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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

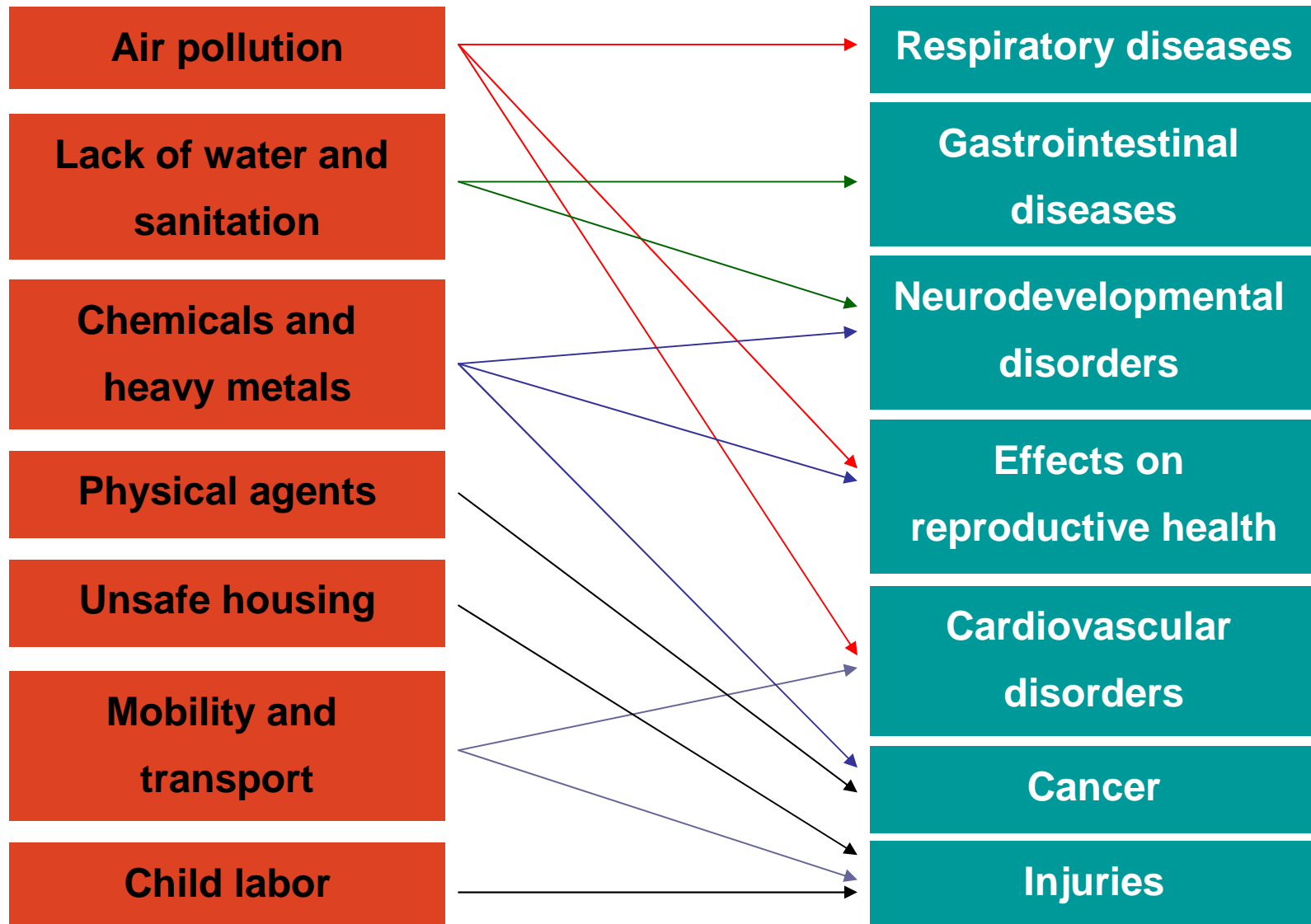
1. rapidly developing organs and systems are uniquely susceptible to toxicants and other environmental influences (**critical windows**)
2. early events may cause, through **biological imprinting**, long-term and potentially irreversible effects
3. early exposure gives time enough for **long latency** 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

Certainties in children's environmental health

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



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)

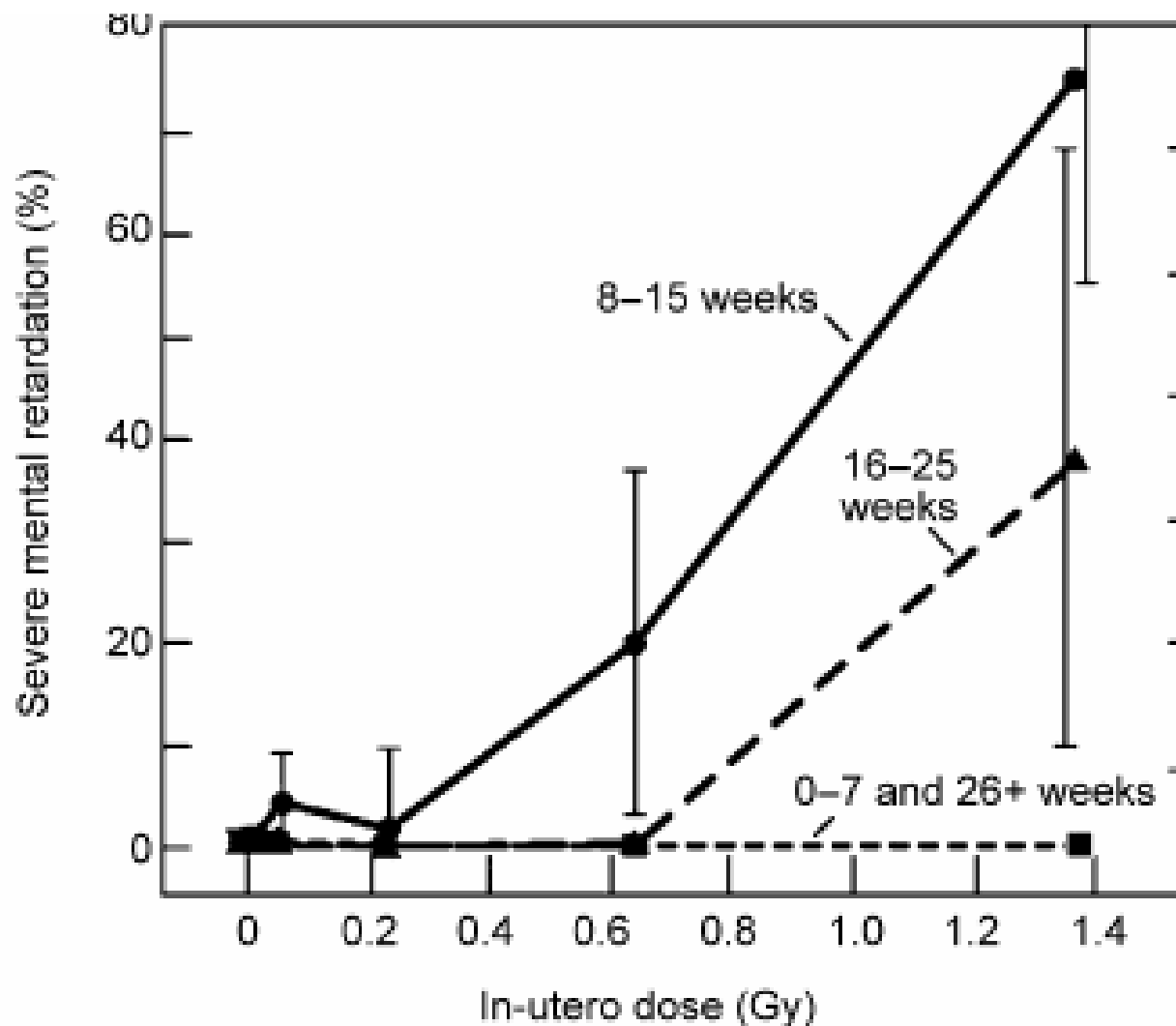


Fig. 5.1. Mental retardation in the atomic bomb in-utero study according to fetal dose and postconception age at irradiation.

Biological effects after prenatal irradiation (embryo and fetus).
Ann ICRP 2003; 33: 5-206.

The fallacies of ecological studies

Research | Children's Health

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

Gayle C. Windham,¹ Lixia Zhang,² Robert Gunier,¹ Lisa A. Croen,³ and Judith K. Grether¹

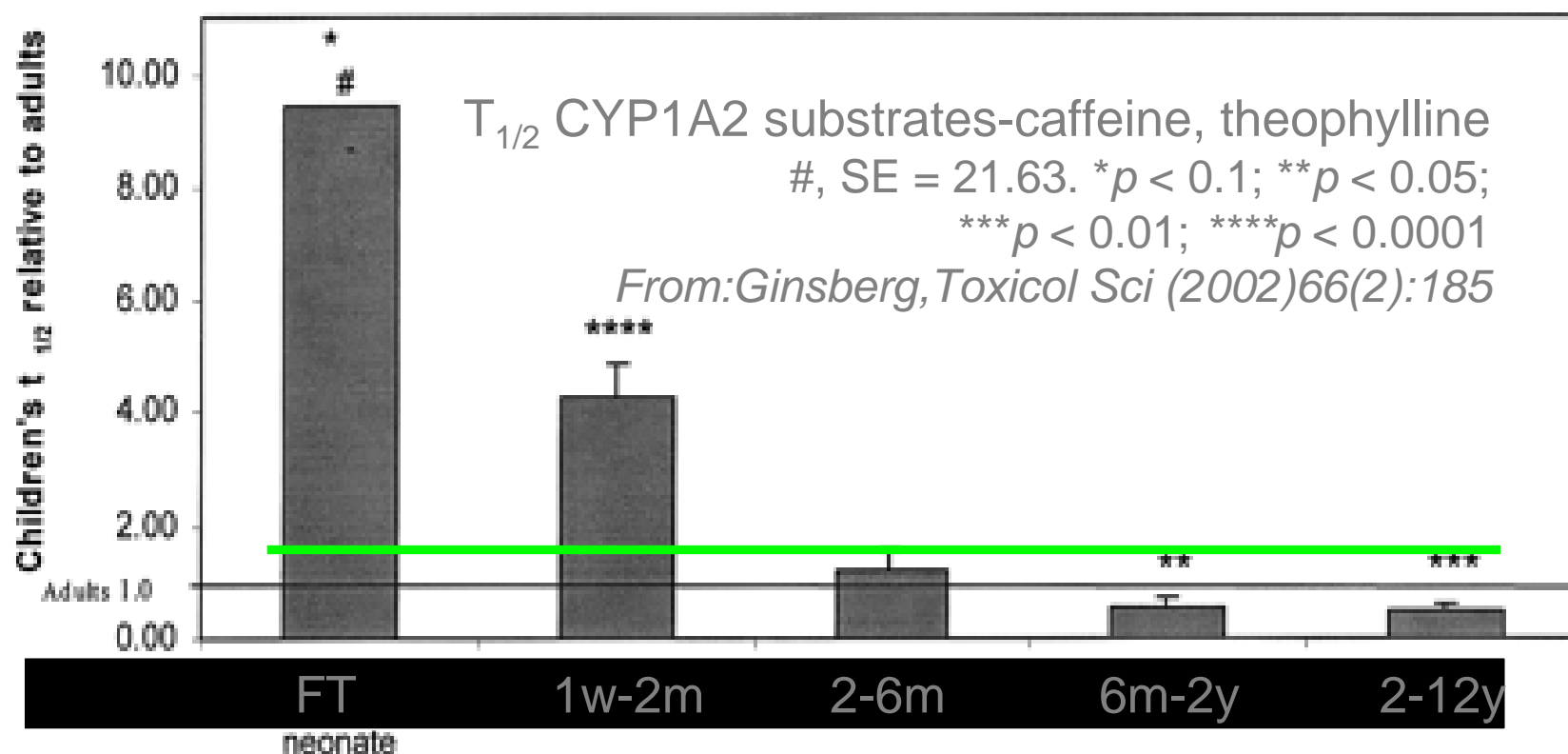
¹Division of Environmental and Occupational Disease Control, California Department of Health Services, Richmond, California, USA;

²Impact Assessment, Inc., La Jolla, California, USA; ³Kaiser Permanente Medical Care Program Division of Research, Oakland, California, USA

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

Causes of uncertainty:

c. variable dose-response estimates

ARTICLES

Burden of disease attributable to selected environmental factors and Injury among children and adolescents In Europe

Francesca Valent, D'Anna Litife, Roberto Bertolini, Leda E Nemer, Fabio Barbone, Giorgio Tamburini

Environmental risk factor	Deaths			DALYs		
	Deaths	% of deaths from all causes	Deaths per 10 000 children	DALYs	% of DALYs from all causes	DALYs per 10 000 children
Outdoor air pollution (0-4 years)	3 861 13 796 ^a	1.8 6.4 ^a	0.7 2.7 ^a			
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

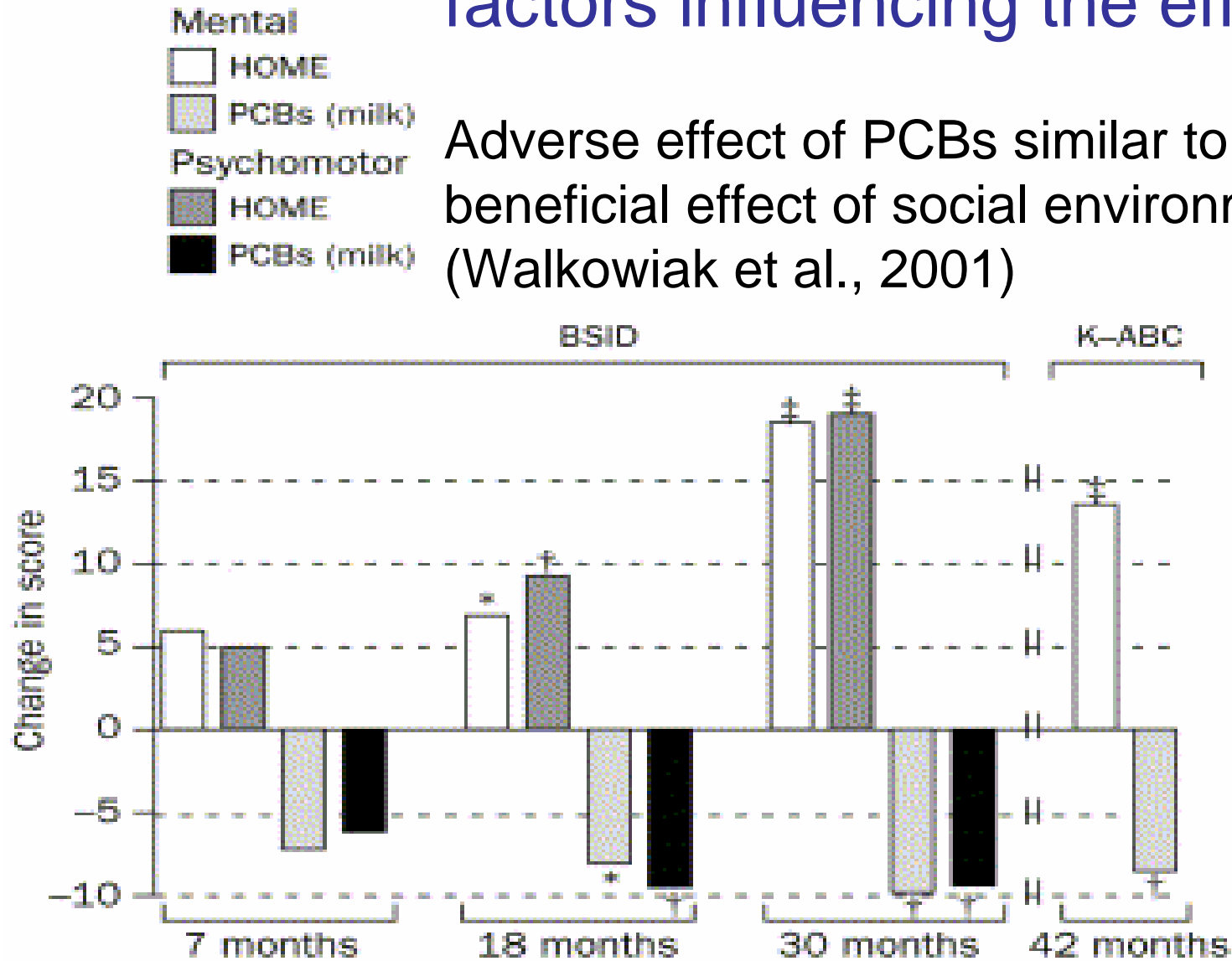
^a Lower and upper estimates.

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)

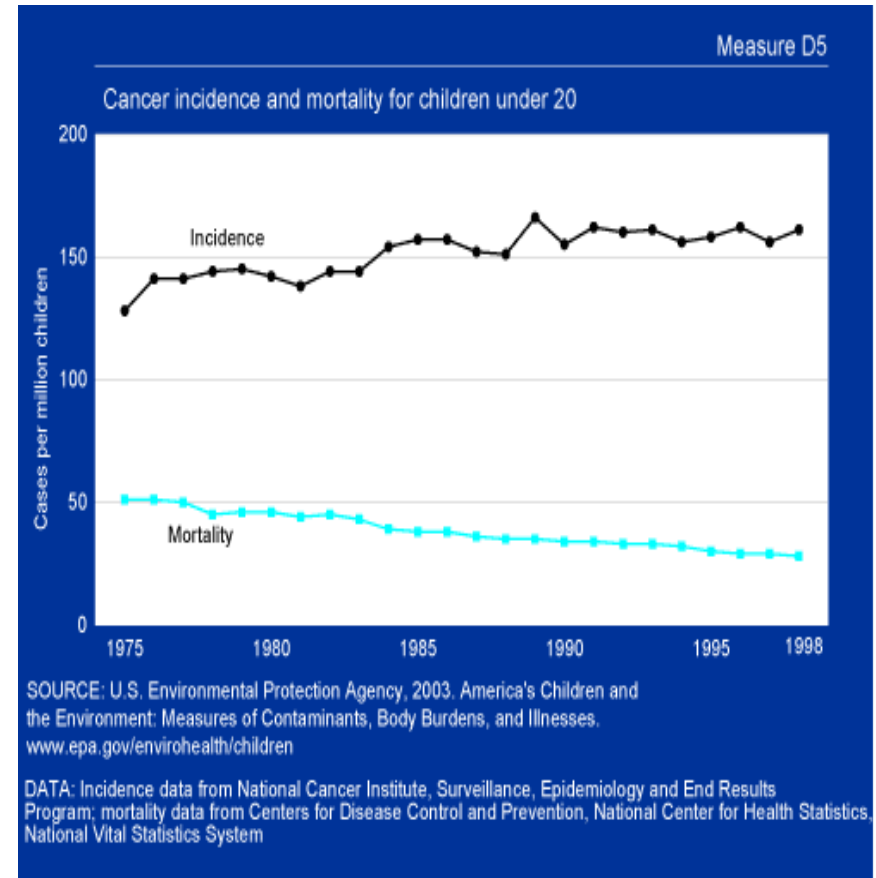


K-ABC was significantly affected by postnatal exposure

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



Several association studies, few certainties

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

Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y, Patte C, Pacquement H, Vérité C, Robert A, Michel G, Margueritte G, Gandemer V, Hémon D, Clavel J.

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

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

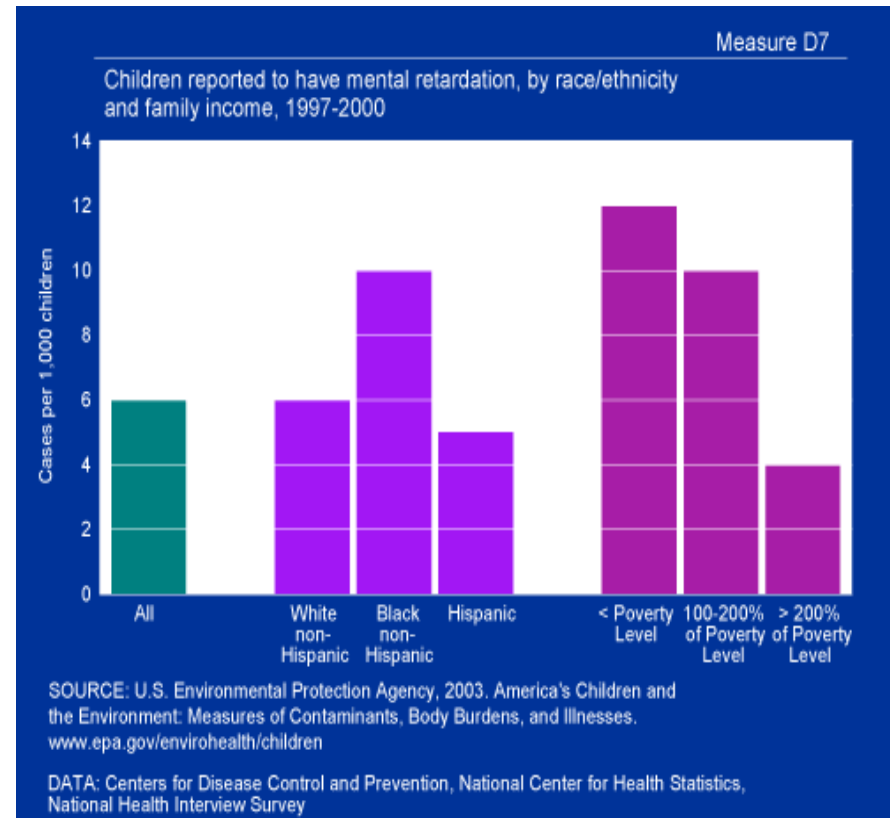
Insecticide use during pregnancy was significantly associated with childhood AL [OR = 2.1; 95% CI 1.7-2.5], both lymphoblastic and myeloblastic, NHL (OR = 1.8; 95% CI, 1.3-2.6), mainly for Burkitt lymphoma (OR = 2.7; 95% CI, 1.6-4.5), and mixed-cell HL (OR = 4.1; 95% CI, 1.4-11.8)

...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



Science...or overstatement?

Scientific Consensus Statement on Environmental Agents Associated with Neurodevelopmental Disorders



Developed by the Collaborative on Health and the Environment's
Learning and Developmental Disabilities Initiative
November 7, 2007

Given the established knowledge, protecting children from neurotoxic environmental exposures from the earliest stages of fetal development clearly is an essential public health measure if we are to help prevent learning and developmental disorders and create an environment in which children can reach and maintain their full potential.

“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 whoel 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)

Maternal fish consumption and children's development

We should take into account all factors influencing neurodevelopment and carefully assess their relative contribution in specific population groups if we want to effectively protect and promote the cognitive development of our children. To start, it will be important to disclose the results of the ALSPAC study with respect to the independent effect of social variables on neurodevelopmental outcomes.

GT and FB are currently involved in PHIME.

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Uncertainties in action: when proof of causality may not be the only key issue)

www.thelancet.com Vol 370 November 3, 2007

Ⓜ 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 Parteous, Emily Prince, Edmund Sonuga-Barke, John O'Warner, Jim Stevenson

VOLUME 114 | NUMBER 9 | September 2006 • Environmental Health Perspectives

Do we need food additives?
Should children be given soft drinks?


In conclusion: several new hypotheses

ehp ENVIRONMENTAL
HEALTH
PERSPECTIVES
ehponline.org

Prenatal Exposure to Airborne Polycyclic
Aromatic Hydrocarbons and Risk of Intrauterine
Growth Restriction

Hyunok Choi, Virginia Rauh, Robin Garfinkel,
Yihuan Tu, and Frederica P. Perera

doi:10.1289/ehp.10958 (available at <http://dx.doi.org/>)
Online 30 January 2008

 **NIHES**
National Institute of
Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services

Cardiovascular and Metabolic Risk

ORIGINAL RESEARCH

A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes

Results from the National Health and Examination Survey 1999–2002

DUK-HEE LEE, MD, PHD¹
IN-KYU LEE, MD, PHD²
KYUNGJUN SONG, MD, PHD³
MICHAEL STEFFES, MD, PHD⁴

WILLIAM TOSCANO, PHD⁵
BETH A. BAKER, MD, PHD^{3,6}
DAVID R. JACOBS, JR., PHD^{1,8}

Persistent organic pollutants (POPs) have become widespread environmental contaminants and now represent a global problem (1). The toxicity of these pollutants in humans and wildlife

Environmental pollution and diabetes: a neglected association

www.thelancet.com Vol 371 January 26, 2008

...but too little action on what is already
known

- Injuries
- Alcohol
- Tobacco smoke
- OAP
- Unsafe Water
- UV
- Lead, arsenic...

Dimensions of certainty-uncertainty

Causality

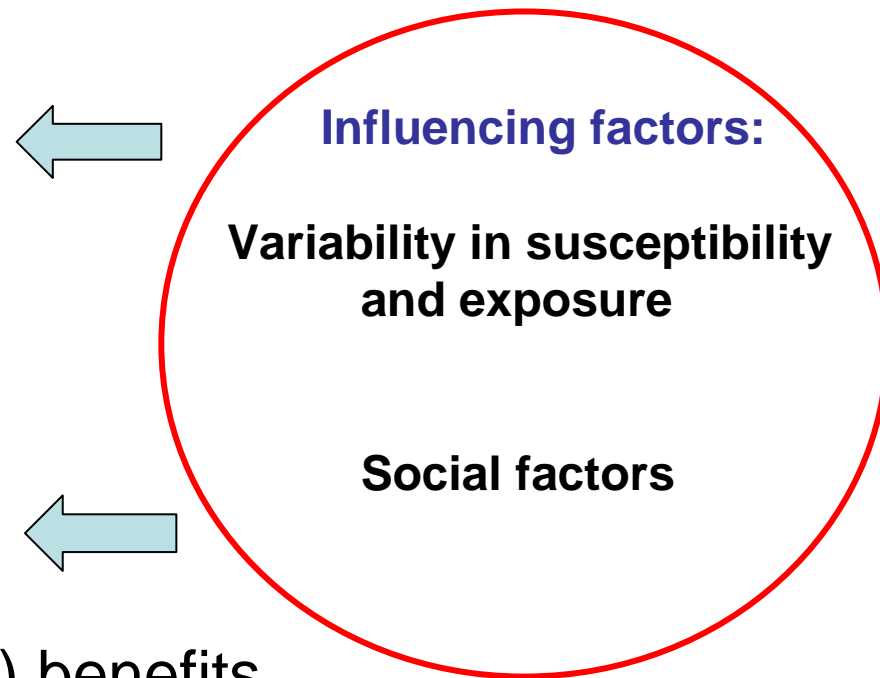
- Association
- Dose-response

Magnitude of effect

- Factor specific BoD
- Pop. Attributable risk
- Comparative risk

Consequences of action

- Expected (comparative) benefits
- Expected (comparative) costs



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

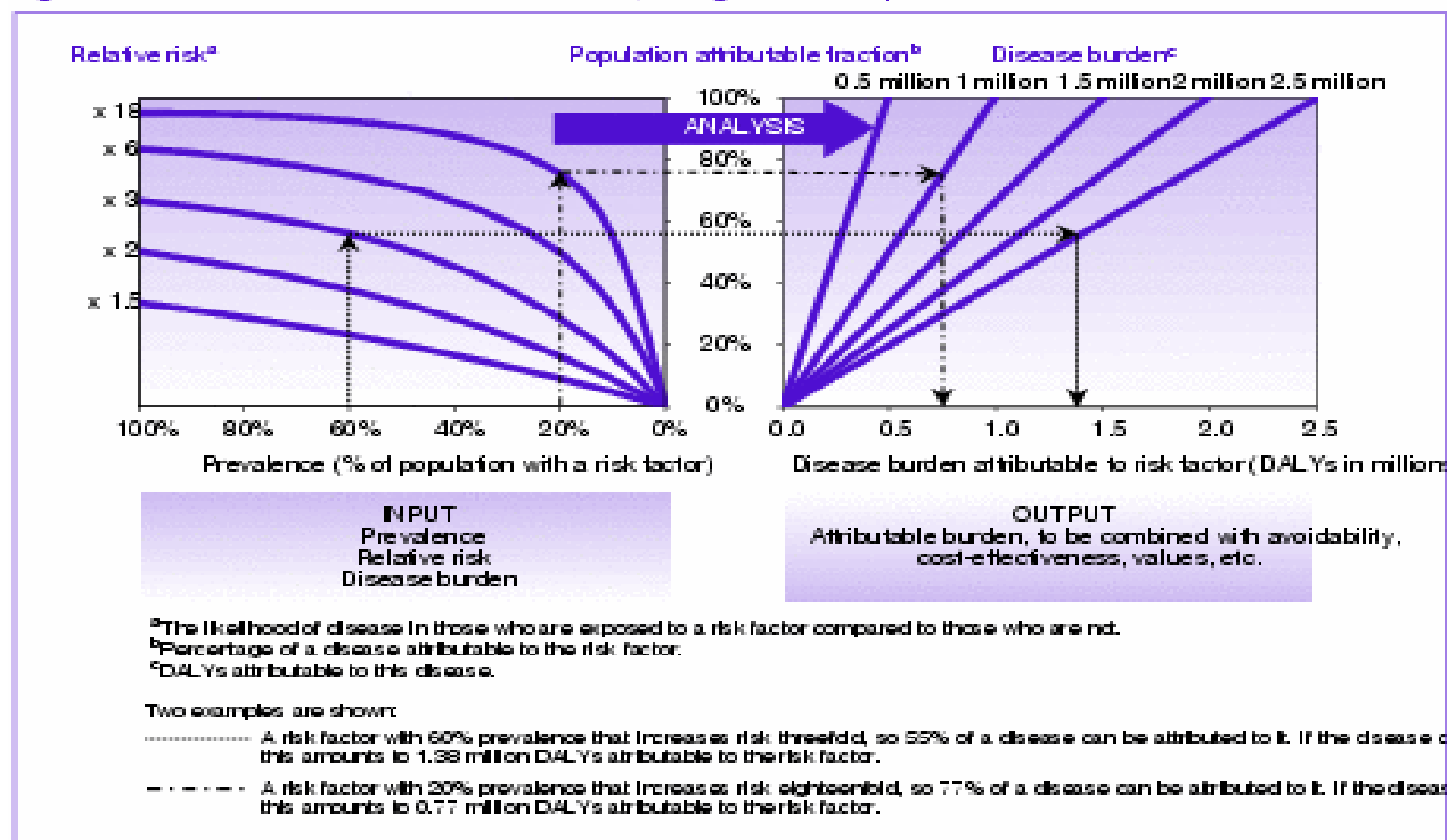
- include ***exposure patterns*** at different stages of development from conception to adolescence
- consider all ***sources of exposure***, such as diet, water, home, day care, school, neighbourhood and working places (for parents)
- reflect 'real world' experiences, including multiple sources of exposure (***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

Figure 2.6 Determination of attributable burden, taking account of prevalence and relative risk



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 microorganisms and other factors influencing the embryo and foetus, and their influence on the neurodevelopmental outcome of children

Conclusions

- 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 proportions is a useful tool