Newest research findings on mercury's health effects

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Historical perspective

Year	Event
1866	First published record of fatal occupational poisoning
1952	First report on developmental neurotoxicity in two infants
1963	Recognition of methylmercury as cause of Minamata disease
1967	Demonstration of mercury methylation in sediments
1972	Experimental demonstration of delayed developmental neurotoxicity
1978	JECFA exposure limit of 3.3 µg/kg per week (based on adults)
1986	First report from New Zealand prospective study
1997	First report on Faroes prospective study
1998	White House workshop identifies uncertainties in evidence
2000	National Research Council supports EPA limit of 0.1 µg/kg per day
2003	JECFA exposure limit of 1.6 µg/kg per week
2004	EFSA recommends that exposures be ‘minimised’
2005	UNEP global program and EU decision to ban mercury exports

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)

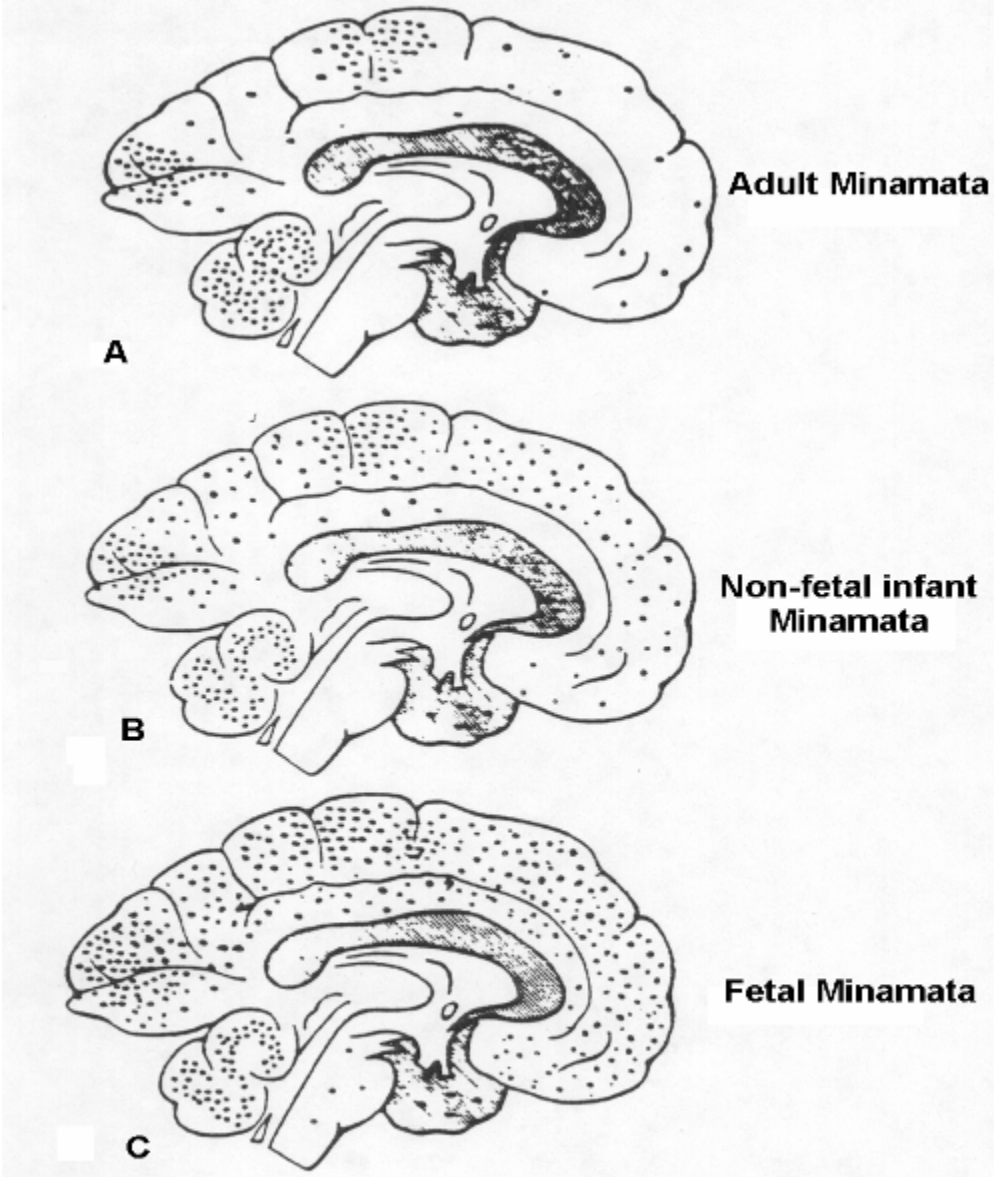


FIG 1: Comparison of the distribution of lesions among the adult (A), non-fetal infantile (B), and fetal infantile (C) Minamata disease. Takeuchi (67), with permission.

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

Poisoning at high doses causes focal damage

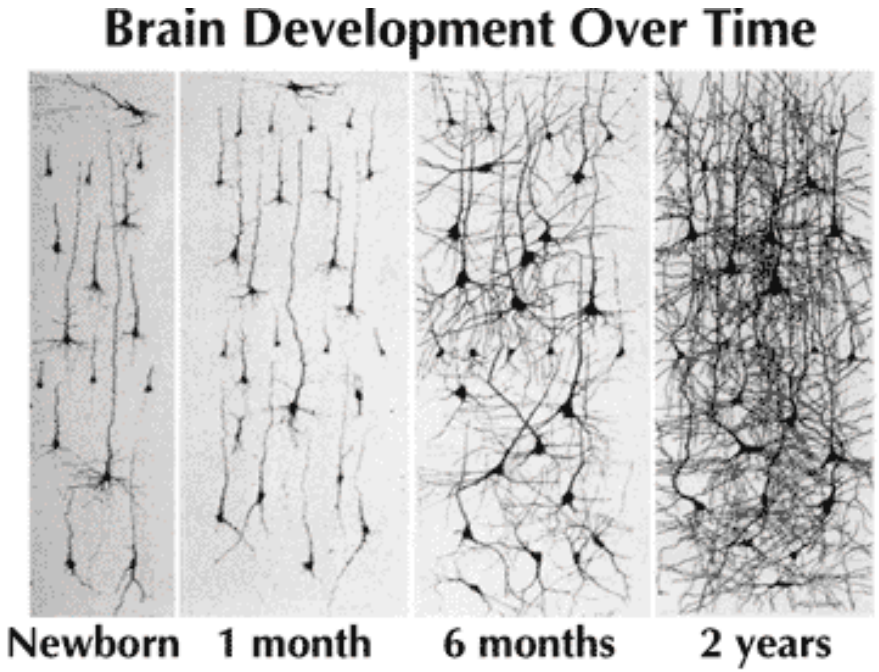
Poisoning at lower doses causes more widespread damage

Poisoning at low doses (the mother is healthy) causes diffuse damage

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
- Not protected by a blood-brain barrier
- Optimal function depends on the integrity of the complete organ

Faroe Islands

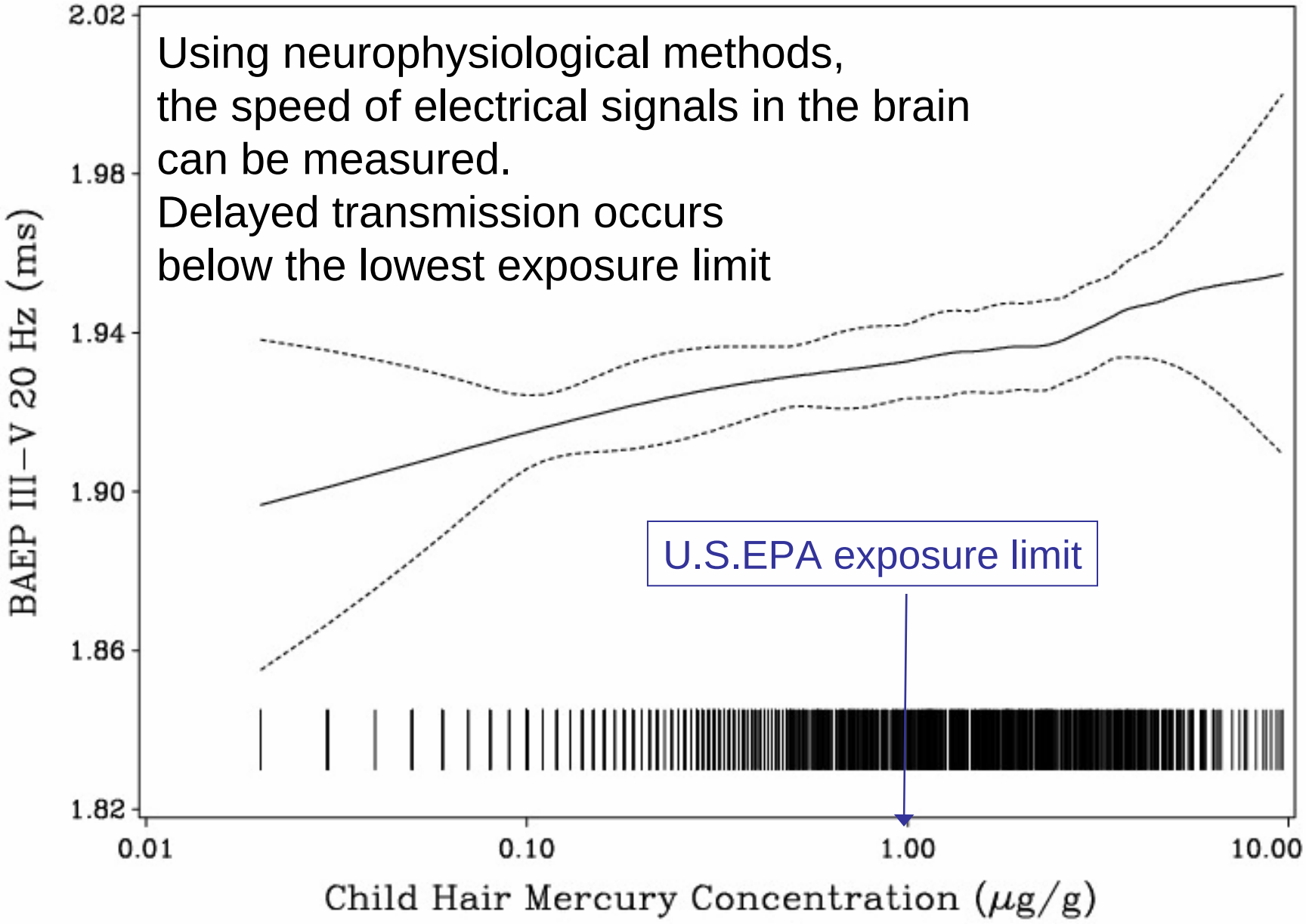
- Homogeneous, western culture
- Scandinavian-type health care and social security
- Traditional food includes pilot whale meat (MeHg) and blubber (POPs)
- Individual reliance on traditional foods varies, depends on seasonal availability, and is weakly associated with confounders

Denmark

Neuropsychological tests are used to assess mercury-linked delays in development.
In Faroese children at age 7 years, each doubling of prenatal exposure corresponds to:

Motor function	0.9 month delay
Attention	1.3 -
Visuospatial function	0.6 -
Language	1.6 -
Verbal memory	2.0 -

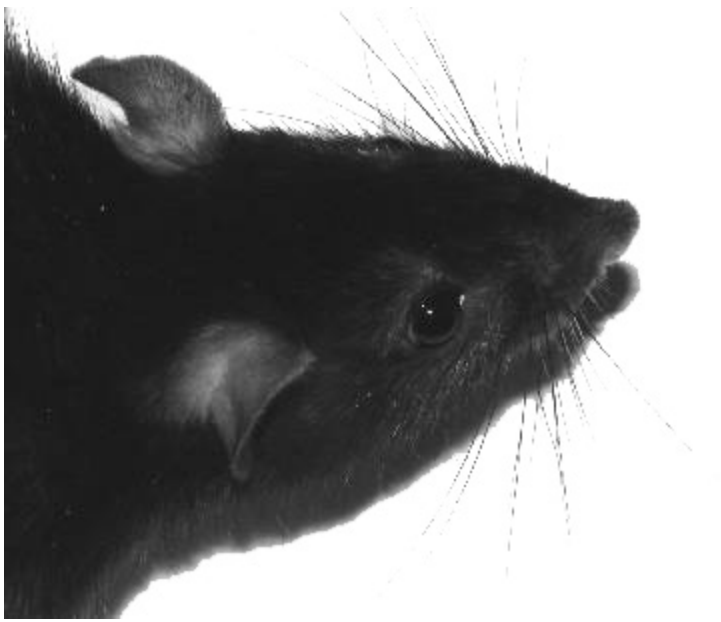
Average effect corresponds to 1.5 IQ points



Murata et al., Journal of Pediatrics, February 2004

The human studies are in agreement with laboratory animal data that developmental mercury exposure causes delayed effects

- Delayed effects of prenatal exposure in rats (Spyker, 1972)
- Monkeys exposed from birth to age 7 yrs showed adverse effects at age 14 yrs (Rice, 1996)



- Increased age-related hearing impairment in monkeys at age 19 yrs (Rice,1998)
- Unmasking of developmental toxicity in rats at 1.5 yrs of age (Newland & Rasmussen, 2000)

Risk assessments have stressed uncertainties in the documentation

- 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)
- …a National Academy of Sciences committee … failed to provide any justification or explanation … (Clarkson et al., 2003)

Possible discrepancy between 'sound science' and responsible risk assessment

Specific concerns that a mercury effect may be overestimated

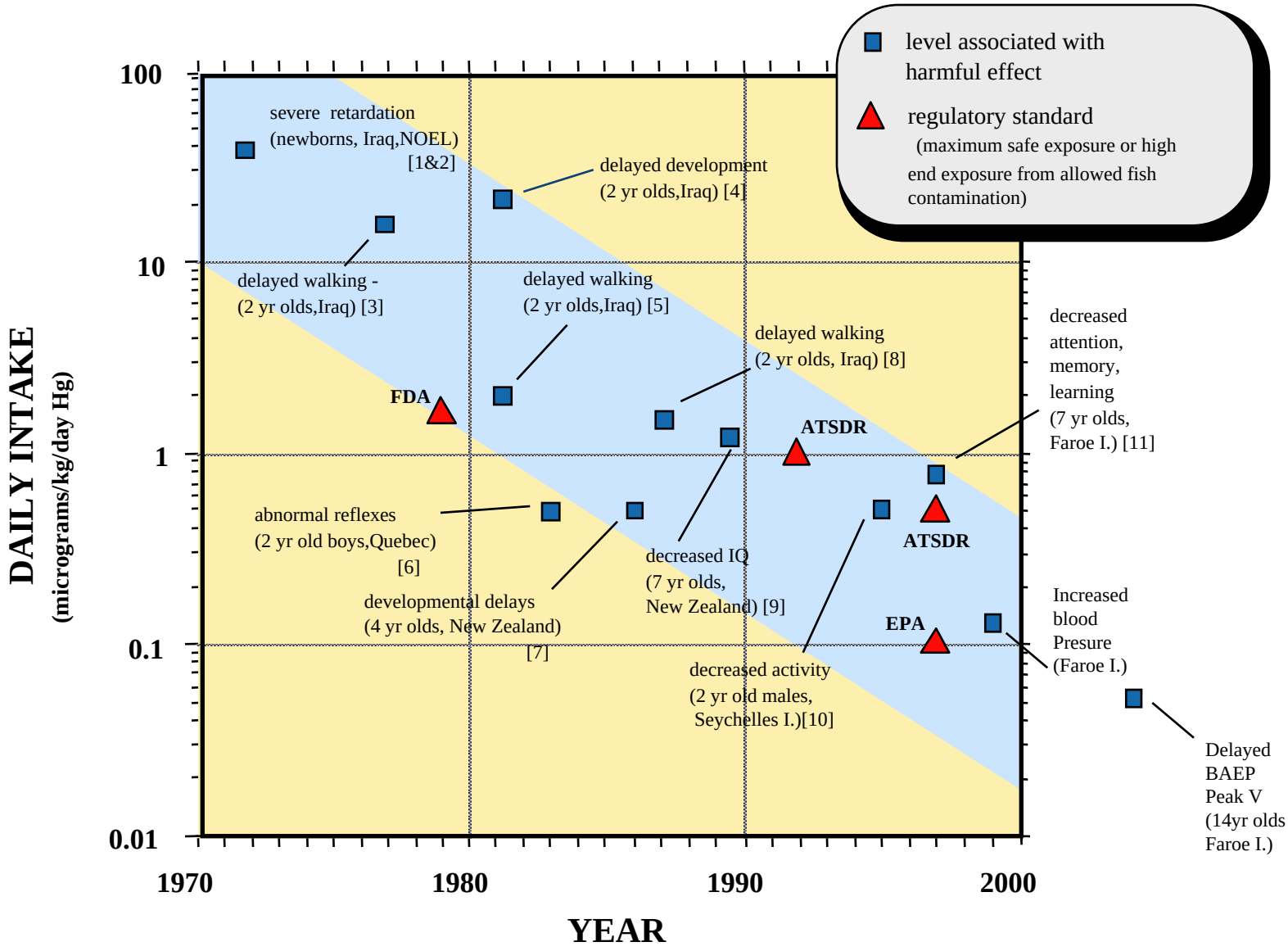
- Association with other neurotoxic seafood toxicant(s)
- Other residual confounding (residence, transportation)
- Failure to adjust for multiple comparisons

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

Better studies - declining thresholds



From: In Harm's Way, 2002

NRC exposure limit calculated from the benchmark dose (and our update)

Mercury concentrations	NRC	Updated
BMDL (µg/L cord blood)	58	43^{+}
Cord blood adjustment (1.5*)	-	29
Uncertainty factor	(10)	(10)
Exposure limit (µg/L blood)	5.8	2.9
Converted to µg/kg*d	0.1	0.05

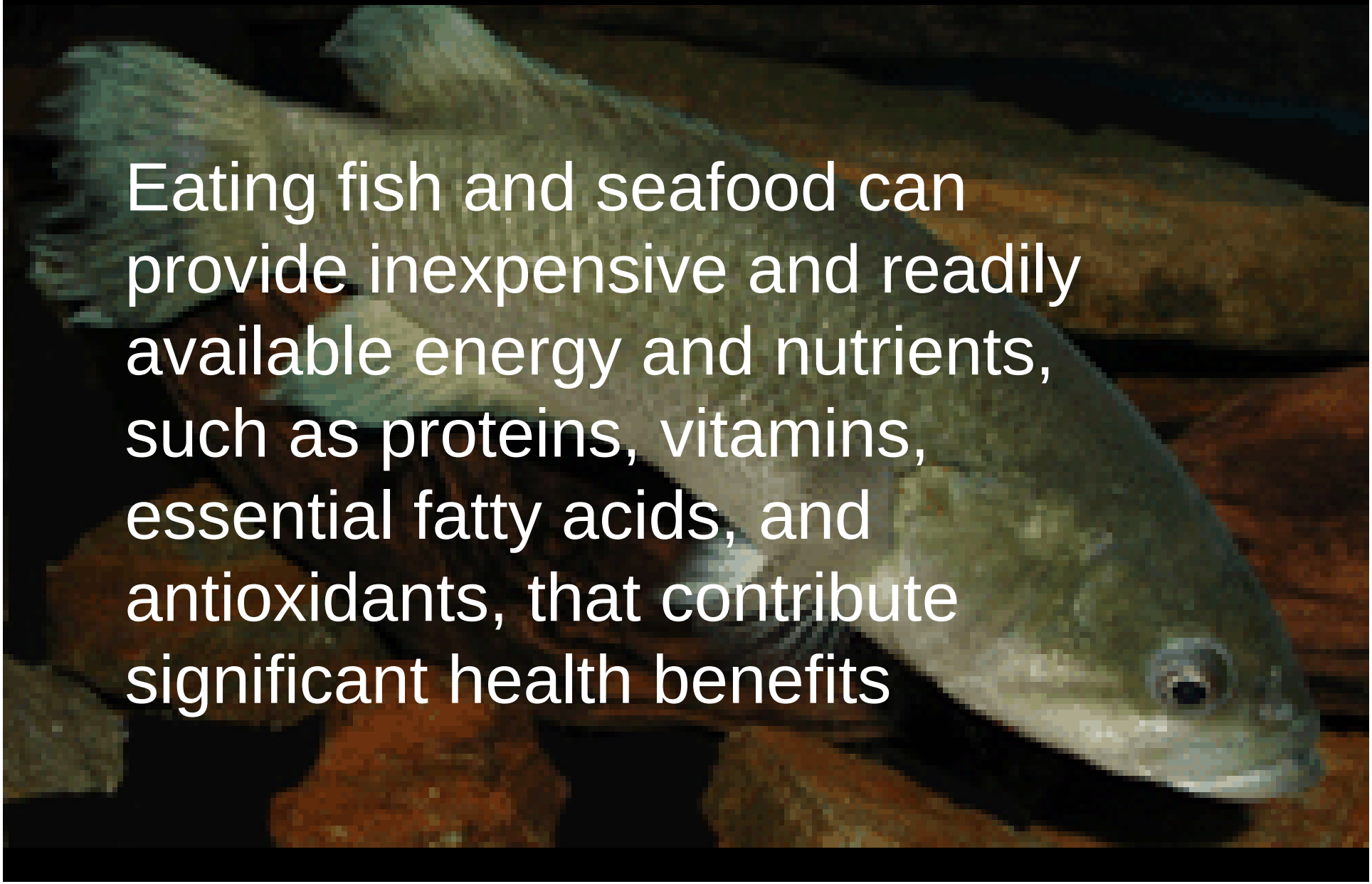
EPA RfD

BMDL: P_0 = 0.05, BMR = 0.05, linear slope for BNT

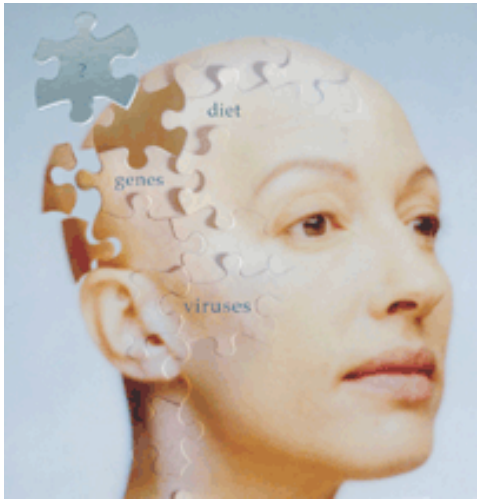
$^{+}$Adjusted for exposure assessment imprecision by SEM

*Based on hair-to-blood ratios in pregnant and non-pregnant subjects

The benefits of a seafood diet



Eating fish and seafood can provide inexpensive and readily available energy and nutrients, such as proteins, vitamins, essential fatty acids, and antioxidants, that contribute significant health benefits



Brain development is affected by beneficial effects of nutrients and toxicity from pollutants

Maternal fish intake

Nutrient and energy supplies

Cellular differentiation
Organ development
Growth

Maturation
Adaptation
Compensation

Adult functioning
Disease risk

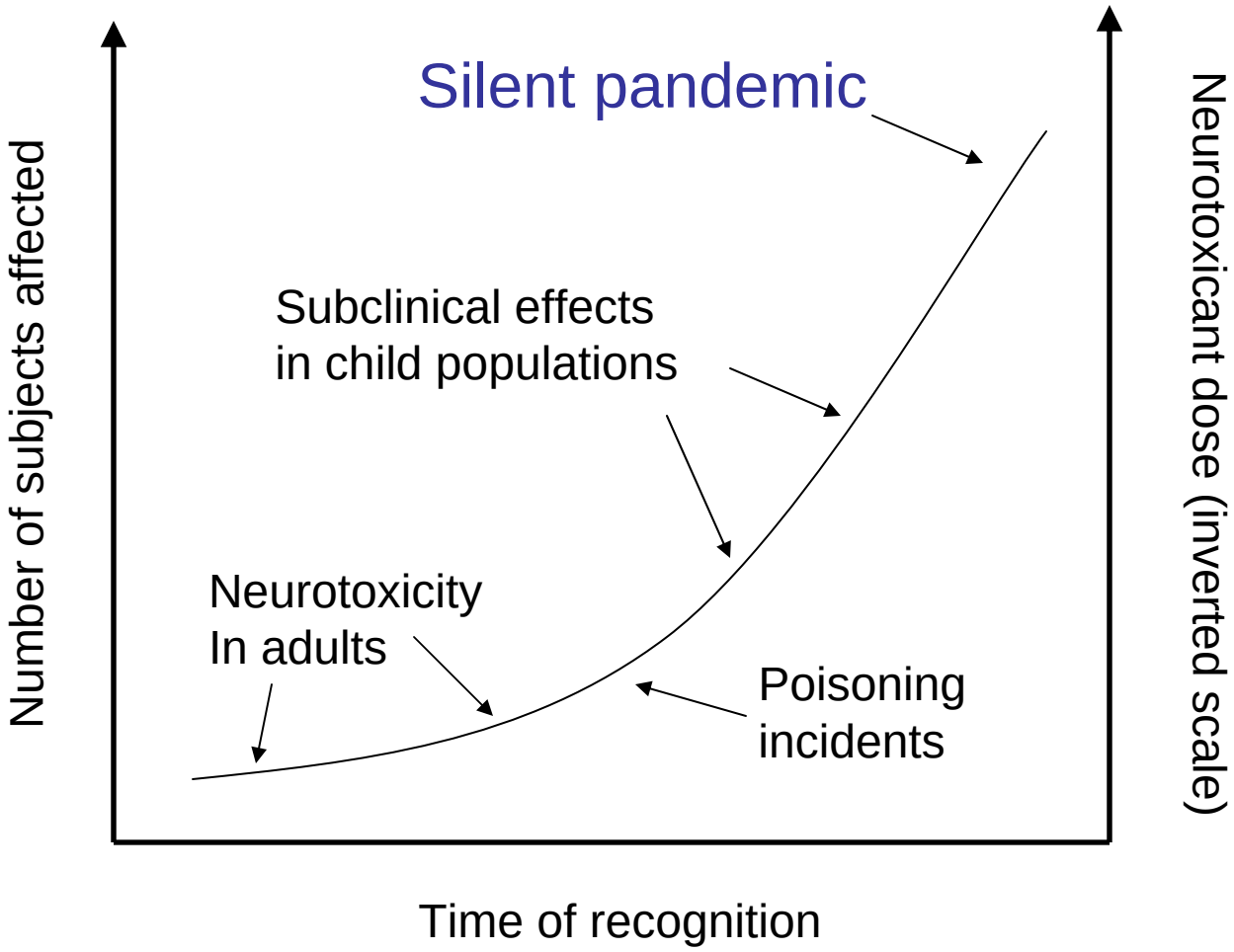
Toxicant exposures

Methylmercury exposure biomarkers

Faroes:
r = 0.25

Calculated mercury effects on motor function in the Faroes double when account is taken of the benefits from nutrients in maternal fish intake during pregnancy

Time course of recognition of methylmercury as a developmental neurotoxicant



Grandjean & Landrigan, in press

Significant health effects of developmental mercury exposure

- Loss of IQ – *the silent pandemic*:
  - A doubling of MeHg exposure corresponds to a loss of ~1.5 IQ points
  - Economic value of one IQ point: $8,350 (U.S. EPA, 1998)
- Developmental neurological disease affects one of six children
- Degenerative neurological disease?
- Cardiovascular disease?