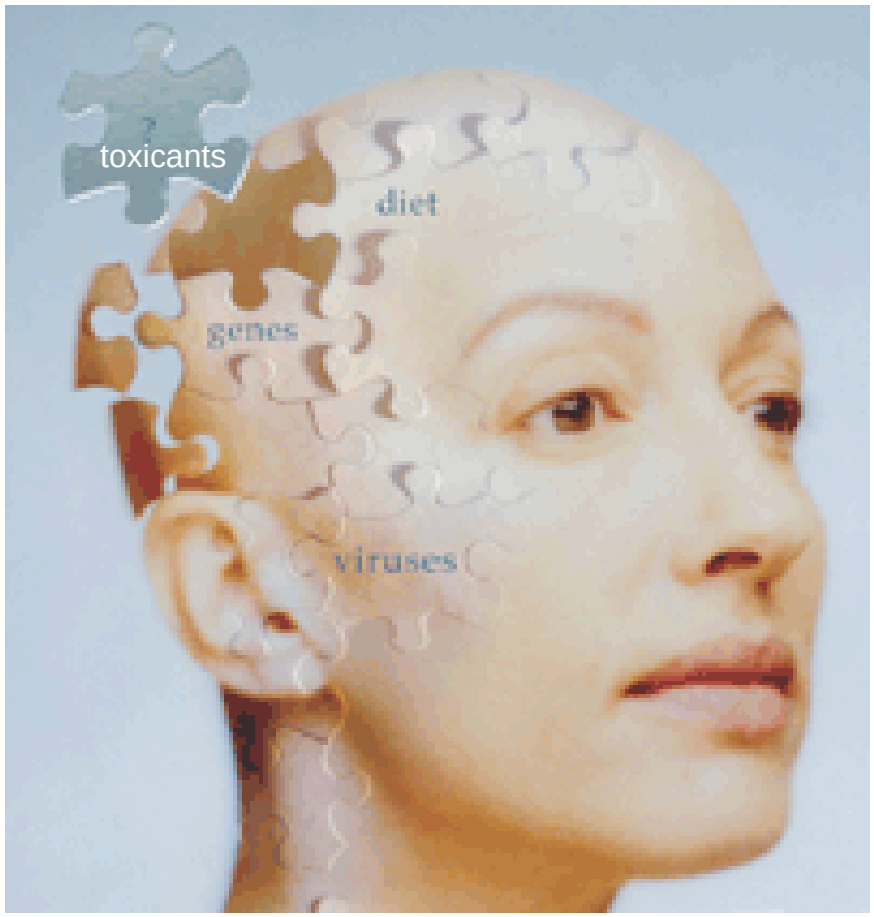


Chemical brain brain:

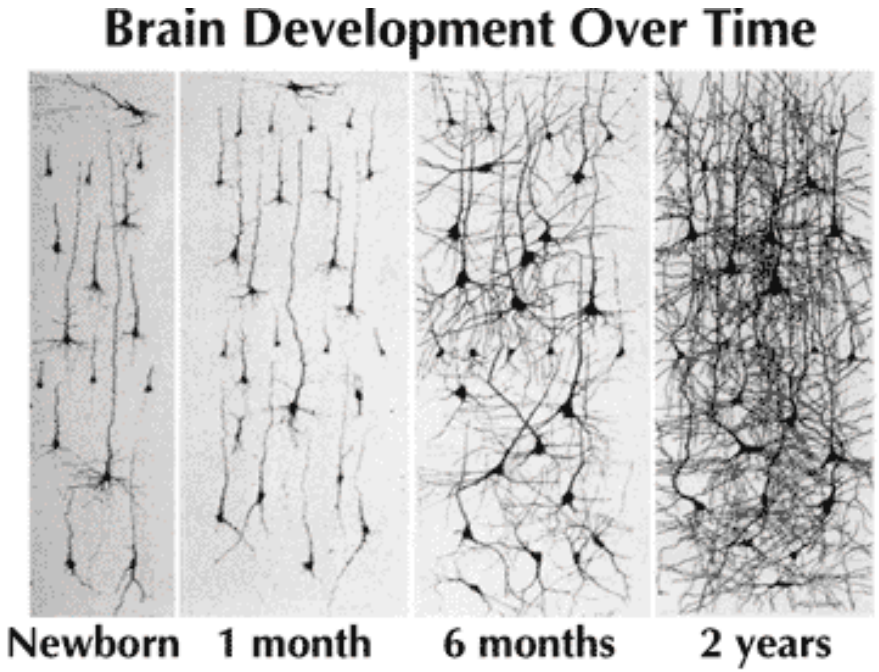
Significance of neurotoxicity for children's environmental health

Philippe Grandjean, MD, DMSc
(University of Southern Denmark and Harvard School of Public Health)

Susceptibility of the nervous system

- Designed to be uniquely sensitive to external stimuli, thereby likely also vulnerable to adverse stimuli

…in particular during development

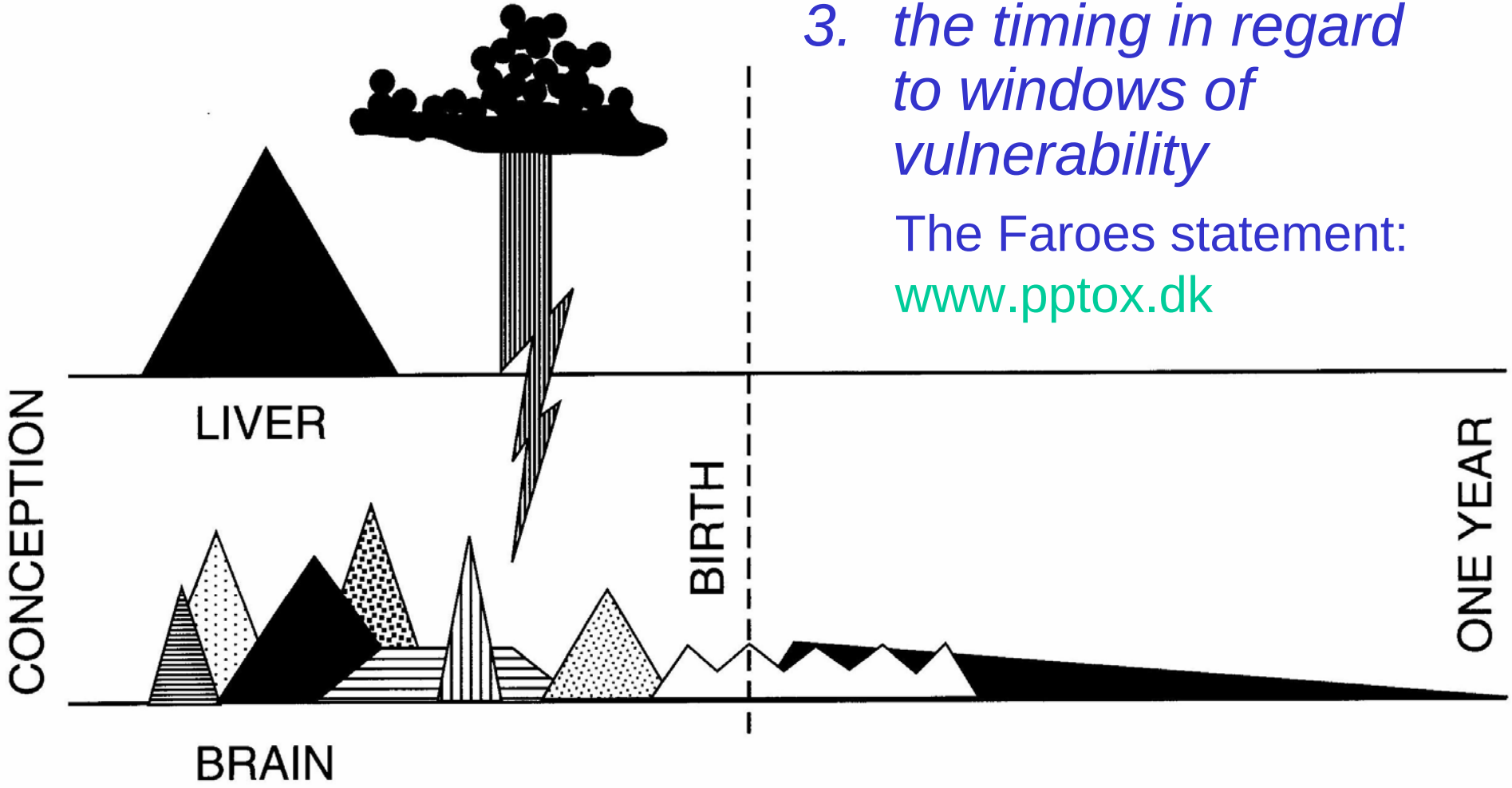


- Development involves multiple stages to be completed sequentially
- Optimal function depends on the integrity of the complete organ

Neurotoxic effects are determined by:

1. the neurotoxicant
2. the dose
3. *the timing in regard to windows of vulnerability*

The Faroes statement:
www.pptox.dk



Learning from Minamata:

…in every case the mother was healthy, and it was not until more than three months after birth that the symptoms were recognized

Shoji Kitamura (1959)

Focal

Widespread

Diffuse

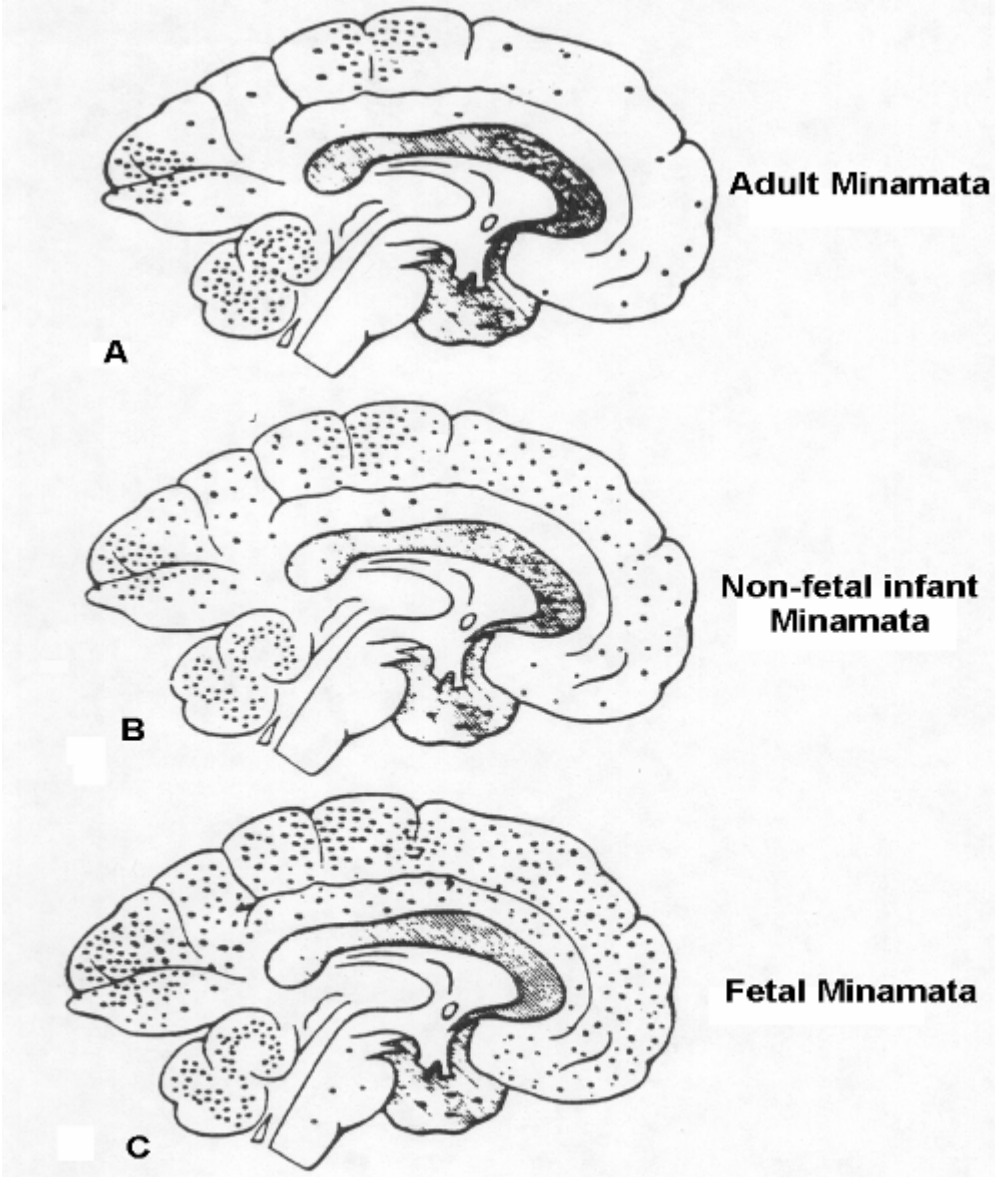


FIG 1: Comparison of the distribution of lesions among the adult (A), non-fetal infantile (B), and fetal infantile (C) Minamata disease. Takeuchi (67), with permission.

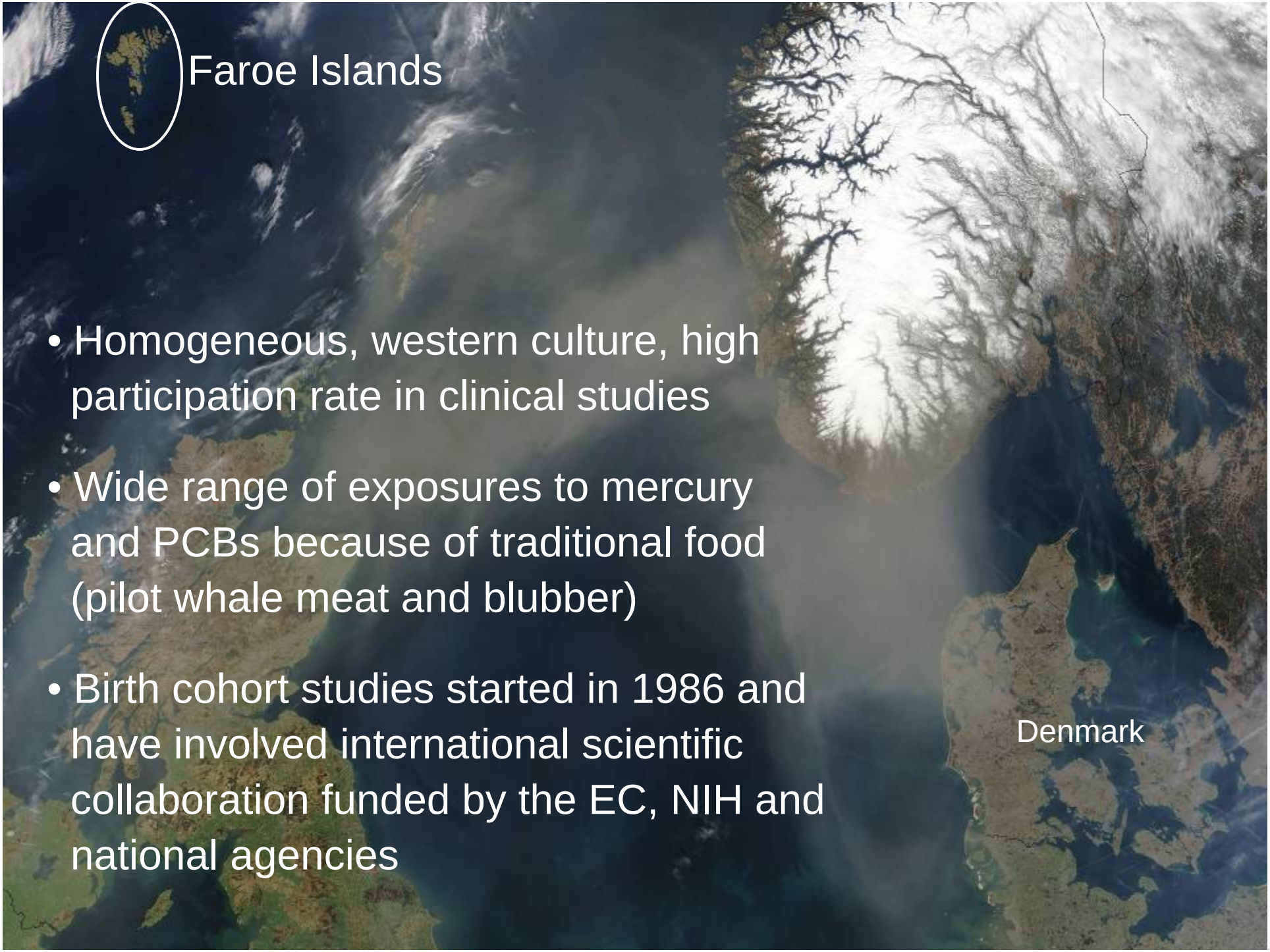
From: Choi, BH. Progress in Neurobiology, 32: 447-490, 1989.

Congenital Minamata disease
patient Shinobu Sakamoto
at the UN Environment Conference,
Stockholm, 1972

…and in 1992
with the
Danish
physician
she inspired

Challenges in assessing clinical manifestations of developmental toxicity

- Non-specific effects are sensitive to confounders
- Effects may depend on the exact time of exposure
- Effects may not be immediately apparent, because the organ system must mature to express relevant functions
- Influence of compensation / reversibility, reserve capacity, and unmasking



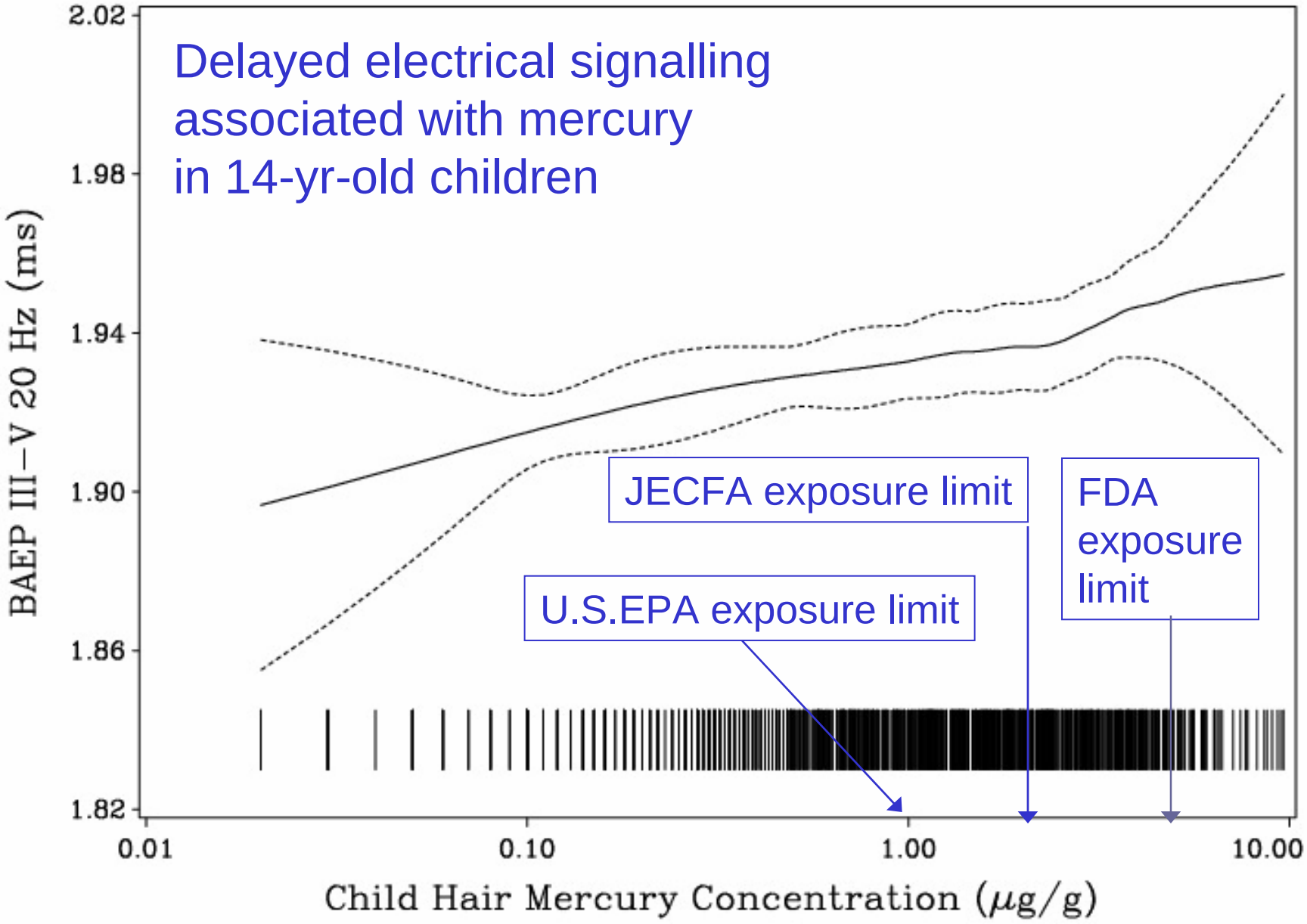
- Homogeneous, western culture, high participation rate in clinical studies
- Wide range of exposures to mercury and PCBs because of traditional food (pilot whale meat and blubber)
- Birth cohort studies started in 1986 and have involved international scientific collaboration funded by the EC, NIH and national agencies

Delay in development (months) at age 7 yrs for each doubling of the prenatal MeHg exposure

Motor (Finger tapping, preferred hand)	0.9
Attention (CPT-reaction time)	1.3
Visuospatial (Bender errors)	0.6
Language (Boston Naming)	1.6
Verbal memory (CVLT short delay)	2.0

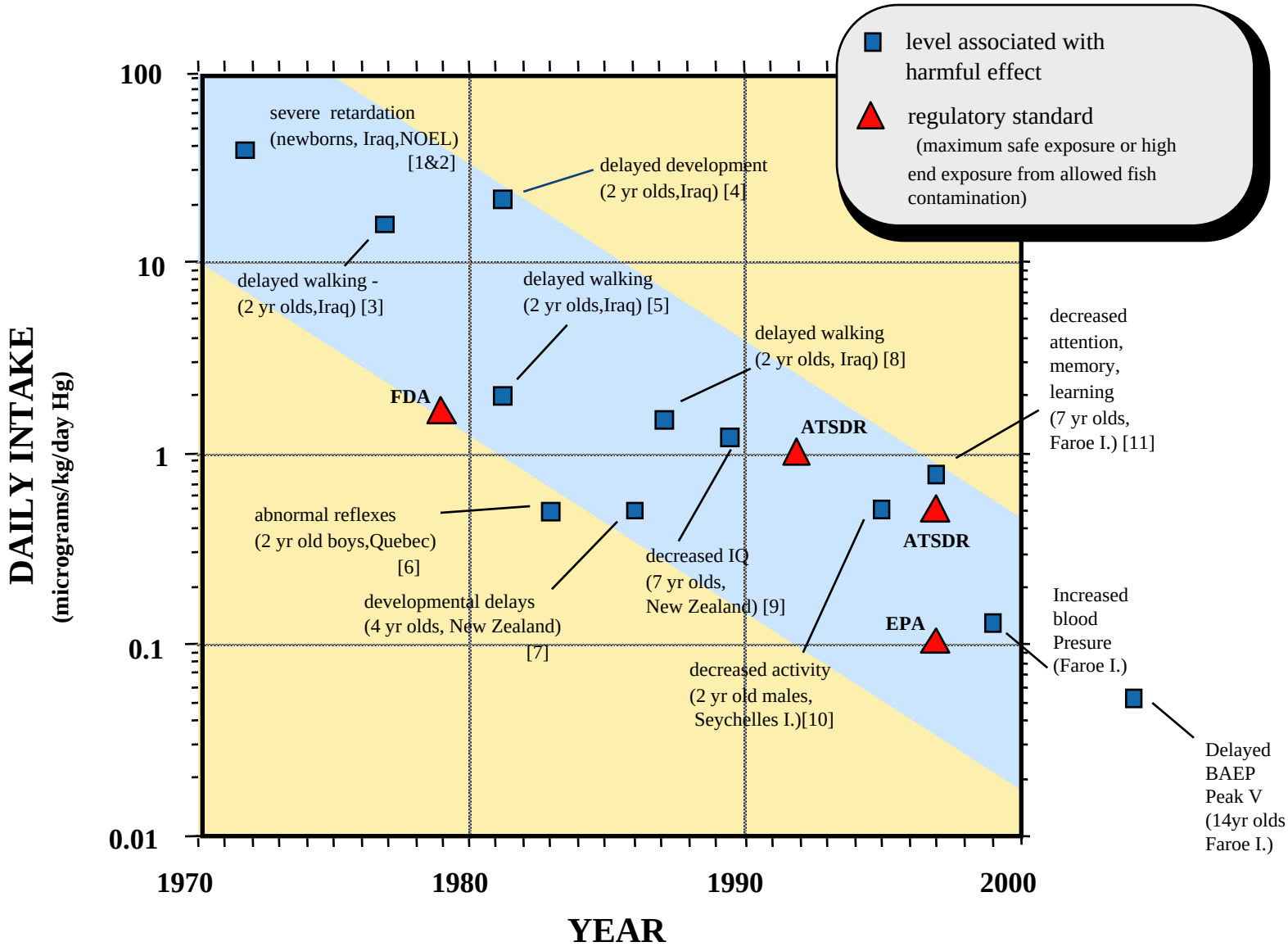
(Average effect ~10% of s.d. or ~~1.5 IQ points)

Methylmercury exposure was indicated by the mercury concentration in cord blood



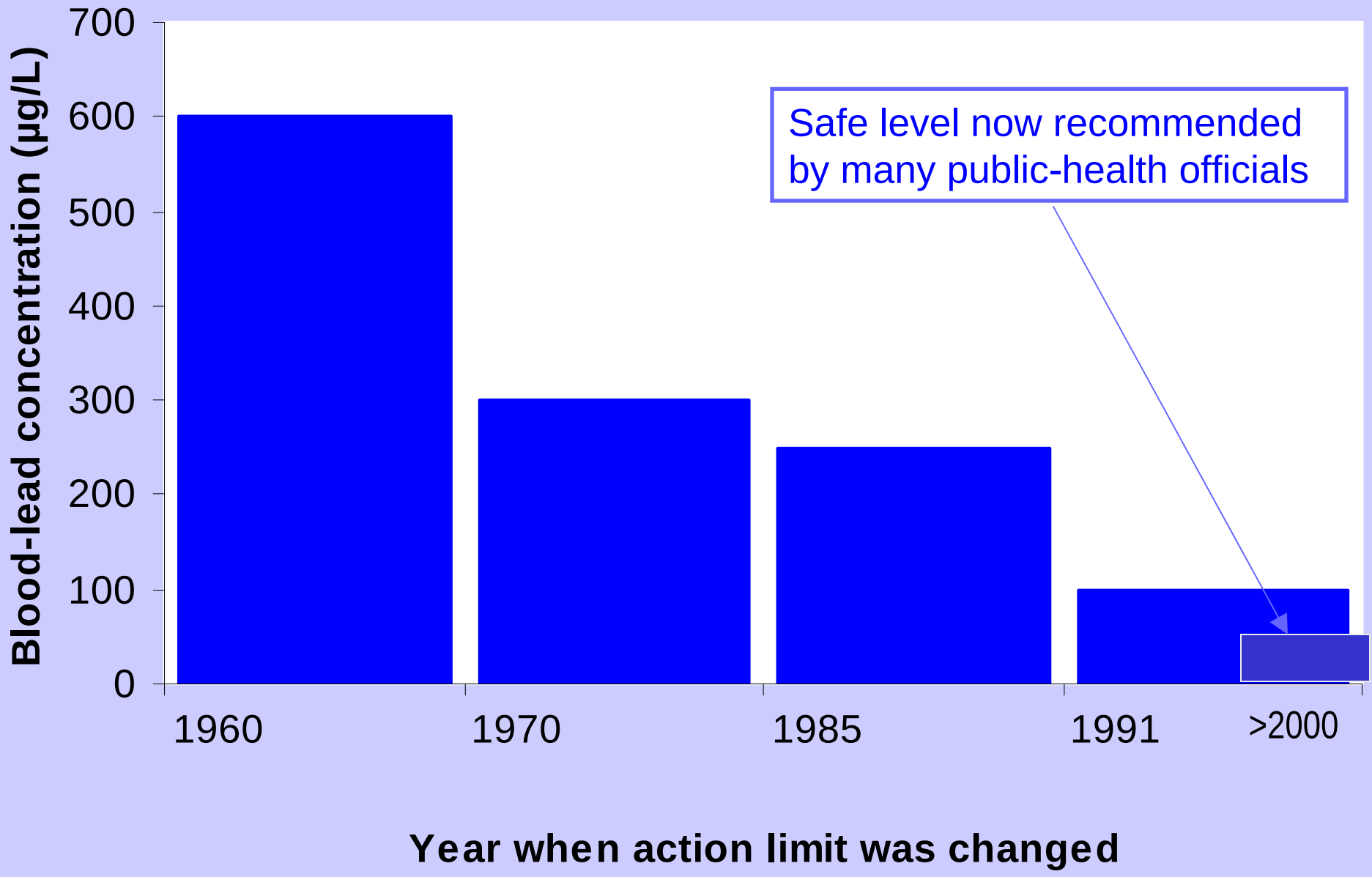
Murata et al., Journal of Pediatrics, February 2004

Declining threshold with time



From: In Harm's Way, 2002

Decreases in lead exposure limits show how slow reaction to science endangered a whole generation of children



REVIEW & OUTLOOK

The Mercury Scare

If you've read a newspaper lately, chances are you've seen an ad claiming that millions of women who eat tuna and other fish with mercury are poisoning their children. That sure sounds bad. Only problem is, it's a whole lot abalone.

About the only thing the ads do prove is that trusting "environmentalists" in a political debate is harmful to your health and the national well being. Their fury this time is directed at Bush Administration plans to *reduce* mercury emissions from utilities 70% by 2018. They want the regulation to go even further—never mind that the Clinton Administration did nothing to reduce emissions—and their strat-

Meet the new Chicken-Littles of the sea.

The super-greens base their misinformation on a problematic study of Faroe Island children. The Faroe mothers also consumed enormous amounts of mercury, though from seafood (such as whale) most Americans don't eat. When their children were given 17 neuropsychological tests, some scored slightly below-average on three. Scientists have since disputed whether there was ever a statistical correlation and note that, even if there was, it's impossible to know it was caused by mercury (the mothers were consuming high levels of such other toxins as PCBs and DDT). Either way, the kids who scored marginally below peers on a few

Specific concerns that a mercury effect may be overestimated

- Association with other neurotoxic seafood toxicant(s)
- Other residual confounding (residence, transportation)
- Failure to adjust for multiple comparisons

Subsequent studies failed to demonstrate overestimation

Reasons that a mercury effect may be *under*estimated

- Association with beneficial seafood nutrient(s)
- Other residual confounding (e.g., toxicants in non-seafood)
- Failure to include multiple outcomes in joint analyses
- Exposure misclassification

How many human neurotoxicants?

- NLM Hazardous Substances Data Bank
- Industrial chemicals only (no biological toxins or drugs)
- Evidence from human poisoning cases or epidemiological studies
- Published in peer-reviewed literature
- 201 human neurotoxicants identified

(Grandjean & Landrigan, The Lancet, 2006)

Types of neurotoxic chemicals (N = 201)

- Pesticides (N = 90)
- Metals and inorganics (N = 25)
- Solvents (N = 43)
- Other industrial chemicals (N = 43)

~50% are HPV chemicals

How many of these neurotoxicants cause *developmental* effects?

- Neurotoxic substances identified in HSDB with synonyms and CAS numbers
- PubMed, TOXNET, and TOXLINE
- Primary search terms: “Prenatal Exposure Delayed Effects”[MeSH] and “Neurotoxicity Syndromes”[MeSH]
- Limiters “All Child: 0-18 years, most recent 10 Years, English, Human”

Search results: Documented developmental neurotoxicants

- **Lead**
- **Methylmercury**
- **PCBs**
- Arsenic
- Toluene
- *Manganese (?)*
- *OP pesticides (?)*

Grandjean & Landrigan, The Lancet, 2006

#7 IN A SERIES

She's the test subject for thousands of toxic chemicals. Why?

Industry falsely discredits current animal testing.

In previous ads in this series, we physicians and scientists have presented a body of scientific evidence linking toxic chemicals to a wide range of health problems in humans, from learning disabilities and brain injury in children to certain cancers in both children and adults.

We have emphasized that these health problems are preventable. We have stressed that thorough pre-market testing of chemicals is a critical component of disease prevention.

There is a well-established and respected FDA approval process that a company must follow before it can market a chemical as a medicine. That process includes testing at various doses on animals. Only if the medicine is shown to be safe for animals is it approved for tests on humans.

America's pharmaceutical industry acknowledges, indeed embraces, these animal testing regimes for medicines. At the same time, however, certain segments of the chemical industry are making false claims about similar pre-market testing for chemicals other than medications.

They claim that testing has little value "because at a high enough dose all chemicals cause cancer." That's not true. The National Cancer Institute and the National Toxicology Program find that only 5-10% of commercial chemicals cause cancer at any dose. The industry also claims that animal testing bears little connection to human risk. That's not true either – the Human Genome Project has shown that laboratory animals and humans have very great genetic similarity and share very similar endocrine, immune and nervous systems.

The industry claims that testing has little value unless it involves tens of thousands of animals at low dose levels. Not true – the National Toxicology Program has developed sophisticated technologies for testing chemicals at a range of doses in small numbers of animals and then predicting human risk.

Inaccurate and false as all these claims are, they have found a certain audience in government and the press. These claims have paralyzed the regulatory process. They are preventing whole classes of chemicals from being properly tested. And that puts everybody's health at risk, especially the health of our children.

What We Know

– Every known human carcinogen causes cancer in animals.

– Every chemical known to cause brain damage in humans causes damage to the brain and nervous system in animals.

– Every chemical known to interfere with reproductive function in humans interferes with reproduction in animals.

– Almost every known cause of birth defects in humans also causes birth defects in animals.

– And, with few exceptions, when toxic chemicals harm animals, they almost always cause similar harm in humans.

What We Can Do

Parents should limit their children's exposure to synthetic chemicals. They should minimize use of pesticides outside and inside the house. They should choose safe cleaning products. Wherever possible, they should purchase organically produced food. Fish from contaminated waters should be avoided. There are more suggestions at www.childenvironment.org.

We must do more. The evidence is incontrovertible. We must move quickly to phase out those toxic chemicals that are known to pose a danger to human health. And we must institute a system of regulation that tests new synthetic chemicals and proves them safe before they are allowed to be sold, before our children are exposed. Isn't that the system you thought we already had?

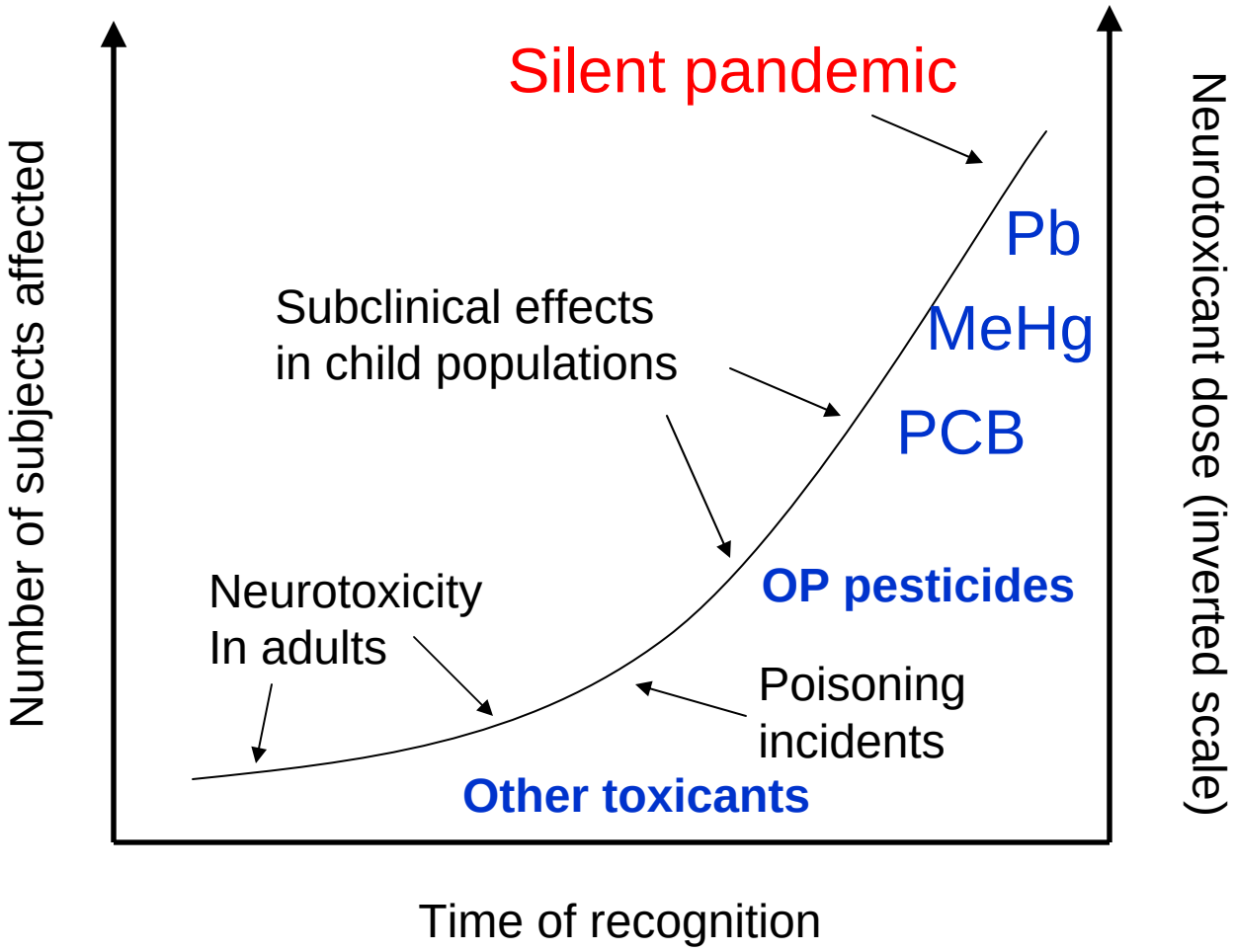
MSSM

MOUNT SINAI SCHOOL OF MEDICINE

Center for Children's Health and the Environment

Box 1043, One Gustave Levy Place, New York, NY 10029 • **www.childenvironment.org**

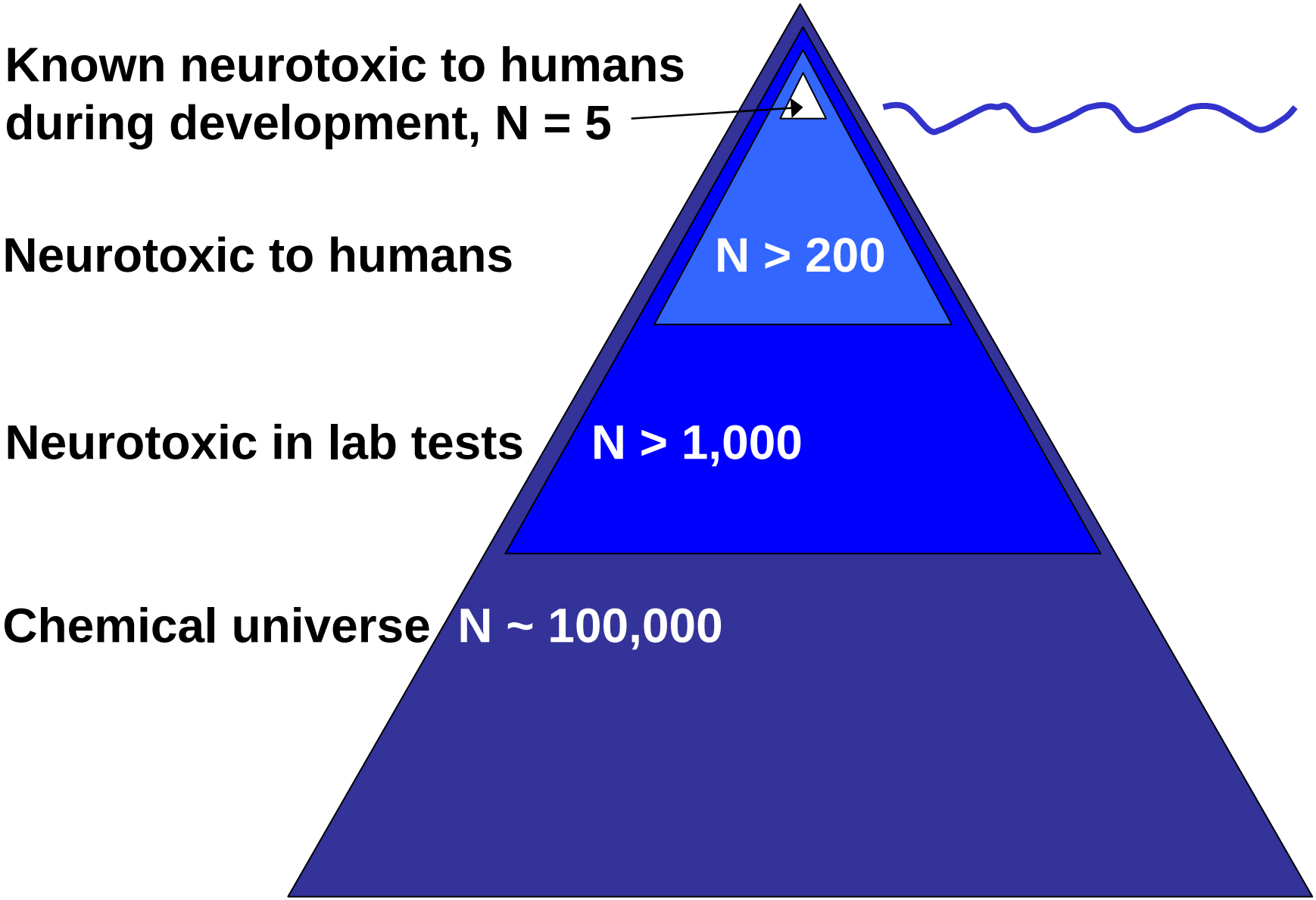
Emerging paradigm: Time course of recognition (of developmental neurotoxicants)



Grandjean & Landrigan, The Lancet, 2006

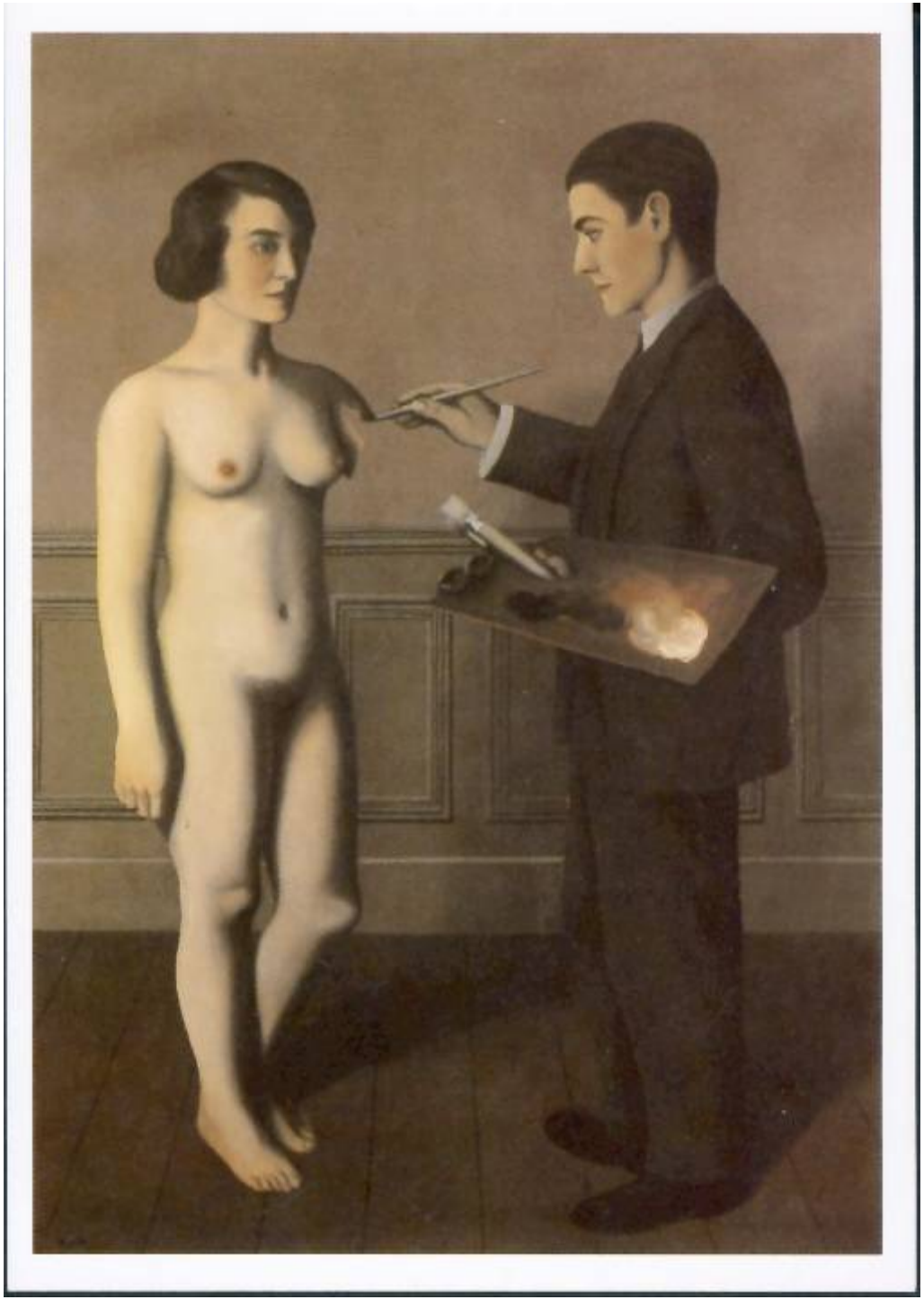
"I've learned a lot in sixty-three years, But, unfortunately, almost all of it is about aluminum."

Current status of the documentation



In interpreting research results, we must recognise that a phenomenon may exist, even if we cannot see it:

What could be known, given our study opportunities and methodologies?



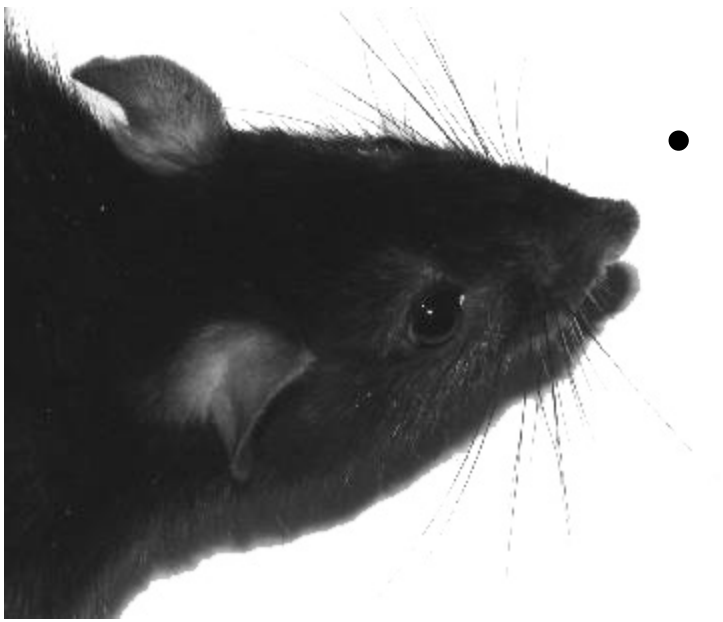
René Magritte

Public health significance of developmental neurotoxicants

- Loss of 1 IQ point:

  Economic value: $8,350 (U.S. EPA, 1998)
- Developmental neurological disabilities (including dyslexia, mental retardation, ADHD, autism spectrum disorders)
  - Affect one of out six children - possibly increasing in incidence
- Susceptibility to degenerative CNS disease or heart disease in later life?

Experimental identification of developmental neurotoxicants



- Cell-based systems for screening
- U.S. EPA protocol (rarely used)
- REACH: rodent toxicity includes brain weight, gross morphology
- OECD effort to harmonize protocols initiated in 1996
  – a revised protocol is currently under final review

Plan of action

- Identify human neurotoxicants
- Document human exposures
- Record long-term consequences of developmental neurotoxicity
- Screen chemicals for neurotoxicity

Target prevention to protect brains

Only one chance to develop a brain