



Summary



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



World Health
Organization

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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- <i>p</i> -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.

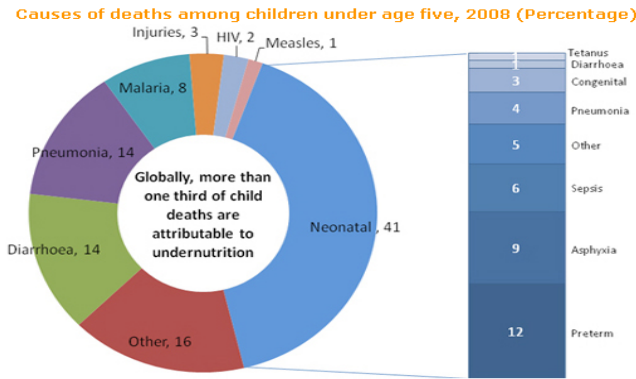
Exposure to environmental hazards underlies ill-health in children in all regions of the world, but particularly in those who are impoverished and

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 acetylcholinesterase - 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 (Hyttén, 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:	↑↑↑	↑↑	↑	↑	↑
- Body water					
- Body fat	↓↓	↓	↓ (Slight)	↔	↔
- Plasma albumin	↓	↓	↓ Slight	↔	↔
Biotransformation:	↓↓↓	↓↓	↑↑ (After some weeks)	↑	↑ Slight
- Oxidation/hydrolysis					
- <i>N</i> -demethylation	↓↓↓	↓	↑↑	↑	↔
- Acetylation	↓	↓	↑	↑	↔
- Conjugation- glucuronidation	↓↓	↓	↑	↑	↔
Renal excretion:					
- 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 (Harbst 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 Ekbon, 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 methoxychlor (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-Slechta 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 doses 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, triiodothyronine; 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 & Ekblom, 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 PM₁₀) 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 et 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 discordance 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

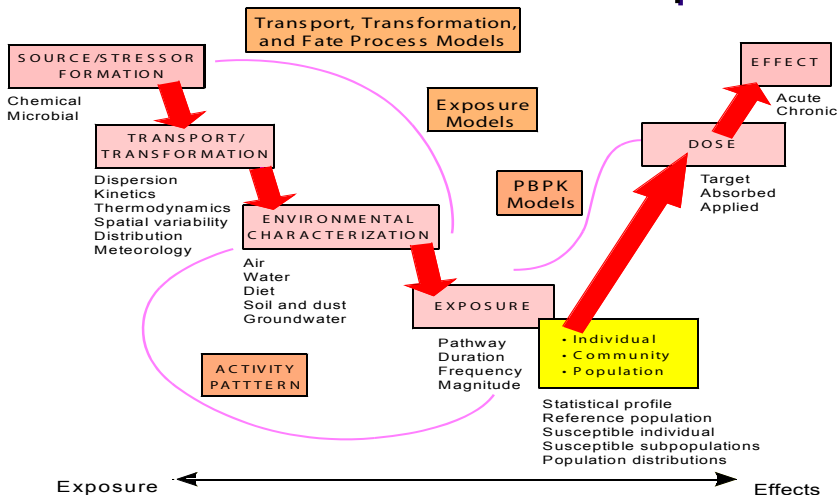
The timing of exposure to chemicals is critical in determining the consequences to children’s health. Manifestation of effects often occurs much later than the life stage when the critical exposure took place. As opposed to what is generally seen in adults, transient changes in physiology at critical 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

Scientific Elements of Exposure



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.

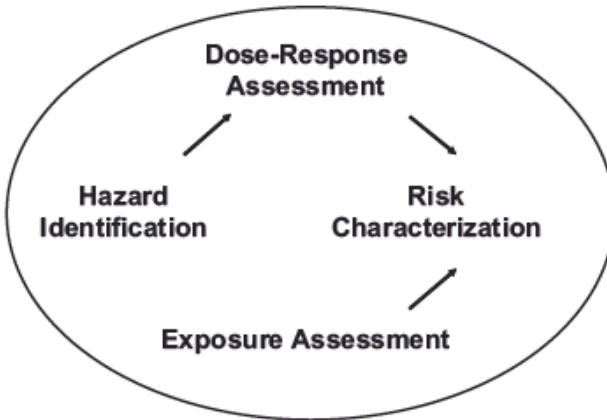
Summary

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

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