Lesson 5: The Health Impacts of PFAS

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Background Information and References for Lesson 5

Introduction

This lesson will focus on two primary objectives:

1) What is known about the health impacts of PFAS as emerging contaminants? What can we learn from data collected from Pittsboro residents? Other towns with similar exposure?
    a) What are the properties that make PFAS harmful?
    b) How does it enter the body and cause harm? Under what circumstances is exposure likely to lead to disease?
    c) How does the use of animal models help us address these questions?
2) What is known about the health impacts of PFAS on wildlife? What are the implications of such impacts?

Students will have an opportunity to review data from national studies as well as preliminary data from Pittsboro. By the end of this lesson, they should be able to:

- Discuss potential risks associated with PFAS exposure based on research studies
- Consider the impact of high-profile cases on the perspectives of local residents
- Make recommendations to residents about how best to minimize exposure
- Discuss the implications of PFAS exposure on wildlife health

Background Information: Human Health

This lesson will introduce students to the complex processes involved in linking exposure to environmental toxins with health effects. To frame our work, we will start with a health phenomenon that is likely well known to the students - the idea of a **cancer cluster**. While many communities have made claims about the presence of unusually high rates of cancers and potential links to environmental facilities, spills, or other sources of exposure, proving this connection is extremely difficult.

One clear example comes from Toms River, NJ, where an extraordinary number of childhood cancers was linked to pollution dumped in the town's drinking water.

Toms River:
A Town Fights Back: The Toms River Story: https://www.youtube.com/watch?v=NtENUFwoT4s

- Video Timestamps: (total playtime: ~ 18 minutes)
    - Opening/Hook: 0:00 - 1:13
    - Background: 1:13 - 2:25

- Don Bennet's story about swimming in the river: 2:25 - 3:02
- Don Bennet's story about reporting on the pollution: 3:02 - 3:42
- Don Bennet/ Peter Hibbart share anecdotes: 3:42 - 4:48
- Why Toms River was ideal/how the contaminants got into the drinking water: 4:48 - 6:10ish
- Illegal dumping began in NJ: 6:10 - 7:33
- Rise in cancer in NJ/Intro to Michael/pipeline leak mobilizes the community/rise in cancer in children: 7:33 - 12:48
- State health authorities designated Toms River a cancer cluster: 12:48 - 13:38
- Remediation/finding the chemical culprit: 13:38 - 15:30
- Cleanup efforts/Call to Action to other communities: 15:30 - 17:52

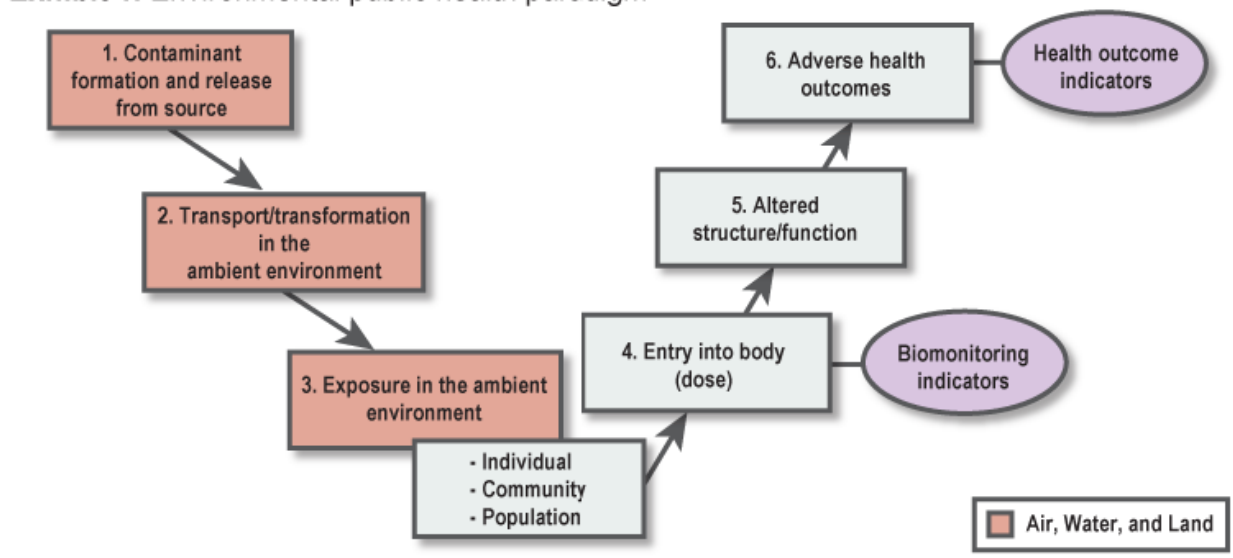
The Toms River story is far from clear cut. Several researchers and analysts are hesitant to label Toms River a cancer cluster, arguing that state health officials buckled under pressure to find someone to blame for the slightly higher than expected rates of childhood cancers. The Slate article linked here covers much of this perspective. A broader critical perspective on the difficulty of proving cancer clusters is given in this NY Times article.

In general, it is important to know that finding a clear, definitive link between exposure to environmental toxins and adverse health outcomes is extremely difficult. In the 1970's public attention on environmental issues and studies linking environmental triggers and human health impacts (e.g smoking and cancer, coal dust and COPD, etc.). The EPA was born during this time in order to consolidate the federal government's environment-related duties. As part of its "Report on the Environment", the EPA investigates exposures to contaminants and their potential impacts on human health.

Show students the environmental public health paradigm to illustrate the factors that may be involved in the development of disease as a result of exposure. In order for a link to be made, all 6 blocks must be clearly established and understood. Of course, real-life examples are complex and non-linear. For example,

- we know what other factors (like lifestyle, genetics, and pre-existing conditions) can also lead to disease, and it may not be possible to control or ignore those potential impacts on human health.
- Different contaminants can cause or increase the risk of the same disease
- Not every person who is exposed will experience adverse health outcomes

Exhibit 1. Environmental public health paradigm



Source: https://www.epa.gov/report-environment/human-exposure-and-health

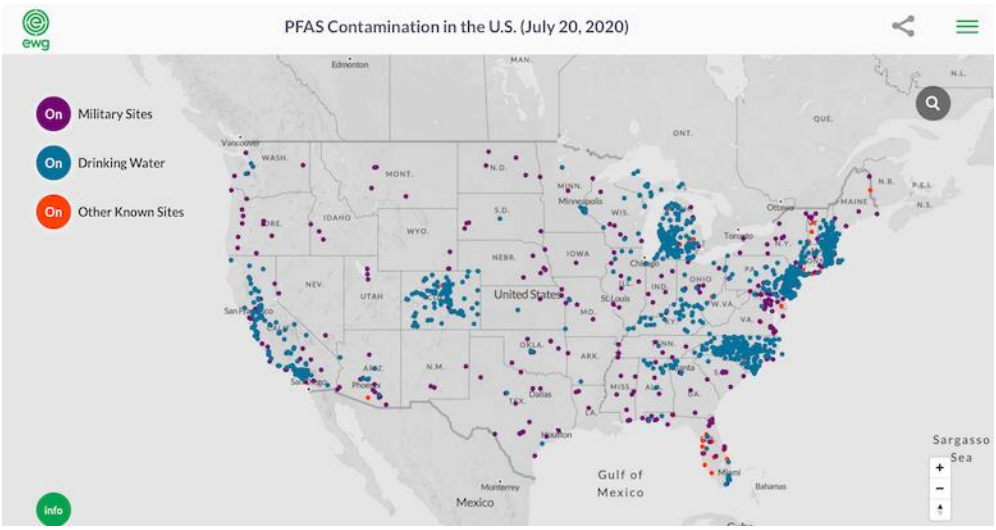
The CDC tracks environmental public health issues, and the data is publically available. Intro to Environmental Public Health Tracking. The video linked here provides an overview.

Prevalence of PFAS in the Human Body

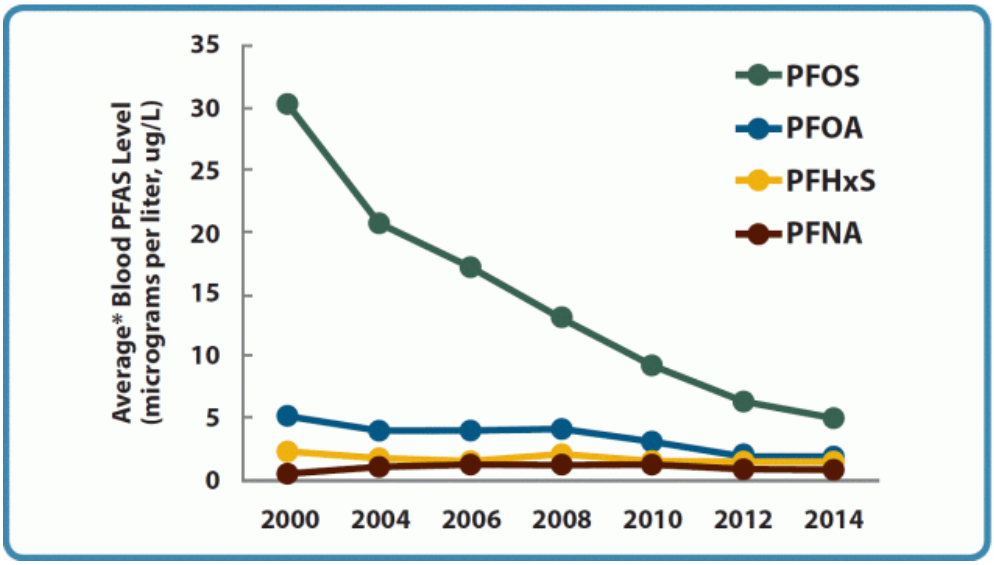
PFAS is detected in human beings across the globe. Based on a 2019 study, more than 98% of American have measurable amounts of PFAS in their blood.

PFOS and PFOA levels have declined over the last decade, but alternative compounds (like short-chain PFAS chemicals) have not. Many researchers are working to determine if detectable amounts of PFAS chemical are linked (and potentially lead) to dangerous health outcomes. So far, we know (without question) that PFAS chemicals are found in detectable amounts. We also know that some correlational data supports a positive association between them and adverse health outcomes. However, very few studies have been able to draw conclusions about causality. Here are some some fast facts about the prevalence of PFAS in humans:

Fact 1: PFAS is everywhere. At least one type of PFAS compound is found in 98% of the US population. Concentrations differ by race/ethnicity, sex, and geographic location. The map below is from the summer of 2020, and shows the location of PFAS exposure in drinking water, military sites, and “other” (ewg.org)



Fact 2: Generally, exposure is in decline for the "oldest" and most common varieties (PFOA, PFOA). The figure below from the CDC shows blood levels of the four most common PFAS from 2000 - 2014.

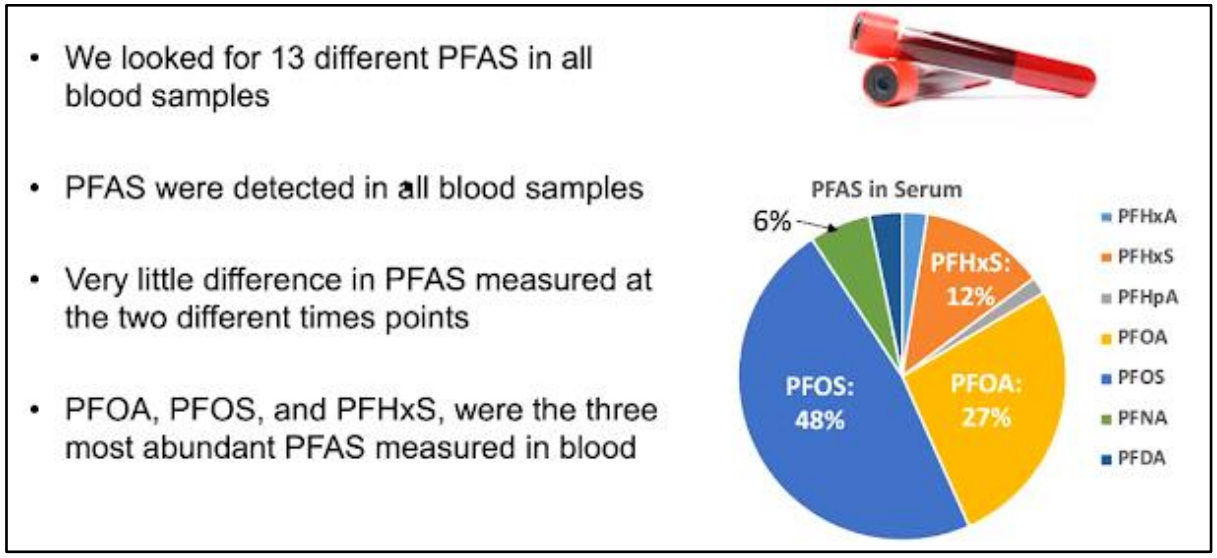


Fact 3: Exposure to newer varieties of PFAS has not decreased, and are detectable in the blood of Pittsboro residents

While much is known about long chain PFAS chemicals, less is known about short chain alternatives. A review form Brendel et al (2018), proposes the following concerns Short-chain PFAS compounds:

- are extremely persistent (they do not undergo degradation)
- have low adsorption and high mobility (they don't stick to media in filters well)
- have the potential for long-range transport
- Pose a risk of adverse health effects on humans and the environment

Data from Stapleton lab presentation shows that Pittsboro residents have both long- and short-chain PFAS compounds in their blood. Note: PFHxA, PFHxS are considered “short chain” PFAS compounds. Full screenshot shown in the Data Packet - Source 5.



Fact 4. Exposure to PFAS is not limited to drinking water. Recall: there are numerous sources of PFAS exposure, including dust, diet, food packaging, inhalation, and others. Here is data from a 2018 study by Suderland et al.

Table 1 Literature estimates of sources contributions (%) to adult PFAS exposures

PFAS	Diet	Dust	Tap water	Food Pkg.	Inhalation	Dermal	Other	Reference
PFOA	16	11		56	14		2[a]	Trudel et al. [25]
PFOA	85	6	1	3[b]			4[c]	Vestergren and Cousins [74]
PFOA	77	8	11		4			Haug et al. [23]
PFOA	66	9	24		<1	<1		Lorber and Egeghy [76]
PFOA	41		37				22[d]	Tian et al. [163]
PFOA	99		<1					Shan et al. [164]
PFOS	66	10	7		2		16[d]	Gebbink et al. [165]
PFOS	72	6	22		<1	<1		Egeghy and Lorber [75]
PFOS	96	1	1		2			Haug et al. [23]
PFOS	81	15					4[a]	Trudel et al. [25]
PFOS	93		4				3[d]	Tian et al. [163]
PFOS	100		<1					Shan et al. [164]
PFBA		4	96					Gebbink et al. [165]
PFHxA	38	4	38		8		12[d]	Gebbink et al. [165]
PFOA	47	8	12		6		27[d]	Gebbink et al. [165]
PFDA	51	2	4		15		28[d]	Gebbink et al. [165]
PFDoDA	86	2	2		4		5[d]	Gebbink et al. [165]

[a]Carpet
[b]Consumer goods
[c]Precursors
[d]Indirect

Links to Human Health Outcomes

While there are few definitive studies linking PFAS exposure to adverse health impacts in humans, there are numerous studies that show associations between these variables (see the TEDX database). The table from Sunderland et al (2018) shows some of the most commonly listed health concerns and the number of studies that report adverse, null, or protective associations.

Table 2 Summary of the epidemiologic literature on PFAS exposures and metabolic outcomes

Outcome	# of total studies	# of studies by results				Other PFASs
		PFOA	PFNA	PFHxS	PFOS	
Lipid profile[a]	39	21/10/1[b]	8/1/2	4/4/2	20/9/3	Inconsistent results for PFDA, PFUnDA, PFTeDA
Insulin resistance and diabetes	18	6/9/1	3/5/0	1/2/1	7/4/1	Mostly null for PFDA, PFUnDA, PFDoDA, N-EtFOSAA, N-MeFOSAA; One positive finding for PFDoDA and insulin resistance
Hypertension, vascular disease and stroke	10	3/5/1	3/0/1	0/3/1	1/3/1	Only one study reported null for PFDA and PFUnDA
Thyroid disease	8	4/3/0	1/2/0	1/2/0	1/3/0	Positive finding for PFDA and PFUnDA in two studies. Null for PFTrDA
Cardiovascular disease	6	1/4/1	1/0/0	0/1/0	0/1/0	No other PFASs have been investigated
Uric acid	5	4/0/0	0/0/0	0/1/0	2/2/0	No other PFASs have been investigated
Overweight and obese	4	1/3/0	1/1/0	1/1/0	3/1/0	Positive finding for PFDA in only one study (Liu et al. [134])

Details of the studies examined are provided in the Supporting Information Table S1

[a]Lipid profile includes low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides

[b]Number of studies with adverse/null/protective results

Animals Models to Study Human Health

Common animal models and generalized information about connections between PFAs exposure and adverse health outcomes. Commonly used model organisms include:

- Mouse/rat models
- Zebrafish
- Monkeys and other non-human primates
- Frogs

Results from these studies are highly variable, but many provide a proof-of-concept for the idea that PFAS exposure may directly impact important physiological processes in the body.

Background Information: Wildlife Health

For a detailed summary of current toxicology studies of PFAS in wildlife, see Section 7.2 of the Interstate Technology and Regulatory Council's (ITRC) online documentation on PFAS. The story of how PFAS impacts on wildlife are even more complex than humans due to the behavior of the chemicals in the environment. It can persist for decades, and is able to travel extraordinary distances from its original source without breaking down. On land, high levels of PFAS have been detected in many species, including birds, deer, invertebrates, reptiles and

amphibians, and plants. The same is true in aquatic ecosystems. Some researchers even suggest that the oceans could reach a “maximum capacity”, and begin re-polluting the land. Unlike many other known contaminants like DDT and PCBs, PFAS chemicals are minimally filtered by plants, algae, and sediment. Comparatively, higher concentrations of PFAS are capable of bioaccumulating in the oceans than previously studied contaminants (The Revelator). PFAS has been detected in a wide diversity of aquatic wildlife, including manatees, loggerhead turtles, polar bears, and whales. While many studies show strong correlative trends, the struggle to definitively link PFAS exposure to health impacts is also difficult for wildlife. Studies from NC State University researcher Scott Belcher’s lab shows striped bass with high levels of PFAS also show significant declines in immune and liver function (Guillette et al., 2020; Belcher, 2019). This may also be true in turtles and dolphins in the region (Belcher, 2019). The challenge for wildlife researchers is that there is no easy way to collect “baseline” data to compare their results to. Without robust experimental controls, drawing strong, convincing conclusions is difficult.

An excellent case study comes from Dr. Scott Belcher of NC State, who studies bioaccumlation and adverse impacts of PFAS on the aquatic vertebrates in the Cape Fear River basin of North Carolina. The Belcher lab studies one **sentinel species**, the American Alligator to determine if local individuals show differences in their blood serum and general health data across a concentration gradient. They analyzed several biomarkers for liver, kidney, immune system, and endocrine system function. Results show that PFOS bioaccumulates in both alligators and fish (at the level of parts per billion (ppb) and parts per million (ppm), with alligators located in known contaminated regions possessing 2-3X more PFAS in their blood compared to those living outside of contaminated regions. They also found site specific differences in immune function, liver enzymes, blood chemistry, unhealed lesions and/or poor body condition. A summary of some work from the Belcher Lab can be found here.

While the protection of wildlife and the ecosystems they live in should be enough motivation to take action against emerging contaminants, we can also consider the indirect impacts on human that result from the presence of PFAS in the environment. COnsumption of game and fish in contaminated waters results in an additional source of PFAS exposure. While there are NO Federal regulations pertaining to the hunting or fishing of animals in contaminated environments, some states are taking precautions to inform and protect its residents from this type of exposure. Michigan provides an excellent case study of state-level advocacy and education on PFAS issues. In 2018 Michigan’s Department of the Environment issued a “Do Not Eat” Deer Advisory for the Oscoda Township, home to Clark’s Marsh. The state advises residents to eat NO part of deer found within 5-miles of the marsh due to extremely high levels of PFAS detected in deer living in the area (one study returned an estimate of 547 parts per billion). The advisory also recommends residents refrain from consuming other wildlife, such as muskrats and turtles, as well due to unknown levels of PFAS. In addition to hunting advisories, Michigan also provides information to homeowners and farmers about ways to protect their pets/livestock from exposure to PFAS.

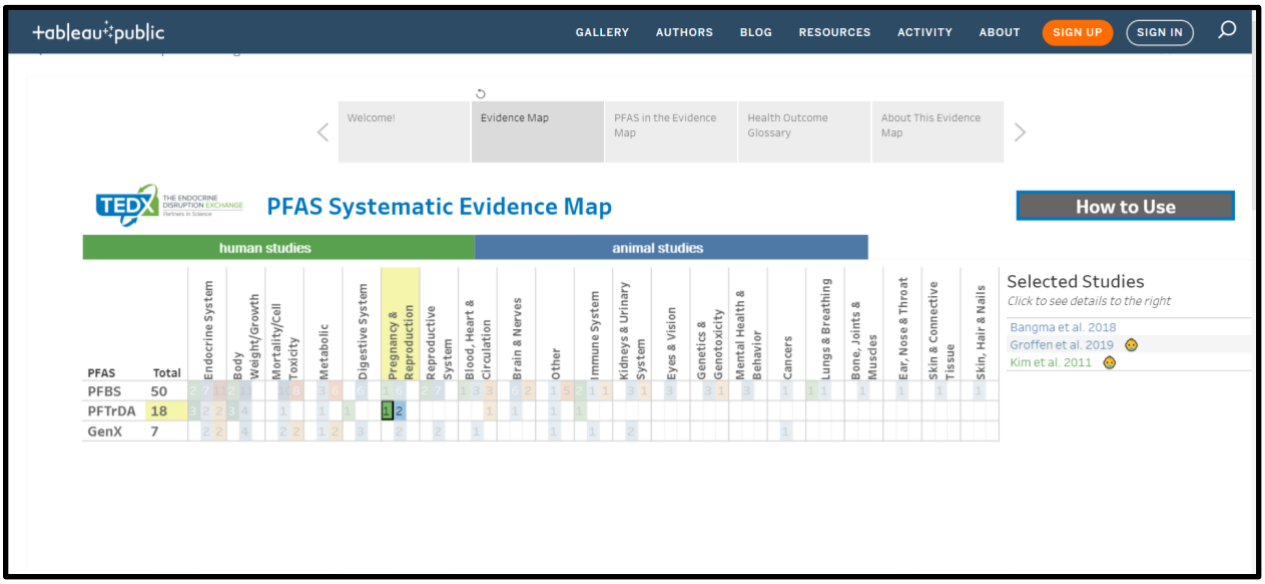
Circling back to considerations for Pittsboro, NC, it is important to consider the impacts on the local ecosystem and the people who rely on it for both sustenance, economic stability, and recreation. Considerations about hunting/fishing, farming, and recreation are relevant as well. As of March 2021, there are no state or federal advisories regarding consumption of wildlife in the area. Concerns are not only limited to the Haw River. Jordan Lake (which receives 70-90% of the Haw River's flow annually) is not only a drinking water source for hundreds of thousands of residents, but it attracts millions of visitors each year. Hunting and fishing are population recreational activities in the region, yet many are unaware of the potential risks posed by PFAS in the water. From an economic standpoint, we must also consider local farms and other businesses who rely on the Haw River and surrounding ecosystems for water and other resources.

Overview of Data Sources for Students

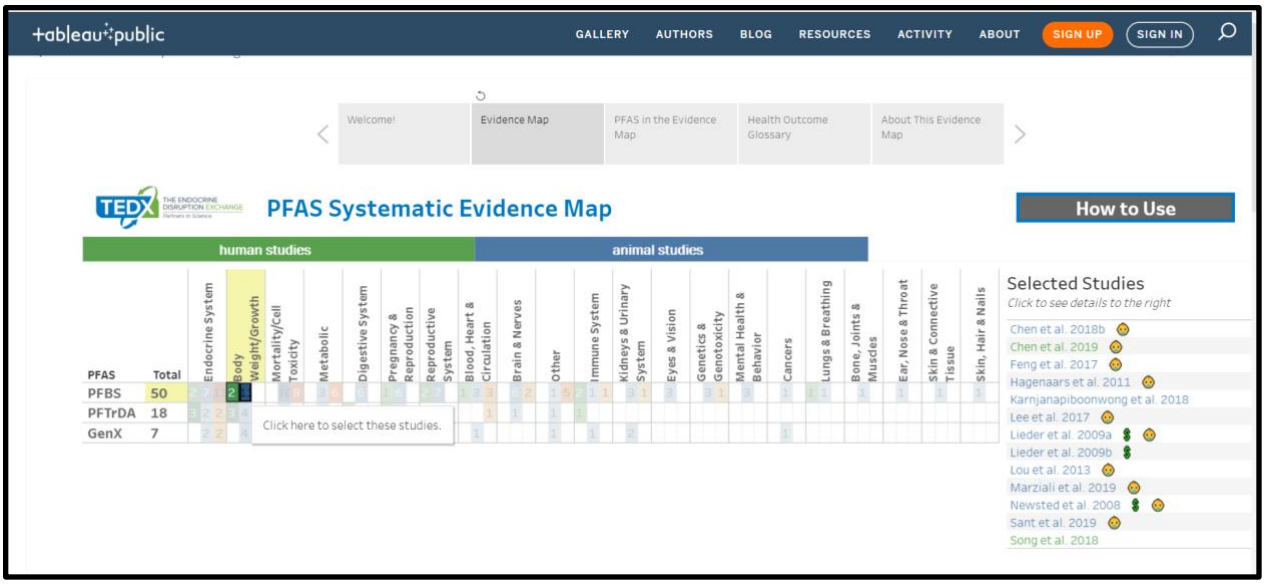
Details below provide some context and tips to help you support students with the assignments in this lesson.

The Endocrine Disruption Exchange's (TEDX) PFAS Systematic Evidence Map

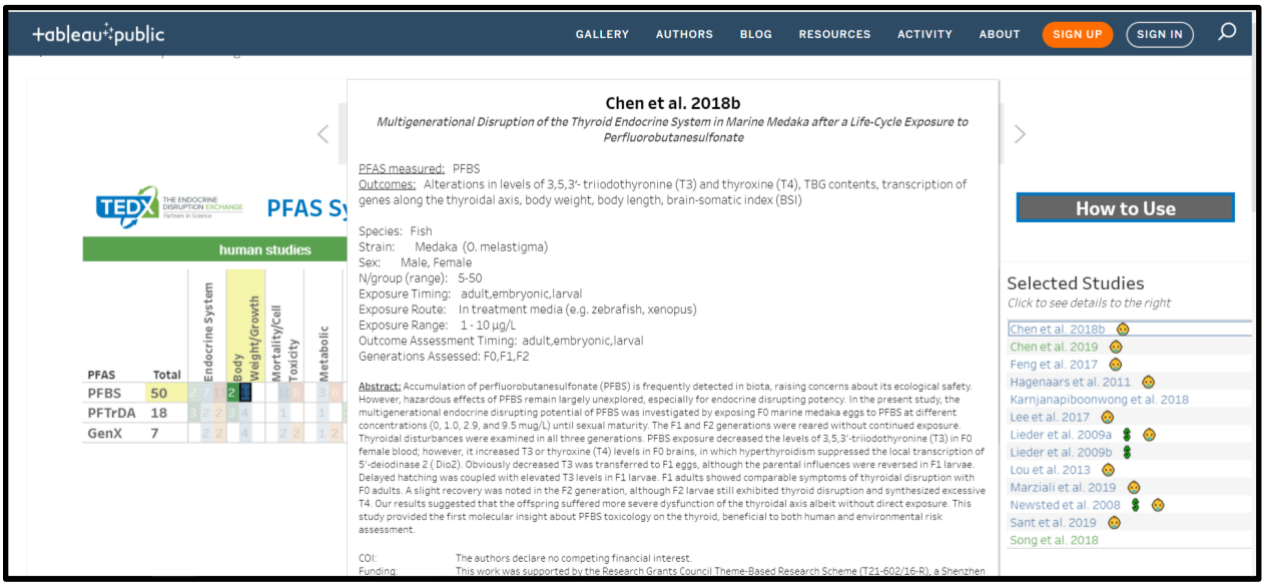
This Tableau features a "evidence map" showing the number of studies that investigate specific health outcomes as a result of PFAS exposure. Here's a screenshot of the evidence map.



The website is interactive. Students can click on a particular set of variables and view the studies that are relevant to their interests. For example, If a student is interested in learning about the impact on body weight due to PFBA exposure, they could click the appropriate cell and see that there are 2 human studies and 11 animal studies on that topic. On the right side of the screen, they will now see a list of those studies, color-coded based on the study subject (human, animal, in vitro)



Now they can get information from each paper by clicking on a reference from the list. Students will use information from these references to complete their homework assignment.



Data Packet Overview

Students will browse select papers from the TEDX database for the in-class assignment. The Data Packet will show the title, abstract, and one or two figures from the paper. The goal of the activity is to give students an opportunity to learn about the current health research on PFAS from primary sources. The abstracts and figures will be challenging to understand, but this is an important lesson in itself. While many people talk and share thoughts about the health impacts of PFAS and other contaminants, very few in the general population are able to digest the primary literature. Instructors should acknowledge that understanding every part of these papers will be hard, but students should focus on skimming for general understanding. Depending on

the amount of time available, instructors may want to model how to extract the relevant information from the abstracts. For example, help students learn to recognize keywords in order to identify the research question, method, findings, and implications. This may also prompt a conversation about the accessibility of scientific research for the general public.

Below is a a quick breakdown/key for each of the references listed in the assignment:

Blood, Heart, and Circulation Data

9.1 Perfluoroalkyl Sulfonates Cause Alkyl Chain Length–Dependent HepaticSteatosis and Hypolipidemia Mainly by Impairing Lipoprotein Productionin APOE*3-Leiden CETP Mice. Bijland et al. *Toxicological Sciences* 123(1), 290–303 (2011)

Study type: mouse model study
Research question: How does PFAS impact levels of non-HDL cholesterol (aka "bad" cholesterol)
Method: mice were fed a diet with one level of PFBS, PFHxS, or PFOS, and various measurements related to cholesterol were taken
Figure note: the bar graphs show the effect of 3 types of PFAS (shaded bars) compared to a control (white bar). Many of the variables measured indicate a significant impact of PFAS after 4 weeks on the prescribed diet.
Take-home points: while there is a lot of technical jargon in this abstract, essentially the authors are telling us that PFAS is associated with "bad" cholesterol, but may not be *causing* it.

9.2 Structure–activity relationship assessment of four perfluorinated chemicals using a prolonged zebrafish early life stage test. Hagenaars and Knapen. *Chemosphere* 82(5), 764-772 (2011)

Study type: zebrafish embryonic development study
Research question: What are the developmental impacts of PFOS, PFOA, PFBS, and PFBA on zebrafish embryos?
Method: compared developmental variables after exposure to various PFAS chemicals
Figure note: Line graph shows that hatching success was impacted at higher concentration (100 mc/l or more); Bar graphs show variation in heart rate at 48 and 72 hours post-fertilization, with some concentrations of each PFAS chemical resulting in significant differences in heart rate.
Take-home points: General effects include tail deformations, uninflated swim bladder, some impacts on hatching rate/success and heart rates.

9.3 Serum polyfluoroalkyl chemicals are associated with risk of cardiovascular diseases in national US population. Huang et al. Environment International (119) 37-46 (2018)

Study type: human serum and survey data
Research question: Are there any associations between serum (a blood product) PFCs levels and prevalence of cardiovascular disease in the US general population?

Method: compared serum PFCs from a random set of survey participants and their self-reported cardiovascular disease outcomes
Figure note: table shows breakdown of demographics and covariates Participants are grouped into quartiles based on their PFC serum levels. P-values show significant trends and interactions across quartiles
Take-home points: Higher PFSc were positively associated with risk of cardiovascular disease (CVD), but this study does not demonstrate *causality.* It does shows however, that these trends persist *independent* of many well-known risk factors associated with CVD (age, sex, race/ethnicity, smoking status, alcohol intake, BMI, diabetes, etc.).

Pregnancy and Reproduction Data

10.1 Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and the risk of hypertensive disorders of pregnancy. Huang et al. Environmental Health 18 (5) (2019)
Study type: humans
Research question: Are there any associations between prenatal PFAS exposure and hypertensive disorders of pregnancy (e.g. preeclampsia)?
Method: Measures PFAS in umbilical cord plasma samples and compared to HDP disorders reported in medical records.
Figure note: table shows breakdown of levels of exposure (T1 (control), T2, and T3) for 4 different PFAS chemicals. P values indicate whether or not the trend is significant
Take-home points: Broadly, women with high levels of PFBS (but not PFHxS, PFDoA, or PFUA) has increased risks of preeclampsia and overall HDP

10.2 Limited reproductive impairment in a passerine bird species exposed along a perfluoroalkyl acid (PFAA) pollution gradient. Groffen et al. Sci Total Environ. (2019)
Study type: passerine birds (wildlife)
Research question: Are there measurable effects of PFAS exposure on reproductive parameters in great tits *(Parus major)?*
Method: Measured various reproductive factors at nests along a gradient of PFAA exposure
Figure note:The graphs show the results along the PFAA gradient. Samples do not fall along an expected distribution, indication no strong correlation between PFAA exposure and detrimental reproductive outcomes.
Take-home points: Compared to other songbirds, there is minimal association between PFAA exposure and reproductive impairment

10.3 Biomonitoring PFAAs in blood and semen samples: Investigation of a potential link between PFAAs exposure and semen mobility in China (Song et al 2018)
Study type: humans
Research question: Is there an association between PFAS levels in blood and semen? Is there a potential link between PFAS exposure and semen quality in a population near the Pearl River Delta region in China?
Method: compared PFAS levels in blood and semen of ~ 100 male participants

Figure note:The table shows the correlation between exposure to 10 different PFAS chemicals and semen concentration and motility. Starts represent significant findings and suggest important implications of PFAS exposure, especially for sperm motility
Take-home points: Blood and semen levels of PFAS were positively correlated. Significant negative correlations were found between exposure tot several PFAS chemicals and sperm motility

Endocrine System Data

11.1 Effects of perfluorooctanesulfonate and perfluorobutane sulfonate on the growth and sexual development of Xenopus laevis. Lou et al Ectoxicology (2013)

Study type: Xenopus laevis (frog)
Research question: what is the effect of PFOS and PFBS on the growth and sexual development of amphibians
Method: Exposed tadpoles to a series of PFAS concentrations and measured variables related to growth and sexual development
Figure note:The graphs show the change in androgen and estrogen receptors at various levels of exposure of PFOS and PFBS compared to the control groups
Take-home points: Neither PFOS nor PFBS had a significant effect on the survival and growth of the frogs. However, they caused hepatohistological (e.g. liver tissue) impairment and impacts on sexual development (by altering the expression of estrogen and androgen receptors) at higher concentrations

11.2 Trans-placental transfer of thirteen perfluorinated compounds and relations with fetal thyroid hormones. Kim et al Environ Sci Technol (2011)

Study type: human (serum and fetal thyroid hormone concentrations)
Research question: What is the relationship between PFCs in human blood serum and fetal thyroid hormones*?*
Method: Measured PFC levels in the blood serum of pregnant women, fetal cord blood serum, and breast milk, and also measured the concentration of various thyroid hormones in pregnant women and their fetuses
Figure note:The graphs show the results along the PFAA gradient. Samples do not fall along an expected distribution, indicating no strong correlation between PFAA exposure and detrimental reproductive outcomes.
Take-home points: Most relationships were non-existent or non-significant, but significant correlations between material PFOS, PFTrDA were linked to higher levels of three thyroid hormone concentrations in the fetus.

11.3 Association of perfluoroalkyl substances exposure with reproductivehormone levels in adolescents: By sex status Zhou et al Environ Int (2016)

Study type: adolescent humans (serum)
Research question: What is the effect of PFASs on reproductive hormones in adolescents*?*

Method: Measured 9 PFAS compounds in the serum of 225 Taiwanese adolescents, and compared the data to their reproductive hormone concentrations
Figure note: The tables show the correlation coefficients for the 9 PFAS compounds and changes in testosterone (Table 2) and estradiol (Table 3).
Take-home points: Higher levels of PFASs coincide with lower testosterone and higher estradiol levels, and more significant associations of PFASs with reproductive hormone were found in males than in females

Glossary of Important Terms

Adverse health outcomes - a health related effect that is attributed to/with a specific context, and has the potential to lower the quality of life, contribute to disabling illness, or lead to premature death

Biomonitoring indicators - in ecology/environmental science, the act of observing/assessing specific factors that illustrate the state of ongoing changes in an ecosystem/environment

Cancer cluster - a greater-than-expected number of cancer cases in a group or geographic region over a period of time

Environmental hazard - a substance or event possessing the potential to threaten the health of the natural environment and/or human health

Epidemiology - study/measurement of the distribution, patterns, and causes of health-related conditions in a defined population

Health outcome indicators - impairments, symptoms, functioning, and other health-related quality of life that are monitored/studied in a specific context

Sentinel species - organisms that can be used to detect risks to humans by providing advance warning of an environmental danger. A common example is the “canary in the coalmine”

Superfund site - a location in the US determined to be polluted with hazardous material and requiring long-term remediation/clean-up.

Toxicology - measurements/analysis of potential toxins and their effects

References

Sunderland, E.M., Hu, X.C., Dassuncao, C. *et al.* A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFASs) and present understanding of health effects. *J Expo Sci Environ Epidemiol* 29, 131–147 (2019). https://doi.org/10.1038/s41370-018-0094-1

Johnson, G. 2013. Cancer Cluster or Chance? The link between environmental contaminants and cancer is surprisingly weak, if not imaginary. Slate.

CDC - PFAS in the US Population. https://www.atsdr.cdc.gov/pfas/health-effects/us-population.html

Sunderland, E., Hu, X., Dassuncao, C., Tokranov, A., Wagner, C., and Allen, T. 2018. A review of the pathways of human exposure to poly- and perfluoroalkyl substances (PFAS) and present understanding of health effects. Journal of Exposure Science and Environmental Epidemiology

The Endocrine Disruption Exchange's (TEDX) PFAS Systematic Evidence Map

Sharpe, R. 2004. How strong is the evidence of a link between environmental chemicals and adverse effects on human reproductive health? BMJ 328 (7437), 447-451.

Heather Stapleton (Duke) Town Hall meeting in Pittsboro (October 2020): https://li.capture.duke.edu/Panopto/Pages/Viewer.aspx?id=255675e7-f96b-4965-9df6-ac710160d5e7

Endocrine Society Presentation with Dr. Scott Belcher, 2019: https://www.youtube.com/watch?v=sdkd8ZRd_eM&t=13s

Guillette, T. C., McCord, J., Guillette, M., Polera, M. E., Rachels, K. T., Morgeson, C., ... & Belcher, S. M. (2020). Elevated levels of per-and polyfluoroalkyl substances in Cape Fear River Striped Bass (Morone saxatilis) are associated with biomarkers of altered immune and liver function. Environment international, 136, 105358. https://www.sciencedirect.com/science/article/pii/S0160412019334762