**Evaluation of Pesticides Risks for Children**

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Introductory

Infants and young children constitute a particular population of concern in terms of exposure to pesticides (including obsolete pesticides). For various reasons (behavioral, anatomical and metabolic) children may have greater susceptibility to the adverse effects of pesticide exposure. This potential for increased susceptibility must be evaluated on a case-by-case basis however, because in some cases children (particularly older children) may have similar or even less susceptibility compared to adults.

Research has also pointed out a number of toxicological modes of action that may be of particular relevance for children's health risks. These include effects on nervous system maturation, endocrine disruption and the influence of early life exposures on development of disease later in life. Although the importance of such modes of action is not yet fully understood, particularly at low levels of exposure, these are areas of expanding research and the data obtained are expected to be useful for improving health risk assessment in this population.

Exposure-Related Susceptibilities

Exposure is a key factor in determining health risks; even the most inherently toxic chemical will pose no risk unless there is sufficient exposure. Many factors which result in an increased potential for exposure during childhood are readily apparent, particularly as regards the oral route. Children are more likely, particularly between the ages of 2 and 6, to crawl on the ground where they may pick up particles of soil, dust or chemical residues (e.g., indoor applied insecticides). They may then ingest these particles or residues via hand-to-mouth behavior, something which occurs in all individuals but is particularly prominent in children.



In addition to soil and dust *ingestion*, children also exhibit a greater intake of food and water (on a per kg-body weight basis) than adults. For example, water intakes of infants and young children are about double that of an adult on a body weight basis and intakes of particular food categories can be many times higher.

Children are also likely to have a more restricted and repetitive diet (e.g., juice rather than water, only fish sticks, only certain vegetables), which could lead to substantially different levels of chemical exposure via the diet compared to a typical adult.

Although the *oral exposure pathway* usually dominates children's exposure, other pathways may be important in certain cases. Children have an *inhalation rate* that is proportionally greater for their body size compared to an adult and thus, on a body-weight basis will have higher exposures. The same applies to *dermal exposure* because the child has a larger surface area when scaled to total body mass.

Age Dependence of Several Key Exposure Variables

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Parameter** | **Infant / Neonate** | **Young Child 3 to 5 years** | **Older Child**  **6 to 10 years** | **Teenager**  **12-18 years** | **Adult** |
| **Body Weight [kg]** | 7 | 17.5 | 29 | 57 | 70 |
| **Water Intake [L/kg.day]** | 00.4 | 00.5 | ND | 0.02 | 0.02 |
| **Breathing Rate [m3/kg.day]** | 0.64 | 0.47 | 0.34 | 0.25 | 0.19 |
| **Skin Surface Area [cm2/kg]** | ND | 417 | 338 | 293 | 257 |
| **Total Vegetable Intake [g/kg.day]** | 6.8 | 7.125 | 5.55 | 3.8 | 3.6 |
| **Total Dairy Intake [g/kg.day]** | 62.7 | 21.15 | 13.3 | 6.3 | 3.4 |

As shown in the table, the skin surface area per kg of body weight of a young child (ages 3 to 5 years) is approximately 60 percent greater than that of an adult. Practically speaking, these differences result in only a slight increase in overall dose, a difference usually overwhelmed by the difference in the *oral pathway.* They may be important in cases where the oral route of exposure is absent.

Infants and neonates also have a unique source of exposure during the early period of life – breast milk and/or baby formula – which they consume at a very high rate relative to their body weight.

Whether the child consumes formula-based milk or maternal milk can have an important bearing on exposure. While maternal milk may involve the transfer of lipophillic toxicants (e.g., chlordane, DDT) from mother to child, use of formula could be associated with increased exposure to a contaminated water supply.

Physiologically-Based Susceptibilities

The moment of birth initiates dramatic changes in physiology. From birth to the late teens, the child's body grows and matures becoming increasingly adult-like. It would be incorrect however to assume that the progression is strictly linear. The pattern of growth and development during childhood varies among different organ systems, and can be quite complex.

*Organ Size Changes*– Patterns of organ growth during childhood are highly organ specific. For example, human babies have brains that are much larger in size relative to their body compared to an adult's. This may have significant implications for chemical distribution; based on their larger relative brain size, children's brains may experience higher doses of a chemical of interest.

*Gastrointestinal System Acidity*– Stomach pH can have significant effects on the absorption of many chemicals, particularly metals and ionizable organic compounds. This would apply to pesticides that are weak acids or bases such as 2,4-D; MCPA; metasulfuron-methyl and glyphosate. The pH of the stomach is fairly neutral (pH 6-8) at birth, becomes acidic (pH 1 to 3) in the first few days of life, but then more basic during the neonatal period (pH >5). Stomach pH reaches adult levels (pH 1-3) by around 2 years of age.

*Body Water/Body Fat*– Body water and body fat percentages play an important role in determining how a chemical is distributed in the body. Tissue hydration decreases consistently with age, from about 74% in the full-term neonate, to approximately 55-60% in the adult. Body fat generally follows a more complex pattern, being relatively low at birth (14%), rising during the first few months of life, leveling off through childhood and then declining around puberty, particularly in males.

*Skin permeability*– In adults, the stratum corneum, a layer of dead highly keratinized cells on the skin surface, constitutes a barrier to *dermal penetration* of many compounds. Although not an absolute barrier (particularly for lipid soluble chemicals) the stratum corneum can substantially attenuate skin permeability. This surface layer is immature in newborns but rapidly develops and thickens during the first four months of life.

*Blood Brain Barrier*– The blood brain barrier is a multicomponent structure that prevents harmful substances from entering the brain from the blood supply. The blood-brain barrier in human infants is relatively undeveloped and displays greater permeability to drugs and other exogenous compounds until about 3 to 4 months of age. Little data exist to quantify the function of the blood-brain barrier at earlier ages.

*Developing Tissues*– Besides the specific example of the blood-brain barrier, the cells of many other tissues in the infant and young child are undergoing rapid division and maturation. These include the cells of the central nervous system, the reproductive organs and the immune system. These highly active cells are susceptible to chemical insult and if eliminated or damaged early in life may leave the individual with diminished capacity later in life.

*Elimination* – Chemicals are cleared from the body primarily via either the urine or feces (biliary excretion). Other forms of elimination, such as the excretion of some metals in the hair, have a relatively minor impact on body burden. Kidney function is relatively immature at birth but rather quickly reaches adult levels: blood filtration ability at about 1 month of age and renal tubular function by about 1 year. Maturation of biliary elimination is much slower and may only approximate adult levels when the child is several years old.

Metabolism-Based Susceptibilities

Another important component of children's potentially increased susceptibility relates to metabolic capacity. At birth, many, although not all, of the metabolic enzymes in the liver (the primary metabolizing organ) have much less capacity compared to the adult. Thus infants may metabolize many chemicals less efficiently than adults, meaning the chemicals are much more slowly eliminated and, consequently, may accumulate to higher levels. This may represent an adverse situation for chemicals which exert a direct toxic effect in the body but a less adverse situation for chemicals which must first be metabolized to a reactive intermediate (e.g., some pyrethroid insecticides).

Toxicological Modes of Action of Particular Concern for Children's Risks

In addition to behavioral or physiological factors of particular interest for assessing children's risks, there are also a number of toxicological modes of action which may be particularly important for children.

*A. Effects on Nervous System Maturation*

The development of the human brain is a remarkable and carefully coordinated process. Over the course of nervous system development, over one hundred billion neurons in the brain must find their proper location and form connections with their neighbors. Nerve fibers must become insulated with myelin in order to transmit signals with proper speed and neurons must develop the proper machinery for producing, secreting and recycling the appropriate neurotransmitters.

Evidence suggests that neurotransmitter activity in early life is necessary for proper neuron connectivity and thus exposures to chemicals which perturb neurotransmitter activity such as insecticides may interfere with this process. Concerns have been raised that doses of insecticides that are too low to cause obvious clinical effects can, if experienced in early life, interfere with neuron conditioning and lead to subtle cognitive effects.

To date, the data indicating that low level insecticide exposures can exert subtle effects on nervous system development have generally been obtained from studies in laboratory rodents. Studies in humans are less definitive, due to the influence of co-exposures to other chemicals and other important co-variables (e.g., socioeconomic status). This remains an area of active research and considerable regulatory interest.

*B. Endocrine Disruption*

The possibility that chemical exposures could disrupt the functioning of the endocrine system is another area of particular concern for children's health risks. Through the secretion of hormones (small molecules with very high affinity for specific cellular receptors), the endocrine system controls or influences many of the body’s most important processes (e.g., *thermal regulation, energy production, blood sugar concentrations, reproductive function, immune response*). Proper functioning of the endocrine system is also critical for both pre-natal and post-natal development. The concept of endocrine disruption postulates that organic chemicals such as pesticides can mimic or interfere with the function of endogenous hormones, thus leading to improper signaling.

One way to measure the ability of a chemical to cause endocrine disruption is via a competitive binding assay. Such an assay examines the ability of the chemical of interest to compete with a hormone for binding to the hormone's normal receptor. A chemical, which has the potential to dislodge a hormone like estrogen from its normal receptor at expected exposure concentrations would be an obvious endocrine disruptor. Studies have shown that pesticides are far less potent and have much lower affinity for the estrogen receptor compared to endogenous estrogen (the estrogen is the primary female sex hormone, responsible for the development and regulation of the reproductive system and the secondary sex characteristics).

The available data indicating that insecticide exposures can cause endocrine disruption in human populations are limited, with many studies in both experimental animals and humans reporting results that are difficult to interpret. The effects that have been observed appear to be associated with fairly high levels of exposure so the relevance to typical human exposures is unclear.

*C. Fetal Basis of Adult Disease*

An emerging concept in both science and regulation is the idea that exposures *in utero* (refers to unborn children)or in early childhood can predispose an individual to a disease that emerges later in life. A theory has focused on early life exposures as causative agents in Parkinson's Disease (PD). It is known that the brain contains a certain number of non-renewable dopamine producing cells and that these cells are lost in PD. When a sufficient number of these cells are lost (typically later in life) the symptoms characteristic of PD (*fine tremor, difficulties in gait*) will become manifest.

Animal studies have shown an association between prenatal exposure to some herbicides (paraquat and maneb) and the emergence of PD-like symptoms in the animals at older ages. Herbicide exposure has also been shown to be a risk factor for PD in a number of epidemiology studies. Obviously there are associations between PD and *various infections*, *brain injury*, and smoking, but nevertheless PD is one of most active areas of research concerning the long term consequences of early life pesticide exposures.

Summary

Infants and young children constitute a particular population of concern in terms of exposure to pesticides. Children may engage in particular activities (crawling, hand-to-mouth activity) that result in increased exposures to chemicals in the environment. Children also have a higher respiration rate, greater relative skin surface area, and higher relative food and water intakes than adults, each of which contributes to a greater exposure potential. Furthermore, the developing physiology and metabolic capacity of infants and young children may also create an increased toxicological susceptibility. The potential for increased susceptibility must be evaluated on a case-by-case basis however, because in some cases certain age groups may have similar or even less susceptibility compared to adults. Research has also pointed out a number of toxicological modes of action that may be of particular concern for children's risks. These include subtle effects on *nervous system development*, *endocrine disruption* and the impact of *pre- and perinatal exposures* on development of disease later in life.



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