Part I — The Basic Science

Chapter 1 — Toxicology 101

Introduction

The whole purpose of this book is to provide information that can help readers discern what factors in the environment are likely to promote effective immunity and corresponding good health in their children from those that are likely to contribute to immune problems and chronic disease. Individual variation certainly exists, and one's genetic background can influence metabolism, organ sensitivity and the impact of chemical exposures and dietary intake. But there is also information that is generally applicable to all pregnant women and children and can help in creating a safer environment for the child's developing immune system. One important step in this process is the identification of what is harmful and what is not, also known as toxicology.

For our purpose of discussing human health risk and particularly that of our children, toxicology can be defined as the study of the adverse health effects resulting from exposure to chemical, physical or biological agents. The interaction between the body and the external environment includes a variety of encounters with chemical, physical and biological factors ranging from pesticides and solvents to drugs and toxin-containing infectious agents. These interactions occur through the foods we eat, the air we breathe, the water we drink and the surroundings we and others create.

These surroundings can range from those found in our home (clothing, cleaning agents, toys and furniture) to those in our workplace environment (computers, copiers, air handling systems, machinery) and those in our neighborhoods (daycare centers, traffic, roadways, shopping areas, golf courses, farms, parks and skyscrapers). Everything we encounter, whether through our lungs, on our skin, via our mouth or through our eyes, becomes an environmental exposure worthy of examination. But each element is not necessarily of equal concern. Some elements carry a significant risk that they may harm the immune system. Other exposures have very little risk for immune damage. Some exposures are beneficial and even necessary for good health. Making those distinctions is why toxicology developed as a science. This concept of risk is discussed further in the next chapter.

The interactions between the body and environmental factors generally follow very simple rules. Some exposures are useful and may play a critical role in promoting good health. Others are problematic and can damage the health of our children. Some exposures are not only beneficial but are necessary for survival (e.g., intake of certain vitamins and minerals). The body, including its immune system, needs certain dietary building blocks or it cannot survive. For example, we must have protein for our immune cells to continue to function and maintain healthy muscles.

At the other extreme, a number of exposures are likely to be harmful for virtually everyone regardless of age, gender or genetic background (e.g., exposure to cyanide or sarin gas). However, there is also a middle ground. There are some environmental factors that can be dangerous, but only for some groups of people. For example, exposure to cytomegalovirus is usually not a big problem for people with a healthy immune system. But for the very young, the very elderly and those with weakened immune systems (e.g., AIDS or chemotherapy patients), exposure to that virus can be life threatening. There are also some substances that may be very toxic but not every exposure to them presents an equal danger. An example of this is botulism toxin.

Botulism toxin is produced by the bacterium, *Clostridium botulinum.* It is also one of the most potent toxins known. Why were people in older generations taught never to buy a canned good with the sides bulging out? Because the bulges were a result of a broken or improper seal and presented the risk of botulism contamination. In the past, people were taught that these products should be avoided at all costs. Or should they?

Ironically, nowadays some people actually pay good money to be exposed to one of the most dangerous toxins we know. The exposures come in the form of BOTOX treatments. Miniscule amounts of the botulism toxin are injected into small areas of the body (generally the face) for cosmetic and medical purposes. The botulism toxin stops signals between the nerves and muscles. This can be used to treat medical problems such as Bell's palsy, lazy eye or cerebral palsy. Of course it has also been used cosmetically to remove wrinkles. But the trick is to ensure the toxic action is only in the local nerves and muscle and can never reach the brain.

Another extremely deadly toxin has also been used for medical treatments. Ricin toxin is the product of castor beans and is a public health concern since it has been produced by terrorist organizations seeking to chemically attack and destroy large populations. But the toxin has medical applications when it can be delivered to cells we want to kill. Very small amounts of the ricin toxin are used to target cancer cells in cancer therapy. Antibodies can be used to direct the ricin poison directly to the cancer cells. In spite of the positive uses for both botulism toxin and ricin toxin, there still remain significant dangers if we encounter them outside of these highly specialized circumstances.

So the trick in toxicology is to know which environmental exposures fall into high health risk categories. What needs to be considered to make this determination? Here are some of the questions that get asked along the way.

1) What is the nature of the environmental factor?
2) What is the way in which the body handles or processes it?
3) How much time does it or its by-products spend in the body?
4) What reactions does this factor undergo in the body?

These questions and the resulting answers help us to place an environmental factor into different categories of potential danger.

One of the misconceptions about chemicals is that we can easily divide them all into a world of inherently good chemicals or despicably evil chemicals. For a few selected chemicals with historic industrial benefits (e.g., the heavy metals lead, mercury, cadmium, arsenic and the dioxins), it is challenging to find any beneficial, let alone "safe" levels.

But for the vast majority of chemicals, blanket good vs. evil labels simply don't apply. The reality is that for most chemicals and drugs, significant health risks occur only for some levels of exposure while other exposure levels are either safe (innocuous to our health) or may be beneficial if not required for good health (e.g., iron, zinc, and vitamin D). In these cases, there is no good or evil label that is useful, only good or bad doses of exposure. For example, one might think that in terms of health, oxygen is inherently good, mercury is inherently evil. But there is more to this story. It is the dose that makes the poison.

The Dose Makes the Poison

In 16th century Germany, a physician and alchemist first began to detail the impact of minerals on human health. This doctor, who revolutionized Medieval thinking about environment and health, eventually became known simply as Paracelsus. Paracelsus recognized that the intake of some minerals was required for good health while other mineral exposures produced illness and even death. He also noted that only certain levels of mineral intake were effective for promoting improved health. Paracelsus essentially became an early version of what we would now call a compounding pharmacist. Among his most significant accomplishments was the coining of what in English translation has become the motto of modern toxicology "the dose makes the poison." This is the entire basis of the field of toxicology, which is founded on the concepts established by Paracelsus. We understand that chemicals and drugs can be safe at some levels of exposure and dangerous at others. Of importance is learning what safe doses are, what dangerous doses are and when we might encounter each of them.

Too Much of a Good Thing

Oxygen is essential for human life; everyone agrees with this. Our atmosphere contains approximately 21% oxygen. The reality is that our bodies need only a certain level of oxygen for optimum health and under normal circumstances, the amount in the air is ideal for our good health. Too little or too much oxygen can be equally harmful. Too little oxygen is technically called hypoxia. With too little oxygen our cells and tissues can literally starve and organs such as the brain become damaged. If the situation continues, organs can fail and we will eventually die.

Oxygen toxicity involves the other extreme of "dose," essentially too much oxygen. The two ways that oxygen toxicity can occur is by forcing it into our lungs at too high a pressure or forcing it into our lungs at too high a percentage over a long period of time. Oxygen toxicity affects the central nervous system (CNS), the lungs and the eyes. Which tissue is most likely to be affected depends upon whether the excess oxygen is at too high a pressure with a higher percentage than normal or whether it is at normal pressure but too high a percentage for a long period of time. It is possible to tolerate 100% oxygen for 24 to 48 hours at sea level. But problems can begin to arise after only a few hours, and the likelihood of severe tissue damage increases as time goes on.

Since the 19th century it has been known that breathing too high a concentration of oxygen for too long a period of time can produce toxicity. In reality, oxygen toxicity is more of a concern for premature newborns in neonatal care units, scuba divers and astronauts. How does this work?

Many premature babies have underdeveloped lungs. They lack lung proteins called surfactants that help to keep the lungs open so air can enter. Without assistance they would suffer from oxygen deficiency. They need oxygen delivered to the lungs and tissues at higher concentrations since their lungs are not mature enough to accomplish what is needed. This is usually performed in the hospital's Neonatal Intensive Care Unit (NICU). In these units, higher concentrations of oxygen can be delivered either via a hood (for babies who can breathe on their own) or though a mechanical ventilator, which helps to fill the collapsed lungs. The latter may also deliver oxygen under high pressure to help the babies breathe. But it is a fine art to provide just enough oxygen and not too much. Under these circumstances, oxygen toxicity can occur that alters lung development, immune system development and the vascular development of the eye. The latter scenario results in vision problems for the child.

Much of the damage caused by oxygen toxicity appears to come from the overproduction of oxygen free radicals and damage to the tissues. Breathing oxygen over 60% for too long can cause multiple problems. The eye is a vulnerable site because premature babies don't have complete blood system development to support the eye. Oxygen toxicity can interfere with and then alter the course of the needed vascular development.

In the case of scuba diving, oxygen is usually carried at either its normal concentration (21%) or at high concentrations for certain periods of time — called hyperbaric oxygen. However, as the diver moves to different depths, the external pressure increases. Diving too deep can cause the oxygen to be under too high a pressure, and toxic amounts can be delivered to the blood and tissues while breathing. The oxygen toxicity created can lead to seizures and brain damage.

For astronauts, breathing oxygen safely depends upon their situation. For example, they are able to safely breathe 100% oxygen for days in the orbiting capsule because the pressure in the capsule is only a fraction of what is found on earth. However, changes during space walks and re-entry mean that the pressure and the concentration of oxygen need to be adjusted to ensure the astronauts both avoid decompression and avoid a lack of oxygen or oxygen toxicity.

Of course, for most of our day-to-day encounters, the oxygen in the air is at a level that is safe, beneficial and required for life. This example with oxygen serves as a reminder that virtually any chemical or drug, even those required for life, can become toxic given a high enough concentration. For this reason, it is important for us to identify which concentrations of chemicals and drugs are safe for our children and which are potential problems for their health and well-being.

Selenium: Deficiency, Health (Immune Protection) and Toxicity

A good example of Paracelsus' idea can be found in our exposure to the mineral, selenium (designated as "Se" on the chemical periodic table). Selenium is an essential micronutrient that is involved with an enzyme (glutathione peroxidase) that is important in the detoxification processes to get rid of oxygen radicals. Glutathione peroxidases are a family of enzymes that, in effect, have antioxidant activity. They convert two dangerous chemicals to safer alternatives. These particular enzymes can take hydrogen peroxide and turn it into water, and they can take very dangerous lipid-radicals and make them into by-products that the body is able to handle. The trick is that the enzymes must have selenium in them to function. For this reason, one of the major roles of selenium is as an antioxidant. Selenium, through its role in glutathione peroxidase, helps to protect our tissues and organs from oxidative damage as our body fights infections and cancer.

Selenium is naturally found in many of the foodstuffs we eat such as cereals (e.g., oatmeal) and grains used to make bread. Selenium content in plants such as wheat is influenced by the soil content where the crop was grown, and this can vary widely. In fact even within the same country, soils in some areas can be deficient in selenium while soils in other regions may contain dangerously high levels of the mineral. At the extremes, this translates directly into the production of selenium-deficient wheat or selenium-toxic wheat depending upon the locale (an example of the latter is found in China). Many individuals also obtain selenium through the food chain (e.g., poultry and other meats) as well as via dietary supplements. This is important because selenium intake is needed for good health. Selenium has a unique antioxidant function that isn't covered by other antioxidants such as vitamin E and vitamin C. So if the level of selenium intake is too low, it results in disease.

Selenium deficiency can affect several different tissues and organs. It leads to diseases such as Keshan Disease, which is associated with an enlarged heart. The disease is given its name after Keshan province in China where the soil is deficient in selenium, and the crops grown locally do not provide sufficient amounts of selenium. Since its naming, the disease has been identified in other countries as well (e.g., New Zealand and Finland). Children and women are particularly susceptible to the disease. Once the heart muscle has been damaged from selenium deficiency, selenium supplementation does not reverse the damage.

In contrast, selenium toxicity, also called selenosis, produces symptoms such as gastrointestinal distress, hair loss, fatigue and neurological damage. Selenium toxicity has been found in certain areas of China where local corn grown in very high selenium soils was a major part of the diet.

As an anti-inflammatory agent, selenium may be important in combating inflammation-related conditions such as cardiovascular disease. Other investigators have reported that selenium levels may be important in certain autoimmune diseases such as autoimmune thyroiditis (Grave's disease and Hashimoto's disease).

Some Factors are Rarely Safe in Nature, Others are Rarely Dangerous

If the dose makes the poison, there are certainly chemicals and drugs that are dangerous at the concentration we usually encounter in nature. Table 1.1 shows a comparison of toxic doses for several chemicals and drugs.

The comparison of relative toxicity for sarin gas vs. vitamin A or for ricin toxin vs. diazepam is remarkable. It highlights the fact that some toxins are only theoretically safe and at the concentration we usually see in nature, they represent significant health hazards. One simply does not want to encounter the botulism toxin or ricin toxin outside of a medical clinic, since a little goes a long way in terms of potential harm to our health.

However, other chemicals and drugs are of little health concern at the levels we are likely to encounter in our daily lives. An example of the latter is amygdalin. This toxin is contained in apple seeds and in some fruit pits. When ingested and in the acid environment of the stomach, amygdalin is converted to cyanide. With enough cyanide, it can kill you. But you would have to eat several buckets full of apple seeds to ingest dangerous levels of amygdalin. So toxicity from amygdalin found in

Table 1.1. Sample adult toxicity of different chemicals (approximate single dose level of each chemical that is considered hazardous to a 170 lb adult).

Toxin	**Dose**	**Toxin**	**Dose**
Botulism toxin	0.4 micrograms	Cyanide	116 milligrams
Ricin	463 micrograms	Acetaminophen	12 grams
VX (nerve gas)	8 milligrams	Aspirin	23 grams
Sarin	15 milligrams	Vitamin A	>39 grams

Botulism toxin is more than 100 million times more toxic than Vitamin A for a single dose.
Note: This table is only provided to illustrate the magnitude of the differences for toxicity and should not be used as a personal safety guide.

apples is a theoretical possibility but not a practical danger. In contrast, many apricot pits contain enough amygdalin to be a practical problem. In the 1990s, some health food products that were imported into the United States were found to contain enough amygdalin-containing apricot pits in one bag to kill several people.

Children are Special in Toxicology

Our children have different safety concerns that must be distinguished from those of adults. They are not simply smaller versions of adults. The challenge for us as a society is that we have been far more successful at defining safe vs. harmful doses for adults than for the various developmental stages of a child's life. This needs to change.

Benefits and Risks of Aspirin: Children are Not Small Adults

Aspirin (or acetylsalicylic acid) would certainly qualify as one of the miracle drugs of the 20th century if not of human civilization. It has been mass-produced as a human therapeutic agent for over 100 years. Even before that, the bark of white willow trees (a source of a precursor to salicylic acid) was used by the ancient Greeks and Native Americans to treat pain. Yet, while it has tremendous potential benefits when used at moderate doses by most adults, safety for children is not simply a matter of lowering the adult dose of aspirin to fit a child's body weight. Instead, we now know that aspirin presents very specific age-related risks for children. Children are not simply smaller versions of adults.

Aspirin blocks the production of inflammatory metabolites called prostaglandins (produced by macrophages and other cells). These metabolites are involved in the chemical cascades that lead to pain and fever. By interfering with these cascades, aspirin is effective at reducing fever (antipyretic activity), alleviating pain (analgesic activity) and reducing the swelling (anti-inflammatory activity) associated with inflammatory reactions. A health risk to adults for consuming moderate doses of aspirin would be an allergic reaction to the drug. At higher levels, thinning of the stomach lining, ulcers, problems with blood clotting and kidney dysfunction are concerns. But the vast majority of adults benefit greatly from the moderate use of aspirin as demonstrated by decades of results.

Yet, this adult miracle drug has added health risks for some children. For children, aspirin presents the risk of Reye's syndrome particularly in children suffering from a fever. The condition connected to Reye's syndrome, as seen in aspirin-treated children from infants to teenagers, often looks similar to a viral illness such as meningitis including symptoms of vomiting, diarrhea and irritability. The actual mechanisms leading to Reye's syndrome are not well known, but mitochondrial toxicity may be involved. However, it is not known if it is a cause of organ damage or one of the effects.

Reye's syndrome is associated with liver degeneration and can lead to brain inflammation, damage and even death if left untreated. The liver problems appear to arise when enzyme activity changes and certain lipids get over-produced in the liver and flood the serum and other tissues. Excess glutamate appears to cause toxicity in the brain particularly to astrocytes (brain macrophages). While Reye's syndrome is relatively rare, it is an excellent example of the difference in health risks for adults as opposed to children. Because of the risk of Reye's syndrome, aspirin use is not recommended for individuals under 20 years of age.

Beyond the immediate uses of aspirin for treating headaches and fevers in adults, regular use of aspirin in adults can have multiple longer-term benefits. In fact, regular use of low dose aspirin is now recommended for middle-aged adults to reduce the risk of heart disease in men and stroke in women. This lesson of age-related risks for aspirin is one that we should apply to the entire spectrum of chemical and drug safety for children.

Understanding the dose and potential health risks can make the difference between a chemical, drug or dietary factor being safe and promoting good health or being toxic and damaging health. A significant amount of time and money has been invested in identifying the risk of environmental exposures relevant to adult populations. Ironically, despite the fact that our children represent our future, we know less about the safety of these factors for the developing immune and neurological systems of children than we do for ourselves.

Conclusions

The legacy of Paracelsus is that we appreciate the value of both natural and synthetic chemicals and drugs and the ways in which they may benefit health. But we also understand that even too much of an otherwise good thing can harm us. Knowing what is safe, what promotes our health and what impairs our health is the minimum of what toxicology can and should tell us. But toxicology has to be used to give us those answers. Safety testing when restricted to adults does little to help us protect our children. The lessons of children's special sensitivities, such as the recently discovered risk of Reye's syndrome, should guide us in the testing lab before medications are approved as safe for children. These lessons should not have to be learned in our homes.

Overview of Toxicology 101

- The motto of toxicology is: the dose makes the poison.
- Specific chemicals and drugs are not necessarily good or bad. But the doses of chemicals and drugs can be good or bad.
- Even too much of a good thing can be bad (e.g., oxygen at 100% can be toxic).
- Knowing what doses may harm children is our goal.
- Basic features of children (e.g., higher breathing rate) make them more sensitive to the environment
- An exposure that is safe for adults may not be safe for children.