 2010 with the Drinking-water Quality Committee and additional experts to review and summarize the available scientific knowledge and evidence.

A literature review was a key source of evidence. This examined the fate and occurrence of pharmaceuticals in water, exposure to pharmaceuticals in drinking-water, assessment of the human health risk associated with pharmaceuticals in drinking-water, removal of pharmaceuticals during wastewater and drinking-water treatment, and preventive management measures to reduce potential exposure to pharmaceuticals in drinking-water.

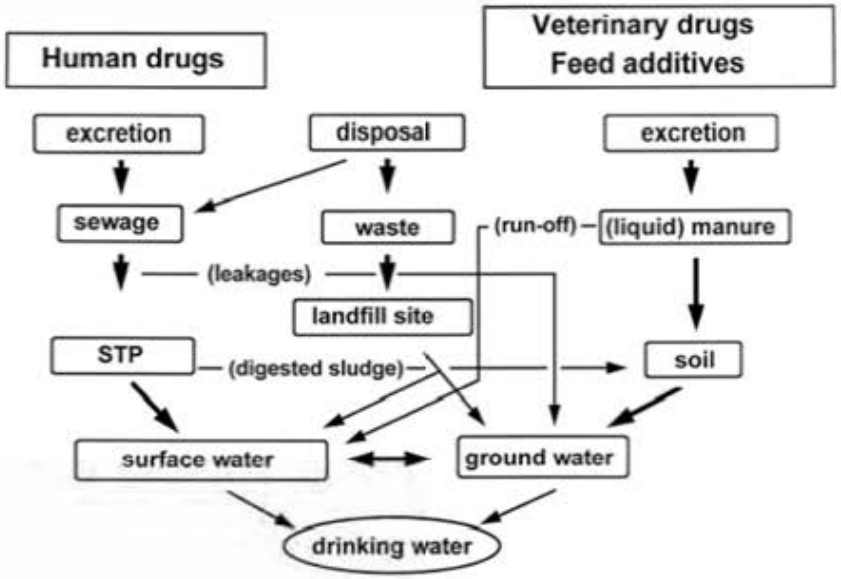
This report contains the key findings and recommendations of the working group and consultations with experts in the Drinking Water Quality Committee. It aims to provide practical guidance and recommendations for managing the emerging concern about pharmaceuticals in drinking-water, taking into consideration the evidence from the literature review. More importantly, it emphasizes the need to prioritize this emerging issue in the overall context of water safety management, which includes microbial and other chemical risks that may threaten the safety of drinking-water.

Scope

This report focuses primarily on reviewing the risks to human health associated with exposure to trace concentrations of pharmaceuticals in drinking-water. It does not discuss the potential impacts on aquatic ecosystems or the broader physical environment.

Occurrence of pharmaceuticals in water

Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs. Pharmaceuticals contain active ingredients that have been designed to have pharmacological effects and confer significant benefits to society. The occurrence of pharmaceuticals in the environment and the water cycle at trace levels (in the range of nanograms to low micrograms per litre) has been widely discussed and published in literature in the past decade. The increase in detection is largely attributable to the advances in analytical techniques and instrumentation. Many surveys and studies have confirmed the presence of pharmaceuticals in municipal wastewater and effluents, and these have been identified as a major source of pharmaceuticals in drinking-water (Figure ES1).



Note: STP is sewage treatment plant.

Figure ES1: Fate and transport of pharmaceuticals in the environment (Ternes, 1998)

Routine monitoring programmes to test drinking-water for pharmaceuticals have not been implemented, as is the case for regulated chemical and microbial parameters. Generally, data on the occurrence of pharmaceuticals in drinking-water have resulted from ad hoc surveys or targeted research projects and investigations. Available studies have reported that concentrations of pharmaceuticals in surface waters, groundwater and partially treated water are typically less than 0.1 µg/l (or 100 ng/l), and concentrations in treated water are generally below 0.05 µg/l (or 50 ng/l).

More systematic studies will help to further our understanding of the transport, occurrence and fate of pharmaceuticals in the environment, especially drinking-water sources. Standardization of protocols for sampling and analysing pharmaceuticals would help to facilitate the comparison of data.

Human health risk assessment for pharmaceuticals in drinking-water

Pharmaceuticals are normally governed by stringent regulatory processes and require rigorous preclinical and clinical studies to assess their efficacy and safety before

commercialization. Therefore, pharmaceuticals are generally better characterized than other environmental contaminants.

This report reviews human health risk assessments of pharmaceuticals in drinking-water conducted in the United Kingdom, Australia and the United States of America (USA). The approaches of acceptable daily intake (ADI) or minimum therapeutic dose (MTD) were adopted as the point of departure in these studies to assess potential risks to human health through exposure to pharmaceuticals in drinking-water. Margins of exposure (MOEs) were derived by comparing measured or modelled exposure levels in drinking-water with a reference exposure concentration, which was usually the ADI or MTD or sometimes a drinking-water equivalent level (DWEL). A judgement of safety could then be based on the magnitude of this MOE for the pharmaceutical under consideration. In other words, screening values to determine whether further action is warranted could be derived from the ADI or the MTD, with uncertainty factors applied as appropriate.

Analysis of the results indicated that appreciable adverse health impacts to humans are very unlikely from exposure to the trace concentrations of pharmaceuticals that could potentially be found in drinking-water. Concentrations of pharmaceuticals in drinking-water are generally more than 1000-fold below the MTD, which is the lowest clinically active dosage. The findings from these three case-studies are in line with the evidence published over the past decade, which suggests that appreciable risks to health arising from exposure to trace levels of pharmaceuticals in drinking-water are extremely unlikely.

Treatment technologies for removal of pharmaceuticals from drinking-water

Having established that raw sewage and wastewater effluents are a major source of pharmaceuticals found in surface waters and drinking-water, it is important to consider and characterize the efficiency of processes for the removal of pharmaceuticals during wastewater and drinking-water treatment. Most of the research has been conducted at the laboratory scale or at full scale in developed countries, including the USA, Japan, the Republic of Korea and countries in Europe.

Even though wastewater and drinking-water treatment processes are not designed specifically to remove pharmaceuticals, they may do so to varying degrees. Pharmaceuticals are not "unusual" chemicals; their removal efficiencies during wastewater and drinking-water treatment are dependent on their physical and chemical properties. In cases where regulations require controls to mitigate risks from exposure to pesticides, treatment barriers may already be optimized to remove pharmaceuticals.

Conventional wastewater treatment facilities generally have activated sludge processes or other forms of biological treatment such as biofiltration. These processes have demonstrated varying removal rates for pharmaceuticals, ranging from less than 20% to greater than 90%. The efficiency of these processes for the removal of pharmaceuticals varies within and between studies and is dependent on operational configuration of the wastewater treatment facility. Factors influencing removal include sludge age, activated sludge tank temperature and hydraulic retention time.

Comparatively, advanced wastewater treatment processes, such as reverse osmosis, ozonation and advanced oxidation technologies, can achieve higher removal rates for pharmaceuticals.

Studies on conventional drinking-water treatment processes have shown that coagulation is largely ineffective in removing pharmaceuticals. Free chlorine is able to remove up to approximately 50% of the pharmaceuticals investigated, whereas chloramines have lower removal efficiency. Compounds that showed high removal by free chlorine but low removal by chloramines include antibiotics, such as sulfamethoxazole, trimethroprim and erythromycin.

Advanced water treatment processes, such as ozonation, advanced oxidation, activated carbon and membranes (e.g. nanofiltration, reverse osmosis), are able to achieve higher removal rates (above 99%) for targeted pharmaceutical compounds in various studies in the published literature.

Advanced and costly water treatment technology will not be able to completely remove all pharmaceuticals to concentrations less than the detection limits of the most sensitive analytical procedures at all times. Therefore, it is imperative that the toxicological relevance of various compounds be considered in the context of appreciable risks to human health. An informed risk assessment is essential before scarce resources are allocated to upgrade or invest in additional advanced treatment processes to reduce trace concentrations of pharmaceuticals in drinking-water.

Preventing pharmaceuticals in drinking-water

Conventional drinking-water quality monitoring that focuses on end-product testing is resource intensive in terms of capital investment and human resources. Coupled with an expanding list of chemical contaminants in drinking-water and water sources that may be of insignificant health concern, an overemphasis on end-product monitoring and the upgrading of treatment infrastructure is not a sustainable, optimal use of limited resources.

As outlined in the WHO *Guidelines for Drinking-water Quality*, the water safety plan approach is "the most effective means of consistently ensuring the safety of a drinking-water supply … through the use of a comprehensive risk assessment and risk management approach that encompasses all steps in the water supply from catchment to consumer". Water safety plans highlight the importance of considering risk assessment and risk management comprehensively from source to tap and adopting preventive measures to address the source of risks.

Adapting the water safety plan approach to the context of pharmaceuticals in drinking-water means that preventing pharmaceuticals from entering the water supply cycle during their production, consumption (i.e. excretion) and disposal is a pragmatic and effective means of risk management. Preventive measures need to be applied as close as possible to the source of the risk and hazard.

Inappropriate disposal practices, such as flushing unwanted or excess drugs down toilets and sinks and discarding them into household waste, are common and may be

the main contributors to pharmaceuticals in wastewater and other environmental media, such as surface waters and landfill leachate.

Preventive measures, such as policies promoting or regulations governing disposal practices at concentrated point sources (e.g. health-care and veterinary facilities), can reduce the amount of pharmaceutical waste entering water bodies. In addition, take-back programmes, guidance and enhanced consumer education will support efforts for the proper disposal of medicines and reduce the impact of pharmaceuticals entering our water sources.

Conclusions

Published literature and national studies have shown that concentrations of pharmaceuticals in surface water and groundwater sources impacted by wastewater discharges are typically less than 0.1 µg/l (or 100 ng/l), and concentrations in treated drinking-water are usually well below 0.05 µg/l (or 50 ng/l). There are few comprehensive, systematic studies on the occurrence of pharmaceuticals in drinking-water. Limited data on the occurrence of pharmaceuticals in drinking-water are a challenge in assessing potential human health risks from exposure to trace concentrations of pharmaceuticals in drinking-water.

Several approaches to screen and prioritize pharmaceuticals have been published in peer-reviewed literature. These approaches usually apply the principles of the point of departure to derive a margin of exposure between the reported worst-case exposure and the MTD, the ADI or sometimes the DWEL.

Targeted investigations conducted in the United Kingdom, the USA and Australia found that pharmaceuticals are largely present in drinking-water at concentrations several orders of magnitude (more than 1000-fold) below the minimum therapeutic dose and largely below the calculated ADIs and DWELs. The substantial margins of safety for individual compounds suggest that appreciable adverse impacts on human health are very unlikely at current levels of exposure in drinking-water.

From a treatment perspective, pharmaceuticals are not unusual organic chemicals, and treatment removal rates depend on the physical and chemical properties of the compounds. Conventional treatment processes with chlorination (free chlorine) can remove about 50% of these compounds, whereas advanced treatment processes, such as ozonation, advanced oxidation, activated carbon and membranes (e.g. reverse osmosis, nanofiltration), can achieve higher removal rates; reverse osmosis, for example, can remove more than 99% of large pharmaceutical molecules.

Recommendations

Trace quantities of pharmaceuticals in drinking-water are very unlikely to pose risks to human health because of the substantial margin of exposure or margin of safety between the concentrations detected and the concentrations likely to evoke a pharmacological effect.

Concerns over pharmaceuticals should not divert the attention and valuable resources of water suppliers and regulators from the various bacterial, viral and protozoan waterborne pathogens and other chemical priorities, such as lead and arsenic.

The current levels of exposure to pharmaceuticals in drinking-water also suggest that the development of formal guideline values for pharmaceuticals in the WHO *Guidelines for Drinking-water Quality* is unwarranted.

Routine monitoring of pharmaceuticals in water sources and drinking-water at the national level and the installation of specialized drinking-water treatment infrastructure to reduce the very low concentrations of pharmaceuticals in drinking-water are not currently deemed necessary given the limited additional health benefits. However, where specific circumstances, such as a catchment survey, indicate a potential for elevated concentrations of pharmaceuticals in the water cycle (surface water, groundwater, wastewater effluent and drinking-water), relevant stakeholders could undertake targeted, well-designed and quality-controlled investigative studies to obtain more information to assess potential health risks arising from exposure through drinking-water. If necessary, screening values could be developed and an assessment of the need for treatment enhancement could also be considered within the context of other risks and priorities using the water safety plan.

Human exposure to pharmaceuticals through drinking-water can be reduced through a combination of preventive measures, such as take-back programmes, regulations, public guidance and consumer education to encourage the proper disposal of unwanted pharmaceuticals and minimize the introduction of pharmaceuticals into the environment.

Enhanced risk communication to the public and public education efforts on water quality issues from the human health standpoint will help the public to better understand this issue relative to other hazards, such as pathogenic microbial risks. This means conveying the risks of exposure to very low concentrations of pharmaceuticals in drinking-water to the public using plain language.

Knowledge gaps and future research

Although current published risk assessments indicate that trace concentrations of pharmaceuticals in drinking-water are very unlikely to pose risks to human health, knowledge gaps exist in terms of assessing risks associated with long-term exposure to low concentrations of pharmaceuticals and the combined effects of mixtures of pharmaceuticals.

Future research in these areas may be beneficial to better characterize potential health risks from long-term, low-level exposure to pharmaceuticals, particularly for sensitive subpopulations.

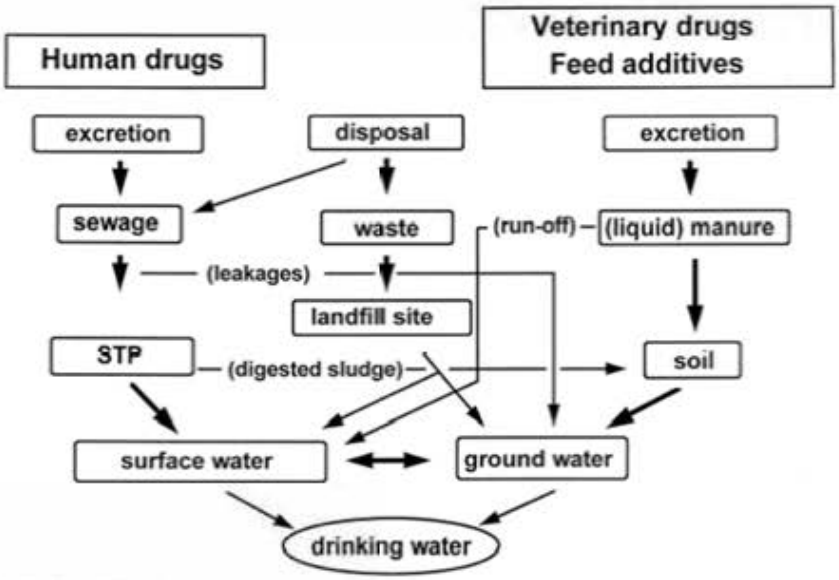
One of the key challenges in estimating exposures to pharmaceuticals in drinking-water and assessing the potential risks to human health is the limited occurrence data for such a diverse group of human and veterinary pharmaceuticals. Implementing monitoring programmes is resource intensive in terms of costs, human resources and infrastructure, and there is also a lack of standardized sampling and analysis protocols

to support monitoring studies. Future research should focus on filling these knowledge gaps, including by providing support to practitioners through the development of cost-effective methods and protocols for prioritizing pharmaceuticals within the context of an overall risk assessment for all drinking-water hazards.

Noting that pharmaceuticals in drinking-water are an emerging issue, WHO will continue to review relevant scientific evidence and, where necessary, update the guidance provided in this report.

1. Occurrence of pharmaceuticals in water

Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs, and they contain active ingredients that evoke pharmacological effects and confer significant benefits to society. The ubiquitous use of pharmaceuticals in human and veterinary medical practices, aquaculture and agricultural products has led to the continual release of a wide array of pharmaceutical chemicals into our environment. As illustrated in Figure 1, pharmaceuticals enter the environment through many routes, including human or animal excreta, wastewater effluent, treated sewage sludge, industrial waste, medical waste from health-care and veterinary facilities, landfill leachate and biosolids.



Note: STP is sewage treatment plant.

Figure 1: Fate of pharmaceuticals in the environment (Ternes, 1998)

Pharmaceuticals and their metabolites undergo natural attenuation by adsorption, dilution or degradation in the environment, depending on their hydrophobicity and biodegradability and on the temperature. Therefore, pharmaceuticals in water sources and drinking-water are often present at trace concentrations, as these compounds would have undergone metabolism and removal through natural processes and, if applicable, wastewater and drinking-water treatment processes.

1.1 Advances in analytical and detection methods

The increase in reported detections of very low concentrations of pharmaceuticals in various environmental matrices, including the water cycle (e.g. surface water, groundwater, treated wastewater effluent and drinking-water), is mainly attributable to technological advances in the sensitivity and accuracy of detection equipment and analytical methods. Gas chromatography with mass spectrometry (GC-MS) or tandem mass spectrometry (GC-MS/MS) and liquid chromatography with mass spectrometry

(LC-MS) or tandem mass spectrometry (LC-MS/MS)[1] are advanced methods that are able to determine target compounds to the nanogram per litre level and are commonly applied for the detection of pharmaceutical compounds in water and wastewater. The selection of methods is dependent on the physical and chemical properties of the target compound. LC-MS/MS analysis is more suitable for measuring target compounds that are more polar and highly soluble in water, whereas GC-MS/MS is better for more volatile target compounds. Figure 2 provides examples of pharmaceuticals in water and wastewater that can be detected using these advanced analytical methods (Fatta et al., 2007).

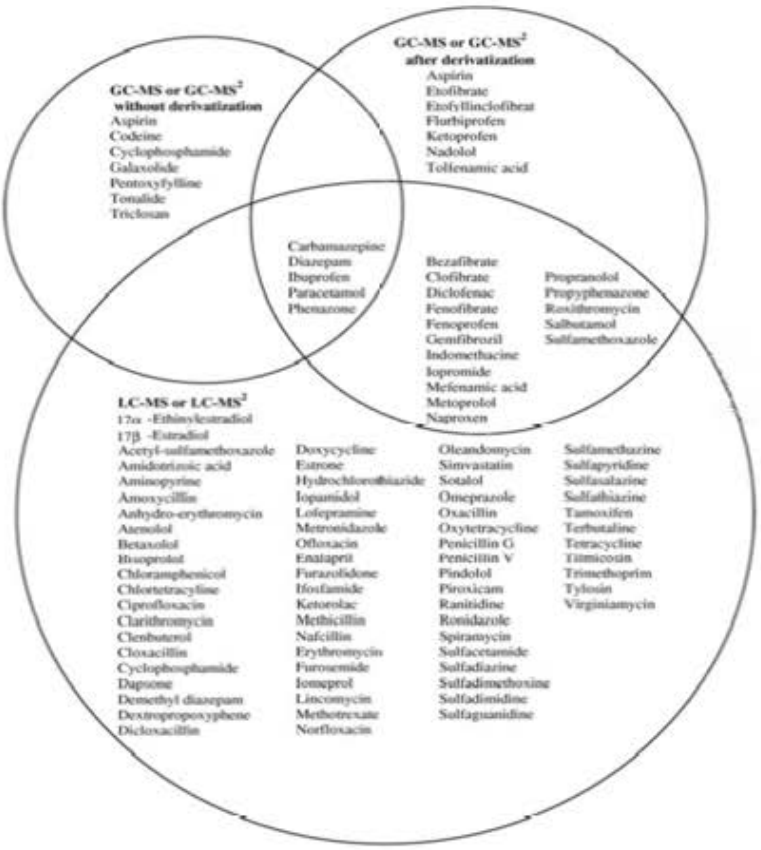


Figure 2. An illustration of analytical methods applied to detect pharmaceuticals in water and wastewater (Fatta et al., 2007)

Whereas improved detection and analytical capabilities will allow us to learn more about the fate and occurrence of pharmaceutical chemicals in the environment, including the water cycle, it is important to recognize that detection of these compounds does not directly correlate to human health risks that could be verified by available human risk assessment methods. In addition, there is currently no standardized practice or protocol for the sampling and analytical determination of pharmaceuticals in water or any other environmental media that ensures the comparability and quality of the data generated.

[1] GC-MS/MS and LC-MS/MS refer to GC-MS² and LC-MS², respectively, in Figure 2.

1.2 Occurrence of pharmaceuticals in surface water

Scientists demonstrated the presence of pharmaceuticals in the environment more than 30 years ago, with studies in the United States of America (USA) in the 1970s that reported the presence of heart medications, pain relievers and birth control medications in wastewater (Tabak & Bunch, 1970; Garrison, Pope & Allen, 1976; Hignite & Azarnoff, 1977). The most cited reference in the peer-reviewed literature on the occurrence of pharmaceuticals in surface waters is the survey by the United States Geological Survey, in which more than 50 pharmaceuticals in 139 streams across 30 states in USA were investigated during 1999 and 2000 (Kolpin et al., 2002).

Many peer-reviewed and published studies have shown that the primary sources of pharmaceuticals entering surface water are from excretion and bathing through treated or untreated municipal wastewater effluent discharges into receiving surface water bodies (Buser, Muller & Theobald, 1998; Ternes, 1998; Buser, Poiger & Muller, 1999; Daughton & Ternes, 1999; Daughton, 2001; Heberer et al., 2001; Heberer, Reddersen & Mechlinski, 2002; Kolpin et al., 2002) and improper disposal of pharmaceutical waste and excess medication by consumers and health-care and veterinary facilities into sewers and drains. Table 1 illustrates several classes of pharmaceuticals found in wastewater influent in a study conducted by the Drinking Water Inspectorate in the United Kingdom.

Table 1. Excretion rates of unmetabolized active ingredients for selected pharmaceuticals

Compound	Pharmaceutical product group	Parent compound excreted (%)	Reference
Amoxycillin	Antibiotic	60	Bound & Voulvoulis (2005)
Atenolol	Beta blocker	90	Bound & Voulvoulis (2005)
Bezafibrate	Lipid regulator	50	Bound & Voulvoulis (2005)
Carbamazepine	Antiepileptic	3	Bound & Voulvoulis (2005)
Cetirizine	Antihistamine	50	Bound & Voulvoulis (2005)
Clofibric acid	Active metabolite	6	Alder et al. (2006)
Diclofenac	Anti-inflammatory	15	Alder et al. (2006)
Erythromycin	Antibiotic	25	Bound & Voulvoulis (2005)
Felbamate	Antiepileptic	40–50	Bound & Voulvoulis (2005)
Ibuprofen	Analgesic	10	Bound & Voulvoulis (2005)

Source: DWI (2007)

A monitoring programme in the United Kingdom focused on 12 pharmaceutical compounds or their metabolites in surface waters (Ashton, Hilton & Thomas, 2004). The results showed that a range of pharmaceuticals from different therapeutic classes were present in both effluents from sewage treatment works and receiving waters in England. The values reported were within the same range as those reported in continental Europe and the USA, where more extensive monitoring has been conducted. Results in the published literature for studies conducted in the USA and Europe also suggest that usage data are positively associated with concentrations of pharmaceuticals measured in effluent and in surface water bodies receiving the treated effluent. Tables 2 and 3 show additional illustrative examples of pharmaceuticals that have been found in the United Kingdom and other European countries, respectively.

Table 2. Measured concentrations of selected pharmaceuticals in the aquatic environment in the United Kingdom

Compound	Median (maximum) concentration (ng/l)		References
	Sewage treatment works effluent	Stream or river waters	
Bleomycin	11 (19)	nd (17)	Aherne, Hardcastle & Nield (1990)
Clotrimazole	14 (27)	21 (34)	Roberts & Thomas (2006)
	—	7 (22)	Thomas & Hilton (2004)
Diclofenac	424 (2349)	< LOQ (568)	Ashton, Hilton & Thomas (2004)
	289 (598)	< LOQ	Roberts & Thomas (2006)
	—	< LOQ (195)	Thomas & Hilton (2004)
Dextropropoxyphene	195 (585)	58 (682)	Ashton, Hilton & Thomas (2004)
	37 (64)	12 (98)	Roberts & Thomas (2006)
Erythromycin	—	< LOQ (80)	Thomas & Hilton (2004)
	< LOQ (1842)	< LOQ (1022)	Ashton, Hilton & Thomas (2004)
Fluoxetine	202 (290)	5 (70)	Roberts & Thomas (2006)
	7.6–52.9	2–43.7	Boucard & Gravell (2006)
Ibuprofen	3086 (27 256)	826 (5044)	Ashton, Hilton & Thomas (2004)
	2972 (4239)	297 (2370)	Roberts & Thomas (2006)
	—	48 (930)	Thomas & Hilton (2004)
Mefenamic acid	133 (1440)	62 (366)	Ashton, Hilton & Thomas (2004)
	340 (396)	< LOQ	Roberts & Thomas (2006)
	—	< LOQ (196)	Thomas & Hilton (2004)
Norfluoxetine	5.2–30.7	4.5–83.0	Boucard & Gravell (2006)
Paracetamol	< 20	—	Roberts & Thomas (2006)
	—	555	Bound & Voulvoulis (2006)
Propanolol	76 (284)	29 (215)	Ashton, Hilton & Thomas (2004)
	304 (373)	61 (107)	Roberts & Thomas (2006)
	—	< LOQ (56)	Thomas & Hilton (2004)
Sulfamethoxazole	< LOQ (132)	< LOQ	Ashton, Hilton & Thomas (2004)
Tamoxifen	< LOQ (42)	< LOQ	Ashton, Hilton & Thomas (2004)
Tetracycline	—	~1000	Watts et al. (1983)
Theophylline	—	~1000	Watts et al. (1983)
Trimethoprim	70 (1288)	< LOQ (42)	Ashton, Hilton & Thomas (2004)
	271 (322)	9 (19)	Roberts & Thomas (2006)
	—	7 (569)	Thomas & Hilton (2004)

LOQ, limit of quantification; nd, not detected (below the detection limit)
Source: DWI (2007)

Table 3. Concentrations of selected pharmaceuticals found in European surface waters

Compound	Median (maximum) concentrations (ng/l)				
	Austria	Finland	France	Germany	Switzerland
Bezafibrate	20 (160)	5 (25)	102 (430)	350 (3100)	—
Carbamazepine	75 (294)	70 (370)	78 (800)	25 (110)	30–150
Diclofenac	20 (64)	15 (40)	18 (41)	150 (1200)	20–150
Ibuprofen	nd	10 (65)	23 (120)	70 (530)	nd (150)
Iopromide	91 (211)	—	7 (17)	100 (910)	—
Roxithromycin	nd	—	9 (37)	< LOQ (560)	—
Sulfamethoxazole[a]	nd	—	25 (133)	30 (480)	—

LOQ, limit of quantification; nd, not detected (below the detection limit)

[a] Includes the human metabolite N^4-acetyl-sulfamethoxazole.

Source: Ternes et al. (2005)

1.3 Occurrence of pharmaceuticals in drinking-water

Most countries (if any) do not have monitoring programmes to routinely test for pharmaceuticals in drinking-water owing to practical difficulties, such as high costs and lack of availability of routine analytical technologies and laboratory infrastructure to detect a diverse range of pharmaceuticals and their metabolites. As a result, the majority of the occurrence data for pharmaceuticals in drinking-water and surface waters come from targeted research projects, targeted investigations and ad hoc surveys, most of which were designed to develop, test and fine-tune detection and analytical methods. Nevertheless, they did provide an initial indication of the presence of pharmaceuticals in the environment.

Studies in the USA have detected very low levels of pharmaceuticals in finished drinking-water. The highest concentration reported was 40 ng/l for meprobamate (Benotti et al., 2009). Studies have also found several pharmaceuticals in tap water at concentrations ranging from nanograms to low micrograms per litre in several countries in Europe, including Germany, the Netherlands and Italy (Huerta-Fontela, Galceran & Ventura, 2011). Two separate studies in Germany (Reddersen, Heberer & Dünnbier, 2002; Zühlke et al., 2004) found phenazone and propylphenazone (an analgesic and an antipyretic drug, respectively) in Berlin drinking-water, with the highest concentration being 400 ng/l for phenazone. This high value was largely attributed to groundwater, used as a drinking-water source, contaminated with sewage (Jones, Lester & Voulvoulis, 2005). In the Netherlands, traces of antibiotics, antiepileptics and beta blockers were detected in the drinking-water supply at concentrations below 100 ng/l, with most concentrations below 50 ng/l (Mons, Hoogenboom & Noij, 2003).

To date, between 15 and 25 pharmaceuticals have been detected in treated drinking-water worldwide, as reported in the peer-reviewed scientific literature (Jones, Lester & Voulvoulis, 2005; Benotti et al., 2009). More pharmaceutical compounds have been detected in untreated water sources, such as wastewater, surface waters and groundwaters (Focazio et al., 2008) in the water cycle, largely attributable to pharmaceuticals of very high usage, including antihyperlipidaemic compounds and non-steroidal anti-inflammatory drugs (NSAIDs).

1.4 Conclusion

The occurrence of pharmaceuticals in the environment, including the water cycle, at concentrations ranging from nanograms to low micrograms per litre has been widely discussed and published in the literature in the past decade (Heberer, Schmidt-Bäumler & Stan, 1998; Zuccato et al., 2000; Heberer, Fuhrmann, Schmidt-Baumier, Tsipi, Koutsouba & Hiski, 2001; Heberer et al., 2004; Stackelberg et al., 2004, 2007; Zühlke et al., 2004; Jones, Lester & Voulvoulis, 2005; Vieno, Tuhkanen & Kronberg, 2005; Loraine et al., 2006; Loraine & Pettigrove, 2006; Snyder et al., 2006; Vanderford & Snyder, 2006; Loos et al., 2007; Pérez & Barceló, 2007; Togola & Budzinski, 2008; Mompelat, Le Bot & Thomas, 2009).

The published literature and national studies have shown that concentrations of pharmaceuticals in surface water and groundwater sources impacted by wastewater discharges are typically less than 0.1 µg/l (or 100 ng/l), and concentrations in treated drinking-water are usually well below 0.05 µg/l (or 50 ng/l).

There are few comprehensive, systematic monitoring studies on pharmaceuticals in drinking-water, and limited occurrence data are a challenge in assessing potential human health risks from exposure to trace concentrations of pharmaceuticals in drinking-water. In addition, there is no standardized protocol for the sampling and analytical determination of pharmaceuticals. More systematic studies, using comparable methods, will help further research on the transport, occurrence and fate of these compounds in various environmental media, and standardization of protocols for their sampling and analytical determination would help to facilitate the comparison of data.

2. Human health risk assessment for pharmaceuticals in drinking-water

2.1 Introduction

Regulatory approval processes for pharmaceuticals require thorough assessments to demonstrate the efficacy and safety of active compounds. These assessments determine the margin of safety associated with human consumption and take into account the risk–benefit equation. Those pharmaceuticals that are most widely used, particularly those approved for over-the-counter sales, require the most stringent assessment and require a substantial margin of safety. Most of the pharmaceuticals that are likely to be found in water fall into the high usage category, because it is those substances that will be present in the greatest quantity. The assessments for approval for particular uses cover a series of preclinical, clinical and sometimes mechanistic studies and are usually performed at doses close to the intended therapeutic dose. For those substances that will be widely used, some studies are also conducted at doses well above those anticipated. Because of these stringent regulatory approval processes, pharmaceuticals will be better characterized and controlled than most environmental contaminants.

Concern has been raised, however, because exposure to pharmaceuticals through drinking-water is an unintended and involuntary exposure over potentially long periods of time. Moreover, there are few scientific risk assessments of exposure to low levels of pharmaceuticals, both as individual species or as mixtures, in drinking-water.

2.2 Assessing risks associated with pharmaceuticals in drinking-water

Chemical risk assessment methods for substances found in food and drinking-water involve establishing an acceptable daily intake (ADI) or tolerable daily intake (TDI) based on a variety of calculations (e.g. from extrapolations, applications of uncertainty factors) applied to a selected point of departure (PoD) from the toxicological and epidemiological database. A common and widely accepted PoD is that concentration at which no adverse effects are detected, which is the no-observed-adverse-effect level (NOAEL), or, less optimally, the lowest concentration at which adverse effects are detected, which is the lowest-observed-adverse-effect level (LOAEL), in combination with an additional uncertainty factor. The PoD may also be derived through a benchmark dose based on statistical evaluation of the dose–response curve of the critical study (FAO/WHO, 2009).

Health risks from pharmaceuticals in water have been most frequently assessed using the minimum therapeutic dose (MTD, the lowest concentration that evokes a desired therapeutic effect among target populations) as the PoD (DWI, 2007; Bull et al., 2011). This is due to practical reasons, including the lack of readily available toxicological data in the public domain that would be necessary to derive a NOAEL/LOAEL or benchmark dose. The MTD is usually a dose below those concentrations where, in rare instances, unacceptable adverse or toxic effects are observed. Therefore, the use of the MTD as a PoD for risk assessment would often result in the development of conservative screening values (reference concentrations used to determine whether further action is warranted, as described below).

The application of the MTD to inform the derivation of screening values does present certain limitations. The MTD is determined by controlled studies in specific preselected populations, which may not be based on the sensitivities of vulnerable subpopulations that would not normally be given the drug. In addition, in specific cases, such as with cytotoxic cancer treatment drugs, the MTD may be at a concentration above which toxic effects are observed. Notwithstanding this, especially in cases where the margins of exposure (MOEs) are substantial, use of the MTD could be considered a pragmatic and sensible method to broadly assess and screen risks.

The main challenges in assessing risks include the limited occurrence data available for pharmaceuticals in drinking-water, the diverse range of pharmaceuticals in use, the wide variation in the use of individual pharmaceuticals between countries, the limited number of data in the public domain and technical limitations relating to assessing risks from chronic exposure to low-dose of pharmaceuticals and mixtures. Nonetheless, several publicly available approaches (USEPA, 2008b) have been used for screening and prioritizing pharmaceuticals for assessing the potential risks to human health from exposure to low concentrations of pharmaceuticals in drinking-water. These reports (DWI, 2007; USEPA, 2008b; Bull et al., 2011) have been subject to scrutiny and peer review. These studies have used the MTD as the PoD for the risk assessment, with subsequent application of uncertainty factors to derive screening values and margins of safety against which to assess the potential risk

These screening values are values against which to judge the likelihood that a particular substance could be of concern at the concentrations observed and so warrant further, more detailed investigation. Screening values are also used to identify those substances from a long list that are the most important and should be considered more closely. As indicated above, there are two approaches that have been used. An ADI or TDI is an amount that can be ingested daily for an extended period, generally a lifetime, without significant risk to health. The large uncertainty factors frequently involved in establishing an ADI or TDI generally serve to provide assurance that exposure exceeding the ADI or TDI for shorter periods, or sometimes for longer periods if the exceedance is small, is unlikely to have any deleterious effect. However, any exceedance of the ADI or TDI needs to be evaluated on a case-by-case basis, as it is very much dependent on the substance and its toxicological profile.

ADIs are typically set by determining the dose at which no adverse effect is observed (the NOAEL) or, less optimally, the lowest level at which an adverse effect is observed (the LOAEL). In both cases, uncertainty factors are applied to reflect uncertainties in extrapolation from experimental animals to humans, in the likely variation within the exposed population or important gaps in the database, to derive the ADI. These uncertainty factors are based on expert judgement, but there is a considerable body of experience in their use. Data from well-conducted studies, where a clear dose–response relationship has been demonstrated, are preferred, typically using experimental animal models; however, where suitable data on human populations are available, these would normally be preferred. The approaches used in developing guideline or screening values for chemicals in drinking-water are described in chapter 8 of the WHO *Guidelines for Drinking-water Quality* (WHO, 2011). Using an ADI to determine a suitable level for drinking-water requires assumptions to be made regarding body weight, as an ADI is usually presented as an

intake per kilogram of body weight. WHO uses a value of 60 kg for an adult and assumes consumption of 2 litres of drinking-water per day. Usually for substances for which an ADI is derived, exposure can also be from food and air, and so a proportion of the ADI is allocated to drinking-water to allow for exposure from other sources. In the case of pharmaceuticals, exposure from other sources is negligible, and so the allocation can be high, even 100%. For individuals taking the pharmaceutical for medical purposes, the additional amount from drinking-water is so small as to make no difference.

The MTD, or the lowest clinically effective dose, is usually equivalent to the lowest dose prescribed or recommended and takes into account the number of doses in a day. These values are derived from an assessment of the balance between efficacy and safety. The approach used to derive a screening value for drinking-water is to divide the MTD by a factor that would provide reasonable assurance that effects, either pharmacological or toxic, would be extremely unlikely. The derivation of this factor is based on expert judgement, as are the uncertainty factors used in the derivation of the ADI. The use of the MTD as a starting point for assessing potential risks of pharmaceuticals to human health or for deriving guideline values has been applied by Schwab et al. (2005) in a human health risk assessment of pharmaceuticals in surface waters in the USA and by Versteegh et al. (2007), Webb et al. (2003), van der Aa NGFM et al. (2009) and Bull et al. (2011). DWI (2007) also used the MTD as the basis for assessing the risk from pharmaceuticals in drinking-water.

The screening values developed are then used as reference points against which the results of monitoring can be judged. In some cases, because monitoring data are so limited, modelling has been used to develop worst-case estimates of potential exposure through water. The screening values are then used as the criteria to support decision-making when a chemical is detected in source water or drinking-water. If the concentration of a particular pharmaceutical exceeds the screening value, then further evaluations of the toxicity and occurrence of the pharmaceutical compound might be warranted. On the other hand, if the concentration is below the screening value, this strongly suggests that adverse health impacts should not be expected.

2.3 Applying the MTD approach: a Drinking Water Inspectorate study[1]

The Drinking Water Inspectorate for England and Wales commissioned a comprehensive desk-based review of current knowledge on and estimation of potential levels of 396 pharmaceuticals and 11 illegal drugs in drinking-water in the United Kingdom based on specific demographic and usage data on active pharmaceutical ingredients and using modelled concentrations based on actual catchments. The DWI (2007) approach was to determine an MOE for each pharmaceutical by comparing the MTD with the theoretical maximum intake from drinking-water.

The modelled concentrations from drinking-water intake were based on two methods: 1) a deterministic method that resulted in estimates of worst-case concentrations in drinking-water and 2) a probabilistic method that resulted in more realistic estimates

[1] This section is based on DWI (2007).

of the concentrations in drinking-water. Pharmaceuticals considered were first evaluated using the deterministic method; for those 24 compounds that had the lowest MOEs, further evaluation was done using the probabilistic method.

The health end-point used in this review was the MTD. Owing to insufficient data, an MTD value of 10 mg per day was used for topically applied pharmaceuticals and a conservative MTD value of 1 mg per day was used for pharmaceuticals for which there were no data, including illegal drugs. For the DWI (2007) evaluation, an uncertainty factor of 1000 was applied for all the compounds as a precautionary value to extrapolate below the level at which effects might be seen. The resultant screening values were used for determining the priority substances for further examination by probabilistic modelling. This additional uncertainty factor, which is widely accepted as a precautionary step by the medical profession, also provides an additional reassurance with regard to exposure of infants and young children.

The MOE for each of the targeted pharmaceuticals was derived by comparing the maximum estimated concentrations in drinking-water with the MTD. The results allow an assessment of the significance of individual pharmaceuticals through drinking-water exposure.

From the worst-case deterministic modelling, only 10 substances showed an MOE less than 1000, of which 4 were illegal drugs, with highly precautionary values for the lowest active dose. In only one case was the exposure ratio less than 100, and this was an unique case, as a combined total for all NSAIDs was used, but compared against the lowest individual MTD for any of the NSAIDs in the group. The results therefore suggested that even in this worst-case situation, there is no significant health risk from intake of pharmaceuticals via drinking-water.

When probabilistic modelling was used to obtain a more realistic estimate of concentrations in drinking-water, the estimated concentrations of all but one substance were significantly lower. The MOEs for all substances were significantly greater than 1000, and only tetrahydrocannabinol and oseltamivir carboxylate had an MOE less than 1000 (Table 4).

The DWI (2007) study led to the conclusion that majority of the pharmaceuticals had MOEs greater than 1000, suggesting a substantial margin of safety against potential adverse health impacts from exposure to trace concentrations of pharmaceuticals in drinking-water.

2.4 Applying the ADI approach

2.4.1 Awwa Research Foundation study[1]

The Awwa Research Foundation commissioned a study to provide critical information regarding the occurrence of and risk assessment for pharmaceuticals and potential endocrine disrupting chemicals (EDCs) in drinking-water. The study examined 62

[1] This section is based on Snyder et al. (2008).

Table 4. Probabilistic modelling data for the top 24 drugs from worst-case deterministic modelling

Drug name	Mean PEC_{dw} (µg/l)	MTD (mg)	MOE	Comments
Total NSAIDs	2.74	7.5	2 737	Combination of 19 anti-inflammatory drugs
Cannabis (tetrahydrocannabinol)	1.377	1	726	Illegal drug
Oseltamivir carboxylate (Tamiflu active metabolite)	107	52	486	Used under pandemic conditions
LSD	0.097	1	10 309	Illegal drug
Cocaine (methylbenzoylecgonine)	0.029	1	34 483	Illegal drug
Aminophylline	0.15	1	6 667	Smooth muscle relaxant
Beclometasone	0.005	0.05	10 000	Anti-asthmatic
Zidovudine	0.057	0.5	8 772	Antiviral
Ecstasy	0.487	1	2 053	Illegal drug
Acamprosate	0.435	1	2 299	Alcoholism treatment
Total statins	1.27	5	3 937	Cholesterol reduction
Nitroglycerine	0.035 4	0.15	4 234	Vasodilator
Heroin (diamorphine)	0.004 49	1	222 717	Illegal drug
Simvastatin	1.18	5	4 227	Cholesterol reduction
Codeine	0.015 7	20	1 277 139	Narcotic analgesic
Ramipril	0.153	1.25	8 177	Diuretic
Lisinopril	0.396	2.5	6 316	Angiotensin converting enzyme inhibitor
Methadone	0.082 2	1	12 173	Opioid agonist
Furosemide	1.74	20	11 507	Diuretic
Amphetamine	0.017 4	1	57 405	Illegal drug
Norethisterone	0.023 6	0.35	14 824	Progesterone derivative
Doxazosin	0.006 81	1	146 843	α-blocker
Bendroflumethiazide	0.275	2.5	9 094	Diuretic
Cyclosporin	0.000 8	2	2 500 000	Immunosuppression

LSD, lysergic acid diethylamide; PECdw, predicted concentration in drinking-water
Source: DWI (2007)

chemicals, including 20 pharmaceuticals and active metabolites, 26 potential EDCs, 5 steroid hormones and 11 phytoestrogens (natural estrogens from plants). The health value applied in this study was the ADI, and a conservative approach was taken in the process of developing the ADI values, as illustrated in Table 5.

In this study, the ADIs were converted to drinking-water equivalent levels (DWELs) in micrograms per litre (or parts per billion) based on assumptions of a 70 kg body weight in adults and consumption of 2 litres per day.

Table 5. Principles for deriving ADIs for compounds considered in this study

Category of analytes	Derivation of ADIs
Compounds that are not carcinogenic	Dividing the highest dose at which an effect was not observed (NOAEL) or the lowest dose at which an effect was observed (LOAEL) in animal or human toxicity studies by uncertainty factors to account for extrapolation to potentially sensitive populations
Compounds with positive evidence of carcinogenicity in high-dose animal studies and data on tumour incidence per dose level	A linear extrapolation model was used to predict the tumorigenic response at low dose level
Carcinogenic compounds with reported evidence in animal studies, but no available tumour incidence data	A safe dose corresponding to a cancer risk of one in a million was estimated

Even with the use of advanced and highly sensitive analytical procedures (with reporting limits in the nanograms per litre or parts per trillion range), none of the pharmaceuticals tested in this study were detected in finished drinking-water above the calculated health risk thresholds. Adopting a conservative worst-case scenario approach, the maximum detected concentrations in finished and piped drinking-water were used to calculate DWELs for each of the target pharmaceuticals. It was found that none of the pharmaceuticals detected in drinking-water exceeded their corresponding ADI.

The minimum margin of safety or MOE for each compound tested was calculated by dividing the DWEL by the maximum detected water concentration. According to United States Environmental Protection Agency (USEPA) policy, compounds with MOEs greater than 100 would generally indicate a low level of concern. Table 6 contains the calculated MOEs for some of the compounds that were detected in drinking-water; these were orders of magnitude above 100, suggesting a low level of concern.

Table 6. MOEs calculated for compounds considered in the Awwa Research Foundation study

Compound	MOE
Atenolol	2 700
Diazepam	110 000
Fluoxetine	41 000
Meprobamate	6 000
Norfluoxetine	44 000
Sulfamethoxazole	6 000 000
Triclosan	2 200 000

2.4.2 Australian Guidelines for Water Recycling[1]

The Australian Guidelines for Water Recycling were developed to serve as an authoritative reference for using recycled wastewater to augment drinking-water supplies. These guidelines were established to protect against microbial and chemical risks, including pharmaceuticals. The pharmaceuticals considered were categorized into two groups: those used solely for humans and those used for agricultural and veterinary purposes.

For veterinary pharmaceuticals, the health end-point is determined based on ADIs established for pharmaceuticals used for agricultural and veterinary purposes by organizations such as the Joint FAO/WHO Expert Committee on Food Additives, the Australian Therapeutic Goods Administration and the European Medicines Agency.

For human pharmaceuticals, the health end-point was a surrogate ADI, which was derived by dividing the lowest daily therapeutic dose by safety factors ranging from 1000 to 10 000. The use of the lowest daily therapeutic dose as a starting point for deriving guideline values or assessing risk has been adopted by others (Webb et al., 2003; Schwab et al., 2005; DWI, 2007; Versteegh et al., 2007; Bull et al., 2011). With respect to pharmaceutical metabolites in source waters, it was considered that the activity of metabolites is generally lower than that of the parent compound, and application of safety factors in the range of 1000–10 000 should provide a safety buffer that is sufficiently conservative.

For most pharmaceuticals, a safety factor of 1000 was applied to the lowest daily therapeutic dose; it consists of a 10-fold factor for sensitive humans, a 10-fold factor for infants and children and a 10-fold factor for the lowest therapeutic dose not being a no-effect level. In addition, a factor of 10 was added for cytotoxic drugs as a result of the higher toxicity associated with these compounds and for hormonally active steroids, which are active at very low concentrations and for which there is a high public perception of adverse effects.

In applying the guidelines, the calculated guideline values for the pharmaceuticals were compared with the highest concentrations measured in secondary treated effluent to derive the MOEs. Most of the calculated MOEs are more than 1000; given that this does not take into account reductions achieved by treatment processes, it is unlikely that pharmaceutical chemicals will be present at levels approaching the recommended guideline values or cause any adverse impacts on human health.

2.5 Conclusion

Risk assessments from the United Kingdom, the USA and Australia have applied the the ADI or the MTD approaches, in conjunction with uncertainty factors, to derive screening values for pharmaceuticals in drinking-water. Analysis of the results indicated that adverse human health impacts are very unlikely from exposure to the trace concentrations of pharmaceuticals that could potentially be found in treated drinking-water. Available data have shown that for those substances that have been

[1] This section is based on NRMMC, EPHC & NHMRC (2008).

detected, the concentrations are more than 1000-fold less than the MTD, which is the lowest clinically active dosage.

These findings are in line with other studies over the past decade that also supported the conclusion that discernible risks to health arising from trace levels of pharmaceuticals in drinking-water are extremely unlikely (e.g. Christensen, 1998; Schulman et al., 2002; Webb et al., 2003; Jones, Lester & Voulvoulis, 2005; Bercu et al., 2008; Snyder, 2010).

Given the low likelihood of human health risk, it is not considered necessary to implement routine monitoring programmes that are resource intensive and detract from other drinking-water concerns that are more important and more acute, particularly the threat of waterborne pathogens. However, where specific circumstances indicate a potential for elevated concentrations, screening values and targeted investigative monitoring could be considered.

Future research could consider investigating the robustness and feasibility of adapting the concept of the threshold of toxicological concern, which is currently more widely used for food additives and contaminants, as an alternative screening-level risk assessment, rather than developing values for each substance individually (Kroes et al., 2004). Research could also look into improvement to risk assessment methodology to address concerns related to pharmaceuticals mixtures and the effects of chronic, low-level exposure to pharmaceuticals, including exposure of sensitive subpopulations, such as pregnant women and patients with particular diseases and medical treatments (Rowney, Johnson & Williams, 2009). The WHO Framework for Risk Assessment of Combined Exposure to Multiple Chemicals (Meek et al., 2011) could be utilized to further consider the issue of mixtures.

3. Treatment technologies for removal of pharmaceuticals from water

3.1 Introduction

Many studies have reported the presence of pharmaceuticals in effluents from wastewater treatment facilities (Ternes, 1998; Andreozzi et al., 2003; Miao et al., 2004; Paxéus, 2004; Castiglioni et al., 2006; Vieno, Tuhkanen & Kronberg, 2007), and identified these effluents as the main conveyors of pharmaceuticals and their metabolites into receiving water sources, such as rivers, lakes, reservoirs and groundwater aquifers, that are used for drinking-water supply (Heberer, 2002; Ternes & Joss, 2006; Xu et al., 2007; Zhang, Geissen & Gal, 2008; Huerta-Fontela, Galceran & Ventura, 2011).

The presence of trace concentrations of pharmaceuticals in the water cycle, typically in the nanogram to low microgram per litre range, has raised questions concerning the efficacy of drinking-water and wastewater treatment processes in removing pharmaceuticals. The majority of research studies on treatment efficacy have been conducted in Europe and the USA, with some studies conducted in developed countries in Asia (Lee et al., 2008; Simazaki et al., 2008; Van De Steene, Stove & Lambert, 2010; Huerta-Fontela, Galceran & Ventura, 2011). In addition, there are more studies that focus on removal efficacies at laboratory scale or by single treatment processes rather than at full scale, especially for drinking-water treatment processes.

This chapter provides an overview of the removal of pharmaceuticals by conventional and advanced wastewater and drinking-water treatment processes based on the published literature.

3.2 Removal of pharmaceuticals by wastewater treatment processes

Conventional wastewater treatment facilities typically have biological degradation using the activated sludge process, whereas advanced facilities have tertiary treatment processes, such as reverse osmosis, ozonation and advanced oxidation technologies. Pharmaceuticals are a diverse group of chemicals, with varying physical and chemical properties (Jelic et al., 2011). Treatment efficacy depends on these physical and chemical characteristics (e.g. hydrophobicity), their reactivity towards different treatment processes and process control, such as solids retention time, temperature and hydraulic retention time. For example, the majority of pharmaceuticals are relatively hydrophobic and therefore less effectively removed by sorption to sludge (Vieno, Tuhkanen & Kronberg, 2007). Treatment removal efficiency could therefore vary significantly between different treatment facilities or at different time periods within the same treatment facility (Vieno, Tuhkanen & Kronberg, 2007).

Table 7 collates the results of several studies to illustrate the removal rates that can be expected by different wastewater treatment processes. These are based on observations of treatment processes ranging from single unit processes to full-scale wastewater treatment facilities found in the various studies.

Table 7. Conventional and advanced wastewater treatment processes and their expected range of removal efficiency for pharmaceuticals

Treatment process	Removal range (%)	Water source	Areas studied	Reference
Conventional wastewater treatment processes				
Activated sludge	11–99	Raw sewage	Australia	Watkinson, Murby & Costanzo (2007)
	7–100	Primary settled sewage	Europe, Japan	DWI (2007)
	< 20–80	Primary settled sewage	France	Gabet-Giraud et al. (2010)
	–193–86[a]	Primary settled sewage	Europe	Vieno, Tuhkanen & Kronberg (2007)
	8–98	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Biological filtration	6–71	Primary settled sewage	Europe	DWI (2007)
Primary settling	3–45	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Coagulation, filtration and settling	5–36	Not specified		
Sand filtration	0–99	Activated sludge effluent		
Advanced wastewater treatment processes				
Ozonation	1–99	Activated sludge effluent	Brazil, Europe, Japan	Ziylan & Ince (2011)
	86–100	Secondary effluent	France	Gabet-Giraud et al. (2010)
Ozonation/ ultrasound and sonocatalysis	23–45	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)
Ozonation and catalytic ozonation	>9–100			
UV irradiation	29	Not specified	Brazil, Europe, Japan	Ziylan & Ince (2011)
Photolysis (UV/ hydrogen peroxide)	52–100	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)
Dark and light Fenton	80–100			
UV/TiO_2	> 95			
Biomembrane	23–99	Treated effluent	Brazil, Europe, Japan	Ziylan & Ince (2011)
Microfiltration and reverse osmosis	91–100	Secondary treated effluent	Australia	Watkinson, Murby & Costanzo (2007)

Table 7 (contd)

Treatment process	Removal range (%)	Water source	Areas studied	Reference
Reverse osmosis	62–97	Secondary treated effluent	France	Gabet-Giraud et al. (2010)
Ultrasound	24–100	Not specified	Europe, India, Japan, Turkey, USA	Ziylan & Ince (2011)

UV, ultraviolet

[a] The removal of some pharmaceuticals appears to be negative. This has been attributed to the way in which removal is calculated, without hydraulic retention time being considered. This means that the effluent sample does not directly correspond to the influent sample. In the case of carbamazepine, the increase observed was consistent, and the most probable cause was reported to be conversion of carbamazepine glucuronides and other conjugated metabolites to the parent compound by enzymatic processes in the treatment plant (Ternes et al., 1999; Vieno, Tuhkanen & Kronberg, 2007).

Table 7 demonstrates that conventional wastewater treatment facilities with activated sludge processes can achieve higher removal efficiency than simple biological filters. Removal rates for pharmaceuticals can vary and could sometimes be limited (Kasprzyk-Hordern, Dinsdale & Guwy, 2009), depending on such factors as sludge age (DWI, 2007), activated sludge tank temperature and hydraulic retention time (Wick et al., 2009; Gabet-Giraud et al., 2010).

Advanced wastewater treatment processes, such as ozonation, membrane treatment and advanced oxidation, can generally achieve higher removal rates (up to 100%) for pharmaceuticals compared with conventional processes. For example, another bench-scale study showed that advanced oxidation processes can achieve up to 100% removal for diclofenac (Klavarioti, Mantzavinos & Kassinos, 2009).

Prediction of removal rates for wastewater treatment processes is possible for pharmaceuticals with very similar chemical structures. However, practical difficulties do exist in predicting removal rates between different wastewater treatment facilities, as highly variable removal rates are obtained for beta blockers, depending on the wastewater treatment facility under consideration. For example, the beta blockers betaxolol, bisprolol, carazolol and metprolol are significantly removed by activated sludge processes, with reported removal rates varying from 65% to about 90% (Ternes, 1998; Gabet-Giraud et al., 2010), whereas low removal rates of less than 20% and approximately 32% are reported for soltalol and propranolol, respectively, in other studies (Bendz et al., 2005; Gabet-Giraud et al., 2010).

3.3 Removal of pharmaceuticals by drinking-water treatment processes

Treated effluents from wastewater treatment facilities that have an impact on receiving water bodies constitute the main source of pharmaceuticals in surface waters, which could be used for drinking-water supply (Rahman, Yanful & Jasim, 2009). Other possible pathways of pharmaceuticals to drinking-water sources include leaching of pharmaceuticals to groundwater (Gomes & Lester, 2003) from sources such as leaking sewage systems and pipes.

None of the wide range of drinking-water treatment processes available have been designed specifically to remove pharmaceuticals that may be present in source waters. Nonetheless, removal of pharmaceuticals during drinking-water treatment is largely dependent on their physical and chemical properties, and treatment processes can therefore achieve some level of removal. For example, biodegradation on slow sand filters and/or sorption to particles removed by coagulation may help reduce the levels of some pharmaceuticals present in drinking-water sources; granular activated carbon (GAC) and powdered activated carbon (PAC) are increasingly adopted in drinking-water treatment to remove pesticides and improve taste and odour, and these processes may remove some pharmaceuticals by sorption (or biodegradation on GAC). Groundwater sources that are used for drinking-water typically have low particulate matter and organic matter content. Therefore, drinking-water treatment is mostly single-stage disinfection, without multiple treatment barriers.

Table 8 summarizes the findings in various published studies on the removal efficiencies of conventional and advanced water treatment processes for pharmaceuticals in drinking-water. The majority of these studies focused on bench-scale removal by spiking water samples with target compounds, subjecting these samples to treatment and measuring the resulting concentrations. However, some full-scale studies at drinking-water treatment facilities have been carried out.

Bench-scale studies using both alum and ferric chloride as coagulants for natural water or pure water samples spiked with pharmaceutical target compounds showed that coagulation (with or without chemical softening) is largely ineffective in removing pharmaceutical target compounds (Westerhoff et al., 2005; Yoon et al., 2006; Snyder et al., 2007). An Awwa Research Foundation project also concluded that coagulation was largely ineffective for pharmaceutical removal in bench-scale, pilot-scale and full-scale investigations (Khiari, 2007).

Chlorination and ozonation can achieve higher removal rates, with efficacy a function of chemical structure and treatment conditions, such as pH and oxidant dose (Zwiener & Frimmel, 2000; Adams et al., 2002; Huber et al., 2003, 2005; Snyder et al., 2003; Ternes et al., 2003; Pinkston & Sedlak, 2004; Kim et al., 2007). In some studies, free chlorine was found to oxidize approximately half of the pharmaceuticals investigated, but chloramine was comparatively less efficient. Antibiotics such as sulfamethoxazole, trimethroprim and erythromycin are among the compounds that showed high removal by free chlorine (Khiari, 2007). Advanced oxidation processes using ozone with hydrogen peroxide greatly improve oxidation and are frequently applied in wastewater recycling processes for indirect potable reuse to convert recalcitrant organic chemicals.

PAC and GAC can achieve high removal of pharmaceutical target compounds, especially hydrophobic compounds. Removal efficacy is a function of contact time, organic loading, chemical structure, solubility and carbon type (Ternes et al., 2002; Yoon Y. et al., 2003; Snyder et al., 2006). Iopromide, ibuprofen, meprobamate, sulfamethoxazole and diclofenac were some of the compounds found to be most resistant to activated carbon removal (Khiari, 2007).

Table 8. Drinking-water treatment processes and their expected range of removal of pharmaceuticals

Treatment process	Removal range (%)	Scale	Country studied (no. of compounds)	Reference
RO	> 99	Pilot	Germany (6)	Heberer, Reddersen & Mechlinski (2002)
RO1	70–91	Bench	Japan (6)	Kimura et al. (2004)
RO2	10–85	Bench		
UV/H_2O_2	3 – > 95	Bench	USA (2)	Rosenfeldt & Linden (2004)
Coag	24–72	Bench	USA (49)	Westerhoff et al. (2005)
PAC (20 mg/l)	> 80	Bench		
PAC (1 mg/l)	40–75	Bench		
Cl_2	25–75	Bench		
O_3	5–95	Bench		
O_3	33–100	Bench	Germany (9)	McDowell et al. (2005)
ClO_2	0–100	Bench	Germany (11)	Huber et al. (2005)
NF1	> 98	Bench	Australia (3)	Nghiem, Schäfer & Elimelech (2005)
NF2	> 80	Bench		
UF	< 30	Bench	USA (27)	Yoon et al. (2006)
NF	30–90	Bench		
Coag	< 5–30	Bench	Finland (5)	Vieno, Tuhkanen & Kronberg (2006)
Cl_2	20–100	Bench	Japan (9)	Simazaki et al. (2008)
PAC	> 98	Bench		
Coag	< 15	Bench		
Constructed wetlands	28–60	Pilot	Singapore (4)	Zhang et al. (2011)
Aeration/SF	25 – > 95	Full	Germany (5)	Reddersen, Heberer & Dünnbier (2002)
O_3/Coag/Sed/Cl_2	100	Full	USA (2)	Boyd et al. (2003)
PAC/Coag/Sed	0	Full	USA (1)	
Cl_2	100	Full	USA (1)	
Coag	0	Full	Republic of Korea (6)	Kim et al. (2007)
UF	0	Full		
GAC	100	Full		
NF	30– > 90	Full	Spain (12)	Radjenović et al. (2008)
RO	45– > 90	Full		
Disinfection	2–97	Full	France (7)[a]	ANSES (2011)
Physical and chemical	31–94	Full		
O_3 + AC	47–97	Full		
Membranes	6–68	Full		
Pre-Cl_2	0 – > 99	Full	Spain (35)	Huerta-Fontela, Galceran & Ventura (2011)
Coag/Floc/SF	< 30–100	Full		
O_3	5 – > 99	Full		

Table 8 (contd)

Treatment process	Removal range (%)	Scale	Country studied (no. of compounds)	Reference
GAC	55 – > 75	Full		
Cl_2	14–100	Full		

AC; activated carbon, Cl_2, chlorine; ClO_2, chlorine dioxide; Coag, coagulation; Floc, flocculation; GAC, granular activated carbon; H_2O_2, hydrogen peroxide; NF, nanofiltration; O_3, ozonation; PAC, powdered activated carbon; RO, reverse osmosis; Sed, sedimentation; SF, sand filtration; UF, ultrafiltration; UV, ultraviolet

[a] Note that this was a national study incorporating 78 instances of pharmaceutical removal.

Membrane treatment is highly effective in removing chemicals from water, and removal efficacy is a function of physical and chemical properties, such as molecular weight, hydrophobicity, polarity, chemical nature and pore size of the membranes. Some studies (Yoon et al., 2006; Khiari, 2007) suggested that nanofiltration (NF) can achieve better removal rates for most target compounds than ultrafiltration (UF)/microfiltration (MF) membranes as a result of both hydrophobic adsorption and size exclusion. Higher molecular weight substances would be removed by size exclusion, especially by NF membranes. Reverse osmosis (RO) was highly effective, despite trace quantities of some target compounds breaching RO membranes. However, a double-pass RO system was reported to remove all target compounds to below detection limits (Khiari, 2007).

Ultraviolet (UV) irradiation at typical disinfection dosages was ineffective for removing most target compounds, even though it can achieve more than 50% removal of sulfamethoxazole (antibiotic), triclosan (antimicrobial) and diclofenac (NSAID). However, a combination of higher-dose UV (400 mJ/cm^2 and higher) with hydrogen peroxide (3 mg/l and above) removed most target compounds (Rosenfeldt & Linden, 2004; Khiari, 2007).

3.4 Conclusion

This chapter has provided an overview of the removal of pharmaceuticals by conventional and advanced wastewater and drinking-water treatment processes based on the published literature.

Conventional wastewater treatment typically consists of activated sludge processes. Biological treatment, such as activated sludge and biofiltration, has demonstrated significant removal rates for pharmaceuticals that are biodegradable or readily bind to particles (Ternes et al., 1999; Joss et al., 2005; Kim et al., 2007). However, removal rates for pharmaceuticals can vary within and between studies (Kasprzyk-Hordern, Dinsdale & Guwy, 2009; Wick et al., 2009), depending on such factors as sludge age (DWI, 2007), activated sludge tank temperature and hydraulic retention time. For example, diclofenac removal in the activated sludge process ranges from 21% to 50%, but this can be optimized by operating the process at a sludge age of eight days or more (Ziylan & Ince, 2011).

Advanced wastewater treatment processes that comprise membranes, advanced oxidation technologies, etc. have shown higher removal efficiencies for pharmaceuticals (e.g. advanced oxidation processes can achieve up to 100% removal

for diclofenac) (Klavarioti, Mantzavinos & Kassinos, 2009). However, conventional treatment is generally sufficient to meet regulatory requirements, and capital-intensive advanced treatment processes are not commonly adopted for wastewater treatment (Spellman, 2010).

With respect to conventional drinking-water treatment, bench-scale studies showed that coagulation (with or without chemical softening) is largely ineffective in removing pharmaceuticals (Westerhoff et al., 2005; Yoon et al., 2006; Snyder et al., 2007). Free chlorine was found to oxidize approximately half of the pharmaceuticals investigated, and chloramine was less efficient. Antibiotics such as sulfamethoxazole, trimethroprim and erythromycin are among the compounds that showed high removal by free chlorine (Khiari, 2007).

Advanced water treatment processes such as ozonation, advanced oxidation, activated carbon and membrane processes (nanofiltration, reverse osmosis) were demonstrated to achieve higher removal rates (above 99%) for targeted pharmaceutical compounds in various published literature studies. However, advanced oxidation processes can lead to incomplete degradation products, such as metabolites, and future research could consider the value and feasibility of studying the formation and impact of these metabolites (Celiz, Tso & Aga, 2009).

For drinking-water sources that are contaminated with pesticides, advanced treatment may already be in place to meet regulations. In such cases, removal of pharmaceuticals during treatment may already be optimized.

Most importantly, it is prudent to note that advanced and costly water treatment technology will not be able to completely remove all micropollutants to concentrations below the detection limits of the most sensitive analytical procedures at all times. Therefore, it is imperative to consider the toxicological relevance of various compounds in the context of appreciable risks to human health. Increased or rapidly changing exposure arising from specific local circumstances (e.g. a significant increase in the concentration of pharmaceuticals in surface waters impacted by wastewater discharge) should be investigated.

An informed risk assessment considering the above principles is essential before allocating scarce resources to upgrade or invest in additional advanced treatment processes to reduce trace concentrations of pharmaceuticals in drinking-water.

In view of the substantial margin of safety for consumption of very low concentrations of pharmaceuticals in drinking-water (Chapter 2 in this report), concerns over pharmaceuticals should not divert the attention and resources of water suppliers and regulators from other chemical and pathogenic microbial priorities. For example, although the government in Australia has issued proposed guideline values for 84 pharmaceuticals for water reuse schemes, but microbial pathogens remain their overriding priority in water reuse (NRMMC, EPHC & NHMRC, 2008).

4. Preventing pharmaceuticals in drinking-water

Conventional drinking-water quality monitoring that places emphasis on end-product testing is very resource intensive in terms of capital investment and human resources. With an expanding list of chemical contaminants detected in drinking-water and water sources that may be of insignificant health concern, an overemphasis on end-product monitoring and the upgrading of treatment infrastructure is clearly not sustainable or an optimal use of limited resources.

Chapter 4 in the fourth edition of the WHO *Guidelines for Drinking-water Quality* states that the water safety plan is "the most effective means of consistently ensuring the safety of a drinking-water supply ... through the use of a comprehensive risk assessment and risk management approach that encompasses all steps in the water supply from catchment to consumer" (WHO, 2011). The key principles of water safety plans underline the importance of looking at risk assessment and risk management across the entire water cycle starting at source. Adapting this full life cycle approach to pharmaceuticals in drinking-water means that preventing pharmaceuticals entering the environment during their production, consumption and disposal is a pragmatic and effective means of risk management.

Inappropriate disposal practices, such as flushing unwanted or excess drugs down toilets and sinks and discarding them in household waste, are common and often a significant contributor of pharmaceuticals present in wastewater and other environmental media (e.g. surface waters and landfill leachate). A survey from Germany's Management Strategies for Pharmaceutical Residues in Drinking Water research programme showed that consumers discarded 23% of liquid pharmaceuticals prescribed and 7% of tablets. While some went into household trash, the equivalent amount of pharmaceuticals that was flushed away is approximately 364 tons every year (Lubick N, 2010). Another survey of households in the United Kingdom in 2003 found that 63% of unwanted pharmaceuticals were discarded in household waste and 11.5% were flushed down sinks or toilets (Bound & Voulvoulis, 2005). Similarly, proper and well-managed disposal practices at concentrated point sources such as health-care and veterinary facilities will help mitigate the entry of pharmaceuticals into our environment.

Currently, tighter rules and regulations apply to controlled substances and cytotoxic drugs than for other pharmaceuticals. Despite this, disposal to sewers is not precluded (USEPA, 2008a). Disposal of non-controlled substances tends to be more variable and is often developed on a local, jurisdictional or regional basis. A scan of the current literature, which is not exhaustive, revealed a few broadly categorized preventive measures in Australia, Canada, the USA and European countries that could potentially reduce the entry of pharmaceuticals into our environment. These measures are described below.

4.1 Improved regulations and guidance on pharmaceutical waste management

All health-care facilities should have policies and procedures in place for the correct management of pharmaceutical waste. In Australia, the Environmental Protection Authority and the National Health and Medical Research Council had guidelines on

the management of waste generated in health-care facilities. The National Health and Medical Research Council stated that, where possible, pharmaceutical waste should be incinerated and should not be sent to landfills or discharged to sewers (NHMRC, 1999). Licensed waste disposal companies collected all clinical and pharmaceutical waste for disposal in authorized waste disposal facilities.

In the USA, frequently used pharmaceuticals, such as epinephrine, warfarin and selected chemotherapeutic agents, are regulated as hazardous waste under the Resource Conservation and Recovery Act. Failure to comply with the regulations under this Act through improper management and disposal of waste can potentially constitute serious violations and incur heavy penalties. To guide stakeholders on acceptable disposal practices, the USEPA supported the development of *Managing Pharmaceutical Waste: A 10-Step Blueprint for Health Care Facilities in the United States*, which recommends a stepwise approach to help health-care facilities develop and implement a comprehensive pharmaceutical hazardous waste management programme. This blueprint adopts the best practices in waste minimization to meet regulatory compliance for pharmaceutical waste disposal and safeguard human health and the environment in a cost-effective manner (Pines & Smith, 2006).

To this end, the USEPA (2010b) has also drafted a guidance document, *Best Management Practices for Unused Pharmaceuticals at Health Care Facilities*, to advise health-care and veterinary facilities on reducing pharmaceutical waste, on pharmaceutical waste management and on application of disposal regulations. The aim is to help reduce the amount of pharmaceuticals that are discharged to water bodies.

4.2 Pharmaceutical take-back programmes

To augment regulations, take-back programmes have been established by government and private organizations in several countries to reduce the amount of drugs entering our environment (Daughton, 2003, 2004; Glassmeyer et al., 2009; Teleosis Institute, 2009). A survey of households in the United Kingdom in 2003 showed that 22% of excess pharmaceuticals were returned to pharmacists; although take-back programmes were effective, further improvement is needed (Bound & Voulvoulis, 2005).

These programmes can be of different scales, ranging from small one-day collection events to regular and systematic regional collection, ongoing return of unused and excess medicines to participating pharmacies and mail-back programmes where excess medicines are returned in prepaid packs to government-supervised mailboxes (SCBWMI, 2005). Several household hazardous waste collection programmes have also added pharmaceuticals to the list over the years (Glassmeyer et al., 2009).

In Australia, the Commonwealth Department of Health & Ageing Services provided funds to establish a system for the collection and disposal of unwanted medicines, known as the Return Unwanted Medicines (RUM) Project. Estimates from RUM showed that in 2010–2011, more than 34 tonnes of unwanted medicines on average are collected monthly by community pharmacies across Australia and subsequently incinerated according to guidelines (RUM, 2011).

In the USA, many scheduled pharmaceutical collection events facilitate prudent disposal of unwanted medications at the regional level, such as the successful "Great Lakes Earth Day Challenge", which collected 4.5 million pills for safe disposal. The USEPA has also awarded grants to support take-back of non-controlled, unused medicines at pharmacies and mail-back of unused medicines with appropriate involvement of law enforcement (USEPA, 2010a). Other mechanisms to reduce the entry of pharmaceuticals into the environment include establishing best management practices for handling solid wastes and minimizing discharge from landfills.

Canada has formal stewardship programmes for household pharmaceutical waste at the provincial level or in cities that provide convenient options for consumers to return pharmaceuticals to community pharmacies for safe disposal.

Europe has widespread standardized take-back programmes. In the 2010 report *Pharmaceuticals in the Environment: Results of an EEA Workshop*, the European Environment Agency (EEA, 2010) stated that most countries in Europe collect unused drugs separately from household waste, usually at pharmacies (a handful also have separate collection sites alongside pharmacies). The national systems are operated and funded by the pharmaceuticals industry, retail pharmacies or the public sector. The operation of the take-back programmes may be the responsibility of the retail pharmacies or of public or private waste contractors (Teleosis Institute, 2009).

4.3 Raising consumer awareness

Consumers are accustomed to disposing of unwanted and expired medicines through household waste and sewers. Such improper disposal practices release pharmaceuticals into our environment, wastewater and water sources. There is therefore a need to raise public awareness and encourage consumers to adopt proper disposal practices for unwanted pharmaceuticals. In Australia, the RUM Project focuses on raising consumer awareness to inform consumers of the appropriate option for drug disposal (RUM, 2010). In addition to regulations under New York's Drug Management and Disposal Act, the New York State Department of Environmental Conservation publishes posters for all pharmacies and retail stores that sell drugs to advise consumers on the proper storage and disposal of unwanted medication (DEC, 2010). Consumers can then serve as environmental stewards to reduce water pollution.

4.4 Conclusion

Appropriate regulations governing disposal practices at point sources of hazards, widespread take-back programmes, guidance and enhanced consumer education will support efforts for the proper disposal of unwanted and excess medicines and reduce the environmental impact of pharmaceuticals entering our environment, including water sources.

As most pharmaceuticals enter the water cycle through wastewater discharges or from poorly controlled manufacturing or production facilities that are primarily associated with generic medicines, the discharge of untreated or poorly treated wastewater to water bodies used as drinking-water sources should be strongly discouraged.

5. Conclusions, recommendations and knowledge gaps

Pharmaceuticals are synthetic or natural chemicals that can be found in prescription medicines, over-the-counter therapeutic drugs and veterinary drugs. They contain active ingredients that are designed to achieve pharmacological effects and confer significant benefits to society. Pharmaceuticals are primarily introduced into the environment via human excretion, sewage effluent, improper drug disposal, agricultural runoff, and livestock and veterinary waste. The ubiquitous use of pharmaceuticals in various settings has resulted in a continuous discharge of pharmaceuticals and metabolites into the environment, leading to their "pseudo-persistence" in the environment. Significant advancements in the sensitivity of detection and analytical technologies and methods have made it possible to detect very low concentrations of pharmaceuticals in the range of nanograms to low micrograms per litre in the water cycle. As pharmaceuticals contain active ingredients that are designed to achieve specific pharmacological effects based on their biological reactivity and biochemical properties, their presence at trace concentrations in the water cycle has generated concerns among various stakeholders, including governments, regulators and the public, over potential risks to human health through very low level exposure via drinking-water.

5.1 Conclusions

Targeted investigative studies conducted in the United Kingdom, the USA and Australia have shown that concentrations of pharmaceuticals in surface water and groundwater sources impacted by wastewater discharges are typically less than 0.1 µg/l (or 100 ng/l). Detection in treated drinking-water is rare; if pharmaceuticals are present, their concentrations are usually well below 0.05 µg/l (or 50 ng/l). There are, however, very few systematic monitoring programmes or comprehensive, systematic studies on the occurrence of pharmaceuticals in drinking-water, and limited occurrence data present one of the key challenges in assessing the potential risks associated with trace concentrations of pharmaceuticals in drinking-water.

Nonetheless, several approaches to screen and prioritize pharmaceuticals have been published in the peer-reviewed literature. MTDs, ADIs and sometimes the DWELs have been used as reference values by which to derive a margin of safety between these and the reported or predicted worst-case exposure in drinking-water.

Targeted investigations conducted in the above-mentioned countries found that traces of pharmaceuticals in drinking-water are largely present at several orders of magnitude (more than 1000-fold) below the lowest therapeutic dose and largely below the calculated ADIs. The substantial margins of safety for individual compounds suggest that appreciable adverse impacts on human health are very unlikely at current levels of exposure in drinking-water.

From a treatment perspective, pharmaceuticals are not unusual organic chemicals, and treatment removal rates are reasonably predictable based upon the physical and chemical properties of the compounds. Conventional treatment processes with coagulation, filtration and chlorination can remove about 50% of these compounds, whereas advanced treatment, such as ozonation, advanced oxidation, activated carbon and membrane processes (e.g. reverse osmosis, nanofiltration), can achieve higher

removal rates; reverse osmosis, for example, can remove more than 99% of large pharmaceutical molecules.

5.2 Recommendations

The substantial margin of safety for consumption of very low concentrations of pharmaceuticals in drinking-water suggests that appreciable adverse impacts on human health are very unlikely. As such, concerns over pharmaceuticals should not divert attention and valuable resources of water suppliers and regulators from other priorities, such as pathogenic microbial water quality issues. The low risk to human health from current levels of exposure in drinking-water suggests that development of formal guideline values for pharmaceuticals in the WHO *Guidelines for Drinking-water Quality* and the installation of specialized treatment processes to reduce trace concentrations of pharmaceuticals are not warranted.

Routine monitoring programmes for pharmaceuticals in water sources and drinking-water and additional or specialized drinking-water treatment to reduce very low concentrations of pharmaceuticals in drinking-water are not deemed necessary due to the limited public health benefits. However, where local circumstances, such as a catchment survey, indicate a potential for elevated levels of pharmaceuticals in the water cycle (surface water, groundwater, wastewater effluent and drinking-water), relevant stakeholders could undertake targeted, well-designed and quality-controlled investigative studies to obtain more information with which to assess the potential health risks arising from exposure through drinking-water. If necessary, screening values could be developed based on the MTD or the ADI approaches, and an assessment of the need for treatment enhancement could also be considered within the context of other risks and priorities using water safety plans.

Reduction of human exposure to pharmaceuticals through drinking-water can be achieved through a combination of preventive measures, such as take-back programmes, regulations, public guidance and consumer education to encourage the proper disposal of unwanted pharmaceuticals and minimize the introduction of pharmaceuticals into the environment. It is also imperative to enhance public communication and education on water quality issues from the human health standpoint. For example, conveying to the public the potential health risks from exposure to very low concentrations of pharmaceuticals in drinking-water will help them to better understand this issue relative to other hazards, such as waterborne pathogenic microorganisms. However, in the long term, improvement of wastewater treatment to more efficiently remove a range of organic substances that are seen as emerging contaminants of concern would provide a more sustainable and comprehensive solution in preventing their entry into the water environment.

5.3 Knowledge gaps and future research

Although current risk assessments indicate that very low concentrations of pharmaceuticals in drinking-water are very unlikely to pose any risks to human health, there are knowledge gaps in terms of assessing the risks associated with long-term, low-level exposures to pharmaceuticals and possible combined effects of chemical mixtures, including pharmaceuticals. Future research investigating the possible additive or synergistic effects of mixtures would be beneficial for an accurate

exposure assessment to determine whether there are any potential risks to human health, taking into account sensitive subpopulations.

One of the key challenges in estimating exposures to pharmaceuticals in drinking-water and assessing the potential risks to human health is the limited occurrence data for the diverse group of human and veterinary pharmaceuticals in use today. Implementing monitoring programmes is resource intensive in terms of costs, human resources and infrastructure, and there is also a lack of standardized sampling and analysis protocols to support monitoring studies. As such, future research looking into cost-effective methods to prioritize pharmaceuticals within the context of an overall risk assessment will benefit our appreciation of low levels of pharmaceuticals in drinking-water from a human health perspective.