Editorial

Children and Increased Susceptibility to Environmental Carcinogens: Evidence or Empathy?

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Introduction

The WHO Task Force for the Protection of Children's Environmental Health declared in its Bangkok statement that "children are not little adults."[1] The premise behind this principle is that children have an exceptional vulnerability to both the acute and chronic effects of environmental hazards and that they are disproportionately susceptible by comparison with adults. Indeed, the Bangkok statement goes on to say that children "are *uniquely* vulnerable to the effects of many chemical, biological and physical agents." The WHO concluded that one third of the global burden of disease can be attributed to environmental risk factors, but whereas children $<$ 5 years of age constitute only 12% of the world population, they represent $>$40% of the environmentally related disease burden. Similar principles to those of the WHO are expounded by other international organizations. The Third European Ministerial Conference on Environment and Health, held in London in 1999, emphasized the importance of protecting children from undesirable environmental exposures in stating: "We recognize the special vulnerability of children and commit to develop policies and actions to achieve a safe environment in which children can develop to their highest attainable level of health." The Fourth Ministerial Conference on Environment and Health will be organized in 2004 in Budapest, Hungary, and will be totally devoted to children's health.

The case for the increased vulnerability of children involves many factors, but these can be grouped in three broad areas. The first is that children are exposed to relatively higher exogenous doses of environmental toxins, *i.e.*, intakes are increased compared with adults. This can be attributed both to lifestyle and physiology (see "Exceptional Exposures").

The second broad area of concern relates to the manner in which environmental toxins are dealt with in the body of a child, *i.e.*, whereas exogenous exposure to a toxin may be similar in children and adults, there may be differences in the amount reaching the target organ, often termed the biologically effective dose (see "Exceptional Susceptibility"). Finally, if exposure begins in childhood, there is plenty of time both for that exposure to be chronic in nature and for the adverse health effects to be manifest, even for diseases with a long latency such as cancer.

Initiatives to promote protection of children's health, in relation to what is a rapidly changing environment in many parts of the world, are both admirable and important. There is an almost intuitive recognition that children, as vulnerable members of society, merit special attention and protection with respect to environmental hazards. This position of defending the vulnerable in society can be supported purely on philosophical and moral grounds. However, the apparent scientific corollary to this position is that children are particularly or even uniquely vulnerable to environmental health hazards, *i.e.*, that the consequences of exposure in children are more severe than the consequences in adults. This latter assertion requires careful scientific evaluation. This is important because in the absence of such evidence it is difficult to form a sound rationale for effective public health decisions to protect child health.

It is worth highlighting the difficulties in terminology with respect to studies of children. Much consideration has been given to defining critical windows of exposure, starting with preconceptual exposure of the gametes of the child's biological parents, through *in utero* exposures and on to the postnatal period (1). This approach recognizes that although childhood is not a series of discrete stages, there are periods of time, sometimes extremely brief, when a child is particularly susceptible to a given exposure. A recent helpful attempt to provide harmonization of terminology for stages of childhood reported five age classes: preterm (*in utero*); term-newborn (0–27 days); infants and toddlers (28 days to 23 months); children (2–11 years); and adolescents (12 to 16–18 years, dependent on region; see Ref. 2). In the discussions, below we have where possible remained consistent with these terms and mainly restrict our discussion to the period between birth and adolescence.

That children suffer disproportionately from many diseases related to environmental hazards is clear; for example, mortality from malaria in parts of Africa is almost two orders of magnitude higher in children $<$ 4 years of age compared with those older $>$ 15 years (3). Social factors, including poverty and inappropriate working environments, as well as climate changes and population migration, will add to both exposure and susceptibility of children to environmental hazards in a wide variety of contexts (3); this is not under dispute or discussion here. However, specifically in relation to environmental carcinogens what is the evidence that children are at higher risk than adults? How strong is the evidence in children that there is an increased exposure and an increased susceptibility once exposed? Here, we draw attention to some of the existing data relating to these questions and point to gaps in knowledge where more research would be valuable.

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[1] Internet address: http://www.who.int/peh/ceh/taskforce.htm.

Epidemiology

In relation to childhood vulnerability and cancer risk, one can discriminate between susceptibility of the child to cancer in childhood and the increased susceptibility of the child to cancer later in life after an exposure in childhood. Cancer in young children is rare, accounting for <1% of new cancers each year in economically developed parts of the world. There are relatively few environmental exposures that have been linked to the etiology of these childhood cancers. Two exceptions, both now only of historical significance, are maternal exposure to ionizing radiation during pregnancy and increased risk of leukemia and other childhood cancers, and the use of diethylstilbestrol by mothers and the increased risk of clear-cell adenocarcinoma of the vagina in their daughters in teenage years or adulthood (1). Furthermore, with respect to children's exposure to ionizing radiation, mortality studies after the 1945 atomic bomb explosions in Hiroshima and Nagasaki revealed that the leukemogenic and carcinogenic risks are greater in those exposed to radiation in the younger age groups (4). The thyroid gland of children is especially vulnerable to the carcinogenic action of ionizing radiation: the incidence of thyroid cancer in children in the Belarus area was <1 case/million/year before the Chernobyl accident, increasing to a peak exceeding 100/million/year in certain areas after the accident (5). In fact, ionizing radiation is the only known thyroid carcinogen and is only effective in children, representing therefore one of the strongest examples of a unique susceptibility in children.

Infections early in life are thought to be related to childhood leukemia (6, 7); the etiology, however, may be infections *per se* rather than specific agents.

Some exposures in childhood may increase risk of cancer decades later. One example is hepatitis B virus where the risk of becoming a chronic carrier and developing hepatocellular carcinoma is greater the earlier in life the infection occurs (8). In developing countries where there is concomitant early life exposure to the dietary hepatocarcinogen, aflatoxin, a synergistic increase in risk is observed. Exposure to both factors leads to a remarkably high liver cancer risk, notably with an increased incidence evident from early adolescence onwards. Another possible example concerns UV light and skin cancer risk. In migrants to Australia, the risk of skin cancer was lower in people who migrated to Australia 10 years after birth than in those who were either born there or migrated in the first 10 years of life (9). In the case of melanoma, this may reflect the fact that melanocytic naevi develop during childhood reaching a maximum density by 10 years of age (10). The case of chemical carcinogen exposure early in life and increased cancer risk is highlighted by the historical example of children used as chimney sweeps in the United Kingdom in the 1700s developing cancer of the scrotum as adults. Some evidence also suggests that exposure to salted fish in the first years of life increases nasopharyngeal cancer risk in Southeast Asia (11). In total, the epidemiological data provide an intriguing indication that low dose exposures early in life may contribute disproportionately to cancer in adulthood, but to date, the effects are difficult to assess; the data on exposures to chemical carcinogens in childhood are particularly sparse.

Exceptional Exposures

The endogenous exposure of a person to any environmental contaminant can be calculated from the concentration of that particular component in environmental media (air, water, soil, and food) and from the intake of these media by that person. It is self-evident that the concentration of a hazardous substance in the environment will be the same for adults and children. However, given the same duration of exposure, profound differences in intakes between adults and children can result. Some examples are considered below.

Per kg body weight, the daily intake of air has been estimated to be 2.3 times higher in small children than in adults, intake of water and fluids 4.8 times higher, and intake of food 6.1 times higher (12). The higher rate of respiration combined with different patterns of behavior in children, *e.g.*, staying outdoors while playing or going to school, may have implications for cancer risk associated with air pollution. Indeed, exposure to potentially carcinogenic air pollutants has been suggested to increase childhood leukemia rates (13). The plausibility of this suggestion is supported by the observation that urinary levels of benzene metabolites in young children (3 years old) from an urban environment appeared to be 1.6–1.8-fold higher than in their parents. This is in turn consistent with the estimated 2.3-fold increased inhalatory intake of benzene in children (14). In contrast, the body burden of polycyclic aromatic hydrocarbons in relation to indoor and outdoor air levels might be similar or even slightly less in children as compared with adults (15). Another example consistent with the greater respiratory rate in children comes from a survey among inhabitants of houses sprayed with methyl parathion. In this instance, young children (<3 years) showed 2.3-fold higher urinary levels of parathion metabolites than older children and adults (16); household insecticide exposure during early life may also be associated with an elevated risk of childhood leukemia (17).

Children show other specific behavioral patterns that may be associated with higher exposure, for instance, mouthing behavior and crawling in relation to soil pollution. In view of their hand- and object-to-mouth behavior, the intake of soil particles by playing children has been estimated to range from several tens of μg to several grams/day; current exposure risk assessment models assume 150 mg/day in contrast to adults who are assumed to ingest 50 mg/day (18). Probably the most extreme example of exposure to soil contaminants relates to children playing in open waste dump areas; very high risks of exposure to dioxins and related compounds have been shown for municipal waste sites in various Asian countries (19). Despite this, direct ingestion of soil does not necessarily present the most important exposure route; for benzo(*a*)pyrene as well as for several metals, it has been demonstrated that consumption of homegrown crops may result in high intake of soil contaminants by children (18, 20, 21).

Children have different nutritional patterns than adults and this can also influence exposure. For instance, children may consume more milk and other dairy products on a daily basis than adults. At the extreme, during early infancy, children may solely ingest breast milk or artificial milk diluted with drinking water. Organochlorine pesticides, polychlorinated biphenyls, polychlorinated dibenzodioxins, polybrominated diphenyl ethers, polycyclic aromatic hydrocarbons, metals such as mercury and lead but also nicotine and some solvents have all been demonstrated to occur at rather high levels in human breast milk because of bioaccumulation in the mother resulting from the environmental persistence of these contaminants. It has been shown that infant exposure to organochlorines through breast milk is associated with early developmental effects (22). To date, no information on long-term health risks, including cancer in relation to this toxic exposure via breast milk, is available and longitudinal epidemiological studies are warranted (23).

In developing countries, many children drink water that has not been purified, thus presenting a myriad of toxic hazards:

the case of arsenic poisoning from well water in Bangladesh is notorious. But also in industrialized countries, despite their advanced drinking water purification technologies, suspected carcinogenic compounds may still be present (24). Bottle-fed infants, who may ingest up to 1.5 liters of drinking water/day, represent a high-risk group for any environmental contaminants in the water supply; however, no information on drinking water pollution-related cancer risks in later life is available. Examples of possibly important exposures include nitrate, which is a substrate for the endogenous formation of carcinogenic *N*-nitroso compounds, pesticides, and trihalomethanes, which are formed as by-products in the course of drinking water disinfection by chlorination. Also inorganic lead, a possible carcinogen, represents an exposure risk as a consequence of the historical use of lead pipes in drinking water supply networks.

In discussing such examples of children's exposures to environmental contaminants, it has to be considered that in everyday life exposure arises from multiple sources, implying that focusing on a single, albeit relevant, exposure route may lead to underestimating exposure levels. Therefore, multipathway exposure assessment as recently has been demonstrated for children's pesticide or polycyclic aromatic hydrocarbon exposure modeling has to be performed to obtain reliable estimates (15, 25).

Additionally, to reduce the uncertainty in current exposure assessments, more information on child behavior and its consequences for the intake of environmental media is required; socioeconomic factors (poverty) and sociocultural factors (religion) will be of major importance in this respect.

Exceptional Susceptibility

Absorption and Distribution. Data from the pharmaceutical field reveal that a child's response to a drug can differ to that of an adult's for a number of physiological reasons, relating to the metabolism and disposition of the drug concerned (2, 26). Although there has been less direct investigation with respect to environmental carcinogens, the changing physiology of the child should equally affect the response to these latter exposures.

A number of physiological changes during childhood can affect absorption and disposition of exogenous agents and some of these are listed in Table 1. It is important to note that this is a continuous and dynamic process with many of these changes evolving over the early months and years of the child's life. In many instances, there is incomplete knowledge as to the timing of the changes. Nevertheless, there is sufficient evidence to indicate that both absorption and distribution of environmental toxins will differ with age and development (2). For example, plasma proteins vary with age in quantity and possibly substrate affinity such that the unbound fraction of administered drugs in plasma from children and adults differs, thus affecting therapeutic response. However, although a child may have an altered susceptibility to a carcinogen compared with an adult, it is difficult to state *a priori* that the child has an increased susceptibility. For example, intestinal transit time may be reduced in children compared with adults (27). This can lead to incomplete absorption and reduced effectiveness of drugs, but the difference may also result in reduced absorption of environmental chemical carcinogens. In a similar vein, experimental studies have shown that more frequent urination results in less time for deconjugation of the carcinogen 4-aminobiphenyl in the bladder, with subsequently lower levels of DNA adducts for a given dose of this bladder carcinogen (28).

Metabolism. The expression of a number of Phase I and Phase II metabolizing enzymes has been shown to alter with age, representing another way in which children may have altered susceptibility to environmental carcinogens (2, 26, 29). In general, the total cytochrome P450 (CYP) level in human liver *in utero* is about one-third that seen in adults. Comparisons of drug metabolism indicate that half-life of drugs is extended in term-newborns but that this difference is significantly reduced during the first 6 months of infancy (26). An interesting example is the changing pattern of hepatic CYP3A enzyme expression with age. CYP3A7 predominates *in utero*. After birth, CYP3A5 increases, but CYP3A4 is the predominant hepatic CYP in adults. CYP1A2 is present at low levels in infants with similar levels to adults from ~3 years of age. These changes might be expected to alter susceptibility to aflatoxin (30). Exposure to aflatoxin increases markedly once a child is weaned on to family foods and this increase has been linked with impairment of growth in these infants and children (31, 32). Aflatoxin is metabolized mainly in the liver by CYP3A4, 3A5, 3A7, and 1A2, with differences in the balance of metabolites produced by each enzyme (33). As each metabolite differs in the formation of DNA adducts, it is reasonable to assume that the carcinogenic effects of exposure will be modulated by age-related changes in CYP expression. It is interesting that expression of the major aflatoxin metabolizing enzymes increase just at the age when the child is exposed to high toxin levels through the switch to family foods.

Phase II enzymes similarly show changes in expression level with age. For example, epoxide hydrolase and glutathione *S*-transferase π are very active in the fetal liver, whereas glutathione *S*-transferase μ and α classes increase in the 3 months or so after birth (34). Although the level of the glucuronidation detoxification pathway is low early in infancy, some of the sulfation enzymes may compensate by their relatively high expression (Table 2).

DNA Repair. Another parameter expected to modulate the effects of exposure to an environmental carcinogen is DNA

Table 1 Factors affecting toxin absorption and distribution in children[a]

Parameter	Observation	Effect
Gastric pH	Less acidic in infants	Altered drug absorption
Gastric emptying	Slower in neonates and infants	Delayed absorption
Intestinal transit time	Shorter in children	Reduced absorption
Body surface area relative to weight	Greater in children	Increased transdermal exposures
Membrane permeability	Greater in neonates	Increased cellular uptake
Plasma protein binding	Reduced in neonates and infants	Increased plasma levels of unbound toxin
Body water	Total body water and extracellular water content higher in neonates and infants	Relatively higher volume of distribution for water soluble toxins

[a] Adapted from Ref. 2.

Table 2 Examples of some alterations in hepatic metabolising enzymes with age[a]

Metabolizing enzyme	Age-related alteration
CYP3A7	High prenatally, low in adults.
CYP3A4	Weak/absent prenatally, low in neonates/infants (40% of adults at age one month); high in adults.
CYP3A5	More commonly expressed in children and adolescents than adults.
CYP1A2	Low pre-natally, low in neonates/infants rising to adult levels (around age 3 years).
CYP2E1	Low prenatally, rising after birth to adult levels (from age 1 year onwards).
Microsomal epoxide hydrolase	Similar or lower level prenatally compared with adults.
N-acetyltransferase	Lower in infants (1–2 years) than adults.
Glucuronidation	Extremely low prenatally, lower in infants than adults.
SULT1A3	Higher prenatally than in adults.
SULT1A1	Lower prenatally than in adults.

[a] Adapted from Refs. 2, 29.

repair. Changes in DNA repair capacity with age have been reported, for example, with UV light-induced damage (35). Studies of the O^6-alkylguanine alkyltransferase enzyme also suggest age-related variations in activity among adults (36). A small study of normal brain tissue samples from infants, children, and adolescents showed no variations with age (37), but overall, there is a notable scarcity of data in this area in relation to children.

Cell Proliferation. The balances between DNA adduct formation, DNA repair, and cell replication will be critical to the development of tumors. Again, there are relatively few direct data on changes in cell replication rate with age. However, inferences can be drawn from the rates of organ weight gain, which show that there are decreases in rates of gain in many organs from birth to 4–6 years of age. Although for organs such as the brain, this is then stable, for others such as the liver, a further growth occurs toward puberty (38). Additional periods of high cell replication exist for reproductive organs around puberty. Despite the absence of precise data, periods of rapid growth *in utero* and infancy will be accompanied by greater cell division rates than in adults for many organs.

Experimental Studies. Most animal cancer bioassays use mature (6–8 weeks old) rodents. In studies of younger animals, the spectrum of tumors is similar to that in older animals, but tumor onset is earlier and incidence is increased (38). Studies of long-term exposures starting at different ages with the same dose are rare. Nevertheless, there are examples with some mutagenic carcinogens (*e.g.*, diethylnitrosamine and vinyl chloride), where the earlier the exposure the greater the tumor incidence (39, 40). In certain tissues, *e.g.*, rat mammary gland, kidney, ovaries and colon, younger animals were more sensitive to tumor formation after treatment with *N*-nitrosomethylurea, whereas for other tissues, *e.g.*, the corpus and cervix, the susceptibility was lower in younger animals (41). Mouse skin applications of 7,12-dimethylbenz(*a*)anthrene resulted in a higher incidence of skin papillomas in older compared with younger mice (42).

In female rats, treatment of 5–8-week-old animals with 7,12-dimethylbenz[*a*]anthrene induced a higher frequency of tumors than in either younger or older animals, reflecting susceptibility in a key period for the development of mammary tissue (43). These subtle differences in susceptibility of a tissue to carcinogenesis with age probably reflect a number of key properties of the tissue at the time of treatment (1, 41). These will include factors discussed above from studies of children, namely the activation and detoxification of the carcinogen, DNA repair activity, and the rate of cell replication but imply additional elements such as the number of target cells in the tissue.

Overall, experimental data are broadly consistent with the hypothesis of age affecting susceptibility to carcinogens in a complex and time-dependent manner. However, there is clearly scope for much more informative data to be generated in this area in relation to childhood susceptibility.

Gaps in Knowledge

The epidemiology both of childhood cancer and of cancer in adults resulting from childhood exposures has a number of limitations. Many of the studies of childhood cancer are based on small numbers because of the relatively low numbers of cancers and their association with rare exposures. In addition, in both situations, accurate information on past exposure is often difficult to obtain, particularly where data are self-reported. This is exacerbated when trying to identify exposures in relation to what may be quite narrow critical windows of exposure.

Biomarkers may potentially improve exposure assessment in cancer epidemiology (44). However, the challenge of assessing past exposure, particularly when reconstructing childhood exposure patterns, is difficult even with biomarkers because of their inherent limited life span. Long-term prospective studies with recruitment at birth and stored biological samples offer possibilities to apply such markers within nested case-control studies (45). Particularly relevant may be the biomarkers such as chromosomal aberrations that have already been associated with increased cancer risk in prospective studies in adults (46).

Where biomarkers may also be valuable is in identifying genetic polymorphisms that confer susceptibility to environmental exposures and permit environmental risk factors to be examined in subgroups of the population. This area may be advanced by the development of high throughput screening of thousands of single nucleotide polymorphisms using DNA microarray technology. In addition, there may be helpful disease markers. For instance, the presence of ALL1/MLL/HRX gene fusions possibly acquired during fetal life, although occurring at a very low incidence rate, are highly predictive for the onset of acute lymphoblastic leukemia or acute myeloid leukemia in later childhood (47). There are some specific ethical issues that need attention in research involving children (48), as well as the practical difficulties of obtaining biological samples from children.

Much of the data on childhood susceptibility points to a need for greater subtly in cancer risk assessment. In particular, the suggestion has been made that risk calculations need to be made for each stage of life, taking into account the variations in pharmacokinetic data (49) and that an addition of these risks at different stages be used in the assessment (38). Nevertheless, there are still many gaps in knowledge that need addressing to permit refinement of such models. Greater knowledge about the

changes in absorption, metabolism, DNA repair, and cell proliferation rates in childhood would be informative. Parallel generation of animal data on age-dependent carcinogen susceptibility would also be useful. Many questions concerning childhood susceptibility relate to infections and chronic inflammatory responses, so greater understanding of the developing immune system would also be valuable.

In summary the available data do suggest that there is a scientific basis to the general concern for special attention to the vulnerability of children to environmental carcinogens and that a greater focus on this research question is justified. However, more data are needed to permit informed assessments of cancer risk in children and to be able to establish a scientific basis for strategies to minimize risk in this vulnerable section of society.

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