

Pesticides and Neurodevelopmental Toxicity

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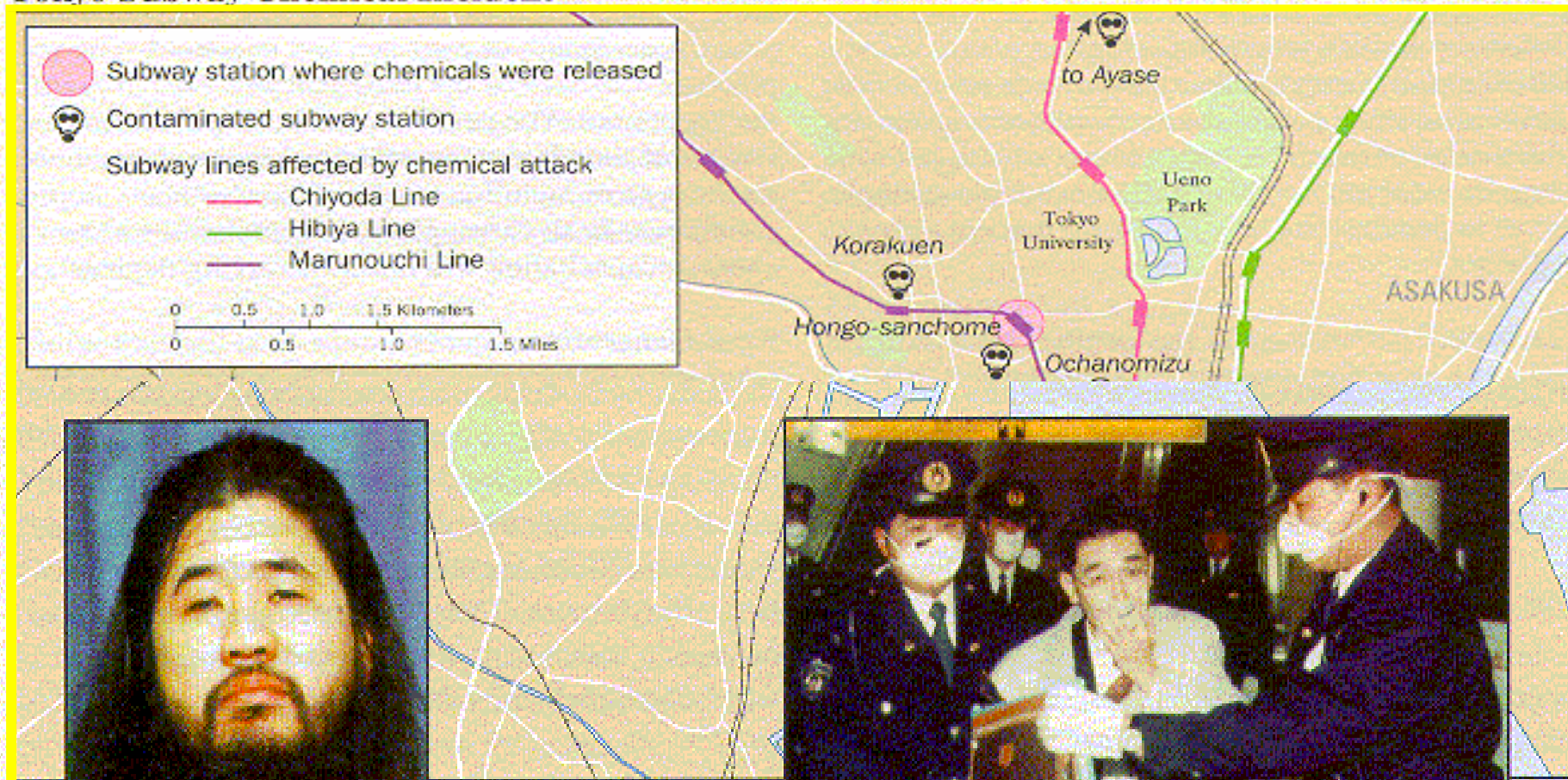
Children and Pesticides

- Pesticides include more than 600 compounds.
- More than 500 m Kg applied each year in USA alone.
- Pesticides include insecticides, herbicides, fungicides, rodenticides – diverse chemicals with diverse effects.
- Children are exposed to pesticides in foods, drinking water, and in homes, schools and communities.
- Children are highly vulnerable to pesticides.
- Developmental toxicity can result from early life exposure.

Origins of Concern about the Neurodevelopmental Toxicity of Pesticides

- The inherent neurotoxicity of many pesticides.
- Recognition of the particular vulnerability to pesticides of fetuses, infants and children.
- Recognition that early exposures to toxic chemicals can injure the developing brain – acute as well as subclinical toxicity.
- New toxicological data.
- New epidemiological findings.

The Neurotoxicity of Pesticides - Chemicals Designed to be Neurotoxic



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Pesticides have a Broad Spectrum of Toxicity

- Acute neurotoxicity
- Delayed neurotoxicity, e.g., OPIDN
- Chronic neurotoxicity
- Cardiac toxicity

Why Children Are Especially Vulnerable to Pesticides and other Environmental Chemicals

- Greater exposure proportionate to body mass—
7 times more water per Kg per day; Hand-to-mouth activity
- Diminished ability to detoxify many chemicals
- Heightened biological vulnerability –
thalidomide, DES, fetal alcohol syndrome
- More years of future life

National Academy of Sciences, 1993

The developing human brain is exquisitely sensitive to toxic chemicals

- This vulnerability is a consequence of the brain's extraordinary complexity, and its openness to external stimuli.
- It is greatest in early life.

Initial recognition of the neurotoxicity caused by chemicals typically occurs in the context of acute, high-dose exposure

A child massively exposed to lead in paint – Queensland Australia, 1904



A child massively exposed to mercury *in utero*
Minamata, Japan, 1960



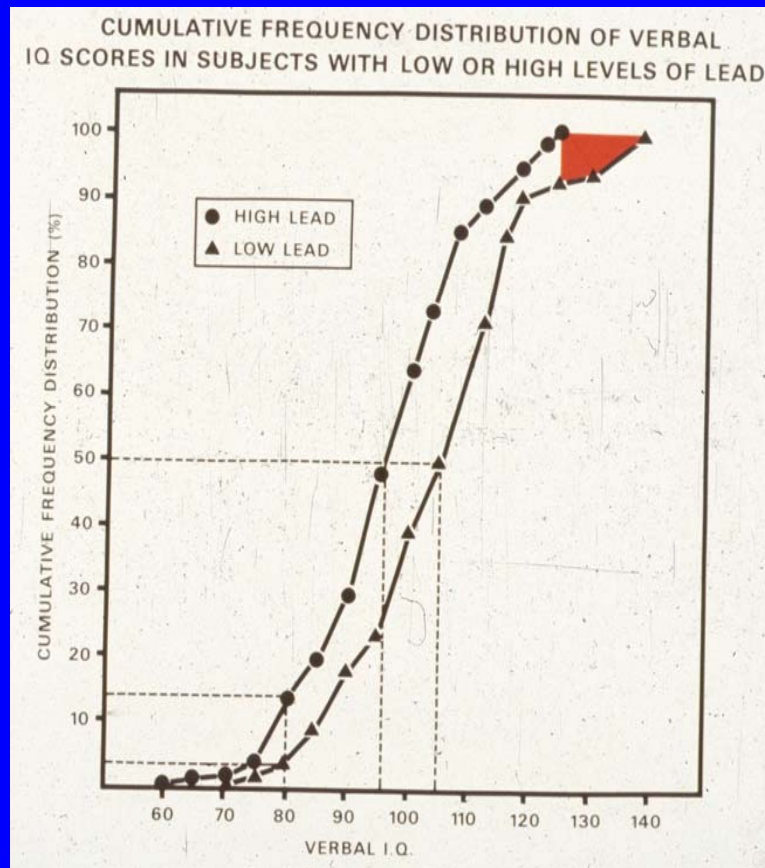
The Spectrum of Neurotoxicity

Subsequent, more sophisticated research demonstrates that neurodevelopmental disability is not limited to clinically obvious conditions, but also includes an entire spectrum of diminished function, termed subclinical toxicity.

Widespread subclinical neurotoxicity can affect the health, well-being, intelligence and even the security of entire societies.

The Needleman Study

Apparently healthy children with increased lead levels have lower IQ



Needleman HL et al. *NEJM*, 1979

The Needleman Study Established the Concept of Subclinical Lead Toxicity

... the concept that relatively low dose exposure to lead... may cause harmful effects to health that are not evident with a standard clinical examination.

The underlying premise is that there exists a continuum of toxicity, in which clinically apparent effects of lead have their asymptomatic, subclinical counterparts.

Subclinical toxicity is now recognized to pertain to all chemicals that are toxic to the brain

Societal impact of 5-point loss in IQ score

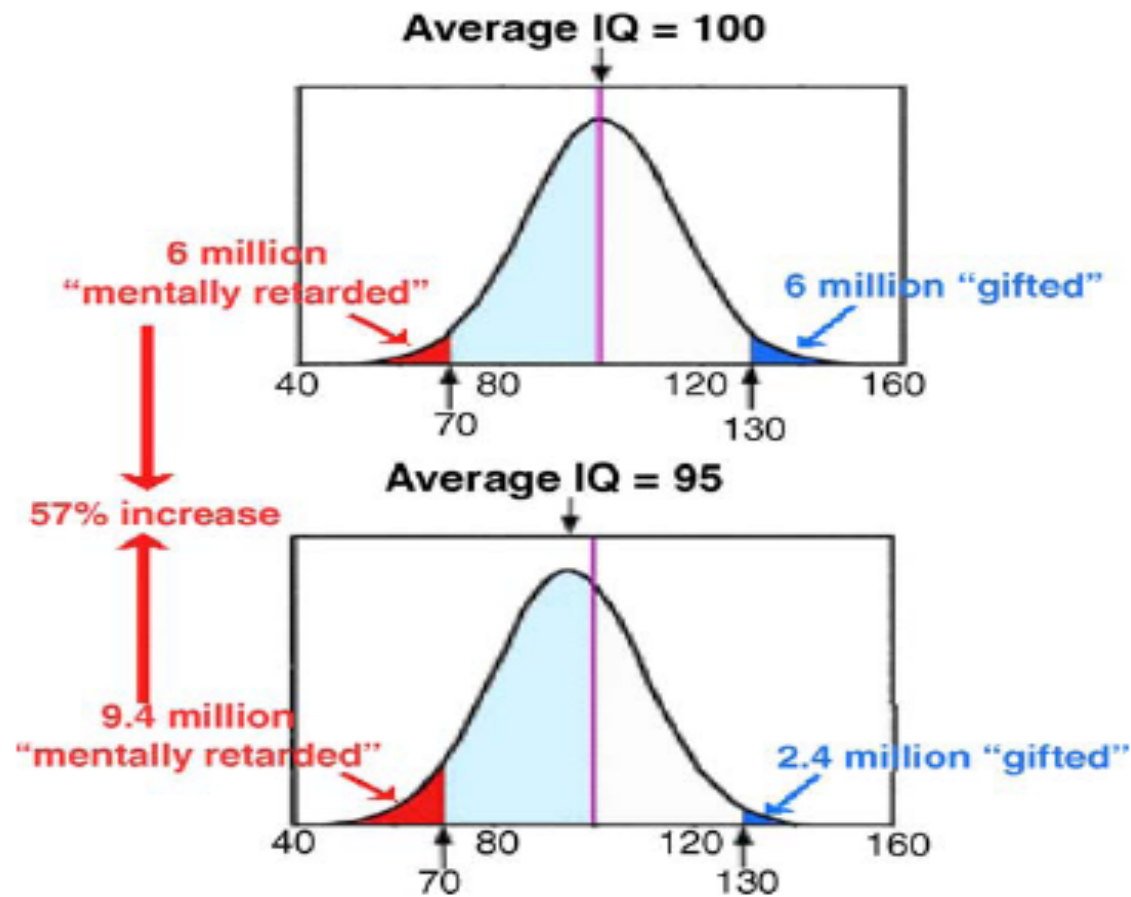


Fig. 3. Losses associated with five-point drop in IQ on a population of 100 million. Based on Weiss (1988) and modified by <http://www.ourstolenfuture.org/NewScience/behavior/iqshift.htm>.

The Concept of Delayed Toxicity

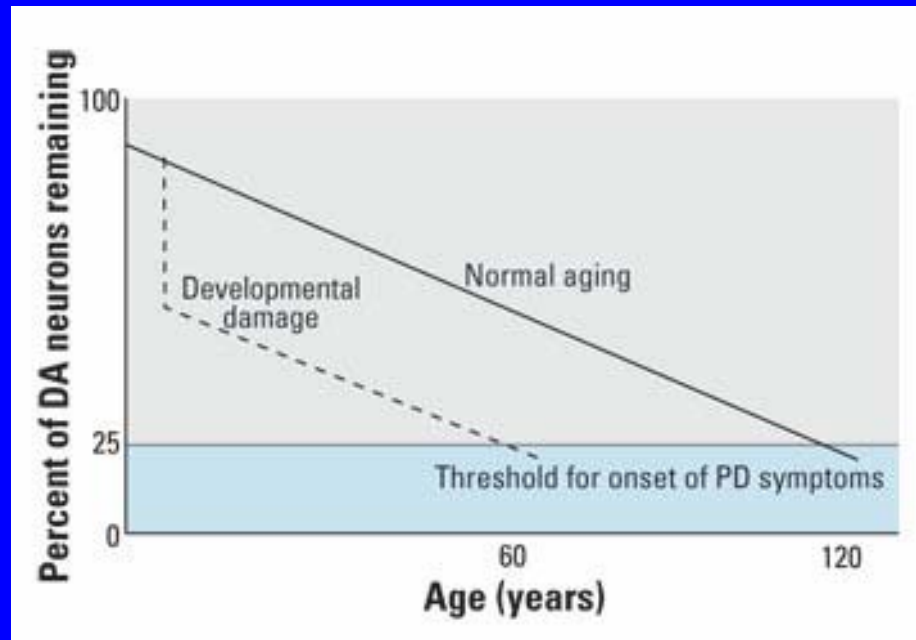
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Early Exposure to Toxic Chemicals May Increase Risk of Neurodegenerative Disease

- Alzheimer's disease
- Parkinson's disease

An emerging area of research

A Proposed Mechanism for the Delayed Appearance of Brain Disease - Early Loss of Neurons Caused by Toxic Chemical Exposure Increases Risk for Later Disease



New Toxicological Evidence for the Developmental Neurotoxicity of Pesticides

Perinatal exposure to low doses of
chlorpyrifos causes:

- Reduced number of neurons
- Decreases in intelligence
- Alterations of behavior

Slotkin T et al

New Epidemiological Findings on the Developmental Neurotoxicity of Pesticides

- Guillette studies of Mexican indigenous children – exposed v. unexposed
- Decreased head circumference in NYC babies exposed *in utero* to OPs – modulated by maternal *PON1* levels.
- Ecuador studies – Grandjean & Harari.
- Developmental delays and Pervasive Developmental Disorder in US birth cohort studies.

The Future - New Toxicity Testing Protocols

- Need to go beyond present crude protocols that examine only brain weight and gross morphology
- Incorporate functional evaluations.
- Expose animals in early life – even prenatally
- Lifelong follow-up
- Detailed pathology

The Future – Prospective epidemiological Studies

- Enroll mothers and babies at or before conception
- Measure exposures as they occur in pregnancy and after birth
- Biomarkers of exposure
- Genetic testing for susceptibilities
- Standardized assessments of babies
- Multi-year follow-up
- Long and expensive, but very powerful

The Future – Prospective Studies The US National Children's Study

- A multi-year prospective epidemiological study that will examine the influences on health, disease and development of exposures in early life
- 100,000 children to be followed from early in pregnancy to at least 18 years of age
- Will explore simultaneous impacts of many risk factors – chemical, social, behavioral
- Will link to prospective studies in many nations through WHO

<http://www.nationalchildrensstudy.gov/>

Critical Research Questions for the National Children's Study

- Contribution of indoor and ambient air pollution to the origins of asthma
- Environmental causes of developmental disabilities – pesticides among them
- Effects of endocrine disruption
- Causes of the rising incidence of certain pediatric cancers

<http://www.nationalchildrensstudy.gov/>

Implications for Developing Nations

- Children in the third world are highly vulnerable to the neurodevelopmental toxicity of pesticides
- Heavy pesticide use
- Exposure of working children and pregnant women
- Use of banned pesticides
- Potential for neurotoxicity to be compounded by undernutrition



Center for Children's Health and the Environment

Mount Sinai School of Medicine