Pediatric Pharmacokinetic Data: Implications for Environmental Risk Assessment for Children

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ABSTRACT. Pharmacology and toxicology share a common interest in pharmacokinetic data, especially as it is available in pediatric populations. These data have been critical to the clinical pharmacologist for many years in designing age-specific dosing regimens. Now they are being used increasingly by toxicologists to understand the ontogeny of physiologic parameters that may affect the metabolism and clearance of environmental toxicants. This article reviews a wide range of physiologic and metabolic factors that are present in utero and in early postnatal life and that can affect the internal dose of an absorbed chemical and its metabolites. It also presents a child/adult pharmacokinetic database that includes data for 45 therapeutic drugs organized into specific children’s age groupings and clearance pathways. Analysis of these data suggests that substantial child/adult differences in metabolism and clearance are likely for a variety of drugs and environmental chemicals in the early postnatal period. These results are also relevant to in utero exposures, where metabolic systems are even more immature, but exposures are greatly modified by the maternal system and placental metabolism. The implications of these child/adult differences for assessing children’s risks from environmental toxicants is discussed with special focus on physiologically based pharmacokinetic modeling strategies that could simulate children’s abilities to metabolize and eliminate chemicals at various developmental stages. Pediatrics 2004;113:973–983; children, metabolism, pharmacokinetics, risk assessment.

ABBREVIATIONS. PK, pharmacokinetics; TK, toxicokinetics; CYP, cytochrome P-450; ADR, adverse drug reaction; Vd, volume of distribution; EH, epoxide hydrolase; CBZ, carbamazepine; 1/2, drug half-life; PBTK, physiologically based toxicokinetic; GI, gastrointestinal.

The fields of pharmacology and toxicology are similarly concerned with human responses to xenobiotics, but there is typically little crossover between these 2 endeavors. As outlined in Fig 1, whereas the starting point in both cases can be the same (eg, a child), the problem addressed and ultimate goals are different. However, pharmacokinetics (PK) offer a linkage in which the principles regarding children’s absorption, distribution, metabolism, and excretion of drugs can be applied to an area where there is typically very little information, the PK handling of environmental toxicants (toxicokinetics [TK]) in children. This critical data gap arises because controlled TK studies are not feasible in children: the intentional exposure of children or pregnant women to toxicants that have no potential benefit, even at low environmental exposure levels, is not ethically acceptable.

In contrast, clinical pediatric drug trials are well accepted for the attainment of PK data and thus provide a data resource for understanding the ontogeny of physiologic/metabolic parameters. This understanding is possible because many drugs are metabolized and cleared by 1 or 2 predominant pathways and so can be used as indicators of PK pathway function.1 Drugs are imperfect surrogates for environmental toxicants in terms of chemical structure, types of biological activity, and size of doses used in clinical trials. However, because environmental toxicants and therapeutic drugs can have the same metabolic pathway, the PK developmental profile observed in drug trials is of relevance to toxicity and risk assessment.

This article summarizes our efforts to better understand children’s PK through the development of a comparative child/adult PK database that encompasses 45 therapeutic drugs.2,3 By combining this in vivo information with in vitro information from liver bank studies on relative protein amounts for key metabolizing enzymes (eg, cytochrome P-450s [CYPs]),4–8 it is possible to draw conclusions about clearance pathway function at various stages of development, from in utero through adolescence. This information has applicability to children’s risk assessment and also as an aid to pediatric drug therapy in terms of understanding how to adjust dosages and the potential for adverse drug reactions (ADRs) and drug–drug or drug–environment chemical interactions. In addition, the PK of the placental–fetal unit can affect in utero exposure to toxicants, and this may contribute to unique sensitivity during this pe-
The excretion of chemicals into breast milk is another pharmacokinetic factor that affects early life exposure and risks, in the realm of both therapeutics and environmental toxicants.

IN UTERO/CHILD/ADULT PK DIFFERENCES: GENERAL OBSERVATIONS

The fetal and early postnatal periods differ from more mature stages of development in a number of ways that can affect chemical clearance, half-life, volume of distribution (Vd), and ultimately plasma or tissue concentration. An overview of these factors in children as compared with adults is presented in Table 1. These differences include basic physiologic properties such as lipid and water composition, organ weights, and blood flows, as well as functional deficits as a result of the immaturity of hepatic and renal systems. The largest differences generally occur in premature and full-term neonates with a progressive shift toward adult values during the first months to years of life.

Physiologic Factors

Neonates and infants have different percentages of body content of water and lipid than older children and adults. At birth, there is a greater percentage of body water and less body lipid. This can increase the volume of distribution of water-soluble chemicals because of expanded water volume but may also decrease the partitioning and thus retention of lipid-soluble chemicals. Limited biomonitoring data for tetrachlorodibenzo-p-dioxin and dioxin-like molecules in the first year of life tends to support this supposition as infants had lower body stores of these lipophilic toxicants than would be expected on the basis of the amount that they were receiving in breast milk. However, another factor, faster biliary excretion, may have accounted for this finding as in-

TABLE 1. Overview of Children’s Developmental Features That Can Affect TK

<table>
<thead>
<tr>
<th>Developmental Feature</th>
<th>Relevant Age Period</th>
<th>TK Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body composition: lower lipid content, greater water content</td>
<td>Birth through 3 mo</td>
<td>Less partitioning and retention of lipid-soluble chemicals; larger Vd for water-soluble chemicals</td>
</tr>
<tr>
<td>Larger liver weight/body weight</td>
<td>Birth through 6 y but largest ratios in first 2 y</td>
<td>Greater opportunity for hepatic extraction and metabolic clearance; however, also greater potential for activation to toxic metabolites</td>
</tr>
<tr>
<td>Immature enzyme function: phase I reactions, phase II reactions</td>
<td>Birth through 1 y but largest differences in first 2 mo</td>
<td>Slower metabolic clearance of many drugs and environmental chemicals; less metabolic activation but also less removal of activated metabolites</td>
</tr>
<tr>
<td>Larger brain weight/body weight; greater blood flow to CNS; higher BBB permeability</td>
<td>Birth through 6 y but largest differences in first 2 y</td>
<td>Greater CNS exposure, particularly for water soluble chemicals which are normally impeded by BBB</td>
</tr>
<tr>
<td>Immature renal function</td>
<td>Birth through 2 mo</td>
<td>Slower elimination of renally cleared chemicals and their metabolites</td>
</tr>
<tr>
<td>Limited serum protein binding capacity</td>
<td>Birth through 3 mo</td>
<td>Potential for greater amount of free toxicant and more extensive distribution for chemicals which are normally highly bound</td>
</tr>
</tbody>
</table>

CNS indicates central nervous system; BBB, blood-brain barrier.
fants are known to more readily excrete lipids and, by inference, compounds that partition into circulating lipids.\textsuperscript{16} The combination of less storage and more rapid biliary excretion of lipophilic toxicans may partially offset the greater dose (per body weight) that infants can receive via breast milk.

Body lipid rises steadily after birth for the first 9 months of life but then decreases steadily until preadolescence, which marks a second period of increasing body lipid.\textsuperscript{5,13} These changes in body composition can also modulate chemical storage, half-life, and \textit{Vd}. Tissue distribution of chemicals can also be affected by differences in organ size across age groups. Liver mass per body weight is higher in infants than in adults,\textsuperscript{17} and tissues such as liver, kidney, and lung undergo rapid growth during the first 2 years.\textsuperscript{18} In contrast, reproductive tissues are generally small per body weight during this period. The brain is disproportionately large in young children. This factor combined with the immaturity of the blood-brain barrier leads to a significant increase in the first 2 years.\textsuperscript{18} In contrast, reproductive tissues are generally small per body weight during this period. The brain is disproportionately large in young children. This factor combined with the immaturity of the blood-brain barrier leads to a significant increase in the first 2 years.\textsuperscript{18} Immaturity of the blood-brain barrier and less plasma protein-binding capacity (see below) may also lead to higher brain concentrations and potential for neurotoxic effects with certain xenobiotics.\textsuperscript{20}

Another factor that can affect the distribution of chemicals is the binding capacity of plasma proteins. A large number of drugs and certain environmental chemicals (eg, organic acids, such as trichloroacetic acid)\textsuperscript{21} are strongly bound to plasma proteins such that there is very little free drug or chemical in the circulation. Because only free drug can cross the placenta, be excreted by the kidney, enter the central nervous system, or be taken up by the liver, extensive protein binding will tend to delay elimination processes that can occur at these sites; it also limits the amount of chemical that is free at any time to exert a toxic effect. Furthermore, extensive protein binding creates the possibility for a drug–chemical or chemical–chemical interaction in which 2 agents compete for the same plasma protein-binding sites. Neutrons have low protein-binding levels, with regard to both albumin and \textit{H}\textsubscript{1}-glycoprotein.\textsuperscript{13,22} This combined with the fact that neonates have immature capability to conjugate and excrete bilirubin, an important endogenous molecule that binds extensively to plasma proteins, may lead to a considerably smaller number of available protein-binding sites in plasma.

**Immaturity of Renal and Hepatic Systems**

Regarding renal clearance, both glomerular filtration rate and transporter (secretory) systems in the proximal convoluted tubule are deficient at birth.\textsuperscript{13,14} In part, renal clearance is impeded by the relatively low percentage of cardiac output reaching this organ in the first weeks to months of life. These factors lead to relatively slow clearance of a wide array of antibiotics and other renally cleared chemicals. Another factor of particular importance to the perinatal period is that certain chemicals can dramatically curtail renal function at this time. This has been observed with angiotensin-converting enzyme inhibitors, which reduce or eliminate urinary flow, resulting in oligohydramnios in utero and no urine output in the newborn.\textsuperscript{23,24}

One might expect metabolic clearance of xenobiotics to be faster in children because, per body weight, smaller organisms generally have greater respiratory rates, cardiac output, nutrient and oxygen demands, and metabolic rates compared with larger species.\textsuperscript{25,26} This seems to be true of children as well because their respiratory rate, cardiac output, and liver mass are greater per body weight than adults.\textsuperscript{17,19,27} However, faster metabolic rates are generally not realized in neonates because of the functional immaturity of a variety of metabolic systems.\textsuperscript{28} The immaturity of hepatic enzymes in neonates has been evidenced as prolonged drug half-life, reduced hepatic clearance, and in select cases a shift in the percentage of formation of various metabolites.\textsuperscript{14,22,28} As discussed further in the next section, this has been seen across a variety of therapeutic drugs and metabolizing pathways, including phase I oxidative systems (various CYPs, flavin monooxygenases), phase II conjugating systems (glucuronidation, N-acetyltransferases), and miscellaneous other systems (eg, alcohol dehydrogenase, serum esterases, epoxide hydrolase).\textsuperscript{6,7,29–31} This suggests that PK immaturity in the perinatal period is a generalized phenomenon that can modulate the metabolism and clearance of numerous environmental toxicants. This could affect the removal of both parent compound and metabolites and alter the degree to which chemicals are converted to toxic metabolites. At later ages, when the immaturity of hepatic systems has been overcome, it is possible for children’s metabolism and clearance of xenobiotics to supersede that in adults.\textsuperscript{27}

**Placental and Fetal Factors**

Many of the PK differences described above for neonates are true and even more dramatically so for the fetus. For example, fetal content of lipid and water, plasma protein binding, integrity of the blood-brain barrier, and hepatic and renal clearance systems are progressively more immature at earlier stages of fetal development.\textsuperscript{6,8,30} These factors are ameliorated to a great degree by the maternal system, which bears the major responsibility for chemical metabolism and clearance. Furthermore, the placenta exhibits an increasing metabolic capacity during development as a wide variety of phase I oxidative (eg, CYPs in the 1A, 2C, and 3A families; alcohol dehydrogenase) and phase II conjugating (eg, glutathione transferases) enzymes have been identified in placental tissues.\textsuperscript{9,32–35} The maternal and placental systems thus decrease the amount of chemical that reaches the fetus, although metabolites formed in the placental or fetal compartments might reach higher local concentration than in the maternal system.

Other factors can affect the propensity for chemicals or their metabolites to reach higher concentration in the fetal compartment. For example, the findings of higher concentrations of weak acids (eg,
valproic acid, glycolic acid after ethylene glycol exposure, methoxyacetic acid) in the fetus as compared with maternal circulation may be related to a slightly higher pH in the fetus with greater ion trapping in that compartment.\textsuperscript{36–39} The generally higher concentrations of mercury in cord blood as compared with maternal blood in various populations\textsuperscript{40–42} is also suggestive of heightened fetal exposure and sensitivity as a result of pharmacokinetic factors. However, these prenatal factors are expected to be at work as well in the rodent test systems used to screen drugs and environmental toxicants for developmental effects. Thus, one might assume that as long as a chemical has been evaluated in well-conducted rodent developmental studies, there should be no surprises, at least from a pharmacokinetic perspective, when the chemical is used in pregnant women. However, this overlooks the uncertainties of relating animal dose–response data to humans; it is possible that the ontogeny of metabolic and other factors differs in the rodent placenta/fetus as compared with that in humans. In fact, it seems that full-term human newborns are more mature than their rodent counterparts with respect to liver metabolism.\textsuperscript{20,43,44} This suggests that the human fetus may also be more metabolically competent than the rodent fetus, leading to cross-species differences in in situ metabolic activation or detoxification in the fetal compartment. Such differences have not been sufficiently studied to enable estimates of how much more or less internal dose of toxicant a human fetus may receive compared with the rodent fetus.

**ADRs Related to Immature Metabolism in Early Life**

The immaturities in metabolic function can affect perinatal susceptibility to ADRs as demonstrated in the well-documented case of chloramphenicol toxicity (anemia) as a result of immature glucuronidation capacity in neonates.\textsuperscript{45,46} This deficiency is critical for chloramphenicol as its primary route of elimination is via conjugation with glucuronide. The immaturity of epoxide hydrolase (EH) in neonates also has implications for ADRs and environmental risk. Fetal and neonatal levels of EH seem to be below adult levels as indicated by in vitro determinations of hepatic protein levels\textsuperscript{47,48} and by the ratio of carbamazepine-epoxide (CBZ-E) to CBZ in blood.\textsuperscript{47,48} Because EH is the primary means for removal of CBZ-E, reports of higher CBZ-E/CBZ ratios in children suggest lower EH activity. Phenytoin toxicity and teratogenicity seem to be related to an oxidative metabolite that requires EH for detoxification with 1 study linking fetal EH deficiency with increased risk for phenytoin’s teratogenic effects,\textsuperscript{49} as originally proposed by Spielberg et al,\textsuperscript{50} in the mouse. Thus, the deficiency of EH that extends into the postnatal period may also predispose neonates to toxicity from epoxides.

Valproic acid is also a case in which young children seem to be more susceptible to ADRs on the basis of pharmacokinetic mechanisms. This antiepileptic drug induces hepatotoxicity most frequently in young children (<2 years of age) who are on multidrug therapy.\textsuperscript{51,52} Although the mechanism for increased sensitivity in children is still under investigation, it seems to be related to the formation of a particular oxidative metabolite (4-ene valproic acid) that can then undergo additional bioactivation.\textsuperscript{53,54} This step seems to be mediated via CYPs 2A6 and 2C9.\textsuperscript{55} Although this reaction can occur in older children and adults, the generally higher activity of CYP metabolism per body weight in the 6-month to 2-year age group suggests that PK factors can contribute to this sensitivity. It may also be possible that CYP inducibility in young children from antiepileptic multidrug therapy is greater than in other age groups.

These examples demonstrate that toxicologists need to take the developmental profile of PK function into consideration when evaluating children’s risks to environmental toxicants. The following section explores further this aspect of children’s susceptibility.

**CHILD/ADULT PK DIFFERENCES: OBSERVATIONS FROM THE THERAPEUTIC DRUG LITERATURE**

We have developed a comparative child/adult database across 45 drugs involving a wide array of clearance mechanisms and children’s age groups.\textsuperscript{2} A similar data set involving 36 drugs has been developed by others\textsuperscript{27,56} with essentially similar results. The age groupings used to organize our data set (Table 2) attempt to capture the rapid physiologic and metabolic changes that occur in the first weeks to months of life while also considering the amount of data available for each period; ie, it would not be useful for comparison purposes to have an age category that contains few data. Of course, individuals within any age group are at slightly different developmental stages. These interindividual differences are evaluated in a variability analysis of this data set.\textsuperscript{3} For each PK study, information was compiled into a central database on drug half-life (t\textsubscript{1/2}), clearance, Vd, peak concentration in plasma, and area under the plasma × time concentration curve. The greatest amount of data were available for t\textsubscript{1/2} (147 data groups involving 41 chemicals and 2090 subjects), and so this summary focuses on across-age comparisons with this endpoint. Clearance results were generally consistent with the t\textsubscript{1/2} data, although in the opposite direction (eg, where children’s drug t\textsubscript{1/2} was prolonged, the corresponding clearance rate

<table>
<thead>
<tr>
<th>Chemical Type</th>
<th>No. of Chemicals</th>
<th>No. of Data Groups</th>
<th>No. of Data Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic Acid</td>
<td>147</td>
<td>41</td>
<td>2090</td>
</tr>
</tbody>
</table>

**TABLE 2. Data Available for Different Age Groups in the Children’s PK Database**

Age Group | Data Groups | Metab/Elim Types* | No. of Chemicals |
-----------|-------------|-------------------|-----------------|
Premature neonates (≤1 wk) | 15 | 5 | 7 |
Full-term neonates (≥1 wk) | 37 | 9 | 19 |
Newborns 1 wk–2 mo | 52 | 7 | 14 |
Early infants 2–6 mo | 22 | 6 | 7 |
Crawlers/toddlers (6 mo–2 y) | 35 | 7 | 14 |
Preadolescents (2–12 y) | 75 | 8 | 26 |
Adolescents (12–18 y) | 12 | 5 | 7 |
Adults | 118 | 11 | 42 |
Total | 366 | 11 | 45 |

* Column lists the number of different metabolism or elimination pathways for which data are available within each age group.
was low). The metabolism and elimination pathways represented in the database include various CYPs as follows: CYP1A2 (2 drug substrates), CYP2C (1 substrate), CYP3A (8 substrates), and multiple/miscellaneous CYPs (6 substrates). The database also includes drug substrates for the glucuronidation pathway (6 substrates) and renal clearance (8 substrates).

Figure 2 summarizes the t½ results across the entire database. The 2- to 4-fold longer t½ in neonates relative to adults reflects immaturity across a broad range of clearance pathways, with this deficit not in evidence by 2 to 6 months of age and a tendency for shorter drug t½ at older ages (6 months to 2 years). This pattern is seen as well for CYP3A substrates (Fig 3), which is despite the fact that neonates have relatively high levels of a fetal form of CYP3A, CYP3A7.4,57 The data in Fig 3 suggest that this fetal CYP is not very active at metabolizing the drug substrates in our database as the child/adult t½ ratios are highest in early life and decrease along a time frame consistent with the onset of CYP3A4 activity.57 Results for CYP1A2 as indicated by 2 drug substrates, caffeine and theophylline, are shown in Fig 4. In this case, the neonate/adult t½ differential is larger, but like the other pathways, a rapid recovery toward and even surpassing of adult levels is seen. The results for other CYPs and for glucuronidation and renal elimination are consistent with the trends shown in the previous figures. This suggests a generalized functional immaturity in PK systems in neonates through 2 months of age, with this differential by an average of 2- to 4-fold (higher in the case of 1A2). The onset of these systems can lead to more rapid clearance (shorter t½) relative to adults by 6 months to 1 year of age, with this continuing for several years.

These findings are consistent with in vitro evidence of the emergence of metabolizing systems in postnatal liver bank samples.4,5,58 A wide variety of CYPs have been found to be deficient in microsomes from fetal and neonatal tissues, with some CYPs barely detectable at birth (eg, CYPs 1A2, 2E1), whereas others are at levels that are 3- to 10-fold below older children and adults (eg, CYPs 2C19, 2D6, 3A4).57,59-62 The CYP2E1 protein content of microsomes increases rapidly during the first weeks of life, but this and the other CYPs studied are still below adult levels of expression through 6 months with a gradual increase toward adult levels by 1 year of age. The rate of development of CYP1A2 protein levels is somewhat slower than that seen for other CYPs. It is important to note that whereas CYP protein levels are still deficient through 6 months of age, the in vivo data (Figs 2-4) suggest attainment and perhaps even surpassing of adult clearance rates via CYPs by this age. At this time, the larger liver mass per body weight that is known to exist in young children17 seems to compensate for the residual deficiencies in CYP levels. Overall, the in vitro CYP protein expression results provide support for the ontologic profile of xenobiotic metabolism shown in Figs 2 to 4 on the basis of in vivo t½ data.

**IMPLICATIONS OF CHILD/ADULT PK DIFFERENCES FOR ENVIRONMENTAL RISK ASSESSMENT**

Modeling Approaches for Incorporating PK Differences Into Children’s Risk Assessments

A critical step in the risk assessment process for children is relating the dose response for toxicity from animal or epidemiology (typically adult worker) studies to children. This can be done with...
the aid of physiologically based toxicokinetic (PBTK) modeling, which simulates blood and tissue concentrations of parent chemical and metabolites.63,64 This is accomplished by organizing the body into compartments that allow for partitioning of chemical from blood into tissues and that model the various clearance processes (metabolism, excretion) to occur within specified compartments. In this way, the physiologic characteristics and metabolic function of a particular species or age group can be used to predict internal dose. The relationship between internal dose and toxic response seen in animal toxicology studies then can be compared with the range of internal doses possible from children’s environmental exposures with the assistance of a working PBTK model in children.

These modeling adjustments to children’s internal dose require knowledge throughout development of the various physiologic and metabolic differences between children and adults. This information can be obtained from the pediatric pharmacokinetic data-base exemplified in Figs 2 to 4 combined with other types of data as described above. Although several modeling efforts have provided screening-level estimates of children’s internal dosimetry to environmental toxicants,65-67 the lack of toxicant exposure data in children has precluded calibration or validation of such models. Furthermore, these approaches will not capture the variability in TK handling of xenobiotics that can be expected to occur across a range of children in any particular age group and across different chemicals. For example, child/adult t½ differences are considerably larger for caffeine (15-fold) than for the closely related xanthine theophylline (3-fold) in the first months of life.2,56 This indicates that risk assessments can obtain misleading information by relying on generalized models of early-life TK function and need to be tailored to specific pathways and chemicals to the extent possible. To this end, it will be advantageous to develop children’s models that are based on actual child and adult PK data for therapeutic drugs, thus providing
a point of calibration for specific pathways of relevance to toxicants. This approach has recently been used to model child/adult differences in the metabolism of caffeine and theophylline.68

A notable exception to the lack of model calibration data in children is with respect to lead. There is considerable blood lead data in children in communities where the degree of exposure from water, soil, food, and air has also been estimated. US Environmental Protection Agency’s Integrated Exposure/Uptake Biokinetic Model for lead has capitalized on these data sets to yield a fairly well calibrated and predictive risk assessment tool for this toxicant.69

Physiologic models describing in utero exposure have also been developed. These models have described the disposition of a number of chemicals in pregnant rodents and their fetuses, as well as the lactating rat and nursing pup.70 Luecke et al71 and Welsch et al72 adapted such models to human pregnancy to forecast potential teratogenic events. O’Flaherty et al73 developed PBPK models that accurately predicted time courses of lead in the blood and its deposition in bone. These models incorporated age-dependent changes in body weight, tissue volumes, blood flows, and bone formation and resorption rates.

Child-Specific Adjustment Factors to Modify Estimates of Exposure and Risk

Children’s risk assessments may also use less quantitative approaches to address TK differences across species and age groups, such as modification of the traditional uncertainty factors used in risk assessment or the application of child-specific uncertainty or adjustment factors.74 The pediatric PK database described in this article can also be used in these applications to describe more generally chemical throughput across various pathways in comparison with adults. This qualitative assessment can determine whether levels of parent compound or key metabolites are likely to be affected by age of exposure and the direction of such differences. Table 3 provides a summary of the in vivo and in vitro data pertinent to pediatric PK function in terms of general trends and how they may affect internal dose and risk in children. The following highlights how these factors can be taken into consideration when assessing children’s risks to environmental toxicants.

Regarding gastrointestinal (GI) absorption, young children may have severalfold greater uptake of toxicants as exemplified by lead, inorganic mercury, and other metals.19,75–78 This differential seems to be related to greater pinocytic activity of intestinal epithelium before closure of the GI tract.19 The possibility of higher GI uptake of ingested chemicals early in life should be evaluated within the context of the chemical’s behavior in the gut. If it is generally well absorbed in rodents and adult humans by the oral route (eg, small organic molecules), then any increase in absorption during early-life stages may not create a large difference in uptake (eg, methyl mercury78). However, for chemicals that are poorly absorbed in adults (eg, inorganic mercury, lead, other metals), increased uptake in children may be an important factor in the exposure and risk assessment.

Because full-term newborns have a well-developed stratum corneum, it is generally assumed that the dermal permeability of full-term newborns and older children is not materially different from in adults.79 This has been shown in vitro test systems using skin from neonates and adults for several different drugs.79–83 However, the skin of premature neonates can be substantially more permeable than that of full-term neonates as a result of immaturity of the stratum corneum.79,84 The data for human skin from premature neonates indicate an inverse correlation between permeability and gestational age. Permeability rates were 100 to 1000 times greater before 30 weeks’ gestation as compared with full-term neonates, with a 3- to 4-fold greater permeation rate seen beyond 32 weeks.81–85 In vivo studies suggest that this increased dermal permeability in premature infants is a short-lived phenomenon with the permeability barrier of even the most premature neonates similar to that of full-term neonates by 2 weeks of postnatal life.83

Inhalation exposure can also be greatest in early life, which in this case is attributable to the greater respiratory volume per lung surface area.19,86,87 Preliminary modeling efforts for young children suggest that this differential can be larger when considering local deposition.86 This exposure dose differential for particles and aerosols may be of particular consequence to young children who are sensitive to respiratory irritants and allergens as a result of asthma or other conditions. Furthermore, in asthma, the changes in breathing pattern and respiratory volume/resistance may create local exposure patterns that are different from that in healthy children or adults. Therefore, it is important to analyze respiratory deposition of particles and aerosols in children, both healthy and those with asthma. This can be aided by the development of regional deposited dose ratio models, which take into account respiratory physiology at different life stages as well as a distribution of particle sizes.89

Table 3 also points out that immaturity of metabolic and renal elimination in early life leads to the potential for prolonged half-life and higher internal exposures to parent compound. This may decrease metabolite formation, which if metabolism is a toxicity process, may lead to less active toxicant being formed. Therefore, it is important to know whether the particular xenobiotic being assessed requires metabolic activation and how clearance of parent compound and activated metabolites is normally accomplished. Given the immaturity of a wide array of metabolic systems in neonates, it is prudent also to consider detoxification reactions (whether phase I or phase II) as immature. Regarding phase II reactions, this seems to be true for glucuronidation, acetylation, certain glutathione transferases, and EH. The combination of less activation via CYPs and also less conjugation and renal elimination in early life leads to the suggestion of no net change in metabolite levels in this age group. This assumption should


<table>
<thead>
<tr>
<th>PK Pathway</th>
<th>Premature Neonates</th>
<th>Neonatal &lt;1 Month</th>
<th>Early Infant 1-2 Months</th>
<th>Mid-Infant 3-5 Months</th>
<th>Late Infant 6-11 Months</th>
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<td>⇐</td>
<td>⇐</td>
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<td>⇐</td>
</tr>
<tr>
<td>N-acetylation</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
</tr>
<tr>
<td>GSTs</td>
<td>Uncertain**</td>
<td>Uncertain**</td>
<td>Uncertain**</td>
<td>Uncertain**</td>
<td>⇐</td>
<td>⇐</td>
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</tr>
<tr>
<td>EH</td>
<td>⇐</td>
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<td>⇐</td>
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<tr>
<td>ADHH+</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
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</tr>
</tbody>
</table>

Trends reflect likely direction of child/adult differences in pathway function.

ADH indicates alcohol dehydrogenase; BW, body weight.

* Applies only when oral absorption is low (e.g., <50%).

† Increases in dermal absorption at 36 wk gestation and earlier, with large increases possible before 32 wk.

‡ Applies to deposition of particles and reactive gases in respiratory tract. Systemic uptake of nonreactive gases can also be increased from short-term acute exposure; however, under steady-state conditions, age group differentials for nonreactive gases cannot be predicted without PBTK modeling.

§ CYP3A pathway activity low unless the chemical can also be a substrate for the fetal isozyme CYP3A7, in which case metabolic rate can be higher in early life.

|| CYP3A7 activity low at these ages, but overlapping substrate specificity with CYP3A4 may keep metabolic activity at or slightly above adult levels.

# Immaturity of N-acetylation conjugating activity during first year of life causes slow acetylator phenotype regardless of genotype.

** GST neonate/adult ratio uncertain because preliminary data suggest that several isozymes are immature at birth, whereas GST pI is high at birth and other isozymes have not been evaluated. Given overlapping function between isozymes, the GST conjugating capacity for any given substrate is currently uncertain.

†† Suggestive evidence for immaturity of ADH system warrants using immaturity factors as for other metabolic systems (CYPs, glucuronidation).
be replaced with specific data for a particular xenobiotic whenever available.

Substrates for the CYP3A family require special consideration because the predominant adult form of the enzyme is deficient in neonates (CYP3A4), but the fetal form of the enzyme (CYP3A7) is highly active in utero and immediately after birth. Because CYP3A7 is capable of activating a number of procarcinogens, it is important to find out whether the chemical under investigation can be activated by this pathway. If this is a data gap but it is known that the activation step can be performed by CYP3A4, then it may be prudent to consider this step also to be active during the perinatal period. This is because of the overlapping substrate specificity between CYP3A4 and 3A7 that often occurs. Because high CYP3A7 activity in early life is present when there is also a larger liver size per body weight and perhaps also poorer detoxification capacity, one should carefully consider the possibility of higher exposure to active metabolites in utero and during the first month of life for CYP3A7 family substrates.

At present, it is difficult to draw quantitative inferences (eg, child-specific TK adjustment factors) from the trends shown in Table 3 because the way in which the various factors interact to modulate internal dose needs to be tested in children’s PBTK analyses. However, the overview shown in Table 3 can be helpful in constructing a qualitative assessment of whether child/adult differences are possible for a given chemical and what direction such differences may take.

SUMMARY

In summary, the various in utero/neonatal/adult TK differences make early-life stages a special concern with respect to both the administration of drug therapies and the assessment of environmental risk. Older children may metabolize and clear xenobiotics faster than adults, which may be protective in some cases but can lead to greater formation of toxic metabolites for other chemicals. Although much has been learned from pediatric pharmacokinetic studies, development of modeling approaches specific to the in utero and postnatal periods is needed to extend these findings and enable the prediction of ADRs and environmental risks for these ages. The general trends in the ontogeny of clearance systems described in this article can be an aid to risk assessors as they evaluate potential susceptibilities and the need for additional data and refinements in analyzing children’s risks.

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Pediatrics 2004;113;973

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