Town of Truro

P.O. Box 2030, Truro, MA 02666
Tel: 508-349-7004 Fax: 508-349-5505

ZONING BOARD OF APPEALS

Agenda

DATE OF MEETING:	**Thursday, June 25, 2020**
TIME OF MEETING:	**5:30 pm**
LOCATION OF MEETING:	**Remote Meeting** **www.truro-ma.gov**

Open Meeting

This will be a remote meeting. Citizens can view the meeting on Channel 18 in Truro and on the web on the "Truro TV Channel 18" button under "Helpful Links" on the homepage of the Town of Truro website (www.truro-ma.gov). Click on the green "Watch" button in the upper right of the page. To provide comment during the meeting please call in toll free at 1-866-899-4679 and enter the following access code when prompted: 746-033-605. Please note that there may be a slight delay (15-30 seconds) between the meeting and the live stream and television broadcast. If you are watching the meeting and calling in, please lower the volume on your computer or television during public comment so that you may be heard clearly. We ask that you identify yourself when calling in to help us manage multiple callers effectively. Citizens may also provide public comment for this meeting by emailing the Town Planner at jribeiro@truro-ma.gov with your comments.

Public Hearing – Continued

2019-008 ZBA – Community Housing Resource, Inc. seeks approval for a Comprehensive Permit pursuant to G.L. c. 40B, §§20-23 to create 40 residential rental units, of which not less than 25% or 10 units shall be restricted as affordable for low or moderate income persons or families, to be constructed on property located at 22 Highland Road, as shown on Assessor's Map 36 and Parcel 238-0 containing 3.91 acres of land area.

Approval of Minutes

June 25, 2018

Adjourn

Office of Town Clerk
Treasurer – Tax Collector
JUN 23 2020
8:35 AM
Received TOWN OF TRURO
By

Planning Department

Town of Truro

24 Town Hall Road
Truro, MA 02666
(508) 349-7004

Zoning Board of Appeals

Meeting Packet – June 25, 2020

Table of Contents

J.M. O'REILLY & ASSOCIATES, INC.
PROFESSIONAL ENGINEERING, LAND SURVEYING & ENVIRONMENTAL SERVICES
Site Development • Property Line • Subdivision • Sanitary • Land Court • Environmental Permitting

MEMORANDUM

June 5, 2020

To: Truro Zoning Board of Appeals

From: John O'Reilly, P.E., P.L.S.
J.M. O'REILLY & ASSOCIATES, INC.

Re: **Supplemental Information**
Cloverleaf Development
Highland Road, Truro, MA
Applicant: Community Housing Resource

On behalf of the applicant, Community Housing Resource, J.M. O'REILLY & ASSOCIATES, INC. is providing the attached revised plans for the above referenced development. The revisions and adjustments to the plans are a result of the Peer Review completed by Horsley-Witten Group on March 3, 2020. The following is a narration of the changes and the responses to the Peer Review Report.

Water Quality Considerations for the Proposed Project.

Wastewater:
As suggested, the disposal of the sewage from the development has been updated to include a Denitrifying treatment process that will reduce the total Nitrogen within the wastewater to 10 ppm at discharge.

Attached, please find a guidance letter by BIO-MICROBICS which summarizes the design parameters so as to achieve a total nitrogen of 10 ppm at the discharge. As support of the design proposal, we have attached the treatment results of a similar development (affordable housing, total flow is 9,990 GPD).

Using the Table 1: TITLE 5 Aggregation of Flows and Nitrogen Loading calculations, as outlined on the Peer Review, and based on a discharge limit of 10 ppm for the wastewater, we have calculated the total nitrogen at the property boundary to be about 9.1 ppm.

Stormwater:
As discussed, we have reviewed and adjusted the stormwater facilities for the development. The major adjustment to the drainage controls is as follows:

- The drainage facilities have been adjusted to accommodate some miscellaneous contributory areas which were omitted from the initial design.

- Grassed swales are proposed for the front and rear drainage facilities.
- Drywells are now shown on Sheet 2 of 5 to accommodate the runoff from the roofed areas of the buildings.
- Drainage facilities are designed for the 50 year storm.

The front drainage facility (DF#1) revisions include the elimination of the two intermediate leaching facilities, (formally DF#2 & DF#3), along the access drive and the enlargement of the lower leaching facility to accommodate the stormwater for the front portion of the site. The stormwater at the entrance into the development is now proposed to be handled by a concrete trench drain. The drainage controls include solid deep sump catch basins with hoods on outflow pipes, a series of drainage manholes and two outfalls into the grassed swale. Stormwater is going to be allowed to pond within the swale for treatment prior to discharge into the subsurface leaching facility.

Outfall into Swale: El = 23.0
Bottom of Swale: EL = 21.0
Inlet into Catch Basin: EL = 22.5 (Max water level in swale is 18 inches)

The two mid-point drainage facilities (DF#2 & DF#3) were adjusted to accommodate the leaching facility locations for the wastewater. The drainage facility was not modified to accommodate a swale. Areas for swales were investigated for the drainage facility, but given the location of the buildings, the necessary grades for the leaching facilities and the buildings, a vegetated swale could not be accommodated. The contributory areas for these two drainage facilities is less than 16% of the total contributory area for the development.

The rear drainage facility (DF#4) revisions include the enlargement of the subsurface leaching facility to accommodate the adjusted contributory areas. Similar to the front drainage facility, the rear facility includes a grassed swale for additional treatment.

Outfall into Swale: EL=43.0
Bottom of Swale: EL=42.0
Inlet into Catch Basin: EL=43.0 (Max water level in Swale is 12 inches)

Specific Comments on the Septic System Design:

1. Reserve Area are shown on Sheets 1 of 5 and 2 of 5. The total capacity for the reserve area is 8,255 GPD. If utilized, the reserve area will be developed using a drip-disposal leaching facility. The drip system is identified as the reserve given the drip system's ability to be installed on slopped ground and around existing trees.
    a. The drip tubing would be mechanically installed along the sloped areas without requiring an open trench.
    b. The drip tubing can be installed around large trees or landscape features so as to not disturb mature vegetation.
    c. The pumps and associated controls that are proposed for the leach field will need to be updated to accommodate the pump controls of the drip tubing, if the reserve area is utilized.

2. Test Pits have not been completed. It is the intention of the applicant to complete the soil testing, as required by Title 5, once access to the areas are available. A hand boring, as previously presented to the town did find suitable soils for the subsurface disposal of wastewater at a percolation rate of less than 2 minutes per inch.
3. Elevations for the top and bottom are provided for the proposed tanks and leaching facilities.
4. Pipe sizes and slopes have been added to Sheet 3 of 5. All sewer pipe shall be 6 inch diameter SDR-35 piping or approved equal.
5. The setbacks from the sewage system to the drainage controls have been added. All required setbacks have been provided.
6. Based on the soil boring and groundwater information within the Peer Report, the groundwater was determined to be about elevation 4.7. The following is offered:
    a. The proposed separation from the bottom of the SAS#1 to groundwater is 46 feet +/-.
    b. The proposed separation from the bottom of the SAS#2 to groundwater is 43 feet +/-.
    c. Front Reserve Area from lowest grade to groundwater is about 28 feet**
    d. Rear Reserve Area from lowest grade to groundwater is about 31**

    ** Drip lines will be set 12 to 18 inches below the existing grade**

    Mounding: Given the depths of the proposed leaching fields (SAS) and lowest reserve area elevations, 28 to 46 feet, mounding of the ground water is not anticipated to result in the bottom of the leaching facilities being within 5 feet of the mounded groundwater.
7. The project now proposes a generator for the operation of the wastewater treatment works during periods of power outage.
8. As part of the submission for a disposal works permit, the applicant shall provide an Operation & Maintenance Agreement with a MA licensed WWTP Operator. The O&M frequency and scope shall conform to the requirements set forth by the manufacturer and the 40B permit. At a minimum J.M. O'REILLY & ASSOCIATES, INC. recommend the following testing for startup;
    a. Sample and Test for Total Nitrogen: Monthly for the first 12 months after start up.
    b. Sample WWTP series: Quarterly after startup or as required by permit.
    c. Sewer Line Inspection: Annually:
       Visual inspect sewer and clean as needed
    d. Pumping: As Required*

    *Evaluate solid accumulations during the first 12 months, operator shall review and confirm pumping schedule.

Specific Comments on Stormwater management Facilities:

1. The drainage facilities have been revised to account for grassed swales in the front and rear drainage controls. The combination of the solid deep sump catch basins with hoods and the grassed swale provides a reduction of almost 78% in the TSS. The two midpoint drainage facilities as still the standard solid deep sump catch basin with hood and a subsurface leaching facility. The available room for a swale was limited in these two areas.

   The four drainage facilities address drainage control for the development. Of the four facilities the project proposed to address 84% of the contributory area with the additional treatment provided with a grassed swale.

2. The contributory areas were reviewed and adjusted to reflect the comments in the Peer report.
3. The offsite areas were reviewed and accounted for, as necessary, please refer to the contributory area sketch with the drainage summary.
4. Roof run off is being controlled through a series of 12'x6' subsurface leach pits. A drainage summary for Building 21 is provided. Based on these calculations a 12'x6' leach pit can handle 1,886 sf of roof area. The building areas have been connected to the respective leach pits to accommodate the sizing.
5. The 50 year rainfall event was taken from the MA Stormwater Handbook. 24 hour, 50 year storm, 6.23 inches.
6. The front drainage facility (DF#1) has been adjusted to add one set of catch basins along the steep part of the access road so as to address the sheet flow comment within the Peer report. The collection points for the remaining drainage areas have not adjusted to add additional catch basins.
7. The issue of the over topping of the catch basin has been resolved with the adjustment in the DF#1.
8. Test Borings have not been completed. It is the intention of the applicant to complete the soil testing, once access to the areas are available. A hand boring, as previously presented to the town did find suitable soils for the subsurface disposal of wastewater at a percolation rate of less than 2 minutes per inch.

Comments on the Other Utilities:

1. Hydrant Flow Tests will be conducted as part of the water main expansion project, the Town of Truro and Environmental Partners is handling the design of the proposed water mains.
2. Street lighting is shown on the landscape planting plan. The lighting posts have been coordinated with the updated site plans.
3. Site Plans 1 and 2 have been updated to show a preliminary layout of the underground utilities. The underground utilities will most likely start at the existing utility pole at Highland and run into the site and terminating in the rear portion of the site adjacent to the control room for the WWTP. The location is not definitive since the utility company will be responsible for the coordination of the utilities once the project receives approval.

   Propane tanks have been shown on Sheet 2 of 5, and on the landscape planting plan.

Other Site Design Comments:

1. A formal phasing plan will be provided to Town once the water main and state highway access permit approval is obtained.
2. Please refer to the Erosion Control Report.
3. Cut and Fill are in the process of being completed by the contractor. It is not anticipated that the volume amounts are going to change significantly from the previous submittal.
4. Please refer to the Erosion Control report.
5. The applicant reviewed the existing vegetation adjacent to the property boundary of the Route 6 corridor. Based on the review the plans have been updated to flip the secondary water services and sewer services. The water services will be installed around the limit of clearing as shown on

sheets 1 and 2 so as to save as much of the natural vegetation as possible. Refer to Landscape Planting Plan for additional plantings to screen Route 6.

6. The Landscape Planting Plan has been updated to specify the planting of shallow-rooted shrubs or trees adjacent to or above the leaching facilities for the wastewater.
7. Plans have been updated to reflect the differences in the proposed pavement pitch.
8. The fire department has reviewed and approved the access drive into the development.
9. The spaces proposed are 20 feet long and 10 feet wide. The parking spaces shown in solid lines are proposed to be paved. The overflow parking spaces, shown in dashed lines are to be finished with native gravel or permeable pavers.
10. No trash "dumpster" is proposed for the site. The area behind Building 21 is a trellis-screened gated "corral" for garbage bins for assigned to units in building 21. Recyclables in Building 21 are handled in a designated area of basement storage. The dwellings in two-unit buildings have individual garbage bin storage areas adjacent to parking. Individual tenants are expected to take trash and recyclables to the Truro Transfer Station. Recyclables are stored/maintained in storage and/or basement areas for individuals or maintenance staff to transport to Transfer Station, Tenants unable to visit Transfer Station will be assisted by Property Maintenance Staff.
11. Cross hatched areas on Landscape Planting Plan and drainage swales are areas for snow storage. These areas are planted with native grasses and will not be damaged by snow storage potential.
12. There are specifically designated playground areas on site. Active recreation areas are off site (Cape Cod National Seashore, Town of Truro Puma Park for example). There is a Bus Stop less than 300 feet west of the entry to the Cloverleaf site. There are no mailboxes locations on site as there is no mail delivery in Truro – individuals pick up at the Post Office less than 1/2 mile west on Highland Road.
13. Sidewalk is shown down to Highland Road. No other connections have been added to the project plans.
14. The site is in a mapped endangered species, the applicant has already received approval and guidance from the Natural Heritage & Endangered Species Program. Refer to the Turtle Protection Plan.
15. Refer to the Landscape Planting Plan.

Summary for Pond 1P: Leaching Facility #1

Inflow	=	2.47 cfs @	12.14 hrs, Volume=	0.143 af
Outflow	=	0.38 cfs @	12.77 hrs, Volume=	0.143 af, Atten= 84%, Lag= 37.9 min
Discarded	=	0.38 cfs @	12.77 hrs, Volume=	0.143 af

Routing by Dyn-Stor-Ind method, Time Span= 0.00-24.00 hrs, dt= 0.01 hrs
Peak Elev= 17.86' @ 12.77 hrs Surf.Area= 1,104 sf Storage= 2,513 cf

Plug-Flow detention time= 69.6 min calculated for 0.143 af (100% of inflow)
Center-of-Mass det. time= 69.5 min (887.6 - 818.1)

Volume	Invert	Avail.Storage	Storage Description
#1	13.50'	1,933 cf	**12.00'W x 92.00'L x 6.00'H Prismatoid** 6,624 cf Overall - 1,792 cf Embedded = 4,832 cf x 40.0% Voids
#2	13.50'	1,527 cf	**6.00'D x 6.00'H Vertical Cone/Cylinder** x 9 Inside #1 1,792 cf Overall - 3.0" Wall Thickness = 1,527 cf
		3,460 cf	Total Available Storage

Device	Routing	Invert	Outlet Devices
#1	Discarded	13.50'	**8.270 in/hr Exfiltration over Wetted area** Phase-In= 0.01'

Discarded OutFlow Max=0.38 cfs @ 12.77 hrs HW=17.86' (Free Discharge)
↑**1=Exfiltration** (Exfiltration Controls 0.38 cfs)

Summary for Pond 2P: Leaching Facility #2

Inflow Area = 0.127 ac, 69.09% Impervious, Inflow Depth > 3.99" for 50-year event
Inflow = 0.70 cfs @ 12.02 hrs, Volume= 0.042 af
Outflow = 0.11 cfs @ 12.48 hrs, Volume= 0.042 af, Atten= 85%, Lag= 27.3 min
Discarded = 0.11 cfs @ 12.48 hrs, Volume= 0.042 af

Routing by Dyn-Stor-Ind method, Time Span= 0.00-24.00 hrs, dt= 0.01 hrs
Peak Elev= 49.91' @ 12.48 hrs Surf.Area= 264 sf Storage= 584 cf

Plug-Flow detention time= 44.6 min calculated for 0.042 af (100% of inflow)
Center-of-Mass det. time= 44.6 min (852.7 - 808.1)

Volume	Invert	Avail.Storage	Storage Description
#1	45.60'	474 cf	**12.00'W x 22.00'L x 6.00'H Prismatoid** 1,584 cf Overall - 398 cf Embedded = 1,186 cf x 40.0% Voids
#2	45.60'	339 cf	**6.00'D x 6.00'H Vertical Cone/Cylinder** x 2 Inside #1 398 cf Overall - 3.0" Wall Thickness = 339 cf
		814 cf	Total Available Storage

Device	Routing	Invert	Outlet Devices
#1	Discarded	45.60'	**8.270 in/hr Exfiltration over Wetted area** Phase-In= 0.01'

Discarded OutFlow Max=0.11 cfs @ 12.48 hrs HW=49.91' (Free Discharge)
↑**1=Exfiltration** (Exfiltration Controls 0.11 cfs)

Summary for Pond 3P: Leaching Facility #3

Inflow Area = 0.118 ac, 67.88% Impervious, Inflow Depth > 3.88" for 50-year event
Inflow = 0.52 cfs @ 12.10 hrs, Volume= 0.038 af
Outflow = 0.10 cfs @ 12.56 hrs, Volume= 0.038 af, Atten= 81%, Lag= 27.7 min
Discarded = 0.10 cfs @ 12.56 hrs, Volume= 0.038 af

Routing by Dyn-Stor-Ind method, Time Span= 0.00-24.00 hrs, dt= 0.01 hrs
Peak Elev= 49.40' @ 12.56 hrs Surf.Area= 264 sf Storage= 515 cf

Plug-Flow detention time= 40.9 min calculated for 0.038 af (100% of inflow)
Center-of-Mass det. time= 40.8 min (856.0 - 815.2)

Volume	Invert	Avail.Storage	Storage Description
#1	45.60'	474 cf	**12.00'W x 22.00'L x 6.00'H Prismatoid** 1,584 cf Overall - 398 cf Embedded = 1,186 cf x 40.0% Voids
#2	45.60'	339 cf	**6.00'D x 6.00'H Vertical Cone/Cylinder** x 2 Inside #1 398 cf Overall - 3.0" Wall Thickness = 339 cf
		814 cf	Total Available Storage

Device	Routing	Invert	Outlet Devices
#1	Discarded	45.60'	**8.270 in/hr Exfiltration over Wetted area** Phase-In= 0.01'

Discarded OutFlow Max=0.10 cfs @ 12.56 hrs HW=49.40' (Free Discharge)
↑**1=Exfiltration** (Exfiltration Controls 0.10 cfs)

Summary for Pond 4P: Leaching Facility #4

Inflow	=	3.62 cfs @	12.03 hrs, Volume=	0.199 af
Outflow	=	0.46 cfs @	12.52 hrs, Volume=	0.199 af, Atten= 87%, Lag= 29.3 min
Discarded	=	0.46 cfs @	12.52 hrs, Volume=	0.199 af

Routing by Dyn-Stor-Ind method, Time Span= 0.00-24.00 hrs, dt= 0.01 hrs
Peak Elev= 38.17' @ 12.52 hrs Surf.Area= 1,224 sf Storage= 3,304 cf

Plug-Flow detention time= 65.7 min calculated for 0.199 af (100% of inflow)
Center-of-Mass det. time= 65.7 min (867.2 - 801.5)

Volume	Invert	Avail.Storage	Storage Description
#1	33.00'	2,141 cf	**12.00'W x 102.00'L x 6.00'H Prismatoid** 7,344 cf Overall - 1,991 cf Embedded = 5,353 cf x 40.0% Voids
#2	33.00'	1,696 cf	**6.00'D x 6.00'H Vertical Cone/Cylinder** x 10 Inside #1 1,991 cf Overall - 3.0" Wall Thickness = 1,696 cf
		3,838 cf	Total Available Storage

Device	Routing	Invert	Outlet Devices
#1	Discarded	33.00'	**8.270 in/hr Exfiltration over Wetted area** Phase-In= 0.01'

Discarded OutFlow Max=0.46 cfs @ 12.52 hrs HW=38.16' (Free Discharge)
↑**1=Exfiltration** (Exfiltration Controls 0.46 cfs)

Summary for Pond 7P: (3) 6'x6' Leach Pits, w/ 3' stone

Inflow Area = 0.135 ac,100.00% Impervious, Inflow Depth > 5.99" for 50-year event
Inflow = 1.41 cfs @ 11.90 hrs, Volume= 0.067 af
Outflow = 0.18 cfs @ 12.01 hrs, Volume= 0.067 af, Atten= 87%, Lag= 6.6 min
Discarded = 0.18 cfs @ 12.01 hrs, Volume= 0.067 af

Routing by Dyn-Stor-Ind method, Time Span= 0.00-24.00 hrs, dt= 0.01 hrs
Peak Elev= 55.28' @ 12.01 hrs Surf.Area= 339 sf Storage= 985 cf

Plug-Flow detention time= 40.2 min calculated for 0.067 af (100% of inflow)
Center-of-Mass det. time= 40.1 min (775.3 - 735.1)

Volume	Invert	Avail.Storage	Storage Description
#1	50.00'	509 cf	**6.00'D x 6.00'H Vertical Cone/Cylinder** x 3 Inside #2
#2	50.00'	611 cf	**12.00'D x 6.00'H Vertical Cone/Cylinder** x 3
			2,036 cf Overall - 509 cf Embedded = 1,527 cf x 40.0% Voids
		1,120 cf	Total Available Storage

Device	Routing	Invert	Outlet Devices
#1	Discarded	50.00'	**8.270 in/hr Exfiltration over Wetted area** Phase-In= 0.01'

Discarded OutFlow Max=0.18 cfs @ 12.01 hrs HW=55.28' (Free Discharge)
↑**1=Exfiltration** (Exfiltration Controls 0.18 cfs)

INSTRUCTIONS:
1. In BMP Column, click on Blue Cell to Activate Drop Down Menu
2. Select BMP from Drop Down Menu
3. After BMP is selected, TSS Removal and other Columns are automatically completed.

Version 1, Automated: Mar. 4, 2008

Location: Drainage Area 1 & 4

TSS Removal Calculation Worksheet

B BMP[1]	C TSS Removal Rate[1]	D Starting TSS Load*	E Amount Removed (C*D)	F Remaining Load (D-E)
Deep Sump and Hooded Catch Basin	**0.25**	**1.00**	**0.25**	**0.75**
Water Quality Swale - Dry	**0.70**	**0.75**	**0.53**	**0.23**
	0.00	**0.23**	**0.00**	**0.23**
	0.00	**0.23**	**0.00**	**0.23**
	0.00	**0.23**	**0.00**	**0.23**

Total TSS Removal = **78%**

Separate Form Needs to be Completed for Each Outlet or BMP Train

Project: Cloverleaf Development
Prepared By: JMO
Date: 5/8/2020

*Equals remaining load from previous BMP (E) which enters the BMP

78% x 84% = 65.5% FOR SITE

Non-automated TSS Calculation Sheet must be used if Proprietary BMP Proposed
1. From MassDEP Stormwater Handbook Vol. 1

DESIGN CALCULATIONS

DESIGN FLOW:

68 BEDROOMS X 110 GPD/BR = 7,480 GPD
OFFICE SPACE (UNIT 21): 279 SF X 75 GPD/1000 SF = 20.9 GPD
TOTAL FLOW: 7,501 GPD

SEPTIC TANK REQUIRED:

FIRST SEPTIC TANK: 7,501 GPD x 200% = 15,002 GALLONS MINIMUM
SECOND SEPTIC TANK: 7,371 X 100% = 7,501 GALLONS MINIMUM

LEACHING FACILITY REQUIRED: 7,501 GPD

LEACHING FACILITY PROVIDED:
TWO (2)- LEACHING FIELDS
ONE (1)- 75' x 92' x 1' LEACH FIELD. Vt = [75' x 92'] x 0.74 GPD/SF = 5,106 GPD
ONE (1)- 75' x 45' x 1' LEACH FIELD. Vt= [75 x 45] x 0.74 GPD/SF = 2,497 GPD
TOTAL = 7,603 GPD

INSTALL:
ONE (1)- 16,000 GALLON SEPTIC TANK (ST1B)
ONE (1)- 8,000 GALLON SEPTIC TANK (ST2B)
ONE (1)- DISTRIBUTION BOX- FLOW SPLITTER
TWO (2)- HSMBR 9.0- N TREATMENT UNITS- DUEL TRAIN
ONE (1)- 6'x6'x4' BLOWER VAULT
ONE (1)- 10,000 GALLON PUMP CHAMBER
TWO(2)- 3 HP EFFLUENT PUMPS WITH LIFT RAILS AND ALARMS
ONE (1)- 5' x 3' ALUMINUM HATCH (H-20 RATED)
THREE (3)- 4' x 4' ALUMINUM HATCH (H-20 RATED)
TWENTY ONE (21)- 24" DIA CAST IRON COVERS (H-20)
ONE (1)- 75' x 92' x 1' LEACH FIELD
TONE (1)- 75' x 45' x 1' LEACH FIELD

G:\AAJobs\Malone- Cloverleaf Utility Plan- 40B- SDS & Drainage- REVISED 5-15-2020.dwg

CLOVERLEAF TRURO RENTAL HOUSING

Community Housing Resource, Inc.; P.O. Box 1015, Provincetown, MA 02657

DRAINAGE- SUBCATCHMENT AREAS

22 HIGHLAND ROAD, TRURO, MA

J.M. O'REILLY & ASSOCIATES, INC.
Professional Engineering & Land Surveying Services
1573 Main Street – Route 6A
P.O. Box 1773
(508)896-6601 Office Brewster, MA 02631 (508)896-6602 Fax

DATE:	SCALE:	BY:	CHECK:	JOB NUMBER:
11-1-2019	As Noted	RFR	JMO	JMO-8446A

16002 West 110th street▪ Lenexa, KS 66219 USA▪ Phone: 913-422-0707▪ Fax: 913-422-0808
E-mail: onsite@biomicrobics.com ▪ www.biomicrobics.com ▪ 800-753-FAST (3278)

May 13, 2020

Lauren D. Usilton
J & R Sales and Service
44 Commercial St.
Raynham, MA 02767

Dear Lauren,

We have received your inquiry regarding the Coverleaf Affordable Housing in Truro, MA. The design flow given to us is 8091 GPD. The influent characteristics used for the design were assumed to be the following concentrations:

- BOD = 300 mg/L
- TSS = 150 mg/L
- TKN = 70 mg/L

We suggest the following system for an effluent of 30/30/10 mg/L BOD/TSS/TN respectively:

- Settling tank of at least 1/2 to 1 time of the daily flow, followed by
- One- BioBarrier® HSMBR® 9.0-N

For an estimated 6 month pump-out frequency, we would suggest a total treatment volume of 16000 gallons where 50% volume is anoxic and 50% is aerobic.

Based on the design flow and influent concentrations stated above, the system proposed should meet the required effluent results assuming there is sufficient alkalinity in the influent wastewater for nitrification and there are no issues with pH, temperature, or toxicity. This also assumes the treatment plant is installed, maintained, and operated correctly. If the influent parameters exceed any of these stated above, additional equipment may be needed.

Please contact me if you have any questions.

Regards,

Minoo Dadman

Sr. Sales & Research Engineer
BioMicrobics, Inc.
Ph.: 913-422-0707
www.biomicrobics.com

Noquochoke Village

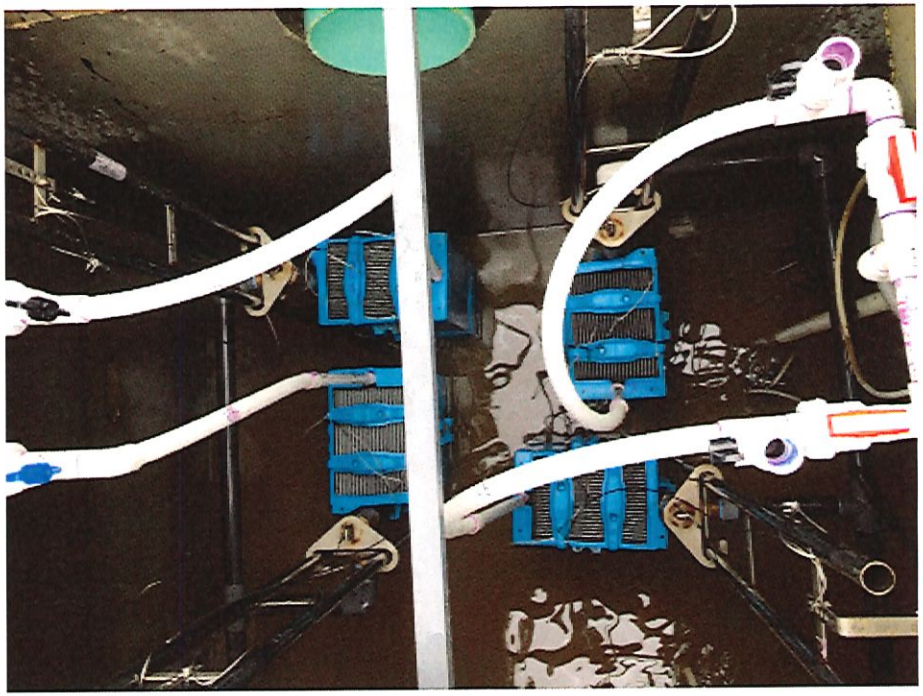
Westport, MA

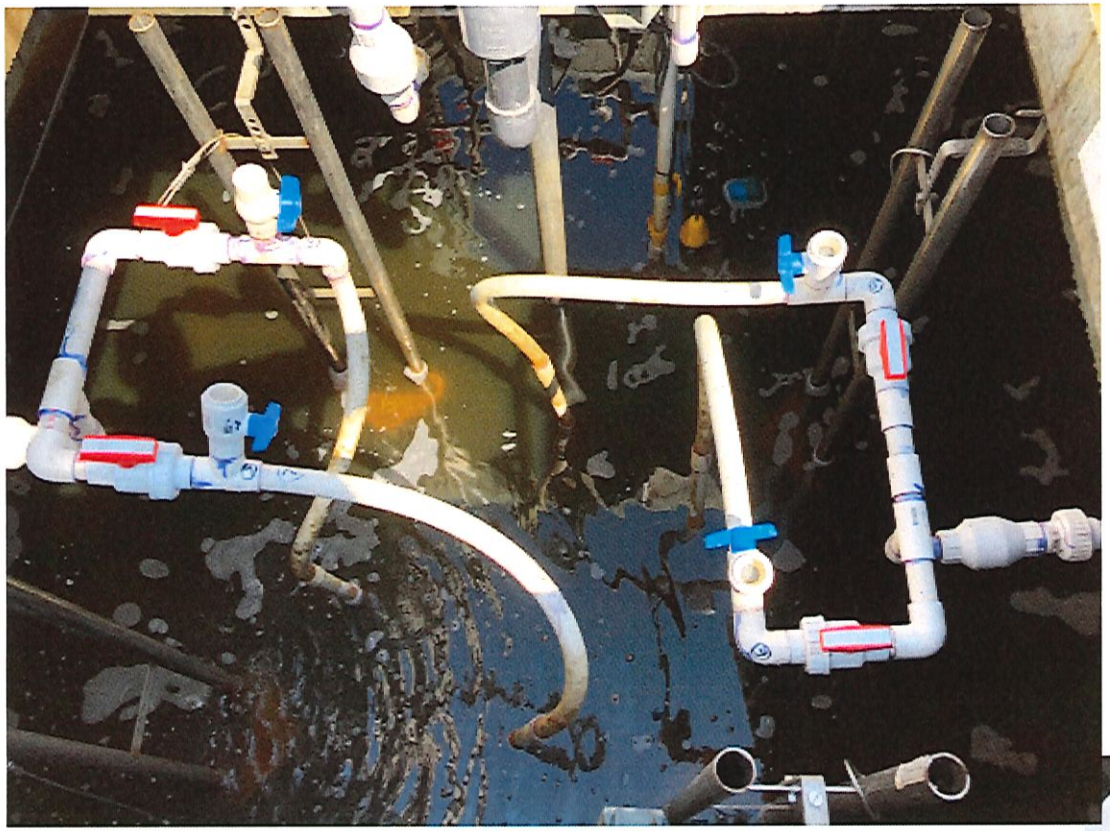
Affordable Housing Apartments – 2018 Installation – 2019 Startup

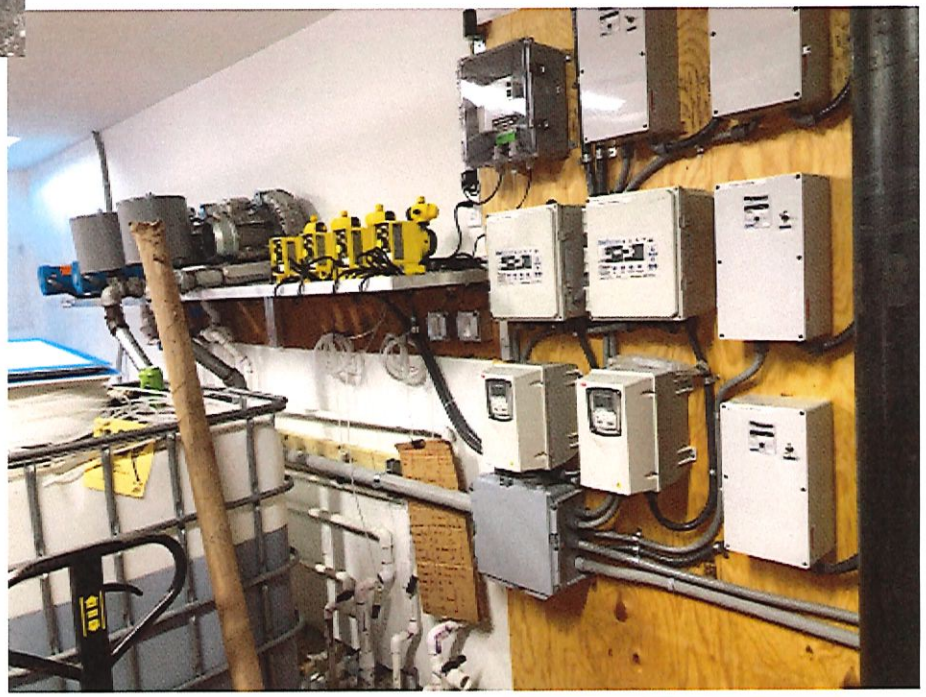
- Design flow 9,990 gpd
- Actual flow ~3,000-4,000 gpd
- Designed on; influent BOD 250 mg/L, Influent TKN 60 mg/L, influent TSS 125 mg/L
- Actual influent numbers: 100 – 800 mg/L BOD; 90-150 mg/L TKN
- Effluent Limits: <30 mg/L BOD, <30 mg/L TSS, <5 mg/L TN
- Effluent results: <4 mg/L BOD, <4 mg/L TSS, <5 mg/L TN

(2) HSMBR 6.0-N with GEOFLOW Drip Dispersal

- 13,000 gallon followed by a 20,000 gallon settling tank - 10,000 gallon flow eq tank – (2) 8,000 gallon three compartment BioBarrier tanks (two anoxic zones and one aerobic zone per tank)- 3,500 gallon pump chamber - dispersed to GEOFLOW Drip Dispersal System
- Local regulators looking for "net zero" nitrogen at the property line
- Seeing a 98% TN removal



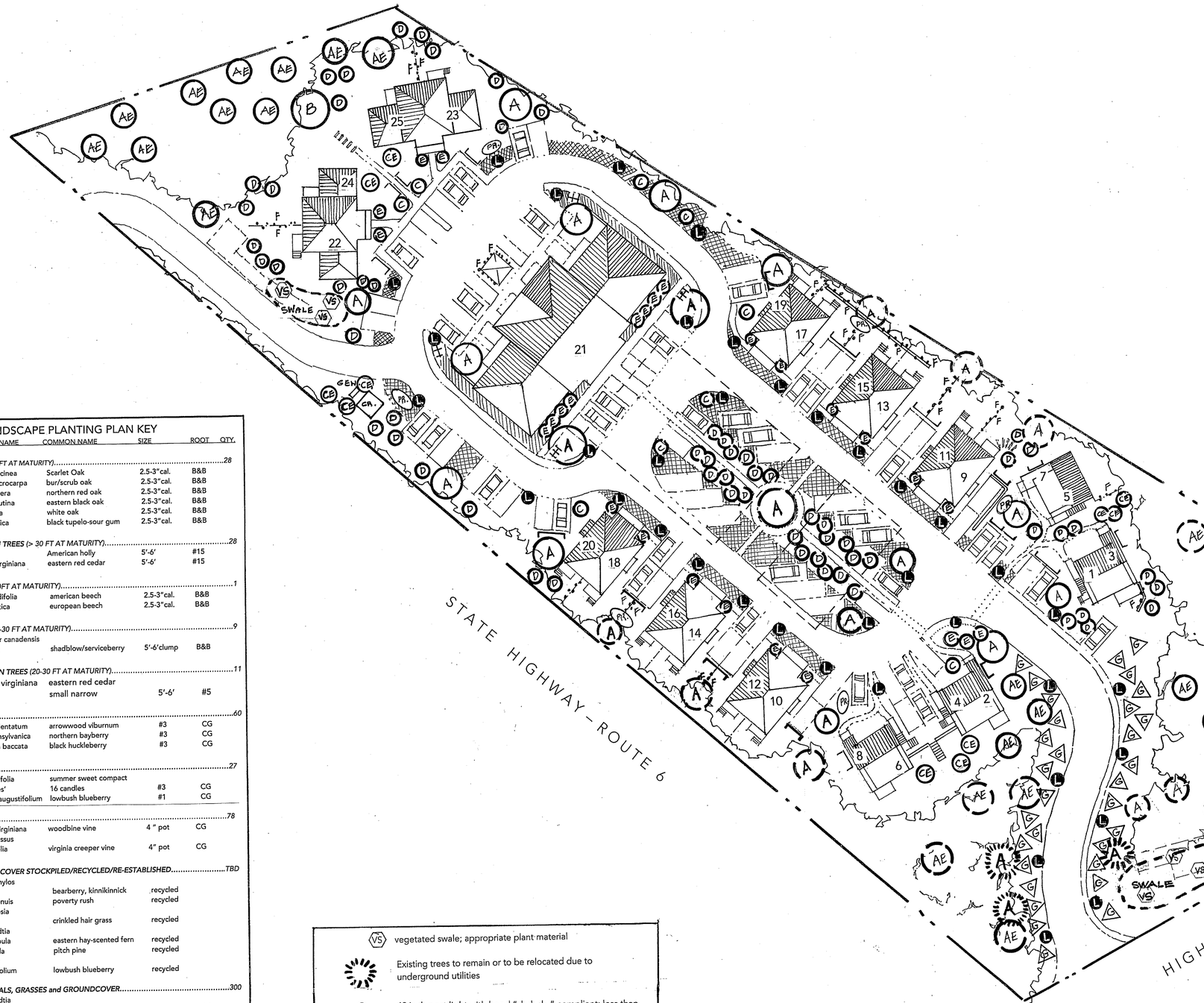




BioMicrobics BioBarrier®

Residential flows - design flow 9,990 gpd

	INFLUENT								EFFLUENT								
	BOD mg/L	TSS mg/L	pH mg/L	TKN mg/L	Nitrate mg/L	Nitrite mg/L	Ammonia mg/L	Alkalinity mg/L	BOD mg/L	TSS mg/L	pH mg/L	TKN mg/L	Nitrate mg/L	Nitrite mg/L	TN mg/L	Ammonia mg/L	Alkalinity mg/L
June 2019	105	16.5	7.3	36.7	ND	ND	30.9	202	<4.0	<4.0	7.6	3.05	9.40	0.34	12.79	1.45	183
July 2019	520	590	7	146.0	ND	ND	83.9	333	<4.0	<4.0	7.8	2.28	4.52	ND	6.80	0.25	94
August 2019	297	54	6.9	97.3	ND	ND	63.6	329	<4.0	<4.0	8.1	1.34	2.57	ND	3.91	0.1	229
September 2019	810	620	6.5	107.0	ND	ND	61.8	255	<4.0	<4.0	7.8	1.11	1.24	ND	2.35	0.17	150
October 2019	403	848	6.9	118.0	ND	0.45	63.7	286	<4.0	<4.0	7.9	0.79	1.11	ND	1.90	0.47	108
November 2019	408	140	6.5	90.4	ND	ND	69.6	337	<4.0	<4.0	7.8	0.76	0.92	ND	1.68	0.11	260
December 2019	146	70	6.8	75.0	ND	ND	47.40	284	4.4	<4.0	7.7	1.62	3.81	ND	5.43	0.27	81
January 2020	*No testing - membrane cleaning performed																
February 2020	31	88	6.9	29.8	0.68	ND	15.60	167	<4.0	<4.0	7.4	2.26	1.23	ND	3.49	ND	81
March 2020	330	7	56	86.5	ND	ND	70.90	345	<4.0	<4.0	7.7	0.88	2.76	ND	3.64	0.31	81
AVG	338.9	270.4	12.31	87.4	ND	ND	56.4	282.00	<4.0	<4.0	7.76	1.57	3.06	0.34	4.98	0.40	141



LANDSCAPE PLANTING PLAN KEY

KEY	BOTANICAL NAME	COMMON NAME	SIZE	ROOT	QTY.
A	*TREES (> 30FT AT MATURITY)*				28
	Quercus coccinea	Scarlet Oak	2.5-3"cal.	B&B	
	Quercus macrocarpa	bur/scrub oak	2.5-3"cal.	B&B	
	Quercus rubera	northern red oak	2.5-3"cal.	B&B	
	Quercus velutina	eastern black oak	2.5-3"cal.	B&B	
	Quercus alba	white oak	2.5-3"cal.	B&B	
	Nyssa sylvatica	black tupelo-sour gum	2.5-3"cal.	B&B	
AE	*EVERGREEN TREES (> 30 FT AT MATURITY)*				28
	Ilex opaca	American holly	5'-6'	#15	
	Juniperus virginiana	eastern red cedar	5'-6'	#15	
B	*TREES (>50FT AT MATURITY)*				1
	Fagus grandifolia	american beech	2.5-3"cal.	B&B	
	Fagus sylvatica	european beech	2.5-3"cal.	B&B	
C	*TREES (20-30 FT AT MATURITY)*				9
	Amelanchier canadensis or A. lavis	shadblow/serviceberry	5'-6'clump	B&B	
CE	*EVERGREEN TREES (20-30 FT AT MATURITY)*				11
	Juniperus virginiana 'taylor"	eastern red cedar small narrow	5'-6'	#5	
D	*SHRUBS*				60
	Viburnum dentatum	arrowwood viburnum	#3	CG	
	Morella pensylvanica	northern bayberry	#3	CG	
	Gaylussacia baccata	black huckleberry	#3	CG	
E	*SHRUBS*				27
	Clethra alnifolia 'I6 candles'	summer sweet compact 16 candles	#3	CG	
	Vaccinium augustifolium	lowbush blueberry	#1	CG	
F	*VINES*				78
	Clematis virginiana	woodbine vine	4 " pot	CG	
	Parthenocissus quinquifolia	virginia creeper vine	4" pot	CG	
G	*GROUND COVER STOCKPILED/RECYCLED/RE-ESTABLISHED*				TBD
	Arctostaphylos uva-ursi	bearberry, kinnikinnick	recycled		
	Juncus tenuis	poverty rush	recycled		
	Deschampsia flexuosa	crinkled hair grass	recycled		
	Dennstaedtia punctilobula	eastern hay-scented fern	recycled		
	Pinus rigida	pitch pine	recycled		
	Vaccinium augustifolium	lowbush blueberry	recycled		
	PERENNIALS, GRASSES and GROUNDCOVER				300
	Dennstaedtia punctilobula	hay-scented fern	#1	CG	
	Dryopteris intermedia	evergreen wood fern	#1	CG	
	Deschampsia flexuosa	crinkled hair grass	flats plugs		
	Deschampsia cespitosa	tufted hair grass	flats plugs		
	Schizachyrium scoparium	little blue stem- 'prairie munchkin'	flats plugs		
	Juncus tenius	poverty rush	seed *		
	Deschampsia flexuosa flexuosa	Colonial Seed Company 'Harmony'or'Pilgrim'mix	seed *		

- Seeded grasses and some mulching at all other disturbed areas around the dwellings

VS vegetated swale; appropriate plant material

Existing trees to remain or to be relocated due to underground utilities

L 42 inch post light with hood "dark sky" compliant; less than 75 watt equivalent

Supplemental trees in undisturbed areas as needed based on site conditions

Seeded area - native grasses/snow storage potential

PR. Underground propane; 250-500 gallon, tbd.

LANDSCAPE PLANTING PLAN

CLOVERLEAF TRURO RENTAL HOUSING
10 JUNE 2020

0 30 60 90

BENCHMARK1
Top of Stone Bound
EL=35.9± (NAVD88 Datum)

BENCHMARK1
Top of Stone Bound
EL=48.5± (NAVD88 Datum)

100' Well Setback

175' To 545 serving MAP: 36 Parcel 170

152' To Well serving Map: 36 Parcel 170

PROPOSED TWO (2)- 2 INCH CLASS 150
H.D.P.E. WATER PIPE
(TYPICAL FOR SERVICES TO BUILDINGS)

N 72°26'56" E 227.86'

RESERVE AREA
Vt=4,285 GPD

PARCEL 238
Area= 3.91 AC±

BUILDING 23-25
FF EL=47.0
TOF EL=46.0
UNIT 25: 4 BR
UNIT 23: 3 BR
TOTAL FLOW: 770GPD

BUILDING 22-24
FF EL=47.0
TOF EL=46.0
UNIT 24: 4 BR
UNIT 22: 3 BR
TOTAL FLOW: 770GPD

PROPOSED HYDRANT

N 58°18'36" W 582.23'

BUILDING 1-21
FF EL=52.0
TOF EL=50.0
UNIT 1: 3 BR + DEN
UNIT 21: 3 BR
TOT. FLOW: 550GPD

BUILDING 3-19
FF EL=50.5
TOF EL=49.0
UNIT 3: 3 BR
UNIT 19: 3 BR
TOT. FLOW: 495GPD

BUILDING 4-18
FF EL=49.0
TOF EL=47.5
UNIT 4: 3 BR
UNIT 18: 3 BR
TOT. FLOW: 495GPD

BUILDING 5-7
FF EL=48.0
TOF EL=46.0
UNIT 5: 2 BR
UNIT 7: 2 BR
TOT FLOW: 220GPD

BUILDING 6-16
FF EL=46.0
TOF EL=44.5
UNIT 6: 3 BR
UNIT 16: 3 BR
TOT FLOW: 385GPD

BUILDING 8-14
FF EL=45.0
TOF EL=43.5
UNIT 8: 3 BR
UNIT 14: 3 BR
TOT FLOW: 385GPD

BUILDING 9-13
FF EL=44.0
TOF EL=42.5
UNIT 9: 3 BR
UNIT 13: 3 BR
TOT FLOW: 385GPD

BUILDING 10-12
FF EL=43.0
TOF EL=41.5
UNIT 10: 3 BR
UNIT 12: 3 BR
TOT FLOW: 330GPD

BUILDING 11
FF EL=42.0
TOF EL=40.5
UNIT 11: 3 BR
TOT FLOW: 165GPD

BUILDING 2-4
FF EL=51.5
TOF EL=50.0
UNIT 2: 3 BR
UNIT 4: 3 BR
TOT. FLOW: 330GPD

BUILDING 6-8
FF EL=52.0
TOF EL=50.5
UNIT 6: 3 BR
UNIT 8: 3 BR
TOT. FLOW: 330GPD

BUILDING 48-20
FF EL=56.0
TOF EL=55.0
UNIT 48: 3 BR DEN
UNIT 20: 3 BR DEN
TOT. FLOW: 550GPD

BUILDING 46-22
FF EL=54.0
TOF EL=52.5
UNIT 46: 3 BR
UNIT 22: 3 BR
TOT. FLOW: 495GPD

BUILDING 44-24
FF EL=52.0
TOF EL=50.5
UNIT 44: 3 BR
UNIT 24: 3 BR
TOT. FLOW: 495GPD

BUILDING 42-26
FF EL=50.0
TOF EL=48.5
UNIT 42: 3 BR
UNIT 26: 3 BR
TOT. FLOW: 495GPD

BUILDING 40-28
FF EL=48.0
TOF EL=46.5
UNIT 40: 3 BR
UNIT 28: 3 BR
TOT. FLOW: 495GPD

BUILDING 38-30
FF EL=46.0
TOF EL=44.5
UNIT 38: 3 BR
UNIT 30: 3 BR
TOT. FLOW: 495GPD

BUILDING 36-32
FF EL=44.0
TOF EL=42.5
UNIT 36: 3 BR
UNIT 32: 3 BR
TOT. FLOW: 385GPD

BUILDING 34
FF EL=42.0
TOF EL=40.5
UNIT 34: 3 BR
TOT. FLOW: 165GPD

FIRST FLOOR GSA EL=47.0'
15 UNITS - 2 BEDROOMS
11,667 S.F. OF OFFICE SPACE
11,667 S.F. COMMUNITY SPACE
TOTAL SEWAGE FLOW=3,640GPD*
*SEWAGE FLOW BASED ON 60 PERSON ASSEMBLY IN COMMUNITY SPACE

TOF=50.0
FF=52.0

PROPOSED HYDRANT

TOW-58.5
BOW-54±

TOW-55.0
BOW-52.5

PROPOSED 8 INCH D.I. WATER PIPE

PROPOSED WATER SERVICE UNITS
4" DIA DOMESTIC
4" FIRE

PROPOSED THREE (3) 2 INCH CLASS 150
H.D.P.E. WATER PIPE
(TYPICAL FOR SERVICES TO BUILDINGS)

N 49°25'22" W 742.30'

STATE HIGHWAY - ROUTE 6

PROPOSED 2 INCH CLASS 150
H.D.P.E. WATER PIPE
(TYPICAL FOR SERVICES TO BUILDINGS)

PROPOSED HYDRANT

PROPOSED 2 INCH CLASS 150
H.D.P.E. WATER PIPE
(TYPICAL FOR SERVICES TO BUILDINGS)

100' Well Setback Map: 36 Parcel: 178

RESERVE AREA
Vt=3,970 GPD

N 13°52'47" W
150.00'

SAS

DB

Existing Gravel Drive
TO BE REMOVED

Edge of Pavement

BENCHMARK1
Top of Mass Highway Bound
EL=27.9± (NAVD88 Datum)

Solid Yellow Lines

N 61°32'11" E 209.61'

Utility Pole

Back of Berm

Existing Catch Basin Rim EL=23.5±

Edge of Pavement

Back of Berm

HIGHLAND ROAD
(60' Wide Town Way)

PLAN
SCALE 1"=30'

SCALE 1"=30'

0 30 60 90

MASS COORD. SYSTEM (NAD83)

TRURO, MA

Head of the Meadow Rd

LOCUS

Highland Rd

6

NOT TO SCALE

PLAN BOOK 672 PAGE 34
ASSESSORS' MAP 36 PARCEL 238

LEGEND

- 32 EXISTING CONTOUR
- 32 PROPOSED CONTOUR
- ×12.34 EXISTING SPOT GRADE
- 24x5 PROPOSED SPOT GRADE
- W WATER SERVICE LINE
- E UNDERGROUND UTILITY SERVICE
- G GAS SERVICE LINE
- TP TEST HOLE / BORING LOCATION
- ST SEPTIC TANK
- DB DISTRIBUTION BOX
- SAS SOIL ABSORPTION SYSTEM
- Reserve RESERVED FOR FUTURE
- UTILITY POLE
- CATCH BASIN
- FIRE HYDRANT
- W WELL
- DRAINAGE MANHOLE
- CONCRETE BOUND, FOUND
- TOP OF BANK
- LIMIT OF WORK
- FENCE
- PT UNDERGROUND PROPANE TANK
- 12' x 6' LEACHING DRYWELL (ROOF)
- TRANSFORMER PAD- UTILITY CLUSTER
- GEN GENERATOR

SHEET 1 OF 5
PERMIT SET- NOT FOR CONSTRUCTION

REVISED 6-5-2020: UPDATED SEWAGE SYSTEM TREATMENT TO INCLUDE 10 PPM NITROGEN LIMIT; ADJUSTED SEWER MANHOLE LAYOUT; ADJUSTED DRAINAGE TO INCLUDE SWALES AND ADDITIONAL CONTRIBUTORY AREAS; UPDATED NOTES AND DETAILS ACCORDINGLY

REVISED 2-14-2020: UPDATED BUILDING LAYOUT, ADJUSTED ENTRANCE; UPDATED SEWAGE SYSTEM COLLECTION AND ADDED I.A. TREATMENT TECHNOLOGY; UPDATED WATER SERVICE LAYOUT AND DRAINAGE ACCORDINGLY

CLOVERLEAF TRURO RENTAL HOUSING

Community Housing Resource, Inc.; P.O. Box 1015, Provincetown, MA 02657

SITE PLAN

22 HIGHLAND ROAD, TRURO, MA

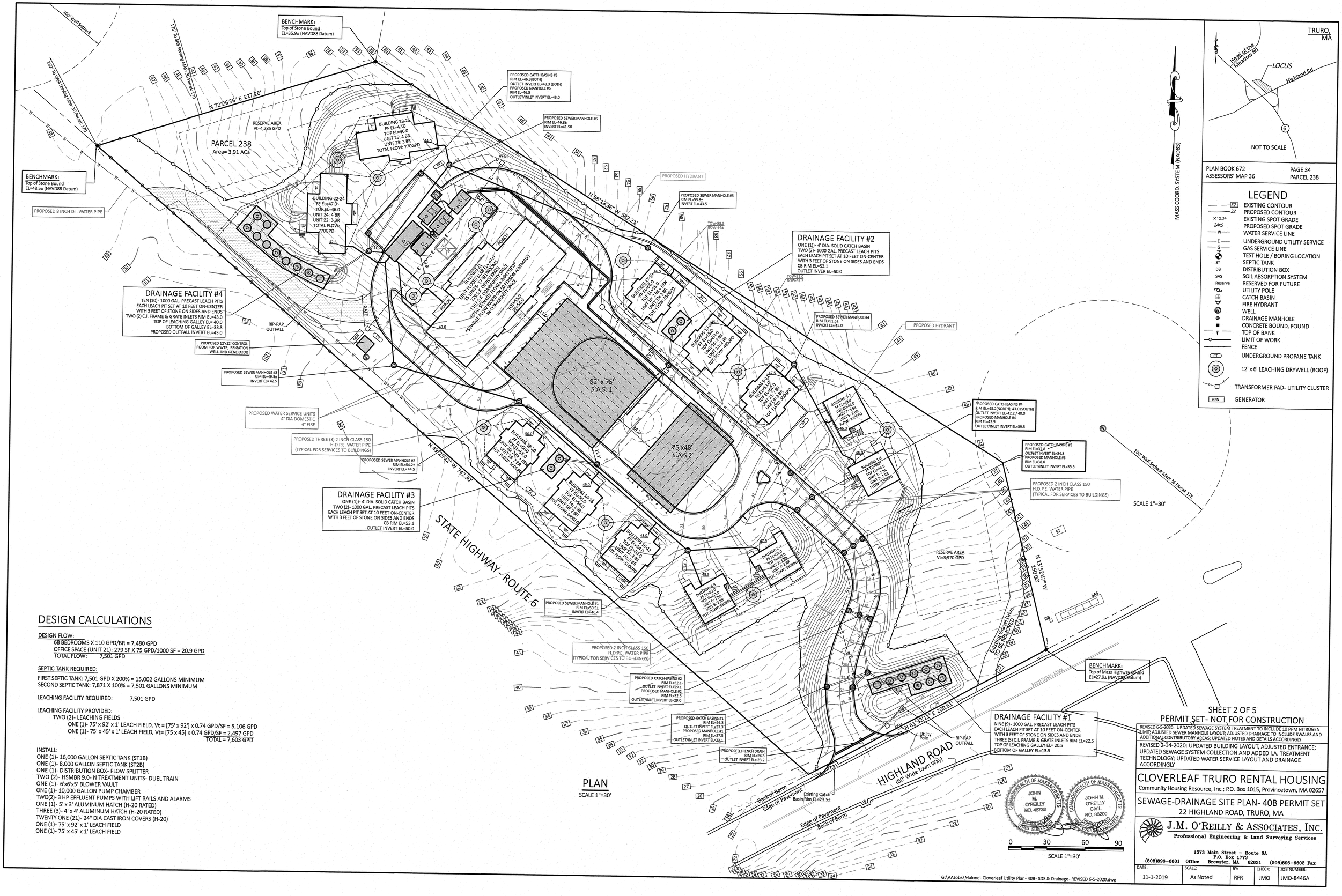
J.M. O'REILLY & ASSOCIATES, INC.
Professional Engineering & Land Surveying Services
1573 Main Street – Route 6A
P.O. Box 1773
Brewster, MA 02631
(508)896-6601 Office (508)896-6602 Fax

DATE:	SCALE:	BY:	CHECK:	JOB NUMBER:
11-1-2019	As Noted	RFR	JMO	JMO-8446A

COMMONWEALTH OF MASSACHUSETTS JOHN M. O'REILLY NO. 46738 PROFESSIONAL LAND SURVEYOR

COMMONWEALTH OF MASSACHUSETTS JOHN M. O'REILLY CIVIL NO. 39000 REGISTERED PROFESSIONAL ENGINEER

G:\AAJobs\Malone- Cloverleaf Utility Plan- 40B- SITE PLAN- REVISED 6-5-2020.dwg



DESIGN CALCULATIONS

DESIGN FLOW:
68 BEDROOMS X 110 GPD/BR = 7,480 GPD
OFFICE SPACE (UNIT 21): 279 SF X 75 GPD/1000 SF = 20.9 GPD
TOTAL FLOW: 7,501 GPD

SEPTIC TANK REQUIRED:

FIRST SEPTIC TANK: 7,501 GPD X 200% = 15,002 GALLONS MINIMUM
SECOND SEPTIC TANK: 7,871 X 100% = 7,501 GALLONS MINIMUM

LEACHING FACILITY REQUIRED: 7,501 GPD

LEACHING FACILITY PROVIDED:
TWO (2)- LEACHING FIELDS
ONE (1)- 75' x 92' x 1' LEACH FIELD, Vt = [75' x 92'] x 0.74 GPD/SF = 5,106 GPD
ONE (1)- 75' x 45' x 1' LEACH FIELD, Vt= [75 x 45] x 0.74 GPD/SF = 2,497 GPD
TOTAL = 7,603 GPD

INSTALL:
ONE (1)- 16,000 GALLON SEPTIC TANK (ST1B)
ONE (1)- 8,000 GALLON SEPTIC TANK (ST2B)
ONE (1)- DISTRIBUTION BOX- FLOW SPLITTER
TWO (2)- HSMBR 9.0- N TREATMENT UNITS- DUEL TRAIN
ONE (1)- 6'x6'x5' BLOWER VAULT
ONE (1)- 10,000 GALLON PUMP CHAMBER
TWO(2)- 3 HP EFFLUENT PUMPS WITH LIFT RAILS AND ALARMS
ONE (1)- 5' x 3' ALUMINUM HATCH (H-20 RATED)
THREE (3)- 4' x 4' ALUMINUM HATCH (H-20 RATED)
TWENTY ONE (21)- 24" DIA CAST IRON COVERS (H-20)
ONE (1)- 75' x 92' x 1' LEACH FIELD
ONE (1)- 75' x 45' x 1' LEACH FIELD

PLAN BOOK 672 PAGE 34
ASSESSORS' MAP 36 PARCEL 238

LEGEND

- EXISTING CONTOUR
- PROPOSED CONTOUR
- EXISTING SPOT GRADE
- PROPOSED SPOT GRADE
- WATER SERVICE LINE
- UNDERGROUND UTILITY SERVICE
- GAS SERVICE LINE
- TEST HOLE / BORING LOCATION
- SEPTIC TANK
- DISTRIBUTION BOX
- SOIL ABSORPTION SYSTEM
- RESERVED FOR FUTURE
- UTILITY POLE
- CATCH BASIN
- FIRE HYDRANT
- WELL
- DRAINAGE MANHOLE
- CONCRETE BOUND, FOUND
- TOP OF BANK
- LIMIT OF WORK
- FENCE
- UNDERGROUND PROPANE TANK
- 12' x 6' LEACHING DRYWELL (ROOF)
- TRANSFORMER PAD- UTILITY CLUSTER
- GENERATOR

SHEET 2 OF 5
PERMIT SET- NOT FOR CONSTRUCTION

REVISED 6-5-2020: UPDATED SEWAGE SYSTEM TREATMENT TO INCLUDE 10 PPM NITROGEN LIMIT; ADJUSTED SEWER MANHOLE LAYOUT; ADJUSTED DRAINAGE TO INCLUDE SWALES AND ADDITIONAL CONTRIBUTORY AREAS; UPDATED NOTES AND DETAILS ACCORDINGLY

REVISED 2-14-2020: UPDATED BUILDING LAYOUT, ADJUSTED ENTRANCE; UPDATED SEWAGE SYSTEM COLLECTION AND ADDED I.A. TREATMENT TECHNOLOGY; UPDATED WATER SERVICE LAYOUT AND DRAINAGE ACCORDINGLY

CLOVERLEAF TRURO RENTAL HOUSING

Community Housing Resource, Inc.; P.O. Box 1015, Provincetown, MA 02657

SEWAGE-DRAINAGE SITE PLAN- 40B PERMIT SET

22 HIGHLAND ROAD, TRURO, MA

J.M. O'REILLY & ASSOCIATES, INC.
Professional Engineering & Land Surveying Services
1573 Main Street – Route 6A
P.O. Box 1773
Brewster, MA 02631
(508)896-6601 Office (508)896-6602 Fax

DATE:	SCALE:	BY:	CHECK:	JOB NUMBER:
11-1-2019	As Noted	RFR	JMO	JMO-8446A

G:\AAJobs\Malone- Cloverleaf Utility Plan- 40B- SDS & Drainage- REVISED 6-5-2020.dwg

GENERAL NOTES:

A.) NEITHER DRIVEWAYS NOR PARKING AREAS ARE ALLOWED OVER SEPTIC SYSTEM UNLESS H-20 COMPONENTS ARE USED.

B.) THE DESIGNER WILL NOT BE RESPONSIBLE FOR THE SYSTEM AS DESIGNED UNLESS CONSTRUCTED AS SHOWN. ANY CHANGES SHALL BE APPROVED IN WRITING.

C.) CONTRACTOR SHALL BE RESPONSIBLE FOR VERIFYING THE LOCATION OF ALL UNDERGROUND AND OVERHEAD UTILITIES PRIOR TO COMMENCEMENT OF WORK.

CONSTRUCTION NOTES:

1.) ALL CONSTRUCTION SHALL CONFORM TO THE STATE ENVIRONMENTAL CODE, TITLE 5, AND THE REQUIREMENTS OF THE LOCAL BOARD OF HEALTH.

2.) SEPTIC TANK(S), GREASE TRAP(S), DOSING CHAMBER(S) AND DISTRIBUTION BOX(ES) SHALL BE SET ON A LEVEL STABLE BASE WHICH HAS BEEN MECHANICALLY COMPACTED, OR ON A 6 INCH CRUSHED STONE BASE.

3.) SEPTIC TANK(S) SHALL MEET ASTM STANDARD C1127-93 AND SHALL HAVE AT LEAST THREE 20" DIAMETER MANHOLES. THE MINIMUM DEPTH FROM THE BOTTOM OF THE SEPTIC TANK TO THE FLOW LINE SHALL BE 48".

4.) SCHEDULE 40 PVC INLET AND OUTLET TEES SHALL EXTEND A MINIMUM OF 6" ABOVE THE FLOW LINE OF THE SEPTIC TANK AND SHALL BE INSTALLED ON THE CENTERLINE OF THE TANK DIRECTLY UNDER THE CLEANOUT MANHOLE.

5.) RAISE COVERS OF THE SEPTIC TANK AND DISTRIBUTION BOX WITH PRECAST CONCRETE WATER TIGHT RISERS OVER INLET AND OUTLET TEES TO WITHIN 6" OF FINISH GRADE, OR AS APPROVED BY THE LOCAL BOARD OF HEALTH AGENT.

6.) PIPING SHALL CONSIST OF 4" SCHEDULE 40 PVC OR EQUIVALENT. PIPE SHALL BE LAID ON A MINIMUM CONTINUOUS GRADE OF NOT LESS THAN 1%.

7.) DISTRIBUTION LINES FOR SOIL ABSORPTION SYSTEM (AS REQUIRED) SHALL BE 4" DIAMETER SCHEDULE 40 PVC LAID AT 0.005 FT/FT. LINE SHALL BE CAPPED AT END OR AS NOTED.

8.) OUTLET PIPES FROM DISTRIBUTION BOX SHALL REMAIN LEVEL FOR AT LEAST 2' BEFORE PITCHING TO SOIL ABSORPTION SYSTEM. WATER TEST DISTRIBUTION BOX TO ASSURE EVEN DISTRIBUTION.

9.) DISTRIBUTION BOX SHALL HAVE A MINIMUM SUMP OF 6" MEASURED BELOW THE OUTLET INVERT.

10.) BASE AGGREGATE FOR THE LEACHING FACILITY SHALL CONSIST OF 3/4" TO 1-1/2" DOUBLE WASHED STONE FREE OF IRON, FINES AND DUST AND SHALL BE INSTALLED BELOW THE CROWN OF THE DISTRIBUTION LINE TO THE BOTTOM OF THE SOIL ABSORPTION SYSTEM. BASE AGGREGATE SHALL BE COVERED WITH A 2" LAYER OF 1/8" TO 1/2" DOUBLE WASHED STONE FREE OF IRON, FINES AND DUST.

11.) VENT SOIL ABSORPTION SYSTEM WHEN DISTRIBUTION LINES EXCEED 50 FEET, WHEN LOCATED EITHER IN WHOLE OR IN PART UNDER DRIVEWAYS, PARKING AREAS, TURNING AREAS OR OTHER IMPERVIOUS MATERIAL; OR WHEN PRESSURE DOSED.

12.) SOIL ABSORPTION SYSTEM SHALL BE COVERED WITH A MINIMUM OF 9" OF CLEAN MEDIUM SAND (EXCLUDING TOPSOIL).

13.) FINISH GRADE SHALL BE A MAXIMUM OF 36" OVER THE TOP OF ALL SYSTEM COMPONENTS, INCLUDING THE SEPTIC TANK, DISTRIBUTION BOX, DOSING CHAMBER AND SOIL ABSORPTION SYSTEM. SEPTIC TANKS SHALL HAVE A MINIMUM COVER OF 9".

14.) FROM THE DATE OF INSTALLATION OF THE SOIL ABSORPTION SYSTEM UNTIL RECEIPT OF A CERTIFICATE OF COMPLIANCE, THE PERIMETER OF THE SOIL ABSORPTION SYSTEM SHALL BE STAKED AND FLAGGED TO PREVENT THE USE OF SUCH AREA FOR ALL ACTIVITIES THAT MIGHT DAMAGE THE SYSTEM.

15.) THE BOARD OF HEALTH SHALL REQUIRE INSPECTION OF ALL CONSTRUCTION BY AN AGENT OF THE BOARD OF HEALTH (OR THE DESIGNER IF THIS SYSTEM REQUIRES A VARIANCE) AND MAY REQUIRE SUCH PERSON TO CERTIFY IN WRITING THAT ALL WORK HAS BEEN COMPLETED IN ACCORDANCE WITH THE TERMS OF THE PERMIT AND APPROVED PLANS. 48 HOURS ADVANCE NOTICE IS REQUESTED.

16.) ONE (1) 4" PVC INSPECTION PORT TO BE RAISED TO WITHIN 3" OF FINISH GRADE FOR EACH LEACHING FIELD. BOTH INSPECTION PORTS TO BE PROVIDED WITH CAST IRON CLEANOUT COVERS AT FINISH GRADE.

17.) INSTALLER TO CONFIRM LOCATION OF ALL UNDERGROUND AND OVERHEAD UTILITIES PRIOR TO START OF CONSTRUCTION.

18.) WATER/SEWER CROSSING: WASTELINE SHALL BE A 20' SECTION OF PVC PIPE CENTERED OVER THE WATER LINE TO MAXIMIZE DISTANCE TO JOINTS.

SOIL LOGS:

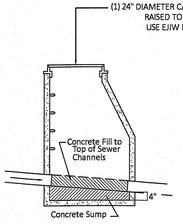
HAND AUGER 1: EL = 58.0±

DEPTH FROM SURFACE (INCHES)	SOIL HORIZON	SOIL TEXTURE (USDA)	SOIL COLOR (MUNSELL)	SOIL MOTTLING	OTHER
0-6	A	FINE LOANY SAND	10YR3/1		
6-24	C1	COARSE SAND	10YR7/8	NONE	
24-186	C2	COARSE SAND	10YR6/4		
					NO WATER ENCOUNTERED

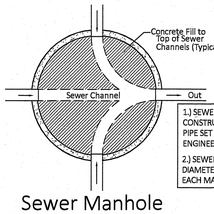
DATE OF TESTING: 10-16-2019
PERCOLATION RATE: LESS THAN 52 MIN/INCH IN C1 LAYERS (ASSUMED)
WITNESSED BY: ROBERT REEDY, EIT, J.M. O'REILLY & ASSOCIATES, INC.
NO GROUNDWATER WAS ENCOUNTERED
USE A LOADING RATE OF 0.74 GPD/SF FOR SIZING OF SOIL ABSORPTION SYSTEM.

PROFILE OF SEWER MANHOLES:

NOT TO SCALE



Sewer Manhole
600 Gallon
Pre-cast Concrete Manhole
with Off-set Cover



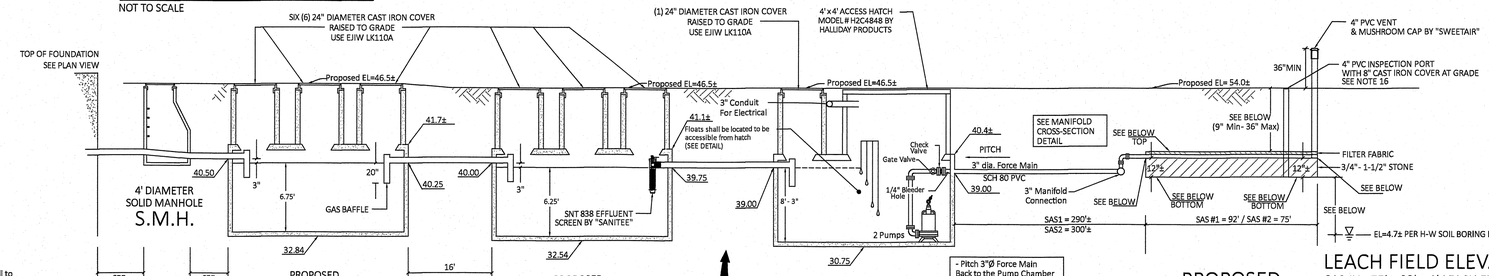
Sewer Manhole
PLAN VIEW
Not To Scale

1.) SEWER CHANNELS SHALL BE CONSTRUCTED OF BRICK OR PVC PIPE SET IN CONCRETE OR OF ENGINEER APPROVED EQUAL.

2.) SEWER CHANNELS MUST MATCH DIAMETER OF OUTLET PIPE FOR EACH MANHOLE

SCHEMATIC FLOW PROFILE:

NOT TO SCALE



LEACH FIELD ELEVATIONS:

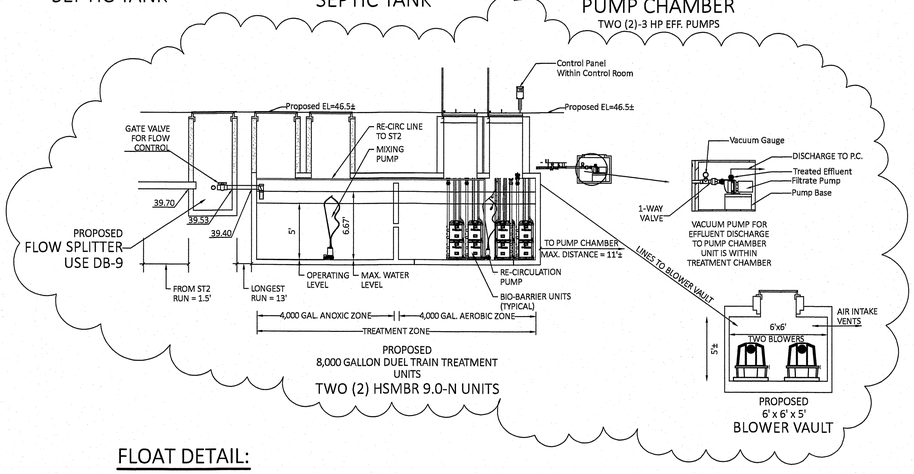
SAS #1- 75' x 92' x 1' LEACH FIELD
TOP OF FIELD = 52.0±
BOTTOM OF FIELD = 51.0±
MAXIMUM GRADE OVER FIELD = 55.0±
DEPTH TO GROUNDWATER = 46'±

SAS #2- 75' x 45' x 1' LEACH FIELD
TOP OF FIELD = 49.5±
BOTTOM OF FIELD = 48.5±
MAXIMUM GRADE OVER FIELD = 52.5±
MINIMUM GRADE OVER FIELD = 50.5±
DEPTH TO GROUNDWATER = 43'±

PUMP DOSING PROGRAM:

1. BOTH PUMPS MUST BE CAPABLE OF PUMPING AT LEAST 90 GPM AGAINST A TOTAL DYNAMIC HEAD OF 30'± (USE (2) MYERS EFF. PUMP- 2 HP OR ENGINEER APPROVED EQUIVALENT).
2. BOTH PUMPS SHALL BE OPERATED ON A TIMER CYCLE.
   SAS #1 PUMP: SHALL RUN FOR MAXIMUM OF 5 MINUTES EVERY 30 MINUTES:
   TOTAL DOSE PER HOUR = 900 GALLONS;
   SAS #2 PUMP: PUMP SHALL RUN FOR A MAXIMUM OF 3 MINUTES EVERY 30 MINUTES:
   TOTAL DOSE PER HOUR = 540 GALLONS
3. FLOAT SYSTEM:
   LOW WATER FLOAT- BOTH PUMPS OFF
   OPERATIONAL FLOAT- BOTH PUMPS ARE AVAILABLE FOR CYCLE PUMPING
   HIGH WATER FLOAT- ALTERNATE PUMP ENGAUGES AND PUMPS TO LOW WATER FLOAT IS ENGAUGED
   HIGH WATER ALARM FLOAT- ALARM SOUNDS- REMOTE DIALER IS ENGAGED TO WWTP OPERATOR.

NOTE:
ONCE PUMPS INSTALLED WITHIN CHAMBER, TIMING AND DOSAGE SHALL BE ADJUSTED TO REFLECT ACTUAL PUMP DISCHARGE AND FLOW RATES.



SEWER MANHOLE ELEVATION SCHEDULE : SMH #1-3			
COMPONENT	RIM EL	PIPE INVERT EL	6" SEWER PITCH (%), LENGTH FROM PREV.
SMH #1	50.5±	46.4±	
SMH #2	54.2±	44.5±	1.1% PITCH , 172' OF 6" SEWER LINE
SMH #3	46.8±	42.5±	2% PITCH, 98' OF 6" SEWER
ST #1 INLET	46.5±	40.5±	2.4% PITCH, 84' OF 6" SEWER

SEWER MANHOLE ELEVATION SCHEDULE : SMH #4-6			
COMPONENT	RIM EL	PIPE INVERT EL	6" SEWER PITCH (%), LENGTH FROM PREV.
SMH #4	51.5±	45.0±	
SMH #5	53.8±	43.5±	1.1% PITCH , 142' OF 6" SEWER LINE
SMH #6	46.8±	41.5±	1.2% PITCH, 164' OF 6" SEWER
ST #1 INLET	46.5±	40.5±	1.2% PITCH, 83' OF 6" SEWER

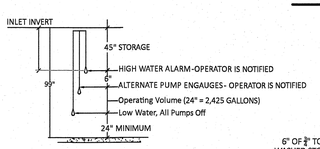
SEWER NOTES:
1.) THE SEWER PIPER SHALL BE 6" DIA. SDR35 PIPE OR APPROVED EQUAL.
2.) EACH WASTE LINE, EXISTING THE BUILDINGS, SHALL BE CONNECTED TO A 6" CLEAN-OUT, TO GRADE, FOR FUTURE MAINTENANCE.

OPERATIONAL NOTES & REQUIREMENTS:

1.) ALL WIRING AND CONNECTIONS SHALL BE IN COMPLIANCE WITH THE MA STATE ELECTRICAL CODE AS WELL AS TO THE MANUFACTURER'S SPECIFICATIONS. ALL WORK SHALL BE COMPLETED BY A LICENSED ELECTRICIAN.
2.) THE ALARM SHALL CONSIST OF A RED WARNING LIGHT, AN AUDIBLE ALARM AND A REMOTE DIALER SO AS TO NOTIFY THE WWTP OPERATOR OF THE ALARM EVENT. LIGHT AND ALARM SHALL BE MOUNTED TO THE SIDE OF THE CONTROL BUILDING.
3.) ALL CORDS FOR PUMPS AND FLOATS SHALL BE CONTINUOUS FROM THE TREATMENT WORKS TO THE JUNCTION DISCONNECT BOX.
4.) JUNCTION DISCONNECT BOX SHALL BE LOCATED ADJACENT TO THE CONTROL BUILDING.

FLOAT DETAIL:

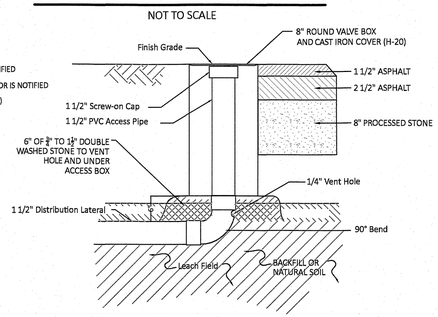
NOT TO SCALE



*FLOAT INSTALLATION NOTES:
1.) FLOATS SHALL BE INSTALLED WITH A CABLE WEIGHT AND SHALL NOT BE TETHERED TO THE DISCHARGE LINE IN ORDER TO ALLOW FOR THEM TO BE PULLED UP TO THE TOP OF PUMP CHAMBER.
2.) FLOATS SHALL BE INSTALLED SO THAT THEY CAN BE ACCESSED FROM OUTLET MANHOLE COVER.
3.) FLOATS MUST BE INSTALLED SO THAT THEY ARE FREE TO MOVE THROUGHOUT IT'S TRAVEL AND NOT CONTACT THE PUMP BODY, PIPING, OR OTHER OBJECTS.

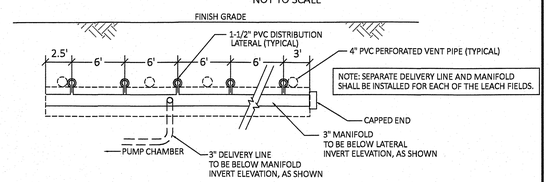
DETAIL OF LATERAL ACCESS CAP

NOT TO SCALE



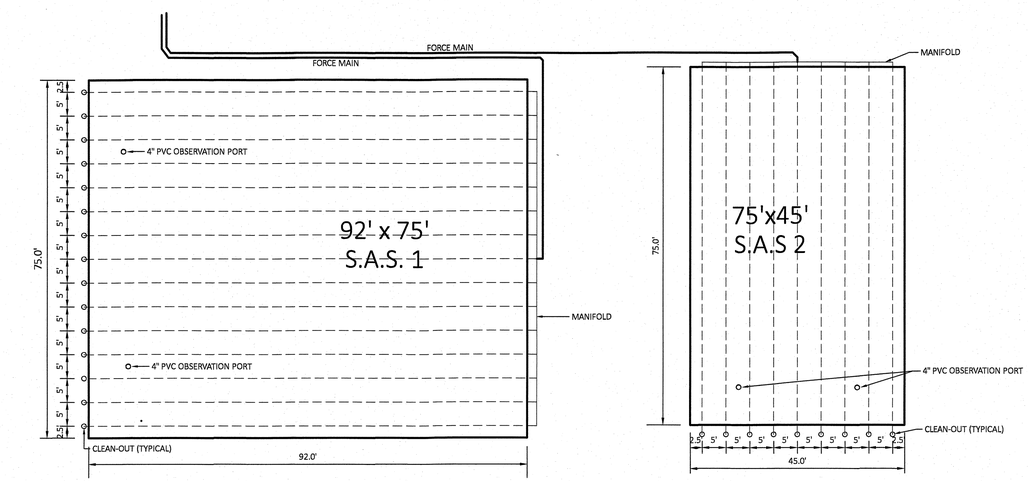
MANIFOLD CROSS-SECTION DETAIL

NOT TO SCALE



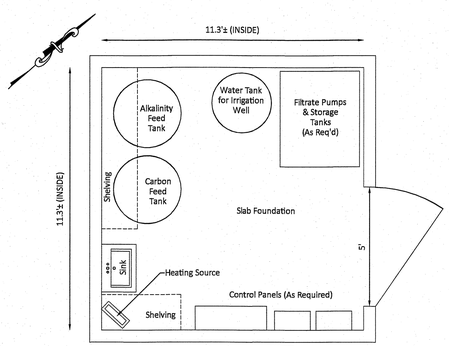
SOIL ABSORPTION SYSTEM DETAIL:

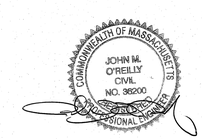
NOT TO SCALE



CONTROL ROOM LAYOUT

SCALE: 1" = 3'





0 30 60 90
SCALE 1"=30'

SHEET 3 OF 5
PERMIT SET- NOT FOR CONSTRUCTION

REVISED 6-5-2020: UPDATED SEWAGE SYSTEM TREATMENT TO INCLUDE 10 PPM NITROGEN LIMIT; ADJUSTED SEWER MANHOLE LAYOUT; ADJUSTED DRAINAGE TO INCLUDE SWALES AND ADDITIONAL CONTRIBUTORY AREAS; UPDATED NOTES AND DETAILS ACCORDINGLY

REVISED 2-14-2020: UPDATED BUILDING LAYOUT, ADJUSTED ENTRANCE; UPDATED SEWAGE SYSTEM COLLECTION AND ADDED I.A. TREATMENT TECHNOLOGY; UPDATED WATER SERVICE LAYOUT AND DRAINAGE ACCORDINGLY

CLOVERLEAF TRURO RENTAL HOUSING
Community Housing Resource, Inc.; P.O. Box 1015, Provincetown, MA 02657

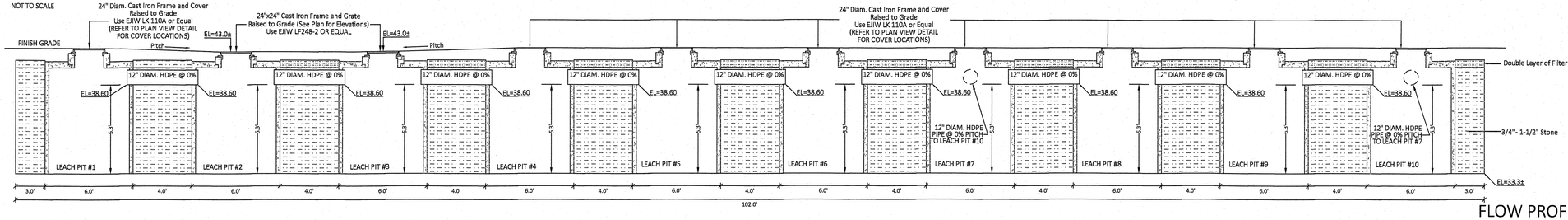
SEWAGE DETAILS- 40B PERMIT SET
22 HIGHLAND ROAD, TRURO, MA

J.M. O'REILLY & ASSOCIATES, INC.
Professional Engineering & Land Surveying Services
1573 Main Street – Route 6A
P.O. Box 1773
(508)896-6601 Office Brewster, MA 02631 (508)896-6602 Fax

DATE:	SCALE:	BY:	CHECK:	JOB NUMBER:
11-1-2019	As Noted	RFR	JMO	JMO-8446A

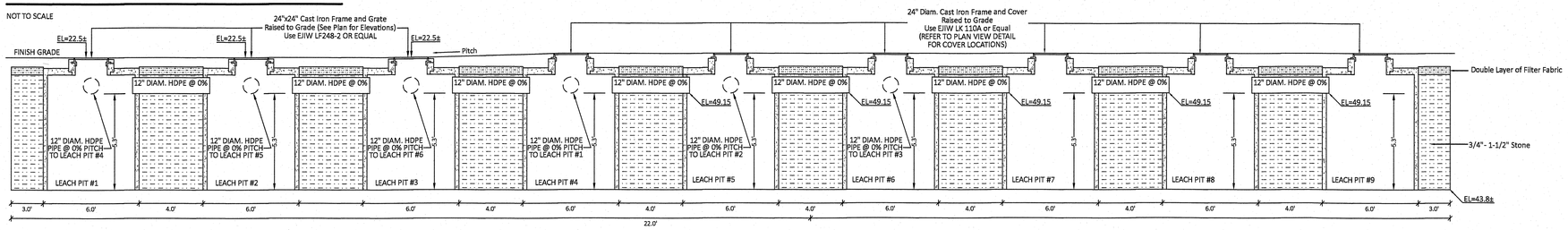
G:\AAJobs\Malone- Cloverleaf Utility Plan- 40B- SDS & Drainage- REVISED 6-5-2020.dwg

FLOW PROFILE OF DRAINAGE FACILITY #4



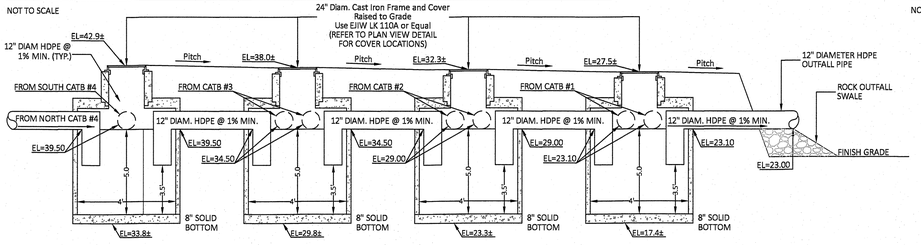
PROPOSED LEACHING FACILITY
USE TEN (10) 1000 GALLON PRECAST LEACHING PIT UNITS
H-20 RATED UNITS AS MFG. BY SHOREY PRECAST OR EQUAL

FLOW PROFILE OF DRAINAGE FACILITY #1



PROPOSED LEACHING FACILITY
USE NINE (9) 1000 GALLON PRECAST LEACHING PIT UNITS
H-20 RATED UNITS AS MFG. BY SHOREY PRECAST OR EQUAL

FLOW PROFILE OF SOLID CATCH BASINS #1 - #4 AND OUTFALL PIPE



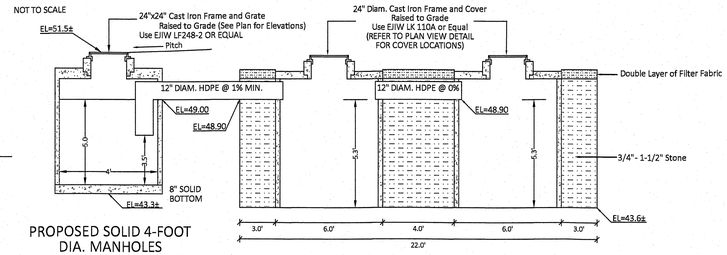
PROPOSED SOLID 4-FOOT DIA. MANHOLE #4
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. MANHOLE #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. MANHOLE #2
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. MANHOLE #1
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

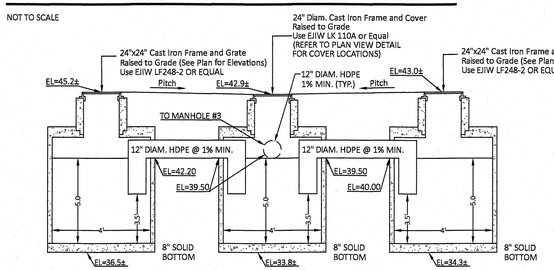
FLOW PROFILE OF DRAINAGE FACILITIES #2 & 3



PROPOSED SOLID 4-FOOT DIA. MANHOLES (CATCH BASINS #5)
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED LEACHING FACILITY
USE TWO (2) 1000 GALLON PRECAST LEACHING PIT UNITS
H-20 RATED UNITS AS MFG. BY SHOREY PRECAST OR EQUAL

FLOW PROFILE OF CATCH BASINS & MANHOLE #4

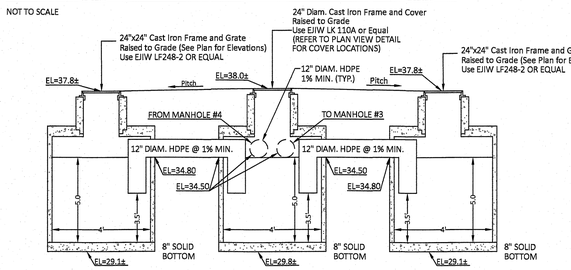


PROPOSED SOLID 4-FOOT DIA. CATCH BASINS #4 (NORTH SIDE)
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. MANHOLE #4
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. CATCH BASINS #4 (SOUTH SIDE)
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

FLOW PROFILE OF CATCH BASINS & MANHOLE #3

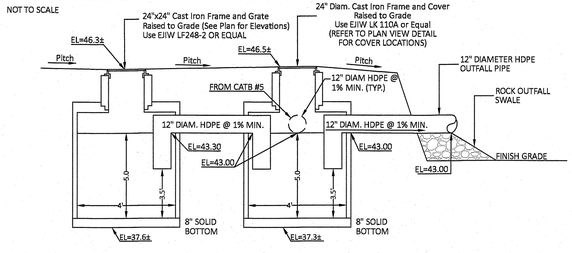


PROPOSED SOLID 4-FOOT DIA. CATCH BASIN #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. MANHOLE #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. CATCH BASIN #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

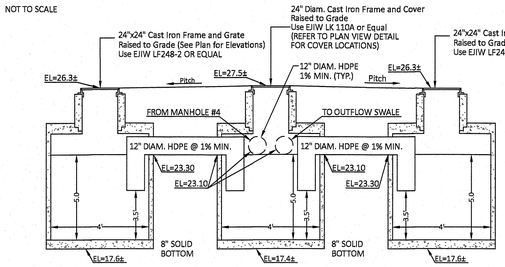
FLOW PROFILE OF SOLID CATCH BASINS #5 MANHOLE AND OUTFALL PIPE



TWO (2) PROPOSED SOLID 4-FOOT DIA. MANHOLE (CATCH BASINS #6)
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. MANHOLE #6
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

FLOW PROFILE OF CATCH BASINS & MANHOLE #1

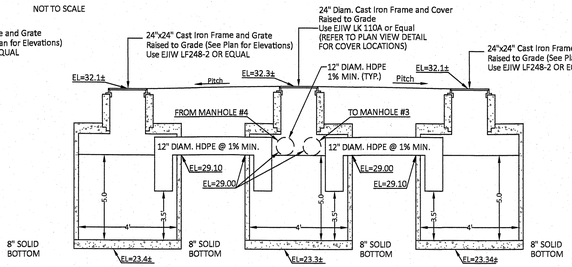


PROPOSED SOLID 4-FOOT DIA. CATCH BASIN #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. MANHOLE #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. CATCH BASIN #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

FLOW PROFILE OF CATCH BASINS & MANHOLE #2



PROPOSED SOLID 4-FOOT DIA. CATCH BASIN #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. MANHOLE #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

PROPOSED SOLID 4-FOOT DIA. CATCH BASIN #3
USE SOLID CATCH BASIN WITH BOTTOM AS MFG. BY SHOREY OR EQUAL 5-FOOT SUMP BELOW INVERT IS REQUIRED

0 30 60 90
SCALE 1"=30'

SHEET 4 OF 5
PERMIT SET- NOT FOR CONSTRUCTION

REVISED 6-5-2020: UPDATED SEWAGE SYSTEM TREATMENT TO INCLUDE 10 PPM NITROGEN LIMIT; ADJUSTED SEWER MANHOLE LAYOUT; ADJUSTED DRAINAGE TO INCLUDE SWALES AND ADDITIONAL CONTRIBUTORY AREAS; UPDATED NOTES AND DETAILS ACCORDINGLY

REVISED 2-14-2020: UPDATED BUILDING LAYOUT, ADJUSTED ENTRANCE; UPDATED SEWAGE SYSTEM COLLECTION AND ADDED I.A. TREATMENT TECHNOLOGY; UPDATED WATER SERRVICE LAYOUT AND DRAINAGE ACCORDINGLY

CLOVERLEAF TRURO RENTAL HOUSING

Community Housing Resource, Inc.; P.O. Box 1015, Provincetown, MA 02657

SITE DETAILS- 40B PERMIT SET

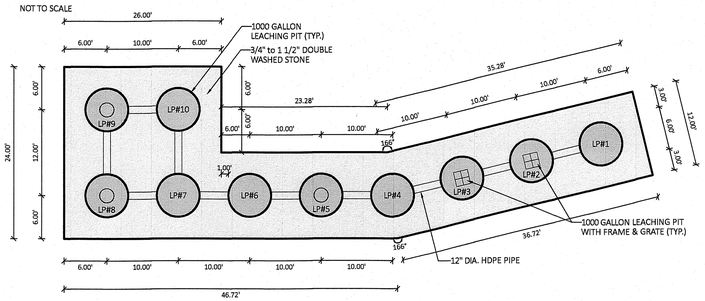
22 HIGHLAND ROAD, TRURO, MA

J.M. O'REILLY & ASSOCIATES, INC.
Professional Engineering & Land Surveying Services
1573 Main Street – Route 6A
P.O. Box 1773
(508)896-6601 Office Brewster, MA 02631 (508)896-6602 Fax

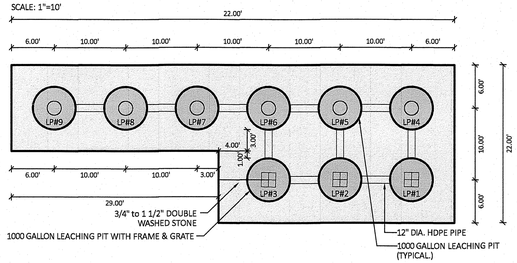
DATE:	SCALE:	BY:	CHECK:	JOB NUMBER:
11-1-2019	As Noted	RFR	JMO	JMO-8446A

G:\AAJobs\Malone- Cloverleaf Utility Plan- 40B- SDS & Drainage- REVISED 6-5-2020.dwg

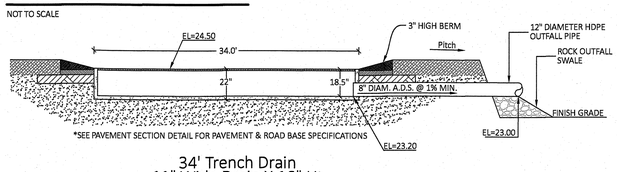
FLOW PROFILE OF DRAINAGE FACILITY #4



LEACHING FACILITY #1

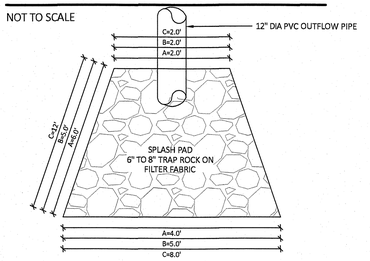


DETAIL OF TRENCH DRAIN:

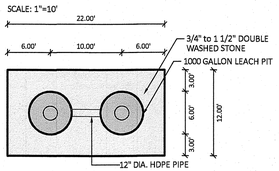


34' Trench Drain
11" Wide Drain X 16" Ht
USE H-20 TRENCH DRAIN
AS MANUFACTURED BY ACME-SHOREY

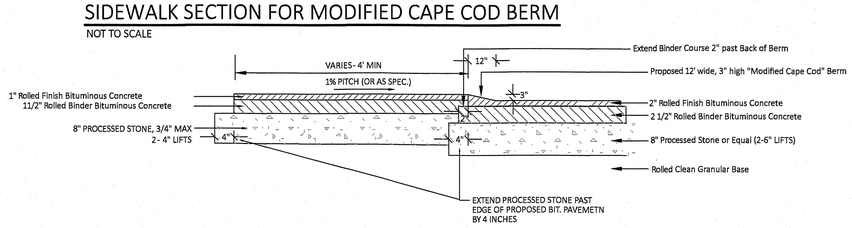
RIP-RAP DETAIL FOR OUTFALL PIPE:



LEACHING FACILITIES #2 & #3

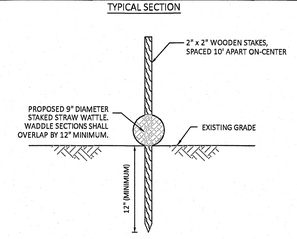


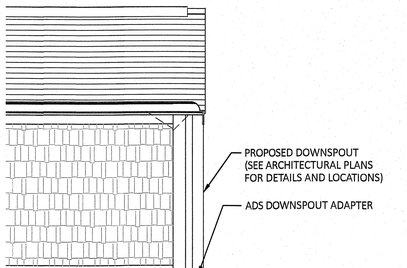
SIDEWALK SECTION FOR MODIFIED CAPE COD BERM



SILT FENCE/EROSION CONTROL DETAIL:

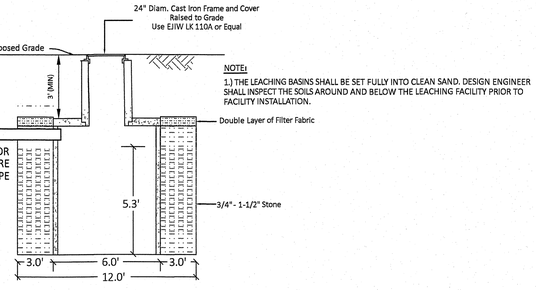
TYPICAL SECTION





ROOF/LAWN DRYWELL DETAIL:

NOT TO SCALE



NOTE:
1.) THE LEACHING BASINS SHALL BE SET FULLY INTO CLEAN SAND. DESIGN ENGINEER SHALL INSPECT THE SOILS AROUND AND BELOW THE LEACHING FACILITY PRIOR TO FACILITY INSTALLATION.

1000 Gallon
Leach Pit
USE (6) LP-1000-H-20
AS MANUFACTURED BY SHOREY OR EQUAL
WITH 4' STONE AROUND

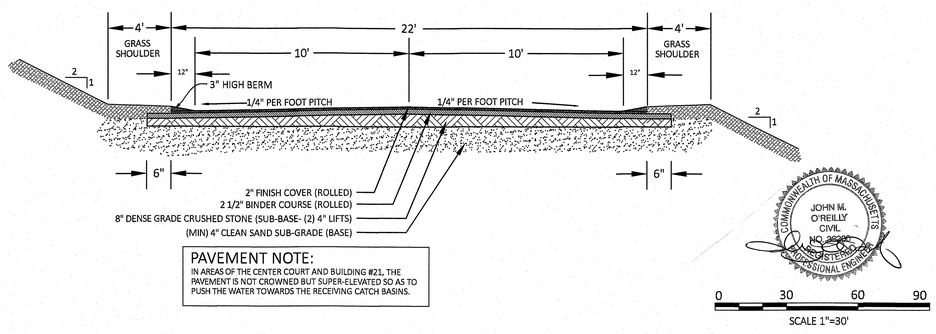
ROOF RUN-OFF:

1.) ALL ROOF GUTTERS SHOULD BE DIRECTLY CONNECTED TO DRYWELLS USING 6" ADS PIPE

2.) DRYWELLS SHALL BE SET FULLY INTO CLEAN SAND. DESIGN ENGINEER SHALL INSPECT THE SOILS AROUND AND BELOW THE LEACHING FACILITY PRIOR TO FACILITY INSTALLATION.

DRIVEWAY PAVEMENT SECTION (WITH CROWN):

NOT TO SCALE



PAVEMENT NOTE:
IN AREAS OF THE CENTER COURT AND BUILDING #21, THE PAVEMENT IS NOT CROWNED BUT SUPER-ELEVATED SO AS TO PUSH THE WATER TOWARDS THE RECEIVING CATCH BASINS.

0 30 60 90
SCALE 1"=30'

SHEET 5 OF 5
PERMIT SET- NOT FOR CONSTRUCTION

REVISED 6-5-2020: UPDATED SEWAGE SYSTEM TREATMENT TO INCLUDE 10 PPM NITROGEN LIMIT; ADJUSTED SEWER MANHOLE LAYOUT; ADJUSTED DRAINAGE TO INCLUDE SWALES AND ADDITIONAL CONTRIBUTORY AREAS; UPDATED NOTES AND DETAILS ACCORDINGLY

REVISED 2-14-2020: UPDATED BUILDING LAYOUT, ADJUSTED ENTRANCE; UPDATED SEWAGE SYSTEM COLLECTION AND ADDED I.A. TREATMENT TECHNOLOGY; UPDATED WATER SERVICE LAYOUT AND DRAINAGE ACCORDINGLY

CLOVERLEAF TRURO RENTAL HOUSING
Community Housing Resource, Inc.; P.O. Box 1015, Provincetown, MA 02657

SITE DETAILS- 40B PERMIT SET
22 HIGHLAND ROAD, TRURO, MA

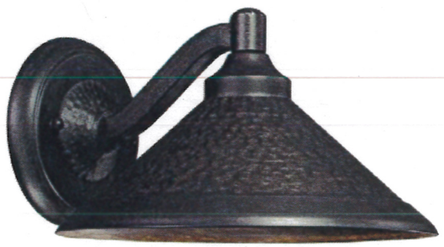
J.M. O'REILLY & ASSOCIATES, INC.
Professional Engineering & Land Surveying Services
1573 Main Street – Route 6A
P.O. Box 1773
(508)896-6601 Office Brewster, MA 02631 (508)896-6602 Fax

DATE:	SCALE:	BY:	CHECK:	JOB NUMBER:
11-1-2019	As Noted	RFR	JMO	JMO-8446A

G:\AAJobs\Malone- Cloverleaf Utility Plan- 40B- SDS & Drainage- REVISED 6-5-2020.dwg

MATERIALS PALETTE

BUILDING EXTERIOR LIGHTING



EXTERIOR LIGHTING

EXTERIOR SITE LIGHTING
42" POST LIGHT WITH HOOD
LESS THAN 75 WATT EQUIV.

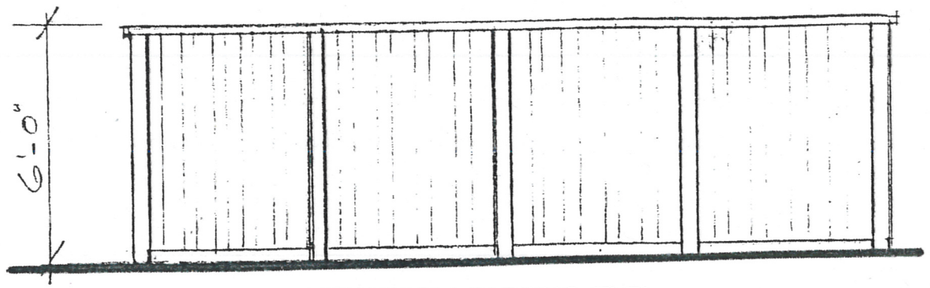
DATE:
06.19.20

EXTERIOR PALETTE/ LIGHTING
CLOVERLEAF TRURO RENTAL HOUSING
TRURO, MASSACHUSETTS

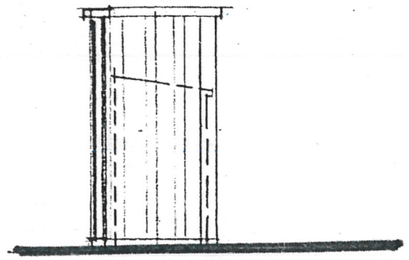
SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

NA

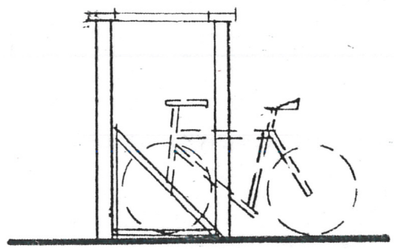
BUILDING FENCING AND TRASH/BIKE STORAGE



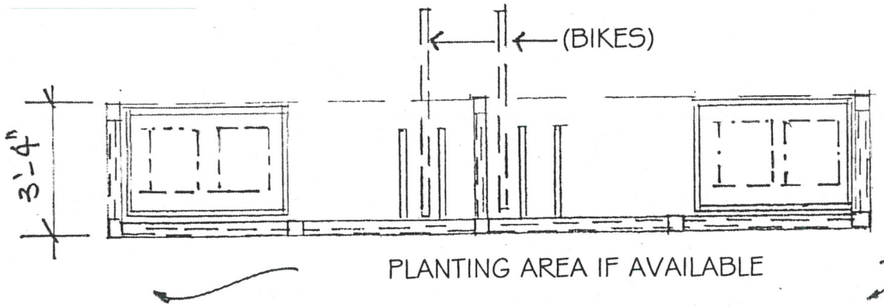
VIEW FROM PARKING (TYP)

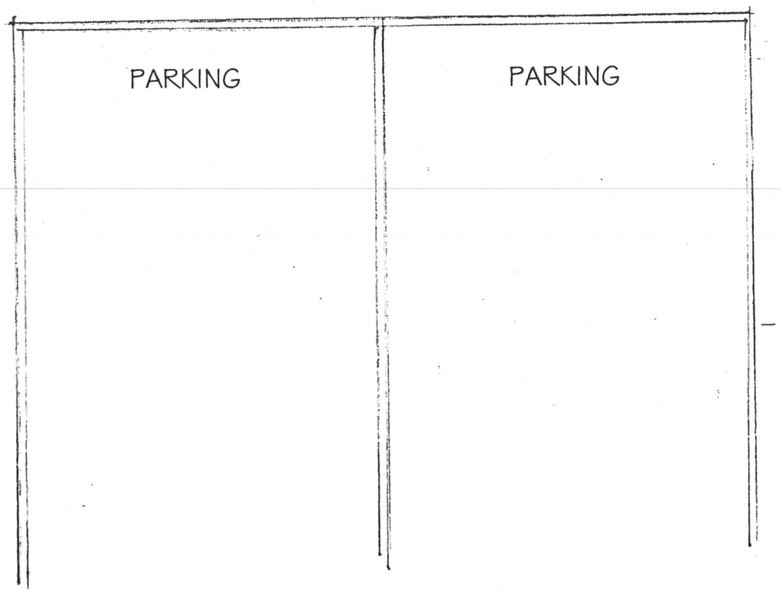


SIDE VIEW



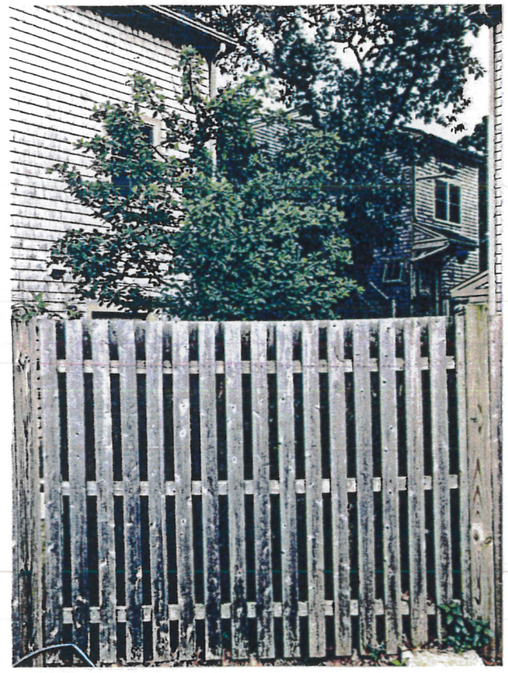
SECTION





BUILDING 21 : EXAMPLE TRASH ENCLOSURE

EXAMPLE TRASH BIN ENCLOSURE



SHADOW BOX PRIVACY FENCING

DATE: 06.19.20

FENCE/STORAGE IMAGES

CLOVERLEAF TRURO RENTAL HOUSING
TRURO, MASSACHUSETTS

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

NA

BUILDING INTERIOR PALETTE

DATE:
06.19.20

INTERIOR PALETTE

CLOVERLEAF TRURO RENTAL HOUSING
TRURO, MASSACHUSETTS

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville ,Massachusetts 02145 ~ 617.623.1833

NA

NHESP File No.: 18-37452

Community Housing Resource, Inc
PO Box 1015
Provincetown MA 02657

Box Turtle Protection Plan for Cloverleaf Affordable Housing Project, Truro, MA.

Turtle Barrier

1. Before construction, install temporary turtle barrier around perimeter of the property or limit of work, as appropriate.
2. Barrier will be high-quality 3' silt fence buried 4-6" deep and backfilled, and will be installed in a way that minimizes habitat disturbance, especially to Box Turtle food plants (mainly Lowbush Blueberry).
3. Fence should be reinforced with hay bales or backer material as appropriate where it is not taut.
4. At the south end of the property fronting Highland Road, where all work vehicles will access the site, a gate for truck access will be included using either silt fence that can be opened, then closed and weighted with sand bags or heavy pipe along the bottom, or a plywood gate at least two feet high (see figure 1).
5. Along the side fronting rt 6, silt fence should bend east at least 50 feet above Highland Rd to keep from directing turtles onto the road.
6. Fence should be inspected once per week during turtle active season (April 1 – October 31) and any holes of gaps repaired.
7. If fence was in place all winter, it will be inspected and repaired in March or early April.

Turtle Surveys

1. All surveys conducted by a biologist pre-approved by MHNESP and in possession of a scientific collecting permit.
2. Approved biologist will conduct 12 hours of pre-construction turtle sweeps inside the fenced 3.9 acre site, spread across 3 non-consecutive visits, during appropriate weather, between May 1 and October 31. Searches occur along both sides of silt fence as well as within the fence.
3. Perimeter fence will be checked for turtles weekly as well as on work days. Work day checks can either be conducted by the MNHESP approved Mass Audubon biologist, another trained staff person, or a member of the construction crew trained by the approved Wellfleet Bay biologist.
4. Conduct half-day sweeps of the area inside the fence twice in June, September, and October, and once in July. August sweep optional.
5. All turtles found will be relocated to appropriate habitat well outside the project area where chance of entering roads is minimal, such as the large areas of National Seashore forest to the north and east. Rare species encounters will be submitted to MNHESP.
6. Reports will be submitted after the first 12 hours of pre-construction searches and after the turtle active season if required by MNHESP.
7. Any questions can be submitted to project manager Mark Faherty, Science Coordinator, Mass Audubon Wellfleet Bay Sanctuary, mfaherty@massaudubon.org.

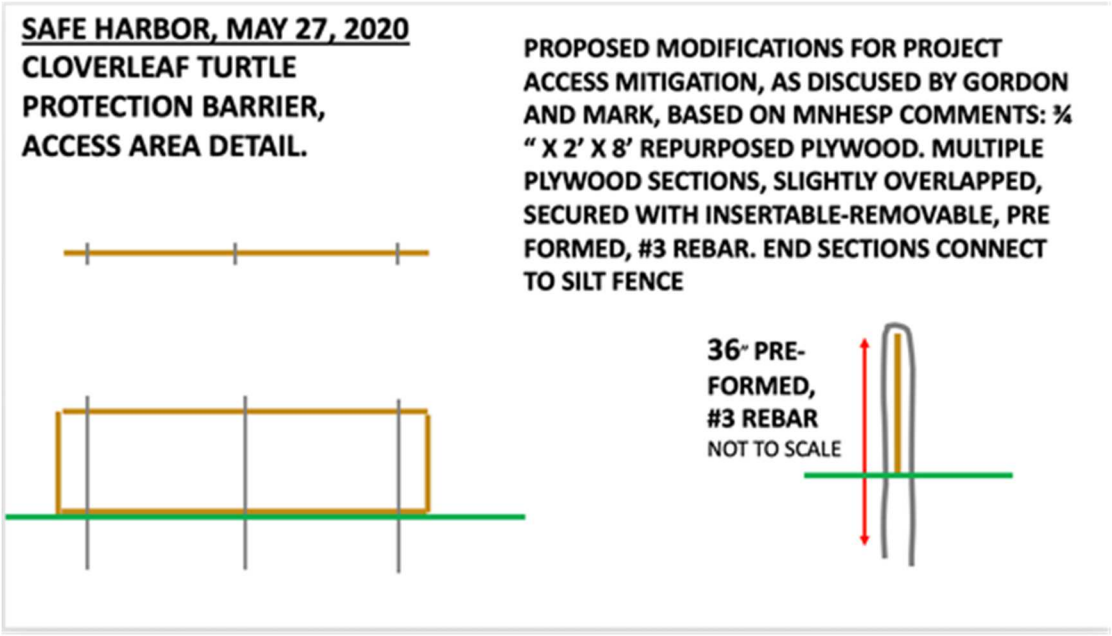


Figure 1. Safe Harbor proposal for plywood access gate for vehicles.

Ted Malone

From: Mark Faherty <mfaherty@massaudubon.org>
Sent: Wednesday, May 27, 2020 5:33 PM
To: Ted Malone; gordon peabody; Jaimie Safe Harbor; Bob Prescott
Subject: Fwd: Box Turtle protection plan NHESP File No.: 18-37452
Attachments: Box Turtle Protection Plan Truro Cloverleaf.docx; ATT00001.htm

Begin forwarded message:

From: "Marold, Misty-Anne (FWE)" <misty-anne.marold@state.ma.us>
Date: May 27, 2020 at 2:24:41 PM EDT
To: Mark Faherty <mfaherty@massaudubon.org>, Bob Prescott <rprescott@massaudubon.org>, "Jones, Michael T (FWE)" <michael.t.jones@state.ma.us>, "Cheeseman, Melany (FWE)" <melany.cheeseman@state.ma.us>, "Holt, Emily (FWE)" <emily.holt@state.ma.us>
Subject: Re: Box Turtle protection plan NHESP File No.: 18-37452

RE: Truro, NHESP 18-37452, TECA protection plan

All,

The Division approves the Box Turtle Protection plan entitled 'Box Turtle Protection Plan for Cloverleaf Affordable Housing Project, Truro, MA.' from MassAudubon received via email on 5/27/2020. I note that if the ground beneath the gate is not level and parallel the bottom of the plywood, you may need to add a 'sweep' to the bottom of the gate to fill any gaps.

Best, Misty-Anne

Important: Our offices are currently closed and all non-essential state employees are working remotely, which includes Environmental Review staff. Governor Baker also suspended state permitting deadlines and response periods with COVID-19 Order No. 17 (March 26, 2020). We will continue to process applications and respond to inquiries and correspondence as quickly as possible, although timelines may be delayed. Thank you for your patience. Please visit our website (www.mass.gov/nhesp) for updates.

Misty-Anne R. Marold, Senior Endangered Species Review Biologist
Massachusetts Division of Fisheries & Wildlife
Natural Heritage Endangered Species Program
1 North Drive, Rabbit Hill Road
Westborough, MA 01581
Direct: 508-389-6356 | Fax: 508-389-7891

From: Mark Faherty <mfaherty@massaudubon.org>
Sent: Wednesday, May 27, 2020 1:41 PM
To: Marold, Misty-Anne (FWE); Bob Prescott; Jones, Michael T (FWE); Cheeseman, Melany (FWE); Holt, Emily (FWE)
Subject: RE: Box Turtle protection plan NHESP File No.: 18-37452

Here is an updated version with a figure of a plywood access gate supplied by Safe Harbors.

Thanks,

Mark

From: Mark Faherty
Sent: Tuesday, May 26, 2020 4:13 PM
To: Marold, Misty-Anne (FWE) <misty-anne.marold@state.ma.us>; Bob Prescott <rprescott@massaudubon.org>; Jones, Michael T (FWE) <michael.t.jones@state.ma.us>; Cheeseman, Melany (FWE) <melany.cheeseman@state.ma.us>; Holt, Emily (FWE) <emily.holt@state.ma.us>
Subject: RE: Box Turtle protection plan NHESP File No.: 18-37452

Hi Misty,

Item #5 included one option I discussed – the silt fence gate that be closed and weighted along the bottom – I'm not sure if that one works for you guys. I combined that option and the plywood option under item 4.

Thanks,

Mark

From: Marold, Misty-Anne (FWE) <misty-anne.marold@state.ma.us>
Sent: Tuesday, May 26, 2020 4:00 PM
To: Bob Prescott <rprescott@massaudubon.org>; Mark Faherty <mfaherty@massaudubon.org>; Jones, Michael T (FWE) <michael.t.jones@state.ma.us>; Cheeseman, Melany (FWE) <melany.cheeseman@state.ma.us>; Holt, Emily (FWE) <emily.holt@state.ma.us>
Subject: Re: Box Turtle protection plan NHESP File No.: 18-37452

All,

If you can revise the Protocol to describe something along the lines we've emailed about here, we can approve this. I'll look through my email to see if I can find an example photo or detail in the meantime.

Misty-Anne

Important: Our offices are currently closed and all non-essential state employees are working remotely, which includes Environmental Review staff. Governor Baker also suspended state permitting deadlines and response periods with COVID-19 Order No. 17 (March 26, 2020). We will continue to process applications and respond to inquiries and correspondence as quickly as possible, although timelines may be delayed. Thank you for your patience. Please visit our website (www.mass.gov/nhesp) for updates.

Misty-Anne R. Marold, Senior Endangered Species Review Biologist
Massachusetts Division of Fisheries & Wildlife
Natural Heritage Endangered Species Program
1 North Drive, Rabbit Hill Road
Westborough, MA 01581
Direct: 508-389-6356 | Fax: 508-389-7891

From: Bob Prescott <rprescott@massaudubon.org>
Sent: Friday, May 22, 2020 11:52 AM
To: Mark Faherty; Marold, Misty-Anne (FWE); Jones, Michael T (FWE); Cheeseman, Melany (FWE); Holt, Emily (FWE)
Subject: RE: Box Turtle protection plan NHESP File No.: 18-37452

Hi Misty-Anne,

I think that's what was used at the Eastham Water Tower construction site and it held up very well. It was a smaller site and we didn't find any box turtles so we don't know of any box turtles got in or out.

I could see a box turtle scaling a hay bale, the fencing maybe more of a challenge.

Bob

From: Mark Faherty
Sent: Friday, May 22, 2020 11:29 AM
To: Marold, Misty-Anne (FWE) <misty-anne.marold@state.ma.us>; Jones, Michael T (FWE) <michael.t.jones@state.ma.us>; Cheeseman, Melany (FWE) <melany.cheeseman@state.ma.us>; Holt, Emily (FWE) <emily.holt@state.ma.us>
Cc: Bob Prescott <rprescott@massaudubon.org>
Subject: RE: Box Turtle protection plan NHESP File No.: 18-37452

Hi Misty-Anne,

We can modify that however you like. I saw one version in an approved TPP where they just used the same silt fence, created a gap as necessary to get vehicles in, then closed the gap at end of day and weighted the bottom of the fencing with sand bags. Safe Harbors said they have done that same method but with heavy pipe to weight the bottom of the silt fence "gate". We can also use plywood if you like. Do you have an example photo? I kbow Safe Harbors could do whatever you want.

Thanks,

Mark

From: Marold, Misty-Anne (FWE) <misty-anne.marold@state.ma.us>
Sent: Thursday, May 21, 2020 3:32 PM
To: Mark Faherty <mfaherty@massaudubon.org>; Jones, Michael T (FWE) <michael.t.jones@state.ma.us>; Cheeseman, Melany (FWE) <melany.cheeseman@state.ma.us>; Holt, Emily (FWE) <emily.holt@state.ma.us>
Cc: Bob Prescott <rprescott@massaudubon.org>
Subject: Re: Box Turtle protection plan NHESP File No.: 18-37452

Mark,

Can you provide a better description of #4? Box turtles can climb hay bales pretty well. Usually, we ask for more rigid system like the using plywood or something taller and more vertical with weighting or bales on the work-side.

Misty-Anne

Important: Our offices are currently closed and all non-essential state employees are working remotely, which includes Environmental Review staff. Governor Baker also suspended state permitting deadlines and response periods with COVID-19 Order No. 17 (March 26, 2020). We will continue to process applications and respond to inquiries and correspondence as quickly as possible, although timelines may be delayed. Thank you for your patience. Please visit our website (www.mass.gov/nhesp) for updates.

Misty-Anne R. Marold, Senior Endangered Species Review Biologist
Massachusetts Division of Fisheries & Wildlife
Natural Heritage Endangered Species Program
1 North Drive, Rabbit Hill Road
Westborough, MA 01581
Direct: 508-389-6356 | Fax: 508-389-7891

From: Mark Faherty <mfaherty@massaudubon.org>
Sent: Friday, May 15, 2020 5:34 PM
To: Marold, Misty-Anne (FWE); Jones, Michael T (FWE); Cheeseman, Melany (FWE); Holt, Emily (FWE)
Cc: Bob Prescott
Subject: Box Turtle protection plan NHESP File No.: 18-37452

Hi Folks,

Please see the proposed turtle protection plan for the Truro Cloverleaf affordable housing project. Happy to amend as necessary.

Thanks,

Mark

****

Mark Faherty

Science Coordinator

Mass Audubon/Wellfleet Bay Wildlife Sanctuary

PO Box 236, State Highway Route 6

South Wellfleet, MA 02663

508-349-2615 x-6110 fax: 508-349-2632

email: mfaherty@massaudubon.org

website: www.massaudubon.org/wellfleetbay

http://www.facebook.com/MassAudubonWellfleetBay

Protecting the Nature of Massachusetts

Stormwater Pollution Prevention Plan (SWPPP)

For Construction Activities At:

CLOVERLEAF PROJECT
22 HIGHLAND ROAD
TRURO, MA

SWPPP Prepared For:

COMMUNITY HOUSING RESOURCE, INC.
Mr. Ted Malone
P.O. Box 1015
Provincetown, MA 02657

SWPPP Prepared By:

J.M. O'Reilly & Associates, Inc.
1573 Main Street
Brewster, MA 02631
Phone #: 508-896-6601
Fax #: 508-896-6602
Email: joreilly@jmoreillyassoc.com

SWPPP Preparation Date:

MONTH XX, 20XX

Estimated Project Dates:
MONTH XX, 20XX

Project Start Date: Unknown
Project Completion Date: Unknown

Contents

SECTION 1: CONTACT INFORMATION/RESPONSIBLE PARTIES

1.1 Operator(s) / Subcontractor(s)

Operator(s):

COMMUNITY HOUSING RESOURCE
Ted Malone
P.O. Box 1015
Provincetown, MA 02657

Subcontractor(s):

Engineer/Surveyor
John O'Reilly
J.M. O'Reilly & Associates, Inc
1573 Main Street 2nd Floor / P.O. Box 1773
Brewster, MA 02631
508-896-6601
508-896-6602 fax
joreilly@jmoreillyassoc.com

Emergency 24-Hour Contact:

T.B.D.

1.2 Stormwater Team

Construction Site Operator: TBD

TBD

OPERATOR will be responsible for implementing the SWPPP: overseeing installation of any structural Stormwater controls, supervising and implementing good housekeeping programs such as site cleanup and disposal of trash and debris, hazardous material management and disposal, vehicle and equipment maintenance, implementing BMPs, overseeing any corrective actions needed. Also responsible for educating all subcontractors on applicable elements of the SWPPP.

John O'Reilly, Civil Engineer & Land Surveyor
J.M. O'REILLY & ASSOCIATES, INC.
1573 Main Street
Brewster, MA 02631
508-896-6601

E-Mail**: joreilly@jmoreillyassoc.com**

J.M. O'REILLY & ASSOCIATES, INC. will be responsible for developing the SWPPP and documenting any changes to the SWPPP

SECTION 2: SITE EVALUATION, ASSESSMENT, AND PLANNING

2.1 Project/Site Information

Project Name and Address

Project/Site Name: CLOVERLEAF PROJECT
Project Street/Location: 22 Highland Road
City: Truro
State: MA
ZIP Code: 02666
County or Similar Subdivision: Barnstable County

Project Latitude/Longitude

(Use **one** of three possible formats, and specify method)

Latitude:	Longitude:
1. xx ° xx ' xx'' N (degrees, minutes, seconds)	1. xx ° xx ' xx'' W (degrees, minutes, seconds)
2. _ _ ° _ _ . _ _ ' N (degrees, minutes, decimal)	2. _ _ ° _ _ . _ _ ' W (degrees, minutes, decimal)
3. _ _ . _ _ _ _ ° N (decimal)	3. _ _ . _ _ _ _ ° W (decimal)

Method for determining latitude/longitude:
☐ USGS topographic map (specify scale: _____) ☐ EPA Web site ☐ GPS
☒ Other (please specify): Google Earth

Horizontal Reference Datum:
☐ NAD 27 ☒ NAD 83 or WGS 84 ☐ Unknown

If you used a U.S.G.S topographic map, what was the scale? _____

Additional Project Information

Is the project/site located on Indian country lands, or located on a property of religious or cultural significance to an Indian tribe? ☐ Yes ☒ No

2.2 Discharge Information

Does your project/site discharge stormwater into a Municipal Separate Storm Sewer System (MS4)? ☐ Yes ☒ No

Are there any surface waters that are located within 50 feet of your construction disturbances?
☐ Yes ☒ No

Table 1 – Names of Receiving Waters

The site will drain into the ground via infiltration. Groundwater flow direction of the project area is due west – southwest towards Cape Cod Bay, per the Cape Cod Commission Groundwater Flow Maps.

Table 2 – Impaired Waters / TMDLs

The TMDL for the Cape Cod Bay. As of this date, no TMDL's for the Cape Cod Bay have been set

Describe the method(s) you used to determine whether or not your project/site discharges to an impaired water:

The above information was taken from The Cape Cod Watershed, August 2009, as prepared by ENSR International

2.3 Nature of the Construction Activity

General Description of Project

This project will consist of clearing land, constructing a roadway, installing utilities and the construction of residential housing units. The housing units will include duplex dwellings, a 15 unit apartment building and a triplex dwelling.

Size of Construction Project

The Construction Site is 3.91 Acres and approximately 82.5% of the lot will be disturbed at one time for the road installation, utilities and the home construction.

2.4 Sequence and Estimated Dates of Construction Activities

THE TIME LINE FOR CONSTRUCTION ACTIVITIES HAS NOT BEEN DETERMINED AT THE TIME OF THIS REPORT

Estimated timeline of activity Construction activity and BMP descriptions

Before any site grading activities begin

1. Install Erosion control Silt Fence (See Section 4.1 & 4.2)
2. Comply with the Natural Heritage – Endangered Species Program's requirements for the site control. NO SITE DISTURBANCE IS ALLOWED PRIOR TO COMPLIANCE WITH THE NHESP PROTOCOL.

2. Construct stabilized construction exits (Section 4.3)

Site grading

1. Begin site clearing and grubbing operations
2. Begin overall site grading and topsoil stripping
3. Establish topsoil stockpile (Section 4.4)
4. Implement stabilization procedures (Section 4.15)

Infrastructure – Utilities

1. Trenching and installation of various utilities (water, electric, etc.)
2. Road Installation

Infrastructure – Foundations

1. Construct temporary concrete washout area (Section 5.6.1)
2. Begin construction of building foundation and capping
3. Remove temporary concrete washout area (Section 5.6.1)

Site stabilization

1. Remove all temporary control BMPs and stabilize any areas disturbed by their removal with erosion controls
2. Prepare final for seeding and landscaping (Section 4.8 & 4.15)
3. Monitor stabilized areas until final stabilization is reached

2.5 Allowable Non-Stormwater Discharges

List of Allowable Non-Stormwater Discharges Present at the Site

Type of Allowable Non-Stormwater Discharge	**Likely to be Present at Your Site?**
Discharges from emergency fire-fighting activities	☐ YES ☒ NO
Fire hydrant flushings	☐ YES ☒ NO
Landscape irrigation	☐ YES ☒ NO
Waters used to wash vehicles and equipment	☐ YES ☒ NO
Water used to control dust	☐ YES ☒ NO
Potable water including uncontaminated water line flushings	☐ YES ☒ NO
Routine external building wash down	☐ YES ☒ NO
Pavement wash waters	☐ YES ☒ NO
Uncontaminated air conditioning or compressor condensate	☐ YES ☒ NO
Uncontaminated, non-turbid discharges of ground water or spring water	☐ YES ☒ NO
Foundation or footing drains	☐ YES ☒ NO
Construction dewatering water	☐ YES ☒ NO

Appropriate BMP's shall be used to minimize the discharge of pollutants. Such control measures will be strictly followed to ensure any impacts from non stormwater discharges are reduced or eliminated. Appropriate BMPs are: **N/A**

2.6 Site Maps

See Appendix A

SECTION 3: DOCUMENTATION OF COMPLIANCE WITH OTHER FEDERAL REQUIREMENTS

3.1 Endangered Species Protection

Eligibility Criterion

Under which criterion listed in Appendix D are you eligible for coverage under this permit?

☐ **A** ☐ **B** ☐ **C** ☐ **D** ☒ **E**

For reference purposes, the eligibility criteria listed in Appendix D are as follows:

Criterion A. No federally-listed threatened or endangered species or their designated critical habitat(s) are likely to occur in your site's "action area" as defined in Appendix A of this permit.

Criterion B. The construction site's discharges and discharge-related activities were already addressed in another operator's valid certification of eligibility for your action area under eligibility Criterion A, C, D, E, or F and there is no reason to believe that federally-listed species or federally-designated critical habitat not considered in the prior certification may be present or located in the "action area". To certify your eligibility under this Criterion, there must be no lapse of NPDES permit coverage in the other operator's certification. By certifying eligibility under this Criterion, you agree to comply with any effluent limitations or conditions upon which the other operator's certification was based. You must include in your NOI the tracking number from the other operator's notification of authorization under this permit. If your certification is based on another operator's certification under Criterion C, you must provide EPA with the relevant supporting information required of existing dischargers in Criterion C in your NOI form.

Criterion C. Federally-listed threatened or endangered species or their designated critical habitat(s) are likely to occur in or near your site's "action area," and your site's discharges and discharge-related activities are not likely to adversely affect listed threatened or endangered species or critical habitat. This determination may include consideration of any stormwater controls and/or management practices you will adopt to ensure that your discharges and discharge-related activities are not likely to adversely affect listed species and critical habitat. To make this certification, you must include the following in your NOI: 1) any federally listed species and/or designated habitat located in your "action area"; and 2) the distance between your site and the listed species or designated critical habitat (in miles). You must also include a copy of your site map with your NOI.

Criterion D. Coordination between you and the Services has been concluded. The coordination must have addressed the effects of your site's discharges and discharge-related activities on federally-listed threatened or endangered species and federally-designated critical habitat, and must have resulted in a written concurrence from the relevant Service(s) that your site's discharges and discharge-related activities are not likely to adversely affect listed species or critical habitat. You must include copies of the correspondence between yourself and the Services in your SWPPP and your NOI.

Criterion E. Consultation between a Federal Agency and the U.S. Fish and Wildlife Service and/or the National Marine Fisheries Service under section 7 of the ESA has been concluded. The consultation must have addressed the effects of the construction site's discharges and discharge-related activities on federally-listed threatened or endangered species and federally-designated critical habitat. The result of this consultation must be either:

i. a biological opinion that concludes that the action in question (taking into account the effects of your site's discharges and discharge-related activities) is not likely to jeopardize the continued existence of listed species, nor the destruction or adverse modification of critical habitat; or

ii. written concurrence from the applicable Service(s) with a finding that the site's discharges and discharge-related activities are not likely to adversely affect federally-listed species or federally-designated habitat.

You must include copies of the correspondence between yourself and the Services in your SWPPP and your NOI.

Criterion F. Your construction activities are authorized through the issuance of a permit under section 10 of the ESA, and this authorization addresses the effects of the site's discharges and discharge-related activities on federally-listed species and federally-designated critical habitat. You must include copies of the correspondence between yourself and the Services in your SWPPP and your NOI.

Supporting Documentation

Provide documentation for the applicable eligibility criterion you select in Appendix D, as follows:

Attached is the response letter from the Natural Heritage Program. See Appendix

3.2 Historic Preservation

Appendix E, Step 1

Do you plan on installing any of the following stormwater controls at your site? Check all that apply below, and proceed to Appendix E, Step 2.

- ☐ Dike
- ☐ Berm
- ☒ Catch Basin
- ☐ Pond
- ☐ Stormwater Conveyance Channel (e.g., ditch, trench, perimeter drain, swale, etc.)
- ☐ Culvert
- ☐ Other type of ground-disturbing stormwater control:

Appendix E, Step 2

If you answered yes in Step 1, have prior surveys or evaluations conducted on the site already determined that historic properties do not exist, or that prior disturbances at the site have precluded the existence of historic properties? ☒ YES ☐ NO

- Soil testing on abutting properties did not reveal the existence of Historic Properties.
- Historic records research found the area was open meadow, vacant of any building and disturbed as part of the Route 6 expansions in the 1960's.

3.3 Safe Drinking Water Act Underground Injection Control Requirements

Instructions (see CGP Part 7.2.14.3):

- If you will use any of the identified controls in this section, include documentation of contact between you and the applicable state agency or EPA Regional Office responsible for implementing the requirements for underground injection wells in the Safe Drinking Water Act and EPA's implementing regulations at 40 CFR Parts 144-147.
- For state UIC program contacts, refer to the following EPA website: http://water.epa.gov/type/groundwater/uic/whereyoulive.cfm.

Do you plan to install any of the following controls? Check all that apply below.

☐ Infiltration trenches (if stormwater is directed to any bored, drilled, driven shaft or dug hole that is deeper than its widest surface dimension, or has a subsurface fluid distribution system)

☒ Commercially manufactured pre-cast or pre-built proprietary subsurface detention vaults, chambers, or other devices designed to capture and infiltrate stormwater flow

☒ Drywells, seepage pits, or improved sinkholes (if stormwater is directed to any bored, drilled, driven shaft or dug hole that is deeper than its widest surface dimension, or has a subsurface fluid distribution system)

Please see below cut and paste email conversation with Local State Agency

Hi Keith,

For any subsurface stormwater infiltration structures (e.g. leaching catch basins, infiltration chambers, drainfields, infiltration trenches that have been backfilled with greater than 18 inches of permeable fill material, etc.), an Underground Injection Control (UIC) registration application submitted to MassDEP is required per MassDEP's UIC regulations, 310 CMR 27.00. The only exemption is for parcels of land that are only used for one, single unit residential dwelling with no additional non-residential activities. If the stormwater conveyance system from a single unit housing development discharges to a subsurface structure on a parcel that receives discharge from multiple parcels, the submittal of the UIC registration application is required.

This is the generic information that I've put together regarding Underground Injection Control (UIC) regulations and UIC Registration application forms for stormwater wells:

All information regarding on-line (eDEP) or paper form UIC registration applications may be obtained at the following web page under the category "Applications & Forms":
http://www.mass.gov/eea/agencies/massdep/water/drinking/underground-injection-control.html

There is one eDEP UIC Registration form that applies to all UIC well types. If filing a paper form, there is a specific UIC form for the registration of stormwater wells (BRP WS 06 UIC Registration – Stormwater Wells) and a UIC

Class V Well Stormwater Technical Compliance Form that must also be completed and submitted with all BRP WS 06 UIC Registration – Stormwater Wells applications. Unfortunately, the stormwater technical compliance form is not currently available through eDEP but an applicant may still file for the UIC Registration for a stormwater well through eDEP and either upload the completed non-exposure form to the eDEP application or mail or email it in separately.

An applicant must determine whether any of the activities occurring within the contributing drainage areas to the well(s) classify the stormwater well as having one or more Land Uses with Higher Potential Pollutant Loads (LUHPPL). Please note that LUHPPL activities or industries do not necessarily make the stormwater well a well with one or more LUHPPL activity. There are instances where the drainage area for the LUHPPL activity is not in the contributing drainage area to the UIC well(s) or does not have the potential to contaminate the well. In these instances the stormwater well is considered to not have any LUHPPL activities for the purpose of registering the UIC well(s) with the MassDEP UIC program.

PDF version of stormwater UIC registration form and instructions (also available as MS Word documents navigating from the main web page):
http://www.mass.gov/eea/docs/dep/water/approvals/year-thru-alpha/t-thru-v/uicstorm.pdf

PDF version of UIC stormwater technical compliance form (also available as MS Word documents):
http://www.mass.gov/eea/docs/dep/water/approvals/year-thru-alpha/m-thru-s/stormexp.pdf

In addition to the stormwater technical compliance form MassDEP requires the submittal of a scaled site plan showing the UIC well locations and a cross sectional schematic showing the UIC well construction details including width and depth dimensions.

Exemptions:
Single family residential use only properties are exempt from filing for UIC Registration.
2 to 4 unit residential use only properties require BRP WS 06 UIC Registration – Stormwater Wells application but don't require the UIC Class V Well Stormwater Technical Compliance Form and Certification Statement.

The application fee associated with the BRP WS06 form for stormwater wells is $110 if there are not LUHPPL activities and $585 if there are one or more LUHPPL activities. If filing by paper as opposed to eDEP on-line filing, you must obtain the one page transmittal form and a unique transmittal number at the following MassDEP web page: http://www.mass.gov/eea/agencies/massdep/service/approvals/transmittal-form-for-payment.html

Important note regarding payment: Only the one page transmittal form with the $110 or $585 check should be sent to the PO Box address shown on the payment transmittal form. Do not send the complete application package to the PO Box as all materials other than the one page transmittal form and check will be discarded. A copy of the transmittal form should be sent with the BRP WS06 application package to the following address:

MassDEP UIC Program
1 Winter Street, 5th Floor
Boston, MA 02108

Joe Cerutti
UIC Program Coordinator
MassDEP
1 Winter Street, 5th Floor
Boston, MA 02108
617 292-5859

fax 617 292-5696 (Note, if faxing, please notify by email or phone)

From: *Keith Fernandes [mailto:kfernandes@jmoreillyassoc.com]*
Sent: *Wednesday, February 03, 2016 7:39 AM*
To: *Cerutti, Joseph (DEP)*
Subject: *NPDES SWPPP Question*

We are currently developing a SWPP for a new subdivision project. We will be installing deep sump catch basins and subsurface infiltration structures in order to handle stormwater run-off. All of this has been designed in accordance with the Massachusetts Stormwater Handbook and meets best management practices.

Section 3.3. of the SWPPP requires that we communicate with the applicable state agency if any controls, such as those referenced above, are installed.

This is what lead me to your email. Not sure what other steps need to take place but please let me know if you need anything else.

Thanks,
Keith E. Fernandes, PE
Civil Engineer

J.M. O'Reilly & Associates, Inc
1573 Main Street 2nd Floor / P.O. Box 1773
Brewster, MA 02631
508-896-6601
508-896-6602 fax
http://www.jmoreillyassoc.com

Confidentiality Notice:
This electronic mail message and any attached files contain information intended for the exclusive use of the individual or entity to whom it was addressed and may contain information that is proprietary, privileged, confidential and/or exempt from disclosure under applicable law. If you are not the intended recipient, you are hereby notified that any viewing, copying, disclosure or distribution of this information may be subject to legal restriction or sanction. Please notify the sender, by electronic mail or telephone, of any unintended recipients and delete the original message without making any copies

Prior to any stormwater being discharged into the proposed stormwater systems the above required permits will be applied for and obtained.

SECTION 4: EROSION AND SEDIMENT CONTROLS

4.1 Natural Buffers or Equivalent Sediment Controls

Buffer Compliance Alternatives

Are there any surface waters within 50 feet of your project's earth disturbances? ☐ YES ☒ NO

4.2 Perimeter Controls

General

- A Silt Fence and a 9" diameter straw waddle shall be installed along the limit of work line as shown on the site plans prepared by J.M. O'REILLY & ASSOCIATES, INC. Any existing catch basins rims shall have filter fabric installed under the rim. Filter fabric shall be installed within the catch basin grates along Highland Road so as to protect the existing drainage system.
- Filter fabric shall be cleaned of any sediment as needed.
- Sediment must be removed from the area of the silt fence/straw waddle if it has accumulated to ½ of the above ground height. Any newly installed catch basins shall be treated the same way.
- Contractor shall have extra silt fence and straw waddles on site during the construction period so as to mitigate any breakdown in erosion controls.

Specific Perimeter Controls

Perimeter Control # 1
Perimeter Control Description

- Please refer to construction plans for details on the silt fence and its installation

Installation

- 5 days prior to the start of construction

Maintenance Requirements

- Filter fabric (under catch basin rims) shall be cleaned of any sediment as needed. Sediment must be removed from the area of the silt fence if it has accumulated to ½ of the above ground height.

EROSION CONTROL

BIOLOG SILT FENCE EROSION CONTROL SYSTEMS" Safe Harbor,2017, 7pages

a. Silt Fencing
    i. 24"-high semi-permeable, geotextile filter fabric shall be installed as a silt fence, as depicted on the approved site plan of record.
    ii. The silt fence filter fabric shall be pushed down into the grade 4-6", with a lawn edger or similar edged-tool.
    iii. The fabric shall be vertically stapled to wooden stakes every 10'.
    iv. Anytime silt buildup against the fabric exceeds 4", the load shall be removed by hand, to a designated area outside the BZ.
    v. All erosion control systems should be removed following site stabilization and successful revegetation.
b. Biologs: Jute netting/straw biologs shall be installed as a sediment barrier, on the activity-area-side of the silt fence, as shown on the site plan.
    i. Biologs shall be 14-16" in diameter, as required by project duration, to maintain zero discharge performance standards.
    ii. These biologs can be recharged with new straw as necessary.
    iii. Biologs shall be secured with 6" cornstarch ground staples, every 2'.
    iv. Anytime sediment buildup exceeds 4", the load shall be removed by hand, to a designated area outside the BZ.
    v. All erosion control systems should be removed following site stabilization and successful revegetation.

4.3 Sediment Track-Out

General

- Please see below for the controls that will be used to minimize the track-out of sediment onto off site streets, other paved areas, and sidewalks from vehicles exiting the construction site.

Specific Track-Out Controls

Track-Out Control # 1

Track-Out Control Description

- For any temporary vehicle exit/entrance location onto the site there shall be an aggregate apron installed
- The aggregate apron will be a min of 15' wide and 12' deep with a min thickness of 6" (aggregate shall consist of ¾" – 1½" native stone)

Maintenance Requirements

- Where sediment has been tracked-out from the project site onto the surface of off-site streets, other paved areas, and sidewalks, you must remove the deposited sediment by the end of the same work day in which the track-out occurs or by the end of the next work day if track-out occurs on a non-work day. Track-out must be removed by sweeping, shoveling, or vacuuming these surfaces, or by using other similarly effective means of sediment removal. You are prohibited from hosing or sweeping tracked-out sediment into any stormwater conveyance (unless it is connected to a sediment basin, sediment trap, or similarly effective control), storm drain inlet, or surface water.")

Steep Slopes

a. Specific, low impact protocols are modeled after successful, exceptionally steep, Safe Harbor slope stabilization projects.
b. Stabilization and revegetation are ongoing, linked projects
c. Slopes shall be stabilized using Safe Harbor natural systems, as described in Safe Harbor Booklet "*Stabilizing Steep and Very Steep Slopes Using Natural Systems*" Safe Harbor, 2017 (15 pages).

4.4 Stockpiled Sediment or Soil

General

- Any stock piles or land clearing debris, associated with the construction of the road, shall comply with the requirements of the NPDES Construction General Permit Parts 2.1.2.4 and 7.2.10

Specific Stockpile Controls

Material Stockpiles shall be located outside any natural buffers established as a requirement of this SWPPP and physically separated from any stormwater controls. Stockpiles shall be protected from contact with stormwater through the use of a temporary perimeter sediment barrier such as a silt fence or duck wattles. Material stockpiles, where practicable, shall be covered or provided with temporary stabilization to avoid direct contact with precipitation or to minimize discharge. Unless infeasible, Material Stockpiles shall contained and securely protected from the wind. Material stockpiles will meet the requirements set forth in the Town of Truro Zoning Regulations.

4.5 Minimize Dust

General

- The generation of dust shall be minimized by using dust suppression techniques, to the extent feasible, shall be used in order to avoid pollutants from being discharged into surface waters.

Specific Dust Controls – If Dust becomes an issue and to the extend feasible

- Covering 30% or more of the soil surface with non-erodible material
- Roughening the soil to produce ridges perpendicular to the prevailing wind. Ridges should be about six (6) inches in height
- Frequent watering of excavation and fill areas
- Providing gravel or paving at entrance/exit drives and parking areas

4.6 Minimize the Disturbance of Steep Slopes

General

- Refer to Site Plan for erosion controls, slope stabilization and re-vegetation.
- Once the side slopes (2:1) have been graded per plan; the areas shall be covered with loam (or onsite "duff" material), seeded with a drought tolerant-slope stability grass seed mix.
- The seeded areas shall be then covered with a bio-degradable erosion control blanket. Blanket shall be secured to surface per manufactures specifications.
- Slopes shall be irrigated, to the best extent possible, until the seed is germinated and is established.

4.7 Topsoil

General

- Topsoil stripped from the construction site will be managed by the following two methods

1. If the material can be used on site the excavating contractor shall either stockpile in an appropriate location with protection against erosion and sedimentation (see section 4.4) until such time as they can use the material or use the material immediately.

2. If the material cannot be used on site, then the excavating contractor shall either stockpile the material in an appropriate location with protection against erosion and sedimentation until such time as the material can be transported off-site. All material transported off-site must be sent to a facility permitted to receive such materials and a copy of the receiving sites provided to the Operator.

<u>Excavation Spoils:</u>

Conservation of Geomass

a. The surface layer of removed overburden in excavation area (Rhizosphere containing native pH levels, nutrients and microorganisms) shall carefully be removed and reused.
b. This project advocates Geocycling of underburden. Disposition rationale is based on natural sediment geo-cycling. This underburden is 100% compatible material with banks.
c. Underburden required for backfill may be left onsite within the L.O.W.
d. Underburden not required for backfill shall be offered to the Town DPW for use as beach nourishment.
e. Underburden not accepted by the Town may be removed from site.

f. Raw areas shall be immediately stabilized, using light straw and jute netting secured with cornstarch ground staples every 4 ft.

4.8 Soil Compaction

General

- In areas where final vegetative stabilization will occur or where infiltration practices will be installed care needs to be taken in order to condition the soil for seeding or planting.

Specific Soil Compaction Controls

Soil Compaction Control # 1-Restrict vehicle/Equipment use
Soil Compaction Control Description

- Restrict vehicle and equipment use in the locations meeting the general description above

Soil Compaction Control # 2-Use Soil Conditioning Techniques
Soil Compaction Control Description

- Prior to seeding or planting areas of exposed soil that have been compacted, rake the area smooth. Planting areas should be seeded with a drought-tolerant seed mix and covered with a biodegradable erosion control blanket, secured in place. Silt fences shall be installed at the tops of slope in these areas to prevent erosion and slow the flow of runoff down the slopes.

4.9 Storm Drain Inlets

General

- Any catch basins rims (within the project site) shall have filter fabric installed under the rim. Filter fabric shall be cleaned of any sediment as needed.

Installation

- 5 days prior to the start of construction (if new catch basins are installed along the roadway during construction they shall have filter fabric installed immediately after installation of rim and grate

Maintenance Requirements

- Clean, or remove and replace, the protection measures as sediment accumulates, the filter becomes clogged, and/or performance is compromised. Where there is evidence of sediment accumulation adjacent to the inlet protection measure, you must remove the deposited sediment by the end of the same work day in which it is found or by the end of the following work day if removal by the same work day is not feasible.

Also, see EPA's *Storm Drain Inlet Protection BMP Fact Sheet* at
www.epa.gov/npdes/stormwater/menuofbmps/construction/storm_drain

4.10 Constructed Stormwater Conveyance Channels

General

- No Stormwater Conveyance Channels are proposed as part of this development

4.11 Sediment Basins

General

- No Sediment Basins are proposed as part of this development

4.12 Chemical Treatment

Use of Treatment Chemicals

Use of treatment chemicals such as polymers, flocculants or other products shall be in addition to conventional erosion and sediment controls and shall be used only where treated stormwater is directed to a sediment control BMP (such as a sediment basin or perimeter control) prior to discharge. Any treatment chemicals selected shall be appropriate for the application, shall comply with state and local requirements, be used in accordance with good engineering practice by properly trained personnel.

If any subcontractors use any treatment chemicals (polymers, flocculants, etc.) the subcontractor must comply with the minimum requirements set forth in Section 2.1.3.3 of the EPA NPDES Construction General Permit

4.13 Dewatering Practices

General

- The development of this site does not require any dewatering

4.14 Other Stormwater Controls

Equipment Service Area

- There are no equipment service areas associated with the development of the three (3) residential homes

Masonry Mixing Area

- Non-stormwater discharges into storm drainage systems or waterways containing slurries from concrete or mortar mixing operations shall not be permitted. Masonry mixing areas shall be located a minimum distance of 100 linear feet from drainage ways, inlets and surface waters and all storm water runoff from these areas shall be contained by a berm or other measures. Run-on water to these areas will be diverted to prevent mixing of clean water and water contaminated with concrete slurry

Equipment and Vehicle Washing

- There are no equipment washing areas associated with the development of the three (3) residential homes

<u>Slope Maintenance</u>

a. Ongoing stabilization shall utilize Native plantings and Native transplants, which will be supervised by Safe Harbor, using established, Safe Harbor protocols.

b. Growing season inspections shall be weekly or as otherwise specified.
c. End of growing season report shall be provided to the Commission.

4.15 Site Stabilization

- Stabilization of disturbed areas must, at a minimum, be initiated immediately whenever any clearing, grading, excavating, or other earth disturbing activities have permanently ceased on any portion of the site, or temporarily ceased on any portion of the site and will not resume for a period exceeding 14 calendar days.
- On areas where work has temporarily ceased, stabilization must begin immediately as soon as it is known that work will be stopped for 14 or more additional calendar days. "Immediately" means as soon as practicable, but no later than the end of the next work day, following the day when the earth-disturbing activities have temporarily or permanently ceased. The deadline to complete stabilization activities is no later than 14 calendar days after initiation of soil stabilization activities such as initially seeding, planting, or providing non-vegetative measures for non-vegetative stabilization.

  The following types of activities shall constitute the initiation of stabilization:
  1. Prepping the soil for vegetative or non-vegetative stabilization;
  2. Applying mulch or other non-vegetative product to the exposed area;
  3. Seeding or planting the exposed area;
  4. Starting any of the activities in # 1 – 3 on a portion of the area to be stabilized, but not on the entire area; and
  5. Finalizing arrangements to have stabilization product fully installed in compliance with the applicable deadline for completing stabilization in the EPA NPDES GCP Parts 2.2.1.2 and 2.2.1.3.

4.16 Long-term Maintenance of Steep Sloped Areas

- In the event of failure of the drought-tolerant seed mix in sections of the steep-sloped areas, the responsible party shall reseed the affected areas and water the areas regularly until seeds have germinated. Additional stabilization controls may also be necessary, including installation of erosion control blanket and/or silt fencing in and around the area. During construction, the contractor shall be responsible for maintenance of steep sloped areas. After construction, the property management company will bear the responsibility.

SECTION 5: POLLUTION PREVENTION STANDARDS

5.1 Potential Sources of Pollution

<u>Spills</u>
a. Mechanized equipment shall be stored within the L.O.W.
b. Mechanized equipment shall be provided with absorbent response materials to protect against unintentional petrochemical leaks.
c. Mechanized equipment shall only utilize the designated access area.

POTENTIAL SOURCES OF POLLUTION

Potential sources of sediment to stormwater runoff include:

- Clearing, grading, and excavating activities, primarily un-stabilized areas, paving operations, demolition and debris disposal, dewatering operations, drilling and blasting, material delivery, storage and use, and landscaping operations.

Potential pollutants other than sediment include the following materials and substances that could be expected to be present on-site during construction:

- Heavy Metals – from concrete additives, concrete washout, material delivery, storage and use, and hazardous substance/waste spills
- pH (Acids and Bases) – from concrete washout, painting and cleaning, drilling operations, material delivery, storage and use, hazardous waste spills, and sanitary/septic waste.
- Paints and Solvents – from concrete washout and waste, painting, concrete polishing, cleaning products, material delivery and use, hazardous waste spills, and sanitary/septic waste
- Trash, Debris and Solids – from clearing and grading, paving, concrete wash waste, construction painting and cleaning, demolition, drilling and blasting, material delivery storage and use, landscaping, and general construction
- Petroleum Based Products – from material delivery storage and use, hazardous waste spills, vehicle and equipment use on site, and vehicle and equipment fueling and maintenance and storage
- Pesticides/Herbicides – from material delivery, storage and use, hazardous waste spills, vehicle use, storage, service, and maintenance
- Fertilizers/Nutrients – from painting, cleaning products, dewatering, material delivery and storage, spills during landscaping operation, sanitary/septic waste

5.2 Spill Prevention and Response

SPILL PREVENTION AND RESPONSE PROCEDURES

a. Mechanized equipment shall be stored within the L.O.W.
b. Mechanized equipment shall be provided with absorbent response materials to protect against unintentional petrochemical leaks.
c. Mechanized equipment shall only utilize the designated access area.

The Contractor or Sub-contractor will be responsible to train all personnel in the proper handling and cleanup of spilled Hazardous Substances or Oil that will be used by them. No spilled Hazardous Substances or Oil will be allowed to come in contact with storm water discharges. If such contact occurs, the storm water discharge will be contained on site by measures such as, but not limited to absorbents, booms, static resistant pads, sump booms and other clean up equipment until appropriate measures in compliance with state and federal regulations are taken to dispose of such contaminated storm water. It shall be the responsibility of the Contractor or Subcontractor to be properly trained, and to train all personnel in spill prevention and clean up procedures in regards to products used by them.

1. In order to prevent or minimize the potential for a spill of Hazardous Substances or Oil to come into contact with storm water, the following steps will be implemented:

a) All Hazardous Substances or Oil (such as pesticides, petroleum products, fertilizers, detergents, construction chemicals, acids, paints, paint solvents, cleaning solvents, additives for soil stabilization, concrete curing compounds and additives, etc.) will be stored in a secure location, with their lids on, preferably under cover, when not in use.
b) The minimum practical quantity of all such materials will be kept at the Project Site.
c) Contractor/Subcontractor responsible for using any Hazardous materials/oil shall have a spill control and containment kit onsite while the Hazardous material/oil is in use.

d) It is the Contractor's responsibility to ensure that all Hazardous Waste discovered or generated at the Project site is disposed of properly by a licensed hazardous material disposal company. The Contractor is responsible for not exceeding Hazardous Waste storage requirements mandated by the EPA or state and local authority.

2. In the event of a spill of Hazardous Substances or Oil, the following procedures must be followed:
a) All measures must be taken to contain and abate the spill and to prevent the discharge of the Hazardous Substance or Oil to storm water or off-site. (The spill area must be kept well ventilated and personnel must wear appropriate protective clothing to prevent injury from contact with the Hazardous Substances.)
b) If the release is equal to or in excess of a reportable quantity, the SWPPP must be modified within seven (7) calendar days of knowledge of the discharge to provide a description of the release, the circumstances leading to the release, and the date of the release. The SWPPP must identify measures to prevent the recurrence of such releases and to respond to such releases. An applicable Critical Incident Form must be completed in accordance with this requirement.
c) If the release is determined to not be reportable (less than a reportable quantity) it shall be noted on a Weekly Inspection Report as an unsatisfactory item with a Task for corrective action and shall be noted and dated when implemented.

3. The Contractor or Subcontractor responsible for the use of Hazard materials/Oil on-site will be the spill prevention and response coordinator for that material/oil. He will designate individuals or himself who will receive spill prevention and response training. These individuals or the contractor/sub-contractor will each become responsible for a particular phase of prevention and response.

5.3 Fueling and Maintenance of Equipment or Vehicles

If you conduct fueling and/or maintenance of equipment or vehicles at your site, you must provide an effective means of eliminating the discharge of spilled or leaked chemicals, including fuel, from the area where these activities will take place.

Examples of effective controls include, but are not limited to, locating activities away from surface waters and stormwater inlets or conveyances, providing secondary containment (e.g., spill berms, decks, and spill containment pallets) and cover where appropriate, and/or having spill kits readily available.

To comply with the prohibition in Part 2.3.1.3 of the EPA NDPES CGP, you must:

a. If applicable, comply with the Spill Prevention Control and Countermeasures (SPCC) requirements in 40 CFR 112 and Section 311 of the CWA;

b. Ensure adequate supplies are available at all times to handle spills, leaks, and disposal of used liquids;

c. Use drip pans and absorbents under or around leaky vehicles;

d. Dispose of or recycle oil and oily wastes in accordance with other federal, state, tribal, or local requirements;

e. Clean up spills or contaminated surfaces immediately, using dry clean up measures where possible, and eliminate the source of the spill to prevent discharge or a furtherance of an ongoing discharge

f. Do not clean surfaces by hosing the area down

CHEMICALS

a. To protect water quality, use of herbicides, pesticides and rodenticides shall be prohibited within the Buffer Zone.
b. BMP and IPM standards shall be utilized for weeds, insects and rodents.
c. Alkaline percolate from concrete may alter nutrient loading of ground water chemistry and impact leaves and roots of vegetation; plastic liners shall be utilized with all concrete formwork to protect ground water from gravity directed, alkaline percolation.
d. Non-leaching decking materials shall be used

5.4 Washing of Equipment and Vehicles

No washing of construction equipment is proposed or allowed within the project activities.

5.5 Storage, Handling, and Disposal of Construction Products, Materials, and Wastes

You must minimize the exposure to stormwater of any of the products, materials, or wastes specified below that are present at your site by complying with the requirements in Part 2.3.3.3 of the EPA NPDES GCP.

Note: These requirements do not apply to those products, materials, or wastes that are not a source of stormwater contamination or that are designed to be exposed to stormwater.

5.5.1 Building Products

For building products: In storage areas, provide either (1) cover (e.g., plastic sheeting or temporary roofs) to prevent these products from coming into contact with rainwater, or (2) a similarly effective means designed to prevent the discharge of pollutants from these areas.

Some examples of building products that are typically stored at construction sites include, but are not limited to, asphalt sealants, copper flashing, roofing materials, adhesives, concrete admixtures.

5.5.2 Pesticides, Herbicides, Insecticides, Fertilizers, and Landscape Materials

No use of Pesticides, Herbicides, Insecticides and Fertilizers is proposed or allowed within the project activities.

Landscape Materials In storage areas, provide either (1) cover (e.g., plastic sheeting or temporary roofs) to prevent these chemicals from coming into contact with rainwater, or (2) a similarly effective means designed to prevent the discharge of pollutants from these areas; and comply with all application and disposal requirements included on the registered pesticide, herbicide, insecticide, and fertilizer label.

5.5.3 Diesel Fuel, Oil, Hydraulic Fluids, Other Petroleum Products, and Other Chemicals

To comply with the prohibition in Part 2.3.1.3 of the EPA NDPES CGP, store chemicals in water-tight containers, and provide either (1) cover (e.g., plastic sheeting or temporary roofs) to prevent these containers from coming into contact with rainwater, or (2) a similarly effective means designed to prevent the discharge of pollutants from these areas (e.g., spill kits), or provide secondary containment (e.g., spill berms, decks, spill containment pallets); and Clean up spills immediately, using dry clean-up methods where possible, and dispose of used materials properly. Do not clean surfaces or spills by hosing the area down. Eliminate the source of the spill to prevent a discharge or a continuation of an ongoing discharge.

5.5.4 Hazardous or Toxic Waste

Examples of hazardous or toxic waste that may be present at construction sites include, but are not limited to, paints, solvents, petroleum-based products, wood preservatives, additives, curing compounds and acids.

(1) Separate hazardous waste from the construction and domestic waste

(2) Store waste in sealed containers, which are constructed of suitable materials to prevent leakage and corrosion, and which are labeled in accordance with the applicable Resource Conservation and Recovery Act (RCRA) requirements and all other applicable federal, state, tribal, or local requirements;

(3) Store all containers that will be stored outside within the appropriately-sized secondary containment (e.g., spill berms, decks, spill containment pallets) to prevent spills from being discharged, or provide a similarly effective means designed to prevent the discharge of pollutants from these areas (e.g., storing chemicals in covered area or having a spill kit available on-site;

(4) Dispose of hazardous or toxic waste in accordance with the manufacturer's recommended method of disposal and in compliance with the federal, state, tribal, and local requirements; and

(5) Clean up spills immediately, using dry clean-up methods where possible, and dispose of used materials properly. Do not clean surfaces or spills by hosing the area down. Eliminate the source of the spill to prevent a discharge or furtherance of an ongoing discharge.

5.5.5 Construction and Domestic Waste

Examples of construction and domestic waste include, but are not limited to, packaging materials, scrap construction materials, masonry products, timber, pipe and electrical cuttings, plastics, styrofoam, concrete, and other trash or building materials.

5.5.6 Waste

a. Onsite trash containers, fitted with a device to secure the lids, shall be used to prevent human food waste from entering the native ecosystem.
b. Worker parking shall be identified, inside the L.O.W.
c. Worker toilet shall be in place.
d. Construction materials storage shall be identified inside the L.O.W. Covered Dumpster shall be stored within the L.O.W.

5.5.7. Concrete Protocols

"*MANAGING CONCRETE*" 2019, Safe Harbor, 7 pages

a. Concrete work shall use Safe Harbor Concrete Management protocols
b. Polyethylene liners shall be used under footings and slabs.
c. This also contributes to the quality of the set by controlling moisture loss.
d. During concrete work, over pour shall be strictly controlled.
e. Concrete over pour shall be directed to forms for moorings, or a tarp for later removal.
f. Concrete over pour on tarps shall be left to harden for recycling.
g. Pumper truck over-pour can be poured onto a tarp dug into a pile of backfill.

h. Overpour is not a waste product. When it has dried and set it may be broken up into pieces and re-used for dry wells.

General

Provide waste containers (e.g., dumpster or trash receptacle) of sufficient size and number to contain construction and domestic wastes. In addition, you must:

(1) On work days, clean up and dispose of waste in designated waste containers; and

(2) Clean up immediately if containers overflow.

5.5.6 Sanitary Waste

Position portable toilets so that they are secure and will not be tipped or knocked over

5.6 Washing of Applicators and Containers used for Paint, Concrete or Other Materials

To comply with the prohibition in Parts 2.3.1.1 and 2.3.1.2 of the EPA NPDES CGP, you must provide an effective means of eliminating the discharge of water from the washout and cleanout of stucco, paint, concrete, form release oils, curing compounds, and other construction materials. To comply with this requirement, you must:

a. Direct all washwater into a leak-proof container or leak-proof pit. The container or pit must be designed so that no overflows can occur due to inadequate sizing or precipitation;

b. Handle washout or cleanout wastes as follows:

i. Do not dump liquid wastes in storm sewers;

ii. Dispose of liquid wastes in accordance with applicable requirements in Part 2.3.3.3 of the EPA NPDES CGP; and

iii. Remove and dispose of hardened concrete waste consistent with your handling of other construction wastes in Part 2.3.3.3 of the EPA NPDES CGP; and

c. Locate any washout or cleanout activities as far away as possible from surface waters and stormwater inlets or conveyances, and, to the extent practicable, designate areas to be used for these activities and conduct such activities only in these areas.

Also, see EPA's *Concrete Washout BMP Fact Sheet* at
www.epa.gov/npdes/stormwater/menuofbmps/construction/concrete_wash

5.6.1 Concrete Wash-out Area

General

Alkaline percolate from concrete may alter nutrient loading of ground water chemistry and impact leaves and roots of vegetation; plastic liners shall be utilized with all concrete formwork to protect ground water from gravity directed, alkaline percolation

The Foundation Contractor (along with any Contractor/Sub-Contractor that will be mixing concrete) shall designate an area (in accordance with section 5.6 (c)) and construct a temporary, above grade concrete wash-out area. The temporary concrete washout area will be constructed as shown in Figure#1, with a recommended minimum length and minimum width of 10', but with sufficient quantity and volume to contain all liquid and concrete waste generated by washout operations. The washout area will be lined with plastic sheeting at least 10 mils thick and free of any holes or tears. Signs will be posted marking the location of the washout area to ensure that concrete equipment operators use the proper facility.

Concrete pours will not be conducted during or before an anticipated storm event. Concrete mixer trucks and chutes will be washed in the designated area or concrete wastes will be properly disposed of off-site. When temporary washout area is no longer needed for the construction project, the hardened concrete and materials used to construct the area will be removed and disposed of according to the maintenance section below, and the area will be stabilized. For design specifications, see Figure #1

Installation

The washout area will be constructed before concrete pours occur at the site

Maintenance and Inspection

The washout areas will be inspected daily to ensure that all concrete washing is being discharged into the washout area, no leaks or tears are present, and to identify when the concrete wastes need to be removed. The washout areas will be cleaned out once the area is filled 70 - 75% of the holding capacity. Once the area's holding capacity has been reached, the concrete wastes will be allowed to harden; the concrete will be broken up, removed, and taken to an appropriate disposal site. The plastic sheeting will be replaced if tears occur during removal of concrete wastes from the washout area.

<u>STORM PULSE INSPECTIONS</u>

a. Additional inspections shall be performed following storm pulse events.

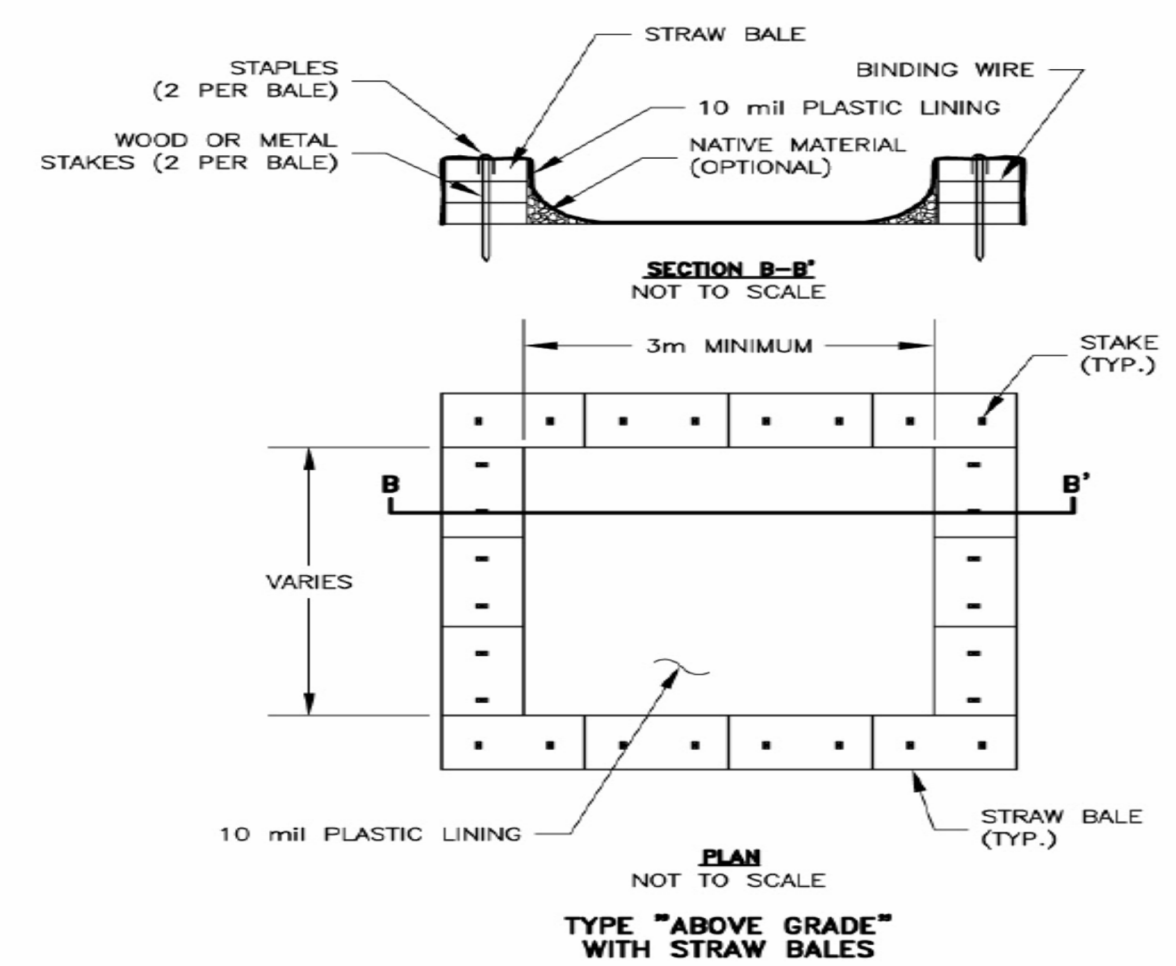


Figure #1

5.7 Fertilizers

The use of fertilizers are not anticipated within the scope of the construction project.

Discharge of fertilizers containing nitrogen or phosphorus shall be minimized. Fertilizers will be applied only in the minimum amounts recommended by the manufacturer. Once applied, fertilizer will be worked in the soil to limit exposure to storm water. Apply only at the time of year appropriate for location. Avoid application during heavy rain and never apply to frozen ground. Application of fertilizer to stormwater conveyance channels or other storm water facilities where water will flow is not permitted. Follow all federal, state and local requirements regarding application. Storage will be in a covered shed. The contents of any partially used bags of fertilizer will be transferred to a sealable plastic bin to avoid spills

5.8 Other Pollution Prevention Practices

No other Pollution Prevention Practices are being proposed at this time

SECTION 6: INSPECTION AND CORRECTIVE ACTION

6.1 Inspection Personnel and Procedures

***Personnel Responsible for Inspections**

T.B.D.

Employees of the above referenced firm shall be responsible for conducting routine site inspections to ensure all BMPs are being implemented and completing inspection reports after each inspection based on established inspection schedule as well conducting spot inspections and informal inspections.

*Note: All personnel conducting inspections must be considered a "qualified person." CGP Part 4.1.1 clarifies that a "qualified person" is a person knowledgeable in the principles and practices of erosion and sediment controls and pollution prevention, who possesses the skills to assess conditions at the construction site that could impact stormwater quality, and the skills to assess the effectiveness of any stormwater controls selected and installed to meet the requirements of this permit.

Inspection Schedule

Per EPA NDPES CGP Section 4.1.2.2 (see below)

Once every 14 calendar days and within 24 hours of the occurrence of a storm event of 0.25 inches or greater. To determine if a storm event of 0.25 inches or greater has occurred on your site, you must either keep a properly maintained rain gauge on your site, or obtain the storm event information from a weather station that is representative of your location. For any day of rainfall during normal business hours that measures 0.25 inches or greater, you must record the total rainfall measured for that day in accordance with Part 4.1.7.1d of the EPA NDPES CGP.

Inspections will be required on a daily basis if any concrete pouring/washing is taking place. Inspections for concrete pouring/washing out shall follow the requirements set forth in section 5.6.1

*Notes: Inspections are only required during the project's normal working hours. "Within 24 hours of the occurrence of a storm event" means that you are required to conduct an inspection within 24 hours once a storm event has produced 0.25 inches, even if the storm event is still continuing. Thus, if you have elected to inspect bi-weekly in accordance with Part 4.1.2.2 of the EPA NDPES CGP and there is a storm event at your site that continues for multiple days, and each day of the storm produces 0.25 inches or more of rain, you are required to conduct an inspection within 24 hours of the first day of the storm and within 24 hours after the end of the storm

Rain Gauge Location (if applicable)

No rain gauge will be installed on site storm event rainfall data will be obtained from a weather station

INSPECTIONS

Project Inspections

a. End of day visual inspections shall prevent unintentional migration on non-indigenous materials beyond the LOW.
b. Regular site inspections, to assure compliance with performance standards, shall be made weekly by Safe Harbor.
c. For the duration of deconstruction, excavation or construction activity, end of day inspections shall be performed by a representative of the contractor on site, to control unintentional migration of non-indigenous materials beyond the Limit of Work
d. The L.O.W. shall be inspected and maintained weekly by Safe Harbor, to maintain zero discharge performance standards, pending site stability with native vegetation.
e. Mechanized equipment shall be inspected daily to prevent unintentional petrochemical discharge.

INSPECTOR RESPONSIBILITIES

The Qualified Inspector/Operator shall have the primary responsibility and significant authority for the implementation, maintenance, inspection, and modifications to the SWPPP. They will be trained in all the inspection and maintenance practices necessary for keeping the Erosion and Sediment Controls that are used onsite in good working order. They will also be trained in the completion of, initiation of actions required by, and the filing of the inspection forms (found in Appendix D & E). Documentation of Qualified Inspector training will be kept on site with the SWPPP.

INSPECTION PROCEDURES

Inspections must include all areas of the site disturbed by Construction Activities and areas used for storage of materials that are exposed to precipitation. Qualified Inspectors must look for evidence of, or the potential for, pollutants entering the storm water conveyance system. Erosion and Sediment Control measures identified in the SWPPP must correspond to those implemented at the site and each measure must be observed to ensure proper operation. Discharge locations must be inspected to ascertain whether Erosion and Sediment Control measures are effective in preventing significant impacts to Waters of the United States, where accessible. Where discharge locations are inaccessible, nearby downstream locations must be inspected to the extent that such inspections are practicable. Locations where vehicles enter or exit the site must be inspected for evidence of off-site tracking. The following inspection and maintenance practices will be used to maintain Erosion and Sediment Controls and stabilization measures:

a. The Person's listed in Section 6.1 will be responsible for these inspections, maintenance and repair activities, and filling out inspection and maintenance reports.

b. All control measures will be inspected at least at the frequency identified in Section 6.1

c. Silt fences will be inspected for depth of sediment, tears, etc., to see if the fabric is securely attached to the fence posts, and to see that the fence posts are securely in the ground.

d. All sediment control measures including silt fence and filter fabric on catch basin rims shall be inspected for built up of sediment. Corrective action will have to be taken if

these inspections reveal that the maintenance requirements set forth in Section 4.2 are met.

e. Temporary and permanent seeding and all other stabilization measures will be inspected for bare spots, washouts, and healthy growth.

f. Concrete wash-out basins shall be inspected daily, when in use, inspections procedures should be followed as set forth in section 5.6.1.

g. An Inspection Report (Appendix D) will be completed after each inspection. Blank copies of the report forms to be completed by the Qualified Inspector(s) are included in this SWPPP in Appendix D.

h. Disturbed Areas and materials storage areas will be inspected for evidence of or potential for pollutants entering stormwater systems.

i. Report to U.S. Environmental Protection Agency within 24 hours of any noncompliance with the SWPPP that will endanger public health or the environment. Complete an applicable Critical Incident and Reportable Quantity Report. Follow up with a written report within 5 days of the noncompliance event.

The following events require 24 hour reporting:

a) any unanticipated bypass which exceeds any effluent limitation in the permit
b) any upset which exceeds any effluent limitation in the permit
c) a violation of a maximum daily discharge limitation for any of the pollutants listed by the EPA in the permit to be reported within 24 hours. The written

j. Spills or Releases of Hazardous Substances or Oil in excess of reportable quantities (as established under 40 CFR Part 110, 40 CFR Part 117 or 40 CFR Part 302) must be reported. Section 5.2 provides further details on the notification and reporting process

k. Vehicle track out areas will be inspected to ensure that the are installed properly

Inspection Report Forms

It is imperative that documentation of the inspection and maintenance of all erosion and sediment control measures be completed as soon as possible after the inspection and/or maintenance is concluded (on form provided in Appendix D), but no more than 2 hours after conclusion of any inspection or maintenance activity. The inspection reports identify any incidents of non-compliance with the permit conditions. Where a report does not identify any incidents of non-compliance, the report must contain a certification that the Project is in compliance with the SWPPP and the Construction General Permit or other applicable State Permit. The report must be signed in accordance with Appendix I, 11 (Signatory Requirements of the Federal NPDES Permit). These records are used to prove that the required inspection and maintenance were performed and shall be printed and placed in the SWPPP Ledger. In addition to inspection and maintenance reports, records should be kept of the Construction Activities that occur on the site. Identified and completed corrective actions will be documented on Form in Appendix E. The Contractor shall retain copies of the SWPPP, all reports and data in paper and CD format for a minimum of **five (5) years** after the Project is complete. Forms found in Appendix

D & E of this SWPPP shall be used by the Qualified Inspector(s) to inventory and report the condition of each measure to assist in maintaining the erosion and sediment control measures in good working order. The following list identifies the required Inspection and Maintenance documentation and record keeping that must be maintained by the Contractor under this SWPPP:

Inspection Reports
- **Bi-Weekly (and Rain Event) Inspection Form (Appendix D)**
- **Corrective Action Log (Appendix E)**

SWPPP Amendment Log
- **SWPPP Amendment Log (Appendix F)**

Training Report
- **Training Report (Appendix I)**

Contractor/Subcontractor Certification Agreement
- **Contractor/Subcontractor Certification Agreement (Appendix G)**

These report forms shall become an integral part of the SWPPP and shall be made readily accessible to governmental inspection officials, the Operator's Engineer, and the Operator for review upon request during visits to the Project site. In addition, copies of the reports shall be provided to any of these persons, upon request, via mail or facsimile transmission. Inspection and maintenance report forms are to be maintained by the permittee for five (5) years following the final stabilization of the site.

OTHER RECORD KEEPING REQUIREMENTS

The Contractor shall keep the following records related to Construction Activities at the site:
- Dates when major grading activities occur and the areas which were graded
- Dates and details concerning the installation of structural controls
- Dates when Construction Activities cease in an area
- Dates when stabilization measures are initiated
- Dates when an areas is stabilized, either temporarily or permanently
- Dates of rainfall and the amount of rainfall
- Dates and descriptions of the character and amount of any spills of Hazardous Substances or Oil
- Records of reports filed with regulatory agencies if reportable quantities of Hazardous Substances or Oil spilled

SWPPP MODIFICATIONS

The inspection report should also identify if any revisions to the SWPPP are warranted due to unexpected conditions. The SWPPP is meant to be a dynamic working guide that is to be kept current and amended by the Qualified Inspector (or other party if so specified below) whenever:

1. There is a change in design, construction, operation (such as new operators becoming active in construction activities), or maintenance at the construction site that has or could have a

significant effect on the discharge of pollutants to the Waters of the United States that has not been previously addressed in the SWPPP. In addition to modifying the SWPPP, the Site Map may also require an amendment. Modifications to the SWPPP and/or Site Map in relation to any change in design, construction, operation, or maintenance at the construction site must be made within 48 hours of such change.
2. Inspections or investigations by site staff, or by local, state or federal officials, determine that the SWPPP modifications are necessary for compliance with the permit. Modifications resulting relation to SWPPP ineffectiveness resulting from an inspection must be initiated within 48 hours.

3. Where EPA (or state regulatory agency) determines it is necessary to impose additional requirements on the discharge, the following must be included in the SWPPP within 48 hours following the determination:

a. A copy of any correspondence describing such requirements
b. A description of the stormwater control measures that will be used to meet such requirements.

4. To reflect any revisions to applicable federal, state or local requirements that affect the stormwater control measures implemented at the site.

5. If applicable, if a change in chemical treatment systems or chemically enhanced stormwater control is made, including use of a different treatment chemical, different dosage rate, or different area of application.

6. BMPs are modified or additional BMPs are designed to correct problems identified during an inspection. Revisions to the SWPPP related to additional or modified BMPs must be completed within 48 hours following the inspection.

7. There is a release involving a Hazardous Substance or Oil in an amount equal to or in excess of a reportable quantity established under either 40 CFR Part 110, 40 CFR Part 117 or 40 CFR Part 302. Revisions to the SWPPP must be completed within seven (7) calendar days of knowledge of the release.

8. A change in design, construction, operation, or maintenance materially affects the site's spill potential per 40 CFR Part 112. Modifications to the SWPPP in relation to such change must be made within 48 hours of the change.

9. The Contractor's failure to modify the SWPPP to include off-site borrow or fill areas used solely for the Project or to monitor or report deficiencies to the Operator will result in the Contractor being liable for fines and construction delays resulting from any federal, state, or local agency enforcement action.

10. Modifications or changes in locations of materials management BMPs shown on the Site Map. Documentation of such modifications or changes must be documented on a Modification Form and depicted on the Site Map within 48 hours of the change. Any such changes to the SWPPP must be made in writing on the SWPP Amendment Log **(Appendix F)** within 48 hours of the date such modification or amendment is made to the SWPPP. Changes must also be drawn on the Site Map within 48 hours of any modification or amendment is made to the SWPPP.

6.2 Corrective Action

Any runoff controls, sediment controls, materials BMPs, or erosion controls found to need corrective action such as replacement, repair, or maintenance shall be entered into the Corrective Action Log Form (Appendix E) and dated upon completion. Any minor corrective action shall be initiated immediately after discovery and completed by the close of the next work day; any major corrective action or replacement shall be initiated within 24 hours and completed within 48 hours.

6.3 Delegation of Authority

Duly Authorized Representative(s) or Position(s):

Mr. Bob Ryley, Construction Manager
HABITAT FOR HUMANITY OF CAPE COD
411 Main Street, Suite 6
Yarmouthport, MA 02675

SECTION 7: TRAINING

Individual Responsible for Initial Training

J.M. O'REILLY & ASSOCIATES, INC. will be responsible for training the Owner/Operator of HABIATATE FOR HUMANITY OF CAPE COD. It will then be his/her responsibility to train any and all contractors/subcontractors that will be working onsite for general stormwater and BMP awareness with detailed training for those contractors/subcontractors with specific stormwater responsibilities. It will also be his/her Responsibility to train the Qualified Inspector.

Training that will be conducted:

- J.M. O'REILLY & ASSOCIATES, INC. will provide information to the Owner/Operator (HABITAT FOR HUMANITY OF CAPE COD) regarding BMP's that will be used onsite and any plans, specifications, and installation requirements.

- The Owner/Operator will conduct informal training for all staff, including subcontractors, on the site. The training will be conducted primarily via tailgate sessions and will focus on avoiding damage to stormwater BMPs and preventing illicit discharges. The tailgate sessions will be conducted as needed and will address the following topics: Erosion Control BMPs, Sediment Control BMPs, Non-Stormwater BMPs, Waste Management and Materials Storage BMPs, and Emergency Procedures specific to the construction site. (See Appendix I – SWPPP Training Log)

SECTION 8: CERTIFICATION AND NOTIFICATION

The following certification statement must be signed and dated by a person who meets the requirements of CGP Appendix I, Part 1.11. This Certification must be resigned in the event of a SWPPP Modification.

Owner/Operator – HABITAT FOR HUMANITY OF CAPE COD

I certify under penalty of law that this document and all attachments were prepared under my direction or supervision in accordance with a system designed to assure that qualified personnel properly gathered and evaluated the information submitted. Based on my inquiry of the person or persons who manage the system, or those persons directly responsible for gathering the information, the information submitted is, to the best of my knowledge and belief, true, accurate, and complete. I am aware that there are significant penalties for submitting false information, including the possibility of fine and imprisonment for knowing violations.

Name: _____ Title: _____

Signature: _____ Date: _____

SWPPP APPENDICES

Attach the following documentation to the SWPPP:

Appendix A – Site Maps

Appendix B – Copy of 2012 CGP

Appendix C – NOI and EPA Authorization Email

Appendix D – Inspection Form

Appendix E – Corrective Action Form

Appendix F – SWPPP Amendment Log

Appendix G – Subcontractor/Contractor Certifications/Agreements

Appendix H – Grading and Stabilization Activities Log

Appendix I – Training Log

Appendix J – Delegation of Authority

Appendix K – Endangered Species Documentation

Appendix L – Historic Preservation Documentation

Appendix A – Site Maps

Appendix B – Copy of 2012 CGP

Appendix C – Copy of NOI and EPA Authorization email

Appendix D – Copy of Inspection Form

Appendix E – Copy of Corrective Action Form

Appendix F – SWPPP Amendment Log

No.	Description of the Amendment	Date of Amendment	Amendment Prepared by [Name(s) and Title]

Appendix G – Subcontractor Certifications/Agreements

SUBCONTRACTOR CERTIFICATION
STORMWATER POLLUTION PREVENTION PLAN

Project Number: _____

Project Title: _____

Operator(s): _____

As a subcontractor, you are required to comply with the Stormwater Pollution Prevention Plan (SWPPP) for any work that you perform on-site. Any person or group who violates any condition of the SWPPP may be subject to substantial penalties or loss of contract. You are encouraged to advise each of your employees working on this project of the requirements of the SWPPP. A copy of the SWPPP is available for your review at the office trailer.

Each subcontractor engaged in activities at the construction site that could impact stormwater must be identified and sign the following certification statement:

I certify under the penalty of law that I have read and understand the terms and conditions of the SWPPP for the above designated project and agree to follow the practices described in the SWPPP.

This certification is hereby signed in reference to the above named project:

Company: _____

Address: _____

Telephone Number: _____

Type of construction service to be provided: _____

_____

_____

Signature: _____

Title: _____

Date: _____

Appendix H – Grading and Stabilization Activities Log

- **Refer to Site Plan for straw waddle, silt fence, erosion control blanket and re-vegetation notes.**

Date Grading Activity Initiated	**Description of Grading Activity**	**Description of Stabilization Measure and Location**	**Date Grading Activity Ceased** (Indicate Temporary or Permanent)	**Date When Stabilization Measures Initiated**

Appendix I – SWPPP Training Log

Stormwater Pollution Prevention Training Log

Project Name:

Project Location:

Instructor's Name(s):

Instructor's Title(s):

Course Location: _____ Date: _____

Course Length (hours): _____

Stormwater Training Topic: *(check as appropriate)*

- ❑ **Sediment and Erosion Controls**
- ❑ **Emergency Procedures**
- ❑ **Stabilization Controls**
- ❑ **Inspections/Corrective Actions**
- ❑ **Pollution Prevention Measures**

Specific Training Objective:_____

_____

Attendee Roster: *(attach additional pages as necessary)*

No.	Name of Attendee	Company
1		
2		
3		
4		
5		
6		
7		
8		

Appendix J – Delegation of Authority Form

Delegation of Authority

I, _____ (name), hereby designate the person or specifically described position below to be a duly authorized representative for the purpose of overseeing compliance with environmental requirements, including the Construction General Permit, at the _____ construction site. The designee is authorized to sign any reports, stormwater pollution prevention plans and all other documents required by the permit.

_____ (name of person or position)
_____ (company)
_____ (address)
_____ (city, state, zip)
_____ (phone)

By signing this authorization, I confirm that I meet the requirements to make such a designation as set forth in Appendix I of EPA's Construction General Permit (CGP), and that the designee above meets the definition of a "duly authorized representative" as set forth in Appendix I.

I certify under penalty of law that this document and all attachments were prepared under my direction or supervision in accordance with a system designed to assure that qualified personnel properly gathered and evaluated the information submitted. Based on my inquiry of the person or persons who manage the system, or those persons directly responsible for gathering the information, the information submitted is, to the best of my knowledge and belief, true, accurate, and complete. I am aware that there are significant penalties for submitting false information, including the possibility of fine and imprisonment for knowing violations.

Name: _____

Company: _____

Title: _____

Signature: _____

Date: _____

Appendix K – Endangered Species Documentation

Appendix L – Historic Properties Documentation

Not applicable

Jeffrey Ribeiro

From: c.e.steinman <c.e.steinman@comcast.net>
Sent: Sunday, June 14, 2020 4:04 PM
To: Jeffrey Ribeiro; Art Hultin
Cc: Rae Ann Palmer
Subject: Comments for the ZBA Public Hearing Regarding the Cloverleaf Project
Attachments: Cloverleaf_Option_6-11-2020.pdf; Original cloverleaf_Site_Plan.pdf

To the Zoning Board of Appeals;:

I request that the following comments be read into the public record regarding the proposed Cloverleaf Project.

I had previously been in support of Building 21 with its fifteen apartments and commons spaces serving as a congregate housing component of the proposed Cloverleaf Project. Having had a 25-year career in the interior design for senior housing, including retirement communities, assisted living, nursing and Alzheimer care projects, I thought the proposal for Building 21 would offer Truro additional housing opportunities for our aging population. However, the devastating impact of the Coronavirus on seniors in congregate housing is a game changer.

With the uncertain future of the COVID-19 pandemic, Building 21 as currently designed might not be manageable, and importantly, not marketable either. Individual-entry apartments as elsewhere on the site are a safer option.

Attached is a concept sketch for replacing the large congregate building with three town-houses, similar in design to units 2, 4 and 6. Taking advantage of the site's topography, there could be six ground-floor apartments entered on the front and back of the town-house buildings that will have at-grade access. Those apartments could be designed for accessibility, similar to unit 2A. This would reduce the number of units in Building 21 from 15 to 9 in the town-houses, resulting in an overall reduction of 6 units. The total units will decrease from 40 to 34. At the same time, the redesign could increase the number of accessible units from 4 to 7.

This proposal is not trying to solve all the water quality issues presented in the peer engineering review, which may require appropriate on-site septic treatment and possibly an overall reduction in the number of units. However, the proposed design change with its reduction in the number of units could be a step in the right direction to help resolve the water quality issue while also making the project more beneficial to our community.

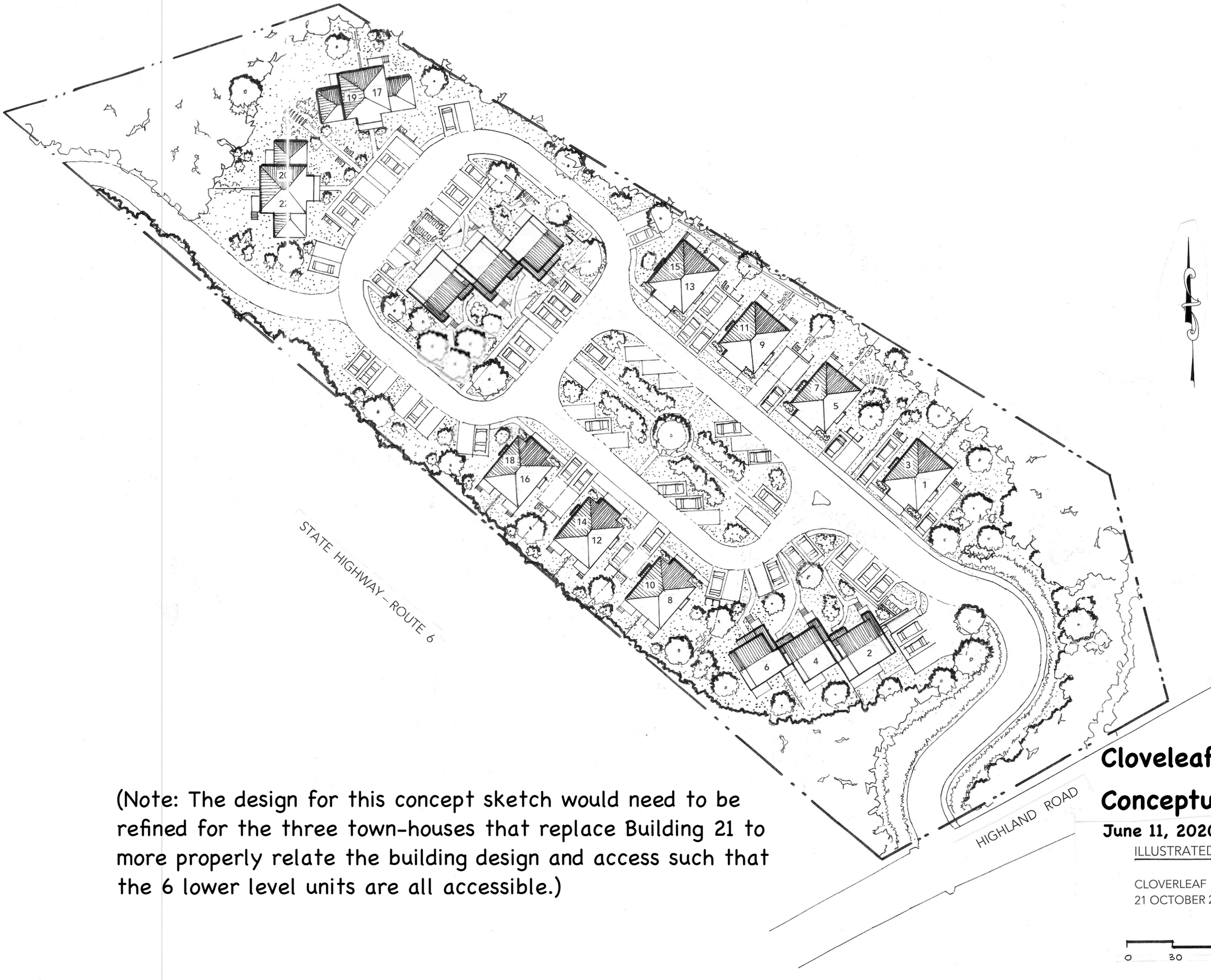
Thank you for the opportunity to comment and for your consideration,

Chuck Steinman
c.e.steinman@comcast.net
cell 617-974-1613

PO Box 781/Shore Road
North Truro, MA 02652

Cloverleaf Option Conceptual Site Plan, Replacing Building 21 with 3 Town-House Buildings:

Cloverleaf Original Illusrative Site Plan Showing Building 21:



Cloveleaf Option
Conceptual Site Plan

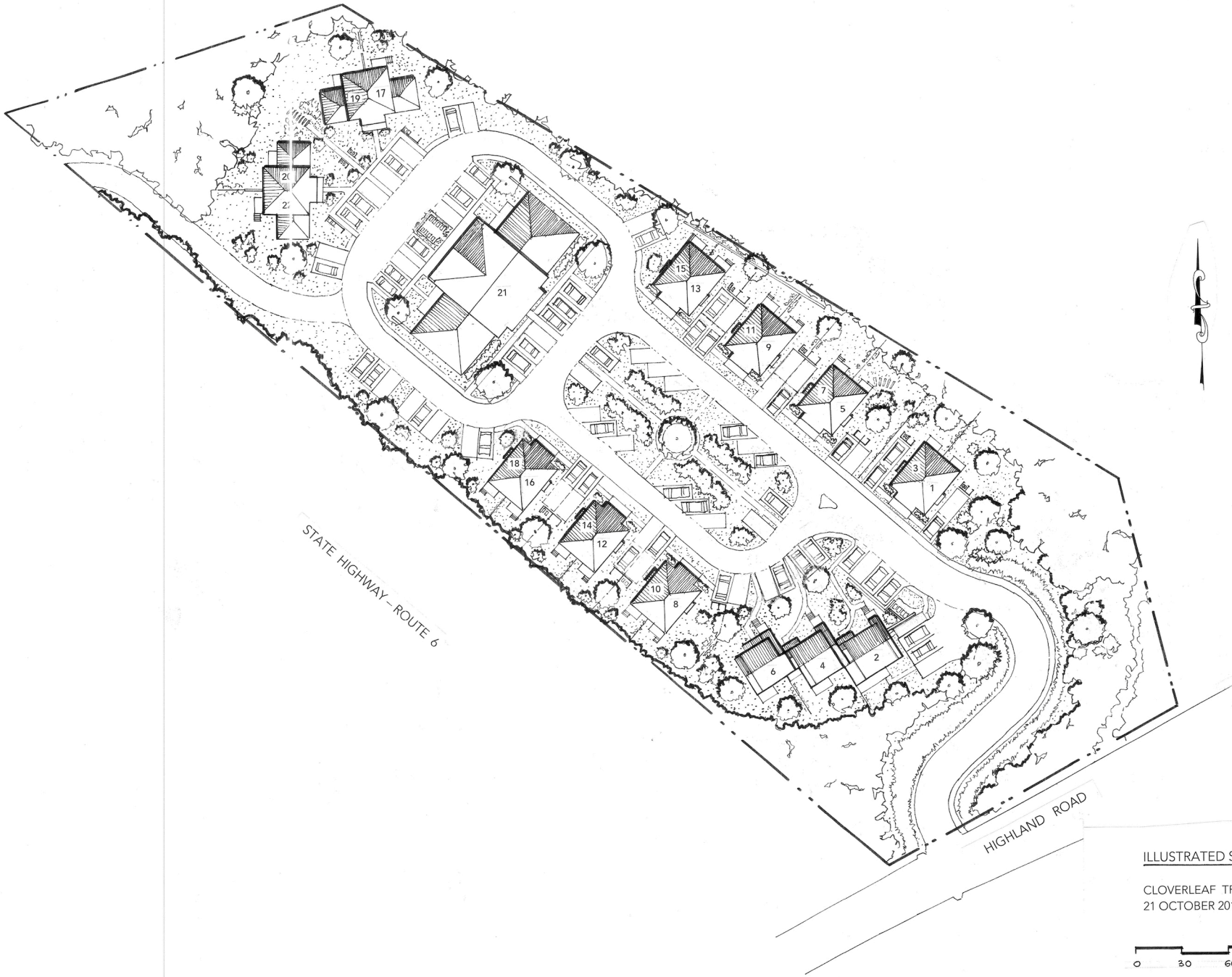
June 11, 2020

ILLUSTRATED SITE PLAN

CLOVERLEAF TRURO RENTAL HOUSING
21 OCTOBER 2019

0 30 60 90

(Note: The design for this concept sketch would need to be refined for the three town-houses that replace Building 21 to more properly relate the building design and access such that the 6 lower level units are all accessible.)



ILLUSTRATED SITE PLAN

CLOVERLEAF TRURO RENTAL HOUSING
21 OCTOBER 2019

0 30 60 90

Submitted by Peter Herridge at 3/12/2020 Hearing

Journal Article submission to the ZBA

This packet contains five recent journal articles from well respected, refereed journals on medicine and environmental research. These articles are being submitted to be made of record in the Public Hearing held by the Zoning Board of Appeals (ZBA) of Truro, Massachusetts concerning the decision to grant a waste water waiver to the proposed Cloverleaf housing project held on March 12, 2020. It is the intention of this submission to demonstrate to the ZBA the fact that nitrate pollution in drinking water poses very serious risks of adverse medical consequences to people who drink this water on both an acute and prolonged basis. These articles also clearly show that even levels of nitrates that are below the maximum nitrate level presently allowed in the US, i.e. 10 mg of nitrogen as nitrate per liter of water, can cause a wide variety of serious medical consequences including cancer, birth defects, spontaneous abortion and thyroid disease.

The contents are:

1) *Exposure-based assessment and economic valuation of adverse birth outcomes and cancer risk due to nitrate in United States drinking water*. Author: Temkin A
2) *Nitrate toxicity and drinking water standards*. Author: Kross BC
3) *Thyroid cancer induction: Nitrates as independent risk factors or risk modulators after radiation exposure, with a focus on the Chernobyl accident*. Author: Drozd VA
4) *Drinking water nitrate and human health: an updated review.* Author: Ward MH
5) *Prenatal nitrate intake from drinking water and selected birth defects in offspring of the participants in the National Birth Defects Prevention Study*. Author: Brender JD

This packet is submitted to the Truro ZBA on March 12, 2020 by Peter Herridge MD, JD.

Prenatal Nitrate Intake from Drinking Water and Selected Birth Defects in Offspring of Participants in the National Birth Defects Prevention Study

Jean D. Brender,[1] Peter J. Weyer,[2] Paul A. Romitti,[3] Binayak P. Mohanty,[4] Mayura U. Shinde,[1] Ann M. Vuong,[1] Joseph R. Sharkey,[5] Dipankar Dwivedi,[4] Scott A. Horel,[1] Jiji Kantamneni,[2] John C. Huber Jr.,[1] Qi Zheng,[1] Martha M. Werler,[6] Katherine E. Kelley,[6] John S. Griesenbeck,[7] F. Benjamin Zhan,[8] Peter H. Langlois,[9] Lucina Suarez,[9] Mark A. Canfield,[9] and the National Birth Defects Prevention Study

[1]Department of Epidemiology and Biostatistics, School of Rural Public Health, Texas A&M Health Science Center, College Station, Texas, USA; [2]Center for Health Effects of Environmental Contamination, and [3]Department of Epidemiology, College of Public Health, University of Iowa, Iowa City, Iowa, USA; [4]Department of Biological and Agricultural Engineering, Texas A&M University, College Station, Texas, USA; [5]Department of Health Promotion and Community Health Sciences, School of Rural Public Health, Texas A&M Health Science Center, College Station, Texas, USA; [6]Slone Epidemiology Center, Boston University, Boston, Massachusetts, USA; [7]III Marine Expeditionary Force, Okinawa, Japan; [8]Department of Geography, Texas State University, San Marcos, Texas, USA; [9]Texas Department of State Health Services, Austin, Texas, USA

Background: Previous studies of prenatal exposure to drinking-water nitrate and birth defects in offspring have not accounted for water consumption patterns or potential interaction with nitrosatable drugs.

Objectives: We examined the relation between prenatal exposure to drinking-water nitrate and selected birth defects, accounting for maternal water consumption patterns and nitrosatable drug exposure.

Methods: With data from the National Birth Defects Prevention Study, we linked addresses of 3,300 case mothers and 1,121 control mothers from the Iowa and Texas sites to public water supplies and respective nitrate measurements. We assigned nitrate levels for bottled water from collection of representative samples and standard laboratory testing. Daily nitrate consumption was estimated from self-reported water consumption at home and work.

Results: With the lowest tertile of nitrate intake around conception as the referent group, mothers of babies with spina bifida were 2.0 times more likely (95% CI: 1.3, 3.2) to ingest ≥ 5 mg nitrate daily from drinking water (vs. < 0.91 mg) than control mothers. During 1 month preconception through the first trimester, mothers of limb deficiency, cleft palate, and cleft lip cases 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 than control mothers to ingest ≥ 5.42 mg of nitrate daily (vs. < 1.0 mg). Higher water nitrate intake did not increase associations between prenatal nitrosatable drug use and birth defects.

Conclusions: Higher water nitrate intake was associated with several birth defects in offspring, but did not strengthen associations between nitrosatable drugs and birth defects.

Citation: Brender JD, Weyer PJ, Romitti PA, Mohanty BP, Shinde MU, Vuong AM, Sharkey JR, Dwivedi D, Horel SA, Kantamneni J, Huber JC Jr., Zheng Q, Werler MM, Kelley KE, Griesenbeck JS, Zhan FB, Langlois PH, Suarez L, Canfield MA, and the National Birth Defects Prevention Study. 2013. Prenatal nitrate intake from drinking water and selected birth defects in offspring of participants in the National Birth Defects Prevention Study. Environ Health Perspect 121:1083–1089; http://dx.doi.org/10.1289/ehp.1206249

Introduction

Nitrate is one of the most widespread chemical contaminants in aquifers around the world (Spalding and Exner 1993). Results from several epidemiologic studies have suggested an association between prenatal exposure to nitrates in drinking water and birth defects in offspring, including neural tube defects (NTDs) (Brender et al. 2004; Croen et al. 2001; Dorsch et al. 1984), central nervous system defects overall (Arbuckle et al. 1988), oral cleft defects (Dorsch et al. 1984), musculoskeletal defects (Dorsch et al. 1984), and congenital heart defects (Cedergren et al. 2002). In these studies, exposure was assigned on the basis of nitrate levels detected in drinking-water sources without further estimating individual consumption of nitrate from such sources. It is noteworthy that previous associations observed between birth defects and nitrates in drinking water were often observed at levels below the current allowable maximum contaminant level for nitrate (10 mg/L as nitrate-nitrogen or 45 mg/L as total nitrate) set by the U.S. Environmental Protection Agency (National Primary Drinking Water Regulations 2010).

Once ingested and absorbed, approximately 25% of nitrate is secreted in saliva (Mensinga et al. 2003), where about 20% is converted to nitrite by bacteria in the mouth (Spiegelhalder et al. 1976). This endogenously formed nitrite, along with nitrite from dietary and drinking-water sources, can react with nitrosatable compounds such as amine- and amide-containing drugs to form *N*-nitroso compounds in the stomach (Gillatt et al. 1985). *N*-Nitroso compounds have been found to be teratogens in animal models (Nagao et al. 1991; Platzek et al. 1983). These compounds are formed to a greater extent in the presence of a nitrosatable compound if nitrite concentration is high (Choi 1985); and when combined with higher nitrite, nitrosatable compounds have been reported to be more strongly associated with exencephaly and skeletal malformations in mice (Teramoto et al. 1980) and with NTDs (Brender et al. 2004, 2011b) and other types of birth defects in humans (Brender et al. 2012). In a small case–control study of Mexican-American women, nitrosatable drug exposure was more strongly associated with NTDs in offspring of women whose drinking-water nitrate measured ≥ 3.5 mg/L than among births to women

Address correspondence to J.D. Brender, Texas A&M University System Health Science Center, 257 SRPH Administration Building, Raymond Storzer/Adriance Rd., College Station, TX 77843-0001 USA. Telephone: (979) 862-1573. E-mail: jdbrender@srph.tamhsc.edu

Supplemental Material is available online (http://dx.doi.org/10.1289/ehp.1206249).

We gratefully acknowledge A. Hansen, I. Mendoza-Sanchez, S. Patil, M. Steck, and S. Tolle for their assistance in exposure assessment and S. Malik for her assistance with the classification of heart defects. We also acknowledge use of the Slone Drug Dictionary under license from the Slone Epidemiology Center at Boston University.

This research was supported by grants 5R01ES015634 and 3R01ES015634-03S1 from the National Institute of Environmental Health Sciences (NIEHS); Centers for Disease Control and Prevention, Birth Defects Branch Cooperative Agreement U01DD000494; and Texas Department of State Health Services Contract 2012-039849.

The content is solely the responsibility of the authors and does not necessarily represent the official views of NIEHS, the National Institutes of Health, or the Centers for Disease Control and Prevention.

J.D.B., B.P.M., and P.J.W. have received travel support from the Woods Hole Research Center to present their work on water nitrates and birth defects at a sponsored workshop. M.M.W. serves on advisory boards of studies that evaluate drugs for rheumatoid arthritis in pregnancy, including several studies sponsored by Amgen, Abbott, and Aventis, companies that may make a product that is included as a nitrosatable drug. The other authors declare they have no actual or potential competing financial interests.

Received: 8 November 2012; Accepted: 11 June 2013; Advance Publication: 14 June 2013; Final Publication: 1 September 2013.

with lower measured nitrate in their drinking water (Brender et al. 2004).

The objectives of our study were to *a*) examine the relation between prenatal exposure to drinking-water nitrate and birth defects in offspring (selected from defect groups previously associated with higher nitrate in drinking water), accounting for maternal water consumption patterns; and *b*) investigate whether higher daily exposure to drinking-water nitrate or total nitrite that included contributions from diet and drinking water strengthened associations between prenatal exposure to nitrosatable drugs and selected birth defects in offspring.

Methods

Study population and design. To address the study objectives, we used data from the Iowa and Texas sites of the National Birth Defects Prevention Study (NBDPS), an ongoing population-based case–control study of birth defects in the United States (includes sites in 10 states) that began in 1997 (Yoon et al. 2001). The Iowa and Texas sites identify deliveries with major birth defects from live births, stillbirths, and elective terminations as part of their population-based birth defect surveillance. In the NBDPS, case classification is standardized, and clinical information on potentially eligible births is evaluated by a clinical geneticist at each study site and also independently reviewed by one or more other clinical geneticists. For the present study, women with estimated dates of delivery from 1 October 1997 through 31 December 2005 who had deliveries with an NTD, oral cleft, limb deficiency, or congenital heart defect were included. Control infants (live births without any major congenital malformations and whose mothers resided in the study area at delivery) were randomly selected from live birth certificates in Iowa and from hospital delivery records in Texas (proportional to the number of births in each hospital in the geographic regions of study). These comparison infants served as controls for all case groups. The institutional review boards (IRBs) at each NBDPS site and the Centers for Disease Control and Prevention approved the NBDPS study protocol, and the IRBs at the University of Iowa, Texas A&M University, and Texas Department of State Health Services also approved the present project.

Data collection. After providing informed consent, case and control mothers were interviewed in English or Spanish by female interviewers using a computer-assisted telephone interview (Yoon et al. 2001). Mothers were questioned about their use of prescription and over-the-counter medications during the index pregnancy, vitamin supplements taken, diet, beverage consumption, work characteristics, and water use. Residential histories were collected for the period 3 months before conception through pregnancy, including the month/year that the mother started and stopped living in each location. A water module was added to the NBDPS interview in 1999, and questions about personal water use were asked of all mothers beginning in 2000, including sources (private well, unfiltered tap, filtered tap, bottled, other); presence and type of filtration; quantity of water drank at home and at work or school on an average day; and any changes including month/year of change in source or quantity of drinking water consumed. Only women who completed the water module were included in the water nitrate analyses, and their estimated dates of delivery ranged from 1998 through 2005.

Assessment of nitrate in municipal tap water. After maternal residential addresses were geocoded, we used an approach developed by the Water Subcommittee of the NBDPS Environmental/Occupational Work Group to link geocoded addresses to municipal water supplies. This included *a*) linking geocoded maternal addresses to public water utilities that had digitized boundary maps available; *b*) if utility boundary maps were not available, linking maternal addresses to water utilities using census place names (census place city boundaries were identified through linkage of municipal water system names to census place names); and *c*) contacting water utilities to confirm whether they provided water for maternal addresses that could not be matched using the first two approaches.

Under the federal Safe Drinking Water Act (SDWA 1974), public water supplies using groundwater are required to sample annually for nitrate, and surface water utilities are initially required to sample quarterly, then annually. In Iowa, SDWA and other public water supply data are maintained by the Center for Health Effects of Environmental Contamination at the University of Iowa (Iowa City, IA, USA). In Texas, routine monitoring data for drinking-water nitrate were obtained from the Texas Commission on Environmental Quality (Austin, TX, USA); public water suppliers are required by Texas law to report water monitoring results to this state agency.

Water samples taken during the actual dates of residence during 1 month before conception (B1) through the end of the third month of pregnancy (P3) were given the highest priority for inclusion and averaged if more than one sample result was available. If sample results for this period (B1P3) were unavailable, results were selected, in order of priority, as *a*) any results of samples up to 12 months before the start of B1 through 12 months after the end of P3, or *b*) results of samples taken closest to the earliest date of B1 and results closest to the last day of P3. Using the same approach, we also obtained water nitrate estimates for 1 month before through 1 month postconception (B1P1) for analyses involving NTDs to better reflect the critical exposure window for these defects.

Assessment of nitrate in bottled water. Analyses of maternal responses to water use indicated that 341 Iowa and 1,069 Texas mothers (with deliveries having the specified birth defects in this project or control births) reported using bottled water exclusively near the beginning of pregnancy, and a large number of participants in both states reported drinking bottled water in addition to tap water. To estimate exposure to nitrate in bottled water, we conducted a bottled water survey in Iowa and Texas from January through May 2010 in which representative samples of bottled water were collected in major metropolitan and municipal areas that women resided in or nearby. In addition, dispensed waters sold by the gallon were obtained in Iowa stores and in Texas stores, water mills, and kiosks. All samples were tested for nitrate at the State Hygienic Laboratory at The University of Iowa with U.S. Environmental Protection Agency Method 300.0 (Pfaff 1993). Median values were assigned for each city based on multiple bottled water samples collected and respective test results. These median levels were assigned to residents of that city; for cities where bottled water was not collected, the median level of the closest city where water was collected was used.

Estimation of nitrate in private well water. Residential addresses of Texas mothers reporting drinking water from private wells were linked to the relevant aquifers. Nearly one-half of the reported private wells were located in the Ogallala Aquifer, with the other reported wells mainly located in five additional major Texas aquifers, including the Edwards-Trinity, Trinity, Carrizo-Wilcox, Gulf Coast, and Hueco-Mesilla Bolson aquifers. We modeled groundwater flow and nitrate transport in these major aquifers and estimated the temporal dynamics of nitrate level at private well locations during the index pregnancies. The modeling effort for individual wells (based on the hydrogeology and the spatial scale of the aquifers) was done separately using two different models: *a*) MODFLOW-MT3DMS (McDonald and Harbaugh 1988; Zheng and Wang 1988) and *b*) HYDRUS-PHRREQC (HP1) model (Jacques and Šimůnek 2005). The wells in the Ogallala Aquifer were modeled using the MODFLOW-MT3DMS because this aquifer encompassed nearly one-half of the private well users, and spanned a large area, which required large scale modeling. Wells in other aquifers were modeled using the HP1 model because the private well users in these aquifers were either localized (e.g., Hueco-Mesilla

Bolson, Trinity) or located on a scattered aquifer such as the Seymour Aquifer. The Seymour Aquifer is known as a scattered aquifer because it is in separate areas of erosional remnants of the Seymour Formation of Pleistocene age in parts of 20 Texas counties. Each model was run for 4–9 years depending on the case or control dates of B1P3 and was validated using available historical sampling data from wells in the respective areas. Daily nitrate concentrations obtained from the models were averaged for the respective exposure windows of each Texas mother who reported drinking private well water.

Estimation of daily intake of nitrate from drinking water. Nitrate levels in drinking water varied considerably by source. Median levels for bottled water, public water supplies, and private wells (estimated through modeling) were respectively 0.33, 5.0, and 17.6 mg/L as nitrate. For mothers living in more than one residence during the two exposure windows of interest, average nitrate levels from reported drinking-water sources at each residence were obtained and weighted by number of months lived at each address. We developed a program for estimating daily intake of nitrate from drinking water during the exposure windows, using STATA® (Release 11; StataCorp, College Station, TX) that took into account the reported sources of drinking water with respective nitrate concentrations and quantity consumed at home and work, use of water filters and type, consumption of tea and coffee, and any reported changes in water consumption or source during 1 month preconception through the first trimester. We developed two environmental exposure metrics including daily intake of nitrate from drinking water (milligrams) during B1P1 that was used in all analyses of NTDs, and water nitrate intake during B1P3 for analyses of heart, limb, and oral cleft defects. Nitrate intake from drinking-water sources was categorized into tertiles for each exposure period based on the control mothers' distributions. We were able to estimate daily intake of nitrate from these sources for 87% of case mothers and 88% of control mothers who completed the water module of the NBDPS interview. Reasons for nonlinkage included nitrate in drinking water of private well users not estimated (9% of the Iowa cases/controls) and insufficient/missing addresses or an address outside the United States during the exposure windows of interest.

Classification of nitrosatable drugs. In the NBDPS interview, mothers were questioned about prescription and nonprescription drugs used (including start and stop dates) for specific illnesses and disorders and were also prompted for specific products. Methods used to classify drugs with respect to nitrosatability have been described in detail in previous publications (Brender et al. 2011a, 2011b). Briefly, the active ingredients of reported medications used were identified, cross-referenced against previously compiled lists of nitrosatable medicinal compounds (Brambilla and Martelli 2007; McKean-Cowdin et al. 2003), and categorized based on the presence of amine (secondary or tertiary) and amide functional groups in their molecular structures. We focused on exposure to any nitrosatable drugs during the month before and after conception in relation to NTDs and during the first trimester for the other birth defects. Approximately 24% of the control mothers in the NBDPS took one or more nitrosatable drugs during the first trimester (Brender et al. 2011a). The most commonly taken nitrosatable drugs included certain types of antiemetic medications, decongestants, antihistamines, and anti-infectives that contained secondary amines, tertiary amines, or amides as part of their molecular structures.

Estimation of total nitrite exposure. To estimate daily intake of nitrate and nitrite from dietary sources, we used a combination of sources, including *a*) the 58-item food frequency questionnaire (FFQ) that elicited information about dietary intake during the year before pregnancy and that was adapted from the short Willett FFQ (Willett et al. 1985), and *b*) additional detailed questions about consumption of breakfast cereals from 3 months before to the end of pregnancy. Procedures were described in detail in a previous publication (Griesenbeck et al. 2009b); briefly, *a*) weighted means for nitrates and nitrites (milligrams/100 g) were calculated for each food item based on the relevant literature; *b*) the respective means were multiplied by the serving size (grams) assigned to each food; *c*) nitrates and nitrites in each serving size were multiplied by the number of servings by month; and *d*) nitrates and nitrites across all food items were summed and then divided by 30 to obtain daily intake of dietary nitrate and nitrite (milligrams). Using the formula suggested by Choi (1985), we estimated total nitrite exposure from food and water as the sum of dietary nitrite intake and 5% of estimated nitrate intake from diet and water sources. Total nitrite intake was further categorized into tertiles based on the control mothers' distributions. In this population, median contributions of food and drinking-water nitrate to daily intake of nitrate were 94% and 6%, respectively. Approximately 97% and 3% of total nitrite exposure was from food and drinking water, respectively.

Statistical analysis. To account for correlation of nitrate intake by geographic location, mixed-effects (random-effects) models for logistic regression were used with mothers nested within cities of residence (nearest city, if rural address) (Goldstein 2010). Mothers in the lowest tertile of nitrate intake from drinking water during B1P1 for analyses of NTDs and B1P3 for the other birth defects served as the referent categories. For limb deficiencies, oral cleft defects, and congenital heart defects, we restricted analyses to isolated birth defects. Covariables were selected *a priori* and based on the literature, and only those cases and controls for which complete data on all pertinent covariables in each analysis were included. For NTDs, covariables included maternal race/ethnicity, education, study site, and any folic acid supplementation during B1P1. In addition to maternal race/ethnicity, education, and study site, covariables for analyses of oral clefts also included maternal age, any smoking 1 month before conception through the first trimester, and folic acid supplementation during the first trimester. Covariables for analyses of limb deficiencies included maternal race/ethnicity, education, age, study site, and multivitamin supplementation during the first trimester. For heart defects, maternal race/ethnicity, education, smoking, study site, and multivitamin supplementation during the first trimester were incorporated into the logistic models. The associations between tertile of prenatal nitrate intake from drinking water and birth defects in offspring were assessed for linear trend by treating the three levels of nitrate intake as a continuous variable in the logistic model and testing the significance of linearity with the z-test in STATA® (equivalent to the Wald chi-square test).

As part of a sensitivity analysis, we repeated the above analyses for the subset of participants who reported drinking only municipal tap water during the period around conception and the first trimester. We also examined the association between measured nitrate (milligrams per liter) in municipal water and selected birth defects for which we used the cut points reported by Croen et al. (2001) and Dorsch et al. (1984) (< 5 mg/L, 5–15 mg/L, and > 15 mg/L).

Nitrosatable drug exposure (any vs. none) during B1P1 and the first trimester was stratified by tertiles of nitrate intake from drinking water and by total nitrite from food and water sources. In analyses involving total nitrite, we excluded women with daily caloric intakes of < 500 or > 5,000 kcal, and also adjusted the odds ratios (ORs) for total energy intake (kilocalories per day). We tested for departure from additivity (biologic interaction) in these associations using a statistical program developed by Andersson et al. (2005) that was adapted for STATA®. This program calculated the relative excess risk due to interaction (RERI) and attributable proportion due to interaction (AP) (and their respective 95% CIs). Departures from additive effects were considered present if the confidence intervals of either measure excluded zero. To

assess multiplicative interaction, the product terms of any nitrosatable drug use with water nitrate and total nitrite intake were included in the logistic models, and multiplicative interaction was considered present if the p-value associated with the interaction term was < 0.05.

Results

Maternal interviews for offspring with estimated dates of delivery from 1997 through 2005 numbered 317 with NTDs, 177 with limb deficiencies, 654 with oral cleft defects, 2,011 with congenital heart defects, and 1,551 unaffected live births. Maternal participation rates for births with NTDs, limb deficiencies, oral clefts, congenital heart defects, and controls were, respectively, 66%, 72%, 74%, 62%, and 64%. Median time from estimated date of delivery to maternal interview ranged from 9 months for control mothers to 13 months for women with NTD-affected pregnancies. Table 1 shows the characteristics of the case and control mothers. Among participants who completed the water module questions, the proportions of control mothers and mothers of babies with heart defects were similar with respect to usual home sources of drinking water. In contrast, mothers of babies with NTDs, limb deficiencies, and oral clefts were more likely than control mothers to report drinking municipal tap water.

Table 1. Selected characteristics of Iowa and Texas case mothers and control mothers in the National Birth Defects Prevention Study, 1997–2005 [*n* (%)].

Characteristic	Controls (*n* = 1,551)	Cases			
		NTDs (*n* = 317)	Limb deficiencies (*n* = 177)	Oral cleft defects (*n* = 654)	Heart defects (*n* = 2,011)
Race/ethnicity					
Non-Hispanic white	901 (58.2)	165 (52.2)	93 (52.5)	393 (60.2)	1,033 (51.5)
Non-Hispanic black	27 (1.7)	9 (2.9)	5 (2.8)	12 (1.8)	60 (3.0)
Hispanic	555 (35.9)	132 (41.8)	67 (37.9)	218 (33.4)	833 (41.5)
Asian/Pacific Islander	21 (1.4)	1 (0.3)	2 (1.1)	12 (1.8)	19 (0.9)
All others	44 (2.8)	9 (2.8)	10 (5.7)	18 (2.8)	62 (3.1)
Missing	3	1	0	1	4
Education (years)					
< 12	286 (18.8)	64 (20.3)	27 (15.6)	138 (21.3)	408 (20.6)
12	443 (29.2)	87 (27.6)	57 (33.0)	192 (29.7)	574 (29.0)
13–15	436 (28.7)	105 (33.3)	57 (32.9)	186 (28.7)	606 (30.6)
> 15	353 (23.3)	59 (18.7)	32 (18.5)	131 (20.2)	390 (19.7)
Missing	33	2	4	7	33
Age at delivery (years)					
< 18	95 (6.1)	11 (3.5)	7 (4.0)	29 (4.4)	98 (4.9)
18–19	130 (8.4)	29 (9.1)	19 (10.7)	61 (9.3)	159 (7.9)
20–24	380 (24.5)	79 (24.9)	48 (27.1)	208 (31.8)	535 (26.6)
25–29	453 (29.2)	100 (31.5)	55 (31.1)	170 (26.0)	551 (27.4)
30–34	344 (22.2)	68 (21.5)	35 (19.8)	114 (17.4)	446 (22.2)
> 34	149 (9.6)	30 (9.5)	13 (7.3)	72 (11.0)	222 (11.0)
Study center					
Iowa	759 (48.9)	146 (46.1)	80 (45.2)	306 (46.8)	769 (38.2)
Texas	792 (51.1)	171 (53.9)	97 (54.8)	348 (53.2)	1,242 (61.8)
Smoking[a]					
No	1,199 (78.7)	259 (82.2)	132 (76.3)	471 (72.6)	1,548 (78.1)
Yes	324 (21.3)	56 (17.8)	41 (23.7)	178 (27.4)	433 (21.9)
Missing/out of range	28	2	4	5	30
Nitrosatable drug exposure[b]					
No	1,166 (77.6)	216 (70.8)	120 (71.9)	482 (76.4)	1,475 (76.2)
Yes	336 (22.4)	89 (29.2)	47 (28.1)	149 (23.6)	460 (23.8)
Total daily nitrite intake[c]					
≤ 4.78 mg/day	726 (66.1)	145 (62.5)	72 (55.8)	334 (68.2)	1,004 (63.5)
> 4.78 mg/day	372 (33.9)	87 (37.5)	57 (44.2)	156 (31.8)	578 (36.5)
Multivitamin use[d]					
No	206 (13.6)	33 (10.6)	22 (12.9)	100 (15.7)	304 (15.5)
Yes	1,308 (86.4)	277 (89.4)	148 (87.1)	537 (84.3)	1,658 (84.5)
Missing	37	7	7	17	49
Usual home source of drinking water[e]					
Tap water, municipal	738 (58.3)	173 (64.3)	96 (64.0)	354 (61.7)	1,011 (56.3)
Tap water, private well	72 (5.7)	19 (7.1)	14 (9.3)	42 (7.3)	99 (5.5)
Bottled water exclusively	455 (36.0)	77 (28.6)	40 (26.7)	178 (31.0)	685 (38.2)
Not available[f]	286	48	27	80	216

[a]Any smoking between date of conception and end of first trimester. [b]Exposure during the first trimester of pregnancy. [c]Total daily nitrite intake = 5% (drinking water nitrate + dietary nitrate) + dietary nitrite. [d]Use during the first trimester of pregnancy. [e]Reported primary drinking water source at the beginning of pregnancy. [f]Water module questions were added in 1999.

Numbers of births with complete information for maternal daily nitrate intake from water sources and other covariables were 227, 94, 415, 1,046, and 1,105, respectively, for all NTDs, isolated limb deficiencies, oral cleft defects, congenital heart defects, and controls. Adjusting for maternal race/ethnicity, education, study site, and folic acid supplementation, maternal nitrate intake of ≥ 5 mg per day from drinking water was associated with NTD-affected pregnancies [adjusted odds ratio (aOR) 1.43; 95% CI: 1.01, 2.04], although this association appeared to be specific to spina bifida (Table 2). Mothers of babies with spina bifida were 1.4 times more likely (95% CI: 0.86, 2.32) than control mothers to ingest between 0.91 and 4.9 mg nitrate per day and 2 times more likely (95% CI: 1.27, 3.22) to ingest ≥ 5 mg nitrate from drinking water around conception (p for trend = 0.003). During B1P3, mothers of babies with isolated limb deficiencies, cleft palate, and cleft lip without cleft palate were, respectively, 1.8 (95% CI: 1.05, 3.08), 1.9 (95% CI: 1.17, 3.09), and 1.8 times (95% CI: 1.08, 3.07) more likely than control mothers to ingest > 5.41 mg per day of nitrate from drinking water. We noted significant linear trends ($p < 0.05$) in the associations between maternal water nitrate and these defects in offspring (Table 2). In contrast, we saw minimal or no associations between maternal nitrate intake from drinking water and congenital heart defects in offspring. Restriction of analyses to women who reported drinking only tap water from municipal water supplies did not materially change the aORs associated with the highest tertile of water intake for spina bifida (aOR = 1.93; 95% CI: 0.99, 3.76), cleft lip without cleft palate (aOR = 1.96; 95% CI: 0.88, 4.36), or cleft palate (aOR = 1.55; 95% CI: 0.78, 3.10), but the aOR for any limb deficiency increased to 3.19 (95% CI: 1.09, 9.35) (see Supplemental Material, Table S1). A significant linear trend was observed for only cleft lip in relation to measured nitrate in drinking water among offspring of women who reported drinking municipal water (see Supplemental Material, Table S2). An aOR of 2.31 (95% CI: 1.20, 4.47) was noted for this defect among offspring of women who consumed water with nitrate levels > 15 mg/L relative to women who drank water with nitrate levels < 5 mg/L.

No specific patterns of stronger associations between nitrosatable drug exposure (any versus none) and birth defects among women with higher daily intake of nitrate from drinking water were evident when aORs were stratified according to tertile of daily nitrate intake from drinking water (see Supplemental Material, Table S3). For several birth defect groups, the strongest associations with

nitrosatable drug exposure were estimated for women in the lowest tertiles of estimated nitrate intake from drinking water [e.g., aORs = 2.54 (95% CI: 1.20, 5.37) and 2.89 (95% CI: 1.15, 7.25) for NTDs and cleft palate, respectively]. The CIs for the RERI and AP included 0, indicating no significant departures from additivity, and the *p*-values for the interaction terms for water and nitrosatable drug exposure were > 0.05, indicating no significant departures from multiplicative effects.

On the other hand, when estimated nitrate from drinking water and diet were combined with dietary nitrite intake to estimate total nitrite exposure from these sources, the strongest associations between nitrosatable drug exposure and several birth defects were observed among women with the highest estimated total nitrite exposure (the lower two tertiles of intake combined because of similarity of ORs) (see Supplemental Material, Table S4). Associations between nitrosatable drug exposure and birth defects were stronger in the highest tertile of total nitrite (vs. the lower two tertiles combined) for NTDs (aOR = 1.76; 95% CI: 0.90, 3.43 vs. aOR = 1.41; 95% CI: 0.87, 2.29), cleft lip without cleft palate (aOR = 2.01; 95% CI: 0.90, 4.48 vs. aOR = 0.80; 95% CI: 0.42, 1.52), cleft palate (aOR = 2.51; 95% CI: 1.24, 5.06 vs. aOR = 0.95; 95% CI: 0.55, 1.64), limb deficiencies (aOR = 1.64; 95% CI: 0.80, 3.35 vs. aOR = 1.00; 95% CI: 0.53, 1.89), atrioventricular septal defects (aOR = 5.10; 95% CI: 1.40, 18.6 vs. aOR = 1.93; 95% CI: 0.76, 4.87), and single ventricle (aOR = 3.25; 95% CI: 1.13, 9.31 vs. aOR = 0.74; 95% CI: 0.27, 2.02). Significant departures from additivity were noted for the joint estimated effects of total nitrite intake and nitrosatable drug exposures for cleft lip, cleft palate, limb deficiencies, and single ventricle; multiplicative interaction was also present in this association with cleft palate (see Supplemental Material, Table S4).

Discussion

Results from this large population-based case–control study suggest that prenatal nitrate intake from drinking water is associated with NTDs, oral cleft defects, and limb deficiencies in offspring. Previous publications that have reported significant associations between drinking-water nitrates and birth defects hypothesized that nitrate might act as a teratogen through its contribution to the endogenous formation of *N*-nitroso compounds (Croen et al. 2001; Dorsch et al. 1984). In the present study, however, higher daily intake of nitrate from drinking water did not strengthen associations between nitrosatable drugs and the various birth defects examined. On the other hand, associations between nitrosatable drugs and birth defects were stronger among women in the highest tertile of estimated total nitrite intake, a measure based on intake of dietary nitrite and nitrate from diet and drinking water. In this study, nitrate levels in the drinking water tended to be low, with a median contribution of nitrate per day from this source of 6% in the study population. In a recent review, the World Health Organization (2011) noted that the contribution of drinking water to nitrate intake is usually < 14%.

Previous studies have assigned exposure based on measured nitrate in drinking water instead of estimating daily ingestion. For

Table 2. Maternal daily nitrate intake from drinking water and selected birth defects in offspring.

Birth defect	Daily nitrate intake from water (mg/day)[a]	Cases [*n* (%)]	Controls [*n* (%)]	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)[b]	*p*-Value for linear trend
Any NTD[c]	< 0.91	67 (29.5)	367 (33.3)	1.00	1.00	0.038
	0.91–4.9	65 (28.6)	360 (32.7)	0.99 (0.68, 1.43)	1.00 (0.68, 1.45)	
	≥ 5.0	95 (41.9)	374 (34.0)	1.39 (0.99, 1.96)	1.43 (1.01, 2.04)	
Spina bifida[c]	< 0.91	30 (22.4)	367 (33.3)	1.00	1.00	0.003
	0.91–4.9	42 (31.3)	360 (32.7)	1.43 (0.87, 2.33)	1.41 (0.86, 2.32)	
	≥ 5.0	62 (46.3)	374 (34.0)	2.03 (1.28, 3.21)	2.02 (1.27, 3.22)	
Anencephaly[c]	< 0.91	31 (43.7)	367 (33.3)	1.00	1.00	0.348
	0.91–4.9	17 (23.9)	360 (32.7)	0.56 (0.30, 1.03)	0.58 (0.32, 1.08)	
	≥ 5.0	23 (32.4)	374 (34.0)	0.73 (0.42, 1.27)	0.78 (0.44, 1.37)	
Any limb deficiency[d,e]	< 1.0	23 (24.5)	370 (33.5)	1.00	1.00	0.028
	1.0–5.41	29 (30.9)	367 (33.2)	1.27 (0.72, 2.24)	1.17 (0.66, 2.07)	
	≥ 5.42	42 (44.7)	368 (33.3)	1.84 (1.08, 3.11)	1.79 (1.05, 3.08)	
Any oral cleft defect[e,f]	< 1.0	122 (29.4)	370 (33.5)	1.00	1.00	0.007
	1.0–5.41	120 (28.9)	366 (33.2)	0.99 (0.74, 1.33)	0.98 (0.73, 1.32)	
	≥ 5.42	173 (41.7)	367 (33.3)	1.43 (1.09, 1.88)	1.45 (1.10, 1.92)	
Cleft lip without cleft palate[e,f]	< 1.0	24 (24.0)	370 (33.5)	1.00	1.00	0.019
	1.0–5.41	29 (29.0)	366 (33.2)	1.22 (0.70, 2.14)	1.13 (0.64, 1.99)	
	≥ 5.42	47 (47.0)	367 (33.3)	1.97 (1.18, 3.30)	1.82 (1.08, 3.07)	
Cleft palate[e,f]	< 1.0	29 (25.2)	370 (33.5)	1.00	1.00	0.007
	1.0–5.41	32 (27.8)	366 (33.2)	1.12 (0.66, 1.88)	1.12 (0.66, 1.90)	
	≥ 5.42	54 (47.0)	367 (33.3)	1.88 (1.17, 3.01)	1.90 (1.17, 3.09)	
Conotruncal heart defects[e,g]	< 1.0	58 (35.4)	370 (33.5)	1.00	1.00	0.403
	1.0–5.41	41 (25.0)	367 (33.2)	0.71 (0.47, 1.09)	0.72 (0.47, 1.11)	
	≥ 5.42	65 (39.6)	368 (33.3)	1.13 (0.77, 1.65)	1.18 (0.80, 1.74)	
Right ventricular outflow tract obstruction heart defects[e,g]	< 1.0	36 (30.0)	370 (33.5)	1.00	1.00	0.083
	1.0–5.41	31 (25.8)	367 (33.2)	0.87 (0.53, 1.43)	0.89 (0.54, 1.48)	
	≥ 5.42	53 (44.2)	368 (33.3)	1.48 (0.95, 2.32)	1.47 (0.93, 2.33)	
Left ventricular outflow tract obstruction heart defects[e,g]	< 1.0	44 (28.2)	370 (33.5)	1.00	1.00	0.522
	1.0–5.41	58 (37.2)	367 (33.2)	1.33 (0.88, 2.02)	1.31 (0.86, 2.00)	
	≥ 5.42	54 (34.6)	368 (33.3)	1.23 (0.81, 1.88)	1.16 (0.75, 1.78)	
Septal heart defects[e,g]	< 1.0	203 (35.8)	370 (33.5)	1.00	1.00	0.853
	1.0–5.41	210 (37.0)	367 (33.2)	1.04 (0.82, 1.33)	0.92 (0.69, 1.22)	
	≥ 5.42	154 (27.2)	368 (33.3)	0.76 (0.59, 0.98)	0.98 (0.71, 1.34)	

[a]For NTDs, water nitrate intake 1 month preconception to 1 month postconception was estimated. For limb, oral cleft, and congenital heart defects, water nitrate intake 1 month preconception through the first trimester was estimated. [b]Crude and adjusted ORs include only cases and controls with complete information for covariates. [c]Adjusted for maternal race/ethnicity, education, study center, and folic acid supplementation. [d]Adjusted for maternal race/ethnicity, education, age, multivitamin supplementation, and study center. [e]Isolated defect. [f]Adjusted for maternal race/ethnicity, education, age, folic acid supplementation, smoking, and study center. [g]Adjusted for maternal race/ethnicity, education, multivitamin supplementation, smoking, and study center.

women who drank water from groundwater sources, measured levels of total nitrate as low as 5–15 mg/L have been significantly associated with birth defects (Dorsch et al. 1984) including anencephaly (Croen et al. 2001). Although we noted significant ORs in the relation between measured nitrate levels at ≥ 5 mg/L and several birth defects, we saw a significant linear trend only for cleft lip without cleft palate in our study population. Other studies have reported elevated, but not statistically significant, ORs for central nervous system defects (Arbuckle et al. 1988) and NTDs (Brender et al. 2004) for measured nitrate levels respectively at 26 mg/L (relative to 0.1 mg/L) and ≥ 3.5 mg/L (relative to < 3.5 mg/L). Positive associations were restricted to groundwater drinkers in several of these studies, and the authors suggested that other agents correlated with nitrate in groundwater might be responsible for the associations noted (Croen et al. 2001; Dorsch et al. 1984).

In contrast to findings from a study of nitrosatable drugs and NTDs in Mexican Americans (Brender et al. 2004), in the present study, higher intake of nitrate from drinking water did not strengthen the association between nitrosatable drug use and NTDs, nor was this pattern noted for the other birth defects examined. In two earlier studies (Brender et al. 2011b, 2012) of NBDPS, which included participants from all 10 sites, associations between prenatal nitrosatable drug exposure and several birth defects, including NTDs, cleft palate, conotruncal heart defects, atrioventricular septal defects, and single ventricle defects were stronger among women with the highest estimated intake of nitrite from dietary sources than in women with lower estimated dietary intakes. Similarly in the present study, associations between nitrosatable drug use and several of the same defects were stronger with higher estimated total nitrite intake, which included intake from drinking-water as well as dietary sources. Water nitrate contributed, on average (median), approximately 3% of total daily nitrite in the present study population. Therefore, water nitrate might be associated with birth defects for reasons other than its contribution to the endogenous formation of *N*-nitroso compounds. Nitrate has been found to occur with other contaminants in drinking water, especially in conjunction with pesticides, arsenic and other trace metals, and water disinfection by-products (Toccalino et al. 2012).

In the present study, we focused on nitrate contamination in drinking-water sources without examining the presence of other water contaminants. Another study limitation was the potential for measurement errors in nitrate content of drinking-water sources and daily consumption of water nitrate. Estimates of nitrate in sources from public water systems were based on data from routine monitoring in which we linked addresses to the most time-relevant sample results available. Our approach for assigning nitrate levels to municipal drinking-water sources was not validated, although we developed and followed a detailed set of standard operating procedures for such assignment (Griesenbeck et al. 2009a). The high percentage of bottled water users presented a challenge in exposure assessment because participants were not specifically questioned about types of bottled water consumed. Therefore, nitrate content from this source was estimated from nitrate measured in bottled water samples from neighborhood grocery store surveys. However, associations noted between nitrate intake from drinking-water nitrate and birth defects changed very little when the analysis was restricted to women who reported drinking tap water from municipal water supplies only. We estimated nitrate content in private wells through complex models that took into account local conditions; however, this modeling effort was restricted to private well users in Texas. Although it is possible that some participants might have not accurately recalled the types and amounts of water that they consumed during early pregnancy, Shimokura et al. (1998) found good agreement (Pearson's $r = 0.78$) between a questionnaire on past use and a 3-day water diary for drinking-water intake in a sample of pregnant women. Given that all exposure assessments in this study of drinking-water nitrate were completed with the study teams blinded to case–control status, misclassification of daily nitrate intake from drinking water would most likely be nondifferential and have led to an underestimation of the true ORs. Measurement error might have also occurred with the estimation of dietary intake of nitrate and nitrite, and this limitation is discussed in detail in previous publications (Brender et al. 2011a, 2012) along with the potential for bias in participant recall of drugs taken during early pregnancy.

Conclusion

In this large, population-based case–control study, women who had babies with NTDs, limb deficiencies, and oral cleft defects were significantly more likely than control mothers to ingest ≥ 5 mg of nitrate per day from drinking water. However, study findings suggest that endogenous formation of *N*-nitroso compounds might not be the underlying mechanism for potential teratogenesis with this water contaminant, because higher intake of nitrate from drinking water did not strengthen associations between prenatal nitrosatable drug exposure and birth defects in offspring. Given that nitrate contamination occurs in conjunction with other water contaminants, future studies of birth defects might focus on prenatal exposure to mixtures of contaminants in drinking water.

References

Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlborn A. 2005. Calculating measures of biological interaction. Eur J Epidemiol 20(7):575–579.

Arbuckle TE, Sherman GJ, Corey PN, Walters D, Lo B. 1988. Water nitrates and CNS birth defects: a population-based case-control study. Arch Environ Health 43(2):162–167.

Brambilla G, Martelli A. 2007. Genotoxic and carcinogenic risk to humans of drug-nitrite interaction products. Mutat Res 635(1):17–52.

Brender JD, Kelley KE, Werler MM, Langlois PH, Suarez L, Canfield MA. 2011a. Prevalence and patterns of nitrosatable drug use among U.S. women during early pregnancy. Birth Defects Res A Clin Mol Teratol 91(4):258–264.

Brender JD, Olive JM, Felkner M, Suarez L, Marckwardt W, Hendricks KA. 2004. Dietary nitrites and nitrates, nitrosatable drugs, and neural tube defects. Epidemiology 15(3):330–336.

Brender JD, Werler MM, Kelley KE, Vuong AM, Shinde MU, Zheng Q, et al. 2011b. Nitrosatable drug exposure during early pregnancy and neural tube defects in offspring: National Birth Defects Prevention Study. Am J Epidemiol 174(11):1286–1295.

Brender JD, Werler MM, Shinde MU, Vuong AM, Kelley KE, Huber JC Jr, et al. 2012. Nitrosatable drug exposure during the first trimester of pregnancy and selected congenital malformations. Birth Defects Res A Clin Mol Teratol 94(9):701–713.

Cedergren MI, Selbing AJ, Lofman O, Kallen BA. 2002. Chlorination byproducts and nitrate in drinking water and risk for congenital cardiac defects. Environ Res 89(2):124–130.

Choi BC. 1985. *N*-nitroso compounds and human cancer. A molecular epidemiologic approach. Am J Epidemiol 121(5):737–743.

Croen LA, Todoroff K, Shaw GM. 2001. Maternal exposure to nitrate from drinking water and diet and risk for neural tube defects. Am J Epidemiol 153(4):325–331.

Dorsch MM, Scragg RK, McMichael AJ, Baghurst PA, Dyer KF. 1984. Congenital malformations and maternal drinking water supply in rural South Australia: a case-control study. Am J Epidemiol 119(4):473–486.

Gillatt PN, Palmer RC, Smith PL, Walters CL, Reed PI. 1985. Susceptibilities of drugs to nitrosation under simulated gastric conditions. Food Chem Toxicol 23(9):849–855.

Goldstein H. 2010. Multilevel Models, 4th ed. New York:Wiley.

Griesenbeck JS, Brender JD, Weyer PJ, Horel SA. 2009a. Standard Operating Procedures for Water and Addresses. Basic Guidelines for Selecting Maternal Addresses and Associated Relevant Water Nitrate Values. Available: http://www.cheec.uiowa.edu/research/SOP%20for%20Assignment%20of%20Drinking%20Water%20Nitrate%20for%20Project.pdf [accessed 31 May 2013].

Griesenbeck JS, Steck MD, Huber JC Jr, Sharkey JR, Rene AA, Brender JD. 2009b. Development of estimates of dietary nitrates, nitrites, and nitrosamines for use with the Short Willett Food Frequency Questionnaire. Nutr J 8:16; doi:10.1186/1475-2891-8-16.

Jacques D, Šimůnek J. 2005. User Manual of the Multicomponent Variably-Saturated Flow and Transport Model HP1, Description, Verification and Examples, Version 1.0. Available: http://www.pc-progress.com/Documents/hp1.pdf [accessed 29 July 2013].

McDonald MG, Harbaugh AW. 1988. A Modular Three-Dimensional Finite-Difference Groundwater Flow Model. Reston, VA:U.S. Geological Survey.

McKean-Cowdin R, Pogoda JM, Lijinsky W, Holly EA, Mueller BA, Preston-Martin S. 2003. Maternal prenatal exposure to nitrosatable drugs and childhood brain tumours. Int J Epidemiol 32(2):211–217.

Mensinga TT, Speijers GJ, Meulenbelt J. 2003. Health implications of exposure to environmental nitrogenous compounds. Toxicol Rev 22(1):41–51.

Nagao T, Morita Y, Ishizuka Y, Wada A, Mizutani M. 1991. Induction of fetal malformations after treatment of mouse embryos with methylnitrosourea at the preimplantation stages. Teratog Carcinog Mutagen 11(1):1–10.

National Primary Drinking Water Regulations. 2010. Maximum Contaminant Levels. 40CFR141. Available: http://www.gpo.gov/fdsys/pkg/CFR-2010-title40-vol22/pdf/CFR-2010-title40-vol22-part141-subpartB.pdf [accessed 29 July 2013].

Pfaff JD. 1993. Method 300.0. Determination of Inorganic Anions by Ion Chromatography. Available: http://water.epa.gov/scitech/methods/cwa/bioindicators/upload/2007_07_10_methods_method_300_0.pdf [accessed 31 July 2013].

Platzek T, Bochert G, Rahm U. 1983. Embryotoxicity induced by alkylating agents. Teratogenicity of acetoxymethyl-methylnitrosamine: dose-response relationship, application route dependency and phase specificity. Arch Toxicol 52:45–69.

SDWA (Safe Drinking Water Act). 1974. Safe Drinking Water Act. Public Law 93-523.

Shimokura, GH, Savitz DA, Symanski E. 1998. Assessment of water use for estimating exposure to tap water contaminants. Environ Health Perspect 106:55–59.

Spalding RF, Exner ME. 1993. Occurrence of nitrate in groundwater—a review. J Environ Qual 22(3):392–402.

Spiegelhalder B, Eisenbrand G, Preussmann R. 1976. Influence of dietary nitrate on nitrite content of human saliva: possible relevance to *in vivo* formation of *N*-nitroso compounds. Food Cosmet Toxicol 14(6):545–548.

Teramoto S, Saito R, Shirasu Y. 1980. Teratogenic effects of combined administration of ethylenethiourea and nitrite in mice. Teratology 21(1):71–78.

Toccalino PL, Normal JE, Scott JC. 2012. Chemical mixtures in untreated water from public-supply wells in the U.S.—occurrence, composition, and potential toxicity. Sci Total Environ 431:262–270.

Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. 1985. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 122(1):51–65.

World Health Organization. 2011. Nitrate and Nitrite in Drinking-water. WHO/SDE/WSH/07.01/16/Rev/1. Geneva:World Health Organization. Available: http://www.who.int/water_sanitation_health/dwq/chemicals/nitratenitrite2ndadd.pdf [accessed 9 August 2013].

Yoon PW, Rasmussen SA, Lynberg MC, Moore CA, Anderka M, Carmichael SL, et al. 2001. The National Birth Defects Prevention Study. Public Health Rep 116(suppl1):32–40.

Zheng C, Wang PP. 1988. MT3DMS Documentation and User's Guide. Tuscaloosa, AL:University of Alabama.

International Journal of
Environmental Research and Public Health

MDPI

Review

Drinking Water Nitrate and Human Health: An Updated Review

Mary H. Ward [1,*], Rena R. Jones [1], Jean D. Brender [2], Theo M. de Kok [3], Peter J. Weyer [4], Bernard T. Nolan [5], Cristina M. Villanueva [6,7,8,9] and Simone G. van Breda [3]

1 Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr. Room 6E138, Rockville, MD 20850, USA; rena.jones@nih.gov
2 Department of Epidemiology and Biostatistics, Texas A&M University, School of Public Health, College Station, TX 77843, USA; jdbrender@sph.tamhsc.edu
3 Department of Toxicogenomics, GROW-school for Oncology and Developmental Biology, Maastricht University Medical Center, P.O Box 616, 6200 MD Maastricht, The Netherlands; t.dekok@maastrichtuniversity.nl (T.M.d.K.); s.vanbreda@maastrichtuniversity.nl (S.G.v.B.)
4 The Center for Health Effects of Environmental Contamination, The University of Iowa, 455 Van Allen Hall, Iowa City, IA 52242, USA; peter-weyer@uiowa.edu
5 U.S. Geological Survey, Water Mission Area, National Water Quality Program, 12201 Sunrise Valley Drive, Reston, VA 20192, USA; btnolan@usgs.gov
6 ISGlobal, 08003 Barcelona, Spain; cvillanueva@isiglobal.org
7 IMIM (Hospital del Mar Medical Research Institute), 08003 Barcelona, Spain
8 Department of Experimental and Health Sciences, Universitat Pompeu Fabra (UPF), 08003 Barcelona, Spain
9 CIBER Epidemiología y Salud Pública (CIBERESP), 28029 Madrid, Spain
* Correspondence: wardm@mail.nih.gov

Received: 17 May 2018; Accepted: 14 July 2018; Published: 23 July 2018

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].

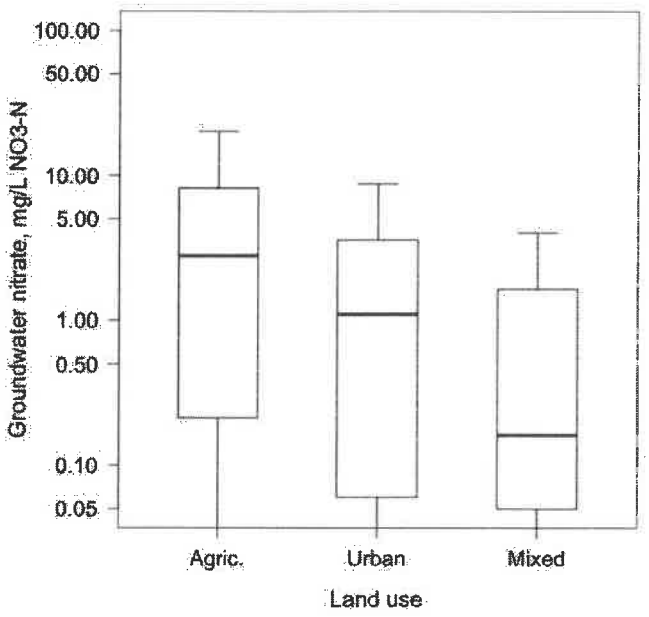


Figure 1. Boxplots of nitrate concentrations in shallow groundwater beneath agricultural and urban land uses, and at depths of private and public drinking water supplies beneath mixed land use. The number of sampled wells were 1573 (agricultural land), 1054 (urban), and 3417 (mixed). The agricultural 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 $\leq$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) ≥5.42 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 $\geq$9.25 mg/L NO_3 ($\geq$2.1 as NO_3-N) and $\geq$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 THM 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 [138]	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 [136]	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.

Acknowledgments: This work was partly supported by the Intramural Research Program of the National Cancer Institute, Division of Cancer Epidemiology and Genetics, Occupational and Environmental Epidemiology Branch. Two authors (TMdK, SvB) acknowledge financial support from the European Commission in the context of the integrated project PHYTOME financed under the Seventh Framework Programme for Research and Technology Development of the European Commission (EU-FP7 grant agreement no. 315683), investigating the possible replacement of nitrite in meat products by natural compounds. CMV notes that ISGlobal is a member of the CERCA Programme, Generalitat de Catalunya.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Davidson, E.A.; David, M.B.; Galloway, J.N.; Goodale, C.L.; Haeuber, R.; Harrison, J.A.; Howarth, R.W.; Jaynes, D.B.; Lowrance, R.R.; Nolan, B.T.; et al. Excess nitrogen in the U.S. environment: Trends, risks, and solutions. In *Issues in Ecology*; Ecological Society of America: Washington, DC, USA, 2012.
2. Vitousek, P.M.; Aber, J.D.; Howarth, R.W.; Likens, G.E.; Matson, P.A.; Schindler, D.W.; Schlesinger, W.H.; Tilman, D. Human alteration of the global nitrogen cycle: Sources and consequences. *Ecol. Appl.* **1997**, *7*, 737–750. [CrossRef]
3. Howarth, R.W. Coastal nitrogen pollution: A review of sources and trends globally and regionally. *Harmful Algae* **2008**, *8*, 14–20. [CrossRef]
4. USEPA. Regulated Drinking Water Contaminants: Inorganic Chemicals. Available online: https://www.epa.gov/ground-water-and-drinking-water/table-regulated-drinking-water-contaminants (accessed on 23 September 2017).
5. International Agency for Research on Cancer (IARC). *IARC Monographs on the Evaluation of Carcionogenic Risks to Humans: Ingested Nitrate and Nitrite and Cyanobacterial Peptide Toxins*; IARC: Lyon, France, 2010.
6. National Research Council (NRC). *The Health Effects of Nitrate, Nitrite, and N-Nitroso Compounds*; NRC: Washington, DC, USA, 1981.
7. Mirvish, S.S. Role of N-nitroso compounds (NOC) and N-nitrosation in etiology of gastric, esophageal, nasopharyngeal and bladder cancer and contribution to cancer of known exposures to NOC. *Cancer Lett.* **1995**, *93*, 17–48. [CrossRef]

8. Ward, M.H.; deKok, T.M.; Levallois, P.; Brender, J.; Gulis, G.; Nolan, B.T.; VanDerslice, J. Workgroup report: Drinking-water nitrate and health-recent findings and research needs. *Environ. Health Perspect.* **2005**, *113*, 1607–1614. [CrossRef] [PubMed]
9. Maupin, M.A.; Kenny, J.F.; Hutson, S.S.; Lovelace, J.K.; Barber, N.L.; Linsey, K.S. *Estimated Use of Water in the United States in 2010*; US Geological Survey: Reston, VA, USA, 2014; p. 56.
10. U.S. Geological Survey. USGS Water Data for the Nation. Available online: https://waterdata.usgs.gov/nwis (accessed on 1 January 2018).
11. Dubrovsky, N.M.; Burow, K.R.; Clark, G.M.; Gronberg, J.M.; Hamilton, P.A.; Hitt, K.J.; Mueller, D.K.; Munn, M.D.; Nolan, B.T.; Puckett, L.J.; et al. *The Quality of Our Nation's Waters—Nutrients in the Nation's Streams and Groundwater, 1992–2004*; U.S. Geological Survey: Reston, VA, USA, 2010; p. 174.
12. Lindsey, B.D.; Rupert, M.G. *Methods for Evaluating Temporal Groundwater Quality Data and Results of Decadal-Scale Changes in Chloride, Dissolved Solids, and Nitrate Concentrations in Groundwater in the United States, 1988–2010*; U.S. Geological Survey Scientific Investigations Report: 2012–5049; U.S. Geological Survey: Reston, VA, USA, 2012; p. 46.
13. Pennino, M.J.; Compton, J.E.; Leibowitz, S.G. Trends in Drinking Water Nitrate Violations across the United States. *Environ. Sci. Technol.* **2017**, *51*, 13450–13460. [CrossRef] [PubMed]
14. Van Grinsven, H.J.M.; Tiktak, A.; Rougoor, C.W. Evaluation of the Dutch implementation of the nitrates directive, the water framework directive and the national emission ceilings directive. *NJAS-Wagening. J. Life Sci.* **2016**, *78*, 69–84. [CrossRef]
15. Vock, D.C. Iowa Farmers Won a Water Pollution Lawsuit, But at What Cost? Available online: http://www.governing.com/topics/transportation-infrastructure/gov-des-moines-water-utility-lawsuit-farmers.html (accessed on 10 February 2018).
16. Des Moines Water Works. On Earth Day, Des Moines Water Works Reflects on Resources Spent to Manage Agrotoxins in Source Waters. Available online: http://www.dmww.com/about-us/news-releases/on-earth-day-des-moines-water-works-reflects-on-resources-spent-to-manage-agrotoxins-in-source-water.aspx (accessed on 10 February 2018).
17. European Commission. The Nitrates Directive. Available online: http://ec.europa.eu/environment/water/water-nitrates/index_en.html (accessed on 10 May 2018).
18. European Union (EU). *Council Directive 91/676/EEC of 12 December 1991 Concerning the Protection of Waters against Pollution Caused by Nitrates from Agricultural Sources*; European Union (EU): Brussels, Belgium, 1991.
19. Hansen, B.; Thorling, L.; Dalgaard, T.; Erlandsen, M. Trend Reversal of Nitrate in Danish Groundwater—A Reflection of Agricultural Practices and Nitrogen Surpluses since 1950. *Environ. Sci. Technol.* **2011**, *45*, 228–234. [CrossRef] [PubMed]
20. European Environment Agency (EEA). Groundwater Nitrate. Available online: https://www.eea.europa.eu/data-and-maps/daviz/groundwater-nitrate#tab-chart_1_filters=%7B%22rowFilters%22%3A%7B%7D%3B%22columnFilters%22%3A%7B%22pre_config_country%22%3A%5B%22Slovenia%22%5D%7D%7D (accessed on 10 February 2018).
21. Schullehner, J.; Hansen, B. Nitrate exposure from drinking water in Denmark over the last 35 years. *Environ. Res. Lett.* **2014**, *9*, 095001. [CrossRef]
22. Vitoria, I.; Maraver, F.; Sanchez-Valverde, F.; Armijo, F. Nitrate concentrations in tap water in Spain. *Gac. Sanit.* **2015**, *29*, 217–220. [CrossRef] [PubMed]
23. Espejo-Herrera, N.; Kogevinas, M.; Castano-Vinyals, G.; Aragones, N.; Boldo, E.; Ardanaz, E.; Azpiroz, L.; Ulibarrena, E.; Tardon, A.; Molina, A.J.; et al. Nitrate and trace elements in municipal and bottled water in Spain. *Gac. Sanit.* **2013**, *27*, 156–160. [CrossRef] [PubMed]
24. Gunnarsdottir, M.J.; Gardarsson, S.M.; Jonsson, G.S.; Bartram, J. Chemical quality and regulatory compliance of drinking water in Iceland. *Int. J. Hyg. Environ. Health* **2016**, *219*, 724–733. [CrossRef] [PubMed]
25. D'Alessandro, W.; Bellomo, S.; Parello, F.; Bonfanti, P.; Brusca, L.; Longo, M.; Maugeri, R. Nitrate, sulphate and chloride contents in public drinking water supplies in Sicily, Italy. *Environ. Monit. Assess.* **2012**, *184*, 2845–2855. [CrossRef] [PubMed]
26. Migeot, V.; Albouy-Llaty, M.; Carles, C.; Limousi, F.; Strezlec, S.; Dupuis, A.; Rabouan, S. Drinking-water exposure to a mixture of nitrate and low-dose atrazine metabolites and small-for-gestational age (SGA) babies: A historic cohort study. *Environ. Res.* **2013**, *122*, 58–64. [CrossRef] [PubMed]

27. Taneja, P.; Labhasetwar, P.; Nagarnaik, P.; Ensink, J.H.J. The risk of cancer as a result of elevated levels of nitrate in drinking water and vegetables in Central India. *J. Water Health* **2017**, *15*, 602–614. [CrossRef] [PubMed]
28. Suthar, S.; Bishnoi, P.; Singh, S.; Mutiyar, P.K.; Nema, A.K.; Patil, N.S. Nitrate contamination in groundwater of some rural areas of Rajasthan, India. *J. Hazard. Mater.* **2009**, *171*, 189–199. [CrossRef] [PubMed]
29. Gupta, I.; Salunkhe, A.; Rohra, N.; Kumar, R. Groundwater quality in Maharashtra, India: Focus on nitrate pollution. *J. Environ. Sci. Eng.* **2011**, *53*, 453–462. [PubMed]
30. Weinthal, E.; Vengosh, A.; Marei, A.; Kloppmann, W. The water crisis in the Gaza strip: Prospects for resolution. *Ground Water* **2005**, *43*, 653–660. [CrossRef] [PubMed]
31. Jones, R.R.; Weyer, P.J.; DellaValle, C.T.; Inoue-Choi, M.; Anderson, K.E.; Cantor, K.P.; Krasner, S.; Robien, K.; Freeman, L.E.B.; Silverman, D.T.; et al. Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa. *Environ. Health Perspect.* **2016**, *124*, 1751–1758. [CrossRef] [PubMed]
32. Schullehner, J.; Hansen, B.; Thygesen, M.; Pedersen, C.B.; Sigsgaard, T. Nitrate in drinking water and colorectal cancer risk: A nationwide population-based cohort study. *Int. J. Cancer* **2018**, *1*, 73–79. [CrossRef] [PubMed]
33. Espejo-Herrera, N.; Cantor, K.P.; Malats, N.; Silverman, D.T.; Tardon, A.; Garcia-Closas, R.; Serra, C.; Kogevinas, M.; Villanueva, C.M. Nitrate in drinking water and bladder cancer risk in Spain. *Environ. Res.* **2015**, *137*, 299–307. [CrossRef] [PubMed]
34. Ward, M.H.; Rusiecki, J.A.; Lynch, C.F.; Cantor, K.P. Nitrate in public water supplies and the risk of renal cell carcinoma. *Cancer Causes Control* **2007**, *18*, 1141–1151. [CrossRef] [PubMed]
35. Ward, M.H.; Cerhan, J.R.; Colt, J.S.; Hartge, P. Risk of non-Hodgkin lymphoma and nitrate and nitrite from drinking water and diet. *Epidemiology* **2006**, *17*, 375–382. [CrossRef] [PubMed]
36. Schullehner, J.; Stayner, L.; Hansen, B. Nitrate, Nitrite, and Ammonium Variability in Drinking Water Distribution Systems. *Int. J. Environ. Res. Public Health* **2017**, *14*, 276. [CrossRef] [PubMed]
37. Ward, M.H.; Kilfoy, B.A.; Weyer, P.J.; Anderson, K.E.; Folsom, A.R.; Cerhan, J.R. Nitrate intake and the risk of thyroid cancer and thyroid disease. *Epidemiology* **2010**, *21*, 389–395. [CrossRef] [PubMed]
38. Brender, J.D.; Weyer, P.J.; Romitti, P.A.; Mohanty, B.P.; Shinde, M.U.; Vuong, A.M.; Sharkey, J.R.; Dwivedi, D.; Horel, S.A.; Kantamneni, J.; et al. Prenatal nitrate intake from drinking water and selected birth defects in offspring of participants in the national birth defects prevention study. *Environ. Health Perspect.* **2013**, *121*, 1083–1089. [CrossRef] [PubMed]
39. Baris, D.; Waddell, R.; Beane Freeman, L.E.; Schwenn, M.; Colt, J.S.; Ayotte, J.D.; Ward, M.H.; Nuckols, J.; Schned, A.; Jackson, B.; et al. Elevated Bladder Cancer in Northern New England: The Role of Drinking Water and Arsenic. *J. Natl. Cancer Inst.* **2016**, *108*. [CrossRef] [PubMed]
40. Nolan, B.T.; Hitt, K.J. Vulnerability of shallow groundwater and drinking-water wells to nitrate in the United States. *Environ. Sci. Technol.* **2006**, *40*, 7834–7840. [CrossRef] [PubMed]
41. Messier, K.P.; Kane, E.; Bolich, R.; Serre, M.L. Nitrate variability in groundwater of North Carolina using monitoring and private well data models. *Environ. Sci. Technol.* **2014**, *48*, 10804–10812. [CrossRef] [PubMed]
42. Eckhardt, D.A.V.; Stackelberg, P.E. Relation of ground-water quality to land use on Long Island, New York. *Ground Water* **1995**, *33*, 1019–1033. [CrossRef]
43. Nolan, B.T.; Hitt, K.J.; Ruddy, B.C. Probability of nitrate contamination of recently recharged groundwaters in the conterminous United States. *Environ. Sci. Technol.* **2002**, *36*, 2138–2145. [CrossRef] [PubMed]
44. Rupert, M.G. *Probability of Detecting Atrazine/Desethyl-Atrazine and Elevated Concentrations of Nitrate in Ground Water in Colorado*; Water-Resources Investigations Report 02-4269; U.S. Geological Survey: Denver, CO, USA, 2003; p. 35.
45. Tesoriero, A.J.; Voss, F.D. Predicting the probability of elevated nitrate concentrations in the Puget Sound Basin: Implications for aquifer susceptibility and vulnerability. *Ground Water* **1997**, *35*, 1029–1039. [CrossRef]
46. Warner, K.L.; Arnold, T.L. *Relations that Affect the Probability and Prediction of Nitrate Concentration in Private Wells in the Glacial Aquifer System in the United States*; U.S. Geological Survey Scientific Investigations Report 2010–5100; U.S. Geological Survey: Reston, VA, USA, 2010; p. 55.
47. Elith, J.; Leathwick, J.R.; Hastie, T. A working guide to boosted regression trees. *J. Anim. Ecol.* **2008**, *77*, 802–813. [CrossRef] [PubMed]
48. Wheeler, D.C.; Nolan, B.T.; Flory, A.R.; DellaValle, C.T.; Ward, M.H. Modeling groundwater nitrate concentrations in private wells in Iowa. *Sci. Total Environ.* **2015**, *536*, 481–488. [CrossRef] [PubMed]

49. Ransom, K.M.; Nolan, B.T.; Traum, J.A.; Faunt, C.C.; Bell, A.M.; Gronberg, J.A.M.; Wheeler, D.C.; Rosecrans, C.Z.; Jurgens, B.; Schwarz, G.E.; et al. A hybrid machine learning model to predict and visualize nitrate concentration throughout the Central Valley aquifer, California, USA. *Sci. Total Environ.* **2017**, *601–602*, 1160–1172. [CrossRef] [PubMed]
50. Leach, S.A.; Thompson, M.; Hill, M. Bacterially catalyzed *N*-nitrosation reactions and their relative importance in the human stomach. *Carcinogenesis* **1987**, *8*, 1907–1912. [CrossRef] [PubMed]
51. Lv, J.; Neal, B.; Ehteshami, P.; Ninomiya, T.; Woodward, M.; Rodgers, A.; Wang, H.; MacMahon, S.; Turnbull, F.; Hillis, G.; et al. Effects of intensive blood pressure lowering on cardiovascular and renal outcomes: A systematic review and meta-analysis. *PLoS Med.* **2012**, *9*, e1001293. [CrossRef] [PubMed]
52. Spiegelhalder, B.; Eisenbrand, G.; Preussmann, R. Influence of dietary nitrate on nitrite content of human saliva: Possible relevance to in vivo formation of *N*-nitroso compounds. *Food Cosmet. Toxicol.* **1976**, *14*, 545–548. [CrossRef]
53. Tricker, A.R.; Kalble, T.; Preussmann, R. Increased urinary nitrosamine excretion in patients with urinary diversions. *Carcinogenesis* **1989**, *10*, 2379–2382. [CrossRef] [PubMed]
54. Eisenbrand, G.; Spiegelhalder, B.; Preussmann, R. Nitrate and nitrite in saliva. *Oncology* **1980**, *37*, 227–231. [CrossRef] [PubMed]
55. Eisenbrand, G. *The Significance of N-Nitrosation of Drugs*; Nicolai, H.V., Eisenbrand, G., Bozler, G., Eds.; Gustav Fischer Verlag, Stuttgart: New York, NY, USA, 1990; pp. 47–69.
56. Ceccatelli, S.; Lundberg, J.M.; Fahrenkrug, J.; Bredt, D.S.; Snyder, S.H.; Hokfelt, T. Evidence for involvement of nitric oxide in the regulation of hypothalamic portal blood flow. *Neuroscience* **1992**, *51*, 769–772. [CrossRef]
57. Moncada, S.; Palmer, R.M.J.; Higgs, E.A. Nitric oxide: Physiology, pathophysiology, and pharmacology. *Pharmacol. Rev.* **1991**, *43*, 109–142. [PubMed]
58. Rees, D.D.; Palmer, R.M.; Moncada, S. Role of endothelium-derived nitric oxide in the regulation of blood pressure. *Proc. Natl. Acad. Sci. USA* **1989**, *86*, 3375–3378. [CrossRef] [PubMed]
59. Palmer, R.M.; Ferrige, A.G.; Moncada, S. Nitric oxide release accounts for the biological activity of endothelium-derived relaxing factor. *Nature* **1987**, *327*, 524–526. [CrossRef] [PubMed]
60. Radomski, M.W.; Palmer, R.M.; Moncada, S. Endogenous nitric oxide inhibits human platelet adhesion to vascular endothelium. *Lancet* **1987**, *2*, 1057–1058. [CrossRef]
61. Radomski, M.W.; Palmer, R.M.J.; Moncada, S. The Anti-Aggregating Properties of Vascular Endothelium—Interactions between Prostacyclin and Nitric-Oxide. *Br. J. Pharmacol.* **1987**, *92*, 639–646. [CrossRef] [PubMed]
62. Larsen, F.J.; Schiffer, T.A.; Weitzberg, E.; Lundberg, J.O. Regulation of mitochondrial function and energetics by reactive nitrogen oxides. *Free Radic. Biol. Med.* **2012**, *53*, 1919–1928. [CrossRef] [PubMed]
63. Ceccatelli, S.; Hulting, A.L.; Zhang, X.; Gustafsson, L.; Villar, M.; Hokfelt, T. Nitric oxide synthase in the rat anterior pituitary gland and the role of nitric oxide in regulation of luteinizing hormone secretion. *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 11292–11296. [CrossRef] [PubMed]
64. Green, S.J.; Scheller, L.F.; Marletta, M.A.; Seguin, M.C.; Klotz, F.W.; Slayter, M.; Nelson, B.J.; Nacy, C.A. Nitric oxide: Cytokine-regulation of nitric oxide in host resistance to intracellular pathogens. *Immunol. Lett.* **1994**, *43*, 87–94. [CrossRef]
65. Langrehr, J.M.; Hoffman, R.A.; Lancaster, J.R.; Simmons, R.L. Nitric oxide—A new endogenous immunomodulator. *Transplantation* **1993**, *55*, 1205–1212. [CrossRef] [PubMed]
66. Wei, X.Q.; Charles, I.G.; Smith, A.; Ure, J.; Feng, G.J.; Huang, F.P.; Xu, D.; Muller, W.; Moncada, S.; Liew, F.Y. Altered immune responses in mice lacking inducible nitric oxide synthase. *Nature* **1995**, *375*, 408–411. [CrossRef] [PubMed]
67. D'Ischia, M.; Napolitano, A.; Manini, P.; Panzella, L. Secondary Targets of Nitrite-Derived Reactive Nitrogen Species: Nitrosation/Nitration Pathways, Antioxidant Defense Mechanisms and Toxicological Implications. *Chem. Res. Toxicol.* **2011**, *24*, 2071–2092. [CrossRef] [PubMed]
68. Mirvish, S.S. Formation of N-nitroso compounds: Chemistry, kinetics, and in vivo occurrence. *Toxicol. Appl. Pharmacol.* **1975**, *31*, 325–351. [CrossRef]
69. Ridd, J.H. Nitrosation, diazotisation, and deamination. *Q. Rev.* **1961**, *15*, 418–441. [CrossRef]
70. Akuta, T.; Zaki, M.H.; Yoshitake, J.; Okamoto, T.; Akaike, T. Nitrative stress through formation of 8-nitroguanosine: Insights into microbial pathogenesis. *Nitric Oxide* **2006**, *14*, 101–108. [CrossRef] [PubMed]

71. Loeppky, R.N.; Bao, Y.T.; Bae, J.Y.; Yu, L.; Shevlin, G. Blocking nitrosamine formation—Understanding the chemistry of rapid nitrosation. In *Nitrosamines and Related N-Nitroso Compounds: Chemistry and Biochemistry*; Loeppky, R.N., Michejda, C.J., Eds.; American Chemical Society: Washington, DC, USA, 1994; Volume 553, pp. 52–65.
72. Qin, L.Z.; Liu, X.B.; Sun, Q.F.; Fan, Z.P.; Xia, D.S.; Ding, G.; Ong, H.L.; Adams, D.; Gahl, W.A.; Zheng, C.Y.; et al. Sialin (SLC17A5) functions as a nitrate transporter in the plasma membrane. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 13434–13439. [CrossRef] [PubMed]
73. Stich, H.F.; Dunn, B.P.; Pignatelli, B.; Ohshima, H.; Bartsch, H. *Dietary Phenolics and Betel Nut Extracts as Modifiers of n Nitrosation in Rat and Man*; IARC Scientific Publications: Lyon, France, 1984; pp. 213–222.
74. Vermeer, I.T.; Moonen, E.J.; Dallinga, J.W.; Kleinjans, J.C.; van Maanen, J.M. Effect of ascorbic acid and green tea on endogenous formation of N-nitrosodimethylamine and *N*-nitrosopiperidine in humans. *Mutat. Res.* **1999**, *428*, 353–361. [CrossRef]
75. Vermeer, I.T.; Pachen, D.M.; Dallinga, J.W.; Kleinjans, J.C.; van Maanen, J.M. Volatile N-nitrosamine formation after intake of nitrate at the ADI level in combination with an amine-rich diet. *Environ. Health Perspect.* **1998**, *106*, 459–463. [PubMed]
76. Chung, M.J.; Lee, S.H.; Sung, N.J. Inhibitory effect of whole strawberries, garlic juice or kale juice on endogenous formation of *N*-nitrosodimethylamine in humans. *Cancer Lett.* **2002**, *182*, 1–10. [CrossRef]
77. Helser, M.A.; Hotchkiss, J.H.; Roe, D.A. Influence of fruit and vegetable juices on the endogenous formation of N-nitrosoproline and *N*-nitrosothiazolidine-4-carboxylic acid in humans on controlled diets. *Carcinogenesis* **1992**, *13*, 2277–2280. [CrossRef] [PubMed]
78. Zeilmaker, M.J.; Bakker, M.I.; Schothorst, R.; Slob, W. Risk assessment of *N*-nitrosodimethylamine formed endogenously after fish-with-vegetable meals. *Toxicol. Sci.* **2010**, *116*, 323–335. [CrossRef] [PubMed]
79. Khandelwal, N.; Abraham, S.K. Intake of anthocyanidins pelargonidin and cyanidin reduces genotoxic stress in mice induced by diepoxybutane, urethane and endogenous nitrosation. *Environ. Toxicol. Pharmacol.* **2014**, *37*, 837–843. [CrossRef] [PubMed]
80. Conforti, F.; Menichini, F. Phenolic Compounds from Plants as Nitric Oxide Production Inhibitors. *Curr. Med. Chem.* **2011**, *18*, 1137–1145. [CrossRef] [PubMed]
81. Abraham, S.K.; Khandelwal, N. Ascorbic acid and dietary polyphenol combinations protect against genotoxic damage induced in mice by endogenous nitrosation. *Mutat. Res.* **2013**, *757*, 167–172. [CrossRef] [PubMed]
82. De Kok, T.M.; (Maastricht, The Netherlands). Unpublished work. 2018.
83. Haorah, J.; Zhou, L.; Wang, X.J.; Xu, G.P.; Mirvish, S.S. Determination of total *N*-nitroso compounds and their precursors in frankfurters, fresh meat, dried salted fish, sauces, tobacco, and tobacco smoke particulates. *J. Agric. Food Chem.* **2001**, *49*, 6068–6078. [CrossRef] [PubMed]
84. Cross, A.J.; Pollock, J.R.; Bingham, S.A. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res.* **2003**, *63*, 2358–2360. [PubMed]
85. Bingham, S.A.; Pignatelli, B.; Pollock, J.R.A.; Ellul, A.; Malaveille, C.; Gross, G.; Runswick, S.; Cummings, J.H.; O'Neill, I.K. Does increased endogenous formation of *N*-nitroso compounds in the human colon explain the association between red meat and colon cancer? *Carcinogenesis* **1996**, *17*, 515–523. [CrossRef] [PubMed]
86. Bingham, S.A.; Hughes, R.; Cross, A.J. Effect of white versus red meat on endogenous *N*-nitrosation in the human colon and further evidence of a dose response. *J. Nutr.* **2002**, *132*, 3522s–3525s. [CrossRef] [PubMed]
87. Bingham, S.A. High-meat diets and cancer risk. *Proc. Nutr. Soc.* **1999**, *58*, 243–248. [CrossRef] [PubMed]
88. Bouvard, V.; Loomis, D.; Guyton, K.Z.; Grosse, Y.; Ghissassi, F.E.; Benbrahim-Tallaa, L.; Guha, N.; Mattock, H.; Straif, K. International Agency for Research on Cancer Monograph Working, G. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol.* **2015**, *16*, 1599–1600. [CrossRef]
89. International Agency for Research on Cancer (IARC). *IARC Monographs on the Evaluation of Carcionogenic Risks to Humans: Red Meat and Processed Meat*; IARC: Lyon, France, 2018.
90. Phytochemicals to Reduce Nitrite in Meat Products (PHYTOME). Available online: www.phytome.eu (accessed on 3 May 2018).
91. Greer, F.R.; Shannon, M. American Academy of Pediatrics Committee on Nutrition and the Committee on Environmental Health. Infant methemoglobinemia: The role of dietary nitrate in food and water. *Pediatrics* **2005**, *116*, 784–786. [CrossRef] [PubMed]
92. Sanchez-Echaniz, J.; Benito-Fernandez, J.; Mintegui-Raso, S. Methemoglobinemia and consumption of vegetables in infants. *Pediatrics* **2001**, *107*, 1024–1028. [CrossRef] [PubMed]

93. Charmandari, E.; Meadows, N.; Patel, M.; Johnston, A.; Benjamin, N. Plasma nitrate concentrations in children with infectious and noninfectious diarrhea. *J. Pediatr. Gastroenterol. Nutr.* **2001**, *32*, 423–427. [CrossRef] [PubMed]
94. Comly, H.H. Landmark article 8 September 1945: Cyanosis in infants caused by nitrates in well-water. By Hunter H. Comly. *JAMA* **1987**, *257*, 2788–2792. [CrossRef] [PubMed]
95. Walton, G. Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. *Am. J. Public Health Nation's Health* **1951**, *41*, 986–996. [CrossRef]
96. Knobeloch, L.; Salna, B.; Hogan, A.; Postle, J.; Anderson, H. Blue babies and nitrate-contaminated well water. *Environ. Health Perspect.* **2000**, *108*, 675–678. [CrossRef] [PubMed]
97. Johnson, C.J.; Bonrud, P.A.; Dosch, T.L.; Kilness, A.W.; Senger, K.A.; Busch, D.C.; Meyer, M.R. Fatal outcome of methemoglobinemia in an infant. *JAMA* **1987**, *257*, 2796–2797. [CrossRef] [PubMed]
98. Lutynski, R.; Steczek-Wojdyla, M.; Wojdyla, Z.; Kroch, S. The concentrations of nitrates and nitrites in food products and environment and the occurrence of acute toxic methemoglobinemias. *Prz. Lek.* **1996**, *53*, 351–355. [PubMed]
99. Ayebo, A.; Kross, B.C.; Vlad, M.; Sinca, A. Infant Methemoglobinemia in the Transylvania Region of Romania. *Int. J. Occup. Environ. Health* **1997**, *3*, 20–29. [CrossRef] [PubMed]
100. World Health Organization. *Water and Health in Europe*; World Health Organization: Geneva, Switzerland, 2002.
101. Abu Naser, A.A.; Ghbn, N.; Khoudary, R. Relation of nitrate contamination of groundwater with methaemoglobin level among infants in Gaza. *East Mediterr. Health J.* **2007**, *13*, 994–1004. [CrossRef] [PubMed]
102. Sadeq, M.; Moe, C.L.; Attarassi, B.; Cherkaoui, I.; ElAouad, R.; Idrissi, L. Drinking water nitrate and prevalence of methemoglobinemia among infants and children aged 1–7 years in Moroccan areas. *Int. J. Hyg. Environ. Health* **2008**, *211*, 546–554. [CrossRef] [PubMed]
103. Zeman, C.; Beltz, L.; Linda, M.; Maddux, J.; Depken, D.; Orr, J.; Theran, P. New Questions and Insights into Nitrate/Nitrite and Human Health Effects: A Retrospective Cohort Study of Private Well Users' Immunological and Wellness Status. *J. Environ. Health* **2011**, *74*, 8–18. [PubMed]
104. Manassaram, D.M.; Backer, L.C.; Messing, R.; Fleming, L.E.; Luke, B.; Monteilh, C.P. Nitrates in drinking water and methemoglobin levels in pregnancy: A longitudinal study. *Environ. Health* **2010**, *9*, 60. [CrossRef] [PubMed]
105. Grant, W.; Steele, G.; Isiorho, S.A. Spontaneous abortions possibly related to ingestion of nitrate-contaminated well water: LaGrange County, Indiana, 1991–1994. *Morb. Mortal. Wkly. Rep.* **1996**, *45*, 569–572.
106. Aschengrau, A.; Zierler, S.; Cohen, A. Quality of community drinking water and the occurrence of spontaneous abortion. *Arch Environ. Health* **1989**, *44*, 283–290. [CrossRef] [PubMed]
107. Albouy-Llaty, M.; Limousi, F.; Carles, C.; Dupuis, A.; Rabouan, S.; Migeot, V. Association between Exposure to Endocrine Disruptors in Drinking Water and Preterm Birth, Taking Neighborhood Deprivation into Account: A Historic Cohort Study. *Int. J. Environ. Res. Public Health* **2016**, *13*, 796. [CrossRef] [PubMed]
108. Stayner, L.T.; Almberg, K.; Jones, R.; Graber, J.; Pedersen, M.; Turyk, M. Atrazine and nitrate in drinking water and the risk of preterm delivery and low birth weight in four Midwestern states. *Environ. Res.* **2017**, *152*, 294–303. [CrossRef] [PubMed]
109. Joyce, S.J.; Cook, A.; Newnham, J.; Brenters, M.; Ferguson, C.; Weinstein, P. Water disinfection by-products and prelabor rupture of membranes. *Am. J. Epidemiol.* **2008**, *168*, 514–521. [CrossRef] [PubMed]
110. Mattix, K.D.; Winchester, P.D.; Scherer, L.R. Incidence of abdominal wait defects is related to surface water atrazine and nitrate levels. *J. Pediatr. Surg.* **2007**, *42*, 947–949. [CrossRef] [PubMed]
111. Waller, S.A.; Paul, K.; Peterson, S.E.; Hitti, J.E. Agricultural-related chemical exposures, season of conception, and risk of gastroschisis in Washington State. *Am. J. Obstet. Gynecol.* **2010**, *202*, e241–e246. [CrossRef] [PubMed]
112. Winchester, P.D.; Huskins, J.; Ying, J. Agrichemicals in surface water and birth defects in the United States. *Acta Paediatr.* **2009**, *98*, 664–669. [CrossRef] [PubMed]
113. Holtby, C.E.; Guernsey, J.R.; Allen, A.C.; VanLeeuwen, J.A.; Allen, V.M.; Gordon, R.J. A Population-Based Case-Control Study of Drinking-Water Nitrate and Congenital Anomalies Using Geographic Information Systems (GIS) to Develop Individual-Level Exposure Estimates. *Int. J. Environ. Res. Public Health* **2014**, *11*, 1803–1823. [CrossRef] [PubMed]

114. Weyer, P.J.; Brender, J.D.; Romitti, P.A.; Kantamneni, J.R.; Crawford, D.; Sharkey, J.R.; Shinde, M.; Horel, S.A.; Vuong, A.M.; Langlois, P.H. Assessing bottled water nitrate concentrations to evaluate total drinking water nitrate exposure and risk of birth defects. *J. Water Health* **2014**, *12*, 755–762. [CrossRef] [PubMed]
115. Yoon, P.W.; Rasmussen, S.A.; Lynberg, M.C.; Moore, C.A.; Anderka, M.; Carmichael, S.L.; Costa, P.; Druschel, C.; Hobbs, C.A.; Romitti, P.A.; et al. The National Birth Defects Prevention Study. *Public Health Rep.* **2001**, *116* (Suppl. 1), 32–40. [CrossRef] [PubMed]
116. Brender, J.D.; Kelley, K.E.; Werler, M.M.; Langlois, P.H.; Suarez, L.; Canfield, M.A. National Birth Defects Prevention Study. Prevalence and Patterns of Nitrosatable Drug Use among U.S. Women during Early Pregnancy. *Birth Defects Res. A* **2011**, *91*, 258–264. [CrossRef] [PubMed]
117. Griesenbeck, J.S.; Brender, J.D.; Sharkey, J.R.; Steck, M.D.; Huber, J.C., Jr.; Rene, A.A.; McDonald, T.J.; Romitti, P.A.; Canfield, M.A.; Langlois, P.H.; et al. Maternal characteristics associated with the dietary intake of nitrates, nitrites, and nitrosamines in women of child-bearing age: A cross-sectional study. *Environ. Health* **2010**, *9*, 10. [CrossRef] [PubMed]
118. Brender, J.D.; Werler, M.M.; Shinde, M.U.; Vuong, A.M.; Kelley, K.E.; Huber, J.C., Jr.; Sharkey, J.R.; Griesenbeck, J.S.; Romitti, P.A.; Malik, S.; et al. Nitrosatable drug exposure during the first trimester of pregnancy and selected congenital malformations. *Birth Defects Res. A* **2012**, *94*, 701–713. [CrossRef] [PubMed]
119. Brender, J.D.; Werler, M.M.; Kelley, K.E.; Vuong, A.M.; Shinde, M.U.; Zheng, Q.; Huber, J.C., Jr.; Sharkey, J.R.; Griesenbeck, J.S.; Romitti, P.A.; et al. Nitrosatable drug exposure during early pregnancy and neural tube defects in offspring: National Birth Defects Prevention Study. *Am. J. Epidemiol.* **2011**, *174*, 1286–1295. [CrossRef] [PubMed]
120. Brender, J.D.; Olive, J.M.; Felkner, M.; Suarez, L.; Marckwardt, W.; Hendricks, K.A. Dietary nitrites and nitrates, nitrosatable drugs, and neural tube defects. *Epidemiology* **2004**, *15*, 330–336. [CrossRef] [PubMed]
121. Dorsch, M.M.; Scragg, R.K.; McMichael, A.J.; Baghurst, P.A.; Dyer, K.F. Congenital malformations and maternal drinking water supply in rural South Australia: A case-control study. *Am. J. Epidemiol.* **1984**, *119*, 473–486. [CrossRef] [PubMed]
122. Croen, L.A.; Todoroff, K.; Shaw, G.M. Maternal exposure to nitrate from drinking water and diet and risk for neural tube defects. *Am. J. Epidemiol.* **2001**, *153*, 325–331. [CrossRef] [PubMed]
123. Arbuckle, T.E.; Sherman, G.J.; Corey, P.N.; Walters, D.; Lo, B. Water nitrates and CNS birth defects: A population-based case-control study. *Arch Environ. Health* **1988**, *43*, 162–167. [CrossRef] [PubMed]
124. Ericson, A.; Kallen, B.; Lofkvist, E. Environmental factors in the etiology of neural tube defects: A negative study. *Environ. Res.* **1988**, *45*, 38–47. [CrossRef]
125. Cantor, K.P. Drinking water and cancer. *Cancer Causes Control* **1997**, *8*, 292–308. [CrossRef] [PubMed]
126. Quist, A.J.L.; Inoue-Choi, M.; Weyer, P.J.; Anderson, K.E.; Cantor, K.P.; Krasner, S.; Freeman, L.E.B.; Ward, M.H.; Jones, R.R. Ingested nitrate and nitrite, disinfection by-products, and pancreatic cancer risk in postmenopausal women. *Int. J. Cancer* **2018**, *142*, 251–261. [CrossRef] [PubMed]
127. Jones, R.R.; Weyer, P.J.; DellaValle, C.T.; Robien, K.; Cantor, K.P.; Krasner, S.; Freeman, L.E.B.; Ward, M.H. Ingested nitrate, disinfection by-products, and kidney cancer risk in older women. *Epidemiology* **2017**, *28*, 703–711. [CrossRef] [PubMed]
128. Inoue-Choi, M.; Ward, M.H.; Cerhan, J.R.; Weyer, P.J.; Anderson, K.E.; Robien, K. Interaction of nitrate and folate on the risk of breast cancer among postmenopausal women. *Nutr. Cancer* **2012**, *64*, 685–694. [CrossRef] [PubMed]
129. Inoue-Choi, M.; Jones, R.R.; Anderson, K.E.; Cantor, K.P.; Cerhan, J.R.; Krasner, S.; Robien, K.; Weyer, P.J.; Ward, M.H. Nitrate and nitrite ingestion and risk of ovarian cancer among postmenopausal women in Iowa. *Int. J. Cancer* **2015**, *137*, 173–182. [CrossRef] [PubMed]
130. Weyer, P.J.; Cerhan, J.R.; Kross, B.C.; Hallberg, G.R.; Kantamneni, J.; Breuer, G.; Jones, M.P.; Zheng, W.; Lynch, C.F. Municipal drinking water nitrate level and cancer risk in older women: The Iowa Women's Health Study. *Epidemiology* **2001**, *12*, 327–338. [CrossRef] [PubMed]
131. Zeegers, M.P.; Selen, R.F.; Kleinjans, J.C.; Goldbohm, R.A.; van den Brandt, P.A. Nitrate intake does not influence bladder cancer risk: The Netherlands cohort study. *Environ. Health Perspect.* **2006**, *114*, 1527–1531. [CrossRef] [PubMed]
132. Ward, M.H.; Mark, S.D.; Cantor, K.P.; Weisenburger, D.D.; Correa-Villasenor, A.; Zahm, S.H. Drinking water nitrate and the risk of non-Hodgkin's lymphoma. *Epidemiology* **1996**, *7*, 465–471. [CrossRef] [PubMed]

133. Ward, M.H.; Heineman, E.F.; Markin, R.S.; Weisenburger, D.D. Adenocarcinoma of the stomach and esophagus and drinking water and dietary sources of nitrate and nitrite. *Int. J. Occup. Environ. Health* **2008**, *14*, 193–197. [CrossRef] [PubMed]
134. McElroy, J.A.; Trentham-Dietz, A.; Gangnon, R.E.; Hampton, J.M.; Bersch, A.J.; Kanarek, M.S.; Newcomb, P.A. Nitrogen-nitrate exposure from drinking water and colorectal cancer risk for rural women in Wisconsin, USA. *J. Water Health* **2008**, *6*, 399–409. [CrossRef] [PubMed]
135. Espejo-Herrera, N.; Gracia-Lavedan, E.; Boldo, E.; Aragones, N.; Perez-Gomez, B.; Pollan, M.; Molina, A.J.; Fernandez, T.; Martin, V.; La Vecchia, C.; et al. Colorectal cancer risk and nitrate exposure through drinking water and diet. *Int. J. Cancer* **2016**, *139*, 334–346. [CrossRef] [PubMed]
136. Fathmawati; Fachiroh, J.; Gravitiani, E.; Sarto; Husodo, A.H. Nitrate in drinking water and risk of colorectal cancer in Yogyakarta, Indonesia. *J. Toxicol. Environ. Health Part A* **2017**, *80*, 120–128. [CrossRef] [PubMed]
137. Brody, J.G.; Aschengrau, A.; McKelvey, W.; Swartz, C.H.; Kennedy, T.; Rudel, R.A. Breast cancer risk and drinking water contaminated by wastewater: A case control study. *Environ. Health-Glob.* **2006**, *5*, 28. [CrossRef] [PubMed]
138. Espejo-Herrera, N.; Gracia-Lavedan, E.; Pollan, M.; Aragones, N.; Boldo, E.; Perez-Gomez, B.; Altzibar, J.M.; Amiano, P.; Zabala, A.J.; Ardanaz, E.; et al. Ingested Nitrate and Breast Cancer in the Spanish Multicase-Control Study on Cancer (MCC-Spain). *Environ. Health Perspect.* **2016**, *124*, 1042–1049. [CrossRef] [PubMed]
139. Mueller, B.A.; Nielsen, S.S.; Preston-Martin, S.; Holly, E.A.; Cordier, S.; Filippini, G.; Peris-Bonet, R.; Choi, N.W. Household water source and the risk of childhood brain tumours: Results of the SEARCH International Brain Tumor Study. *Int. J. Epidemiol.* **2004**, *33*, 1209–1216. [CrossRef] [PubMed]
140. Mueller, B.A.; Newton, K.; Holly, E.A.; Preston-Martin, S. Residential water source and the risk of childhood brain tumors. *Environ. Health Perspect.* **2001**, *109*, 551–556. [CrossRef] [PubMed]
141. De Groef, B.; Decallonne, B.R.; Van der Geyten, S.; Darras, V.M.; Bouillon, R. Perchlorate versus other environmental sodium/iodide symporter inhibitors: Potential thyroid-related health effects. *Eur. J. Endocrinol.* **2006**, *155*, 17–25. [CrossRef] [PubMed]
142. Van Maanen, J.M.; Welle, I.J.; Hageman, G.; Dallinga, J.W.; Mertens, P.L.; Kleinjans, J.C. Nitrate contamination of drinking water: Relationship with HPRT variant frequency in lymphocyte DNA and urinary excretion of N-nitrosamines. *Environ. Health Perspect.* **1996**, *104*, 522–528. [CrossRef] [PubMed]
143. Radikova, Z.; Tajtakova, M.; Kocan, A.; Trnovec, T.; Sebokova, E.; Klimes, I.; Langer, P. Possible effects of environmental nitrates and toxic organochlorines on human thyroid in highly polluted areas in Slovakia. *Thyroid Off. J. Am. Thyroid Assoc.* **2008**, *18*, 353–362. [CrossRef] [PubMed]
144. Tajtakova, M.; Semanova, Z.; Tomkova, Z.; Szokeova, E.; Majoros, J.; Radikova, Z.; Sebokova, E.; Klimes, I.; Langer, P. Increased thyroid volume and frequency of thyroid disorders signs in schoolchildren from nitrate polluted area. *Chemosphere* **2006**, *62*, 559–564. [CrossRef] [PubMed]
145. Aschebrook-Kilfoy, B.; Heltshe, S.L.; Nuckols, J.R.; Sabra, M.M.; Shuldiner, A.R.; Mitchell, B.D.; Airola, M.; Holford, T.R.; Zhang, Y.; Ward, M.H. Modeled nitrate levels in well water supplies and prevalence of abnormal thyroid conditions among the Old Order Amish in Pennsylvania. *Environ. Health* **2012**, *11*, 6. [CrossRef] [PubMed]
146. Longnecker, M.P.; Daniels, J.L. Environmental contaminants as etiologic factors for diabetes. *Environ. Health Perspect.* **2001**, *109* (Suppl. 6), 871–876. [CrossRef] [PubMed]
147. Moltchanova, E.; Rytkonen, M.; Kousa, A.; Taskinen, O.; Tuomilehto, J.; Karvonen, M.; Spat Study, G. Finnish Childhood Diabetes Registry, G. Zinc and nitrate in the ground water and the incidence of Type 1 diabetes in Finland. *Diabet. Med.* **2004**, *21*, 256–261. [CrossRef] [PubMed]
148. Muntoni, S.; Cocco, P.; Muntoni, S.; Aru, G. Nitrate in community water supplies and risk of childhood type 1 diabetes in Sardinia, Italy. *Eur. J. Epidemiol.* **2006**, *21*, 245–247. [CrossRef] [PubMed]
149. Benson, V.S.; Vanleeuwen, J.A.; Taylor, J.; Somers, G.S.; McKinney, P.A.; Van Til, L. Type 1 diabetes mellitus and components in drinking water and diet: A population-based, case-control study in Prince Edward Island, Canada. *J. Am. Coll. Nutr.* **2010**, *29*, 612–624. [CrossRef] [PubMed]
150. Winkler, C.; Mollenhauer, U.; Hummel, S.; Bonifacio, E.; Ziegler, A.G. Exposure to environmental factors in drinking water: Risk of islet autoimmunity and type 1 diabetes—The BABYDIAB study. *Horm. Metab. Res.* **2008**, *40*, 566–571. [CrossRef] [PubMed]

151. Klein, B.E.K.; McElroy, J.A.; Klein, R.; Howard, K.P.; Lee, K.E. Nitrate-nitrogen levels in rural drinking water: Is there an association with age-related macular degeneration? *J. Environ. Sci. Health Part A* **2013**, *48*, 1757–1763. [CrossRef] [PubMed]
152. Ahluwalia, A.; Gladwin, M.; Coleman, G.D.; Hord, N.; Howard, G.; Kim-Shapiro, D.B.; Lajous, M.; Larsen, F.J.; Lefer, D.J.; McClure, L.A.; et al. Dietary Nitrate and the Epidemiology of Cardiovascular Disease: Report From a National Heart, Lung, and Blood Institute Workshop. *J. Am. Heart Assoc.* **2016**, *5*, e003402. [CrossRef] [PubMed]
153. Kapil, V.; Khambata, R.S.; Robertson, A.; Caulfield, M.J.; Ahluwalia, A. Dietary nitrate provides sustained blood pressure lowering in hypertensive patients: A randomized, phase 2, double-blind, placebo-controlled study. *Hypertension* **2015**, *65*, 320–327. [CrossRef] [PubMed]
154. Omar, S.A.; Webb, A.J.; Lundberg, J.O.; Weitzberg, E. Therapeutic effects of inorganic nitrate and nitrite in cardiovascular and metabolic diseases. *J. Intern. Med.* **2016**, *279*, 315–336. [CrossRef] [PubMed]
155. Presley, T.D.; Morgan, A.R.; Bechtold, E.; Clodfelter, W.; Dove, R.W.; Jennings, J.M.; Kraft, R.A.; King, S.B.; Laurienti, P.J.; Rejeski, W.J.; et al. Acute effect of a high nitrate diet on brain perfusion in older adults. *Nitric Oxide* **2011**, *24*, 34–42. [CrossRef] [PubMed]
156. Maas, R.; Schwedhelm, E.; Kahl, L.; Li, H.; Benndorf, R.; Luneburg, N.; Forstermann, U.; Boger, R.H. Simultaneous assessment of endothelial function, nitric oxide synthase activity, nitric oxide-mediated signaling, and oxidative stress in individuals with and without hypercholesterolemia. *Clin. Chem.* **2008**, *54*, 292–300. [CrossRef] [PubMed]
157. Jadert, C.; Phillipson, M.; Holm, L.; Lundberg, J.O.; Borniquel, S. Preventive and therapeutic effects of nitrite supplementation in experimental inflammatory bowel disease. *Redox Biol.* **2014**, *2*, 73–81. [CrossRef] [PubMed]
158. Khademikia, S.; Rafiee, Z.; Amin, M.M.; Poursafa, P.; Mansourian, M.; Modaberi, A. Association of nitrate, nitrite, and total organic carbon (TOC) in drinking water and gastrointestinal disease. *J. Environ. Public Health* **2013**, *2013*, 603468. [CrossRef] [PubMed]
159. De Roos, A.J.; Ward, M.H.; Lynch, C.F.; Cantor, K.P. Nitrate in public water supplies and the risk of colon and rectum cancers. *Epidemiology* **2003**, *14*, 640–649. [CrossRef] [PubMed]
160. Gatseva, P.D.; Argirova, M.D. High-nitrate levels in drinking water may be a risk factor for thyroid dysfunction in children and pregnant women living in rural Bulgarian areas. *Int. J. Hyg. Environ. Health* **2008**, *211*, 555–559. [CrossRef] [PubMed]
161. Toccalino, P.L.; Norman, J.E.; Scott, J.C. Chemical mixtures in untreated water from public-supply wells in the U.S.—Occurrence, composition, and potential toxicity. *Sci. Total Environ.* **2012**, *431*, 262–270. [CrossRef] [PubMed]
162. Joshi, N.; Rhoades, M.G.; Bennett, G.D.; Wells, S.M.; Mirvish, S.S.; Breitbach, M.J.; Shea, P.J. Developmental abnormalities in chicken embryos exposed to *N*-nitrosoatrazine. *J. Toxicol. Environ. Health Part A* **2013**, *76*, 1015–1022. [CrossRef] [PubMed]
163. Mitch, W.A.; Sharp, J.O.; Rhoades Trussell, R.; Valentine, R.L.; Alvarez-Cohen, L.; DSedlak, D.L. *N*-Nitrosodimethylamine (NDMA) as a Drinking Water Contaminant: A Review. *Environ. Eng. Sci.* **2003**, *20*, 389–404. [CrossRef]
164. Krasner, S.W. The formation and control of emerging disinfection by-products of health concern. *Philos. Trans.* **2009**, *367*, 4077–4095. [CrossRef] [PubMed]
165. Hezel, M.P.; Weitzberg, E. The oral microbiome and nitric oxide homoeostasis. *Oral Dis.* **2015**, *21*, 7–16. [CrossRef] [PubMed]
166. Hyde, E.R.; Andrade, F.; Vaksman, Z.; Parthasarathy, K.; Jiang, H.; Parthasarathy, D.K.; Torregrossa, A.C.; Tribble, G.; Kaplan, H.B.; Petrosino, J.F.; et al. Metagenomic analysis of nitrate-reducing bacteria in the oral cavity: Implications for nitric oxide homeostasis. *PLoS ONE* **2014**, *9*, e88645. [CrossRef] [PubMed]
167. Burleigh, M.C.; Liddle, L.; Monaghan, C.; Muggeridge, D.J.; Sculthorpe, N.; Butcher, J.P.; Henriquez, F.L.; Allen, J.D.; Easton, C. Salivary nitrite production is elevated in individuals with a higher abundance of oral nitrate-reducing bacteria. *Free Radic. Biol. Med.* **2018**, *120*, 80–88. [CrossRef] [PubMed]
168. Vogtmann, E.; Chen, J.; Amir, A.; Shi, J.; Abnet, C.C.; Nelson, H.; Knight, R.; Chia, N.; Sinha, R. Comparison of Collection Methods for Fecal Samples in Microbiome Studies. *Am. J. Epidemiol.* **2017**, *185*, 115–123. [CrossRef] [PubMed]

169. Sinha, R.; Abu-Ali, G.; Vogtmann, E.; Fodor, A.A.; Ren, B.; Amir, A.; Schwager, E.; Crabtree, J.; Ma, S.; The Microbiome Quality Control Project Consortium; et al. Assessment of variation in microbial community amplicon sequencing by the Microbiome Quality Control (MBQC) project consortium. *Nat. Biotechnol.* **2017**, *35*, 1077–1086. [PubMed]
170. Hebels, D.G.; Jennen, D.G.; van Herwijnen, M.H.; Moonen, E.J.; Pedersen, M.; Knudsen, L.E.; Kleinjans, J.C.; de Kok, T.M. Whole-genome gene expression modifications associated with nitrosamine exposure and micronucleus frequency in human blood cells. *Mutagenesis* **2011**, *26*, 753–761. [CrossRef] [PubMed]
171. Hebels, D.G.; Jennen, D.G.; Kleinjans, J.C.; de Kok, T.M. Molecular signatures of N-nitroso compounds in Caco-2 cells: Implications for colon carcinogenesis. *Toxicol. Sci.* **2009**, *108*, 290–300. [CrossRef] [PubMed]
172. Vineis, P.; Chadeau-Hyam, M.; Gmuender, H.; Gulliver, J.; Herceg, Z.; Kleinjans, J.; Kogevinas, M.; Kyrtopoulos, S.; Nieuwenhuijsen, M.; Phillips, D.H.; et al. The exposome in practice: Design of the EXPOsOMICS project. *Int. J. Hyg. Environ. Health* **2017**, *220*, 142–151. [CrossRef] [PubMed]
173. Hebels, D.G.; Georgiadis, P.; Keun, H.C.; Athersuch, T.J.; Vineis, P.; Vermeulen, R.; Portengen, L.; Bergdahl, I.A.; Hallmans, G.; Palli, D.; et al. Performance in omics analyses of blood samples in long-term storage: Opportunities for the exploitation of existing biobanks in environmental health research. *Environ. Health Perspect.* **2013**, *121*, 480–487. [CrossRef] [PubMed]
174. International Nitrogen Initiative. Available online: http://www.initrogen.org/ (accessed on 22 April 2018).
175. Dinnes, D.L.; Karlen, D.L.; Jaynes, D.B.; Kaspar, T.C.; Hatfield, J.L.; Colvin, T.S.; Cambardella, C.A. Nitrogen management strategies to reduce nitrate leaching in tile-drained midwestern soils. *Agron. J.* **2002**, *94*, 153–171. [CrossRef]
176. Baron, J.S.; Hall, E.K.; Nolan, B.T.; Finlay, J.C.; Bernhardt, E.S.; Harrison, J.A.; Chan, F.; Boyer, E.W. The interactive effects of excess reactive nitrogen and climate change on aquatic ecosystems and water resources of the United States. *Biogeochemistry* **2013**, *114*, 71–92. [CrossRef]

Clinical Thyroidology / Review

European Thyroid Journal

Eur Thyroid J 2018;7:67–74
DOI: 10.1159/000485971

Received: July 4, 2017
Accepted after revision: December 1, 2017
Published online: January 11, 2018

Thyroid Cancer Induction: Nitrates as Independent Risk Factors or Risk Modulators after Radiation Exposure, with a Focus on the Chernobyl Accident

Valentina M. Drozd[a, b] Igor Branovan[b] Nikolay Shiglik[b] Johannes Biko[c] Christoph Reiners[a, c]

[a]The International Fund "Help for patients with radiation-induced thyroid cancer 'Arnica'", Minsk, Belarus; [b]Project Chernobyl, Brooklyn, NY, USA; [c]Clinic and Polyclinic of Nuclear Medicine, University of Würzburg, Würzburg, Germany

Keywords
Thyroid cancer · Nitrate pollution · Ionizing radiation · Chernobyl · Salivary glands · Risk stratification · Belarus

Abstract
In recent decades, differentiated thyroid cancer (DTC) incidence has been increasing worldwide. The important contributions to this phenomenon of "overdiagnosis" driven by wider use of improved ultrasound systems are amply documented, notwithstanding the "real" carcinogenic effects of ionizing radiation, e.g., from the Chernobyl accident or health care interventions. Less well understood is the role of nitrates – as environmental pollutants, in diet, and in medication – in thyroid carcinogenesis. Increasing exposure to nitrates is associated with rising incidence of esophageal, stomach, bladder, and colon cancers. Recent data suggest that in agricultural areas with higher mean nitrate levels in groundwater, DTC risk is also elevated. Our work in Belarus after Chernobyl has shown that children in districts with high nitrate concentrations in drinking water had significantly higher thyroid cancer incidence after irradiation than did their counterparts in areas with lower nitrate concentrations. Notwithstanding thyroid shielding, increasing use of computed tomography and dental X-rays heightens radiation exposure of the salivary glands in the general population, especially in children and adolescents. When nitrate intake is increased, salivary gland irradiation may potentially result in carcinogenic elevations in plasma nitric oxide concentrations. In conclusion, excess nitrate intake seems to be an independent risk factor for DTC. Additionally, we hypothesize from our data that high nitrate levels modulate the carcinogenic effect of radiation on the thyroid. Cohort studies, case-control studies, or both, are needed to quantify the effects of nitrates on DTC risk in the presence or absence of radiation exposure, e.g., that associated with diagnostic or therapeutic health care interventions.

Introduction

During the last 30 years, the incidence of differentiated thyroid cancer (DTC) has steadily increased worldwide, most markedly in France, Italy, the Republic of Korea, Australia, and the USA [1–8]. In the USA, DTC incidence

KARGER

E-Mail karger@karger.com
www.karger.com/etj

Prof. Valentina M. Drozd, MD, PhD
The International Fund "Help for patients with radiation-induced thyroid cancer 'Arnica'"
Zolotaya Gorka 11, 1, Minsk 220005 (Belarus)
E-Mail vm.drozd@gmail.com

is rising more rapidly than that of any other malignancy except liver cancer [1], with the annual percent change (both genders) increasing from 2.4% in 1980–1997 to 6.6% in 1997–2009 [2, 8]. In Europe, the increase in the last 2–3 decades has ranged from 5.3% (Switzerland) to 155.6% (France).

In Belarus and Ukraine, DTC incidence has also substantially increased in the past 25 years; there is strong evidence that this increase was mainly due to radiation exposure of children and adolescents after the Chernobyl accident [9–11]. Nonetheless, an appreciable proportion of thyroid cancers diagnosed in young people in these countries may be related to screening or other confounders [10, 12].

The main factors contributing to the worldwide increase in the incidence of DTC continue to be debated. Today, it is generally accepted that the widespread use of ultrasound, introduced in the 1980s to diagnose structural thyroid diseases, has led to earlier, more frequent detection of this neoplasm. Better diagnostics were estimated to account for 60% or more of DTC diagnoses in 2003–2007 in women under the age of 80 years in France, Italy, the USA, Australia, and the Republic of Korea, and 30% or more in other very high-income countries [13]. Consistent with these estimates, small thyroid cancers that are best discovered using new technologies (ultrasound and fine-needle aspiration biopsy) have shown a sharply increased incidence [14]. However, improved medical surveillance and "overdiagnosis" do not completely explain the rise in rates of papillary thyroid carcinoma (PTC), since a significant increase also has been observed for larger tumors (>10 mm) [15–18].

DTC and Radiation Exposure

Also well accepted as an explanation for greater frequency of DTC diagnoses is radiation exposure. External radiotherapy in childhood for cancer, tinea capitis, or an enlarged thymus or tonsils has been long known to be associated with an elevated risk of DTC [19–21]. Additionally, DTC was the first solid tumor to be found in excess among atomic bomb survivors in Japan [22]. An updated pooled analysis of 12 studies [23] identified a consistent risk model across the full range of external radiation doses to the thyroid, with relative risk (RR) increasing approximately supralinearly through 2–4 Gy, and then leveling and declining above approximately 30 Gy, although RRs remained elevated. Radiogenic effects occurred for both PTC and nonpapillary thyroid tumors. For doses >0.10 Gy, RRs increased significantly with dose ($p < 0.01$), with no significant departure from linearity. The excess relative risk (ERR) estimate per Gy was significant within 10 years of radiation exposure at 2.76 (95% CI: 0.94–4.98), and remained elevated 50 years and more after exposure [23].

In several other studies, dental radiography was associated with an increased risk of thyroid cancer [24, 25] and parotid gland tumors [26]. One case-control study [24] found a significant association between self-reported dental X-ray exposure, particularly multiple exposures, and DTC risk (odds ratio [OR]: 2.1, 95% CI: 1.4–3.1, $p < 0.001$) with a dose-response pattern ($p < 0.0001$ for trend). American Dental Association recommendations stress the need to shield the thyroid during dental X-ray examination [27].

Pediatric DTC rates in Belarus began to increase as early as 4 years after the Chernobyl accident [28, 29]. Ecological studies of DTC incidence in Belarus and Ukraine following Chernobyl estimated a linear ERR per Gy of 18.9 and excess absolute risk per Gy of 2.7 [9]. Cohort studies with measurement-based individual thyroid dose estimates reported ERRs per Gy of 5.3 and 2.2 for DTC in Ukraine and Belarus [11, 30–35], respectively.

Nitrates as Pollutants, in Diet, and in Medication

Beyond diagnostic activity and radiation exposure, additional factors may contribute to increased DTC incidence, and require further investigation. In particular, nutritional exposure to chemical pollutants such as nitrates in drinking water, specifically during intrauterine life and early childhood, might affect thyroid cell propensity to mutagenesis. In general, there are five primary sources of exposure to nitrate and its metabolite nitrite: environmental/atmospheric exposure to nitric oxide (NO) and nitrogen, dietary exposure to nitrate and nitrite in food and in drinking water, and endogenous production of NO and swallowing of nitrate-rich saliva [36, 37].

The largest proportion of reactive nitrogen, i.e., NO, nitrogen dioxide, nitric acid, nitrous oxide, nitrite, nitrate, ammonia, nitrogen oxides, and organic compounds such as urea, amines, proteins, and nucleic acids, in the environment comes from agriculture in the form of fertilizers and animal waste [38, 39]. The past 60 years have witnessed an exponential increase in the use of nitrogen-rich manure and reactive nitrogen as fertilizers [40]. Although they boost agricultural productivity, nitrogen-

rich fertilizers let nitrates seep through the soil into both groundwater and surface water. There, these substances can accumulate for years until the concentration is adverse to human health. Because of water pollution, high amounts of nitrate might be present in fruits and vegetables, specifically those grown in greenhouses. Additionally, high nitrate levels may be found in cured and processed meats due to the addition of these chemicals as preservatives or color enhancers. Medications, including antidiarrheals, diuretics, vasodilators, and the cytotoxic chemotherapy agent nitrosourea, also contribute to nitrate exposure in humans [39, 41].

In Belarus, between 1960 and 1990, mean use of nitrogen fertilizers increased more than 20-fold, from 4 to 92 kg/hectare, while the average nitrate concentration in groundwater rose almost 40-fold, from 1.1 to 41.6 mg/L [42]. Groundwater from open wells is the main source of drinking water in rural Belarus. According to the Belarusian Ministry of Health, about 1% of pipeline water samples have nitrate concentration exceeding the World Health Organization (WHO)-recommended maximum contaminant level of 45 mg/L [43]. In contrast, about 40% of water samples from open wells exceed that maximum contaminant level. In Brest and Gomel Oblasts, the proportion of such samples reaches 40–60%, while in Mogilev Oblast, it is about 20% [43].

Physiology and Pathophysiology of Nitrates

In the past 30 years, the roles of NO in physiology and pathophysiology have been extensively studied. Nitrate is metabolized by the nitrate-nitrite-NO pathway. As a gas (in the pure state and under standard temperature and pressure conditions) with an unshared electron, NO participates in various biological processes. In the body, under normal oxygen pressure, NO is produced by NO synthetase from L-arginine. In hypoxia, nitrite is reduced by a variety of reductases, including deoxyhemoglobin, to produce NO. Further reduction/oxidation of NO can lead to metabolite production (nitrogen dioxide, nitrate) [44].

Nitrate and NO are known to affect the iodine metabolism of the thyroid. Nitrate is a competitive inhibitor of the sodium-iodine symporter and prevents iodide uptake by the gland. Thyroid hormone synthesis is thereby compromised, leading to thyrotropin elevation. The resultant chronic thyroid stimulation can lead to proliferative changes, including hypertrophy and hyperplasia as well as neoplasia [45–47].

There are other mechanisms by which ingested nitrate may produce detrimental effects on health. One is through formation of methemoglobin, which inhibits the oxygen-carrying capacity of blood; another is through endogenous formation of N-nitroso compounds that may act as carcinogens [41, 46]. Nitrosamine synthesis depends on temperature and pH, and may be stimulated by low-level gamma radiation [48–50].

The salivary glands play a very important role in the metabolism of nitrate and the nitrate-nitrite-NO pathway [36, 37]. Dietary nitrate is rapidly completely absorbed in the upper gastrointestinal tract. Sixty percent of ingested nitrate is excreted in the urine within 48 h [36, 37]. However, approximately 25% of circulating nitrate is taken up by the salivary glands and secreted into the mouth in saliva. Salivary nitrate concentrations are 10- to 20-fold above blood levels, and may reach several millimolars. Oral facultative anaerobic bacteria, residing mainly in the tongue's crypts, then reduce nitrate to nitrite and NO via nitrate-reducing enzymes. This relatively effective process results in nitrite levels that are 1,000-fold higher in saliva than in plasma.

Nitrates and Radiotherapy

Therapeutic irradiation increases NO levels in salivary gland tissue. NO produced in irradiated tissues mediates cellular regulation through posttranslational modification of a number of proteins [44]. Evidence exists for the role of NO as an intrinsic radiosensitizer [51]. On the other hand, administration of an NO synthesis inhibitor ameliorated the dysfunction of irradiated salivary glands, indicating that NO helps mediate the dry mouth symptoms occurring after irradiation [52].

Radiation-induced bystander effects may be modulated by NO [53–56]. NO synthase activation and NO overproduction after exposure to ionizing radiation not only affect bystander cells with activated NO synthase, but also can stimulate specific cell-signaling mechanisms. These NO-dependent effects include the promotion of genomic instability and the accumulation of DNA reduplication errors in bystander cells, without the direct DNA damage seen in irradiated cells. Hydrophobic properties of NO, permitting the diffusion of the substance through the cytoplasm and plasma membranes, allow this signaling molecule to easily spread from irradiated cells to bystander cells without the involvement of gap-junctional intercellular communication [56].

Nitrate Carcinogenicity: Relation to DTC

The first report of negative health effects of nitrate, namely, methemoglobin formation, was in 1945, after observation of cyanosis in infants in Iowa, USA [57]. Long-term exposure to nitrate and nitrite has been evaluated in relation to multiple tumor types; positive associations were reported for cancers of the esophagus, stomach, bladder, and colon [41, 50].

NO as a carcinogen heavily depends on concentration in a nonlinear manner: the specific activity of this analyte at very low levels blocks tumor growth, while moderate concentrations promote tumor angiogenesis and cell survival via lymphocyte suppression [44]. High NO levels may induce chromosomal breaks directly, or indirectly by inhibiting DNA repair activities [58]. NO can cause irreversible injury to several fundamental cancer control genes. The substance plus superoxide rapidly react to form peroxynitrite, which can cause oxidative damage to DNA. NO can also block DNA synthesis through inhibition of ribonucleotide reductase, the rate-limiting enzyme in DNA production [58–60]. Additionally, NO can directly inhibit enzymes in the mitochondrial electron transport chain or act indirectly by interfering with DNA repair mechanisms, leaving the cell susceptible to other DNA-damaging agents [59]. NO has been shown to have a role in stimulating vascular endothelial growth factor-D (VEGF-D) expression in vitro [61]. The formation of the NO biomarker, nitrotyrosine, was also correlated with VEGF-D expression in human PTC. In that setting, NO may induce lymph node metastasis via VEGF-D stimulation. In vitro, NO has both genotoxic and metastasis-promoting properties. Increased NO generation in cancer cells may contribute to tumor hemangiogenesis or lymphangiogenesis by upregulating VEGF-D [61]. The effects of NO are mediated in part by its metabolites, such as peroxynitrite. Data suggest that NO stimulates CXC chemokine receptor 4 (CXCR4) expression in vitro [62]. Nitrotyrosine formation was also correlated with CXCR4 expression and lymph node metastasis in human PTC [62].

Regarding DTC, Ward et al. [63] found an increased risk of this neoplasm in agricultural areas with higher mean nitrate levels in public water supplies and with longer-term consumption of water with nitrate-N concentrations exceeding 5 mg/L (subjects with ≤5 years' consumption at levels of >5 mg/L, RR: 2.6, 95% CI: 1.1–6.2). Increased dietary nitrate intake was associated with a heightened risk of DTC (RR: 2.9, 95% CI: 1.0–8.1, $p = 0.046$) and with the prevalence of hypothyroidism (OR: 1.2, 95% CI: 1.1–1.4), but not hyperthyroidism [63].

With regard to thyroid radiation dose, de Vathaire et al. [64] investigated potential modifiers of the thyroid dose response to radiation therapy in survivors of pediatric solid tumors other than thyroid cancer. The risk of DTC as a second primary malignancy increased with a thyroid dose of up to 10 Gy, then leveled off for higher doses. The excess RR per Gy of radiation to the thyroid was 4.7 (95% CI: 1.7–22.6). Patients also receiving nitrosourea chemotherapy had a 6.6-fold (95% CI: 2.5–15.7-fold) higher risk than those who did not.

Exposure to Nitrates and Radiation after Chernobyl

Recently published data suggest a synergistic influence of nitrates in drinking water and the thyroid radiation dose on the incidence of childhood DTC in Belarus after the Chernobyl accident [12]. The highest mean thyroid dose (320 mGy) and the highest incidence of pediatric thyroid cancer in 1986–2005 (11 per 100,000 patient-years) was found in the most contaminated area, Gomel Oblast [12]. However, there was a notable exception to the general dose-incidence rate pattern, i.e., substantial difference in rates of pediatric thyroid cancer in Mogilev versus Brest Oblasts (1.50 vs. 5.51 per 100,000 patient-years). Whereas the estimated thyroid doses from iodine-131 were comparable in the two regions (65 vs. 51 mGy), nitrate contamination of drinking water significantly differed (mean levels in open well water, 40 vs. 185 mg/L). Radiation dose was significantly associated with thyroid cancer incidence ($p = 0.029$), but the effect of radiation significantly varied according to the nitrate concentration in drinking water ($p = 0.004$). A plausible interpretation of these observations is that the radiation effect on thyroid cells might be modified by patients' ingestion of nitrate from drinking water [12]. Comparison of maps respectively showing levels of groundwater pollution by nitrates (Fig. 1a) and Chernobyl-related radiation doses (Fig. 1b) also suggests that both factors may influence DTC risk.

Conclusions

Based on our own experience and on published data, we hypothesize that thyroid cancer may be induced by coincidence of several conditions: (1) excessive nitrate uptake via drinking water increases nitrite production,

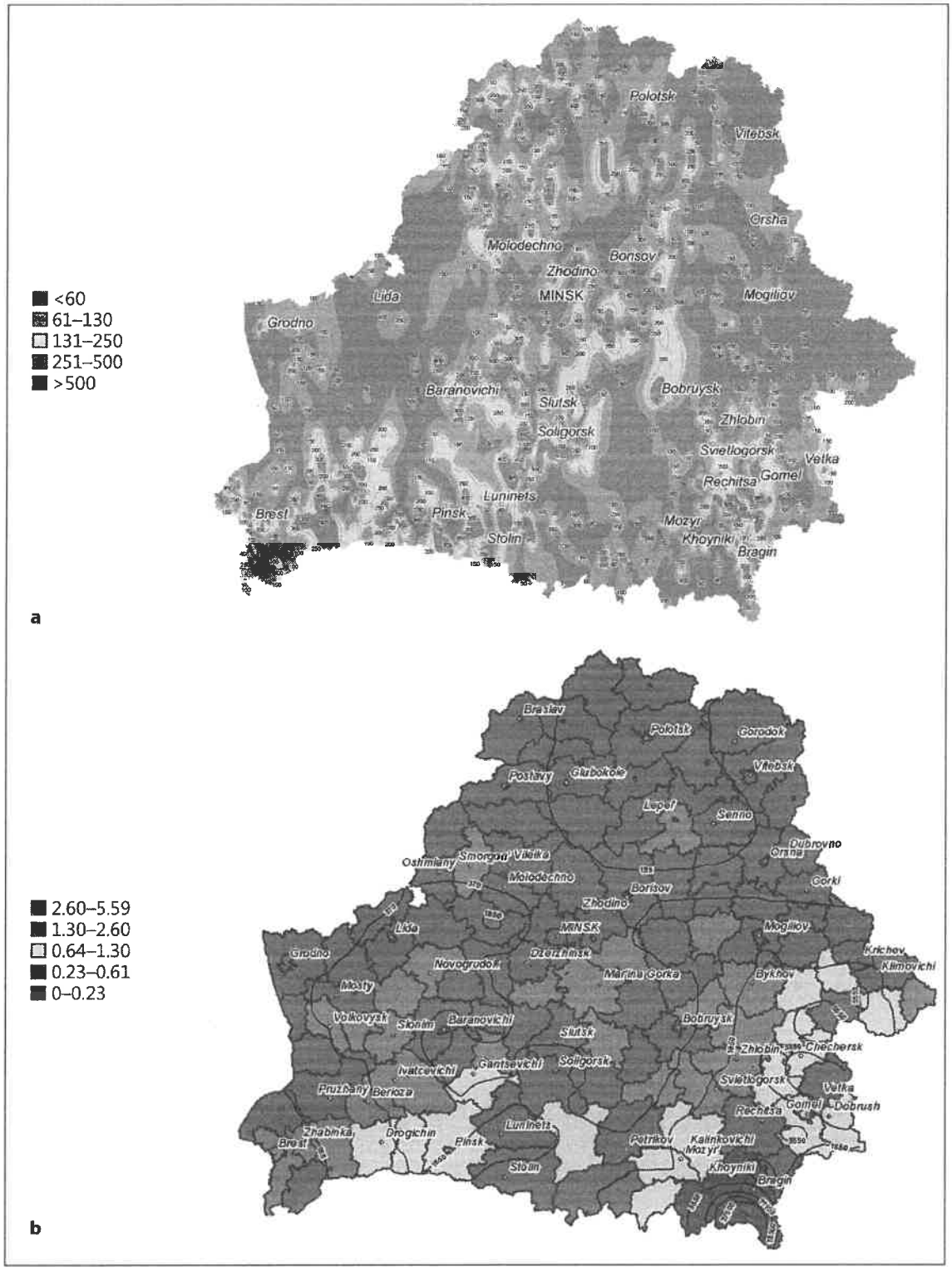


Fig. 1. Maps of Belarus depicting by district (oblast) the level of groundwater pollution with nitrate (mg/L) measured in open wells in 1988–1990 (**a**) and the prevalence (per 1,000) of pediatric thyroid cancer in 1986–2005 in the cohort ages 0–18 years at exposure to radioactive fallout from the Chernobyl accident (**b**). In **b**, areas exposed to such fallout are bounded with black lines, and radioactive contamination due to radioiodine in 1986 (in kBq/m^2) is shown in small numerals. Notably, areas of greatest pediatric thyroid cancer prevalence tend to coincide with areas characterized by both a high radiation exposure and high nitrate pollution of groundwater.

which leads to the development of hypoxia in the blood, especially in children, and to overproduction of NO, which is carcinogenic per se; (2) radiation exposure of the salivary glands, e.g., by dental X-ray examination, may also lead to increased plasma levels of NO; and (3) if one or both of these processes coincide with radiation exposure of the thyroid, the considerably increased NO concentrations in the body presumably enhance the carcinogenic effect of the radiation.

The role of radiation in thyroid carcinogenesis is well documented. The influence of other factors and confounders and their synergistic effects is less well understood. Studies of radiation-induced DTC in Belarus after the Chernobyl accident have shown that children living in areas with high nitrate concentration in drinking water have a significantly elevated thyroid cancer risk. A plausible interpretation is that the radiation effect might be modulated by ingested nitrates. Further cohort studies or case-control studies with individual exposure estimates are required to quantify the effect of nitrate on DTC risk in the context of growing use of medical radiation for diagnostic and therapeutic purposes. Such studies examining the increasing exposure to nitrates alone and in combination with ionizing radiation may provide a better understanding of the considerable increase in thyroid cancer incidence in many countries.

Acknowledgments

The authors are grateful for the important suggestions and contributions of Mary H. Ward, Senior Investigator, Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA. Robert J. Marlowe edited this paper.

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Merlo DF, Filiberti R, Kobernus M, Bartonova A, Gamulin M, Ferencic Z, Dusinska M, Fucic A: Cancer risk and the complexity of the interactions between environmental and host factors: HENVINET interactive diagrams as simple tools for exploring and understanding the scientific evidence. Environ Health 2012; 11(suppl 1):S9.

2 Pellegriti G, Frasca F, Regalbuto C, Squatrito S, Vigneri R: Worldwide increasing incidence of thyroid cancer: update on epidemiology and risk factors. J Cancer Epidemiol 2013; 2013:965212.

3 Nagataki S, Nystrom E: Epidemiology and primary prevention of thyroid cancer. Thyroid 2002;12:889–896.

4 World Health Organization: United Nations Environment Programme (WHO-UNEP), State of the Science of Endocrine Disrupting Chemicals. 2012. http://www.who.int/ceh/publications/endocrine/en/index.html.

5 Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP: Systematic review of trends in the incidence rates of thyroid cancer. Thyroid 2016;26:1541–1552.

6 Cramer JD, Fu P, Harth KC, Margevicius S, Wilhelm SM: Analysis of the rising incidence of thyroid cancer using the Surveillance, Epidemiology and End Results National Cancer Data Registry. Surgery 2010;148:1147–1152; discussion 1152–1143.

7 Roche LM, Niu X, Pawlish KS, Henry KA: Thyroid cancer incidence in New Jersey: time trend, birth cohort and socioeconomic status analysis (1979–2006). J Environ Public Health 2011;2011:850105.

8 SEER: Cancer of the thyroid SEER Stat Fact Sheets. http://seer.cancer.gov/statfacts/html/thyro.html (accessed February 14, 2017).

9 Jacob P, Bogdanova TI, Buglova E, Chepurniy M, Demidchik Y, Gavrilin Y, Kenigsberg J, Meckbach R, Schotola C, Shinkarev S, Tronko MD, Ulanovsky A, Vavilov S, Walsh L: Thyroid cancer risk in areas of Ukraine and Belarus affected by the Chernobyl accident. Radiat Res 2006;165:1–8.

10 Jacob P, Bogdanova TI, Buglova E, Chepurniy M, Demidchik Y, Gavrilin Y, Kenigsberg J, Kruk J, Schotola C, Shinkarev S, Tronko MD, Vavilov S: Thyroid cancer among Ukrainians and Belarusians who were children or adolescents at the time of the Chernobyl accident. J Radiol Protect 2006;26:51–67.

11 United Nations Scientific Committee on the Effects of Atomic Radiation: Sources and Effects of Ionizing Radiation, UNSCEAR 2008 Report to the General Assembly with Scientific Annexes. Annex D: Health effects due to radiation from the Chernobyl accident. New York, United Nations, 2008.

12 Drozd VM, Saenko VA, Brenner AV, Drozdovitch V, Pashkevich VI, Kudelsky AV, Demidchik YE, Branovan I, Shiglik N, Rogounovitch TI, Yamashita S, Biko J, Reiners C: Major factors affecting incidence of childhood thyroid cancer in Belarus after the Chernobyl accident: do nitrates in drinking water play a role? PLoS One 2015;10: e0137226.

13 Vaccarella S, Dal Maso L, Laversanne M, Bray F, Plummer M, Franceschi S: The impact of diagnostic changes on the rise in thyroid cancer incidence: a population-based study in selected high-resource countries. Thyroid 2015; 25:1127–1136.

14 Ahn HS, Kim HJ, Welch HG: Korea's thyroid-cancer "epidemic" – screening and overdiagnosis. N Engl J Med 2014;371:1765–1767.

15 Chen AY, Jemal A, Ward EM: Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. Cancer 2009;115: 3801–3807.

16 Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, Devesa SS: Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. Cancer Epidemiol Biomarkers Prev 2009;18:784–791.

17 17 Pathak KA, Leslie WD, Klonisch TC, Nason RW: The changing face of thyroid cancer in a population-based cohort. Cancer Med 2013;2:537–544.

18 Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM: Trends in thyroid cancer incidence and mortality in the United States, 1974–2013. JAMA 2017;317:1338–1348.

19 Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, Schneider AB, Tucker MA, Boice JD Jr: Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res 1995;141:259–277.

20 Shore RE, Woodard E, Hildreth N, Dvoretsky P, Hempelmann L, Pasternack B: Thyroid tumors following thymus irradiation. J Natl Cancer Inst 1985;74:1177–1184.
21 Favus MJ, Schneider AB, Stachura ME, Arnold JE, Ryo UY, Pinsky SM, Colman M, Arnold MJ, Frohman LA: Thyroid cancer occurring as a late consequence of head-and-neck irradiation. Evaluation of 1,056 patients. N Engl J Med 1976;294:1019–1025.
22 Socolow EL, Hashizume A, Neriishi S, Niitani R: Thyroid carcinoma in man after exposure to ionizing radiation. A summary of the findings in Hiroshima and Nagasaki. N Engl J Med 1963;268:406–410.
23 Veiga LH, Holmberg E, Anderson H, Pottern L, Sadetzki S, Adams MJ, Sakata R, Schneider AB, Inskip P, Bhatti P, Johansson R, Neta G, Shore R, de Vathaire F, Damber L, Kleinerman R, Hawkins MM, Tucker M, Lundell M, Lubin JH: Thyroid cancer after childhood exposure to external radiation: an updated pooled analysis of 12 studies. Radiat Res 2016; 185:473–484.
24 Memon A, Godward S, Williams D, Siddique I, Al-Saleh K: Dental X-rays and the risk of thyroid cancer: a case-control study. Acta Oncol 2010;49:447–453.
25 Wingren G, Hallquist A, Hardell L: Diagnostic X-ray exposure and female papillary thyroid cancer: a pooled analysis of two Swedish studies. Eur J Cancer Prev 1997;6:550–556.
26 Preston-Martin S, Thomas DC, White SC, Cohen D: Prior exposure to medical and dental X-rays related to tumors of the parotid gland. J Natl Cancer Inst 1988;80:943–949.
27 American Dental Association Council on Scientific Advisory Affairs: The use of dental radiographs: update and recommendations. J Am Dent Assoc 2006;137:1304–1312.
28 Kazakov VS, Demidchik EP, Astakhova LN: Thyroid cancer after Chernobyl. Nature 1992; 359:21.
29 Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, Drozdovitch V, Maceika E, Zvonova I, Vlassov O, Bouville A, Goulko G, Hoshi M, Abrosimov A, Anoshko J, Astakhova L, Chekin S, Demidchik E, Galanti R, Ito M, Korobova E, Lushnikov E, Maksioutov M, Masyakin V, Nerovnia A, Parshin V, Parshkov E, Piliptsevich N, Pinchera A, Polyakov S, Shabeka N, Suonio E, Tenet V, Tsyb A, Yamashita S, Williams D: Risk of thyroid cancer after exposure to ^{131}I in childhood. J Natl Cancer Inst 2005;97:724–732.
30 Beal SH, Chen SL, Schneider PD, Martinez SR: An evaluation of lymph node yield and lymph node ratio in well-differentiated thyroid carcinoma. Am Surg 2010;76:28–32.
31 Astakhova LN, Anspaugh LR, Beebe GW, Bouville A, Drozdovitch VV, Garber V, Gavrilin YI, Khrouch VT, Kuvshinnikov AV, Kuzmenkov YN, Minenko VP, Moschik KV, Nalivko AS, Robbins J, Shemiakina EV, Shinkarev S, Tochitskaya SI, Waclawiw MA: Chernobyl-related thyroid cancer in children of Belarus: a case-control study. Radiat Res 1998;150:349–356.
32 Tronko MD, Howe GR, Bogdanova TI, Bouville AC, Epstein OV, Brill AB, Likhtarev IA, Fink DJ, Markov VV, Greenebaum E, Olijnyk VA, Masnyk IJ, Shpak VM, McConnell RJ, Tereshchenko VP, Robbins J, Zvinchuk OV, Zablotska LB, Hatch M, Luckyanov NK, Ron E, Thomas TL, Voilleque PG, Beebe GW: A cohort study of thyroid cancer and other thyroid diseases after the Chernobyl accident: thyroid cancer in Ukraine detected during first screening. J Natl Cancer Inst 2006;98: 897–903.
33 Little MP, Kwon D, Zablotska LB, Brenner AV, Cahoon EK, Rozhko AV, Polyanskaya ON, Minenko VF, Golovanov I, Bouville A, Drozdovitch V: Impact of uncertainties in exposure assessment on thyroid cancer risk among persons in Belarus exposed as children or adolescents due to the Chernobyl accident. PLoS One 2015;10:e0139826.
34 Zablotska LB, Ron E, Rozhko AV, Hatch M, Polyanskaya ON, Brenner AV, Lubin J, Romanov GN, McConnell RJ, O'Kane P, Evseenko VV, Drozdovitch VV, Luckyanov N, Minenko VF, Bouville A, Masyakin VB: Thyroid cancer risk in Belarus among children and adolescents exposed to radioiodine after the Chernobyl accident. Br J Cancer 2011;104: 181–187.
35 Zablotska LB, Nadyrov EA, Rozhko AV, Gong Z, Polyanskaya ON, McConnell RJ, O'Kane P, Brenner AV, Little MP, Ostroumova E, Bouville A, Drozdovitch V, Minenko V, Demidchik Y, Nerovnya A, Yauseyenka V, Savasteeva I, Nikonovich S, Mabuchi K, Hatch M: Analysis of thyroid malignant pathologic findings identified during 3 rounds of screening (1997–2008) of a cohort of children and adolescents from Belarus exposed to radioiodines after the Chernobyl accident. Cancer 2015;121:457–466.
36 Lundberg JO, Weitzberg E, Gladwin MT: The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov 2008;7:156–167.
37 Bryan NS, Loscalzo J (eds): Nitrite and Nitrate in Human Health and Disease. New York, Springer, 2011, p 306.
38 UNEP/WHRC: Reactive Nitrogen in the Environment: Too Much of a Good Thing? Paris/Falmouth, United Nations Environment Programme and the Woods Hole Research Center, 2007. http://www.unep.fr/scp/publications/details.asp?id=DTI/0904/PA (accessed April 12, 2012).
39 World Health Organization: Evaluation of certain food additives and contaminants. Forty-fourth report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series 1995; No. 859. Geneva, WHO, 1995.
40 Townsend AR, Howarth RW: Fixing the global nitrogen problem. Sci Am 2010;302:64–71.
41 World Health Organization; International Agency for Research on Cancer: IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2010, V. 94: Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins. Lyon, IARC, 2010.
42 Kudelsky AV, Pashkevich VI, Kapora MS, VKavalenka MK: Quality of drinking groundwater of Belarus. Nat Res 2009;1:53–61.
43 Drozdova EV, Buraya VV, Rudik VA: Nitrate pollution of drinking water in Belarus: the analysis of the problem and arguments for further studies. Health Environ 2010;15:56–61.
44 44 Scicinski J, Oronsky B, Ning S, Knox S, Peehl D, Kim MM, Langecker P, Fanger G: NO to cancer: The complex and multifaceted role of nitric oxide and the epigenetic nitric oxide donor, RRx-001. Redox Biol 2015;6:1–8.
45 Capen CC: Mechanistic data and risk assessment of selected toxic end points of the thyroid gland. Toxicol Pathol 1997;25:39–48.
46 Costamagna ME, Cabanillas AM, Coleoni AH, Pellizas CG, Masini-Repiso AM: Nitric oxide donors inhibit iodide transport and organification and induce morphological changes in cultured bovine thyroid cells. Thyroid 1998;8:1127–1135.
47 van Maanen JM, van Dijk A, Mulder K, de Baets MH, Menheere PC, van der Heide D, Mertens PL, Kleinjans JC: Consumption of drinking water with high nitrate levels causes hypertrophy of the thyroid. Toxicol Lett 1994; 72:365–374.
48 Ward MH: Too much of a good thing? Nitrate from nitrogen fertilizers and cancer. Rev Environ Health 2009;24:357–363.
49 Ohashi K, Tsutsumi M, Tsujiuchi T, Kobitsu K, Okajima E, Nakajima Y, Nakano H, Takahashi M, Mori Y, Konishi Y: Enhancement of N-nitrosodiethylamine-initiated hepatocarcinogenesis caused by a colchicine-induced cell cycle disturbance in partially hepatectomized rats. Canc Res 1996;56:3474–3479.
50 Agency for Toxic Substances and Disease Registry (ATSDR): Toxicological Profile for N-Nitrosodimethylamine (Final Report). Atlanta, ATSDR, 1989.
51 Jordan BF, Sonveaux P, Feron O, Gregoire V, Beghein N, Dessy C, Gallez B: Nitric oxide as a radiosensitizer: evidence for an intrinsic role in addition to its effect on oxygen delivery and consumption. Intl J Cancer 2004;109:768–773.
52 Takeda I, Kizu Y, Yoshitaka O, Saito I, Yamane GY: Possible role of nitric oxide in radiation-induced salivary gland dysfunction. Radiat Res 2003;159:465–470.
53 Nagasawa H, Little JB: Induction of sister chromatid exchanges by extremely low doses of alpha-particles. Cancer Res 1992;52:6394–6396.
54 Nagasawa H, Little JB: Unexpected sensitivity to the induction of mutations by very low doses of alpha-particle radiation: evidence for a bystander effect. Radiat Res 1999;152:552–557.
55 Azzam EI, Little JB: The radiation-induced bystander effect: evidence and significance. Hum Exp Toxicol 2004;23:61–65.

56 Yakovlev VA, Mikkelsen RB: Reactive nitrogen posttranslational modifications of proteins in carcinogenesis; in Laher I (ed): Systems Biology Free Radicals and Antioxidants. Springer, 2014, pp 2873–2891.
57 Comly HH: Landmark article Sept 8, 1945: Cyanosis in infants caused by nitrates in well-water. By Hunter H. Comly. JAMA 1987;257:2788–2792.
58 Roy B, Guittet O, Beuneu C, Lemaire G, Lepoivre M: Depletion of deoxyribonucleoside triphosphate pools in tumor cells by nitric oxide. Free Radic Biol Med 2004;36:507–516.
59 Ghafourifar P, Colton CA: Compartmentalized nitrosation and nitration in mitochondria. Antioxid Redox Signal 2003;5:349–354.
60 Xu W, Liu LZ, Loizidou M, Ahmed M, Charles IG: The role of nitric oxide in cancer. Cell Res 2002;12:311–320.
61 Nakamura Y, Yasuoka H, Zuo H, Takamura Y, Miyauchi A, Nakamura M, Kakudo K: Nitric oxide in papillary thyroid carcinoma: Induction of vascular endothelial growth factor D and correlation with lymph node metastasis. J Clin Endocrinol Metab 2006;91:1582–1585.
62 Yasuoka H, Kodama R, Hirokawa M, Takamura Y, Miyauchi A, Sanke T, Nakamura Y: CXCR4 expression in papillary thyroid carcinoma: Induction by nitric oxide and correlation with lymph node metastasis. BMC Cancer 2008;8:274.
63 Ward MH, Kilfoy BA, Weyer PJ, Anderson KE, Folsom AR, Cerhan JR: Nitrate intake and the risk of thyroid cancer and thyroid disease. Epidemiology 2010;21:389–395.
64 de Vathaire F, Haddy N, Allodji RS, Hawkins M, Guibout C, El-Fayech C, Teinturier C, Oberlin O, Pacquement H, Diop F, Kalhouche A, Benadjaoud M, Winter D, Jackson A, Bezin Mai-Quynh G, Benabdennebi A, Llanas D, Veres C, Munzer M, Nguyen TD, Bondiau PY, Berchery D, Laprie A, Deutsch E, Lefkopoulos D, Schlumberger M, Diallo I, Rubino C: Thyroid radiation dose and other risk factors of thyroid carcinoma following childhood cancer. J Clin Endocrinol Metab 2015;100:4282–4290.

THE JOURNAL OF PREVENTIVE MEDICINE
2002; 10 (1): 3-10

NITRATE TOXICITY AND DRINKING WATER STANDARDS – A REVIEW

B.C. Kross

USA

Abstract. The current US EPA maximum contaminant level (MCL) for public drinking water supplies and the health advisory level (HAL) for other private water supplies is 10 mg/L, expressed as NO_3-N. Unlike other drinking water standards, the nitrate standard has no safety factor, which typically is about a 10-fold safety factor to account for differences in human susceptibility. Guidance, action, or advisory levels for nitrate in drinking water are lower in several countries, including Germany (4.4 mg/L), South Africa (4.4 mg/L), and Denmark (5.6 mg/L). Clearly health and regulatory officials in other countries believe that the current WHO and USA drinking water standard for nitrate is not adequate to protect their most susceptible population from methemoglobinemia. In addition to acute methemoglobinemia, other potential health effects of nitrate exposure in drinking water include cancer, disruption of thyroid function, birth defects, and developmental disorders in children. Is the current drinking water standard in the US and World Health Organization for nitrate adequate? I think not! Clearly the most susceptible human population (infants under four months of age with existing diarrhea conditions) is not adequately protected from methemoglobinemia. In addition, recent studies suggest other possible linkages between nitrate in drinking water and adverse health consequences for adults. Particularly troublesome is the finding of a positive association between nitrate in drinking water (at levels below the USA drinking water standard) and bladder cancer and ovarian cancer in a large cohort of women in Iowa, USA. Given this framework, the regulatory authorities should establish a safety factor of two, which would reduce the current MCL and HAL for nitrate to 5.0 mg/L NO_3-N. This regulatory mandate would encourage a prudent public health strategy of limiting human nitrate exposure.
Key words: nitrate, drinking water, safety factor, methemoglobinemia

Rezumat. Nivelul maxim admis de contaminare a sistemelor publice de aprovizionare cu apă potabilă, stabilit de Agenţia de Protecţie a Mediului din SUA pentru nitraţi, ca şi nivelul maxim recomandat pentru alte sisteme particulare de apă este de 10 mg/l, exprimat în NO_3-N. Spre deosebire de alte standarde pentru apa de băut, în standardul american pentru nitrat nu s-a aplicat un **factor de siguranţă** (de regulă, cu valoarea 10) pentru a se lua în considerare diferenţele de susceptibilitate existente în populaţie. Nivelurile maxime acceptate pentru nitraţi în apa de băut sunt mai mici în unele ţări ca Germania (4,4 mg/l), Africa de Sud (4,4 mg/L) şi Danemarca (5,6 mg/L). Aceasta înseamnă că, în aceste ţări, nivelul maxim acceptat în SUA nu este considerat suficient de scăzut pentru a proteja de methemoglobinemie grupele cele mai susceptibile ale populaţiei. Pe lângă methemoglobinemie, ca efect acut, există şi alte patologii asociate expunerii la nitraţii din apă, cum sunt cancerul, unele disfuncţii tiroidiene, malformaţii congenitale şi tulburări de dezvoltare la copii. La întrebarea dacă limita admisă în SUA şi recomandată de OMS pentru nitraţi în apă, este corespunzătoare, răspunsul este negativ, fiindcă nu asigură o protecţie suficientă, astfel încât grupele cele mai susceptibile ale

populației (copii sub vârsta de 4 luni, cu factori favorizanți ai diareei) să nu facă methemoglobinemie. În plus, studii recente sugerează existența unor posibile asocieri între nitrații din apă și o serie de efecte adverse asupra sănătății adulților. Sunt relevante, în acest sens, rezultatele care indică o asociere pozitivă între nitrații din apă (în concentrații sub limita admisă în SUA) și cancere de vezică și ovariene, constatată într-un studiu de cohortă efectuat pe femei în statul Iowa, SUA. Având în vedere aceste aspecte, consider că se impune stabilirea unui factor de siguranță în valoare de 2, care ar reduce limita maximă admisă pentru nitrați la 5,0 mg/L NO_3-N. Această decizie de reglementare ar încuraja o strategie prudentă pentru limitarea expunerii populației la nitrați.
Cuvinte cheie: nitrați, apă de băut, factor de siguranță, methemoglobinemie

Health Effects

The current US EPA maximum contaminant level (MCL) for public drinking water supplies and the health advisory level (HAL) for other private water supplies is 10 mg/L, expressed as NO_3-N. These health-based standards and advisory levels are intended to prevent infant methemoglobinemia. Nitrate generally has a low human toxicity, but becomes a hazard when it is reduced to nitrite by bacterial action in the human gastrointestinal tract. Nitrite coverts oxygen-carrying hemoglobin to methemoglobin, which then cannot transfer oxygen. The resulting condition is methemoglobinemia, or the so-called blue baby disorder.

The most susceptible population to nitrate/nitrite toxicity is infants less than four months of age. Their high sensitivity is due to a combination of factors: higher gastric pH which allows greater bacterial activity in the stomach and subsequent enhanced conversion of ingested nitrate to nitrite, higher proportion of fetal hemoglobin which is more readily oxidized to methemoglobin than adult hemoglobin, and infant NADH - dependent methemoglobin reductase (the enzyme responsible for converting methemoglobin to normal hemoglobin) has about half the activity of the adult enzyme (1).

Several thousand cases of infant methemoglobinemia have been reported in the literature, with an overall case fatality rate of about 5-10 percent. Recent outbreaks have been reported in Central and Eastern Europe, especially in rural areas utilizing private well-water supplies (2,3). The most recent fatal case of methemoglobinemia in the United States occurred in South Dakota in 1986 (4).

The major source of nitrate intake for infants is from drinking water mixed with infant formula. Boiling of drinking water to kill bacteria (a common practice in rural areas) concentrates the nitrate that is present. Feeding practices that include early introduction of certain fruits and vegetables, which contain naturally high nitrate levels (beets, spinach, carrot or apple juice), can also enhance the risk of infant methemoglobinemia (5,6).

There is presently no evidence to support earlier hypotheses that breast-fed infants may develop

methemoglobinemia when their mothers consumed nitrate contained in well water. So far, available data from experimental animals and limited human studies indicate that neither nitrate nor nitrite accumulate or concentrate in the mammary gland or milk (7).

Methemoglobinemia is a syndrome of elevated methemoglobin level, high blood nitrite, and frequently is associated with acute diarrhea. A newly proposed hypothesis being advanced by the Center for Global Food Issues is that nitrates in water or food are not the cause of infant methemoglobinemia, but rather the infant's own body is the primary culprit as it responds to pathogens or an indigestible protein (8). In brief, this theory suggests that when an infant has acute diarrhea or other severe gastrointestinal disturbance, either from a bacterial infection in the gut or a protein intolerance (perhaps from cow's milk supplemental feedings) (9), the entire metabolism of the infant is altered in such a way as to cause methemoglobin formation, irrespective of the infant's nitrate intake from food or water. The proposed mechanism of methemoglobinemia in this case is the release of nitric oxide from the white blood cells responding to the inflammation in the gastrointestinal system. The nitric oxide is converted by the body into nitrate, then to nitrite, and finally to ammonia, which is cleared by the kidneys. This process is known as endogenous nitrate production, and has been described recently in the literature for about 45 infants studied in Israel (10). During such episodes of severe gastrointestinal disturbances, the nitric oxide is overproduced, resulting in an accumulation of nitrite in the body. The outcome has been called endogenous methemoglobinemia.

In addition to acute methemoglobinemia, other health effects including cancer (11,12), disruption of thyroid function (13), birth defects (14), developmental disorders in animals (15) and developmental disorders in children (16) are under current study with respect to their relationship to nitrate exposures in drinking water. Although the recent National Research Council report concluded that the current drinking water standards for nitrate were adequate to protect human health in the United States, this conclusion was hedged somewhat by this same subcommittee's recommendation that limiting infant exposure to nitrate would be a sensible public-health measure (17).

Basis for Drinking Water Standard

The current nitrate standard established in 1987 is based on a literature review of 278 cases of methemoglobinemia reported in the United States between 1945 and 1950. The study reported that none of these cases occurred when nitrate concentrations in drinking water were below 10 mg/L (18). Unlike other drinking water standards, the nitrate standard has **no safety factor**, which typically is about a 10-fold safety factor to account for differences in human susceptibility.

Other studies and case reports in the literature strongly suggest that a safety factor is needed. Studies conducted in Germany in 1964 indicated that about 4% of the 249 cases of methemoglobinemia occurred in infants consuming water containing less than 11 mg/L. of nitrate (19). Other case reports in the literature indicated that infants with severe diarrhea are also susceptible to methemoglobinemia following ingestion of drinking water containing less than 10 mg/L. of nitrate-N (20). A recent report of methemoglobinemia in Wisconsin involved an infant consuming formula mixed with private well water containing 9.9 mg/L of nitrate-N and up to 7.8 mg/L of copper (21). Guidance, action, or advisory levels for nitrate in drinking water are lower in several countries, including Germany (4.4 mg/L), South Africa (4.4 mg/L), and Denmark (5.6 mg/L). Clearly health and regulatory officials in other countries believe that the current drinking water standard for nitrate is not adequate to protect their most susceptible population from methemoglobinemia.

Extent of Nitrate Contamination

Another important issue related to nitrate toxicity and drinking water resources is the current extent of groundwater and surface water contamination in the United States. A national drinking water survey conducted by the US EPA indicated about 1.2% of community-water wells and about 2.4% of rural domestic wells have nitrate levels that exceed the health advisory level. It is estimated that about 1.5 million people, including about 22,500 infants, are served by rural domestic wells and that another 3 million people, including about 43,500 infants, are served by community water wells that exceed health advisory levels for nitrate (22).

An Environmental Working Group review of nearly 200,000 public water sampling records found that nearly 2-million people - including an estimated 15,000 infants under the age of four months - drank water from 2,016 water systems that were reported to the US EPA for violating the nitrate standard at least once between 1986 and 1995. All of these water systems were termed "significant noncompliers" by the US EPA and 60% were repeat violators. An additional 3.8 million people drink water from private wells that are contaminated above the 10 mg/L nitrate standard. In seven states - California, Pennsylvania, New York, Illinois, Wisconsin, Minnesota, and Iowa - more than 100,000 rural residents are exposed to nitrate above the federal standard via private drinking water (23).

In a statewide survey conducted in Iowa, about 18% of rural domestic wells had nitrate contamination above the 10 mg/L. limit (24). Similarly, an assessment of Safe Drinking Water Act database in Iowa indicates that from 1988 to 1995, the MCL was exceeded in 21% of the samples, and was greater than 5 mg/L in 43% of the samples. Some trends in the data were also noted. The median concentration of nitrate in finished water supplies

decreased from 1991 to 1995, which was also represented in a decline in the percentage of samples exceeding the MCL - 21% in 1991 to 4% in 1995 (25). However, in another study of groundwater sources in Iowa, the trend for nitrate contamination is not as clear. Since 1982 multiple samples of untreated groundwater used for Iowa municipal water supplies indicate no significant temporal trends in either the frequency of detection or median nitrate concentrations in these wells (26).

In the rural areas of America, nitrate contamination of drinking water supplies continues to be an important public health issue. In the event that future research proves a relationship between nitrate exposure to infants and subsequent adverse health effects such as cancer or developmental disorders, the population at risk to excess nitrate exposures will indeed be huge.

Naturally occurring groundwater resources without influence from anthropogenic pollution sources such as fertilizer, sewage sludge, and animal manure generally contain nitrate at levels below 3.0 mg/L (27). For example, the natural background concentration of nitrate in Iowa groundwater is typically less than 2.0 mg/L (28).

Sources of Nitrate in Drinking Water

Within the US, each year there are about 8-billion pounds more nitrogen available in farm fields than can be utilized by the crops (29). This excess nitrogen generally moves through the soil into groundwater, or is transported during rainfall events into surface waters. Some natural degradation (denitrification) also occurs. Other sources of nitrate such as sewage treatment plants, private septic systems, animal manure, legume crops, and atmospheric deposition can be important in specific, localized groundwater systems. In Iowa, the Department of Natural Resources estimates that about 55-60% of the nitrate environmental loading is from commercial fertilizer applications. Moreover, these area sources of nitrate contamination appear to be more significant than point sources or poor well construction. For example, in Iowa's statewide rural well water study, single source problems such as locating near or in animal feedlots accounted for only 3% of the total rural wells, and accounted for only about 1% of the wells exceeding the nitrate standard (1).

Policy Issues

In order to protect pristine groundwater resources and to recognize the uncertainty in current human health-based standards for nitrate toxicity, a non-degradation groundwater protection strategy for nitrate should be established for all areas where the existing groundwater quality is better than the current drinking water standard. In other words, industrial, municipal, and agricultural pollution sources should not be allowed to contaminate groundwater resources up to the current 10 mg/L level for nitrates. A

regulatory framework that accepts or encourages the so-called license to pollute concept is unwise, particularly if an allowable level of nitrate pollution is based on the flawed assumption that the current drinking water standard for nitrate is adequate to protect human health.

Is the current drinking water standard for nitrate adequate? I think not! Clearly the most susceptible human population (infants under four months of age with existing diarrhea conditions) is not adequately protected from methemoglobinemia. In addition, recent studies suggest other possible linkages between nitrate in drinking water and adverse health consequences for adults. Particularly troublesome is the recent finding of a positive association between nitrate in drinking water (at levels below the drinking water standard) and bladder cancer and ovarian cancer in a large cohort of women in Iowa (12). If further studies confirm strong associations between nitrate in drinking water and cancer, then a revised regulatory safety factor would be applied. However, in the meantime, a safety factor of at least two is needed to adequately protect the vulnerable, helpless infant population. Given this framework, the regulatory authority should implement a maximum contaminant level goal (MCLG) of 3 mg/L of NO_3-N in order to limit infant exposures to nitrate.

By mandating a safety factor of two, which would reduce the current MCL and HAL for nitrate to 5.0 mg/L NO_3-N, and by promulgating a MCLG of 3.0 mg/L of NO_3-N; the United States regulatory approach for nitrate in drinking water would become consistent with other European countries and would encourage the prudent public health strategy of limiting human nitrate exposure.

REFERENCES

1. Kross B.C., Ayebo A.D., Fuortes L.J. (1992) - *Methemoglobinemia: nitrate toxicity in rural America*, Am. Fam. Physician, 46: 183-88.
2. Ayebo A., Kross B.C., Vlad M., Sinca A. (1997) - *Infant methemoglobinemia in the Transylvania region of Romania*, Int. J. Occup. Env. Hlth., 3: 20-29.
3. Vasilov M., Condrea St., Cristea A., et al. (2001) - *Trend of methemoglobinemia cases in eastern Romania*, J. of Preventive Medicine, 9 (2): 11-19.
4. Johnson C.L., Bonrud P.A., Doisch T.L. (1987) - *Fatal outcome of methemoglobinemia in an infant*, J.A.M.A., 257: 2796-2797.
5. Keating J.P., Lell M.E., Strauss A.W., et al. (1973) - *Infantile methemoglobinemia caused by carrot juice*, New Eng. J. Med., 288 (16): 824-26.
6. Dusdieker L.B., Getchell J.P., Liarakos T.M., et al. (1994) - *Nitrate in baby foods - Adding to the nitrate mosaic*, Arch. Pediatr. Adolesc. Med., 148(5): 490-494.
7. Dusdieker L.B., Stumbo P.J., Kross B.C., Dungy C.I. (1996) - *Does increased nitrate ingestion elevate nitrate in human milk?* Arch. Ped. Adoles. Med., 150 (3): 311-315.
8. Avery A.A. (1999) - *Infantile methemoglobinemia: reexamining the role of drinking water nitrates*, Environmental Health Perspectives 107 (7): 583-586.

9. Murray K.F., Christle D.L. (1993) - *Dietary protein intolerance in infants with transient methemoglobinemia and diarrhea*, J. Pediatr., 122: 90-92.
10. Hanukoglu A., Danon P.N. (1996) - *Endogenous methemoglobinemia associated with diarrheal disease in infancy*. J. Ped. Gastroenterology & Nutrition, 23 (1): 1-7.
11. Weisenburger D.D. (1990) - *Environmental epidemiology of non-Hodgkin's lymphoma in eastern Nebraska*, Am J Ind Med, 18:303-306.
12. Weyer P.J., Cerhan J.R., Kross B.C., et al. (2001) - *Municipal drinking water nitrate level and cancer risk in older women: the Iowa Women's Health Study*, Epidemiology 11: 327-338.
13. Van Maanen et al. (1994) - *Consumption of drinking water with high nitrate levels causes hypertrophy of the thyroid*, Toxicology Letter, 72: 365-374.
14. Arbuckle T.E., Sherman G.J., Corey P.N., et al. (1988) - *Water nitrates and CNS birth defects: a population-based case-control study*, Arch. Environ. Health, 43: 162-67.
15. Markel E., Nyakas C., Ormai S. (1989) - *Nitrate induced changes in sensorimotor development and learning behavior in rats*, Acta. Physiol. Hung., 74: 69-75.
16. Harper D., Sinca A. (1999) - *Methods of neuropsychological assessment. Unpublished proceedings from Workshop entitled "Environmental and developmental issues in the identification and prevention of methemoglobinemia in Romanian infants"*, October 19-21, 1999 in Satu Mare, Romania.
17. NRC - National Resource Council (1995) - *Nitrate and nitrite in drinking water*, National Academy Press: Washington DC, p 49.
18. Walton G. (1951) - *Survey of literature related to infant methemoglobinemia due to nitrate contaminated water*. Am. J. Pub. Health 41: 986-96.
19. Simon C., Manzke H., Kay H., Mrowetz G. (1964) - *Uber vorkommen, pathogenese and Moglichkeiten zur prophylaxe der durch nitrit verursachten methamoglobinamie*. Zeitschrift fur Kinderheilkunde 91: 124-38.
20. Dagan R., Zaltzstein E., Gorodischer R. (1988) - *Methemoglobinemia in young infants with diarrhea*, Eur. J. Pediatr. 147: 87-89.
21. Knobeloch L., Krenz K., Anderson H. (1993) - *Methemoglobinemia in an infant*, Wisconsin, 1992, MMWR 42: 12, p. 217-219.
22. US Environmental Protection Agency Washington DC. (1992) - *Another look: national pesticide survey*. Phase II report.
23. Environmental Working Group (1996) - *Pouring it on - nitrate contamination of drinking water*, edited by BA Cohen, R Wiles, and C Campbell, Washington, DC, p.1-70.
24. Kross B.C., Hallberg G.R., Bruner D.R., et al. (1993) - *The nitrate contamination of private well water in Iowa*, Am. J. Pubic Health, 83: 270-272.
25. Hallberg G.R., Riley D.G., Kantamneni J.R., et al. (1996) - *Assessment of Iowa Safe Drinking Water Act monitoring data: 1988-1995*, University of Iowa Hygienic Laboratory, Research Report 97-1, Iowa City, IA, p. 1-132.
26. Kolpin D.W., Sneck-Fahrer D., Hallberg G.R., Libra R.D. (1997) - *Temporal trends of selected agricultural chemicals in Iowa's*

groundwater, 1982-1995: Are things getting better? J. Environ Qual, 26: 1007-1017.

27. Madison R.J., Brunett J.O. (1985) - *Overview of the occurrence of nitrate in ground water of the United States*. In: National Water Summary 1984, Reston, VA: US Geological Survey, Water Supply Paper 2275, p. 93-105.
28. Hallberg G.R., Libra R.D., Long K.R., Splinter R.C. (1987) - *Pesticides, groundwater, and rural drinking water quality in Iowa: In Pesticides and Groundwater: A Health Concern for the Midwest*. Navarre, Minn: The Freshwater Foundation and US Environmental Protection Agency, p. 83-104.
29. NRC - National Resource Council Board of Agriculture (1993) - *Soil and Water Quality: An agenda for agriculture*. National Academy Press, Washington DC.

Environmental Research 176 (2019) 108442

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

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

Alexis Temkin[a,*], Sydney Evans[a], Tatiana Manidis[b], Chris Campbell[a], Olga V. Naidenko[a]

[a] Environmental Working Group, 1436 U Street NW Suite 100, Washington, DC, 20009, USA
[b] Duke University, Nicholas School of the Environment, 9 Circuit Dr, Durham, NC, 27710, USA

ARTICLE INFO

Keywords:
Nitrate
Drinking water
Economic analysis
Colorectal cancer –reproductive outcomes

ABSTRACT

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

1. Introduction

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

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

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

* Corresponding author.
E-mail address: alexis@ewg.org (A. Temkin).

https://doi.org/10.1016/j.envres.2019.04.009
Received 21 December 2018; Received in revised form 9 April 2019; Accepted 10 April 2019
Available online 11 June 2019

List of abbreviations

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

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

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

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

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

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

2. Methods

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

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

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

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

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

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

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

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

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

2.3. Calculation of nitrate-attributable cases of disease

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

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

where.

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

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

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

where,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

where.

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

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

CSF = cancer slope factor.

BR = background cancer rate.

WCA = water consumption adjustment factor between populations.

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

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

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

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

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

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

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

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

3. Results

3.1. Annual nitrate-attributable disease cases

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

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

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

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

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

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

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

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

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

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

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

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

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

3.3. Meta-analysis of colorectal cancer studies

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

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

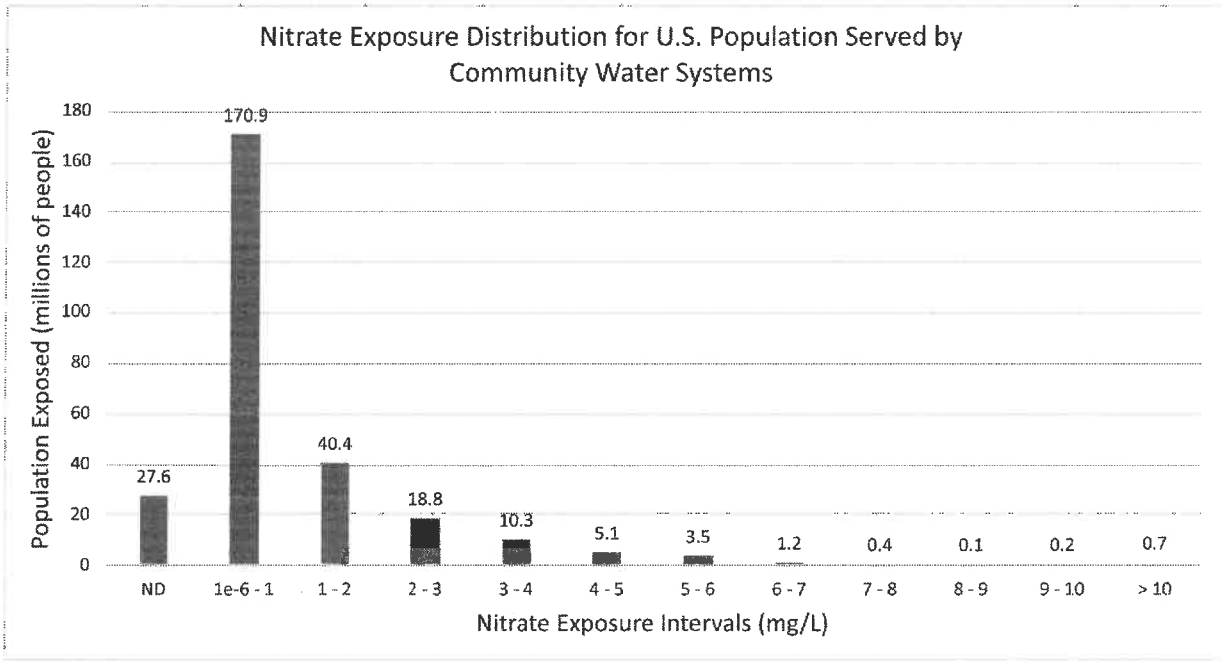


Fig. 1. U.S. population distribution for exposure to nitrate in drinking water at specific concentration ranges. Data from 2010 to 2017 for community water systems for all 50 states. The lower range of the nitrate exposure intervals represents the lowest average calculated. ND = non-detect. Source of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

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

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

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

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

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

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

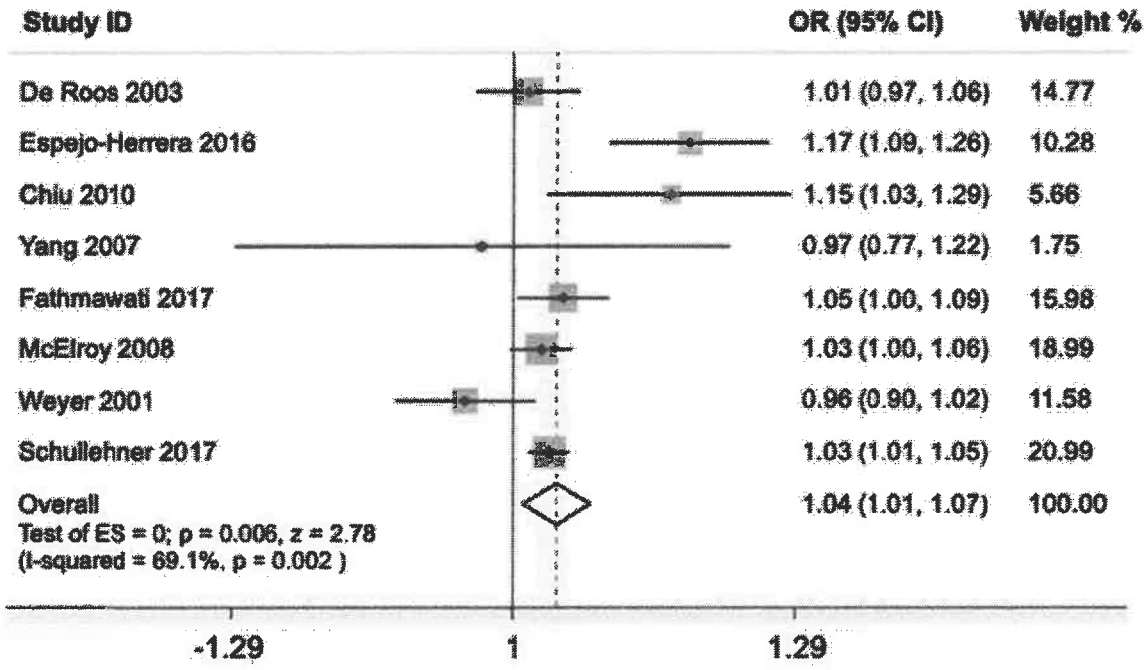


Fig. 2. Odds ratio (OR), 95% confidence intervals (95% CI), study weight within the overall meta-analysis and overall risk estimate based on studies of nitrate exposure from drinking water and colorectal cancer risk. ORs were obtained by exponentiating the study-specific slope estimates from generalized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

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

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

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

3.4. Risk-based drinking water benchmarks for nitrate

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

4. Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Availability of data and materials

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

Declarations of interest

None.

Authors' contributions

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

Submission declaration

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

Funding

This research was supported by grants from the Park Foundation and the Leon Lowenstein Foundation.

Ethics approval and consent to participate

Not applicable.

Acknowledgements

The authors gratefully acknowledge the help of Tasha Stoiber Ph.D. and David Andrews Ph.D. for assistance with technical review of the manuscript.

This research was supported by grants from the Park Foundation and the Leon Lowenstein Foundation.

Appendix A. Supplementary data

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

References

Brender, J.D., Weyer, P.J., Romitti, P.A., Mohanty, B.P., Shinde, M.U., Vyong, A.M., Sharkey, J.R., Dwivedi, D., Horel, S.A., Kantamneni, J., Huber Jr., J.C., Zheng, Q., Werler, M.M., Kelley, K.E., Griesenbeck, J.S., Zhan, F.B., Langlois, P.H., Suarez, L., Canfield, M.A., 2013. The national birth defects prevention study. Prenatal nitrate intake from drinking water and selected birth defects in offspring of participants in the national birth defects prevention study. Environ. Health Perspect. 121 (9), 1083–1089.

Camargo, M.C., Stayner, L.T., Straif, K., Reina, M., Al-Alem, U., Demers, P.A., Landrigan, P.J., 2011. Occupational exposure to asbestos and ovarian cancer: a Meta-analysis. Environ. Health Perspect. 119 (9), 1211–1217.

Cao, Y., Blount, B.C., Valentin-Blasini, L., Bernbaum, J.C., Phillips, T.M., Rogan, W.J., 2010. Goitrogenic anions, thyroid-stimulating hormone, and thyroid hormone in infants. Environ. Health Perspect. 18 (9), 1332–1337.

Chang, C., Chen, C., Wu, D., Yang, C., 2010. Nitrates in drinking water and the risk of death from rectal cancer: does hardness in drinking water matter? J. Toxicol. Environ. Health, Part A. 73, 1337–1347.

Chiu, H., Tsai, S., Wu, T., Yang, C., 2010. Colon cancer and content of nitrates and magnesium in drinking water. Magnes. Res. 23 (2), 81–89.

Cochrane Collaboration, 2011. Cochrane Handbook for Systematic Reviews of Interventions. Available at: http://handbook-5-1.cochrane.org/, **Version 5.1.0.**

De Roos, A.J., Ward, M.H., Lynch, C.F., Cantor, K.P., 2003. Nitrate in public water supplies and the risk of colon and rectum cancers. Epidemiology 14 (6), 640–649.

Deeks, J.J., Higgins, J.P., Altman, D.G., Green, S., 2011. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaborative.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Contr. Clin. Trials 7 (3), 177–188.

Desaigues, B., Ami, D., Bartczak, A., Braun-Kohlová, M., Chilton, S., Czajkowski, M., Farreras, V., Hunt, A., Hutchison, M., Jeanrenaud, C., Kaderjak, P., Máca, V., Markiewicz, O., Markowska, A., Metcalf, S., Navrud, S., Nielsen, J.S., Ortiz, R., Pellegrini, S., Rabl, A., Riera, R., Scasny, M., Stoeckel, M.E., Szántó, R., Urban, J., 2011. Economic valuation of air pollution mortality: a 9-country contingent valuation survey of value of a life year. Ecol. Indica 902–910.

Dunn, A., Grosse, S.D., Zuvekas, S.H., 2018. Adjusting health expenditures for inflation: a review of measures for health services research in the United States. Health Serv. Res. 53 (1), 175–196.

Edwards, T.M., Hamlin, H.J., Freymiller, H., Green, S., Thurman, J., Guillette Jr., L.J., 2018. Nitrate induces a type 1 diabetic profile in alligator hatchlings. Ecotoxicol. Environ. Saf. 147, 767–775.

Espejo-Herrera, N., Gracia-Lavedan, E., Boldo, E., Aragones, N., Perez-Gomez, B., Pollan, M., Molina, A.J., Fernandez, T., Martin, V., La Vecchia, C., et al., 2016. Colorectal cancer risk and nitrate exposure through drinking water and diet. Int. J. Cancer 139, 334–346.

Fathmawati, Fachiroh J., Gravitiani, E., Sarto, Husodo, A.H., 2017. Nitrate in drinking water and risk of colorectal cancer in Yogyakarta, Indonesia. J. Toxicol. Environ. Health, Part A. 80 (2), 120–128.

Grandjean, P., Bellanger, M., 2017. Calculation of the disease burden associated with environmental chemical exposures: application of toxicological information in health economic estimation. Environ. Health 16 (1), 123.

Grosse, S.D., Berry, R.J., Mick Tilford, J., Kucik, J.E., Waitzman, N.J., 2016. Retrospective assessment of cost savings from prevention: folic acid fortification and spina bifida in the U.S. Am. J. Prev. Med. 50 (5 Suppl. 1), S74–S80.

Gulis, G., Czompolyvova, M., Cerhan, J., 2002. An ecologic study of nitrate in municipal drinking water and cancer incidence in Trnava District, Slovakia. Environ. Res. Sec. A 88, 182–187.

Hamlin, H.J., Edwards, T.M., McCoy, J., Cruze, L., Guillette Jr., L.J., Nov 2016. Environmentally relevant concentrations of nitrate increase plasma testosterone concentrations in female American alligators (Alligator mississippiensis). Gen. Comp. Endocrinol. 1 (238), 55–60.

Health Canada, 2013. Guidelines for Canadian Drinking Water Quality. Guideline Technical Document. Nitrate and nitrite. Available at: http://healthycanadians.gc.ca/publications/healthy-living-vie-saine/water-nitrate-nitrite-eau/alt/water-nitrate-nitrite-eau-eng.pdf.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altma, D.G., 2003. Measuring inconsistency in meta-analyses. Br. Med. J. 327, 557–560.

Horton, M.K., Blount, B.C., Valentin-Blasini, L., Wapner, R., Whyatt, R., Gennings, C., Factor-Litvak, P., Nov 2015. Co-occurring exposure to perchlorate, nitrate and thiocyanate alters thyroid function in healthy pregnant women. Environ. Res. 143 (Pt A), 1–9.

IARC (International Agency for Research on Cancer), 2010. Ingested Nitrate and Nitrite, and Cyanobacterial Peptide Toxins. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. v. 94 Available at: https://monographs.iarc.fr/monographs-and-supplements-available-online/.

Inoue-Choi, M., Jones, R.R., Anderson, K.E., Cantor, K.P., Cerhan, J.R., Krasner, S., Robien, K., Weyer, P.J., Ward, M.H., 2015. Nitrate and nitrite ingestion and risk of ovarian cancer among postmenopausal women in Iowa. Int. J. Cancer 137 (1), 173–182.

Institute for Clinical and Economic Review, 2017. Final Value Assessmnet Framework: Updates for 2017-2019. Available at: https://icer-review.org/wp-content/uploads/2017/06/ICER-value-assessment-framework-Updated-050818.pdf.

Institute of Medicine, 2007. Preterm Birth: Causes, Consequences, and Prevention. The National Academies Press, Washington, DC.

Jensen, V.B., Darby, J.L., Seidel C Gorman, C., 2012. Technical Report 6: Drinking Water Treatment for Nitrate. Center for Watershed Sciences, University of California, Davis Available at: groundwaternitrate.ucdavis.edu/files/139107.pdf.

Jones, R.R., Weyer, P.J., DellaValle, C.T., Inoue-Choi, M., Anderson, K.E., Cantor, K.P., Krasner, S., Robien, K., Freeman, L.E., Silverman, D.T., Ward, M.H., 2016. Nitrate from drinking water and diet and bladder cancer among postmenopausal women in Iowa. Environ. Health Perspect. 124 (11), 1751–1758.

Jones, R.R., Weyer, P.J., Dellavalle, C.T., Robien, K., Cantor, P., Krasner, S., Beane Freeman, L.E., Ward, M.H., 2017. Ingested nitrate, disinfection by-products, and kidney cancer risk in older women. Epidemiology 28 (5), 703–711.

Jones, R.R., DellaValle, C.T., Weyer, P.J., Robien, K., Cantor, K., Krasner, S., Beane Freeman, L.E., Ward, M.H., May 2019. Ingested nitrate, disinfection by-products, and risk of colon and rectal cancer in the Iowa Women's Health Study cohort. Environ. Int. 126, 242–251.

Kenny, J.F., Barber, N.L., Hutson, S.S., Linsey, K.S., Lovelace, J.K., Maupin, M.A., 2009. Estimated use of water in the United States in 2005: U.S. Geological survey circular 1344. Available at: https://pubs.usgs.gov/circ/1344/pdf/c1344.pdf.

Khatri, J., Mills, C.E., Maskell, P., Odongerel, C., Webb, A.J., 2017. It is rocket science - why dietary nitrate is hard to 'beet'! Part I: twists and turns in the realization of the nitrate-nitrite-NO pathway. Br. J. Clin. Pharmacol. 83 (1), 129–139.

Kormos, C.E., Wilkinson, A.J., Davey, C.J., Cunningham, A.J., 2014. Low birth weight and intelligence in adolescence and early adulthood: a meta-analysis. J. Public Health 36 (2), 213–224.

Kuo, H., Wu, T., Yang, C., 2007. Nitrates in drinking water and risk of death from rectal cancer in Taiwan. J. Toxicol. Environ. Health A Curr. Issues 70 (20), 1717–1722.

Malits, J., Blustein, J., Trasande, L., Attina, T.M., 2018. Perfluorooctanoic acid and low birth weight: estimates of US attributable burden and economic costs from 2003 through 2014. Int. J. Hyg Environ. Health 221 (2), 269–275.

March of Dimes, 2019. Peristats. Available at: https://www.marchofdimes.org/peristats/Peristats.aspx.

Mariotto, A.B., Yabroff, K.R., Shao, Y., Feuer, E.J., Brown, M.L., 2011. Projections of the cost of cancer care in the United States: 2010-2020. J. Natl. Cancer Inst. 103 (2), 117–128.

Marseille, E., Laarson, B., Kazi, D.S., Kahn, J.G., Rosen, S., 2015. Threshold for the cost-effectiveness of interventions: alternative approaches. Bull. World Health Organ. 93, 118–124.

McElroy, J.A., Trentham-Dietz, A., Gangnon, R.E., Hampton, J.M., Bersch, A.J., Kanarek, M.S., Newcomb, P.A., 2008. J. Water Health 6 (3), 399–409.

Migeot, V., Albouy-Llaty, M., Carles, C., Limousi, F., Strezlec, S., Dupuis, A., Rabouan, S., 2013. Drinking-water exposure to a mixture of nitrate and low-dose atrazine metabolites and small-for-gestational age (SGA) babies: a historic cohort study. Environ. Res. 122, 58–64.

Mirvish, S.S., Grandjean, A.C., Moller, H., Fike, S., Maynard, T., Jones, L., Rosinsky, S., Nie, G., 1992. N-nitrosoproline excretion by rural Nebraskans drinking water of varied nitrate content. Cancer Epidemiol. Biomark. Prev. 1 (6), 455–461.

Morales-Suarez-Varela, M.M., Llopis-Gonzalez, A., Tejerizo-Perez, M.L., 1995. Impact of nitrates in drinking water on cancer mortality in Valencia, Spain. Eur. J. Epidemiol. 11 (1), 15–21.

National Cancer Institute, 2018. Iowa Women's Health Study: Epidemiology of Cancer in a Cohort of Older Women. Available at: https://epi.grants.cancer.gov/Consortia/members/iowawomen.html.

National Research Council, 1993. Pesticides in the Diets of Infants and Children. The National Academies Press, Washington, DC Available at: https://www.nap.edu/catalog/2126/pesticides-in-the-diets-of-infants-and-children.

National Research Council, 1997. Safe Water from Every Tap: Improving Water Service to Small Communities. The National Academies Press, Washington, DC. https://doi.org/10.17226/5291.

National Research Council (NRC) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, 2009. Science and Decisions: Advancing Risk Assessment. National Academies Press (US), Washington (DC) Available at: https://www.ncbi.nlm.nih.gov/books/NBK214630/.

Oakeshott, P., Hunt, G.M., Poulton, A., Reid, F., 2010. Expectation of life and unexpected death in open spina bifida: a 40-year complete, non-selective, longitudinal cohort study. Dev. Med. Child Neurol. 52 (8), 749–753.

OEHHA (California Office of Environmental Health Hazard Assessment), 2004. Public Health Goal for Arsenic in Drinking Water. Available at: https://oehha.ca.gov/water/public-health-goal/public-health-goal-arsenic-drinking-water.

OEHHA (California Office of Environmental Health Hazard Assessment), 2018a. Nitrate and Nitrite in Drinking Water. Available at: https://oehha.ca.gov/media/downloads/crnr/nitratephg051118.pdf.

OEHHA (California Office of Environmental Health Hazard Assessment), 2018b. Public Health Goals (PHGs). Available. https://oehha.ca.gov/water/public-health-goals-phgs.

Pennino, M.J., Compton, J.E., Leibowitz, S.G., 2017. Trends in drinking water nitrate violations across the United States. Environ. Sci. Technol. 51, 13450–13460.

Poulsen, R., Cedergreen, N., Hayes, T., Hansen, M., 2018. Nitrate: an environmental endocrine disruptor? A review of evidence and research needs. Environ. Sci. Technol. 52 (7), 3869–3887.

Rose, G., 2001. Sick individuals and sick populations. Int. J. Epidemiol. 30 (3), 427–432.

Rupert, M.G., 2008. Decadal-scale changes of nitrate in ground water of the United States, 1988–2004. J. Environ. Qual. 37 (Suppl. 5) S-240-S-248. https://dl.sciencesocieties.org/publications/jeq/abstracts/37/5_Supplement/S-240.

Schullehner, J., Hansen, B., Thygesen, M., Pedersen, C.B., Sigsgaard, T., 2018. Nitrate in drinking water and colorectal cancer risk: a nationwide population-based cohort study. Int. J. Cancer 143 (1), 73–79.

SEER, 2018. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Available at: https://seer.cancer.gov/.

Soerjomaataram, I., Lortet-Tieulent, J., Ferlay, J., Forman, D., Mathers, C., Parkin, D.M., Bray, F., 2012. Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer. BMC Med. Res. Methodol. 12, 125.

STATA Community-contributed Packages for Meta-Analysis in Stata. Available at: https://www.stata.com/support/faqs/statistics/meta-analysis/, Accessed date: 6 November 2018.

Stayner, L.T., Almberg, K., Jones, R., Graber, J., Pedersen, M., Turyk, M., 2017a. Atrazine and nitrate in drinking water and the risk of preterm delivery and low birth weight in four Midwestern states. Environ. Res. 152, 294–303.

Stayner, L., 2017b. Review of the Draft Public Health Goal for Nitrate and Nitrite in Drinking Water by Leslie Stayner. PhD Professor of Epidemiology University of Illinois at Chicago School of Public Health. June 19, 2017. Available at: https://oehha.ca.gov/media/downloads/crnr/peerreviewstayner061917.pdf.

Tonacchera, M., Pinchera, A., Dimida, A., Ferrarini, E., Agretti, P., Vitti, P., Santini, F., Crump, K., Gibbs, J., 2004. Relative potencies and additivity of perchlorate, thiocyanate, nitrate, and iodide on the inhibition of radioactive iodide uptake by the human sodium iodide symporter. Thyroid 14, 1012–1019.

U.S. Cancer Statistics Working Group U.S. Cancer, 1999-2015. Statistics Data Visualizations Tool, Based on November 2017 Submission Data. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute Available at: www.cdc.gov/cancer/dataviz.

U.S. Department of Labor Bureau of Labor Statistics, 2017. Consumer Price Index. US Department of Labor Bureau of Labor Statistics Available at: http://data.bls.gov/cgi-bin/surveymost?cu.

U.S. EPA, 1992. EPA's Approach for Assessing the risks associated with Chronic Exposure to Carcinogens. Background Document 2. January 17, 1992. Available at: https://www.epa.gov/iris/epas-approach-assessing-risks-associated-chronic-exposure-carcinogens.

U.S. EPA, 2002. Review of the Reference Dose and Reference Concentration Processes Document. Available at: https://www.epa.gov/risk/review-reference-dose-and-reference-concentration-processes-document.

U.S. EPA, 2005. Economic Analysis for the Final Stage 2 Disinfectants and Disinfection Byproducts Rule. Available at: https://nepis.epa.gov/Exe/ZyPDF.cgi?Dockey=P1005OOX.txt.

U.S. EPA, 2010. Guidelines for Preparing Economic Analyses. Available at: https://www.epa.gov/environmental-economics/guidelines-preparing-economic-analyses.

U.S. EPA, 2011. Nutrient Indicators Dataset. Estimated Nitrate Concentrations in Groundwater Used for Drinking. Available at: https://www.epa.gov/nutrient-policy-data/estimated-nitrate-concentrations-groundwater-used-drinking.

U.S. EPA, 2015a. Benefit and Cost Analysis for the Effluent Limitations Guidelines and Standards for the Steam Electric Power Generating Point Source Category. Available: https://www.epa.gov/sites/production/files/2015-10/documents/steam-electric_benefit-cost-analysis_09-29-2015.pdf.

U.S. EPA, 2015b. Regulatory Impact Analysis of the Final Revisions to the National Ambient Air Quality Standards for Ground-Level Ozone. Available at: https://www3.epa.gov/ttnecas1/docs/20151001ria.pdf.

U.S. EPA, 2018a. 2018 Edition of the Drinking Water Standards and Health Advisories Tables. Available at: https://www.epa.gov/sites/production/files/2018-03/documents/dwtable2018.pdf.

U.S. EPA, 2018b. Enforcement and Compliance Online (ECHO) Database. Analyze Trends: Drinking Water Dashboard. Available at: https://echo.epa.gov/trends/comparative-maps-dashboards/drinking-water-dashboard.

van Grinsven, H.J., Rabl, A., de Kok, T.M., 2010. Estimation of incidence and social cost of colon cancer due to nitrate in drinking water in the EU: a tentative cost-benefit assessment. Environ. Health 9, 58.

van Maanen, J.M., Welle, I.J., Hageman, G., Dallinga, J.W., Mertens, P.L., Kleinjans, J.C., 1996. Nitrate contamination of drinking water: relationship with HPRT variant frequency in lymphocyte DNA and urinary excretion of N-nitrosamines. Environ. Health Perspect. 104 (5), 522–528.

Villanueva, C.M., Fernandez, F., Malats, N., Grimalt, J.O., Kogevinas, M., 2003. Meta-analysis of studies on individual consumption of chlorinated drinking water and bladder cancer. J. Epidemiol. Community Health 57, 166–173.

Viscusi, V.K., Aldy, J.E., 2003. The value of a statistical life: a critical review of market estimates throughout the world. J. Risk Uncertain. 27 (1), 5–76.

Ward, M.H., Rusiecki, J.A., Lynch, C.F., Cantor, K.P., 2007. Nitrate in public water supplies and the risk of renal cell carcinoma. Cancer Causes Control 18, 1141–1151.

Ward, M.H., Kilfoy, B.A., Weyer, P.J., Anderson, K.E., Folsom, A.R., Cerhan, J.R., 2010. Nitrate intake and the risk of thyroid cancer and thyroid disease. Epidemiology 21 (3), 389–395.

Ward, M.H., Jones, R.R., Brender, J.D., de Kok, T.M., Weyer, P.J., Nolan, B.T., Villanueva, C.M., van Breda, S.G., 2018. Drinking water nitrate and human health: an updated review. Int. J. Environ. Res. Public Health 15 (7), E1557 Jul 23.

Weir Schechinger, A., Cox, C., 2018. America's Nitrate Habit Is Costly and Dangerous. Available at: https://www.ewg.org/research/nitratecost/.

Weyer, P.J., Cerhan, J.R., Kross, B.C., Hallberg, G.R., Kantamneni, J., Breuer, G., Jones, M.P., Zhen, W., Lynch, C.F., 2001. Municipal drinking water nitrate level and cancer risk in older women: the Iowa women's health study. Epidemiology 12 (3), 327–338.

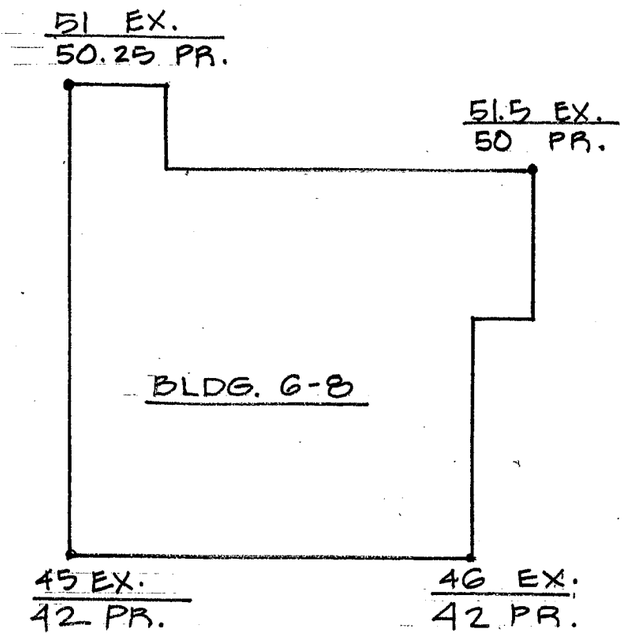
World Health Organization (WHO), 2018. Health Statistics and Information Systems. Metrics: Disability-Adjusted Life Year (DALY). Available at: https://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/.

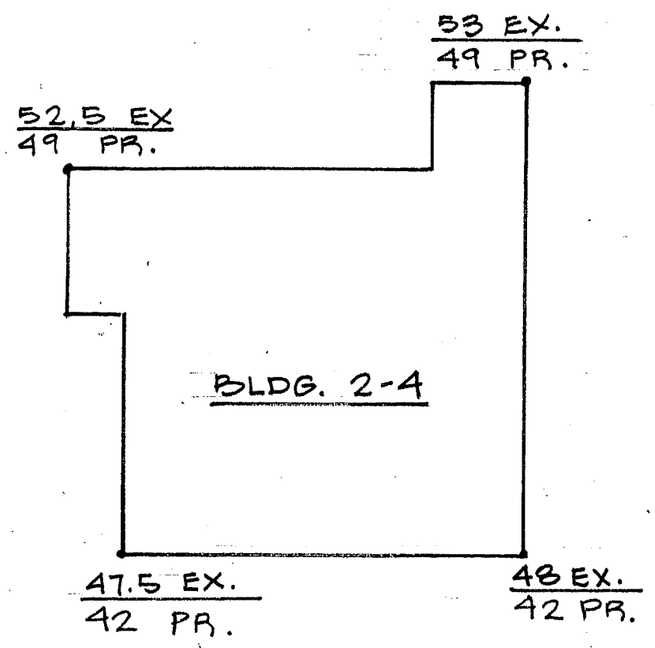
Yabroff, K.R., Bradley, C.J., Mariotto, A.B., Brown, M.L., Feuer, E.J., 2008. Estimates and projections of value of life lost from cancer deaths in the United States. J. Natl. Cancer Inst. 100 (24), 1755–1762.

Yabroff, K.R., Lund, J., Kepka, D., Mariotto, A., 2012. Economic burden of cancer in the US: estimates, projections, and future research. Cancer Epidemiol. Biomark. Prev. 20 (10), 2006–2014.

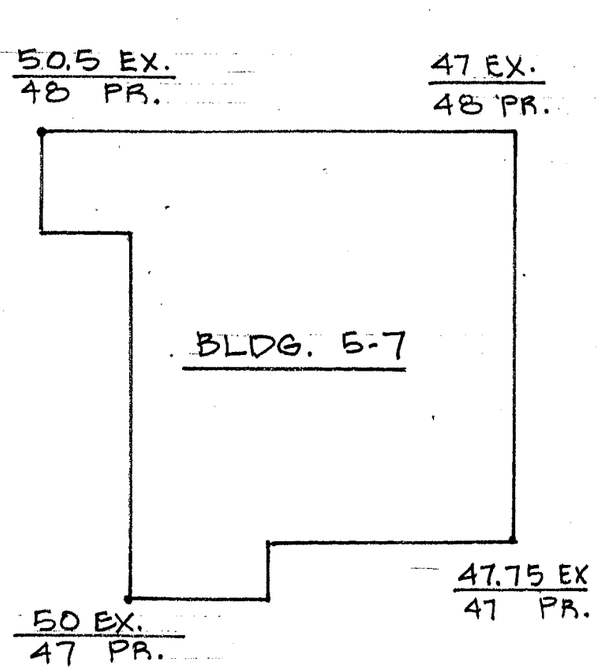
Yang, C., Wu, D., Chang, C., 2007. Nitrate in drinking water and risk of death from colon cancer in Taiwan. Environ. Int. 33, 649–653.

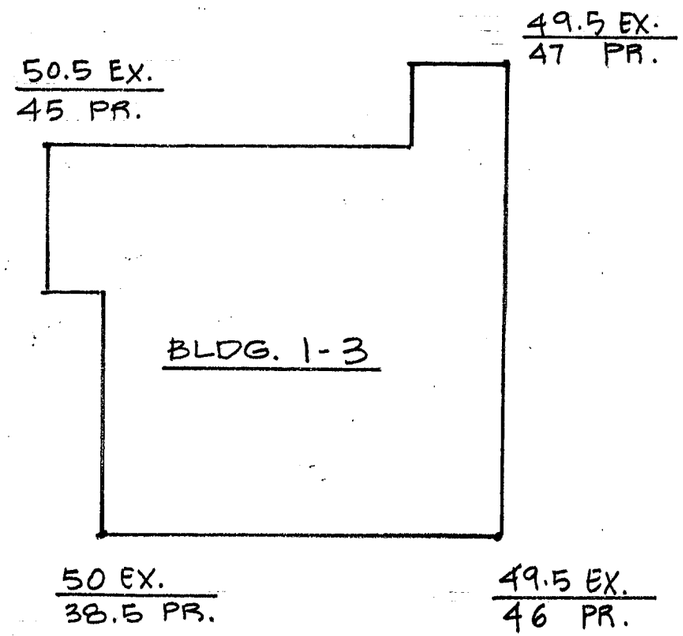
Zeise, L., Wilson, R., Crouch, E.A., 1987. Dose-response relationships for carcinogens: a review. Environ. Health Perspect. 73, 259–306.





	6-8	2-4	5-7	1-3
AVERAGE EXISTING GRADE	48.3	50.25	48.8	49.8
AVERAGE PROPOSED GRADE	46	45.5	47.5	44.12
AVG. BUILDING HEIGHT ABOVE EXISTING GRADE	26.2	23.25	22.7	21.7
AVG. BUILDING HEIGHT ABOVE PROPOSED GRADE	28.5	28	24	27.38
ACTUAL ELEVATION ABOVE SEA LEVEL TO PROPOSED RIDGE LINE	74.5	73.5	71.5	71.5





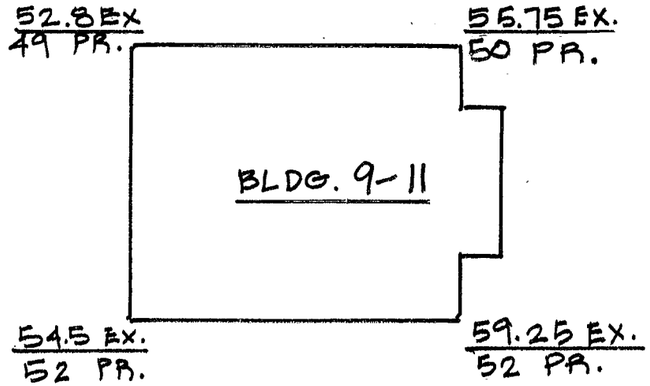
BUILDING HEIGHT CALCULATIONS

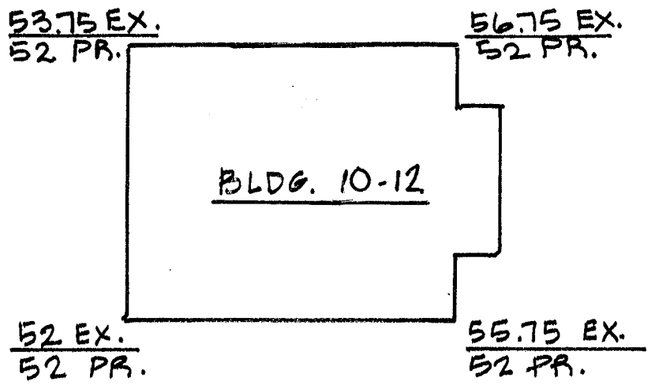
BUILDINGS 1-3, 2-4, 5-7, 6-8
CLOVERLEAF TRURO RENTAL HOUSING

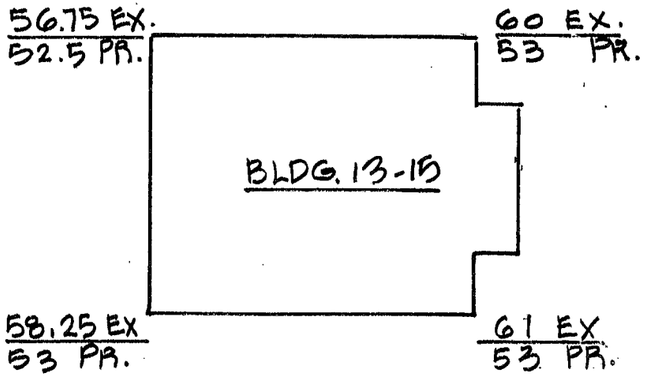
SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street Somerville, Massachusetts 02145 ~ 617.623.1833

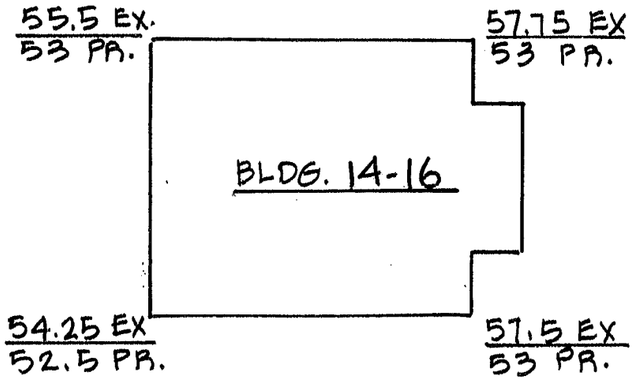
2.20.20

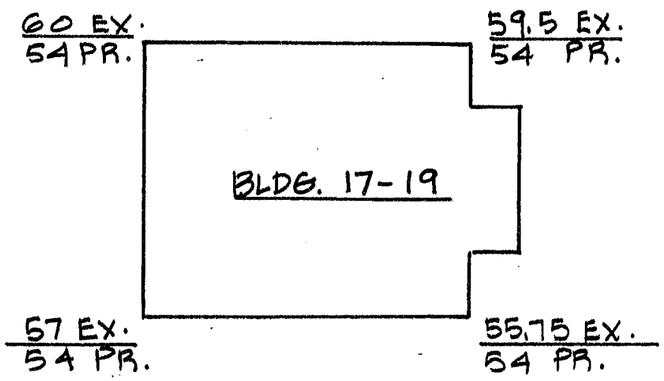
A-3

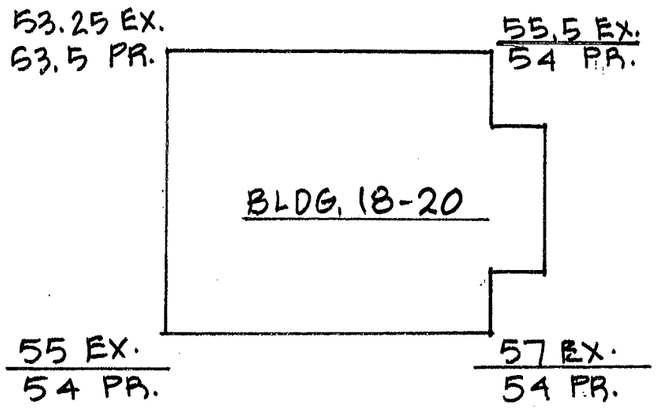












	9-11	10-12	13-15	14-16	17-19	18-20
AVERAGE EXISTING GRADE	55.5	54.5	59.0	56.25	58.0	55.18
AVERAGE PROPOSED GRADE	50.75	52.0	52.8	52.8	54.0	53.87
BLDG. HEIGHT ABOVE EXISTING GRADE	24'-0"	26'-0"	22'-6"	25'-3"	24'-6"	27'-3"
BLDG. HEIGHT ABOVE PROPOSED GRADE	28'-3"	28'-6"	28'-6"	28'-8"	28'-6"	28'-6"
ACTUAL ELEVATION ABOVE SEA LEVEL TO PROPOSED RIDGELINE	79.0	80.0	81.0	81.0	82.0	82.0

BUILDING HEIGHT CALCULATIONS

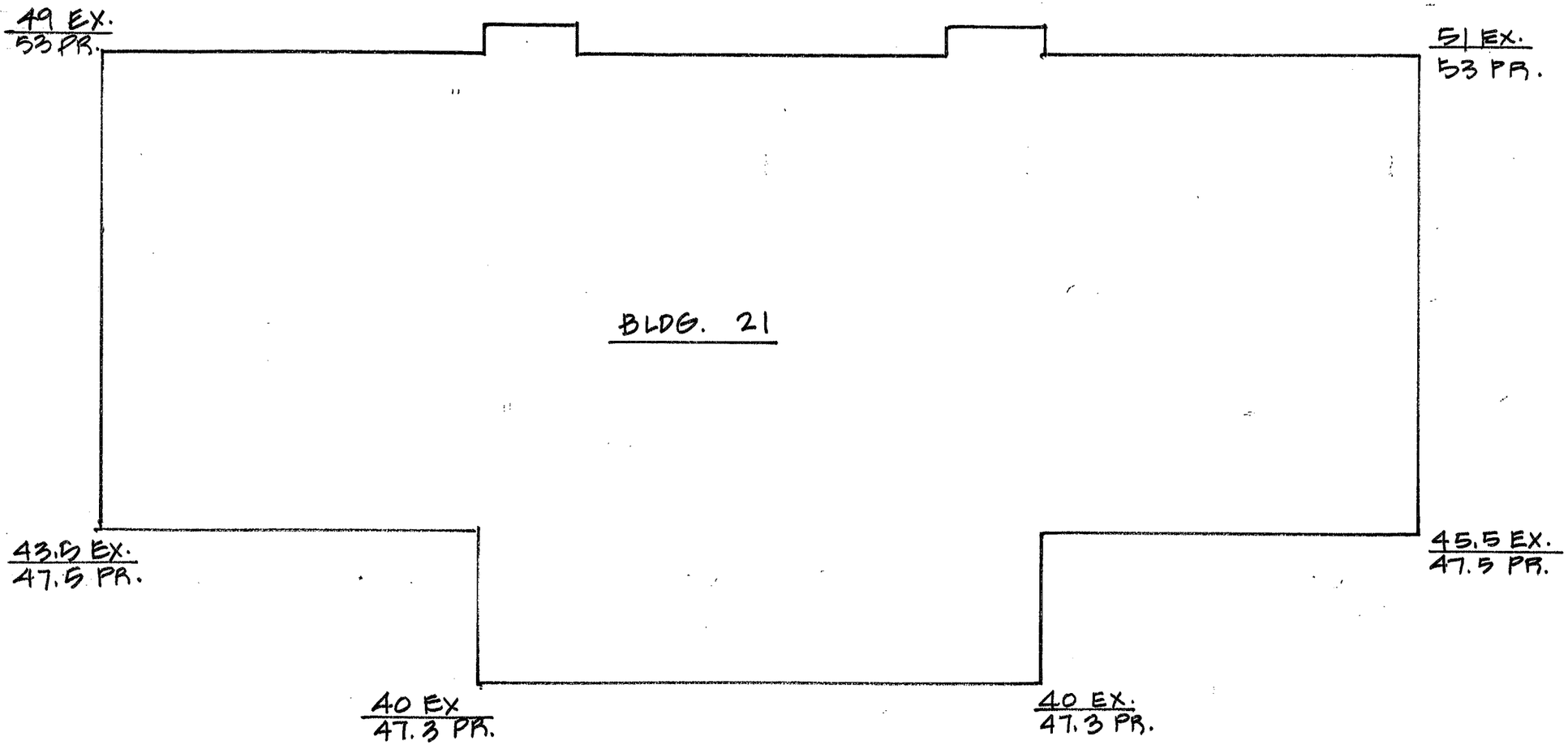
CLOVERLEAF 9-11, 10-12, 13-15, 14-16, 17-19, 18+20
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street Somerville, Massachusetts 02145 ~ 617.623.1833

2-20-20

A3

AVERAGE EXISTING GRADE	44.8
AVERAGE PROPOSED GRADE	49.2
BLDG. HEIGHT ABOVE AVG. EXISTING GRADE	41'-5"
BLDG. HEIGHT ABOVE AVG. PROPOSED GRADE	37'-0"
ACTUAL ELEVATION ABOVE SEA LEVEL TO PROPOSED RIDGELINE	86.3

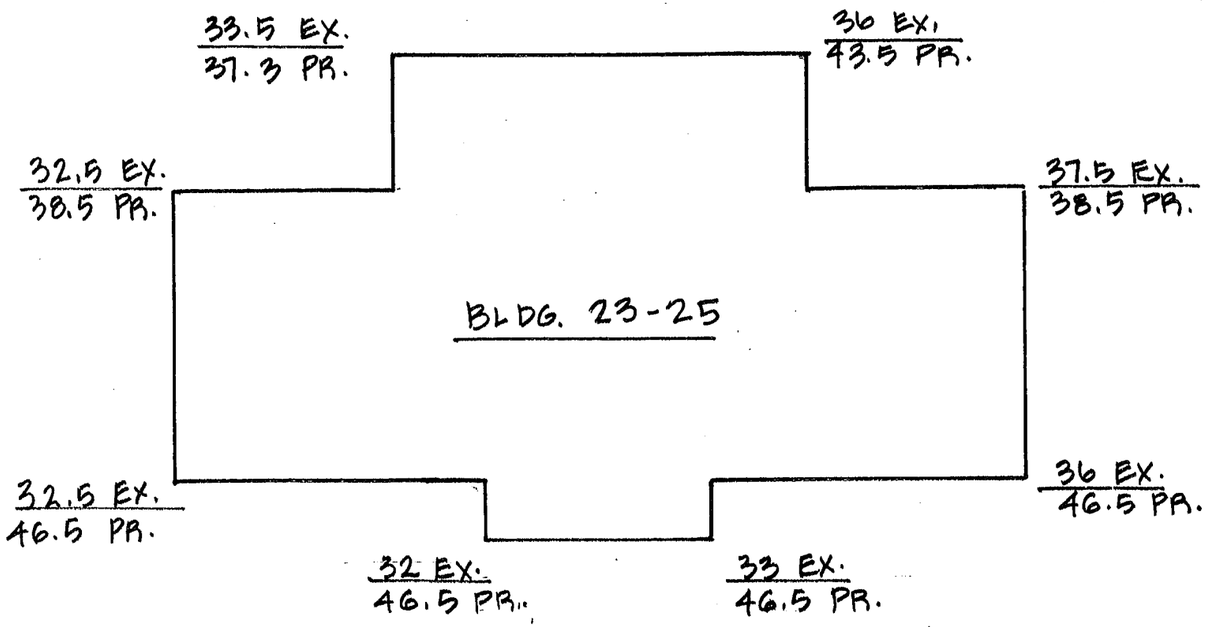


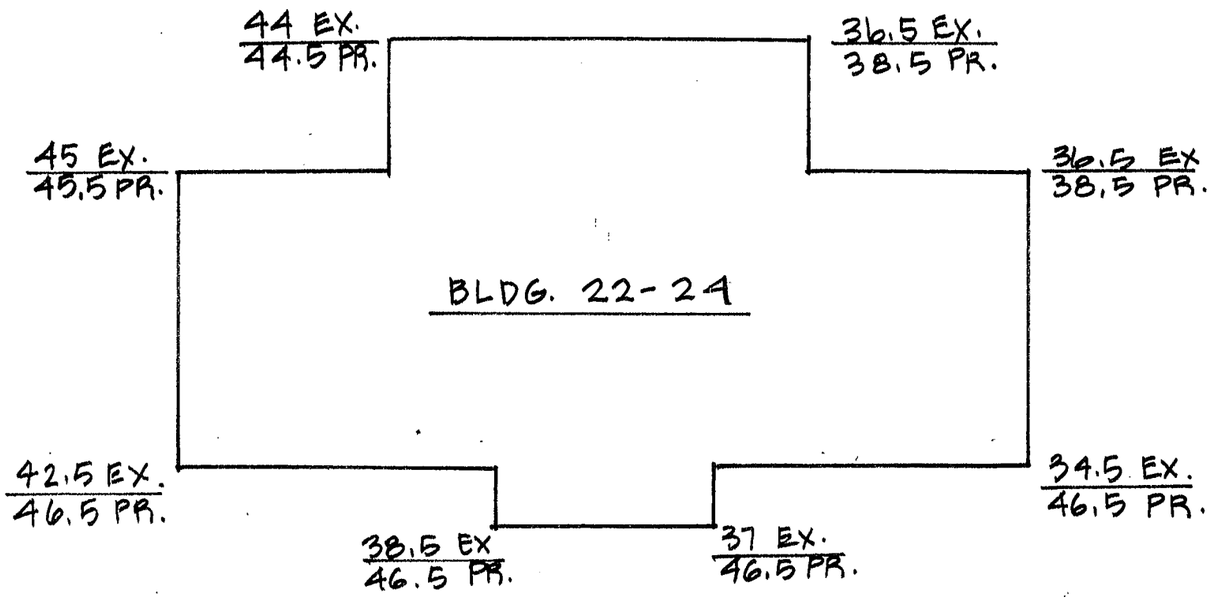
BUILDING HEIGHT CALCULATIONS
CLOVERLEAF BLDG. 21
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street Somerville, Massachusetts 02145 ~ 617.623.1833

2-20-20

A3





	23-25	22-24
AVERAGE EXISTING GRADE	34.75	39.7
AVERAGE PROPOSED GRADE	43.0	44.12
BLDG. HEIGHT ABOVE EXISTING GRADE (AVG.)	36'-11"	31'-11"
BLDG. HEIGHT ABOVE PROPOSED GRADE (AVG.)	28'-8"	29'-6"
ACTUAL ELEVATION ABOVE SEA LEVEL TO PROPOSED RIDGELINE	71.8	71.8

BUILDING HEIGHT CALCULATIONS

CLOVERLEAF 22-24, 23-25

CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street Somerville, Massachusetts 02145 - 617.623.1833

JESSICA ROMUALDI SNARE
REGISTERED ARCHITECT
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

2-20-20

A3

CLOVERLEAF TRURO RENTAL HOUSING
BUILDINGS 1-3, 2-4, AND 6-8 (Buildings may be mirrored)

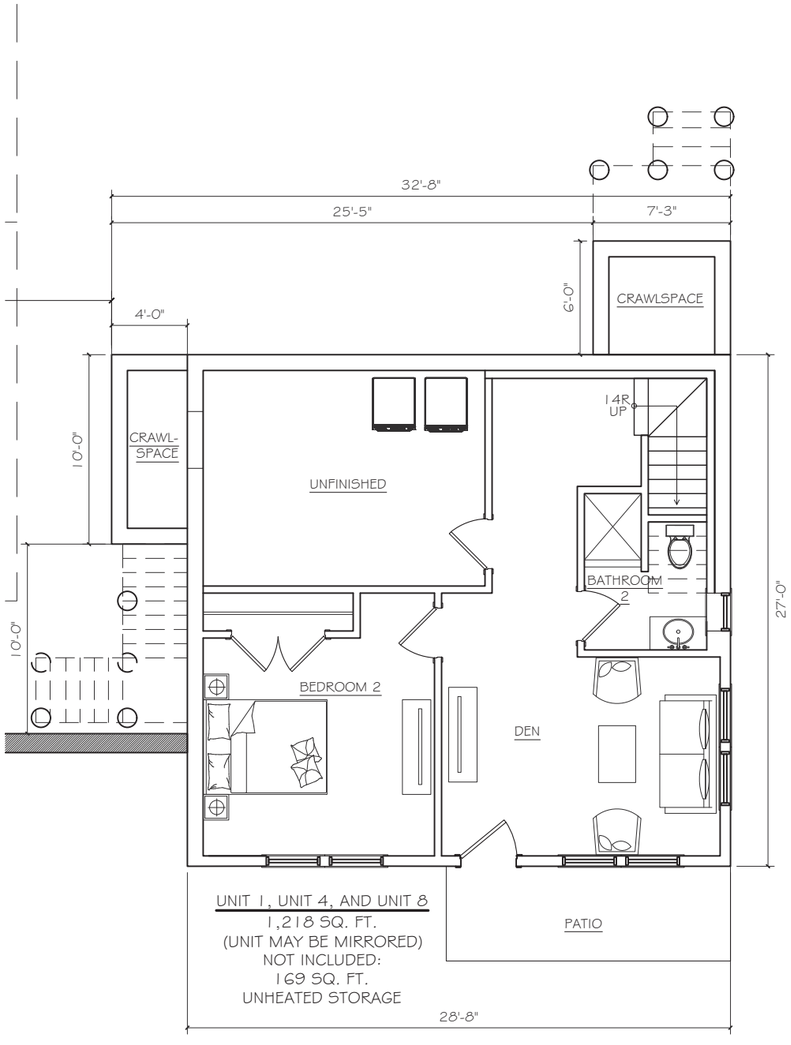
Truro, Massachusetts

Thursday, February 20, 2020

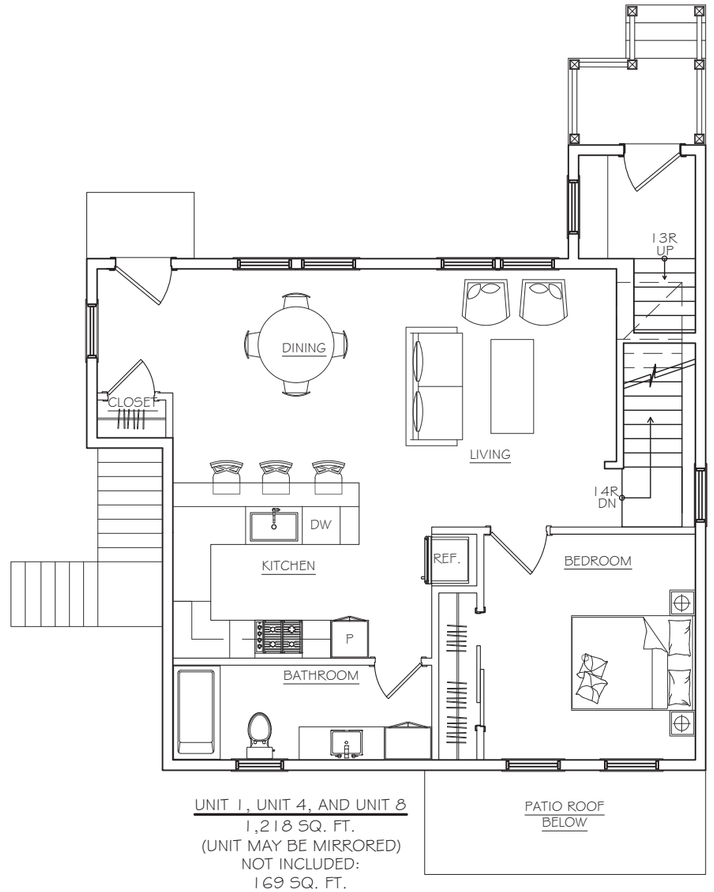
Spring Hill Design

INTERIORS ARCHITECTURE SPACE PLANNING

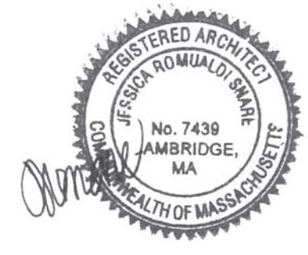
21 Dartmouth Street, Somerville, MA, 02145 ~ 617.623.1833



1 FIRST/GARDEN LEVEL PLAN UNIT 1, UNIT 4, AND UNIT 8
SCALE: 1/8" = 1'-0"



2 SECOND/MAIN ENTRY LEVEL PLAN UNIT 1, UNIT 4, AND UNIT 8
SCALE: 1/8" = 1'-0"



DATE:
02.20.20

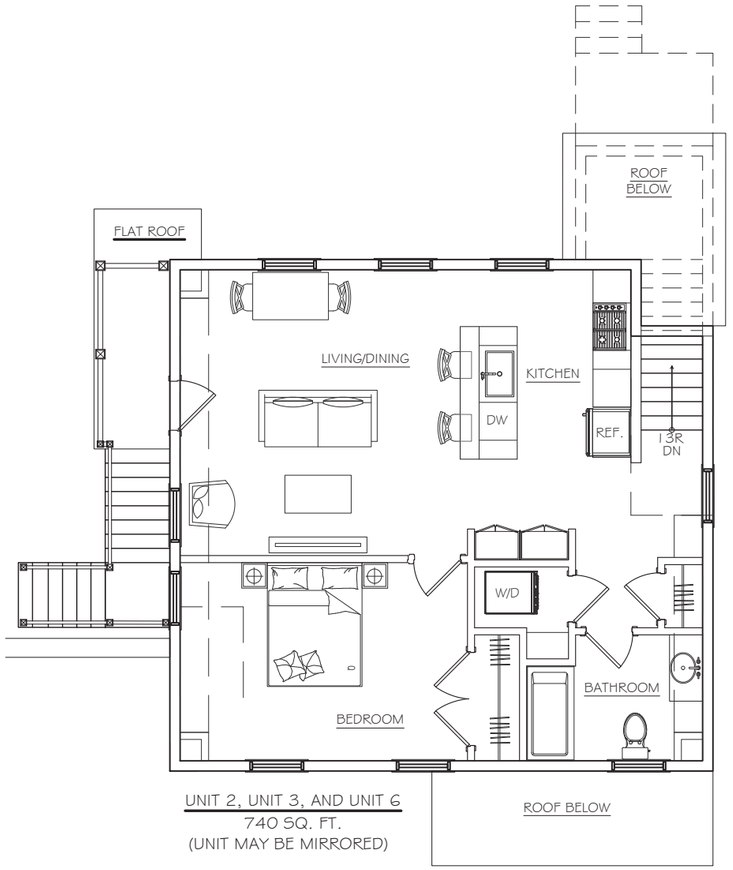
UNIT 1, UNIT 4, AND UNIT 8 PLANS

CLOVERLEAF BUILDINGS 1-3, 2-4, AND 6-8
CLOVERLEAF TRURO RENTAL HOUSING

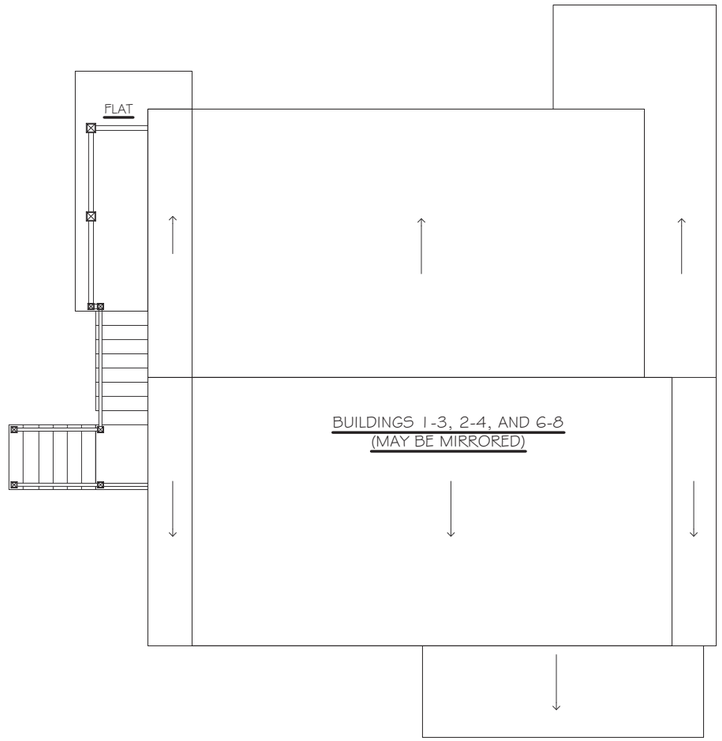
SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A1.1



1 THIRD LEVEL PLAN UNIT 2, UNIT 3, AND UNIT 6
SCALE: 1/8" = 1'-0"



2 BUILDINGS 1-3, 2-4, AND 6-8 ROOF PLAN
SCALE: 1/8" = 1'-0"

THIRD LEVEL AND ROOF PLANS

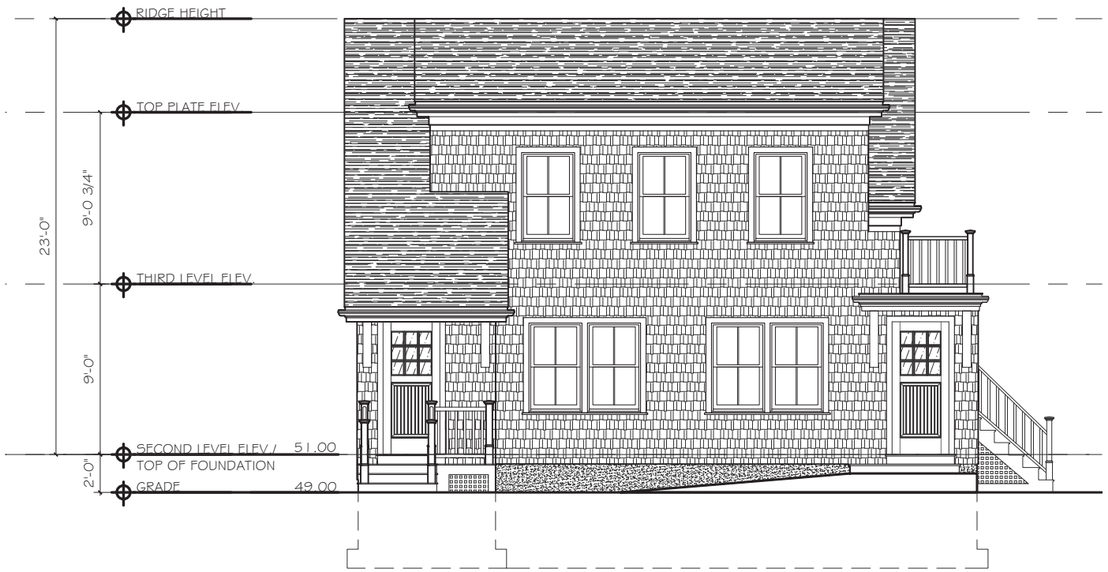
CLOVERLEAF BUILDINGS 1-3, 2-4, AND 6-8
CLOVERLEAF TRURO RENTAL HOUSING

DATE: 02.20.20

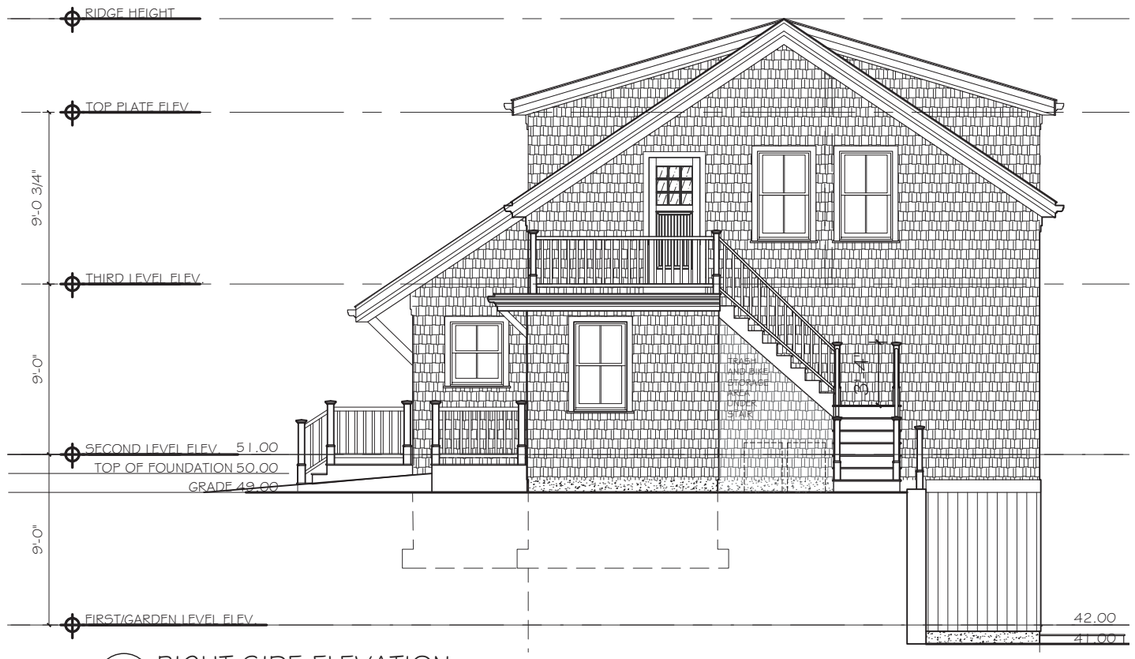
SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

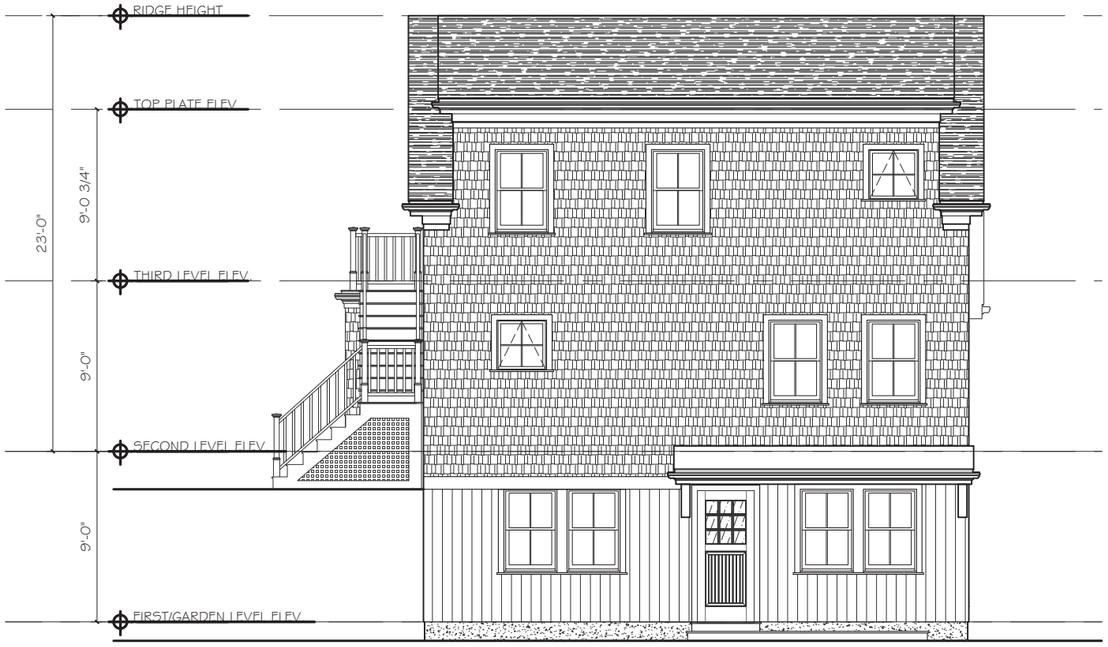
A1.2



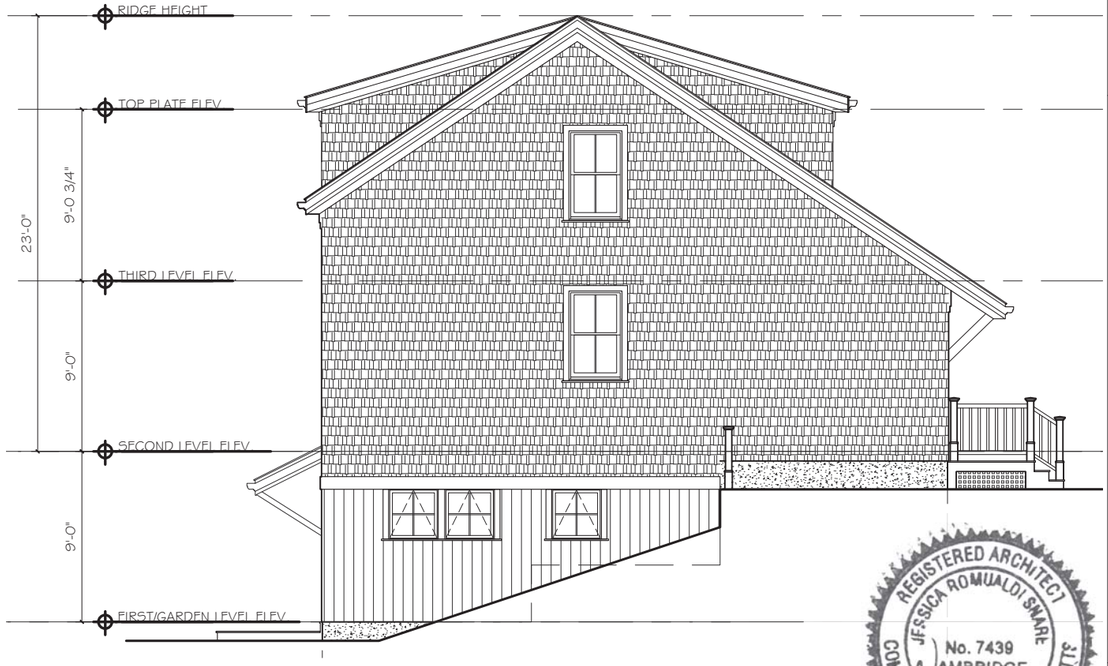
1 FRONT ELEVATION
SCALE: 1/8" = 1'-0"



2 RIGHT SIDE ELEVATION
SCALE: 1/8" = 1'-0"



3 BACK ELEVATION
SCALE: 1/8" = 1'-0"



4 LEFT SIDE ELEVATION
SCALE: 1/8" = 1'-0"

DATE:
02.20.20

FRONT ELEVATION

CLOVERLEAF BUILDINGS 1-3, 2-4, AND 6-8
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/4" = 1'-0"

A2.1

CLOVERLEAF TRURO RENTAL HOUSING
BUILDING 5-7

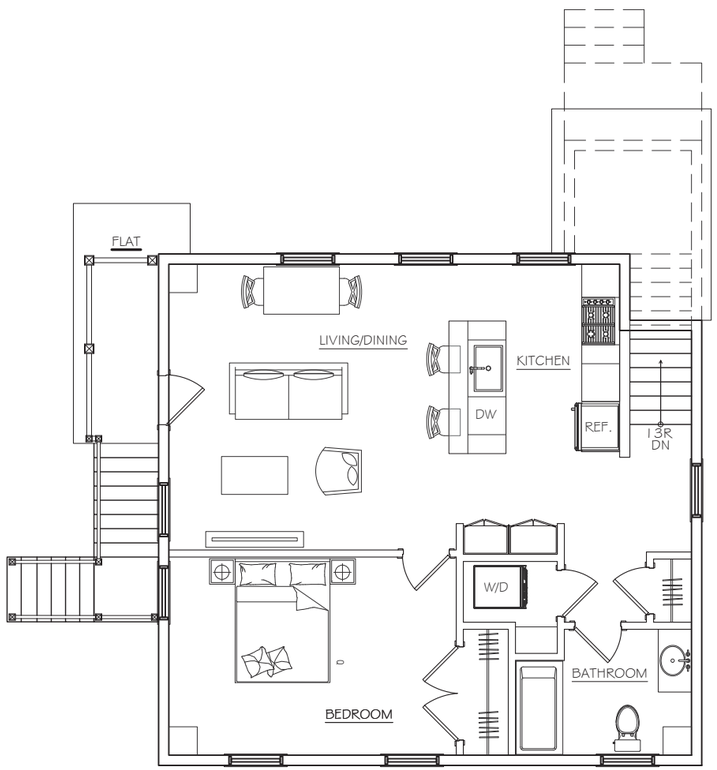
Truro, Massachusetts

Thursday, February 20, 2020

Spring Hill Design

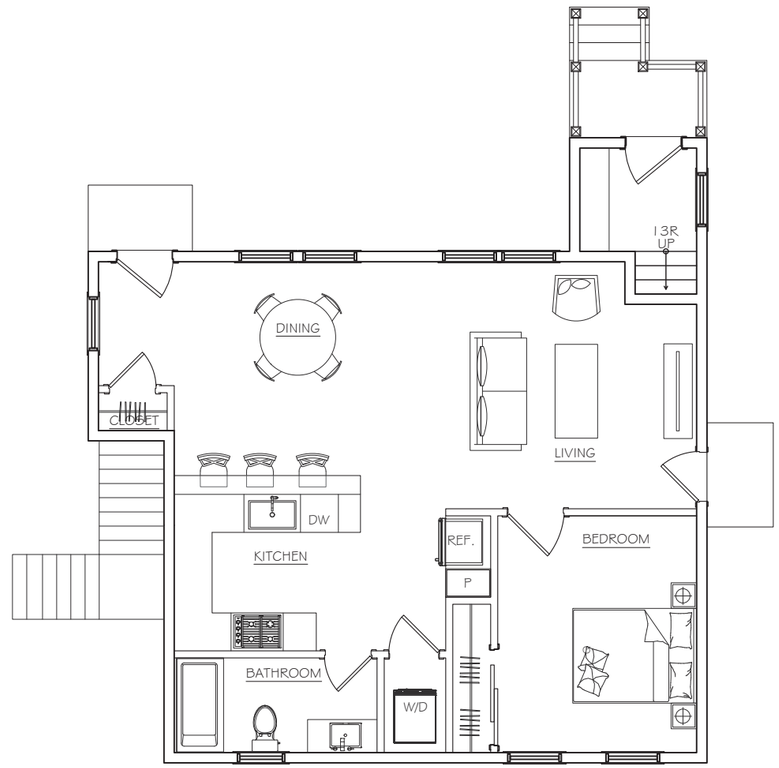
INTERIORS ARCHITECTURE SPACE PLANNING

21 Dartmouth Street, Somerville, MA, 02145 ~ 617.623.1833



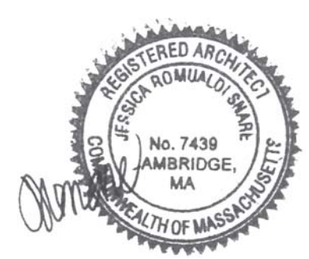
UNIT 5
752 SQ. FT.

1 UNIT 5 FLOOR PLAN
SCALE: 1/8" = 1'-0"



UNIT 7
742 SQ. FT.

2 UNIT 7 FLOOR PLAN
SCALE: 1/8" = 1'-0"



DATE:
02.20.20

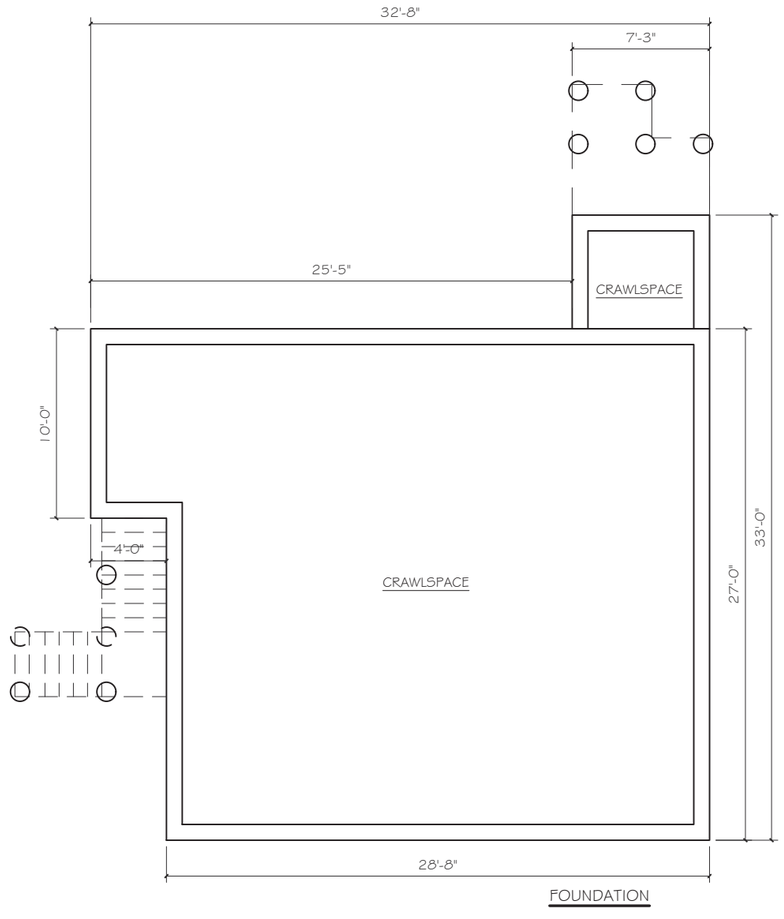
UNITS 5 AND UNIT 7 FLOOR PLANS

CLOVERLEAF BUILDING 5-7
CLOVERLEAF TRURO RENTAL HOUSING

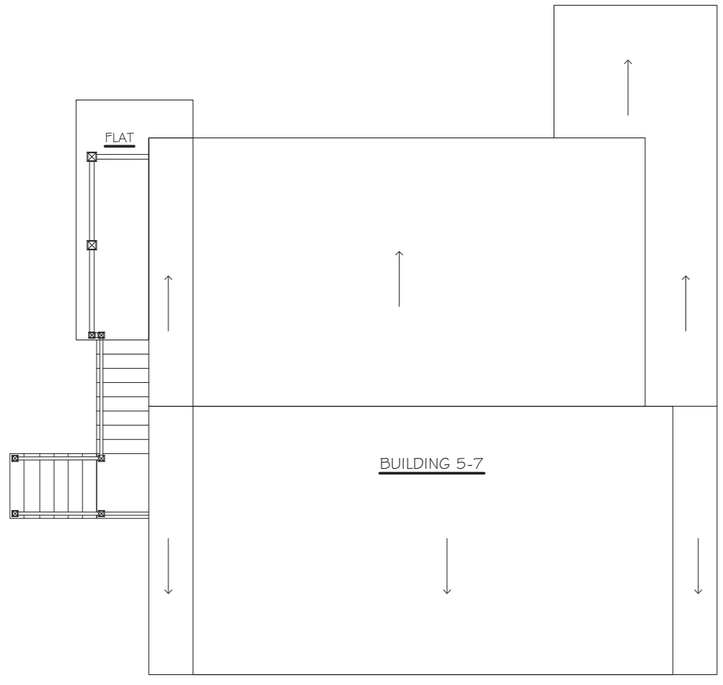
SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A1.1



1 FOUNDATION PLAN
SCALE: 1/8" = 1'-0"



2 BUILDING 5-7 ROOF PLAN
SCALE: 1/8" = 1'-0"

JESSICA ROMUALDI SNARE
REGISTERED ARCHITECT
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

DATE:
02.20.20

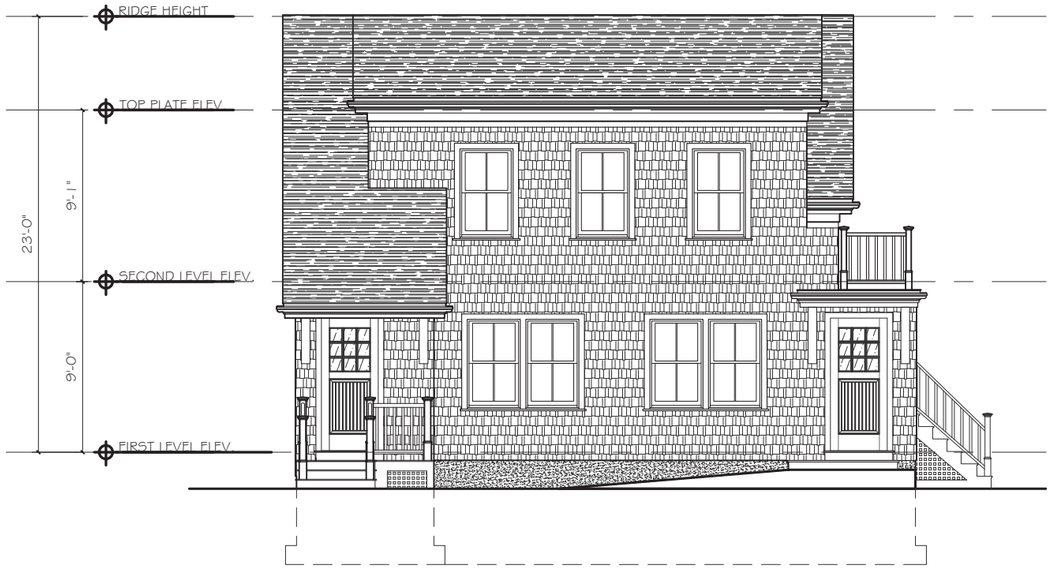
FOUNDATION AND ROOF PLANS

CLOVERLEAF BUILDING 5-7
CLOVERLEAF TRURO RENTAL HOUSING

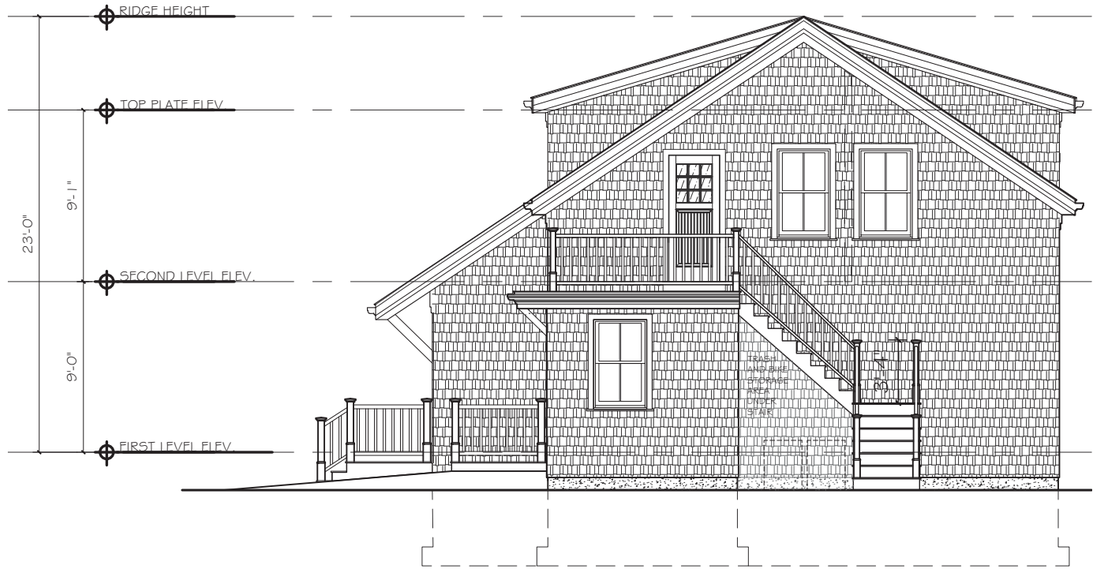
SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

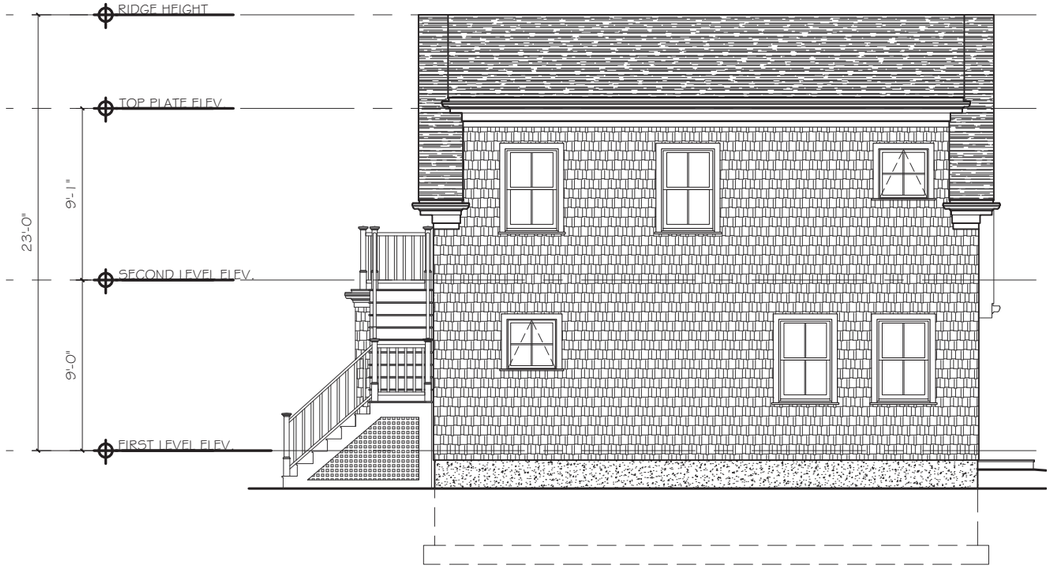
A1.2



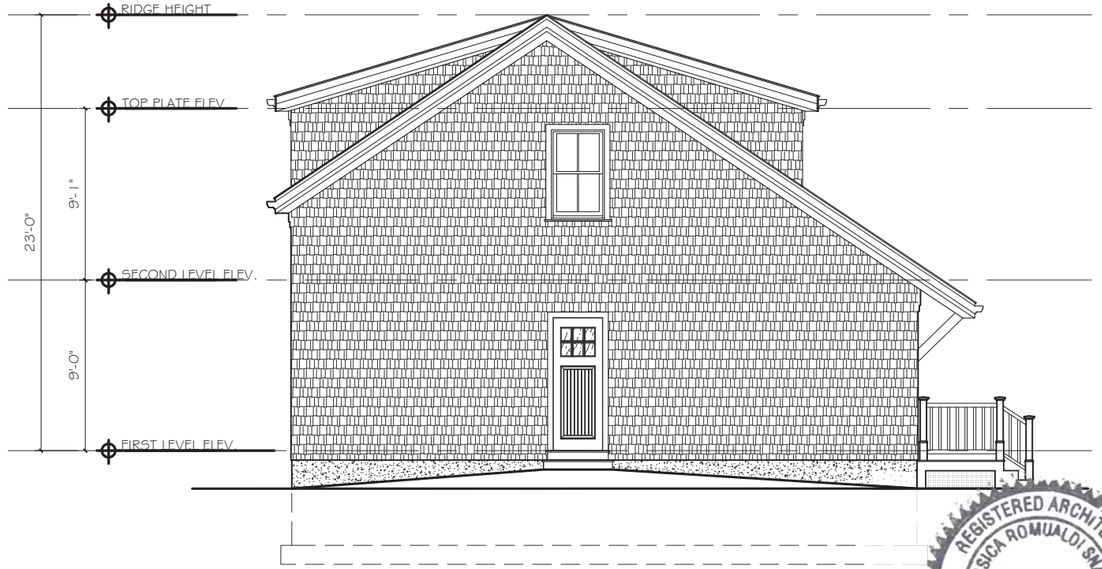
1 FRONT ELEVATION
SCALE: 1/8" = 1'-0"



2 RIGHT SIDE ELEVATION
SCALE: 1/8" = 1'-0"



3 BACK ELEVATION
SCALE: 1/8" = 1'-0"



4 LEFT SIDE ELEVATION
SCALE: 1/8" = 1'-0"

REGISTERED ARCHITECT
JESSICA ROMUALDI SNARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

DATE:
02.20.20

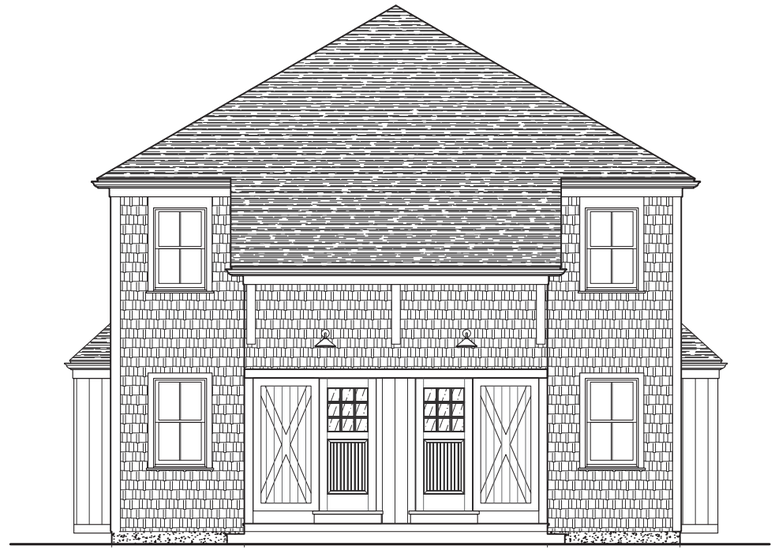
FRONT ELEVATION

CLOVERLEAF BUILDING 5-7
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A2.1



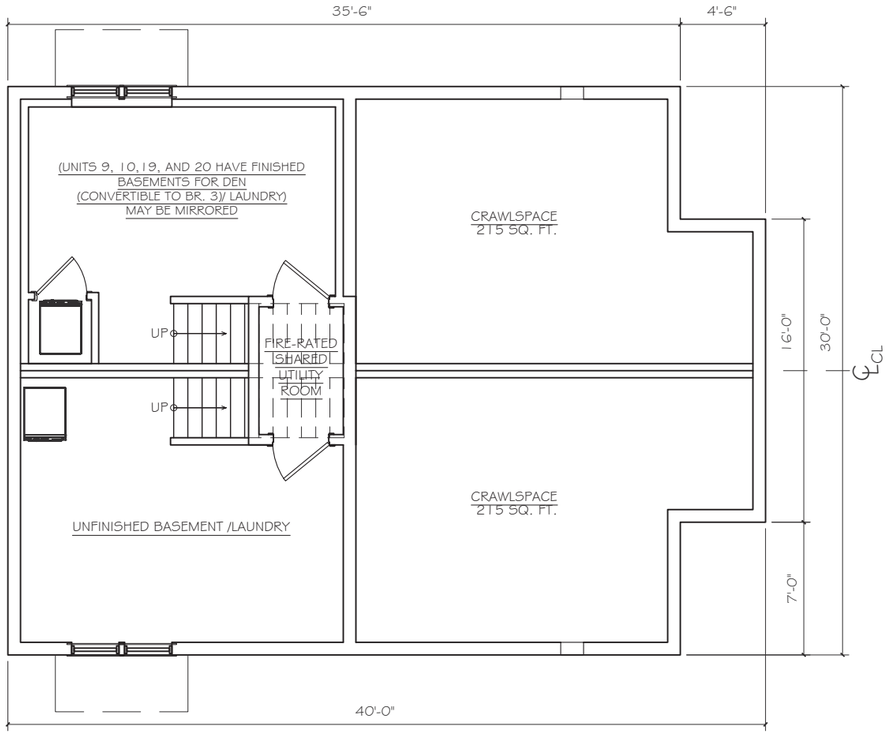
CLOVERLEAF TRURO RENTAL HOUSING
BUILDINGS 9-11, 10-12, 17-19, AND 18-20
Truro, Massachusetts

Thursday, February 20, 2020

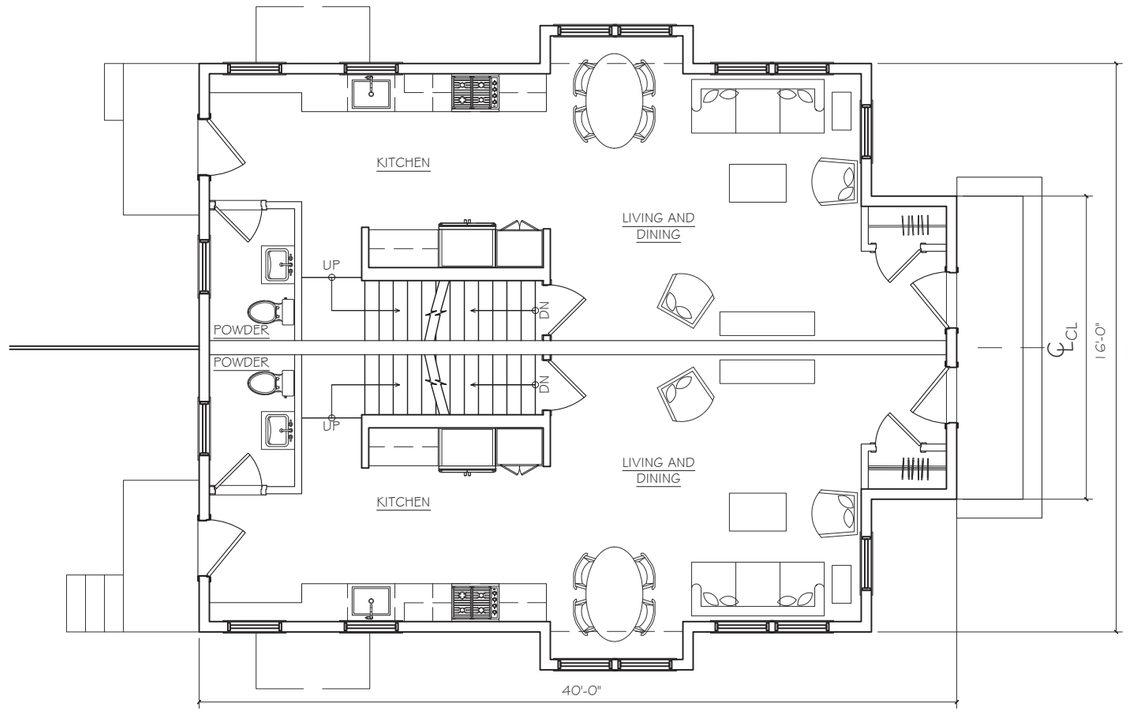
Spring Hill Design

INTERIORS ARCHITECTURE SPACE PLANNING

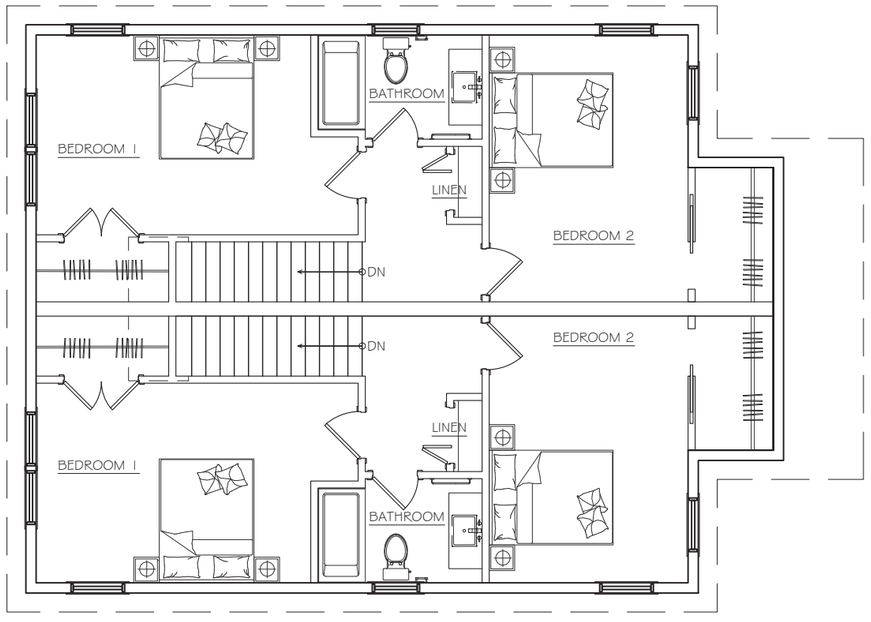
21 Dartmouth Street, Somerville, MA, 02145 ~ 617.623.1833



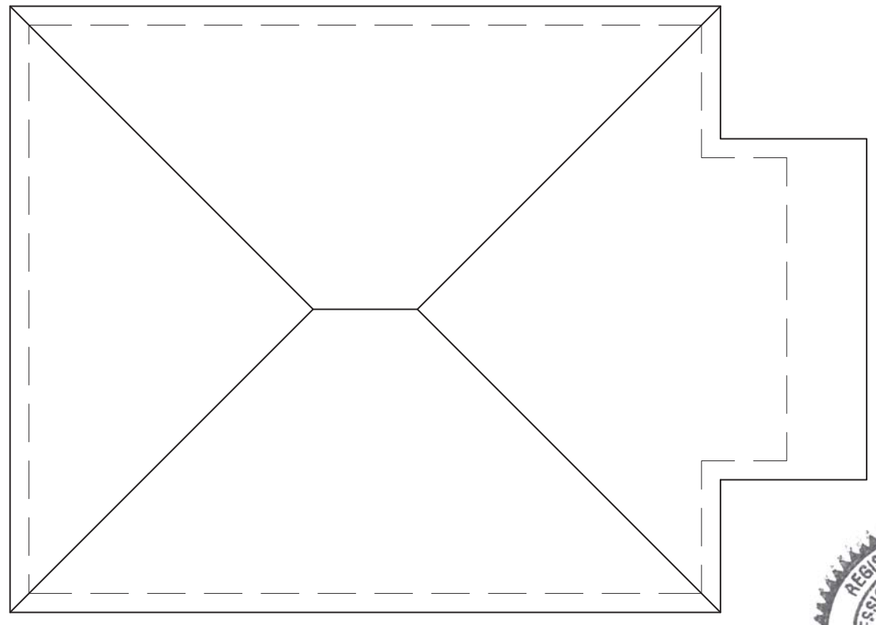
1 BASEMENT PLAN
SCALE: 1/8" = 1'-0"



2 FIRST LEVEL PLAN
SCALE: 1/8" = 1'-0"



3 SECOND LEVEL PLAN
SCALE: 1/8" = 1'-0"



2 ROOF PLAN
SCALE: 1/8" = 1'-0"

DATE:
02.20.20

FLOOR PLANS

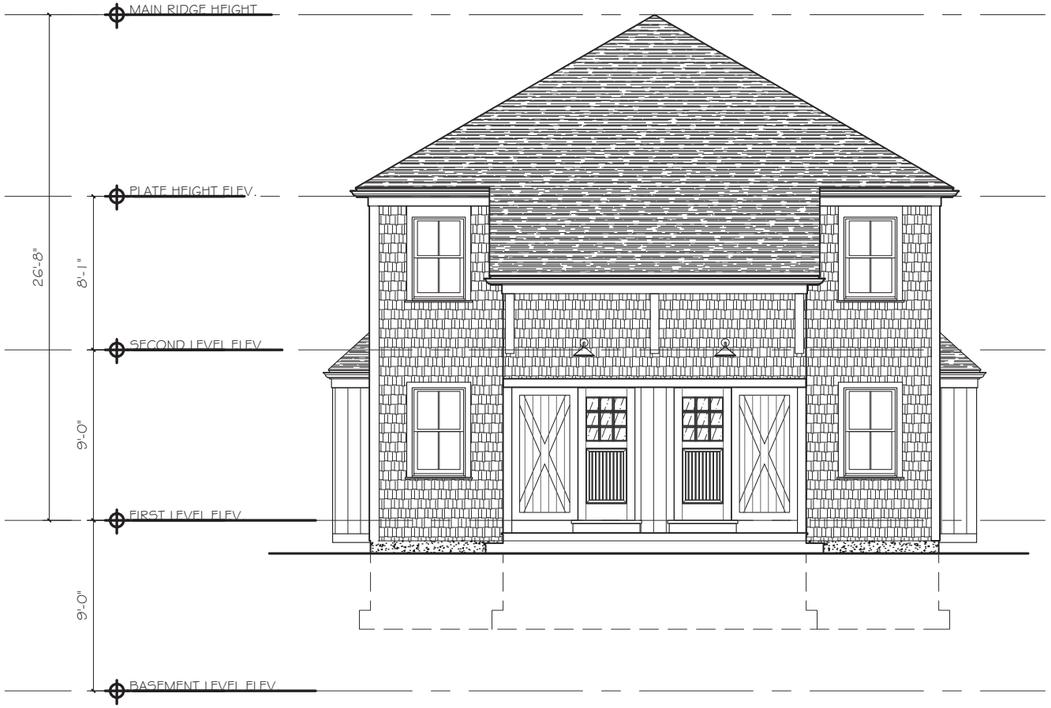
CLOVERLEAF BUILDINGS 9-11, 10-12, 17-19, AND 18-20
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

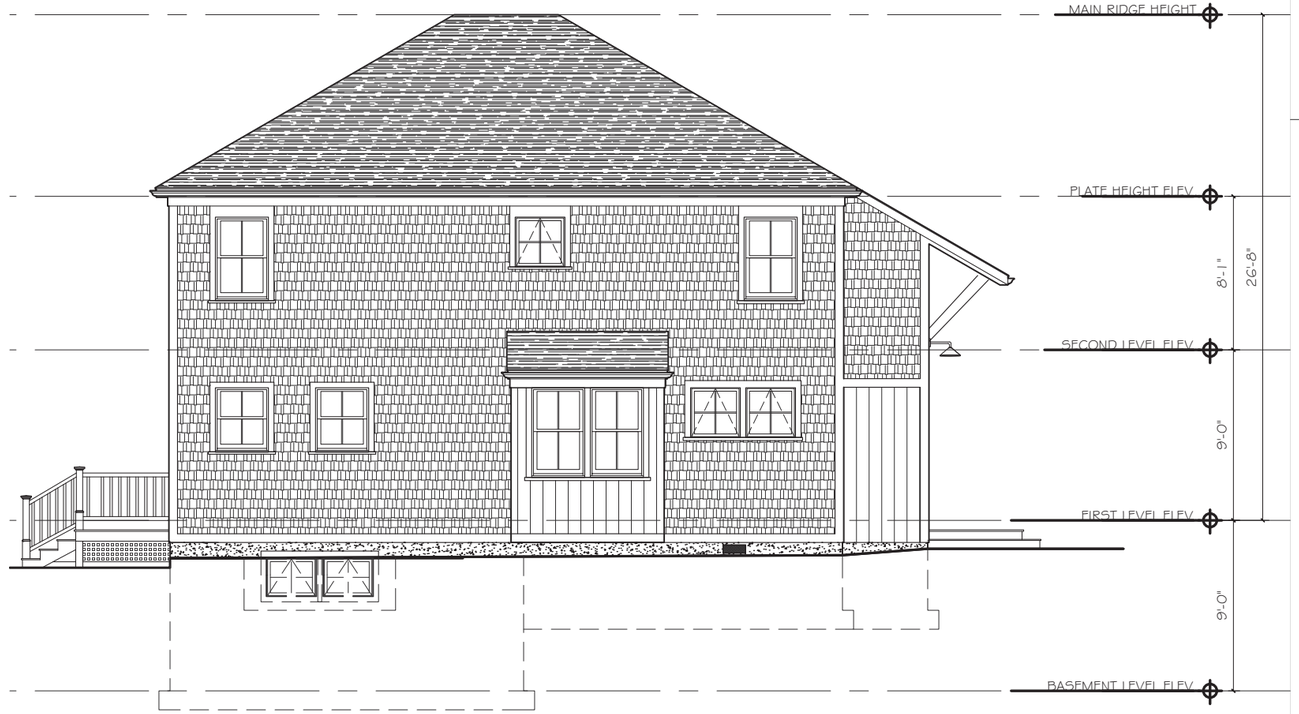
REGISTERED ARCHITECT
JESSICA ROMUALDI SNARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

1/8" = 1'-0"

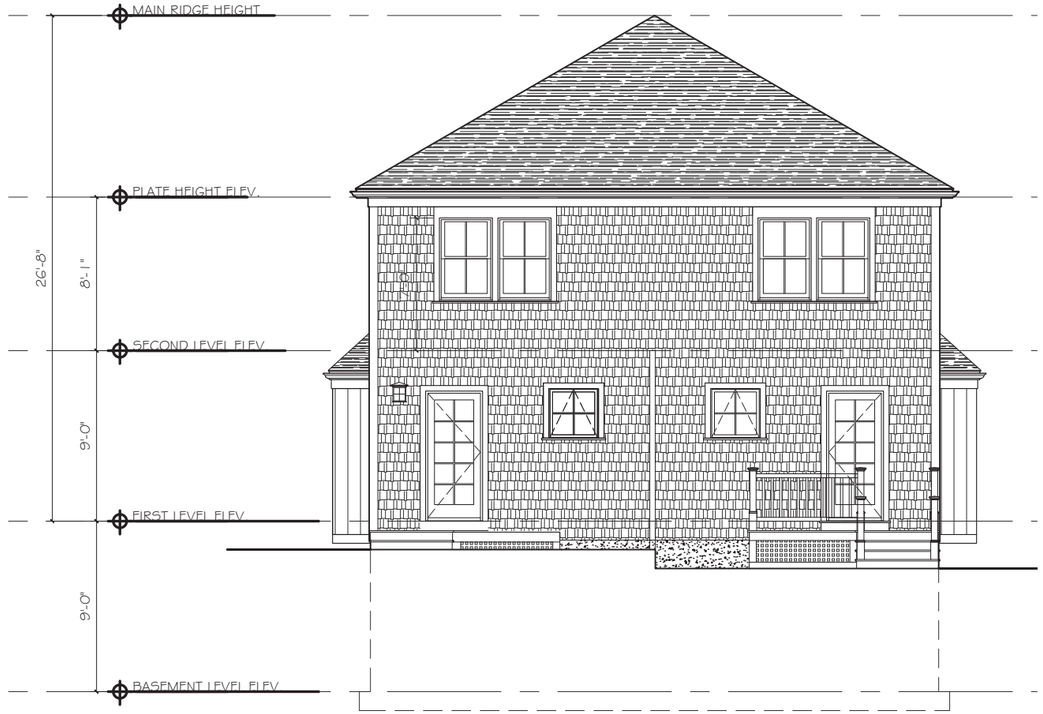
A1.0



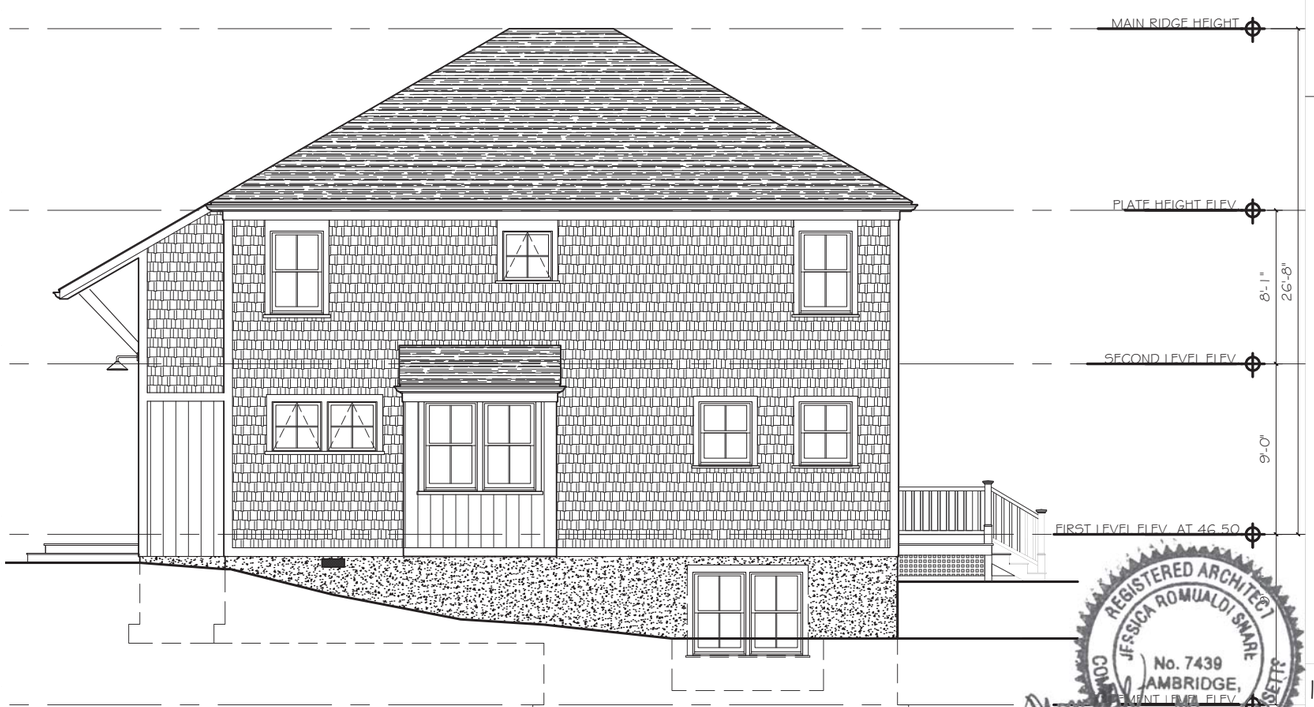
1 FRONT ELEVATION
SCALE: 1/8" = 1'-0"



2 SIDE ELEVATION 1 (SIDE MAY BE MIRRORED DEPENDING ON THE BUILDING)
SCALE: 1/8" = 1'-0"



3 BACK ELEVATION
SCALE: 1/8" = 1'-0"



4 SIDE ELEVATION 2 (SIDE MAY BE MIRRORED DEPENDING ON THE BUILDING)
SCALE: 1/8" = 1'-0"

DATE:
02.20.20

ELEVATIONS

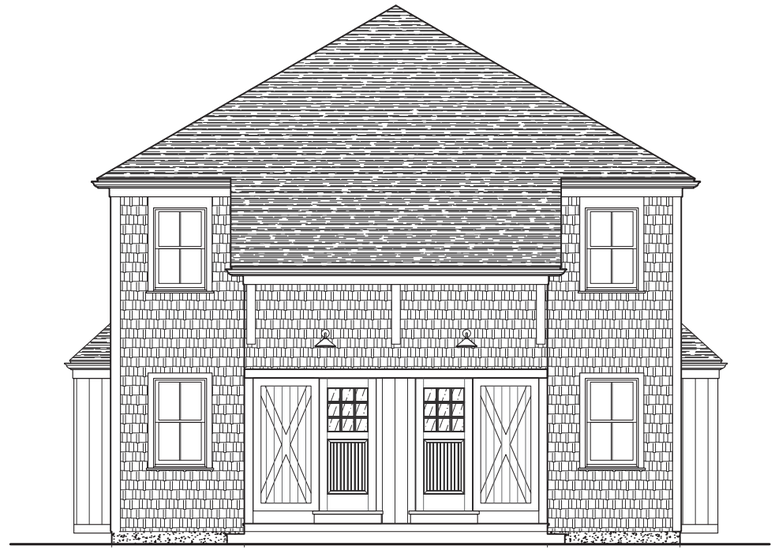
CLOVERLEAF BUILDINGS 9-11, 10-12, 17-19, AND 18-20
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

REGISTERED ARCHITECT
JESSICA ROMUALDI SNARE
No. 7439
CAMBRIDGE,
COMMONWEALTH OF MASSACHUSETTS

1/8" = 1'-0"

A2.1



CLOVERLEAF TRURO RENTAL HOUSING
BUILDINGS 13-15 AND 14-16

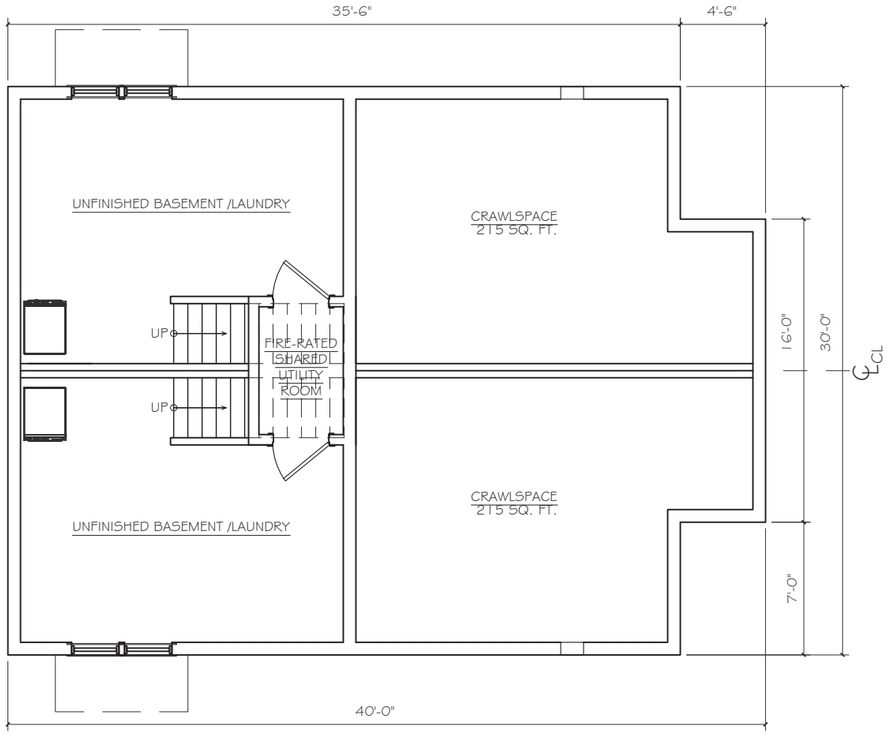
Truro, Massachusetts

Thursday, February 20, 2020

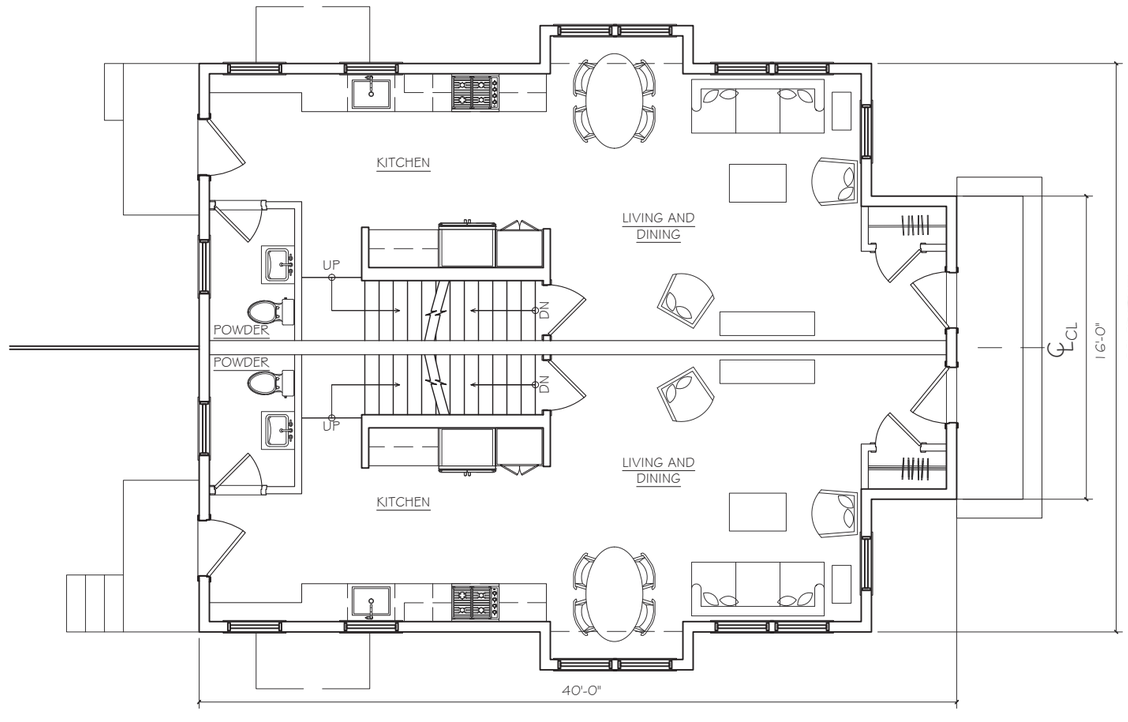
Spring Hill Design

INTERIORS ARCHITECTURE SPACE PLANNING

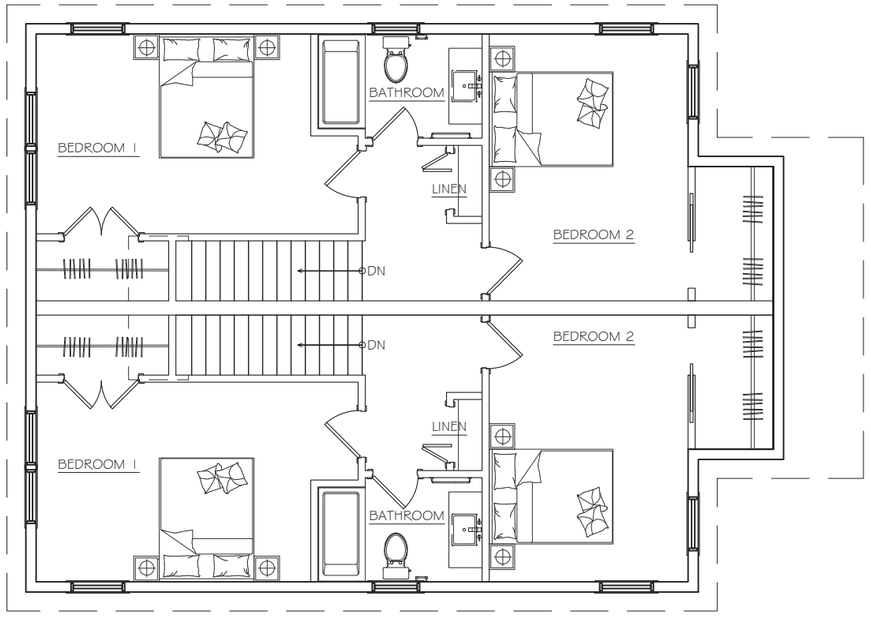
21 Dartmouth Street, Somerville, MA, 02145 ~ 617.623.1833



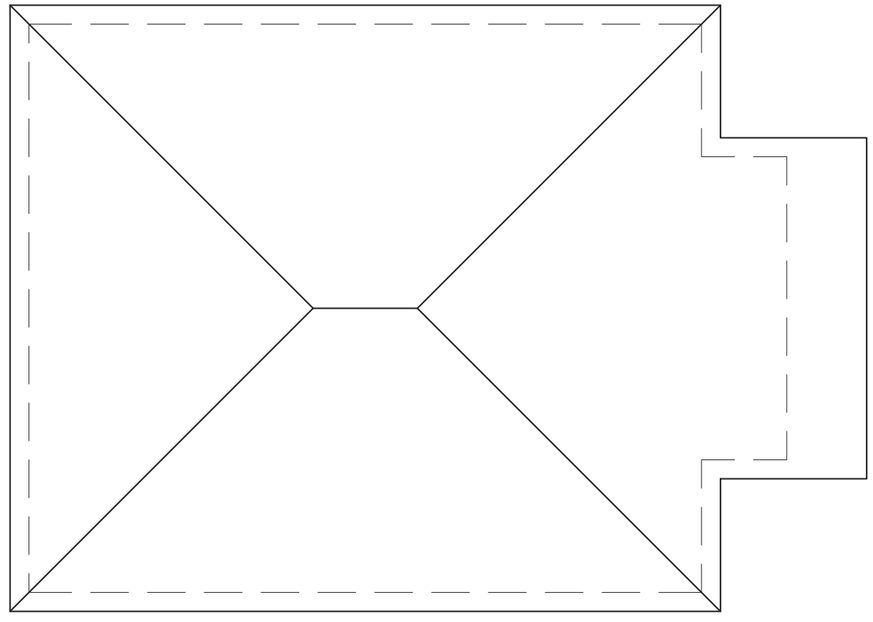
1 BASEMENT PLAN
SCALE: 1/8" = 1'-0"



2 FIRST LEVEL PLAN
SCALE: 1/8" = 1'-0"



3 SECOND LEVEL PLAN
SCALE: 1/8" = 1'-0"



2 ROOF PLAN
SCALE: 1/8" = 1'-0"

DATE: 02.20.20

REGISTERED ARCHITECT
JESSICA ROMUALDI SHARP
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

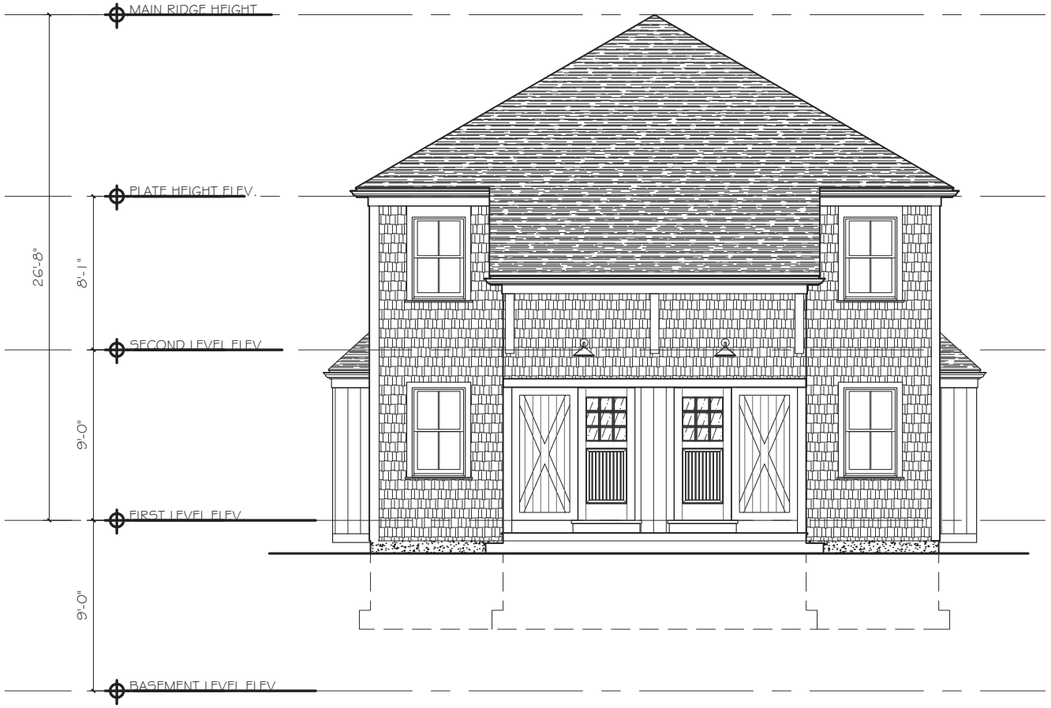
FLOOR PLANS

CLOVERLEAF BUILDINGS 13-15 AND 14-16
CLOVERLEAF TRURO RENTAL HOUSING

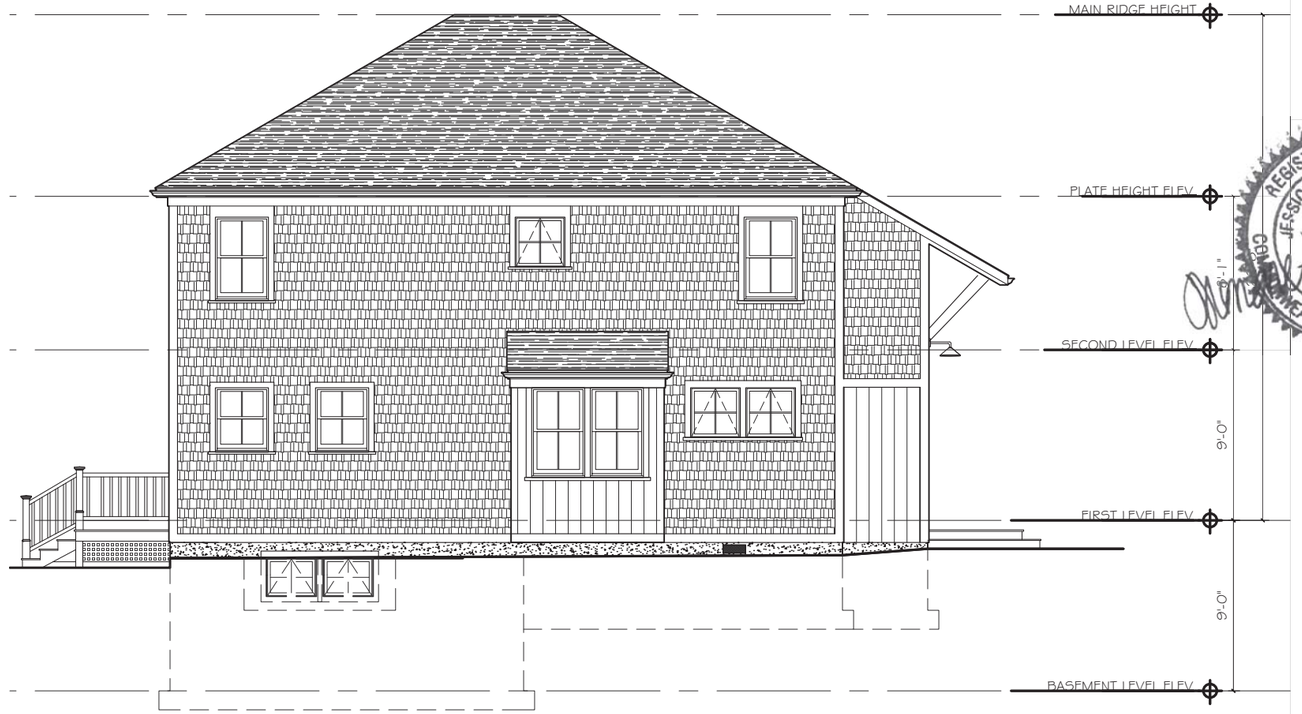
SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

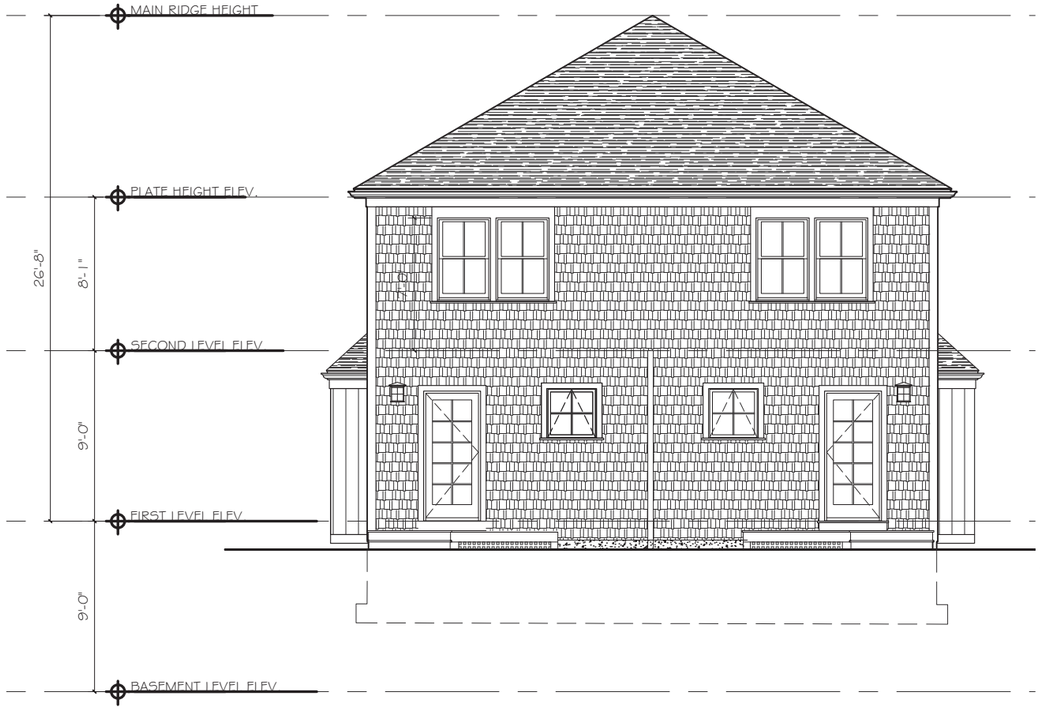
A1.0



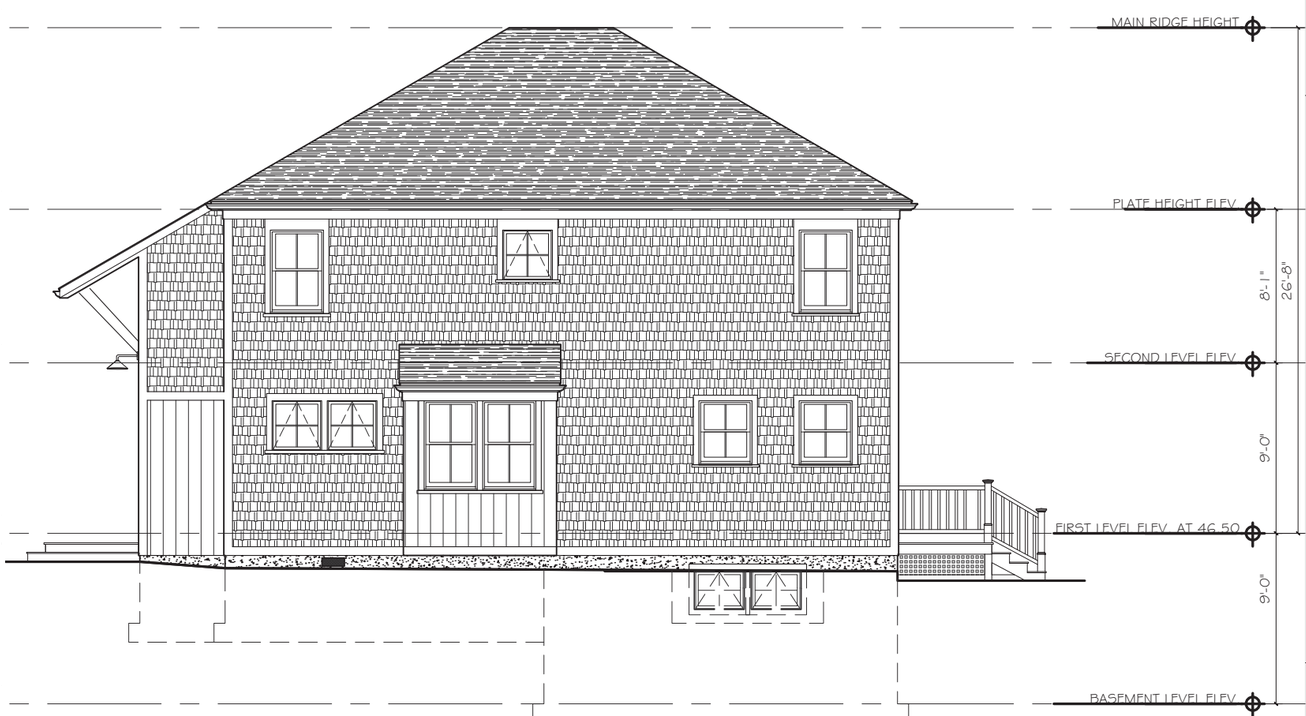
1 FRONT ELEVATION
SCALE: 1/8" = 1'-0"



2 SIDE ELEVATION 1 (SIDE MAY BE MIRRORED DEPENDING ON THE BUILDING)
SCALE: 1/8" = 1'-0"



3 BACK ELEVATION
SCALE: 1/8" = 1'-0"



4 SIDE ELEVATION 2 (SIDE MAY BE MIRRORED DEPENDING ON THE BUILDING)
SCALE: 1/8" = 1'-0"

DATE: 02.20.20

REGISTERED ARCHITECT
JESSICA ROMUALDI SWARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

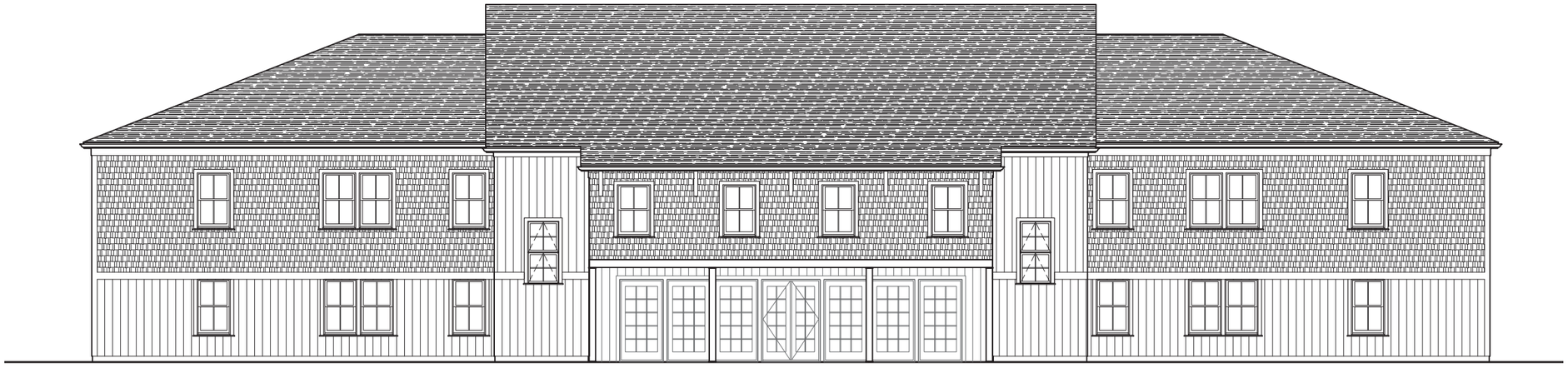
ELEVATIONS

CLOVERLEAF BUILDINGS 13-15 AND 14-16
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A2.1



CLOVERLEAF TRURO RENTAL HOUSING
BUILDING 21

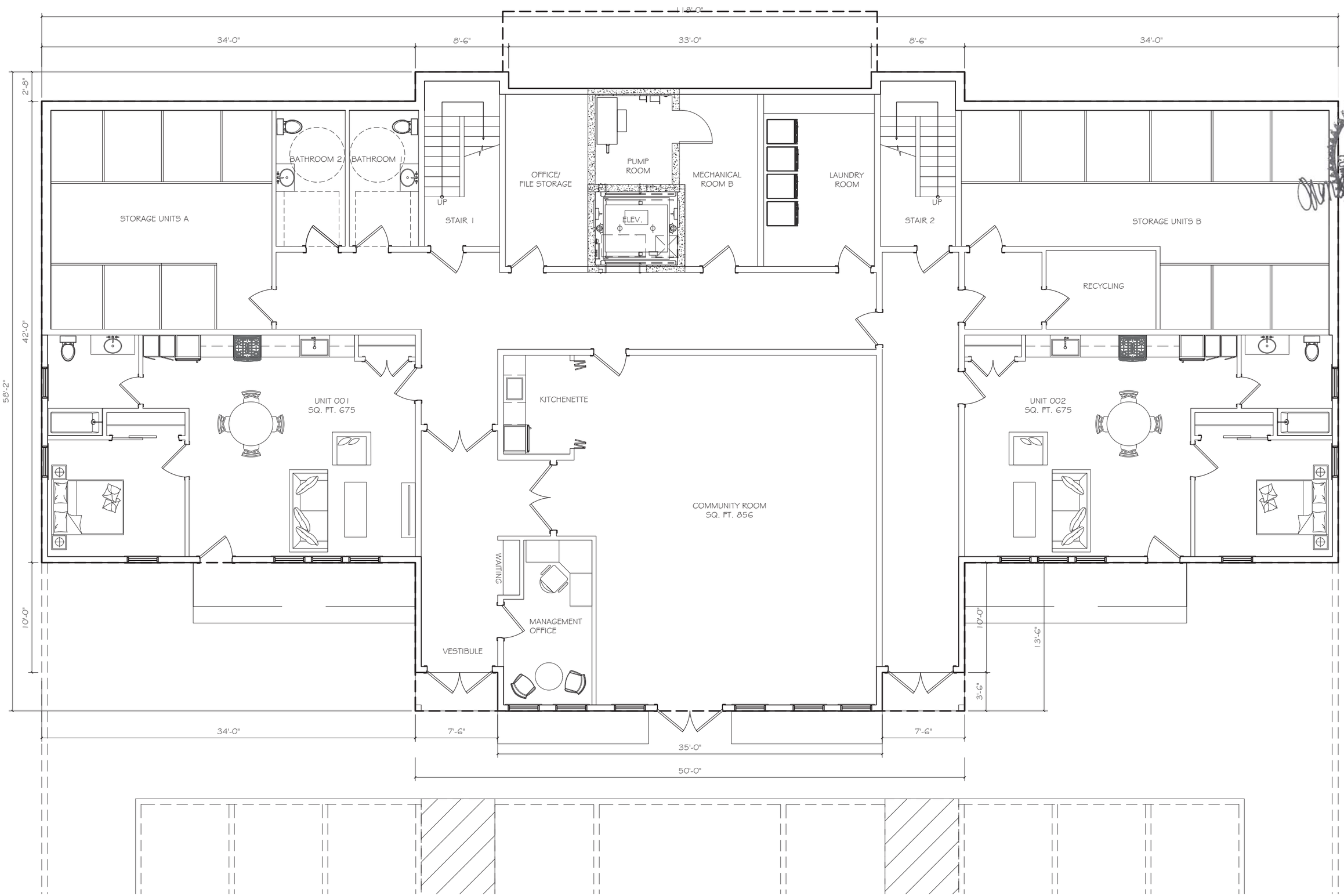
Truro, Massachusetts

Thursday, February 20, 2020

Spring Hill Design

INTERIORS ARCHITECTURE SPACE PLANNING

21 Dartmouth Street, Somerville, MA, 02145 ~ 617.623.1833



1 BASEMENT FLOOR PLAN
SCALE: 1/8" = 1'-0"

DATE: 02.20.20

REGISTERED ARCHITECT
JESSICA ROMUALDI SHARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

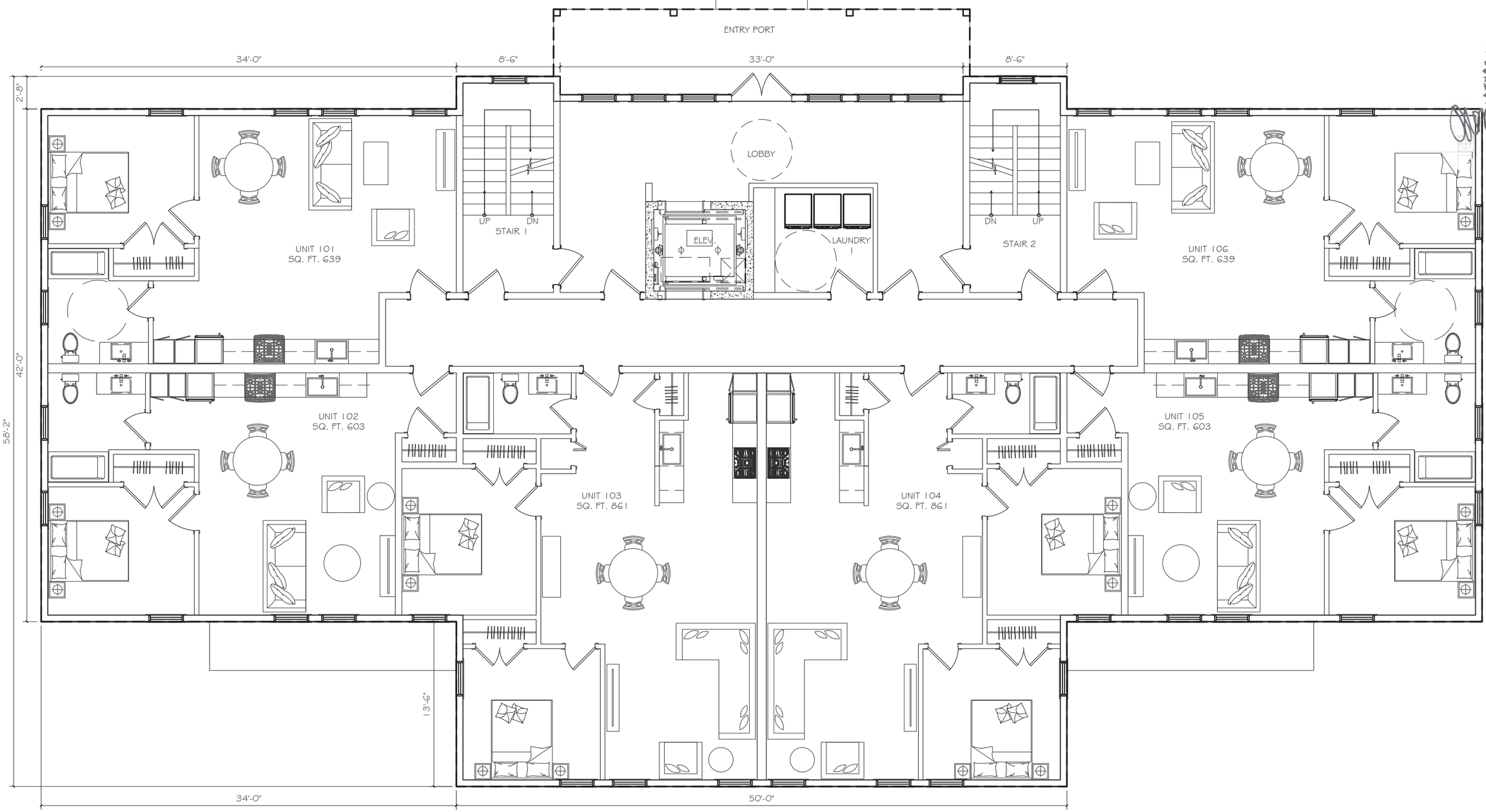
BASEMENT FLOOR PLAN

CLOVERLEAF BUILDING 21
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A1.0



1 FIRST FLOOR PLAN
SCALE: 1/8" = 1'-0"

DATE: 02.20.20

REGISTERED ARCHITECT
JESSICA ROMUALDI SWARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

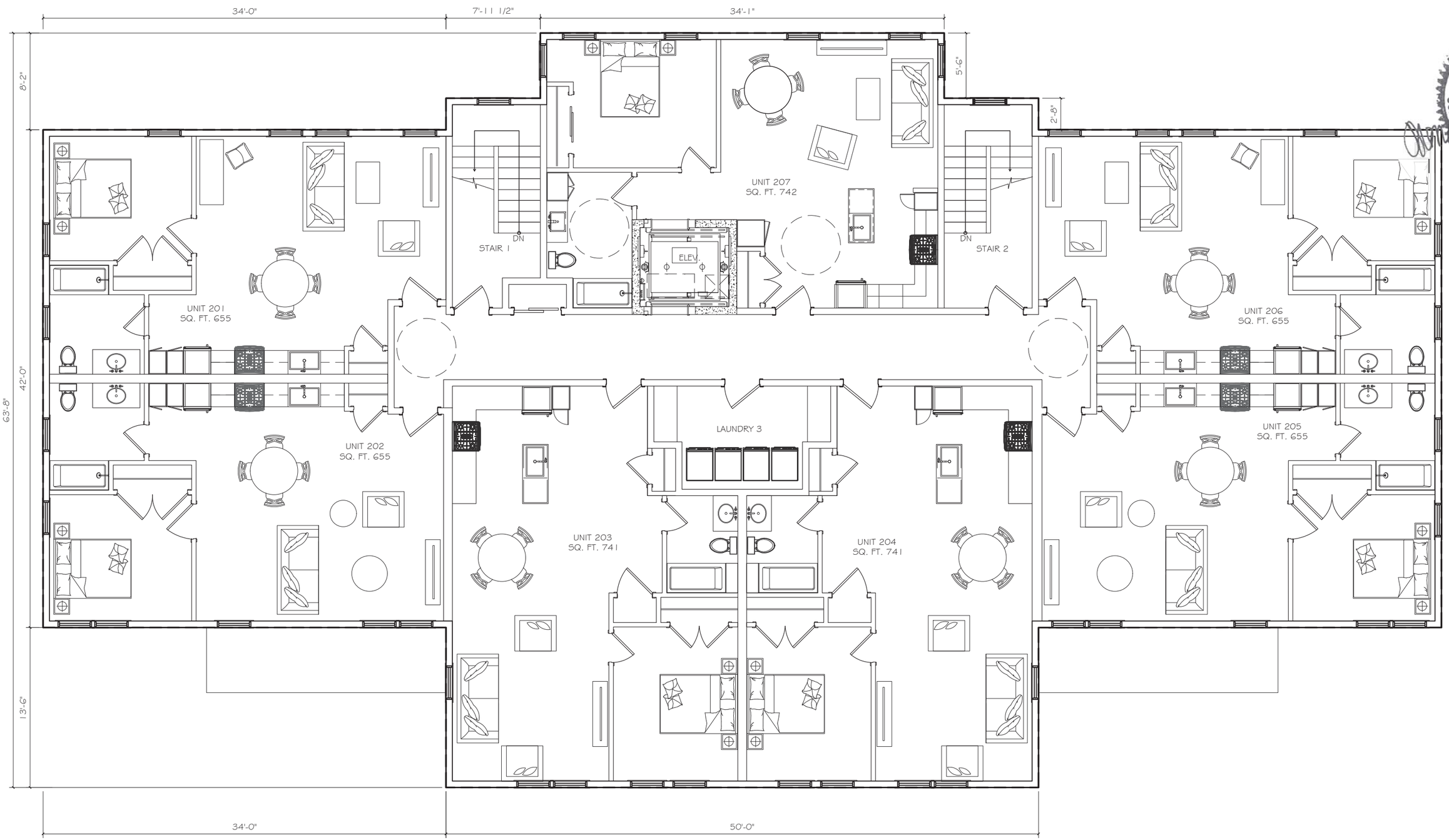
FIRST FLOOR PLAN

CLOVERLEAF BUILDING 21
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A1.1



1 SECOND FLOOR PLAN
SCALE: 1/8" = 1'-0"

DATE: 02.20.20

REGISTERED ARCHITECT
JESSICA ROMUALDI SWARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

SECOND FLOOR PLAN

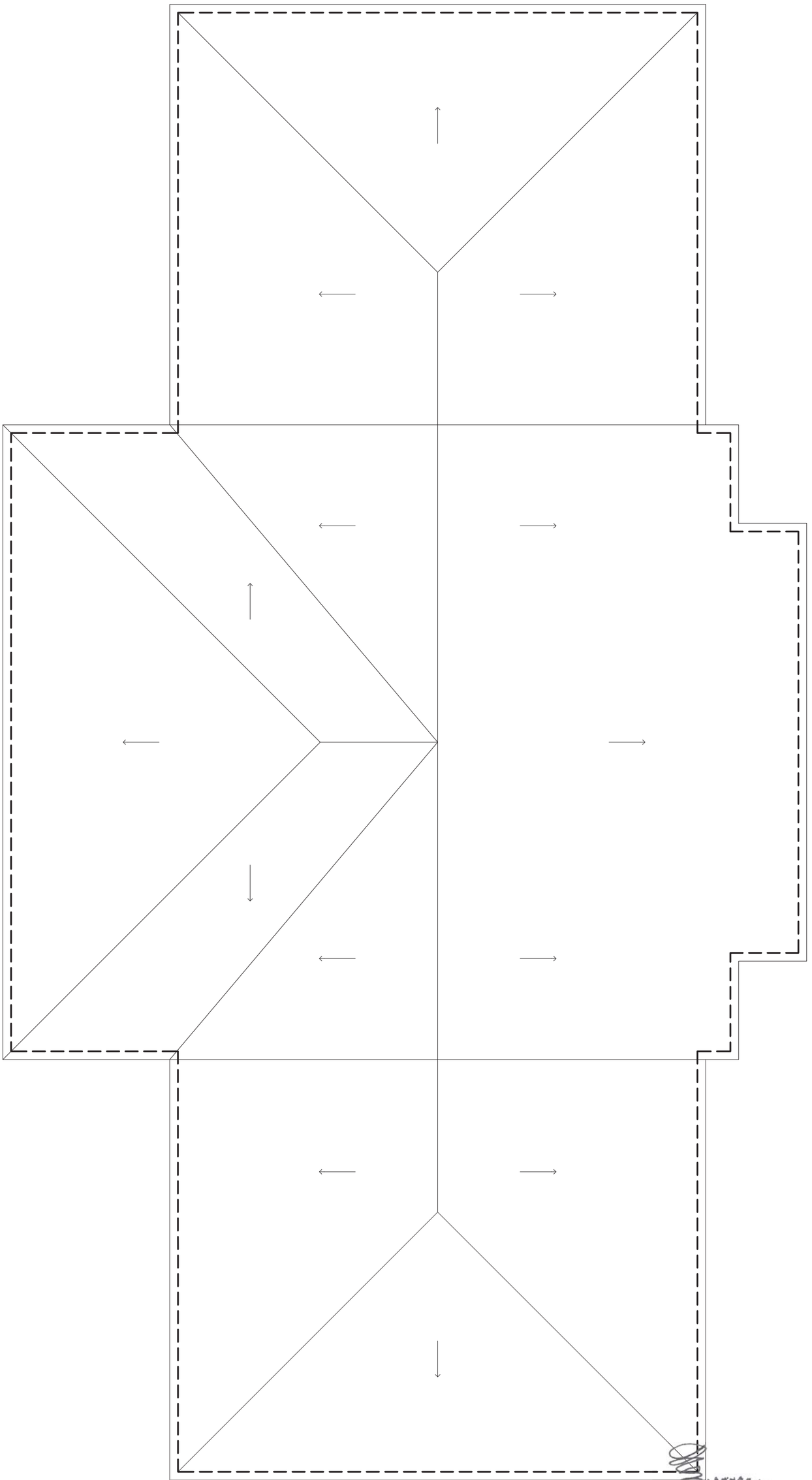
CLOVERLEAF BUILDING 21
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A1.2

1 ROOF PLAN
SCALE: 1/8" = 1'-0"



SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville ,Massachusetts 02145 ~ 617.623.1833

ROOF PLAN

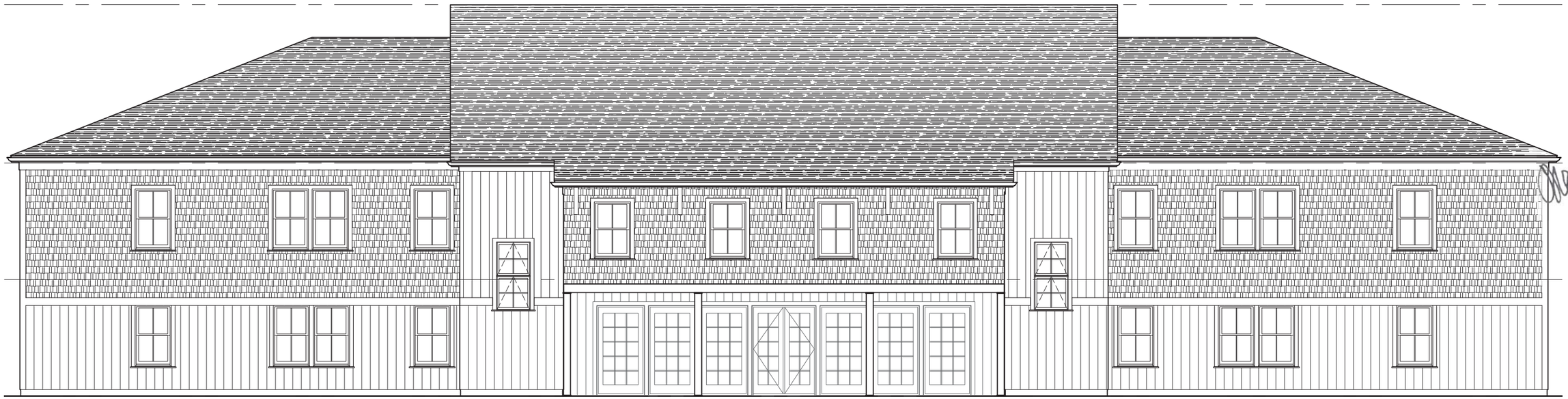
CLOVERLEAF BUILDING 21
CLOVERLEAF TRURO RENTAL HOUSING

REGISTERED ARCHITECT
JESSICA ROMUALDI SHAAF
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

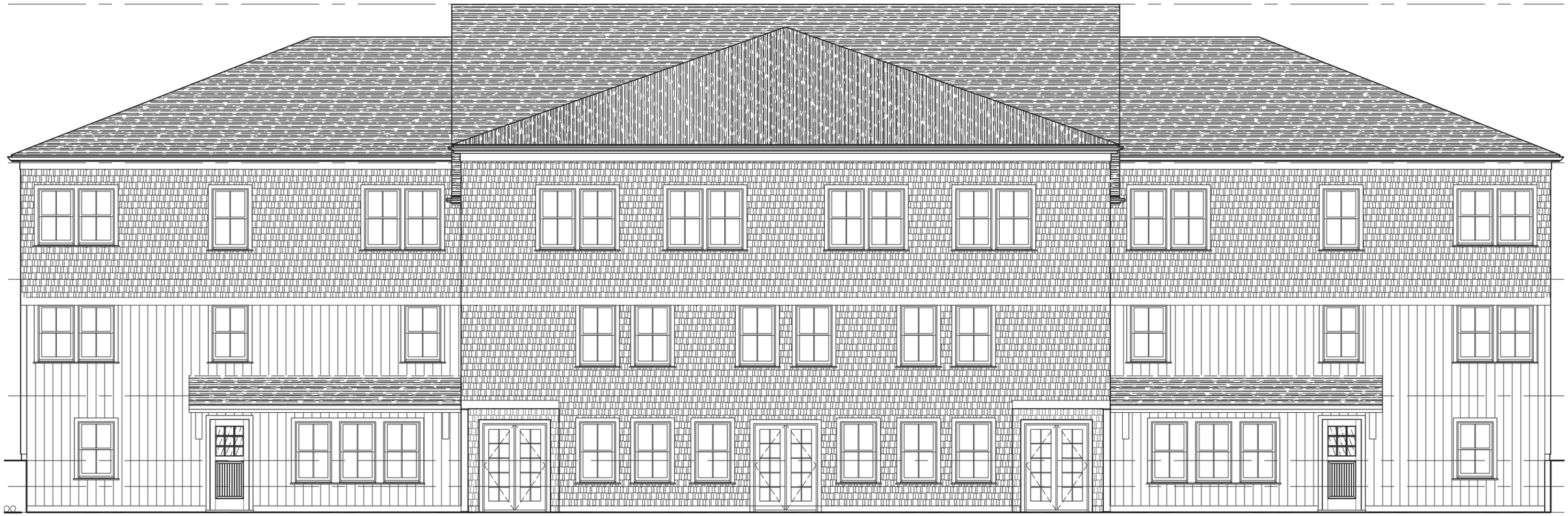
DATE:
02.20.20

A1.3

1/8" = 1'-0"



1 FRONT ELEVATION
SCALE: 1/8" = 1'-0"



2 BACK ELEVATION
SCALE: 1/8" = 1'-0"

FRONT AND BACK ELEVATIONS

CLOVERLEAF BUILDING 21
CLOVERLEAF TRURO RENTAL HOUSING

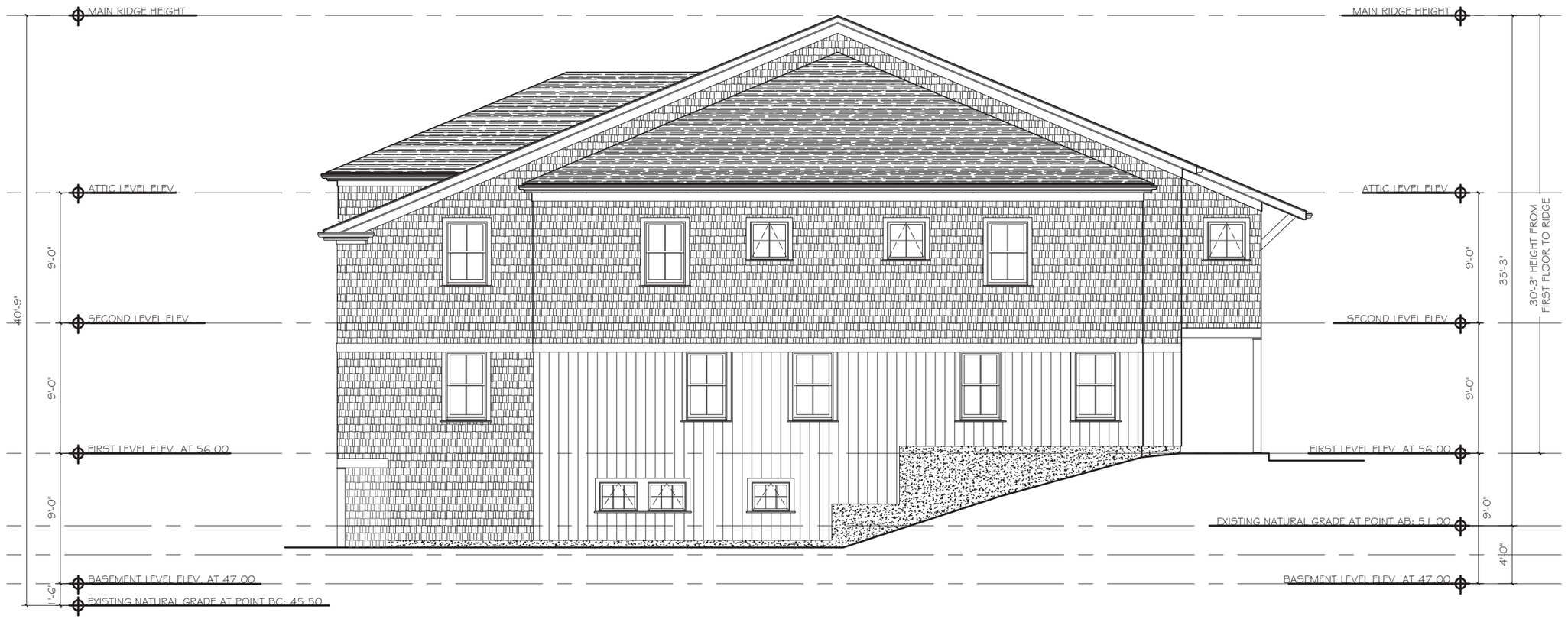
DATE: 02.20.20

REGISTERED ARCHITECT
JESSICA ROMUALDI SHARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A2.1



1 LEFT SIDE ELEVATION
SCALE: 1/8" = 1'-0"

DATE: 02.20.20

REGISTERED ARCHITECT
JESSICA ROMUALDI SWARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

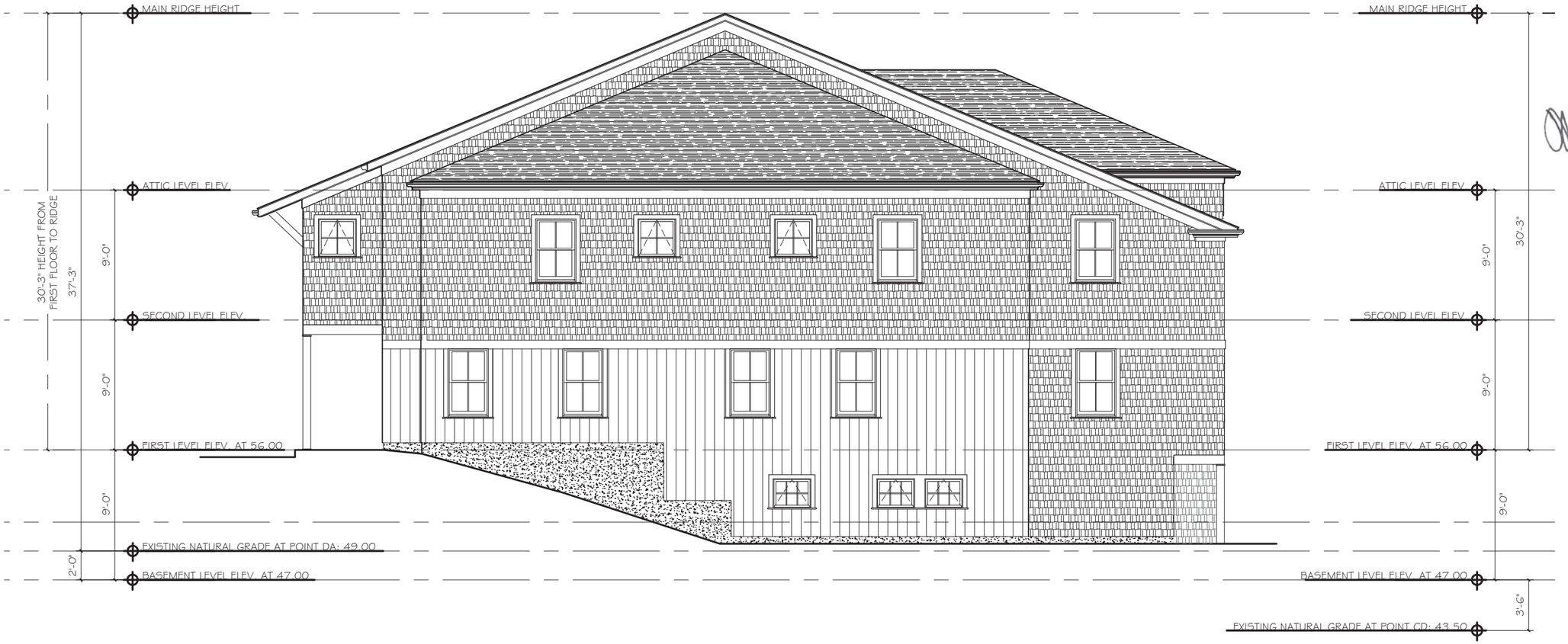
LEFT SIDE ELEVATION

CLOVERLEAF BUILDING 21
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

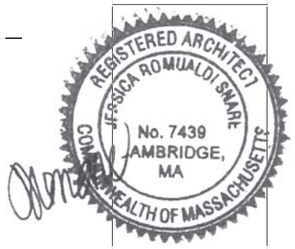
1/8" = 1'-0"

A2.2



1 RIGHT SIDE ELEVATION
SCALE: 1/8" = 1'-0"

DATE: 02.20.20



RIGHT SIDE ELEVATION

CLOVERLEAF BUILDING 21
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A2.3

CLOVERLEAF TRURO RENTAL HOUSING
BUILDING 22-24 AND 23-25(MIRRORED)

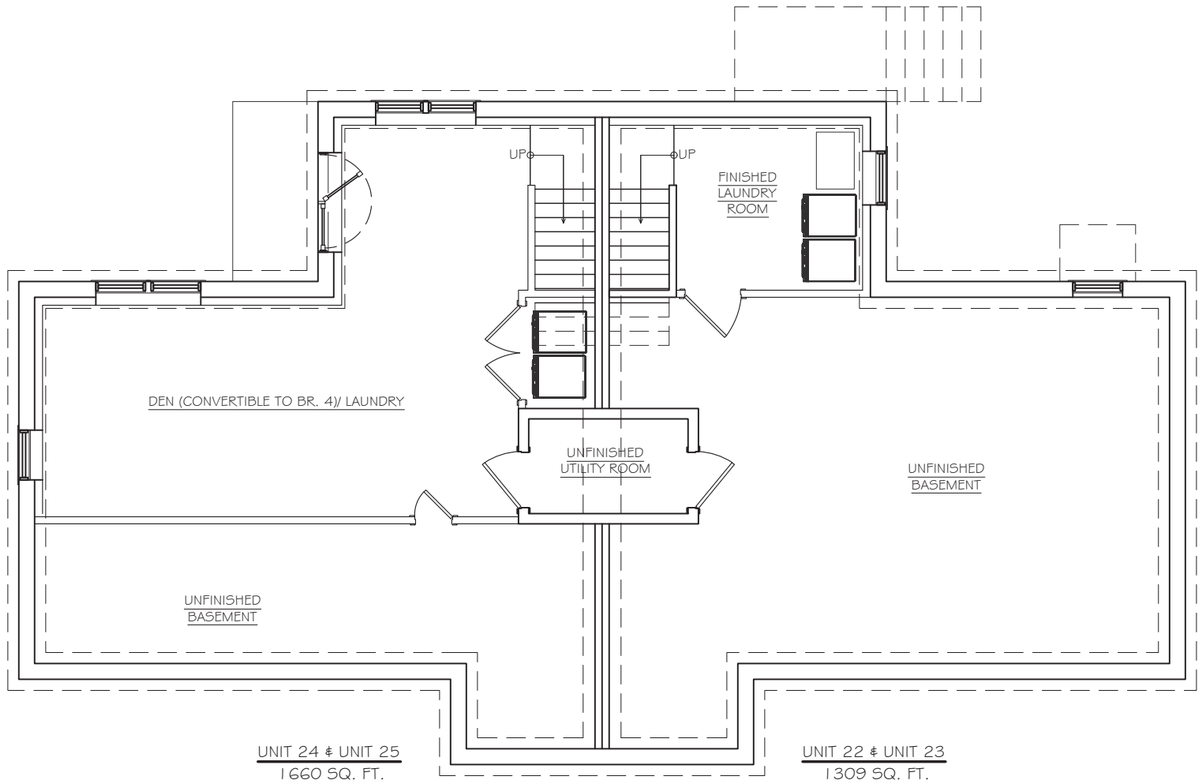
Truro, Massachusetts

Thursday, February 20, 2020

Spring Hill Design

INTERIORS ARCHITECTURE SPACE PLANNING

21 Dartmouth Street, Somerville, MA, 02145 ~ 617.623.1833



1 BASEMENT FLOOR PLAN
SCALE: 1/8" = 1'-0"

BASEMENT FLOOR PLAN

CLOVERLEAF BUILDING 22-24 AND 23-25 (MIRRORED)
CLOVERLEAF TRURO RENTAL HOUSING

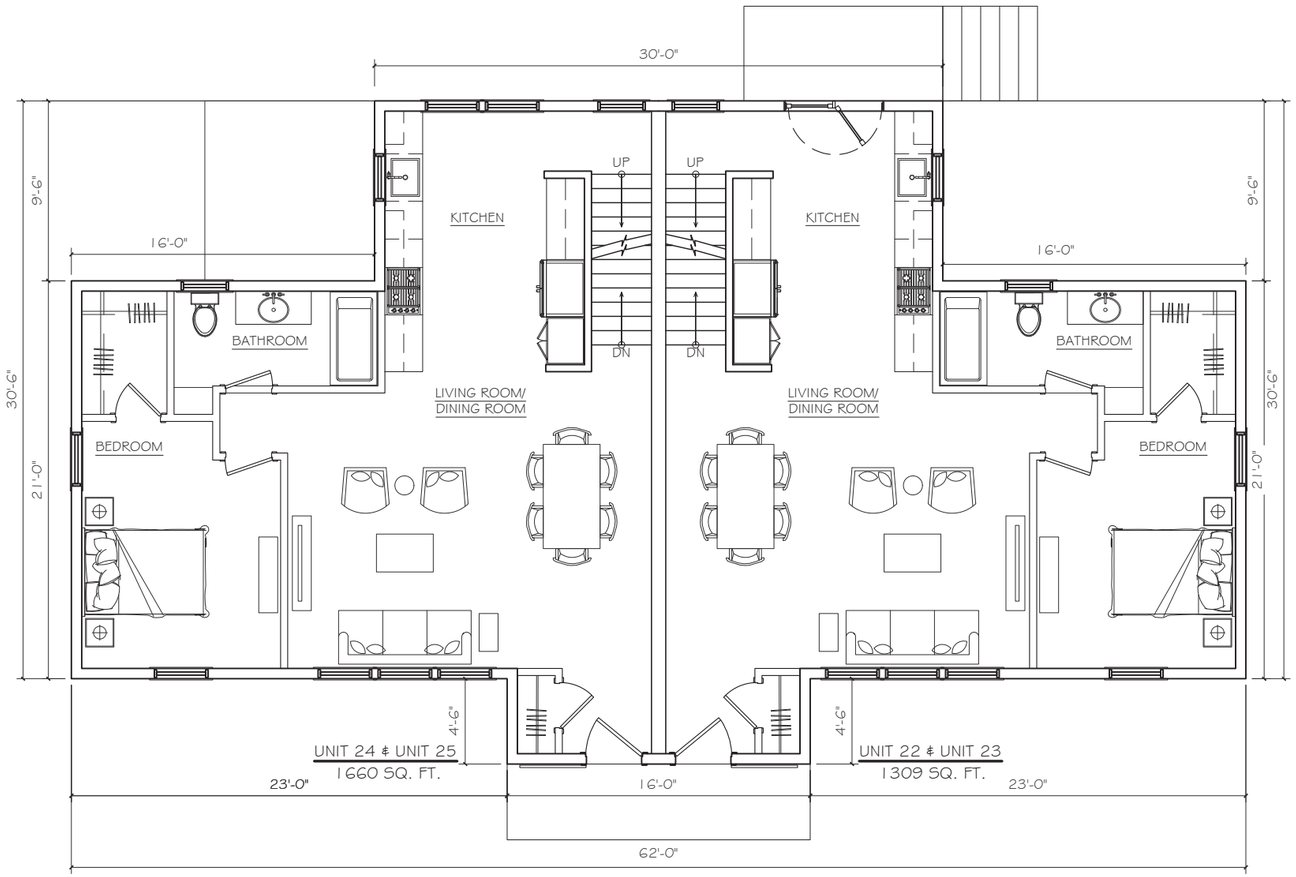
DATE:
02.20.20

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

REGISTERED ARCHITECT
JESSICA ROMUALDI SNARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

1/8" = 1'-0"

A1.0



1 FIRST FLOOR PLAN
SCALE: 1/8" = 1'-0"

FIRST FLOOR PLAN

CLOVERLEAF BUILDING 22-24 AND 23-25 (MIRRORED)
CLOVERLEAF TRURO RENTAL HOUSING

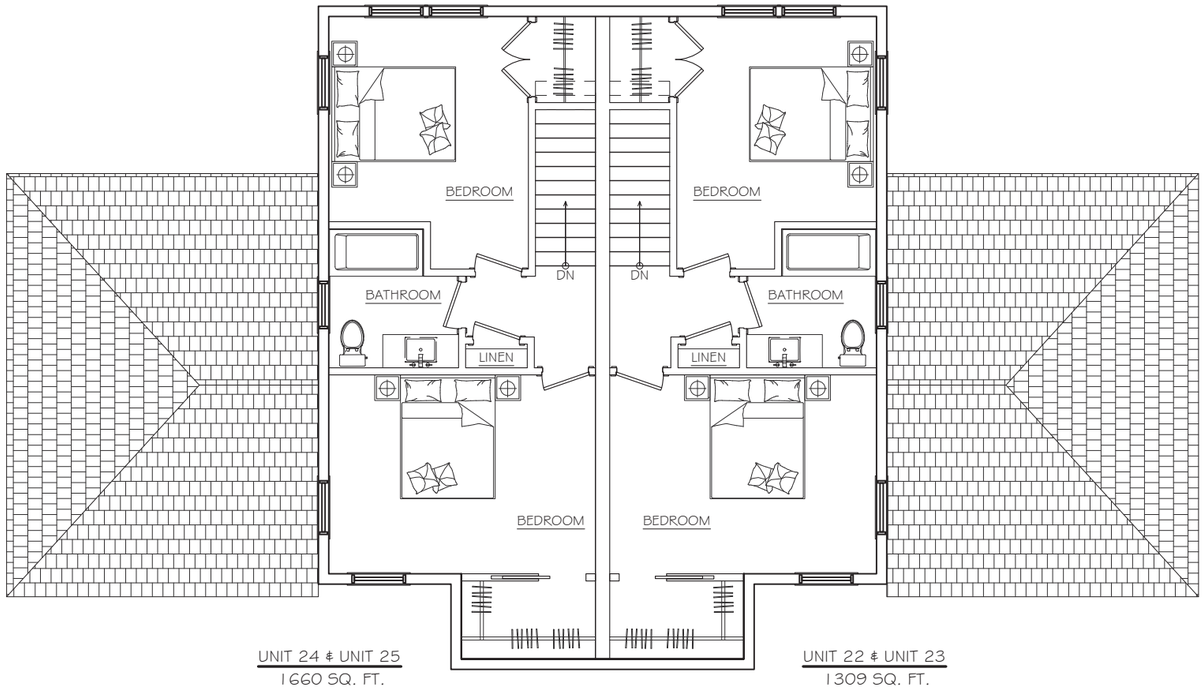
DATE:
02.20.20

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville ,Massachusetts 02145 ~ 617.623.1833

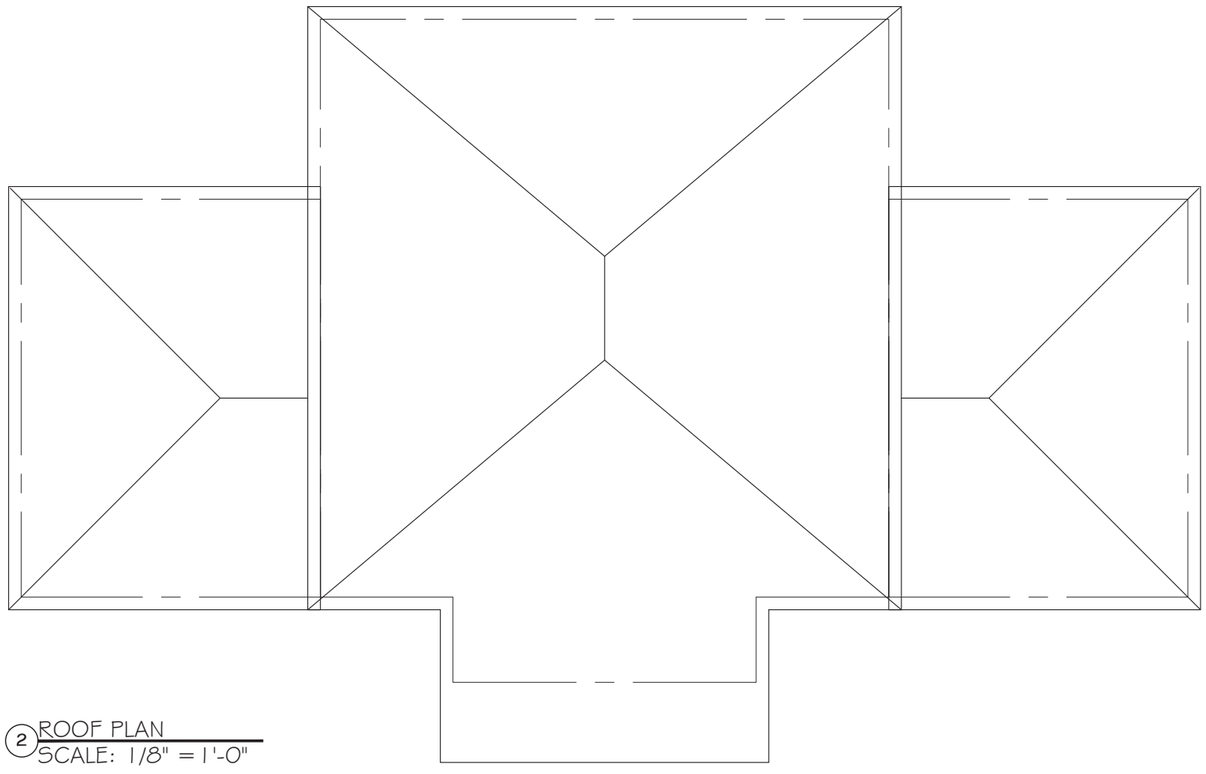
1/8" = 1'-0"

A1.1

REGISTERED ARCHITECT
JESSICA ROMUALDI SMART
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS



1 SECOND FLOOR PLAN
SCALE: 1/8" = 1'-0"



2 ROOF PLAN
SCALE: 1/8" = 1'-0"

DATE:
02.20.20

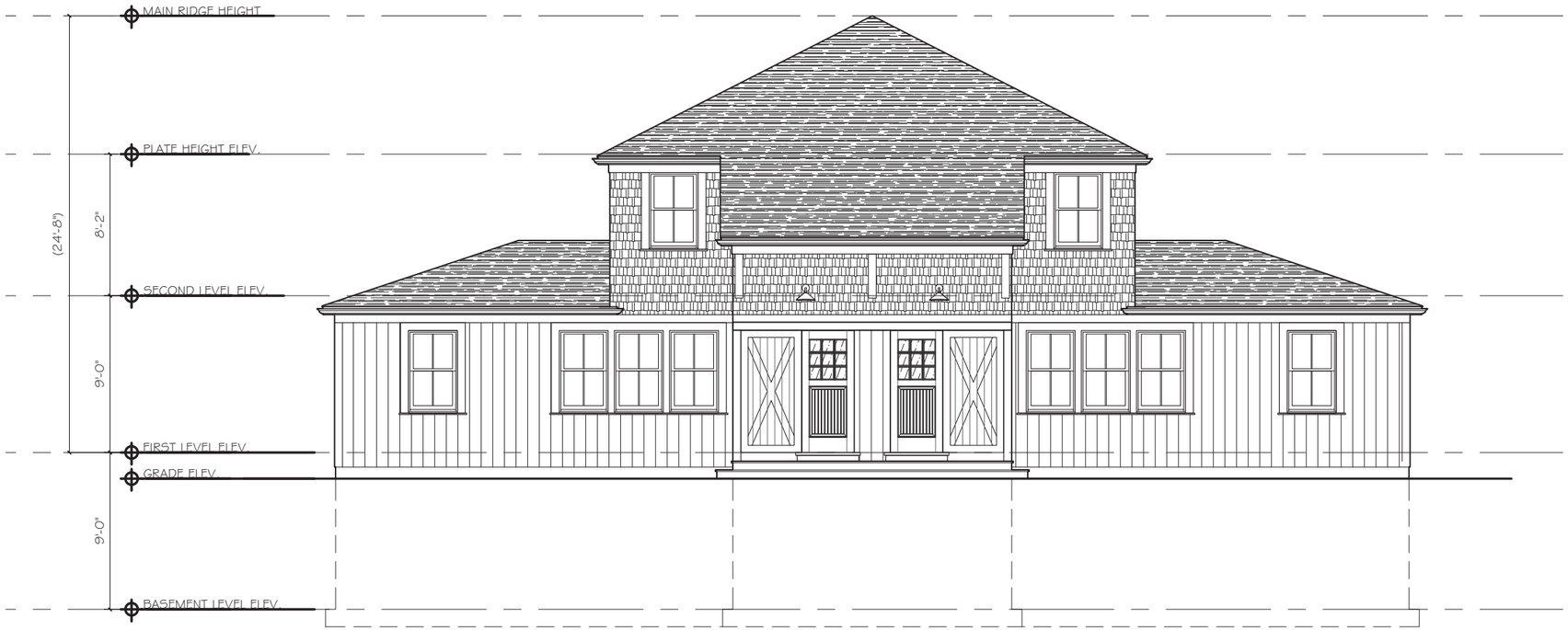
SECOND FLOOR AND ROOF PLANS

CLOVERLEAF BUILDING 22-24 AND 23-25 (MIRRORED)
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville ,Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A1.2



1 FRONT ELEVATION
SCALE: 1/8" = 1'-0"

1 BACK ELEVATION
SCALE: 1/8" = 1'-0"

REGISTERED ARCHITECT
JESSICA ROMUALDI SMART
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

DATE:
02.20.20

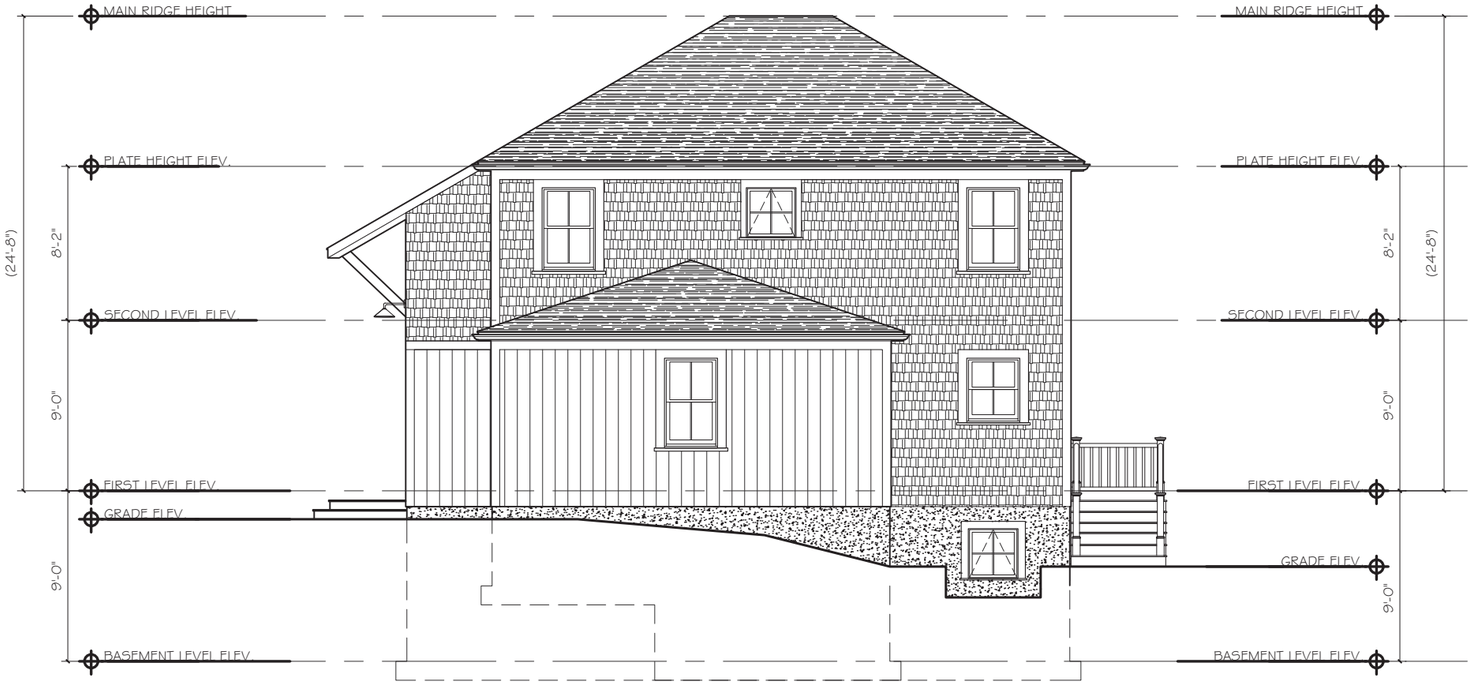
FRONT AND BACK ELEVATIONS

CLOVERLEAF BUILDING 22-24 AND 23-25 (MIRRORED)
CLOVERLEAF TRURO RENTAL HOUSING

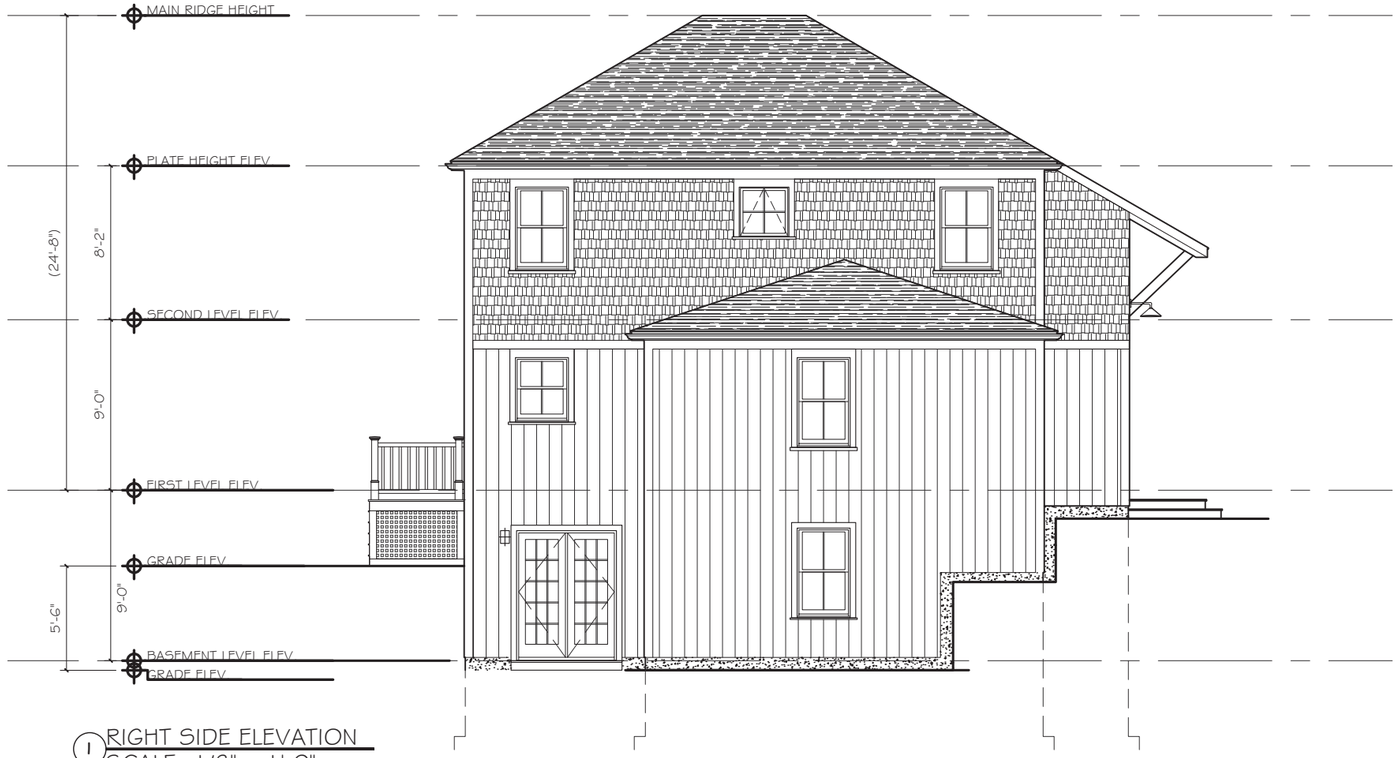
SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A2.1



1 LEFT SIDE ELEVATION
SCALE: 1/8" = 1'-0"



1 RIGHT SIDE ELEVATION
SCALE: 1/8" = 1'-0"

DATE:
02.20.20

SIDE ELEVATIONS

CLOVERLEAF BUILDING 22-24 AND 23-25 (MIRRORED)
CLOVERLEAF TRURO RENTAL HOUSING

SPRING HILL DESIGN
ARCHITECTURE INTERIORS SPACE PLANNING
21 Dartmouth Street, Somerville, Massachusetts 02145 ~ 617.623.1833

1/8" = 1'-0"

A2.2

REGISTERED ARCHITECT
JESSICA ROMUALDI SHARE
No. 7439
CAMBRIDGE, MA
COMMONWEALTH OF MASSACHUSETTS

TOWN OF TRURO
ZONING BOARD OF APPEALS
MEETING MINUTES
June 25, 2018
TRURO TOWN HALL

Members Present: Chair-Bertram Perkel, Art Hultin, John Dundas, Fred Todd, John Thornley, Alternate-Susan Areson

Members Absent: Chris Lucy

Others Present: Interim Town Planner-Jessica Bardi, Atty. Christopher Snow, Kevin Shea, Atty. Liz McNichols, Judy Richland, Atty. Benjamin Zehnder, Fred Gaechter, Atty. David Reid, Frank Dubinski, Regan McCarthy, Nathalie Ferrier, Joanne Barkan, Joan Holt

Chair Perkel called the meeting to order at 5:30 pm.

Chair Perkel advised the audience that the Stephens Way item (2nd item listed on the agenda) was going to be continued. The ZBA received an application to continue.

Chair Perkel made a motion to continue 2018-003/ZBA-Susan Solomont to the next available meeting. Member Thornley seconded.
So voted; 5-0-0, motion carries.

Chair Perkel then stated that the ZBA would take the next item out of order to discuss.

2018-007/ZBA – Kevin R. Shea and Judith Richland, for property located at 402 Shore Road (Atlas Sheet 10, Parcel 22, Registry of Deeds title reference, Book 13530, Page 012). Applicants are seeking a variance or amendment to the variance, whichever the Board deems appropriate, w/ref. to Section 50.1 (lot size) of the Zoning Bylaw that was granted on January 30, 2017 (docket #2016-013/ZBA) to construct a single family residence as per plans filed and extended to July 30, 2018. The applicant is requesting to substitute the previously approved plans and to amend the period to exercise the variance to January 30, 2019.

Atty. Christopher Snow approached the Board. He represents the applicants. He stated that he did not find that the Public Hearing had been published. Chair Perkel said that if Atty. Snow thinks that is a defect, then the Board will advertise and place the hearing on another agenda, however there is some sense that it was not necessary to advertise. Atty. Snow stated that not advertising could pose a significant hazard to the petitioner. If the petitioner waits the specified 20 days without an appeal, then pulls a building permit, then a person can come along and claim a defective notice and challenge the building permit for a period of up to 90 days. He would like the public hearing advertised for the next meeting of July 30th, 2018. Chair Perkel stated that they would advertise for the next meeting.
Interim Town Planner Bardi interjected to say that she had confirmation from the Cape Cod Media Group of the public hearing being published on June 9th and June 16th. She brought forth a copy of the publication for Atty. Snow to review. Upon review, he stated that the ZBA could go forward with hearing the public hearing.
Atty. Snow said that Kevin Shea and Judith Richland have a Purchase and Sale agreement for the property next door, owned by Siniscalco and Rybeck. As he mentioned in an earlier presentation, the

problem with the variance of Siniscalco and Rybeck expires July 30, 2018 and is tied (he thinks accidentally) to a particular set of building plans. Atty. Snow's clients have different plans for this lot, all within zoning setbacks and dimensional requirements. The client has entered into an agreement that is contingent upon the Zoning Board of Appeal's approval of extending the variance. If the delay in acting upon the variance is without the fault of the landowner and is the fault entirely (or nearly entirely) of third parties over which the landowner has no control, that delayed time period can be forgiven, and the variance extended. The delay is only on the Siniscalco/Rybeck lot.
Member Dundas stated that based upon what counsel said, it makes sense to him.
Member Hultin has no problem with the extension of time to the variance.
Member Todd had a question regarding what's stated under Chapter 40 which says that they are not allowed to do a second extension. Atty. Snow explained that it has been interpreted under the equitable eyes of the highest court in the Commonwealth to apply their equitable powers to allow relief under an equitable principle.
Chair Perkel asked the attorney what he wanted the ZBA to do for them. Atty. Snow believes they are entitled to the fourteen-month extension that was lost to the Planning Board but deferred to his client. Mr. Shea would also like the fourteen months. During further discussion, Mr. Shea announced he would be applying to the Conservation Commission to build a sea wall. If that were approved, he would then be changing the situs of the house by moving the deck. Chair Perkel stated that if the Board is to equitably extend the variance, he does not think it would be appropriate for them to consider time for Mr. Shea to do something else. Chair Perkel then asked what the minimum extension time would be (the response was unintelligible) and asked if the Board would consider an eight-month extension. The Board was amenable to an eight-month extension. Atty. Snow then pointed out that they still had the issue regarding the plan. He asked if the Board would approve the plans Mr. Shea brought in with him and filed with his application. Chair Perkel recalled there was some discussion about the height of one of the structures, and he wondered whether they should start from scratch. Atty. Snow suggested perhaps holding another meeting before July 30th where public comment would be heard, regarding the new plan.
Atty. Liz McNichols approached the Board. She represents Barbara Rybeck and Joan Siniscalco. She is here to support Mr. Shea's application for the equitable tolling. The owners want to see the agreement with Mr. Shea go through, and they support the application to amend the variance. It is Atty. McNichols' understanding that the footprint Mr. Shea is considering is within the footprint of the plans originally submitted by Rybeck/Sinscalco. It complies with all zoning and setback requirements and he is not asking for any further relief. She pointed out that the proposed plan fits within the footprint of the plan they already approved. She would like to see the eight-month extension granted so they can exercise those rights granted by the Board.
Judy Richland, Mr. Shea's wife, had a question. She stated that the Zoning Board did approve the building on 408 Shore Road. They listened to the public and gave in to all their issues regarding building height. The building that's proposed at 402 Shore Road is exactly like the house on 408 Shore Rd. It is no larger, in fact it is smaller. She does not understand why the Zoning Board would not approve it.
It was determined to continue this hearing to the July 23, 2018 meeting. No vote was taken.

Continuation – 2018-003/ZBA – Susan Lewis Solomont, by Atty. Sarah Turano-Flores, for property located at 37 Stephens Way (Atlas Sheet 58, Parcel 1, title reference: Book 10986, Page 185). Applicant is seeking to overturn the Building Commissioner's decision to not issue a permit and is also requesting a Special Permit and/or Variance, whichever the Board deems appropriate, w/ref. to Sec. 10.2 and 50.1A of the Truro Zoning Bylaw to construct a single-family dwelling.
As noted at beginning of meeting, the ZBA received an application to continue this to their next available meeting.

At this time, Member Thornley left the meeting.

Continuation – 2018-002/ZBA – Timsneck LLC, by Atty. Benjamin Zehnder, for property located at 10 Thornley Meadow Road (Atlas Sheet 53, Parcel 87, title reference: Book 30529, Page 134). Applicants are seeking a Special Permit and/or Variance, whichever the Board deems appropriate, w/ref to Sections 10.4 and 30.7B of the Truro Zoning Bylaw for additions to a pre-existing, non-conforming single-family dwelling.

Atty. Benjamin Zehnder approached the Board. His client has decided to redesign the project eliminating the swimming pool entirely, as the client and abutters were unable to come to an agreement. The plan in front of the Board is identical in all respects to what they have seen before except the pool, the pool house, and the pool deck, have been removed from the plan. What has been added is an at-grade paver sitting area. They have also created notes in the site plan in order to protect the conservation restricted area. They are going to install a four-foot high wooden snow fence, a geo-textile silt fence, as well as signage stating, "Do Not Enter-Conservation Restriction Area". There is also a new landscaping plan which shows a significant amount of screening between this property and the neighbor to the north.
Chair Perkel asked to see where the paved sitting area would be located. Atty. Zehnder located the correct plan and pointed out the location.
Member Areson had a question about the berm. She believed there had been some discussion about the removal of that berm between the two properties. Atty. Zehnder confirmed that the berm was indeed being removed. Member Todd asked whether the height of the berm was being used as part of the grade calculations in determining the building height. Atty. Zehnder stated that he didn't believe it was but had not specifically asked the engineers that question. Member Dundas asked what the Conservation Trust comments regarding the screening were based upon. Atty. Zehnder believes the Conservation Trust is saying that the natural flora and fauna area is a sandy heath, so extensive vertical planting would change the nature of that environment.
Fred Gaechter approached the Board. He wished to pass out a report which the Conservation Trust commissioned from a consultant regarding the plantings, so they would have it for the record. The gist of it is indeed the quantity of the plantings, and not necessarily the species. There were 46 plantings proposed for the lot, which appeared excessive to the Trust. The Trust would like it reduced significantly because those plantings could adversely impact the heathland. They would also like to see some conditions added if the plan is to be approved, with regard to the plantings such as; all plantings would be hand dug (no heavy equipment on the property), proper irrigation and replacement of any plants that fail, and other conditions that make it a viable plan. He also passed out a diagram of the neighborhood as it's important from a conservation perspective, to indicate what they are talking about. Mr. Gaechter proceeded to give a brief description of the properties in the neighborhood regarding locales of other conservation restrictions. The Trust would like the Zoning Board to consider this application not only in the context the legality of the amplification and the physical construction, but also the neighborhood in which it will reside and the mind-set of the Trust, the neighbors, and the Town.
Chair Perkel asked how one would enforce the replacement of plants that fail. Mr. Gaechter stated that as a holder of the conservation restriction, which is approved by the Selectmen and the State, the Trust is required by State law to make an annual visit. They are to request the property owner for access, the Trust goes out and conducts their inspection of the land and puts together a formal report that goes to the State to ensure the Trust is doing their stewardship under the terms of that conservation restriction. The Trust's interest is only in the conservation restricted portion of the property. Member Hultin pointed out that the wording for that condition would be quite specific, to which Mr. Gaechter stated that the Trust would be happy to put something together.

Atty. David Reid approached the Board. He represents John and Yvette Dubinski who are the immediate abutters to the North. He stated that while certainly the pool, pool house, and pool deck are the biggest concerns of his clients, they are not the only concerns. He pointed out that there was a lot of time spent discussing the fact that under the special permit criteria, in addition to the Board's assessment of whether there is a detriment, they must also find (in order to grant a special permit) is what's proposed is in harmony with the intent and purpose of the Zoning Bylaw. The Comprehensive Plan says that the rural character of this neighborhood is a critical factor. One of the largest threats to that character is the over-development of residential sites, particularly in prominent locations of hilltops, shorelines, and more visible locations like that. This project is all of those. With the removal of the pool and the pool house a lot of that is eliminated from his client's perspective. The other concern they have is the lower exercise area. If you look at the North and West elevation, it's a point sticking out from the house in the direction of his client's property. The room appears to be all glass on the two sides which point toward the abutter and, as discussed with Atty. Zehnder, an open patio. His clients continue to have concerns that this very visible, very open, very bright glass area will continue to have an adverse effect on the area. There is also the legitimate question as to whether the exercise level constitutes a third floor. The addition that's proposed has two sides fully exposed, above grade. A third story is not permitted under the height regulations of the bylaw.

Atty. Reid then went on to discuss when the lot was created (in 2007, not in 1993 as Atty. Zehnder stated). It is a further subdivision of the original lot. When created in 2007 it did not have 150 feet of frontage on any road. The definition of lot frontage is that it must be measured along one road. Because the lot was created in 2007 without complying with the quantity requirement of frontage at that time, it is not a lawfully, pre-existing non-conforming lot. Chair Perkel asked if that were true in light of the amendment of 40A Section 7. Atty. Reid stated yes. Chair Perkel continued, stating that the amendment mentioned a ten-year statute of limitations, and if you count from 2007 to 2018 you get to ten. Atty. Reid countered that in March of this year the Appeals Court stated that it's not the correct measurement. In the case of a non-conformity by an ANR plan the statute of limitations does not begin to run until there is a severance of the two lots from common ownership. That did not occur, in this case, until 2017. The statute of limitations has not run out. It does not qualify for a special permit, only a variance. Member Todd stated in looking at the elevations he sees three stories, despite what the height regulations say.

Chair Perkel stated that Atty. Reid was presenting a jurisdictional issue, in a sense. Atty. Reid agreed. Chair Perkel said he was not prepared to put this to a vote by the ZBA until he gets the opinion of counsel. The Board needs to have another meeting, and to have an opinion. He also believes there will be a fair amount of conditions which will need to be reviewed before they vote on them. Chair Perkel said the hearing would need to be continued with Atty. Zehnder's approval. Atty. Zehnder will consent to a continuance but would like to be heard on legal issues before the Board breaks.

Frank Dubinksi, son of Yvette and John Dubinski, asked to say a few words. His parents have lived at their current address for approximately 17 years. He is the generation who will inherit the house. He feels the important thing to note is the rural character of the town. People come to Truro for a reason. He has looked at the plans. He feels there are a lot of unanswered questions when it comes to the plan.

Regan McCarthy approached the Board. She asked what would be the total square footage of the structures and the square footage of the impervious land covering? She stated that the largest square footage house in Truro is 9400 square feet. She believes that this house will be larger than that, and that it would be helpful for the public to know the facts on that.

Nathalie Ferrier approached the Board. She asked who on the Board would like to be a neighbor of a house with nine bedrooms, nine bathrooms, and a large exercise room. She is concerned with the approval of another large structure in Truro and would like the ZBA to consider what they are doing.

Joanne Barkan approached the Board. She understands that the Board will probably put conditions on the approval of the project if they vote to approve it. She would like to know if there is a condition that can be put on that would make it quite secure that a pool would not be put in later.
Joan Holt approached the Board. She'd like to discuss the issue of detriment to the neighborhood. She stated that everyone in South Truro understands that the reason Truro has these large "monstrosities" is because of the business of people deciding that it's not a detriment to the neighborhood. Even though there is no house size limit bylaw yet, there is a lot which the ZBA could rely on in saying that the expansion of the house will be a detriment to the neighborhood. She'd like the Board to tell the neighbors why they feel it will not be a detriment. The neighborhood was unable to prevent the house at the end of Cooper Road, nor the Klein house, from being built. Most of the houses in the area are under 2000 square feet.
Atty. Zehnder wished to respond. He's listened to people come up and say that the house is too big, the neighborhood is changing, etc. but that's not the Zoning Board of Appeals job. That is the Planning Board's job. The ZBA's job is to look at the application and consider the facts. In regard to whether the exercise room creates a third story, he read a portion of the bylaw which states "*A basement, at its narrowest, may have its full height above ground on not more than one side and which may not have more than half of its height above mean ground on the second side.*". Yes, there are two sides exposed, but one of those sides doesn't have more than half of its height exposed. It meets the basement definition.
The statute of limitations case which Atty. Reid referenced is a different statute then the 10-year statute which Chair Perkel alluded to earlier, and the property does indeed qualify for a special permit.
Atty. Zehnder stated that the Dubinski's son came up and stated that this project will change the rural characteristics of the neighborhood however, the Dubinski's property has a main dwelling of 2,652 square feet, 2 bedrooms, a cottage with 2 bedrooms (689 square feet), and a potting shed, all on a lot of 62,000 square feet. They didn't feel they were changing the rural character of the Town. The applicant for 10 Thornley Meadow road is applying for a single-family dwelling with six (not 9 as previously stated) bedrooms. The gross floor area of the first floor is 4,009 square feet. The second floor has 2,976 square feet, and the finished basement has 1,167 square feet. Total gross floor area is 8,152.

Member Hultin made a motion to continue 2018-002/ZBA-Timsneck LLC, for property located at 10 Thornley Meadow Road to the next regularly scheduled meeting (July 30th at 5:30pm).
Member Areson seconded.
So voted; 5-0-0, motion carries.

Chair Perkel asked Atty. Zehnder to grant the Board a time extension. Atty. Zehnder agreed to a time extension of 60 days after the meeting with the understanding that the Board could ask for more time if needed, and Atty. Zehnder would consider it at that time.

Member Todd made a motion to adjourn at 7:30pm.
Member Hultin seconded.
So voted; 5-0-0, motion carries.

Respectfully Submitted,
Noelle L. Scoullar