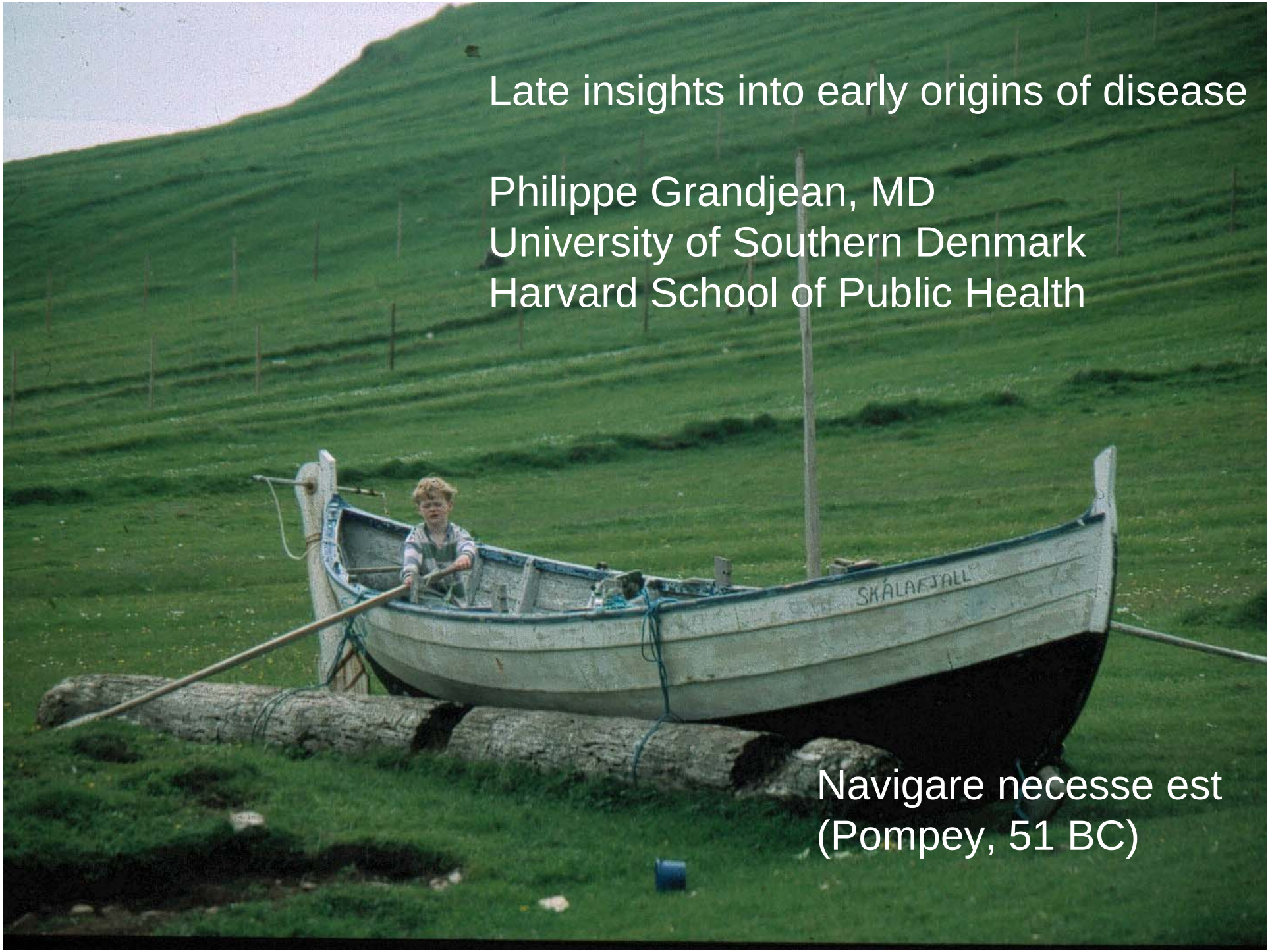


Late insights into early origins of disease

Philippe Grandjean, MD
University of Southern Denmark
Harvard School of Public Health

Navigare necesse est
(Pompey, 51 BC)

Lead: Early stages in the recognition of programming effects

1943	Byers and Lord report lasting brain damage in lead-poisoned children
1965	Patterson reports that current lead exposures are 100-fold above ‘natural’ levels
1979	Needleman and colleagues report dose-related mental deficits in children with previous lead exposure at ‘background’ levels

The only form of lead poisoning that is lethal - according to the automobile and petroleum industries (Denmark, about 1975)

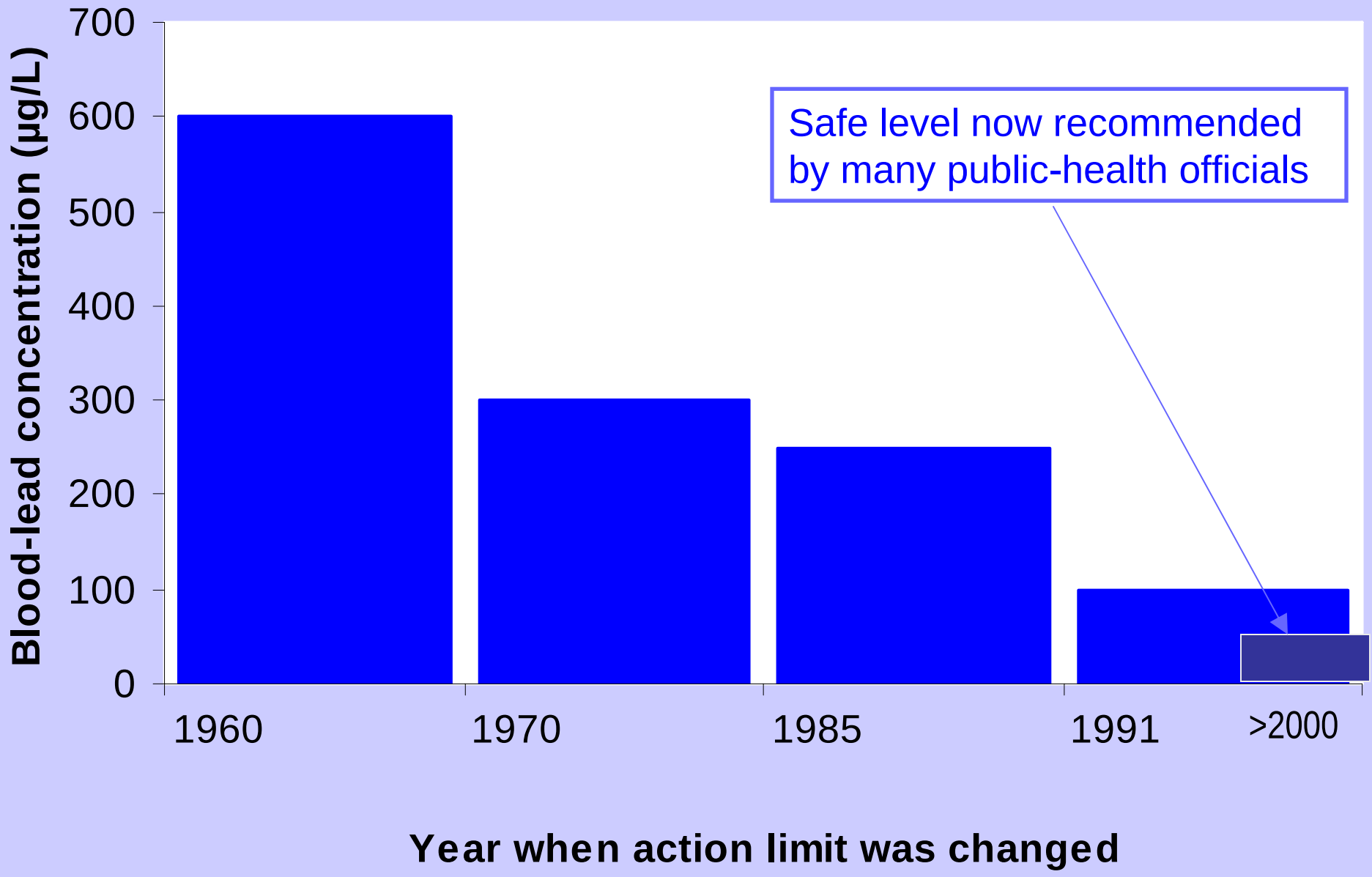
The 25-year perspective:

Professor of Environmental Medicine,1982

In hindsight, we underestimated developmental lead neurotoxicity - quotation from Danish study:

> ”The results obtained in this study ***do not suggest*** that the lead exposures caused any ***severe*** intellectual reduction, although in this ”normal” range, the high-lead children ***showed*** lower functioning, as compared to the low-lead group. Thus, even in a minimally-polluted area, ***some*** children ***appear to be at risk*** for neuropsychological deficits due to ***long-term*** lead exposure.”

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



Methylmercury: Early stages in the recognition of programming effects

1952	Developmental neurotoxicity in two Swedish infants
1963/68	Formal recognition of the Minamata disease causation
1972	Rodent experiments show delayed developmental neurotoxicity
1986	Adverse effects observed in children from methylmercury in maternal fish intake during pregnancy

The message on developmental methylmercury neurotoxicity was challenged

- Science first rejected our manuscript (it was later published in Neurotoxicol Teratol 1997; 19: 417-28)
- Science instead offered to present our unpublished results in their News section (which we refused)

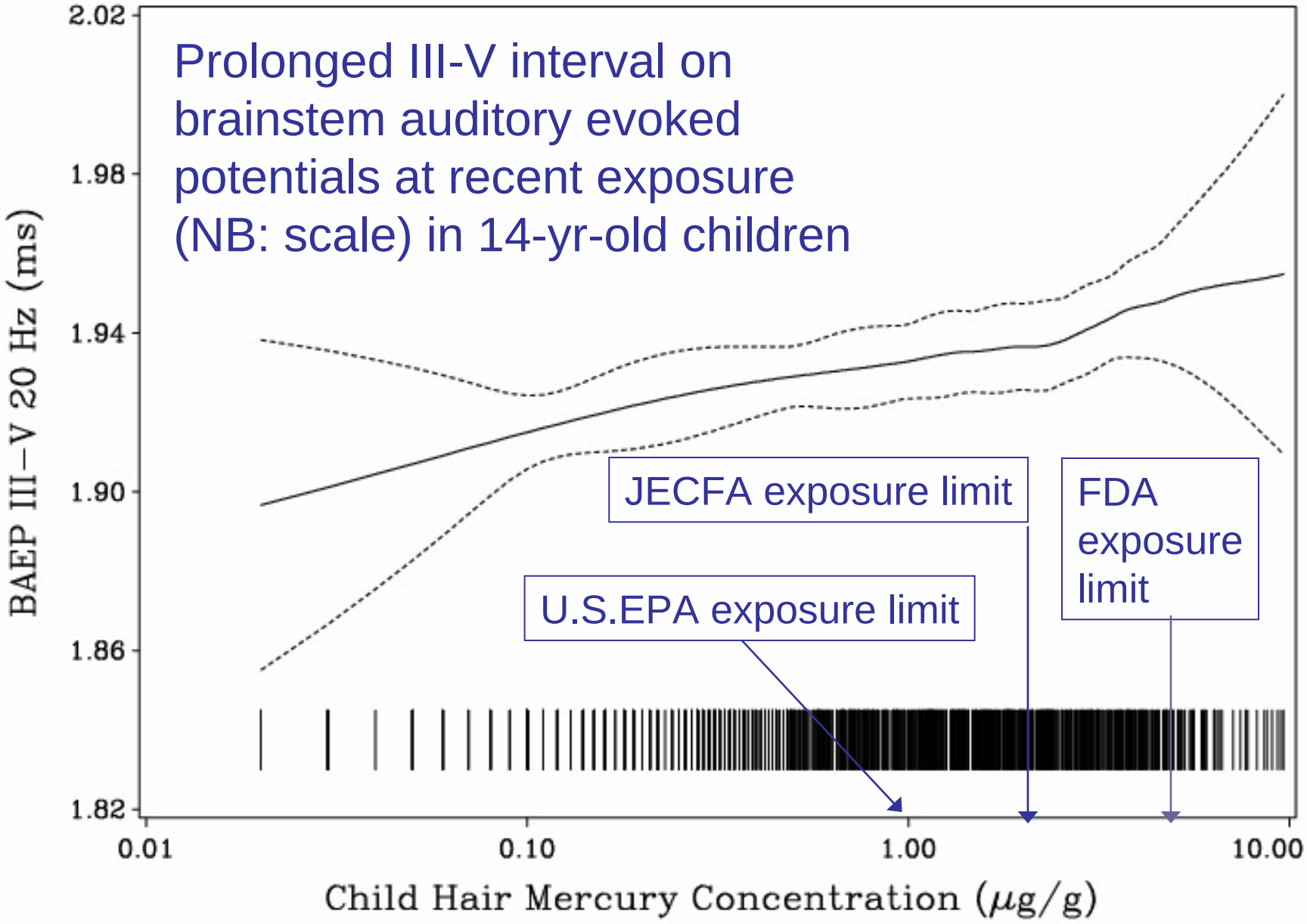
Science 12 December 1997:
Vol. 278. no. 5345, pp. 1904 - 1905
DOI: 10.1126/science.278.5345.1904

POLICY FORUM

Balancing Fish Consumption Benefits with Mercury Exposure

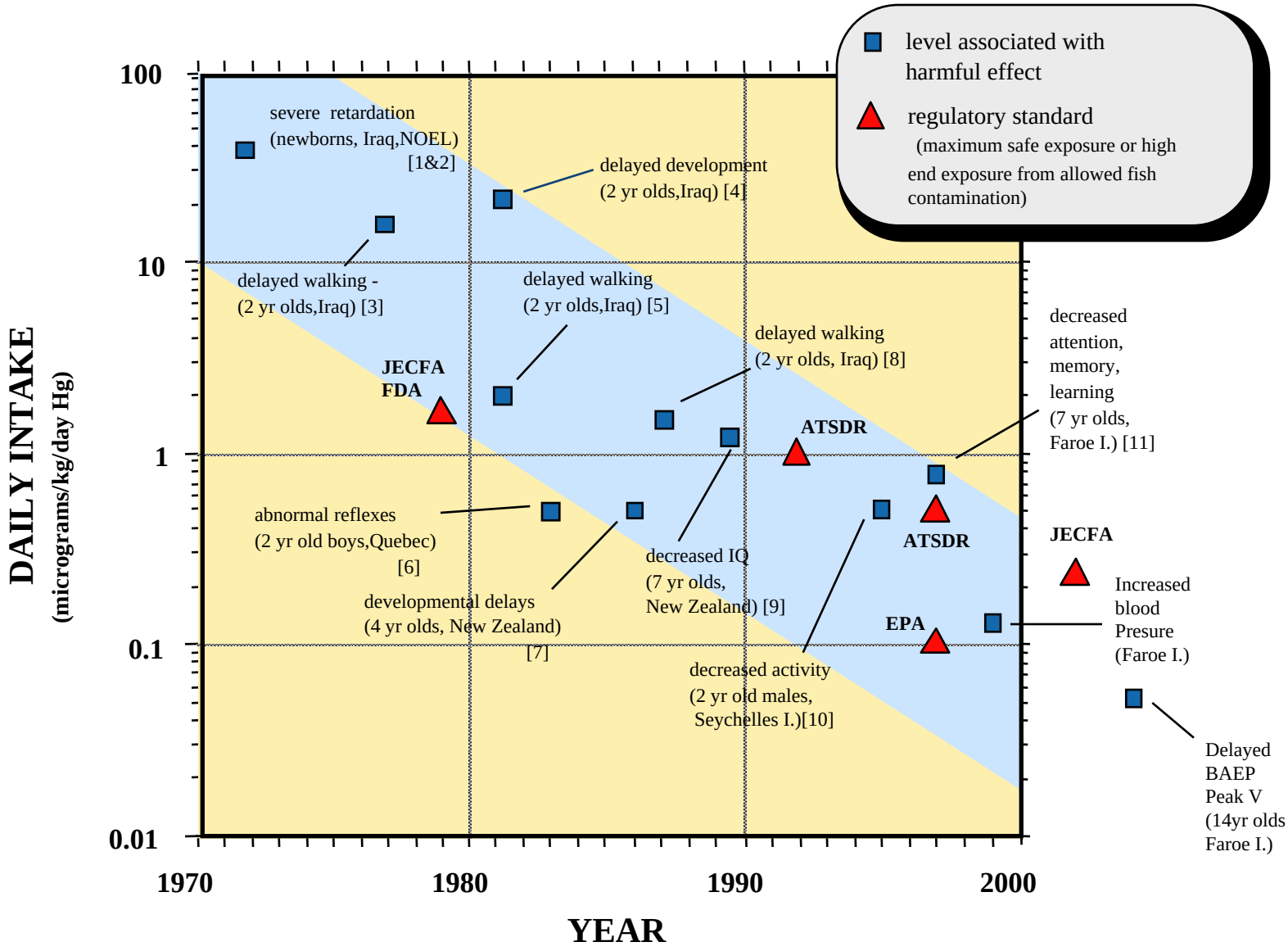
Grace M. Egeland and John P. Middaugh

P. Grandjean, P. Weihe, R. F. White, *Neurotoxicology* 20, 1 (1997).



Murata et al., Journal of Pediatrics, February 2004

Thresholds decline due to better science



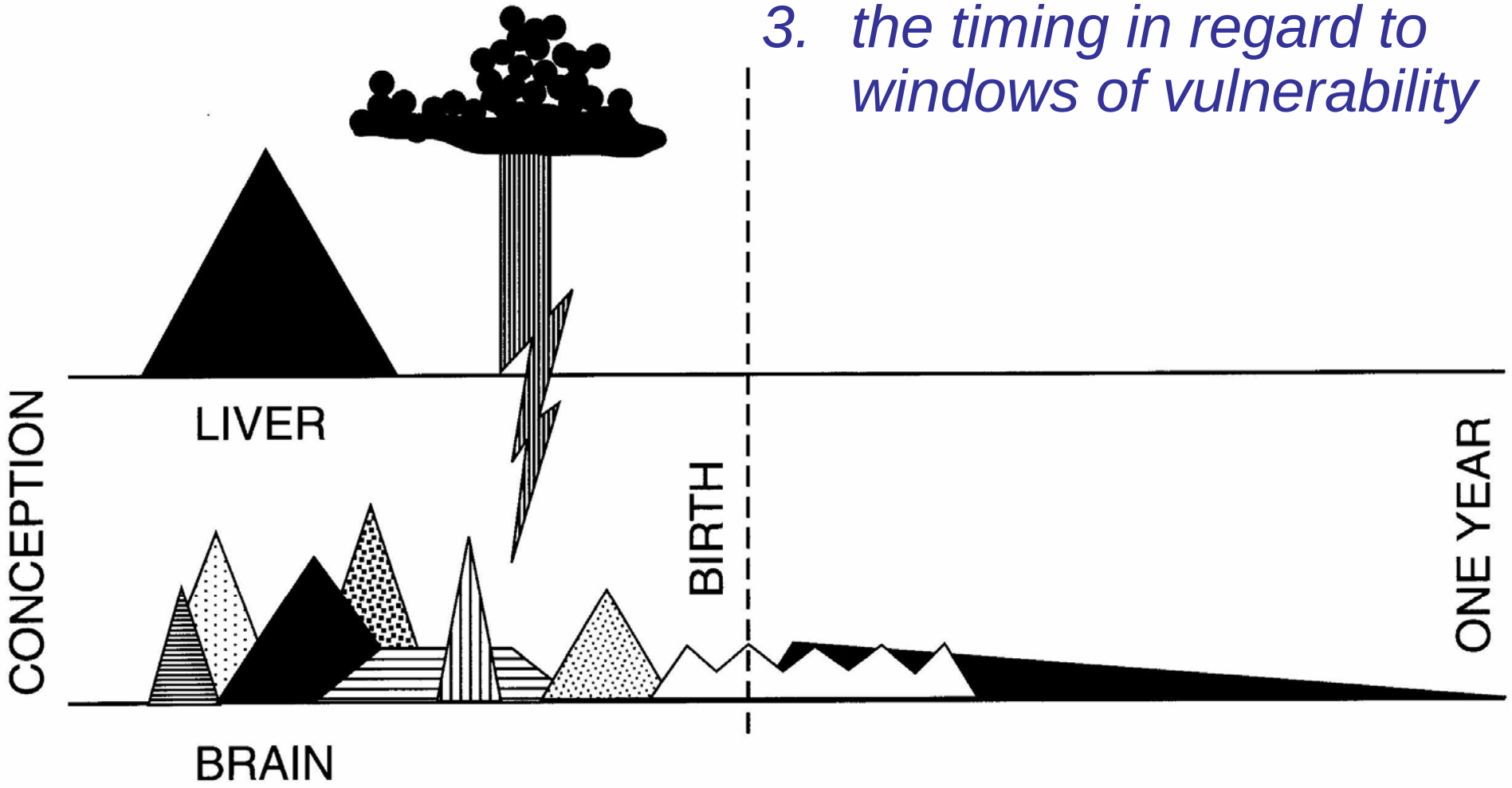
Updated from: In Harm's Way, 2002

Other risk factors: Early stages in the recognition of programming effects

1968	Fetal alcohol syndrome described in case series
1971	Clear-cell carcinoma discovered in girls whose mothers used diethylstilbestrol in pregnancy
1973	Permanent damage in survivors of infancy arsenic poisoning from milk powder
1977	Forsdahl reports that infant mortality in a birth cohort is linked to adult mortality
1985	The Jacobsons report cognitive deficits in children exposed to PCB from Great Lakes
1987	Skakkebæk reports carcinoma in situ in fetal testicular gonocytes

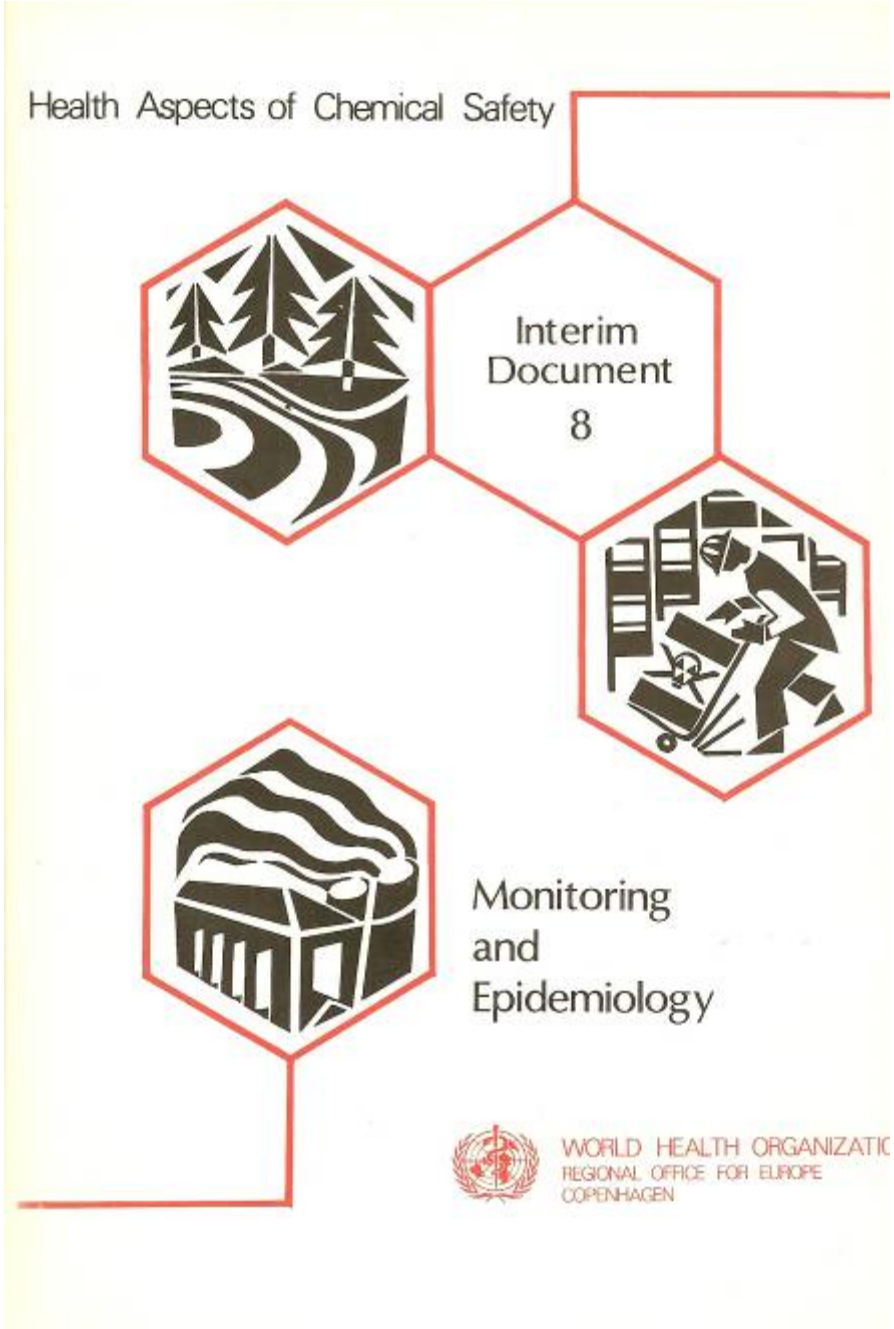
Toxic effects are determined by:

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



WHO-EURO initiative to conduct ’Integrated monitoring of exposure to selected chemicals and their health effects’ (1982)

- Lead
- Mercury
- Pesticides
- Others…

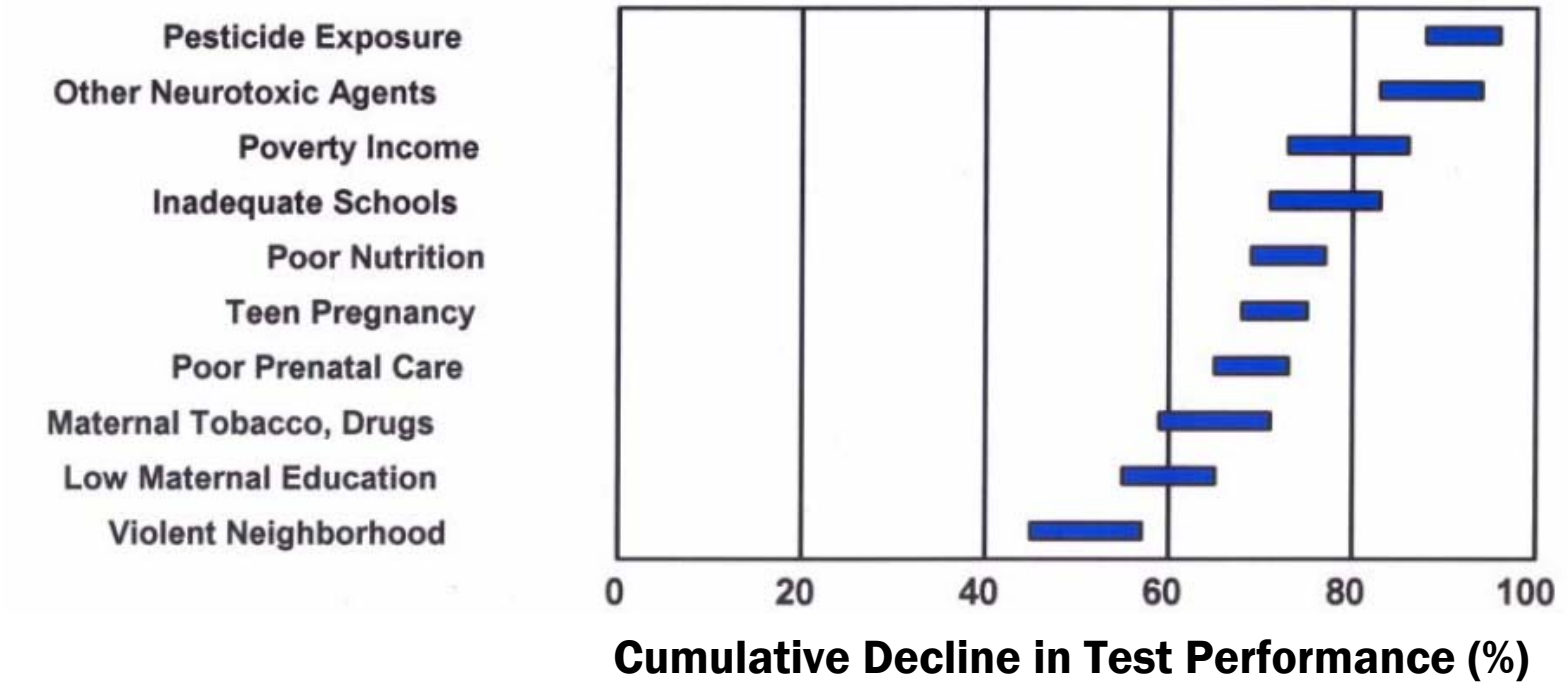


Challenges in assessing clinical manifestations of developmental toxicity

- 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

Challenges from multifactorial causation

Each individual risk factor may not induce any serious adverse effect, but a combination of risk factors may.
Because of associations between risk factors, and imprecision in the assessment of each exposure, the effects of individual hazards will be underestimated.



From Weiss et al., 2001

Challenges from inherent biases toward the null hypothesis*

- Low statistical power
- Overzealous use of 5 % probability level
- Use of 20% probability level to minimize risk of type II error
- Imprecise exposure data
- No adjustment for negative confounding
- Short and incomplete follow-up
- …

*From a list developed with David Gee (EEA) and Collegium Ramazzini colleagues

Challenges from the desire for less uncertainty and more research

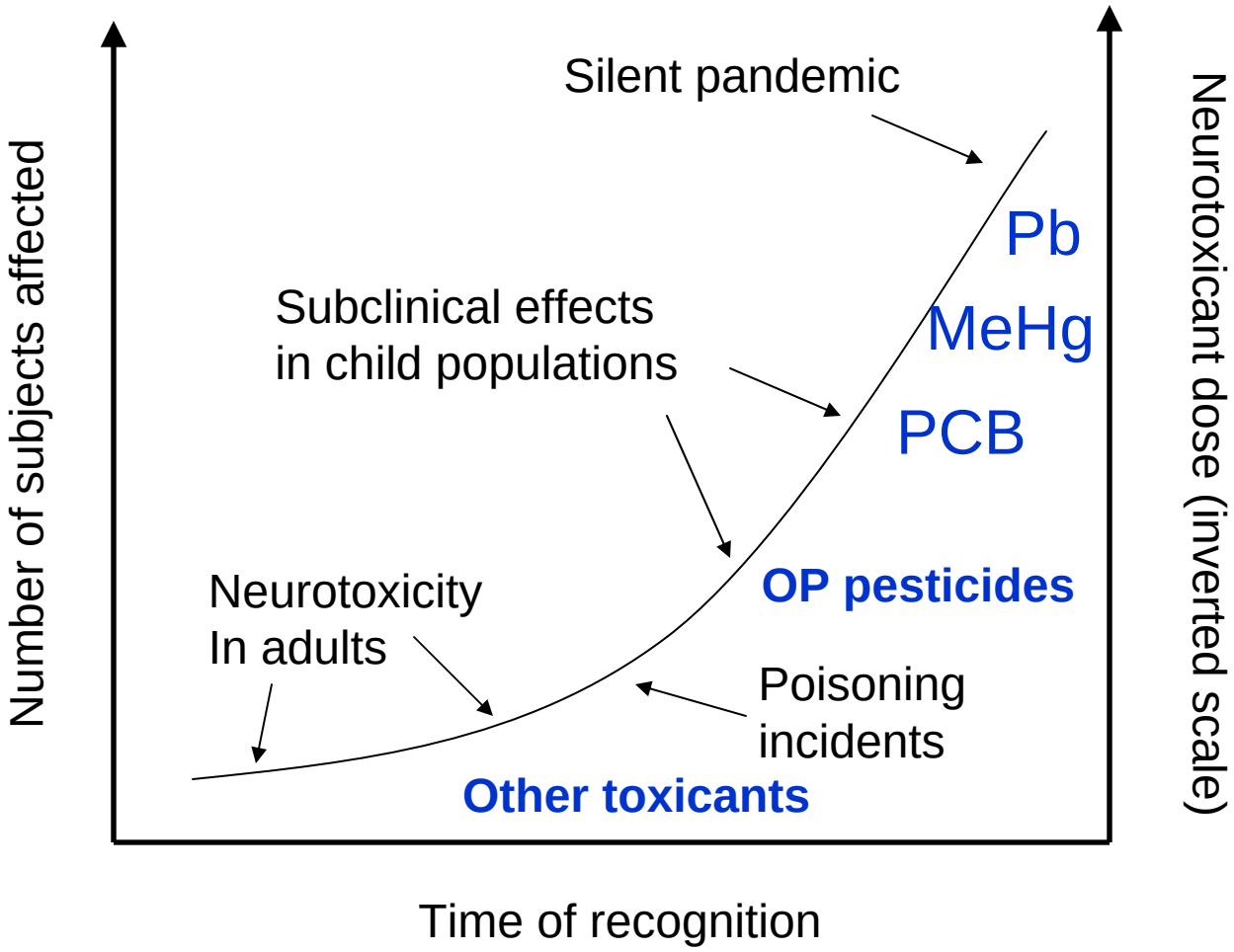
- “The foetus *may be* more susceptible to methylmercury toxicity than the adult…” (JECFA, 1978)
- “Significant uncertainties remain because of issues related to exposure, neurobehavioral endpoints, confounders and statistics, and design…”

  (NIEHS / White House workshop, 1998)

Challenges from the desire for replication in science – thereby creating inertia

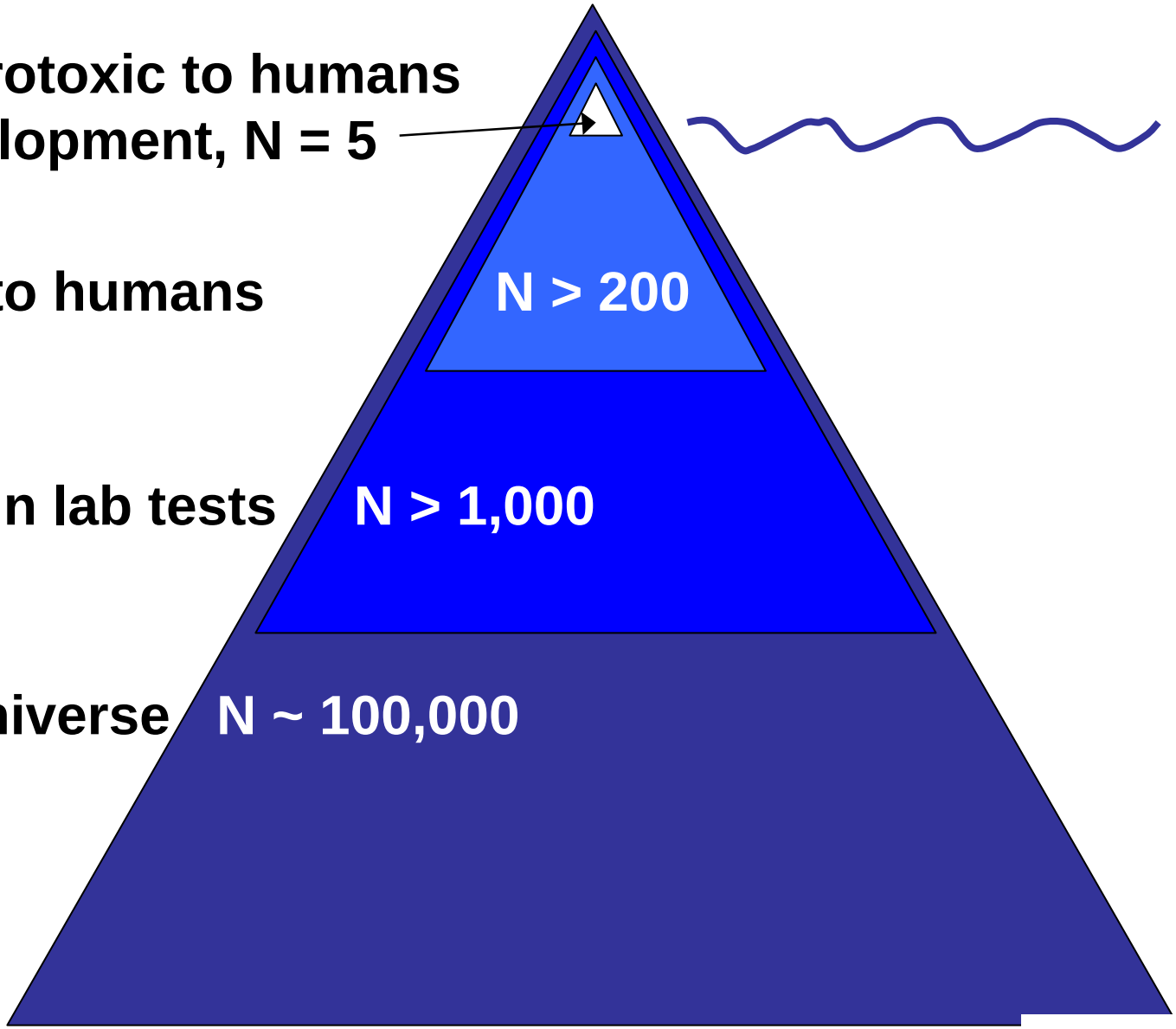
- The majority of published papers in environmental health journals deals with a limited, rather stable list of pollutants
- PubMed lists over 15,000 scientific publications on lead
- Other toxicants are very poorly studied in comparison

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



Grandjean & Landrigan, The Lancet, 2006

Number of environmental toxicants

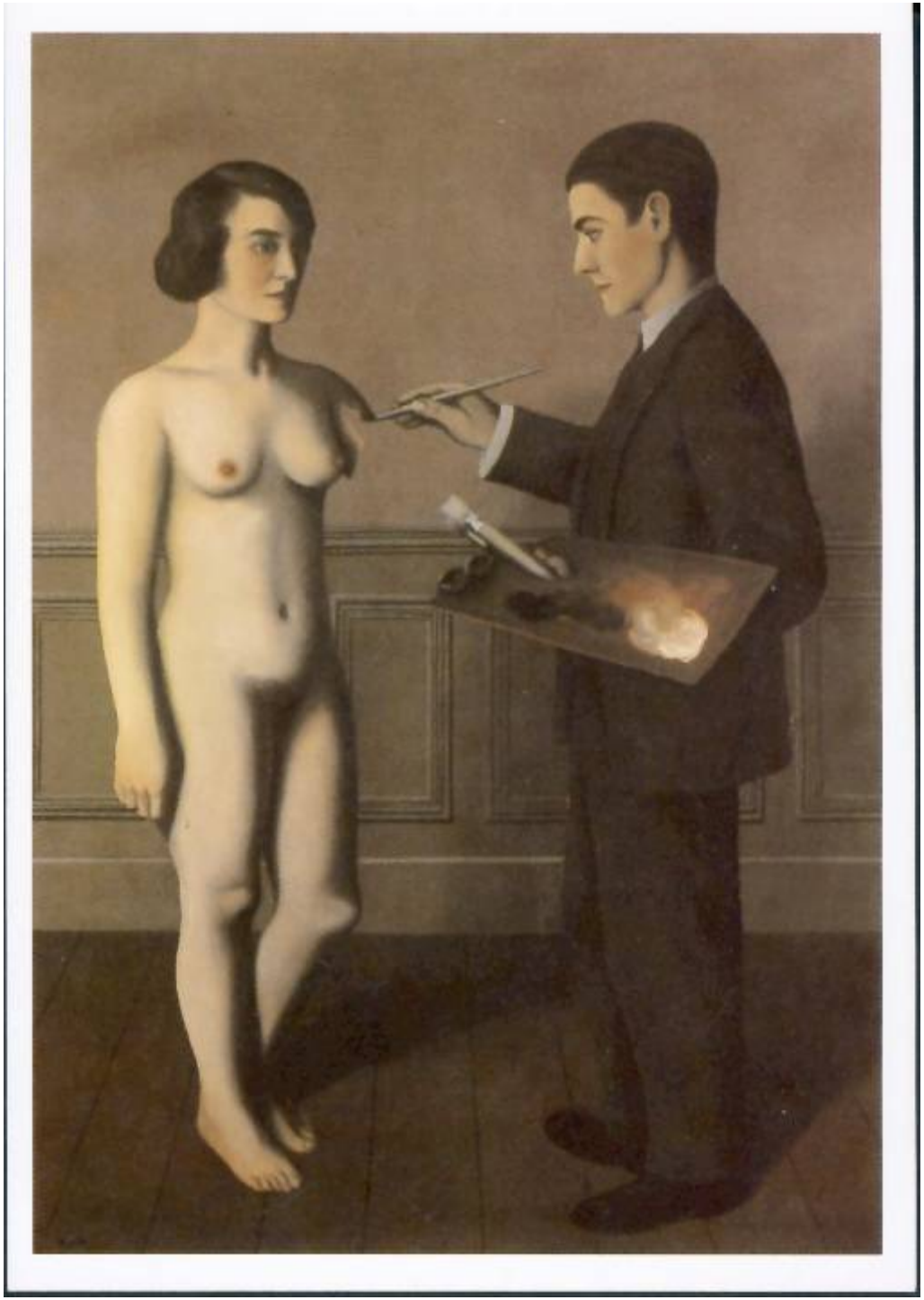


Late lessons on the developmental origin of human health and disease

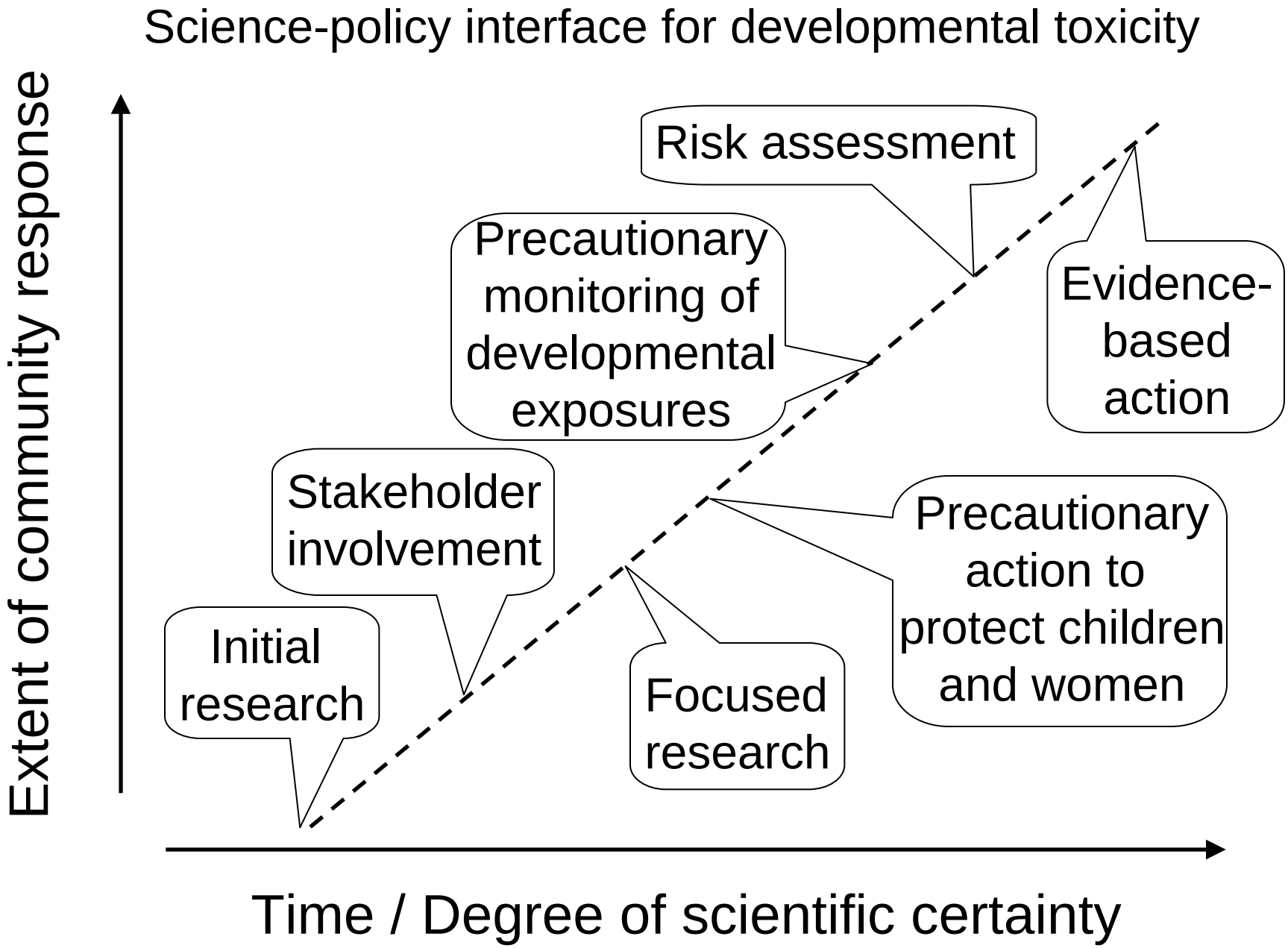
- Significance of early case reports was overlooked
- Human health implications of experimental evidence were only slowly appreciated
- Conclusions emphasised the *p* value, while the upper confidence limit was ignored
- Absent or uncertain evidence was thought to support the null hypothesis
- Environmental risks considered one by one

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


Science-policy interface for developmental toxicity
Extent of community response
Risk assessment
Precautionary monitoring of developmental exposures
Evidence-based action
Stakeholder involvement
Precautionary action to protect children and women
Initial research
Focused research
Time / Degree of scientific certainty

The 25-year delayed message:

- Expand research to understand better the developmental origin of human health, organ function, and disease

- Include developmental exposure in standard testing of chemicals

- Emphasise life-time exposures in epidemiological studies

- Aim at protecting the most vulnerable human populations