

FACTORS INFLUENCING PESTICIDE RISKS FOR CHILDREN

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Abstract. 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.

Keywords: children, risk assessment, susceptibility

1. Introduction

Society regards with exceptional unease concerns about the effects of pesticides and other chemicals on children's health (Slovic, 1987). While children have long been regarded as a key population at risk for certain chemicals (*e.g.*, lead, methylmercury), children are a population subgroup which increasingly drives

regulations for a much broader set of chemicals. This increased emphasis may be traced to a 1993 US National Research Council (NRC) report, *Pesticides in the Diets of Infants and Children*, which considered the extent to which children differ from adults in terms the potential adverse health effects of pesticide exposures. The NRC report noted that while there is clear evidence of adult-child differences in susceptibility, children's susceptibility to pesticide exposure does not always lie in the same direction; in some cases, children may be less susceptible than adults (NRC, 1993). Relative susceptibility must therefore be examined on a case-specific basis, considering the age group of concern, the chemical in question, and the types of health effects associated with the chemical (Scheuplein et al., 2002).

Although it is common to discuss risks for "children" as a general category, this approach lacks precision because it encompasses a very diverse range of individuals, including premature infants, infants and neonates, juveniles from the ages of 1 to 12 years and teenagers. Individuals in this range exhibit an exceptionally diverse range of behaviors and physiology. Furthermore the age range of concern may be variable; in addressing soil lead exposures the USEPA focuses on children ages 0 to 6 years of age (because soil ingestion exposures in older children are similar to those in adults) whereas concerns for endocrine disruption might focus on children around the age of puberty. Thus, the first step in discussing children's risks from pesticide exposure is to recognize that risks will be age-specific and broad statements relating to "children" as a generic term may be incorrect in some cases. Given this caveat, it is correct to state that at specific ages, children may be more susceptible to certain chemical exposures than adults. This may be due to differences in behavior that contribute to chemical exposures (*e.g.*, soil ingestion), anatomical differences (*e.g.*, increased skin permeability) or metabolic differences (*e.g.*, differences in metabolic capacity). Each of these broad bases for increased susceptibility is discussed below.

2. 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. For example, studies conducted by Stanek, Calabrese

and colleagues have estimated that on a typical day, the average child might ingest between 28 and 45 milligrams of soil or dust via hand-to-mouth activity (Stanek and Calabrese, 1995). The corresponding estimate for adults is 10 mg (Stanek et al., 1997). Furthermore, while all young children engage in putting non-food objects in their mouth, some children may do so to an extreme degree, an activity known as pica (Bartrop, 1966). For such children, soil ingestion can be as high as 10-13 grams of soil or dust per day (Calabrese and Stanek, 1992). The extent of hand-to-mouth activity is highly age dependent and primarily involves children between 1 and 6 years of age. Infants do not begin crawling until 6 to 10 months of age and therefore have very limited contact with soil or flooring surfaces. Children older than 6 years have generally very limited hand-to-mouth behavior and have soil/dust ingestion levels approaching that of an adult.

TABLE 1. Age Dependence of Several Key Exposure Variables

Parameter	Infant/ Neonate	Young Child 3 to 5 years	Older Child 6-10 years	Teenager 12-18 years	Adult
Body weight (kg)	7	17.5 *	29	57	70
Water intake (L/kg-day)	0.04	0.05	ND	0.02	0.02
Breathing rate (m ³ /kg-day)	0.64	0.47	0.34	0.25	0.19
Skin surface area (cm ² /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

Source: USEPA (1997); ND – no data available

Values are approximate ratios of parameter to average body weight estimated for that age range; values were averaged for males and females where gender-specific values were provided separately.

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 (Table 1). 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. 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 (Table 2). 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 lipophilic toxicants (*e.g.*, chlordane, DDT) from mother to child, use of formula could be associated with increased exposure to a contaminated water supply.

TABLE 2. Age Dependence of Breast Milk Intake

	Infant Age			
	1 month	2 months	3 months	4 months
Breast milk intake (g/kg-day)	159 ± 24	129 ± 19	117 ± 20	111 ± 17

Source: USEPA (1997)

Data from infants that were exclusively breast fed during the first four months of life.

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 (US EPA, 1997) 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 (US EPA, 1997). As shown in Table 1, 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.

3. 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 (Figure 1). Examples include:

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.

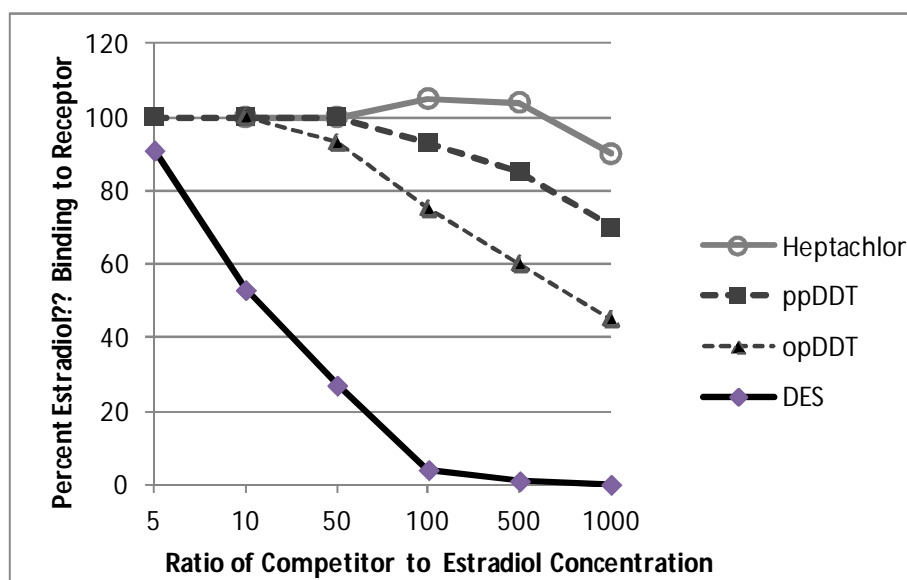


Figure 1. Important Physiological Changes Occurring During Development

GI 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 (Alcorn and McNamara, 2003).

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 (Alcorn and McNamara, 2003). 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 (Maples et al., 2005).

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 (Statz and Felgenhauer, 1983). Little data exist to quantify the function of the blood-brain barrier at earlier ages (Webster, 2008).

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 (discussed in greater detail in Section 5).

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 (Alcorn and McNamara, 2003). Maturation of biliary elimination is much slower and may only approximate adult levels when the child is several years old (Alcorn and McNamara, 2003).

4. 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).

Metabolism of many compounds involves two primary phases. Phase I reactions typically involve either breaking the molecule into smaller parts or adding oxygen to the molecule to create a reactive site (*e.g.*, heptachlor is oxidized to heptachlor epoxide). Phase II reactions typically involve attaching

a more water soluble ligand to the reactive site to enhance elimination via either the urine or bile.

Maturation of the ability to carry out Phase I reactions develops during the first few years of life. Many important Phase I reactions are carried out by a family of enzymes known as cytochrome P450s (CYP 450s). The different members of this family (called isoforms) possess substrate specificity and metabolize different types of chemicals. For example, CYP1A2, CYP2C19 and CYP3A4 are responsible for metabolism of many pesticides and other xenobiotics whereas CYP2D6 is important in the metabolism of many pharmaceuticals (Abass et al., 2012). Maturation of the CYP450 isoforms is age dependent, although many reach adult activity levels by the end of the first year of life, as indicated in Figure 2 (Alcorn and McNamara, 2002). Some isoforms (*e.g.*, CYP3A7) are also present during the fetal period and then decline over the first few months of life as adult forms become more active.

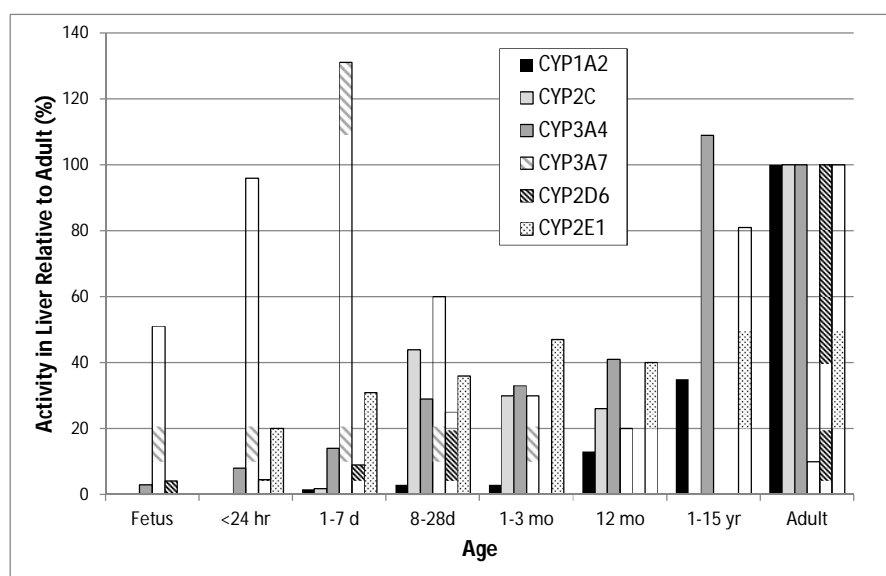


Figure 2. Maturation Pattern of Several CYP Enzymes During Development. Adapted from Alcorn and McNamara (2002).

The progression in enzyme maturation can also be illustrated with data obtained for a different Phase I enzyme, hepatic carboxylesterase. This enzyme carries out important Phase I reactions on a number of pesticides (the pyrethroids and pyrethrins) as well as a number of prodrugs (*e.g.*, the antiviral

drug oseltamivir). Pharmaceutical metabolism studies used for evaluating drug safety and efficacy allow such enzyme maturation data to be collected where it could not be ethically collected in controlled studies with pesticides. As shown in Figure 3, activity of the hCE-2 isoform of hepatic carboxylesterase is below adult levels for the first few years of life but appears to achieve adult levels (or near adult levels) for the remainder of the juvenile period. The hCE-1 isoform appears to mature somewhat later but nonetheless reaches 80% of adult levels by age 6 to 9 (Zhu et al., 2009). The phenomenon of increased enzymatic capacity during later childhood is common to many Phase I enzymes.

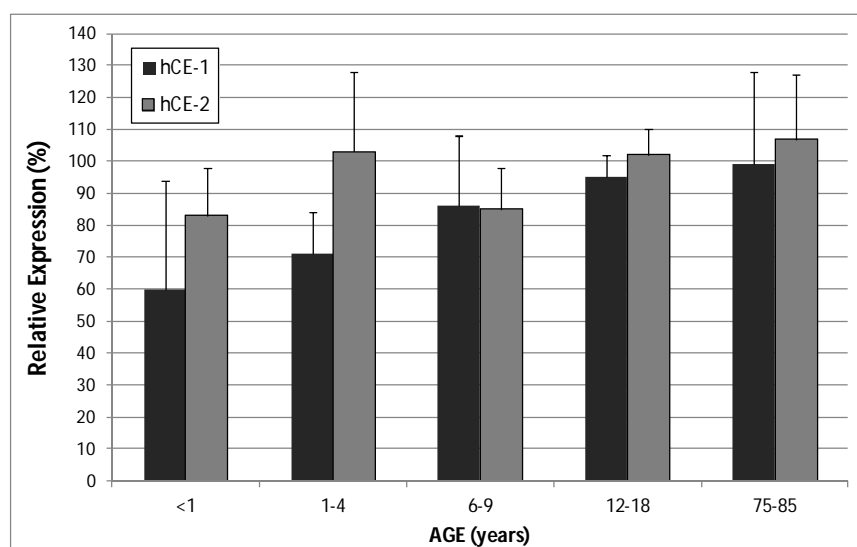


Figure 3. Maturation Pattern of Human Hepatic Carboxylesterases (CE) During Development. Relative expression of hCE isoforms in hepatic s9 fractions. Data from Zhu et al. (2009). Error bars = standard deviation.

The maturation of Phase II enzymes is typically a somewhat slower process. In adults, activated molecules (*i.e.*, Phase I reaction products) are most commonly combined with ligands such as glucuronic acid, glycine or bile salts prior to being eliminated from the body. For example, glucuronidation is important in the elimination of pyrethroids and also appears to be significant for DDT (ATSDR, 2002; 2003). The glucuronidation pathway matures rather slowly in children, not reaching adult levels until 6 to 30 months of age, depending on how competency is measured (Alcorn and McNamara, 2002). However, conjugation with sulfate is an alternative metabolic pathway that is

very active in infants and which may partially compensate for the limited glucuronidation capacity (Alcorn and McNamara, 2002; de Zwart et al., 2004). For example, the drug acetaminophen is excreted primarily as a glucuronate conjugate in adults but primarily as a sulfate conjugate in infants (Miller et al., 1976). The extent to which sulfation can be used for pesticide metabolism in infants is currently not well understood.

The examples given above indicate that, in general, the period of susceptibility in childhood may be relatively short, involving only the first few years of life. Consistent with the NRC's findings, case-specific factors may nonetheless be important. For example, a recent study has suggested that children's paraoxonase activity (an enzyme important in the toxicity of some organophosphates and carbamates) does not reach adult capacity until age 9 (Gonzalez et al., 2012). Situation-specific factors to consider include the dissociation constant (pKa), the lipid and water solubility, the distribution in the body and the specific enzymes responsible for the pesticide's metabolism. When such data are not available, they should be considered research priorities so that the potential risks for children can be reliably assessed.

5. 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. Many of these are relatively new considerations that may not have been well investigated for obsolete pesticides, most of which underwent their primary toxicological evaluation in decades past. Recent data have suggested, however, that these critical modes of action should not be overlooked.

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 (Saunders et al., 2012).

It is clear that pre-natal or post-natal insecticide exposure can have persistent effects on brain neurotransmitter activity. For example, Tang et al., (2003) exposed neonatal rats to the insecticide methyl parathion at doses ranging from 0.3 to 0.9 mg/kg-day from day 1 to 21 after birth. These treatments produced observable clinical symptoms (tremor) in the pups after treatment although they resolved between treatments. The authors observed that rats tested at post-natal day 40 showed persistent decreases in acetylcholinesterase activity and acetylcholine receptor binding at all doses tested. Although all groups showed some recovery by postnatal day 40, results for all treated animals remained statistically different from those in control animals. In another study, Gupta et al. (1985) exposed pregnant rats to methyl parathion from day 6 to 20 of pregnancy. The two doses studied were selected as either producing no frank maternal toxicity (1.0 mg/kg-day) or causing minimal visible maternal toxicity (1.5 mg/kg-day). Activity of acetylcholinesterase and choline acetyl transferase (the key enzyme in acetylcholine synthesis) was assessed in offspring at postnatal days 1, 7, 14, 21, and 28. Both doses resulted in reduced acetylcholinesterase activity on postnatal day 1 but only 1.5 mg/kg-day resulted in persistent reduction in acetylcholinesterase as well as increases in choline acetyl transferase. In parallel experiments examining behavioral effects, Gupta et al. also reported that methyl parathion exposure was not associated with behavioral deficits in most tests conducted (*e.g.*, startle response, passive avoidance, rotarod performance) but that operant behavior (assessed as learning to press a bar in response to a reward), cage emergence and accommodated locomotor activity were impaired at 1.0 mg/kg-day but not at 1.5 mg/kg-day. Operant behavior was assessed at 3 to 6 months of age, well beyond the period of exposure. The authors could not explain the paradoxical dose-response pattern but noted that U shaped dose-response curves are commonly seen in dose response curves for psychoactive drugs.

While data from animal studies suggest an effect of pre-natal or postnatal pesticide exposure on brain physiology and function, data from human studies are less definitive. For example, Rauh et al. (2006) conducted a study of 254 inner city children in the USA with potential exposures to chlorpyrifos from home application. The authors measured chlorpyrifos levels in cord plasma after birth, thus obtaining a surrogate measure of *in utero* exposure. To assess potential effects on cognitive development they used the Bailey Scales of Infant Development administered at 12, 24, and 36 months of age. Using the resulting data they developed multivariate regression models which included race,

gender, maternal IQ and education, tobacco smoke exposure and home environment as co-variables. Chlorpyrifos cord blood was divided into 2 groups, high exposure (>6.17 pg/g) and low exposure (<6.17 pg/g). The overall range in cord blood values was from <1 pg/g to 63.3 pg/g. Rauh et al. reported that prenatal chlorpyrifos exposure was associated with increased odds of some adverse neurodevelopmental outcomes. For example mental development index (MDI) and psychomotor development index (PDI) scores were significantly decreased in the high chlorpyrifos exposure group at 36 months of age, although this was not observed at 12 or 24 months. The authors also reported that the high category of gestational chlorpyrifos exposure was also associated with increased odds of developing attention problems, ADHD or pervasive developmental delay (PDD), although the confidence intervals for these outcomes were very wide (e.g., odds ratio for diagnosis of ADHD: 6.50 [1.09–38.69]).

Another human study, Torres Sanchez et al. (2007) evaluated prenatal DDT and DDE exposures and their potential effects on psychomotor development in 244 mother-child pairs living in an area of Mexico with endemic malaria. Mean serum DDE levels in the maternal population were approximately 7 ng/mL. Cognitive development was evaluated in children at different times during the first year of life using the MDI and PDI scores noted above. The authors reported that only 1st trimester DDE concentrations were associated with decreased PDI scores (-0.52 points, $p = 0.02$), MDI scores were not associated with estimates of pre-natal exposure. The authors noted their results were somewhat at odds with results of two earlier studies, one of which found no association between prenatal DDE levels and PDI and MDI scores, the other finding both scores affected. Torres-Sanchez *et al.* subsequently conducted a follow up study of this population, examining MDI and PDI scores at 12, 18, 24 and 30 months after birth. The researchers found that the previously observed effect on psychomotor development did not persist beyond 12 months of age, although it seems likely that the exposure would have continued after birth (Torres-Sanchez et al., 2009).

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 covariables (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 (USEPA, 2011). 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. For example, Blair et al. (2000) demonstrated that while the non-pesticide diethylstilbestrol (DES) was able to substantially displace estrogen from its receptor at only a 10 times higher concentration, a hundred-fold excess concentration of o,p'-DDT was required to have even a limited effect on estradiol-estrogen receptor binding (Figure 4). p,p'-DDT and heptachlor were even less effective competitors for estradiol. Thus, at very low concentrations in plasma, these pesticides would not pose a concern as anti-estrogens. However, circulating levels of estrogen/estradiol are extremely low, in the tens to hundreds of pg/mL range, and at sufficient exposure, plasma concentrations of pesticide might be substantially higher. Thus it is not only the relative binding affinity but also the circulating concentrations that must be considered when examining potential risks.

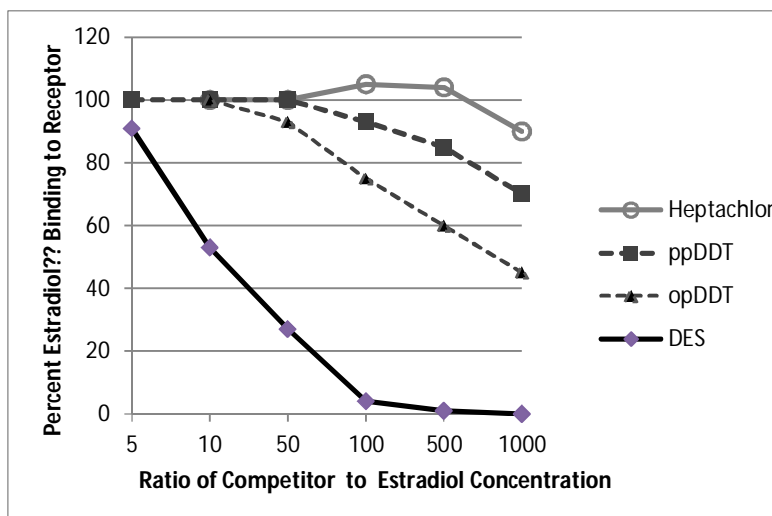


Figure 4. Relative Estrogen Receptor Binding Affinity of Several Pesticides

Beyond receptor binding studies, studies conducted in whole animals have suggested that DDT has the potential to disrupt reproductive development. For example, Hojo et al. (2006) reported delays in sexual maturation in male rats exposed *in utero* to 50 or 350 ppm DDT in the diet, although there were no deficits in reproductive function. These doses also caused alterations in serum estradiol and progesterone levels in female animals. However, both doses also caused systemic toxicity to the parental animals (tremors, liver toxicity, mortality), suggesting a limited relevance to potential human environmental exposures which would be expected to occur at levels below those causing such significant toxicity.

Studies of potential DDT effects on reproduction have also been conducted in human populations. For example, Bhatia et al. (2005) conducted a case-control study of male reproductive tract abnormalities in the San Francisco area. They reported no association between maternal serum DDT/DDE concentrations and deformities of the male reproductive system. On the other hand, Cohn et al. (2003) reported a decreased probability of pregnancy in women exposed to DDT as babies *in utero*. Maternal serum samples were drawn 1 to 3 days after delivery and analyzed for DDT and DDE. Time to pregnancy was then assessed 28-31 years later in 289 daughters of the women enrolled in the study. Median o,p'-DDT, p,p'-DDT and DDE concentrations in maternal blood were 0.49, 13.05, and 48.19 $\mu\text{g/L}$, respectively. Cohn et al.

reported a decrease of 32% in the probability of pregnancy per 10 µg/L p,p'-DDT in maternal serum (95% CI: 11-48%). However, they also observed a 16% increase in probability of pregnancy per 10 µg/L p,p'-DDE in maternal serum (95% CI: 6-27%). This rather paradoxical finding (which the authors discuss could be due to an anti-androgenic effect of p,p'-DDE) illustrates the difficulty in understanding the complex nature of potential endocrine disruption.

As with the subtle neurological effects discussed earlier, the 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. The data appear to be substantially stronger for effects on wildlife (*e.g.*, in amphibians, fish) which may be more sensitive to such effects (NAS, 1999).

C. Fetal Basis of Adult Disease

An emerging concept in both science and regulation is the idea that exposures *in utero* or in early childhood can predispose an individual to a disease that emerges later in life (Heindel, 2008). This has been described as a fetal basis for adult disease (FeBAD). Recent speculation has focused on early life exposures as causative agents in Parkinson's Disease (PD) (Landrigan et al., 2005; Logroscino, 2005; Barlow et al., 2007; Miller and O'Callaghan, 2008). 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. The new theory suggests that early life insults (*e.g.*, infections, chemicals, injuries) which destroy some of these cells may either cause an individual's PD to appear earlier or, when combined with normal age-related loss, may shift an individual into the symptomatic pool. The data supporting this hypothesis remain limited. A number of animal studies have shown an association between prenatal exposure to several herbicides (paraquat and maneb) and the emergence of PD-like symptoms in the animals at older ages (Barlow et al., 2007). Herbicide exposure has also been shown to be a risk factor for PD in a number of epidemiology studies (reviewed in Elbaz and Tranchant, 2007). However, these studies have also shown associations between PD and various infections, brain injury, and smoking (Elbaz and Tranchant, 2007). The data are therefore somewhat muddled. Nonetheless, PD is one of most active areas of research concerning the long term consequences of early life pesticide exposures.

The case with PD involves destruction of cells. An alternative mechanism under consideration involves early life alterations in cellular components (usually DNA) which only manifest themselves late in life. As we learn more about how DNA is used in our cells it has become apparent that the genetic code itself is only part of the story. Epigenetic mechanisms such as the addition of methyl groups to DNA can alter gene expression and are used by normal cells to regulate their internal processes. Several recent studies have suggested that prenatal exposure to arsenic, which is known to interfere with DNA methylation, can predispose an individual to lung disease or cancer as an adult (reviewed in Vahter, 2008). With specific reference to obsolete pesticides, a recent animal study conducted by Zama and Uzumcu (2009) showed that prenatal and perinatal exposure (gestational day 19 to postnatal day 7) of rats to methoxychlor (20 or 100 $\mu\text{g}/\text{kg}\text{-day}$), resulted in persistent hypermethylation of ovarian genes later in adult life. A number of studies have also suggested the possibility of obesogens, chemicals which alter fat metabolism and predispose an individual to weight gain, obesity and a constellation of related diseases (*i.e.*, diabetes, heart disease, certain cancers) later in life. A recent review by Slotkin (2011) has suggested that organophosphate exposure could be linked to later life development of diabetes and obesity. Slotkin summarized studies which showed that 1 mg/kg-day of chlorpyrifos, administered on the first four days after birth, resulted in a pre-diabetic state in rats when tested as adults. Similar findings were reported by this research group in rodent studies of diazinon and parathion.

The FeBAD hypothesis remains largely speculative. Findings from animal studies are suggestive but difficult to extrapolate to humans. Conducting good epidemiology studies, which can be more informative, will be challenging. The long time interval between exposure and disease appearance will entail considerable expense, potential loss of subjects, and challenges in terms of controlling potential confounders (*e.g.*, diet, genetics). What is very clear is that the FeBAD concept is proving to be particularly appealing to researchers and regulatory scientists, combining as it does two key populations of interest (children and the elderly).

6. Conclusions

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. Although the importance of such modes of action is not fully understood, particularly at low levels of exposure, further research in these areas is warranted.

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