Environmental contaminants and children's health: Cause for concern, time for action

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The present paper provides an outline of the developmental and behavioural characteristics that make children, especially the fetus and young child, more vulnerable to contaminants than adults. The major categories of contaminants are briefly described. The evidence for their possible effects on neurobehavioural development; immune, endocrine and respiratory systems; childhood cancer based on research studies with animals; children exposed to catastrophic 'accidents' involving overdose exposures; and pregnant women and children from communities with high 'background' levels of contamination who participated in studies is reviewed. While the data are worrisome, especially for children living in northern and certain urban communities, much remains to be learned about possible subtle effects and the potential for long term effects of the current background contamination experienced by the majority of Canadian children before its significance to their health can be fully evaluated. The present regulatory processes, which are based on risk assessment, are so cumbersome and costly that the great majority of chemicals in use have not been fully evaluated, and the ingenuity of new chemical production continually exceeds the capacity to test the new chemicals. Moreover, despite past insistence on scientific proof of adverse effects and safety, unanticipated effects have occurred that will threaten the sustainability of human life unless more effective control measures are taken to limit the release of toxic substances and persistent chemicals into the environment. Therefore, the shortcomings of risk assessment are discussed, and the precautionary principle, which is used in some countries and is proposed for use internationally as an alternative measure that may offer improved control for the future, is outlined. Finally, opportunities for physician action are suggested.

Key Words: *Children's environmental health; Environmental contaminants; Precautionary principle; Risk assessment; Toxicant effects; Toxicant vulnerability*

Les contaminants environnementaux et la santé des enfants : Une cause d'inquiétude, le temps d'agir

RÉSUMÉ : Le présent article donne un aperçu des caractéristiques développementales et comportementales qui rendent les enfants, et surtout les fœtus et les jeunes enfants, plus vulnérables aux contaminants que les adultes. Les principales catégories de contaminants sont brièvement décrites. On examine des données quant à leurs effets possibles sur le développement neurocomportemental, sur les systèmes immunitaire, endocrinien et respiratoire, sur le cancer infantile d'après des études sur des animaux, sur les enfants exposés à des «accidents» catastrophiques donnant lieu à une exposition à surdose ainsi que sur les femmes enceintes et les enfants de collectivités au taux de fond élevé de contamination qui ont participé à des études. Bien que les données soient inquiétantes, surtout dans le cas d'enfants vivant dans le Grand Nord et dans certaines collectivités urbaines, il reste beaucoup à apprendre sur les effets subtils possibles et le potentiel d'effets à long terme de la contamination de fond que subissent la plupart des enfants canadiens avant qu'il soit possible d'en évaluer l'importance sur leur santé. Les processus de réglementation actuels, fondés sur l'évaluation des risques, sont si lourds et si coûteux que la majorité des produits chimiques utilisés n'ont pas été évalués et que l'ingéniosité de production des nouveaux produits chimiques est toujours supérieure à la capacité d'effectuer des essais sur ces produits chimiques. De plus, malgré une insistance antérieure à obtenir des preuves scientifiques de leurs effets néfastes et de leur innocuité, des effets inattendus se sont manifestés, lesquels menaceront la viabilité de la vie humaine, à moins que des mesures de contrôle plus efficaces soient prises pour limiter l'émission de substances toxiques et de produits chimiques persistants dans l'environnement. Par conséquent, les lacunes de l'évaluation des risques sont abordées, et le principe de précaution, utilisé dans certains pays et proposé à l'échelle internationale comme mesure de rechange afin d'améliorer le contrôle dans l'avenir, est souligné. Enfin, des possibilités d'action de la part des médecins sont suggérées.

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"By default we are conducting a massive toxicological experiment, and our children are the 'experimental animals'" (1)

Of the determinants of child health and well being, it is now widely acknowledged that the environment rates highly; optimal conditions are essential for children's healthy growth and development. About 60 years ago, relatively few environmental chemicals were recognized as being hazards to the growing child; lead, mercury and arsenic are obvious examples that most rapidly come to mind. Beginning with the Second World War, industrial chemicals and chemicals intended for use in war to kill humans began to be 'modified' for peaceful uses to control 'pests' in the environment, and were produced in increasing numbers. It was not long before serious 'accidents' involving spills or inappropriate application occurred. Examples include consumption by pregnant mothers of fish in Japan (Minamata disease) (2) and grain in Iraq (3) contaminated with methylmercury; and rice in Taiwan (4) and Lake Michigan fish (5) contaminated with polychlorinated biphenyls (PCBs). These tragic events resulted in various, often serious, neurobehavioural disorders in children. They served to warn society of the possible hazards of new chemicals and, in particular, it became clear that the fetus was vulnerable to maternal exposure to environmental chemicals. Today, many thousands of manufactured chemicals are in our environments, the majority of which have not been stringently tested for safety, and, of those that have, relatively few have been confirmed to be safe for the young child and fetus.

Despite the lessons of the past, standards designed to protect humans from overexposure to environmental contaminants are designed, essentially, for the safety of the adult working male. To attempt to protect the child, a 'factor of 10', which is unsubstantiated in most instances, is applied to adult standards. Most often, safety has not been evaluated for pregnant women who are told to avoid chemical exposures, advice that is difficult to follow in view of the ubiquitous distribution of many potentially hazardous substances.

The present overview describes for paediatricians why children, especially the fetus and the young child, require special consideration; it outlines the main classes of contaminants and their important toxic effects; it illustrates why regulatory reliance on risk assessment is fraught with difficulty; and it describes the precautionary principle, which should overarch it, especially when considering children's environmental health. Finally, measures are suggested that physicians can take as health care providers, advocates and community leaders to improve the safety of children's environments.

CHILDREN'S VULNERABILITY

The fact that children are growing and developing makes them more vulnerable than adults to the adverse effects of environmental chemicals (6). Viewed very simplistically, cellular growth involves response to and acquisition of nutrients and chemicals in the cell's environment. Consequently, cells that are growing and replicating rapidly are more likely than cells that are quiescent to be influenced by chemicals, including substances that may not be beneficial. Growth is most rapid in utero and in early childhood, with a further spurt at puberty, and it is at these stages that environmental chemicals can have their most damaging effects. Brain growth, while continuing beyond adolescence, is maximal in the fetus and young child, and although some plasticity is preserved into adult life, it is essentially a one-time event. It has become clear that the placenta is not protective against simple molecules or more complex molecules whose physicochemical characteristics, including their state of ionization, allows them to be transported easily across cell membranes (7).

Growth requirements and the physiology of the young child demand much higher intakes of water and other nutrients per unit body weight than those required by the adult – sevenfold and threefold, respectively, for the infant and young child (8). Heat loss from higher surface area to body mass ratio and metabolic processes of growth result in a higher metabolic rate in the child, causing increased oxygen requirements and, hence, a higher resting minute volume; oxygen requirements are further increased by the higher activity levels of childhood (8). Young infants' low plasma protein-binding capacity, renal clearance, hepatic conjugation activity and immature blood-brain barrier add to their vulnerability. In early childhood, hepatic detoxification mechanisms, such as glutathione S-transferase (9) and P450 cytochrome enzyme system (10) activities, rise rapidly to exceed adult values, a potentially beneficial feature if the substance concerned is converted to a less toxic metabolite and readily excreted. Conversely, some degradation products may be more toxic than the original compounds from which they are derived. Small size, crawling and exploratory activities increase the exposure of the young child to heavy volatile substances, chemicals used on lawns and residual compounds in carpets (11).

At a more fundamental level, individual genetic differences may place the young child at increased risk. Genetic differences are now recognized in enzymes that catabolize toxic substances – for example, a genetic polymorphism that influences the rate of ability to hydrolyze organophosphates (12). Hence, in addition to vulnerability resulting from their early growth, some children will show greater susceptibility to certain compounds.

CONTAMINANTS OF CONCERN

Environmental contaminants are recognized to affect organ systems rather than to produce specific disease entities. Moreover, some of the contaminants affect several organs. Thus, depending on the substance, and the extent, timing and duration of exposure, effects may be en-

countered on the brain, respiratory system, immune system, reproductive and endocrine systems, and the kidney and liver. Several classes of contaminants can be defined:

- certain metals;
- persistent organic pollutants (POPs);
- pesticides (herbicides, insecticides, fungicides and rodenticides);
- polyhalogenated byphenyls;
- solvents and volatile organic compounds (VOCs); and
- airborne pollutants.

METALS

Metals with recognized toxic effects include lead, mercury, arsenic, cadmium and manganese.

Lead: Lead is an environmental contaminant of antiquity. Since the 1950s, paediatricians have witnessed a progressive reduction in 'acceptable' blood lead levels from the 'intervention' level of 60 μg/dL of that time to the current view that lead should not be in the body in measurable quantities; however, if it is present, blood levels must not exceed 10 μg/dL. Globally, lead pollution continues to result from its use in gasoline, paints, industrial processes and products. In Canada, the use of lead is still permitted in some industrial products and in paints that are used where children are considered unlikely to encounter them; it is also intermittently found in imported goods. American data show that a direct relationship exists between the progressive reduction in lead use for gasoline production from 1976 to 1980 and in blood lead values in the general population (13). While lead has immunosuppressive and endocrine disruptor effects (14), the toxic effects of primary concern affect the developing nervous system of the fetus, the infant and the young child; these effects are discussed below.

Mercury: Mercury is a ubiquitous pollutant; about 50% of that found in the environment originates from natural sources, and the remainder originates from industrial processes, including paper and pulp production and coal burning furnaces. Catastrophic 'accidents' have resulted from industrial release – for example, the Japanese Minamata Bay disaster of the late 1950s during which maternal ingestion of heavily polluted fish resulted in the births of 23 infants with severe neurological damage, including mental disability and cerebral palsy (15). Metallic mercury travels widely in air and water, and is converted in water by bacterial action to the more readily absorbed methylmercury and then bioconcentrated through the aquatic food chain (16). High intakes occur in people for whom fish, and fat and meat from predatory animals and sea mammals (the so-called 'country foods') form the staple diet.

Neurodevelopmental tests on 73 children from New Zealand (17), 738 children from the Seychelles (18) and 917 children from Faroe Island (19) born to apparently healthy mothers who ate mercury-contaminated fish during pregnancy showed effects that correlated with the extent of maternal exposures. Exposure during pregnancy was assessed on the basis of maternal hair mercury content. Values were quoted in parts per million in two of the reports and in micrograms per gram in the Faroe Island study (18), making a comparison of the exposures difficult. The values of hair mercury content of the mothers in the Seychelles study (0.5 to 26.7 ppm) (17) were lower than those of the New Zealand mothers (6.0 to 86.0 ppm) (16). Fifteen per cent of the Faroe Island maternal hair values were higher than 10 μg/g (18). Cord blood values quoted in the Faroe Island study ranged up to 350 ug/L. The effects on the children included decreased scores on the Wechsler intelligence test, inattentiveness and poor memory. These changes persisted at seven years of age, with the exception of the Seychellois children – the values of maternal hair methylmercury had been relatively lower than that reported in the other studies when the children were originally tested (20).

Mercury levels averaging 14.2 μg/L and 10.4 μg/L, respectively, were found in cord blood samples from 475 Nunavik and 67 Baffin Island newborns, and about 2.0 ug/L in samples from 243 North Shore Quebec infants (21). In a large epidemiological study of Northern Cree children and adults, lower blood mercury levels were noted after a reduction in dietary fish consumption (22). The significance of the above findings with regard to neurological development of children of Canada's northern peoples and others whose diet contains large quantities of ocean or lake fish is uncertain. The New Zealand investigators (17) noted a dose-dependent relationship between mercury levels and neurological effects – 61 of the 73 children who showed neurobehavioural effects were from mothers with hair mercury levels of 20 to 80 ppm. A similar maternal hair mercury dose-dependent effect was found in the Faroe Island children when they were tested at age seven years (19). However, the consumption of fish confers definite nutritional benefits, and some restraint may, therefore, be necessary in cautionary statements on fish consumption that are intended to protect pregnant women (23). Measures being taken to minimize the exposure of Canadians to methylmercury were summarized recently (24).

Arsenic: Arsenic is found in rocks and soil, but human sources, such as coal-fired power plants, domestic and industrial wastes, metal mining and arsenic-containing pesticides, are the principal sources of environmental arsenic. Consequently, aresenic levels are increasing. Concentrations above safety standards may occur in drinking water from private wells (24). Chronic arsenic exposure is associated with damage to the kidneys, liver and brain; however, general environmental arsenic contamination has not yet risen to levels that pose a threat to Canadian children's health.

Cadmium: Cadmium is released from fossil fuel-burning, mining and waste incinerators. Leafy vegetables and grains take up soil cadmium; thus, most human exposure is dietary. Animal studies show that cadmium is poten-

tially more toxic to an infant than to a fetus, apparently because it induces anorexia in pregnant animals that ingest it, resulting in low uptakes (26). Rat pups receiving low-level exposure show varying neurological deficits, depending on the dose and route of exposure (27). Human studies are difficult to evaluate because of the usual co-occurrence of cadmium with raised lead levels.

Manganese: Manganese, unlike lead and mercury, is a physiological requirement because it is a catalyst for certain enzyme reactions. Elevated manganese blood levels were reported in two studies of 30 (28), and 16 (29) children with hyperactivity and learning disorders. Although dietary manganese is absorbed more efficiently by young children than adults, the relevance of the raised values, if any, needs to be confirmed by larger, better documented longitudinal studies. Symptomatic 'manganism' in adults occurs essentially as a consequence of inhaled manganese. In Canada, manganese remains a pollutant of concern because of its continued use in methylcyclopentadienyl manganese tricarbomyl (MMT) to replace ethyl lead as an octane enhancer in gasoline.

Persistent organic pollutants

A vast array of manufactured organic substances degrade very slowly in the natural environment, some have half-lives of many centuries (eg, chloroform, 1850 years; and hexachlorethane and trichlorethylene, 1.8 billion and 1.3 million years, respectively) (30). POPs include many organochlorine pesticides such as Mirex, Chlordane, hexachlorobenzene and DDT; polyhalogenated biphenyls such as PCBs; and numerous unintentional by-products of pulp and paper, pesticide, and plastic manufacturing, including dioxins and furans. The latter are also produced in the combustion of coal and gas for energy production, and in waste incinerators.

POPs include particularly dangerous contaminants, such as dioxins, that pose great threats to humanity because of their persistence, ubiquitous distribution, resistance to attempts at destruction, lypophilic nature, tendency to bioaccumulate and toxic effects. Although most have not been used in the Arctic, air and oceanic transport, long half-lives, together with bioaccumulation through the food chain, have given rise to special concern for the indigenous peoples of the North. Their dependence on traditional food sources such as seal, Beluga whale and Arctic fish has resulted in body burdens of certain POPs that greatly exceed those of people living in southern Canada (31). POPs accumulate in adipose tissue and are mobilized during lactation; the concentration of PCBs in a study of breast milk from Nunavik mothers was fourfold that of southern Quebec mothers (32). While Inuit people have levels that are of concern, trace quantities of a large number of POPs are detected in most humans tested.

Although the production and use of some POPs, for example DDT, have ceased in the developed world, their withdrawal from use has been selective. For example, although no longer manufactured, PCBs are still widely found in transformers. As noted above, dioxins and furans continue to be released; one often unrecognized source is the burning of vinyl plastics in municipal, hospital and industrial incinerators. POPs have numerous possible adverse health effects that are discussed below, including neurobehavioural developmental disabilities, effects on the developing immune system, cancer promotion and endocrine disruption. Because of their acknowledged toxicity, 12 POPs, including organochlorine pesticides, industrial hexachlorobenzene, PCBs, dioxins and furans, were the subject of a recent international treaty under the United Nations Environment Program to cease their production and to eradicate them where possible (33).

Pesticides

The number of pesticides in use has steadily increased over the past 50 years. They are used as herbicides, fungicides, insecticides and rodenticides. While pesticide poisoning may have acute life-threatening effects, only the possible long term effects are discussed in this paper. Three major chemical classes of pesticide are recognized.

Organochlorines: Examples of organochlorines include DDT, Chlordane, Aldrin, hexachlorobenzene and pentachlorophenol. Pentachlorophenol is a wood preservative that is widely detectable in the Canadian population (34). While primarily active on nerve conduction chemistry, these substances are acknowledged carcinogens (35), and, based mainly on animal studies, are suspected teratogens (36), immunotoxins (37) and endocrine disrupters (38). Many persist in the environment and continue to be manufactured for use in developing countries, for example, DDT for mosquito control. The search for affordable alternatives should be an international concern.

Organophosphates and carbamates: Organophosphates and carbamates, such as Chlorpyriphos, Malathion, Diazinon, and Carbaryl, are cholinesterase inhibitors; the primary concern is for potential effects on acetylcholine-dependent features of the developing nervous system. While no confirmed effects on humans appear to have been reported, animal studies confirm fetal effects; offspring of pregnant mice given 0.18 mg/kg/day of Diazinon showed behavioural disturbances (39). Some organophosphates are teratogenic in animals, and there is concern about the possible long term influence on immune system development (40). Chlorpyriphos was, until recently, widely used as a domestic insecticide; it has been withdrawn from use in the United States and is being phased out in Canada.

Pyrethroids: Examples of pyrethroids, such as Pyrethrin and Cyfluthin, may be produced from natural sources or manufactured. They have generally been regarded as having low toxicity. However, mice given relatively low doses have shown behavioural disturbances (41), and the substances are also viewed as being potential endocrine disrupters (42).

Phenoxy herbicides: 2,4-Dichlorophenoxyacetic acid

(2,4-D) is a widely used example of this class. 2,4-D has a half-life of five to 10 days in soil and is almost completely excreted unchanged following absorption. A reduced sperm count (43) and an association with non-Hodgkins lymphoma have been reported in farm workers (44,45), apparently related to crop spraying; however, until relatively recently, 2,4-D was contaminated by dioxins. Consequently, the earlier literature on its toxicity is difficult to evaluate. 2,4-D is listed among known or suspected human endocrine disrupters by Environment Canada (46).

Polyhalogenated byphenyls

As noted above, polyhalogenated biphenyls such as PCBs and their related degradation products, dioxins and furans, are recognized to be particularly hazardous, persistent and ubiquitous toxicants. They accumulate in adipose tissue and are mobilized during lactation. The effects of PCBs on the developing fetal nervous system were clearly seen in the previously mentioned disaster with rice oil in Taiwan (4), after which 118 children underwent long term follow-up, 27 of whom were paired with carefully matched control children and were shown to have definite cognitive and neurobehavioural difficulties. Studies of children with lower levels of in utero exposure are also of concern. Children of two groups of mothers who were relatively highly exposed through the consumption of fish from the Great Lakes showed reduced performance on newborn assessment (n=115, [47]), and on intelligence quotient (IQ) testing at age 11 years (n=211 [48]). Multivariate analysis of results from 395 Dutch children aged 42 months born to mothers who were environmentally exposed to 'background' levels of PCB and dioxin showed cognitive effects that were proportional to the degree of in utero exposure (49). A recent report of 171 mother-infant pairs from Germany (50), noted a negative association between prenatal and postnatal PCB exposure and Bayley Scales of Infant Development scores. In this study, assessment using the HOME scale indicated a positive effect from 30 months that was equal to the negative impact of PCB exposure. While the Great Lakes' (48) and Dutch (49) authors found no significant effects from postnatal exposure through breast milk, the authors of the German study (50) reported a negative effect related to the PCB content of breast milk received postnatally. The basic chemical structure of PCBs has some resemblance to thyroxin. While the mechanism of action of PCBs on the developing nervous system is not fully understood, there is evidence that at least some of the effect is due to influences on thyroid metabolism and thyroid hormone action (51).

Solvents

Organic solvents are widely used in industry in the manufacture of rubber, plastics, degreasing and cleansing agents. They are also used in dry cleaning. Many solvents, such as benzene, toluene, xylene and trichloroethylene, are highly volatile (the so-called VOCs), and most are lipophylic. The majority are neurodepressants. The adverse effects of ethyl alcohol on the developing nervous system are too well known to be discussed in the present paper. Studies indicate that other solvents, such as toluene (52) and xylene (53), are also neurotoxic to animal fetuses, and result in neuromotor and behavioural effects. Features, including intrauterine growth restriction, microcephaly, neurodevelopmental defects and dysmorphism resembling that of fetal alcohol syndrome were described in 18 children after heavy maternal exposure to toluene from regular glue or spray-paint sniffing during pregnancy (54). Additionally, some are carcinogens, for example benzene (55), which is used in the rubber industry, present in paints, vehicle emissions and tobacco smoke. The benzene metabolite muconic acid was found in the urine of 57 young inner city children identified as being 'at risk' on the basis of high blood lead levels; the levels varied with the time of day and duration of street activity. The benzene exposure was presumed to be due to the inhalation of vehicle exhaust fumes and tobacco smoke (56).

Airborne pollutants

Airborne pollutants include particulates, sulfur dioxide, oxides of nitrogen, acid aerosols, ground-level ozone, and 'air toxics' such as tobacco smoke and VOCs, including benzene, which may be transported in air currents. They vary in quantity, depending on location and the prevailing circumstances. Both outdoor and indoor air pollution are important, but the latter is especially important because children spend up to 90% of their time in the home, at school and on transportation vehicles (57).

Particulates: Particulates vary in size and chemical composition. They originate from many sources, especially the burning of fossil fuels in vehicle engines, furnaces and gas-stoves, electricity production and incinerators. Smaller particles, those less than 2.5 microns in diameter (particulate matter [PM] 2.5), reach the distal airways and are more damaging than larger PM 10 particles. Inhalation of PM2.5 particles results in reduced pulmonary function and distal airway disease (58).

Sulfur dioxide: Sulfur dioxide originates from coal and oil burning furnaces, the burning of natural gas and, to a varying extent, from diesel fumes. While sulfur dioxide is a direct respiratory irritant, it readily dissolves in water and reacts to form acid aerosol particulates, including sulfuric acid.

Oxides of nitrogen: Nitrous oxide and nitrogen dioxide result mainly from the burning of fossil fuels. Nitrogen dioxide is an airway irritant and at a concentration of 0.3 ppm (comparable to peak urban values), it was shown to potentiate exercise-induced bronchospasm in 15 subjects with asthma (59). While they are present in indoor air from gas stoves, kerosene heaters, Zambonis, etc, nitrogen oxides have a particular role in the formation of ground level ozone in outdoor air.

Ground level ozone: Ground level ozone is formed when

oxides of nitrogen react with oxygen and VOCs under the influence of sunlight and warmth. This mixture, combined with other particulates, comprises the 'smog' of the hot summer months (60). Ozone levels are highest during the daytime in the summer and especially downwind from coal-burning power plants and industries, and around major traffic arteries and interchanges. After 18 h of inhaling 0.2 ppm of ozone, 14 healthy patients showed migration of inflammatory cells into bronchial lavage and acute inflammation of the mucosa in bronchial biopsies (61). Increased mucosal permeability also occured in another study of eight healthy adults (62). It has been suggested that ozone affects lung growth through effects that occur at the alveolar level (63).

MAJOR HEALTH EFFECTS

While there is very extensive research and clinical literature on the health effects of environmental contaminants, until recently it mainly referred to work with adult animals and humans. More recently, there has been a rapid expansion of research involving pregnant and young animals, and in studies involving pregnant women and their children, for example, through the use of biomarkers and case control studies. However, it is clear that there is a need for more laboratory, clinical and epidemiological research in this area, and especially into fetal effects. Information on the long term implications of fetal and early childhood exposures for the adult is particularly lacking. Prospective, long term population studies with exposure data that are collected during fetal life or during early infancy are urgently needed.

The major effects discussed below are those on neurobehavioural development, the immune and endocrine systems, childhood cancer, asthma and congenital malformations.

Neurobehavioural developmental effects

The effects of metals, especially lead, on the developing nervous system have been the subject of intensive clinical research. The long story of attempts to prove the serious effects of environmental lead on children's health was one of persistence by paediatric clinical researchers and biochemists to overcome enormous resistance from industrial interests. It is a 'cautionary tale' that has recently been well described (13). The acute neurotoxic effects of lead are well known and will not be discussed. Subclinical chronic lead toxicity has affected many North American children in the past and is a continuing problem for children in the developing world. Body burdens of lead in children that were formerly deemed acceptable have been shown to be associated with behavioural problems. High bone lead concentrations in 212 children aged seven to 11 years involved in a longitudinal study of the developmental course of delinquency correlated with increased easy distractibility, attention deficit disorder with hyperactivity, delinquent behaviour and aggression (64). Based on a meta-analysis of studies of lead exposure, it was calculated that for the rise from 10 μg/dL to 20 μg/dL in blood lead values, there is an average loss of 2.6 IQ points (65). As noted above, the burden of lead in the environment has been reduced substantially over the past 20 years. Despite this reduction, the prevalence of neurobehavioural disorders appears to have risen (66). Several factors could be responsible, including increased reporting; major social changes affecting families; the fact that the population affected were mainly children living in disadvantaged circumstances where other environmental contaminants may now be problematic; and the widespread presence of other contaminants, such as pesticides and incineration products, in the typical environments of children.

Research in the past 20 years on the cellular processes involved in brain growth has enabled a much better understanding of the effects of pollutants on the growing brain. Lead, for example, is known to interfere with cell proliferation, cell differentiation, synapse formation and apoptosis, and to alter the levels of neurotransmitters and the density of dopamine receptors (67,68). Similarly, understanding of the importance of neurotransmitters in the control of fetal neuronal proliferation and differentiation (69) may explain some of the toxic effects observed in animals exposed to pesticides that act through acetylcholinesterase.

Exposures to toxic levels of mercury and PCBs that have occurred through environmental 'accidents' have been shown to result in IQ deficits and neurobehavioural disabilities such as ataxia, Parkinsonism, attention deficit disorders and poor school performance (3,4). However, the effects of simultaneous low level exposure to a wide range of environmental contaminants in utero and in early infancy, which is now the international norm (24,70,71), are as yet uncertain. The concerning findings in children that were reported in the Great Lakes, Dutch and German studies noted above, indicated an effect on IQ of ambient PCBs. The possibility of effects on Canadian Aboriginal children, especially those of the Arctic who are at the high end of this norm, are of concern (32). The use of pesticides to control garden and lawn weeds must be questioned because it adds unnecessarily to children's total exposure to contaminants. Reduced coordination, memory deficits, poor control of fine movements and the inability to 'draw a man', were recently reported in 33 Mexican children, who along with their families, had been regularly exposed to mixtures of pesticides in agricultural use (72).

Immune system effects

Once again, the majority of studies have, until recently, involved human adults and animals. A report of a recent workshop on developmental immunotoxicology reviewed animal studies, mainly with rodents (73). The effects of Chlordane, a dioxin, lead, benzene, and diethylstilbestrol (DES) suppressed normal development of mouse thymus (37) and specific progenitor cells of the T and B lympho-

cyte series. The suppression of cell-mediated immunity (graft versus host responses) and of natural killer cell activity were also seen (74). The report proposed the existence of multiple toxicological-dependent 'windows' of increased vulnerability that could contribute to the postnatal effects of developmental immunotoxicant exposure.

The young infants born to the Taiwanese mothers exposed to high levels of PCBs in pregnancy experienced excessive episodes of bronchitis and pneumonia. The affected children had reduced serum immune globulin A and immune globulin M concentrations, and reduced T-cell series compared with matched control children, indicating that cell-mediated immunity was dysfunctional (73). A recent report of a study of 118 Nunavik infants followed completely for one year did not find a relationship between total first year infections and intrauterine organochlorine exposure, as was indicated by early breast milk sampling. However, while otitis media affected about 80% of all infants in the study (those who were breast milk and formula fed), the risk of acute and recurrent episodes between age four and seven months correlated with prenatal exposure to organochlorines (75). While white blood cell concentrations, especially CD4 lymphocytes, were lower in breastfed babies during their first three months in this study, there were no clinically relevant differences noted with regard to immunological parameters, nor were they associated with prenatal organochlorine exposure.

Although widely suspected, to date it seems that it has not been possible to demonstrate a mechanism, if any exists, to relate immunotoxicant exposure to the enhanced T helper cell (Th) 2 responsiveness described in atopic disorders (76).

Endocrine disruption

The estrogenic effects of DDT on wildlife have been recognized for many years, and the tragic results of DES that was given to pregnant women are well known. The effects of pesticides and many industrial chemicals on the endocrine system were recently summarized (77,78). Endocrine disrupters can act directly by blocking natural hormones from binding with their receptors and by mimicking natural hormones through binding to receptors. Indirectly, they can interfere with hormone production and with transport-binding proteins. Experimental studies, mainly with rodents, have confirmed that some former pesticides, including DDT, Chlordane and methoxychlor, and dioxins, have many adverse effects, depending on their enhancing or inhibiting effects, which include early or late onset of puberty, abnormal ovarian cycling, hypospadias, hypospermia, delayed testicular descent and abnormal sex differentiation (78).

There are few reports of direct endocrine disruptive effects on children. These include the effects of DES, and the disruption of thyroid hormone production by PCB and PCB congeners that occur in utero through several mechanisms such as displacement from transthyretin, increased thyroxine turnover (51), or other more complex endocrine-mediated effects (79) that may result in intellectual impairment (48,49,50). One of the reviews referred to above (78), tabulated very worrisome trends in the general population that are presumed to be related to disturbed endocrine function. These trends include the increasing prevalence of hypospadias, cryptochidism, testicular, breast and prostate cancer, reduced sperm count, earlier onset of pubertal breast changes, and a shift toward females in the human sex ratio. The rate of change noted in some of the studies was up to 5%/ year, a rate that cannot be sustained for long without major effects on the health of societies. International control of the release of the offending substances has, therefore, become vital. Because endocrine disrupting chemicals are already widely distributed throughout the world, measures must also be sought to reduce or minimize their effects.

Childhood cancer

The relative rarity of cancer in childhood has made it difficult to evaluate the role of toxicants in its etiology. While it has been suggested that a 25% increase has occurred in the past 25 years (80), this assessment is currently under review. Three instances of prenatal exposure resulting in childhood cancer are well recognized. First, DES resulted in clear cell adenocarcinoma of the vagina in daughters of treated women (74). Second, it is generally accepted that the risk of leukemia in childhood is increased by the exposure of the fetus to prenatal maternal diagnostic x-rays (82). Third, gamma radiation from the Chernobyl disaster has resulted in up to a 15-fold increase in thyroid cancer in children throughout the region affected, and much higher increases in the most highly exposed areas (83). Several recent discussions of childhood cancer in the Amercian literature have noted an increased incidence of acute lymphatic leukemia, non-Hodgkin's lymphoma, and tumours of the brain and bone (84-86). According to Statistics Canada, similar increases of these specific cancers have not been seen in children in this country (87); an increase in the age-adjusted rates for the general population was noted in a recent review (55).

An analysis of parental occupational exposure as a risk factor for childhood cancers concluded that there was evidence linking early childhood leukemia with parental exposure to solvents, paints and the motor vehicle industry in mechanics, painters and service station operators; and childhood neural tumours with paternal paint exposure (88). With regard to other contaminants, a recent review of human epidemiological studies of children was inconclusive, noting methodological challenges and inadequacies. Studies of experimental animals included in this review showed definite evidence of effects, but at higher exposures than would usually occur (78). A further review of studies of pesticides with regard to specific, common childhood cancers, while recognizing methodological limitations, stated that "increased risks

are of greater magnitude than those observed in pesticide-exposed adults", and concluded that there is potential to prevent at least some childhood cancer by limiting pesticide exposure (88). The reviews repeatedly note uncertainty due to the lack of adequate exposure data in case control studies, and the need for large numbers of subjects in both case control and cohort studies. Clearly, there is a need for prospective collection of exposure information and extensive studies of biomarkers from large numbers of children, such as could occur through a national collaborative research program.

Asthma

The effects of indoor and outdoor pollution on respiratory symptoms of childhood were touched on above, and include a nonspecific increase in coughing, increased rate and severity of asthma attacks, increased use of asthma medications and physician and hospital visits, permanent reduction in lung function, and increased mortality (58). It is now accepted that the worldwide prevalence of asthma in childhood has definitely increased in the past 20 years. Health Canada reported a prevalence of 11.2% in children from birth to 14 years of age in 1994/95 compared with 2.4% in 1978/79 (87). The reasons for the increase are unknown, but because such a change is not likely to be genetic, environmental factors are being sought. The airborne pollutants discussed above, and biological contaminants such as toxigenic moulds (90), are linked with exacerbations and the severity of asthma attacks rather than its etiology.

A recent report of 1035 children followed from birth suggested that exposure to infections in early infancy, through siblings or childcare, protects from wheezing and asthma in later childhood (91). The authors proposed that the stimulation of type 1T helper cells' response by early infection inhibits Th 2 helper cells predominant in early childhood, thereby allowing expansion and maturation of Th 2 memory cells with the development of an atopic phenotype. Other authors have suggested that immunotoxicants, such as lead, polyaliphatic hydrocarbons from diesel fumes and tobacco smoke, operate through a similar process (92).

An understanding of the factors that underlie the increase in asthma, a troubling disease that affects children, requires more research; however, in the interim, children need protection from the many factors in their indoor and outdoor air environments that aggravate their condition (93,94).

Congenital malformations

Although teratogenic effects of organochlorine pesticides have been recognized in birds, animals and reptiles since the 1950s, the relationship of the present day maternal body burden of contaminants to malformations in humans, if any, is yet to be defined. The increased prevalence of genital abnormalities and a possible association to endocrine disruptors was discussed above. A recent Canadian prospective controlled study of 75 women who developed symptoms from occupational exposure to organic solvents noted a 13-fold increase in major congenital malformations (95). Attempts have been made to link clusters of specific anomalies to specific contaminants, for example, an attempt was made during litigation to link the recent sudden excess of anophthalmia to the herbicide Benomyl which was reported in the media, but definite proof of association was lacking.

CHILDHOOD TOXICANT EXPOSURES IN THE CANADIAN CONTEXT

The above discussion focused on accepted research findings about the effects of toxicants on the fetus and child. Of necessity, most of the data refer either to definite episodes involving specific communities where pregnant women and/or children have been affected by notable overdose exposures or to research with animals. Data involving Canadian children are relatively limited, and comparable poisoning events have not been reported. Moreover, with few exceptions, such as children of Inuit and other Aboriginal families, and children living around toxic waste sites, exposure of Canadian children is limited to the very low doses of the numerous toxicants encountered in their parents' and their own environments. Canadian environments range from natural pristine to downtown urban and obviously polluted areas; none are entirely free of contamination, but the degree varies greatly, and even pristine areas have yielded worrisome findings. Some urban areas are so affected that considerations of environmental justice have been invoked (96).

The possible effects on Canadian children of their multiple, low-dose childhood exposures are essentially unknown, especially with regard to the developing fetal brain and adult-onset disorders. Effects on wildlife, the few animal studies of multiple exposures undertaken, and data from studies of children and adults cited in this review suggest that the responsible attitude is to suspect the possibility of covert effects, make every effort to limit exposures, and to eliminate or restrict the use of substances now known to have toxic effects or to be converted into active chemicals such as endocrine disrupters, carcinogens and immunotoxins. Clearly, the great need for an expansion of research in this area of health effects is being recognized by universities and Canada's national research bodies.

CONTROL OF ENVIRONMENTAL CONTAMINANTS: RISK ASSESMENT AND THE PRECAUTIONARY PRINCIPLE

It is evident from the information given above that contamination of the global environment with toxic chemicals, many of which are extraordinarily persistent, has reached a level where control has become vital, and that control measures used to date have been insufficient to protect human life into a sustainable future. Physicians, especially those caring for children and pregnant women,

need to become involved in advocating for efforts to contain and curtail chemical pollution of the earth's ecosystems. The following section of the present paper briefly describes the limitations of risk assessment that currently guides regulatory measures; provides an overview of the precautionary principle, agreeing with its proponents that it should be accepted into legislation and overarch other regulatory policies; and, finally, suggests ways in which physicians can take action to promote safer environments for children.

Limitations of risk assessment

When science-based risk assessment followed by risk management was introduced about 50 years ago, it was intended to guide regulations for aircraft safety and the safety of nuclear power production. However, its use quickly spread to applications in the environment, health education and transportation. In a recent publication by the Network for Environmental Risk Assessment and Management, it was stated that "The essence of risk management is the systematic and comprehensive identification, estimation and evaluation of risk scenarios followed by careful selection of risk control options to reduce risks" (97). Unfortunately, although this process claims to be 'scientifically sound' and deals "exclusively with numerically quantifiable scientific data and statistical methods to analyze that data", it is inordinately slow, is often prohibitively expensive and, eventually, is shown to have been inadequate. For example, it failed to anticipate such serious effects as endocrine disruption, Arctic drift and the bioaccumulation of pollutants, and the loss of stratospheric ozone.

Risk assessment cannot respond to the diversity, complexity and rate of introduction of today's biological and chemical products, particularly in view of the many unknown factors that are related to effects on human health. Insofar as human health is concerned, risk assessment is based mainly on research with animals and observations of toxic effects in humans. The majority of exposure studies are with a single chemical under question; they do not mimic concurrent exposure to multiple synthetic substances that is today's human experience. In this regard, the adipose tissue of American citizens is stated to contain about 700 synthetic organic chemicals (98). While it is usually assumed that effects are simply additive or inhibitory, in fact, the most common effect is at least multiplicative. An extreme example of this synergy is the effect of PCBs on hepatic porphyrins in the presence of dioxin. A dose of PCB that alone will cause a 1.5 times increase in porphyrins will, in the presence of dioxin at a dose that alone produces no measurable effect, result in a 650-fold porphyrin increase (98). The majority of known chemicals have yet to be toxicity tested. Such chemicals are presumed to be harmless until a hazard becomes apparent, are assigned zero risk and then are essentially unrestricted (98). Moreover, in industrial processes, many chemicals are produced that have yet to be identified. For example, while over 300 organochlorine by-products of chlorine-bleach pulp mills have been identified and include chlorinated dioxins, furans and methylsulphones, these identified substances account for only 3% to 10% of all organically based chlorine in the effluent (98).

Both cost-benefit and risk-benefit analyses are carried out on the basis of risk assessment and, indeed, are viewed as being important in regulatory policy formulation. The foregoing discussion indicates that, in most instances, such analyses inevitably are simplistic and naive. While individual studies may present their results with accuracy, the variability of results from other authors using subtle differences in data, weighting and/or included variables may result in radically different interpretations. For example, risk-benefit costs associated with electrical energy production from the use of coal power quoted in the literature range from $20 to less than 0.04 cents/kW h (99).

The *Domestic Substances List of the Canadian Environmental Protection Act* contains about 23,000 substances; most of the many thousands of substances identified in the period before current regulations came into effect and have yet to be fully assessed. The regulation of the production and release of chemicals through the risk assessment process has major limitations – it proceeds far slower than human ingenuity in inventing the chemicals. Thus, although between 500 and 1000 new substances are produced in the United States each year, the United States National Toxicology Program fully assesses only 10 to 20 new substances per year (98). The costs of full risk assessment, even of newly produced chemicals are prohibitive; in the United States National Toxicology Program, an abbreviated 13-week single species toxicology test of all the interactions in a mixture of 25 chemicals would require 33 million experiments at a cost of three trillion dollars (98).

Although it has obviously served industry well, risk assessment has placed humans, especially children, at risk from unknown and unanticipated effects. Moreover, demand by industrial interests for scientific proof of direct causal association has resulted in long delays in the introduction of controls or withdrawal of some substances shown to be toxic. Those interested in further information on risk assessment are referred to *Enivronmental Health Risk Management: A Primer for Canadians* (97), *Environment Standard Setting and Children's Health (*the recent report of the Canadian Environmental Law Association and Ontario College of Family Physicians) (100) and a recent series of articles on the topic (98,99,101-106). Risk assessment certainly has a place in the regulatory process and must continue, but society currently needs policies that are more responsive to early warning signs. Dr Herbert Needleman's statement (1) quoted at the beginning of this paper must be viewed with enormous concern by all who care for children's health and well-being. Of particular concern to paediatricians must be that, in the past, the focus of regu-

latory measures was on the working adult, and the special vulnerability of the developing child was inadequately recognized. The precautionary principle discussed briefly below and in greater detail in the references quoted appears to offer a means to move forward with greater hope for safety in the regulation of chemicals.

The precautionary principle

The precautionary principle was introduced in Germany as the 'Vorsorgeprinzip' or 'foresight principle' about 30 years ago to speed the regulatory process for assessing policy decisions. It has undergone much discussion and modification since it was introduced. One widely adopted version resulted from a United Nations meeting in Rio de Janiero in 1992; the United Nations *Declaration on the Environment and Development*, Principle 15, states:

> *In order to protect the environment the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost effective measures to prevent environmental degradation. (107)*

While this 'Rio version' of the principle recognized the need to take protective measures in the absence of full scientific certainty, the definition refers to an *approach* rather than a *'principle'*, and it requires *threats of serious or irreversible damage* and that measures *should be cost effective.* Physicians, especially those who work with children (who mostly lack autonomy), must question whether this utilitarian position is ethical when dealing with threats against human life, particularly of future generations. Although this restrictive version of the principle has offered a compromise acceptable to many industrial interests vis-à-vis risk management, it is seen by others in industry to be 'protectionist', and not to be 'least-trade-restrictive', a standard applied by the World Trade Organization (103). It has, however, been adopted into law by several European countries and is referred to in the recently revised *Canadian Environmental Protection Act* (108).

Compared with risk assessment, the precautionary principle has been viewed by some of its critics as being invalid and simplistic, and likely to promote dubious science (109,110). The intent of the precautionary principle is not to abandon scientific assessment, but it does challenge scientists to think differently about the conduct of studies and communication of their results (111). It proposes earlier acknowledgement of possible risk, and greater caution regarding the introduction of substances and activities with action based on the weight of evidence when a potential for adverse effects is recognized in related compounds, in animal studies and/or from human surveillance. In the past, under risk assessment, major industrial investment in a new product has often occurred while the risk assessment process was still in progress. The demonstration of potential harms has then been met with calls for absolute proof of toxicity that may be impossible to fill because of prohibitions against the 'necessary' controlled studies in human subjects. The protracted history of the reduction of the use of lead referred to previously exemplifies such a process. The individual, societal and economic costs, calculated to be billions of dollars (112), were too great for a similar disaster ever to be repeated. Compared with risk assessment, the precautionary principle attempts to take account of a wider array of variables, including the uncertainties related to the effects of toxic substances and health outcomes, and, consequently, is even less suited to cost-benefit or risk-benefit analysis. Where cost-benefit analyses are available and deemed valid, however, they would be useful input into decision-making based on the precautionary principle. Once it has been applied to a member of class of chemicals or activities, generalization to the class or activity may be possible. An interesting case study of its application to the use of genetically modified crops is available (99).

The precautionary principle is being viewed as the overarching principle to protect future societies while enabling continued cautious production and use of new chemicals to serve them (93). A more recent version of it has been widely promulgated following a 1998 meeting of the United States Science and Environmental Health Network at Racine, Wisconsin. The so-called 'Wingspread version' states:

> *When an activity raises threats of harm in human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof. The process of applying the Precautionary Principle should be open, informed, and democratic and must include potentially affected parties. It must also involve an examination of the full range of alternatives, including no action. (113)*

Important features of this version of the precautionary principle are that it is indeed a *principle*, not simply an *approach*; that it does not require 'evidence of *serious or irreversible* threat'; that *burden of proof and persuasion lies with the proponent of the activity*; and that it does not require that measures should be *cost effective*. It has four critical elements of precaution: prompt action, even in scientific uncertainty; burden of proof and persuasion on proponents; transparency; and the assessment of alternatives (102). This recent version of the principle has been

widely welcomed in international environmental circles and, will be used to guide future environmental policies for societies seeking greater safety for their members.

PHYSICIANS' OPPORTUNITIES TO MINIMIZE CONTAMINANT RISKS TO CHILDREN

Many opportunities exist for physicians to improve their understanding of the role of contaminants in childhood illness while at the same time reducing the likelihood that future patients will be affected by environmental contaminants. Suggestions include the following.

- Follow a program of personal education with regard to the issues of environmental contamination.
- Exemplify environmental concern through self-discipline with regard to environmental contamination. Whether working in an office or a hospital, certain questions should be asked. Is the production of waste minimized? Is waste disposed of appropriately? Is plastic separated from materials to be incinerated? Are all suitable materials recycled?
- Provide patient educational materials, and offer educational sessions to office and hospital staff, and community groups on the broad issues regarding children's environmental health and on measures to minimize children's exposures to contaminants.
- Establish an exposure database by seeking a history of environmental exposures when taking a child's medical history. Such a history should include the following:
  - housing conditions, including proximity to sources of contaminants such as industries, waste dumps, municipal incinerators and major traffic interchanges;
  - the possibility of toxic exposures of the child's mother before or during her pregnancy;
  - a history of the occupations of parents, including industrial and farming activities;
  - the use of pesticides in the child's home or other environments;
  - possible school, hobby or sports exposures;
  - age at, circumstances and duration of actual exposures; and
  - recent or distant history of dietary exposure, for example, regular consumption of sport fish or 'country foods'.

While such an enquiry will not be feasible in all instances, such detail becomes essential when assessing children with congenital malformations, neurobehavioural disorders, neoplasia, allergies or features compatible with endocrine dysfunction.

CONCLUSIONS

The present paper has provided a brief overview of the susceptibility of the fetus and child to environmental contaminants, briefly described the principal contaminants and their known effects on children's health, and has tried to place this knowledge in the context of Canada in 2001. Additionally, because physicians are in a strong position to effect change, the vital need for improved regulation and control of the production and use of chemicals – new and old – has been addressed. The limitations of the system under which most industrialized countries currently operate in this regard, and the potential for improvement have been described. In addition to the educational opportunities and need for patient advocacy that it creates, environmental contamination is clearly a huge area of rapidly expanding knowledge, with many opportunities for much needed further research. Aspects relating to the environment, such as the impact of climate change, ecosystem health or sustainable development, have not been addressed. These topics are addressed in many other sources; for example, they were briefly summarized in the third edition of *The Health of Canada's Children* (66).

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