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Communities advancing the studies of Tribal nations across their lifespan: Design, methods, and baseline of the CoASTAL cohort

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ABSTRACT

The CoASTAL cohort represents the first community cohort assembled to study a HAB-related illness. It is comprised of three Native American tribes in the Pacific NW for the purpose of studying the health impacts of chronic, low level domoic acid (DA) exposure through razor clam consumption. This cohort is at risk of DA toxicity by virtue of their geographic location (access to beaches with a history of elevated DA levels in razor clams) and the cultural and traditional significance of razor clams in their diet. In this prospective, longitudinal study, Wave 1 of the cohort was comprised of 678 members across the human lifespan, with both sexes represented within child, adult, and geriatric age groups. All participants were followed annually with standard measures of medical and social history; neuropsychological functions, psychological status, and dietary exposure. DA concentrations were measured at both public and reservation beaches where razor clams are acquired. Multiple metrics were piloted to further determine exposure. Baseline data indicated that all cognitive and psychological functions were within normal limits. In addition, there was considerable variability in razor clam exposure. Therefore, the CoASTAL cohort offers a unique opportunity to investigate the potential health effects of chronic, low level exposure to DA over time.

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1. Introduction

The role that ocean waters play in global health is increasingly recognized as an important public health issue (Knap et al., 2002). The growing demand for fish and shellfish, coupled with widespread contamination and development in coastal areas, has challenged the fragile ecological balance that exists between land-dwelling and marine populations. Health concerns stemming from the ocean generally revolve around exposure to agents in the marine ecosystem such as environmental pollutants, metals, and biotoxins. Marine scientists have identified the phenomenon of harmful algal blooms (HABs) as an important source of marine biotoxins (Erdner et al., 2008). While microscopic algae are essential for ocean life, there are a few dozen species that produce powerful biotoxins. When these algae bloom in excess, there can be devastating health effects in seabirds, marine mammals, and humans. Harmful algal blooms have been linked to human death and illness, and mass killings of fish, marine mammals, and seabirds (Stommel and Watters, 2004). Oceanographic monitoring data suggest that there are more toxic algal species, frequency of HABs appears to be increasing, and toxic strains of algae are spreading across new geographical regions (Luckas et al., 2005).

There are five clinical poisoning syndromes associated with HABs, but only one, amnesic shellfish poisoning, has a well-defined neurologic, gastrointestinal, and neuropsychological syndrome characterized by profound memory disorder. Domoic acid (DA), the causative agent in amnesic shellfish poisoning, is produced by microscopic algae of the genus, *Pseudo-nitzschia* (Bates et al., 1989). The potential risk of DA to human health was discovered in 1987 on Prince Edward Island, Canada, where 153 cases of acute intoxication were documented (including 4 deaths) (Perl et al., 1990a,b; Teitelbaum, 1990; Teitelbaum et al., 1990). These clinical cases were linked to the consumption of DA-contaminated mussels

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harvested from the Cardigan River. Symptomology included nausea, vomiting, abdominal cramping, excessive respiratory secretions, coma, and death. Neurological symptoms such as headaches, hallucinations, confusion, and memory impairment were also reported in exposed individuals. Clinical evaluations of 14 adults after the outbreak revealed that 12 had severe antegrade memory deficits with relative preservation of higher cortical functions (Teitelbaum, 1990; Teitelbaum et al., 1990). Affected individuals had difficulty remembering events that had occurred after DA exposure. Subsequent to this incident, environmental sampling revealed blooms of *Pseudo-nitzschia* at the locations where the mussels had been harvested. This episode firmly established the serious and complex health effects associated with the oral ingestion of DA-contaminated shellfish.

In response to the Canadian episode of DA poisoning, scientific investigations of DA toxicity and neurotoxicity were initiated in the laboratory with animal models. The neurobehavioral signature of this compound has been detailed by Grant et al. (2010). DA acts as a strong emetic and is associated with adverse changes in both brain and behavior. The hippocampus is the primary site of injury in the central nervous system (CNS). The adverse consequences of DA exposure are not limited to a single behavioral effect, and treatment-related changes have been documented in motor, cognitive, and emotionality domains. Research has also demonstrated that functional losses can be persistent and injuries to the CNS can be progressive over time. Given that DA is an increasingly prevalent biotoxin in the world's oceans (Trainer et al., 2012), there is an urgent need to identify study populations that have documented (and measurable) low-dose, chronic exposures to DA. Ideally these populations can be assessed for evidence of clinical (and subclinical) exposure effects and can be followed longitudinally to evaluate changes across time. We report here the identification and initial characterization of such an exposure cohort, as well as details regarding the methodology of this study. Since a wide range of specialized methods are used to describe the cohort and measure cognition as well as exposure across the lifespan, baseline cohort results will immediately follow each category of measurement.

2. Methods and results

2.1. Study background and community involvement

The Communities Advancing the Studies of Tribal Nations Across the Lifespan (CoASTAL) cohort evolved from a community based, environmental health initiative of the Quileute Indian Nation in response to concerns about rising levels of DA in the Pacific Northwest, USA. Shellfish managers, Tribe Council members, and the Quileute Health Clinic participated in the design, implementation, and interpretation of a pilot study that raised the possibility of DA neurotoxicity among some people in their community. However, since exposure and cognition are both complex processes, further investigation with a larger sample over time was needed to clarify and extend the findings. Subsequently, neighboring Pacific coast Tribal Nations both north (Makah Tribe) and south (Quinault Indian Nation) joined the study team to further examine the potential health effects of low levels of DA exposure by razor clam consumption.

Using a community-based participatory model, the contributions of these Tribal Nations to the cohort study included assistance with research design and implementation, including recruitment, data collection, interpretation of results, and community outreach and education. This was facilitated through hiring local study coordinators (Tribal members) and assembling local data collection field teams, community advisory boards, and medical advisory groups. Tribal fisheries experts, shellfish researchers, and environmental health managers assisted with providing environmental, razor clam harvest and DA data, and critical linkages with Tribal Councils and other community leaders. Community events such as health fairs, elder dinners, and treaty celebrations were used as venues to introduce the study to the Tribal Nations and to distribute informational brochures about the study and educational materials about memory, DA and healthy diets. The CoASTAL cohort study was funded by the National Institute of Environmental Health Science and data collection began in the summer of 2005 in the areas depicted below in Fig. 1.

2.2. The CoASTAL cohort

2.2.1. Recruitment

This study represents the methodology and baseline data collection for Wave 1 (the first 5 years) of a prospective longitudinal cohort study of DA neurotoxicity in the Pacific Northwest. The cohort was comprised of 678 participants. Initially recruitment was limited to individuals in the following age groups: school age children (6–12 years), adults (18–64 years), and geriatric (65+ years). Sampling frames for each site were derived through tribal registries from the Quinault, Quileute, and Makah reservations. After sorting by age, potential participants were randomly selected based upon the total number of enrolled members for each study site. A letter of invitation was sent to each selected adult participant and to the parents or primary caregivers of child participants. The letter of invitation explained the nature, purpose, and general procedures of the study.

Field coordinators scheduled baseline visits for all study participants. If a participant declined participation, their name was removed from the list and an alternate was randomly selected within their age group. This sequence was continued until the goal recruitment numbers were met at each location or until the lists of potential participants were exhausted. An alternative methodology was used to recruit the infant sample as they were not included on the tribal enrollment registries. Flyers were posted in health clinics, on bulletin boards, and in local newspapers on each reservation asking parents/primary caregivers to volunteer their

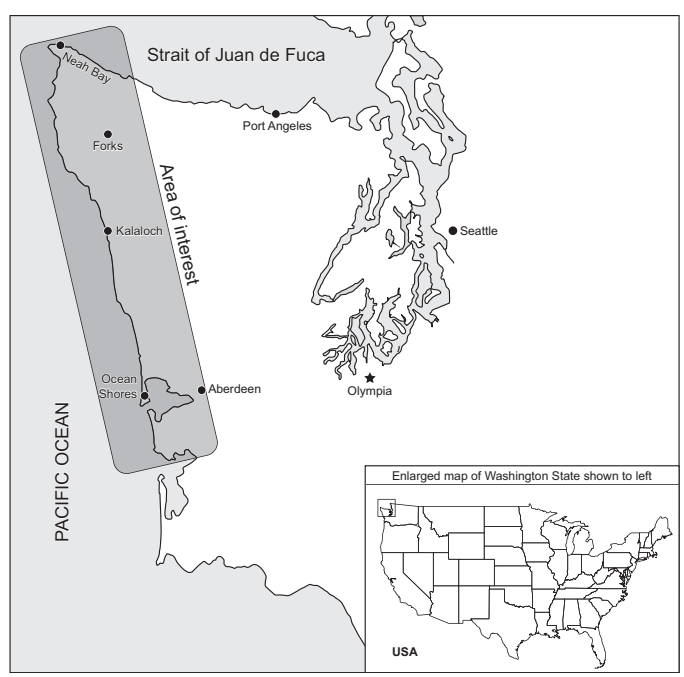

Fig. 1. Study region.

infants (ages 9–16 months) for participation in the study. Infant participants received the same reimbursement as child participants for the completion of the developmental exam and exposure history (obtaining mother's shellfish consumption and nursing history).

2.2.2. Cohort characteristics

Fig. 2 provides a summary of cohort enrollment ($N = 678$). One hundred and eight children between the ages of 6 and 12, 507 adults between 18 and 64 years, 31 geriatric participants, and 32 infants were enrolled in the CoASTAL study. The cohort consisted of 58% women and 42% men; this is similar to the population distribution of cohorts previously reported for tribal people (e.g., Slattery et al., 2007). Descriptive data for the characteristics of participants enrolled in the cohort are presented in Tables 1–4. The average age of adult participants was 40.4 years with a range of 18–83 years. The majority of adults had at least a high school education, and women had significantly more years of education than men ($p < 0.01$). At the time of enrollment, 48% of participants were unemployed. The mean age of children was 8.4 years and 35% of child participants were girls. A limited number of infants were also included in the cohort at this study phase and their mean age was 10.8 months.

2.2.3. Baseline visit procedures

Written informed consent was obtained from all participants at the beginning of their baseline visit in compliance with standard procedures required by the University of Maryland Institutional Review Board. All visits were conducted by trained examiners in private offices at the participant's respective field site. Exclusionary criteria included a history of severe dementia, severe head injury, or other psychiatric or neurological disorder which precluded understanding informed consent or assessment procedures. Consent was obtained from the parents or primary caregivers for each child and the cognitive exam procedures were explained to all children to ensure they were comfortable taking part in the study.

The baseline evaluation for the school age children, adults, and geriatric samples included a background/medical history and confounding exposure questionnaire; shellfish consumption, dietary intake questionnaires and records; and a cognitive screening exam. Parents or primary caregivers completed all questionnaires based on their child's history. All adult participants received $50 each year for the completion of a cognitive exam and for providing medical history and dietary consumption data. In addition, adult participants received $10 for each one-day food intake record four times a year. Child participants received a $50 gift card (upon completion of the annual exam) and a $10 gift card (upon providing a one-day food record) as reimbursement.

Total time for the baseline visit was approximately 2.5 h; 75 min for obtaining informed consent and completing the surveys and questionnaires, and an additional 75 min for the cognitive screening exam with rest breaks as needed. Upon completion of the exam, participants were also asked to take home and complete a one-day food record to be returned within 5 days. The same consenting procedure used for the school age children was replicated for the infants. The infants' parent or primary caregiver was required to be in the testing room and to take part in the developmental exam. The exam took approximately 1.15 h, which included a 15 min play

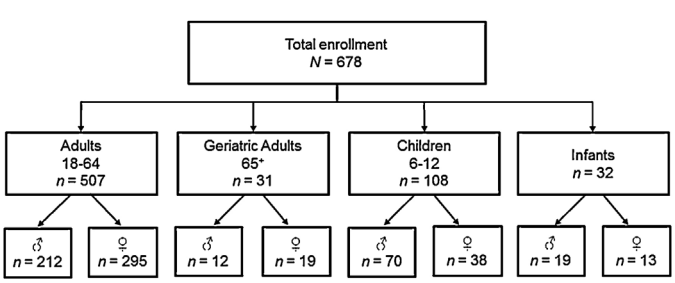

Fig. 2. Cohort enrollment by age and sex.

Table 1
Characteristics of adult and geriatric participants enrolled in the CoASTAL cohort.

Characteristic	Full sample $n = 538$	Men $n = 224$	Women $n = 314$	p value[a]
Age	40.4 ± 14.7	39.6 ± 14.8	41.0 ± 14.5	0.30
Gender (female)	58	0	100	–
Employed	52	48	55	0.11
Educational level	<0.01			
<High school	25	26	24	
High school	37	46	31	
Vocational/technical/ Associate's degree/ Some college	33	25	38	
Bachelor's/master's	6	4	8	

Data are presented as percentages, except for age which is shown as mean ± SD.
[a] p values from Chi-squared test, Fisher's exact test, or t-test, as appropriate.

Table 2
Characteristics of children enrolled in the CoASTAL cohort study.

Characteristic	Full sample $n = 108$	Boys $n = 70$	Girls $n = 38$	p value[a]
Age	8.5 ± 1.5	8.4 ± 1.5	8.5 ± 1.5	0.75
Gender (female)	35	0	100	–
Body mass index[b]	20.5 ± 4.7	20.1 ± 4.2	21.2 ± 5.4	0.29
Normal	79	79	78	
Overweight	14	16	10	
Obese	7	4	12	
Pre-term birth	16	15	16	1.00
Birth weight (g)[c]	3490 ± 600	3510 ± 630	3460 ± 600	0.69
Attend tribal school	19	17	21	0.80
Received tutoring	25	30	16	0.16
Diagnosed with learning disability	9	13	3	0.10
Difficulty with speech	12	17	3	0.03
Difficulty with language	7	10	0	0.05
Birth trauma	11	10	11	1.00
Asthma	18	24	8	0.06
Exposed to hazardous chemicals	2	3	0	0.54

Data presented as percentage, except age, body mass index (BMI), and birth weight presented as mean ± SD.
[a] p values from chi-square test, Fisher's exact test, or t-test, as appropriate.
[b] BMI calculated by this formula: weight (kg)/height (m)^2. Classifications of BMI: Normal BMI-for-age from the 5th to the 85th percentile, overweight BMI-for-age from the 85th up to the 95th percentile, obese BMI-for-age at or above the 95th percentile.
[c] $n = 84$ (53 males, 31 females).

Table 3
Characteristics of infants enrolled in the CoASTAL cohort.

Characteristic	Full sample $n = 32$	Boys $n = 19$	Girls $n = 13$	p value[a]
Gender (female)	10.8 ± 1.7	10.8 ± 1.6	10.8 ± 1.9	0.99
Premature birth	30	25	36	0.68
Birth weight (g)	3470 ± 670	3520 ± 690	3410 ± 650	0.67
Breastfed	77	88	62	0.19
Exposed to hazardous chemicals	3	0	8	0.43
Mother smoked tobacco during pregnancy	55	50	63	0.68

Data presented as percentage, except age and birth weight presented as mean ± SD.
[a] p values are from t-test or Fisher's exact test, as appropriate.

Table 4
Health and medical history of adult and geriatric participants.

	Full sample	Men	Women	*p* value[a]
	n = 538	*n* = 224	*n* = 314	
Body mass index[b]	32.4 ± 7.4	31.2 ± 6.4	33.2 ± 7.9	0.003
Normal	13	15	12	
Overweight	29	30	28	
Obese	57	54	60	
Current smoker	47	47	47	0.951
Alcohol use				<0.001
Never	51	39	59	
Monthly	21	25	19	
2–4 times a month	20	26	16	
2–3 times a week	6	8	5	
4 or more times a week	2	3	1	
Ever smoked marijuana				0.019
Never	34	35	34	
Fewer than 3 times	22	16	26	
More than 3 times	44	50	41	
Ever tried cocaine	36	36	36	0.841
Ever tried heroin	4	3	5	0.208
Ever tried other hallucinogen	19	25	15	0.016
Ever tried other non-prescription psychotropic drug	19	18	20	0.732
Ever diagnosed with or received treatment for alcohol or substance abuse problems	29	36	24	0.02
Co-morbid medical conditions				
Continuous	1.63 ± 1.84	1.33 ± 1.94	1.83 ± 1.74	0.006
Number of co-morbidities				0.004
0	29	38	24	
1	30	32	30	
2	17	13	19	
3	24	18	28	
Diabetes	14	13	15	0.464
Cancer	6	3	7	0.083
Stroke	5	6	5	0.668
Seizures/epilepsy	4	7	3	0.028
Multiple sclerosis	0.9	1.2	0.8	0.646
Dementia (AD, PD, HD)[c]	0.5	1.2	0.0	0.153
Lupus	1.4	0.6	1.9	0.411
Head injury	12	14	11	0.331
Loss of consciousness due to head injury (*n* = 64)	3	0	5	0.510
High blood pressure	26	26	25	0.846
Memory problems (*n* = 56)	13	16	10	0.688
Tremors	1.2	1.0	1.3	1.000
Depression, anxiety, and other psychiatric problems	25	12	34	<0.001
Taking anti-convulsants[d]	14	5	9	–
Taking anti-depressants	75	12	63	–
Taking anti-hypertensives	89	34	55	–

Data are presented as percentages, except body mass index which is presented as mean ± SD.
[a] *p* values from chi-square test, Fisher's exact test, or *t*-test, as appropriate.
[b] Body mass index (BMI) calculated by this formula: weight (kg)/height (m)^2. Classifications of BMI: Normal = 18.5–24.9, overweight = 25–29.9, and obese ≥30.
[c] Dementia diagnoses: Alzheimer's disease, Parkinson's disease, and Huntington's disease.
[d] Value reported is total number of individuals that reported taking the drug in question.

break for the infant. Infant participants also received a $50 and a $10 gift card, as well as a blanket and small toy.

2.2.3.1. Measures. All data were collected using standardized instruments, interviews, or cognitive assessment procedures. Measurement selection for cognitive instruments was based upon the following criteria: (1) the ability to screen the major functional domains of human cognition in standard fashion without redundancy; (2) the ability to assess memory functions; (3) suitability of measures for each age group; (4) well documented reliability and validity for cognitively intact or neurologically impaired populations; (5) cross-cultural validity and suitability of measures for the assessment of Native Americans; and (6) brevity to minimize participant burden (maximum length of 75 min for the cognitive exam). Data for all measures described below were collected for all participants at the baseline visit and each year thereafter for a total of 4 visits. Univariate analyses were performed to describe demographic characteristics, health history, psychological functioning, and dietary characteristics of the cohort. Differences on categorical variables were examined using Pearson's chi-squared test; differences in continuous variables were evaluated by Student's two-sample *t*-test. All statistical analyses were performed using Stata 10 software (Stata Corp, 2007). Statistical significance for all analyses was defined as $p < 0.05$.

2.2.3.2. Health history. Demographic data, developmental, academic, social, occupational, medical, neurologic, and psychiatric history were assessed using a modified version of the Boston Occupational and Environmental Health Questionnaire (Feldman, 1999) for adults and a modified version of the Pediatric Neuropsychology and Environmental Questionnaire (Feldman, 1999) for children. The Brief Michigan Alcohol Screening Test (BMAST; Pokorny et al., 1972) and Alcohol Use Disorders

Identification Test (AUDIT; Babor et al., 2001) were used to identify individuals with alcohol use problems.

2.2.3.3. Anthropometry. Trained field coordinators measured weight and height. Participants wore lightweight clothing, removed their shoes, and emptied their pockets prior to measurements. Height was measured to the nearest inch using a portable stadiometer (Shorr Infant/Child/Adult Portable Height-Length Measuring Board, Olney, Maryland). Weight was measured on a calibrated electronic scale and recorded to the nearest pound (SECA Digital Floor scale, Hanover, Maryland). Body mass index (BMI) was calculated using the formula weight (kg)/height $(m)^2$.

Health status and medical history of adult participants are summarized in Table 4. The mean BMI was 32.4; 29% of adults were categorized as overweight and 57.3% were categorized as obese. Women were significantly more likely than men to be categorized as obese (60% vs. 54%, respectively). Among adult participants, 47% were current smokers, and 49% reported at least monthly alcohol use; men drank significantly more often than women ($p < 0.001$). With respect to substance use, 66% reported some marijuana use, 36% reported previous cocaine use, 19% reported previous use of hallucinogens, and 19% reported use of non-prescription psychotropic drugs. Twenty-nine percent of participants reported previous diagnosis or treatment for an alcohol or substance use problem. Men reported history of diagnosis or treatment for alcohol or substance use more frequently than women ($p = 0.002$). Twenty-five percent of participants reported a history of hypertension and 14% reported a history of diabetes.

Health status and medical history of children and infants enrolled in the cohort are summarized in Tables 2 and 3. For school age children, the mean BMI was 20.5, with 14% of children categorized as overweight and 7% categorized as obese. Sixteen percent of children were born prematurely. Boys were significantly more likely than girls to be diagnosed with a learning disability (13% vs. 3%, respectively) and to have difficulties with speech or language.

2.2.3.4. Cognitive assessment. Cognitive functions were assessed with standardized neuropsychological test batteries conducted by trained examiners unaware of exposure data. The critical cognitive domains assessed included: *Simple and Complex attention* and *Concentration* [Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Digit Span, WAIS-III Coding (Wechsler, 1997); Trail Making Test, Parts A and B; Kiddie Trails (Reitan, 1992)], *Constructional praxis* [WAIS-III Block Design (Wechsler, 1997), Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) Block Design (Wechsler, 2003)], *Verbal memory* [California Verbal Learning Test, Second Edition (CVLT-II) Standard, Short and Children's versions (Delis et al., 2000)] *Visual memory* [Children's Memory Scale (CMS) Dot Location Test (Cohen, 1997)], *Psychomotor speed* [Trail Making Test, Part A] *and Dexterity* [Lafayette Grooved Pegboard (Lafayette Instrument Company, 2002)] and *Cognitive flexibility* [Trail Making Test, Part B (Reitan, 1992)]. Intelligence quotient (IQ) estimates were made from the WAIS-III subtests. Assessment of early learning, memory, and intelligence in infants was evaluated with the Mullen Scales of Early Learning (Mullen, 1995). Overall, the baseline cognitive status was normal for all participants. For the cognitive status of adults, please refer to Fig. 3.

2.2.3.5. Psychological adjustment. Psychological functioning was measured using standard measures of depression and anxiety in both adults and children. Depression was assessed using the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) in adults and the Children's Depression Inventory (CDI; Kovacs, 1992) in children. The BDI-II is a 21 item self-report inventory that measures severity

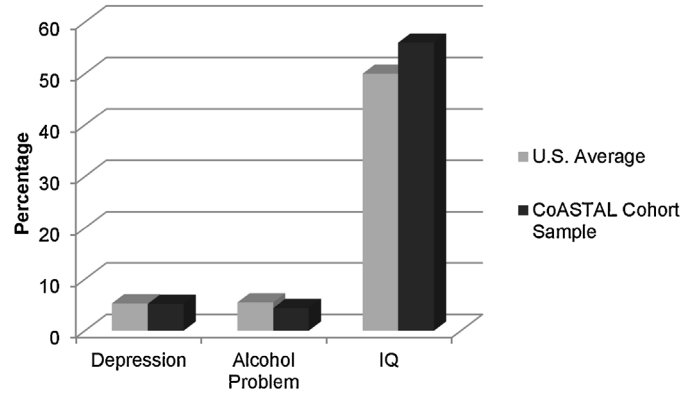

Fig. 3. Behavioral findings of adults in the CoASTAL cohort.

of depressive symptoms. Respondents were asked to rate each question on a scale from 0 to 3, which reflects varying degrees of agreement with depressive symptoms. The total score ranged from 0 to 63 with higher total scores suggesting more severe symptoms of depression. Scores in the range of 14–19 indicate mild depression, scores from 20 to 28 indicate moderate levels of depression, and scores from 29 to 63 indicate severe depression. CDI scores ranged from 0 to 54. Both the BDI-II and CDI evaluate the individual's mood in the 2 weeks prior to the assessment. Symptoms of anxiety were assessed using the Spielberger State-Trait Anxiety Inventory (STAI; Spielberger et al., 1983). The STAI is a 40-item self-report measure designed to measure an individual's current anxiety level as well as his/her typical anxiety levels. Items are scored on a 4-point Likert-type scale (1 = not at all; 4 = very much so).

Children's overall behavioral adjustment was assessed with the Achenbach Child Behavior Checklist (Achenbach and Rescorla, 2001). The CBCL is a 118 item questionnaire designed to assess children's social competence and behavior problems as reported by parents (Achenbach and Rescorla, 2001). Items are rated on a 3 point scale (0 = not true; 2 = very true or often true). The CBCL yields scores for internalizing behavior problems, externalizing problems, and total behavior problems as well as subareas of social withdrawal, somatic complaints, anxiety and depression, destructive behavior, social problems, thought problems, attention problems, aggressive behavior, and delinquent behaviors. Test–retest reliabilities range from 0.95 to 1.00; internal consistency reliability coefficients for subscales range from 0.78 to 0.97; and criterion validity has been found to be acceptable (National Center for Community-Based Child Abuse Prevention, 2005). T-scores were used for all analyses as demonstrated in Table 5.

Table 5
Findings of children in the CoASTAL cohort.

Measure and subscales	Full sample $n = 108$	Boys $n = 70$	Girls $n = 38$	p value[a]
Child depression inventory				
Total symptoms	47	47	46	0.564
Negative mood	48	49	48	0.756
Interpersonal problems	50	49	52	0.442
Ineffectiveness	46	46	46	0.928
Anhedonia	51	52	49	0.288
Negative self-esteem	44	45	42	0.135
Child behavior checklist				
Internalizing problems	48	49	48	0.678
Externalizing problems	50	51	49	0.521
Total behavior problems	48	49	48	0.798

[a] p values from chi-square test, Fisher's exact test, or t-test, as appropriate.

In summary, findings of psychological adjustment indicated that 25% of adults reported a history of depression, anxiety, or other psychological problems, with women reporting significantly more symptoms of depression than men (BDI: mean = 11.8 vs. 8.3, $p < 0.01$). Men and women reported similar levels of state anxiety, and women reported significantly higher trait anxiety (STAI: mean = 54.4 vs. 51.9, $p = 0.01$). Both boys and girls scored in the average range for total symptoms of depression, negative mood, interpersonal problems, ineffectiveness, anhedonia, as measured on the CDI; scores on the negative self-esteem scale were slightly below average for both boys and girls. No significant differences were noted between boys and girls for any of the CDI scale scores. Similarly, scores on the Internalizing, Externalizing, and Total Behavior problem scales of the CBCL were also in the average range with no significant differences in behavior problems noted between boys and girls.

2.2.3.6. Domoic acid exposure assessment. Since the primary mechanism for DA exposure is through razor clam consumption, shellfish consumption, and general dietary intakes, these exposures were assessed using multiple methods. The utility of the dietary assessment methods used in the CoASTAL cohort has been previously described (Fialkowski et al., 2010a) and will be briefly summarized here. Environmental data with respect to DA levels were also obtained.

2.2.3.7. Food frequency questionnaire. Participants completed the Block Food Frequency Questionnaire (FFQ; Block et al., 1986) to characterize usual frequency of consumption of specific foods or food groups. The Block FFQ is a self-administered, quantitative food frequency questionnaire that asks respondents to recall their usual frequency of consuming specific foods or food groups; it also asks respondents to provide estimates of portion sizes using standardized portion photos. The period of dietary recall was the year prior to the baseline study visit. The Block FFQ has been extensively validated with diverse populations of adults (Cummings et al., 1987; Sobell et al., 1989; Block et al., 1990, 1992; Coates et al., 1991; Subar et al., 2001). The Block FFQ compares favorably with other FFQ instruments (Subar et al., 2001). For participants with self-identified limitations in reading skills, the Block FFQ was completed by a standardized interview developed specifically for this study.

2.2.3.8. Dietary records. Dietary records were completed every 4 months as two 1 day dietary records and one set of 2 day dietary records, for a total of 4 dietary records over 1 year. Respondents were assigned a grouping of days of the week based on the day of their first visit. At least one of the assigned days included a weekend day. This approach was designed to capture seasonal and day of the week variation and decrease respondent fatigue. Field coordinators trained the participants in record keeping techniques, provided a tool kit of calibrated utensils (e.g., measuring cups and spoons), provided recording materials, followed up with phone calls, and reviewed the dietary record upon completion. Data coding and entry were performed by staff trained in the use of the Nutrition Data System for Research (NDS-R) Database Version 4.07 (© Regents of the University of Minnesota). The intakes from the dietary records were calculated as the mean of the number of days reported. At least 2–4 days were reported by all respondents. The results for the dietary intakes as assessed with the dietary records among the adults of the CoASTAL cohort have been reported previously (see Fialkowski et al., 2010a,b, 2012). In general, the men and women did not record intakes that met Dietary Reference Intake (DRI) recommendations for total fat, saturated fat, cholesterol, protein, vitamin A, vitamin E, vitamin C, magnesium, and zinc (Fialkowski et al., 2010b). A dietary pattern reflecting the presence of indigenous foods was not detected (Fialkowski et al., 2012).

Estimates from the FFQ of the dietary intakes of the men and women are shown in Table 6. These intakes from the CoASTAL cohort were compared to the intakes of men and women, ages 20 years and older, that were reported in the What We Eat in America (WWEIA), National Health and Nutrition Examination Survey (NHANES) from 2011 to 2012. The intakes of dietary cholesterol for both men and women were higher than the intakes reported in NHANES, i.e., 338 mg for men, 229 mg for women. For dietary fiber, the cohort men's intakes were slightly lower than men in NHANES at 20.3 g; however, the intakes for women were similar to women in NHANES at 16.1 g. For the fatty acids, the intakes of omega-3 fatty acids were similar to the men and women in NHANES. For example, the men from the NHANES sample had a mean intake of 2.4 g and the women 1.8 g. Given the access to seafood rich in omega-3 fatty acids among the Tribal Nations of the Pacific Northwest, this is surprising. However, the FFQ may have underestimated the seafood consumption by limiting choices of fish relevant to the Pacific coastal waters. On the other hand, the intakes of the monounsaturated fatty acids (MUFA) were high among the men compared to NHANES, i.e., 34.8 g MUFA and the polyunsaturated fatty acids (PUFA) were lower, i.e., 28.7 g. The women were consistently higher than their NHANES counterparts, i.e., 24.3 g MUFA and 16.8 g PUFA. The Acceptable Macronutrient Distribution Range (AMDR) set as the Dietary Reference Intakes (DRI) for fat is 20–35% of energy (kcal). Both the men and women of the CoASTAL cohort at 37.2% and 36.5%, respectively, had slightly higher fat intake than the acceptable range.

The dietary intakes of the boys and girls from the CoASTAL cohort displayed in Table 7 were also compared to intakes reported in the WWEIA, NHANES from 2011 to 2012 for boys and girls ages 2–19. The intakes of dietary cholesterol for both boys and girls were higher than the intakes reported in NHANES, i.e., 250 mg for boys, 197 mg for girls. For dietary fiber, the boy's intakes were slightly higher than boys in NHANES, 15.9 g and the intakes for girls were slightly higher than girls in NHANES, 12.9 g. For the fatty acids, the intakes of omega-3 fatty acids were slightly higher compared to the boys and girls in NHANES. For example, the boys had a mean intake of 1.73 g and the girls 1.45 g. In contrast to the adults, the children's intakes of omega-3 fatty acids were more consistent with the access to seafood rich in omega-3 fatty acids among the Tribal Nations of the Pacific Northwest. The intakes of the MUFA were higher among the boys compared to NHANES, i.e., 28.1 g MUFA and the PUFA were higher, i.e., 18.0 g. The girls were also consistently higher than their NHANES counterparts, i.e., 22.5 g MUFA and 15.0 PUFA. The Acceptable Macronutrient Distribution Range (AMDR) set as the Dietary Reference Intakes

Table 6
Mean dietary intakes for adults from a food frequency questionnaire.

Nutrient	Total $n = 538$	Men $n = 221$	Women $n = 308$	p value[a]
Cholesterol (mg)	311 ± 287	367 ± 317	271 ± 256	<0.001
Dietary fiber (g)	17.0 ± 13.4	17.7 ± 14.4	16.6 ± 12.7	0.348
Omega-3 fatty acids (g)	2.1 ± 1.9	2.2 ± 1.9	1.9 ± 1.8	0.145
MUFA (g)	37.8 ± 32.9	41.3 ± 35.1	35.2 ± 31.1	0.034
PUFA (g)	22.3 ± 19.0	23.6 ± 20.0	21.3 ± 18.3	0.180
% energy from fat	36.8 ± 6.5	37.2 ± 6.2	36.5 ± 6.8	0.225
% energy from saturated fatty acids	11.4 ± 2.4	11.7 ± 2.2	11.2 ± 2.5	0.043
% energy protein	14.2 ± 3.2	14.9 ± 3.2	13.7 ± 3.1	<0.001
% energy carbohydrate	49.6 ± 8.4	47.9 ± 7.9	50.9 ± 8.5	≤0.001

Data presented as mean ± SD. Abbreviations: MUFA = Monounsaturated fatty acids; PUFA = Polyunsaturated fatty acids.
[a] Probability associated with t-scores.

Table 7
Mean dietary intakes for children 5–17 years old from a food frequency questionnaire.

Nutrient	Total $n = 99$	Boys $n = 65$	Girls $n = 34$	p value[a]
Cholesterol (mg)	269 ± 160	279 ± 178	249 ± 117	0.390
Dietary fiber (g)	17.2 ± 10.1	17.6 ± 11.2	16.4 ± 7.9	0.566
Omega-3 fatty acids (g)	1.73 ± 1.20	1.83 ± 1.42	1.59 ± 0.70	0.422
MUFA (g)	36.9 ± 22.3	38.6 ± 25.4	33.8 ± 14.5	0.311
PUFA (g)	21.2 ± 13.7	22.4 ± 15.8	18.9 ± 8.1	0.234
% energy fat	36.5 ± 4.9	36.6 ± 4.9	36.4 ± 4.8	0.810
% energy saturated fatty acids	12.0 ± 2.0	11.9 ± 1.9	12.1 ± 2.0	0.688
% energy protein	14.3 ± 2.5	14.3 ± 2.6	14.4 ± 2.4	0.736
% energy carbohydrate	50.8 ± 6.3	50.8 ± 6.3	50.8 ± 6.3	0.980

MUFA = Monounsaturated fatty acids; PUFA = Polyunsaturated fatty acids.
[a] Probability associated with t-scores.

(DRI) for fat is 20–35% of energy (kcal). Both the boys and girls, at 36.6% and 36.4%, respectively, were slightly higher than the acceptable range. Thus, the greater intakes in fatty acids observed among the Native American children can partially be explained by the higher proportion of fat consumed in the diets.

2.2.3.9. Shellfish consumption. Shellfish consumption was assessed using the Shellfish Assessment Survey (SAS), specifically developed and validated in collaboration with participating tribes for this population (Fialkowski et al., 2010a). The SAS was piloted on each reservation and adjustments were made for clarity, readability, and relevance. The final version of the questionnaire asked for the frequency, types, and preparation of shellfish, as well as locations from which shellfish were harvested. Each participant took 10–15 min to complete the SAS upon entry into the cohort, reporting their consumption of shellfish over the previous month.

Shellfish consumption for adults and children is summarized in Tables 8 and 9. The majority of adults and children reported consumption of fish and/or shellfish (96% and 92%, respectively). Razor clam consumption was also relatively high, with adults consuming more razor clams (83%) than children (58%). However, there was considerable variability in the number of razor clams consumed annually and/or seasonally.

2.2.3.10. Shellfish sampling and analyses. Shellfish samples were collected twice monthly to coincide with the summer-fall HAB season (June–October) and on a monthly basis the remainder of the year. The shellfish of greatest interest were razor clams because razor clams can hold DA in tissue for up to one year and thus produce the greatest human health risk. DA sampling occurred on a weekly basis during the summer-fall HAB season.

2.2.3.11. Domoic acid sampling data. Serial samples were collected from 11 beach areas on the North, North Central, and Central Region Pacific coast of Washington where people reported sourcing razor clams. Concentrations of DA in razor clams were determined by the Shellfish Program in the Office of Environmental Health and Safety (Washington State Department of Health) and the Northwest Fisheries Science Center (National Oceanic and Atmospheric Administration) using the method described by Hatfield et al. (1994), which uses a methanol/water extraction and analysis by high-performance liquid chromatography. Mean levels of DA across all sites were 4.04 ppm (SD = 4.97 ppm) during the first year of the study, with the highest median level reported from a single sample collected at Second Beach (13.59 ppm) and the most consistent elevation level noted in samples obtained from Kalaloch Beach (mean = 15.69 ppm). These beaches historically have the highest elevations of DA, are closely monitored by regulatory agencies, and are closed to shellfish harvesting when levels reach the regulatory guidance level of 20 ppm or greater.

2.2.3.12. Exposure assessment. In addition to examining levels of razor clam consumption (the primary vector of DA exposure), DA toxicity level data were collected from 11 beaches of eight regions of the northwest coast of Washington where razor clams were sourced. Data collection ranged from the Columbia River to Neah Bay (Fig. 1) and included tribal as well as non-tribal beaches. Since there was considerable variability in the sources of razor clams among participants, three exposure methods were studied in Wave 1. The first involved defining exposure as the product of (the average number of razor clams consumed per month that year) multiplied by the mean measured DA concentration in razor clams at all beaches from which the participant ate clams that year. The second involved establishing a "typical" exposure level based upon DA concentrations in regions of most frequently sourced clams. Finally, the third exposure method was based on consumption data, dividing the group into high and low consumers based upon the overall distribution of scores. Individuals consuming 15 or more razor clams/month were considered high consumers and people who ate fewer were categorized as low consumers.

2.2.3.13. Mercury exposure. Fish and seafood comprise a large part of the CoASTAL cohort's diet. Therefore this population as a whole may be at risk of methylmercury exposure. Since elevated levels of methylmercury exposure may also be associated with cognitive and neurological symptoms, this metal is a potential confounding factor in this study. For this reason, the concentration of total mercury in hair samples was analyzed for 20% of adults and children at all study sites. Of the 228 samples, more than half were below the level of quantification and more than one-third of these were below the level of detection. Where levels were detected for women and children, they remained below the means reported by the 1999–2000 NHANES in each age group (McDowell et al., 2004; Centers for Disease Control and Prevention, 2005). Moreover, the adult women from the CoASTAL cohort had an approximately 4-fold lower mean concentration than the means reported from NHANES. There was no difference in the means between men and women. The reason for the relatively low mercury concentrations in the CoASTAL cohort is most likely because the Tribal Nations are located in a remote part of Northwest Washington state, where there is a relatively low risk for exposure to toxicants due to the absence of mining and industrial sources.

3. Discussion

The CoASTAL cohort represents the first community cohort of Native Americans assembled to study a HAB-related illness, specifically amnesic shellfish poisoning. The cohort is unique to the extent that it is geographically located in a region where humans are exposed to low-level DA exposures through razor clam consumption. The demographics of this coastal area include a wide range of consumers as well as non-consumers. Moreover, by virtue of tribe membership and reservation living, the cohort is relatively stable for longitudinal studies. Finally, close monitoring of DA levels in razor clams from both tribe and state natural resources and fisheries programs provide frequent and geographically widespread measures of DA levels. Thus, this region provides access to the best available DA exposure data in the United States and possibly the world. From a public health perspective, this cohort is particularly important to study as they are at greatest potential risk for chronic, low level DA-related toxicity.

DA levels during the study period remained relatively low, thus direct comparison to the documented cases of amnesic shellfish poisoning associated with the Prince Edward Island outbreak

Table 8
Adult seafood consumption as reported on shellfish assessment survey.

	Total	Men	Women	*p* value[a]
	n = 526	*n* = 217	*n* = 309	
Eat fish and/or shellfish (%; *n* = 524)	96	97	95	0.229
Eat razor clams (%; *n* = 519)	83	87	80	0.025
Razor clams consumed/month Fall/Winter (mean ± SD; *n* = 492)	13 ± 16	15 ± 17	13 ± 16	0.139
Razor clams consumed/month annually (mean ± SD; *n* = 455)	13 ± 15	14 ± 16	12 ± 14	0.087
Razor clam meals/month during Fall/Winter (%; *n* = 505)				0.018
0	18	14	21	
1 to 2	36	40	33	
3 to 4	24	29	21	
5 to 6	11	8	13	
7 to 8	5	4	5	
9 to 10	6	5	7	
Number of razor clams per meal in Fall/Winter (%; *n* = 498)				<0.001
0	18	14	21	
1 to 2	18	15	21	
3 to 5	41	40	42	
6 to 9	15	18	12	
10 or more	8	13	4	
Eat razor clam chowder (*n* = 473)	78	80	76	0.369
Razor clam chowder meals/month in Fall/Winter (%; *n* = 470)				0.488
0	22	20	24	
1 to 2	40	43	37	
3 to 4	22	24	21	
5 to 6	9	7	10	
7 to 8	5	4	5	
9 to 10	2	3	2	
Cups of razor clam chowder per meal in Fall/Winter (%; *n* = 479)				0.011
0	23	20	25	
1	20	18	22	
2	35	32	37	
3	15	19	12	
4	7	11	4	
Razor clam meals/month in Spring/Summer (%; *n* = 479)				0.062
0	19	15	22	
1 to 2	42	46	39	
3 to 4	26	28	24	
5 to 6	6	7	6	
7 to 8	3	1	5	
9 to 10	4	4	4	
Number of razor clams per meal in Spring/Summer (%; *n* = 471)				0.001
0	19	15	22	
1 to 2	19	18	20	
3 to 5	41	38	43	
6 to 9	15	19	12	
10 or more	6	1	3	
Eat crab (%; *n* = 496)	22	25	20	0.199
Number of crab meals in Fall/Winter (mean ± SD; *n* = 487)	0.6 ± 1.7	0.8 ± 2.1	0.5 ± 1.3	0.049
Number of crab meals in Spring/Summer (mean ± SD; *n* = 483)	0.5 ± 1.6	0.5 ± 1.4	0.5 ± 1.8	0.868
Number of little neck clams consumed yearly (mean ± SD; *n* = 229)[b]	19 ± 40	19 ± 36	19 ± 43	0.956
Number of butter clams consumed yearly (mean ± SD; *n* = 225)[b]	20 ± 42	19 ± 34	20 ± 48	0.917
Number of horse clams consumed yearly (mean ± SD; *n* = 221)[b]	5.7 ± 29	7.0 ± 36	4.9 ± 23	0.600

Data presented as percentage or mean ± SD; varies by row.
[a] *p* values from chi-square test, Fisher's exact test, or *t*-test, as appropriate.
[b] Clam data is very unstable due to a few large values.

(Perl et al., 1990a,b; Teitelbaum et al., 1990) cannot be made. However, since the convergence of data from human autopsy and non-human primate studies suggests temporal lobe abnormalities at the root of the serious and persistent memory difficulties (Sutherland et al., 1990; Cendes et al., 1995; Slikker et al., 1998a,b;), lower level exposures might be expected to contribute to milder forms of memory problems after DA exposure. Currently, there is no available biomarker of human exposure to DA; therefore measures of exposure are necessarily linked to razor clam consumption and estimates of DA levels established from sourced beach sampling.

Overall, baseline cognitive data with the CoASTAL cohort suggests scores well within the average range for age and educational level for children and adults on all cognitive measures. Psychological assessment data found that one-fourth of adults reported a history of depression, anxiety, or other psychological problems, with women reporting more symptoms of depression than men. Men and women reported similar levels of state anxiety (current), and women reported significantly higher trait anxiety (long term, stable). Despite these statistical differences, scores on the psychological measures remained within normal limits. Similarly, the children demonstrated no evidence for problems with depression or interpersonal problems. Their relatively low scores on the negative self-esteem scale suggest a healthy sense of liking themselves and feeling loved. Overall, the psychological adjustment of this cohort further supports their suitability for prospective studies.

Dietary data for the CoASTAL cohort sample shown in the Tables 6 and 7 were derived from FFQs, whereas, the national data from NHANES used for comparison were derived from 24-hour dietary recalls. Although some of the observed differences may

Table 9
Children's seafood consumption as reported on shellfish assessment survey.

	Total	Boys	Girls	*p* value[a]
	n = 108	*n* = 70	*n* = 38	
Eat fish and/or shellfish (%; *n* = 108)	92	90	95	0.489
Eat razor clams (%; *n* = 105)	58	56	62	0.533
Razor clams consumed/month Fall/Winter (mean ± SD; *n* = 99)	4.6 ± 6.6	4.0 ± 5.5	5.6 ± 8.0	0.256
Razor clams consumed/month annually (mean ± SD; *n* = 97)	4.3 ± 6.9	4.0 ± 6.5	4.9 ± 7.5	0.535
Razor clam meals/month during Fall/Winter (%; *n* = 103)				0.487
0	43	45	38	
1 to 2	29	30	27	
3 to 4	20	20	22	
5 to 6	6	5	8	
7 to 8	1	0	3	
9 to 10	1	0	3	
Number of razor clams per meal in Fall/Winter (%; *n* = 99)				0.205
0	44	48	38	
1 to 2	30	26	38	
3 to 5	22	24	19	
6 to 9	2	0	5	
10 or more	1	2	0	
Eat razor clam chowder (*n* = 94)	63	63	62	0.922
Razor clam chowder meals/month in Fall/Winter (%; *n* = 91)				0.927
0	38	38	39	
1 to 2	37	38	36	
3 to 4	19	16	22	
5 to 6	4	5	3	
7 to 8	1	2	0	
9 to 10	0	0	0	
Cups of razor clam chowder per meal in Fall/Winter (%; *n* = 92)				0.711
0	38	38	38	
1	34	31	38	
2	24	27	19	
3	3	4	3	
4	1	0	3	
Razor clam meals/month in Spring/Summer (%; *n* = 102)				0.573
0	43	45	39	
1 to 2	38	35	44	
3 to 4	14	15	11	
5 to 6	2	2	3	
7 to 8	2	3	0	
9 to 10	1	0	3	
Number of razor clams per meal in Spring/Summer (%; *n* = 99)				0.274
0	44	48	38	
1 to 2	33	30	39	
3 to 5	18	21	14	
6 to 9	4	2	8	
10 or more	0	0	0	
Eat crab (%; *n* = 106)	16	19	11	0.285
Number of crab meals in Fall/Winter (mean ± SD; *n* = 106)	0.6 ± 1.5	0.7 ± 1.7	0.4 ± 1.1	0.346
Number of crab meals in Spring/Summer (mean ± SD; *n* = 106)	0.5 ± 1.3	0.6 ± 1.5	0.2 ± 0.8	0.187
Number of little neck clams consumed yearly (mean ± SD; *n* = 73)[b]	5.2 ± 17	4.3 ± 13	7.1 ± 21.9	0.510
Number of butter clams consumed yearly (mean ± SD; *n* = 74)[b]	5.0 ± 12.9	3.1 ± 8.6	8.9 ± 18.7	0.072
Number of horse clams consumed yearly (mean ± SD; *n* = 69)[b]	0.6 ± 2.4	0.4 ± 1.6	1.1 ± 3.8	0.262

[a] *p* values from chi-square test, Fisher's exact test, or *t*-test, as appropriate.
[b] Clam data is very unstable due to a few large values.

reflect an artifact of the different methodologies, previously published studies from this research team concluded that the dietary data from the CoASTAL cohort and NHANES yielded similar results with respect to dietary intakes (Fialkowski et al., 2010b). Collectively, these results show the merits of methods used in the CoASTAL cohort study compared to other nationally vetted methods.

With respect to exposure assessment, there is currently no available method for detection of DA in human body fluids. Although environmental exposures are historically very difficult to assess (Nitta et al., 2010), every effort is made in this investigation to use the best available methods and models. However, as new methods become available, this well studied cohort would be in an optimal position to participate in validation studies and would benefit from evolving science. Meanwhile, the best available method for assessing exposure is through dietary consumption and razor clam source data. Pilot testing a technology assisted dietary assessment (TADA) method to potentially increase the accuracy of dietary consumption data and make real time links to memory functions will be initiated during the next wave of this study (Boushey et al., 2016). Finally, the cumulative effects of past DA exposure history remain an unknown in this study. Questions still remain regarding generalizability of this cohort to other, non-American Indian people. This is particularly relevant as 26% of the cohort believes that Pacific Northwest coastal Native American Indians have developed immunity to DA throughout many years and generations of exposure (see Roberts et al., 2016). In fact, the genetic basis for immunity to paralytic shellfish toxins was tested in a Makah Tribe cohort (Adams et al., 2016). The potential for immunity of Native American Indians to DA can only be answered

with future comparative studies (behavioral and genetic) within the context of more advanced detection methods and exposure models.

Meanwhile, the CoASTAL cohort offers a unique opportunity to investigate the potential health effects of chronic low level exposure to DA over time. Specifically, these methods will provide the basis for determining the extent to which continuous exposure to low levels of DA may be associated with memory problems. Findings may be relevant to protecting the health of this vulnerable population and the high risk groups within it (infants, children, and elderly), as well as other populations. Moreover, the results of this study may also be of public health significance by establishing guidelines for preventing DA illnesses associated with potential long-term chronic exposure. This is particularly important as DA-related harvesting closures have been reported in more regions of the United States (e.g., Trainer et al., 2007; Fernandes et al. (2013)).

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