Why screening for developmental neurotoxicity? – A few thoughts from an epidemiological perspective

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One reason why are we here

Grandjean P and Landrigan PJ  *Lancet* 2006

**Developmental neurotoxicity of industrial chemicals**

*P Grandjean, PJ Landrigan*

Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are common, costly, and can cause lifelong disability. Their causes are mostly unknown. A few industrial chemicals (e.g.,

“*Exposure during fetal development may cause brain injury at doses much lower than those affecting adults ....*”

*.... still only few chemical are recognized as neurotoxic*”
Recognized chemicals ...

They identified 5 chemicals in 2006 (known knowns):

- Lead
- Methyl-mercury
- Arsenic
- Polychlorinated biphenyls (PCBs)
- Toluene

- … and a long list of known unknowns (n>1000).

- … and unknown unknowns (n>80000)!!
Identification of chemicals follows a pattern which has a lot to do with dose

Figure 1: The effects of a neurotoxic chemical on a population over time
For identification of chemicals toxic to neurodevelopment, the first evidence dealt with adverse effects of high doses on the adult nervous system, and was followed by case reports and epidemiological evidence on developmental toxicity at successively lower doses, to which childhood populations of increasing magnitude were exposed. Recognition of inorganic lead, methylmercury, and polychlorinated biphenyls as neurotoxic followed this curve.
Early-life exposures
Short and long term consequences

Figure 1: Effect of neurotoxicants during early brain development
Exposures in early life to neurotoxic chemicals can cause a wide range of adverse effects on brain development and maturation that can manifest as functional impairments or disease at any point in the human lifespan, from early infancy to very old age.
And a few years later they added more chemicals

Grandjean P and Landrigan PJ  *Lancet Neurol* 2014

- Manganese
- fluoride,
- chlorpyrifos,
- Dichlorodiphenyltrichloroethan
- Tetrachloroethylene,
- polybrominated diphenyl ethers
And a few years later they added more chemicals

Grandjean P and Landrigan PJ *Lancet Neurol* 2014

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**Neurobehavioural effects of developmental toxicity**

*Philippe Grandjean, Philip J Landrigan*

*Lancet Neurol* 2014; 13: 330-38  Neurodevelopmental disabilities, including autism, attention-deficit hyperactivity disorder, dyslexia, and other

- Manganese
- fluoride,
- chlorpyrifos,
- Dichlorodiphenyltrichloroethan
- Tetrachloroethylene,
- polybrominated diphenyl ethers

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**BUT ….. (there's always a but)**
Lack of balance!

- For some of the compounds identified, many of the epidemiological studies were of low quality
- Non-confirmative studies were often not cited and ignored
- Uncertainty not given much weight
Lack of balance!

• For some of the compounds identified, many of the epidemiological studies were of low quality

• Non-confirmative studies were not often cited and ignored

• Uncertainty not given much weight

• But they are making a valid point ....

• And regardless of how we weight the evidence some of the facts cannot be ignored
Perinatal exposures to Pb

- IQ, concentration, memory, cognition, and behavior
  (Landrigan PJ, 1975; Needleman HL, 1979)

- Even at low concentrations (<10μg/dL)
  (Lanphear BP et al EHP 2005)

- For compounds that can easily be quantified and concentration reflect exposure over reasonable time ....

- ...it is not difficult to evaluate long term consequences of developmental exposures (even at low concentrations)

- ....it just takes time
Same goes for methyl-mercury
(also a question of dose)

• High exposures (Minamata 1960)
  – profound mental retardation (Harada M, 1995).

• Seafood, particularly predator fishes:
  – impairment in memory, attention, language, and visuospatial perception documented in children (Grandjean P, 1997).

• “Normal Seafood”
  – Endless discussion of benefits and risk of fish consumption (as we approach “zero”)
For organic chemicals the picture is more complex

- Even for persistent chemicals such as the PCBs quantifying exposure is complex.
- Divergent findings on neurotoxicity
For organic chemicals the picture is more complex

- For non-persistent compounds obtaining a reliable exposure estimates is very challenging
What about pesticides (OPs)
- a more balanced review-

A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure

B. González-Alzaga\textsuperscript{a}, M. Lacasaña\textsuperscript{a,b,*}, C. Aguilar-Garduño\textsuperscript{c}, M. Rodríguez-Barranco\textsuperscript{a,b}, F. Ballester\textsuperscript{b,c,d}, M. Rebagliato\textsuperscript{b,e}, A.F. Hernández\textsuperscript{f}

"Prenatal and to a lesser extent postnatal exposure to OPs may contribute to neurodevelopmental and behavioral deficits in preschool and school children."
The overall take home message

….. in terms of regulating chemicals we occasionally make mistakes ….
The overall take home message

….. in terms of regulating chemicals we occasionally make mistakes …..

"DDT is good for me-e-e-e!" ??

The great expectations held for DDT have been realized. During 1946, exhaustive scientific tests have shown that, when properly used, DDT kills a host of destructive insect pests, and is a benefactor of all humanity.

Time Magazine (June 30, 1947)
The overall take home message

….. in terms of regulating chemicals we occasionally make mistakes ….. **repeatedly**
Conclusions

- There is sufficient evidence to suggest that early life exposures to certain chemicals (including pesticides) may have long term adverse health consequences for the developing offspring.

- Quality of existing studies equally reflects the complexity of capturing these effects.

- A multidisciplinary approaches is needed and in vitro screening for neurotoxicity is a logical step in that direction.