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Chemical Safety in a Vulnerable World

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Protecting Children from Harmful Chemical Exposures
Chemical Safety and Children's Health

Prepared by: IFCS FSC Working Group Chaired by Hungary

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Protecting Children from Harmful Chemical Exposures *Chemical Safety and Children's Health*

This paper is intended to provide background information and scientific rationale for the Decision Paper, "Protecting children from harmful chemical exposures," (IFCS/FORUM-IV/14w). Both papers were prepared by the Forum Standing Committee Working Group, chaired by Hungary, for the Fourth Session of the Intergovernmental Forum on Chemical Safety (Forum IV) Bangkok, Thailand, 1-7 November 2003. The major sections and headings in this information paper are harmonized with the decision paper.

I. Issues for consideration

Sustainable development is "a form of development which meets the needs of the present without compromising the ability of future generations to meet their own needs."⁽²²⁾ Sustainable development rests on three pillars, namely the economy, the society and the environment.^(135, 165) Humankind stands in the centre of the prosperous economy, the future oriented society, and the sound environment. Our children and grandchildren, the heart and the soul of sustainable development, will inherit the future society, operate the future economy and manage the environment for the future of mankind. (Figure 1) Therefore, it is an intrinsic component of sustainable development to protect the health of children and ensure that children live in environments that allow them to reach their full potential as individuals and contributing members of these societies.

The World Health Organization (WHO) defines the interaction between environment and health as both the direct pathological effects of environmental exposures to chemicals, radiation and some biological agents, and the effects on health and well-being of the broad physical, psychological, social and aesthetic environment, which includes housing, urban development, land use and transport.⁽¹⁶⁹⁾ As scientific knowledge defining the relationship between health and the environment expands, it becomes increasingly apparent that the developing foetus and children can be especially vulnerable to environmental chemical exposures. The effects of such exposures are determined in part by chemical toxicity, dose, timing and duration of exposure ^(19, 34, 61, 121, 130, 134-6, 139, 151, 154-6, 158, 160-1). Poverty, malnutrition and related stress factors can further increase the vulnerability of children to environmental exposures, directly by exacerbating adverse health effects and indirectly by perpetuating the cycle of poverty, poor health and environmental degradation.^(23, 35, 54, 104, 140-1, 169, 172) Central to protecting children's environmental health is the eradication of poverty. Appropriate partnerships should be established between the governments of the developed and developing countries, UN organizations, multi-interest economic organizations, the three sides of the world of work (labour, employer and regulatory authority), non-governmental organizations, and the public to ensure that the most serious environmental threats to children's health are identified and addressed. Such partnerships can develop innovative solutions that lead to sustainable environmental health and labour policies and programmes to prevent harmful chemical exposures, and to preserve and protect children's health. However, these partnerships will function only if governments ensure definite resources for the development and implementation of specific actions. Governments should connect economic progress with social evolution to make the education of children, and the protection of their mental, psychological and physical health the central elements of poverty eradication⁽¹⁴¹⁾

II. Background and the current situation

It has been over a decade since the first global conferences emphasized that special attention should be paid to children's interests in the preservation of the environment and sustainable development. (The *World Summit for Children*, UNGASS (137) and the *UN Conference on Environment and Development*, UNCED – *Earth Summit* (138)). The June 2002 United Nations Special Session on Children reviewed the progress made in improving the lives of children around the globe since 1990, and concluded there is a long way to go. For example, the Report of the Secretary-General noted that in over 100 countries the mortality of children under 5 was reduced by 20 per cent.(63) Likewise, there was significant reduction in deaths from diarrhoeal diseases, and there were improvements in health from immunisation and vitamin supplement programmes. However, the Report also notes that malnutrition, war, HIV-AIDS and poverty minimized any gains made.

A. Environmental Health Risks to Children

Environmental Conditions – Quality of the Environment. Environmental conditions are the chemical, physical and biological threats present in the places where children live, play, learn and work (including the threats to the developing fetus). Children may be exposed to environmental health risks within a variety of environments (including the home, school and workplace), via multiple media (such as food, air, water, objects, animals) and during the performance of any activity (e.g. eating, sleeping, working, playing) (Figure 2). When environmental quality is poor, children suffer. Environments with inadequate sanitation and lack of clean and sufficient supplies of water; poor hygiene; inadequate housing; climate change leading to the proliferation of disease vectors; ozone layer depletion; indoor air pollution; and exposure to hazardous chemicals all contribute to childhood mortality and morbidity and play a role in preventing children from reaching their full potential (139). A major requirement of improving the lives of children globally is to improve the environments in which they live.

Mortality. Over five million children between the ages of 0 to 14 die every year from illnesses that relate directly to environmental conditions, mainly in the developing world.(23) This means, on average, 13,000 child deaths daily – the equivalent of one jumbo-jet full of children crashing every 45 minutes.(139, 166) Mortality from all causes for children under age five is currently over 10 million deaths per year, and many of these deaths could be prevented if environmental conditions were improved. Figure 3 shows the top killers of children in developing countries. Acute respiratory infections, diarrhoeal diseases and malaria account for approximately 40 per cent of post-neonatal, under-five child deaths worldwide. These three categories of disease are closely related to environmental factors. Acute respiratory infections account for two thirds of all deaths in children from birth to age 14 years and are strongly linked to indoor and outdoor air pollution. In India, for example, it is estimated that up to 440,000 children under five years of age die each year due to exposure to air pollution from solid fuel use in household cooking.(139) UNICEF has reported a direct link between access to safe drinking water and mortality in children under the age of 5 who die from diarrhoeal disease. Improved water treatment and sanitation could reduce these deaths by up to one third.(170)

While acute and chronic exposures to chemicals are not the main cause of child mortality in the world, unintentional poisonings account for tens of thousands of deaths in children before the age of 14 years. (see Section D, Acute poisonings).

Morbidity. A large fraction of all disease is related to the environment in a broad sense(139). It is estimated that globally, about 43% of the environmental disease burden falls on children under 5 years of age, though they constitute only 12% of the world's population(119). A large number of illnesses related to childhood environmental chemical exposures are not fatal, but contribute disproportionately to the environmental burden of disease during childhood and later life. For instance, the World Health Report 2002 estimated that a range of effects of the heavy metal lead may cause about 2% of the environmental burden of disease for children.(167) As nations make the transition from high mortality developing countries (where factors related to communicable diseases, maternal and perinatal conditions and nutritional deficiencies dominate) to more developed countries, there is a transition in risk factors, and chemical exposures become comparatively more prominent. Taking action to reduce all environmental threats, including exposures to toxic chemicals, could make a major contribution to child health.(137)

B. Chemical Hazards and Sustainable Development

Benefits of chemicals. Synthetic chemicals are integral to some of the most important societal advances and economic development. The use of chemicals is critical to the construction, transportation, communications, and production industries. Pesticides and fertilisers are widely used, and they help to lessen the physical burden of agricultural activities(51). Chemicals provide benefits in many aspects of daily life, including health care, hygiene, and public health measures, such as vaccinations, medication, and sanitation and water disinfection. In all regions of the world, chemicals provide significant contributions to disease cure, prevention, and control.

Risks of chemicals. While chemical use has brought societal benefits, it also creates risks. Acute and chronic toxicity are increasingly associated with chemical exposures in all age groups. Children may be at increased risk of adverse health outcomes and developmental consequences from environmental chemical exposures(14, 113, 121). Balance between the benefits and risks of chemical use must be sought to support the best possible conditions that promote public health and environmental integrity. Specifically, it is imperative that safer chemical and non-chemical alternatives be explored and promoted, and that chemicals, when necessary, be used safely and judiciously to protect children's health and to promote sustainable development.

Number and level of knowledge about the toxicity of chemicals. There are tens of thousands of synthetic chemical substances in commerce. For many chemicals in commerce, safety screening data and hazard information either have not been generated or are not available to the public.(28, 53, 58, 84)ⁱ However, only a relatively small number of these chemicals are produced in high volumes. A subset of these chemicals, the High Production Volume Chemicals (HPVCs),ⁱⁱ have been targeted for coordinated international evaluation based upon the assumption that production volume can be used as a surrogate for exposure. International authorities agree, under the Organization for Economic Cooperation and Development's Screening Information Data Set (OECD/SIDS) program, that six basic datasets are necessary for a minimum understanding of a chemical's potential toxicity. These test batteries are used to "screen" the chemicals and set priorities for further testing or risk assessment/management activities. They are designed to evaluate aspects of acute toxicity, chronic toxicity, developmental and reproductive toxicity, mutagenicity, ecotoxicity, and environmental fate. Where available, the rodent reproduction/developmental toxicity screening testsⁱⁱⁱ would provide data relevant to examining the potential for early life stage toxicity.

Estimates are that globally there are approximately 5000 HPVCs, and recent studies show that large data gaps exist.(93)

- A 2002 study by the European Chemicals Bureau concluded that 14% of the European Union HPVCs had a complete SIDS data set available to the public, 65% had partial SIDS data, and 21% had none.(1)
- A similar study by the United States Environmental Protection Agency (USEPA) in 1998, found full public SIDS data sets available for 7% of HPVC, partial SIDS data sets for 50% and no SIDS data for 43% of chemicals. www.epa.gov/chemrtk/hazchem.htm

While efforts such as the HPV Challenge Program (145) are working toward making more screening toxicity data available, there remains basic uncertainty related to the safe use and sound management of HPVCs. Furthermore, although HPVC represent a large portion of manmade chemicals in use, human exposure to lower production volume chemicals may be significant because of the category of use or specific physicochemical properties. Less is known about these lower production volume chemicals.(107)

Evaluating the health risks of chemical contaminants in the environment depends upon relating toxicity (adverse health outcome(s) at various doses) to human exposure (route, dose, timing and life stage). Toxicity data are most often generated from adult animal testing(147, 161), or in vitro experiments. Exposure estimates are modeled from a variety of data inputs including production and use data, environmental monitoring data, estimates of activity and dietary patterns, and, when available, human biomonitoring^{iv} measurements.(144) Until recently, determination of safe exposure has most commonly been based upon modeling averaged exposures over a standard 70 year lifetime.(147) Standard risk assessment practices have been developed to estimate safe exposure levels from these types of data. For example, US EPA calculates an expected safe exposure level for humans, known as a Reference Dose (RfD) for chemicals thought to exhibit threshold phenomena by dividing the animal No Adverse Effects Level or model derived benchmark dose by adjustment factors (typically 10-fold) to account for (1) the uncertainty and variability in toxicokinetics^v and response, when extrapolating from animal studies to humans; and (2) inter-individual variability in toxicokinetics and response in humans. With new scientific knowledge and insight gained from genomics, as well as information related to understanding the implications of metabolic pathway development(44), the appropriateness of these “standard” 10-fold adjustment factors is being questioned, particularly when exposures may occur during critical periods of development early in life.(25, 49, 147) There is mounting evidence to suggest that exposure to environmental contaminants during fetal development can have a profound impact on disease later in life.(16) Further, the health consequences of exposure to very low doses of multiple chemicals is often not well understood.(13, 147)

Increasing concern about the degree to which standard risk assessment approaches protect children has led to a variety of new approaches. For example, in 1996, the U.S. Food Quality Protection Act (FQPA)^{vi} established special provisions for the protection of infants and children. FQPA implemented key recommendations of the National Academy of Sciences report(83), "Pesticides in the Diets of Infants and Children," by (1) requiring an explicit determination that tolerances are safe for children, (2) including the use of an additional safety factor of up to ten-fold, if necessary, to account for uncertainty in data relative to children; and (3) requiring consideration of children's special sensitivity and exposure to pesticide chemicals. A second example is the Voluntary Children's Chemical Evaluation Program (VCCEP),^{vii} launched as a "pilot" by US EPA in 2000, which is intended to provide data to enable the public to understand the potential health risks to children associated with certain chemical exposures. Currently, VCCEP is beginning to evaluate available data through a process of Peer Consultation by a group of scientific experts with extensive and broad experience in toxicity testing and exposure

evaluations. The VCCEP pilot will be evaluated to identify efficiencies which can be applied to any subsequent implementation of the program. Section C below discusses in detail the ways in which children may be more vulnerable to chemical exposures than the general population.

C. Why Are Children Particularly Vulnerable To Chemicals?

Children (from the prenatal period through adolescence) often react differently to chemicals than do their adult counterparts because, compared to adults, they have different exposures, different metabolism, different vulnerabilities determined by critical windows of development, and a longer life expectancy. These differences may render children more or less likely to be damaged by a xenobiotic^{viii} than an adult.

To protect children's environmental health (especially for the foetus and the small child), it is important to understand when and how they can be particularly vulnerable to chemical exposures.*(19, 38, 113, 121)*

Understanding the rapidly changing nature of the child is essential to understanding vulnerability to chemicals. One way to categorize the elements of this changing sensitivity is as follows:

- i. **Biology:** Vulnerability to toxic exposures during critical periods of ontogenesis^{ix}, and characteristics of metabolism at various stages of development affecting the fate of xenobiotics inside the human body (age-related toxicokinetics).
- ii. **Physiology:** Functional features of the developmental stages of the child affecting body burden and internal dose of xenobiotics;
- iii. **Behaviour:** Age-related exposure patterns of the child including physical location in the environment, activity patterns, and behaviours typical of different life stages.

While these categories overlap and interact, the discussion below examines each of these areas individually in detail.

i. Biology.

Vulnerability to toxic exposures during critical periods of ontogenesis. On-going organ and tissue differentiation, organization and cell development in the foetus and child result in unique periods of either heightened vulnerability during which chemical toxicants can disrupt normal development and cause permanent damage *(94, 136, 152)*, or periods during which, in theory, systems are resistant to damage by virtue of their immaturity.*(112)* The outcome of a particular exposure during the pre-embryonic, embryonic or foetal stages may be different. The organs (e.g. lungs, kidney, liver) of newborns, both premature and term, are immature. Maturation of the major organ systems is rapid in the first 2 to 3 postnatal years, but significant development of the central and peripheral nervous systems, the immune system, the endocrine system and the pulmonary system continues through puberty.*(114)* During morphological and biological developmental phases children may have a different sensitivity to exposures to xenobiotics, often increased and unique.*(117, 121, 128-9, 136)* Thus, the timing of exposures during development can significantly affect toxicity.

Metabolism and Age-related Toxicokinetics. Toxic effects exerted on any organism (including every developmental stage of the child) depend on the functions and capacity of that organism with respect to absorption, distribution, biotransformation, and elimination of a given toxicant. Just as with pharmaceutical agents, children may metabolise xenobiotics differently than healthy adults depending upon the route, timing, dose and duration of exposure.*(101)*

Absorption. The absorption of xenobiotics often varies with age. Gastric acid secretion, gastric emptying time, intestinal motility and biliary function are all reduced in the newborn but emptying time is increased in the infant and child. The lack of intestinal flora in newborns affects the distribution of xenobiotics in the gastrointestinal tract. All of these variables can affect gastric absorption.

Distribution. The distribution of xenobiotics in the body is likely to change with age-dependent variables such as size and composition of body water compartments, protein binding characteristics, haemodynamic factors such as cardiac output and regional blood flow, and membrane permeability. For example, the total body water compartment, including the extracellular space in newborns is larger than in adults affecting the distribution of water-soluble compounds. Lipophilic^x xenobiotics may more readily penetrate the central nervous system in infants and young children until the blood-brain barrier reaches maturity in the third year of life.(127) The strength of affinity for and extent of binding to plasma proteins of a particular xenobiotic are important because only unbound chemicals can be distributed from the vascular space to other body fluids and tissues. In infants, some important serum proteins such as albumin are decreased and only approach adults values by age 10-12 years. Others, such as alpha-1-acid glycoprotein achieve adult levels by 12 months of age. Thus, tissue distribution may vary significantly with age at exposure.

Biotransformation. Xenobiotics often undergo “activation” or “detoxification” via biotransformation in the liver. The metabolic profile of the developing human presents a constantly changing picture; certain enzymes are activated while others are repressed. This explains the markedly different sensitivities to various toxicants that are exhibited throughout the developmental period.(77) Metabolic enzyme systems change significantly during development: generally the foetus and newborns show decreased activity, and reach near adult level days to months after birth (e.g. cytochrome P450 enzymes).(30) In neonates immaturity of conjugating enzymes (glucuronidyl transferase) along with low metabolic capacity may increase the risk of toxic effects from xenobiotics which are detoxified by this mechanism. The relative lack of UDP-glucuronic acid can also be one of the causes of insufficient conjugation(127) When metabolism is required to detoxify a xenobiotic, immature pathways constitute an increased risk to the newborn. When the metabolite of the xenobiotic and not the parent compound exerts the toxic effect, immature biotransformation activity is protective. Little information exists on the role of enzyme system changes on the biotransformation of specific xenobiotics during development.

Elimination. Elimination is most often either renal or via the gut. Both the liver and the kidneys are immature at birth, especially so in the pre-term neonate. Neither glomerular filtration nor tubular secretion in the kidney reaches adult levels until roughly one year of age. Thus, infants may have decreased excretion and clearance of xenobiotics, prolonging half-life and potentially increasing toxicity.(127) Conversely, rapid maturation occurs during the first six months of life, and the elimination/clearance of many chemicals is higher in children than in adults.(44, 102, 105)

Placenta and metabolic activity. The placenta plays a determining role in the protection and damage of the foetus partly by its barrier-function, partly by its metabolic activity.^{xi} (Figure 4) There is no direct mixing of fetal and maternal blood, but the intervening tissue (*the placental barrier*) is sufficiently thin to permit the absorption of nutritive materials and oxygen into the fetal blood and the elimination of carbon dioxide and nitrogenous waste from it. The barrier function of the human placenta with haemochorial^{xii} structure is much higher than that of the

rodent's placenta of haemoendothelial^{xiii} structure.^{xiv} Despite this barrier function, many pharmaceuticals and xenobiotics do traverse the human placenta, most commonly by passive diffusion, where they can exert harmful effects.(112) For example, the placenta often does not prevent mother to baby transfer of carcinogens.(6, 150) Metabolic activity of the placenta may transform xenobiotics from harmless to toxic forms; e.g. transformation of non-carcinogenic substances into carcinogens, the so-called transplacental carcinogenic effects.(7, 76, 168)

In summary, children, especially foetuses and neonates in the first six months life, can be particularly vulnerable to the effects of chemicals due to their immature metabolism and decreased or absent ability to detoxify and eliminate xenobiotics. Metabolic immaturity can be protective when a xenobiotic requires metabolic activation to be toxic. Consequently, generalisations with respect to metabolic differences between children and adults are difficult, but the capacity of infants to inactivate many toxic xenobiotics is lower than that of the adults.(113, 136)

ii. Physiology.

Children grow and develop very rapidly in the first three years of life and again during puberty. They are anabolic,^{xv} have rapid and efficient energy metabolism, and may absorb xenobiotics more completely than adults. For example, for a given oral dose of lead, a toddler will absorb 50% compared to an adult who will absorb 5-15 %.(47, 143) Small children breathe more quickly, and consume more food and water than adults in proportion to their body weight.(Figures 5, 6) Infants and young children have higher surface area to body weight ratios than adults resulting in greater weight-adjusted absorption through the skin.(61, 112, 139) (Figure 7) Consequently, xenobiotics in air, water, or food, or that come in contact with the skin may be delivered in higher weight-adjusted amounts to the youngest individuals.(83)

iii. Behaviour.

As with adults, children's exposure to chemicals occurs through different routes, circumstances and settings. However, normal behaviour and activities of children in different life stages can significantly affect exposure patterns. For example, children spend more time outdoors than adults and engage in play and learning through hand-to-mouth exploration. Thus, exposures through non-nutritive ingestions may be significant. Hand to mouth activity can, for example, lead to ingestion of contaminated soil.(Figure 8) Children live and breathe closer to the ground than adults, so toxicants that tend to accumulate at ground level will be more accessible to the curious small child than to adults. Finally, children are cognitively immature and unable to understand and avoid risks. Thus, a wide range of exposure scenarios must be considered in order to determine the degree to which children at various stages are exposed to chemical hazards.(Figure 2)

A critical element of a child's vulnerability to chemicals relates to the timing of the exposure with respect to development. This is discussed more comprehensively in section D.

D. Chemical Exposures and Children's Health

A wide spectrum of exposures must be considered to understand chemical risks to children's health. Chemical exposures experienced by men and women prior to conception, and by women during pregnancy can adversely affect survival and long-term health. As children grow and

develop after birth, they become increasingly mobile, independent and curious. Their environments expand in variety and scope. Their natural curiosity and learning behaviours may cause children to be exposed to chemicals in products that are used or stored in households, schools, parks, rural environments, in swimming and recreational areas, or applied on pets or animals. Other types of exposure occur through chemical releases to the environment from manufacture or use of products, or from accidental (or intentional) chemical spills. Children in some populations may have relatively higher exposures to chemicals of concern due to particular cultural practices or diets.⁽¹³⁹⁾ Extreme poverty often forces children to work to help their families to survive. Work places that use child labour are often congested, dusty, inadequately ventilated and, in some instances, require the handling of hazardous chemicals.

i. Exposure in different stages of ontogenesis

Chemical exposures can be conveniently considered using a life stage approach, which highlights the differences in sources and routes of exposure and vulnerability by age.

▪ Gestation

During pregnancy, chemicals that enter a mother's body have the potential to adversely affect the development of a foetus.^(127, 136) Disturbances occurring during the different stages of prenatal development are manifested in characteristic morphologic changes.^(Figure 9) Both endogenous (genetic) and environmental factors may cause pathologic development.^(96, 116, 136)

In the pre-embryonic (zygote) stage (gestation days 1-14) cells are totipotential and tend to respond to chemical exposures in an all-or-none fashion; the cells either die resulting in pregnancy loss, or survive with damage or intact.^(31-2, 134, 136) ^(Figure 10) The main event of the embryonic stage (2nd to 10th week of gestation) is organogenesis. If an appropriate dose/concentration of a teratogenic substance crosses the placenta during a critical period of organogenesis, major anomalies will be induced in the embryo. Higher exposures to hazardous substances may even cause embryonic death.^(65-7, 74, 136, 156, 161) In the foetal stage (11th week of gestation to birth), exposure to a hazardous substance may retard foetal growth, (small for gestational age) or cause functional deficits (e.g. reduced mental capacity, enzyme abnormalities).^(31-2, 135-6, 151-2, 156, 158-60) Some xenobiotics produce toxicity following a deterministic dose-response relationship,^{xvi} while others are mutagenic and follow a stochastic dose-response relationship at lower doses and a more deterministic dose-response relationship at high doses.^{xvii} ^(Figure 10)

Congenital anomalies are among the leading causes of death in children living in high-income countries where infectious disease deaths are now rare. It has been estimated that around 20% of all birth defects are due to gene mutations, 5-10% to chromosomal abnormalities, and another 5-10% to exposure to a known teratogenic agent or maternal factor.^(10, 88) Together, these percentages account for only 30-40%, leaving aetiology of more than half of all human birth defect unexplained.⁽¹⁷⁾ Some of the remaining 60-70% may be related to chemical exposures during gestation. Some portion of functional defects such as mental retardation and developmental disorders, are also known sequelae of certain prenatal exposures to xenobiotics.^(19, 121, 139)

- Infancy

Healthy babies double their birth weight in the first 6 months of life and triple it by one year. Chemical exposures in infant food, water and air can affect normal growth and development. Exposure patterns change rapidly in the infant period as the variety of foods taken increases and motor development allows for increasing mobility.

Unique chemical exposures occur during infancy through mother's breast milk. Clinicians recognize that medications given to a lactating mother may pass to the infant through the breast milk(72), and exercise caution when prescribing pharmaceuticals. Similarly, persistent lipophilic environmental contaminants such as dioxins and PCBs may accumulate in breast milk and cause exposures in breast-fed infants.(79) Heavy metals such as methylmercury and lead are also secreted in breast milk. These exposures are ubiquitous. A striking example is the presence of environmental chemicals in the breast milk of the Inuit peoples of the Arctic region. Although the region is largely free from polluting industries, some persistent organic chemicals undergo global transport and bioaccumulation^{xviii} in foods ingested by people living in the remotest locations.(36) Trend data show that restricting or banning specific chemicals can result in decreased breast milk contamination over time, and that continued use is associated with increased breast milk contamination.(120)

Nonetheless, breast-feeding is strongly recommended, and has been shown to decrease the risk of gastrointestinal and respiratory diseases in infancy (105) and to increase IQ.(70) Based on available evidence, two separate WHO/EURO consultations noted that infant exposure through breast milk was considerably less important than exposure *in utero*, and that risk management should thus aim to limit intake of contaminated food by the mother rather than restrict breast-feeding.(100)

- Early Childhood

Medical and educational research has shown that the development of intelligence, personality and social behaviour occurs most rapidly during the first three to four years in humans. It is estimated that half of all intellectual development potential is established by the age of four years.(121) According to recent research, brain development is much more vulnerable to environmental influence, including toxic chemical exposures, than was previously suspected, and the influence of early environmental exposures on brain development is long lasting.(154)

Psychosocial and cognitive development begins at birth and parents are the children's earliest teachers. Therefore, strengthening the ability of all family members to care for and stimulate their children and encourage them to learn can set the stage for adult success. However, the ability to care for children is greatly influenced by the physical environment. In many countries, particularly those where the environment is seriously degraded, collecting water, gathering firewood and tending crops take up large amounts of time and energy. When those tasks fall without relief on women, they have too little time to spend on ensuring the best possible care for their children. When parents are absent or ill, they may be unable to keep children safe as they explore their world.(139)

- Children of school age

More than 1.4 billion children from age five to 14 years – approximately 87 per cent of all children – live in developing countries, where many of the biggest environmental challenges exist. School age children's environments expand beyond their homes and care centres, giving them frequent interaction with a wider range of people in more places than when they were younger.(139)

Injury (usually road traffic injuries, falls and drowning) is now the number-one killer of children aged 5 to 14 years.(95) Environmental factors such as exposed cooking set-ups, dangerous tools and equipment, open sewers, heavy traffic, dangerous construction or electrical sites, and hazardous chemicals pose threats. In developing countries a child's health and growth may also be affected when he or she engages in wage-earning work or domestic chores unsuitable for his/her age and ability, such as working long hours in a field, carrying heavy loads, and walking long distances for fuel wood or water.

In developed countries asthma and childhood cancers are now major concerns. In the United States, cancer is the second biggest killer of children between 5 and 14 years of age, after accidents, with the median age of child victims of cancer being six years old. Acute leukaemia is the most common type of cancer found in children, and its incidence appears to be rising in some developed countries.(139) Chemical exposures before birth or early in childhood may be contributing to this growing problem.

- Adolescence

During the critical phase of adolescence, the ability of young people to develop their capacities and life skills and to participate meaningfully in society hinges on a number of cultural, socio-economic and environmental factors.(139) In addition, adolescence is a time when young people often need to work to support their families. Poverty and resource degradation in an adolescent's community can significantly diminish employment possibilities. Hazardous working conditions are also of prime concern for this age group. Adolescents' lighter body weight and lack of skills may predispose them to injuries in the workplace.

In this age group child labour and employment involving chemical exposure may increase chemical risks significantly.(55) Adolescence is the last period of rapid somatic growth as well as the time of complete differentiation of the organs of reproduction. Exposures, particularly potentially high level exposures incurred during child labour, to pesticides, neurotoxicants, endocrine disruptors, allergens and carcinogens, during this critical period may be especially dangerous.

Child labour. It has been recently estimated by the International Labour Organization (ILO/IPEC) that out of 352 million children aged 5-17 years more than 171 million are exposed to dangerous conditions and poisonings.(55) The 1999/2000 Multiple Indicator Cluster Surveys (MICS) of 49 developing countries revealed that 23 per cent of rural children (5 to 14 years old) and 13 per cent of urban children worked. Saharan African countries showed the highest proportion of children working.

Being tender physically, children are susceptible to various work-related injuries and illnesses, more than adults doing the same kind of work. Also, because they are not yet matured mentally, they are less aware, and in some cases unaware, of the potential risks

involved in their specific occupations or in the workplace itself. As a result, a large number of working children are affected by various hazards in the workplace; information published by ILO in 1998 indicates that more than two-thirds of children are affected in some countries. Recent surveys at the national level have demonstrated that a very high proportion of the children suffered physical injuries or fell ill while working, and some of them stopped working permanently. There is a need to determine more specifically how many children and youth suffer from work-related injuries.(55) Infectious diseases (e.g. gastro-intestinal illnesses and tuberculosis), and acute poisonings due to dangerous chemicals are more frequent among working children. There are currently no studies documenting patterns and/or frequency of illnesses in adults who as children laboured with dangerous materials.(136)

ii. Role of chemicals in environmentally related diseases in children

- Asthma

The prevalence of asthma in people aged 5-34 years is high in many countries. In the USA in 1992, 49.4 people per 1000 population suffered from asthma, representing a 42 per cent increase over the previous ten years.(9, 78, 97) While this is probably partly due to changes in diagnostic practices, it does not explain the dramatic increased incidence of asthma over a ten year period.

There is a great divergence between countries in terms of asthma prevalence: in the USA it is higher than in Japan or among the Eskimos, but lower than in New Zealand. We do not know whether these differences are of genetic or environmental origin.(52) The asthma mortality rate among children in the USA increased twofold between 1980 and 1993 (40) . The number and severity of acute asthma episodes in children is linked to ambient air pollutants, and a number of studies suggest that both indoor and outdoor air pollutants can contribute to the increased incidence of the disease.(41, 73, 96)

- Acute poisoning

Unintentional acute poisonings among children are serious consequences of modern chemical use. Poisonings are often caused by household chemicals (cleaning agents, disinfectants, washing-machine detergents, and kerosene), medicines, and pesticides. Improper packaging and storage, and children's exploratory behaviours, together with their ignorance about risks are important reasons leading to increased risk to children. Poisonings tend to be under reported, and differences in definition and surveillance by country make it difficult to determine global rates of childhood poisonings with precision.(99) Examples of country specific poisoning data as reported by poison centres are:

- Brasil (2001): 12,471 poisonings were reported in children under age five which represented 27.6% of all reported cases.(89)
- Hungary (2001-2002): 8,030 and 8,690 poisoning cases were reported in 2001 and in 2002, respectively; 20-21 per cent of these afflicted children younger than 14 years. The majority of child poisoning cases were accidental and only 7 per cent of them were suicide attempts.(2)
- Portugal (1999): 16,916 poisonings were reported of which 42% occurred in children under age five years.(20)
- Sri Lanka (2001): Of the 500 poisonings reported, 23.4% occurred in children under five years.(3)

- Sweden (2001-2002): The annual rate of inquires to the poison centre concerning non-pharmaceutical chemicals was about 14,000 per million children aged 0 through 9 years. Of these, about one-tenth, or 1,500, had or were recommended contact with health care advice.(125)
- Switzerland (2000): 12,448 poisonings were reported in children amounting to 52.6% of all poisonings.(126)
- USA (2001): A large surveillance network reported 2.2 million human poison exposure cases, of which 85.2 % were unintentional and 0.05 % were fatal. Over 1.1 million poisonings (51.6%) occurred in children less than 5 years and another 326,000 occurred between ages of 6 and 12 years.(68)

The most serious cases of poisonings tend to be hospitalised, but represent only a portion of total poisonings.

While acute and chronic exposures to chemicals are not the main cause of child mortality and illness in the world, the World Health Organization (WHO) estimated for 2000 and 2001 that unintentional poisonings account for 50,000 deaths of children aged 0 to 14 years, per year.(163-4, 167) In OECD countries (excluding Turkey), injury is the principal cause of child death during 1991-1995. More than 20,000 children between the ages of 1 and 14 died each year from injuries; 2 % of these deaths were from poisonings.(103) Regardless of conflicting estimates, childhood chemical poisonings are a serious problem worldwide.

- Chronic poisoning and delayed toxic effects

Both short and long-term exposures to chemicals early in life may result in delayed toxic effects which become manifest in later childhood, adulthood or in subsequent generations depending upon the mechanism of toxicity and the latency period of the environmental disease. Chronic, low-level exposures to chemical pollutants occur constantly via the inspired air, drinking and bathing water, and food. Sources of pollution vary regionally and locally. For example, lead exposure in developed countries is usually related to lead paint in old housing stock, whereas in the developing world it may be caused by backyard battery recycling facilities or lead fittings in grinding stones or water pumps.(42) Food and drinking water may become contaminated when improperly stored in containers that originally held toxic chemicals or pesticides, which is a common practice in poor communities despite of the fact that it is prohibited in most countries. Children may be exposed to hazardous chemicals in their dwelling place, at the workplace (child labour, accompanying working parents) or through parents' work clothes taken home. The levels of ambient chemical pollution of air, water and soil add to total exposures and further endanger children's health.

Several successful efforts have been mounted to stop the increase of environmental pollution: contamination of the environment by heavy metals has been reduced; factory releases have declined; lead and benzene content of petrol have been reduced; use of some persistent organic pollutants is declining; production and use of a number of other hazardous chemicals (e.g. asbestos, carcinogenic pesticides, substances subjected to Rotterdam Convention Prior Informed Consent(III) procedure) have been decreased. Despite these successes, the heavy metal or polycyclic aromatic hydrocarbon pollution of the Earth's soil is significant. Dioxins, PCBs, persistent pesticides, and heavy metals bioaccumulate and biomagnify^{xix} in the food web. Pollution of indoor and out-door air is at unacceptable levels in many places where biomass fuels are used for cooking, and traffic-related pollution is uncontrolled. Other emissions such as

brominated diphenyl ethers used as flame-retardants continue to increase. In many places unacceptable levels of arsenic, other anthropogenic and naturally occurring metals, and organic material contaminate drinking water. Pollution caused by war may disproportionately endanger the health of children and subsequent generations thus threatening sustainable development.(139)

In this environment of multiple chemical exposures, there is a strong concern about specific chemicals known to have adverse effects on the basic intellectual capabilities of children. New research has raised very substantial concerns that chemical contaminants are contributing to a wave of behavioural disorders. The social costs of caring for a larger fraction of the population classified as mentally retarded far exceeds the cost needed for environmental protection and prevention. A country or city with large percentages of children growing up intellectually impaired by lead poisoning, PCB exposure, or by the absence of essential nutrients like iodine in their diets, will increasingly be economically disabled. That community will bear the cost of caring for those with severe disabilities, struggle with the social impacts of violent behaviour, and be deprived of the full complement of the very workforce - intelligent and technologically competent - that is essential for global competitiveness in an information-based economy. These issues also tap a deep well of social injustice since the burden falls disproportionately on socially disadvantaged families.(13, 121)

Section E illustrates these concepts with specific examples of chemicals proven to be harmful to children even at low exposure levels.

E. Selected examples of chemical substances of concern

Metals such as mercury, arsenic, cadmium, manganese, chromium and their derivatives are widely used in modern society. These metals may, at sufficient exposure levels, negatively affect children's health.(43, 57).

- *Lead*

Lead has been known as an acute occupational and environmental poison for thousands of years. Lead is found everywhere in nature, in rocks, soil, water, air and in any living creature. Human activity has brought about an alarming increase of lead concentration in our environment. Millions of tonnes of lead are produced and used in the world annually.(91)

Lead enters the human body mainly by food, drinking water and inspired air. In adults, about 5 to 15 per cent of lead presented to the gut is absorbed, whilst in children absorption is estimated to be 30 to 50 per cent.(39, 143) About 40 per cent of inspired lead is absorbed from the lung. Dermal absorption of inorganic lead is insignificant, but organic lead is readily absorbed through the skin. Once absorbed, lead is transported via the blood to internal organs (e.g. liver and kidneys) and the bones, where it is deposited. The half-life of lead in the blood is estimated at 20-40 days. It is excreted (mainly by urine) very slowly; therefore, even low level, chronic lead exposure leads to the accumulation of lead in the body.

Effects of lead exposure are summarized in Table 1. Lead has an adverse effect both on the central and peripheral nervous system.(56) Classic symptoms are lead-encephalopathy, weakness and paralysis of the extensor muscles and lead colic. Young children are especially vulnerable to the adverse effect of chronic low-level exposure to lead on the central nervous system(18, 34, 45, 71, 87, 123,-4) Hyperactivity(33), impaired psychometric intelligence and cognitive ability(85-7), learning difficulties(71), and hearing loss have been reported in lead exposed school children. Lead also crosses the placenta(46, 108), and impairs the foetal nervous system.

The consequences of prenatal lead-exposure manifested during postnatal development are documented in several long term cohort studies.(8, 11, 17, 21, 37, 75, 118, 128-9)

For example, in the Port Pirie Cohort Study(129) children from urban and rural communities surrounding a large smelter were followed from birth to the age of 11to13 years. Analysis of these children found an inverse relationship between blood lead levels (expressed as the average of the concentration at 15 months, 2, 3 and 4 years) and IQ. After adjustment for a wide range of confounders, full scale IQ in these children declined by 3 points (95% confidence interval 0.07-5.93) from expected with an increase of 10 micrograms/dl (ug/dl) lifetime average blood lead(128) The cognitive deficits first demonstrated at the age of seven years(8), persisted into later childhood.(128) It should be noted, however, that blood lead concentrations recorded in Port Pirie were higher than the 5 to 10 ug/dl mean values characteristic to most urban populations today.

A similar relationship was described by *Lanphear et al.*(64), and *Canfield et al.*(24) who followed a group of children from birth to the age of 60 months and found an average 5.5 point reduction in IQ for every 10 micrograms/dl increase in blood lead. These investigators documented that the lead associated cognitive deficit occurred at blood lead levels less than 10 ug/dl.

In a cohort study in Denmark, where the mean blood lead concentration of children born in 1987 was about 3 ug/dl, *Nielsen et al.*(90) found that while neurotoxic effects of lead may occur at such low exposure levels, they are difficult to demonstrate unequivocally because the greater influence of other predictors (e.g. birth weight, gestational age, hearing problems, single parent household, older siblings, breastfeeding, somatic illness, maternal intelligence). *Wassermann et al.*(153) studied the behaviour problems of children in association with blood lead concentrations from birth to the age of three years. It was found that adverse impact of lead exposure on behaviour is significant, but small in comparison to more powerful social determinants.

Evolution of knowledge. At the turn of the 20th century, lead poisoning was considered an acute occupational disease of adults.(15)^{xx} Despite reports of “seasonal colic” from Queensland, Australia which described a symptom profile in lead poisoned children different from the adult pattern, risk parallels were drawn between levels seen in children and levels seen in occupationally exposed adults. Lead levels below 80 ug/dl were considered “normal” because lead was a ubiquitous exposure and universally found at lower levels in people without overt symptoms. The concept that there was a threshold of lead toxicity was widely accepted, and the threshold level was set at the lowest level associated with symptoms of acute poisoning.

The enduring effects of acute lead poisoning on child development became apparent only with the publication of longer follow-up observations in the 1940s, which noted persistent impairments in intellect, behaviour, and sensory-motor function. From 1950 to 1990 information about the dangers of lead poisoning in children exploded.(15) With the advent of effective chelation treatment beginning in the 1950s, physicians increased screening, and developed treatment and follow-up programs. Data began to accumulate showing long-term morbidity following acute lead poisoning in children. During this period the differences in absorption, distribution and metabolism of lead in infants and children compared to adults were discovered, and long-term, chronic toxicities particularly to the central nervous system were described. The independent, prospective cohort studies of the 1970s and 1980s described above showed the deficits in IQ and neurobehavioral measures in children who were exposed to lead but never demonstrated acute symptoms. The “threshold” level for lead toxicity began to fall as the special

vulnerabilities of children were increasingly defined.(143) (Figure 11) The toxic threshold for lead was most recently set at 10 µg/dl, the 1990 World Health Organisation standard that still holds today (Note: WHO is planning to review the standard.). Subsequent meta-analyses have quantified the risk of low-level lead exposure estimating that an increase in blood lead from 10 to 20 µg/dl is associated with an average IQ loss of 2 to 3 points.(121) With additional studies it may be shown that lead exposure at any level can cause measurable damage to cognitive function in children when analysed at the population level.(24) This is of particular importance because current data suggest that the neurotoxicity of childhood lead exposure is not reversible with treatment.(109)

Significance. Although an IQ loss of a few points may have minimal significance for the average individual, it has profound implications when applied to large populations. When the population distribution curve for IQ, or any other neurobehavioral endpoint, is shifted by even a small amount there are dramatic effects at the high and low ends of the distribution, often referred to as the "tails." As shown in a hypothetical example in Figure 12 a downward shift of a mere 5 points in the mean IQ results in a greater than 50 per cent increase in the numbers of functionally mentally retarded individuals and a comparable decrease in the numbers of gifted individuals in the population. In theory, this small shift in average IQ may have enormous implications for society, translating, for example, into increased needs for special education and services, as well as a significantly diminished intellectual capacity within the population as a whole.(121) In addition, the social and economic costs of such a shift are staggering. For a decline of 3 points in average population IQ, it is estimated that there is a 28% increase in the prevalence of high school dropouts, a 25% increase in prevalence of poverty and a 25% increased prevalence of males being jailed.(81) Estimated percentage earnings loss associated with a 3 point average IQ decrease range from 5 to almost 11% decrease annually.

- *Mercury/methylmercury*

Like lead, mercury is a heavy metal that disrupts brain development. Of the various species of mercury, organic mercury, specifically methylmercury, is the most dangerous to the developing brain. High dose exposure causes severe disabilities such as mental retardation and cerebral palsy, whereas the more commonly encountered low levels of exposure can contribute to attention, memory, and language impairments.(27)

The effects of methylmercury on the developing brain were first observed in the tragic poisoning epidemic in Minamata Bay, Japan, during the 1950s. In this episode, residents regularly consumed fish that were highly contaminated with methylmercury from industrial discharges into the bay. Infants born to mothers who consumed the fish exhibited a variety of neurological abnormalities, including mental retardation, disturbances of gait, speech, sucking, swallowing, and abnormal reflexes, whereas their mothers often showed no signs of mercury poisoning. Because methylmercury was not identified as the cause until very late in the course of the epidemic, mercury exposures were never quantified, and a toxic threshold for the effects seen at Minamata was never established.(74, 82)

The quantitative study of methylmercury neurotoxicity began with a second major poisoning epidemic in Iraq in 1972.(14) In this tragic incident, infants were born with severe disabilities, including mental retardation, cerebral palsy, seizures, blindness, and deafness, after their mothers consumed bread contaminated with a methylmercury fungicide. As in Minamata, many mothers of affected infants suffered minimal or no symptoms of mercury toxicity.

An apparent toxic threshold, implied in the first case reports of severely retarded infants, soon became obsolete. Within a few years it was evident that many children exposed prenatally to lower levels of mercury suffered delays in walking and talking despite apparently "normal" development in infancy. Most recently, a large study in the Faroe Islands has identified deficits in language, memory, and attention that occur at low levels of prenatal methylmercury exposure.⁽¹²¹⁾ While the studies of low-dose prenatal and perinatal methylmercury exposure remain inconsistent, the WHO has recently revised downward the provisional weekly tolerable intake (PWTI) for methylmercury from 3.3 to 1.6 ug/kg bw/week reflecting the increasing weight of evidence showing adverse effects on neurologic tests in infants and children exposed at low doses.⁽⁶⁰⁾

- *Polychlorinated biphenyls*

Polychlorinated biphenyls (PCBs) are a large group of fat-soluble chemicals previously produced for industrial use as lubricants and insulators in electrical equipment, as flame retardant heat transfer and hydraulic fluids, and as plasticizers in a variety of applications. Although their production has been banned in most of the industrialized world for decades, their environmental persistence and bioaccumulation within the food chain have resulted in ubiquitous low-level human exposures, particularly from the consumption of beef, dairy products, and fish that are relatively high in fat. PCBs cross the human placenta and are excreted in human breast milk. The potential effects of PCBs on child development were first brought to attention by poisoning episodes in Japan in the late 1960s and Taiwan in the late 1970s.. In those incidents, several thousand people ingested rice oil accidentally contaminated with thermally degraded PCB-containing heat transfer fluid. The fluid contained relatively high amounts of thermal degradation products of the PCBs. As with other neurotoxicants, the developing foetus proved to be much more sensitive than the mother. Exposed newborns had a variety of developmental effects, including reduced birth weight, hyperpigmentation, early tooth eruption, deformed nails, and gum hypertrophy. In childhood, they also exhibited IQ impairment, poor health, and increased behaviour problems.^{xxi}⁽¹²¹⁾ (Figure 13)

Subsequent studies of environmentally exposed populations have reported additional associations, although the findings can be subtle and are inconsistent among studies. In the newborn, the reported effects of prenatal PCB exposure include decreased birth weight, head circumference, and gestational age, as well as motor immaturity, increased lability, and increased startle and decreased reflexes on the Brazelton Neonatal Behavioural Assessment Scale. In early childhood, prenatal PCB exposure is associated in some studies with a variety of cognitive impairments (reduced memory and attention, decreased verbal ability, impaired information processing) and developmental delays (reduced psychomotor development), as well as adverse behavioural and emotional effects (decreased sustained activity, decreased high-level play, increased withdrawn and depressed behaviour, increased activity level). In preteen years, prenatal PCB exposure is associated with decreased word and reading comprehension, decreased full-scale and verbal IQ, and reduced memory and attention.⁽¹²¹⁾ Other researchers, however, have reported that effects noted at birth or in early childhood disappeared as the children aged.⁽⁶⁹⁾

Studies have reported that maternal PCB body burden also alters thyroid hormone status in mothers and infants. Higher maternal PCBs are associated with small but significant reductions in total thyroid hormone in mothers and infants, as well as higher levels of thyroid stimulating hormone (TSH) in the infants. Thyroid hormone is critical to brain development, and elevated maternal TSH levels during pregnancy, with or without reductions of thyroid hormone, are associated with reduced IQ in offspring years later. These observations suggest that the adverse

developmental effects of PCBs may be at least partly mediated through impacts on thyroid hormone. PCB exposures also modulate neurotransmitter levels, which may be another mechanism by which PCBs affect neurodevelopment.(121)

While there is general agreement, supported by acute poisoning events and corroborating animal testing, that high exposures to PCBs *in utero* are neurotoxic to humans, there is less consistency among studies of lower dose exposures. Differences in study design, population evaluated, exposure measures, and outcome measures among epidemiologic studies make direct comparisons difficult and increase uncertainty about the existence of and/or threshold for toxic exposure levels. Recent uniform determinations of exposure in ten studies of PCB and neurodevelopment will facilitate making direct comparison.(69) This sort of uncertainty is common as knowledge of environmental toxicity evolves (as seen in the case of lead) and highlights the importance of continuing research and reinterpretation of data as science matures, in order to protect children from harmful exposures.

- *Pesticides*

Pesticides are widely used in agriculture and vector-control programs globally, and have extensive home, school, and industrial uses. The incidence of pesticide poisoning is significant in developing countries, including accidental exposure in children, occupational exposure of young farm workers, and exposure resulting from un-used, obsolete pesticides. For some pesticides, chronic low dose exposures may cause effects, such as impaired development of the nervous system, compromised immune system, or cancer.

Since synthetic pesticides were first introduced in the early 1940s, their worldwide consumption has grown markedly, with total consumption reaching 2.6 million metric tons of active ingredients in 1995, increasing at about one per cent per year.(139, 171) Developed countries have been the major users of pesticides, consuming about three-quarters of the world total. Once released in the environment, pesticides can pollute rivers, groundwater, air, soil, and food. Human exposure occurs from breathing, drinking, eating, or through skin absorption.

Children can, in certain exposure scenarios, be uniquely susceptible to the health threats posed by pesticides.(98) A child's exposure to pesticides can occur as early as the prenatal phase, and during infancy they may be exposed to pesticides through breast-feeding, mouthing activities and skin contact.(83)

The impact on human health from pesticide exposure depends on a number of factors, including the kind of pesticide involved and its toxicity, the amount or dose of the exposure, the length and timing of exposure, and the way in which the exposure occurs. Epidemiological studies have described statistical associations between various prenatal and/or low dose childhood pesticide exposures and increases in pregnancy loss, congenital malformations, childhood cancers and neurodevelopmental disabilities. Additional concerns about pesticide exposures causing changes in immune response or endocrine function have been raised. There are frequently limitations to epidemiological studies in this area, including uncertain and nonspecific exposure assessment, lack of specificity in disease classification, and lack of control for confounding factors.(110) Animal research supports many of these findings. Further work is required to link precise exposure measures to adverse outcomes in humans from specific classes of pesticides, but sufficient data exist to support a precautionary approach where children's exposures are concerned.(40, 173) If environmental exposures compromise the immune system, the risk of infectious disease and cancer may increase, thus increasing mortality rates. This is of special

concern in developing countries where people can be simultaneously exposed to both pesticides and infectious pathogens when their immune systems are already compromised by other factors, such as malnutrition.(80)

- *Persistent Organic Pollutants (POPs)*

Organic compounds that persist in the environment tend to accumulate in the body fat of animals and humans, and can be highly toxic at very low concentrations. They include pesticides containing polychlorinated hydrocarbons, such as DDT, industrial chemicals such as PCBs used for example in transformer oil, and by-products of industrial processes such as dioxins. There is a significant level of concern that these chemicals could cause long-term health effects, such as reproductive and neurological disorders (see PCBs above).

- *Nitrates*

Nitrate pollution is now considered to be one of the most serious water quality problems in the world. Nitrogen is a basic ingredient in artificial fertilisers. The use of fertilisers has been rapidly increasing, causing excessive nitrogen loading of the environment on a global scale. Global fertiliser use soared from less than 14 million tonnes in 1950 to 135 million tonnes in 1996.(139)

As a result, nitrogen levels have risen in surface and groundwater sources resulting in elevated nitrate levels in drinking water supplies. Untreated wastewater discharge has also contributed to the nitrate pollution of water resources.

Excess nitrate absorption is mostly associated with the "blue baby syndrome" (methaemoglobinaemia). Nitrates are reduced to nitrites in the body, and nitrite interferes with the blood's ability to carry oxygen to the body tissues, resulting in a bluish colour of a baby's skin. Infants under six months of age who are not exclusively breast-fed are particularly vulnerable to high levels of nitrates in drinking water for several reasons.(4, 139) First, the gut flora, which convert the non-toxic nitrates to toxic nitrites, flourish in the less acidic neonate gut. Second, foetal haemoglobin which persists for several months after birth is more easily oxidized to methaemoglobin than adult haemoglobin. Third, one of the two enzyme systems responsible for reducing methaemoglobin to functional ferrous haemoglobin operates at only about 50% of the adult capacity in young infants. Finally, because infants have high water requirements, non-breastfeeding infants exposed to nitrate contaminated drinking water will have much higher exposures per unit body weight than older children or adults. Levels higher than 10 milligrams of N/litre (US Standard) can have toxic effects on infants. Adults and older children are able to withstand much higher levels with no risk of methaemoglobinaemia.

- *Household products*

Kerosene, solvents, pharmaceuticals, cleaners and other chemical products are dangerous to children if they are kept in inappropriate containers and places that are accessible to children. Children, who like to play, explore and test what they find may ingest dangerous chemicals and suffer acute poisoning with severe consequences.(19. 136)

- *Waste sites*

Improper waste disposal can result in the release of hazardous chemicals into the environment. Chemicals, such as PCBs, can seep from waste sites into soil and water. Open burning of materials can release chemicals, including dioxins, heavy metals and particulate matter into the

environment. These pose a potential risk to the health of children, especially to those who live and scavenge in poor areas.

- *Chemical terrorism and children*

Chemical and biological weapons used by terrorists against the public pose an increasing threat. The number of victims may be significant – in a chemical terror-action in 1995 committed against the underground in Tokyo proved, the number of child poisonings may be considerable (over 5000 adults and children injured, 12 people died). As chemical weapons cause disproportional large effect in children, governments should urgently elaborate the mechanism for protecting children and both provide information to, and collect information from those who deal with children's exposures and health effects, such as paediatricians, nurses and toxicologists.(29)

F. International action to protect children from harmful chemical exposures

In *Priorities for Action beyond 2000*, IFCS recognizes that to protect the health of the general public, chemical safety issues regarding susceptible groups (including pregnant women, foetuses, and children) need to be clearly addressed in the assessment and management of risks.(53) Global accords have highlighted the concern and the need for action to improve children's environmental health. The following examples are representative of other international statements supporting these themes.

- The United Nations General Assembly Special Session on Children (2002) (UNGASS) recognized that exposure to hazardous chemicals needs to be addressed to ensure the health and well-being of children and pledged to protect the environment in a sustainable manner.(142)
- The 2002 World Summit on Sustainable Development (WSSD) recognized the need to reduce environmental health threats, taking into account the special needs of children and the linkages between poverty, health and environment. At that Summit, the Healthy Environments for Children Alliance (HECA) was announced.(166)
- Other important international activities include the United Nations Millennium Developmental Goals(141) and the Organization for Economic Cooperation and Development program.(92)

III. What can be done to increase Chemical Safety for Children?

The dynamic nature of the developing foetus, infant and child and the complex and interdependent relationship between environmental integrity and human health make understanding how to protect these future adults from chemical harms extremely challenging. The intricate balance between the benefits and risks of modern chemical must be constantly evaluated. Local and regional differences in climate, disease vector populations, water and food supply, level of development, industrial controls, and public health infrastructure affect chemical management choices and are also continuously changing. Finally, the large number of specific chemicals and the millions upon millions of chemical containing products and processes overwhelm our ability to develop precise and complete information about the chemical risks posed to children from conception to adulthood. It is the responsibility of today's adults to protect our children and grandchildren, the heart and the soul of sustainable development, and ensure that they can achieve their full potential in a safe environment. There is no one solution for all cases. Rather, governments, individual citizens, parents and teachers, communities, non-

governmental organizations, industries that make and use chemicals, and multilateral organizations must all continue to engage in open creative dialog, and free information and idea exchange in order to explore and create ever better ways to safeguard our children from unnecessary or unacceptable levels of chemical risks.

Prevention is better than cure. The most effective means of protecting children from chemical risks is by preventing hazardous exposures. This can best be achieved by: identifying risks and implementing preventive measures that will reduce or eliminate unsafe exposure and minimize risks; promoting safer chemical and non-chemical alternatives and clean production; applying the precautionary approach;^{xxii} and promoting transparent science-based risk evaluation procedures. Understanding the range of potential exposure sources is important in assessing cumulative exposure of single chemicals and exposure to mixtures of chemicals. In addition, there are many uncertainties about the health effects in children from exposures to chemicals. In many countries, current chemical regulations require the use of safety factors in an attempt to ensure that sensitive sub-populations are protected. Nevertheless, the magnitude of scientific uncertainty requires that new, child-specific, protective strategies be developed which will prevent irreversible long-term injury before full scientific knowledge is available. Significant research is needed to reduce these uncertainties.

Actions that can be taken to improve chemical safety for children can be placed into the following categories: prevention of exposure and reduction of risk; education and training; data and research needs; and indicators of environmental health. A selection of specific examples of actions that would promote and enhance children's environmental health and minimize chemical harms follows.

A. Prevention of exposure and reduction of risk.

- Adopt the precautionary approach in the context of children's environmental health.
- Promote non-chemical alternatives, and integrated pest management strategies which include safe and judicious use of pesticides.
- Promote clean production and adopt pollution prevention and other appropriate management strategies that prevent or reduce children's unsafe exposure to chemicals, in particular to those chemicals of highest concern.
- Prepare national action plans to address child labour which include specific reference to hazardous chemicals in the workplace.^{xxiii}
- Ensure that effective safety information labels are included on consumer products that are potentially hazardous to children, providing guidance on handling, transport, use and disposal, and information about first aid and contacting poison information centres.
- Strengthen community right-to-know where children are potentially exposed so that parents and others responsible for children have adequate and reliable information on emissions and discharges and on the safety and safe use of products, including, where appropriate, relevant information on chemical constituents of consumer products, to take action to protect children
- Further support the creation and/or strengthening of poison control centres in developing countries, and their active role in the protection of children's environmental health.

B. Education and training.

- Educate parents, children, teachers, and communities about types and routes of exposure and how to recognize and avoid unsafe levels of exposure, e.g. safe chemical use and distribution, disposal, and appropriate alternatives.
- Design educational materials and implement school programs and media campaigns in the local language, taking into account local needs, to alert and teach children, parents and the public about the potential dangers of improper chemical use and potential unintentional chemical exposures.
- Encourage further industry participation in educational campaigns to raise awareness about children's special vulnerability and the need to protect them through safe use of chemicals.
- Offer education to representatives of industry, public interest groups, the media, policy-makers and other professionals about chemical risks and risk communication.
- Raise the awareness of decision-makers about the risks to children's health and development associated with chemical use and encourage policies that take into account any specific vulnerabilities to chemicals that children may have.
- Train health professionals about children's unique vulnerabilities to certain chemicals and the risk of chemical exposures in different settings, the most common exposure pathways, as well as how to diagnose, identify the cause, prevent and treat exposures.
- Encourage donors to fund innovative educational programmes incorporating children and chemicals into development assistance programmes, and taking the opportunities offered through existing convention funding mechanisms to address children and chemicals issues.

C. Data and research needs

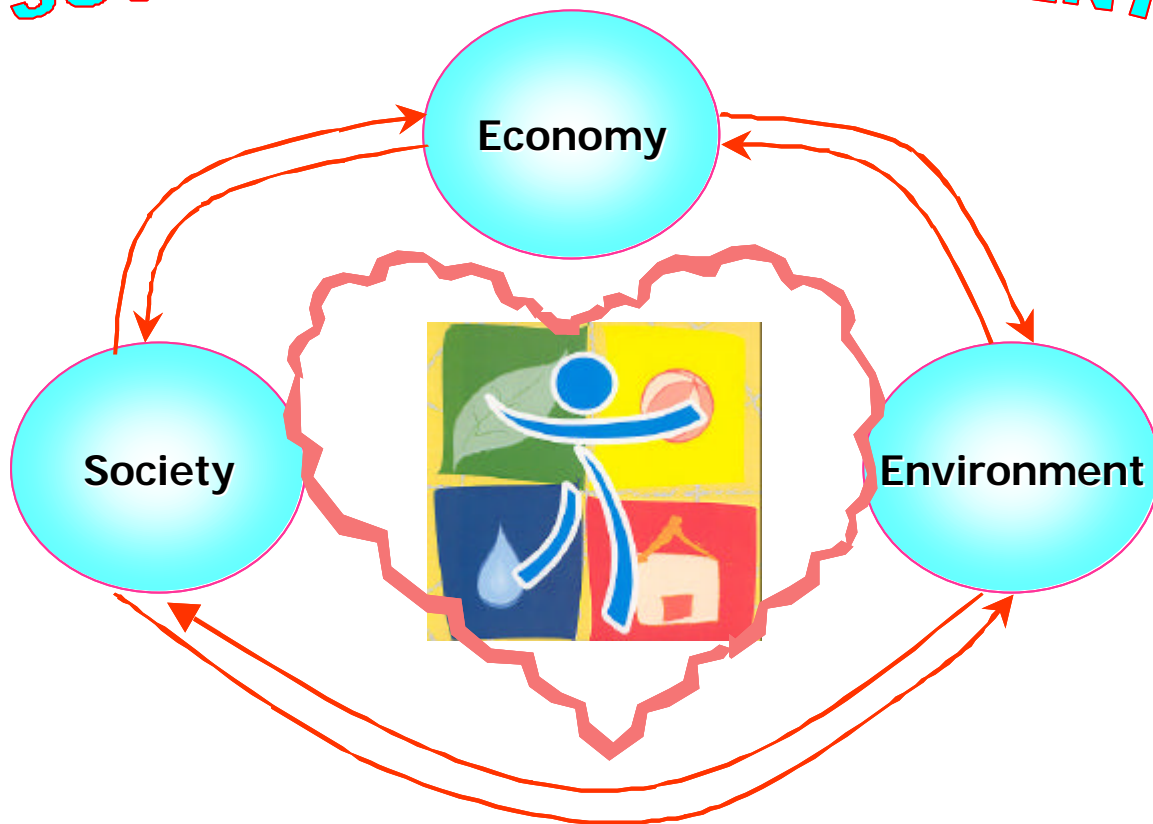
- Increase and support further scientific research on the link between chemical exposure and health outcomes in different age groups, and in different settings.
- Continue to improve and implement risk assessment approaches that account for child-specific issues.
- Develop a better understanding of foetal (maternal) and early childhood exposure.
- Develop toxicity testing data which further explore the toxicological impact of early life exposure.
- Determine how to incorporate new scientific information (i.e. genomics, proteomics) toward understanding the mechanisms of toxic action which are associated with early life exposure and their risks.
- Encourage donors to fund innovative research incorporating children and chemicals into development assistance programmes, and taking the opportunities offered through existing convention funding mechanisms to address children and chemicals issues.

D. Indicators of environmental health

- Develop appropriate indicators of chemical safety and children's health.
- Use appropriate indicators of chemical safety and children's health to measure progress in protecting children from chemical hazards
-

In addition, to protect children's health, Chapter 19 of Agenda 21 should be further implemented and countries should sign, ratify and implement existing international treaties regarding certain chemicals such as the Rotterdam Convention on Prior Informed Consent(*111*) and the Stockholm Convention on Persistent Organic Pollutants.(*122*)

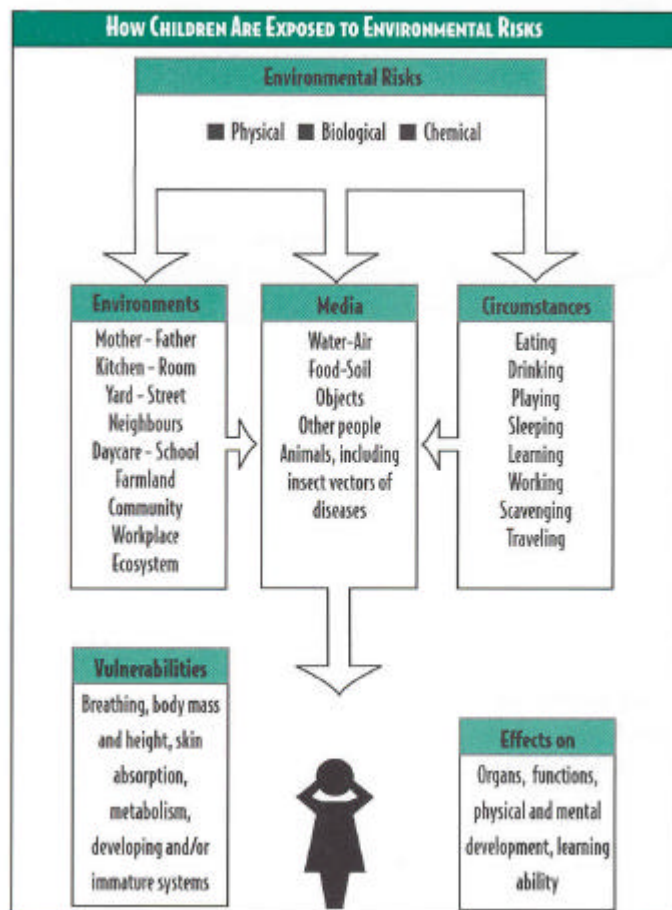
SUSTAINABLE DEVELOPMENT



Three pillars of the sustainable development are: society, economy and environment; the “heart” of the sustainable development is the future generation (children).

Figure 1.

How Children are Exposed to Environmental Risks

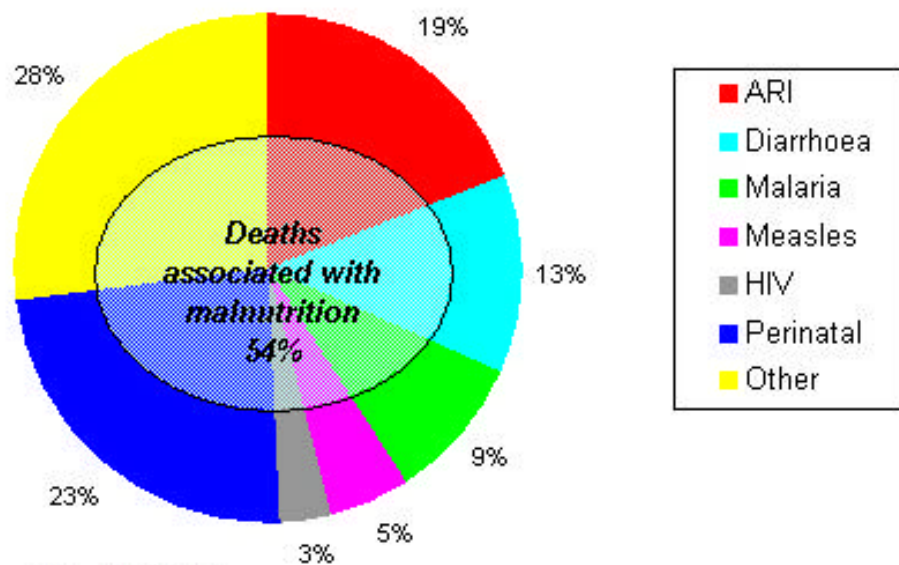


Source: adapted from the World Health Organization

Source: United Nations Environment Program, UNICEF, World Health Organization: *Children in the New Millennium. Environmental Impact on Health*, 2002. UNEP, UNICEF & WHO. Printed in the Republic of Malta. <http://www.unep.org/ceh/> Accessed 23 Sept 2003.

Figure 2.

Proportional Mortality Among Under Fives, Worldwide, 2001



Sources:

For cause-specific mortality: EIP/WHO

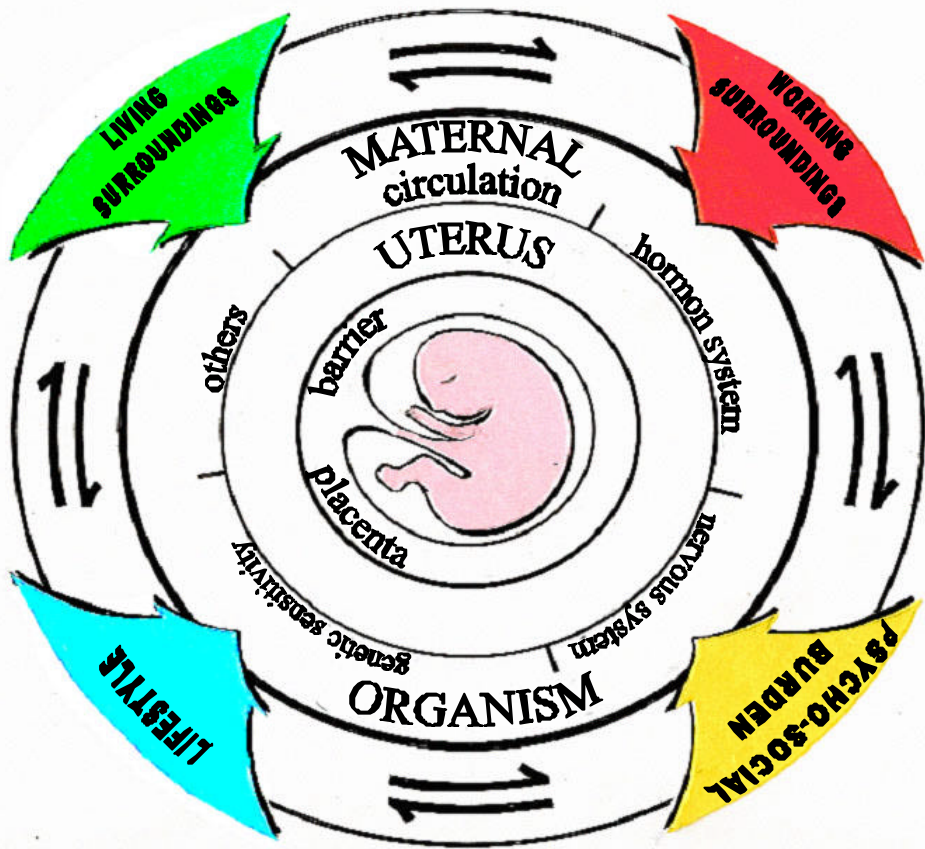
For malnutrition: Pelletier DL, et al. *AMJ Public Health* 1993, 83: 1130-3

Top killers of children. Causes of death for ~10 million children under – five years in worldwide in 2001. ARI: Acute Respiratory Infection; HIV/AIDS: Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome.

Source: EIP/WHO, Pelletier DL, et al. Epidemiologic evidence for a potentiating effect of malnutrition on child mortality. Am J Public Health (1993)83:1130-3.

Figure 3.

Dangerous substances



blood-brain barrier

placenta barrier

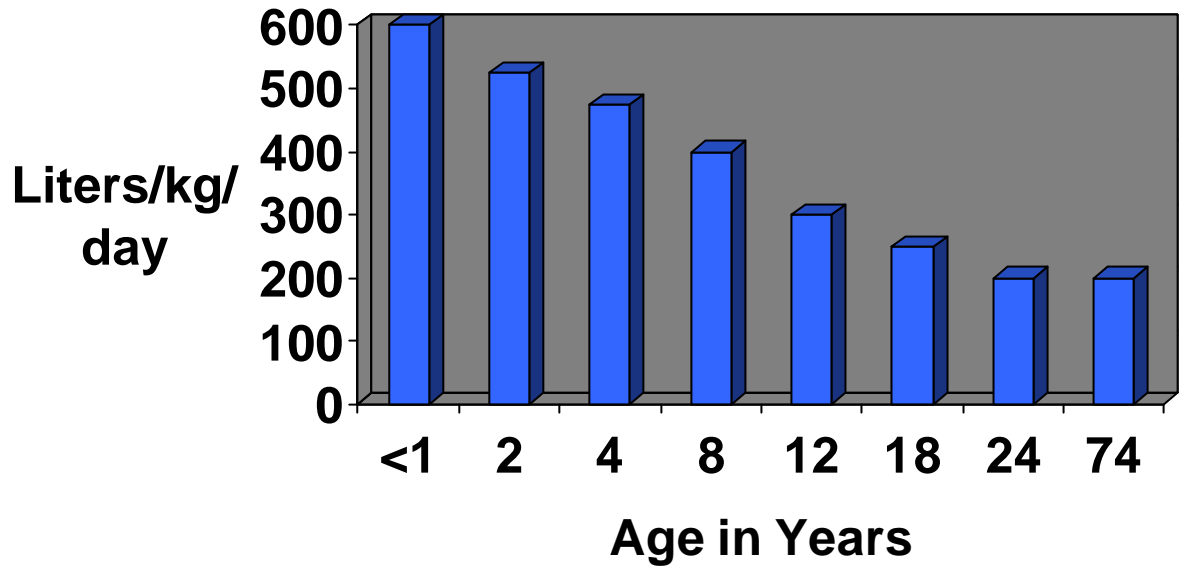
(vulnerable foetal organs, tissues)

The embryo is defended by several “membranes” against the environmental agents. None the less, if the mother exposed to high dose of dangerous substance, the first “protective reaction” of the mother is the abortion of embryo.

Source: after Prof. G.-H Schumacher – Ungváry Gy.: Embryotoxicity and hepatotoxicity. Thesis. Budapest. pp. 1-205. (1985) (in Hungarian)

Figure 4.

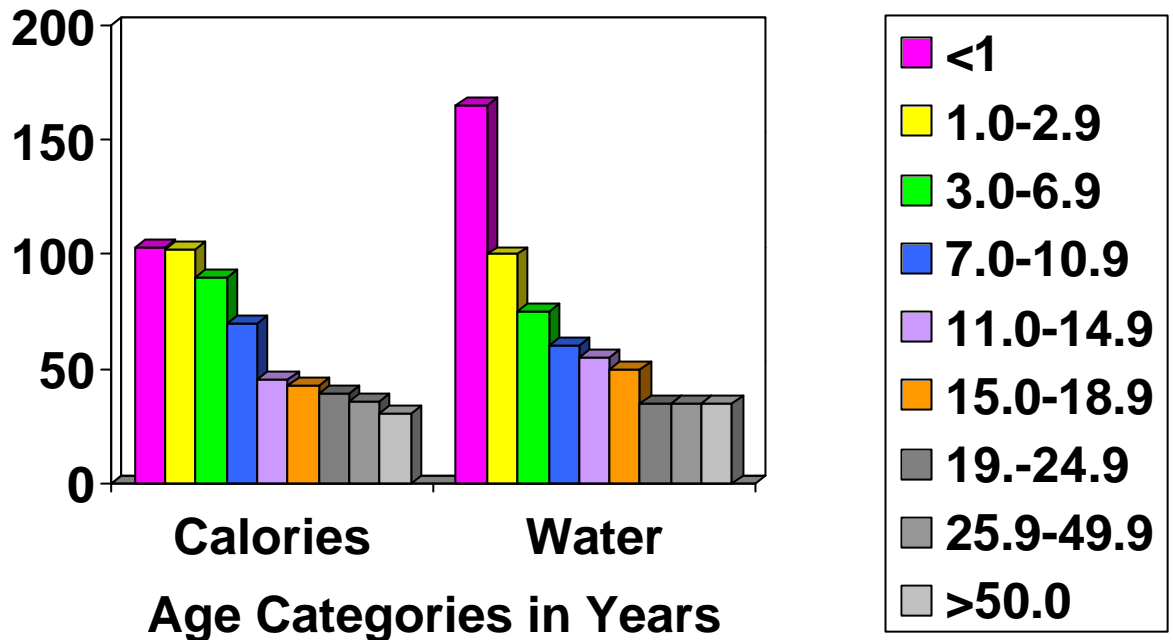
Breathing Rates by Age Group



Source: Miller MD, et al. "Differences Between Children and Adults: Implications for Risk Assessment at California EPA. *Int J Toxicology* (2002) 21:1-16.

Figure 5

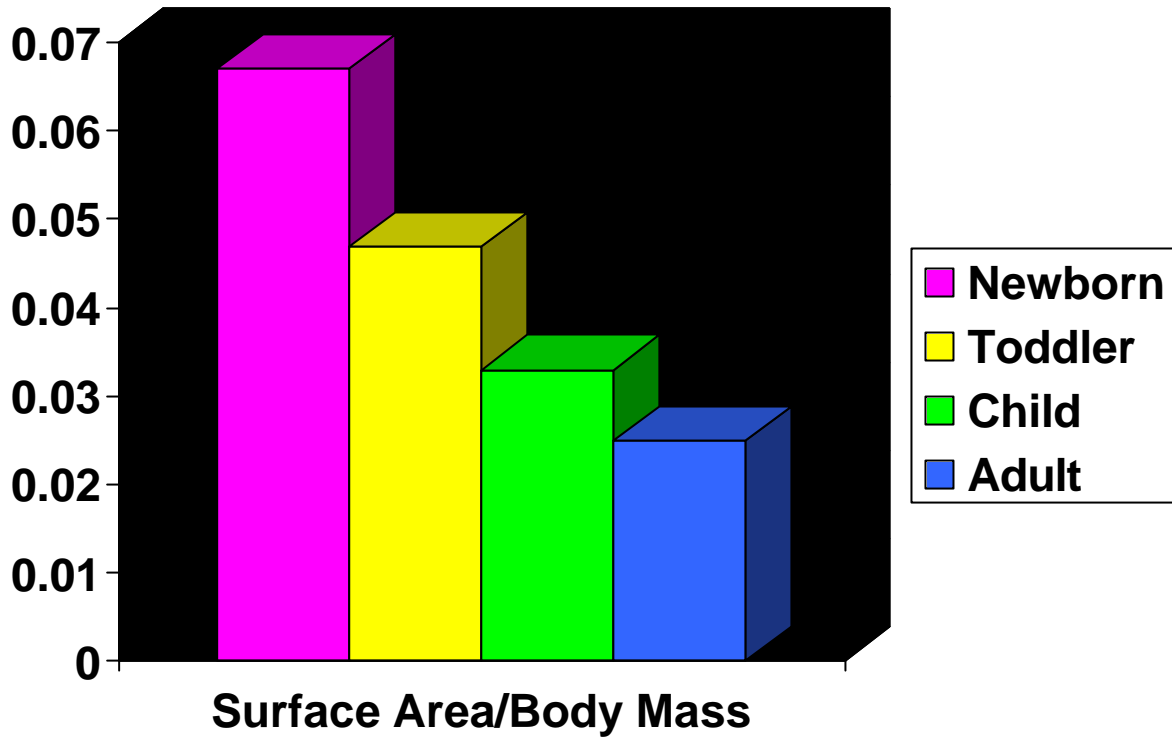
Maintenance Requirements



Daily caloric and water maintenance requirements as a function of age.

Sources: Johnson KB. *The Johns Hopkins Hospital The Harriet Lane Handbook*. 13th Edition. Mosby: St. Louis; 1993. and Miller MD, et al. "Differences Between Children and Adults: Implications for Risk Assessment at California EPA. *Int J Toxicology* (2002) 21:1-16.

Figure 6

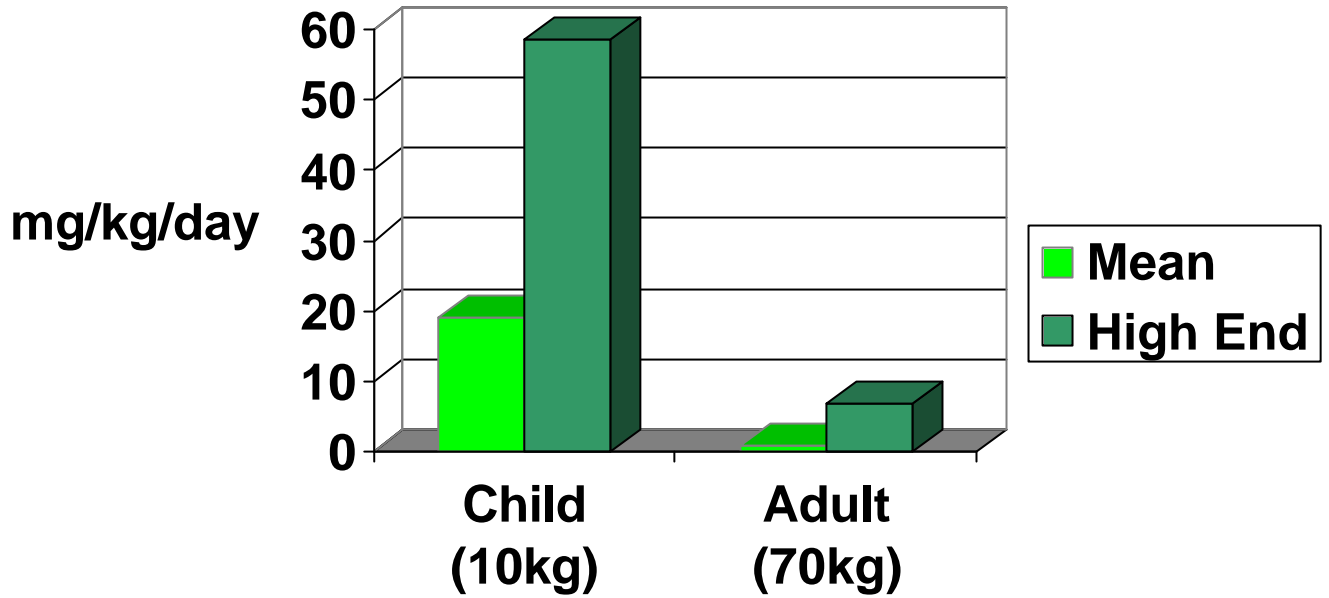


Surface Area to Body Mass Ratios as function of age.

Source: Selevan SG, et al. Identifying critical windows of exposure for children's health. *Environ Health Perspect* (2000)108(Suppl 3):541-455.

Figure 7

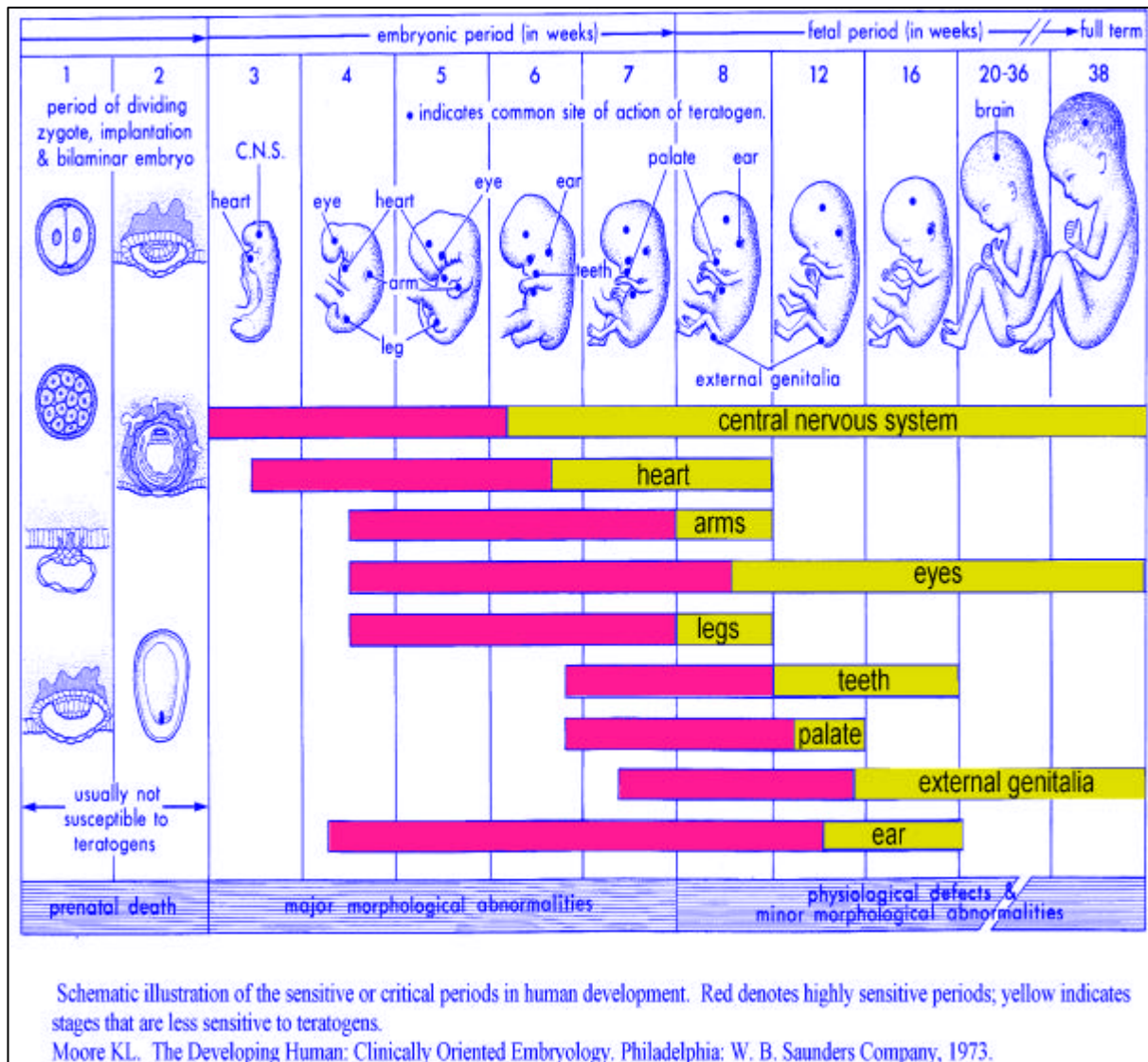
Soil Consumption



Soil Consumption in children and adults.

Source: United States Environmental Protection Agency. *Child-specific Exposure Factors Handbook (Interim Report)*
<http://www.epa.gov/ncea/pdfs/efh/front.pdf>

Figure 8



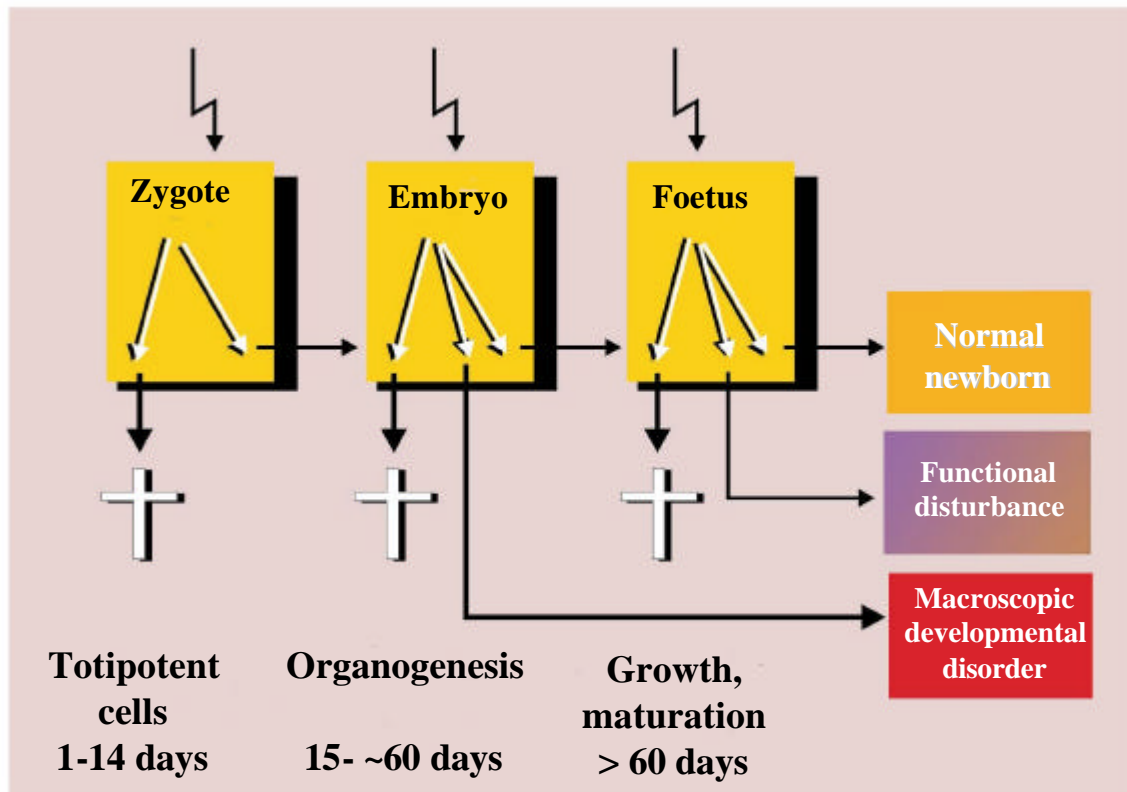
Weeks represented as post-conception.

Weeks of Gestation are by convention, post conception weeks plus 2.

Note: In black & white - Dark gray denotes highly sensitive periods;
 light gray indicates stages that are less sensitive to teratogens.

Source: Reprinted from Moore, KL, Persaud TVN. *The Developing Human: Clinically Oriented Embryology*. Philadelphia, WB Saunders, 1973, page 98. with permission from Elsevier as it appears in Selevan SG, et al. *Identifying critical windows of exposure for children's health. Environ Health Perspect (2000)108(Suppl 3):541.*

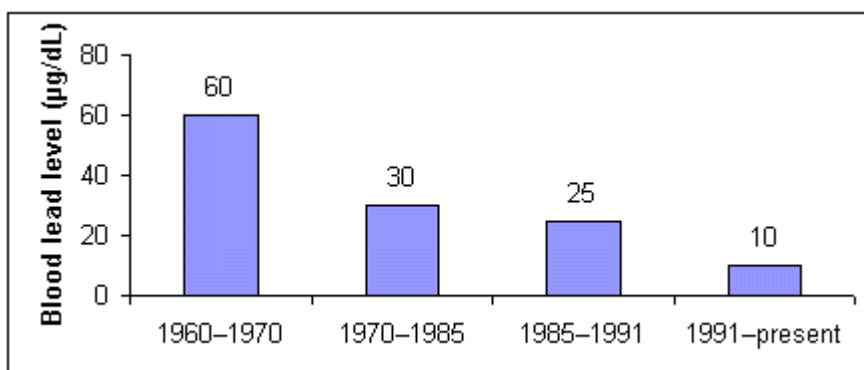
Figure 9



In the three phases of gestation, the reaction to xenobiotics of developing embryo is dose-dependent. Disturbances occurring during the different stages of prenatal development are manifested in characteristic (morphologic and/or functional) changes. Abnormalities of pre-embryonal development are named zygopathies; these are followed by embryopathies up to the 10th week, and foetopathies up to the delivery.

Sources: Czeizel E, et al. Congenital anomalies. Medicina: Budapest; 1973. (in Hungarian) and Ungváry Gy, et al. Combined embryotoxic action of toluene a widely used industrial chemical and acetylsalicylic acid (Aspirin). Teratology (1983)27:261-269.

Figure 10.



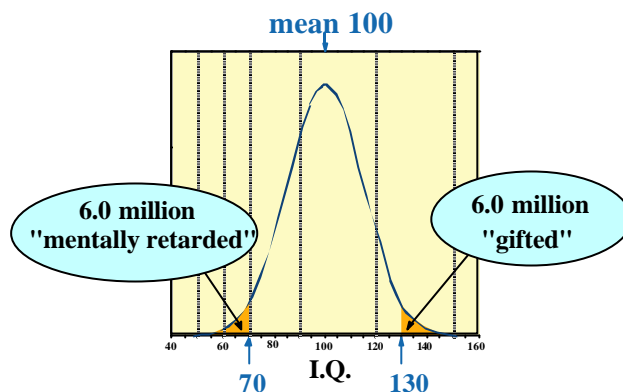
Lowering of the Centers for Disease Control and Prevention
Recommended Action Level for Blood Lead in Children.

Source: *Case Studies in Environmental Medicine Lead Toxicity*,
ATSDR

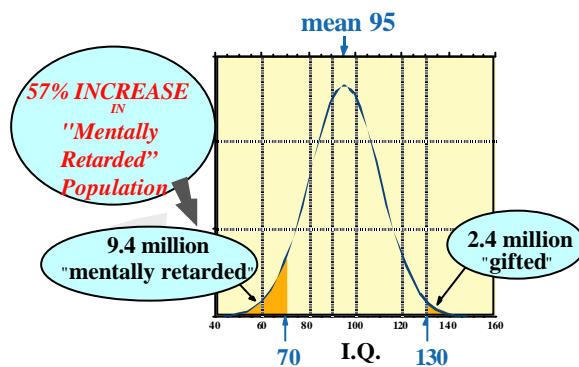
[http://www.atsdr.cdc.gov/HEC/CSEM/lead/standards_regulations.html#
Figure%2](http://www.atsdr.cdc.gov/HEC/CSEM/lead/standards_regulations.html#Figure%2)

Figure 11

The Significance of Small Effects: EFFECTS OF A SMALL SHIFT IN IQ DISTRIBUTION IN A POPULATION OF 260 MILLION



5 Point Decrease in Mean IQ

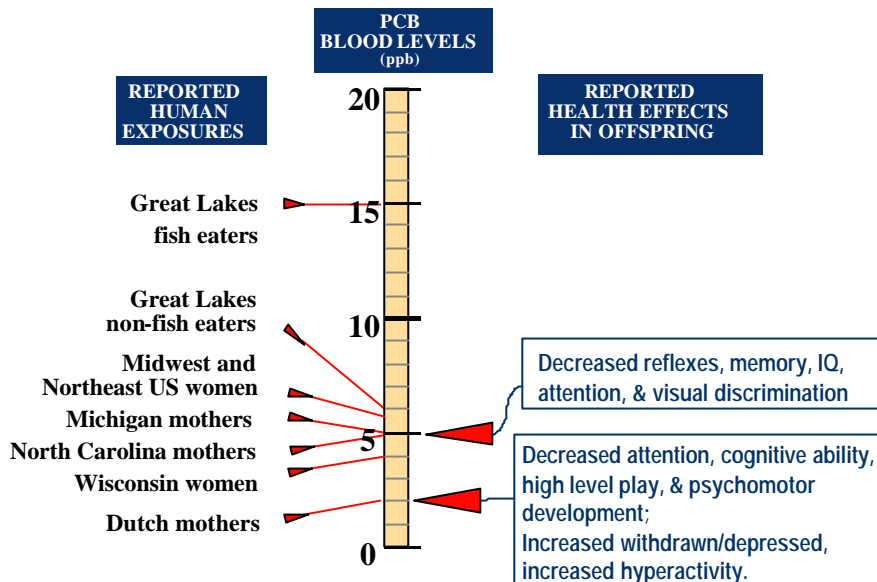


Population effects of a small shift in average IQ. The upper chart shows the distribution of IQ scores in a hypothetical population where the average IQ is 100 and the standard deviation is 15. The gray area under the left “tail” of the curve represents the 2.3 % of the population with an IQ <70, the score used to define mental retardation. In a population of 260 million, approximately 6 million people would fall below this line. The lower chart depicts an IQ distribution that results from lowering the average IQ by 5 points from 100 to 95. Now, 3.2 % of the population, or 9.4 million people, have an IQ below 70. This represents more than a 50 % increase in the numbers of mentally retarded. The numbers of gifted, defined as those with IQs greater than 130, have declined by more than 50 % from 6 million to 2.4 million. Thus, a small shift in average IQ results in a greatly increased need for special education and services, as well as diminished intellectual capacity within the population as a whole.

Source: Greater Boston Physicians for Social Responsibility, *In Harm's Way*
Download at <http://psr.igc.org/ihwpp2.ppt> Accessed 30 Sept 2003

Figure 12

PCBs: Inadequate Margin of Safety



Polychlorinated biphenyls (PCBs): inadequate margins of safety (serum levels). Prenatal exposure to background levels of PCBs has been shown to adversely affect reflexes, memory, and neurological function as assessed by physical examination of infants and toddlers. Adverse effects on attention, memory, intelligence, and reading comprehension have been demonstrated in children followed-up to age 11 years. Note: All health effects shown are associated with prenatal PCB exposure, except hyperactivity, which is associated with blood levels at 42 months of age. While adverse effects have been associated with real-world exposures in specific populations, uncertainty remains about the precise dose-effect relationships in humans.

Source: Greater Boston Physicians for Social Responsibility, *In Harm's Way Download* at <http://psr.igc.org/ihwpp2.ppt> Accessed 30 Sept 2003

Figure 13

TABLE 1: WHAT IS KNOWN ABOUT LEAD AND LEAD POISONING?

At low levels, lead poisoning in children causes:	At high levels, lead poisoning in children causes:	Effects of lead poisoning on children can be:
<ul style="list-style-type: none">• Reduction in IQ and attention span;• Reading & learning disabilities;• Hyperactivity & behavioural problems;• Impaired growth;• Impaired visual & motor functioning;• Hearing loss.	<ul style="list-style-type: none">• Anaemia;• Brain, liver, kidney, nerve damage;• Coma;• Convulsions;• Death.	<ul style="list-style-type: none">• Long-term and potentially irreversible;• Intensified with repeated exposure & accumulation of lead in body.

Source: United Nations Children's Fund and United Nations Environment Programme, Childhood Lead Poisoning: Information for Advocacy and Action, UNICEF and UNEP, New York, 1997.

Annex 1. Human teratogens with mutagenic or epigenetic genotoxic activity

Agent	CAS Reg. No.	Mutagenic effects	Epigenetic effects
Aminopterin and methotrexate	54-62-6 59-05-2	Clastogenic	Folic acid antagonist
Busulphan (Myleran)	55-98-1	Gene mutagen	no effect
Captopril	62571-86-2	questionable effect	ACE inhibitor, alteration of gene expression
Carbamazepine	298-46-4	SCE inducer	no effect
Cigarette smoking		Clastogenic and gene mutagen	no available data
Cocaine	50-36-2	no effect	Alteration of gene expression and programmed cell death
Cyclophosphamide (Endoxan)	50-18-0	DNA base modification	no effect
Cytarabine (Cytosine arabinoside, ARA-C)	147-94-4	Nucleoside analogue	no effect
Daunorubicine and doxorubicine	20830-81-3 23214-92-8	Clastogenic and gene mutagen	Topoisomerase antagonist
Diethylstilbestrol	56-53-1	no effect	Microtubuline polymerisation and depolymerisation
Diphenylhydantoin	57-41-0	questionable effect	Alteration of gene expression
Ethanol (i.e. acetaldehyde)	64-17-5	Clastogenic (effect depends on metabolism)	questionable effect
Indomethacin	53-86-1	Clastogenic	Antimutagenic (!)
Iodide		questionable effect	questionable effect
Lithium	7439-93-2	questionable effect	questionable effect
6-Mercaptopurine	50-44-2	Purin analogue	questionable effect
Methimazole and propylthiouracil	60-56-0 51+52-5	no effect	Antimutagenic (!) Alteration of gene expression
Methyl mercury		C-mitoses	nd
Methylene blue	61-73-4	Gene mutations	Guanosine monophosphate synthesis inhibition
Penicillamine	52-67-5	Oxidative radicals	questionable effect
Polychlorinated byphenyls (PCB)		questionable effect	no available data
Primidone and phenobarbital	125-33-7 50-06-6	questionable effect	P ₄₅₀ enzyme inducer
Quinine	130-95-0	Clastogenic?	DNA repair inhibitor
Retinoids (tretinoin)	302-79-4	no effect	Alteration of gene expression
Testosterone, methyltestosterone, danazol, 17 α -ethinyl-testosterone	58-22-0 58-18-4 1723-88-5 434-03-7	no effect	Alteration of gene expression and programmed cell death
Tetracycline-HCl, oxytetracycline, doxycycline	60-54-8 79-57-2 564-25-0	questionable effect	questionable effect
Thalidomide	50-35-1	Germ cell mutagen?	no available data
Trimethadione and paramethadione	127-48-0 115-67-3	no available data	no available data
Valporic acid	99-66-1	SCE inducer	Alteration of gene expression
Warfarin and dicumarol	81-81-2 66-76-2	Clastogenic	DNA repair modifier

Source: Bishop JW, et al. Genetic Toxicities of human Teratogens. *Mutat Res* (1997)396:9-43.

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- Healthy Environments for Children Alliance www.who.int/heca/en/;
- Children's Environmental Health in Latin America and the Caribbean www.cepis.org.pe/bvsana/i/chelac.html;
- International Research and Information Network on Children's Health, Environment and Safety www.inchesnetwork.org;
- International Society of Doctors for the Environment www.isde.org.

ENDNOTES

ⁱ This has prompted the IFCS to adopt a Priority for Action (A3) to address the situation. A report has been prepared for Forum IV and is available on http://www.who.int/ifcs/Documents/Forum/ForumIV/Meeting_docs/Working_docs/09w-F4_en.doc. The direction was that for all chemicals in commerce, appropriate data detailing the inherent hazards of those chemicals should be made available to the public. Highest priority should be given to hazard information for those chemicals that have greatest potential for substantial exposures. Several concrete suggestions to this end are detailed in the report and should be kept in mind when discussing the specific data needs to address hazards for children.

ⁱⁱ HPVCs: Chemicals placed on the EU market in volumes exceeding 1000 tonnes per year per producer or importer, and chemicals produced or imported into the USA at or above 1 million pounds per year.

ⁱⁱⁱ For further explanation see OECD Guidelines 421 (<http://www.oecd.org/dataoecd/18/14/1948474.pdf> Accessed 29 September 2003) and 422 (<http://www.oecd.org/dataoecd/18/30/1948410.pdf> Accessed 29 September 2003)

^{iv} Biomonitoring: Analysis for example of blood, urine, tissues, to measure chemical exposure in humans.

^v Toxicokinetics: The study of the way that xenobiotics move through the body after they are swallowed or absorbed.

^{vi} For full text of the Food Quality Protection Act, 1996: <http://www.epa.gov/oppfead1/fqpa/gpogate.pdf> Accessed 24 Sept 2003

^{vii} For more information on Voluntary Children's Chemical Evaluation Program see: <http://www.epa.gov/chemrtk/vccep/> Accessed 24 Sept 2003.

^{viii} Xenobiotic: a chemical foreign to the biological system.

^{ix} Ontogenesis: the development of an individual organism.

^x Lipophilic: having an affinity for fat.

^{xi} The organ has a portion of embryonic origin, derived from a highly developed area of the outermost embryonic membrane (chorion frondosum), and maternal portion formed by a modification of the part of the uterine mucosa (decidua basalis) in which the chorionic vesicle is implanted. Within the placenta the chorionic villi with their contained capillaries carrying blood of the embryonic circulation are exposed to maternal blood in the sinusoidal spaces in the decidua basalis.

^{xii} Haemochorial: denoting the type of placenta in which maternal blood comes in direct contact with the chorion (the outermost extraembryonic membrane)

^{xiii} Haemoendothelial: denoting the type of placenta in which maternal blood comes in contact with the endothelium of chorionic vessels.

^{xiv} This species differences in placental structure explains, for example, why acetylsalicylic acid (ASA) is a strong teratogen in rats and mice, but hardly teratogenic in humans. Teratogenic levels of free salicylic acid (is the component responsible for the teratogenic effect of ASA) are not attained in the human fetus. (131, 157)

^{xv} Anabolic: a state of construction by which simple substances are converted by living cells into more complex compounds; body-building

^{xvi} *Embryotoxic, teratogenic materials*. During organogenesis, one group of chemicals may affect the embryo, directly dose-dependently or by way of cytotoxicity (*direct embryotoxic and teratogenic effects*), or indirectly, through their maternal toxic effects (*indirect embryotoxic and teratogenic effects*). *Embryotoxic effects* inhibit embryonic and fetal growth, and cause either malformations or death of the embryo (*growth retardation, teratogenic and embryo-lethal effects*). Owing to its importance, the teratogenic effect of chemicals is treated by some authors separately from the other two embryotoxic effects (growth retardation, embryo-lethal). The effects manifest usually proportionally to the dose entering the body. Doses just above the threshold dose (minimal effective dose) induce congenital anomalies (Annex 1) and/or growth retardation. Higher doses cause death of the embryo. If the substance does not have teratogenic effects, the embryo-lethal effect is preceded only by growth retardation further increase of the dose leads to the intoxication, even death of the mother (maternal toxic and maternal lethal effects). Sometimes the embryo-damaging and maternal toxic effects overlap. (116, 131, 158)

In case of dangerous substances the effects of which appear only above the so called threshold dose but become more and more seriously damaging with increasing the dose up to a maximal level (which means often the death of the living organism), the relationship between the effects and the dose is termed deterministic dose-effect relationship, characterized by a flattened, "S"-shaped dose-effect curve.

In regard to the everyday practice it is important to understand that teratogenic substances have threshold dose (e.g. in contrast to genotoxic carcinogens, mutagens, which do not have no-effect dose). In doses below the threshold dose level, these substances do not harm the embryo. It is important also from a practical view, that direct (or specific) teratogens are more dangerous than indirect (or non-specific) ones. While the former damage the embryo without adversely affecting the mother, in case of the latter adverse fetal effects appear in addition to maternal toxicity.

^{xvii} *Mutagenic embryotoxic and teratogenic substances.* Another group of dangerous substances possibly getting into the body during gestation is made by those teratogens which are mutagens at the same time (Annex 1). These may exert their effect anytime during ontogenesis. Mutagenic embryotoxic and teratogenic substances may have teratogen, transplacental carcinogen or generation-toxic effects, as well. These have no threshold dose (theoretically, their effect may manifest due to exposure to a single molecule) and the frequency of their effect increases with the increase of the exposure concentration or the exposure time, but the 100 % frequency is never reached (substances characterized by so called stochastic dose-response). The substances with stochastic effect, cause acute intoxication above a certain dose, which is characterized by a deterministic relationship (similar to the effect of higher doses of ionizing radiation).

^{xviii} Bioaccumulate: the process by which substances increase in concentration in living organisms as they take in contaminated air, water, or food because the substances are very slowly metabolized or excreted.

^{xix} Biomagnify: Refers to the process whereby certain substances such as pesticides or heavy metals move up the food chain, work their way into rivers or lakes, and are eaten by aquatic organisms such as fish, which in turn are eaten by large birds, animals or humans. The substances become concentrated in tissues or internal organs as they move up the chain.(148)

^{xx} Additional histories: Warren C. Brush with Death: A social history of lead poisoning. The Johns Hopkins University Press: Baltimore; 2000. English PC. Old Paint: A medical history of childhood lead-paint poisoning in the United States to 1980. Rutgers University Press: New Brunswick; 2001.

^{xxi} It is now widely accepted that the thermal degradation products were the causative factors in these poisoning episodes. (PCBs and the Environment, Vol. 3, edited by J.S. Waide, CRC Press, "Differences between Yusho and other kinds of poisonings involving only PCBs" by T. Kashimoto and H. Miyata, pp. 1-26 (1987)

^{xxii} Rio Declaration on Environment and Development Principle 15: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation"

^{xxiii} ILO Convention 182, which calls for immediate action to ban the worst forms of child labour.

<http://www.ilo.org/public/english/standards/ipecc/ratification/convention/text.htm>