

# Toxicology News

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## Distinguishing Children from Adults in Toxicology: Part 1

By Robert Middleberg

**T**he phrase “children are not small adults” is understood in clinical and laboratory medicine. Pediatrics is a medical specialty with its own strict training and professional guidelines, and pediatric laboratory medicine has methods, procedures, and reference ranges to accommodate this special population.

This author’s experience, however, is that in postmortem forensic matters, children are often treated as adults. The following is a brief overview of the pathological and toxicological issues in this regard.

Part one of this article addresses some of the differences between adults and children. Part two will deal with the challenges unique to the pediatric population in postmortem forensic toxicology and suggest ways to address some of the issues.

### Background statistics

Each year, about 2 million poisoning exposures are reported to U.S. poison control centers. Children generally account for about 65% of these exposures, with about 100 fatalities. Therefore, children comprise the majority of reported poisonings, but most poisonings are not fatal (1). Between the ages of one and five years, there is a significant rise in poisonings, peaking at two to three years (2).

Self-mediated poisonings are rare under the age of one year. Between one and five, there is a significant rise in poisoning exposures, especially those that are self-mediated but unintentional. At this age, children are becoming mobile and orally fixated, tending to put most things they contact into their mouths.

From age six to the adolescent years, there is a significant decrease in self-mediated, unintentional poisonings, but a slight rise in intentional poison-

ings. From adolescence to adulthood, there is a large increase in intentional poisonings, mainly due to experimentation and suicide. By far the greatest preponderance of poisoning deaths in the pediatric population occurs among adolescents (1).

Homicidal poisonings in the United States have been estimated to be about 0.2% of all homicides in people aged 10–50. Of all deaths in children ages one through four in 2001, 7.9% were homicides (3). It is difficult to glean what subpercentages of poisonings and deaths in children are non-accidental. Of all the childhood exposures reported by the U.S. poison control centers in 2002, four were listed as malicious (1). Based on this author’s experience, that is an underestimate of such events.

Between 1992 and 1994, 44 non-accidental poisonings of children in the home were reported in the United Kingdom and the Republic of Ireland, resulting in five deaths (4). Considering historical and empirical evidence, as well as medicolegal and social issues, the rate of non-accidental poisonings in the pediatric population is likely underreported.

### Historical events

A review of historical and reported individual cases demonstrates numerous instances of accidental and purposeful poisonings of children. While space prevents a total accounting, a few notable cases indicate that pediatric poisoning is likely more common than one might think.

Humans have been aware of poisons for a long time, as revealed in the earliest deciphered writings of the Sumerians (4500 B.C.). The perfection of poisoning through the Greek and Roman civilizations and during the Renaissance in Italy and France is well-described (5). That children were the victims of such poisonings is both likely and documented, es-

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## Inside...

**Dietary Supplements ..... 2**

## Abuse of Dietary Supplements Is Common and Dangerous

By Karen E. Simone

From the beginning of recorded history, humans have used plants to alter consciousness and treat illness. Plants are the original source of many currently used medications. The opium poppy contains morphine and codeine. Aspirin is derived from white willow bark. Foxglove is the original source of the heart medication digoxin. Although “natural,” not all plants are safe. Many poisons, such as hemlock and strychnine, are plant-derived.

Plants contain many potentially active alkaloids. The amounts and types vary depending on sun, soil, rainfall, and many other environmental conditions. As a result, predictable and accurate dosing with plant material is difficult. Technology has improved the safety and efficacy by allowing reliable extraction and synthesis of the specific chemicals thought to have the desired effect. Dietary supplements, many of which use crude plant material, recreate the unpredictability of historic times. Chemical content, doses, efficacy, and safety often are not known with certainty.

### Dietary Supplement Health and Education Act

The Dietary Supplement Health and Education Act of 1994 was enacted to ensure the availability of safe and appropriately labeled dietary supplements. It defines “dietary supplement,” and provides guidelines for appropriate labeling and accompanying literature. Unfortunately, the act also removed the pre-marketing safety evaluation requirement for most products. As a result, government regulation of dietary supplements is poor. The Food and Drug Administration (FDA) can remove a dietary supplement from the market only if it presents “a significant or unreasonable risk of illness or injury.”

According to the legal definition, dietary supplements are products meant to supplement the diet to maintain health. Vitamins, minerals, herbs, botanicals, amino acids, enzymes, organ tissues, glandulars, and metabolites are dietary supplements. The products cannot claim to diagnose, treat, cure, or prevent an illness. Labeling may make “structure or function” or “well-being” claims. Ingredients must be listed. Labeling must be truthful and not misleading.

### Abuse

The public uses dietary supplements not only to promote good health, but also to obtain a more

“natural,” legal high. According to the American Association of Poison Control Centers’ Toxic Exposure Surveillance System, in 2002, deliberate misuse was the cause of poisoning by dietary supplements more often than it was the poisoning cause for all other drugs combined, whether over-the-counter, prescription, or illicit. In the poisoning cases in which dietary supplements were the agents, 12% involved abuse or misuse (2,694 of 22,928). Of the other drugs, 6% of cases involved abuse or misuse (75,357 of 1,258,407). Ephedrine products accounted for 77% of the cases of abused or misused dietary supplements.

In the 1980s, teens and young adults used over-the-counter “look-alike” drugs to obtain a “legal” high. Manufacturers designed tablets and capsules to look like more desirable prescription medications, such as amphetamines. The ingredients were usually over-the-counter medications, such as ephedrine, caffeine, or phenylpropanolamine, sometimes in combination. Users could purchase these products at head shops, gas stations, or truck stops, or from magazines or catalogs. “Magnum 357” and “White Cross” are popular look-alike stimulants.

Since the 1990s, the natural, legal high has become popular. “Herbal Ecstasy,” “Ultimate XPhoria,” and “Cloud Nine” are examples of products. Manufacturers promote products as stimulants, depressants, hallucinogens, entactogens (sensation enhancers), or aphrodisiacs. In addition, manufacturers offer natural and “safe” alternatives for weight loss, body building, other athletic performance enhancement, sexual enhancement, and management of psychiatric disorders.

Although many of the ingredients are plants, the alkaloids in the plants are sometimes the same as ingredients in over-the-counter and prescription medications. Table 1 summarizes the herbs discussed below, providing common plant names, effects, and examples of prescription and over-the-counter medications that contain the same key ingredients.

### Stimulants

Stimulants are the most commonly abused dietary supplements. Most contain ephedrine, synephrine, caffeine, or yohimbine. The FDA prohibited the sale of all ephedrine-containing dietary supplements as of April 12, 2004. The manufacturers of ephedrine-containing products will most likely replace the ephedrine with other stimulants, probably synephrine or caffeine. The risks of use or abuse are those associated with enhanced stimulation, which increases heart rate and blood pressure, and can cause seizures and psychosis. Heart attack, stroke, and arrhythmias can occur. Manufacturers often combine

several separate sources of stimulants in one product. Ephedrine or synephrine is combined with caffeine, yohimbine, or both, increasing the risk of serious adverse events.

### Depressants

Manufacturers also offer depressants. Unlike stimulants, depressants typically do not contain the same ingredients as over-the-counter or prescription medications. Most are only slightly effective and minimally toxic. Commonly used depressants include valerian, kava-kava, passion flower, melatonin, and skullcap.

Although the mechanism of action is unclear, valerian's effects may be partially due to enhancement of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Alcohol, benzodiazepines, and barbiturates also work through GABA. Some clinical trials suggest mild efficacy in treating insomnia and anxiety. Two case reports, one oral and one parenteral, documented overdose. Abdominal and chest pain, dilated pupils, fatigue, tremor, and dizziness occurred. Withdrawal, which may have been related to long-term valerian use, was reported after abrupt discontinuation. Tachycardia and delirium resolved after treatment with a benzodiazepine. Chronic use may be associated with headache, hyperexcitability, and insomnia.

Kava-kava is a plant that grows throughout the Pacific islands, where it is used socially the way Americans use alcohol. The plant is pulverized or chewed, steeped in water, filtered, and served at room temperature. The dietary supplements are usually in the form of tablets, capsules, or extracts. Kava is a depressant with some local anesthetic effect. It may block sodium channels, enhance inhibitory neurotransmitters (GABA and glycine), or antagonize excitatory neurotransmitters (glutamate and aspartate). Most reported effects are from the homemade brew, not tablets or capsules.

Kava-kava numbs the mouth and induces alcohol-like effects, including mild euphoria, contentment, and talkativeness. Chronic use can cause a red, scaly rash, problems with visual accommodation, and liver dysfunction or failure. Hallucinations or delusions can occur with chronic heavy use. Extrapyrmidal effects and reversible paralysis have been reported with heavy use. Unstable gait and impairment of motor control can also occur, especially with high doses. It is questionable whether dietary-supplement forms cause significant effects.

Passion flower can have mild sedative and anxiolytic properties. Significant drowsiness, as well as decreased or irregular heart rhythms, can occur in large overdose.

Melatonin is not usually abused. Skullcap probably does not cause significant central nervous system effects in regular doses, although chronic use may cause liver dysfunction. Overdose is not well-documented, but may cause giddiness, stupor, confusion, and seizures.

### Hallucinogens

Many products are promoted for hallucinogenic properties. Morning glory seeds, Hawaiian baby woodrose seeds, nutmeg, damiana, and salvia are touted as natural hallucinogens. Morning glory and Hawaiian baby woodrose seeds contain *d*-lysergic acid and related alkaloids. The ability of morning glory seeds to cause hallucinations is questionable. When a subject ingested 250 morning glory seeds, anxiety, tension, and diarrhea resulted.

Morning glory is sometimes confused with the more potent woolly morning glory (Hawaiian baby woodrose). A subject who ingested 100 Hawaiian baby woodrose seeds experienced nausea and vomiting, dilated pupils, tachycardia, agitation, and paranoia. The potential for a significant LSD-like effect is questionable, especially when the alkaloids are included as components of a tablet or capsule.

Nutmeg causes considerable toxicity when the powdered spice is ingested in large quantity, approximately one to three tablespoonfuls. Capsules and tablets are unlikely to contain enough nutmeg to cause hallucinations.

Salvia is becoming more popular. Those who chew or smoke it report LSD-like effects. Swallowing it is thought to inactivate the components necessary for a high.

Most of the hallucinogens require a fairly pure form of plant or seed to have significant effects. Tablets and capsules are unlikely to cause hallucinations.

### Summary

Some manufacturers and users promote dietary supplements as safer than pharmaceutical or illicit drug alternatives, whether used "appropriately" or to obtain a legal high. Although dietary supplements are probably safe in most cases, significant toxicity is possible.

Depending on the dietary supplement and the dose, it appears that the greatest effects are obtained directly from pure plant products or home-brewed beverages. Tablets and capsules contain such small amounts of plant alkaloids that their effects are limited. Stimulants are notable exceptions, and are more likely than other abused dietary supplements to cause significant effects.

Learning a few of the common and scientific

Table 1. Common dietary supplements

Scientific Name (Common/Other Names)	Selected Ingredients	Intended Effects	Toxic Effects	Medications and Dietary Supplements Containing
Ephedra sinica, intermedia, equisetina (Ephedra, ma huang, yellow horse, yellow astringent, epitonin)	Ephedrine, pseudoephedrine	Stimulant, weight loss, enhanced athletic performance	Increased HR, BP, and T; seizures	OTC medication: Ephedrine sulfate (oral)  Supplements: Herbal Ecstasy (previously), Metabolife, Stacker, Yellow Jacket, Xenadrine, Uraeus Liquid Speed
Pinellia ternate (Ban xia)	Ephedrine, pseudoephedrine?	Stimulant, weight loss, enhanced athletic performance	Increased HR, BP, and T; seizures	OTC medication: Ephedrine sulfate (oral)  Supplements: Cold Snap, No Cigarettes with Menthol and Clove, Minor Bupleueum
Sida cordifolia (Heartleaf, country mallow)	Ephedrine, pseudoephedrine?	Stimulant, weight loss, enhanced athletic performance	Increased HR, BP, and T; seizures	OTC medication: Ephedrine sulfate (oral)  Supplements: Herbal Ecstasy, Bliss Extra, EX:1, Road Runner Super, Metabolife, Stacker, Yellow Jacket, Xenadrine, Trip-E
Citrus aurantium (Bitter orange)	Synephrine	Stimulant, weight loss, enhanced athletic performance	Increased HR, BP, and T; seizures	OTC medications: 357 Magnum, Vivarin, Molie, Overtime, NoDoz  Supplements: Xenadrine EFX, Trip2Night (ephedra-free)
Paullinia cupana (Guarana, zoom, Brazilian cocoa)	Caffeine, theophylline, theobromine	Stimulant, weight loss, enhanced mental alertness and athletic performance	N, V, increased HR, increased or decreased BP, arrhythmias, seizures	OTC medications: 357 Magnum, Vivarin, Molie, Overtime, NoDoz  Supplements: Xenadrine NRG, Grand Prix, Road Runner Super, Awake, Herbal Xtreme, Colt Liquid Extreme, Organic Ecstasy
Camellia sinensis (Green tea)	Caffeine, theophylline, theobromine	Stimulant, weight loss, enhanced mental alertness and athletic performance	N, V, increased HR, increased or decreased BP, arrhythmias, seizures	OTC medications: 357 Magnum, Vivarin, Molie, Overtime, NoDoz  Supplements: Xenadrine EFX, Xenadrine NRG, Organic Ecstasy
Cola nitida (Kola nut, cola nut)	Caffeine, theobromine	Stimulant, weight loss, enhanced mental alertness and athletic performance	N, V, increased HR, increased or decreased BP, arrhythmias, seizures	OTC medications: 357 Magnum, Vivarin, Molie, Overtime, NoDoz  Supplements: Xenadrine NRG, Herbal Xtreme, Colt Liquid Extreme
Ilex paraguariensis (Yerba mate, mate, Paraguay tea, St. Bartholomew's tea, Jesuit's tea)	Caffeine, theophylline, theobromine	Stimulant, weight loss, enhanced mental alertness and athletic performance	N, V, increased HR, increased or decreased BP, arrhythmias, seizures	OTC medications: 357 Magnum, Vivarin, Molie, Overtime, NoDoz  Supplements: Xenadrine EFX, Xenadrine NRG, Colt Liquid Extreme, Organic Ecstasy
Corynanthe yohimbe, Pausinystalia yohimbe (Yohimbe)	Yohimbine	Aphrodisiac, stimulant, hallucinogen	Increased HR and BP, N, V, D, palpitations, dizziness, hallucinations	RX medications: Yocon, Aphrodyne  Supplements: Herbal V, Ecstatic, Stay Erect, Nymphomax, Aphrodisiac "Boom!"

Scientific Name (Common/Other Names)	Selected Ingredients	Intended Effects	Toxic Effects	Medications and Dietary Supplements Containing
Valerian officinalis (Valerian, baldrian)	Valerenic acid, valtrate, acevaltrate, didrovaltrate	Sleep aid, anxiolytic	Chronic: headaches, excitability; OD: tight chest, decreased BP, dilated pupils, abdominal pain, tremors, lightheadedness; withdrawal possible	Medications: None  Supplements: Benzo Berries, Blue Berries
Piper methysticum (Kava-kava, awa, kawain, kavain, yangona)	Kawain, dihydrokawain, methysticin, dihydromethysticin, yangonin, demethoxyyangonin	Social drink for mild euphoria, anxiolytic, anti-stress, for restlessness	Acute: N, sedation, numb mouth, temporary paralysis, extrapyramidal effects; Chronic: shortness of breath, gastritis, liver/renal dysfunction, weight loss, skin rash, disorientation, hallucinations; OD: visual effects, ataxia, paralysis	Medications: None  Supplements: Waka, HTP. Calm, Happy Camper, Liquid Lust, Benzo Berries, Blue Berries
Passiflora incarnata (usually) (Passion flower, passion fruit, granadilla, water lemon, maypop, apricot vine)	Passiflorine, harmans, maltol, flavonoids	Sedative, anxiolytic	Allergy, drowsiness, fatigue, N, V, decreased HR; OD: arrhythmia possible	Medications: None  Supplements: HTP.Calm, Happy Camper, Algerian Blend, Sativah (herbal smoke), Ecstasy Cigarettes, Pipe Dreams Smoking Blend
Scutellaria laterifolia (Scullcap, skullcap, helmet flower, hoodwort, mad-dog weed)	Scutellarein, wogonin, baicalin, scuterivulactone	Herbal tranquilizer (ineffective) and rabies treatment (ineffective)	Chronic: hepatotoxicity possible; OD: giddiness, stupor, confusion, seizures possible	Medications: None  Supplements: Algerian Blend, Sativah (herbal smoke), Pipe Dreams Smoking Blend
Salvia divinorum (Salvia, diviners sage, yerba de maria)	Salvinorin-A,	Hallucinogen	Flashbacks	Medications: None  Supplements: Sage Extract 5X, Sativah (herbal smoke)
Myristica fragrans (Nutmeg, mace, nuxmoschata)	Camphene, dipentene, myristicin, elemicin	Hallucinogen	N, V, flushing, increased HR, dry mouth, giddiness, disorientation, chest pressure; then delirium, stupor and deep sleep	Medications: None  Supplements: Liquid Lust, Herbal Xtreme, Colt Liquid Extreme
Ipomoea violacea (Morning glory)	$\alpha$ -lysergic acid	Hallucinogen	D, anxiety, tension	Medications: None  Supplements: Druids Fantasy, Space Cadets
Argyrea nervosa (Hawaiian baby woodrose, woolly morning glory)	$\alpha$ -lysergic acid	Hallucinogen	N, V, increased HR, dilated pupils, agitation, paranoia	Medications: None  Supplements: Trip-E
Turnera diffusa (Damiana, old woman's broom, rosemary, herba de la pastora)	1,8-cineol, pinenes, damianin, others	Aphrodisiac, hallucinogen	Unknown, probably minimal to none	Medications: None  Supplements: Algerian Blend, Liquid Lust, Sativah, Ecstasy Cigarettes, Erotic, Pipe Dreams Smoking Blend

Key: OTC, over-the-counter; RX, prescription; N, nausea; V, vomiting; D, diarrhea; HR, heart rate; BP, blood pressure; T, temperature; OD, overdose.

names will help readers anticipate the effects of dietary supplements by monitoring labeled ingredients.

### Suggested Reading

1. Drug facts and comparisons. eFacts online. Wolters Kluwer Health ([www.wkhealth.com](http://www.wkhealth.com)). [www.factsandcomparisons.com/ProdPage.asp?ID=1042](http://www.factsandcomparisons.com/ProdPage.asp?ID=1042). Accessed April 15, 2004.
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## Pediatric Toxicology

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pecially since children were considered a form of property in many cultures. Roman law ("Patria potestas") gave exclusive rights to men over children, including power of life and death (6).

The poisoning of children has continued through time with some very notable cases. Roman emperor Claudius was poisoned by his second wife so her son, Nero, could gain the throne. To avoid competition, Nero had his half-brother Britannicus, the rightful heir, poisoned at the age of 12 (7). During the heyday of the French female poisoners, Catherine Deshayes Monvoisin, alias La Voisine (the neighbor), was a well-known poisoner for hire. In perfecting her "art," she reportedly poisoned to death some 2,000 infants (5). For these and other offenses, she was burned at the stake in 1680 (8).

Mary Cotton was perhaps England's most notorious female poisoner. In addition to murdering three husbands and a few other adults, from 1842 to 1872 she managed to poison to death with arsenic 12 children, a few of them stepchildren, but many her own. Forensic toxicological evidence in specimens from her last victim, as well as from four exhumed previous deaths, led to her hanging in 1873 (9). In England, between 1863 and 1887, children under five were more likely to be the victims of homicide than all other age groups combined, with poisoning being a significant means. Children too young to work were often insured and then poisoned to relieve ailing family finances (10).

In the United States, Genene Jones, a pediatric nurse in Texas, was suspected in the deaths of 47 children at a hospital and several more at a nearby clinic. She was found guilty of murder in 1983 for the death of one child from the clinic through the use of succinylcholine. She was also convicted of inflicting injury to a child through the use of heparin (11, 12).

### The basis of differences

There are many anatomical, physiological, and psychosocial reasons why children should not be considered small adults. While space limits this discussion, some important differences relevant to post-mortem forensic toxicology should be stressed. From the time of birth through entry into adulthood, the human body goes through an incredible metamorphosis. Blood volume increases from approximately 0.3 liters at birth to 4–5 liters in adults, while the body surface area increases about eightfold (13). Other significant differences are best described as toxicokinetic or toxicodynamic in nature.

### Toxicokinetic differences

Toxicokinetics is defined as the dynamic behavior and movement of toxic substances and their metabolites within a living system (14). The four main processes involved are absorption, distribution, metabolism, and elimination. These processes vary greatly through the developmental stages. Absorption differences between children and adults are greatest in the very young, especially during the neonatal period.

During the first year or so of life, notable differences in gastric emptying time, exocrine pancreatic function, bile acids, and bacterial flora lead to adults and children differing significantly in the onset of action and bioavailability of administered or exposed substances. For example, in the first few days of life, the gastric pH may be neutral or basic, thus facilitating absorption of basic and acid-labile compounds. It takes about three months for gastric secretions in the infant to reach the lower limit of acidity found in adults. In addition, neonates and infants have longer gastric emptying times and irregular peristalsis (15).

The distribution of toxic substances in the young child is also affected by maturing processes, especially in regard to such parameters as body water (16):

Age	% Total Body Water
Premature	85–90%
<1 year	70–80%
1 year	60%
Adult	55%

Adipose tissue in the neonate can contain as much as 57% water and 35% lipids, whereas the corresponding values in adults are 25% and 70%. Protein-binding in neonates, depending on the protein involved, may be greater or less. Some of these differences are maintained through infancy (16). All these factors can have significant effects on the bioavailability and resulting blood concentrations of various toxicants, such as ethyl alcohol, phenytoin, phenobarbital, and salicylate.

### Differences in metabolism

The metabolism (including biotransformation) of toxic substances can be qualitatively and quantitatively different in numerous organs and tissues in a child compared with an adult, and a good example is hepatic function. Phase I hepatic biotransformations mature rapidly and reach adult capacity by six months of age. At birth, however, total neonatal hepatic cytochrome P450 concentration is only about 30% that of adult levels, so neonates have less xenobiotic oxidation capability with resulting longer half-lives or lower renal clearance. Some examples of compounds affected by this immature CYP activity include caffeine, diazepam, fentanyl, midazolam, nicotine, phenytoin, and theophylline (17).

Some phase II biotransformation reactions are significantly lower in young children than adults, with some not reaching adult capacity until three to four years of age. Glucuronidation processes, the predominant phase II reactions in adults, have only 10–30% activity in the neonate and take years to fully mature. Compounds affected by this lack of glucuronidation include bilirubin, acetaminophen, morphine, chloramphenicol, salicylate, oxazepam, and naloxone. The almost always fatal gray baby syndrome following chloramphenicol administration is a result of the inability to glucuronidate significantly.

On the other hand, sulfation is a quantitatively and qualitatively important phase II reaction in children. Sulfation of acetaminophen remains the primary phase II conjugate up to age nine; thereafter, glucuronidation is the predominant conjugate (17).

### Elimination of toxic substances

The body's ability to eliminate toxic substances is a critical factor in ameliorating potential chemical-induced damage. While the body has numerous means to eliminate xenobiotics, including through exhalation, sweat, and feces, the kidney is the primary excretory organ for many compounds. Such factors as renal blood flow, glomerular filtration, tubular secretion, and reabsorption all play significant roles in renal excretion. Renal blood flow approximates that of adults at five to 12 months of life while

glomerular filtration rates reach maturation from three to five months of age. However, tubular secretion and reabsorption appear to mature at much slower rates. Such factors can significantly affect the residence time of toxic agents such as aminoglycosides (16, 18, 19).

Overall, differences in toxicokinetic variables lead to significant differences in the residence time of numerous substances. For example, the half-life of caffeine in adults is about six hours, whereas in newborns it is approximately 103 hours (20).

### Toxicodynamics

Toxicodynamics is defined as what effects the toxin or toxicant has on the organism, and these effects are more difficult to quantify in children than are the toxicokinetic variables. Much of this difficulty has to do with the inability to test the effects of xenobiotics in this population prior to actual exposure. Legislation on the issue of premarket testing of drugs in children in the United States is constantly in turmoil. The majority of pediatric studies of drugs are performed in children with pre-existing pathology, thus introducing potential unknown factors. Virtually no exposures to environmental/occupational toxicants are tested in children. Notwithstanding, some empirical observations have led to some important conclusions.

The most important conclusion is that, in general, effects in children may be significantly different from those in adults. The paradoxical effects of some central nervous system stimulants and depressants clearly demonstrate such differences. On a cellular level, age-related sensitivity of receptors has been demonstrated in animals (21). Such differences probably exist in humans as well. A number of medications are administered in higher or lower doses compared with adults to elicit desired effects in children, such as digoxin. Toxicologically, the age-related sensitivities to lead exposure present a significant age-related toxicodynamic difference.

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