Recognition by regulators and the regulated community alike that children’s sensitivity and susceptibility to certain substances may be much different from those of adults is changing the face of risk assessment around the world. From lead-paint mitigation efforts in older neighborhoods, to recalls of toys and other children’s products, ongoing study of children’s health issues is changing the regulatory climate and the way the world does business.

Issues

Development from ovum to adult occurs over a relatively brief, but crucially important, span of a mammal’s lifetime. Development is a fascinating, complex process that has unique vulnerabilities. Science has come to realize that development does not stop at birth when the fetus separates from the maternal organism, but continues throughout childhood and adolescence to sexual and cognitive maturity. This realization has fueled development of a study field centered on children’s health. While children share the genome of adults and express many of the same metabolic capabilities, it is clear that children are not simply small adults. In children, enzymatic pathways, organ systems, and even blood flow have not reached the full functional capacity of adults. This leads to potential differences in response to environmental challenges. The responses may be inconsequential, or they may be manifested in a variety of diseases or conditions with long-lasting impacts on health or quality of life. Thus, children’s health issues span a wide range of topics, including diseases such as asthma and childhood cancer, conditions such as low birth weight, congenital anomalies, and neurodevelopmental defects including autism and ADHD, as well as effects on the endocrine, reproductive, and immune systems.

A few examples of emerging children’s health issues are summarized below.

Lead—An Ancient and Continuing Danger for Children’s Health

The dangers of lead have been recognized among miners for centuries, and plumbism (lead toxicity) as a result of cooking in lead pots has been hypothesized to have contributed to the fall of Rome. Although the occupational hazard of lead has been well known,
it has only been in the last 50 years or so that we have understood the health effects of even very low environmental exposures and the potential for subtle neurological effects in children. Exposures to lead still occur at toxic levels and sometimes come from unexpected sources. Lead from paint and dust in older housing, lead in dust from outdoor paint, lead in the air from leaded gasoline (still used in some developing countries), lead in toys imported from other countries, and lead in water from older plumbing all may contribute to subtle but significant exposures in terms of risk to children.

EPA has regulated the amount of lead that is acceptable in paint and other environmental sources. The Department of Housing and Urban Development has developed regulations regarding sources of lead in housing. Also, the Consumer Product Safety Commission (CPSC), on several separate occasions, has recalled toys that were found to have unacceptable levels of lead in paint or decorations. Most recently, children’s cloth books, toy military figures, and wooden toy trains have been recalled because of components or paint found to have high lead contents.

Development of Epithelial Barrier Functions of Brain and Gut

Epithelia are important boundary layers that separate and isolate important regions of the body from each other and from the environment. Their role as barriers matures during gestation and the perinatal period. Because the barrier functions are not fully mature at birth, the neonate and infant differ from adults with respect to the ability of agents to enter important tissue spaces. An important example of this concept is the central nervous system (CNS), which requires a specialized, highly controlled environment in order to function effectively. Disruptions of the homeostatic condition of the CNS can result from disease or other pathological conditions and can lead to further physiological compromise. The tissue environment of the mature CNS is maintained by barriers that restrict the entry and exit of nutrients and other substances to and from the blood (blood-brain barrier) and to and from the cerebrospinal fluid (cerebrospinal fluid-brain barrier). The blood-brain barrier arises as the walls of the developing CNS thicken and become vascularized. In rodents, invasion of the CNS by blood vessels occurs around gestational days 10–11, the same time that increased neurogenesis begins. The permeability of the blood-brain barrier changes throughout the latter part of gestation and during the immediate postnatal period, such that the permeability of the blood-brain barrier small molecules and albumin decreases markedly (~68% decline) between the last day of gestation and 2 days after birth. Permeability diminishes further until postnatal day 10, followed by a more gradual decline over the next few weeks until the adult permeability status is attained.

A major difference between rodent and human development is the timescale over which the embryo/fetus develops. Rodent gestation is approximately 3 weeks long, whereas human development occurs over 38 weeks. Many structures that develop in utero in humans mature postnatally in rodents, leading to difficulties in using rodent data to predict hazards for humans. The rodent CNS matures predominantly after birth, whereas the human blood-brain barrier is considerably more advanced at birth. The state of the barrier function of the absorptive epithelium of the gastrointestinal tracts of experimental animals and humans, while not as well-studied as those of the CNS, also undergo differential schedules of development.

ADAF—What Is It?

In 2005, EPA refined its approach to cancer risk assessment by publishing the Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens. This guidance is intended to take into account the potential that early-life exposures may have greater potency, leading to an increased risk for cancer.
Within this guidance, EPA describes an age-dependent adjustment factor (ADAF) as a default adjustment to be used when the mode of action is determined to be mutagenic, but chemical-specific data to evaluate the difference between adults and juveniles are not available.

Several EPA regions are now including an additional safety factor (ADAF) for cancer-causing substances with a mutagenic mechanism of action, and the California Department of Environmental Protection (Cal EPA) has published a support document for derivation of adjustments that allow for early-life-stage exposures. In the Cal EPA document, the application may be extended to non-mutagenic agents and may include exposure during the third trimester of pregnancy. Also, the document discusses the possibility of applying larger factors to exposures around the time of puberty, especially in cases where mammary or reproductive organ tumors are induced. Both federal and state regulators are beginning to apply the ADAF, so it is important that scientists and managers involved in developing and assessing children’s health data understand the development and ramifications of this adjustment factor.

**The FQPA Safety Factor—Impact of Developmental Neurotoxicity Testing**

As part of the Food Quality Protection Act (FQPA) passed by Congress in 1996 for regulation of pesticides, EPA was directed to “use an additional tenfold margin of safety in assessing the risks to infants and children to take into account the potential for pre- and postnatal toxicity and the completeness of the toxicology and exposure databases.” This additional safety factor could be reduced or replaced “only if, based on reliable data, the resulting margin would be safe for infants and children.” EPA’s approach is to apply the factor, then reduce or remove it based on the data or uncertainty factors applied in the process of developing a reference dose or margin of exposure.

The potential for neurotoxic effects in the young (developmental neurotoxicity; DNT) is an area that has been of increasing concern to EPA. DNT testing guidelines were published in 1991, and data from DNT studies are often pivotal in determining the size of the FQPA factor that is retained for various pesticides. In some cases, it is clear from adult neurotoxicity data and other developmental and reproductive toxicity studies that neurotoxic effects are part of the general toxicity profile, rather than indicating greater sensitivity or susceptibility in the young. The interpretation of data from the literature, in addition to data from reports of guideline-compliant safety tests, is another area that requires evaluation for relevance and impact on the FQPA factor. In other cases, the results need to be evaluated taking into account the types of statistical analyses conducted and the overall pattern of effects within and across different neurotoxicity endpoints to determine if there is an adverse effect.

**The Technical Approach**

To assist our clients in understanding various issues in the area of children’s health, Exponent is developing webinars on specific topics that are of interest to the children’s health, regulatory, and legal communities. Each of our webinars in this series on children’s health will consist of a focused presentation of 20–25 minutes followed by 15–20 minutes of questions and discussion. The authors/presenters are listed below:

**Lead—An Ancient and Continuing Danger for Children’s Health**

Dr. Carole Kimmel

**Development of Epithelial Barrier Functions of Brain and Gut**

Dr. John DeSesso
ADAF—What Is It?
Dr. Gary Kimmel

The FQPA Safety Factor—
Impact of Developmental Neurotoxicity Testing
Drs. Carole Kimmel and Abby Li

A schedule of times and dates will be finalized and sent out under separate cover.

Exponent’s Expertise
Exponent’s Reproductive and Developmental Toxicology team is led by a multidisciplinary group of senior scientists with technical insight; analytical skills; and regulatory, academic, and laboratory capabilities to address these issues. Team members average more than 25 years of experience in their complementary disciplines, and each member has contributed to one or more of the following: technical, regulatory (EPA, FDA, CSPC, EU), and expert consultancy support on health and environmental issues to commercial clients, trade associations, law firms, and government clients. Using an integrated approach, our staff advises clients on issues involving data and literature analyses concerning potential children’s health issues, testing registration, product stewardship, and litigation support.

The team includes other distinguished scientists in related scientific areas, including reproductive toxicology and risk assessment, endocrine modulation, clinical epidemiology, medical toxicology, exposure assessment, and general toxicology. The team has lent its expertise to solving challenges related to pharmaceuticals, pesticides, industrial chemicals, environmental contaminants, and medical devices. A selection of the team’s publications over the past few years is provided below. It demonstrates the breadth and depth of our capabilities.

Recent Exponent Publications and Presentations Related to Children’s Health


About Exponent Health Sciences

Exponent is a leading engineering and scientific consulting firm dedicated to providing solutions to complex problems. Exponent has one of the foremost health sciences consulting practices in the United States. Our scientists, physicians, and regulatory specialists evaluate a full range of environmental and public health issues, including potential health effects associated with environmental agents, chemicals, consumer products, food safety and nutrition, and pharmaceutical products. Our clients rely on us for incisive and objective assessments that address physical, chemical, and biological phenomena in order to arrive at solutions that can be relied upon to make important decisions. In addition, Exponent performs research and analysis in more than 90 science-and engineering-related technical disciplines.

More information about our Health practice, as well as our other capabilities, can be found at www.exponent.com.

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