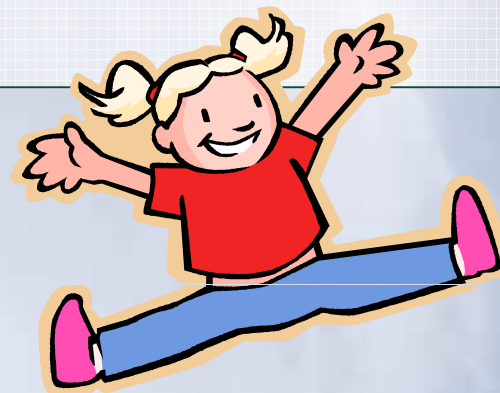


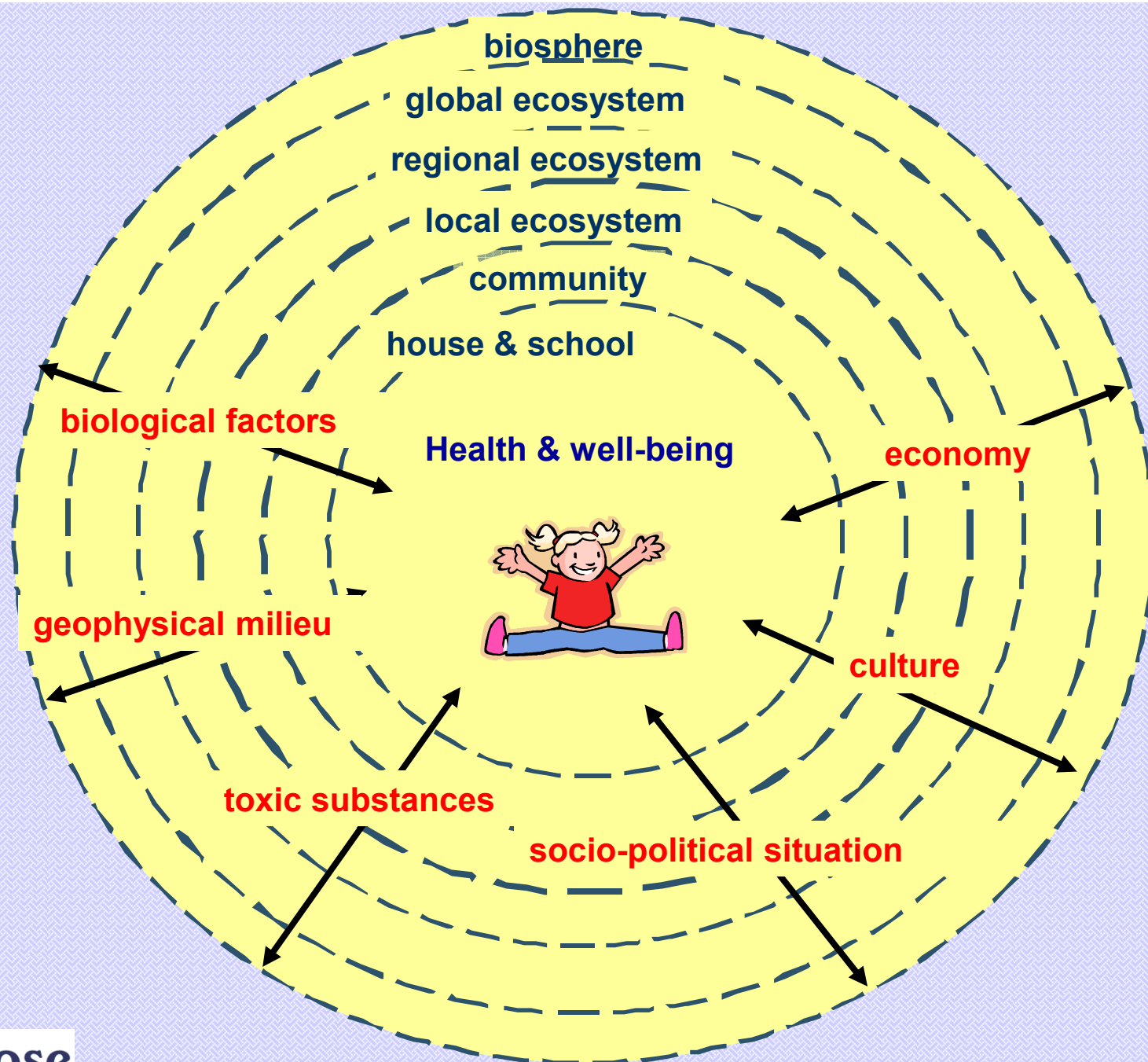
# **An ecosystem approach to neurotoxic effects of metals in children**



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CINBIOSE**

**WHO-PAHO Collaborating Centre for the Prevention of Work  
and Environment Related Illnesses**

**University of Québec at Montréal**





# Ecosystem approach to health

- ✧ Recognises the **dynamic interaction** between human health and well-being and the different components of the ecosystem.
- ✧ Integrates **gender-based concerns** and analyses and **participative methods**;
- ✧ Requires **new disciplinary and transdisciplinary methodologies** to examine and combine these various elements;
- ✧ Adopts a finality of seeking viable **short, medium and long term solutions**.

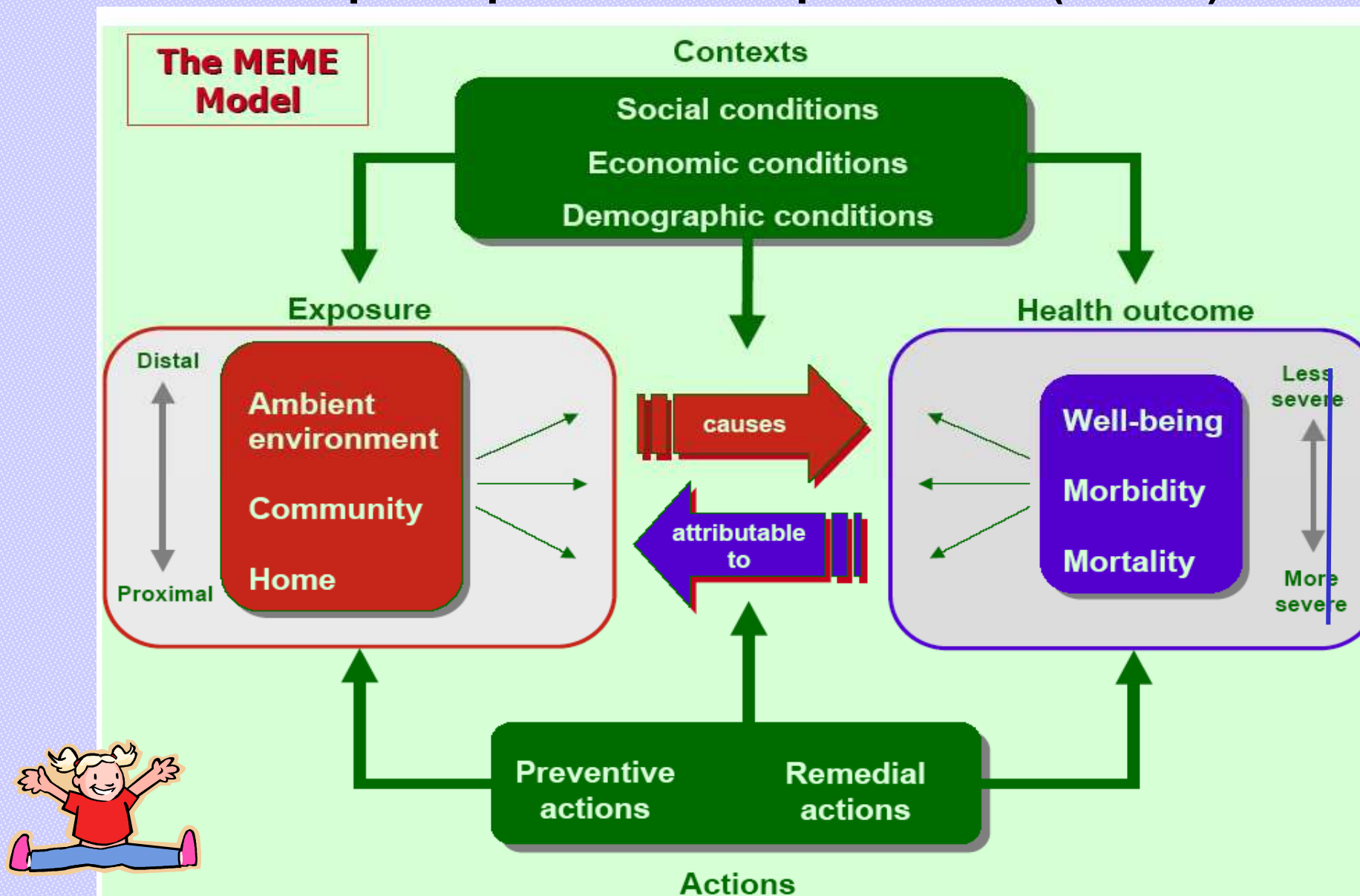


# Global Initiative on Children's Health Indicators

- ✧ launched at the World Summit on Sustainable Development in September 2002.
- ✧ Multiple Exposures  
Multiple Effects (MEME)  
Complex Model



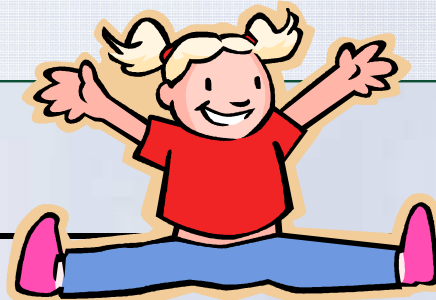
# Multiple Exposures Multiple Effects (MEME)





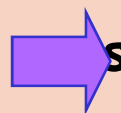
# Children's exposure to metals and neurobehavioral performance

- ✧ Metals such as lead (Pb) and mercury (Hg) can interfere with normal functioning of the developing nervous system.
- ✧ These effects have been observed on a continuum of dysfunction, with increasing exposure.
- ✧ We do not know if excess manganese can have similar effects....

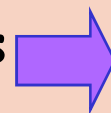


# A continuum of deterioration

Subtle changes in  
neurophysiological &  
neuropsychological  
parameters



Sub-clinical signs &  
symptoms in individuals



Neurologic and  
neuropsychiatric  
disorders

sensitive tests of subtle  
changes in performance



specific diagnostic  
criteria

continuous variables



dichotomous data

possibility to carry out  
studies on small  
populations

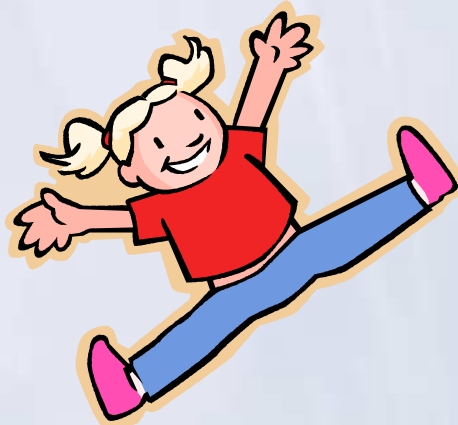


large populations (or  
very high exposures)



# Neurobehavioral tests

*What do they tell us?*





A Bird was felling a tree  
 and the tree was sick in  
 a tree. then the bird  
 up the tree and the bird  
 and only if the bird god  
 get his dad



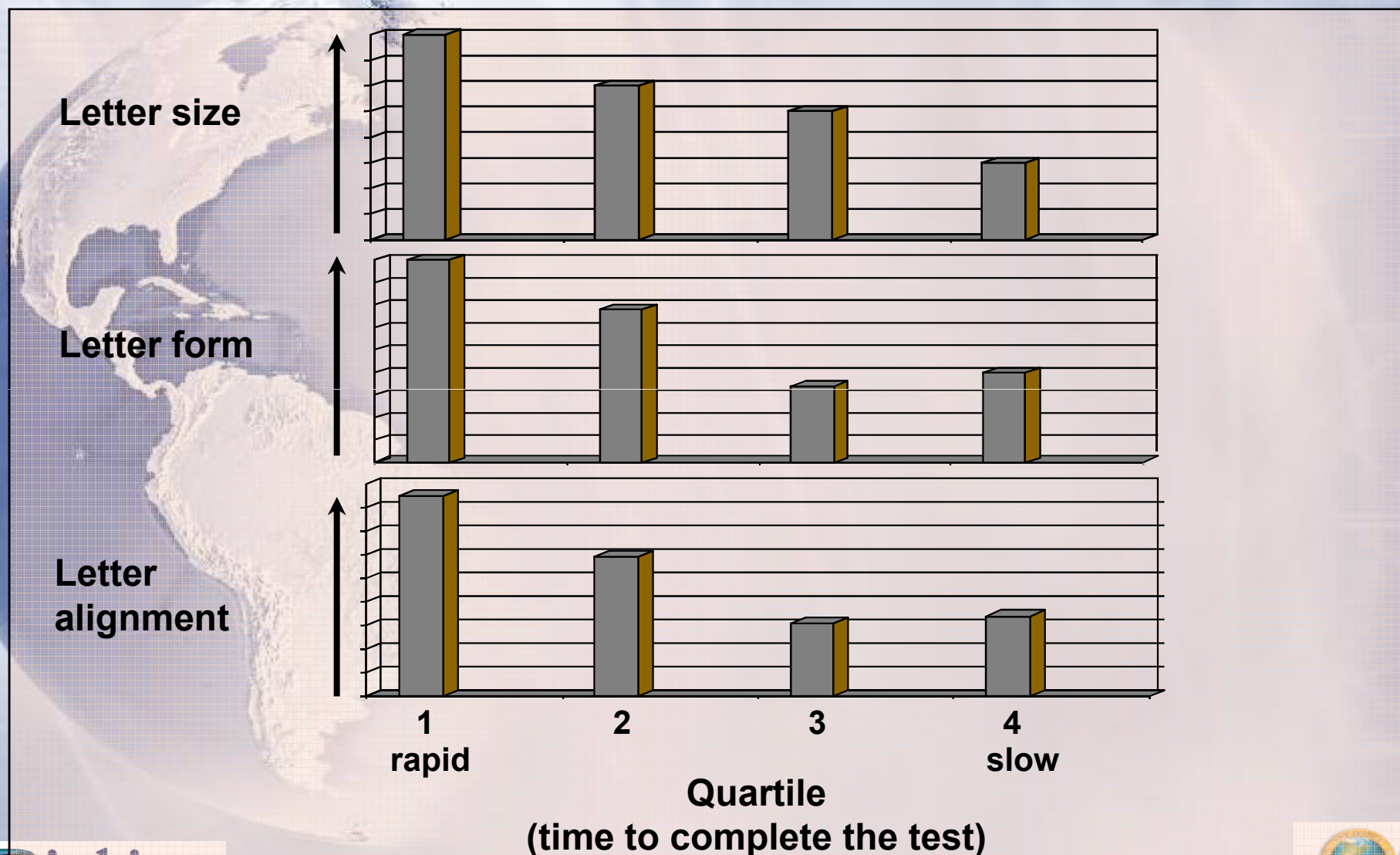
The Sore Yit a Bæ  
 The B are wen i +  
 to fix the kits of his did  
 we sex got it up a lie Bæ  
 Bæ a lie.  
 we ix a the of hid it up with a lie

# Fine motor movement: Grooved Pegboard





# Writing and Grooved Pegboard results



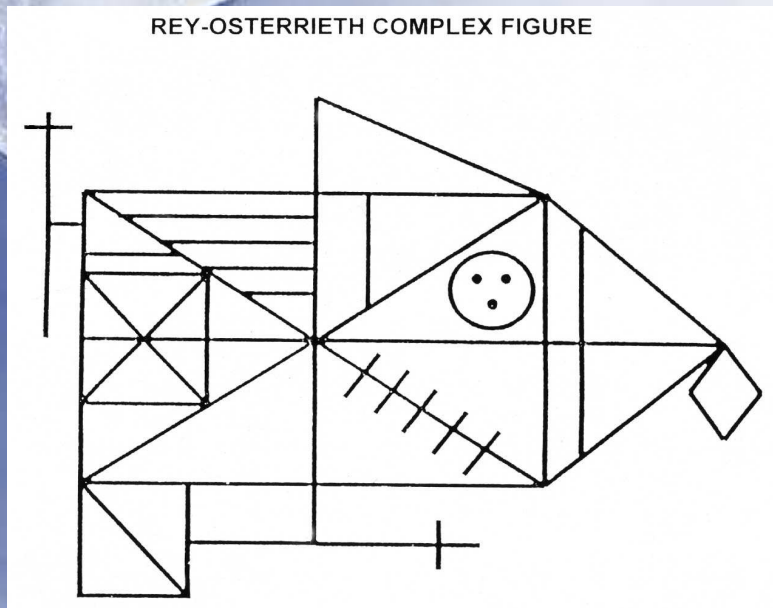


# **Predictability of neuropsychological tests with respect to learning needs**



# Predictability of neuropsychological tests with respect to learning needs

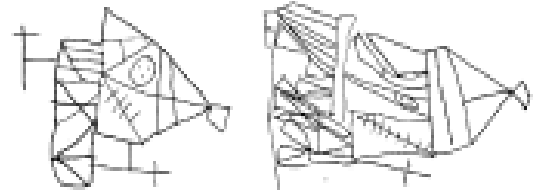
## Rey–Osterriech complex figure



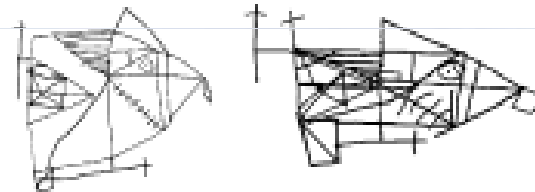
Category 1



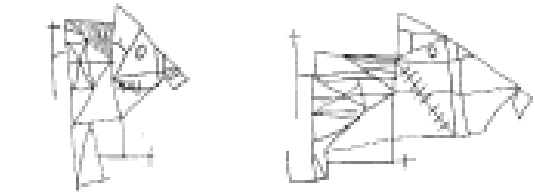
Category 2



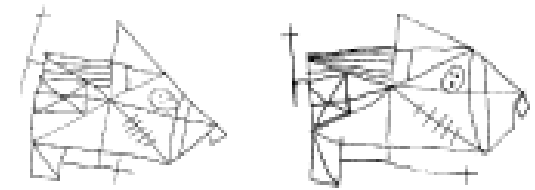
Category 3



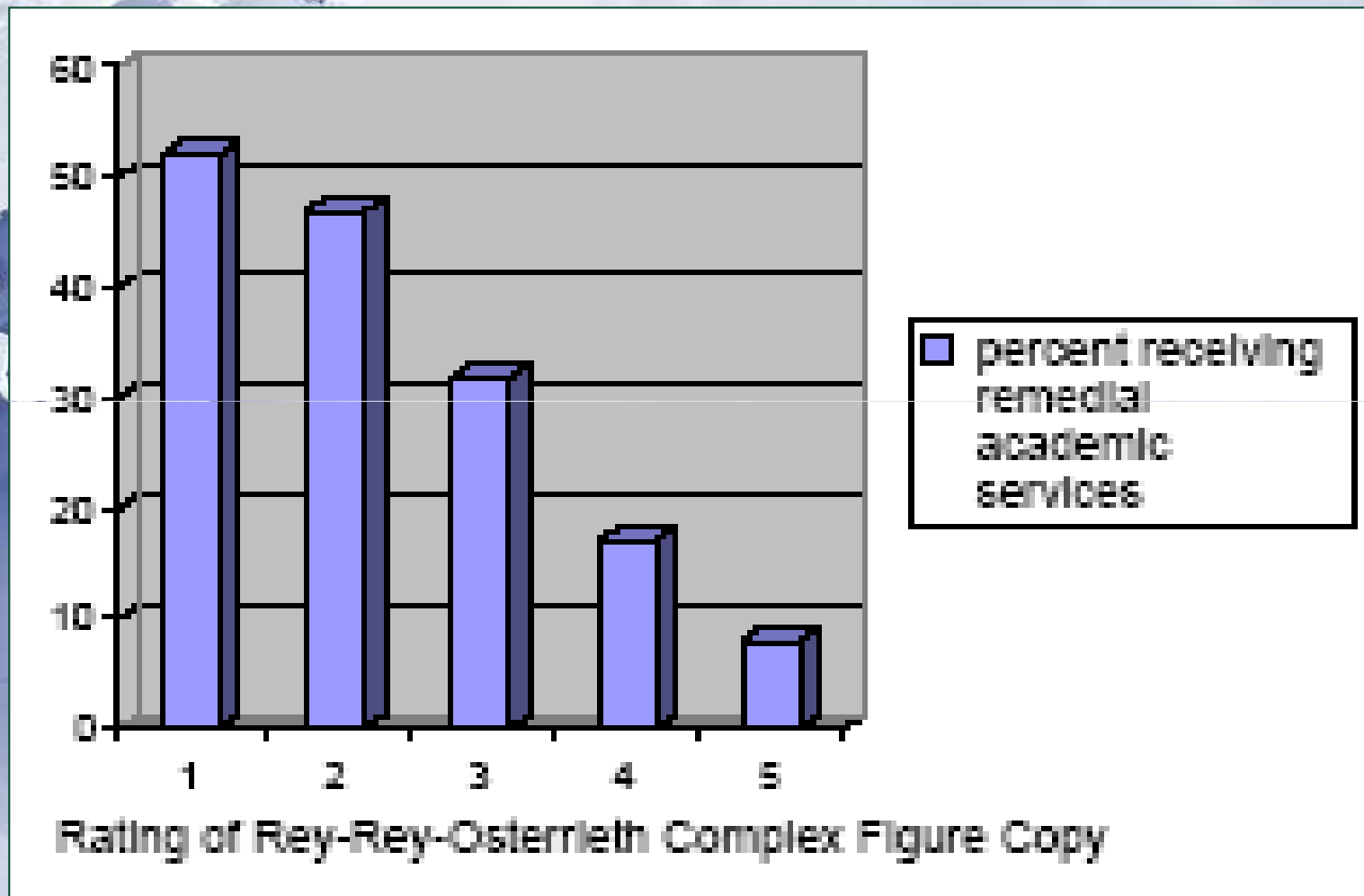
Category 4



Category 5



# Predictability of neuropsychological tests with respect to learning needs

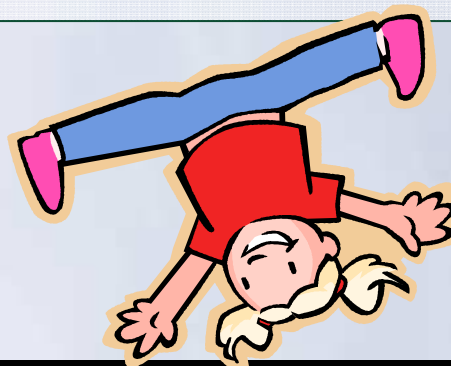


(Bellinger et al. 2003)

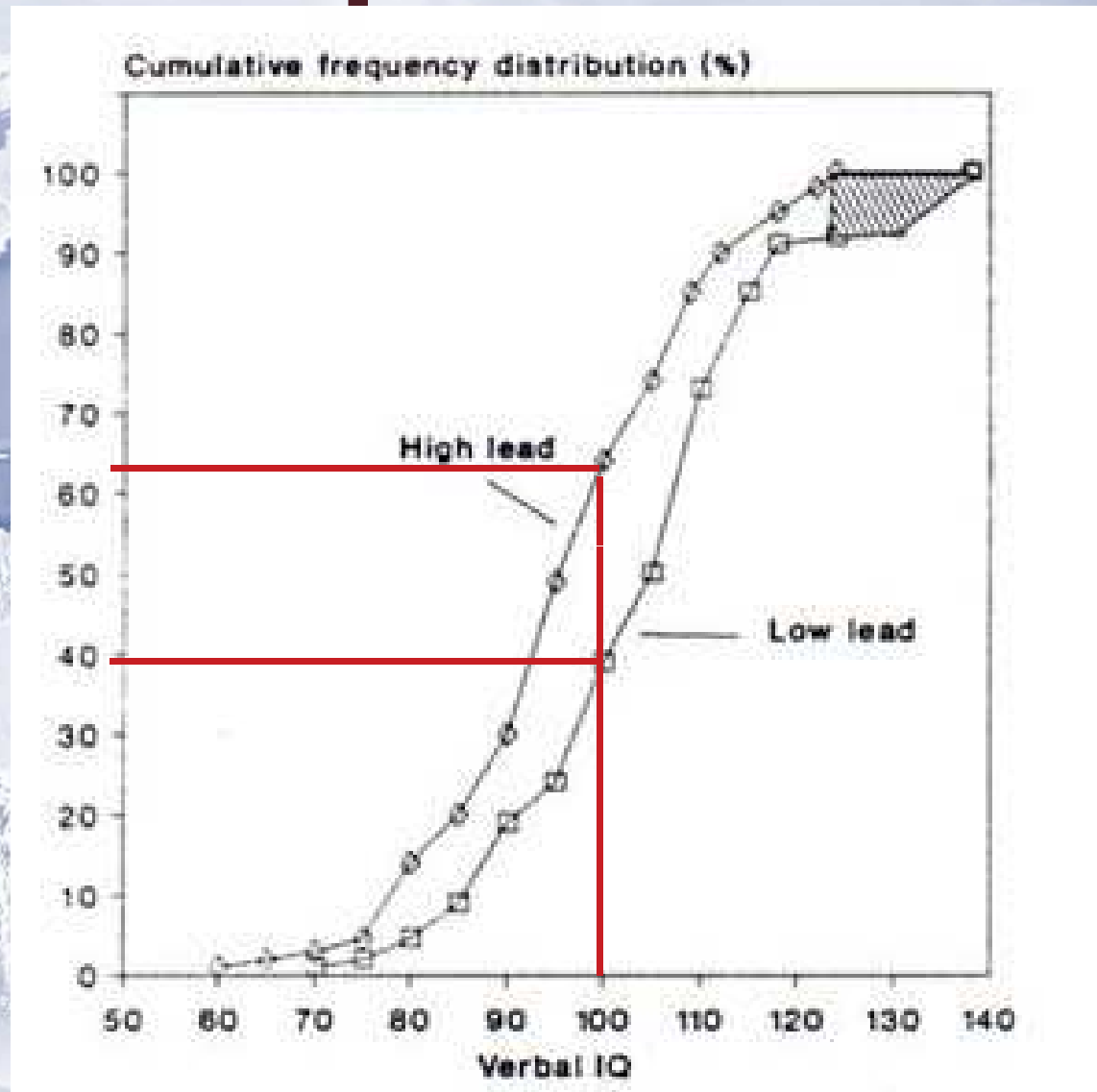
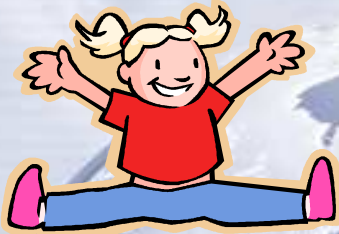


# Lead (Pb) and children

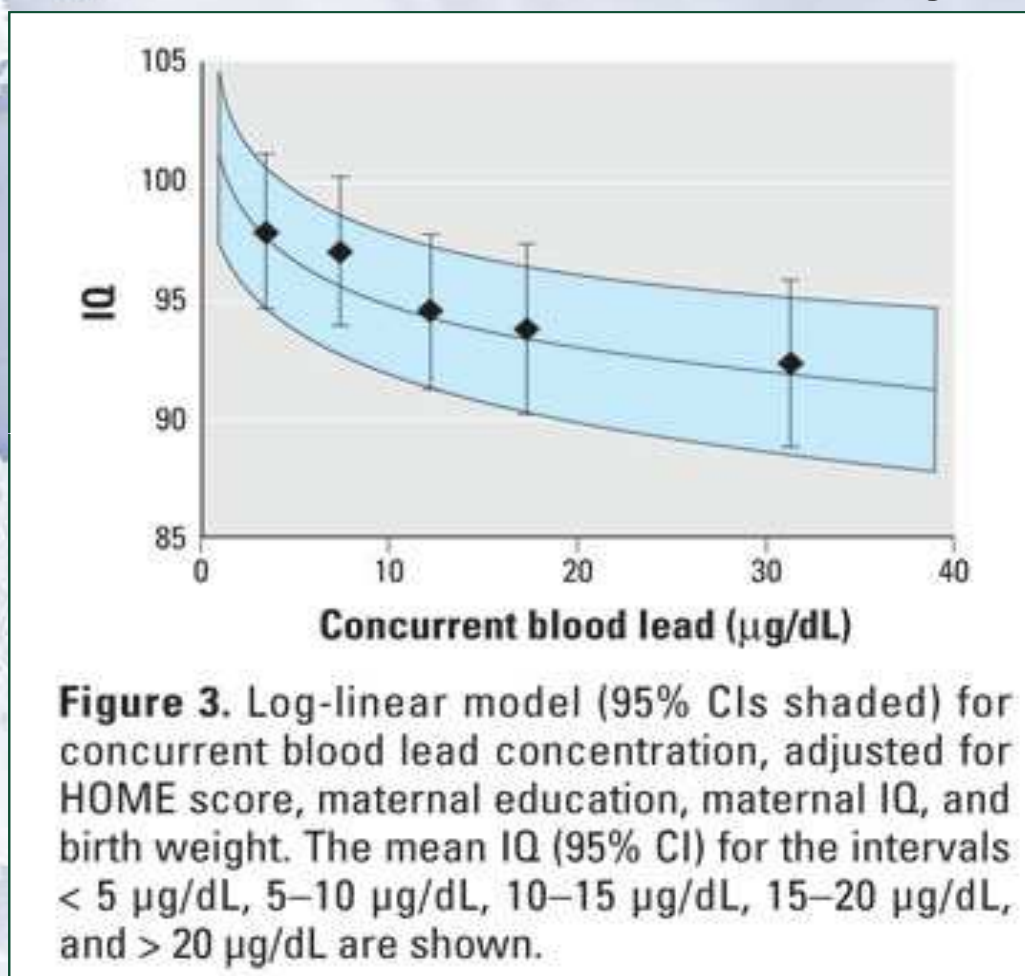
- ✧ **Pb was removed from gasoline in many countries because of its effects on children's IQ**
- ✧ **Pb exposure has been associated with a large number of cognitive, motor and sensory deficits, as well as behavioral problems**



# Lead exposure & verbal IQ



# Current studies on IQ lead exposure: an international pooled analysis



(n = 1331)

7 cities:  
Boston,  
Cincinnati,  
Cleveland,  
Mexico, Port  
Pirie,  
Rochester,  
Yugoslavia





# Many studies throughout the world have shown relations between Pb exposure and children's neurodevelopment for:

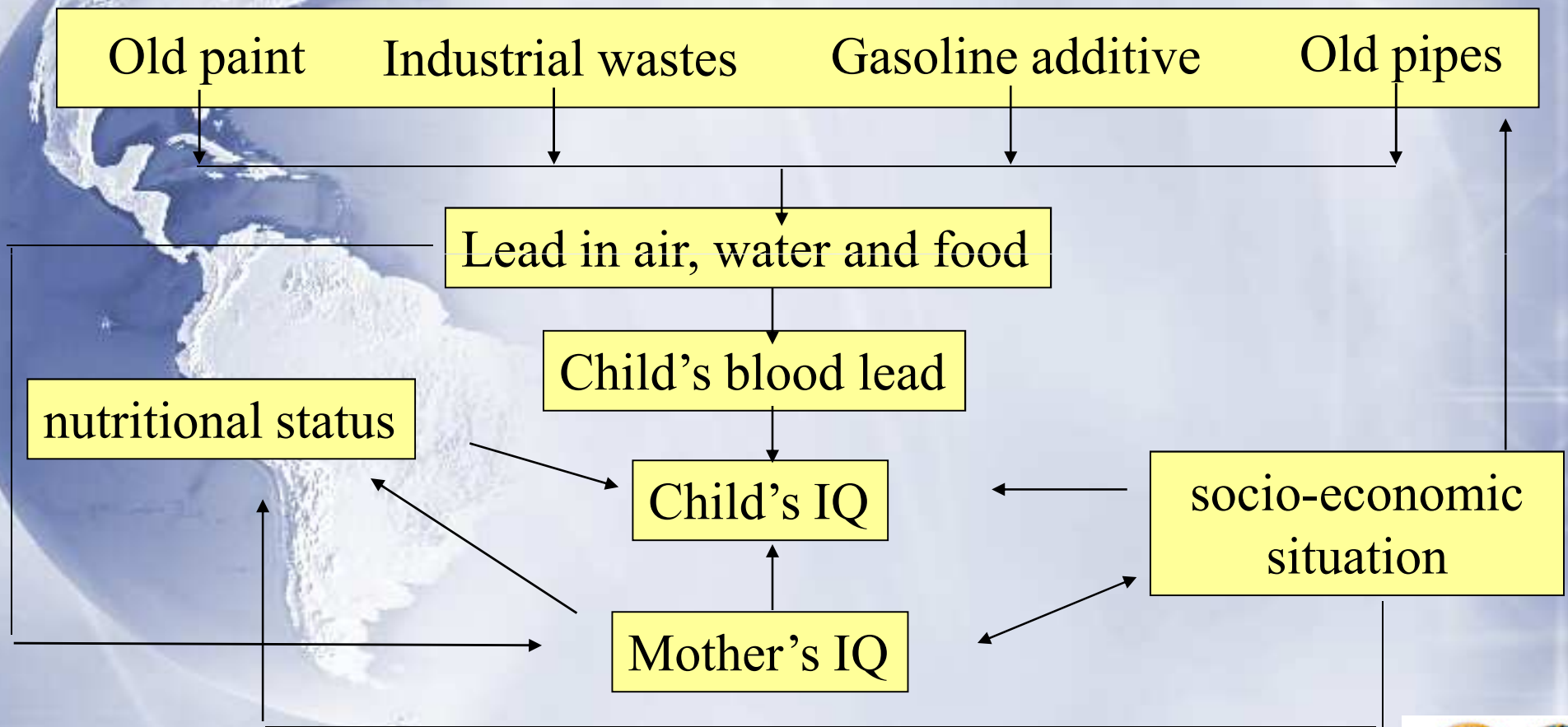
- ✧ **Executive function**
- ✧ **Attention/vigilance**
- ✧ **Reading and spelling**
- ✧ **Pattern recognition**
- ✧ **Word recognition**
- ✧ **Fine motor movements**
- ✧ **Visuo-motor skills**

- ✧ **Hyperactivity**
- ✧ **Impulsivity**
- ✧ **Distractibility**
- ✧ **Social skills**
- ✧ **Antisocial behavior**

- ✧ **Evoked potentials**
- ✧ **Nerve conduction velocity**



# An ecosystem approach to lead and health



# Manganese in tap water

An interdisciplinary study of children's exposure and effects in Quebec





# Ingested Manganese: Without risk?

- ✧ Manganese is an essential element, necessary for a large number of functions
- ✧ Common dietary sources of manganese
  - ✧ Nuts, grains, green leafy vegetables, tea
  - ✧ Drinking accounts for 1-20% of ingested manganese
- ✧ Homeostatic control through absorption and excretion
  - ✧ In adults, 3-10% is retained from food
  - ✧ In infants, 20% is retained from milk formula (Corner et al., 1989)

***The "safe level of intake" (NOAEL 11 mg/d) based on fragile scientific ground. Studies used to derive safe levels did not look for adverse effects of manganese intake***

# Neurotoxic effects of Mn in children: studies raising cause for concern

- ✧ Early studies among hyperactive and learning disabled children reported higher [Mn] in hair; no source of exposure was identified<sup>1,2</sup>
- ✧ In China<sup>3</sup>: children exposed to water from toxic dumpsite with Mn (240-350 ug/L) compared to matched-pair referents:
  - ✧ Increased [Mn] in hair
  - ✧ Significantly poorer performance on several neurobehavioral tests and scores correlated with hair Mn
- ✧ In Bangladesh<sup>4</sup>: exposed to Mn in water (4–3,908 µg/L; mean 795)
  - ✧ ↓ IQ with concentration of Mn in well water

<sup>1</sup> Collipp et al 1983, <sup>2</sup> Pihl et al 1977, <sup>3</sup> He et al 1994, <sup>4</sup> Wasserman et al 2006



# Guidelines for max [Mn] in water

## ✧ Guideline values:

- ✧ WHO 400 ug/L (recently lowered, was 500 ug/L)
- ✧ Canada: no health based guideline
- ✧ USA 300 ug/L (Health based guideline EPA)
  - ✧ In USA, 6% of private wells have >300 ug Mn/L
  - ✧ Distribution of [Mn] is poorly characterized in Canada

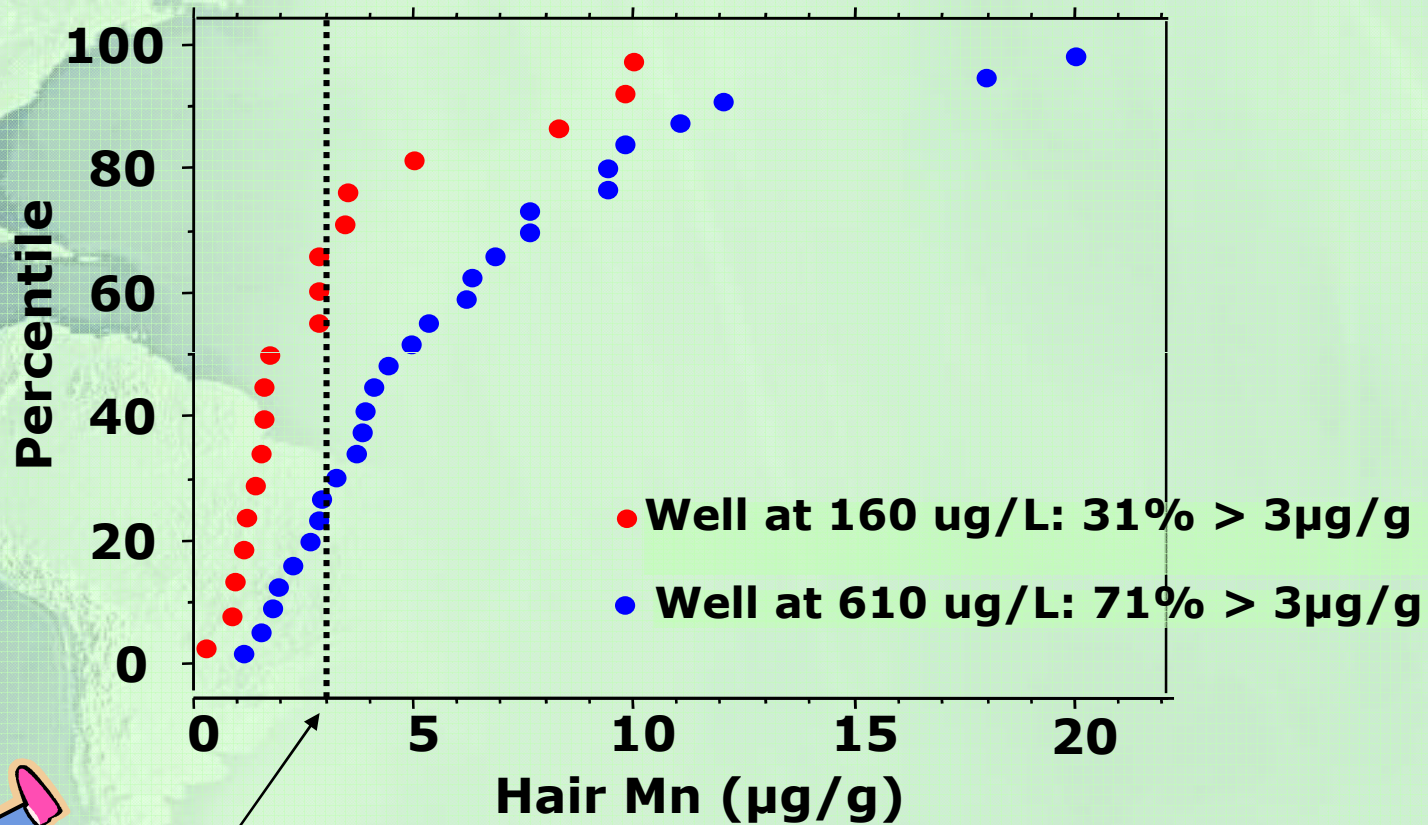


# Pilot study: Context and methods

- ✧ **Public water system of a community in Quebec had high levels of manganese from natural sources**
- ✧ **We proposed a pilot project to a primary and a high school**
- ✧ **Teachers who agreed sent letters inviting parents to participate**
  - ✧ **45 children were assessed (23 boys, 22 girls)**
  - ✧ **Mean age: 11 y (6 – 15 y)**
  - ✧ **Use of tap water:**
    - ✧ **Only 9% drank water from tap**
    - ✧ **96% uses tap water to cook**



# Children's hair Mn with respect to wells with different Mn levels





# Elevated Conners' scores & elevated hair Mn

Conners subscales		Hair Mn (ug/g)		Fisher's Exact Test ( <i>p</i> )
		< 3.0 n (%)	≥ 3.0 n (%)	
Oppositional (n = 45)	< 64	19	18	<b>0.014</b>
	≥ 65	<b>0</b>	<b>8</b>	
Hyperactivity (n = 45)	< 64	19	17	<b>0.006</b>
	≥ 65	<b>0</b>	<b>9</b>	
Cognitive problems (n = 40)	< 64	12	19	ns
	≥ 65	<b>5</b>	<b>4</b>	
ADHD Index (n = 45)	< 64	17	15	<b>0.024</b>
	≥ 65	<b>2</b>	<b>11</b>	



# Follow-up after installation of a filtration system

- ✧ Four months after reduction of exposure, 33/46 children were followed-up.
- ✧ **Hair manganese decreased markedly**
  - ✧ Mean went from 5.0 ug/g (SD 4.3) to 0.7 ug/g (SD 0.6); no value exceeded the upper limit of the normal range (i.e. 3.0 ug/g).
- ✧ No significant relationship between hair Mn and Conners scores
- ✧ No significant change in Conners scores (teachers or parents)



# **New study on manganese exposure through tap water and children's neurodevelopment**

**Financed by CIHR**

## ✧ Study sites

- ✧ Communities using groundwater to feed the municipal aqueduct
- ✧ Communities chosen to form a gradient [Mn] water aqueduct (0 - 1,230 ug/L)
- ✧ Total number of sites will depend on participation rate (estimate: 8 sites)

## ✧ Study population

- ✧ **400 children** in primary school (6 - 12 y)
  - ✧ 172 children seen so far
  - ✧ Participation rate 25 – 37%
- ✧ Recruitment through schools
- ✧ Inclusion criteria: live in the same house since 4 months



# Neurobehavioral Test Battery

## **Cognitive tests**

- ✧ **IQ: Wechsler Abbreviated Scale of Intelligence (WASI)**
- ✧ **Memory: California Verbal Learning Test–Children's Version**
- ✧ **Inhibition: D-KEFS Color-Word Interference Test**
- ✧ **Attention/impulsivity: Conners' Continuous Performance Test II**

## **Motor tests**

- ✧ **Items from the Luria Nebraska Motor Scale**
- ✧ **Manual dexterity: Santa Ana**
- ✧ **Motor speed: Fingertapping**

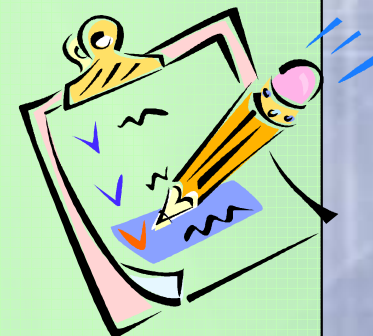
## **Questionnaires administered to parent and teacher**

- ✧ **Conners Rating Scales (long form; revised version)**
- ✧ **School motivation, psychosocial adaptation and school performance (Bouffard)**

# Information collected

## Structured Interview with mothers:

- ✧ Raven (mother IQ)
- ✧ Beck Depression Inventory
- ✧ Hollingshead (socioeconomic status)
- ✧ HOME (stimulation at home)
- ✧ Child medical history (including perinatal stress and birth weight, etc.)
- ✧ Exposure to neurotoxics *in utero* and perinatally (alcohol, tobacco, lead, pesticides, etc.)
- ✧ Health services usage and school support





# Manganese exposure assessment

## ✧ Homes tap water sampling

- ✧ Measurement of Mn, Pb, Fe, Ca, Cu, Zn, As, Mg (ICP-MS)

## ✧ Children hair sampling

- ✧ 2 cm closer to the scalp (=exposure from 2 last months)
- ✧ Measurement of Mn, Pb, Fe, Cu, Zn, As (ICP-MS)

## ✧ Residency history

- ✧ length of exposure to current manganese levels

## ✧ Assessment of dietary intake of manganese and iron

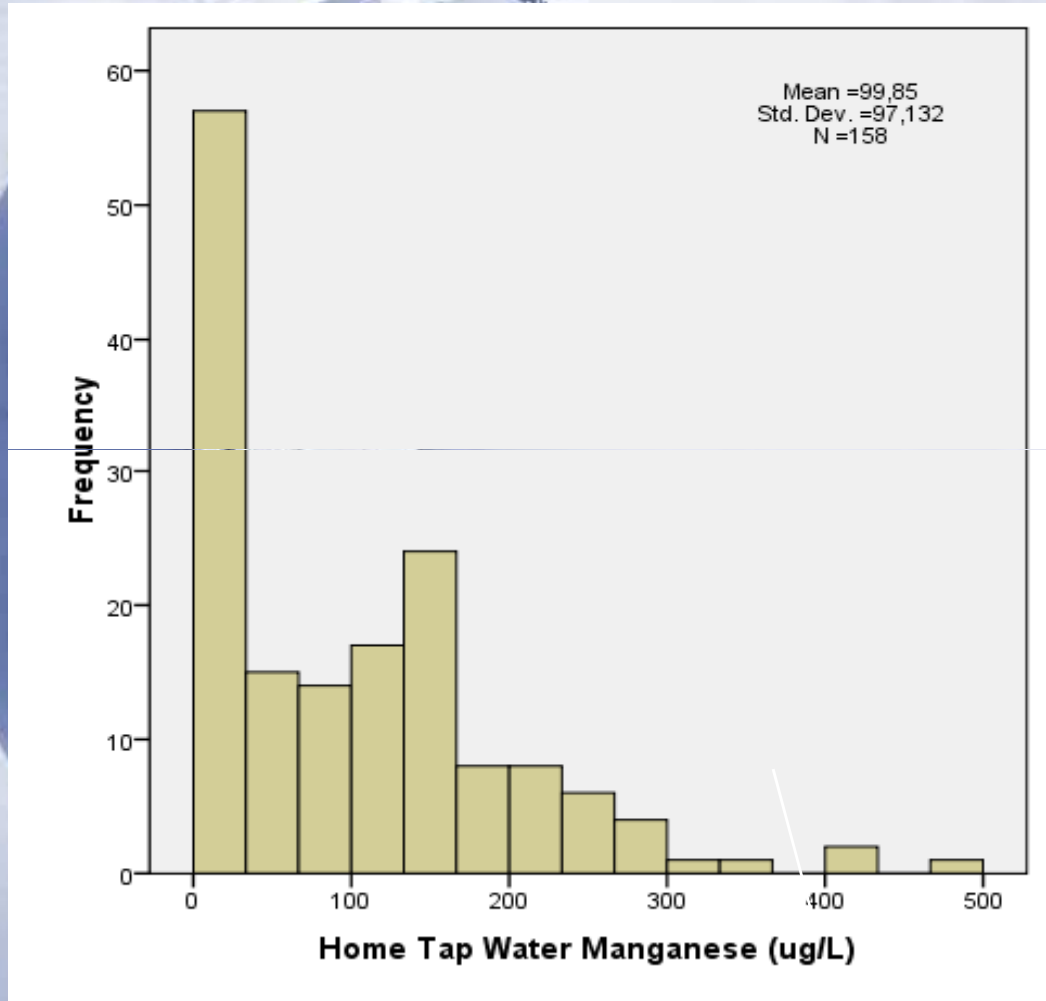
- ✧ Food frequency questionnaire
- ✧ Focus on consumption of foods providing elevated intake of manganese and iron
- ✧ Assessment of indirect and indirect intake of tap water



# Preliminary results

- ✧ **89 boys and 72 girls**
- ✧ **mean age= 8.8 y (SD 1.8, range 6 -13)**

# Distribution of [manganese] in tap water

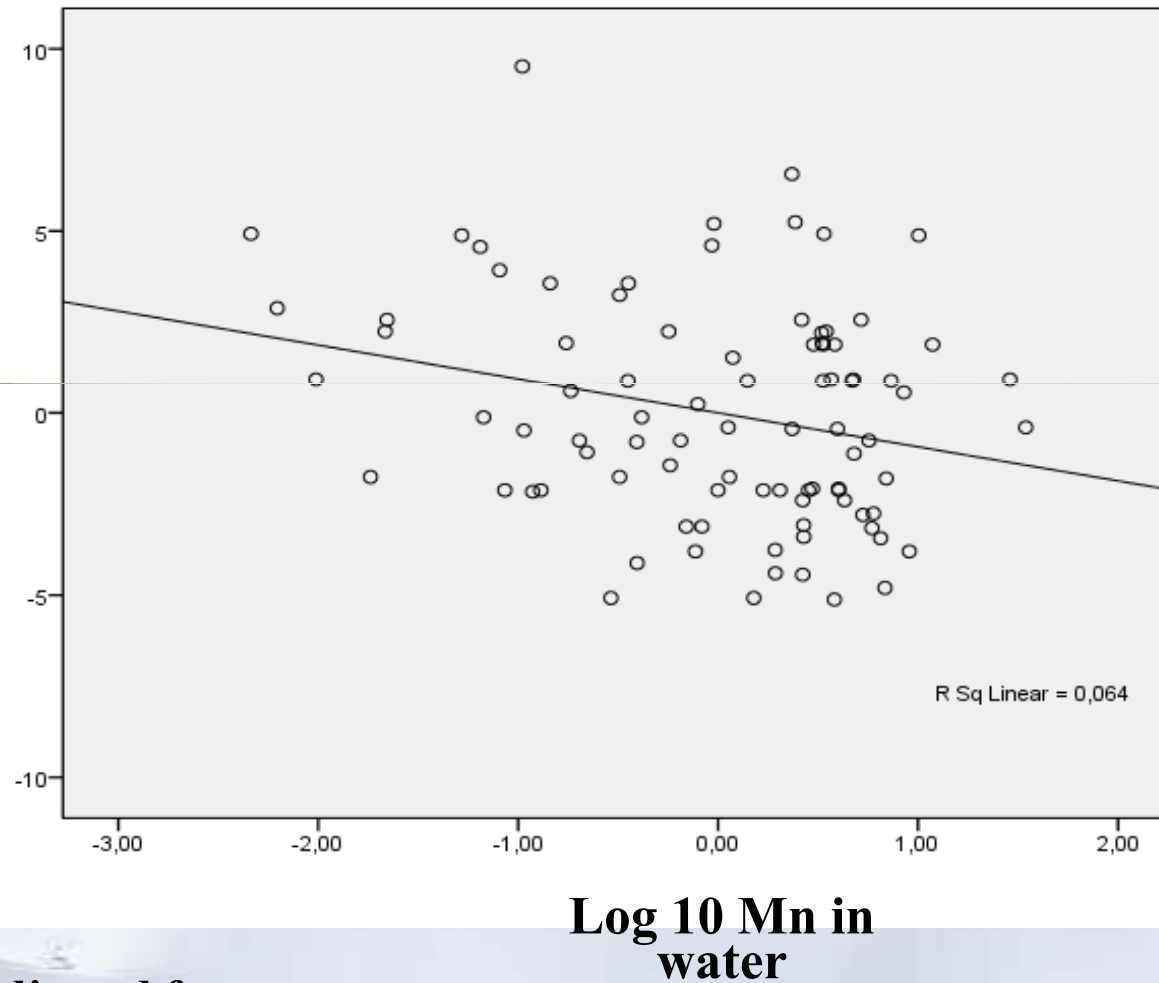


- ✧ **Mean=100 ug/L (SD 97)**
- ✧ **Median = 90.4 ug/L**
- ✧ **Range (0 – 1800)**
  - ✧ **2 values >1000 ug/L**



# Motor abilities

Luria Test  
Score\*



Log 10 Mn in  
water

\*adjusted for age



**For several tests the relation with manganese is different for girls and boys  
BUT all preliminary results show an inverse relation between manganese in drinking water and performance**

✧ Boys:

- ✧ Verbal memory

✧ Girls:

- ✧ Santa Ana motor test
- ✧ Block design
- ✧ Performance IQ

# Special Education

Has received Special Ed.		Water Mn tertiles			
		Lowest tertile ≤ 22 ug/L	Middle tertile 22 – 152 ug/L	Highest tertile >152 ug/L	Total
no	Count	38	36	30	104
	%	90%	69%	67%	75%
yes	Count	4	16	15	35
	%	10%	31%	33%	25%
Total	Count	42	52	45	139
	%	100%	100%	100%	100%

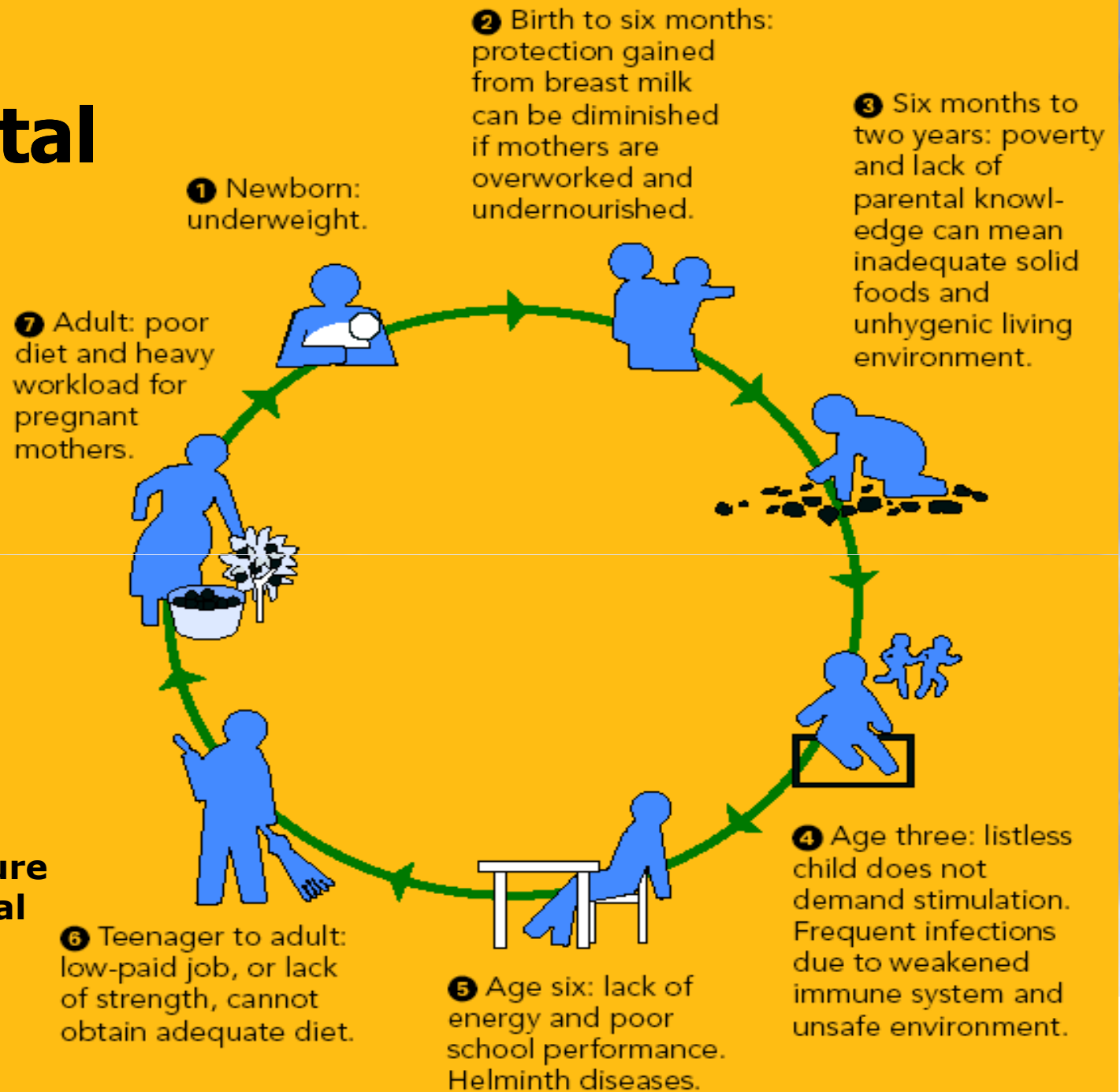
**Step 1: Logistic reg [Mn] continuous  $p_{[Mn]} = .003$  Covariates: income, family rank**

**Step 2: Logistic on [Mn] grouped into tertiles; OR for middle tertile = 6.3 [1.7-23.8]; OR for highest tertile = 7.7 [2.0-30.0]**



# The cycle of environmental disease

Using Indicators to Measure Progress on Environmental Health, WHO, UNEP, 2002



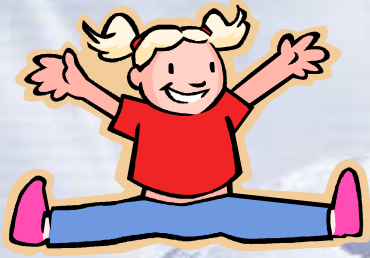












# Methylmercury (MeHg) Exposure

- ✧ **Consumption of fish and marine mammals is the primary source of MeHg exposure in humans.**
- ✧ **But:** fish is a very healthy food, with important nutrients and for many peoples throughout the world, the major source of animal protein.
- ✧ **Challenge:** Maximize nutritional input from fish consumption and minimize toxic risk