# Summary

## of Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals

**World Health Organization**

# Summary of Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals

**World Health Organization**

# Contents

# Contributors to Environmental Health Criteria 237

## Experts

Tom Burbacher, Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, Washington, USA

George Daston, Procter & Gamble Company, Cincinnati, Ohio, USA

Rodney Dietert, Department of Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, New York, USA

Agneta Falk-Filipsson, Karolinska Institutet, Stockholm, Sweden

Fernando Froes, USP School of Medicine, Sao Paulo, Brazil

Gonzalo Gerardo Garcia Vargas, Universidad Juarez del Estado de Durango, Gomez Palacio, Mexico

Kimberly Grant, University of Washington, Seattle, Washington, USA

Tony Myres, Ottawa, Ontario, Canada

Asher Ornoy, Hebrew University, Jerusalem, Israel

Susan Ozanne, University of Cambridge, Cambridge, United Kingdom

Jerry Rice, Washington, D.C., USA

Peter Sly, Department of Pediatrics and Physiology, Telethon Institute, Perth, Australia

Jorma Toppari, University of Turku, Turku, Finland

## Advisory group members

Patric Amcoff, Organisation for Economic Co-operation and Development, Paris, France

Bingheng Chen, Environmental Health, Fudan University School of Public Health, Shanghai, People's Republic of China

Thea De Wet, Department of Anthropology and Developmental Studies, Rand Afrikaans University, Auckland Park, South Africa

Agneta Falk-Filipsson, Utredningssekretariatet, Institutet förmiljömedicin (IMM), Karolinska Institutet, Stockholm, Sweden

Elaine Faustman, Pediatric Environmental Health Research Center, University of Washington, Seattle, Washington, USA

Ryuichi Hasegawa, Division of Medicinal Safety Science, National Institute of Health Sciences, Tokyo, Japan

Carole Kimmel, Office of Research and Development, National Center for Environmental Assessment, Environmental Protection Agency, Washington, D.C., USA

Kannan Krishnan, University of Montreal, Montreal, Quebec, Canada

Irma Makalinao, National Poisons Control & Information Service, Philippines General Hospital, Manila, Philippines

Mathuros Ruchirawat, Chulabhorn Research Institute, Bangkok, Thailand

Radim J. Sram, Institute of Experimental Medicine, Academy of Sciences of the Czech Republic, Prague, Czech Republic

William Suk, Division of Extramural Research and Training, National Institute for Environmental Health Sciences, Department of Health and Human Services, Research Triangle Park, North Carolina, USA

Jan E. Zejda, Department of Epidemiology, Medical University of Silesia, Katowice, Poland

## Secretariat

Terri Damstra, World Health Organization, Research Triangle Park, North Carolina, USA (deceased)

## Contributors to Summary document

Miao Yu, New Haven, Connecticut, USA

James Listorti, Washington, DC, USA

## Secretariat

Nida Besbelli, Department of Public Health and Environment, World Health Organization, Geneva, Switzerland

Ruth A Etzel, Department of Public Health and Environment, World Health Organization, Geneva, Switzerland

Marie Noel Brune, Department of Public Health and Environment, World Health Organisation, Geneva, Switzerland.

# Acronyms and Abbreviations

| | |
|---|---|
| ACE | angiotensin converting enzyme |
| AGD | anogenital distance |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BMD | benchmark dose |
| DDE | dichlorodiphenyldichloroethene |
| DDT | dichlorodiphenyltrichloroethane |
| DES | diethylstilbestrol |
| EHC | Environmental Health Criteria |
| EPA | Environmental Protection Agency (USA) |
| EU | European Union |
| hCG | human chorionic gonadotropin |
| IARC | International Agency for Research on Cancer |
| IPCS | International Programme on Chemical Safety |
| IUGR | intrauterine growth restriction |
| NRC | National Research Council |
| OECD | Organisation for Economic Co-operation and Development |
| PAH | polycyclic aromatic hydrocarbon |
| PBB | polybrominated biphenyl |
| PBPK | physiologically based pharmacokinetic |
| PCB | polychlorinated biphenyl |
| $PM_{10}$ | particulate matter less than 10 μm in diameter |
| POP | persistent organic pollutant |
| RfD | reference dose |
| T3 | triiodothyronine |
| T4 | thyroxine (tetraiodothyronine) |
| TCDD | 2,3,7,8-tetrachlorodibenzo-$p$-dioxin |

| | |
|---|---|
| TDI | tolerable daily intake |
| Th1 | T helper 1 |
| Th2 | T helper 2 |
| UN | United Nations |
| UNEP | United Nations Environment Programme |
| UNICEF | United Nations Children's Fund |
| USA | United States of America |
| USEPA | United States Environmental Protection Agency |
| VOC | volatile organic compound |
| WHO | World Health Organization |

# Preface

WHO has been concerned for many years about the adverse effects of chemical exposures on susceptible populations, including children. Past Environmental Health Criteria (EHC) publications addressing methodologies for risk assessment in children include EHC 30, *Principles for Evaluating Health Risks to Progeny Associated with Exposure to Chemicals during Pregnancy* (IPCS, 1984), and EHC 59, *Principles for Evaluating Health Risks from Chemicals during Infancy and Early Childhood: The Need for a Special Approach* (IPCS, 1986). Since these monographs were published in the 1980s, new data and methodologies have emerged, indicating that children are a vulnerable population subgroup with special susceptibilities and unique exposures to environmental factors that have important implications for public health practices and risk assessment approaches.

Environmental Health Criteria 237 *Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals* (IPCS, 2006) was intended for use by public health officials, research and regulatory scientists, and risk assessors. This document provides a summary of the findings from Environmental Health Criteria 237 and was prepared for use by a wider audience. For detailed information, the reader should consult the full document, available at http://www.inchem.org/documents/ehc/ehc/ehc237.pdf.

# Summary of Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals

## Summary

Environmental factors play a major role in determining the health and well-being of children. Accumulating evidence indicates that children, who comprise over one third of the world's population, are among the most vulnerable of the world's population and that environmental factors can affect children's health quite differently from adults' health. The disease burden estimates from environmental risks highlight the particular vulnerability of children when facing environmental risks. For example, while 24% of the global burden of disease is attributable to the environment, as much as 33% is attributable to the environment for children (WHO, 2006). Poor, neglected, and malnourished children are most severely affected. These children often live in unhealthy housing, lack clean water and sanitation services, and have limited access to health care and education.

This booklet summarizes the scientific principles to be considered in assessing health risks in children from environmental chemicals and provides information for public health officials, research and regulatory scientists, and others responsible for protecting children's health.

# Introduction and background

## Introduction and background

Environmental factors play an important role in determining the health of children, who are among the most vulnerable of the world's population. This document focuses on the relationship between exposure(s) to environmental factors at a specific stage of fetal/child development and health outcomes through the life span, rather than on a single environmental hazard and related disease or outcome.

Exposure to environmental hazards underlies ill-health in children in all regions of the world, but particularly in those who are impoverished and

malnourished, and those who face a confluence of both traditional and emerging environmental exposures. Greater awareness in recent years about the special vulnerability of children has led to an increased number of new research programmes, international agreements, and international alliances that specifically address and promote healthy environments for children.

In 2002, the WHO launched the Healthy Environments for Children Alliance, which seeks to mobilize support and intensify global action to provide healthy environments for children. During the same year, the Bangkok Statement was declared at the World Health Organization (WHO) International Conference on Environmental Threats to Children: Hazards and Vulnerability, held in Bangkok, Thailand. In 2005 and 2009, the Second and Third International Conferences on Environmental Threats to Children were held in Buenos Aires, Argentina, and Busan, Republic of Korea, respectively. At these conferences, the wide range of international participants approved the 'Buenos Aires Declaration' and the 'Busan Pledge for Action' prompting WHO and partners to act for healthier environments for children. These three conferences contributed to identifying the need for improved risk assessment methodologies in children, and determining priority areas for research collaboration. In addition, many countries have established specific regulations to protect children from exposure to certain environmental hazards, such as banning of heavy metals (such as lead in paint) in toys. The initiatives of the last decade make it clear that a comprehensive assessment of environmental risk in children, based on the most recent research findings, is essential to provide scientific and systematic advocacy for policy to improve children's environmental health and safety.

Despite remarkable advances in recent decades, it is estimated that nearly 11 million children under five years of age die annually from causes that are largely preventable. Most of these occur in African and South-east Asian regions of the world (UNICEF, 2010; WHO, 2005). Figure 1 shows the major causes of death in children under five years of age. The primary environmental threats continue to be the 'traditional' risks including unsafe drinking-water, poor sanitation, indoor air pollution, infectious and vector-borne diseases and contaminated food supplies. However, 'emerging' risks, including exposure to human-made toxic substances in the environment, pose an increasing threat to children's health.

**Figure 1.** Estimated distribution of major causes of death among children under five years of age and neonates in the world, 2008 (WHO and UNICEF 2010)
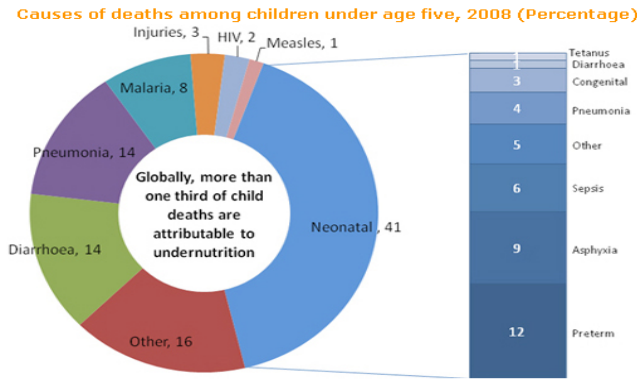


Note: Based on the Child Health Epidemiology Reference Group of WHO and UNICEF estimates, 2010.

(Updated version after EHC 237)

Chemical hazards, social and economic factors all have effects on children's health. There is clear scientific evidence that exposure to environmental chemical hazards during different developmental stages has resulted in an increased incidence of certain childhood diseases. A wide range of chemicals can affect children's health, but a few chemical classes are of particular concern. These include heavy metals, persistent organic pollutants, pesticides, and air pollutants. Heavy metals and lipophilic persistent organic pollutants (POPs) cross the placenta and also favour transfer into breast milk, usually the primary source of food for infants. Heavy metals and POPs are known to interfere with the normal growth and development of children (Damstra et al., 2002; Coccini et al., 2006).

Beyond environmental exposures, other risks play a part in children's ill-health. Social and cultural factors are considered as the cause behind causes of child morbidity and mortality. Economic and nutritional factors, especially poverty, are key among the driving forces that create unhealthy environmental conditions for children. In addition to these extrinsic factors, intrinsic factors such as genetic makeup that controls the dynamics of development play a key role in determining the susceptibility of children to environmental exposures at different life stages. For example, the presence of a gene that results in lower levels of acetycholinesterase - the target enzyme of organophosphates - would increase the vulnerability of the developing brain to organophosphate pesticides (Costa et al., 2005; Costa et al., 2003).

Adverse effects in children may result from exposure prior to conception (paternal and/or maternal), during prenatal development, or postnatally to the time of full maturity. Even within a given developmental stage, shorter intervals of exposure may determine susceptibility for particular outcomes. Different organ systems develop at different rates, but it has been shown that for each developmental stage, there are both broad windows of susceptibility and more specific periods of susceptibility (Faustman et al., 2000; Selevan et al., 2000).

Adverse health outcomes from early exposures may become apparent at any point in the lifespan. In some instances, they may be apparent only after long latency periods. The effects of toxic exposures on developmental processes may result from different mechanisms of action, and the toxic exposures may produce different health outcomes compared with the same exposures in adults.

## Summary

Environmental threats to the health of today's children result from a complex interaction of influences in children's biological, social, behavioural, physical, and economic environments.

It is clear that:

- environmental exposures play a significant role in the production of adverse health outcomes in children and that this is a serious public health concern,

- due to health, wealth, or opportunity, many children are disadvantaged from the time of conception,

- the health of the "child" at each stage of development will set the stage for and affect future health

# Unique Biological Characteristics of Children

Children are not simply little adults; they possess distinct characteristics across life stages that contribute to their different susceptibility to environmental exposures. For example, infants gain more weight during the first four to six months than during the rest of their lives and organ systems grow at different rates at any time from infancy to early childhood. Looking at organ growth, although the absolute brain weight does not change much with age, the brain to body weight ratio decreases with age. In contrast, the absolute weights of kidney and liver increase with age, but their relative weights show little change. Skin is similar in adults and infants in terms of barrier properties. Neonates and infants in general have a larger surface area relative to body weight than do adults.

With respect to anatomical and functional characteristics, most organ systems lack structural or functional maturity at birth. The gastrointestinal, endocrine, and reproductive systems are all immature at birth. The blood–brain barrier is also immature, and the development of this barrier and the nervous system in general continues in postnatal life.

Physiologically, neonates have fewer alveoli and a faster breathing rate than adults; the heart rate is greater in newborn infants than in older children (Emery & Mithal, 1960); and the rate of blood flow to organs changes with age. For tissue composition, the water contents of liver, brain, and kidneys decrease from birth to adulthood, while overall composition of muscle in terms of lipid and water does not seem to vary (Dickerson & Widdowson, 1960). The bones of infants contain more water and less fat, protein, and minerals than adult bones.

Metabolism is also a function of age, with most metabolizing enzyme systems developing from the middle of gestation until a few months after birth. Neonates and young children may be better or less able than adults to deal with toxic substances, owing to differences in metabolic capacity (Spielberg, 1992; NRC, 1993; Dorne et al., 2005).

Absorption of chemicals occurs through routes such as oral, dermal, and pulmonary. Toxicokinetics – the process of absorption, distribution, metabolism and elimination of a chemical - directly affects the outcome of chemical insult and differs between children and adults. The developing organs are particularly susceptible to toxic insult, given the increased rate of cell division and immaturity of some functional excretion systems. Uptake of chemicals is also likely to vary between children and adults.

For example, the respiratory ventilation rate in infants is significantly larger relative to lung surface compared with adults. Therefore, infants potentially have greater uptake of airborne compounds on a body weight basis (Bennett et al., 1996).

The physiological distribution volume for chemicals may vary between children and adults because of differences in water and lipid content as a function of age. For example, the relatively larger extracellular fluid volume of the infant means somewhat greater dilution of water-soluble chemicals (Friis-Hansen, 1971; Rylance,1988; Kearns et al., 2003). However, the lipid-soluble substances would be distributed in a smaller volume of fat in infants relative to adults (Alcorn & McNamara, 2003). In addition, renal clearance has been shown to be lower in neonates than in older children and adults, for all chemical classes: lipophilic, hydrophilic, and organic ions (Clewell et al., 2002).

Physiological changes during pregnancy would influence the toxicokinetics of the mother and the growing fetus as well (Hytten, 1984; Krauer, 1987; Mattison et al., 1991). For instance, the renal blood flow and glomerular filtration rate are increased during pregnancy, which may enhance renal clearance of certain xenobiotics, thus protecting the fetus from exposure to chemicals in the systemic circulation. The complex interplay of molecular and physiological factors in the functional and structural development of various organ systems ultimately influences the toxicokinetics and toxicodynamics of chemicals. Table 1 gives a summary of the age dependency of the determinants of toxicokinetics in children.

Breastfeeding plays a critical role in human infant development, since it provides not only essential nutrition but also protection against infection and other immunological disorders (Lawrence, 1989). Unfortunately, the nursing mother can also serve as a source of infant exposure to drugs, chemicals, and environmental exposures which may be continuous and chronic in nature. However, based on the numerous advantages of breastfeeding, the benefits exceed the potential risk (Kacew, 1992; Pronczuk et al., 2004).

**Table 1.** Summary of the age dependency of the determinants of toxicokinetics in children in comparison with normal adults[a]

| | Age of child | | | | |
|---|---|---|---|---|---|
| | Newborn preterm | Term (0-4 weeks) | Infancy | 1-4 years | 5-12 years |
| Oral absorption | ↓ | ↔ | ↔ | ↔ | ↔ |
| Distribution:<br>- Body water | ↑↑↑ | ↑↑ | ↑ | ↑ | ↑ |
| - Body fat | ↓↓ | ↓ | ↓ (Slight) | ↔ | ↔ |
| - Plasma albumin | ↓ | ↓ | ↓ Slight | ↔ | ↔ |
| Biotransformation:<br>- Oxidation/hydrolysis | ↓↓↓ | ↓↓ | ↑↑ (After some weeks) | ↑ | ↑ Slight |
| - *N*-demethylation | ↓↓↓ | ↓ | ↑↑ | ↑ | ↔ |
| - Acetylation | ↓ | ↓ | ↑ | ↑ | ↔ |
| - Conjugation-glucuronidation | ↓↓ | ↓ | ↑ | ↑ | ↔ |
| Renal excretion:<br>- Glomerular filtration | ↓↓ | ↓ | ↓ | ↔ | ↔ |
| - Tubular secretion | ↓↓ | ↓ | ↓ (Slight to 6 months) | ↔ | ↔ |

[a] Based on Rylance (1988).   ↑ = increased,   ↓ = decreased,   ↔ = unaltered.

# Developmental Stage-specific Susceptibilities and Outcomes in Children

The timing of exposure to chemicals or other insults is  critical in determining the consequences to children's health.  Due to differing windows of susceptibility the same dose of the same chemical during different periods of development can have very different consequences. Windows of susceptibility in children are broad, and extend from the preconception period through to the end of the adolescent period.

Structural or functional alteration of organs may result from chemical insult.  Structural malformations are likely to occur as a result of exposure to chemicals during the embryonic and fetal periods, when the basic structure of organs is being formed. However, even after an organ has been established,

**Table 2.** Examples of adverse effects of developmental stage-specific exposures on various organ systems[a]

| Period of susceptibility for exposure | Neurological | Reproductive | Renal | Endocrine | Cardiac | Immune | Respiratory | Cancer |
|---|---|---|---|---|---|---|---|---|
| Pre-conception | Periconceptional use of folic acid supplements decreases rate of neural tube defects (Bailey et al., 2003) | | | | | | | |
| Preimplantation | | | | | | | | Exposure of male mice to x-rays or urethane causes cancer in their offspring (Anderson et al., 2000) |
| Embryonic age | Neural tube defects from retinoic acid, arsenic, and valproic acid (Adams,1993; Bennet & Finnell, 1998) | Decreased fertility in female rats exposed to dioxin (TCDD) (Gray & Ostby, 1995) | Hydronephrosis with dioxin exposure during embryonic or fetal periods in rats (Couture-Haws et al., 1991; Birnbaum, 1995) | | | | | |
| Fetus | Decreased intelligence, increased behavioural problems with lead (Bellinger et al., 1994; Rice, 1996) Cerebral palsy, mental retardation with high-dose methylmercury (Harada, 1978); subtle neurobehavioural effects with low doses (Grandjean et al., 1997) | Exposure to several phthalates induces reduced AGD and malformations in male rats (Mylchreest et al, 1999; Gray et al, 2000) Delay in pubertal development from exposure to PBBs Vaginal adenocarcinoma in young women due to DES (Herbst et al, 1971) | ACE fetopathy with neonatal renal failure from maternal exposure to angiotensin inhibitors (Tabacova et al, 2003) | Maternal smoking causes decreased birth weight and increased risk for later diabetes (Montgomery and Ekbom, 2002) and osteoporosis (Cooper et al, 2002). Decreased T3/T4 levels in infant and juvenile rats (Brouwer et al, 1998) exposed to PCBs | Decreased heart rate variability in children exposed prenatally to methylmercury (Grandjean et al., 2004) Intrauterine growth retardation (IUGR) (e.g. due to poor maternal malnutrition) increases risk of coronary heart disease in adulthood (Lau and Rogers, 2005) | Decreased cell-mediated immunity in males following perinatal exposure of rats to methoxchlor (Chapin et al., 1997) and heptachlor (Smialowicz et al., 2001, Smialowicz, 2002) Lead exposure reduces Th1 immune capability, causing a shift towards increased Th2, responses in rats (Dietert et al., 2004; Dietert & Lee, 2005). | Altered airway growth with increased collagen deposition in airway walls with exposure to maternal smoking (Sekhon et al., 2001) Altered control of breathing with diminished hypoxic response postnatally with maternal smoking in utero (Ueda et al., 1999) | Inorganic arsenic in drinking-water caused adrenal tumours in male offspring and ovarian and lung tumours in female offspring as adults (Waalkes et al., 2003). |
| Neonate | | | Hydronephrosis with dioxin exposure during neonatal and infantile periods in rats (Birnbaum, 1995) | | | | Increased incidence of respiratory mortality following exposure to particulates in the air (Glinianaia et al., 2004) | |
| Infant | Exposure of juvenile mice to pesticides caused Parkinson-like declines in dopaminergic neurons in adulthood (Cory-Slecta et al., 2005) | | | Maternal grooming affects ability to respond to stress in adulthood in rats (Gilbert, 2005) | | | | |
| Child | Brain tumors and meningiomas after therapeutic high does ionizing radiation to the head (Ron et al., 1988b; Kleinschmidt and Lillehei, 1995) | | | Lead poisoning causes abnormal bone structure and poor growth (Osterloh, 1991) | | Leukemia in children due to radiation from atomic bomb (IARC, 2000) | Exacerbation of pre-existing asthma from exposure to particulates in the air (Parnia et al., 2002) Chronic ozone exposure decreases lung function (Kunzli et al., 1997) | Ionizing radiation and leukemia in childhood and adulthood (Chow et al., 1996; Ron et al.,1988a). Radioisotopes of iodine from Chernobyl disaster and thyroid carcinoma (Pacini et al., 1997) |
| Adolescent | | Delayed puberty with ethanol consumption (Dees et al., 1998) Delayed puberty with atrazine exposure in rats (Laws et al., 2000; Ashby et al., 2002) | | | | | | Breast cancer in adulthood with high-dose ionizing radiation (Boice et al., 1996) |

ACE, angiotensin converting enzyme; AGD, anogenital distance; DES, diethylstilbestrol; IUGR, intrauterine growth restriction; PBBs, polybrominated biphenyls; PCBs, polychlorinated biphenyls; T3, triodothyronine; T4, thyroxine; TCDD, tetrachlorodibenzo-p-dioxin; Th1, T helper 1; Th2, T helper 2

[a] This table is not intended as a comprehensive review. Only selected examples are provided.

disruption of cell growth and cell migration can have lifelong consequences on key organ systems. Exposure to chemicals during early life stages can result in adverse effects during the stage when exposure occurred, or the effects may not manifest themselves until later stages. Each organ system has its particular developmental state-specific susceptibility, and outcomes, in children (see Table 2 for examples). Depending on the dose of the chemical and the susceptibility of the host, immediate and/or long-term adverse effects can range from functional deficits to malformations, even to mortality.

Side-effects from prenatal chemical exposures may cause mortality, growth restriction and birth defects. It is often stated that exposures occurring between conception and implantation result either in the death of the embryo, or have no effects. However, animal studies shows that certain mutagens would also cause malformations during the implantation period (Rutledge & Generoso, 1998). About one third of post-implantation pregnancies end in spontaneous abortion, and occupational exposure of the mother to a variety of agents during pregnancy has been demonstrated in epidemiological studies to be associated with spontaneous abortion (Pastides et al., 1988; Taskinen et al., 1989; Lindbohm et al., 1990; Lipscomb et al., 1991; Windham et al., 1991 Schenker et al., 1995).

The effects of prenatal chemical exposure on growth have most commonly been measured as changes in birth weight. Maternal smoking, exposure to polluted air and exposure to persistent organochlorine compounds have been associated with the reduction of fetal birth weight (Bosley et al., 1981; Wang et al., 2002; Sram et al., 2005; Rylander et al., 1995).

Birth defects, or congenital anomalies, are the result of a disturbance in normal developmental processes, and may be the outcome of a combination of intrinsic factors and environmental influences. For example, excess amounts of retinoic acid or inadequate periconceptual folic acid intake was shown to be responsible for a higher incidence of birth defects (Shenefelt, 1972; Matt et al, 2003). Public health efforts to ensure that all women of childbearing age have adequate folic acid intake have been effective in reducing defects such as those of the neural tube (Botto et al, 2004).

It is extremely helpful to understand what occurs physiologically in major organ systems (nervous, reproductive, endocrine, cardiovascular, immune, respiratory, kidney) during critical periods of susceptibility, and the possible consequences of exposure.

The developing nervous system is more susceptible than the adult brain to the disrupting effects of toxic chemicals. Levels of exposure that produce few, or no, obvious effects on the mature nervous system in adults may pose a serious risk to the developing nervous system (Faustman et al., 2000). The lengthy period of brain development and the extensive number of neural processes available for disruption during development contribute to the susceptibilities of the developing nervous system to toxicants (Rodier, 1994).

Neurogenesis of different areas of the brain continues to occur throughout gestation, and postnatally. Exposure to environmental chemicals such as methylmercury, lead, or certain pesticides may produce cellular or molecular changes that are expressed as neurobehavioural (functional) deficits (Adams et al., 2000), or as increased susceptibility to neurodegenerative diseases later in life (Cory-Slechta et al., 2005).

The effects of prenatal chemical exposure can be expressed across several domains of behaviour and can include adverse effects on intelligence/cognition, social behaviour or temperament, sensory development (vision, hearing), and physical growth (Vreugdenhil et al., 2004). Depending on the timing and nature of the neurotoxicity, behavioural deviations in the developing child can range from mild (e.g. learning disabilities) to severe (e.g. mental retardation).

The fetus is particularly sensitive to methylmercury exposure, and adverse neurobehavioural effects in infants have been associated with exposure levels that result in few, if any, signs of maternal clinical illness or toxicity. Early life stage exposure to this organometal, primarily through the consumption of fish, produces a broad spectrum of dose-dependent neurobehavioural effects (NRC, 2000; Davidson et al., 2004).

Aside from mercury, lead is perhaps the best-studied toxicant that has been clearly linked to central nervous system injury and adverse neurobehavioural outcomes in exposed children. It has long been recognized that high exposure to lead can result in encephalopathy, coma and death (Needleman, 2004). The relationship between environmental lead exposure and intellectual deficits in children was confirmed in an international pooled analysis (Lanphear et al., 2005). It is generally accepted in the scientific and medical communities that the adverse neurobehavioural consequences associated with developmental lead exposure are not reversible and remain in place across the human lifespan (Bellinger, 2004).

There is also mounting evidence from Taiwan, China, the United States, the Netherlands, Germany and the Faroe Islands on the developmental toxicity of polychlorinated biphenyls (PCBs) (Schantz et al., 2003). Commonly occurring environmental pollutants, PCBs pose potential health risks to both humans and wildlife (Kuratsune et al., 1971; Hsu et al., 1985). Infants born to mothers who consumed PCB-contaminated rice oil during pregnancy were found to be at increased risk of low birth weight and neurobehavioural deficits such as delayed attainment of developmental milestones, lower scores of intelligent tests (Guo et al., 2004).

The consumption of alcohol during pregnancy can have a profound impact on childhood development (Burbacher & Grant, 2006). The effects of ethanol are dose dependent, and children born to alcoholic or ethanol-abusing mothers are at highest risk for poor developmental outcomes (Stratton et al., 1996). The most serious clinical outcome for infants who have been exposed in utero to alcohol is the development of fetal alcohol syndrome (Jones & Smith, 1973).

Reproductive organs develop throughout gestation with a series of accurately timed gene activities. Adverse effects can manifest at birth, during puberty, or in adulthood, depending on the action of agents and the timing of exposure and dose of the chemical. For example, *in utero* exposure of men to Diethylstilbestrol (DES) has been linked to meatal stenosis, testicular hypoplasia and sperm abnormalities (Henderson et al., 1976; Gill et al., 1977, 1979; Stillman, 1982). In females, adenosis, clear cell adenocarcinoma, and structural defects of the cervix, vagina, uterus, and fallopian tubes have been linked to in utero exposure to DES (Stillman, 1982). Exposure to high levels of polybrominated biphenyls (PBBs) *in utero* and via breastfeeding has been linked to an early menarche in girls (Blanck et al, 2000).

Men whose mothers smoked tobacco during pregnancy were more likely to have reduced semen quality, smaller testis size, and reduced fecundability (Jensen et al., 1998, 2005).

The endocrine system regulates metabolic, nutritional, reproductive and behavioral processes, as well as growth, responses to stress, and the function of the digestive, cardiovascular, renal and immune systems. The endocrine glands have early windows of susceptibility during the embryonic period, when the glands first begin to develop. The later period of differentiation of the glands, which occurs mostly during the fetal period, constitutes another set of susceptible periods for the endocrine system. Programming

of the endocrine system occurs during the period of fetal/neonatal development, and disruption by exposures to toxicants during this critical period can result in severe abnormalities in endocrine function. Evidence from epidemiological studies demonstrates that exposures during early life stages can create susceptibility to diabetes and obesity later in life (Lau & Rogers, 2005). Poor maternal nutrition, especially during the last trimester of pregnancy, has been linked to poor glucose tolerance and insulin resistance in the offspring (Montgomery & Ekbom, 2002).

The first organ system in a fetus to develop is the cardiovascular system as it is necessary for the delivery of oxygen and nutrients to the rapidly developing cells of the embryo. The heart begins to beat at three weeks of embryonic age. The most susceptible period of prenatal heart development of the heart occurs between week 2 and 8 in humans; developmental cardiac anomalies have been associated with a broad spectrum of agents such as carbon monoxide, monocrotaline and catecholamines (Lau & Kavlock, 1994). There are suggestions that environmental contaminants such as ambient air pollution (carbon monoxide, nitrogen dioxide, ozone, and $PM_{10}$) can affect cardiac development in humans (Ritz et al, 2002).

The development of the immune system is a dynamic process and involves a variety of cellular activities such as cellular proliferation, migration, recognition, clonal expansion and apoptosis. Environmentally induced events can be directed at immune cells, or may arise as a result of essential alterations in the physiological microenvironment to promote immune cell migration. Immune system development can be divided into five stages, from initiation of haematopoiesis to the establishment of immune memory (Dietert et al., 2000); exposure to an immunotoxicant during different windows of susceptibility might be expected to produce different outcomes. Epidemiologic studies have documented an increased risk of otitis media during the first year of life, associated with increasing prenatal exposure to PCBs and DDE (Dewailly et al., 2000; Dallaire et al., 2004).

In summary, early life stage exposure to environmental hazards can produce significant immunotoxicity, whereas the same effects are not always seen in adults. The consequences of early exposure could include increased susceptibility to infectious disease and cancer, increased risk of asthma and atopy, and an increase in some forms of autoimmune disease. Evidence suggests that the expected outcome of exposure can differ depending upon the window of immune development when exposure occurs. Hence,

the developmental status of the immune system during environmental insult is a key factor in determining the likely health risk (Dietert, 2000).

Lung development continues from the embryonic phase until the age of 18-20 years. As it is a continuous process from embryo to adolescence, it is logical to surmise that children may be more susceptible to the effects of respiratory toxicants than adults, whose lung growth is complete. Immature differentiating cells of the respiratory tract are more sensitive to respiratory toxicants than mature cells, and at dose levels that cause no effects in adult cells (Plopper at al., 1994). Many studies try to distinguish between environmental exposures that induce a disease in previously normal hosts, and those that trigger exacerbations of pre-existing disease. The distinction is more likely to result from the developmental phase of the host when the exposure took place than from any intrinsic properties of the exposure.

Both indoor and outdoor air pollution have been identified as risk factors for the induction and the exacerbation of respiratory disease, especially asthma. Irritants of respiratory diseases include the combustion-related products formed by the burning of organic fuels, including nitrogen dioxide, particulate matter, and diesel exhaust particulates; bioaerosols such as moulds, allergens and bacterial products; air toxics, including formaldehyde and other volatile organic compounds (VOCs); pesticides, PCBs and heavy metals (Volkmer et al., 1995; Salome et al., 1996; Rumchev et al., 2000, 2002; Garrett et al., 1999; Sporik & Platts-Mills, 2001).

Second-hand smoke, which contains not only combustion-related pollutants but also a large number of air toxics and carcinogens, is an important contributor to indoor air pollution. The effects of passive smoking begin in utero, where constituents of tobacco smoke, such as PAHs, nicotine, and carbon monoxide, cross the placenta and are concentrated in the fetal circulation (Perera et al., 1999). The potentially mutagenic effects of tobacco smoke may impair normal cellular division and differentiation in the respiratory tree, leading to reduced lung function and increased bronchial hyperresponsiveness (Collins et al., 1985; Young et al., 1991; Cook et al.,1998).

Another source of exposure to pollutants in the indoor environment is via the combustion of biomass (such as dung, charcoal, wood, or crop residues) or coal. Women and young children are most heavily exposed to indoor air pollution from biomass combustion. Children under five years of age, particularly in developing countries, who are exposed to biomass

fuel combustion  have an elevated risk of  acute lower respiratory tract infections.

There is a consistent body of  evidence that exposure to ambient air pollution is associated with symptoms of  cough, bronchitis, respiratory infection, and upper respiratory tract illness in children (Dockery et al., 1989; Raizenne et al., 1996; Schwela, 2000). Although the effects of pollutants appear small, they occur at levels within the national ambient air quality standards of  most countries and have the potential to affect large populations of children.

Exposures during early kidney development tend to cause the most severe structural and functional alterations, and have the most profound consequences. Direct-acting cytotoxicants (e.g. chlorambucil)  are very effective at disturbing development during periods of  rapid cell proliferation, which occurs during induction of  the anlagen. Several drugs used to treat sick, and often premature, infants also pose a risk of  compromising renal function due to poorly developed feedback loops (Guignard & Gouyon, 1988). As a result of  the different cellular processes involved in organ development versus organ function, there seems to be disconcordance between agents inducing renal toxicity in adults, and those that do so in children.

Cancers are uncommon during the first two decades of  life. Exposures to cancer-causing agents preconceptionally, during intrauterine life, or in early childhood may result in the development of cancer during later childhood or during subsequent adult life. There is direct evidence that children are more susceptible than adults to at least some kinds of  carcinogens, including certain chemicals and various forms of  radiation (Tomatis & Mohr, 1973; Napalkov et al, 1989; Birnbaum & Fenton, 2003). Prenatal diagnostic X-rays have also been linked to increased risk of  leukemia in offspring (Ron et al, 1988; Chow et al, 1996). There is evidence of  increased or even unique early-life susceptibility to cancers that result from infection with certain oncogenic viruses, including Epstein-Barr virus and hepatitis B virus.

Exposures to carcinogens during childhood have caused tumours that appear chiefly in adulthood. Examples include tumours of  the brain, cranial nerves, and meninges after therapeutic irradiation of  the head; thyroid carcinoma after therapeutic and environmental exposures to ionizing radiation; leukaemia and solid tumours in adult survivors of  the

## Summary

The timing of exposure to chemicals is critical in determining the consequences to children's health. Manifestation of effects often occurs much later than the life stage when the critical exposure took place. As opposed to what is generally seen in adults, transient changes in physiology at critical periods of child development can result in permanent changes in organ function. As impacts of childhood environmental hazards may manifest throughout the lifespan, the importance of understanding the contribution of environmental chemicals to the total disease burden is considerable.

# Exposure Assessment of Children

Exposure is defined as the contact of an individual with a pollutant for specific durations of time (IPCS, 2004). It can be described in terms of intensity, frequency, and duration (USEPA, 1992). Figure 2 shows how exposure links contaminant sources to health effects in an environmental health framework. Exposure assessment in environmental studies identifies potentially exposed populations, potential pathways of exposure, and quantifies the magnitude, frequency, duration and time pattern of contact with a contaminant.

**Figure 2.** Scientific elements for estimating exposure and source: Environmental health framework
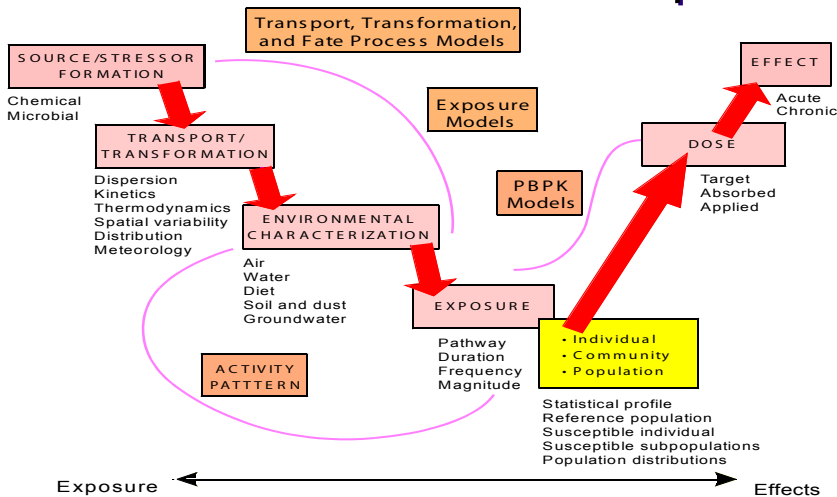
Environmental exposure of children to contaminants is a complex process due to the variety of possible pollutant sources, different routes and pathways (Cohen Hubal et al., 2000b). For example, pesticide exposure may result from agricultural use, or from use in homes, schools and recreational centers. Additional exposure of children of agricultural workers is possible if the parent transports pesticides into the home via his or her skin or clothing.

Cumulative risk assessments evaluate the health risk from aggregate exposures accumulated over time, and for multiple contaminants or stressors. This is an important concept in understanding environmental health risks to children in different settings, particularly in developing countries where children may face multiple stressors.

'Route of exposure' is defined as the portal of entry to the body, while 'pathway' is defined as the course that the contaminant takes from its source to the exposure medium, and then to the portal of entry. For a given source, exposure media and exposure routes can define the pathways. Depending upon the life stage of the child, exposure media can include amniotic fluid, breast milk, air, water, soil/dust/ sediments, food, and objects/surfaces.

Exposure routes include transplacental transfer, inhalation, ingestion, dermal absorption, and indirect (non-dietary) ingestion. 'Exposure factors' are factors related to human behaviour, and the characteristics that determine an individual's exposure to a contaminant. For instance, a child's exposure to ozone through inhalation is determined by factors such as the duration of time spent in different indoor and outdoor locations, and the child's breathing rate during the period of exposure.

There are various methods of assessing exposure. 'Direct assessment' measures the contact between an individual and a chemical in the exposure media over an identifiable period of time. It is important to collect all data on exposure media concentrations, activities, and exposure factors that are required to quantify exposure (Cohen Hubal et al, 2000a; USEPA, 2001). Biomarker methods do not measure the exposure directly, but are indicators of an absorbed dose (IPCS, 1993, 2001). Urine, blood, nails, saliva, hair and faeces are common media for biomarker measurements. Maternal biomarkers of exposure can also be measured in amniotic fluid and breast milk. When appropriately used, biomarkers are an objective method of indicating an absorbed dose from a variety of sources; however,

they cannot themselves provide information on the source, route or duration of exposure.

Mathematical expressions to quantify the exposure processes and doses are known as the modeling method of exposure assessment. Different models are used for specific purposes. For example, 'deterministic models' provide a point estimate of exposure or dose from single value input variables, while 'probabilistic models' take into account the distribution of values that input variables will have. There are crop-specific models to assess children's exposure to environmental chemicals through diet (Legind & Trapp, 2009). While these models can be used to predict individual exposure and dose, they are generally most effectively used at the population level (IPCS, 2005).

The unique physiological and behavioral characteristics of children influence their exposure to environmental toxicants. Physiological characteristics affect the exposure-uptake relationship in children. For example, children have a larger surface area, relative to body weight, than do adults which provides more area for dermal absorption. In addition the larger relative surface area of children means that body heat loss will be more rapid, requiring a higher rate of metabolism. Their oxygen and food requirements are greater per kilogram of body weight. The higher breathing rate and food consumption rate required to meet these physiological needs can result in higher exposures to environmental contaminants in air and food relative to adults.

Children's behaviour and the way they interact with the environment may also play an important role in determining their exposure to toxicants. Children crawl, roll and climb over contaminated surfaces, so have higher dermal contact than adults in the same environment. They eat different foods, which may result in higher dietary ingestion (Cohen Hubal et al., 2000b). Other factors, such as geography, climate, culture, socioeconomic status, gender, seasonality, and areas (i.e. urban versus rural) may all contribute to children's total environmental exposure.

Proximity to sources of contamination, and/or high concentrations in air, water, soil and biota will result in high exposure of children who live in those areas. For example, in mining areas, children can be exposed to metals as a result of contact with contaminated air, soil, and dust. Similarly, in agricultural areas, children could have high exposures to the pesticides that are applied to crops in the area.

Ambient air exposure pathways include air emission from production processes, as well as volatilization of organic compounds, airborne particulates, acid gases and open burning (ATSDR, 1994). A considerable burden of disease from ambient air pollution has been reported for cities such as New Delhi, India (Pande et al, 2002); Santiago, Chile (Ostro et al, 1999) and Mexico City, Mexico (Borja-Aburto et al, 1998).

Indoor exposure pathways are very important, because children spend more than 90% of their time indoors in most regions of the world. Rural households in developing countries still rely on coal or unprocessed biomass material in the form of wood, dung, and crop residues for fuel (Bruce et al., 2000). High levels of indoor air pollutants result from the use of either open fires or poorly functioning stoves to burn biomass or coal (Ezzati & Kammen, 2001). Many of the substances in smoke from either biomass or coal burning can be hazardous to humans. The most important are suspended particulate matter, carbon monoxide, nitrous oxide, sulfur oxides (coal), formaldehyde, and PAHs (Bruce et al., 2000; Smith et al., 2000).

Second-hand smoke is an indoor air pollutant that is a major concern. Especially in developing countries, people smoke indoors where they live and work, thus resulting in a high percentage of homes with second-hand smoke pollution and high inhalation exposures for children.

House dust as an important route of exposure for many chemical contaminants. Various levels of pesticides, PCBs, PAHs, plasticizers (phthalates, phenols), flame retardants, other organic xenobiotics, and inorganic constituents have been reported in house dust (Butte & Heinzow, 2002; USEPA, 2004).

Pesticide exposure in children could potentially be increased if they live in homes in close proximity (60 m) to pesticide-treated farmland (Fenske et al., 2002). Usually, applications of insecticides and herbicides in and around the home are a more likely source for children's exposures.

The indoor environment can serve as an important pathway for exposures to moulds as well as chemical contaminants. Fungal toxins (e.g. aflatoxin) contaminate food and are a particular problem in African and South-east Asian countries (Egal et al., 2005).

Ingestion of contaminants is the primary exposure pathway for drinking-water. Dermal absorption and inhalation of contaminants during bathing are other common pathways.

Industrial effluent, agricultural runoff (pesticides), and oil and mining wastes are important sources for surface water contamination. Hazardous waste sites are a recognized source of groundwater contamination. The natural pollution of aquifers with metals such as fluoride and arsenic is an important source of contamination in many countries. High levels of fluoride in water sources have been identified in at least 25 countries. Also, high natural levels of arsenic in drinking-water have been found in some countries, such as China, India, Bangladesh and Romania (UN, 2001; Smedley & Kinniburgh, 2002).

Contaminated soils containing metals, organochlorine pesticides and other persistent organic pollutants (POPs) may expose children to health hazards. The most important sources of metals in soil are mine tailings, smelter wastes, and atmospheric fallout (Nriagu & Pacyna, 1988). Ingestion of contaminated surface soil is a primary exposure route, while inhalation and dermal contact with contaminated soils can also lead to elevated exposure.

The Agency for Toxic Substances and Disease Registry in the United States has confirmed that children living near hazardous waste sites may have higher exposures to environmental chemicals, which may result in a greater potential for health problems (ATSDR, 1997).

The food-chain exposure pathway may lead to environmental hazards to children, as many contaminants, particularly fat-soluble substances and heavy metals, are concentrated there. These may reach concentrations in animal tissues thousands of times higher than those found in water, soil, and sediment (Damstra et al., 2002). For example, methylmercury accumulates in the tissues of fish (UNEP, 2002) and persistent organic chemicals accumulate in tissues of certain wildlife species. Children can be exposed to biological as well as chemical contaminants through the food-chain.

Human to human exposure pathways usually involve maternal exposure, or occupationally-related exposure that occurs when a parent brings contaminants from the workplace to the home on their skin and clothes.

In addition to investigation of various exposure pathways, the study of microenvironments, or settings, is critical to understanding exposure patterns in children. These include residential, school, child-care centers and recreational settings. For example, additional sources of chemicals are associated with school settings such as laboratories, activity rooms, or

school equipment. Exposure to volatile compounds has been reported in art buildings (Ryan et al., 2002). Moreover,  in various parts of the world children are exposed to toxic chemicals in unique circumstances such as those of street children and refugee children (UNICEF, 2004). These children may not have access to education or health care, and may lack basic sanitation, nutrition, and normal opportunities for recreation and social interaction (UNICEF, 2001). Globally, millions of children live under these conditions. There is, therefore, a tremendous need to understand chemical exposures and other health stressors in particular settings throughout the world.

**Summary**

Because of differences in physiology, behaviours, body weight, and body surface area, the exposure levels in children may be different from and often higher than exposures in adults. Furthermore, in terms of risk, children may also be more susceptible to environmental pollutants because of differences in absorption, metabolism, and excretion. More information is needed about the behavioural and cultural factors that influence the exposure to chemicals in children.

Children's exposure will differ according to geographic area, different activities undertaken, the settings they live in, and the different social realities they experience.  Risk assessment is, therefore, a highly complex matter. More research is needed to assess levels of exposure to environmental chemicals on a global scale, particularly in developing countries.

# Methodologies to Assess Health Outcomes in Children

Children's health status is an important population marker of environmental threats to human health. Only recently have investigators focused on methodologies designed specifically to address the unique characteristics of children and the need to consider exposures in the context of life stages. The same methodologies used for assessing adult health status in relation to environmental factors can be used for children, but they must be adapted to reflect the rapid rate of growth and development characteristics of infants and children. Measurements of exposure and outcomes may need to be more frequent than in adults and timed to reflect the key stages of human growth and development: i.e. embryonic, fetal, neonatal, infant, childhood, adolescence, and adulthood.

Epidemiological methods can ensure the validity and reliability of study results. The choice of epidemiological study design is dependent upon a number of factors, including the research question and type of study covariates, selection of an appropriate sample. With regard to infants and children, the biological plausibility underlying the timing and dose of exposure at critical developmental windows needs careful attention in both study design and result interpretation (IPCS, 2002). Although experimental study designs remain the optimal choice for establishing causality, such designs are considered unethical for most environmental health research. Thus, only observational study designs are discussed here.

Descriptive studies are designed to generate hypothesis or assess research questions for subsequent testing; this group of study designs includes ecologic design, cross-sectional design and linkage studies. These designs have been powerful in identifying patterns of disease occurrence and in identifying potentially at-risk subgroups.

Analytic studies, such as case-control and prospective/retrospective cohort studies, test formal hypotheses requiring the establishment of a temporal ordering between exposure and outcome. During this process, the selection of a control group is extremely difficult and requires careful consideration of the issue of comparability between the control and treatment groups. In addition, key issues facing analytic studies include errors associated with the measurement of exposures, the requirement for complete evaluation of all health outcomes, the capture of relevant covariates, and the need to select the most appropriate statistical model.

## Growth and development

Growth and development in humans are dynamic processes involving numerous bodily functions. The timed processes underlying human development are therefore important considerations when designing epidemiological studies focusing on growth and developmental endpoints. Established embryonic critical windows typically begin with early pregnancy or approximately two weeks post-conception. Unfortunately, investigators are often unable to capture exposures during this interval, because women may not recognize their pregnancy at this early point. As a result, retrospective collection of information is required, which assumes that women can accurately report exposures in the periconception period. Application of the human chorionic gonadotropin (hCG) biomarker gives investigators an opportunity to define periconception critical windows

using prospective cohort designs. Once exposure is measured and defined, it is necessary to determine how best to measure growth and development. Repeated fetal measurements at standardized intervals will be needed in a study population of pregnant women.

A number of well-defined anthropometric methodologies using standardized scales are available to measure growth in studies of infants and children. Unlike adults (Hutchinson et al., 1992), there is no universally accepted methodology for measuring infant and child development in relation to environmental exposures. The selected approach included in any methodology for measuring infant and child development must be age, gender and culturally appropriate.

Onset and progression of puberty can be used for both boys and girls to measure the influence of exposures relating to this developmental milestone. Birth defects are also indicators of developmental outcomes, but given the rarity of major malformations, case-control studies remain the design of choice for such investigations.

## Reproductive development and function

Two broad categories of outcomes -fecundity and fertility - can be studied in assessing the reproductive toxicity of an environmental agent. Fecundity can be estimated or approximated by assessing reproductive hormonal profiles of men and women, semen quality in men, or menstruation in women or by measuring time to pregnancy for couples interested in becoming pregnant. Time to pregnancy can be measured in calendar time or menstrual cycles, and has proved a reasonable estimate of cycle-specific probability of conception when comparing exposed and unexposed couples (Baird et al., 1986).

Fecundity end-points are not necessarily adverse health states, and may also include puberty, sexual libido, gynaecological or urological disorders fecundity impairments, and premature reproductive senescence. The need to consider fecundity end-points is supported by the possible relation between consumption of PCB-contaminated fish and diminished fecundability (Axom et al, 2000; Buck et al, 2000). Male fecundity impairments have been associated with both birth defects and chronic disease. For example, cryptorchidism has been associated with impairments in male fecundity and testicular cancer. Fertility end-points include live births, plurality of births, and secondary sex ratio (the ratio of male to female live births). Xenobiotics that selectively impact the X or Y chromosome may result

in decrements of the sex ratio, possibly due to differences in rates of conception or pregnancy loss.

## Neurological and behavioural effects

Environmental agents such as diethylstilbestrol (DES) and polychlorinated biphenyls (PCBs) have been associated with alterations in gender-specific behaviour (Collaer & Hines, 1995; Guo et al, 1995; Longnecker et al, 2003). Given the ability of these agents to affect a number of target sites or pathways (e.g. autonomic, peripheral, or central nervous system), a diverse range of outcomes should be considered. Clinical assessment coupled with standardized assessment tools are likely to be needed for end-point measurements.

## Cancer

Since childhood cancers are relatively rare, case-control study designs are primarily used for assessing environmental carcinogens. Cancer registries can be used for ascertaining cases in a defined population over time. Siblings, neighbours, schoolmates, or children seeking medical services from the same clinic can be selected as controls. In some cases, a linkage study can be used to assess possible new exposures, but might be limited by data scarcity on the exposure and other etiologic factors impacting the couple's fecundity.

## Immune system effects

No universal guidelines for assessing immune function in children in relation to environmental agents have been established. Diagnostic approaches used by clinicians can be adopted for research purposes, and may include alterations in B and T lymphocytes or T helper/T suppressor cell ratios. Age-appropriate assessments should recognize the ongoing development of the immune system during fetal development and childhood (Holladay & Smialowicz, 2000).

## Respiratory system effects

The mature respiratory system evolves throughout fetal life, childhood, and early adulthood. Exposure to environmental chemicals can affect a number of respiratory processes, such as cellular differentiation and lung growth, underscoring the need to select age-specific end-points for infant and children (Fanucchi et al, 1997; Smiley-Jewell et al, 1998). Although no universal guidelines are provided, symptom inventories along with field-

based spirometry and adapted diagnostic approaches could be used for research. Exposure during critical periods of lung development may have effects that would not be seen if the same exposure were to occur in adulthood (Dietert et al., 2000).

### Haematopoietic/cardiovascular, hepatic/renal, skin/musculoskeletal, and metabolic/endocrine system effects

For haematopoietic/cardiovascular, hepatic/renal, skin/musculoskeletal, and metabolic/endocrine system effects, there are no established universally accepted guidelines or study protocols for assessing organ-specific health end-points.

### Summary

There is no universally-defined methodology for assessing children's overall health status in relation to environmental factors. For many aspects of child health, such as growth and development, a number of assessment tools may be used for research purposes. For other aspects, such as the endocrine system, no assessment tools are currently available. As children are undergoing continuous development, health assessment methodologies geared to their needs should be responsive to all organ systems. Prospective studies are particularly important, as they can capture time-varying covariates in children. The short interval between many exposures and outcomes (e.g. in utero exposures and infant birth size) further supports the use of prospective studies.

Challenges remain regarding the impact of the environment on children's health during development such as the need to identify critical windows, including those before, during, or shortly after conception, for the spectrum of health end-points relevant for child health.

# Implications and Strategies for Risk Assessment for Children

WHO has defined risk assessment as an empirically based paradigm that estimates the risk of adverse effects from exposure of an individual or population to a chemical, physical, or biological agent. It includes components of hazard identification, dose-response assessment, exposure assessment, and risk characterization (see Figure 3) (NRC, 1983; IPCS, 2000). In the current document, this risk assessment model is being extended to cover potentially vulnerable life cycle stages such as pregnancy, childhood, and adolescence (see Table 3).

**Figure 3.** Risk assessment paradigm for human health



Problem formulation to establish the goals, breadth and the focus of the assessment is the first step in any risk assessment (Olin & Sonawane, 2003; Renwick et al, 2003). A risk assessment on the health effects of chemical exposures to children should focus on the identification of life stages, the timing of and response to the exposures, and the integral relationship among them. Children's particular vulnerability, and their unique exposure pathways, must be addressed during problem formulation. Problem formulation should serve as a qualitative screen to identify the exposure scenarios that need to be considered (including settings unique to children) and whether or not there is a potential for higher exposures or greater susceptibility in children. It should result in a conceptual model, based on the qualitative characterization of hazard and exposure (Olin & Sonawane, 2003; Daston et al., 2004; USEPA, 2005).

From the risk management perspective, there may be regulatory, judicial, economic, and social considerations that influence the timing and breadth of the assessment. For example, a specific regulatory requirement, a community need, a health crisis, or some other factor may drive the risk assessment. Hazard identification, as defined by the International Programme on Chemical Safety (IPCS), identifies the inherent capacity of a substance to cause adverse effects in an organism, system, or sub-population exposed to that substance. The specific developmental vulnerability of children, and the long-term consequences of early exposure as precursors for later onset of adult disease, must be considered. In addition, a wide range of developmental end-points and critical periods of susceptibility need to be taken into account in assessing risk in children.

**Table 3.** Risk assessment paradigm for human health

### Characterization of the overall risk assessment

Define the purpose of the risk assessment, including the regulatory and/or public health need. Consider the historical perspective and whether other assessments of the same or comparable exposures have been carried out. Define the life stages of interest.

### Characterization of the health hazard

*Characterize the entire database that provides information on the potential for health concerns in children. Specifically, describe:*

- the quantity and quality of the data;

- whether the data are from human or laboratory animal studies (single or multiple species);

- the appropriateness of the life stages studied and how inclusive the end-points are with respect to defining alterations in development for a given life stage;

- the potential for not only immediate, but also delayed, effects following an exposure.

*With specific reference to the available human data, describe:*

- the types of data used (e.g. ecologic, case–control, or cohort studies; or case-reports or case-series);

- the degree to which developmental stages are addressed;

- the degree to which exposures are detailed;

- the degree to which confounding/modifying factors are accounted for;

- the degree to which other causal factors are excluded.

*Characterize the dose–response nature of the effects of an exposure, including:*

- the data used;

- any model(s) used to develop the dose–response curve(s) and the rationale and chemical-specific information supporting the choice(s).

While human studies are preferable for determining the potential health effects of exposure, these are often limited by ethical considerations and the complexity of establishing exposure conditions. Toxicity testing in experimental animals therefore continues to play an important role in characterizing developmental hazards in children. When extrapolating from animal data, it is important to ascertain the concordance of adverse developmental effects between animals and humans. This requires detailed knowledge of the comparative stages of organ system development (Morford et al., 2004).

Reversibility and latency of childhood exposure are rarely evaluated directly in risk assessment for children. Yet either event could have a major impact on hazard identification. Additional studies from less than lifetime exposures to evaluate latency to effect and reversibility of effect are a critical research need (Damstra et al, 2002; USEPA, 2002).

Following a review of toxicity data in humans and animals, the health-related database is characterized as being sufficient or insufficient to proceed further in the risk assessment (USEPA, 2005; Kimmel et al, 2006). Where data are considered adequate, a dose-response relationship is evaluated. The dose-response relationship can be studied via health outcome data from human studies, and various quantitative evaluations. The dose-response evaluation has traditionally been based on health-based guidance values such as the tolerable daily intake (TDI) or reference dose (RfD). Where sufficient data are available, use of the benchmark (BMD) approach is preferable (IPCS 1999, 2005; USEPA, 2000; Sonich-Mullin et al, 2001). Biologically based dose-response models are considered a major advance for evaluating the dose-response relationship (Shuey et al., 1994; IPCS, 2000). Duration adjustment and toxicokinetic approaches can also be used (Kimmel et al., 2006; Daston et al, 2004; Ginsberg et al., 2004).

The exposure assessment characterizes the pathways, magnitude, frequency, and duration of human exposures from various sources. The age/developmental stage of the child must be a primary consideration when conducting exposure assessment, since the outcome will be affected by the child's anatomy, physiology, and metabolism change over time, as well as their interactions with their environment. Socioeconomic, cultural, and physical conditions can also influence exposure levels. In addition, exposure of either parent may affect the germ cells that form the child. As prenatal and postnatal exposure occur through the maternal system, maternal toxicokinetics and placental/lactational metabolism and transfer

must be taken into consideration.

Direct methods, biomarkers of exposure  and mathematical methods can be used to assess exposure. Direct methods of assessment measure the contact of the child with the agent and can identify exposure concentrations in a particular medium over an identifiable period of time. Biomarkers of exposure are indicators of absorbed dose and demonstrate that internal exposure has occurred and can be used to estimate chemical uptake over time and help establish the relationship between exposure and effect. Mathematical models can be used to quantify the processes leading to exposure (and internal dose).

Risk characterization is the final phase of the risk assessment process. It involves the  synthesis of critically evaluated information from exposure assessment, hazard identification and dose-response considerations into an overall evaluation of the assessment that can be communicated to health professionals. The risk characterization should incorporate all life stages that were identified in the problem formulation stage, and, if part of a larger risk assessment, it should place the vulnerability of the child in perspective with the other populations being considered.  Ultimately, the risk characterization results in a statement of the potential susceptibility of children to specific effects of specific exposures to environmental agents, on the basis of which regulatory decisions will be made. Frequently, however, the risk manager is not a specialist in children's health; it is therefore imperative that the risk characterization be clear, definitive and unencumbered by scientific jargon.

In summary, life-stage-specific risk assessments are only beginning to be incorporated into the overall risk assessment process. Many gaps in knowledge and use remain to be addressed. These include efforts to incorporate data from molecular studies and new technologies into a meaningful framework for children's health risk assessment; a greater sensitivity to effective communication among individuals of varying backgrounds, and the development of new conceptual frameworks with a particular focus on the uniqueness of early life stages.

With recognition of children's special susceptibility, it is better to prevent than to treat environmental diseases. In developing countries, the most important issue may be to prioritize which exposure reductions will have the greatest overall impact with the limited resources available. It is important to identify the exposures that pose the greatest health risks, as

well as the sources and pathways for these exposures. This information can then be used to make choices that lead to health benefits for children around the world.

# Conclusions and Recommendations

Although substantial knowledge has been gained on the prevention of environmental hazards to children, much remains to be learned. Further research is needed in the following areas:

- design and implement prospective cohort studies of pregnant women, infants, and children with a longitudinal capture of exposures at critical windows and sensitive health end-points along the continuum of human development. Efforts to recruit couples prior to conception are needed to address critical data regarding periconceptional exposures and children's health

- continue to develop and enhance population-based surveillance systems for the real-time capture of sentinel health end-points. This includes current surveillance systems such as vital registration for birth size and gestation and birth defects registries for capturing major malformations. Also, the consideration of emerging sentinel end-points such as fecundability, as measured by time to pregnancy and sex ratios, should receive added research consideration

- strengthen exposure monitoring efforts in children during different developmental stages, including efforts to assess aggregate and cumulative exposures

- strengthen exposure monitoring efforts in developing countries

- identify subpopulations with the highest exposure levels

- develop validated, sensitive, and cost-effective biomarkers of exposure, susceptibility, and effects, particularly during early developmental stages

- improve characterization of the differences in toxicokinetic and toxicodynamic properties of xenobiotics at different developmental stages. Also, to develop databases of developmental stage–specific physiological and pharmacokinetic parameters in both human and animal studies

- conduct studies focusing on mechanisms of action during different developmental stages by which exposures may cause adverse outcomes

- develop end-points that can be used to assess organ system functions in both humans and animal species and to identify analogous periods of development across species

- examine the utility of newer molecular and imaging technologies to assess causal associations between exposure and effect at different developmental stages. Also, to improve characterization of the windows of susceptibility of different organ systems in relation to structural and functional end-points

- develop and validate biological models and animal testing guidelines that can address health outcomes at different developmental stages

- determine which exposure reductions will have the greatest overall impact on children's health

# References

Adams J (1993). Structure–activity and dose–response relationships in the neural and behavioral teratogenesis of retinoids. Neurotoxicol Teratol, 15(3): 193–202.

Adams J et al. (2000). Workshop to identify critical windows of exposure for children's health: work group summary. *Environmental Health Perspectives*, 108(Suppl 3):535–544.

Alcorn J & McNamara PJ (2003). Pharmacokinetics in the newborn. Adv Drug Deliv Rev, 55(5): 667–686.

Anderson LM et al. (1989). Transplacental initiation of liver, lung, neurogenic, and connective tissue tumors by *N*-nitroso compounds in mice. *Fundamental and Applied Toxicology*, 12(3): 604–620.

Anderson LM, Diwan BA, Fear NT, & Roman E (2000). Critical windows of exposure for children's health: Cancer in human epidemiological studies and neoplasms in experimental animals. Environ Health Perspect, 108(Suppl 3): 573–594.

Ashby J, Tinwell H, Stevens J, Pastoor T, & Breckenridge CB (2002). The effects of atrazine on the sexual maturation of female rats. Regul Toxicol Pharmacol, 35: 468–473.

ATSDR (1994). *Environmental data needed for public health assessments. A guidance manual.* Atlanta, GA, United States Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

ATSDR (1997). Healthy children — toxic environments. Acting on the unique susceptibility of children who dwell near hazardous waste sites. Report of the Child Health Workgroup.

Atlanta, GA, United States Department of Health and Human Services, Agency for Toxic Substances and Disease Registry.

Axom A et al. (2000). Time to pregnancy and infertility among women with a high intake of fish contaminated with persistent organochlorine compounds. *Scandinavian Journal of Work, Environment & Health*, 26: 199–206.

Bailey LB, Rampersaud GC, & Kauwell GP (2003). Folic acid supplements and fortification affect the risk for neural tube defects, vascular disease and cancer: *Evolving science. J Nutr, 133(6): 1961S–1968S*

Bellinger D, Leviton A, Allred E, & Rabinowitz M (1994). Pre- and postnatal lead exposure and behavior problems in school-aged children. Environ Res, 66(1): 12–30.

Bennett WD, Zeman KL, & Kim C (1996). Variability of the fine particle deposition in healthy adults: Effect of age and gender. *American Journal of Respiratory and Critical Care Medicine,* 153:1641-1647

Bennett GD & Finnell GD (1998). Periods of susceptibility to induced malformations of the developing mammalian brain. In: Slikker WJ & Chang LW eds. Handbook of developmental neurotoxicology. San Diego, CA, Academic Press, pp 189–208.

Birnbaum L (1995). Developmental effects of dioxin. Environ Health Perspect, 103(Suppl7): 89–94.

Birnbaum LS & Fenton SE (2003). Cancer and developmental exposure to endocrine disruptors. *Environmental Health Perspectives*, 111(4): 389–394.

Blanck HM et al. (2000). Age at menarche and Tanner stage in girls exposed in uteroand postnatally to polybrominated biphenyl. *Epidemiology*, 11: 641–647.

Boice JD Jr, Land CE, & Preston DL (1996). Ionizing radiation. In: Schottenfeld D & Fraumeni JF Jr eds. Cancer epidemiology and prevention, 2nd ed. New York, Oxford University Press, pp 319–354.

Bolognesi C, Rossi L, & Santi L (1988). A new method to reveal the genotoxic effects of *N*-nitrosodimethylamine in pregnant mice. *Mutation Research*, 207(2): 57–62.

Borja-Aburto VH et al. (1998). Mortality and ambient fine particles in southwest Mexico City, 1993–1995. *Environmental Health Perspectives*,106(12): 849–855.

Bosley AR, Sibert JR, & Newcombe RG (1981). Effects of maternal smoking on fetal growth and nutrition. *Archives of Disease in Childhood*, 56: 727–729.

Botto LD, Olney RS, & Erickson JD (2004). Vitamin supplements and the risk for congenital anomalies other than neural tube defects. *American journal of medical genetics. Part C, Seminars in medical genetics*, 125(1): 12–21.

Brouwer A, Morse DC, Lans MC, Schuur AG, Murk AJ, Klasson-Wehler E, Bergman A, & Visser TJ (1998). Interactions of persistent environmental organohalogens with the thyroid

hormone system: Mechanisms and possible consequences for animal and human health. Toxicol Ind Health, 14: 59–84.

Bruce N, Perez-Padilla R, & Albalak R (2000). Indoor air pollution in developing countries: A major environmental and public health challenge. Bull World Health Organ, 78: 1078–1092.

Buck GM et al. (2000). Parental consumption of contaminated sport fish from Lake Ontario and predicted fecundability. *Epidemiology*, 11: 388–393.

Burbacher TM & Grant KS (2006). Neurodevelopmental effects of alcohol. In: Davidson PW, Myers GJ, & Weiss B eds. Neurotoxicity and developmental disabilities: individual differences in personality and motivational systems. San Diego, CA, Elsevier Academic Press.

Butte W & Heinzow B (2002). Pollutants in house dust as indicators of indoor contamination. *Reviews of Environmental Contamination & Toxicology*, 175: 1–46.

Chapin R, Harris M, Davis B, Ward S, Wilson R, Mauney M, Lockhard A, Smialowicz R, Moser V, Burka L, & Collins B (1997). The effects of perinatal/juvenile methoxychlor exposure on adult rat nervous, immune and reproductive system function. Fundam Appl Toxicol, 40: 138–157.

Chow WH et al. (1996). Cancers in children. In: Schottenfeld D & Fraumeni JF Jr eds. *Cancer epidemiology and prevention, 2nd ed.* NewYork, Oxford University Press, pp 1331–1369.

Clewell HJ et al. (2002). Review and evaluation of the potential impact of age- and gender-specific pharmacokinetic differences on tissue dosimetry. *Critical Reviews in Toxicology*, 32: 329-389

Coccini T et al. (2006). Effects of developmental co-exposure to methylmercury and 2,2',4,4',5,5'-hexachlorobiphenyl (PCB153) on cholinergic muscarinic receptors in rat brain. Neurotoxicology, 27(4): 468–477.

Cohen Hubal EA et al. (2000a). The challenge of assessing children's residential exposure to pesticides. *Journal of Exposure Analysis and Environmental Epidemiology*, 10: 638–649.

Cohen Hubal EA, et al. (2000b). Children's exposure assessment: A review of factors influencing children's exposure, and the data available to characterize and assess that exposure. *Environmental Health Perspectives*, 108(6): 475–486.

Collaer ML & Hines M (1995). Human behavioral sex differences: A role for gonadal hormones during early development. *Personality and Social Psychology Bulletin*, 118: 55–107.

Collins MH, Moessinger AC, Kleinerman J, Bassi J, Rosso P, Collins AM, James LS, & Blanc WA (1985). Fetal lung hypoplasia associated with maternal smoking: Amorphometric analysis. Paediatr Res, 19: 408–412.

Cook DG, Strachan DP, & Carey IM (1998). Parental smoking and spirometric indices in children. Thorax, 53: 884–893.

Cooper C et al. (2002). The fetal origins of osteoporotic fracture. *Calcified Tissue International,* 70: 391–394.

Cory-Slechta DA, Thiruchelvam MT, Richfield EK, Barlow BK, & Brooks AI (2005). Developmental pesticide exposures and the Parkinson's disease phenotype. Birth Defects Res A Clin Mol Teratol, 73: 136–139.

Costa LG, Cole TB, & Furlong CE (2003). Polymorphism of paraoxonase (PON1) and their significance in clinical toxicology of organophosphates. *Journal of Toxicology - Clinical Toxicology*, 41:37-45

Costa LG et al. (2005). Measurement of paraoxonase (PON1) status as a potential biomarker of susceptibility to organophosphate toxicity. *Clinica Chimica Acta*, 352:37-47

Couture-Haws L, Harris MW, McDonald MM, Lockhart AC, & Birnbaum LS (1991).Hydronephrosis in mice exposed to TCDD-contaminated breast milk: Identification of the peak period of sensitivity and assessment of potential recovery. Toxicol Appl Pharmacol, 107(3): 413–428.

Dallaire F et al. (2004). Acute infections and environmental exposure to organochlorines in Inuit infants from Nunavik. *Environmental Health Perspectives*, 112(14): 1359–1365.

Damstra T et al. (2002). *Global assessment of the state-of-the-science of endocrine disruptors.* Geneva, World Health Organization (WHO/PCS/EDC/02.2).

Daston G et al. (2004). A framework for assessing risks to children from exposure to environmental agents. *Environmental Health Perspectives*, 112(2): 238–256.

Davidson PW, Myers GJ, & Weiss B (2004). Mercury exposure and child development outcomes. Paediatrics, 113(Suppl 4): 1023–1029.

Dees WL, Hiney JK, & Srivastava V (1998). Alcohol's effects on female puberty: The role of insulin-like growth factor 1. Alcohol Health Res World, 22(3): 165–169.

Dewailly E et al. (2000). Susceptibility to infections and immune status in Inuit infants exposed to organochlorines. *Environmental Health Perspectives*, 108(3): 205–211.

Dickerson JWT & Widdowson EM (1960). Chemical changes in skeletal muscle during development. *Biochemical Journal*, 74:247-257.

Dietert RR et al (2000). Workshop to identify critical windows of exposure for children's health: Immune and respiratory systems work group summary. *Environmental Health Perspectives*, 108(Suppl 3): 483–490.

Dietert R & Lee J-E (2004). Toxicity of lead to the developing immune system. In: Holladay S ed. Developmental immunotoxicology. Boca Raton, FL, CRC Press.

Dietert RR, Lee J-E, Hussain I, & Piepenbrink M (2004). Developmental immunotoxicology of lead. Toxicol Appl Pharmacol, 198(2): 86–94.

Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, & Ferris BG Jr (1989). Effects of inhalable particles on respiratory health of children. Am Rev Respir Dis, 139(3):587–594.

Dorne JL, Walton K, & Renwick AG (2005). Human variability in xenobiotics metabolism and pathway-related uncertainty factors for chemical risk assessment: A review. Food Chem Toxicol, 43(2): 203–216.

Egal S, Hounsa A, Gong YY, Turner PC, Wild CP, Hall AJ, Hell K, & Cardwell KF (2005). Dietary exposure to aflatoxin from maize and groundnut in young children from Benin and Togo, West Africa. Int J Food Microbiol, 104(2): 215–224.

Emery JL& Mithal A (1960). The number of alveoli in the terminal respiratory unit of man during late intrauterine life and childhood. *Archives of Disease in Childhood*, 35:544-547

Fanucchi MV et al. (1997). Naphthalene cytotoxicity of differentiating Clara cells in neonatal mice. *Toxicology and Applied Pharmacology*, 144: 96–110.

Faustman EM et al. (2000). Mechanisms underlying children's susceptibility to environmental toxicants. Environ Health Perspect, 108(Suppl 1): 13–21.

Fenske RA et al. (2002). Children's exposure to chlorpyrifos and parathion in an agricultural community in central Washington State. *Environmental Health Perspectives*, 110(5): 549–553.

Friis-Hansen B (1971). Body composition during growth. In vivo measurements and biochemical data correlated to differential anatomical growth. Paediatrics, 47(Suppl 2): 264–274.

Garrett MH et al. (1999). Increased risk of allergy in children due to formaldehyde exposure in homes. *Allergy*, 54(4): 330–337.

Gilbert SF (2005). Mechanisms for the environmental regulation of gene expression. Birth Defects Res C Embryo Today, 72: 291–299.

Gill WB, Schumacher GF, & Bibbo M (1977). Pathological semen and anatomical abnormalities of the genital tract in human male subjects exposed to diethylstilbestrol in utero. *Journal of Urology*, 117: 477–480.

Gill WB et al. (1979). Association of diethylstilbestrol exposure in utero with cryptorchidism, testicular hypoplasia and semen abnormalities. *Journal of Urology*, 122: 36–39.

Ginsberg G et al. (2004). Incorporating children's toxicokinetics into a risk framework. *Environmental Health Perspectives*, 112(2): 272–283.

Glinianaia S, Rankin J, Bell R, Pless-Mulloli T, & Howel D (2004). Does particulate air pollution contribute to infant death? Environ Health Perspect, 112(14): 1365–1370.

Grandjean P, Weihe P, White RF, Debes F, Araki S, Yokoyama K, Murata K, Sorensen N, Dahl R, & Jorgensen PJ (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol, 19(6): 417–428.

Grandjean P, Murata K, Budtz-Jorgensen E, & Wihe P (2004). Cardiac autonomic activity in methylmercury neurotoxicity: 14-year follow-up of a Faroese birth cohort. J Paediatr, 144: 169–176.

Gray LE Jr & Ostby JS (1995). In utero 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) alters reproductive morphology and function in female rat offspring. Toxicol Appl Pharmacol, 133(2): 285–294.

Gray LE Jr, Ostby J, Furr J, Price M, Veeramachaneni DN, & Parks L (2000). Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol Sci, 58: 350–365.

Guignard JP & Gouyon JB (1988). Adverse effects of drugs on the immature kidney. Biol Neonate, 53(4): 243–252.

Guo YL, Lambert GH, & Hsu CC (1995). Growth abnormalities in the population exposed in utero and early postnatally to polychlorinated biphenyls and dibenzofurans. *Environmental Health Perspectives*, 103(Suppl 6): 117–122.

Guo YL, Lambert GH, Hsu C-C, & Hsu MM (2004). Yucheng: Health effects of prenatal exposure to polychlorinated biphenyls and dibenzofurans. *Int Arch Occup Environ Health,* 77: 153–158.

Harada M (1978). Congenital Minamata disease: intrauterine methylmercury poisoning. Teratology, 18(2): 285–288.

Hatch MC, Warburton D, & Santella RM (1990). Polycyclic aromatic hydrocarbon–DNA adducts in spontaneously aborted fetal tissue. *Carcinogenesis*, 11(9): 1673–1675.

Henderson BE et al. (1976). Urogenital tract abnormalities in sons of women treated with diethyl-stilbestrol. *Pediatrics*, 58: 505–507.

Herbst AL, Ulfelder H, & Poskanzer DC (1971). Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med, 284: 879–881.

Holladay SD & Smialowicz R (2000). Development of the murine and human immune system: Differential effects of immunotoxicants depend on time of exposure. Environ Health Perspect, 108(Suppl 3): 463–473.

Hsu ST et al. (1985). Discovery and epidemiology of PCB poisoning in Taiwan: A four-year followup. *Environmental Health Perspectives*, 59: 5–10.

Hutchinson LJ, Amler RW, Lybarger JA, & Chappell W (1992). Neurobehavioral test batteries for use in environmental health field studies. Atlanta, GA, United States Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Hytten FE (1984). Physiological changes in the mother related to drug handling. In: Krauer B, Krauer F, Hytten FE,& del Pozo E eds. *Drugs and pregnancy: Maternal drug handling: Fetal drug exposure*. New York, Academic Press, pp7-17.

IARC (2000). Ionizing radiation, Part 1: X- and gamma ($\gamma$)-radiation, and neutrons. Lyon, International Agency for Research on Cancer (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 75).

IPCS (1984). *Principles for evaluating health risks to progeny associated with exposure to chemicals during pregnancy*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 30).

IPCS (1986). *Principles for evaluating health risks from chemicals during infancy and early childhood: The need for a special approach*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 59).

IPCS (1993). *Biomarkers and risk assessment: concepts and principles*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 155).

IPCS (1999). *Principles for the assessment of risks to human health from exposure to chemicals*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 210).

IPCS (2000). *Human exposure assessment*. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 214).

IPCS (2001). *Biomarkers in risk assessment*: Validity and validation. Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 222).

IPCS (2002). Global assessment of the state-of-the-science of endocrine disruptors. Geneva, World Health Organization, International Programme on Chemical Safety.

IPCS (2004). *IPCS risk assessment terminology*. Part 1: IPCS/OECD key generic terms used in chemical hazard/risk assessment; Part 2: IPCS glossary of key exposure assessment terminology. Geneva, World Health Organization, International Programme on Chemical Safety (Harmonization Project Document No. 1)

IPCS (2005). *Chemical-specific adjustment factors for interspecies differences and human variability: Guidance document for use of data in dose/concentration–response assessment.* Geneva, World Health Organization, International Programme on Chemical Safety (Harmonization Project Document No. 2).

IPCS (2006). *Principles for evaluating health risks in children associated with exposure to chemicals.* Geneva, World Health Organization, International Programme on Chemical Safety (Environmental Health Criteria 237).

Jensen TK, Henriksen TB, Hjollund NH, Scheike T, Kolstad H, Giwercman A, Ernst E, Bonde JP, Skakkebaek NE, & Olsen J (1998). Adult and prenatal exposures to tobacco smoke as risk indicators of fertility among 430 Danish couples. Am J Epidemiol, 148:992–997.

Jensen TK, Joffe M, Scheike T, Skytthe A, Gaist D, & Christensen K (2005). Time trends in waiting time to pregnancy among Danish twins. Hum Reprod, 20(4): 955–964.

Jones KL & Smith DW (1973). Recognition of the fetal alcohol syndrome in early infancy. Lancet, 2: 999–1001.

Kacew S (1992). General principles in pharmacology and toxicology applicable to children. In: Guzelian PS, Henry CJ, & Olin SS eds. Similarities and differences between children and adults: Implication for risk assessment. Washington, DC, ILSI Press.

Karube T et al. (1989). Analyses of transplacentally induced sister chromatid exchanges and micronuclei in mouse fetal liver cells following maternal exposure to cigarette smoke. *Cancer Research*, 49(13): 3550–3552.

Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, & Kauffman RE (2003). Developmental pharmacology — drug disposition, action, and therapy in infants and children. N Engl J Med, 349: 1157–1167.

Kimmel CA, Kimmel GL, & Euling SY (2006). Developmental and reproductive toxicity risk assessment for environmental agents. In: Hood RD ed. *Developmental and reproductive toxicology, a practical approach*. Boca Raton, FL, CRC Press.

Kleinschmidt D & Lillehei KO (1995). Radiation-induced meningioma with a 63 year latency period. Case report. J Neurosurg, 82: 487–488.

Krauer B (1987). Physiologiacl changes and drug disposition during pregnancy. In: Nau H& Scott WJ eds. *Pharmacokinetics in teratogenesis*. Vol.1. Boca Raton, FL,CRC Press, pp3-12.

Kunzli N, Lurmann F, Segal M, Ngo L, Balmes J, & Tager IB (1997). Association between lifetime ambient ozone exposure and pulmonary function in college freshmen — results of a pilot study. Environ Res, 72: 8–23.

Kuratsune M et al. (1971). Yusho, a poisoning caused by rice oil contaminated with polychlorinated biphenyls. *Health Services and Mental Health Administration Health Reports,* 86(12): 1083–1091.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J, & Roberts R (2005). Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. Environ Health Perspect, 113(7): 894–899.

Lau C & Kavlock RJ (1994). Functional toxicity in the developing heart, lung, and kidney. In: Kimmel CA & Buelke-Sam J eds. *Developmental toxicology*, 2nd ed. New York, Raven Press, pp 119–188.

Lau C & Rogers JM (2005). Embryonic and fetal programming of physiological disorders in adulthood. Birth Defects Res C Embryo Today, 72: 300–312.

Lawrence RA (1989). Breast-feeding and medical disease. Med Clin North Am, 73: 583–603.

Laws SC, Ferrell JM, Stoker TE, Schmid J, & Cooper RL (2000). The effects of atrazine on female Wistar rats: An evaluation of the protocol for assessing pubertal development and thyroid function. Toxicol Sci, 58: 366–376.

Legind CN & Trapp S (2009). Modeling the exposure of children and adults via diet to chemicals in the environment with crop-specific models. *Environment Pollution*, 157(33):778-85

Lindbohm M-L et al. (1990). Spontaneous abortions among women exposed to organic solvent. *American Journal of Industrial Medicine*,17: 449-463

Lipscomb JA et al. (1991). Pregnancy outcomes in women poetentially exposed to occupational solvents and women working in the electronics industry. *Journal of Occupational & Environmental Medicine*, 33 (5):597-604

Longnecker MP et al. (2003). Comparison of polychlorinated biphenyl levels across studies of human neurodevelopment. *Environmental Health Perspectives*, 111(1): 65–70.

Maltoni C et al. (1981). Carcinogenicity bioassays of vinyl chloride monomer: A model of risk assessment on an experimental basis. *Environmental Health Perspectives*, 41: 3–29.

Matt N et al. (2003). Retinoic acid– induced developmental defects are mediated by RARb/RXR heterodimers in the pharyngeal endoderm. *Development*, 130: 2083–2093.

Mattison DR, Blann E, & Malek A (1991). Physiological alterations during pregnancy: impact on toxicokinetics. *Fundamental and Applied Toxicology*, 16: 215-218

Montgomery SM & Ekbom A (2002). Smoking during pregnancy and diabetes mellitus in a British longitudinal birth cohort. *British Medical Journal*, 324: 26–27.

Morford LL et al. (2004). Hazard identification and predictability of children's health risk from animal data. *Environmental Health Perspectives*, 112(2):266–271.

Mylchreest E, Sar M, Cattley RC, & Foster PM (1999). Disruption of androgen-regulated male reproductive development by di(*n*-butyl) phthalate during late gestation in rats is different from flutamide. Toxicol Appl Pharmacol, 156: 81–95.

Napalkov NP et al. (1989). *Perinatal and multigeneration carcinogenesis*. Lyon, International Agency for Research on Cancer (IARC Scientific Publications No. 96).

NRC (1993). *Pesticides in the diets of infants and children*. Report of the Committee on Pesticides in the Diets of Infants and Children, Board on Agriculture and Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council. Washington, DC, National Academy Press.

NRC (1983). *Risk assessment in the federal government: Managing the process*. Reportof the Committee on the Institutional Means for the Assessment of Risks to Public Health, Commission on Life Sciences, National Research Council. Washington, DC

NRC (2000). Toxicological effects of methylmercury. Report of the Committee on the Toxicological Effects of Methylmercury, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council. Washington, DC, National Academy Press.

Needleman HL (2004). Lead poisoning. *Annual Review of Medicine*, 55: 209–222.

Nriagu JO & Pacyna JM (1988). Quantitative assessment of worldwide contamination of air, water, and soils by trace metals. Nature, 333: 134–139.

Olin SS & Sonawane BR (2003). Workshop to develop a framework for assessing risks to children from exposure to environmental agents. *Environmental Health Perspectives*, 111(12):1524–1526.

Osterloh JD (1991). Observations on the effect of parathyroid hormone on environmental blood lead concentrations in humans. *Environmental Research*, 54: 8–16.

Ostro BD et al. (1999). Air pollution and health effects: A study of medical visits among children in Santiago, Chile. *Environmental Health Perspectives*, 107(1): 69–73.

Pacini F, Vorontsova T, Demidchik EP, Molinaro E, Agate L, Romei C, Shavrova E, Cherstvoy ED, Ivashkevitch Y, Kuchinskaya E, Schlumberger M, Ronga G, Filesi M, & Pinchera A (1997). Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: Comparison with naturally-occurring thyroid carcinoma in Italy and France. J Clin Endocrinol Metab, 82: 3563–3569.

Pande JN et al. (2002). Outdoor air pollution and emergency room visits at a hospital in Delhi. *Indian Journal of Chest Disease and Allied Sciences*, 44: 13–19.

Parnia S, Brown JL, & Frew AJ (2002). The role of pollutants in allergic sensitization and the development of asthma. Allergy, 57(12): 1111–1117.

Pastides H et al. (1988). Spontaneous abortion and gengeral illness symptoms among semiconductor manufacturer. *Journal of Occupational Medicine*, 30(7): 543-551

Perera FP, Jedrychowski W, Rauh V, & Whyatt RM (1999). Molecular epidemiologic research on the effect of environmental pollutants on the fetus. Environ Health Perspect, 107(Suppl 3): 451–460.

Plopper CG et al. (1994). Elevated susceptibility to 4-ipomeanol cytotoxicity in immature Clara cells of neonatal rabbits. *Journal of Pharmacology and Experimental Therapeutics*, 269: 867–880.

Pronczuk J, Moy G, & Vallenas C (2004). Breast milk: An optimal food. Environ Health Perspect, 112(13): A722–A723.

Raizenne M, Neas LM, Damokosh AI, Dockery DW, Spengler JD, Koutrakis P, Ware JH, & Speizer FE (1996). Health effects of acid aerosols on North American children: Pulmonary function. Environ Health Perspect, 104(5): 506–514.

Renwick AG et al. (2003). Risk characterisation of chemicals in food and diet. *Food and Chemical Toxicology*, 41(9): 1211–1271.

Rice DC (1996). Behavioral effects of lead: Commonalities between experimental and epidemiologic data. Environmental Health Perspectives, 104(Suppl 2): 337–351.

Risau W (1998). Development and differentiation of endothelium. *Kidney International Supplement*, 67:S3–S6.

Ritz B et al. (2002). Ambient air pollution and risk of birth defects in Southern California. *American Journal of Epidemiology*, 155: 17–25.

Robbiano L et al. (1989). Comparison of DNA alkylation,fragmentation, and repair in maternal and fetal tissues of pregnant rats treated with a single dose of ethyl methanesulfonate, ethyl-*N*-nitrosourea, *N*-nitrosodiethylamine, and methyl-*N*-nitrosourea. *Teratogenesis Carcinogenesis and Mutagenesis*, 9(3): 157–166.

Rodier PM (1994). Vulnerable periods and processes during central nervous system development. Environ Health Perspect, 102(Suppl 2): 121–124.

Ron E, Modan B, & Boice JD (1988). Mortality after radiotherapy for ringworm of the scalp. *American Journal of Epidemiology*, 127: 713–725.

Rumchev K et al. (2000). Childhood asthma and exposure to formaldehyde and volatile organic compounds. *Respirology*, 5(Suppl): A26.

Rumchev KB et al. (2002). Domestic exposure to formaldehyde significantly increases the risk of asthma in young children. *European Respiratory Journal*, 20(2): 403–408.

Rutledge JC& Generoso WM (1998). Malformations in pregastrulation developmental toxicology. In: Korach KS ed. *Reproductive and developmental toxicology*. New York, Marcel Dekker, pp73-86

Ryan TJ, Hart EM, & Kappler LL (2002). VOC exposures in a mixed-use university art building. Am Ind Hyg Assoc J, 63: 703–708.

Rylance GW (1988). Prescribing for infants and children. Br Med J, 296: 984–986.

Rylander L, Stromberg U, & Hagmar L (1995). Decreased birthweight among infants born to women with a high dietary intake of fish contaminated with persistent organochlorine compounds. *Scandinavian Journal of Work Environment & Health*, 21: 368–375.

Salome CM et al. (1996). Effect of nitrogen dioxide and other combustion products on asthmatic subjects in a home-like environment. *European Respiratory Journal*, 9(5): 910–918.

Schantz SL, Widholm JJ, & Rice DC (2003). Effects of PCB exposure on neuropsychological function in children. *Environmental Health Perspectives*, 111(3): 357–576.

Schenker MB et al. (1995). Association of spontaneous abortion and other reproductive effects with work in the semiconductor industry. *American Journal of Industrial Medicine*, 28:639-659

Schwela D (2000). Air pollution and health in urban areas. Rev Environ Health, 15: 13–42.

Selevan SG et al., (2000). Identifying critical windows of exposure for children's health. Environ Health Perspect, 108(Suppl 3): 451–455.

Sekhon HS, Keller JA, Benowitz VL, & Spindel ER (2001) Prenatal nicotine exposure alters pulmonary function in newborn rhesus monkeys. Am J Respir Crit Care Med, 1645:989–994.

Shenefelt RE (1972). Morphogenesis of malformations in hamsters caused by retinoic acid: Relation to dose and stage at treatment. *Teratology*, 5(1): 103–118.

Shuey DL et al. (1994). Biologically-based dose–response modeling in develop mentaltoxicology: Biochemical and cellular sequelae of 5-fluorouracil exposure in the developing rat. *Toxicology and Applied Pharmacology*, 126: 129–144.

Smedley PL & Kinniburgh DG (2002). A review of the source, behaviour and distribution of arsenic in natural waters. *Applied Geochemistry*, 17: 517–568.

Smialowicz R (2002). The rat as a model in developmental immunotoxicology. Hum Exp Toxicol, 21: 513–519.

Smialowicz R, Williams W, & Copeland C (2001). Effect of perinatal/juvenile heptachlor exposure on adult immune and reproductive system function in rats. Toxicol Sci, 61:164–175.

Smiley-Jewell S, Nishio S, Weir AJ, & Plopper CG (1998). Neonatal Clara cell toxicity by 4-ipomeanol alters bronchiolar organisation in adult rabbits. *The American Journal of Physiology*, 274(4 Pt 1):L485–L498

Smith KR, Samet JM, Romieu I, & Bruce N (2000). Indoor air pollution in developing countries and acute lower respiratory infections in children. Thorax, 55: 518–532.

Sonich-Mullin C, et al. (2001). IPCS conceptual framework for evaluating a mode of action for chemical carcinogenesis. *Regulatory Toxicology and Pharmacology*, 34: 146–152.

Spielberg SP (1992). Anticonvulsant adverse drug reactions: Age dependent and age independent. In: Guzelian PS, Henry CJ, & Olin SS eds. Similarities and differences between children and adults: Implication for risk assessment. Washington, DC, International Life Sciences Institute, ILSI Press, pp 104–106.

Sporik R & Platts-Mills TA (2001). Allergen exposure and the development of asthma. *Thorax*, 56(Suppl 2): 58–63.

Srám RJ et al. (2005). Ambient air pollution and pregnancy outcomes: A review of the literature. *Environmental Health Perspectives*, 113(4): 375–382.

Stillman RJ (1982). In utero exposure to diethylstilbestrol: Adverse effects on the reproductive tract and reproductive performance and male and female offspring. *American Journal of Obstetrics and Gynecology*, 142: 905–921.

Stratton K, Howe C, & Battaglia F (1996). Fetal alcohol syndrome: Diagnosis, epidemiology, prevention and treatment. Washington, DC, National Academy Press.

Tabacova S, Little R, Tsong Y, Vega A, & Kimmel CA (2003). Adverse pregnancy outcomes associated with maternal enalapril antihypertensive treatment. Pharmacoepidemiol Drug Saf, 12: 633–646.

Taskinen H et al. (1989). Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. *Scandinavian Journal of Work Environment & Health*, 15: 345-352

Tomatis L & Mohr U (1973). *Transplacental carcinogenesis*. Lyon, International Agency for Research on Cancer (IARC Scientific Publications No. 4).

Ueda Y, Stick SM, Hall G, & Sly PD (1999). Control of breathing in infants born to smoking mothers. J Pediatr, 135(2 Pt 1): 226–232.

UN (2001). United Nations synthesis report on arsenic in drinking water (draft). Developed on behalf of the United Nations Administrative Committee on Cooperation Sub-Committee on Water Resources, with active participation of UNICEF, UNIDO, IAEA, and the World Bank. Geneva, World Health Organization (http://www.who.int/water_sanitation_health/dwq/arsenic3/en/).

UNICEF (2001). *Partnerships to create child-friendly cities: Programming for child rights with local authorities.* Florence, International Union of Local Authorities and United Nations Children's Fund (http://www.childfriendlycities.org/pdf/brochure.pdf)

UNICEF (2004). *Child labour*. New York, United Nations Children's Fund (http://www.unicef.org/protection/index_childlabour.html).

UNICEF (2010). Childinfo.org: *Statistics by Area/Child Survival and Health*. New York, United Nation Children's Fund.

UNEP (2002). *Global mercury assessment*. Geneva, United Nations Environment Programme.

USEPA (1992). Guidelines for exposure assessment. Fed Regist, 57(104): 22888–22938.

USEPA (2000). Benchmark dose technical guidance document (external review draft). Washington, DC, United States Environmental Protection Agency (EPA/630/R-00/001; http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=20871).

USEPA (2001). *Draft protocol for measuring children's non-occupational exposure to pesticides by all relevant pathways*. Research Triangle Park, NC, United States Environmental Protection Agency, Office of Research and Development (EPA/600/R-03/026).

USEPA (2002). *Child-specific exposure factors handbook (interim report).* Washington, DC, United States Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment (EPA-600-P-00-002B).

USEPA (2004). *A pilot study of children's total exposure to persistent pesticides and other persistent organic pollutants (CTEPP).* Washington, DC, United States Environmental Protection Agency (EPA/600/R-04/193).

USEPA (2005). *A framework for assessing health risks of environmental exposures to children.* Washington, DC, United States Environmental Protection Agency, Office of Research and Development (EPA/600/R-05/093A).

Volkmer RE et al. (1995). The prevalence of respiratory symptoms in South Australian children. II. Factors associated with indoor air quality. *Journal Pediatrics and Child Health*, 31: 116–120.

Vreugdenhil HJ, Mulder PG, Emmen HH, & Weisglas-Kuperus N (2004). Effects of perinatal exposure to PCBs on neuropsychological functions in the Rotterdam cohort at 9 years of age. Neuropsychology, 18(1): 185–189.

Waalkes MP et al. (2003). Transplacental carcinogenicity of inorganic arsenic in the drinking water: Induction of hepatic, ovarian, pulmonary and adrenal tumors in mice. *Toxicology and Applied Pharmacology*, 186: 7–17.

Wang X et al. (2002). Maternal cigarette smoking, metabolic gene polymorphism, and infant birth weight. *The Journal of American Medical Association*, 287: 195–202.

WHO (2005). The world health report: Make every mother and child count. Redesigning child care: Survival, growth and development. Geneva, World Health Organization (http://www.who.int/whr/2005/en/).

WHO (2006). Pruss-Ustun A, Corvalan C *Towards an estimate of the environmental burden of disease.* WHO Geneva. Available at: http:// www.who.int/ quantifying_ ehimpacts/publications/preventingdiseasebegin.pdf (accessed 4 January 2011)

Windham GC et al. (1991). Exposure to organic solvents and adverse pregnancy outcome. *American Journal of Industrial Medicine*, 20: 214-259

Young S, Le Souef PN, Geelhoed GC, Stick SM, Turner KJ, & Landau LI (1991). The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. New England Journal of Medicine, 324: 1168–1173.

For further information:
www.who.int/ceh

World Health
Organization