



THE NEED FOR A LIFE-STAGE APPROACH TO ASSESS RISKS FROM CHEMICAL EXPOSURES IN CHILDREN

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Children have **different susceptibilities during different life-stages** -from conception to adolescence- due to their dynamic growth and developmental processes, as well as physiological, metabolic and behavioural differences, and unique exposure pathways.

This recognition has raised international concern and identified the need to develop ***risk assessment approaches that take into account the special vulnerabilities of children at each developmental stage*** in order to adequately protect children.

The stages of “childhood” can be viewed from a variety of perspectives: chronological, developmental, legal, educational,...

WORKING DEFINITIONS FOR STAGES IN HUMAN DEVELOPMENT

DEVELOPMENTAL STAGE/EVENT

TIME PERIOD

PRE-CONCEPTION

Pre-fertilization

PREIMPLANTATION EMBRYO

Conception to implantation

POSTIMPLANTATION EMBRYO

Implantation to 8 weeks pregnancy

FETUS

8 weeks to birth

PRE-TERM BIRTH

24–37 weeks

NORMAL TERM BIRTH

40+ 2 weeks

PERINATAL STAGE

29 weeks pregnancy to 7 days after birth

NEONATE

birth to 28 days

INFANT

28 days to 1 year

CHILD

Young child

1 – 4 years

Toddler

2 – 3 years

Older child

5 – 12 years

ADOLESCENT

2ry sexl traits to maturity (12 to 18)

ADULT

after 18-21 (certain systems continue to develop, e.g., skeleton, brain)

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Major environmental threats to children:

- ② Economic and nutritional
- ② Social, cultural, demographic, lifestyle
- ② Physical – "built environment"
- ② Chemical hazards

Intrinsic factors

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Nutritional factors

- **In pregnant women**

Protein malnutrition results in anemia that impairs foetal growth and development:

LBW or size and increased child morbidity

- **In Infants**

LBW linked to developmental and learning deficits

- **In the 2-3 y.o.**

Chronic under-nutrition may delay growth and learning abilities.

An impaired immune system favors infections.

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Nutritional factors

Iron deficiency:

Main cause of anemia, over 2 billion people (WHO, 2002b).

1/5 of perinatal mortality attributed to iron deficiency.

Reduces intelligence in mid-childhood

Increases susceptibility to lead

Vit A deficiency:

Main cause of preventable blindness in children (WHO, 2002b).

Low folic acid:

Pre-conception/early pregnancy: birth defects (neural tube)

WHO data base: <http://www3.who.int/whosis/micronutrient/>

Obesity in children: health threat in developed countries, increasing in developing (de Onis et al., 2004; Koplan et al., 2005)

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Intrinsic factors: genetics

- Control the dynamics of development
- May determine the susceptibility of children to environmental exposures at different life-stages
- Outcome of exposure influenced significantly by genetics
- Most frequent genetic polymorphisms: differences in the capacity to metabolize toxicants over the course of various developmental stages.



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Intrinsic factors: genetics

- ***Ex: heavy maternal cigarette smoking (> 10/day) and cleft lip/palate in the offspring when an allelic variant for TGF-alpha is present***
(Hwang et al., 1995; Shaw et al., 1996).
- ***Ex: 4% of the population carries a gene that results in lower levels of acetylcholinesterase (target enzyme of OPs) increasing the vulnerability of the developing brain to OPs***
(Costa et al., 2003).

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Establishing causal links between specific environmental exposures and complex, multifactorial health outcomes is difficult and challenging, particularly in children

- For children, the stage in their development when the exposure occurs may be as important as the magnitude of exposure
- Exposures to the same environmental factor can result in very different health outcomes in children - some being irreversible and persistent
- Different organ systems mature at different rates: the same dose of an agent during different periods of development can have very different consequences
- Long latency period between exposure and effects, with some outcomes not apparent until later in life.

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Different organ systems develop at different rates, and for each developmental stage there are both broad windows of susceptibility and more specific periods of susceptibility

(Selevan et al., 2000; Faustman et al., 2000).

However, in most cases, the exact time when organ systems are susceptible to toxic chemicals is unknown

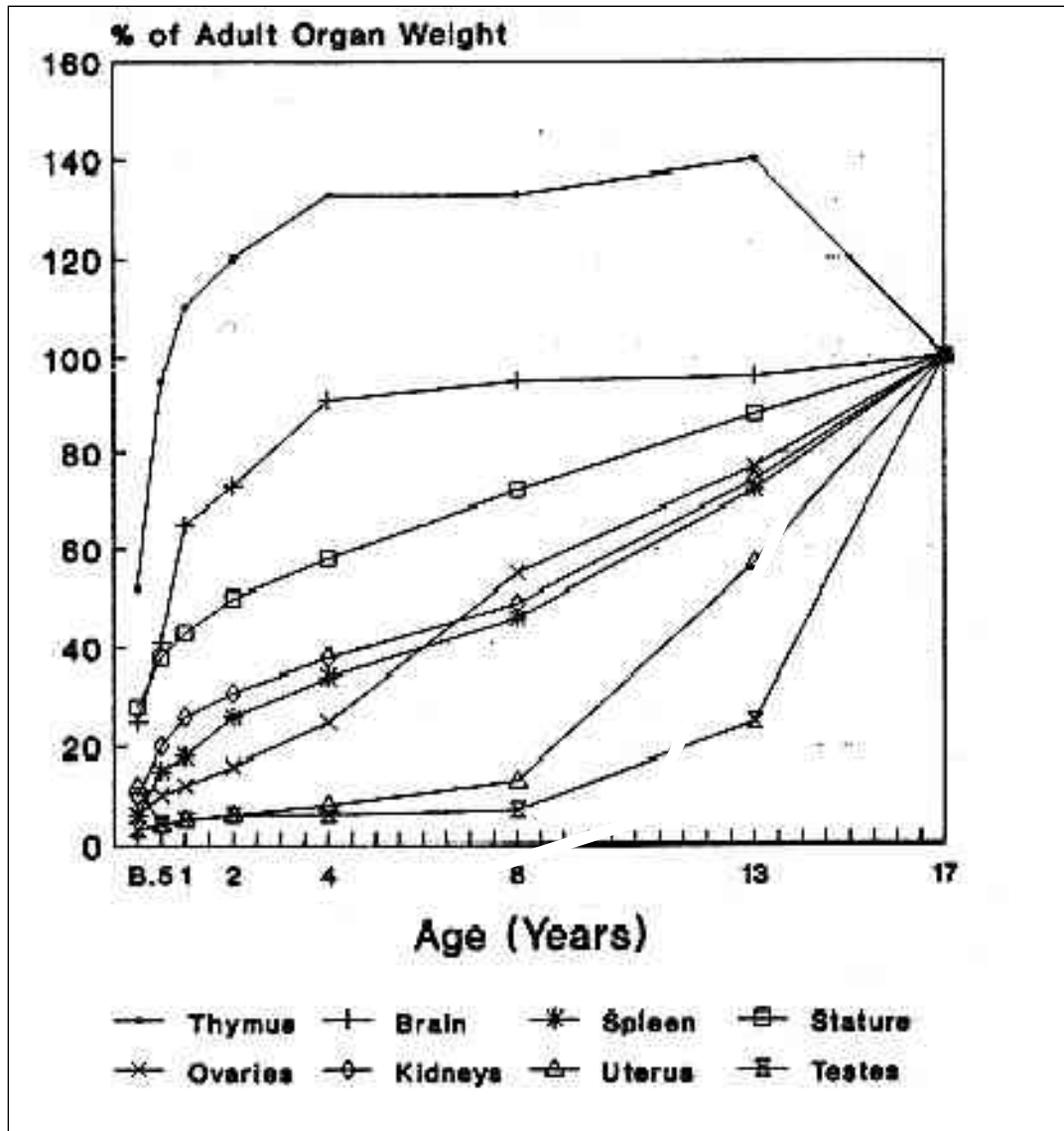
- **Know in some detail for CNS development & radiation exposure**
- **More will be known on adolescence – greater interest in the effects of hormonally active agents and more information available.**

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Adverse effects in children may result from exposure:

- **Prior to conception (paternal or maternal)**
- **During prenatal development**
- **Postnatally - to the time of full maturity**

WINDOWS OF DEVELOPMENT: BIRTH TO ADOLESCENCE



- ❖ **Vital organ growth**
 - Brain
 - Lungs
 - Kidneys
 - Reproductive organs
- ❖ **Physiological function**
 - CNS
 - Immune system
 - Endocrine system

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Adverse health outcomes from early exposures may become apparent at any point in the life-span, even after long latency periods.

Ex. health effects resulting from developmental exposures:

- Prenatally/at birth miscarriage, stillbirth, LBW, birth defects
- In young children asthma, neurobehavioural and immune impairment
- In adolescents precocious or delayed puberty
- In adults diabetes, heart disease

DEVELOPMENTAL STAGE SPECIFIC SUSCEPTIBILITIES AND OUTCOMES IN CHILDREN

SPECIFIC ORGAN SYSTEMS –

Periods of susceptibility & consequences of exposure

Growth restriction and birth defects

Nervous system

Reproductive system

Endocrine and metabolic disorders

Cardiovascular system

Immune system

Respiratory system

Kidney

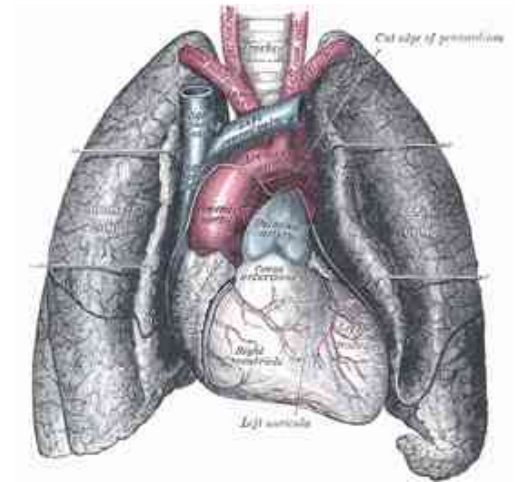
Cancer

Childhood cancers that may have environmental causes

Adult cancers related to childhood exposures

Chemical exposures of special concern

Normal development of the lungs in humans



Prenatal

8-10 w: functional smooth muscle

16 w: airway branching

17 w: blood vessels

24 w: lamellar bodies in Type II cells

26 w: respiratory bronchioles

28 w: cartilage

30-50% of alveoli

Postnatal

Increase in airway size parallels somatic growth

Alveolarisation up to 2y

Lung volume:

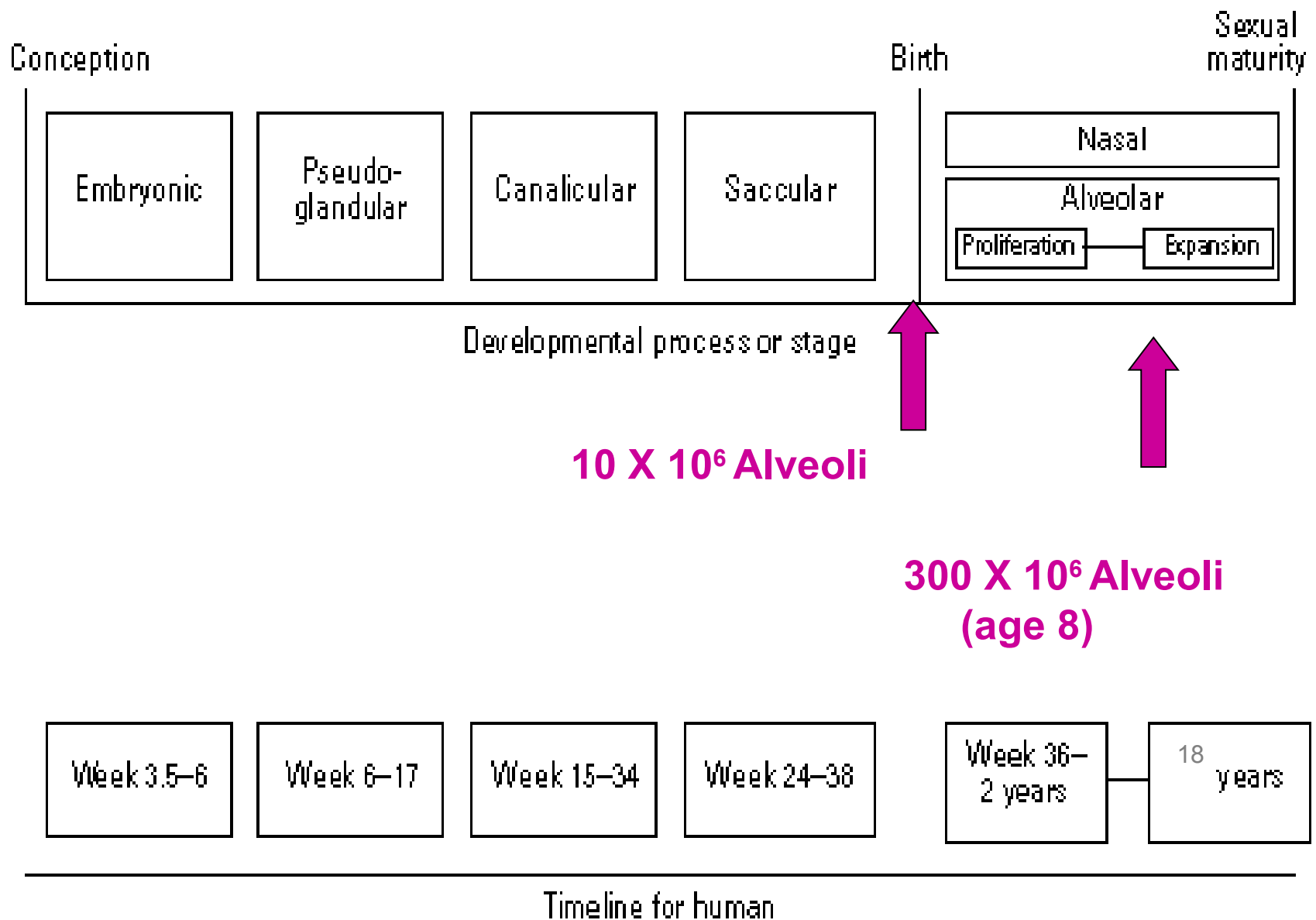
X2 from birth to 18 months

X2 again to 5 y

Lung growth up to

18 y in females

20-23 y in males.



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Environmental tobacco smoke (ETS): toxics and carcinogens, incl. PM, NO_x, aldehydes and oxygen free radicals that are irritants or cilio-toxics

In utero

- PAHs, nicotine and CO cross the placenta and concentrate in the foetal circulation. Foetal enzymes are immature and metabolites accumulate at a period of intense cellular differentiation and growth

(Perera et al 199; Ruhle et al., 1995).

Mutagenic effects of smoke may impair cellular division and differentiation in the respiratory tree leading to reduced lung function and increased bronchial hyper-responsiveness

(Cook et al., 1998).

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Environmental tobacco smoke (ETS)

Infants

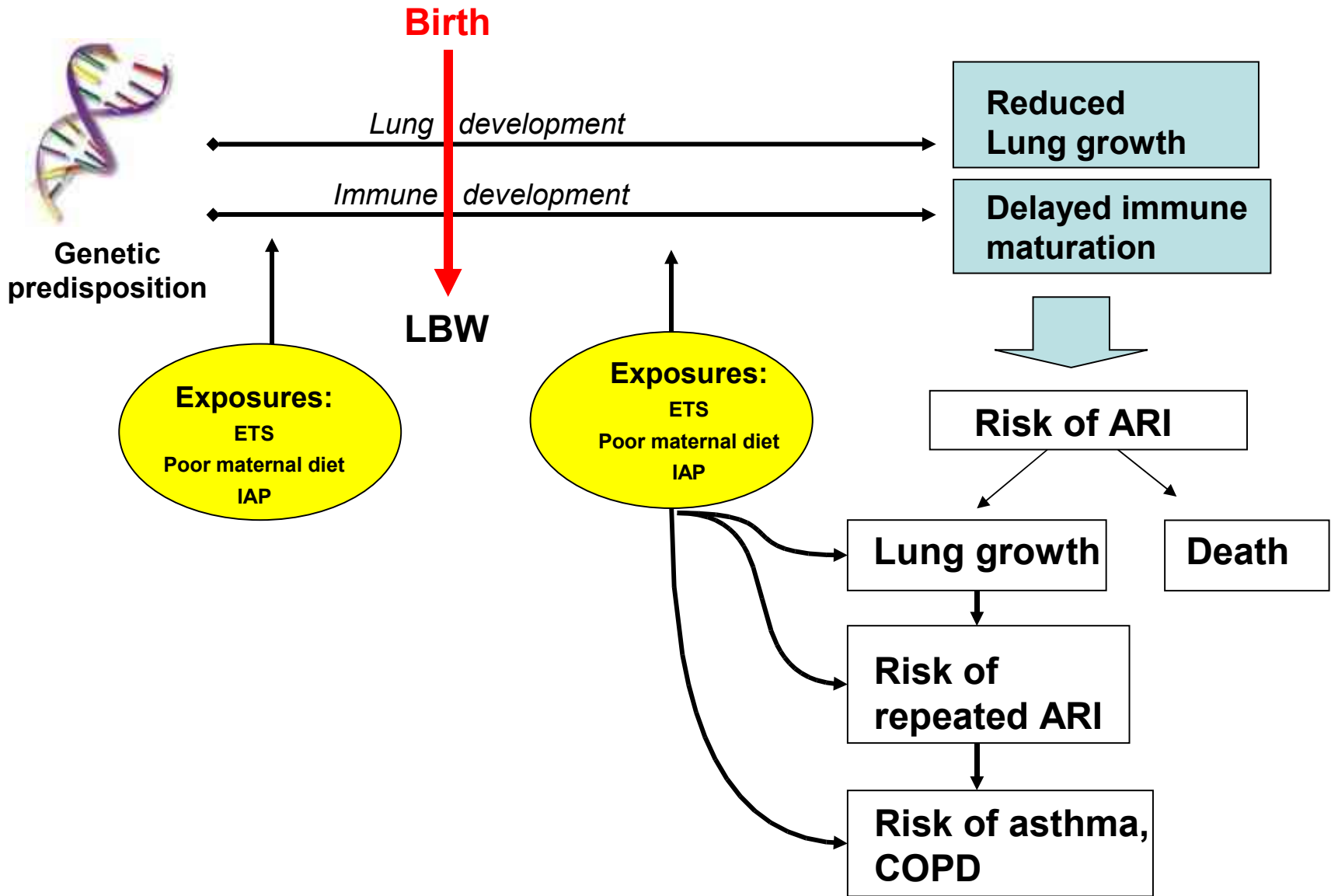
decreased lung function and increased bronchial hyper-responsiveness when mothers smoked in pregnancy and predisposition to wheezing and lower respiratory illnesses (*Tager et al., 1995*).

Children

Parental smoking over 10/day increases the risk of asthma X 2.5 and may increase their risk of atopic sensitization (*Braback et al., 1995*)

LRTI 60% higher amongst children exposed to ETS during the first 18 months of life

Risks of chronic and recurrent otitis media increased



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Exposure Assessment of Children

- **Direct methods**
- **Biomarkers of exposure**
- **Modeling**

Unique characteristics of children that affect exposure

Exposure as it relates to children around the world

Sources/geographical location

Pathways of exposure (air, water, soil, food...)

Settings/microenvironments (home, school, child care centre, recreations, special settings)

Environmental equity factors (vulnerable communities)

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Limitations in knowledge – Why?

- Research on the impact of environmental factors on children's health focuses on specific exposures (e.g. lead, pesticides) or a particular organ system or endpoint.
- No prospective longitudinal studies capturing exposures over key developmental windows or life stages.
- Few studies on peri-conceptual exposures

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The way ahead - Opportunities

- New technologies and methodologies may allow to study exposures during these critical windows.
- The special vulnerability of children and the life-stage approach to be considered for child-protective policies and in risk assessment

However: lack of full proof for causal associations should not prevent efforts to reduce exposures or implement intervention and prevention strategies.

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The way ahead – What needs to be done

- Design and implement prospective cohort studies of pregnant women, infants & children with longitudinal capture of exposures at critical windows and sensitive health endpoints – *E.g. recruiting couples prior to conception to address peri-conceptual exposures and children's health.*
- Enhance population based surveillance systems for the real time capture of sentinel health endpoints.
Eg. birth size & gestation, birth defects registries, fecundability and sex ratios
- Strengthen exposure monitoring efforts in children during different developmental stages, incl.aggregate and cumulative exposures.

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The way ahead – what needs to be done

- Strengthen exposure monitoring efforts in developing countries.
- Identify subpopulations with the highest exposure levels.
- Develop validated, sensitive and cost-effective biomarkers of exposure, susceptibility, and effects (in early ages).
- Improve characterization of the different toxicokinetic and toxicodynamic properties of xenobiotics at different developmental stages
- Study mechanisms of action during different developmental stages by which exposures may cause adverse outcomes.

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WHO Environmental Health Criteria (EHC) 237

Scientific principles that need to be considered when assessing the potential health risks in children from exposure to environmental agents during distinct developmental stages.

EHC 30, “Principles for Evaluating Health Risks to Progeny Associated with Exposure to Chemicals During Pregnancy” (IPCS, 1984)

EHC 59, “Principles for Evaluating Health Risks from Chemicals During Infancy and Early Childhood: The Need for a Special Approach” (IPCS, 1986a).

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ENVIRONMENTAL HEALTH CRITERIA 237

PRINCIPLES FOR EVALUATING HEALTH RISKS IN CHILDREN ASSOCIATED WITH EXPOSURE TO CHEMICALS

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Available at: www.who.int/ipcs