HEALTH RISK ASSESSMENT OF CHEMICAL HAZARDS

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Epidemiology and Environmental Health

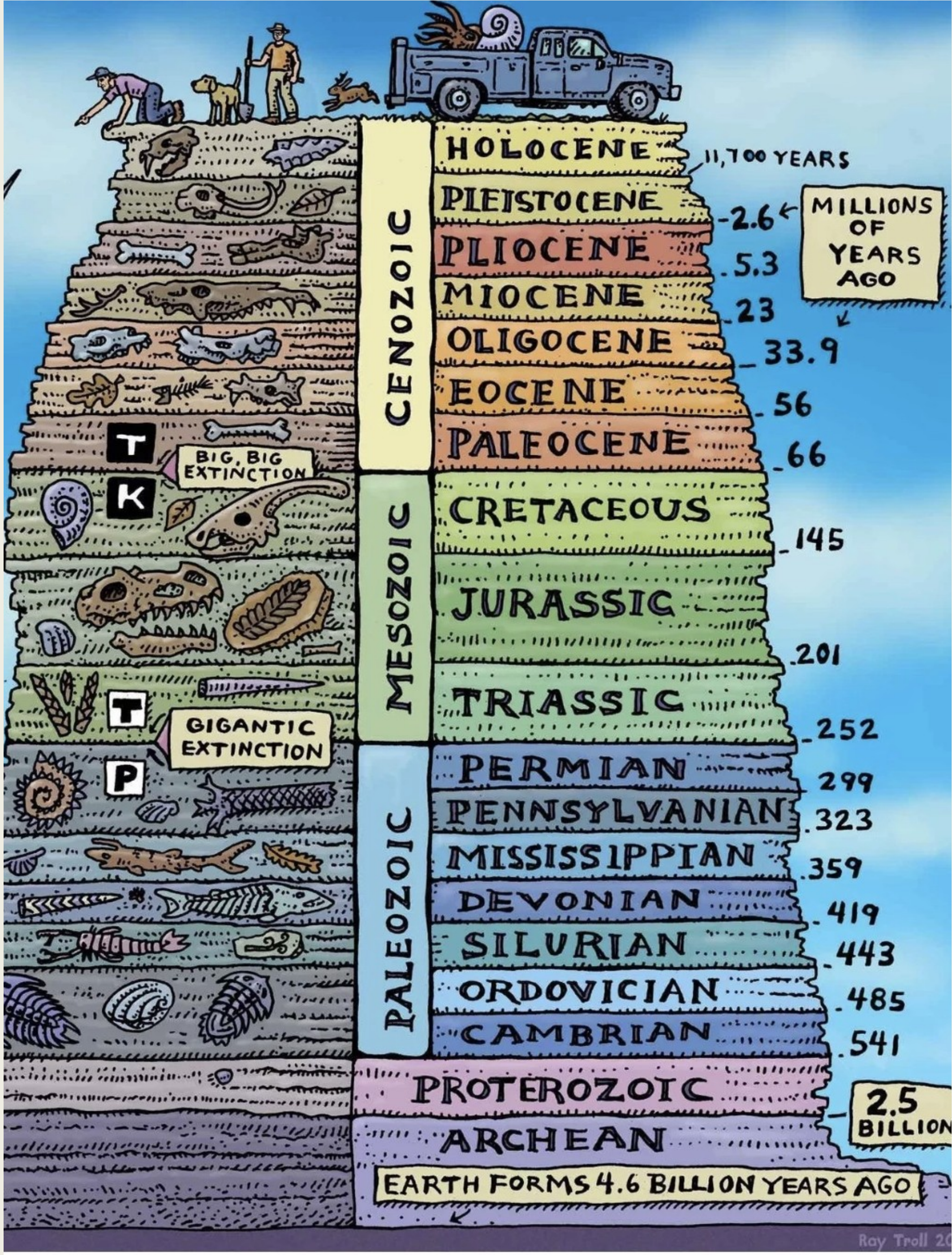
October 26, 2023

We have been producing chemical pollutants for generations

LEEMAGE/CORBIS VIA GETTY IMAGES

THE ANTHROPOCENE IS CHEMICAL

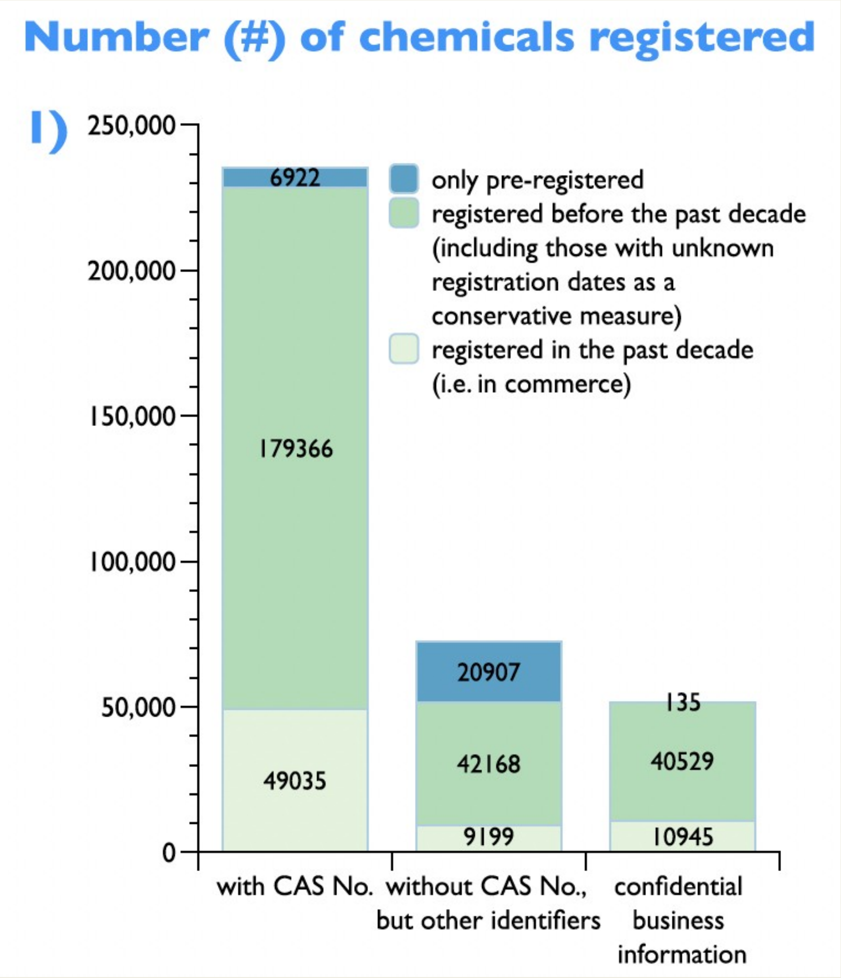
https://www.npr.org/sections/13.7/2016/10/01/495437158/climate-change-and-the-astrobiology-of-the-anthropocene



f Earth. Note the timescales. We are currently in the Holocene, which has been warm and moist
w human civilization. But the activity of civilization is now pushing the planet into a new epoch
e Anthropocene.

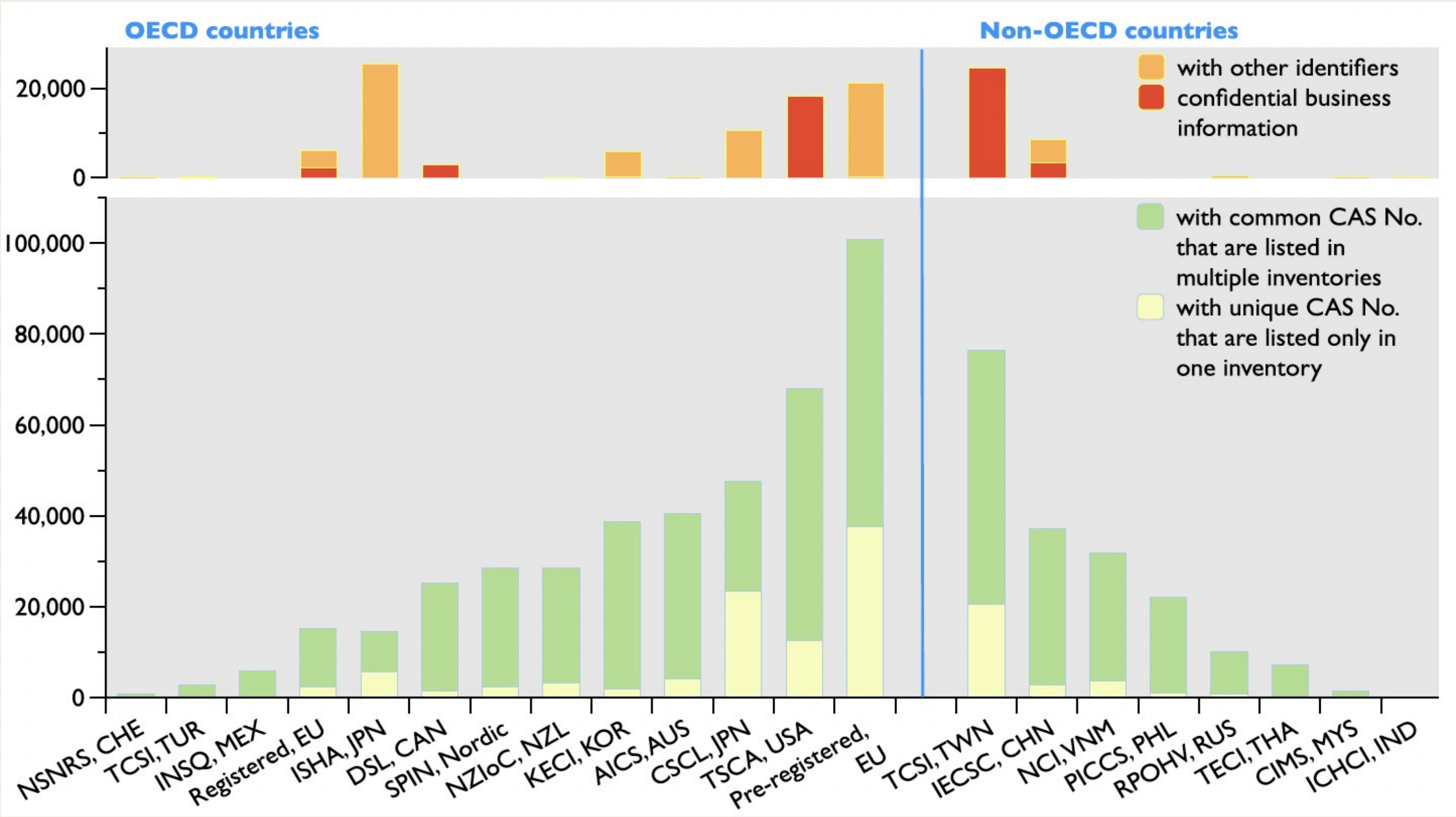
Humans produce thousands of chemicals

- Trillions of tons of chemically active material discharged by mining, mineral processing, farming, construction and energy production.
- Humans have synthesized potentially as many as 350,000+ chemicals.
  - >50,000 chemicals remain publicly unknown because they are “confidential”.
  - Up to 70,000 chemicals are poorly/ambiguously described.
- New synthetic chemicals are constantly developed: the USA alone recently produced an average of 1500 new substances a year.



Naidu R et al. Chemical pollution: A growing peril and potential catastrophic risk to humanity. *Environment International* 2021; 156:106616. Wang Z et al. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. *Environmental Science and Technology* 2020; 54, 2575–2584.

Number of modern chemical producers and users is growing



Up to early 2000, main manufacturers were: US, Canada, Western Europe and some other members of the Organisation for Economic Cooperation and Development (OECD).

Increasingly, production and export occurs in BRICS countries (Brasil, Russia, India, China, South Africa).

Wang Z et al. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. *Environmental Science and Technology* 2020; 54, 2575–2584.

Exposures, developed countries

- In the US, 1242 sites listed on the National Priorities List as worst hazardous waste sites.
- 3-4 million children estimated to live within 1 mile of at least one hazardous waste site.
- Lead, arsenic, and mercury are listed as toxicants of greatest concern at these sites.
- The likelihood of vulnerable populations, including women of reproductive age and young children, being exposed to at least 1 chemical is very high.

Grandjean P, Landrigan PJ. Developmental neurotoxicity of industrial chemicals. *Lancet* 2006; 368: 2167-78.

LA OROYA, PERU

Potentially affected people: 35,000
Type of pollutants: Lead, copper, zinc, and sulfur dioxide.

LINFEN, SHANXI PROVINCE, CHINA

Potential population affected: 200,000
Type of pollutants: PM-2.5, PM-10, volatile organic compounds, arsenic, lead.

HAINA, DOMINICAN REPUBLIC

Potentially affected people: 85,000
Type of pollutants: Lead.

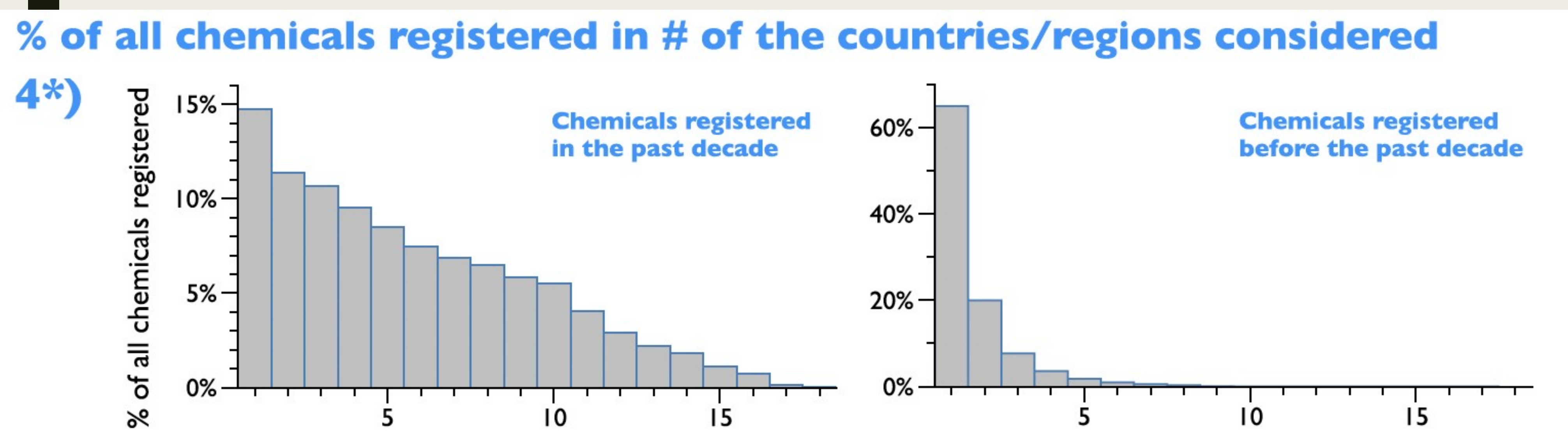
[“Jardines de plomo” https://vimeo.com/157555416](https://vimeo.com/157555416)

Source: www.blacksmithinstitute.org

The chemical world has no boundaries

Country A
- Produce
- Release
- Use
- Dispose
- Export
- Import

Country B
- Produce
- Release
- Use
- Dispose
- Export
- Import



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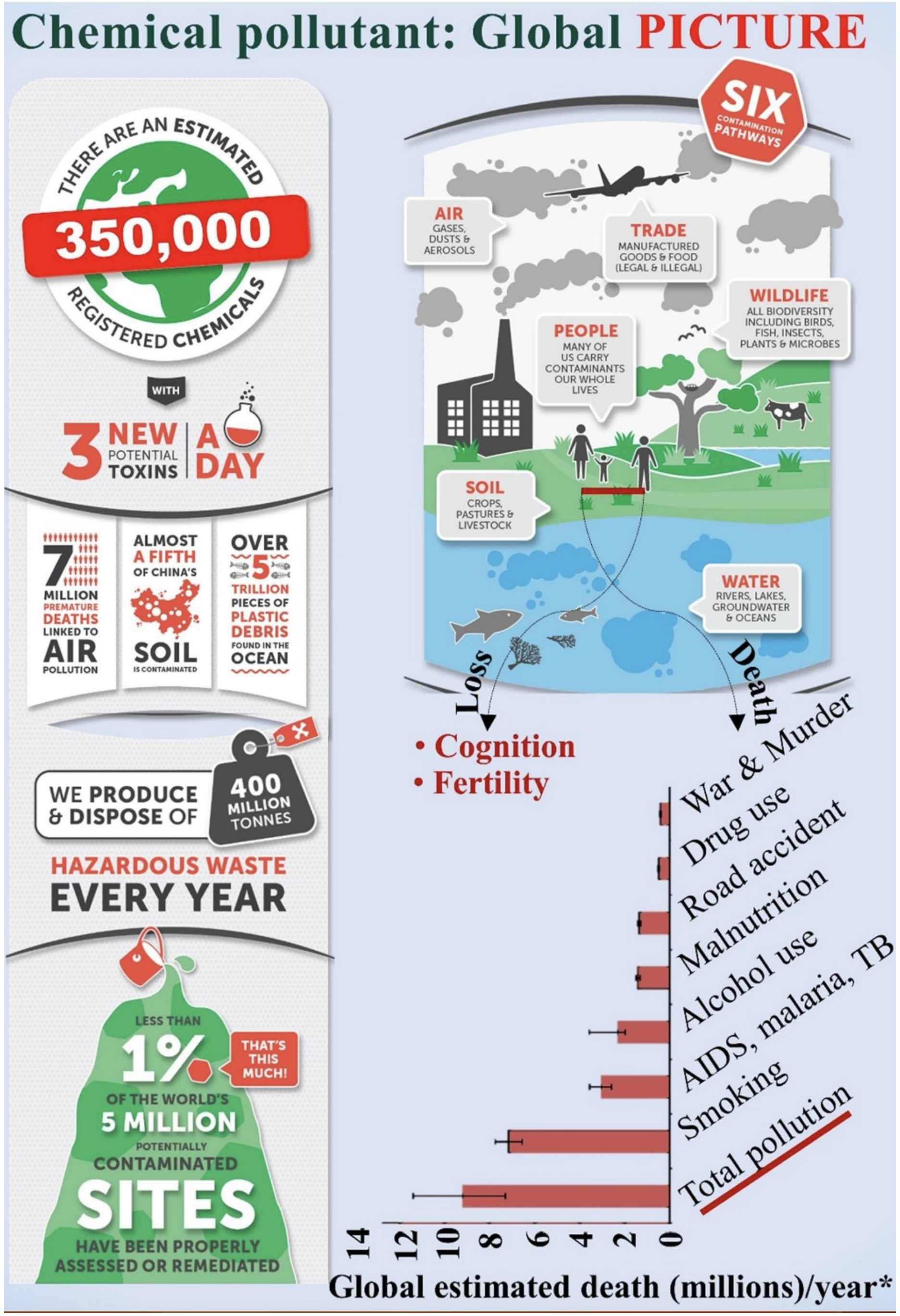


Naidu R et al. Chemical pollution: A growing peril and potential catastrophic risk to humanity. *Environment International* 2021; 156:106616.

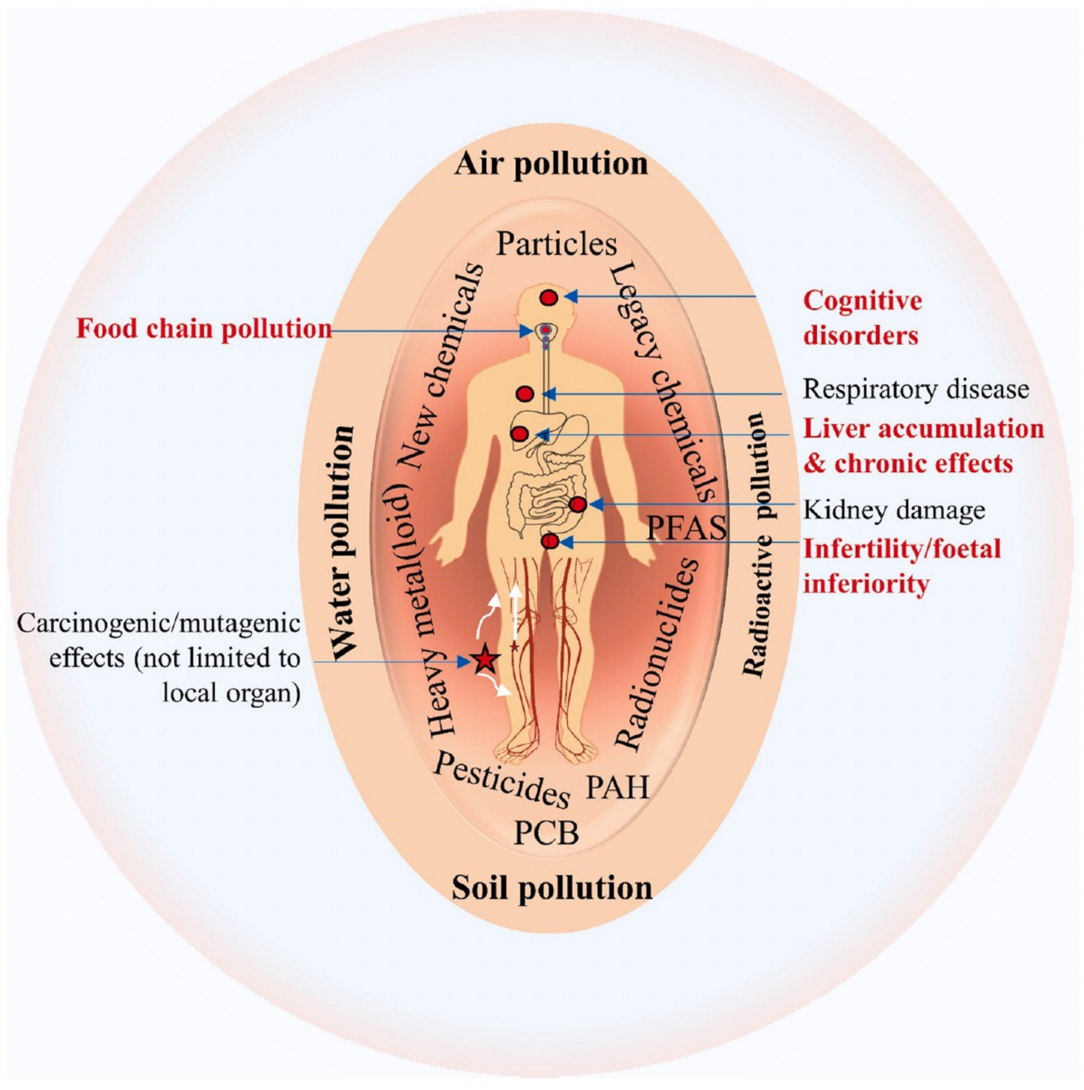
Top polluters and associated haza

The top ten polluters and potential impacts on human life (as proposed by Pure Earth/Blacksmith Institute ((Pure Earth and Green Cross Switzerland 2016)).

Rank	Industries	DALYs*	Potential pollutants
1	Used lead acid batteries	2,000,000–4,800,000	Pb
2	Mining and ore processing	450,000–2,600,000	Pb, As, Cd, Hg, hexavalent chromium (Cr(VI))
3	Lead smelting	1,000,000–2,500,000	Pb, Cd, Hg
4	Tanneries	1,200,000–2,000,000	Cr(VI)
5	Artisanal small-scale gold mining	600,000–1,600,000	Hg
6	Industrial dumpsites	370,000–1,200,000	Pb, Cr(VI)
7	Industrial estates	370,000–1,200,000	Pb, Cr(VI)
8	Chemical manufacturing	300,000–750,000	Pesticide, volatile organic compounds (VOCs), heavy metal(loid)s
9	Product manufacturing	400,000–700,000	Pb, Hg, Cr(VI), dioxins, VOCs, sulphur dioxide
10	Dye industry	220,000–430,000	Pb, Hg, Cd, chlorine compounds

* Disability-Adjusted Life Years - a measure of human disease burden attributed to pollution. The more DALY, the more burden it causes.

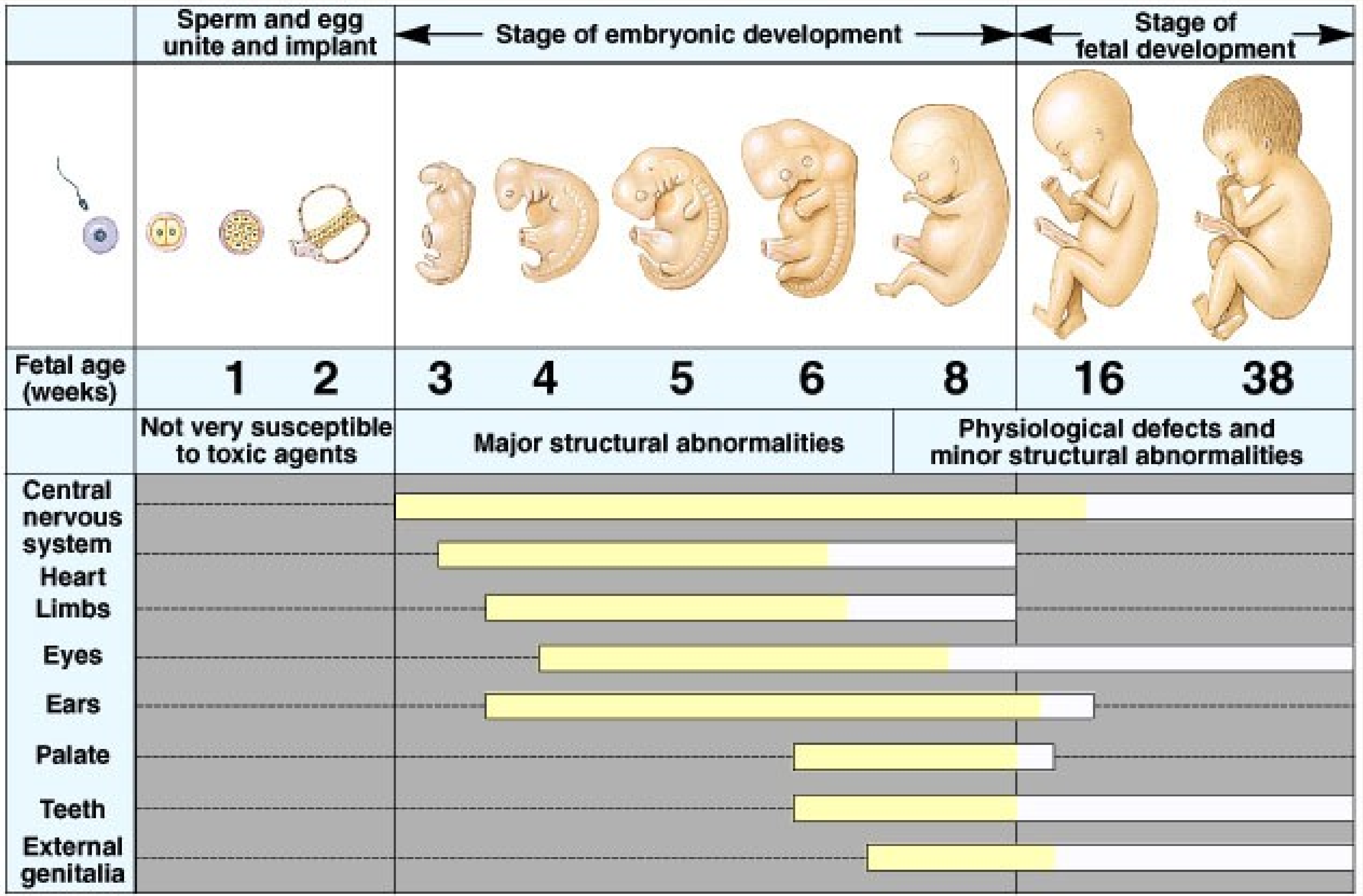
Naidu R et al. Chemical pollution: A growing peril and potential catastrophic risk to humanity. *Environment International* 2021; 156:106616.



EVIDENCE OF HEALTH EFFECTS

Naidu R et al. Chemical pollution: A growing peril and potential catastrophic risk to humanity. *Environment International* 2021; 156:106616.

The very nature of human development makes us vulnerable to toxic exposures



How do we sort out what is harmful and what is not?

- Individual or community concerns
- Scientific studies
  - *Exposure occurrence or characterization*
  - *Health effects – animal models and humans*
- Exposure monitoring by governmental agencies or NGOs
- Formal process of health risk assessment by regulatory agencies
  - *United States Environmental Protection Agency*

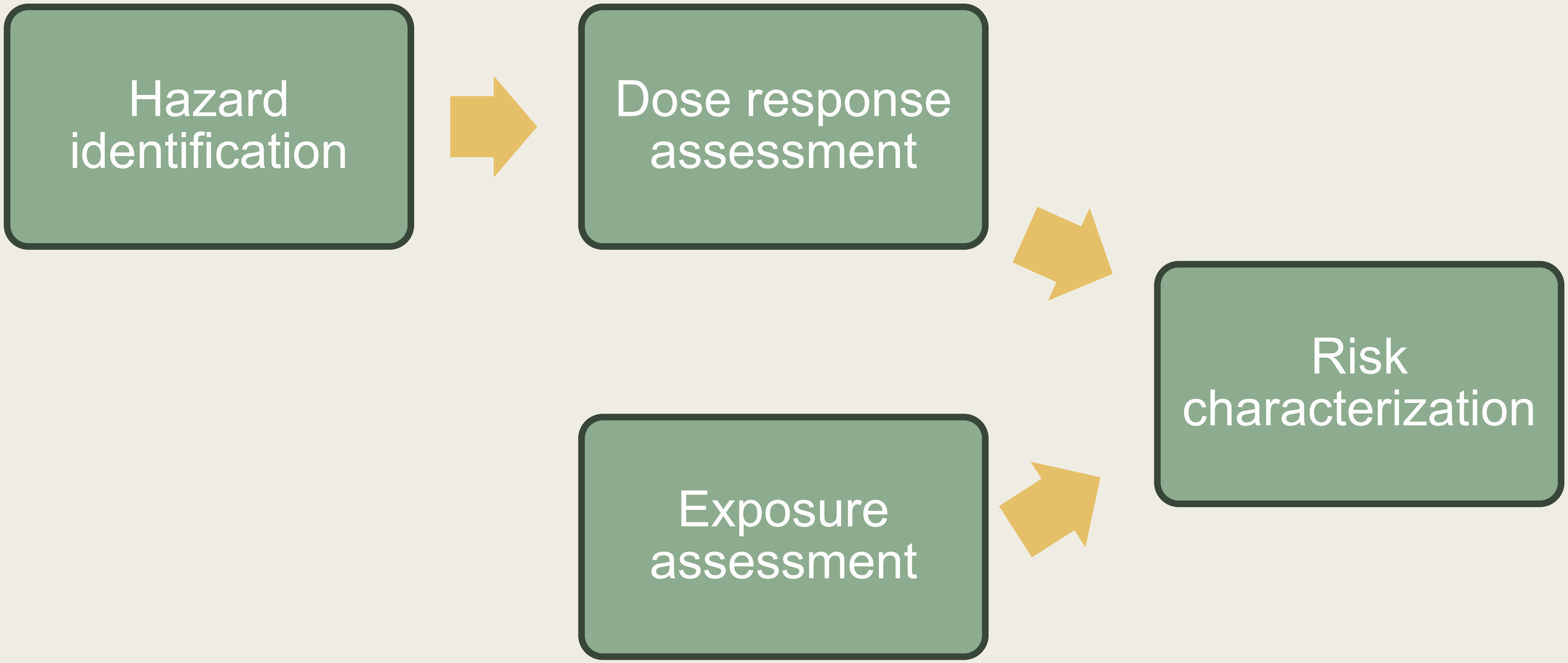
Toxic Substances Control Act (TSCA)

ith

Chemical Name	CASRN	Chemical Group	Date Initiated	Docket Number(s)	Status*	Agency Contact
1-Bromopropane	106-94-5	Solvents	December 2016	EPA-HQ-OPPT-2019-0235; EPA-HQ-OPPT-2016-0741	Final risk evaluation (August 2020)	Amy Shuman Email: Shuman.Amy@epa.gov Phone: (202) 564-2978
1,1-Dichloroethane	75-34-3	Solvents	December 2019	EPA-HQ-OPPT-2018-0426	Final scope (August 2020)	Clara Hull Email: Hull.clara@epa.gov Phone: (202) 564-3954
1,1,2-Trichloroethane	79-00-5	Solvents	December 2019	EPA-HQ-OPPT-2018-0421	Final scope (August 2020)	Matthew Lloyd Email: Lloyd.matthew@epa.gov Phone: (202) 566-2389
1,2-Dichloroethane	107-06-2	Solvents	December 2019	EPA-HQ-OPPT-2018-0427	Final scope (August 2020)	Simon Regenold Email: Regenold.Simon@epa.gov Phone: (202) 566-1537

Human health risk assessment process by the USEPA

- Planning



https://www.epa.gov/risk/conducting-human-health-risk-assessment#tab-1

Planning

Component	Details
Who, what where	General population vs. occupational groups Life stages: children, pregnant/nursing women Population sub-groups (highly susceptible or highly exposed)
What is the hazard of concern?	Chemical (single or mixture) Physical (dust, heat) Microbiological/biological
Source of hazard	Point sources (factory, Superfund site) Non-point sources (automobile exhaust, agricultural runoff) Natural sources
How does exposure occur	Pathways (air, water, soil, solid waste, food, consumer products Routes (ingestion, dermal contact, inhalation, non-dietary ingestion)
What does the body do with the environmental hazard	Is it absorbed by the body? Is it distributed throughout the body? Does the body breakdown the environmental hazard? How does the body get rid of the hazard?
Health effects	What are the health effects (ex., heart disease, liver disease, etc.)
Time to effect	Is timing of exposure important (critical window)? How long until health effects are observed (acute, sub-chronic, chronic)?

https://www.epa.gov/risk/conducting-human-health-risk-assessment#tab-1

Hazard identification

- Process to determine whether exposure can increase the incidence of adverse health effects (e.g., cancer, birth defects).
- Examines the available scientific data for a given chemical (or group of chemicals) and develops a weight of evidence to characterize the link between the negative effects and the chemical agent.
  - Epidemiological studies (observational)
  - Animal studies
    - Often conducted at higher doses than experienced by humans; difficult to extrapolate
  - Toxicokinetics (how the body absorbs, distributes, metabolizes, eliminates a chemical)
  - Toxicodynamics (mechanisms by which a chemical may impact human health)

https://www.epa.gov/risk/conducting-human-health-risk-assessment#tab-1

Dose-response assessment

dose–response relationship

The resulting biological responses in an organ or organism expressed as a function of a series of doses.

Things to consider:

1. There may be too many health outcomes to study, so only some are selected
   1. The adverse effect or precursor response that occurs at lowest dose is selected.
2. There may not be a clear dose-response relationship for all selected outcomes
   1. Nonlinear effects.
   2. Thresholds.

Kordas K et al. Iron and zinc supplementation does not improve parent or teacher ratings of behavior in first grade Mexican children exposed to lead. *Journal of Pediatrics* 2005; 147: 632-9.

Dose-response assessment may lead to establishment of No-Observed-Adverse-Effect-Level and Reference-Dose

NOAEL

The highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control; some effects may be produced at this level, but they are not considered adverse or precursors of adverse effects.

RfD

Oral or dermal dose derived from the NOAEL that represents the estimated daily exposure to humans (including sensitive groups) that is likely to be without appreciable risk of deleterious effect

RfD = NOAEL/Uncertainty factor (typically 100) that represents variability of exposure & effect

Expressed as mg/kg body weight/day

https://www.epa.gov/risk/conducting-human-health-risk-assessment#tab-1

Exposure assessment

- **P**rocess of measuring or estimating the magnitude, frequency, and duration of human exposure to an agent in the environment.
- Includes some discussion of the size, nature, and types of human populations exposed to the agent, as well as discussion of the uncertainties in the above information.
- "Central Tendency" -- average exposure experienced by the affected population, based on the amount of agent present in the environment and the frequency and duration of exposure.
- "High End" – estimated highest dose experienced by some individuals (90th percentile exposure).

Risk characterization & determination

risk characterization

The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.

1. Draft determination
   - EPA determines if chemical presents unreasonable risk
   - Undergoes peer review
2. Published in Federal Register
3. 60-day public commenting period
4. Final Risk Evaluation
   - Published within 3-3.5 years of chemical identification

https://www.epa.gov/chemicals-under-tsca

Examples of final rules & dockets

Hexachlorobutadiene (HCBD)	HCBD is used as a halogenated aliphatic hydrocarbon that is produced as a byproduct during the manufacture of chlorinated hydrocarbons, particularly perchloroethylene, trichloroethylene, and carbon tetrachloride and is subsequently burned as a waste fuel. Learn more about HCBD uses. *Identified Hazards* – HCBD is toxic to aquatic invertebrates, fish, and birds, and has been identified as a possible human carcinogen. Data indicate the potential for renal, reproductive, and developmental effects.	EPA prohibited the manufacturing (including import), processing, and distribution in commerce of HCBD and HCBD-containing products or articles, except for the unintentional production of HCBD as a byproduct during the production of chlorinated solvents, and the processing and distribution in commerce of HCBD for burning as a waste fuel.
Pentachlorothiophenol (PCTP)	PCTP, which is also called PCTP, is used to make rubber more pliable in industrial uses. Learn more about PCTP uses. *Identified Hazards* – PCTP is toxic to protozoa, fish, terrestrial plants, and birds. Data for analogous chemicals (pentachloronitrobenzene and hexachlorobenzene) indicate the potential for liver and reproductive effects. However, no animal or human hazard data has been identified.	EPA prohibited the manufacture (including import), processing, and distribution in commerce of PCTP, and products or articles containing PCTP, unless PCTP concentrations are at or below 1% by weight.

Dockets

- DecaBDE – EPA-HQ-OPPT-2016-0724
- PIP (3:1) – EPA-HQ-OPPT-2016-0730
- 2,4,6-TTBP – EPA-HQ-OPPT-2016-0734
- HCBD – EPA-HQ-OPPT-2016-0738
- PCTP – EPA-HQ-OPPT-2016-0739

https://www.epa.gov/chemicals-under-tsca

Beyond the US/EPA

- ECHA – European Chemicals Agency
- REACH establishes procedures for collecting and assessing information on the properties and hazards of substances.
- Companies need to register their substances.
- ECHA receives and evaluates individual registrations for their compliance. Authorities and ECHA's scientific committees assess whether the risks of substances can be managed.
- Authorities can ban hazardous substances if their risks are unmanageable. They can also decide to restrict a use or make it subject to a prior authorisation.

https://echa.europa.eu/en/regulations/reach/understanding-reach

In your own backyard, RECETOX at the forefront of chemical monitoring, risk assessment & regulation

Innovate beyond PFAS

New proposed legislation on "forever" chemicals is under consideration in Europe and the United States, where per- and polyfluoroalkyl substances (PFAS) are a hot topic for regulators and lawmakers. On both sides of the Atlantic, regulation of widely used PFAS has been complex and evolving. Their presence in hundreds of different products—from nonstick cookware to food packaging to fire-fighting foam—and their persistence in food, drinking water, and the environment have resulted in a pollution problem of unprecedented scale. Recently, for example, it was reported that 45% of the tap water in the United States contains at least one type of PFAS. Because these compounds are so chemically stable that they do not degrade in the environment (including in the human body), PFAS seriously challenge long-established ideas of how chemicals can be used, assessed, and regulated, and it remains to be seen whether the new regulations will solve this problem.

Chemicals assessment traditionally has been centered around toxicity and physical hazards such as flammability. Chemicals that are carcinogenic, mutagenic, or toxic for reproduction (so-called CMR chemicals), as well as chemicals with high acute toxicity such as many neurotoxicants, stand

The implications are substantial. One aspect is that chemicals that are only moderately toxic, but highly persistent, cannot be used in open and dispersive applications as has been the case for PFAS, but have to be used in closed systems, such as industrial equipment without any leaks or vents (which is required for highly toxic chemicals). Another aspect is that persistence does not carry sufficient weight in the assessment and regulation of chemicals. Persistence should be seen as a direct element of chemical hazard. The current approach of treating persistence only as a factor that modulates exposure to a chemical is not adequate. Under this approach, low persistence leads to lower estimated exposure and, thereby, a rating of lower risk in current chemicals assessment, whereas high persistence does not lead to a "red flag."

Accordingly, the way forward should include changes to the established system of chemicals assessment and regulation that go beyond the case of PFAS. For the specific problem of PFAS, it will be necessary to develop PFAS-free alternatives for many of the current PFAS uses. In general, this is possible for the vast majority of cases. Even for challenging and demanding uses such as fire-fighting foams for

> **"…persistence acts as a multiplier of toxicity. This insidious aspect…has been underestimated…"**

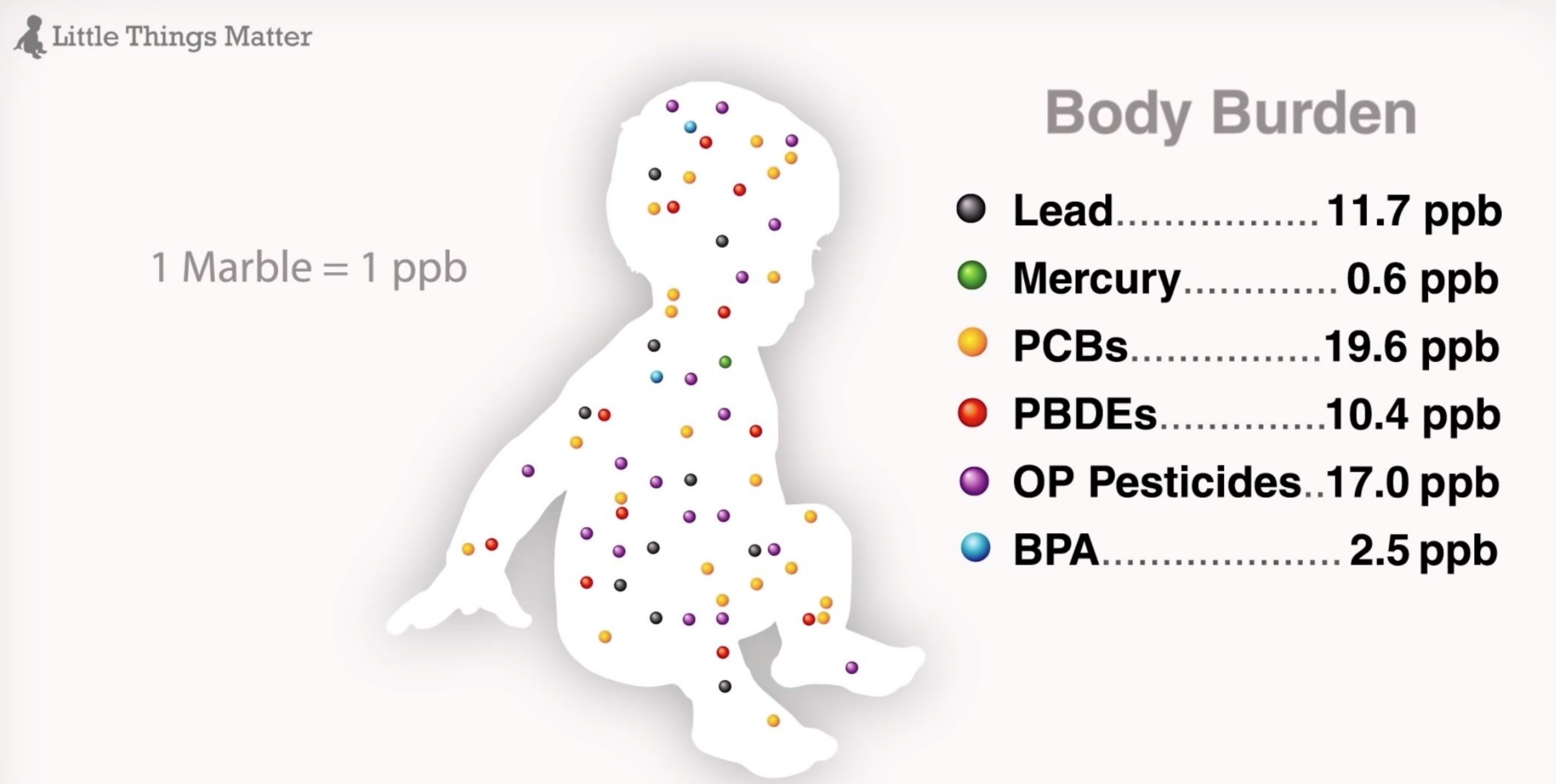
Martin Scheringer is a professor of environmental chemistry at RECETOX, Masaryk University, Brno, Czech Republic, and a senior scientist and group leader at ETH Zürich, Zürich, Switzerland. He is also the chair of the International Panel on Chemical Pollution and a co-coordinator of the Global PFAS Science Panel. scheringer@usys.ethz.ch

Future of risk assessment

- People are exposed to many environmental chemicals throughout their lives.
- Very often, these exposures occur at the same time.
- Concern over higher risk of adverse health outcomes from simultaneous exposures to many environmental chemicals.

Braun JM et al. What can epidemiological studies tell us about the impact of chemical mixtures on human health? *Environmental Health Perspectives* 2016; 124: A6-A9.

Children are exposed to "mixtures" of chemicals



http://littlethingsmatter.ca/2018/02/13/the-impact-of-toxins-on-the-developing-brain/

ONE EXAMPLE OF HAZARDOUS CHEMICAL: LEAD

Lead exposure around the world

In 2000, estimated 120 million people had BLL 5-10 g/dL

- *40% of all children had BLL ≥ 5 g/dL.*
- *97% of those children lived in developing countries.*

Pruss-Ustun et al. (2004) Lead exposure. In: Ezzati M et al., eds. *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors.* Geneva, WHO: 1495-1542.

Projections for global lead exposure (g/dL) among children, 2010-30

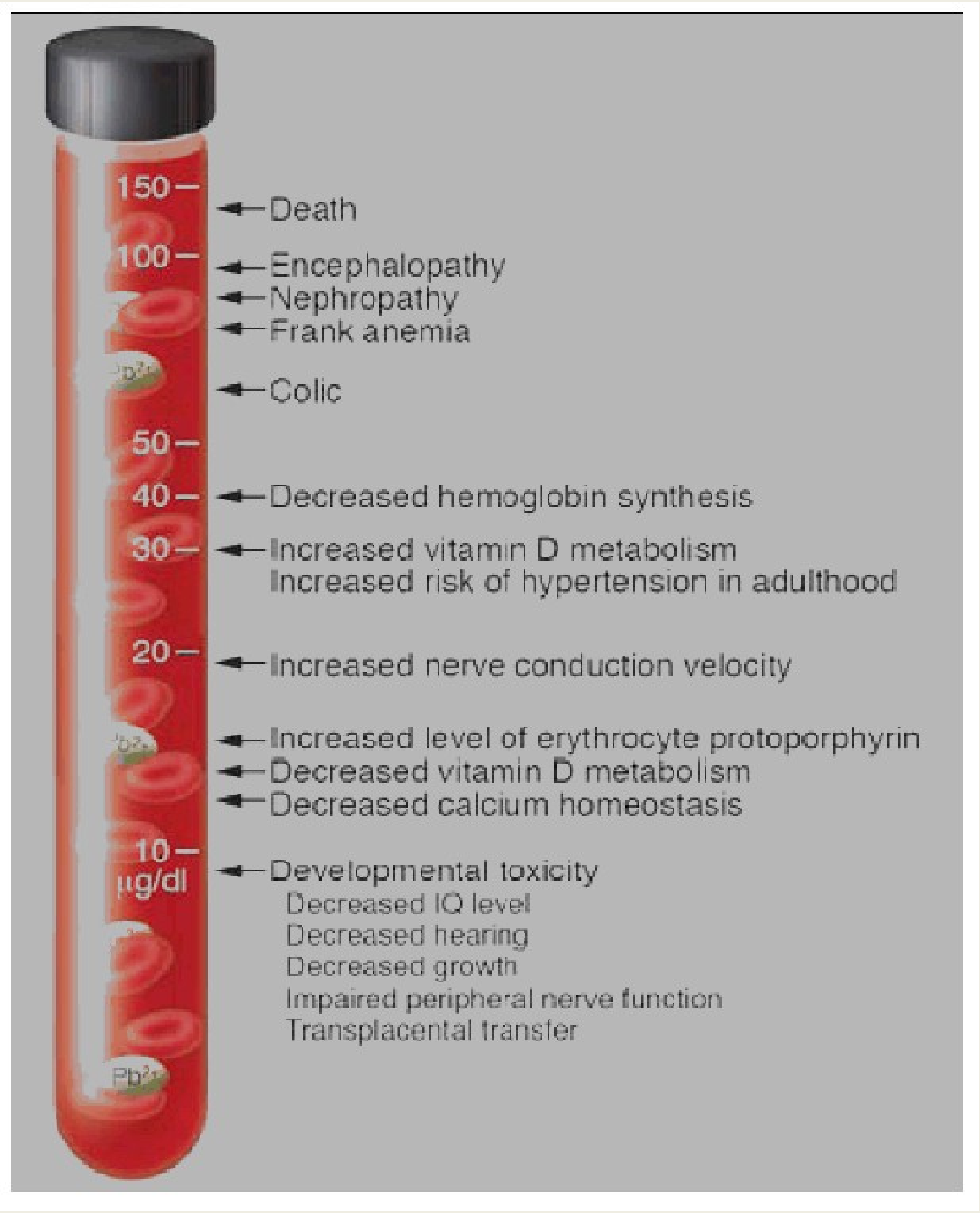
Pruss-Ustun et al. (2004) Lead exposure. In: Ezzati M et al., eds. *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors.* Geneva, WHO: 1495-1542.

Sources of exposure to lead

Global consequences of lead exposure

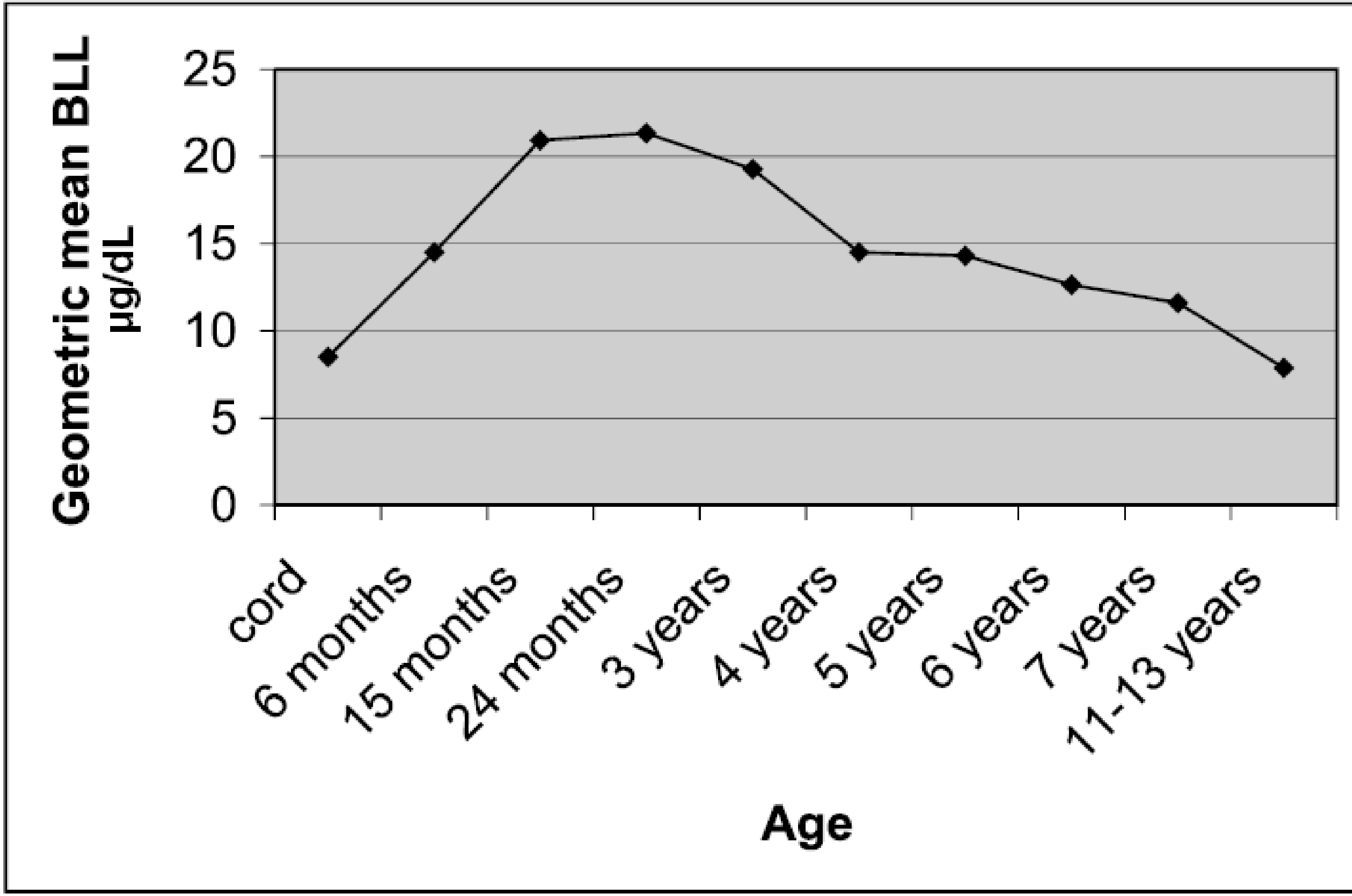
0.6% of the global burden of disease is attributable to lead-exposure

- *9.8 million DALYs due to mild mental retardation.*



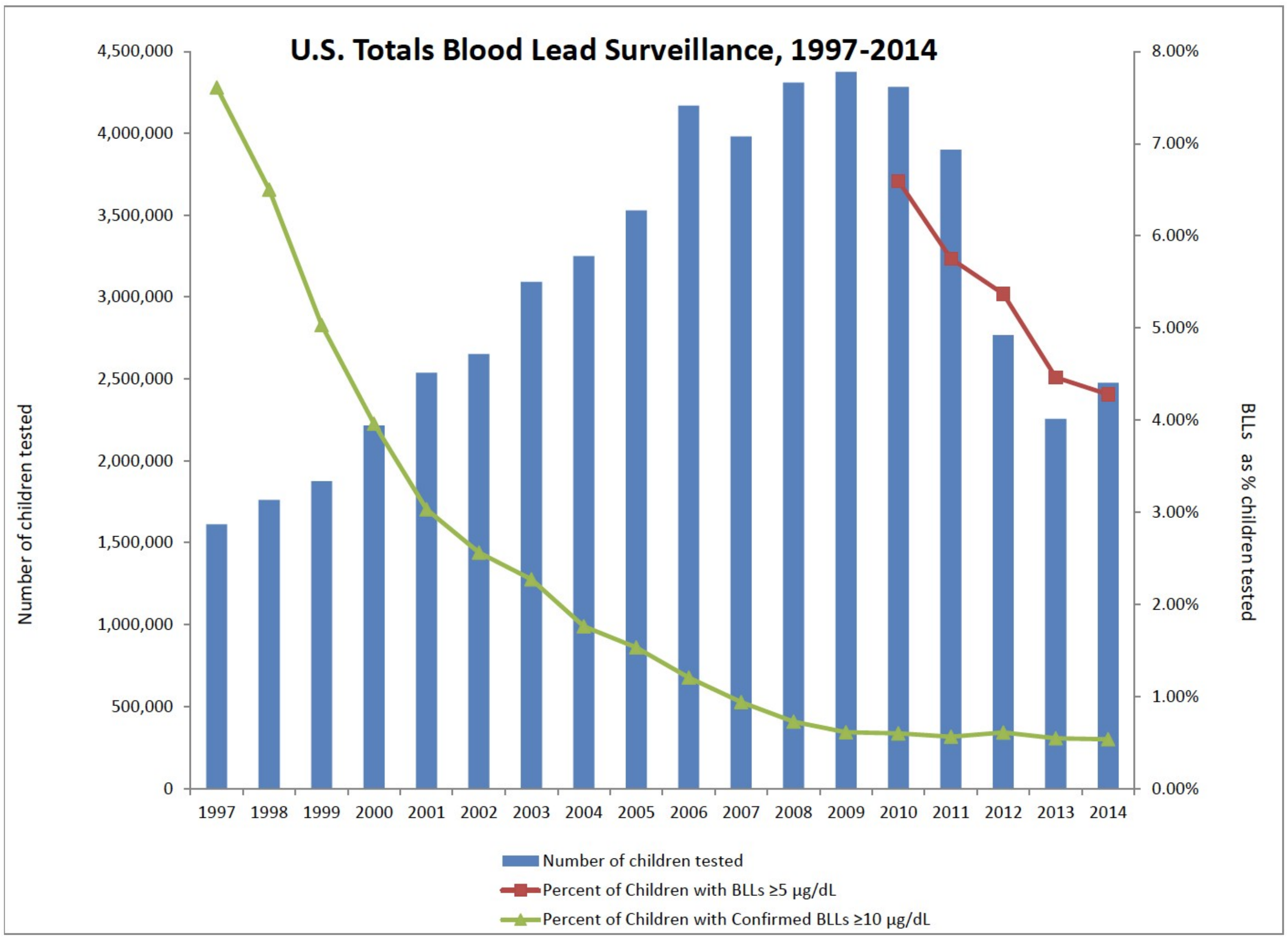
Pruss-Ustun et al. (2004) Lead exposure. In: Ezzati M et al., eds. *Comparative quantification of health risks: global and regional burden of disease attributable to selected major risk factors.* Geneva, WHO: 1495-1542. WHO 2010. Childhood lead poisoning.

Figure 4. Age trend in blood lead levels (BLLs).



Source: Tong et al. 1996.

The problem of lead, US



Elevated BLLs among US children, 2009-15:

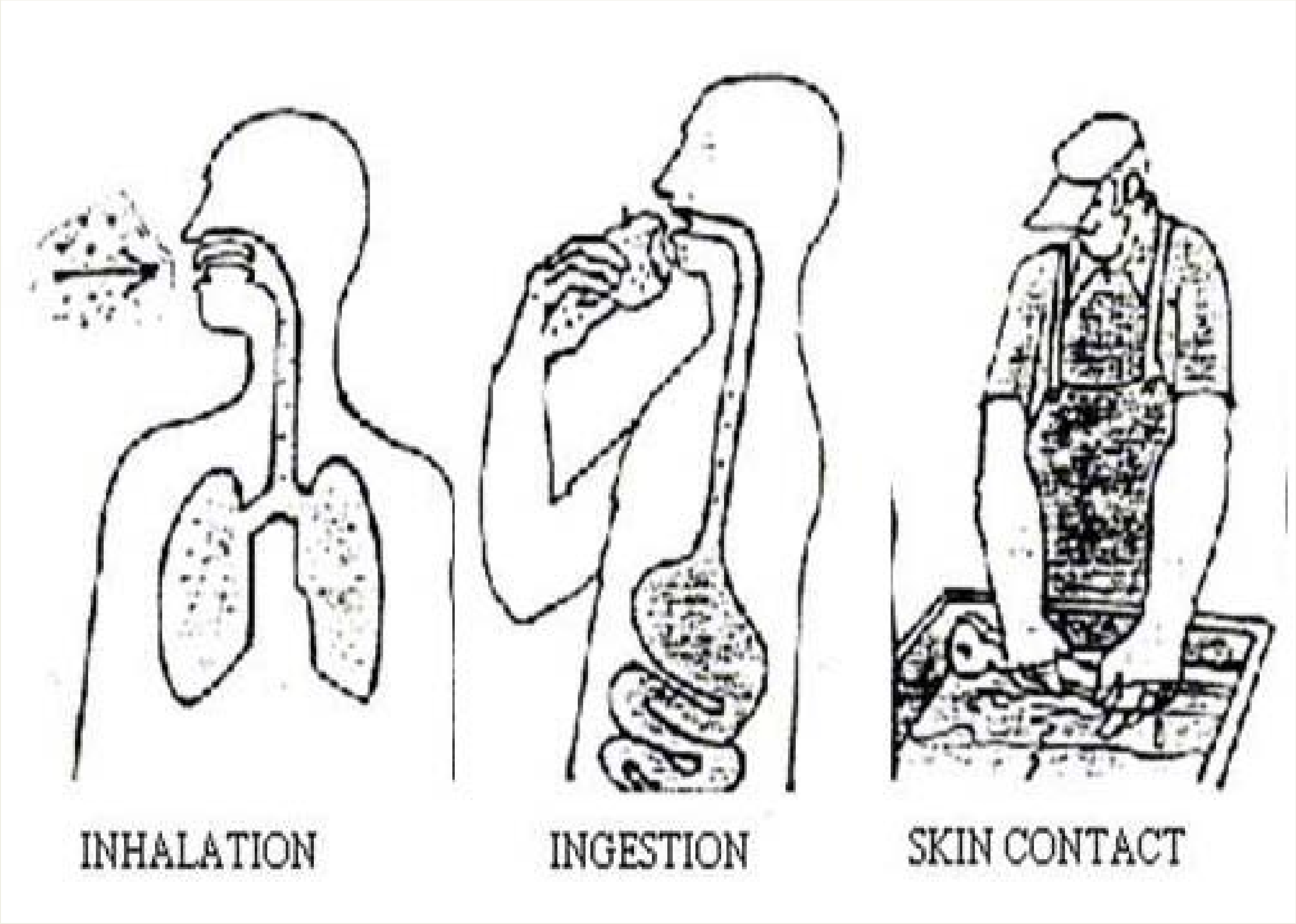
≥ 10 g/dL – 0.58%
≥ 5 g/dL – 2.95%

CDC. National Surveillance Data (1997-2014). McClure, Niles, Kaufman. Blood lead levels in young children: US, 2009-2015. *Journal of Pediatrics* 2016; 175: 173-81.

Lead exposure is a social justice issue

Ireland & Palmer (2016). The full picture of our lead problem. www.nrdc.org/stories

How lead enters the body



Maternal lead exposure contributes to exposure in the fetus

Lead accumulated in bone is released during pregnancy and lactation.

- *Contributes around 30%.*
- *Mobilization continued up to six mo during lactation.*

Maternal lead levels and infant (cord blood) lead levels are highly correlated.

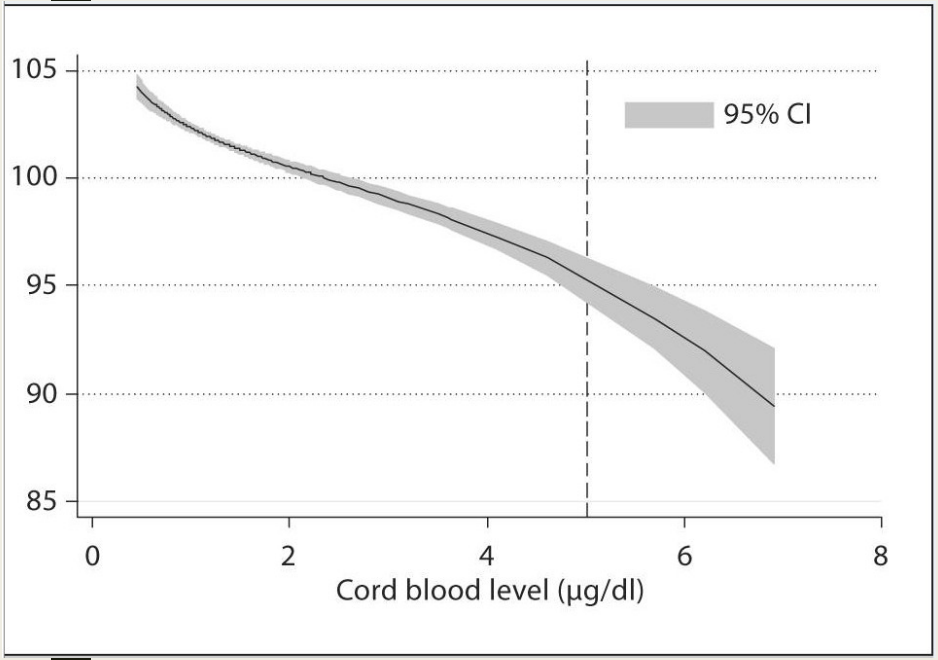
- *r^2=0.87 in 500 mother-infant pairs from Mexico.*

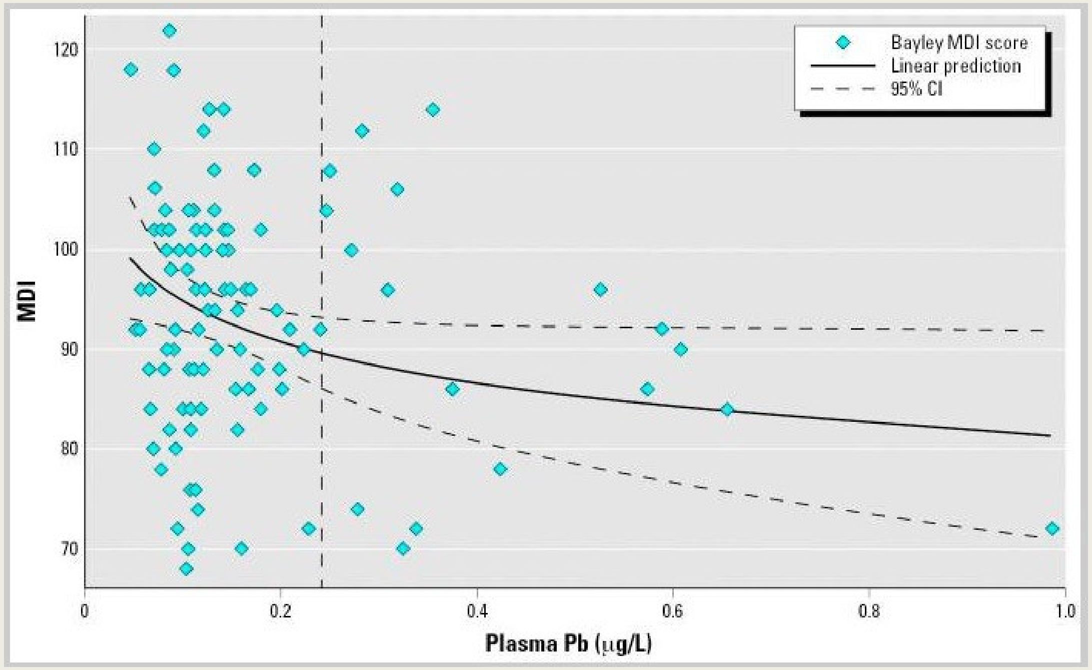
Maternal bone lead levels are related to lower birth weight in their children.

- *In Mexico women, 4-7 g decrease in BW for every 1 µg/g increase in bone lead.*

Higher lead exposure also associated with slower growth post-partum.

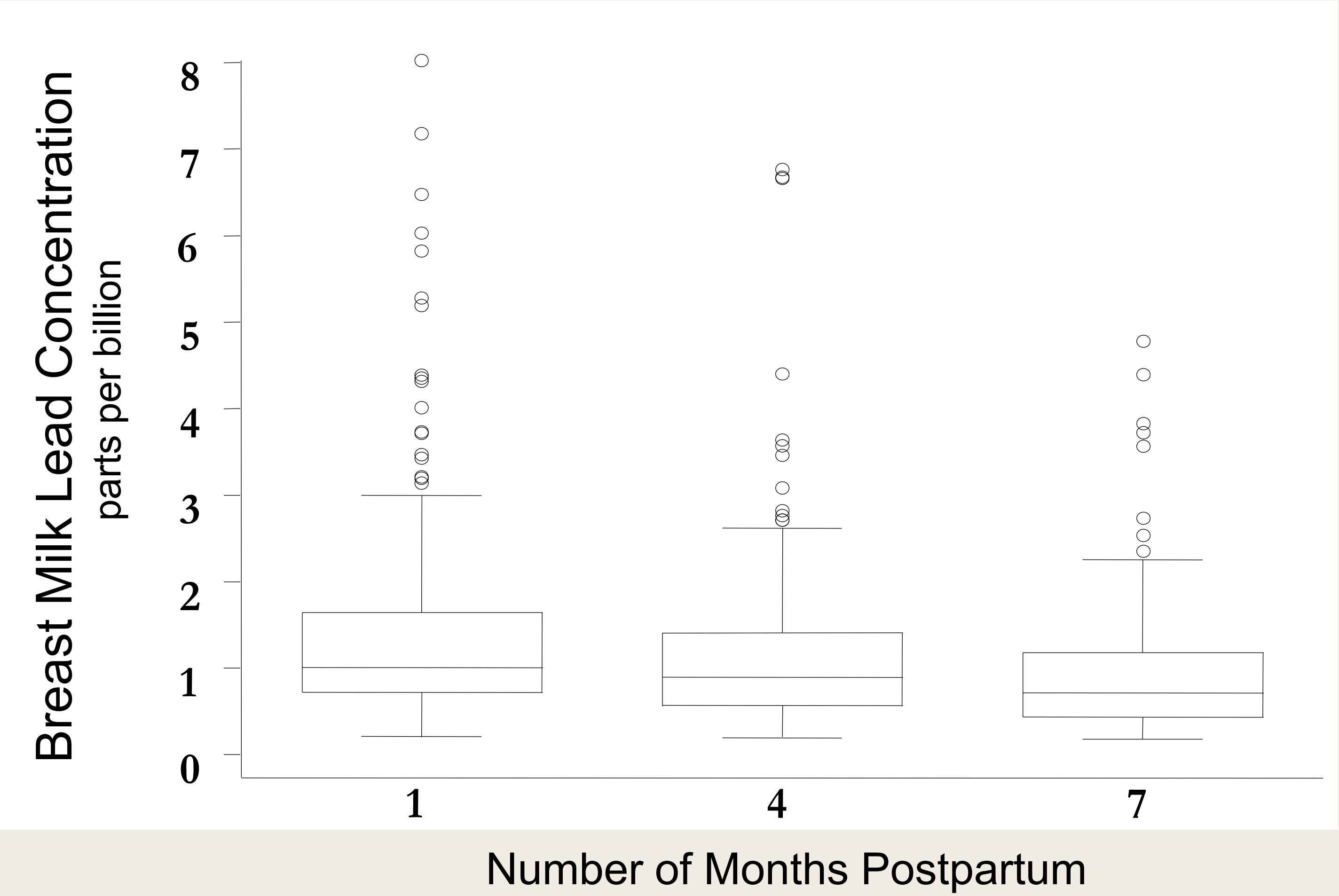
Prenatal lead exposure, is related to lower neurodevelopmental scores





Jedrychowski et al. Very low prenatal exposure to lead and mental development of children in infancy and early childhood: Krakow prospective cohort study. *Neuroepidemiology 2009;* 32: 270-8. Hu et al. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental development *Environmental Health Perspectives* 2006; 114: 1730-5.

Maternal body lead burden contributes to infant exposure through breast milk



Ettinger AS et al. Influence of maternal bone lead burden and calcium intake on levels of lead in breast milk over the course of lactation. *American Journal of Epidemiology* 2006; 163: 48-56.

ß = -0.36***

ß = -017***

Kordas et al., Blood lead, anemia and short stature are independently associated with cognitive performance in Mexican school children. *Journal of Nutrition* 2004; 134: 363-71.

Contrary to previous belief, low-level exposure to lead is associated with poor outcomes—pooled analysis of cohort studies

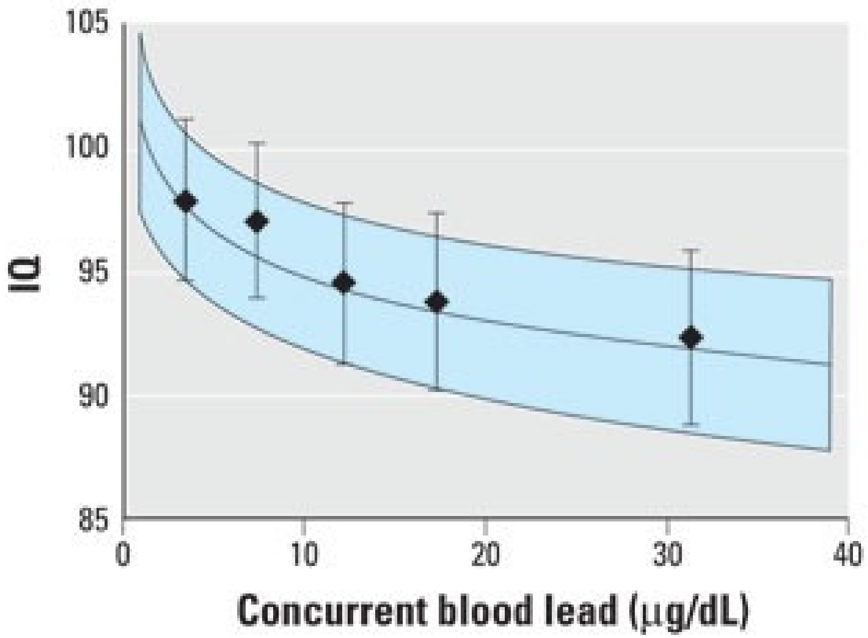


Figure 3. Log-linear model (95% CIs shaded) for concurrent blood lead concentration, adjusted for HOME score, maternal education, maternal IQ, and birth weight. The mean IQ (95% CI) for the intervals < 5 μg/dL, 5–10 μg/dL, 10–15 μg/dL, 15–20 μg/dL, and > 20 μg/dL are shown.

<u>IQ points associated with concurrent PbB:</u>

- *2.4 – 30 ug/dL—6.9 [4.2-9.4]*

- *2.4 – 10 ug/dL—3.9 [2.4-5.3]*
- *10 – 20 ug/dL—1.9 [1.2-2.6]*
- *20 – 30 ug/dL—1.1 [0.7-1.5]*

Lanphear BP et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect* 2005; 113: 894-9.

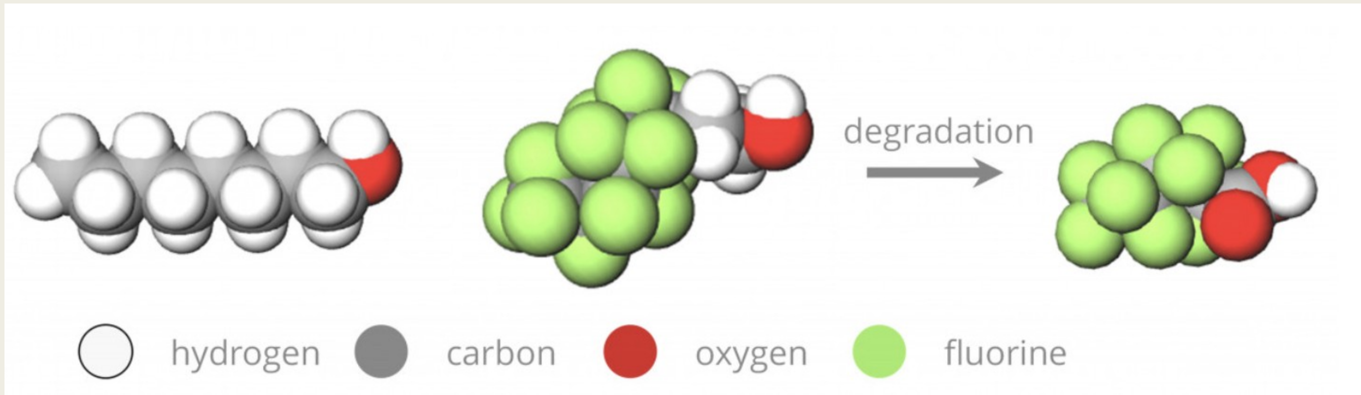
SHIFTING THE IQ DISTRIBUTION

What has been/is being done?

- Leaded gasoline phased out
  - *Not in airplane engines*
- Lead-based paint banned for interior applications
  - *Not exterior*
- Lead poisoning prevention programs
- Gradual lowering of “level of concern”
- Educational and awareness campaigns

ANOTHER EXAMPLE OF HAZARDOUS CHEMICAL(S): PFAS

What are PFAS & why are we concerned?



DISSOLVE BUT STAY IN WATER

BIOACCUMULATE IN ECOSYSTEMS INCLUDING HUMANS

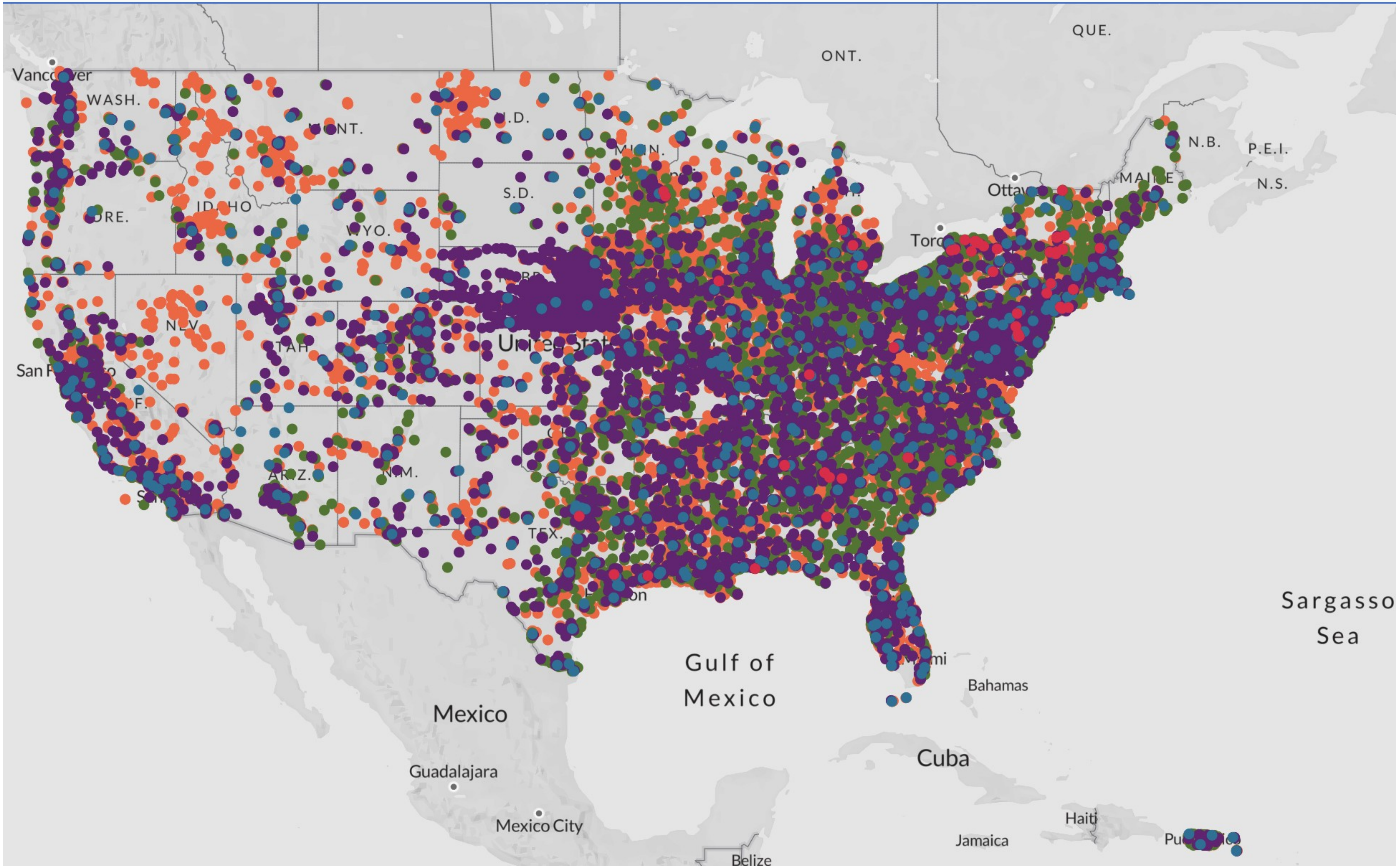
VERY MOBILE

VOLATILE AND CAN BECOME AIRBORNE

https://eeb.org/work-areas/industry-health/pfas/#

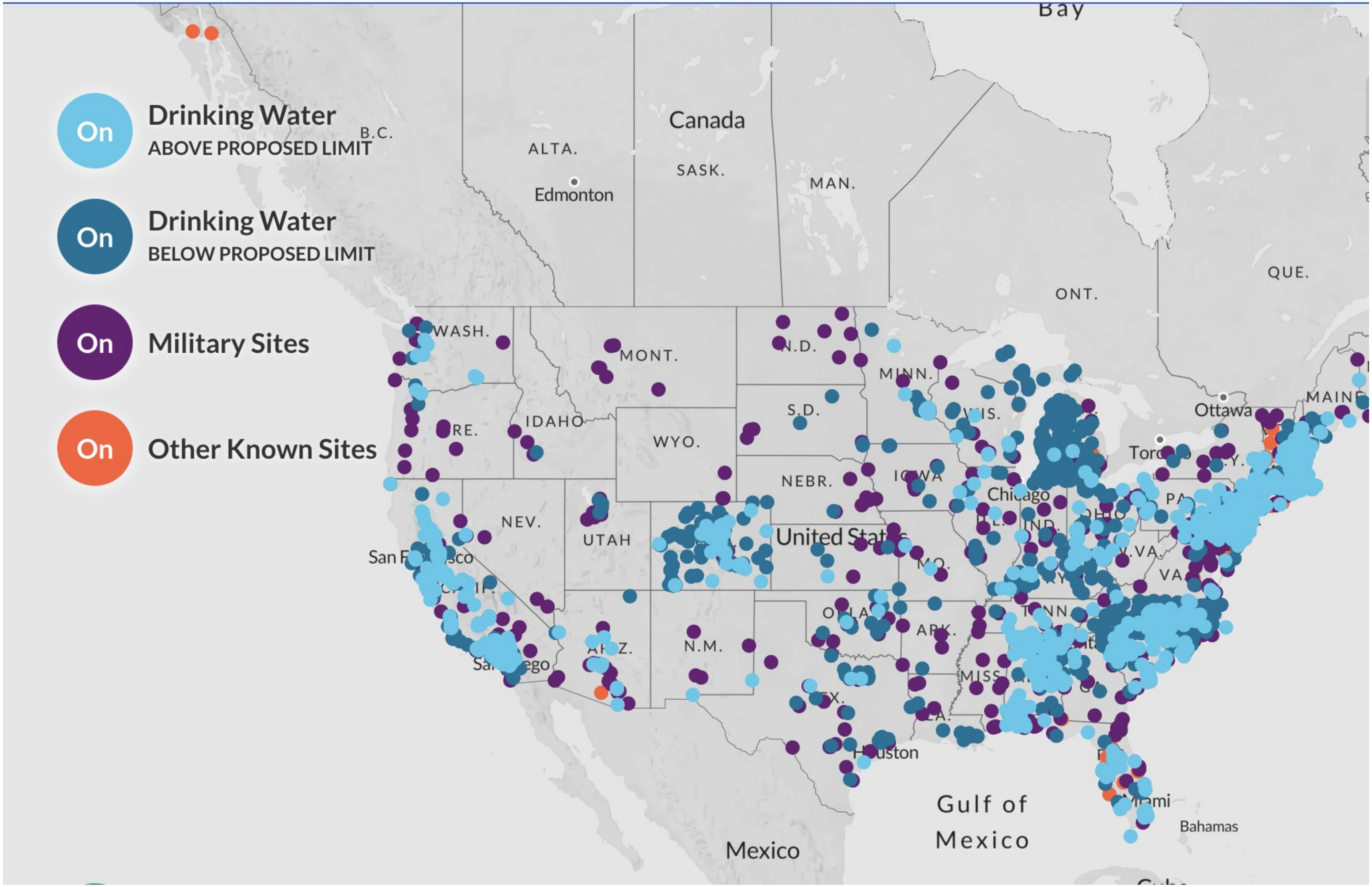

Time to phase out
PFAS
#ForeverChemicals

Suspected industrial discharges of PFAS



https://www.ewg.org/interactive-maps/2021_suspected_industrial_discharges_of_pfas/map/

PFAS Contamination in the U.S. (August 17, 2023)



https://www.ewg.org/interactive-maps/pfas_contamination/map/

Actions in Europe

- https://www.rivm.nl/en/pfas/video-european-ban-on-pfas

Latest updates

Universal PFAS restriction proposal:

- ECHA receives more than 5 600 comments on PFAS restriction proposal, 26 Sept 2023
- Listen to our podcast: committee chairs María Ottati and Roberto Scazzola give an update on the universal restriction proposal, 20 Sept 2023
- Q&As from the info session online, 28 June 2023
- Watch the info session on the proposed PFAS restriction
- ECHA publishes PFAS restriction proposal, 7 February 2023

Restriction proposal on PFAS in firefighting foams:

- ECHA's committees: EU-wide PFAS ban in firefighting foams warranted, 22 June 2023

Other:

- Perfluoroheptanoic acid (PFHpA) and its salts added to Candidate List of substances of very high concern, 17 January 2023

https://echa.europa.eu/hot-topics/perfluoroalkyl-chemicals-pfas