Certainties and uncertainties on children’s environmental health

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Conclusions
(in advance, for those who prefer to take a break)

- Certainty is at odd with intelligence
- Research must address all areas of uncertainty
- Action must be informed by priority setting
- Scientists should feel responsible for the overall consequences of their messages
- Sense of proportion is a useful tool
Outline

• Dimensions of certainty/uncertainty and influencing factors

• (Quasi-)certainties in children’s environmental health

• Examples of uncertainties

• Causes of uncertainties

• Challenges for research and for action in the context of uncertainty
Dimensions of certainty-uncertainty

Causality
- Association
- Dose-response

Magnitude of effect
- Factor specific burden of disease
- Population attributable risk/comparative risk

Prioritization in action
- Expected (comparative) benefits
- Expected (comparative) costs
Certainties in children’s environmental health

1. rapidly developing organs and systems are uniquely susceptible to toxicants and other environmental influences (critical windows)

2. early events may cause, through biological imprinting, long-term and potentially irreversible effects

3. early exposure gives time enough for long latency agents to produce adverse health effects

4. air, fluid and food intakes and specific behaviours make children more exposed to several environmental toxicants

*stays for the whole developmental period from (pre)conception to adolescence
5. there is an important variability across individuals and population groups in both susceptibility and exposure

6. variability may be qualitative or quantitative, i.e. they may regard the nature or the amount of the effect

7. The environmental burden of disease for children is 25 to 35 % of the total burden of diseases for children

8. Social factors are important effect modifiers
Certainties in children’s environmental health: causality links

- Air pollution
- Lack of water and sanitation
- Chemicals and heavy metals
- Physical agents
- Unsafe housing
- Mobility and transport
- Child labor

- Respiratory diseases
- Gastrointestinal diseases
- Neurodevelopmental disorders
- Effects on reproductive health
- Cardiovascular disorders
- Cancer
- Injuries
Causes of uncertainty: a. causality links

- Effects which may arise only for exposure during very narrow susceptibility windows, particularly *in utero*, may be missed by toxicology testing (underestimate).

- Effects that have a very long (i.e. several decades) latency period, that are prolonged into adult life or that can be observed only in the offspring (intergenerational effects) may also be missed (underestimate).

- Effects may be attributed to specific exposures while they are due to other factors not considered in the design of the study and/or in the analysis of results (overestimate).
Biological effects after prenatal irradiation (embryo and fetus).
Ann ICRP 2003; 33: 5-206.

Fig. 5.1. Mental retardation in the atomic bomb in-utero study according to fetal dose and postconception age at irradiation.
The fallacies of ecological studies

Autism Spectrum Disorders in Relation to Distribution of Hazardous Air Pollutants in the San Francisco Bay Area

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Causes of uncertainty:
b. variable susceptibility

- Existence of great variability in susceptibility to different toxicants among children of different age groups due to rapid changes in metabolism, distribution, excretion etc.

- Existence of genetic variability in susceptibility. Existence of biological factors (ex. nutritional status) that can modify susceptibility
High variability in the immature metabolism: lessons from pharmaceuticals

- High Variability even for closely related drugs
- Neonate/adult difference for caffeine 13X greater than for theophylline

$$T_{1/2} \text{ CYP1A2 substrates-caffeine, theophylline}$$

#, SE = 21.63. *p < 0.1; **p < 0.05; ***p < 0.01; ****p < 0.0001

Causes of uncertainty:
c. variable dose-response estimates

<table>
<thead>
<tr>
<th>Environmental risk factor</th>
<th>Deaths</th>
<th>% of deaths from all causes</th>
<th>Deaths per 10 000 children</th>
<th>DALYs</th>
<th>% of DALYs from all causes</th>
<th>DALYs per 10 000 children</th>
</tr>
</thead>
</table>
| Outdoor air pollution (0–4 years)                | 3 861  
13 796\(^a\) | 1.8  
6.4\(^a\) | 0.7  
2.7\(^a\) | 340 818 | 3.1 | 66.1                     |
| Indoor air pollution (0–4 years)                 | 9 845  | 4.6                         | 1.9                        | 340 818 | 3.1 | 66.1                     |
| Water, sanitation and hygiene (0–14 years)       | 13 548 | 5.3                         | 0.8                        | 549 940 | 3.5 | 31.53                    |
| Lead (0–4 years)                                 |        |                             |                            | 156 619 | 1.4 | 3.0                      |
| Injuries (0–4 years)                             | 75 159 | 22.6                        | 3.1                        | 4 793 557 | 19.0 | 200.4                    |

\(^a\) Lower and upper estimates.
Causes of uncertainty: d. effect modifiers

- When exposure to an hazardous agent is sufficient to produce toxicity, the ultimate health effect can be **modified** by factors that, in children to a much greater extent than in adults, can increase **susceptibility** (i.e. concomitant disease or malnutrition) and/or overall **vulnerability** (i.e. lack of adequate access to quality health care) and/or **modify the ultimate effect** (e.g. quality of parenting).

- This is particularly important because it introduces further factors of variability with respect to socio-economic factors (exposure scenarios).
Existing areas of uncertainty: factors influencing the effect

Adverse effect of PCBs similar to beneficial effect of social environment (Walkowiak et al., 2001)

K-ABC was significantly affected by postnatal exposure
Open issues

1. child cancers and environmental exposures

- In Europe, the incidence of child cancer increased from 120 (1978) to 140 (1997) cases per million; a similar trend was shown in USA.

- Several pollutants (radiation, PAHs, some pesticides) are known carcinogenics, many others are suspected.

- To which extent is the increase attributable to environmental pollutants? Other factors related to western life style (mother’s age, no. siblings, hygiene) can contribute to the increase.


DATA: Incidence data from National Cancer Institute, Surveillance, Epidemiology and End Results Program; mortality data from Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System.
Several association studies, few certainties

Household Exposure to Pesticides and Risk of Childhood Hematopoietic Malignancies: The ESCALE Study (SFCE)

INSERM (Institut national de la santé et de la recherche médicale), Villejuif, France.

*Environ Health Perspect.* 2007 Dec;115(12):1787-93.

Insecticide use during pregnancy was significantly associated with childhood AL [OR = 2.1; 95% CI 1.7-2.5], both lymphoblastic and myeloblastic, NHL (OR = 1.8; 95% CI, 1.3-2.6), mainly for Burkitt lymphoma (OR = 2.7; 95% CI, 1.6-4.5), and mixed-cell HL (OR = 4.1; 95% CI, 1.4-11.8)

…but enough for a precautionary approach
Open issues

2. developmental disorders and exposures to environmental pollutants

• Several neurotoxicants (Pb, MeHg, PCBs) are associated to Dev. Disorders, Dev. delay and mild mental retardation

• The proportion of DD/MMR caused by environmental pollutants is likely to be little. Most of the causes of DDs are genetic, perinatal and social

• New hypotheses are made and new concerns arise while little is done on well known causes
“research definitively shows that environmental agents such as lead, mercury, manganese, arsenic, PCBs, alcohol, toluene, tobacco smoke and many pesticides are capable of disrupting human brain development, resulting in negative impacts on the functions controlled by the brain”. (OK)

Henvinet (a network financed by the EU proposes the following definition: 
neurodevelopmental disorders are those that affect the central nervous 
system of the offspring as a result of maternal exposure to chemicals during 
gestation or lactation (not OK: the statement attributes to pollution the whole 
responsibility of the DDs)
Causes of uncertainty:
e. insufficient knowledge about absolute and comparative risks, benefits and overall impact of actions

- The assessment of the possible risks and benefits of each recommended action should include the overall impact of the action

- Resources, political commitment, attention of the public are all limited; prioritization should be carefully based on comparative assessment of the health benefits of a menu of actions
Uncertainties in action: the case of fish, mercury and child development

Should we restrict fish intake in pregnancy?

• yes (earlier studies, US FDA)
• no (ALSPAC Study, NYC study)
Uncertainties in action: when proof of causality may not be the only key issue

Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial

Donna McCann, Angelina Barrett, Alison Cooper, Debbie Crumpler, Lindy Dalen, Kate Grimshaw, Elizabeth Kitchin, Kris Lok, Lucy Porteous, Emily Prince, Edmund Sonuga-Barke, John O'Warner, Jim Stevenson

Do we need food additives?
Should children be given soft drinks?
In conclusion: several new hypotheses
...but too little action on what is already known

- Injuries
- Alcohol
- Tobacco smoke
- OAP
- Unsafe Water
- UV
- Lead, arsenic...
**Dimensions of certainty-uncertainty**

Causality
- Association
- Dose-response

Magnitude of effect
- Factor specific BoD
- Pop. Attributable risk
- Comparative risk

Consequences of action
- Expected (comparative) benefits
- Expected (comparative) costs

**Influencing factors:**
- Variability in susceptibility and exposure
- Social factors
Conclusions

• the wide variability in sensitivity and exposure, the multifactorial nature of many health effects and the lack of adequate developmental testing of many chemicals, all contribute to a considerable amount of uncertainty on the existence and magnitude of the health effects of environmental contaminants in developing organisms.

• uncertainties must be addressed by adopting distinct but complementary approaches including child focused toxicological testing, epidemiological and policy research, precautionary approaches and preventive policies.
Addressing uncertainties:

1. child specific risk assessment process

- include *exposure patterns* at different stages of development from conception to adolescence

- consider all *sources of exposure*, such as diet, water, home, day care, school, neighbourhood and working places (for parents)

- reflect ‘real world’ experiences, including multiple sources of exposure (*aggregate exposure*), simultaneous exposure to several compounds with similar action (*cumulative exposure*) and additive, or multiplicative, toxic effects

- extend and improve *biomonitoring*

- consider different *exposure scenarios*, in order to take into account *aggregate* and cumulative exposure and *socioeconomic factors* that may influence exposure and effect
Addressing uncertainties: 2. epidemiological and policy research

- examine and better quantify the association between environmental factors and health effects, in different exposure scenarios
- assess the efficacy of single-factor and possibly multifactor interventions, including long-term effects
- assess the comparative impact of different policies
action: the crucial aspect is the population attributable fraction and ultimately the disease burden
Keep an eye on the size of the effect/burden of disease!

The environmental burden may vary by a factor of 100 - 1000 among different population groups and different exposures.

E.g. UV and EMF exposure: a considerable difference in health effects, but public (and scientists’) attention is not proportionate to what we know.
Addressing uncertainties:

3. risk regulation and preventive policies

- risk regulation approaches, which include the adoption of extra safety factors, the precautionary principle and other precautionary approaches

- preventive policies aimed at decreasing the emissions of, and/or reducing the exposure to, potentially toxic compounds. These policies cannot be effective without a wide collaboration of all stakeholders including legislators, communities, and the industry
Addressing uncertainties:
4. Research challenges

• Children’s exposure to environmental pollutants needs a stronger research effort

• Research should not be limited to causality, but should include exposure estimates, attributable burden, identification of effective interventions

• Action must take into account the comparative dimensions of risk to identify correctly the priorities, and communicate effectively with the population
Addressing uncertainties: the role of longitudinal studies

- **Longitudinal studies** investigating at the same time several factors may provide answers to several questions regarding causality and health effects.

- **The Trieste birth cohort** investigates the exposure to heavy metals as well as to microrganisms and other factors influencing the embryo and foetus, and their influence on the neurodevelopmental outcome of children.
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