

Investigating How Age and Gender Affect Internal Doses of Chemicals

Physiologically based modeling is a tool ideally suited to assessing the potential that age and gender may predispose individuals to toxic effects of chemicals. The tool also leads to more scientifically based risk assessments.

—Harvey J. Clewell III, ENVIRON Health Sciences Institute

Background

Chemical manufacturers are under increasing pressure to provide evidence that their products do not pose a particular risk to children or other populations of concern. Assessments of the potential risks from exposure to chemicals must take age- and gender-related factors into account. But that's easier said than done. Researchers are still developing an understanding of the processes that contribute to age- and gender-based differences in susceptibility to risk including differences in tissue concentrations following exposure to chemicals.

Currently, most risk assessments of chemical exposures apply crude default uncertainty factors when adjusting for variability between age groups or genders. The LRI-supported research described here has resulted in new techniques that can be used to develop refined chemical-specific adjustment factors for age and gender, improving the accuracy of risk assessments and quantifying differences in sensitivity associated with target tissue dose between different populations or life stages.

Young children and adults differ in how they absorb and metabolize nutrients, environmental contaminants, pharmaceuticals, and other chemicals. These differences can lead to age-related variations in the concentration of chemicals at the site of sensitive tissues—and thus the associated risk—when people are exposed to chemicals in the environment.

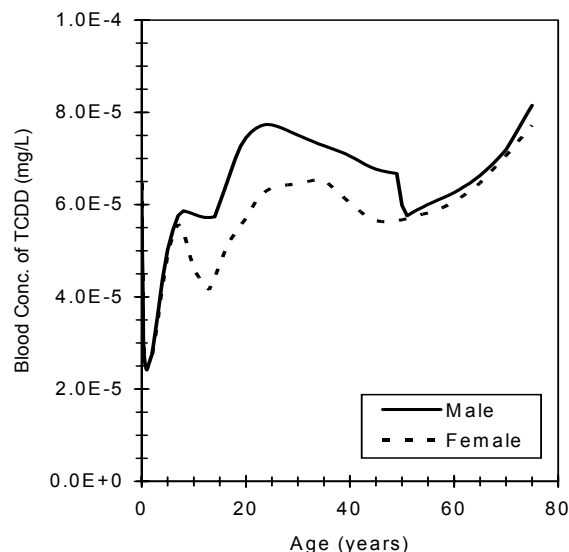
Variations in risk due to physiological or biochemical differences also may occur between males and females, and between elderly individuals and adults. Older individuals may be less efficient at detoxifying and eliminating contaminants than younger adults are, and researchers have observed gender differences in the metabolism and elimination of some compounds.

In this research, a team led by Harvey Clewell III of ENVIRON Health Sciences Institute developed models that include pharmacokinetic,

What makes some populations more biologically sensitive than others?

The level of risk associated with a given exposure to a particular chemical depends not only on what the chemical does to the body (known as pharmacodynamics or toxicodynamics) but also what the body does to the chemical (pharmacokinetics). Pharmacokinetics describes the rates at which a chemical is absorbed, distributed, metabolized, and excreted by the body. These rates and factors that affect them—such as body weight, breathing rate, blood flow, metabolism, tissue volumes—differ between young and old, as well as between males and females.

For example, below are modeled blood concentrations as a function of age for continuous oral exposure of males (solid line) and females (dashed line) to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, commonly known as dioxin) at a constant daily intake of 1 nanogram per kilogram of body weight (Clewell *et al.* 2004).



physiological, and biochemical data for different life stages. These models allow the researchers to simulate how physiological and biochemical processes change over time due to growth and aging.

Approach

Clewell and his colleagues first reviewed the scientific literature to identify available data on age- and gender-specific differences in physiological and biochemical processes that affect doses received by tissues. Based on these data, they developed mathematical equations to describe age- or gender-related changes, and incorporated the equations into a much larger physiologically based pharmacokinetic (PBPK) model. PBPK models are used widely in risk assessments for extrapolating dose-response relationships across species, such as from mouse to human. The same qualities that make PBPK models attractive for such extrapolations make them useful for predicting age- and gender-specific differences in pharmacokinetics.

The researchers applied the PBPK model to three case studies. The first case study modeled and compared changes in pharmacokinetics for a range of environmental chemicals over various life stages. The hypothesis tested was that many of the pharmacokinetic differences across age and gender are due to fundamental changes in physiological and biochemical processes. The second case study modeled the impact of age- and gender-related differences in the form and structure of the lung, along with differences in breathing rates, on the pharmacokinetics of inhaled vapors. The third case study used PBPK models to compare exposures received by the fetus through the placenta versus exposures received by the infant from its mother's milk, to demonstrate critical periods of exposure from a pharmacokinetic perspective.

Results and Implications

The results of all three case studies suggested that age-related variations in tissue doses of the chemicals tested (e.g., measured by concentrations of the chemical or its metabolized byproducts in blood or urine) generally are within a factor of two over the course of a lifetime. However, there were exceptions in very early childhood in which the dose varied by approximately a factor of ten.

These larger differences were seen shortly after birth. The models predicted that infants clear the chemicals from their systems more slowly than adults, a difference that appears to be related mainly to the immaturity of the infant's metabolic enzyme systems. The child's clearance systems mature rapidly, however, resulting in smaller differences in pharmacokinetics compared with adults (generally on the order of a factor of two or three) by the time children reach six months of age. In later years, children actually may clear chemicals more quickly than adults, apparently due to physiological changes associated with growth and activity.

In general, the models predicted fewer differences in tissue dose between males and females, although some chemicals showed significant contrasts. The concentration of perchloroethylene in the blood of females, for example, rose more rapidly than in males between ages 10 and 20. Perchloroethylene is stored in body fat, and females typically develop more body fat between ages 10 and 20 compared to males.

The results of the case studies suggest that exposure during early childhood (birth to five years) contributes only a small fraction to an individual's total lifetime exposure for a cumulative effect. However, exposure during infancy may present a window of susceptibility for short-term effects, due to the immaturity of the infant's clearance systems.

PBPK models provide a cost-effective way to obtain initial estimates of how populations at different life stages or of different genders may vary in their sensitivities to the effects of a chemical. The models also can help researchers identify and prioritize areas in which more experimental data are needed to better characterize a chemical's potential to be of special concern for a particular age group or gender.

This research provides regulatory agencies and health authorities with a scientifically defensible basis for replacing the default uncertainty factors used to develop acceptable exposure levels to chemicals.

References

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