

The Faroes Statement: Human Health Effects of Developmental Exposure to Chemicals in Our Environment

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The periods of embryonic, foetal and infant development are remarkably susceptible to environmental hazards. Toxic exposures to chemical pollutants during these windows of increased susceptibility can cause disease and disability in infants, children and across the entire span of human life. Among the effects of toxic exposures recognized in the past have been spontaneous abortion, congenital malformations, lowered birthweight and other adverse effects. These outcomes may be readily apparent. However, even subtle changes caused by chemical exposures during early development may lead to important functional deficits and increased risks of disease later in life. The timing of exposure during early life has therefore become a crucial factor to be considered in toxicological assessments.

During 20–24 May 2007, researchers in the fields of environmental health, environmental chemistry, developmental biology, toxicology, epidemiology, nutrition and paediatrics gathered at the International Conference on Fetal Programming and Developmental Toxicity, in Tórshavn, Faroe Islands. The conference goal was to highlight new insights into the effects of prenatal and early postnatal exposure to

chemical agents, and their sustained effects on the individual throughout the lifespan. The conference brought together researchers to focus on human data and the translation of laboratory results to elucidate the environmental risks to human health.

Research State of the Art

The developing embryo and foetus are extraordinarily susceptible to perturbation of the intrauterine environment. Chemical exposures during prenatal and early postnatal life can bring about important effects on gene expression, which may predispose to disease during adolescence and adult life. Some environmental chemicals can alter gene expression by DNA methylation and chromatin remodelling. These epigenetic changes can cause lasting functional changes in specific organs and tissues and increased susceptibility to disease that may even affect successive generations.

New research on rodent models shows that developmental exposures to environmental chemicals, such as hormonally active substances (endocrine disruptors), may increase the incidence of reproductive abnormalities, metabolic disorders such as diabetes, and cancer, presumably through epigenetic mechanisms that do not involve changes to DNA sequences but which may, nevertheless, be heritable.

Prenatal exposure to diethylstilboestrol, an oestrogenic drug no longer used during pregnancy, has been shown to cause an increased risk of vaginal, uterine and breast cancer

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in human beings and animal models. In animal models, low-level developmental exposure to a plastics ingredient, bisphenol A, may increase the susceptibility to breast or prostate cancer, and prenatal exposure to vinclozoline, a common fungicide, may also promote later development of cancer. These substances are only weak carcinogens, if at all, in the adult organism but are nonetheless hazardous to the growing foetus. In addition, when exposure to a carcinogenic substance occurs during early development, the expected lifespan will exceed the normal latency period for development of the disease.

The human reproductive system is highly vulnerable to changes in the intrauterine hormonal environment. In men, there is an increase in the occurrence of testicular cancer, poor semen quality and cryptorchidism, jointly termed the testicular dysgenesis syndrome. In animals, a similar combination of outcomes is replicated by developmental exposure to certain phthalate esters. However, links between environmental chemicals and the testicular dysgenesis syndrome in human beings are still unclear, although suggestive associations have been found with maternal smoking, fertility treatment of the mother, phthalate exposure and occupational exposure to pesticides with suspected oestrogenic and anti-androgenic activity. Perinatal exposure to endocrine-disrupting chemicals, such as polychlorinated or polybrominated biphenyls or dichlorodiphenyltrichloroethane compounds, may affect puberty development and sexual maturation at adolescence. Many other environmental chemicals can cause such effects in animal models. Expression of some of these effects may be promoted by predisposing genetic traits.

The brain is particularly sensitive to toxic exposures during development, which involves a complex series of steps that must be completed in the right sequence and at the right time. Slight decrements in brain function may have serious implications for future social functioning and economic activities, even in the absence of mental retardation or obvious disease. Each neurotoxic contaminant may perhaps cause only a negligible effect, but the combination of several toxic chemicals, along with other adverse factors, such as poor nutrition, may trigger substantial decrements in brain function.

The immune system also undergoes crucial developmental maturation both before and after birth. New evidence suggests that a number of persistent and non-persistent environmental pollutants may alter the development of the immune system. Studies in a variety of species of experimental animals indicate polychlorinated biphenyls to be highly immunotoxic. While exposures of human adults show little indication of such effects, early life exposures appear capable of inducing similar aberrations in children as seen in other species. Asthma, allergic sensitization or greater susceptibility to infections may be linked to prenatal or early postnatal chemical exposures. In addition, because of multiple interactions between the immune and nervous systems, abnormal maturation of immune responsiveness may also be implicated in some neurodevelopmental disorders.

While the research on developmental toxic effects has, to date, emphasized maternal exposures and the infant environment, the possibility exists that paternal exposures may also

affect the child's development. Experimental studies suggest that ionizing radiation, smoking and certain environmental chemicals may be of importance, and that some exposures may affect the health and development of children, as well as the sex ratio of the offspring.

Conclusions

Three aspects of children's health are important in conjunction with developmental toxicity risks. First, the mother's chemical body burden will be shared with her foetus or neonate, and the child may, in some instances, be exposed to larger doses relative to the body weight. Second, susceptibility to a wide range of adverse effects is increased during development, from preconception through adolescence, depending on the organ system. Third, developmental exposures to environmental chemicals can lead to life-long functional deficits and disease.

Research into the environmental influence on developmental programming of health and disease has, therefore, led to a new paradigm of toxicologic understanding. The old paradigm, developed over four centuries ago by Paracelsus, was that 'the dose makes the poison'. However, for exposures sustained during early development, another critical, but largely ignored, issue is that 'the timing makes the poison'. This extended paradigm deserves wide attention to protect the foetus and child against preventable hazards.

These insights derive in part from numerous animal studies indicating that events during the foetal and early postnatal period may be responsible for reproductive, immunological, neurobehavioural, cardiovascular and endocrine dysfunctions and diseases, including certain cancers and obesity. Some of these adverse effects have been linked to environmental chemicals at realistic human exposure levels (i.e. levels similar to those occurring from environmental sources).

Among the mechanisms involved, particular concern is raised about changes in gene expression due to altered epigenetic marking, which not only may lead to increased susceptibility to diseases later in life, but may, in some cases, also affect subsequent generations.

Most chronic disease processes are characterized by multi-causality and complexity. Understanding such processes requires a broad systems approach that focuses on integrative biology within socio-environmental contexts.

Recommendations

Studies on the aetiology of human disease need to incorporate early development and characterize appropriately the factors that determine organ functions and subsequent disease risks. Such associations can best be examined in long-term prospective studies, and existing and planned pregnancy or birth cohorts should be utilized for this purpose.

The aetiology of human disease can be better understood through cross-disciplinary approaches, translation of animal data, better exposure biomarkers and understanding individual susceptibility. Improved communication needs to be

stimulated among the scientific disciplines involved and between scientists and policy-makers.

Environmental chemical exposure assessment should emphasize the time period of early development. Exposure data already routinely collected should be applied, when feasible, in epidemiological studies. In addition, cord blood, cord tissue, human milk and other biological samples should be collected for assessment of exposure biomarkers and for determination of gene expression changes.

Because human beings are exposed to numerous chemicals during development and throughout life, mixed exposures need to be considered in a life-course approach to disease. Other factors, such as nutrition, other lifestyle factors and societal environment, need to be considered for additive or interactive effects. This research should also capitalize on the ability of genetic variation and gene–environment interaction to explore the causal nature of environmental exposures with respect to health outcomes.

Risk assessment of environmental chemicals needs to take into account the susceptibility of early development and the long-term implications of adverse programming in a variety of organ systems. Although test protocols exist to assess reproductive toxicity, neurodevelopmental toxicity and immune toxicity, such tests are not routinely used, and the potential for such effects is, therefore, not necessarily considered in decisions on safety levels of environmental exposures.

The accumulated research evidence suggests that prevention efforts against toxic exposures to environmental chemicals should focus on protecting the embryo, foetus and small

child as highly vulnerable populations. Given the ubiquitous exposure to many environmental chemicals, there needs to be renewed efforts to prevent harm. Healthier solutions should be researched and proposed in future work. Prevention should not await definitive evidence of causality when delays in decision-making would lead to the propagation of toxic exposures and their long-term, harmful consequences. Current procedures, therefore, need to be revised to address the need to protect the most vulnerable life stages through greater use of precautionary approaches to exposure reduction.

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