

***Training Course in Reproductive Health Research
19 February 2008, WHO HQ***

**FETAL/ENVIRONMENTAL
ORIGINS OF ADULT DISEASE**

Children's Health and the Environment

WHO Training Package for the Health Sector

World Health Organization

www.who.int/ceh

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WHAT IS THE ENVIRONMENT?

"Everything that surrounds anything"

web.mala.bc.ca

All the physical, chemical, biological and social factors that may affect the origin, growth, development and survival of an organism in a given setting.

Fetal Origins of Adult Disease

Causes and estimated number of deaths/year in children 0 to 4 yrs

Acute respiratory infections:	1 000 000
Diarrhoeal diseases:	1 600 000
Malaria and other vector-borne:	1 000 000
Injuries (non-intentional)	300 000
Poisonings	16 000

www.who.int/evidence 2002 data

The environment and health for children and their mothers, Fact sheet WHO/284, 2005

Diseases strongly linked to environmental threats are present in places where children grow, live, learn and... work

WHO ACTIVITIES ON CHILDREN'S HEALTH & THE ENVIRONMENT

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WE KNOW MORE! New recognition of:

❖ **Special vulnerability of child/fetus to environmental influences**

Chemicals, radiations, noise, climate change,...

❖ **Effects related to toxicity, dose, type of exposure and timing**

❖ **Effects exacerbated by:**

- **Poverty**
- **Malnutrition**
- **Urbanization**
- **Degraded environments**
- **Stressful circumstances**
- **Ignorance**

MAIN GLOBAL ENVIRONMENTAL HEALTH RISKS

- ❖ Poor hygiene and sanitation
- ❖ Household water insecurity
- ❖ Air pollution – indoor and outdoor
- ❖ Disease vectors
- ❖ Chemical hazards
- ❖ Injuries and accidents
- ❖ *EMERGING ISSUES!*

Over 5 000 000 children under 14 years die every year from diseases that relate to environmental conditions, mainly in the developing world.

www.who.int/world-health-day/2003

HEALTH EFFECTS OF GLOBAL WARMING:

□ Direct Effects

- Thermal extremes: heat stroke
- Weather disasters: drowning, and psychological trauma
- Dehydration and Diarrhoeal disease

□ Indirect Effects

- Food availability: malnutrition, growth retardation, and developmental delay
- Increased aeroallergens: allergies
- Malaria, dengue fever, and other vector-borne diseases

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COMBINATION OF ENVIRONMENTAL RISK FACTORS

Heavy traffic

+

Toxic waste site, industrial effluent

+

Contaminants (in water, food, objects)

+

Malnutrition

+

Genetic predisposition



1. No effects
2. No obvious effects – *disease later in life!*
3. Developmental problems
4. Disease

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**COMPLEX ENVIRONMENTS,
MULTIPLE PROBLEMS,
STRATEGIC APPROACHES**

RISKS

Physical
Chemical
Biological
Social

MEDIA

Water, Air, Food
Soil, Objects

SETTINGS

Rural/urban
Home, Park,
Field, Street,
Work

ACTIVITIES

Eating, Drinking, Working,
Hobbies, Habits,

EFFECTS ON

Organs
Systems
Functions
Well-being
Development
Survival

SUSCEPTIBILITY

Critical windows
Nutrition
Poverty
Ethnic minorities



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ARE ENVIRONMENTAL THREATS SIMILAR AROUND THE WORLD?

KEY GLOBAL RISK FACTORS (WHO)

- ❖ Water safety
- ❖ Hygiene and sanitation
- ❖ Air pollution
- ❖ Disease vectors
- ❖ Chemical hazards
- ❖ Injuries and accidents
- ❖ **EMERGING ISSUES!**

CEH CONCERNS IN INDUSTRIALIZED COUNTRIES

- ❖ Respiratory disease and air quality
- ❖ Obesity/nutrition/diabetes
- ❖ "Built" environment
- ❖ Neurological impairment
- ❖ Birth defects
- ❖ Autism
- ❖ Fetal origin of adult disease
- ❖ Childhood cancer
- ❖ Endocrine disruption

MILLENNIUM DEVELOPMENT GOALS (MDGs)

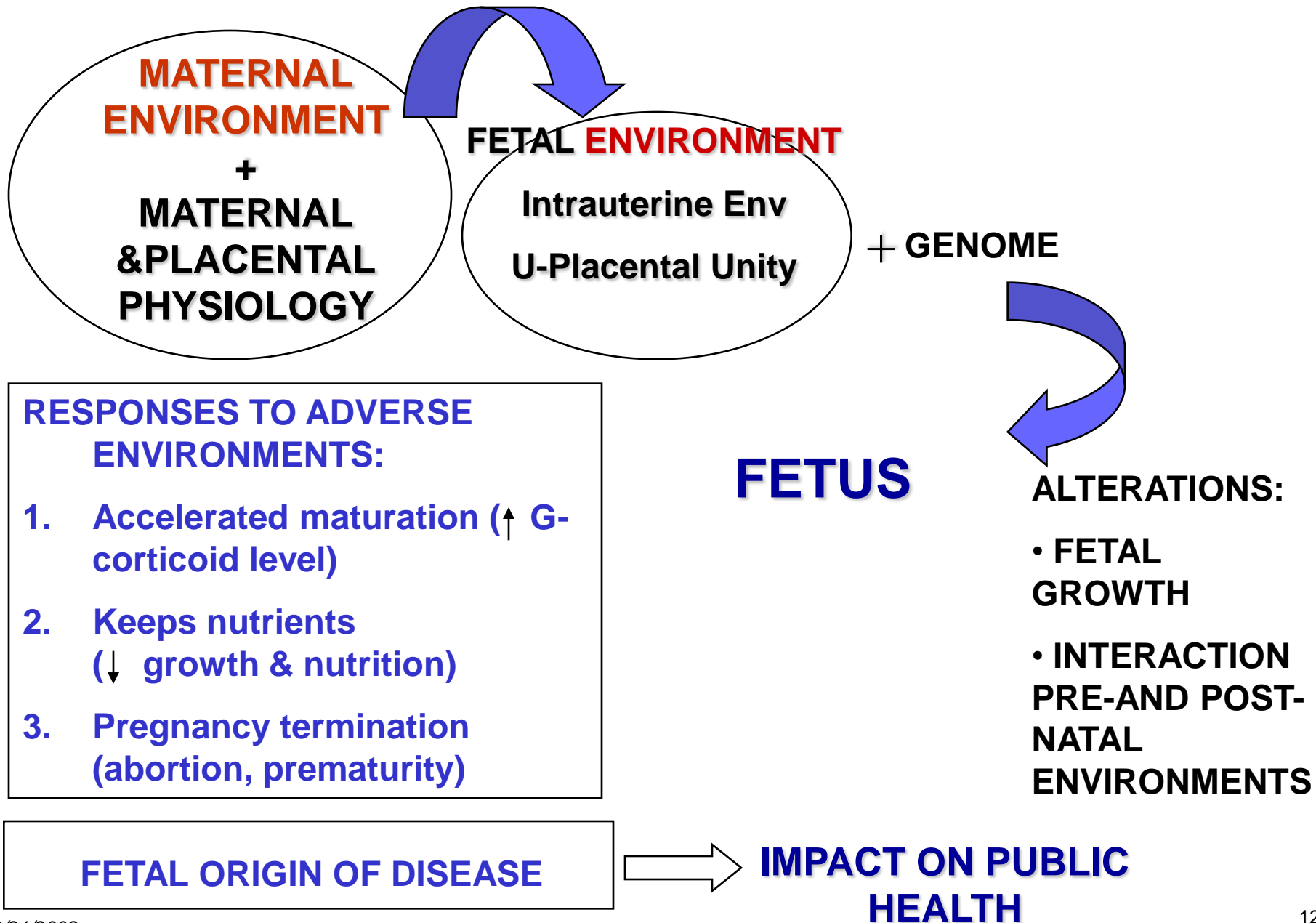
1. Eradicate extreme poverty and hunger
2. Achieve universal primary school education
3. Promote gender equality and empower women
4. Reduce child mortality
5. Improve maternal health
6. Combat HIV/AIDS, malaria and other diseases
7. Ensure environmental sustainability
8. Develop a global partnership for development

BARKER HYPOTHESIS

Low birthweight linked to hypertension, cardiopathy, type II diabetes and osteoporosis later on in life

Wit JM. Implications of the Barker hypothesis for general practitioners. Ned Tijdschr Geneeskd. (2000) 144(52):2491.

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GENETIC MODIFICATIONS

Epigenetics:

Heritable changes in gene function that cannot be explained by changes in chromosomal system

3 Main types of epigenetic information:

- ❖ DNA methylation
 - ❖ genomic imprinting
 - ❖ Histone modification
-
- **Changes can be permanent or transient**
 - **Some of them are part of normal development**
 - **Some are affected by environment → altered gene expression (suppression/activation of genes)**

THRIFTY PHENOTYPE HYPOTHESIS

How does the fetus respond to an adverse environment?

By making irreversible changes in its development

- ❖ **Abnormal insulin secretion/action**
- ❖ **Reduced vascularity**
- ❖ **Reduced number of nephrons**

•Gluckman, The fetal, neonatal and infant environments – the long-term consequences for disease risk, Early Human Development (2005) 81:51.

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PREDICTIVE ADAPTIVE RESPONSES (PARs)

- ❖ The developing organism predicts its future environment
- ❖ Embryo/fetus depend on the information transmitted by the mother/placenta to evaluate/predict the present and future environments.
- ❖ **PARs**: decisions to change the course of development for future advantages
 - **Appropriate PARs**
 - **Inappropriate PARs**

•Gluckman, *The fetal, neonatal and infant environments – the long-term consequences for disease risk*, *Early Human Development* (2005) 81:51.

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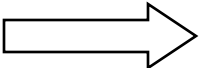
❖ Key concept: match/mismatch PARs

Relationship between real and predicted postnatal environments determines disease risk

✓ **Match: low risk of disease**

✓ **No match: higher risk of disease**

❖ Nutritional signals:

low food availability  insulin resistance

•Gluckman, *The fetal, neonatal and infant environments – the long-term consequences for disease risk*, *Early Human Development* (2005) 81:51.

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❖ Very adverse environment →

Death

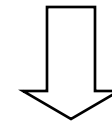
❖ Less adverse environment →

Alterations of

- Maturity

- Size

- Growth



Small newborn
(Prematurity)



Long-term
consequences

Compensatory growth



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IMPLICATIONS OF THESE MODELS

- ❖ "Lifestyle" disease
- ❖ Improve maternal and child health
- ❖ More research needed in:
 - Genetic changes
 - Windows of opportunity during plasticity periods?
 - Peri-conception period
 - Father and mother's exposure
 - Women's nutrition
 - Metabolic, cardiovascular, skeletal & other systems



WHO

BUT THE TIME FOR ACTION IS NOW

EXAMPLE OF AN INORGANIC CHEMICAL ARSENIC (AS)

- ❖ From natural erosion, pesticide run-off, coal burning, smelting, glass and electronic production waste
- ❖ Skin lesions and cancer, vascular and neurological disease, increased risk of cancer
- ❖ WHO guideline: 0.01 mg/L (ppm)
- ❖ Arsenic crosses the placenta
- ❖ Previous studies: *In utero* exposure to Arsenic linked to increased risk for stillbirth, and spontaneous abortion

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EXAMPLE: ARSENIC AND THE ANTOFAGASTA STUDY

- ❖ High Arsenic exposure in Antofagasta (Chile) from 1958 to 1970
- ❖ Study of exposed children (1958 – 1971): Increase in mortality from lung cancer and bronchiectasis when *in utero* + childhood exposure to arsenic in drinking water

- Exposure in:

Early childhood

In utero and early childhood

- Mortality due to:

cancer SMR=7

SMR=6.1

bronchiectasia SMR=12

SMR=46.2

Smith. A. Increased Mortality from Lung Cancer and Bronchiectasis in Young Adults after Exposure to Arsenic in Utero and in Early Childhood, EHP

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EXAMPLE: TOBACCO SMOKE

❖ **Lung development is a multievent process that begins at the first month of gestation and continues postnatally.**

- Toxicants to developing lungs: ETS, bioactivated compounds and oxidant gases
- Targets: epithelial cells that are maturing and/or proliferating

❖ **Developing fetus more susceptible than adult to PAHs carcinogenicity:**

- Increased susceptibility of the fetus to DNA damage
- Reduced ability to clear ETS constituents

❖ **Tobacco metabolites in the fetus: toxic effects.**

Perera, Biomarkers in maternal and newborn blood indicate heightened fetal susceptibility to procarcinogenic DNA damage, EHP (2004) 112 (10)

Pinkerton, The mammalian respiratory system and critical windows of exposure for children's health, EHP (2000) 108 (S3).

Jaakkola, Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration,

EHP (2001) 109 (6).

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EXAMPLE: TOBACCO SMOKE

- ❖ **Maternal smoking is risk factor for:**
low lung function, low birth weight, pre-term delivery, sudden death, lower respiratory illness, wheezing and asthma in children, debilitating asthma, obstructive pulmonary disease, cancer in adults.

- ❖ **Effects on lung development:**
 - diminishing airway and alveolar growth
 - Structural alterations
 - Interference with control of respiration and developing immune system
 - Reduction in fetal breathing movements: exposure to hypoxia even 1 hr after cigarette was smoked
 - Changes in CNS sensitivity to blood gases = impaired control of breathing
 - Reduced placental blood flow, reduced supply of nutrients and oxygen to the fetus and growth retardation: **Fetal origins of disease**

•A. Hoo. *Respiratory function among preterm infants whose mothers smoked during pregnancy. American Journal of Respiratory and Critical Care Medicine.* (1998) 158 (3): 700.

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EXAMPLE: TOBACCO SMOKE

- ❖ **Secondhand smoke + urban air pollutants:**
 - Effect greater than the sum of individual effects
 - Reduced fetal growth, lower birth weight
 - Problems in learning and school performance
- ❖ **Women who quit smoking during pregnancy and who are exposed to second-hand smoke: babies born with more gene mutations (umbilical cord blood studies)**
- ❖ **High doses of vitamin C can be beneficial**

Grant, Qualitatively and Quantitatively Similar Effects of Active and Passive Maternal Tobacco Smoke Exposure on In Utero Mutagenesis at the HPRT Locus, BMC Pediatrics (2005), 5 (20).

Proskocil, Vitamin C prevents the effects of prenatal nicotine on pulmonary function in newborn monkeys. Am J Respir Crit Care Med. (2005) 171(9):1032

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OTHER EXAMPLES

- ❖ **Radiation: exposure *in utero* in Nagasaki led to mental retardation and small head size**

- ❖ **Ethyl alcohol: array of congenital malformations in children of heavily alcoholic mothers**
 - Mental retardation
 - Microcephaly
 - Short palpebral fissures
 - Intrauterine and postnatal growth retardation.

- ❖ **Noise, heat: impacts that harm mother's health can indirectly have detrimental effects on fetus.**

Miller, How environmental hazards in childhood have been discovered: carcinogens, teratogens, neurotoxicants and others, Pediatrics (2004) 113 (4): 945.

WHAT IS AN ENDOCRINE DISRUPTING CHEMICAL? (EDCS)

Exogenous substance or mixture that alters the function(s) of the hormonal system and consequently causes adverse effects in an intact *organism*, or its *progeny* or its *sub-population*

Natural

- **Phytoestrogens**
- **Fungal estrogens**

Synthetic

- **Hormones**
- **Some pesticides**
- **Industrial by-products ("dioxin-like")**
- **Pharmaceuticals**
- **Some persistent organic pollutants (POPs)**

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EXAMPLES OF EFFECTS ON WILDLIFE

REPTILES: decline in alligator population by 90% after difocol, DDT, DDE chemical spill

- ❖ Smaller penis size
- ❖ Abnormal gonad morphology
- ❖ Altered sex steroid concentrations

FISH: reproductive alterations when exposed to sewage treatment waste

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Another type of cancer: Diethylstilbestrol as a model for environmental estrogens

- ❑ DES administered to pregnant women 1940-1960 for high-risk pregnancies but later to promote "healthier babies" as well.
- ❑ Female offspring developed clear-cell carcinoma of the vagina, vaginal adenosis, cervical ectropion, and other abnormalities.
- ❑ Males: reproductive tract abnormalities.

Has human cancer incidence resulting from DES exposure peaked? DES daughters are reaching post-menopause, the age of endometrial carcinoma...

- ❑ DES may be a model compound for other environmental agents with estrogenic potential.

PLASTICS

- ❖ Phthalates: solvents, soft plastics, and cosmetics
- ❖ Most US population exposed to phtalates
- ❖ Special population highly exposed
- ❖ Animals: reproductive and developmental toxicities
- ❖ Human studies: possible associations with
 - Altered semen quality
 - Shortened gestation
 - Reduced anogenital distance in baby boys
 - Premature breast development
 - Obesity

*Hauser, Occupational and Environmental
Medicine 2005*

REPORT DETAILS ENVIRONMENTAL HARM TO FETUSES

❖ Study by the Environmental Working Group and Commonweal on 10 babies born in 2004 (USA)

❖ Findings:

- 287 chemicals found.
- 200 industrial chemicals and pollutants found in umbilical cord blood, as an average.
- Among them: pesticides, consumer product ingredients and wastes from burning coal, gasoline and garbage.
- 180 of these cause cancer in humans or animals,
- 217 are toxic to the brain and nervous systems
- 208 cause birth defects or abnormal development in animal tests.

Houlihan, Body Burden, The pollution in newborns, EWG, 2005

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IF PREGNANT

Many pregnancy/birth problems could be avoided through:

- **Family planning,**
- **Balanced, organic diet**
- **Management of maternal health problems**
- **Avoiding maternal infection**

Usual advice:

- ✓ Folic acid in flour to prevent neural tube defects,
- ✓ Iodine in salt to prevent congenital hypothyroidism,
- ✓ Vit B12 (methyl donor important for DNA and protein modification) around conception
- ✓ Rubella vaccinations prevents congenital rubella syndrome.

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HOW TO REDUCE EXPOSURE?

- ❖ Don't smoke! Nor stay near smokers
- ❖ Eat food without additives
- ❖ ...organic (without pesticides and preservers)
- ❖ Eat less meat and fat products
- ❖ Avoid fish rich in POPs and Hg (salmon, tuna,...)
- ❖ Avoid microwaving plastics
- ❖ Filter water at home
- ❖ Use few cosmetics and fragrances
- ❖ Don't use solvents
- ❖ Reduce the number of chemical cleaners at home



WHO

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CHILDREN'S HEALTH AND THE ENVIRONMENT

WHO - Tools and mechanisms available to promote CEH

- ❖ Training Package for the Health Sector
- ❖ National Profiles on the status of CEH
- ❖ CEH Indicators
- ❖ Promotion of the Environmental History taking: "*Green page*"
- ❖ EH components into the IMCI
- ❖ Guidelines for setting up CEH Centres
- ❖ Technical assistance to countries
- ❖ Collaborative research: Longitudinal Cohort Studies on CEH

Through: Partnerships and alliances with NGOs and IGOs

Applying a PREVENTIVE AND EDUCATIONAL APPROACH

WHO: Training for the Health Sector

Improving the capacity to diagnose, prevent and manage paediatric diseases linked to the environment

New training materials:

➤ **Reproductive health and the Environment**

➤ **Environmental Health Criteria 237:**

Principles for Evaluating Health Risks in children Associated with Exposure to Chemicals

<http://www.who.int/ipcs/publications/ehc/ehc237.pdf>

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HECANET NEWSLETTER

- ❖ **HECANET is an international mailing list dedicated to promoting healthy environments for children.**
 - ❖ The list provides updates on:
 - ❖ the activities in the area,
 - ❖ advocacy tools and information resources,
 - ❖ relevant meeting announcements,
 - ❖ and reports on technical research and monitoring related to environmental risks to children's health
- ❖ **www.who.int/heca/infomaterials/hecanet/en/index.html**
- ❖ **To subscribe, send an email to: heca@who.int**

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CEH WEBSITE



The screenshot shows a Microsoft Internet Explorer browser window displaying the WHO website for Children's Environmental Health (CEH). The browser's address bar shows the URL <http://www.who.int/ceh/ev/>. The website header features the WHO logo and the text "World Health Organization" in multiple languages: Arabic, Chinese, English, Français, Русский, and Español. A search bar is located to the right of the language options. Below the header, a navigation menu on the left lists various sections: Home, About WHO, Countries, Health topics, Publications, Research tools, WHO sites, Children's environmental health (highlighted), Risks, National profiles, Indicators, Capacity building, Publications, and Research. The main content area is titled "Children's environmental health" and features a photograph of diverse children. Below the photo, there is a paragraph of text: "Children are our future, numbering over 2.3 billion worldwide (aged 0-19) and representing boundless potential. Child survival and development hinge on basic needs to support life; among these, a safe, healthy and clean environment is fundamental." Another paragraph follows: "Children are exposed to serious health risks from environmental hazards. Over 40% of the global burden of disease attributed to environmental factors falls on children below five years of age, who account for only about 10% of the world's population. Environmental risk factors often act in concert, and their effects are exacerbated by adverse social and economic conditions, particularly conflict, poverty and malnutrition. There is new knowledge about the special susceptibility of children to environmental risks: action needs to be taken to allow them to grow up and develop in good health, and to contribute to economic and social development." A bullet point at the bottom of the main text states: "Each year, at least three million children under the age of five die due to environment-related diseases." On the right side of the page, there are sections for "NEW" and "OTHER RECENT NEWS". The "NEW" section includes a link for a "North American report: Children's Health and the Environment in North America - A First Report on Available Indicators and Measures" with a "Full text" link. The "OTHER RECENT NEWS" section includes links for "Information package on environmental and occupational health", "CEHI & HELI consultation in Jordan", "The environment and health for children and their mothers", and "CEHI Newsletter". At the bottom of the page, there is a link for "Posters and maps adapted from Inheriting". The browser's status bar at the bottom shows "Done" and "Local intranet".

www.who.int/ceh

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WHO

"Improving children and mothers' (and fathers') environmental health by addressing and tackling issues affecting their health, presents an essential contribution towards the achievement of the Millennium Development Goals (MDGs)"

<http://www.who.int/ceh/publications/factsheets/fs284/en/>