

BC Centre for Disease Control

An agency of the Provincial Health Services Authority

*Domoic Acid Exposure Among the
First Nation Population in BC*

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Workshop on Marine Biotoxins
October 24-25 2016

Conflict of interest;

None

Target audiences of this talk are different; therefore, technical slides are marked with this sign to avoid confusion.



Contents

The following three questions would be addressed in this talk.

1. What is domoic acid (DA) / amnesic shellfish poisoning (ASP)?
2. What are the risk factors related to ASP
 - 2.1. currently included in the regulatory values
 - 2.2. currently are not included in the regulatory values
3. What are the important differences between First Nation population and General population as regard to DA exposure?

What is domoic acid (DA)?

History




Moses...lifted up the staff and struck the water that was in the Nile, in the sight of Pharaoh ...(Exodus 7:20)



“The History of Great Japan”
(Dai Nihon Shi, 1715, Tsunaeda)
Harmful algal bloom (red tide)



Alfred Hitchcock's "THE BIRDS", 1969

 The NEW ENGLAND JOURNAL of MEDICINE






HOME ARTICLES & MULTIMEDIA ▾ ISSUES ▾ SPECIALTIES & TOPICS ▾ FOR AUTHORS ▾ CME ▶

ORIGINAL ARTICLE

An Outbreak of Toxic Encephalopathy Caused by Eating Mussels Contaminated with Domoic Acid

Trish M. Perl, M.D., Lucie Bédard, M.S.N., Tom Kosatsky, M.D., M.P.H., James C. Hockin, M.D., Ewen C.D. Todd, Ph.D., and Robert S. Remis, M.D., M.P.H.

N Engl J Med 1990; 322:1775-1780 | June 21, 1990 | DOI: 10.1056/NEJM199006213222504

Share:     

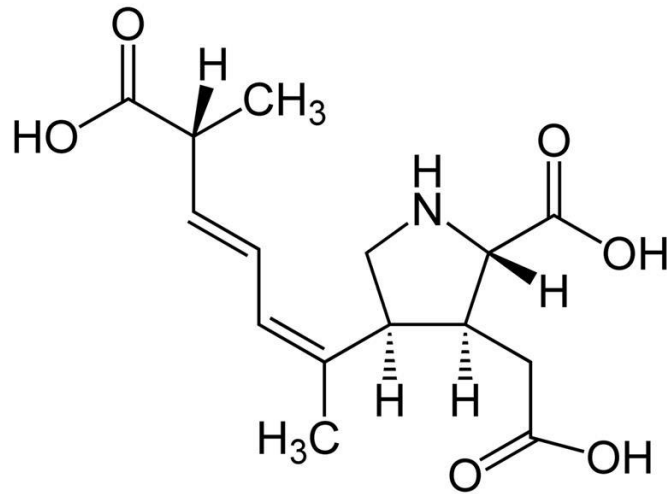
Abstract Article References Citing Articles (294) Letters

Clinical syndrome defined in 1990

What is Domoic acid (DA)?



- Neurotoxin
- Kainic acid analog
- Isolated from red algae (1959, Japan)



(2S,3S,4S)-3-(carboxymethyl)-4-
[(1Z,3E,5R)-6-hydroxy-1,5-
dimethyl-6-oxo-hexa-1,3-
dienyl]pyrrolidine-2-carboxylic acid

IUPAC name

There are myths regarding Domoic acid!

Myths

Keeping Shellfish in ambient temperature, exposure to light, freezing or storing it for a long time destroys potential domoic acid contamination.

True

False

Myths

Keeping Shellfish in ambient temperature, exposure to light, freezing or storing it for a long time destroys potential domoic acid contamination.

True

False

?

DA is persistent (freezing or storing food would not fully destroy it)

Myths

Cooking, boiling and steaming shellfish destroys any potential domoic acid contamination.

True

False

Myths

Cooking, boiling and steaming shellfish destroys any potential domoic acid contamination.

True

False

DA is persistent (cooking food would not destroy it)

Myths

Episodes of high Domoic acid concentration dose not happen in the colder months of the year (autumn and winter).

True

False

Myths

Episodes of high Domoic acid concentration dose not happen in the colder months of the year (autumn and winter).

True

False ?

While the prevalence of the reported high Domoic acid concentration in shellfish is more common in warmer months of the year, many episodes, including the original major outbreak of 1987 [November and December] happened in cooler months of the year.

Myths

Stomach acids in sea animals (sea lions) and human can destroy the DA

True

False

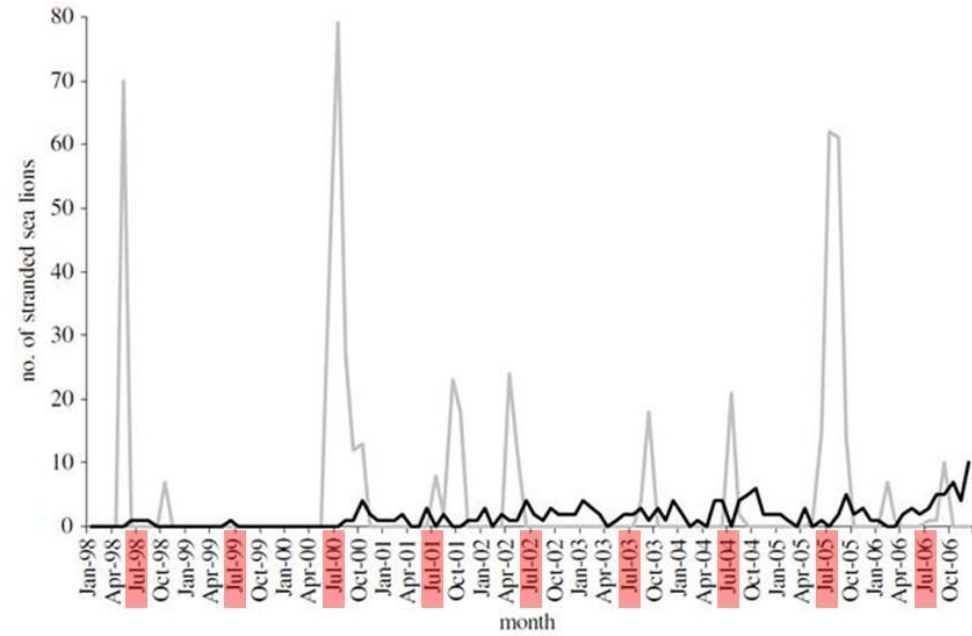
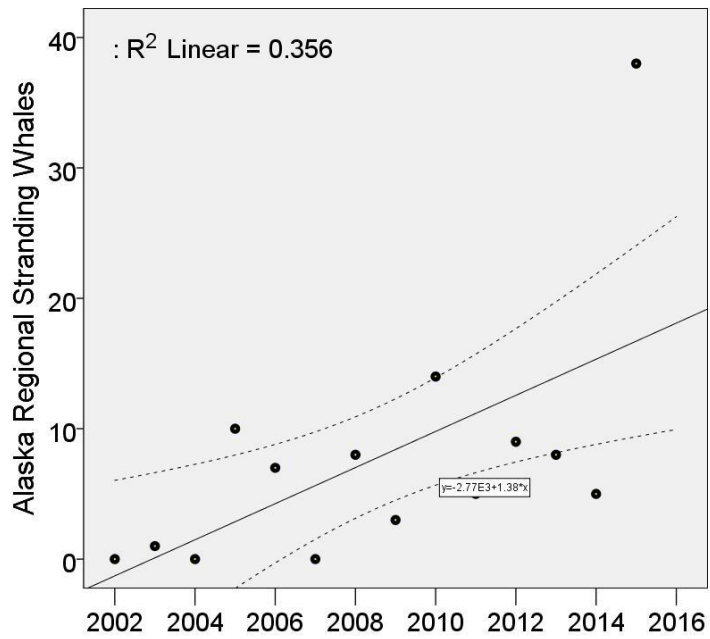
Myths

Stomach acids in sea animals (sea lions) and human can destroy the DA

True

False

Not to a clinically important extent in high dose exposure.



Personal communication

Goldstein et al. Comparison of monthly acute (gray line) and chronic (black line) neurological cases admitted to the Marine Mammal Center from 1998 to 2006.

Myths

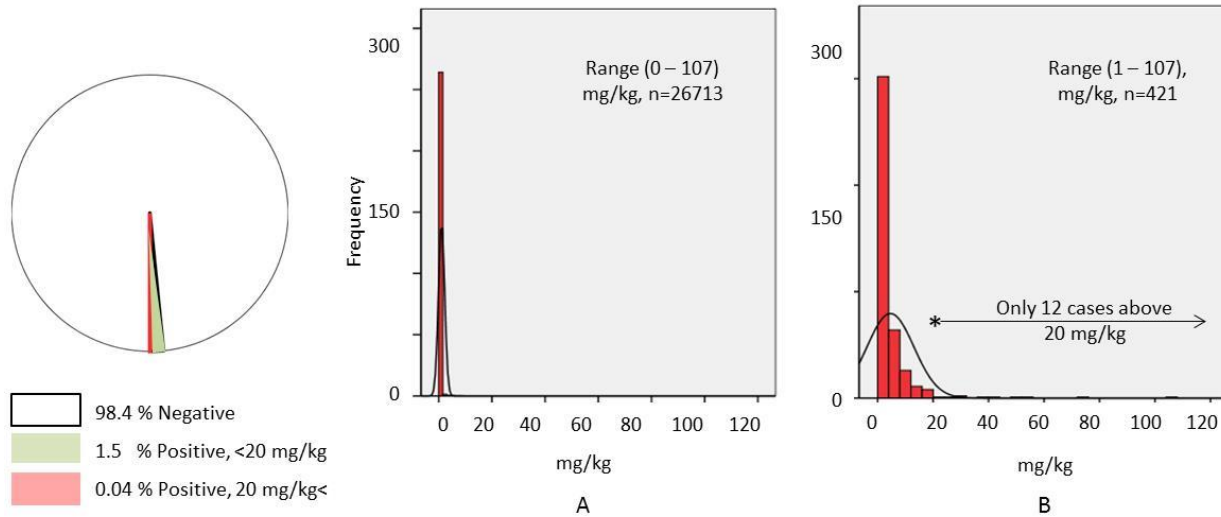
High concentration of DA in shellfish is reported EVERY YEAR from BC.

True

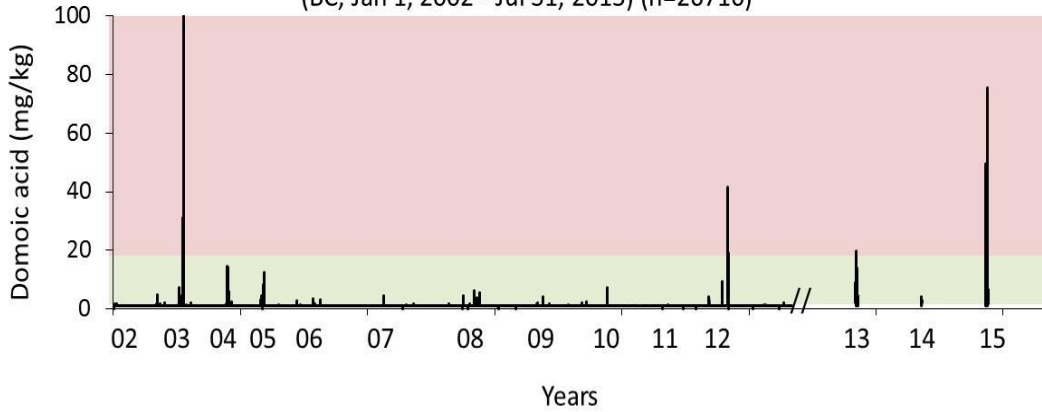
False

Domoic acid concentration in shellfish in BC (2002-2015)

Domoic acid concentration in shellfish samples BC-Jan 2002 to Aug 2015 (n=26716)

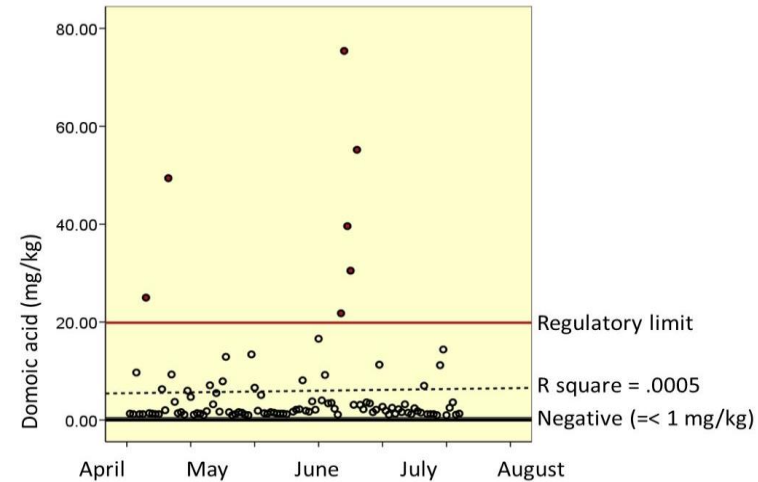


Domestic Acid Concentrations in Mussels and Razor Clams (BC, Jan 1, 2002 - Jul 31, 2015) (n=26716)



Detected Samples

Concentration of Domoic Acid in BC Shellfish, 2015



Total number of samples for each year was different from 2002 to 2012. Annual number samples 2013 to 2015 were not known. They were assumed to be equal to the average of the past 10 years. Values below $1 \mu\text{g}/\text{kg}$ are considered to be negative. This graph is subjected to minor changes.

Myths

High concentration of DA in shellfish is reported EVERY YEAR from BC.

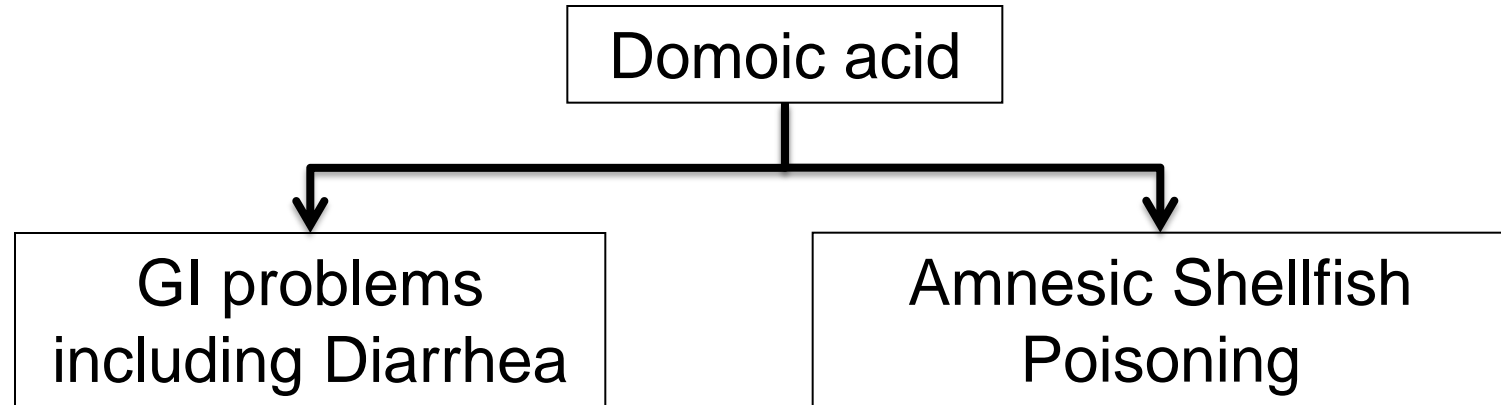
True

False

- ✓ Positive samples True
- ✓ Above 20 ppm False

What is amnesic shellfish poisoning (ASP)?

Clinical findings



107 admission – 3 died (soon after)

Risk factors old age and chronic renal failure

Myths

Majority of Amnesic Shellfish Poisoning cases could be diagnosed based on “short term memory loss”.

True

False

Myths

Majority of Amnesic Shellfish Poisoning cases could be diagnosed based on Short term memory loss.

True

False

Gastrointestinal symptoms including “diarrhea” is more common and happens at lower exposure doses of Domoic acid.

Myths

Amnesic Shellfish Poisoning is a frequently reported from the

Developed countries

True

False

Developing countries

True

False

Myths

Amnesic Shellfish Poisoning is a frequently reported from the

Developed countries

True

False

Developing countries

True

False

Myths

Amnesic Shellfish Poisoning is a frequently reported from the

Developed countries

True

False

Developing countries

True

False

ASP is rarely reported because

- (1) Regulations are in place
- (2) Underdiagnoses is common (non specific manifestation)
- (3) Under reporting of plausible cases
- (4) Ecological determinants for production of very high concentration of DA are rarely materialised

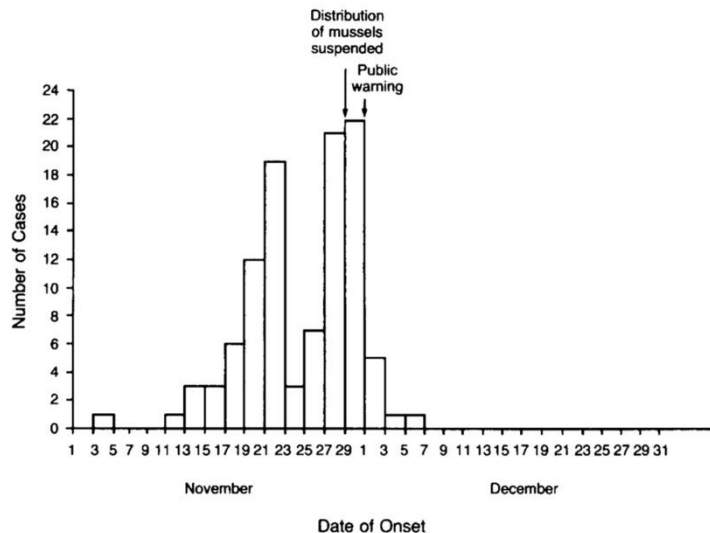


Figure 1. Cases of Mussel-Associated Intoxication, According to the Date of Onset of Symptoms, in Canada in November and December 1987. A total of 105 cases are shown, since the date of mussel consumption was not known for two patients.

Table 1. Symptoms of Illness among 99 Patients after the Consumption of Mussels.*

SYMPTOM	NO. OF YES RESPONSES	TOTAL RESPONSES	%
Nausea	75	98	77
Vomiting†	74	97	76
Abdominal cramps†	48	95	51
Diarrhea†	41	97	42
Headache	40	93	43
Memory loss†	24	96	25

*The results were obtained from the standardized questionnaires completed for 99 of the 107 patients. Total responses do not add to 99 because not all questions were answered for each patient.

†Criterion for inclusion as a case.

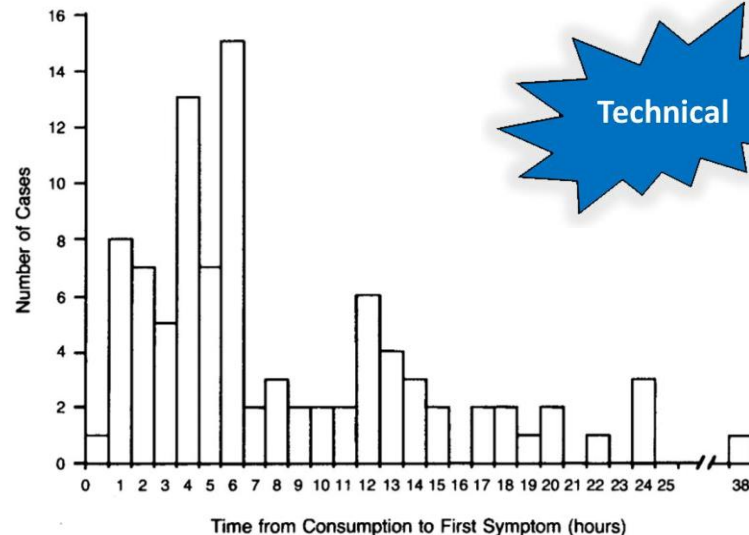


Figure 2. Interval between Mussel Ingestion and the Onset of the First Symptom (Incubation Period).

The data shown are based on responses to 91 questionnaires.

Table 3. Clinical Course and Estimated Quantity of Domoic Acid Ingested by Nine Patients Who Became Ill after Mussel Consumption and a Control Who Did Not.*

SUBJECT	AGE	ESTIMATED WEIGHT OF MUSSELS CONSUMED†	DOMOIC ACID IN SAMPLE	ESTIMATED DOMOIC ACID CONSUMED	CLINICAL COURSE‡			
					GI LOSS	MEMORY LOSS	HOSPITALIZATION	ICU
	yr	g	mg/100 g	mg				
Control	60	35	52	20	-	-	-	-
Patient no.								
1	72	120	52	60	+	-	-	-
2	62	150	45	70	+	+	-	-
3	70	150	52	80	+	-	-	-
4	61	300	31	90	+	-	-	-
5	67	160	68	110	+	-	-	-
6	61	360	31	110	+	-	-	-
7	74	400	68	270	+	+	+	-
8	68	225	128	290	+	+	+	+
9	84	375	76	290	+	+	+	+

*The analysis was limited to persons for whom a sample of uneaten mussels was available.

†The weight of the mussels eaten was estimated when the portion size was unknown.

‡GI denotes gastrointestinal symptoms (vomiting, diarrhea, or abdominal cramps), and ICU admission to the intensive care unit.

LOAEL; 1.00 mg/kg NOAEL; 0.33 mg/kg

Myths



Regulatory toxicological values related to DA are based on experimental animal models.

True

False

Myths



Regulatory toxicological values related to DA are based on experimental animal models.

True

False

If human data is available and if the quality of these data is good, regulatory toxicology values would be developed based on human data.

In addition, experimental animal toxicological values are not protective enough in human.

Risk factors related to ASP

Included in the current toxicological regulations

1. Elderly

- In the original ASP outbreak, 3 out of 107 confirmed cases (2.8%) died in the early stages, all of whom were over 65 y [71, 82, and 84 y]
- In experimental mice models, age-related super sensitivity to DA has been observed
- Age-dependent neurotoxic effects
- Similarly, kainate, which is similar to DA, induced more severe symptoms in older rats

2. Kidney failure

- One of the 3 cases who died soon after 1987 ASP outbreak had presented with chronic renal failure
- Serum and brain DA analysis indicated that age-related super sensitivity to DA in mice is related to reduced clearance rather than increased neuronal sensitivity.

Risk factors related to ASP

NOT included in the current toxicological regulations

3. DA in Pregnancy

- Crosses the placenta
 - Accumulates in the amniotic fluid
 - Long half life in the amniotic fluid
- } fetus may be
Continually re-exposed
- Intraperitoneal DA to pregnant mice → severe impairment of learning and memory, anxiety-related behaviors
 - Brain of prenatally exposed mice → myelination failure and the overgrowth of neuronal processes of the limbic cortex neurons (irreversible, and include structural and functional damage to offspring which becomes monitor able in their adulthood)

4. Breast fed neonates

- Low level DA has been detectable in milk up to 24 hr after exposing the mothers in rat models
- Blood levels of DA in neonates are higher as renal clearance of toxin is insufficient. Following maturation of renal function, their susceptibility diminishes
- Neonatal animals have been shown to be 40 times more sensitive to DA than adults

5. Repeated doses

Current risk assessment is based on ingestion of a single batch of shellfish

- Consume multiple doses before the half-life of the toxin, for example, consuming shellfish for lunch and dinner
- Frequent doses could also be used in consecutive days in which the next dose is consumed after the toxin has been partly bio-metabolised in the body.
- The half-life of DA in rats and monkeys was estimated to very short to 4 h. These findings are reasonable enough to assume similar values for human.

6. Chronic low dose exposure (i)

There is evidence that after the first dose of DA is being washed off from the plasma and exceeded impact may remain consistent with presence of a long term pharmacologic effect in chronic shellfish consumers.

- Low-level repetitive DA exposure on gene transcription and mitochondrial function in the vertebrate CNS using a zebrafish model → subthreshold DA aggravates toxicity, depended on dose, duration of exposure and prior history of DA.

6. Chronic low dose exposure (ii)

- Chronic exposure in zebrafish caused increased neurologic sensitivity to DA
- Alters gene transcription and impairs mitochondrial function in the CNS
- A novel DA-specific antibody response that is a signature of chronic low-level exposure has been identified initially in a zebrafish exposure model and observed in naturally exposed wild sea lions
- Behavioural and structural changes in later stages of life if exposed during pregnancy

Regulations



When toxicology regulations develop

- ✓ Assumptions are being made
 - ✓ Robust methods are being followed
 - ✓ Uncertainties are addressed
- If these steps are followed, it is expected that those limits are safely protecting the whole population.
 - However, if the primary assumptions are not correct, applying uncertainty factors might not be protecting enough.

Concerns

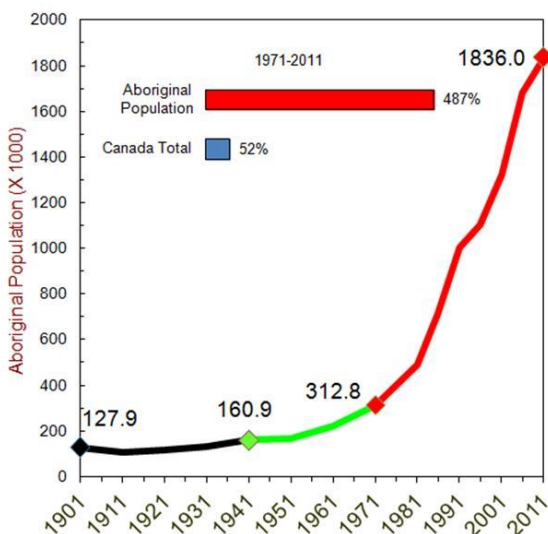
- ✓ Portion size and frequency of consumption were assumed for commercial consumption, and back extrapolated to 250 g (FDA involved calculations and 400 g EFSA).
- ✓ At risk population (pregnancy and breast feeding) were not discussed
- ✓ Chronic low dose toxicity was not discussed
- ✓ Advances in epidemiology and toxicology were not available

What are the important differences between the First Nation population and General population in regard to DA exposure?

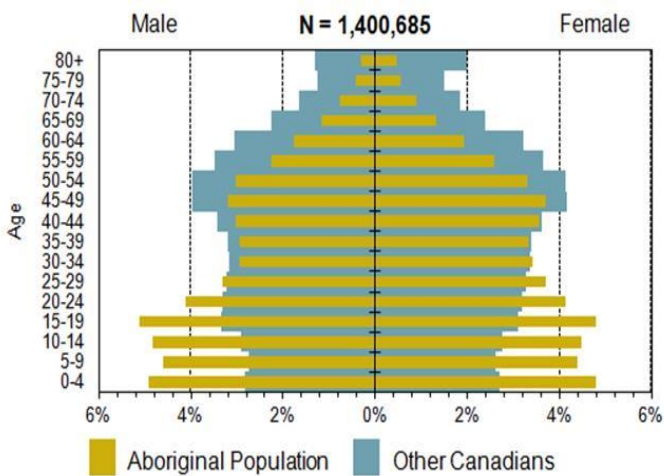
What has changed from 1987 to 2016 that may affect the risk?

Population trends

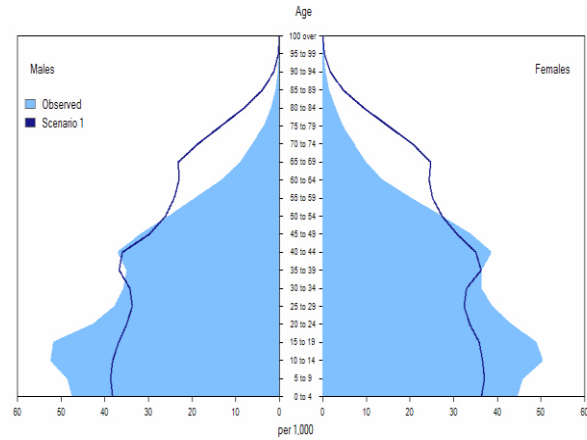
As compared to the general population, “Population” growth rate among the First Nation is higher leading to an extra increased risk.



Population Growth - Aboriginal Ancestry Population, 1901-2011



Age Pyramid of Aboriginal Population, 2011



Aboriginal population Canada, 2006 and 2031 (assuming no ethnic mobility and constant fertility)

By 2031; The % of seniors would remain lower for Aboriginal peoples & the % of youths under 15 years of age would remain considerably higher

<https://www.aadnc-aandc.gc.ca/eng/1370438978311/1370439050610>
<http://www.statcan.gc.ca/pub/91-552-x/2011001/c-g/c-g04-eng.htm>

“Population” at risk is increasing

- ✓ Prevalence of older population is increasing
 - ✓ Prevalence of pregnancy is increasing
 - ✓ Prevalence of neonates under breast feeding is increasing
 - ✓ Prevalence of renal failure (longer life) is increasing
-
- ✓ Pregnancy could be an independent risk factor

**Risk related to Domoic acid among pregnant first nation women
could be “higher”**

Summary of potential differences

✓ **Self harvesting as compared to commercial use**

- ✓ Portion sizes
 - Target communities
 - Individuals
- ✓ Frequency of shellfish consumption
- ✓ Chronic low dose additional effects
- ✓ Population structure differences
- ✓ Prevalence of chronic renal diseases (and risk factors including high blood pressure and diabetes)
- ✓ Prevalence of pregnancy and breast feeding
- ✓ Case findings and health inequalities
- ✓ Political and macro social policies, and intersectionality
- ✓ Potential differences as for the mechanism of toxicity is not clear
- ✓ Barriers to implement recommended action

**Changes in the population structure among First Nation
Population has shifted the domoic acid exposure risk
towards them, as compared to general population
(Population at risk has increased to a higher extent)**

"It is time for a renewed, nation-to-nation relationship with First Nations peoples, one that understands that the constitutionally guaranteed rights of First Nations in Canada are not an inconvenience but rather a sacred obligation"

Prime Minister Justin Trudeau

Dec 08 2015



Environmental inequity in toxic high dose exposure

Inequity in high dose exposure to chemicals and medications are already known in:

- ✓ **Intentional acute high dose exposure (overdose)**
- ✓ **Accidental acute high dose exposure**
- ✓ **Occupational acute and chronic high dose exposure**
- ✓ **Environmental exposure acute and chronic high dose exposure**
 - Industrial hazardous waste sites
 - Industrial pollution risks (A report from Seattle, Washington)
 - Environmental/agricultural exposure to pesticides

A new concept:

- To our knowledge, the current report is the first one on **“inequity as regard to food toxicity”**

“inequity as regard to food toxicity”

Prior to 1989 both commercial and self harvest consumer were at risk of high exposure to Domoic acid



Majority of the population

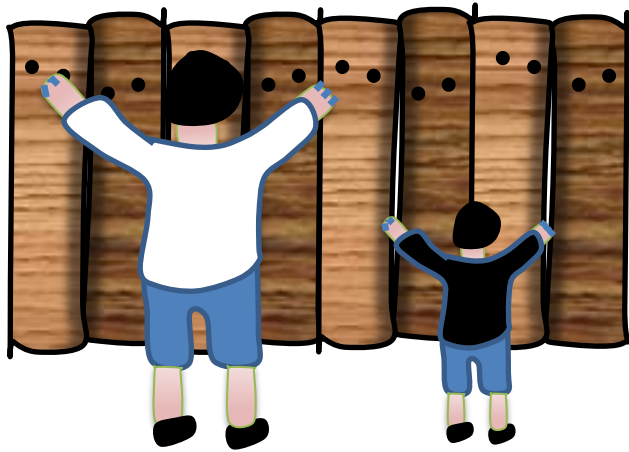


Commercial consumers

Fewer people who self harvest



Self harvesting consumers



Before 1987
No regulation

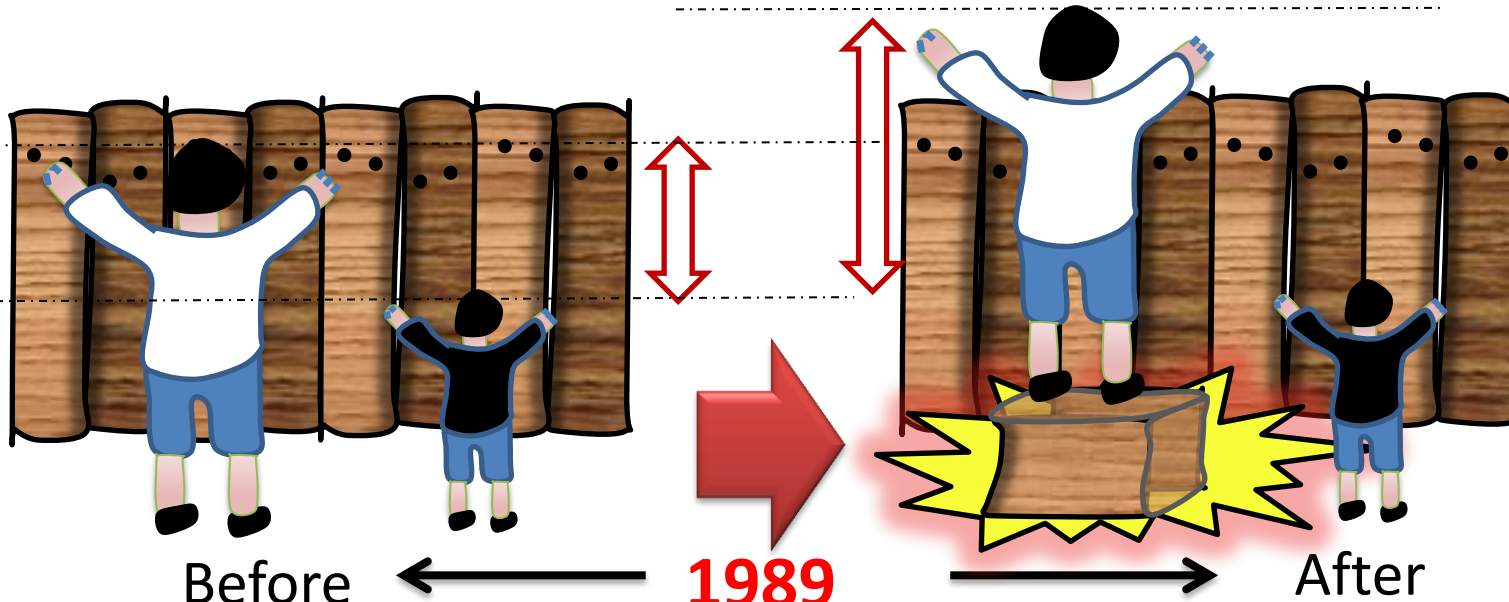
“inequity as regard to food toxicity”



Commercial consumers



Self harvesting consumers



Before

1989

After

No regulation

implementing regulation for commercial product

Beaches close for commercial harvesting if the Domoic acid concentration is more than 20 ppm

Inequity has increased between commercial users and self harvesting population



Commercial consumers



Self harvesting consumers



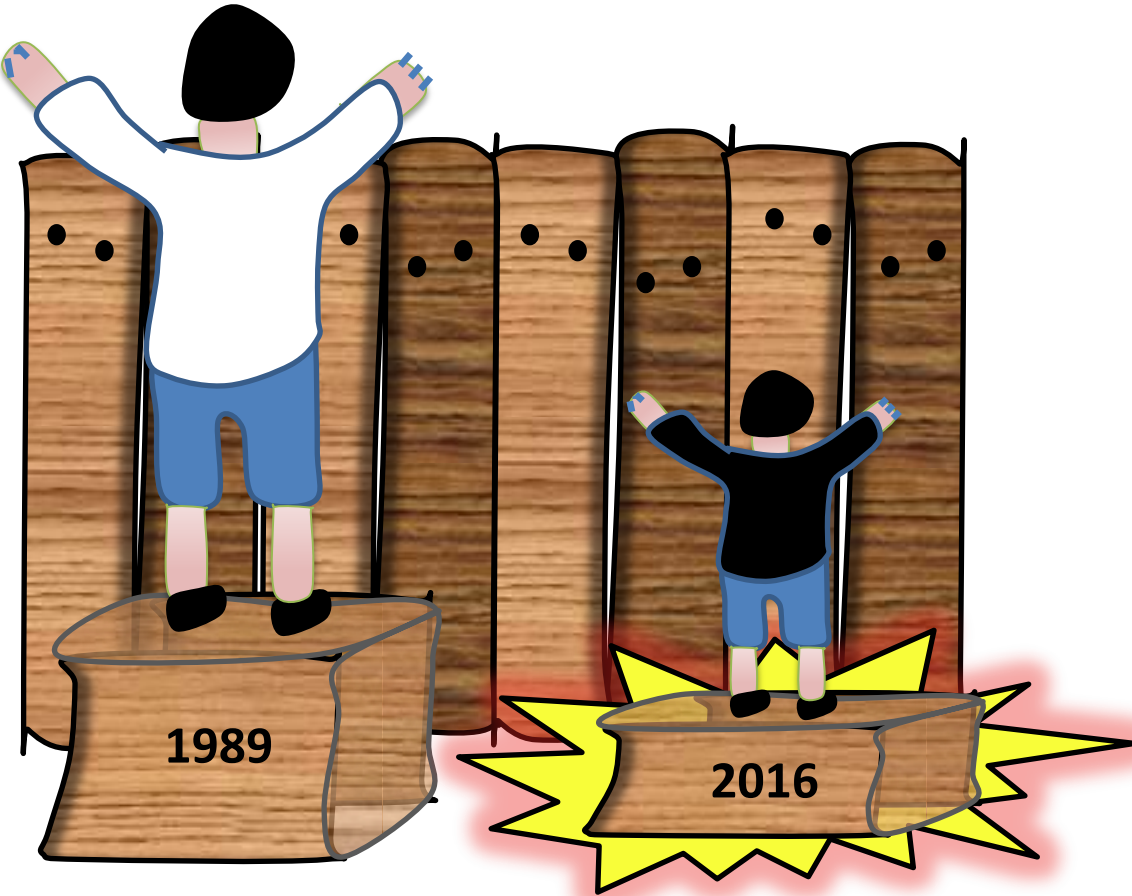
Regulation for commercial consumers



Commercial consumers



Self harvesting consumers



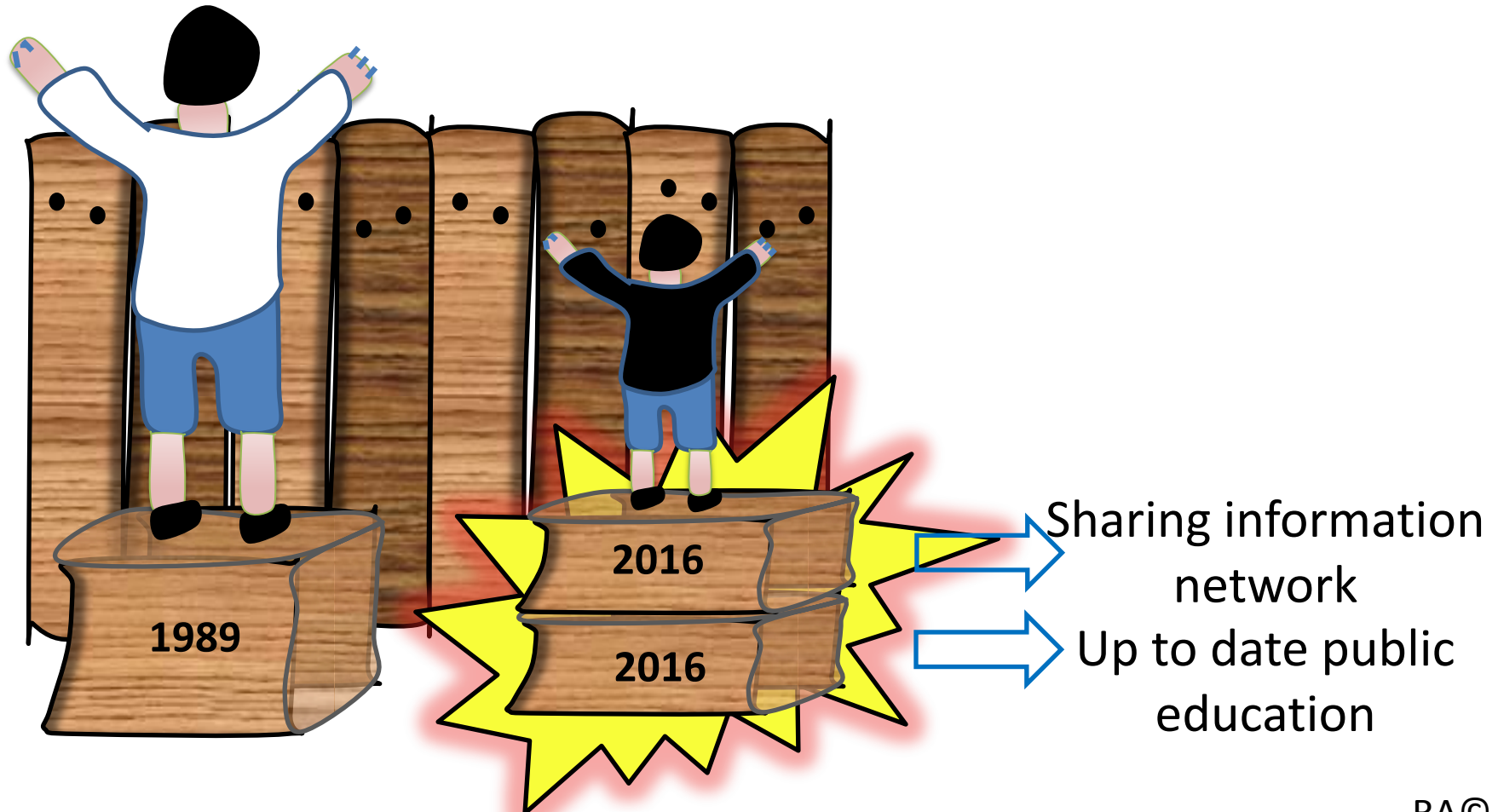
More effective Education



Commercial consumers



Self harvesting consumers

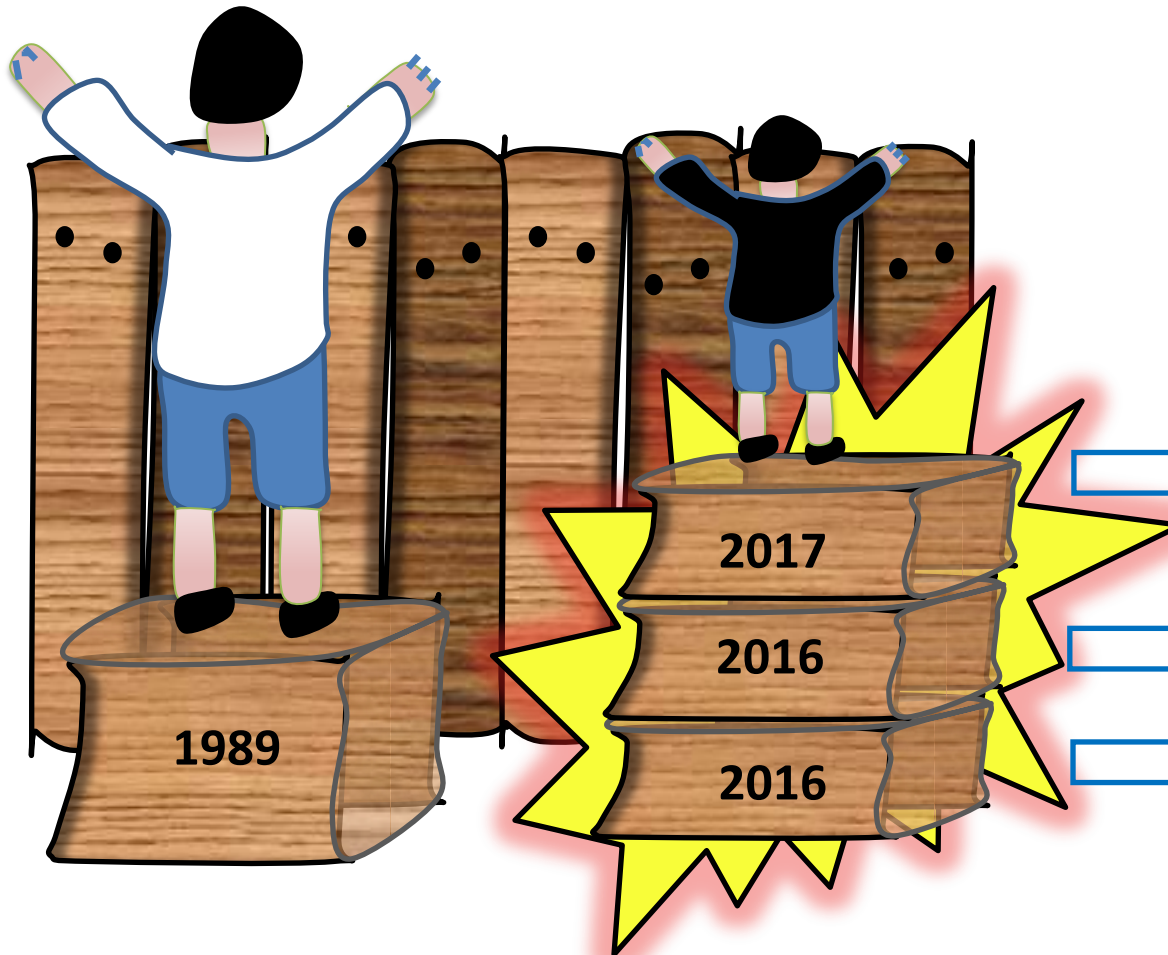




Commercial consumers



Self harvesting consumers



Opening a new review to the regulation?

Sharing information network

Up to date public education

Limitations

Benefits and risks for self harvesting

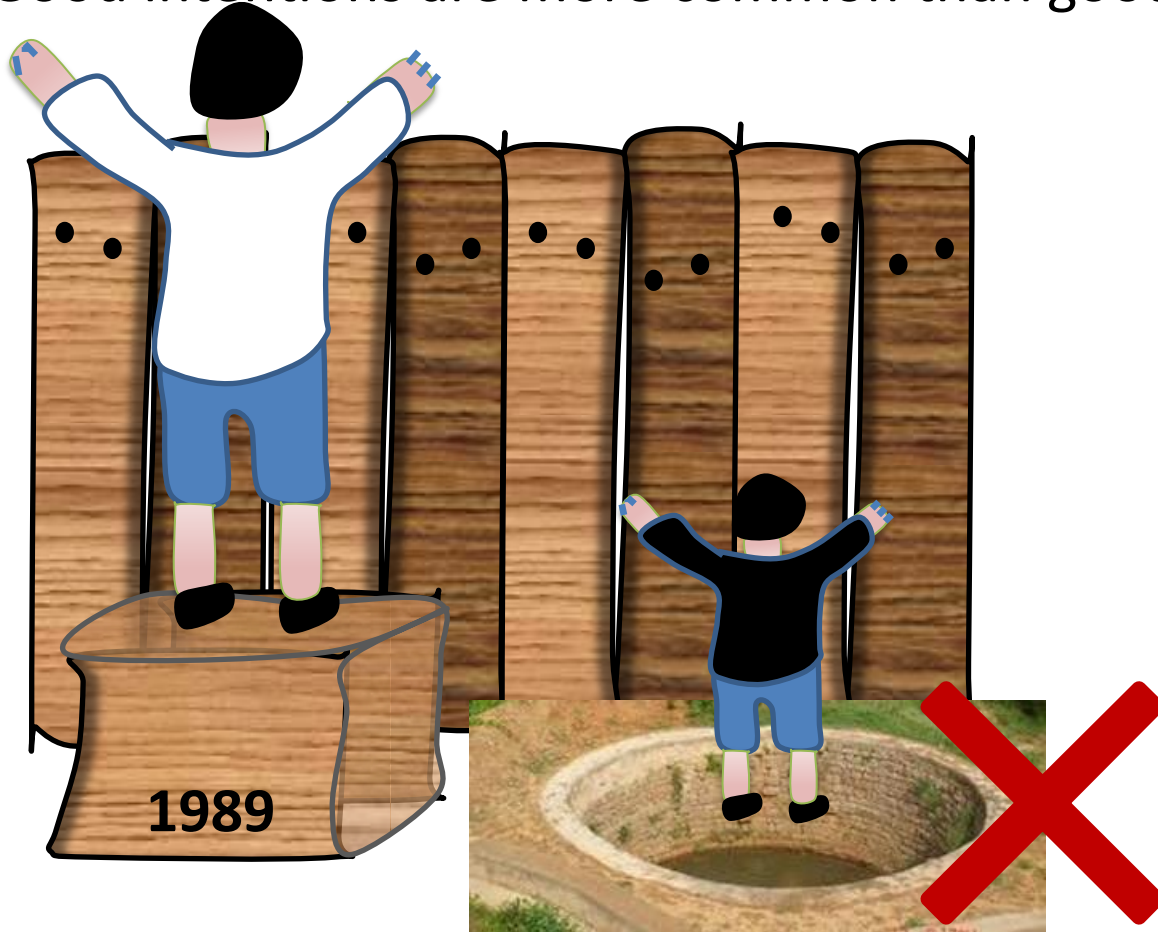


Commercial consumers



Self harvesting consumers

- ✓ A message of “do not eat” Shellfish is wrong!
- ✓ Shellfish is a good source of protein
- ✓ Get updates of the time and places which are risky
- ✓ Good intentions are more common than good outcomes



“What to do?” Road-map

A) Further dialogue and collaboration with First Nations Health Authority is needed to decide collaboratively on appropriate intervention approaches.

[TODAY (October 24, 2016)

Jane Philpott, Canadian Minister of Health, announced that Health Canada started a process to revise Canada’s Food Guide to

- ✓ Reflect the latest scientific evidence on diet and health,
- ✓ Better support Canadians in making healthy food choices.
- ✓ Protecting vulnerable populations]

B) Opening a new review to the regulation of Domoic acid

BC Centre for Disease Control

An agency of the Provincial Health Services Authority

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