

## **Appendix F**

# **General Issues in the Evaluation of Children's Environmental Health**

**December 22, 2000**

## F.1 Introduction

Under the mandates of the Children's Environmental Health Protection Act (SB25, 1999), OEHHA must consider age-related differences in exposure patterns and in susceptibility to pollutant toxicity, focusing on infants and children. To this end, we have taken into account relevant published epidemiological, toxicological, and behavioral data, where available. As noted in section 4.2.1, examining age-dependent toxicity in children is a difficult task. In this Appendix, we highlight a few of the principal differences between infants and children relative to adults that may result in differential responses to ambient air pollutants and make it difficult to extrapolate effects from one age group to another.

Investigating potential air pollution-related effects in children presents challenges due to the numerous physiological factors that must be considered, including rapid growth, changes in fluid and protein content, organ function, metabolic rates and enzymatic function that characterize childhood. A child's behavior patterns, as well as his or her environment, allow for exposures that are both quantitatively and qualitatively different than adults. Premature infants, term newborns, young children, and adolescents are age groups unique in all these respects. Inter-individual variability in response due to genetic polymorphisms creates an additional dimension of complexity.

## F.2 Children's Exposure Patterns

Children's exposures are influenced by their activities and where these activities take place. Compared to adults, they spend more time outdoors and in active play and sports. A study of activity patterns in California found that children under 12 years of age spent an average of 124 minutes per day engaged in active sports, hiking, or outdoor activities compared with only 21 minutes for adults (Wiley et al. 1991; see also Section 3.6 regarding indoor exposures).

Newborns and young infants spend considerable time in a single environment (e.g. a crib) compared with more mobile older children. An infant or toddler may be unable to remove him or herself from an irritating stimulant, leading to increased exposure. Infants and young children frequently play on the floor, where they may contact and assimilate (via inhalation, ingestion, or percutaneous absorption) cleaning agents, formaldehyde, and possibly pesticide residues. Vapors that are heavier than air can concentrate in the breathing zone of young children near the floor. While the breathing zone for an adult is four to six feet above the floor, for an infant it may be inches (Bearer 1995).

Infants and younger children have especially high breathing rates related to their levels of oxygen consumption. Their relatively large body surface area per unit body weight and high activity levels result in greater energy expenditure for thermogenesis than that required by adults. The average daily breathing rates of children aged 3 to 12 years are approximately twice those of adults (452 vs. 232 L/kg-d) (OEHHA 2000b). Comparison of the average breathing rates for these two groups suggests that over a one-hour period, a playing child three to twelve years of age may breath 4.5 times as much air as a sedentary adult (OEHHA 2000b). Figure 1 depicts how air intake per unit body weight declines with increasing age.

### **F.3 Absorption and Volume of Distribution**

Characteristics of absorption of chemicals show age-related trends from birth through early childhood. The structure of the conducting airways develops completely prenatally; however, 85% of alveoli form in the postnatal period. While the full-term infant has about 50 million alveoli, some may have as few as 10 million. In contrast, the adult has approximately 300 million, though there is considerable variability (Wohl and Mead 1990). Most of the adult complement of alveoli develops in early childhood, but in some cases the number may increase to age eight or beyond (Thurlbeck 1988). As much of this growth occurs during the first three years of life, young children have a large alveolar surface per unit body weight relative to an adult for absorption of chemicals into the systemic circulation. Therefore, when viewed on the basis of dose per unit of lung surface area, the disparities between the adult and child are even greater than on a body weight basis (Plopper and Thurlbeck 1994). Alveolar multiplication coincides with postnatal increases in elastin and collagen, which contribute to the development of the mature lung's volume-pressure relationships and compliance (Wohl and Mead 1990).

Total body water as a percentage of body weight decreases from the young fetus to adulthood. At term, water constitutes 75% of body weight and fat constitutes 15%. By six months of age these percentages are 60% and 30% respectively. The proportion of extracellular fluid decreases from gestation (65%) to puberty (20%). As a consequence, water-soluble chemicals will tend to have a larger volume of distribution and slower clearance rates in younger infants and children.

### **F.4 Metabolism**

The ontogeny of metabolic pathway development during early life may result in important changes in rates of activation to toxic intermediates, detoxification, and clearance of xenobiotic compounds. Total cytochrome P450 content of human liver microsomes is unchanged from fetal life through the first year of post-gestational life and is approximately 1/3 the total adult content (Treluyer et al., 1991). Although total content of these enzymes is relatively stable, P450 enzymes can be divided into at least three major groupings: fetal, early neonatal (which surges during the first day following parturition), and neonatal (whose activity increases during the weeks to months after birth). CYP1A2, a neonatal enzyme, is undetectable up to 1 month of age (Cresteil 1998).

There has been little research about the timing of development of cytochrome p450 activity in tissues other than the liver. In one study, sex- and age-related differences in CYP1A1 activity in the human brain were documented (Watzka et al. 1999). During childhood, enzyme activity increased dramatically and reached adult levels by puberty. In the lung, animal studies have shown that exposure to environmental toxicants (sidestream tobacco smoke) can alter the developmental profile of cytochrome P450 enzymes, inducing earlier activity (Gebremichael et al. 1995). Repair of injured pulmonary Clara cells by toxicants activated by cytochrome p450 enzymes is decreased in the early postnatal period in rabbits and neonatal injury alters bronchiolar organization in the adult (Smiley-Jewell et al. 1998, 2000). In general, the range of inducibility of fetal CYP forms is unknown (Hakkola et al. 1998).

Epoxide hydrolase and some glutathione S-transferases are active in fetal life while other glutathione-S-transferases and UDP-glucuronyltransferases develop in the months following birth. Metabolism of exogenous proteins and bilirubin remains extremely low in neonates less than 10 days of age (Omiencinski et al., 1994; Cresteil, 1998).

As a result of differing enzyme activity, some chemicals are metabolized by wholly different metabolic pathways at different ages. In infants, theophylline is N-methylated to caffeine. In adults this is a minor pathway, the majority being N-demethylated or C-oxidized to monomethylxanthines or methyl-uric acid. A pattern of metabolism similar to adults is achieved by seven to nine months of age (Reed 1996).

While children in general may be at increased risk for pharmacokinetic/dynamic reasons, subsets of children may be yet more sensitive due to genetic susceptibility. In an elegant set of studies, Pereira has shown significant transplacental transfer of polyaromatic hydrocarbons (PAHs) and environmental tobacco smoke constituents from mother to fetus, increased PAH DNA adduct formation in maternal and newborn white blood cells related to environmental exposure, and increased fetal sensitivity to genetic damage relative to the mother. Newborns with a specific restriction length polymorphism (CYP 1A1 Msp1), had elevated numbers of adducts compared to those without the polymorphism (Pereira 1999).

## **F.5 Critical Period Programming**

Biologists have described sensitive time periods during which certain stimuli create irreversible effects that sometimes may not be noted until much later in life. One example is the development of functional sweat glands. While we are all born with approximately the same number of sweat glands, none respond to heat at birth. Gradually, they become functional in response to heat over the first two or three years of life. Warmer conditions during this developmental interval are associated with an increasing number of sweat glands becoming activated. By three years of age, the functional number of sweat glands is fixed irreversibly (Diamond 1991).

Early development involves rapid cell proliferation, migration, and differentiation, processes uniquely sensitive to disruption. In the brain these processes are unidirectional and occur at very specific times for different structures. Unlike many other cell types, neurons have long been considered to proliferate only during development, and each specific cell type only during a limited period. Structural maturation of neural pathways, including an increase in the diameter and myelination of axons, continues through adolescence. Chemical exposures can have profound effects on all of these neurological developmental processes (Rodier 1994, 1995; Paus et al. 1999; Golub 2000).

The development of the immune system results from a series of carefully timed and coordinated events during embryonic, fetal, and early postnatal life. Exposure of pregnant animals to immunotoxic chemicals at doses causing only transient effects in adults can produce long-lasting or permanent immune deficits in their offspring. Examples of agents for which prenatal exposure appears to produce lifelong immunosuppression include chlordane, benzo[a]pyrene, and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) (Holladay and Smialowicz, 2000). Development of the allergic phenotype appears to be related to aeroallergen exposure during infancy (Holt 1998). Recent data suggest that childhood exposures to several air pollutants (particulate matter, nitrogen dioxide, and acid aerosols) may result in permanent lung function deficits, with unknown clinical consequences (Gauderman et al. 2000). Other organ systems also show unique long-term consequences of early life chemical exposures that are not seen in the mature animal.

In general, however, there are few data delineating precise windows of susceptibility during gestation or post-natally.

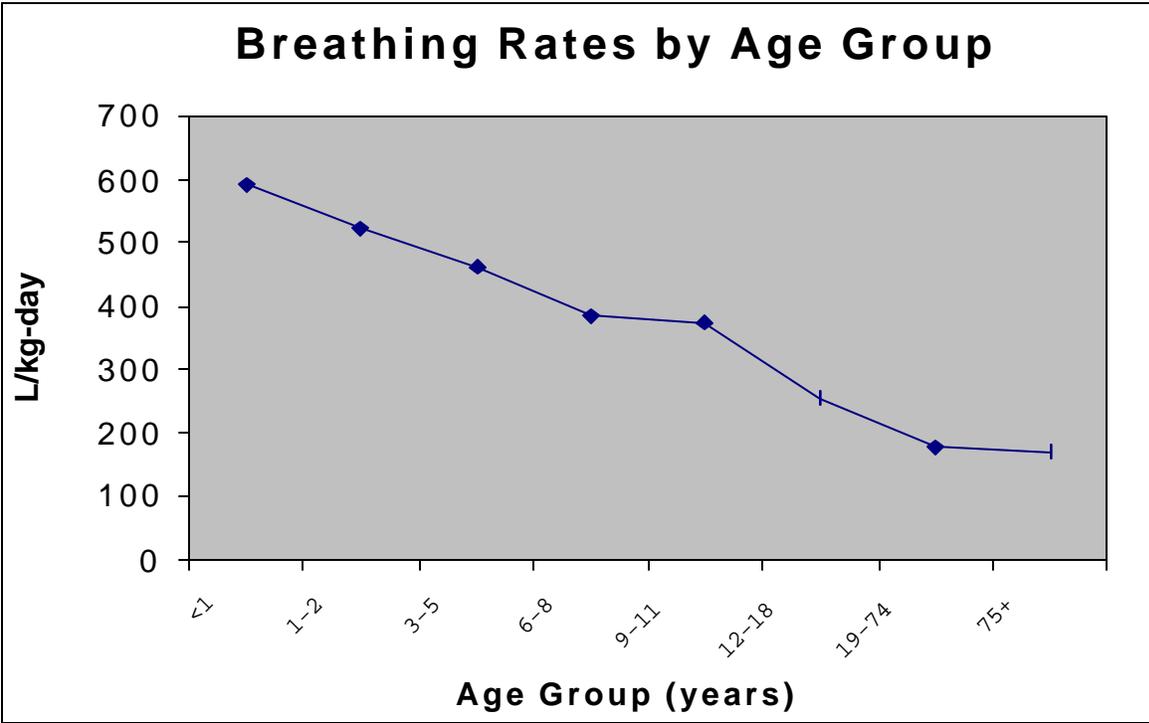


Fig.1: Breathing rates calculated by dividing daily inhalation rates ( $\text{m}^3/\text{day}$ ) from Table 5 of Layton (1993) by body weights presented in Table 3 of Layton (1993) (original data from National Food Consumption Survey 1977-1978).

## F.6 References

- Bearer, C. 1995. How are children different from adults? *Environ. Health Perspect.* 103 (suppl 6): 7-12.
- Cresteil, T. 1998. Onset of xenobiotic metabolism in children: Toxicological implications. *Food Additives and Contaminants.* 15:Suppl., 45-51.
- Diamond, J. 1991. Pearl Harbor and the emperor's physiologists. *Natural History.* Dec. 2-7.
- Gauderman, W.J., McConnell, R., Gilliland, F., London, S., Thomas, D., Avol, E., Vora, H., Berhane, K., Rappaport, E.B., Lurmann, F., Margolis, H.G., Peters, J. 2000. Association between air pollution and lung function growth in Southern California children. *Am. J. Respir. Crit. Care Med.* 162:1383-1390.
- Gebremichael, A., Chang, A.M., Buchpitt, A.R., Plopper, C.G., Pinkerton, K.E. 1995. Postnatal development of cytochrome P450 1A1 and 2B1 in rat lung and liver: Effect of aged and diluted sidestream cigarette smoke. *Toxicol. Appl Pharmacol.* 135(2):246-253.
- Golub, M. 2000. Adolescent health and the environment. *Environ. Health Perspect.* 108:355-62.
- Hakkola, J., Tanaka, E., Pelkonen, O. 1998. Developmental expression of cytochrome P450 enzymes in human liver. *Pharmacol. Toxicol.* 82:209-217.
- Holladay, S.D., Smialowicz, R.J. 2000. Development of the murine and human immune system: Differential effects of immunotoxicants depend on time of exposure. *Environ. Health Perspect.* 108 (suppl. 3): 463-473.
- Holt, P.G. 1998. Programming for responsiveness to environmental antigens that trigger allergic respiratory disease in adulthood is initiated during the perinatal period. *Environ. Health Perspect.* 106 (suppl. 3): 795-800.
- OEHHA. 2000b. Air Toxics Hot Spots Program Risk Assessment Guidelines. Part IV: Technical Support Document for Exposure Assessment and Stochastic Analysis. Office of Environmental Health Hazard Assessment, Cal/EPA. September 2000. Available at [www.oehha.ca.gov](http://www.oehha.ca.gov).
- Omiencinski, C.J., Aicher, L., Swenson, L. 1994. Developmental expression of human microsomal epoxide hydrolase. *J. Pharmacol. Exp. Therap.* 269 (1): 417-23.
- Paus, T., Zijdenbos, A., Worsley, K., Collins, D.L., Blumenthal, J., Giedd, J.N., Rapoport, J.L., Evans, A.C. 1999. Structural maturation of neural pathways in children and adolescents: In vivo study. *Science.* 283:1908-11.
- Pereira, F. 1999. Molecular epidemiologic research on the effects of environmental pollutants on the fetus. *Environ. Health Perspect.* 107 (S3): 451-460.

- Plopper, C.G., Thurlbeck, W.M. 1994. Growth, Aging, and Adaptation. In: Textbook of Respiratory Medicine, 2<sup>nd</sup> Edition. Eds., Murray and Nadel. W. B. Saunders, Philadelphia.
- Reed, M. 1996. Principles of Drug Therapy. In: Nelson's Textbook of Pediatrics 15<sup>th</sup> Ed. W.B. Saunders, Philadelphia.
- Rodier, P. 1994. Vulnerable periods and processes during central nervous system development. Environ. Health Perspect. 102 (suppl. 2): 121-124.
- Rodier, P. 1995. Developing brain as a target of toxicity. Environ. Health Perspect. 103 (suppl. 6): 73-76.
- Rodier, P.M., Ingram, J.L., Tisdale, B., Croog, V.J. 1997. Linking etiologies in humans and animal models: Studies of autism. Repro. Toxicol. 11:2/3.417-422.
- Smiley-Jewell, S.M., Nishio, S.J., Weir, A., Plopper, C.G. 1998. Neonatal Clara cell toxicity by 4-ipomeanol alters bronchiolar organization in adult rabbits. Am. J. Physiol. 274:L485-498.
- Smiley-Jewell, S.M., Liu, F.J., Weir, A., Plopper, C.G. 2000. Acute injury to differentiating Clara cells in neonatal rabbits results in age-related failure of bronchiolar epithelial repair. Toxicol. Pathol. 28(2): 267-76.
- Thurlbeck, W.M. Growth, aging and adaptation. In: Murray, J.F., Nadel, J.A., editors: Textbook of respiratory medicine, Philadelphia, 1988. W.B. Saunders Company, pp. 37-46.
- Treluyer, J.M., Jacqz- Aigrain, E., Alvarez, F., Cresteil, T. 1991. Expression of CYP2D6 in developing human liver. Eur. J. Biochem. 202:583-88.
- Watzka, M., Bidlingmaier, F., Schramm, J., Klingmuller, D., Stoffel-Wagner, B. 1999. Sex and age-specific differences in human brain CYP11A1 mRNA. Expr. J. Neuroendocrin. 11:901-905.
- Wiley, J.A., Robinson, J.P., Cheng, Y.T., Piazza, T., Stork, L., Pladsen, K. 1991. Study of children's activity patterns. Contract number A733-149. Final Report. California Environmental Protection Agency, Air Resources Board.
- Wohl, M.E.B., Mead, J. Age as a factor in respiratory disease. In: Chernick, V., Kendig, E.L., editors: Kendig's disorders of the respiratory tract in children. Philadelphia, 1990, W.B. Saunders, pp. 175-182.