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A SMALL DOSE OF TOXICOLOGY

The Health Effects of Common Chemicals

2nd Edition

HWP | Healthy World Press

A Small Dose of Toxicology, 2nd Edition
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Preface to the 2nd Edition

My goal has always been to make toxicology both relevant and interesting to the casual reader. Toxicology is the study of how chemicals affect the body. Science and our use of chemicals are integral to modern life; the more we understand how chemicals affect our health and well-being, the more we can do to make smart choices as consumers and to advocate for human and environmental health.

After finishing the first edition of *A Small Dose of Toxicology* (published by Taylor & Francis in 2006) I created a website to support the book and make PowerPoint presentations readily and freely available for each chapter of the book. I wanted to build a tool to help people become better acquainted with the principles of toxicology and to provide something both teachers and students would find useful. In the spirit of creating tools that are both useful and fun, I also created an interactive poster on toxicology that allows the user to click on a square and get more information on a particular subject.

One of the important aspects of science and of toxicology is how our understanding of chemicals has evolved over time. The lessons we have learned with the use of chemicals, sometimes unhappy ones, are often incorporated into present-day regulation and best practices to protect human and environmental health. To highlight toxicological history through the ages, toxicologist Toni Hayes and I created another interactive poster, "Milestones of Toxicology," which has been translated into Arabic by Ansam Sawalha. Often our challenge is not only to generate new information, but to better use what we already know in order to make the best possible decisions and policies for our families and future generations.

While pondering how to create a collection of interactive information that would integrate science with chemicals' health effects and historical lessons learned, I became increasingly fascinated with wiki technology and wiki websites. Sites like Wikipedia allow a community of people to build a broad base of interactive, dynamic, and connected knowledge. This fascination led to the creation of Toxipedia, a wiki-based site to encourage information sharing among toxicologists, scientists, and others and to put toxicological sciences in the context of history, society, and culture. A primary goal was to create a website that would support the toxicological community in building a trusted base of knowledge that would help individuals to educate themselves and make informed decisions to protect their health and the health of the environment. It was also hoped that Toxipedia would be a useful resource for students, teachers, the general public, and policy makers.

The exciting possibility of creating an interactive toxicology e-book occurred when the copyright for *A Small Dose of Toxicology* was returned to me. Given the challenge of keeping textbooks current and integrating them with the material already available on the Web, it is my view that most textbooks will ultimately become e-books. *A Small Dose of Toxicology, 2nd Edition* is our effort to respond to this challenge. All the chapters of the book have been updated and new chapters added, but most importantly, the text has been linked into Toxipedia. This will allow readers to easily

explore topics of interest in more depth. Our goal is to make *A Small Dose of Toxicology* a dynamic and evolving resource. Scientists, students, and teachers will be able to add new material to future editions to help build the knowledge base.

A Small Dose of Toxicology, 2nd Edition will be released only as an e-book by Healthy World Press, a division of the Institute of Neurotoxicology and Neurological Disorders (INND). INND is a Seattle-based nonprofit organization that makes scientific information freely accessible in order to help support a more healthy and peaceful world. There is no charge for downloading *A Small Dose of Toxicology, 2nd Edition* or the supporting PowerPoint presentations, but we do ask that you consider making a small donation to support our work to regularly update both the book and Toxipedia.

Acknowledgments

This 2nd edition of *A Small Dose of Toxicology,* which is the first e-book edition, evolved with the development of Toxipedia. Toxipedia has been possible only with the support of Darryl Duke and his company Stepstone Technologies Inc., and I owe Darryl a huge thanks for his technical support as well as his ongoing encouragement. Another big thanks to Kelli Lewis of Kelli Lewis Design who created all the logos for the Toxipedia suite of websites as well as the new book cover. Philip Dickey was once again generous enough to read and comment on the entire edition. Maria M. Williams did a final edit before preparing material for the web site and the e-book. Jeff Williams was the master of preparing the e-book and creating the final epub files. Finally, I want to thank Janice Camp for her ongoing support in all ways large and small.

Toxicology and You

or

An Introduction to a Small Dose of Toxicology

Introduction

Toxicology originally developed as the study of poisons and is now more formally described as the study of the adverse effects of chemical or physical agents on living organisms. During our lives, most of us begin to develop an intuitive sense of toxicology that guides many of our personal day-to-day decisions. This process can start first thing in the morning over a cup of coffee or tea or a can of cola. These common beverages contain caffeine, the most widely consumed stimulant in the world. Most consumers of caffeine are well aware of the benefits of this drug as well as the consequences of consuming too much. Through trial and error we have learned how to moderate our consumption of caffeine to avoid any undesirable effects. In regulating our consumption of caffeine we are applying the most basic principle of toxicology: dose/response. We apply this principle when we judge how much and what to eat or drink, or how much suntan lotion we should use before going to the beach. As we shall see in a later chapter, caffeine provides an excellent example of how we knowingly or unknowingly apply the principles of toxicology. When we understand how caffeine interacts with the body, we see why coffee and soda companies make so much money from this amazing drug. Looking at the world through the lens of toxicology provides a very interesting perspective on current and historical events and our own lives.

The purpose of *A Small Dose of Toxicology* is to build upon our intuitive understanding of toxicology, applying the principles of toxicology with knowledge and comfort. This will allow more critical analysis of not only our immediate environment but many of the current events that shape our society. Toxicological considerations directly or indirectly influence many decisions that shape our home, play, school, and work environments. As citizens in a democratic society, we must be able to meaningfully engage decision makers in industry, government, and the news media. This book is not about the thousands of commercial chemicals that are in use, but rather about the principles that guide decisions about their use and distribution. A little knowledge about toxicology will allow us to better judge the potential effects of chemical exposures on our lives, ask insightful questions, and ultimately, influence the decision makers.

Historical and Current Events

Historically, toxicology was typically concerned with determining the amount of a substance that would be fatal. Literature has some splendid examples of the awareness of naturally occurring poisons. The ancient Greeks were very

knowledgeable about the properties of hemlock, part of the parsley family, even though they did not know what specific chemical in it caused death. In 399 BC Socrates was condemned to die by hemlock after being charged with religious heresy and corrupting the morals of local youth. We now know that the active chemical is the alkaloid coniine, which when ingested causes paralysis, convulsions, and potentially death. More modern examples of the knowledge of poisons can be seen in the following from Act 5 of *Romeo and Juliet* by Shakespeare:

> • • •
>
> Come bitter pilot, now at once run on
> The dashing rocks thy seasick weary bark!
> Here's to my love! O true apothecary!
> Thy drugs are quick. Thus with a kiss I die.
>
> • • •

Historical events can also be interpreted from the perspective of toxicology. For example, Great Britain acquired Hong Kong during the Opium War of 1839-42. Medical uses of opium included the treatment of diseases such as dysentery and cholera. Users soon found that smoking a mixture of tobacco and opium increased the absorption of opium, resulting in a more rapid onset of its effects. The Chinese government was trying to curb the smoking of opium because of its debilitating effects, which was at odds with the British desire to increase the opium trade. Knowledge about the physiological and toxicological properties of drugs (legal or illegal) is important in developing sound public policy. Looking at historical and current events through the filter of toxicology (see below) provides a new perspective on the underlying issues.

Everyday Examples of Toxicology

Below are a few examples (Table 1.1); there are many more and they make the news daily. Can you add to this list? What toxicology-related issues have been in the news recently?

Table 1.1 Every Day Examples of Toxicology

Topic	Comment
Thalidomide	Developed as a sedative in the early 1960s but found to cause a rare birth defect, phocomelia. In 1962 legislation was passed by the FDA requiring new drugs to undergo sufficient animal and human testing prior to approval for use.
Hong Kong	1. Many chickens and birds in Hong Kong were killed to stop the spread of an avian virus potentially deadly to humans. 2. Why was Hong Kong a British colony? This was in part due to the Opium Wars, when

	England and other countries wanted to promote the use of opium among the Chinese population.
Princess Diana	At the time of death her driver may have been intoxicated.
Ambassador to Mexico	A number of years ago a former governor of Massachusetts (Weild) was denied the opportunity to become the ambassador to Mexico because US Senator Jesse Helms thought he was "soft on drugs." Yet this senator was from a key tobacco-growing state and a major supporter of the tobacco industry (and hence nicotine). Who is soft on drugs?
$276 Billion	Money lost or spent due to the consumption of alcohol or dug abuse, car accidents, lost work, etc...
$65 Billion	Money lost or spent due to tobacco-related illnesses or disease.
Food	Our food supply is dependent on, and contaminated with, pesticides. Artificial sweeteners, flavors, and colors are used. Mercury contaminates some fish.
Noise	Loud noise can damage hearing and can cause an even greater effect in combination with certain drugs.
Dust	The dust in your home may contain many hazardous contaminants, e.g. lead or pesticides. Many of these can be tracked in the home on shoes or by pets. Removing shoes can reduce contamination in the home.
12,000 children	Estimated number of children with Fetal Alcohol Syndrome.

Coeur d'Alene, Silver Valley, ID	352,000 pounds of lead from mining pollution washed into Lake Coeur d'Alene.
Solar radiation (ultraviolet light)	May cause sunburn, cancer.
Arsenic	Found in drinking water and old smelter and mining sites; causes skin disease and cancer.

The Definition of Toxicology

Toxicology, while formally considered a new science, has ancient roots and is closely linked to medicine. Toxicology's counterpart in medicine is pharmacology, the study of the beneficial and adverse effects of medicinal drugs. The adverse effects of drugs, often termed side effects, are really the toxicological or undesired aspects of the drug that one must endure along with the benefits. The basic principles of pharmacology and toxicology are very similar, with just a different emphasis on the outcome. For example, one can study the pharmacological or beneficial aspects of caffeine or the undesired or toxicological aspects of too much caffeine. Caffeine at the right dose is commonly consumed for its stimulant effects on the nervous system, but too much produces equally recognizable and undesirable effects.

As knowledge of the effects of poisons grew, so did the definition of toxicology. A more contemporary definition of toxicology is the study of the adverse effects of chemical and physical agents on living organisms. While this definition may appear relatively simple there are important aspects worth exploring. "Adverse effects" can range from obvious ones like death, cancer, an injury such as an acid burn, or the undesired effects of too much caffeine. We quickly note these unpleasant effects and easily relate them to exposure to the agent. As our understanding of toxicology has increased, there has been a shift in focus to recognizing the unique sensitivity of individuals and the more subtle adverse effects such as a decrease in learning and memory. Subtle damage to the nervous system, which can result in a decrease in intelligence, is more difficult to assess in an individual and to relate to exposure. To assess subtle changes it is often necessary to evaluate exposure and effect in a large group or population of people. Our increased awareness of the adverse effects of lead exposure on young children is an excellent example of toxicology's shift in perspective. It is not nearly as important to know how much lead will kill a child as it is to understand the sensitivity of the child's developing brain to even low levels of exposure. Harming the learning and memory of a child results in a lifetime of undesirable effects and consequences for the individual and society.

The child pictured in Figure 1.1 working in a lead battery recycling factory illustrates the global implications of toxicology. This child will suffer from the effects of lead poisoning for a lifetime and will not be able to reach his intellectual potential.

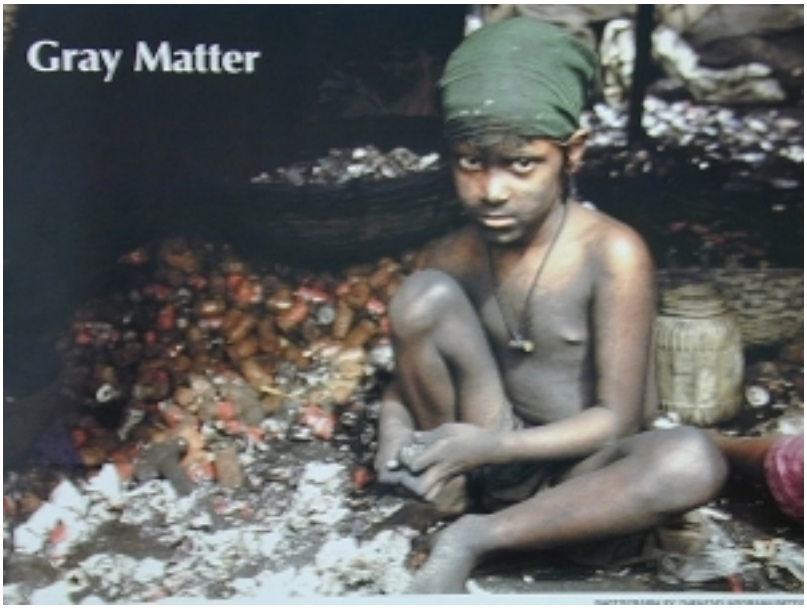

Figure 1.1 Child working in a lead battery recycling factory
Child Labour, Bangladesh. - Child working in a lead battery recycling factory. - S118-4. - [Copyright by the Photographer and/or Peter Arnold, Inc. (used with permission)]

The second part of the definition of toxicology concerns "chemical or physical agents." Chemical agents can be either naturally occurring or manufactured. Hazardous naturally occurring agents produced by living organisms are called toxins, while hazardous manufactured agents are called toxicants. Naturally occurring agents can be as benign and essential as water or as deadly as the venom of a coral snake. Plants, animals, and bacteria produce a range of chemical substances or toxins that usually aid in their survival or defense. Humans and even other animals have learned to use these agents to cure disease as well as poison other plants and animals. Several different plants produce caffeine, a bitter compound, mostly likely to protect them from insects. Digitalis, from foxglove, is used in treating heart disease. Bacteria, such as botulism or anthrax, produce toxins that can kill humans, but we take advantage of the yeast that produces alcohol.

Our industrial society has learned to manufacture a wide range of chemicals designed for specific purposes. Much of our food supply depends on the use of pesticides. Our households, schools, and workplaces contain numerous chemicals that are potentially hazardous. The laptop computer essential for writing this book contains thousands of different chemicals. The manufacture of many of the items we depend upon, and their subsequent disposal, can create additional hazards. There are examples around the world of contaminated areas that are potentially hazardous to animals, plants, and humans.

Physical agents represent a different set of challenges for a toxicologist and are often related to occupational health issues. Temperature and noise are the two most common physical agents that must be considered. In the past decade there has been a growing recognition of the harmful effects of loud noise on hearing and, even more important, a willingness to promote the use of hearing protectors. Excessive temperature in the work environment or from wearing protective clothing can decrease performance. Both noise and temperature can increase the stress in the

environment and interact with other agents to produce a significant decline in performance. Some drugs can interact with noise to produce greater hearing loss. Sleep deprivation or jet lag can also have serious undesirable effects or a temporary loss of performance.

Toxicology has progressed, along with the biological sciences, to place a greater emphasis on understanding the mechanism of action of an agent and the subtle responses of the organism, and on recognizing the sensitivity of individuals. Thus toxicology has moved away from death as an endpoint to focus on work performance and quality of life. For example, exposure to hazardous vapors may cause impaired judgment or slowed reaction time, resulting in serious injury to the person responding to an emergency. The child exposed to alcohol during gestation may have permanent learning disabilities because of the sensitivity of the developing brain at that particular point. Recognition that the sensitivity of the individual depends on stage of development, age, or genetic makeup has become one of the most important principles of toxicology. This has modified the thinking and application of the principle of dose/response.

It is possible to take an even broader view of toxicology by defining it as the study of the response of a defined system to some event or exposure to an agent. The principles of toxicology are now applicable to vast phenomena such as global warming or deforestation: increased atmospheric carbon dioxide is a toxic event and a rain forest can sustain logging only at certain levels. The basic principles of toxicology are a framework for considering both local and global events, many of which raise ecological considerations. This more ecological perspective on toxicology is not the subject of the book but is worth keeping in mind as one applies the principles of toxicology on a day-to-day basis.

Environmental Health

An underlying theme behind this book is to place toxicology in the context of environmental health. How do you define environmental health? What environment are we considering: home, school, workplace, outdoors, indoors, the oceans, the air, or water? I define environmental health as "conditions that ensure that all living things have the best opportunity to reach and maintain their full genetic potential." While this is a very broad approach to environmental health, its value can be best illustrated by looking at children. How do we ensure that our children can reach their "full genetic potential"? For example, children exposed to even very low levels of lead may develop learning disabilities, and the detrimental changes may affect the child for a lifetime. How do we as individuals and as a society work to ensure that children are not adversely affected by exposure to lead? This is a complex issue that goes well beyond toxicology, but knowing more about toxicology can help in making small decisions that can influence a child's future quality of life. The same is true of larger environmental issues. *A Small Dose of Toxicology* strives to apply the principles of toxicology with the broader goal of increasing the potential for all living things to have an opportunity to reach and maintain their full genetic potential. We will examine the effects of exposure to specific agents on living systems and emphasize resulting changes in performance and function.

Ensuring environmental health is a complex interaction between the individual and society and ranges from local to global issues. Gold miners in the Amazon use mercury to extract the gold. As the mercury evaporates to reveal the gold, it harms the miners as they breathe it in. But the mercury is also going into the atmosphere: the wind may take it far away but eventually it falls back to the ground, where it is modified by bacteria and taken up by fish. Government agencies must then regulate the amount of mercury acceptable in certain species of fish such as tuna and swordfish. Broken thermometers, fluorescent light bulbs, and a variety of consumer products release mercury into the environment. As a society, how much do we spend to curb the release or even the sale of mercury?

Pesticides are chemicals designed to kill unwanted plants, insects, and animals. While necessary in some situations, their widespread use has had unintended consequences. DDT, widely used to kill mosquitoes, is but one example. Initially thought to be harmless to other organisms, it was subsequently found to weaken the shells of bird eggs, causing serious declines in populations of predatory birds. An interesting property of DDT and a number of related pesticides is that they are stored in fat. As the DDT moves up the food chain from smaller to larger animals, more and more accumulates in the animals' fat. During breastfeeding, fat is mobilized and along with it the DDT, which appears in breast milk and is consumed by the infant. These are two of the many issues that we must confront as we begin to appreciate the global implications of toxicology and environmental health, which in turn impact us as individuals.

Regulation

State and national government agencies spend our tax dollars on environmental and toxicology issues. Both the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) were formed in an effort to protect the health and well-being of people and the environment. For both agencies, 1962 was a year to remember. A turning point in the regulation governing the FDA occurred in 1962 when a new sleeping pill, thalidomide, was shown to cause birth defects. Infants in Europe and Australia whose mothers used thalidomide while pregnant were born with birth defects. Fortunately, Dr. Frances O. Kelsey, an FDA scientist, kept this drug off the American market despite the best efforts of industry to have the drug approved. Following this incident, regulation was passed that significantly strengthened the FDA's control over approval of new drugs.

Also in 1962, Rachel Carson published her landmark book *Silent Spring*, which dramatically documented the impact of chemicals on the environment and raised concerns about the effect of pesticides on human health. In a delayed political response, the EPA was created in 1970 to administer a variety of laws to protect human health and the environment. The EPA is responsible for regulating pesticides, industrial chemicals, hazardous waste, drinking water quality, air pollutants, and other environmental hazards.

Summary

The title of this book identifies a primary aim of the book, which is to provide a small but useful introduction to toxicology. Many of the examples were selected to emphasize how toxicology fits into everyday events and life choices. Do we take one or two cups of coffee? What are the consequences of drinking alcohol or consuming other recreational drugs? Why are some individuals more sensitive to chemical or physical agents than others? Is our food cooked long enough to ensure that all bacteria are killed? My focus is on the practical application of toxicology in our day-to-day lives, but another aim is to apply the principles of toxicology to bigger societal issues. Understanding the principles of toxicology can provide the power to discover new insights into decision-making. The principles of toxicology can then be continually applied to ever-changing circumstances as we strive to understand the issues. The power lies in having the knowledge to evaluate a new situation.

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> "It is not the truth that makes you free. It is your possession of the power to discover the truth. Our dilemma is that we do not know how to provide that power."
>
> - Roger Lewontin, New York Review of Books, Jan. 7, 1997

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Each of us can benefit from discovering how and why our bodies interact with an agent and understanding how various compounds impact the environment. Appreciating the impact of dose/response and individual susceptibility provides a basis for taking action to improve our own health and well-being and that of the environment. Knowing that infants are more susceptible than adults to agents such as lead because of their low weight and their developing nervous systems can result in small but important actions that reduce the infants' exposure and thus improve their quality of life. This knowledge may also spur changes in the workplace or regulatory action by government agencies. Knowledge can provide the power to shape and influence environmental health.

The reader is encouraged to pick and choose specific chapters of interest; toxicology is fun when explored out of curiosity. One unique feature of the book is that each chapter has a corresponding PowerPoint presentation. This presentation material was designed to aid the student or the teacher by providing a concise overview of the material in the chapter and, in some cases, provide information from a slightly different perspective. As a teacher myself, I have always wondered how many times the same material has been reproduced to accommodate a lecture.

I omitted some of the details on the chemistry and mechanism of action of specific agents, knowing that this information is available from other sources. A list of references includes a number of excellent books that contain more specific information on both common and obscure toxic agents. This edition of "A Small Dose of Toxicology" is designed to take advantage of the extensive information in Toxipedia, a wiki-enabled web site that is designed to grow as our understanding of toxicology expands. Toxipedia's mission is to place scientific information in the context of history, society, and culture and thereby allow us individually and collectively to make better decisions about human and environmental health. It has been said that toxicology can

be learned in two easy lessons of only ten years each (I think it may be three lessons now). This book is an introduction to the first ten years.

Additional Resources

Below is a list and brief description of a very few of the more detailed web sites and references. Each chapter of has additional specific recourses and reference while the below are more general in nature.

Teaching Resources

• A Small Dose of Toxicology presentation material and references. Website contains presentation material related to this book for each chapter.
• University of Washington. Center for Ecogenetics and Environmental Health. K-12 teacher resources and student aids that address toxicology.
• US National Library of Medicine. Toxicology Tutorials. Site offers three tutorial lessons on toxicology. [accessed December 27, 2011]
• Toxicology Education Foundation (TEF). TEF provides grants and resources for education in toxicology. [accessed December 27, 2011]
• Society of Toxicology (SOT). K-12 Resources. US toxicology organization site has a variety of useful information and links to educational resources on toxicology and related biological sciences. [accessed December 27, 2011]

European, Asian, and International Agencies

• Organization For Economic Co-Operation And Development (OECD). Chemical Safety and Biosafety. OECD Site contains general information on environmental and chemical health and safety. [accessed December 27, 2011]
• European Commission. Public Health. European Commission has extensive health-related information in many languages. [accessed December 27, 2011]
• European Environment Agency. European Environment Agency has extensive environmental health-related information in many languages. [accessed December 27, 2011]
• National Institute for Clinical Excellence (NICE). NICE was set up as a Special Health Authority for England and Wales and its role is to provide patients, health professionals, and the public with authoritative, robust, and reliable guidance on current "best practice." [accessed December 27, 2011]
• UK Department of Health (DOH). The aim of DOH is to improve the health and well-being of people in England. [accessed December 27, 2011]
• National Institute for Occupational Safety and Health. International Chemical Safety Cards. This international site has information on a large number of agents. [accessed December 27, 2011]
• Toxicology Excellence for Risk Assessment. International Toxicity Estimates for Risk (ITER). "ITER is a compilation of human health risk values from a number of international health organizations and independent groups." [accessed December 27, 2011]
• Chemical Safety Information from Intergovernmental Organizations. INCHEM is a means of rapid access to internationally peer-reviewed information on chemicals commonly used throughout the world, which may also occur as contaminants in the environment and food. It consolidates information from a number of

intergovernmental organizations whose goal it is to assist in the sound management of chemicals. [accessed December 27, 2011]
• International Programme on Chemical Safety (IPCS). Pesticide Data Sheets. Site has large list of pesticide data sheets. [accessed December 27, 2011]
• International Agency for Research on Cancer (IARC). IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. [accessed December 27, 2011]
• World Health Organization (WHO). The World Health Organization, the United Nations' specialized agency for health, was established on April 7, 1948. WHO's objective, as set out in its constitution, is the attainment by all peoples of the highest possible level of health. Information is in English, Spanish, and French. [accessed December 27, 2011]
• International Programme on Chemical Safety (IPCS). IPCS is a joint programme of three Cooperating Organizations - ILO, UNEP and WHO, implementing activities related to chemical safety. [accessed December 27, 2011]
• Encyclopaedia of Occupational Health and Safety. Published by the International Labour Office to promote "the protection of the worker from sickness, disease and injury arising out of employment." [accessed December 27, 2011]
• European Environment Agency. Site has information on improving Europe's environment. [accessed December 27, 2011]
• Institute for Global Communications (IGC). EcoNet is part of IGC and was the world's first computer network dedicated to environmental preservation and sustainability. [accessed December 27, 2011]
• Human and Environmental Risk Assessment (HERA). HERA is a voluntary industry program to carry out Human and Environmental Risk Assessments on ingredients of household cleaning products. It is a unique European partnership established in 1999 between the makers of household cleaning products (AISE) and the chemical industry (CEFIC) that supplies the raw materials. [accessed December 27, 2011]
• Australian Institute of Health and Welfare. Australia's national agency for health and welfare statistics and information. [accessed December 27, 2011]
• Japanese Ministry of Health, Labour and Welfare (MHLW). Japan's MHLW regulates drug, food and labor safety. [accessed December 27, 2011]
• Japanese National Institute of Health Sciences (NIHS). Japan's NIHS regulates drugs and chemicals. [accessed December 27, 2011]

North American Agencies

• Health Canada. Health Canada provides extensive health-related information in English and French. [accessed December 27, 2011]
• The Canadian Centre for Occupational Health and Safety (CCOHS). CCOHS provides information and advice to promote safe and healthy working environments. [accessed December 27, 2011]
• Canadian CHEMINDEX database. [accessed December 27, 2011] The CHEMINDEX database contains information on over 200,000 chemicals; record contains identification information on a unique chemical substance, including chemical names and synonyms, the CAS registry number, and a list of the CCINFO databases containing information on that substance. [accessed December 27, 2011]
• Canadian MSDS Database. Material Safety Data Sheets on over 120,000 compounds

from 600 North American manufacturers and suppliers. [accessed December 27, 2011]
• US National Library of Medicine. This site provides access to probably the greatest sources of reference material in the world. The Health Information section has specific areas related to toxicology as well as many searchable databases. [accessed December 27, 2011]
• US Environmental Protection Agency (EPA). Contains a wealth of information on many common environmental pollutants such as lead, mercury, and pesticides, including regulatory information. The site also has a great kids section. [accessed December 27, 2011]
• US Environmental Protection Agency (EPA). Integrated Risk Information System (IRIS). "IRIS is a database of human health effects that may result from exposure to various substances found in the environment." An excellent source of information about many compounds and a great starting place. [accessed December 27, 2011]
• US Environmental Protection Agency (EPA). Toxics Release Inventory (TRI) Program. "The Toxics Release Inventory (TRI) is a publicly available EPA database that contains information on toxic chemical releases and other waste management activities reported annually by certain covered industry groups as well as federal facilities." [accessed December 27, 2011]
• US Food and Drug Administration (FDA). All you would ever want to know about the drug approval process as well as basic information on diseases and current event topics. [accessed December 27, 2011]
• US Food and Drug Administration (FDA). Milestones in Food and Drug Law History. Site contains an interesting historical perspective on the US FDA. [accessed December 27, 2011]
• US Occupational Safety and Health Administration (OSHA). OSHA is responsible for regulating the workplace environment. The site has information on current standards and business requirements. [accessed December 27, 2011]
• US National Institute for Occupational Safety and Health (NIOSH). NIOSH is responsible for conducting research and making recommendations for the prevention of work-related disease and injury. [accessed December 27, 2011]
• US Centers for Disease Control and Prevention (CDC). CDC is recognized as the lead federal agency for protecting the health and safety of people of the United States. [accessed December 27, 2011]
• US Consumer Product Safety Commission (CPSC). CPSC works to save lives and keep families safe by reducing the risk of injuries and deaths associated with consumer products. [accessed December 27, 2011]
• US National Toxicology Program (NTP). In 1978 the Department of Health and Human Services (DHHS) established the NTP to coordinate toxicological testing programs, strengthen the science base in toxicology, develop and validate improved testing methods, and provide information about potentially toxic chemicals to health regulatory and research agencies, the scientific and medical communities, and the public. [accessed December 27, 2011]
• US National Institute of Environmental Health Sciences (NIEHS). Wide range of information linking the environment, toxicology, and health. [accessed December 27, 2011]
• California Environmental Protection Agency (CalEPA). "The CalEPA mission is to restore, protect, and enhance the environment to ensure public health, environmental

quality, and economic vitality." [accessed December 27, 2011]
• California Office of Environmental Health Hazard Assessment (OEHHA). The OEHHA mission is to "protect and enhance public health and the environment by scientific evaluation of risks posed by hazardous substances." [accessed December 27, 2011]

Non-Government Organizations

• Environmental Defense Fund. The Environmental Defense Fund is dedicated to protecting the environmental rights of all people, including future generations. Among these rights are clean air and water, healthy and nourishing food, and a flourishing ecosystem. [accessed December 27, 2011]
• Scorecard: The Pollution Information Site. Site has information on health effects and state exposure issues. [accessed December 27, 2011]
• Toxicology Excellence for Risk Assessment (TERA). "TERA is a nonprofit (501(c)(3)) corporation dedicated to the best use of toxicity data for the development of risk values." [accessed December 27, 2011]
• North American Association for Environmental Education (NAAEE). NAAEE is a network of professionals, students, and volunteers working in the field of environmental education throughout North America and in over 55 countries around the world. Since 1971, the association has promoted environmental education and supported the work of environmental educators. [accessed December 27, 2011]
• American Lung Association (ALA). ALA fights lung disease in all its forms, with special emphasis on asthma, tobacco control and environmental health. [accessed December 27, 2011]
• Society of Toxicology. US-based international professional organization for toxicologists. [accessed December 27, 2011]
• DRCNet Online Library of Drug Policy. Offers an incredible history and information on commonly used recreational drugs. [accessed December 27, 2011]

Library References

• National Library of Medicine. Site provides easy access to medical and scientific literature and numerous databases. [accessed December 27, 2011]
• National Library of Medicine. US TOXNET. TOXNET is a cluster of databases on toxicology, hazardous chemicals, and related areas. [accessed December 27, 2011]
• National Library of Medicine. Environmental Health & Toxicology. Site has links to many sites on a variety of toxicology information. [accessed December 27, 2011]

Introductions to Toxicology and Risk

Ottoboni, Alice. *The Dose Makes the Poison: A Plain Language Guide to Toxicology, 2nd Edition*. New York: Van Nostrand Reinhold, 1991. A very good introduction to toxicology.
Berger, Bob. *Beating Murphy's Law: The Amazing Science of Risk*. New York: Delta, 1994. A fun look at risk in everyday life.
Morgan, M. Granger. "Risk Analysis and Management". *Scientific American* 269, (1993): 32-41. This is a good short overview of many of the issues in risk analysis.
Kent, Chris. *Basics of Toxicology*. New York: Wiley, 1998. More detailed overview but still accessible.

Reference Books

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Principles of Toxicology

or

A Small Dose of Toxicology

Introduction and History

There are three basic and interwoven principles of toxicology: 1) dose/response, 2) hazard X exposure = risk, and 3) individual sensitivity. While these principles may form much of the foundation of toxicology, when it comes to any specific substance there is likely to be controversy. Disagreement may arise on the relative importance of any one of these principles when trying to evaluate implications for public health. Exploring these principles is an essential first step before examining their application to any specific substance. This chapter will explore some of the details and issues surrounding these principles, but first it is appropriate to put them in historical context.

Our ancient ancestors worried about being poisoned, either accidentally or on purpose. The formal study of poisons (and thus toxicology) began 500 years ago during the Renaissance, a period of incredible change and challenge to traditional thought. Phillippus Aureolus (Figure 2.1) was born in Switzerland in 1493. He took the pseudonym of Theophrastus Bombastus von Hohenheim and still later invented the name Paracelsus (1493-1541). This name may signify his desire to move beyond the Roman philosopher and medical writer Aulus Cornelius Celsus (c 3-64 [AD]), who promoted cleanliness and recommend the washing of wounds with an antiseptic such as vinegar. Paracelsus's claim to toxicology is that he elegantly stated the principle of dose/response as "All substances are poisons; there is none, which is not a poison. The right dose differentiates a poison from a remedy." This often-used quote accurately states that too much of anything, even drinking too much water, can be harmful. (It should be noted that too little of some substances can also be harmful.)

Figure 2.1: Paracelsus
In this portrait Paracelsus is surrounded by various philosophical symbols. From *Paracelsus: Etliche Tractaten, zum ander Mal in Truck auszgangen. Vom Podagra und seinem Speciebus* (Coln, 1567). Washington University Collection. (from website)

What Paracelsus failed to emphasize is the variation in sensitivity of the individual. A bee sting can be deadly for some individuals while only annoying for most people. There are now numerous examples demonstrating that the developing infant is very sensitive to the poisonous effects of substances that do not harm the adult. For example, alcohol consumption during pregnancy can result in permanent harm to the infant without affecting the mother. The brain of the developing infant is sensitive to low levels of lead exposure, which is not the case for the adult. Another approach to the principle of dose/response might look like this: "The sensitivity of the individual differentiates a poison from a remedy. The fundamental principle of toxicology is the individual's response to a dose." The principle of dose/response is useful only when linked to the sensitivity of the individual.

Individual sensitivity to a hazardous agent depends on age, genetics, gender, current or prior illness, nutrition, and current or history of exposure to chemical agents. The developing nervous system of the infant is more susceptible than the mature nervous system to a range of agents. Our metabolism of agents slows as we age and our bodies again become more vulnerable to the effects of an agent. Our gender and genetics dictate our ability to metabolize agents, either more quickly or even not at all. For example, some people metabolize alcohol more slowly than other people because of their genetics. All these factors are important when we judge our susceptibility to a particular hazard.

An agent or situation is hazardous when it can produce an adverse or undesirable effect. Hazard is a property of a particular agent or situation. Early in our lives we learn about the hazards of crossing the street, falling off a ladder, or stumbling down the stairs. Learning about the hazards of a chemical agent is not so easy. Defining the hazard of a chemical agent requires experience in human exposures or careful study in experimental models. Through personal experience we gain an understanding of the hazards of some agents like alcohol or caffeine.

We routinely combine our knowledge of hazard, exposure, and individual susceptibility to judge the possibility or risk of harm. A young person judges the speed of the approaching car and decides to run across the street while an elderly person waits for the traffic light to change. This decision is based on a judgment about the risk of being struck by the car. An experienced mountain climber will judge the risk of harm on a difficult climb very differently from someone with no experience. Judging the risk of harm from a chemical agent is often far more difficult because the adverse effects may not be immediately obvious or may depend on individual sensitivity.

The ability of an agent to damage the nervous system or to cause cancer ten years after exposure is clearly not obvious. The formal process of determining the potential of agents to cause harm is called risk assessment. Risk assessment is the process of combining all the known information about the hazard of an agent and making a determination of the potential for harm to people, animals, or the environment. The risk assessment process is complicated and often controversial because needed data may not be available or there is conflicting information.

Risk management combines the risk assessment with economic and political concerns, public opinion, and other considerations to determine a course of action. These judgments seldom satisfy everyone. The principles of toxicology form the foundation for the risk assessment and ultimately for the risk management decisions. Individual and community involvement in the decision-making process is a critical part of developing sound policies to minimize risks to people and the environment.

Dose/Response

The two most important words in toxicology are dose and response; in other words, how much of an agent will produce what reaction. In toxicology the focus is usually on adverse reaction or response, but it is equally useful to consider a full range of responses from desirable to undesirable. Experience teaches us how to moderate the dose to achieve a desired result or avoid an undesirable effect. Eating one apple is beneficial, but eating five apples may produce a stomachache. One cup of coffee in the morning may be just right, but if you drink three cups too quickly you will suffer the consequences. For light-skinned people, acquiring a tan without getting sunburned requires careful management of exposure to the sun. While Paracelsus stated correctly that the "… dose differentiates a poison from a remedy," it is the individual who must constantly be aware of the dose and his or her particular response.

Defining the dose is a critical first step in the effort to predict a response. Dose is the amount of exposure to an agent, a quantitative measure of the exposure related to

the subject or individual. For a chemical agent or drug the dose is the amount of the material in relation to body weight. Typically the amount of material is measured in grams or thousandths of a gram (milligrams, mg) and body weight is measured in kilograms (kg), equal to one thousand grams. The dose is the amount of material consumed divided by body weight, or mg/kg.

Calculating the Dose

- Oral dose = amount of material consumed (mg)/body weight (kg)

By knowing just a couple of facts we can turn our everyday exposure to caffeine into a dose. There are approximately 100 mg of caffeine in a cup of coffee. The actual amount of caffeine in a cup of coffee depends on the coffee bean, how the coffee was prepared, and the size of the cup. An adult weighing 155 lbs (about 70 kg) who consumes this cup of coffee would receive a dose of 100 mg divided by 70 kg, or 1.4 mg/kg of caffeine. The importance of including body weight becomes clear if you consider a child who weighs only 5 kg (11 lbs). If this child consumed the same cup of coffee, the dose would be 100 mg/5 kg or 20 mg/kg, more than ten times higher than the adult's.

The difficult part of calculating the dose is often determining the exact amount of exposure to the agent. Very sensitive instrumentation is now available to analytical chemists in order to accurately determine the amount of a specific agent in a material. If the agent is pure, it is relatively easy to determine the amount of the substance and then calculate the dose. Some foods, such as table salt or sugar, are relatively pure and the dose can easily calculated by weighing the material. Package labeling for medicine usually indicates how many milligrams of a drug each pill contains, so the dose can be calculated. An infant formulation of a medicine contains much less drug per pill, but because of the difference in weight between the infant and the adult, the dose is similar.

Calculating the dose following workplace or environmental exposure can be far more difficult. If the agent is in the air, then calculation of the dose must consider not only the concentration in the air but also the duration of the exposure, rate of breathing, and body weight. The amount of air inhaled over a period of time is estimated from laboratory data. Given this information, it is possible to estimate the dose according to the following formula:

Inhalation dose (mg/kg) =

- Air concentration of agent (mg/ml) X volume of air inhaled per hour (ml/hr) X duration of exposure (hr)/body weight (kg)

For non-chemical exposures, other variables and different units of measurement are required. For example, exposure to sunlight could be measured in hours, but to determine the dose would require knowing the intensity of the light as well as the exposed skin surface area.

Workplace and environmental exposures are often repeated and occur over an extended period of time. The health effects of repeated long-term exposures can be very different from one short-term exposure.

Duration of exposure, frequency of exposure, and time between exposures are important determinants of dose and response. Four beers in one hour would produce a very different response than four beers over four days. Many years of repeated high levels of alcohol exposure can lead to serious liver damage as well as other health complications quite different from the short-term consequences of one exposure to a high level of alcohol. *Acute exposure* is a single or very limited number of exposures over a short period of time. C*hronic exposure* is repeated exposure over a long period of time. The effects of acute or chronic exposure, as in the case of alcohol, are often very different. We consume common painkillers with the desire to quickly stop our headache. Long-term repeated use, however, can have undesirable effects on the stomach or liver. Tobacco users desire the acute effect of the nicotine but inevitably suffer the chronic effects of long-term use such as lung cancer and heart disease. It is also possible to have a delayed response to an acute exposure. For example, a laboratory researcher died several months after an acute exposure to a small amount of ethyl mercury. Detailed knowledge about the hazards of a substance is necessary in evaluating exposure, effect, and dose/response relationships. This includes information about the consequences of acute or chronic exposure.

There is often a range of responses associated with any particular agent. The acute response to a single dose is often the easiest to characterize, but the response to multiple exposures over a long period of time may be the most important. For example, an emergency response worker who is exposed acutely to a solvent in the air may have her or his judgment impaired, resulting in a serious mistake. However, over the long term this exposure is of no consequence, assuming the worker survives any mistake in judgment. In contrast, long-term exposure to coal dust can lead to black lung and severe disability. Also, for a long time it was thought that the only serious complication from childhood lead exposure was death resulting from high exposure. Subsequent research demonstrated that even small amounts of lead exposure during childhood could result in brain damage that lasts a lifetime. Determining what responses are most important is a central aspect of many debates in toxicology.

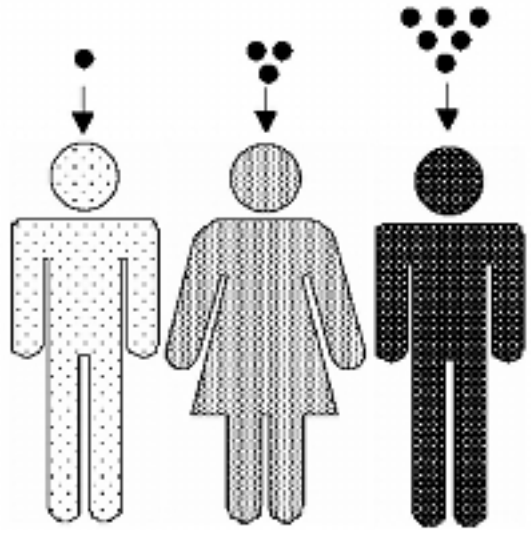
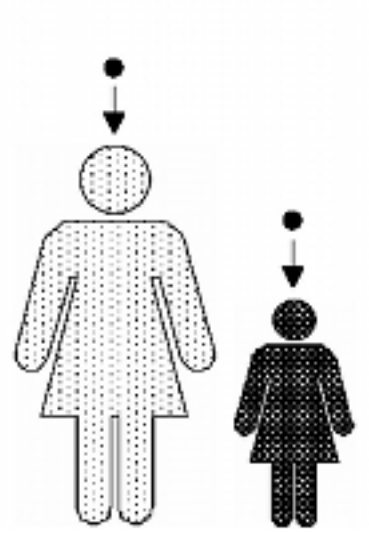
Demonstrating Dose/Response

In general, it is true that for any individual, the greater the dose, the greater the response. This concept can be easily demonstrated in the home or classroom with a few simple items (see appendix, Dose/Response Demonstration). Caffeine, which distributes evenly throughout total body water, is a good illustration of dose/response. A can of cola contains approximately 50 mg of caffeine (about 4 mg per ounce of cola). Consumption of the first can of cola delivers an exposure of 50 mg per total body weight. Assuming a 100 kg person, this would be 50 mg/100 kg or 0.5 mg/kg. Consumption of three cans of cola would result in a dose of 1.5 mg/kg and six cans of cola a dose of 3 mg/kg of caffeine. You can almost imagine the change in shade depicted in Figure 2.2 as the concentration of the caffeine in the blood increases. An individual's response to the caffeine varies with the dose and corresponding amount of circulating caffeine.

The right panel (Figure 2.2) illustrates the effect of body size on the dose. When the

adult and the child receive the same amount of caffeine, the exposure is the same but the dose is dramatically different. A child who weighs only 10 kg receives a dose of 5 mg/kg after one can of cola. An adult who weighs 100 kg must drink 10 cans of cola to receive an equivalent dose. Body size is a critical factor in determining dose and any subsequent response. For the equivalent exposure to any substance such as lead or a pesticide, the child will receive a much greater dose than the adult. As we shall discover, there are other important physiological factors that also make children more susceptible than adults to the effects of an agent.

Figure 2.2 The Effect of Dose and Body Size on Response

The Importance of Dose	The Importance of Size
	
The larger the dose, the greater the effect	The smaller the size, the greater the effect

For a given body size, the larger dose produces a greater effect (left), and for a given exposure, the smaller body size receives a greater effect and larger dose (right).
The next figure (Figure 2.3) illustrates the critical relationship between dose and response. In this case, we define the response as difficulty in walking and the dose of, or exposure to, alcohol as a glass of wine. If we selected a group of people at random and offered them wine, no one (most likely) would have difficulty walking after one drink (depending of course on how big the glass was). The number of people responding, or in this case having difficulty walking, is a percentage of the total number of people in our study population. As exposure to wine increases, more and more people would have difficultly walking until finally, everyone was affected.

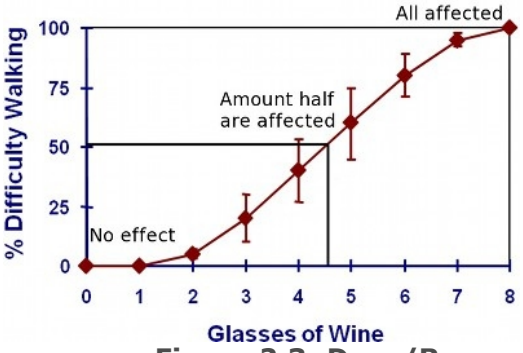


Figure 2.3: Dose/Response Graph for Drinking Wine
Dose/response function for difficulty in walking and number of glasses of wine consumed. This is an idealized curve, but it illustrates the principle that at low doses (i.e. A few glasses) there is little response, then an increasing response to a maximum response. Note that this figure does not take into consideration body weight or any other variables such as gender or frequency of exposure (i.e. time between drinks).

In toxicology, the dose at which one half or 50% of the population is affected is often calculated and used to compare the toxicity of different agents. In this example, 50% of the population is affected after exposure to 4.5 glasses of wine. The vertical bars represent the variability from one test group to the next. If we repeat this experiment with a different group of people, the actual data points could be somewhat different but should generally fall within the range spanned by the vertical bars or error bars. There are many possible reasons for this variation, including body weight (which changes dose), food consumption prior to drinking, past use of alcohol, genetics, and gender. Technically this figure is an exposure/response graph because the dose is not calculated; the number of glasses of wine represents a measure of exposure, not dose. To change from exposure to dose we would need to know the participants' body weight and the amount of alcohol in the glass of wine.

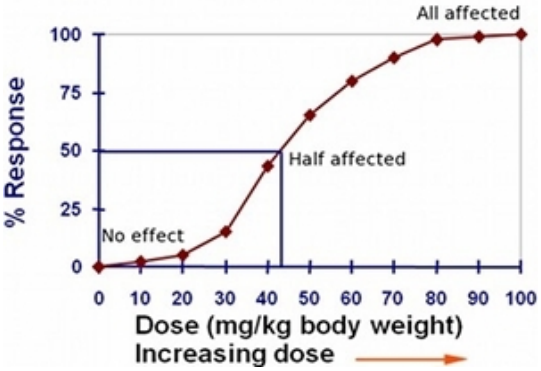


Figure 2.4: An Idealized Dose/Response Graph
The horizontal axis indicates the dose in mg/kg of body weight, while the vertical axis is the percent of maximum response. For a very low dose there is no or little response. The response increases with the dose until the maximum response is reached and increasing the dose has no additional effect.

Figure 2.4 demonstrates an "S"-shaped idealized dose/response graph, which is typical of most types of exposure. In this figure the percentage responding is plotted

against the dose in mg/kg. This "S" shaped curve illustrates that at low doses there is little or no response, while at high doses all individuals respond or demonstrate the effect. The line drawn at 50% determines at what dose 50% of the population would demonstrate this response. In this situation, 50% of the subjects respond at a dose of 42 mg/kg, while 99% of the subjects respond at 90 mg/kg. It is important to emphasize that if we repeat this experiment the results would be slightly different. Each individual varies from one time to the next, and there is even greater variability among different people. Variability is a consistent theme in biology, complicating data analysis and interpretation of results. These variations lead to the need for statistical evaluation of data.

Hazard and Risk

Risk is the probability of injury, disease, loss of function, or death for an individual or population exposed to a hazardous substance or situation. An agent or situation that can produce or cause a harmful or adverse effect is a h*azard*. Hazard is an intrinsic property of a substance and any particular substance may have a range of hazards associated with it, depending upon specific conditions or circumstances. On a daily basis, we routinely confront a range of potentially hazardous agents, including the fire we cook with, the electricity that lights our homes, the household chemicals we use for cleaning, the chemicals that run our cars, the drugs in the medicine we take, and the list goes on. We use these potentially hazardous agents but are careful to avoid conditions that will result in the expression of their hazardous properties. Gasoline is a good example of an agent with multiple hazards. We depend on its flammability to make our cars run but that same flammability can be hazardous in an uncontrolled fire. Sniffing gasoline, undertaken by some people for effects on the nervous system, represents a very different hazard. Problems develop when we do not fully appreciate an agent's potential to cause harm or the conditions under which the agent can cause harm. Problems can also occur when products or mechanical systems malfunction.

In the past, the hazard associated with any particular substance was related to immediate or obvious harm. As our knowledge and experience increase, so too does our appreciation of an agent's ability to produce unexpected consequences or harm. Take for example DDT, a very powerful pesticide useful in the eradication of mosquitoes. As Rachel Carson so eloquently pointed out, DDT devastated bird populations not directly but indirectly, by thinning eggshells to such an extent that the eggshells failed. This resulted in a devastating decline in bird populations, particularly of birds that feed on animals. Still later we learned that DDT was a very persistent chemical and highly soluble in fat. DDT thus accumulated up the food chain: in this case, birds were at the top of the food chain and most affected. Humans are also at the top of the food chain, and through a variety of means, DDT ends up in the food supply and becomes stored in body fat. When women are breastfeeding, fat and DDT are mobilized and become the food of nursing infants, for whom the exposure represents a large dose. We are still unsure of the consequences of fetal exposure to DDT and its effects on the developing organism. Many other fat-soluble chemicals such as dioxin and PCBs are known to contaminate breast milk. Lead is another example of a major public health disaster that occurred because the consequences of low-level exposure to the developing nervous system were not appreciated.

Recognition of the potential harmful effects of agents—from drugs to pesticides—resulted in new research efforts and the formation of government agencies responsible for regulating hazardous substances. The Food and Drug Administration (FDA) is responsible for ensuring that all drugs and food additives are both efficacious and safe. The Occupational Health and Safety Administration (OSHA) establishes rules to control or limit exposures to a variety of chemicals in the workplace, based upon toxicology data. The Consumer Product Safety Commission (CPSC) works to reduce injury from consumer products. The US Environmental Protection Agency (EPA) governs the release of chemicals into the environment to protect soil, water and air. It also regulates the cleanup of hazardous chemicals in the environment.

While science plays an important role in characterizing the harmful effects of an agent, society also establishes laws to regulate or limit exposure to known hazards. Tobacco and alcohol consumption are legal despite recognized hazards that pose a considerable cost to society. It was only recently that the government forced the tobacco industry to acknowledge the addictive properties of nicotine and began to recover healthcare costs through litigation. While the adverse effects of excessive alcohol consumption have been recognized for a long time, it was only in the 1970s that birth defects related to alcohol consumption during pregnancy were recognized. However, the US government has declared that marijuana and many other recreational drugs are illegal based upon their known hazard characteristics. Obviously, this is a controversial area, with many people (and even countries) having very different opinions and laws.

Hazard and risk are linked by exposure. Reducing the hazard, the exposure, or both can lower risk. If there is no exposure, then there is no risk or possibility of harm. Knowledge and experience allow one to judge the potential for harm or risk associated with exposure to a substance. In this way we are all toxicologists, always judging the potential for harm against the benefit of exposure. This is often easier said than done, but being knowledgeable about an agent can lead to the development of specific strategies to reduce the potential for harm. Since one cannot necessarily foresee all possible exposures to a hazardous substance, choosing less hazardous substances is also a vital part of risk reduction.

The beneficial use of radiation is one of the best examples of how careful characterization of a hazard is essential for its safe use. A radioactive substance can be safely stored or transported if appropriately contained. Depending on the characteristics of the radioactive material, it can be safely handled by using appropriate shielding and safety precautions. Laboratory workers usually wear special badges that quantify radiation exposure to ensure that predetermined levels of exposure, which are considered safe, are not exceeded. Unfortunately, after more than 50 years, society has not yet been able to design and implement a safe way to dispose of radioactive waste. The hazardous properties of radiation are explored further in chapter 13.

Historically, potentially toxic agents have been ranked by their lethality, or the amount of material that causes death. In this measure, hazard is defined only as death, obviously only the grossest measure of an agent's effect. Because of individual

variability or susceptibility, a standardized measure is the dose (in units of mg/kg) that produces death in half of the subjects, a 50% response. This is called an LD50 or lethal dose for 50% of the population. The LD50 is one measure of the *toxicity* of a substance, its capacity for causing illness or death. The LD50 is usually determined using populations of test animals such as rats and mice and is based on a single acute exposure to an agent and the single response of death. Although the LD50 can be useful in comparing the gross hazards of agents, it is not necessarily relevant to a response produced by low-level chronic exposure. For example, the LD50 of lead is not particularly important, given its adverse effects on the developing nervous system even at very low levels of exposure. LD50s are misleading if used as the only characterization of the toxicity of a substance. Aspirin is a commonly used over-the-counter medicine, while DDT is a pesticide that has been banned because of its toxic effects and persistence in the environment. Yet they have similar LD50s.

Table 2.1 lists the LD50s of a variety of common agents. Since the LD50 is the amount of material required to produce death, a higher LD50 implies a lower toxicity and vice versa. Note how high the LD50 is for alcohol, which is fortunate given its widespread consumption. This explains why so few people die as a result of acute alcohol consumption. Generally, people lose consciousness at high blood alcohol levels and die not directly from the alcohol but from suffocating on their own vomit as the body tries to rid itself of this toxicant. Note also the low LD50 (high toxicity) for nicotine, the most active and addictive ingredient in cigarettes.

Table 2.1. Approximate Acute LD50s of Some Common Chemical Agents

Agent	LD50 (mg/kg)
Ethyl alcohol	10,000
Salt (sodium chloride)	4,000
Iron (ferrous sulfate)	1,500
Morphine	900
Mothballs (paradichlorobenzene)	500
Aspirin	250
DDT	250
Cyanide	10
Nicotine	1

Tetrodotoxin (from fish)	0.01
Dioxin (TCDD)	0.001 (for some species)
Botulinum toxin	0.00001

Fortunately, the LD50 is no longer recognized as an adequate or even particularly useful assessment of an agent's ability to cause harm. Toxicologists have developed a wide array of tests to determine if an agent can produce an adverse effect across all organ systems. If any hint of adverse effects is observed, further testing is done to carefully characterize and understand the effect. Ultimately, the hazard must be judged on the sensitivity of the individual.

Routes of Exposure and Absorption

An agent exerts its effects when it enters or comes into contact with the body, or in other words, when an individual has been exposed to it. Although we are primarily concerned with effects on humans, the same principles apply to all living organisms and, indeed, to the entire environment. *Exposure*, like many of the terms in toxicology, has several different aspects, the most important of which are 1) route of exposure, 2) frequency of exposure, and 3) duration of exposure. Exposure is also affected by *absorption*. Even though we may come in contact with an agent, if little is taken up into the body (or absorbed), there is little effect. For example, the metallic mercury from a broken thermometer, if swallowed, is very poorly absorbed by the gut and will be excreted in the feces. However, if this same amount of mercury were allowed to evaporate and be inhaled, there would be very serious health consequences. This example shows that metabolism and excretion modify absorption. What is not absorbed (and even some of what is absorbed) may be excreted from the body by various routes, including through urine, feces, sweat, or exhalation. *Excretion* reduces the effect because it lowers the amount of toxicant in the body, thus reducing exposure to sensitive organs.

There are three main *routes of exposure*: 1) skin (or dermal) exposure, 2) lung (inhalation) exposure, or 3) oral (gastrointestinal) exposure. A fourth route of exposure is by injection, which is used for delivery of drugs or medication that cannot be taken orally. Injections can take several forms. An injection directly into a blood vessel bypasses most of the absorption barriers and the drug will have almost full and immediate access to the most organs of the body. Some medications are injected into the muscle (intramuscularly or IM), which slows absorption as the drug is slowly taken up by the blood supplying the muscle. Finally, injections can be made just under the skin (subcutaneous or SC). This method is commonly used for allergy testing or tuberculin (TB) tests.

Skin is the largest organ of the body and does an amazing job of protecting us from most agents. However, the skin is an important route of exposure to some agents and

also a site of highly adverse reactions. For example, the adverse effect of too much exposure to the sun is well known. In many cases, the skin is an excellent barrier to chemical agents, but some solvents can readily penetrate the skin. Solvents such as gasoline or chemical cleaners can readily remove the natural oils of the skin and result in adverse skin reactions, as well as chemical absorption. The labels of many pesticides state that gloves and other skin protection should be worn because of the risk of pesticide absorption through the skin or allergic reaction such as a rash. A number of medications can now be applied through a skin patch, such as nicotine patches to curb the desire to smoke cigarettes. The advantage of a skin patch in that the drug will be absorbed at a constant slow rate, thus keeping the drug blood levels relatively constant. This system helps smokers by keeping their blood nicotine levels elevated and constant, curbing the desire to smoke.

Inhalation is an excellent route of exposure to many agents, including the oxygen essential for life. The lungs are very rich in blood to facilitate the absorption of oxygen and thus allow the rapid absorption of other agents directly into the bloodstream, quickly producing an effect. Carbon monoxide is a potentially lethal gas that can be generated in the home by poorly ventilated heaters, faulty furnaces, or a car idling in an attached garage. It is readily taken up by the blood cells by the same mechanism as oxygen. In fact, carbon monoxide binds to the hemoglobin in the blood cells better than oxygen, so exposure can cause serious injury and even death through lack of oxygen intake. Cigarette smokers become dependent on the nicotine absorbed through the lungs from tobacco smoke. Marijuana users hold their breaths to allow additional absorption of the active ingredient THC. The lungs can also excrete some agents, although this is usually in very small amounts. The excretion of alcohol forms the basis for the alcohol Breathalyzer test, which quantifies the amount of alcohol in the body by measuring what is exhaled.

Ingestion of substances orally allows absorption from the stomach and intestines. This is a critical route of exposure for many agents, from essential carbohydrates, proteins, and vitamins, to unwanted pesticides and lead. All that is ingested is not necessarily absorbed, and absorption can be dependent on age. For example, in an adult, only about 10% of the lead ingested is absorbed, but up to 50% may be absorbed by an infant or a pregnant woman. In this case, unabsorbed lead is passed through the intestine and excreted in the feces. The increased absorption of certain agents at different times of life is related to the body's demand for important elements: the intestines are able to absorb increased amounts of calcium and iron but will take lead as a poor substitute. Alcohol and caffeine are readily absorbed by the stomach, making for two of the most popular drugs in our culture. Oral exposure also occurs through our food and drinking water, so it is imperative to have unpolluted water and a safe food supply.

The other two aspects of exposure are frequency and duration. Frequency can refer not only to the number of times the exposure occurred, but also to the time between exposures. For example, drinking four beers within 15 minutes is quite different from drinking four beers in four days. Frequent exposure of a short duration results in rapidly elevated blood levels of any agent (assuming it's absorbed). Two quick cups of coffee in the morning serve to elevate blood caffeine levels, whereas slowly sipping a

cup of coffee will not have the desired stimulating effect. It takes approximately 30 minutes to absorb the caffeine from a cup of coffee and reach peak blood caffeine levels. The harmful or toxic effects of an agent are often dependent on the frequency of exposure and the time between exposures.

Duration of exposure is a closely related factor. In toxicology, duration is usually divided into three periods: 1) acute exposure (usually just one or two exposures of short duration); 2) sub-chronic exposure (multiple exposures over many days or perhaps months); and 3) chronic exposure (long-term or even lifetime exposure). The terms acute and chronic are also used to characterize the time delay between exposure and the onset of symptoms. Acute effects are those noticed directly following exposure and are usually easily related to the agent. The chronic or long-term effects of an agent may occur years later and are often very difficult to attribute to a particular cause. For example, the acute effects of alcohol consumption or exposure to the solvent in glue are obvious in the drunkenness produced. The effects of chronic exposure to these compounds, as observed in alcoholics, are very different: specifically, cirrhosis of the liver. The chronic effect of childhood lead exposure can be impaired learning that will be an influencing factor throughout an individual's lifetime. The chronic effects of food additives and pesticides are evaluated in lifetime animal studies to assess the carcinogenic (cancer-causing) potential of these agents.

There are two types of exposure that deserve special attention: fetal exposure during pregnancy and exposure to the brain. For a long time it was thought that the placenta offered the developing fetus significant protection from hazardous agents. We know now that the majority of agents readily cross the placenta and expose the developing fetus to whatever the mother has been exposed to. For compounds that readily distribute throughout body water, such as caffeine, the fluid surrounding the infant (amniotic fluid) will have the same level of the compounds as the mother's blood. Thus the infant is literally swimming in caffeine and its metabolites. Fetal exposure to methylmercury can actually be higher than that of the mother because the developing infant acts as a storage site for maternal mercury.

The brain in the adult, but not in the fetus, is afforded some extra protection from hazardous agents. This barrier is known as the blood-brain barrier because of its ability to keep some agents from moving from the blood vessels into the brain tissue. This barrier works primarily on large molecules but does not stop water-soluble agents such as caffeine from entering the brain. While there are obviously many good aspects to the blood-brain barrier, it has also proven to be very challenging to move desirable drugs into the brain to treat disease.

From a scientific perspective, single exposures to chemicals are investigated to understand how the body reacts to a specific chemical. In real life, however, we are often exposed to a mixture of chemical agents. Multiple agents may interact and affect absorption or how the body reacts to the chemical. The body has a very sophisticated system to metabolize and eliminate chemicals form the body; this system plays an important role in protecting us from hazardous substances.

Metabolism, Distribution, and Excretion

Fortunately, living organisms have developed elaborate systems to defend themselves from toxic agents. In biology, *metabolism* refers to an organism's ability to change a substance into different chemical parts, or metabolites, that are usually less toxic. The body metabolizes the food we consume to recover energy and basic elements necessary for our well-being. In toxicology, metabolism refers to the body's ability to reduce an agent into parts that are either less harmful or more readily excreted, a process called *detoxification*. The most common route of excretion is through urine, although some agents can be excreted in the feces, sweat, or even the breath. For toxic agents, metabolism is beneficial, but it can also reduce the benefits of a drug needed to aid in the recovery from an illness.

Distribution refers to where an agent goes in the body. Some agents such as pesticides and PCBs accumulate in the fat. Other agents such as lead can accumulate in the bone in the place of calcium. Agents stored in the body may never be fully excreted; as we age, we continue to accumulate a body burden of these stored agents like PCB or lead. Metabolism, distribution, and excretion are linked aspects that are essential to predicting the adverse effects of an agent and thus determining the risk of exposure to it.

Although most cells in the body are capable of metabolism, the primary organ for detoxification is the liver. The liver has a variety of specialized cells that produce enzymes to aid in the metabolism of toxic agents. These enzymes can break down toxic agents into smaller elements, making them less toxic. In some cases the compounds are changed so that they are more easily filtered by the kidney and excreted in the urine. Alcohol and caffeine, for example, are metabolized in the liver. The liver is a remarkable organ but can be permanently damaged by diseases such as hepatitis or through long-term alcohol consumption. Liver damage can be detected in the blood by looking for elevated levels of compounds produced by the liver. Insurance companies use liver function tests to evaluate the possibility of chronic drug consumption.

Not all agents can be readily metabolized. The toxic metals lead and mercury are elements that cannot be degraded but must still be removed from the body. Another important mechanism of detoxification is the attachment or binding of another compound to a toxic chemical to make it easier for the kidney to filter the compound out of the blood and excrete in the urine. A primary purpose of the kidney is to screen the blood of waste products and concentrate them in the urine for excretion, as occurs, for example, with mercury. Caffeine is excreted in the urine at approximately the same concentration of the blood because the kidney cannot concentrate caffeine. Vitamins, however, are readily concentrated and excess amounts are quickly eliminated in the urine.

Chelators bind to metals so that they are more readily excreted in the urine. In the past, chelators were routinely prescribed to people with elevated blood lead levels in an effort to accelerate the excretion of lead in the urine. Unless the blood levels are excessively elevated, the current treatment is to determine the source of the lead

exposure and take remedial action. The problem with chelators is that they are non-specific and bind useful agents such as calcium.

Half-life is a measure of the length of time an agent stays in the body before being metabolized and eliminated. More precisely, the half-life of an agent refers to the time it takes to reduce the level of the agent by one half. For example, if the amount of caffeine in your blood were measured as 12 units (the particular units are not important), it would take approximately five hours for that level to be reduced to six units. In this case, five hours represents the half-life of caffeine. Another five hours later the amount would be reduced in half to three, and so on until it approaches zero. The half-life of an agent, either toxic or beneficial, is a critical aspect of its ability to produce and maintain an effect. There can be considerable individual variability in the ability to metabolize an agent; this variability is reflected in the half-life for that particular individual. For example, someone who rapidly metabolizes caffeine (meaning someone for whom caffeine has a short half-life, say three hours) may want to drink more coffee more rapidly to elevate and maintain high caffeine blood levels and achieve the desired effect. Others may find that one cup of coffee every three or four hours is adequate. A variety of factors, such as liver disease or even pregnancy, can decrease the metabolism or excretion of an agent and thus increase the half-life. During pregnancy the half-life of caffeine increases to approximately seven hours, resulting in higher blood caffeine levels for a longer period of time. While the half-life of agents such as caffeine and alcohol are relatively short, many of the most serious environmental toxicants have much longer half-live values. For example, the half-life of lead is approximately 30 days. Many pesticides and PCBs are also readily stored in the body and have long half-life values. Careful consideration of the half-life of a drug is an important aspect during medical treatment. The half-life of a hypothetical drug is illustrated in Figure 2.5.

Figure 2.5. A Characterization of Half-life
A substance is consumed at time zero (for example, a cup of coffee) and blood samples are collected at every hour. Concentration of the agent is plotted against time. The black line represents the half-life when the blood concentration has dropped by one half its maximum. Thus, in this example, the half-life is four hours.

The ability of an agent to get into a specific organ of the body often dictates its effect. For example, alcohol and caffeine would not be consumed were they not readily

distributed to the brain, where they produce a considerable effect. As already mentioned, lead can be exchanged for calcium and accumulate in the bone, while many pesticides and PCBs are stored in fat cells. These patterns of distribution and the storage of compounds in the body can have serious toxicological implications. During rapid weight loss, excess toxicants can be redistributed into the blood supply as fat is metabolized. Lead in the bone can also be mobilized if there is heavy demand for calcium, as occurs during pregnancy. To further complicate matters, each area of the body—in this case the fat and bone—can have its own half-life that can differ from that in blood. The half-life of lead in the blood is measured in days, while that in bone is measured in years.

Sensitivity, Susceptibility, and Variability

Susceptibility refers to the differences in sensitivity to toxic agents, causing some people to suffer greater effect from the same exposure than others. This is a key concept in toxicology and risk analysis/management. Susceptibility is primarily related to several factors, including age, sex, health, and genetic background. *Sensitivity* is related to susceptibility but generally refers to special cases of extreme susceptibility to certain agents by some people. Someone who is allergic to bee stings can have a fatal reaction when stung by just one bee, while for most others a sting is of little concern. Enhanced sensitivity to a compound can develop after repeated exposure to it or a similar agent. Allergies to animals such as cats and dogs are examples of specific sensitivities to an agent called animal dander. Other individuals may develop a sensitivity to dust mites.

In general the young and elderly are most susceptible to the adverse effects of an agent. The young, particularly the very young, are more susceptible because the organs are still rapidly developing, and dividing cells are more easily harmed than mature cells. For example, lead affects the developing nervous system to a much greater degree than the adult brain. The brain is rapidly growing during and after birth, particularly throughout the first seven years of life. The brain is not fully developed until the late teens. During the first year of life the metabolism of agents by the liver is also reduced. This is why the half-life of caffeine can be measured in days for the newborn while it is hours for the adult. The elderly are more sensitive to agents because of a decreased ability to metabolize them and to compensate for the effects.

Gender can also play an important role in susceptibility to agents, in part due to hormonal influences. The classic example is the female birth control pill. In this case, a very small exposure to specific hormones has a very large influence on fertility. Other agents such as PCBs also appear to affect some of the female hormones. Some athletes use hormones called steroids to increase muscle mass: these agents have different toxic side effects for males and females. Females have additional issues related to pregnancy, which causes many changes in physiology that can alter the absorption, distribution, and metabolism of an agent and thus dramatically influence its effects. For example, during pregnancy there is a decrease in liver metabolism that increases the half-life of caffeine. Calcium mobilization during pregnancy can also redistribute lead from the bone if there has been previous lead exposure.

Personal health is another factor that can influence susceptibility to an agent. A compromised liver or immune system can make exposure to even low levels of an agent completely intolerable. Someone who is diabetic may find sugar toxic and may enjoy considerable benefit from artificial sweeteners. On the other hand, someone who cannot metabolize phenylalanine, a naturally occurring and essential substance, may find the common artificial sweetener in some soda toxic. An individual who suffers from asthma may find exposure to wood smoke extremely harmful, whereas many people can tolerate short exposures to it fairly well. (Wood smoke is nevertheless toxic in either case, and chronic exposure can lead to health problems.) The physiological changes of disease or chronic illness are thus are very important considerations in assessing the exposure to an agent.

Finally, our genetic variability may make us more or less prone to disease or the effects of a toxic agent. Some can tolerate caffeine before bed, while for others such exposure would result in a restless night. It is always important to consider the individual and the individual characteristics of a situation.

Applying the Principles

Multiple Chemical Exposure

In the real world we are not exposed to only one chemical at a time. The air we breathe contains many separate chemicals. Indoor air in homes can contain chemicals from smoke, molds, carpet glue, mothballs, and cleaning products, to name only a few. Determining the risk from such multiple exposures is difficult because the body does not necessarily respond to each chemical in the mixture in the same way it would if the others were not present. Sometimes one chemical can cause the body to respond more strongly to another chemical, generating a synergistic effect. We know, for example, that exposure to environmental tobacco smoke greatly increases the risk of cancer from asbestos. The increase is not additive—that is, it is not equal to the risk from tobacco plus the risk from asbestos—but is actually much greater than the sum of the two risks.

There are also cases where exposure to two chemicals reduces toxic effects. Methanol (wood alcohol) causes blindness if ingested. Methanol poisoning is treated by administering ethanol (common alcohol), which competes for metabolism in the body, thus slowing the formation of toxic byproducts of methanol and keeping their levels low enough to avoid damage to the optic system. This is sometimes referred to as an antagonistic effect.

When more than two chemicals are involved, the problem of determining risks becomes increasingly complex. Scientific study of chemical mixtures has been relatively limited because of the sheer number of combinations possible. Even if the exact effects of exposure to mixtures are unknown, reducing exposure is still a good strategy to lower risk.

Multiple Chemical Sensitivity

Multiple chemical sensitivity (MCS) is characterized by a variety of adverse effects

upon multiple organs that result from exposure to levels of common foods, drugs, and chemicals that do not affect most people. Symptoms following exposure include headaches, fatigue, lack of concentration, memory loss, asthma, and other often subjective responses. MCS has remained controversial because standard medical evaluations, such as blood biochemical screens, have failed to identify consistent physical or laboratory test abnormalities that would account for the symptoms. MCS is thought to develop following sensitization to one chemical, a sensitivity that then is generalized so that chemicals of a similar class and lower concentrations of exposure come to elicit the response. Researchers have been working to develop a mechanism of action for these responses and have focused on immune system responses and, more recently, on involvement of the nervous system. Other investigators postulate that the responses are due to some forms of psychological illness. Whatever the mechanism of action, it is important to attempt to associate cause-and-effect relationships and apply the principles of toxicology. Identification of the agents that may be causing the symptoms can result in plans to reduce exposure to these agents and thus reduce symptoms and improve the quality of life. In addition, reductions in the exposure to toxic chemicals for all people may help reduce the incidence of MCS.

Assessing and Managing Risk

As we have seen, risk is closely related to hazard and is defined as the probability of the recognized hazard occurring. *Risk assessment* is the process by which the nature and magnitude of risk are identified, while r*isk management* is the process of determining whether or how much to reduce risk through our actions. Evaluation of the potential adverse effects of some activity or exposure (risk assessment) is something we all do informally on a day-to-day basis. What we decide to do is in part the result of an ongoing risk management decision. It can be as simple as crossing the street against a red light or as complex as spending extra money for organically grown foods to reduce our exposure to pesticides. Many of the risks associated with chemical exposure are indirect or subtle effects on health; in other words, conditions, situations, or exposures to an agent that affect the quality of life. Table 2.2 lists some of the factors that can influence a person's perceptions and views about health concerns.

Table 2.2. Considerations That Influence Acceptability of Risk

More-Acceptable Risk	Less-Acceptable Risk
Benefits understood	Benefits unclear
No alternatives	Alternatives available
Risk shared	Risk affects few
Voluntary	Involuntary

Can be controlled by individual	Uncontrollable
Familiar	Unfamiliar
Low dread	High dread
Affects everybody	Affects children
Occurs naturally	Of human origin (synthetic)
Little media attention	Much media attention
Understood	Not understood
High trust	Low trust

Risk analysis and risk management play an important role in public policy. The debates range from the development of environmental impact statements for the location of buildings to those on household lead abatement and what chemicals can be allowed in the food supply. Quality of life issues such as asthma and mental impairment are now recognized as important components of risk assessment. For example, childhood exposure to lead can result in reduced IQ, which can affect individuals throughout their lifetimes. Childhood asthma can have a severe impact on an individual's ability to play and socialize.

In the past, much of formal risk assessment concerned an estimation of the risk of cancer and subsequent death and then deciding what was acceptable. Typically, a risk of death of less than 1 in 100,000 (10^{-5}) or 1 in 1 million (10^{-6}) is considered an "acceptable" level of risk for exposure to a chemical. In comparison, the risk of death in an automobile accident is 1 in 4000 and the risk of death from lightning is 1 in 2 million. Comparisons like these above are sometimes used to argue that the risk of exposure to a chemical agent is negligible. Such comparisons can be misleading, however, if the conditions of the two risks are different. For example, if they affect different populations unequally, say falling disproportionately on those of a particular ethnic background, the risks may be more likely to be judged unacceptable. Or if one risk is the result of voluntary choice (drinking alcohol) and another is not (eating food contaminated with bacteria), it cannot be assumed that an individual would be equally willing to tolerate them.

Risk assessment is a complex area that requires the application of all the principles of toxicology. It is often divided into four somewhat overlapping areas: 1) hazard identification, 2) dose/response assessment, 3) exposure assessment, and 4) risk characterization. Hazard identification is the process of collecting and evaluating

information on the effects of an agent on animal or human health and well-being. In most cases, this involves a careful assessment of the adverse effects and what is the most sensitive population. The dose/response assessment involves evaluation of the relationship between dose and adverse effect. Typically, an effort is made to determine the lowest dose or exposure at which an effect is observed. A comparison is often made between animal data and any human data that might be available. Next is exposure assessment, in which an evaluation of the likely exposure to any given population is assessed. Important parameters include the dose, duration, frequency, and route of exposure. The final step is risk characterization, in which all the above information is synthesized and a judgment made on what is an acceptable level of human exposure. In the simplest terms, risk is the product of two factors: hazard and exposure (i.e. hazard x exposure = risk). In real risk assessments, all hazards may not be known and exposure is often difficult to quantify precisely. As a result, the calculated risk may not accurately reflect the real risk. The accuracy of a risk assessment is no better than the data and assumptions upon which it is based.

Risk management is the political or social process of deciding how the benefits balance the associated risks. Risk management is also concerned with how the public perceives risk and how we judge and perform our own risk assessments. An example of risk management was the decision to remove lead from gasoline. After a great deal of research it was demonstrated that low levels of lead exposure are harmful to the developing nervous system. It was then determined that the benefits of removing lead from gasoline were greater than the costs. A program was developed to gradually phase out lead from gasoline, design new engines not requiring lead, and replace old cars.

Summary

The principles of toxicology are summarized as follows: **dose/response**, **risk= hazard X exposure** and **individual sensitivity**. Many of us have an excellent intuitive sense of the principles of toxicology from experience with caffeine, alcohol, or other drug exposures. These experiences form a foundation upon which to build a formal understanding of toxicology that is applicable to many situations. We make many personal decisions based on dose/response and risk consideration, and as citizens we are also confronted with many broader concerns about environmental exposures. How much do we invest to limit the spread of environmental contaminants? Should coal-fired power generating facilities be required to invest in more sophisticated smoke stack scrubbers to remove mercury? Advances in the toxicological and biological sciences provide new knowledge and understanding upon which to make both personal and societal decisions.

A Small Dose of Toxicology History

or

An Introduction to the History of Toxicology and Lessons Learned

Milestones of Toxicology Interactive Poster

Introduction

Antiquity

The history of toxicology is rich with personalities, political intrigue, warfare, regulation, and, most importantly, lessons learned. It begins with early humans' need for survival, which required an understanding of the potential hazards of the plants and animals they encountered. Early experimentation with plants was driven by an interest in curing various ailments of body and spirit. Shen Nung, the father of Chinese medicine (approximately 2695 BCE), who was noted for tasting 365 herbs and dying

from a toxic overdose, also wrote an early treatise, *On Herbal Medical Experiment Poisons*. This work was modified though the ages and ultimately helped to established China as a leader in herbal medicine.

The Ebers papyrus, an ancient Egyptian record dated from approximately 1500 BC, contains 110 pages on anatomy and physiology, toxicology, spells, and treatment. The papyrus has a fascinating history: it changed hands and was lost and found again after it first surfaced in 1862. It documents a wide range of toxic substances including hemlock, the state poison of the Greeks, and aconite, a poison used by the Chinese to tip their arrows.

Early Poisons

An array of poisons have been used for assassinations throughout history. Mithridates VI, who was the King of Pontus in Asia Minor from 120 BCE to 63 BCE, took increasing concentrations of various poisons in an effort to protect himself from poisoning attacks. Legend has it that Mithridates attempted suicide by poison but failed and ultimately died by the sword.

Some of the first laws related to toxicology were directed at poisons. Sulla (138-78 BCE) created laws such as the *Lex Cornelia de sicariis et veneficis*, which made it illegal to poison people, including prisoners, and to buy, sell, or purchase poisons. In the 1400s arsenic became a common poison, sometimes used by women to assassinate inconvenient husbands for their wealth. The trend of using poisons for murder continues to modern times, as exemplified by the 2006 poisoning of Alexander Litvinenko, who was poisoned by exposure to the radioactive alpha-particle emitter polonium 210. There is also increasing concern for the potential use of biological weapons to kill people or disrupt society. A strain of anthrax, the bacterium *Bacillus anthracis*, killed several people in the US in 1991. Louis Pasteur developed a vaccine for anthrax in 1881, but research continues to develop and produce more effective vaccines. Unfortunately, the search for more powerful and exotic means of poisoning people continues along with advances in science and technology.

Toxicological Sciences

As scientific methodology advanced, the toxicological sciences became more rigorous. Paracelsus (1493-1541), sometimes called the father of toxicology, articulated the now famous saying "the dose makes the poison." In 1775 the first recognition of an occupational exposure to cancer was made by Percivall Pott, an English surgeon. He observed that exposure to soot was related to scrotal cancer in chimney sweeps. Mathieu J. B. Orfila (April 24, 1787 - March 12, 1853), a French toxicologist and chemist, is credited with founding the modern science of toxicology, in part through analytical work in forensic toxicology related to the poison of the day, arsenic.

Discovery of individual chemicals such as caffeine, nitroglycerin, cocaine, and saccharin increased in the 1800s and accelerated during the 1900s. The German military, supported by a robust chemical industry, was the first to use chemical weapons in World War I. On April 22, 1915, it released chlorine gas over the battlefield at Ypres Salient in Belgium, killing an estimated 5,000 French and Algerian troops.

World War II stimulated the start of the chemical revolution, which included the development of very powerful nerve gases. The aftermath of WWII also stimulated the development of an array of pesticides and an enormous global chemical industry. Chemical weapon stockpiling was an integral part of the arms race throughout the Cold War, and the destruction of these weapons has proven challenging, costly, and time consuming. The Chemical Weapons Convention of 1993 outlaws the production, stockpiling, and use of chemical weapons by all signatories.

Recognizing Hazards

As the use of chemicals and other agents such as metals became widespread, it became clear that they could cause ecological damage and affect human health. Advances in methods to detect chemicals spurred research on the mechanisms of action of many early chemical formulations. In addition, advances in medicine and toxicological sciences led to a better understanding of the health effects of chemical exposures on individuals and populations.

Several incidents brought into sharp focus the potential hazards associated with chemical exposures. During prohibition in 1929, an alcohol tonic called Ginger Jake was contaminated with tri-ortho cresyl phosphate (TOCP), a paralyzing organophosphate chemical. This incident damaged the nervous systems of an estimated 50,000 people. Alice Hamilton, MD (1869-1970), the first female member of Harvard Medical School, documented the health effects of occupational exposure to chemicals such as lead. In the 1950s mercury was released into the environment of Minamata Bay in Japan. The mercury was taken up by fish in the form of methylmercury and caused tragic effects on the developing fetus and on some adults in the area who depended on fish in their diet.

The publication of Rachel Carson's *Silent Spring* in 1962 marked a turning point in the management of chemicals in the United States and ultimately led to the banning of the pesticide DDT. In 1978, the contamination of Love Canal in upstate New York vividly demonstrated the consequences of improperly managing chemical waste. Industrial accidents such as the 1984 release of methyl isocyanate by a Union Carbide subsidiary manufacturing pesticides in Bhopal, India resulted in the death of thousands and injury of hundreds of thousands. The challenge now is to recognize the more subtle effects of chemical exposures that might cause cancer or affect the nervous system of children and to develop appropriate regulation to prevent delayed or longer-term harm from chemical exposures.

Regulation

The incidents mentioned earlier, and others as well, generated public outrage and political pressure that sometimes led to policies to regulate the use of chemicals. In 1906, the Pure Food and Drugs Act was enacted with the support of the Department of Agriculture's chief chemist Harvey W. Wiley. This act established the basis for the Food and Drug Administration (FDA) to protect consumers from potentially dangerous drugs and food and stipulated that the consumer be given warning about the toxic or addictive nature of certain products. Most countries adopted the Geneva Protocol in

1925 to limit the use of chemical and biological weapons in warfare. The federal Food, Drug, and Cosmetic Act (FD&C) was passed by Congress in 1938, giving authority to the FDA to oversee the safety of food, drugs, and cosmetics. This policy effort followed the 1937 introduction of Elixir Sulfanilamide, a medicine that contained diethylene glycol as a vehicle. Over one hundred people, including many children, died when it was distributed and consumed without testing or warnings of the hazard. The Occupational Safety & Health Act (OSHA), passed on December 29, 1970, was intended to ensure every worker a safe and healthful workplace by preventing work-related injuries, illnesses, and deaths. OSHA functions by issuing and enforcing rules (called standards) for workplace safety and health, including exposure to hazardous chemicals. The Environmental Protection Agency (EPA) was officially formed as a result of a law passed in 1970 by the Nixon administration. The EPA would be responsible for maintaining clean air, land, and water and for regulating pollutants in the environment. In the 1990s the European Union moved forward with a more comprehensive chemical use policy through the REACH program (Registration, Evaluation, and Authorization of Chemicals). REACH shifted the momentum and innovation in protecting human health and the environment from the United States to Europe, with the European Union embracing a more precautionary approach to managing chemicals.

Conclusion

The history of toxicology provides a revealing window into our scientific understanding of how chemicals affect health and well-being and how society responds to this new information or experience. The interactive poster depicted in figure 1 provides an opportunity for a more in-depth exploration of toxicology's fascinating history. Many of the unfortunate lessons learned spurred the development of regulatory standards to protect human health and the environment.

Additional Resources

There is a large and ever-growing body of information on the history of toxicology, particularly on the World Wide Web (e.g. Toxipedia). Introductory chapters to major textbooks are also an excellent source of information.

Web-based References

• Toxipedia. History of Toxicology. Toxipedia provides a comprehensive resource on the history of toxicology divided by era. Page also features Milestones of Toxicology Interactive Poster, an interactive pdf file that presents a colorful review of toxicology and allows the user to click on topics for additional information. A high-resolution version suitable for printing is also available. [accessed August 4, 2008]

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A Small Dose of Alcohol

or

An Introduction to the Health Effects of Alcohol

Ethyl Alcohol (CH_3-CH_2-OH): Quick Facts
Uses: solvent, commonly found in beverages
Source: home, industry, pharmacies, and alcoholic beverages
Recommended daily intake: none (not essential)
Absorption: readily absorbed by intestine, food will delay absorption
Sensitive individuals: fetus (Fetal Alcohol Spectrum Disorder [FASD])
Toxicity/symptoms: developing nervous system very sensitive to low levels of exposure; children – lowered IQ, learning and behavioral problems; adults – inebriation, memory loss, liver disease, cancer
Regulatory facts: government agencies recommend women not consume alcohol during pregnancy; blood alcohol when operating motor vehicle regulated by local governments
General facts: long history of use, consumed worldwide, 1 to 3 infants per 1000 globally affected by FASD
Environmental concerns: voluntarily consumed
Recommendations: limit consumption, do not consume alcohol during pregnancy, do not operate motor vehicles after drinking

Introduction

Viewed through the lens of toxicology, alcoholic beverages provide a fascinating window into our relationship with a substance that many of us consume because of its intoxicating properties. Our relationship with alcoholic beverages began over 10,000 years ago with the accidental fermentation of grain. But despite our great familiarity with the use of alcohol, it was not until the early 1970s that we realized that alcohol consumption during pregnancy severely affected the developing infant, with no apparent harm to the mother. Worldwide, 9.1 infants per 1000 are affected by Fetal Alcohol Spectrum Disorder (FASD).

The word alcohol comes from the Arabic *al-kuhul* originally referring to a white powder of antimony used as eye makeup. It was not until the middle of the 18th century that alcohol took on its current meaning of the fermented and intoxicating ingredient found in many common beverages. Fermentation occurs when microorganisms such as yeast, fungi, or bacteria break down complex molecules to produce energy in the absence of oxygen. During fermentation, certain strains of yeast produce ethyl alcohol and carbon dioxide in their quest for energy from available sugars. Below is a table of common fermentation starting points and the end products either as a direct result of fermentation or from further distillation.

Table 4.1 Types of Distilled Spirits

Base Ingredient	End Product
Cereal grains	Beers and whiskeys
Honey	Mead
Grapes	Wine and brandy
Root vegetables	Vodka
Sugar Cane	Rum

Alcohol is also an excellent and widely used solvent, appearing in many products from gasoline to drugs. Industrially, it is produced by chemical reactions using acetaldehyde or petroleum byproducts and more recently from biomass, such as corn or sugar cane. In the United States, annual corn ethanol production for use in fuel has grown from 175 million gallons in 1980 to nearly 9.3 billion gallons in 2008.

Worldwide production is estimated at over 16 billion gallons and is expected to continue to grow.

Case Studies

Fetal Alcohol Syndrome Disorder

Despite alcohol's long history of use, its effects on the developing fetus were not recognized until the early 1970s. Fetal Alcohol Syndrome Disorder (FASD) is the result of maternal consumption of alcohol during pregnancy and is one of the leading causes of permanent learning disabilities and physical growth deficiency. Some believe that 1% of the US population may be affected and a greater percentage are affected worldwide (Wattendorf and Muenke, 2005). FAS is identified by characteristic changes in facial features, particularly around the mouth and eyes. A milder form without the facial deformities, but associated with learning disabilities and CNS dysfunction, is called Fetal Alcohol Effect (FAE) or Alcohol-Related Neurodevelopmental Disorder (ARND). In the US, it is estimated that between 4,000 and 12,000 infants suffer from FAS and 36,000 children have milder forms of alcohol-related disabilities. Worldwide, as many as three infants per 1,000 births have FAS, and an unknown number are afflicted with milder forms of disability related to maternal alcohol consumption. The effects of alcohol on the infant illustrate the sensitivity of the developing fetus to chemical exposure. The tragedy is two-fold: 1) the effects of alcohol on the fetus are preventable, and 2) the effects last a lifetime, robbing individuals of the opportunity to express their full genetic potential.

Alcohol and the Liver

Alcohol has a range of effects in addition to the effects on the developing fetus: for some, desirable acute effects; and with long-term consumption, effects on the liver and other organs. In the US, over 2 million people experience alcohol-related liver disease. Effects of alcohol on the liver are dose related: the more consumed, the greater the effects. Early on there is an accumulation of fat in the liver as a result of the metabolism of alcohol. Metabolites of alcohol, produced by the liver, are toxic to liver cells. Some heavy drinkers develop an inflammation (alcoholic hepatitis) of the liver. As consumption continues, the liver becomes less functional and a process starts that can lead to cirrhosis, or scarring of the liver. Continued drinking can result in death, but if the drinking stops, functioning of the liver can improve; however, the underlying damage is not reversible.

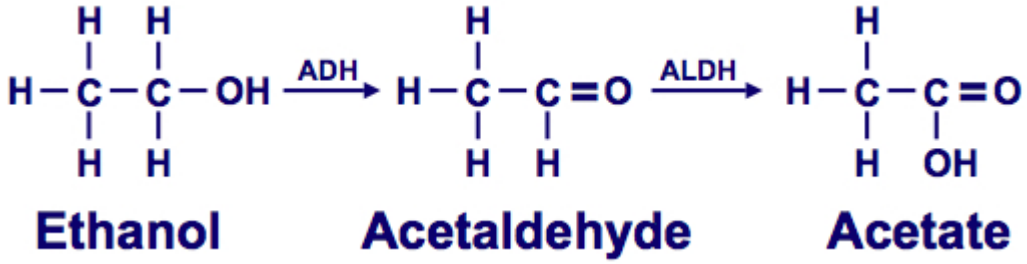
Biological Properties

Alcohol is readily absorbed from the stomach and the intestine, and the highest blood level occurs about 30 minutes from the time of the last drink. Alcohol absorption is slowed by the presence of food in the stomach; however, once it reaches the small intestine, alcohol absorption is rapid. Alcohol vapors can be inhaled and absorbed by

the lungs and can be a significant occupational hazard where used industrially.

After consumption and absorption the majority of alcohol distributes into body water, and like most solvent and anesthetics some distributes into fat. It is excreted in the urine and breath, hence the utility of the taking breath samples to evaluate alcohol exposure. Your breath alcohol level is directly related to your blood alcohol level. The majority of alcohol in your body is metabolized in the liver. An enzyme, alcohol dehydrogenase (ADH), metabolizes alcohol to acetaldehyde. Acetaldehyde is toxic, with elevated levels causing flushing, headache, nausea, and vomiting. Acetaldehyde is in turn quickly metabolized to the less toxic metabolite acetate by another enzyme acetaldehyde dehydrogenase (ALDH) (Figure 4.1).

Figure 4.1 Metabolism of Alcohol



Humans have varying amounts and types of ALDH which affects their ability to metabolize the toxic metabolite acetaldehyde. For example of approximately 50% of people of Asian heritage have a single base change in a gene that encodes for ALDH resulting in an inactive form of ALDH, which makes alcohol consumption very unpleasant. Antabuse (disulfiram), a common drug prescribed to discourage alcohol consumption, blocks ALDH and causes blood levels of acetaldehyde to rise. The subsequent toxic side effects discourage continued alcohol consumption. Disulfiram was a chemical originally used in the rubber industry. Workers inadvertently exposed to disulfiram accidentally discovered its effects when they became sick after drinking alcoholic beverages.

The metabolism of most drugs or chemicals is proportional to the concentration of the compound in the blood. This allows us to calculate the rate of metabolism or a half-life. However, ethanol is different; its metabolism is relatively constant over time and the rate of metabolism does not increase with rising blood concentrations. We also know that metabolism is proportional to body weight; thus the bigger you are, the higher the rate of metabolism, but on average, ethanol is metabolized at a rate of 120 mg/kg per hour or about 1 oz (30 ml) in 3 hours.

Ethanol is easily measured in the blood and reported as milligrams per milliliter (mg/ml)of blood. Current laws regulating driving after drinking specify specific blood alcohol concentration (BAC) as unacceptable when operating a motor vehicle. Most

states set 0.08 or 0.1, which is equivalent to 80 mg/100 ml or 80 milligrams per deciliter (mg/dL) of blood. Alcohol content of exhaled breath is about 0.05% of the BAC.

Another factor that influences blood alcohol concentrations and thus the effects of alcohol is gender. Drink for drink, a female will have a higher BAC than a male. First, women tend to be smaller, so by body weight they receive a higher dose of alcohol. Second, women metabolize less alcohol in the intestine than men, which results in great absorption of alcohol and a higher BAC. Finally, women usually have a greater proportion of body fat per body weight, which results in lower volume of fluid by weight. An average male of medium weight (160-180 pounds) must consume almost four drinks in an hour to reach an a BAC of 0.08, whereas an average female weighing 130 to 140 pounds requires on only 3 drinks within one hour to reach a BAC of 0.08. The exact number of drinks to reach a BAC of 0.08 of course depends on many variables, not the least of which is the percent alcohol in the drink.

How alcohol affects the central nervous system is still not completely clear. For some time, researchers thought that the depressant affects of alcohol, like other anesthetic agents, was caused by the dissolving of cells' lipid membranes and the disruption of the function of various proteins. More recently, researchers have focused on specific receptors such as glutamate (excitatory) and GABA (inhibitory). Despite intensive research, the mechanism by which alcohol affects the developing fetus is still unknown.

Health Effects

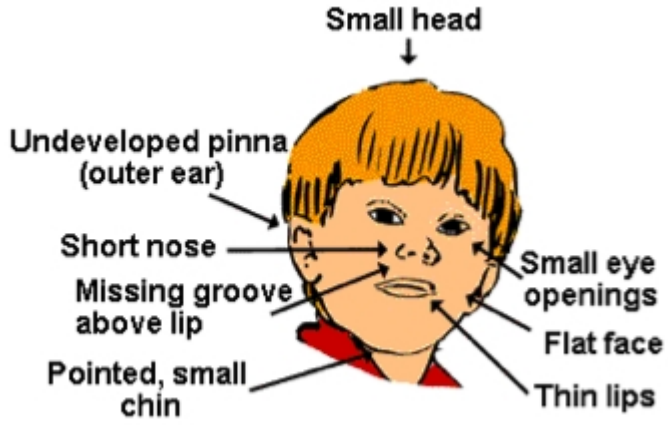
By any measure, alcohol has an enormous impact on our society: it contributes to at least 100,000 premature deaths, and economic costs are estimated to be over $275 billion a year, including medical expenses, lost worker productivity, automobile accidents, and crime. The toxic effects of alcohol have resulted in efforts and laws to control and regulate its consumption. While alcohol affects the individual consumer, two areas are of particular concern for the greater society: 1) the effects of alcohol on the developing infant from maternal alcohol consumption and 2) the death and injury caused by driving motor vehicles following drinking. This section is divided into the health effects of alcohol on children and adults to emphasize the sensitivity of fetal exposure to alcohol during pregnancy.

Before starting, it is necessary to define what a drink means. This is not as straightforward as it might seem given the wide range of beverages that contain varying concentrations of alcohol. One common definition of a drink is a beverage that contains 0.5 oz or 15 ml of ethanol.

Children

Despite alcohol's long history of use, the adverse effects of maternal alcohol consumption on the developing fetus wasn't described until 1968, by French researchers at the University of Nantes. In 1972, the cluster of effects was further described and named Fetal Alcohol Syndrome (FAS) by researchers at the University of Washington in Seattle, USA. FAS is characterized by physical and facial abnormalities (Figure 4.2), slow growth, central nervous system dysfunction, and other disabilities. The related brain damage can be severe, leaving the child with serious learning and functional disabilities that have lifelong impacts. Another form of alcohol-related effects is Fetal Alcohol Effect (FAE), where children are born with learning or memory disabilities, but without the characteristic physical abnormalities. The disabilities associated with fetal alcohol exposure are now described as Fetal Alcohol Spectrum Disorder (FASD), which recognizes the range of effects alcohol has on development. In addition, alcohol consumption during pregnancy causes an increase in stillbirths and spontaneous abortions. It is extremely important to recognize that alcohol consumption during pregnancy results in the largest number of preventable mental disabilities in the world.

Figure 4.2 Physical Characteristics of FAS



In 1981 the US Surgeon General first advised that women should not drink alcoholic beverages during pregnancy because of the risks to the infant. In 1989 warning labels were mandated on all alcoholic beverages sold in the United States, and since 1990 the US government policy has clearly stated that women who are pregnant or planning to become pregnant should not drink alcohol.

It is difficult to determine exactly how many young children and subsequent adults are handicapped by fetal exposure to alcohol because the diagnosis of less severe forms of the disease is imprecise. Worldwide, alcohol consumption affects between 1 and 3 out of 1,000 infants. In the United States, 4,000 to 12,000 infants per year are born with FAS and as many as three times of that with minor disabilities. Recent studies in the United States estimate that 14 to 22.5 percent of women report drinking some alcohol during pregnancy. An additional concern is that a woman is often not aware she is

pregnant during the first few very vulnerable weeks of pregnancy.

The consequences of maternal alcohol consumption are tragic and last a lifetime for the exposed infant. In 1989, Michael Dorris described the life of his adopted son Able, who had FAS, as that of a drowning man, one "conceived in an ethanol bath" and unable to find the shore.

Adults

Alcohol, a toxic solvent, flows freely in our society. Because it is heavily advertised, easy to make, easy to purchase, and widely consumed across all ages because of its neuroactive properties, we struggle to address adverse health consequences of consumption. In the United States the legal drinking age is 21 years, but illicit consumption of alcoholic beverages often starts much earlier. In Europe and other parts of the world the legal drinking age is generally 18 and sometimes 16 years of age.

The acute effects of alcohol consumption are associated with mild nervous system effects such as relaxation and reduced inhibitions that many people find desirable. Additional consumption results in sleepiness and reduced motor and reaction time, which effects the ability to operate a motor vehicle or engage in complex tasks. Continued consumption can result in drunkenness, which is often associated with uncontrolled mood swings and emotional responses and sometimes violence. Excessive alcohol consumption can result in violence, spousal and child abuse, crime, motor vehicle accidents, workplace and home accidents, drowning, suicide, and accidental death. Rapid consumption of large quantities of alcohol sometimes seen on college campuses can result in respiratory depression, coma, and possibly death due to depressed respiration. Vasodilation also occurs especially in vessels near the skin, which gives the drinker false feeling of warmth. Contrary to popular belief, sexual function is decreased for both men and women after alcohol consumption.

The chronic effects of alcohol consumption include alcoholism, liver disease, various cancers, brain disorders, cardiovascular disease, absence from or loss of work, family dysfunction, and malnutrition. Chronic consumption of alcohol can result in a tolerance to its overt effects, but it still affects functional ability, such as that required to drive a vehicle. Tolerance can develop to such an extent that an individual can have very high alcohol levels (300 to 400 mg/dl) and still not appear to be physically affected. However, the ability to tolerate high blood alcohol levels does not change the level necessary to produce death from acute consumption.

Chronic excessive consumption of alcohol can result in physiological dependence or alcoholism. There is often a steady progress in the need to consume alcohol, so that

the person starts drinking early in the day to maintain blood alcohol levels and avoid withdrawal effects. Alcoholism often results in a variety of organ system effects, some of which are related to accompanying malnutrition. Treatment for alcoholism must address the withdrawal effects as well as associated vitamin deficiencies associated with any malnutrition.

Alcohol Withdrawal Effects

- Tremor
- Nausea
- Irritability
- Agitation
- Tachycardia
- Hypertension
- Seizures
- Hallucinations

Alcohol affects a number of organs, but the liver is most commonly affected. Initially there is accumulation of fat in the liver. Cellular damage appears to be associated with increased levels of acetaldehyde. This in turn results in a scarring or hardening of the liver called cirrhosis. All these changes to the liver result in decreased ability to metabolize alcohol as well other drugs; the toxicity of some drugs, such as the pain reliever Tylenol (acetaminophen), is enhanced.

The International Agency for Research on Cancer (IARC) states that "alcoholic beverages are carcinogenic to humans (Group 1)" and concluded that "the occurrence of malignant tumors of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and female breast is causally related to alcohol consumption." Alcohol is also associated with a general increase in cancer of other organs and interacts synergistically with smoking, putting smokers who drink at a greater risk for developing cancer. There is increasing evidence that alcohol consumption by women increases the risk for breast cancer.

Regulatory Standards

Advice or regulation related to alcohol consumption during pregnancy was slow to arrive even following the documentation of fetal effects, and more needs to done to discourage alcohol consumption during pregnancy.

- 1981: US Surgeon General first advised that women should not drink alcoholic

beverages during pregnancy.

- 1988: US required warning labels on all alcoholic beverages sold in the United States.
- 1990: US Dietary Guidelines stated that women who are pregnant or planning to become pregnant should not drink alcohol.
- 1998: 19 states required the posting of alcohol health warning signs where alcoholic beverages are sold.

Recommendations and Conclusions

Reducing Exposure

Reducing exposure is easy in concept but is usually more difficult in practice. Most importantly, women who are planning on becoming pregnant or who are pregnant should not consume alcohol. Men need to support and encourage women's avoidance of alcohol consumption during pregnancy. For many who consume alcohol, it is important to learn how to manage exposure. Food consumption slows alcohol absorption, so eat when drinking and do not to consume alcohol on an empty stomach. There is a great amount of variability in the percent of alcohol in drinks. It is a good practice to consume fewer drinks that have high alcohol content.

Conclusion

Alcohol is a readily available toxic chemical that can yield pleasurable experience or disastrous effects that can cause enormous suffering. The most tragic effects occur when a woman consumes alcohol during pregnancy, producing irreversible harm to the developing fetus. The consumption of alcohol during pregnancy is the single greatest cause of preventable birth defects and learning and performance disabilities. Alcohol is associated with motor vehicle accidents and a range of other detrimental effects. While government regulatory agencies and policy responses have worked to reduce the adverse health and societal effects, over $1 billion is spent every year advertising the consumption of this chemical. In conclusion, consume with caution and beware of your individual sensitivity.

Additional Resources

Slide Presentation and Online Material

A Small Dose of Alcohol presentation material and references. Website contains presentation material related to the toxicity of alcohol.

European, Asian, and international Agencies

• UK Department of Health (DOH). Alcohol Misuse Information. The DOH provides extensive information on the health effects of alcohol. [accessed July 13, 2008]
• International Council on Alcohol and Addictions (ICAA). "ICAA is a non-governmental organization in consultative status (Category Special) with the Economic and Social

Council of the United Nations and in official relations with the World Health Organization." [accessed July 13, 2008]

North American Agencies

- Health Canada. Fetal Alcohol Spectrum Disorder (FASD). This site provides tools to reduce and manage the effects of fetal exposure to alcohol. [accessed July 13, 2008]
- US Centers for Disease Control (CDC). Fetal Alcohol Syndrome: Guidelines for Referral and Diagnosis. [accessed July 13, 2008]
- US Department of Justice (DOJ). Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF). ATF's unique responsibilities include protecting the public, reducing violent crime, and enforcing the federal laws and regulations relating to alcohol and tobacco diversion, firearms, explosives, and arson. [accessed July 13, 2008]
- US National Institute on Alcohol Abuse and Alcoholism (NIAAA). "The NIAAA supports and conducts biomedical and behavioral research on the causes, consequences, treatment, and prevention of alcoholism and alcohol-related problems." [accessed July 13, 2008]
- National Toxicology Program. Health Assessment and Translation. Website has information for parents about the effects of alcohol on reproduction and development. [accessed July 13, 2008]
- US Department Of Health And Human Services (HHS). Substance Abuse and Mental Health Services Administration (SAMHSA) Center for Substance Abuse Prevention. "The CSAP mission is to decrease substance use and abuse by bringing effective prevention to every community." [accessed July 13, 2008]

Non-Government Organizations

- Alcoholics Anonymous (AA). An international organization dedicated to helping people with alcohol consumption concerns. [accessed July 13, 2008]
- Center for Science in the Public Interest (CSPI). "CSPI is an advocate for nutrition and health, food safety, alcohol policy, and sound science." [accessed July 13, 2008]
- Mothers Against Drunk Driving (MADD). "MADD's mission is to stop drunk driving, support the victims of this violent crime, and prevent underage drinking." [accessed July 13, 2008]
- National Council on Alcoholism and Drug Dependence, Inc. (NCADD). NCADD provides education, information, help and hope to the public and advocates prevention, intervention and treatment. [accessed July 13, 2008]
- Rutgers, The State University of New Jersey. Center of Alcohol Studies (CAS). The Center of Alcohol Studies is a multidisciplinary institute dedicated to acquisition and dissemination of knowledge on psychoactive substance use and related phenomena with primary emphasis on alcohol use and consequences. [accessed July 13, 2008]
- FAS Bookshelf, Inc. Website devoted to providing resources on Fetal Alcohol Syndrome. [accessed July 13, 2008]
- National Organization on Fetal Alcohol Syndrome. "NOFAS is dedicated to eliminating birth defects caused by alcohol consumption during pregnancy and improving the quality of life for those affected individuals and families." [accessed July 13, 2008]
- Alcohol and Drugs History Society (ADHS). ADHS, formerly Alcohol and Temperance History Group, is an international group of alcohol, temperance, and drug history scholars founded to foster the exchange of ideas among scholars of all disciplines who are interested in any aspect of past alcohol use, abuse, production, and control within

given societies or countries and online home of The Social History of Alcohol and Drugs: An Interdisciplinary Journal (SHAD). [accessed July 13, 2008]

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National Institute on Alcohol Abuse and Alcoholism (NIAAA), National Institutes of Health. *Alcohol and Health, 10th Special Report to the US Congress. Highlights from Current Research*. Department of Health and Human Services, June 2000. [accessed July 13, 2008]

Astley, S.J. (2004). *Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code*. Seattle: University of Washington, 2004.

Stratton, Kathleen, Howe, Cynthia, and Frederick C. Battaglia, eds. *Fetal Alcohol Syndrome: Diagnosis, Epidemiology, Prevention, and Treatment*. Washington, DC: The National Academy Press, 1996. [accessed July 13, 2008]

World Health Organization. *Global Status Report on Alcohol 2004*. [accessed July 13, 2008]

Wattendorf, D. J., and M. Muenke. "Fetal alcohol spectrum disorders". *American Family Physician* 72 (2005): 279-82, 285. [accessed July 13, 2008]

A Small Dose of Caffeine

or

An Introduction to the Health Effects of Caffeine

Caffeine (1,3,7-trimethylxanthine): Quick Facts
Uses: most widely used stimulant in the world
Source: coffee, tea, cola and other soft drinks, chocolate, stimulant pills, some analgesics
Recommended daily intake: the US Food and Drug Administration (FDA) advises pregnant women to "avoid caffeine-containing foods and drugs, if possible, or consume them only sparingly"
Absorption: rapid following oral consumption
Sensitive individuals: fetus, children, some adults
Toxicity/symptoms: high dose:agitation, tremors; withdrawal:headache
Regulatory facts: GRAS (Generally Recognized as Safe)
General facts: long history of use; related xanthines: theobromine (3,7-dimethylxanthine) and theophylline (1,3-dimethylxanthine)
Environmental concerns: contaminates sewage discharge
Recommendations: be thoughtful about consumption

• • •

Caffeine Industry

"The coffee and cola industries owe their wealth to the physiological properties of the drug caffeine."

- S.G. Gilbert (2001)

• • •

Coffee

"Black as hell, strong as death, sweet as love."

- Turkish proverb.

"Often coffee drinkers, finding the drug to be unpleasant, turn to other narcotics, of which opium and alcohol are most common."

- *Morphinism and Narcomanias from Other Drugs* (1902) by T. D. Crothers, M.D.

"Coffee, which makes the politician wise/And see through all things with his half-shut eyes."

- Alexander Pope (1688–1744), English satirical poet. *Rape of the Lock,* cto. 3 (1712).

"The morning cup of coffee has an exhilaration about it which the cheering influence of the afternoon or evening cup of tea cannot be expected to reproduce."

- Oliver Wendell Holmes Sr. (1809–94), US writer, physician. *Over the Teacups,* ch. 1 (1891).

• • •

Tea

"Is there no Latin word for Tea? Upon my soul, if I had known that I would have let the vulgar stuff alone."

- Hilaire Belloc (1870–1953), British author. *On Nothing,*"On Tea" (1908).

"It has been well said that tea is suggestive of a thousand wants, from which spring the decencies and luxuries of civilization."

- Agnes Repplier (1858–1950), US author, social critic. *To Think of Tea!* ch. 2 (1932).

"Tea, though ridiculed by those who are naturally coarse in their nervous sensibilities will always be the favorite beverage of the intellectual."

- Thomas De Quincey (1785–1859), English author. *Confessions of an English Opium-Eater,*"The Pleasures of Opium" (1822).

• • •

Introduction and History

Caffeine, a naturally occurring chemical found in a number of plants, has a long and illustrious history and continues to have an enormous impact on our society. It has gone from being vilified, compared to alcohol and nicotine, to becoming the most widely accepted and consumed neuroactive drug in the world. Caffeine is available in a wide range of products with no regulations on its sale or use. Even more than alcohol and nicotine, caffeine demonstrates our interest in, and capacity to consume, drugs that affect our nervous system.

In this chapter we will explore the physiological reasons why we so readily consume

caffeine. The economics are staggering.: coffee alone is one of the largest cash crops in the world, with global production in 2006/2007 estimated at greater than7 billion kilograms (more than 14 billion pounds). This translates to over a trillion cups of coffee and literally tons of caffeine, and does not even take into consideration the caffeine consumed from cola beverages, tea, and chocolate. Our brains and our wallets are hooked on caffeine.

Historically, caffeine has played an important role in trade and politics and even now, the export of coffee is an extremely important part of world trade for many countries. The health effects of caffeine have been the subject of numerous scientific inquiries; perhaps the best book addressing both the historical and health aspects of caffeine is *The World of Caffeine: The Science and Culture of the World's Most Popular Drug* by Bennett Alan Weinberg and Bonnie K. Bealer. Published in 2001, this book gives a wonderful account of the interaction between caffeine and society, from its ancient roots to present times. A book devoted almost entirely to the health effects of caffeine is *Caffeine and Health* by Jack E. James, published in 1991.

Given the many plants that contain caffeine, some have speculated that even Stone Age humans chewed the leaves and fruit of caffeine-producing plants to enjoy its stimulant properties. Although this early consumption is speculative, it is clear that caffeine consumption has been with us for a long time.

Tea appears to be the most ancient of caffeinated drinks. The first documented use is in China by its first great emperor, Shen Nung, in about 2700 B.C., and there are many references to tea and its many benefits throughout Chinese history Tea became popular with Buddhist monks to keep them awake during long hours of meditation. Despite the association of tea with China, some believe that tea was actually introduced into China from Northern India.

In the 5th century, tea was an important item of trade on the Silk Road, and in about 800 A.D., tea was introduced to Japan, where the consumption of powdered green tea evolved into an elaborate ceremony that is still practiced today. The Dutch brought tea to Europe in 1610, and the Americans revolted over taxes on tea in 1773. A few years later, England sent the first opium to China in payment for tea, which ultimately resulted in the Opium Wars and England's control of Hong Kong.

Coffee's history is equally rich and savory. According to legend, in about 850 A.D., an Ethiopian goatherd (or shepherd depending on your source) noticed that his goats seemed more alert after consuming wild berries. Wishing to increase his own performance, he tried the berries himself, constituting the first occupational consumption of coffee.

The cultivation of coffee trees and the roasting of coffee beans was developed by 1100. Four hundred years later, Mecca, Cairo, and Constantinople were the sites of the first coffee shops. Coffee came to Europe in the 1600s and quickly spread to the Americas, where coffee trees were introduced in 1723. By the 1700s there were coffee shops throughout Europe; the first espresso machines were made in France in the early 1800s, and the early 1900s saw the introduction of instant coffee. In 1971, the

first Starbucks coffee shop opened in Seattle, Washington, and now there are thousands of Starbucks around the world, as well as many other local coffee shops. In many parts of the world, coffee shops are an important gathering place for discussion and relaxation, an integral aspect of people's culture. In this respect, the United States is just catching up to the rest of the world.

Chocolate provides much less caffeine than tea or coffee and people all over the world consume it not so much for the caffeine but for the taste. Archaeological evidence indicates that the Olmec people of Mexico harvested the cacao bean to make a drink in 400 B.C. or perhaps earlier. By 250 A.D., the Mayans of Mexico were cultivating the cacao tree. The Aztec people used the cacao bean as currency and equated it to a drink form the Gods. The scientific name for the cacao bean tree is *Theobroma cacao*. *Theobroma* is Greek for "Food of the Gods." Theobromine, the primary caffeine-like compound found in chocolate, also derives its name from *Theobroma*. The Spanish explorer Hernando Cortés brought cocoa to Spain in 1528, where it was kept secret from the rest of Europe until 1600, when it quickly became very popular, so popular that the Pope had to declare that chocolate drinks did not break a fast. The first English chocolate houses opened in 1657, and in 1828, shortly after the invention of the first espresso machine, the screw press for extracting cocoa butter from the beans was invented in Holland. Chocolate as a solid was invented in the 1840s and soon became a common food item.

The amount of caffeine in a particular product, as well as the amount consumed, can vary enormously (see Table 5.1). The amount in a cup of coffee varies with the type of bean, and the roasting and brewing methods. Tea leaves actually have a higher concentration of caffeine than coffee beans, but the extraction of caffeine from coffee is more efficient. (However, brewing tea for a longer period releases more caffeine.) By weight, cocoa has the least amount of caffeine, but it also contains the structurally similar compound theobromine.

Caffeine is also added to many colas and other soda-like beverages. Some are known specifically for their high caffeine concentration, and it is now possible to buy water-based drinks fortified with caffeine. Over-the-counter pills of caffeine are also available, and many analgesic medications contain caffeine, in part to alleviate headaches caused by caffeine withdrawal.

Table 5.1 Common products and caffeine concentration

Product	Caffeine	Size
Coffee	50-150 mg	Cup (about 8 ounces or 225 ml)
Tea	20-100 mg	Cup (about 8 ounces or 225 ml)
Cola drinks	20-100	8 ounces or 225 ml

Energy drinks	120-300	12 ounces
Chocolate (cocoa)	1-35 mg	Ounce or 28 grams

Table 5.2 History of Caffeine Consumption (T=Tea, Co=Coffee, Ch=Chocolate)

Date	Type	Event
3000 BC	T	Tea discovered in China or introduced from India
350 BC	T	First written description of tea-drinking in China
400 BC	Ch	Olmec people of Mexico made chocolate drinks
250 AD	Ch	Mayans of Mexico cultivated cocoa crops
450	T	Turkish traders bargained for Tea and the Silk Road was born
800	T	Tea introduced to Japan
850 (about)	Co	Coffee beans discovered: the fable says that an Ethiopian herder noticed that goats were more alert after eating the wild berries; he then sampled this new delicacy
1100 (about)	Co	First coffee trees grown and coffee beans roasted
1450	T	Japanese tea ceremony created and popularized
1475	Co	World's first coffee house established in Constantinople
1528	Ch	Cocoa brought to Spain by Hernando Cortés
1600s	Co	Coffee introduced to Europe and moved quickly to the Americas

1600s	Ch	Chocolate drinks introduced to Europe
1610	T	Dutch brought tea to Europe
1657	Ch	First English chocolate houses opened
1700s	Co	Coffee houses opened throughout Europe
1723	Co	First coffee plants introduced to the Americas
1773	T	Boston Tea Party, rebellion against England's tea tax
1776	T	England sent first opium to China to help pay for tea
1822	Co	First espresso machine created in France
1828	Ch	Screw press that extracted cocoa butter from the beans invented in Holland
1835	T	First experimental tea plantations established in Assam, India
1840s	Ch	Chocolate as solid developed
1908	T	Tea bags invented in New York
1938	Co	First instant coffee invented by the Nestlé company
1971	Co	Starbucks opened its first location in Seattle, Washington's Pike Place Market

Case Studies

The Individual

With as commonly consumed and easily available a drug as caffeine, the very best case study is yourself, your family, or your friends. Ask the following questions and

carefully consider the implications of these answers. Have you ever drunk too much caffeine? If so, how did you know you had too much? If the answer to the first question is yes, then you are on your way to becoming a toxicologist. If you have felt the jitters or agitation of too much caffeine, then you have experienced the nervous system effects and are a case study in the neurotoxicology of this drug.

What happens when you stop drinking caffeine? Do you get a headache? If the answer is yes then you are dependent on the drug caffeine. Some of your caffeine consumption is driven by a desire to avoid a caffeine-induced headache.

How many hours elapse before you reach for that second cup of coffee? Many of us have learned by practice that when our blood caffeine levels decline too far, we need to boost them back up with a second cup of coffee, tea, or a can of soda.

The above factors make caffeine the most widely consumed stimulant drug in the world. The stimulant and other basic biological properties of caffeine make it an almost ideal money-making drug for many large corporations and small businesses.

Society

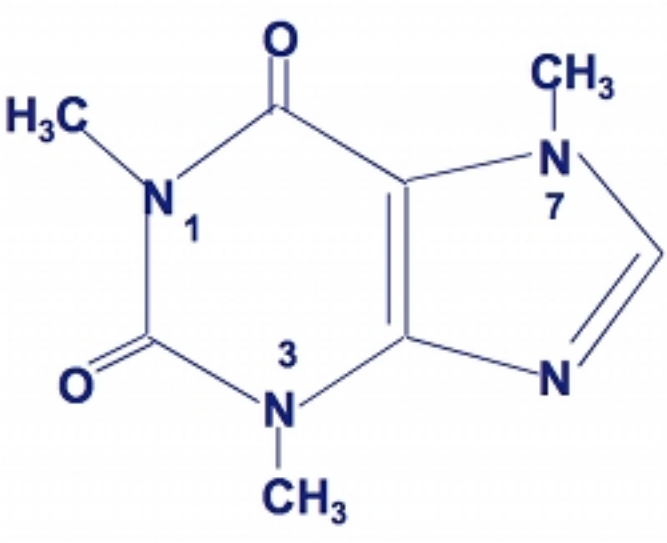
The study of caffeine is a window into our culture and society. Why do so many people consume caffeine and what does that say about our drug consumption? What are the basic biological properties that make caffeine the most widely consumed stimulant in the world?

Many people start consuming caffeine at an early age. It is not uncommon for schools to have soda machines, and coffee stands are often found close to schools. Middle and high school students are well aware of the stimulant properties of caffeine. Is it appropriate for schools to have soda machines, which encourages caffeine consumption?

Biological Properties

Caffeine is a naturally occurring chemical manufactured by a number of plants in either the fruit—as in coffee bean, cola nuts, and coca beans—or the leaves—as in tea. The global use of caffeine-bearing substances at the start of the 19th century coincided with a period of great discovery in the physical and chemical sciences. Caffeine was isolated from coffee beans in 1819 by Friedlieb Ferdinand Runge, a young German physician and chemist. Caffeine derives its name from the German *Kaffeine*, which is in turn from *Kaffee*, or coffee. In 1827 the active ingredient in tea was isolated and called "thein," but was later found to be identical to the caffeine of coffee.

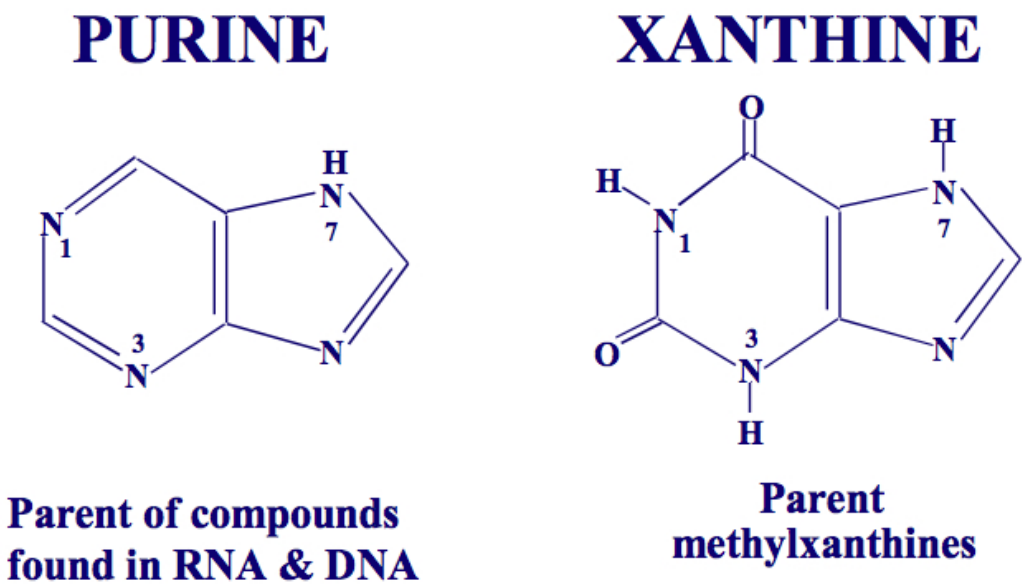
Figure 5.1 Caffeine or 1,3,7-trimethylxanthine



Purified, caffeine (Figure 5.1) is a white crystalline powder with a bitter taste. Caffeine is not particularly soluble in water and is extracted from plant material with hot water; the longer the extraction period, the greater the amount of caffeine extracted. In plants, caffeine's purpose may be to discourage consumption by predators with its bitter taste and mild nervous system effects. But with humans it clearly has the opposite effect of encouraging consumption of the plant.

The chemical name of caffeine is 1,3,7-trimethylxanthine, and caffeine's basic chemical structure is similar to the purine structure found in DNA (see below). This similarity in structure generated speculation that caffeine may somehow cause cancer by interacting with DNA or RNA. Despite this similarity in structure, there is no indication that caffeine is mutagenic or causes cancer.

Figure 5.2 Chemical Structures of Purine and Xanthine



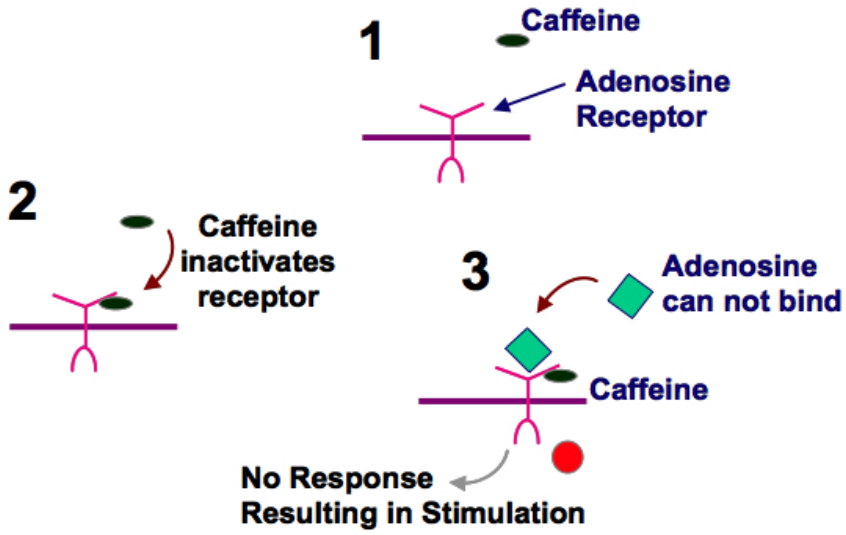
Closely related methylxanthines include theophylline (1,3-dimethylxanthine), theobromine (3,7-dimethylxanthine), and paraxanthine (1,7-dimethylxanthine). Theobromine is found primarily in chocolate. These derivatives of caffeine are important because they are pharmacologically active and also are caffeine's common metabolites.

Caffeine is readily and completely absorbed from the intestine following oral ingestion. It distributes throughout body water, so blood, urine, and breast milk will all have about the same concentration of caffeine. Metabolism varies between individuals, but on average the caffeine from a cup of coffee will produce peak blood caffeine levels in about 30 minutes. This peak level will drop by one half in 4-5 hours, the so-called half-life. In smokers caffeine is metabolized more quickly, usually with a half-life of about three hours, whereas during pregnancy, the half-life increases to 8-10 hours. Newborns cannot metabolize caffeine and rely solely on excretion of caffeine in the urine, which means the half-life of caffeine is measured in days, not hours. Metabolism occurs primarily in the liver and starts with the removal of one or two of the methyl (CH_3) groups to make di- or mono-methylxanthines, which are excreted in the liver. The relatively short half-life of caffeine accounts for its repeated consumption.

Caffeine and the related dimethylxanthines have similar pharmacological, therapeutic, and toxic effects. The primary actions include stimulation of the central nervous system, relaxation of bronchial muscles, mild cardiac muscle stimulation, and diuretic effects on the kidney.

There are a number of possible ways that caffeine can exert its effects, but the most probable action, particularly at concentrations from common consumption, is blockage of the adenosine receptor. Adenosine is a neurotransmitter that produces a calming effect; caffeine blocks the receptors that are activated by adenosine, which results in stimulation (Figure 5.3). There is additional evidence that over time, the cells of the nervous system respond to the blockage of adenosine receptors by increasing the number of adenosine receptors or regulating their activity.

Figure 5.3 Mechanism of Action of Caffeine



Caffeine and theophylline are the most active on the central nervous system, while theobromine is much less active. Caffeine and theophylline also appear to stimulate the respiratory centers, making them useful in treating of infants who stop breathing for extend periods of time (sleep apnea, which can lead to sudden infant death).

Methylxanthines also affect smooth muscles and the cardiovascular system. The most notable effect on smooth muscles is relaxation of the bronchi of the lungs, and theophylline is prescribed to treat mild forms of asthma. While both caffeine and theophylline will relax the bronchial smooth muscles, theophylline is used therapeutically because of its longer half-life. This allows the drug to stay in the therapeutic range longer. Individuals may notice some changes in heart rate following consumption of a strong cup of coffee. Most caffeine users have developed a tolerance to the cardiovascular effects, but these effects may occur if there is elevated consumption.

Health Effects

Most people experience the stimulant effects of caffeine as an increase in alertness and energy, and possibly an increase in concentration. What many like most is gaining the ability to stay awake. Long-term consumption of caffeine does not result in tolerance to the desirable stimulatory effects. This is important for the caffeine industry because if we developed tolerance to this drug, we would stop consuming it due to lost effectiveness.

Another important aspect of caffeine is that repeated consumption does not change the metabolism of caffeine. From individual to individual, the half-life of caffeine in the blood—how fast it is removed—does not change with repeated use. If the half-life of caffeine decreased and the metabolism were faster, we would have to drink even more caffeine to maintain our blood caffeine levels.

The adverse effects of caffeine are a common experience for most caffeine consumers.

Too much caffeine results in central nervous system effects ranging from uncomfortable to adverse. These effects include restlessness, tension, and mild tremor or the jitters, and may progress to feelings of anxiety and even fear. Regular caffeine users soon learn how to manage their caffeine consumption to maintain blood caffeine levels at a desirable level that produces mild stimulation without the uncomfortable neurotoxic effects. Fortunately, the half-life of caffeine is short, so that any undesirable effects soon decline. Many people also experience insomnia from caffeine consumption. Caffeine's effect on sleep varies from individual to individual: some people can consume caffeine late in the evening and sleep well, while others cannot.

Many people experience undesirable withdrawal effects when they stop consuming caffeine. The most prominent undesirable effect is a headache. Additional effects may include feelings of fatigue and irritability. Relief from symptoms usually occurs with resumption of caffeine consumption, which is a classic sign of drug dependence. Awareness of your individual potential to suffer from withdrawal effects is important. This knowledge can often explain the onset of a headache when there is a sudden or unexpected cessation of caffeine consumption.

Most of the overt toxicity of caffeine, theophylline, or theobromine is associated with the cardiovascular effects. Sensitive individuals may experience elevated or irregular heartbeats and elevated respiration. A good example of the cardiovascular effects of theobromine is evident when dogs consume chocolate. Milk chocolate contains about 45 mg/oz (150 mg/100 g) of theobromine and baking chocolate has about 400 mg/oz (1400 mg/100 g). The lethal effect of theobromine for dogs is 100-150 mg/kg. In addition, the half-life of theobromine for dogs is about 17 hours. For a small dog, it does not take much to produce serous toxic effects from the accidental consumption of chocolate. For example, 1 ounce of baker's chocolate could be fatal for a dog weighing 22 pounds. For humans the lethal effects of caffeine occur at between 5 to 10 grams, which on a mg/kg basis is similar to the 100-150 mg/kg of theobromine for dogs.

- In 1980, the US Food and Drug Administration (FDA) advised pregnant women to "avoid caffeine-containing foods and drugs, if possible, or consume them only sparingly."

There are several good reasons to consider the potential for caffeine to affect the developing fetus. First, caffeine and its metabolites distribute throughout body water. This means that the fluid surrounding the fetus contains caffeine and its metabolites at levels similar to those in the mother's blood: the fetus is literally swimming in and breathing caffeine. Second, during the last two trimesters of pregnancy, maternal caffeine metabolism decreases, and the half-life increases to about twice normal, or 8-10 hours. This means that after caffeine consumption both the maternal blood caffeine levels and the infant's exposure will stay higher for a longer period of time. Third, caffeine clearly interacts with the nervous system by affecting the adenosine receptor. The consequences of having the fetal brain develop while being influenced by a drug that is blocking the adenosine receptor are not yet clear. There is, however, some human and animal data indicating that high levels of caffeine may adversely affect the infant. The US FDA advises pregnant women to avoid or limit caffeine consumption in

an effort to address these concerns.

Excessive consumption of caffeine is a near-perfect example of the fundamental dose/response principle of toxicology: sudden reduction in caffeine consumption by the regular consumer can lead to the onset of headaches. It can be argued that many people are dependent on their caffeine consumption to maintain their body in a comfortable, pain-free state. There is disagreement about the mechanism responsible for the caffeine-induced headache. One possibility is that caffeine causes a small constriction of cerebral blood vessels; when caffeine consumption is stopped for an extended period of time these vessels enlarge, causing a headache.

Reducing Exposure

Many of us consume caffeine throughout our lives. Through experience we learn how much to consume to achieve the desired effects and avoid the undesirable ones. The first step in reducing exposure to any agent is being aware of the exposure and our response to it. It is simple to say that reducing exposure to caffeine only requires reduction in the consumption of caffeinated beverages. But in reality it is more complicated. For example, should caffeinated products be readily available in high schools? What are the consequences of caffeine exposure for high school students?

Regulatory Standards

The US Food and Drug Administration classifies caffeine Generally Recognized As Safe (GRAS). This designation means that there is sufficient data and history of use to indicate that caffeine is safe to consume in the amounts commonly found in foods and beverages. The FDA allows caffeine to be added to cola drinks.

Recommendation and Conclusions

Caffeine is the perfect moneymaking drug. First, it has very desirable stimulatory effects on the central nervous system. Second, you cannot consume too much at one time because the drug produce undesirable nervous system effects. Third, you cannot stop drinking it because you will get a headache. Fourth, the half-life of the drug is relatively short, so that you must go back for more. Fifth, you don't lose your craving for it. And finally, it is a naturally occurring substance with a long history of use that is recognized by the regulatory authorities as being safe. The coffee, tea, and cola industries benefit enormously from our desire for this drug.
Each of us should be aware of our dose/response to caffeine and limit our consumption accordingly. Over 200 foods, beverages, and over-the-counter medications contain caffeine, which means it is important to read the labels. If you are pregnant, think about whether you want your fetus swimming in caffeine and its metabolites.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Caffeine presentation material and references. Website contains presentation material related to the health effects of caffeine.

European, Asian, and International Agencies

• International Food Information Council (IFIC) Foundation. IFIC's mission is to communicate science-based information on food safety and nutrition to health and nutrition professionals, educators, journalists, government officials and others providing information to consumers. IFIC is supported primarily by the broad-based food, beverage and agricultural industries. [accessed April 2, 2003]
• UK Department of Health Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Reproductive Effects of Caffeine 2008. Excellent report on the reproductive effects of caffeine. [accessed July 16, 2008]

North American Agencies

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Non-Government Organizations

• Center for Science in the Public Interest: Nutrition Action. Caffeine: The Good, the Bad, the Maybe. Article on caffeine and its health effects. [accessed July 16, 2008]
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• I Need Coffee. Non-commercial Caffeination Information. A humorous but factual look at coffee consumption. [accessed July 16, 2008]
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A Small Dose of Nicotine

or

An Introduction to the Health Effects of Nicotine

Nicotine: Quick Facts
Uses: pesticide, drug in tobacco
Source: tobacco
Recommended daily intake: none (not essential)
Absorption: lungs, skin, stomach (poor absorption in stomach because nicotine is a strong base), intestine (better)
Sensitive individuals: fetus, children
Toxicity/symptoms: dependency-producing; acute effects: salivation, weakness, mental confusion, dizziness, nausea, vomiting, diarrhea
Regulatory facts: RfD: none, LD50: 10 mg/kg, not currently regulated but legislation is under consideration to allow FDA regulation
General facts: long history of use, addictive
Environmental concerns: growing demand for cigarettes in developing countries
Recommendations: avoid

Overview

Nicotine is one of the most potent, toxic, and readily available drugs today. The history of tobacco use dates back over two millennia; its psychoactive and medicinal properties were discovered by indigenous peoples of the Americas. Nicotine is highly toxic, with only 60 mg potentially deadly to an adult. On March 21, 2000, the US Supreme Court ruled that the US Food and Drug Administration did not have the authority to regulate tobacco. On June 22, 2009, President Obama signed the Family Smoking Prevention and Tobacco Control Act, landmark legislation that gives the US Food and Drug Administration authority to regulate the manufacturing and marketing of tobacco.

Introduction and History

Nicotine was isolated from tobacco leaves (*Nicotiana tabacum*) in 1828, but the powerful effects of nicotine were already well recognized. The tobacco plant is native to the Americas and its use as a medicine and stimulant goes back at least 2000 years and most likely many millennia before that. South American temple carvings show Mayan priests enjoying the benefits of this drug from smoking tobacco through a pipe. Tobacco appears as part of the healing arts and sacred rituals of many of the native peoples of the Americas.

Use in Europe and the American Colonies

There are various theories of how tobacco was introduced to Europe, but Christopher Columbus and his crews undoubtedly sampled this native weed and succumbed to its spell. Once introduced into Europe, tobacco for use in pipes and as cigars spread rapidly. Some thought it was powerful medicine and might even cure the Plague, while others saw it as an evil and nasty habit.

By the early 1600s tobacco had become an important cash crop exported to Europe by the new colonies in North America. Some historians believe the colonies would not have prospered without the money from this toxic crop. Tobacco is a demanding crop to grow, and as tobacco farming spread south there was a growing demand for workers. In the 1700s tobacco plantation farmers began importing African slaves to work the tobacco farms. Tobacco became important not only for local economies, but also for national governments as soon as it became apparent that one could tax the people's habit.

The Invention of Cigarettes

It took many years to refine and develop tobacco consumption as a means of drug delivery. Tobacco consumption was initially confined to chewing or smoking with a pipe or cigar. Cigarettes were invented in 1614 by beggars in Seville, Spain, who collected scraps of cigars and rolled the tobacco into small pieces of paper. Cigarette

consumption grew gradually in popularity, but cigarettes were expensive to produce until 1880, when a machine to roll cigarettes was patented. This invention ushered in cheaper cigarettes and major tobacco corporations. Sir Walter Raleigh popularized pipe smoking in England. He was beheaded on October 28, 1618, but before his head dropped he requested to smoke a final bowlful of tobacco.

The Beginnings of Regulation

The undesirable health effects of tobacco consumption were not entirely unrecognized. By 1890, 26 states had passed laws banning the sale of cigarettes to minors. Cigarette consumption increased steadily, spurred along by both world wars and relentless marketing by the tobacco companies. In 1964, the US Surgeon General issued a report linking smoking with lung cancer and heart disease, which triggered a slow recognition among policy makers of the true cost of smoking and efforts to reduce consumption. It was not until 1994 that the US Food and Drug Administration officially determined that nicotine was a dependency-producing drug. The US Supreme Court subsequently ruled that the FDA could not regulate nicotine as a drug. However, all this attention did encourage legal action that resulted in the tobacco companies paying billions of dollars to cover health care costs of tobacco-related diseases. On June 22, 2009, President Obama signed the Family Smoking Prevention and Tobacco Control Act, landmark legislation that gives the US Food and Drug Administration authority to regulate the manufacturing and marketing of tobacco. While tobacco consumption is declining in North America and parts of Europe, it continues to increase in many parts of the world.

Use as an Insecticide

The widespread personal consumption of nicotine is not its only role. In 1763 nicotine was first used as an insecticide. The potent nervous system effects of nicotine kill or deter insects; these are the same effects that attracted people to nicotine. Nicotine is extracted from tobacco leaves by steam or solvent treatment and then sprayed on vegetation where it comes in contact with and is readily absorbed by insects. Nicotine-based pesticides are no longer registered by the US (EPA, 2008).

Rates of Global Tobacco Use

The maps below indicate the use of tobacco products by men and women in countries around the world. The data is based on surveys taken from the WHO Report on the Global Tobacco Epidemic, 2008.

Figure 6.1 Smoking any Tobacco Product, %, Males

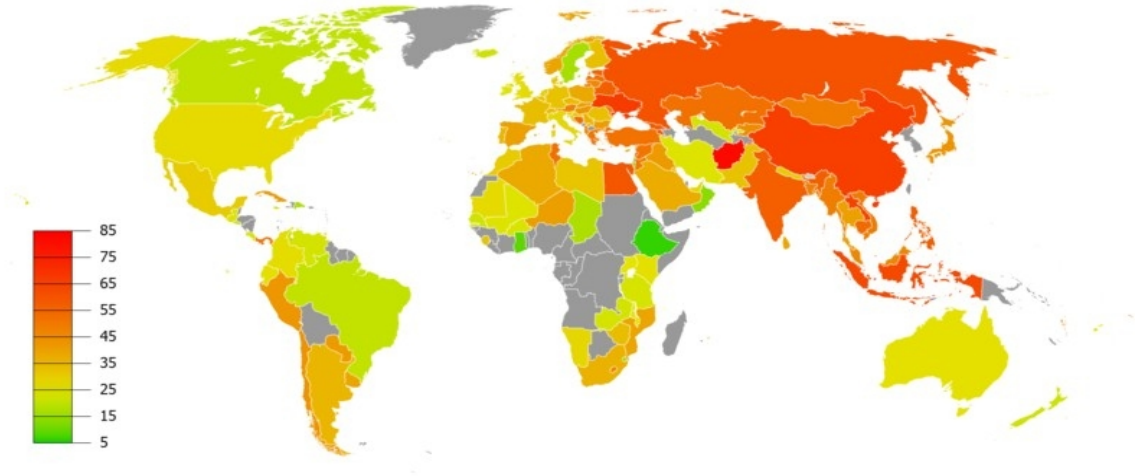
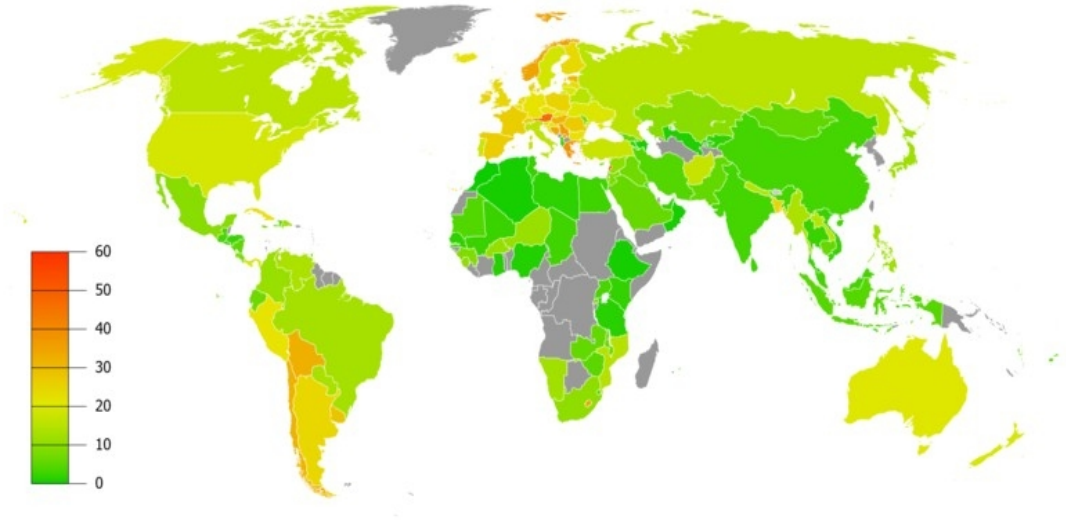


Figure 6.2 Smoking any Tobacco Product, %, Females



Case Studies

The Divine Origin of Tobacco

Tobacco was a powerful medicine for the first people of the Americas. Native California tribal legend traces the origins of tobacco to sacred immortals that they believed first inhabited the land. The immortal ancestors gave tobacco to the humans to heal and guide them from the ancient past to the present and beyond; tobacco was an important part of creation. Native medicine doctors and shamans relied upon tobacco for guidance, a source of strength, and healing rituals. Tobacco was sacred, not to be rapidly consumed in the doorway of a back alley. As Native American author Julian Lang suggested, the warning on a pack of cigarettes should be "Use of this product should be restricted to prayerful or religious activity, or social activity which reflects aspects of the Creation." (Lang, 1997)

Green Tobacco Sickness

Green tobacco sickness (GTS) afflicts workers harvesting tobacco when nicotine is absorbed through the skin from handling wet tobacco leaves. Workers report symptoms of nausea, vomiting, weakness, dizziness, headache, and, depending on the amount of exposure, decreases in heart rate and blood pressure. These are the classic signs of nicotine poisoning. This illness often lasts for several days, and some workers require hospital treatment. Workers that used tobacco products were less like to suffer from GTS because they developed a tolerance to the effects of nicotine. In addition, longer-term workers are less likely to report GTS, possibly because younger workers who are sensitive to nicotine tend to drop out of the work force. The incidence of GTS would be reduced by appropriate worker education about the absorption of nicotine through the skin and the use of protective clothing. For more information, see the CDC's Morbidity and Mortality Weekly Report on GTS.

Biological Properties

Nicotine has a range of physiological effects and has provided researchers with an opportunity to learn nervous system function. It is readily absorbed through the skin and lungs, but because it is a strong base is not well absorbed in the acidic environment of the stomach. Nicotine travels from the lungs to the brain in about 7 seconds, thus each puff produces a reinforcing effect. The positive effects of nicotine are associated with a complex balance of stimulation and relaxation. For example, depending on the dose, it can increase or decrease the heart rate. One of the most prominent reactions of first-time users is nausea and vomiting. This reaction is due to stimulation of both the central and peripheral nervous systems, which triggers a vomiting reaction. The underlying mechanism of action is its effect on acetylcholine-like receptors, sometimes referred to as nicotinic receptors.

Nicotine is metabolized in the liver, lung, and kidney. It has a relatively short half-life of about 2 hours, which greatly contributes to the desire to have another smoke in an effort to restore blood nicotine levels. The primary metabolite of nicotine is cotinine, which has a much longer half-life than nicotine. Because of cotinine's longer half-life, insurance companies will typically test urine or blood samples for cotinine to determine if someone has been smoking. Nicotine and its metabolites are readily excreted in the urine. Nicotine is also excreted in the breast milk of nursing mothers, with heavy smokers having up to 0.5 mg of nicotine per liter of milk. Given the infant's small size, this can represent a significant dose of nicotine for the baby.

The skin absorption of nicotine and subsequent adverse effects make it an effective pesticide. Nicotine poisoning occurs primarily from children coming in contact with nicotine insecticides or tobacco products.

Health Effects

Nicotine is a highly toxic drug, with only 60 mg being lethal to an adult. The average cigarette contains 8 to 9 mg of nicotine; so one pack of cigarettes contains enough nicotine to kill the average adult, to say nothing of a child. Depending on smoking technique, a smoker receives about 1 mg of nicotine per cigarette. The effects of nicotine are complex but are similar to acetylcholine poisoning. Acute effects of nicotine poisoning include nausea, vomiting, salivation, diarrhea, dizziness, mental confusion, and weakness. At high levels of exposure, nicotine causes decreased blood pressure, difficulty breathing, irregular pulse, convulsions, respiratory failure, and death.

Nicotine is probably the most addictive drug readily available to the average person. The nicotinic effects from smoking are highly reinforcing, with some users comparing the effects to cocaine or amphetamine. Regular smokers consume nicotine for stimulation but also to avoid the withdrawal effects. The withdrawal effects include irritability, anxiety, restlessness, impatience, increased appetite and weight gain. Nicotine patches take advantage of nicotine's ability to cross the skin barrier and are used to maintain a steady state blood level of nicotine and thus reduce the desire to smoke. Nicotine gum and now nicotine drinks are often used as an alternative to smoking.

Nicotine also affects the developing fetus. Adverse effects of chronic nicotine consumption during pregnancy include reduced infant birth weight, attention deficit disorders, and other cognitive problems. Nicotine receptors are expressed early during development, and it is not clear what effects nicotine exposure during development has on the fetus.

The health effects of nicotine cannot be entirely separated from the effects of cigarettes as a whole. Nicotine keeps people smoking, but the many other compounds found in cigarettes that are inhaled when smoking contribute to respiratory disease, cardiovascular disease, and lung cancer. The carcinogenic properties of nicotine alone have yet to be evaluated independent of tobacco smoke.

Regulatory Standards

Concerns over the hazards of secondhand smoke are now widely accepted, which has resulted in increased restrictions on indoor smoking. Some US states have laws limiting smoking outdoors near doorways and more recently have even limited smoking in cars when children are present.

On March 21, 2000, the US Supreme Court ruled that the US Food and Drug Administration did not have the authority to regulate tobacco. On June 22, 2009, President Obama signed the Family Smoking Prevention and Tobacco Control Act, landmark legislation that gives the US Food and Drug Administration authority to regulate the manufacturing and marketing of tobacco.

Recommendation and Conclusions

Given the serious health effects associated with cigarette smoking, primarily maintained by the addictive properties of nicotine, the best advice is not to start. Unfortunately, despite the obvious health problems and cost to society, thousands of young people start smoking each year.

All nicotine-containing products should be handled with care and kept out of the reach of children. Secondhand smoke should be avoided, particularly for children, and laws limiting exposure to secondhand smoke should be encouraged.

Nicotine is a very potent drug—highly addictive when regularly consumed—and its use should be avoided. Laws restricting or defining smoking areas that reduce exposure to secondhand smoke should be encouraged.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Nicotine presentation material and references. Website contains presentation material related to the health effects of nicotine.

European, Asian, and International Agencies

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A Small Dose of Pesticides

or

An Introduction to the Health Effects of Pesticides

Introduction

Definition

The purpose of a pesticide is usually to kill or repel some form of life. The US Environmental Protection Agency's definition of a pesticide is as follows: "A pesticide is any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest. Though often misunderstood to refer only to insecticides, the term pesticide also applies to herbicides, fungicides, and various other substances used to control pests." Pesticide formulations contain both "active" and "inert" ingredients. Active ingredients are what kill the pest, and inert ingredients help the active ingredients to work more effectively.

Types

The two largest classes of synthetic pesticides are insecticides, which are designed to kill insects, and herbicides, which are designed to kill plants. Other classes of pesticides include fungicides (for molds and fungi), rodenticides (for mammals), and antimicrobials (for microorganisms such as bacteria and viruses). Antimicrobial pesticides are used as preservatives, sterilizers, and disinfectants in home, institutional, and commercial environments. (For more information on antimicrobial pesticides, see this EPA website. Note that pharmaceuticals intended to kill organisms in the body, such as bacteria and parasitic worms, are not defined as pesticides and are regulated as drugs.)

How Pesticides Work

Pesticides work by interfering with an essential biological mechanism in the pests, but because all living organisms share many biological mechanisms, pesticides are never specific to just one species. While pesticides may kill pests, they may also kill or harm other organisms that are beneficial or at least not undesirable. They may also harm people who are exposed to pesticides through occupational or home use, through eating foods or liquids containing pesticide residue, or through inhaling or contacting pesticide-contaminated air. The ideal pesticide would be highly specific to only the target organism, be quick acting, and would degrade rapidly to harmless, inert materials in the environment.

Case Studies

Cats, Dogs and Fleas

Fleas have a complex life cycle and reproduce rapidly, so flea control is a challenging issue in any household with pets, particularly if pets spend any time outside. A common insecticide used to kill fleas on cats is imidacloprid. This insecticide is also used to control insects such as aphids, whiteflies, termites and a range of other soil insects, and some beetles. It is also very toxic to honey bees.

Imidacloprid is toxic to the nervous system, causing an overstimulation of acetylcholine and consequent paralysis and death in insects. When used to control fleas, it is typically applied to the back of the pet's neck, where it is absorbed through the skin and circulates in the blood. It takes only a very small amount of the pesticide in the blood of the cat or dog to kill the flea, which gets exposed when biting the pet and consuming the insecticide-infused blood. Because of the flea's very small size (the average flea weighs between 0.5 mg and 1 mg, though they can double their body weight when feeding), it receives a large does relative to its body weight. In contrast, the pet appears to be unaffected by its exposure to this pesticide primarily because it receives a very small amount of chemical relative to its larger body weight. However, if overexposed, the effect to an animal like a small cat would include muscle weakness, fatigue, and twitching.

Farm Worker Illness from Pesticides

The total use of pesticides in the United States is about 6 billion pounds a year, 1.2 billion pounds of which is used in agriculture. Worldwide agricultural pesticide use amounts to an additional 5 billion pounds of active ingredient each year. The active ingredients in pesticide formulations often make up less than 1% of the material applied, so these estimates do not include other ingredients used in pesticide products. These additional ingredients, sometimes called inert ingredients, may have their own hazards. Determining the exact amount of pesticides used by the agriculture industry is difficult because there is no national requirement for users to report the amount of pesticide applied. Pesticides are also used by homeowners, commercial real estate managers, government, and industry on lawns, gardens, golf courses, and inside buildings.

The use of pesticides in large agricultural settings requires special training and knowledge to ensure that farm workers' and crop pickers' exposure is minimized. For example, carbofuran (n-methyl carbamate) is a broad-spectrum insecticide used on rice, alfalfa, table and wine grapes, cotton, potatoes, and soybeans. Carbofuran insecticide inhibits cholinesterase, causing an increase in the neurotransmitter acetylcholine. Elevated acetylcholine levels cause tremor, paralysis, and death in insects, and can have similar effects on wildlife, such as birds, as well as humans. Due to its toxicity to humans and mammals, the US EPA moved to ban all use of carbofuran in 2008.

Farm workers come into contact with pesticides during pesticide application or when

entering the fields too soon after an application. Carbofuran is used on cotton; the EPA requires a 48-hour waiting period after application before farm workers are allowed to enter the field. This is to allow the pesticide to dissipate and degrade, reducing workers' exposure to the active ingredient.

In 1998, carbofuran was applied aerially to a California cotton field. Within hours of the spraying, 34 farm workers entered the cotton field to weed the cotton plants. Several hours later the workers reported symptoms including nausea, headache, eye irritation, muscle weakness, salivation, and decreased heart rate. These symptoms are consistent with poisoning from a cholinesterase inhibitor such as carbofuran. The majority of the workers were decontaminated and hospitalized; unfortunately, several workers went home without being decontaminated, potentially exposing their families to the pesticide still on their work clothes and shoes. Infants or young children are more susceptible to the effects of pesticides than adults and are very vulnerable to this type of take-home exposure from the workplace. For more information on this incident see the US Centers for Disease Control report (MMWR, 1999).

History

Minerals and Metals

One of the first pesticides was sulfur, used by the Chinese in around 1000 BC to control bacteria and mold (fungus). Sulfur is still widely used today. For example, it is used in fungicides to control diseases on both agricultural and ornamental plants, and in the wine industry, sulfur is used to control unwanted bacterial growth in empty wine barrels and is commonly added to wine to kill unwanted yeast. The Chinese also pioneered the use of arsenic-containing compounds to control insects. Arsenic has a long history of use both as an insecticide and herbicide, and also as a medicine. Arsenic trioxide was used as a weed killer (herbicide) in the late 1800s, and lead arsenate, containing both lead and arsenic, was used as an insecticide, particularly in orchards, prior to the development of synthetic pesticides following WWII. Some of the first concerns about pesticide safety were raised over lead arsenate residue on fruit and in orchards, and to this day, some orchard soils remain contaminated with lead and arsenic. Arsenic in the form of chromated copper arsenate (CCA) is used today as a wood preservative (to keep wood in contact with soil or moisture from rotting).

Plant-based Pesticides

Plants have provided several other important nonsynthetic pesticides. In the late 1600s nicotine, an extract from tobacco leaves, was recognized as a potent insecticide and is now in limited use as a pesticide. Another group of nonsynthetic insecticides is pyrethrums, which are harvested and refined from chrysanthemums. The Strychnine tree, *Nux vomica*, contains strychnine used to kill rodents. Finally, rotenone, an insecticide and fish poison, is extracted from the root of *Derris elliptica*, a climbing plant from Southeast Asia. Plant extracts are useful for controlling pests, but they are often difficult to purify and produce in large quantities. Consequently, the modern use

of plant-based pesticides didn't significantly increase until advances were made in synthetic chemistry and pest biology.

Synthetic Pesticides

Synthetic chemistry advanced rapidly in the 1930s and by the early 40s, a range of new pesticides had been developed, including organochlorine insecticides like DDT. In 1937 the first organophosphate compounds were synthesized by a group of German chemists. These very potent compounds were kept secret during World War II and were originally developed as potential chemical warfare agents. After the war, these organophosphate compounds were re-purposed as insecticides, and many organophosphate insecticides continue to be used today.

Herbicides were developed after WWII in order to increase food production and create possible warfare agents. In 1946, the first commercially available chlorine-based herbicides were marketed to kill broadleaf plants. This class of compounds includes 2,4-D (2,4-Dichlorophenoxyacetic acid) and 2,4,5-T (2,4,5-Trichlorophenoxyacetic acid), synthetic auxins (plant hormones) that disrupt plant growth. These herbicides have been extensively utilized in agriculture and to clear roadsides and rights of way. 2,4,5-T was used extensively during the Vietnam War to defoliate jungle plants. During the manufacturing process, 2,4,5-T was often contaminated with the persistent and very toxic dioxin, TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin). Dioxins, like other chlorinated compounds including DDT, bioaccumulate in body fat and persist in the environment for many years (the soil half-life is 10 to 12 years). Dioxins are classified as carcinogens and are also known to affect the reproductive and immune systems.

The US EPA cancelled the use of 2,4,5-T because of the dioxin contamination, but 2,4-D is still one of the most widely used herbicides.

Pesticide Use Statistics

Both the volume of pesticides used and the amount of money spent on pesticides demonstrate our dependency on these chemicals.

Amount of Pesticides Used in the US and Worldwide

The EPA reported that 4.9 billion pounds of pesticide products were used in the United States in 2001, which is equivalent to 4.5 pounds per person. Approximately 888 million pounds of active ingredients and 600 different chemical compounds were included in these pesticides. The agriculture industry used about 675 million pounds of pesticide active ingredient (76% of total active ingredients used) and 102 million pounds (11.5%) were used on lawns and gardens by homeowners and by government and general industry. Another 2.6 billion pounds were used in disinfectants, and 0.80

billion pounds were used for wood preservatives.

Worldwide, about 5.05 billion pounds of pesticide active ingredient were used in agriculture in 2001.

Table 7.1 Pesticide Use in the United States (2001 estimates)

Type	Billions of Pounds	Percentage
Conventional pesticides (herbicides, insecticides, fungicides, etc.)	0.89	17.7
Other pesticide chemicals (sulfur, petroleum oil, etc.)*	0.32	6.4
Wood preservatives	0.8	16.1
Specialty biocides (antimicrobial pesticides)	0.35	7.2
Chlorine/hypochlorites (used in water disinfection)	2.61	52.5
TOTAL	4.97	100

*This category is defined by EPA as follows: "The pesticides in this group include sulfur and petroleum oil and other chemicals used as pesticides, such as sulfuric acid, insect repellents (e.g., DEET), moth control products (e.g., paradichlorobenzene), and others." Source: EPA Pesticides Industry Sales and Usage 2000 and 2001 Market Estimates, Table 3.3 (2004)

US and Global Expenditures

In 2001, total expenditures for pesticides in the US were $11.09 billion, of which $7.4 billion was spent by the agricultural industry. Worldwide, the cost of pesticides used for agriculture in 2001 was US $31.8 billion.

Home Use of Pesticides

Home use of pesticides is widespread, and unfortunately there are many examples of home poisoning with pesticides. Consumers who use pesticides often apply them at much greater rates per acre than do farmers and professional pesticide applicators. Children are at particularly increased risk to pesticides that have been tracked in from outdoors as well as from pesticides that are used inside the home.

Efforts to Reduce Exposure and Use

Increased understanding of the possible health and environmental effects of pesticides is driving the demand for tighter regulation of pesticides use and is motivating efforts to reduce exposures, especially to children. Some communities are moving to ban the use of pesticides on lawns and landscaping, along roadsides to control weeds, and in and near schools, among other initiatives. People worldwide are recognizing the effects of pesticides on water quality and the health of wildlife, and there is increasing awareness of occupational hazards, especially to workers in developing nations. While pesticides may be needed to help protect crops and control indoor pests, they need to be used prudently and with knowledge of their potential harm. We need to continue to reduce unnecessary pesticide use, find safer and more selective pest management tools, and protect sensitive populations from exposure.

Biological Properties of Insecticides

Most chemical insecticides act by poisoning the nervous system. The central and peripheral nervous system of insects is fundamentally similar to that of mammals. A small amount of pesticide can be fatal to an insect, primarily because of the insect's small size and high rate of metabolism. While that same amount will not be fatal to a person, it may still cause harm.

The similarities of nervous system structure make it nearly impossible to design insecticides that affect only target insect pests; consequently, insecticides may affect non-pest insects, people, wildlife, and pets. Some insecticides harm water quality or affect organisms in other ways; for example, the insecticide carbaryl (a carbamate insecticide, further discussed below) is listed as a carcinogen by the state of California and as a possible hormone disruptor by the state of Illinois' EPA. The newer insecticides are designed to be more specific and less persistent in the environment.

The most prominent classes of insecticides are organochlorines, organophosphates, carbamates, and pyrethroids.

Organochlorines

The chemical structure of organochlorines is diverse, but they all contain chlorine,

which places them in a larger class of compounds called chlorinated hydrocarbons. Organochlorines, which include DDT, demonstrate many of the potential risks and benefits of insecticide use.

While organochlorines have the advantage of being cheap to manufacture and are effective against target species, they have serious unintended consequences. Organochlorines disrupt the movement of ions such as calcium, chloride, sodium, and potassium into and out of nerve cells. Depending on the specific structure of the organochlorine chemical, it may also affect the nervous system in other ways. At one time organochlorines were thought to be ideal because they are very stable, slow to degrade in the environment, dissolve in fats (and are therefore readily taken up by insects), and seemingly harmless to mammals. Unfortunately it eventually became clear that the attributes of persistence and fat solubility were actually very undesirable: the organochlorines passed up the food chain, where they bioaccumulated in the fat of large animals and humans and were passed on to nursing young. The global use and transport of organochlorines resulted in the contamination of wildlife around the globe, including in Arctic and Antarctic regions where these insecticides are rarely if ever used. A decline in the number of birds that prey on animals exposed to DDT was one of the first signs of the unintended consequences. Unexpectedly, DDT caused a thinning of the birds' eggshells and resulted in the death of their developing young.

Organochlorines like DDT are now largely banned in industrialized countries but they are still manufactured and used in developing countries. (Banned pesticides are still manufactured in some industrialized countries and exported.) Organochlorine insecticides provide many important lessons about the desirable and undesirable properties of pesticides.

Organophosphates and Carbamates

Organophosphates and carbamates have very different chemical structures, but share a similar mechanism of action and will be examined here as one class of insecticides.

Organophosphates were initially developed in the 1940s as highly toxic biological warfare agents (nerve gases). Modern derivatives, including sarin, soman, and VX, were stockpiled by various countries and now present some difficult disposal problems. Researchers created many different organophosphates in their search for insecticides that wouldtarget selected species and would be less toxic to mammals. When the organophosphate parathion was first used as a replacement for DDT, it was believed to be better as it was more specific. Unfortunately there were a number of human deaths because workers failed to appreciate the fact that parathion's short-term (acute) toxicity is greater than DDT's.

The problem with organophosphates and carbamates is that they affect an important

neurotransmitter common to both insects and mammals. This neurotransmitter, acetylcholine, is essential for nerve cells to be able to communicate with each other. Acetylcholine released by one nerve cell initiates communication with another nerve cell, but that stimulation must eventually be stopped. To stop the communication, acetylcholine is removed from the area around the nerve cells, and an enzyme, acetylcholinesterase, breaks down the acetylcholine. Organophosphates and carbamates block the enzyme and disrupt the proper functioning of the nerve cells. Hence, these insecticides are called acetylcholinesterase inhibitors.

Structural differences between the various organophosphates and carbamates affect the efficiency and degree to which the acetylcholinesterase is blocked. Nerve gases are highly efficient and permanently block acetylcholinesterase, while the commonly used pesticides block acetylcholinesterase only temporarily. The toxicity of these pesticides presents significant health hazards, and researchers continue to work to develop new insecticides that have fewer unintended consequences.

Pyrethroids

One of the newer classes of insecticide, synthetic pyrethroids are loosely based upon the naturally occurring pyrethrum found in chrysanthemum flowers. Synthetic pyrethroids were first developed in the 1980s, but the naturally occurring pyrethrum was first commercially used in the 1800s. Their use has increased significantly over the last 20 years. The chemical structure of pyrethroids is quite different from that of organochlorines, organophosphates, and carbamates but the primary site of action is also the nervous system. Pyrethroids affect the movement of sodium ions (Na^+) into and out of nerve cells, causing the nerve cells to become hypersensitive to neurotransmitters. Structural differences between various pyrethroids can change their toxic effects on specific insects and even mammals.

Synthetic pyrethroids are more persistent in the environment than natural pyrethrum, which is unstable in light and breaks down very quickly in sunlight.

Biological Properties of Herbicides

Herbicides are used to kill or damage plants and are the most rapidly growing type of pesticide. Prior to the 1930s, herbicides were nonspecific and often very toxic to humans as well as other animals. In the 1930s, researchers discovered several chemicals that selectively killed plants while developing new insecticides. These chemicals are now widely used to increase food production by killing weeds that choke out or compete with food crops.

The most well known herbicides are the chlorophenoxy compounds that include 2,4-D

and 2,4,5-T. This herbicide mixture, sometimes called Agent Orange in the 1960s, was widely used to kill broadleaf plants in agricultural fields, along roadsides, and on rights of way for power lines. It was also extensively used as a chemical warfare agent to kill unwanted vegetation, for example in jungles. The mechanism of action of this class of chemicals is poorly understood, but the herbicides appear to interact with plant growth hormones. (See Pesticides - History for discussion of the contamination of 2,4,5-T with dioxin.)

Paraquat and the related chemical diquat are nonselective herbicides that are also toxic to mammals. Occupational or accidental exposure to paraquat can occur by ingestion, skin exposure, or inhalation, all of which can cause serious illness or death. While seldom used in the United States at this time, paraquat is still widely used in developing countries. At one time it was used in marijuana plant eradication programs, but it was discontinued when a number of fatalities were observed in smokers of paraquat-contaminated marijuana.

There are many other herbicides in widespread use, such as alachlor, glyphosate, and atrazine, and they have a range of actions on plants and animals.

Herbicides have become an essential part of the agriculture business and are thought by some to be necessary for high crop yields. However, a serious limitation of many herbicides is their lack of specificity; in other words, herbicides can damage the crops of interest. The manufacturers of herbicides are working to address this problem and are increasingly turning to biotechnology to create genetically modified crops that are herbicide resistant. For example, Monsanto produces the glyphosate-based herbicide RoundUp. The company also manufactures a genetically modified soybean that is resistant to RoundUp. This allows farmers to use RoundUp herbicide with the RoundUp Ready soybean plants and not have to worry about killing the soybean plants. The genetically modified RoundUp Ready soybean is now widely planted, though the practice has generated considerable controversy internationally.

Biological Properties of Fungicides

Fungicides were developed to control the fungi and mold that may grow on crops, stored foods and seeds, and in our bodies. Control of plant fungus in agriculture is important not only because fungi can damage crops, but also because some fungi produce toxic chemicals (mycotoxins). One fungus, *Aspergillus flavus*, often contaminates nuts (e.g. peanuts) and grains (e.g. corn). This fungus produces aflatoxin, a compound that can cause liver disease and in some situations, liver cancer. Another naturally occurring grain fungus produces an ergot alkaloid that can cause hallucinations.

Early fungicides were sulfur, copper sulfate, and mercury-based compounds. In the 1940s and 50s, hexachlorobenzene, a synthetic fungicide, was widely used to protect seed grain from fungal rot. Mercurial compounds were also applied to seed grains to protect them from soil fungus. Both of these chemicals caused severe illness when people ate treated grains intended for planting as crops. These two fungicides are now rarely used and have been replaced by less-toxic ones, but careful harvest and storage procedures for seeds are necessary to prevent potential contamination of food supplies. The overall need for fungicides in seed and crop storage can be reduced by controlling environmental conditions that encourage the growth of fungi, and Integrated Pest Management reduces the need to use dangerous fungicides on growing plants.

Biological Properties of Rodenticides

Rodenticides are a broad class of pesticides designed to kill small mammals such as rats and mice. Some rodenticides are anticoagulants and work by inhibiting blood-clotting; these are often used to control rat populations. One of the first anticoagulant rodenticides was warfarin, which is related to plant-derived coumadin (from spoiled sweet clover). Inthe 1950s rats developed resistance to warfarin, which prompted scientists to develop more potent anticoagulants, which are termed second-generation anticoagulants. Other rodenticides include fluoroacetic acid and zinc phosphide (which are both very toxic), and thiourea-based compounds.

One of the problems of rodenticides is that they may also harm wildlife that mistake pesticide-containing baits or pellets for food. Wildlife, such as wolves or birds of prey, may also be harmed by eating rodents or other animals that have been poisoned. The primary alternative to using chemical rodenticides is trapping.

Biological Properties of Molluscicides

Molluscicides are used to control slugs and snails. Mollusks are a group of invertebrate animals that include shellfish, cephalopods (such as squid and octopus), slugs, and snails.

The most commonly used active ingredient in molluscicides is metaldehyde, which disrupts the gastric organs of slugs and snails, causing death. This product is often manufactured as brightly colored pellets, which has the unfortunate unintended consequence of being attractive to children, wildlife, and pets. Some manufacturers have added a bitter agent to make the products unpalatable.

Alternatives to chemical molluscicides include using traps or barriers, or designing

gardens that are less attractive to slugs. Slug and snail baits containing iron phosphate as the active ingredient are also available and are less toxic than metaldehyde.

Effects of Pesticides on Human Health

Introduction

Pesticides are designed to kill and because their mode of action is not specific to one species, they often kill or harm organisms other than pests, including humans. The World Health Organization estimates that there are 3 million cases of pesticide poisoning each year and up to 220,000 deaths, primarily in developing countries. The application of pesticides is often not very precise, and unintended exposures occur to other organisms in the general area where pesticides are applied. Children, and indeed any young and developing organisms, are particularly vulnerable to the harmful effects of pesticides. Even very low levels of exposure during development may have adverse health effects.

Pesticide exposure can cause a range of neurological health effects such as memory loss, loss of coordination, reduced speed of response to stimuli, reduced visual ability, altered or uncontrollable mood and general behavior, and reduced motor skills. These symptoms are often very subtle and may not be recognized by the medical community as a clinical effect. Other possible health effects include asthma, allergies, and hypersensitivity, and pesticide exposure is also linked with cancer, hormone disruption, and problems with reproduction and fetal development.

Pesticide formulations contain both "active" and "inert" ingredients. Active ingredients are what kill the pest, and inert ingredients help the active ingredients to work more effectively. These "inert" ingredients may not be tested as thoroughly as active ingredients and are seldom disclosed on product labels. Solvents, which are inert ingredients in many pesticide formulations, may be toxic if inhaled or absorbed by the skin.

Children are at greater risk from exposure to pesticides because of their small size: relative to their size, children eat, drink, and breathe more than adults. Their bodies and organs are growing rapidly, which also makes them more susceptible; in fact, children may be exposed to pesticides even while in the womb.

Insecticides

Organochlorines

Acute ingestion of organochlorine insecticides can cause a loss of sensation around the mouth, hypersensitivity to light, sound, and touch, dizziness, tremors, nausea,

vomiting, nervousness, and confusion.

In 1975, over 70 workers manufacturing Kepone, an organochlorine insecticide, in Hopewell, Virginia, developed a variety of neurological symptoms, the most prominent of which became known as the "Kepone shakes." The workers' symptoms started about 30 days after their first exposure to Kepone. Subsequent testing also revealed decreases in sperm count and motility. In 1976, Kepone was discontinued and substituted with organophosphates.

Organophosphates and Carbamates

Acute organophosphate and carbamate exposure causes signs and symptoms of excess acetylcholine, such as increased salivation and perspiration, narrowing of the pupils, nausea, diarrhea, decrease in blood pressure, muscle weakness, and fatigue. These symptoms usually decline within days after exposure ends as acetylcholine levels return to normal.

Some organophosphates also have a delayed neurological reaction characterized by muscle weakness in the legs and arms. During Prohibition, people consumed a homemade alcoholic drink made out of Jamaican ginger that was contaminated with the organophosphate triorthocresyl phosphate (TOCP). More than 20,000 people were affected by a condition called "Ginger Jake paralysis." Later research found that these effects could be reproduced in animals, and the US government required that organophosphates be tested for delayed effects during the registration process. The human toxicity of organophosphates caused a decline in their use and spurred the search for new alternatives.

Pyrethroids

Among the most promising alternatives to organophosphates were synthetic pyrethroids. However, pyrethroids can cause hyper-excitation, aggressiveness, incoordination, whole-body tremors, and seizures. Acute exposure in humans, usually resulting from skin exposure due to poor handling procedures, usually resolve within 24 hours. Pyrethroids can cause an allergic skin response, and some pyrethroids may cause cancer, reproductive or developmental effects, or endocrine system effects.

Herbicides

Herbicides are generally less toxic to mammals than insecticides. Most herbicides interfere with plant hormones or enzymes that do not have any direct counterpart in animals. The most serious human health concerns have been related to chemical contaminants in the active ingredient. Military personnel and others exposed to Agent Orange, a mixture of the herbicides 2,4-D and 2,4,5-T that was contaminated with dioxin (TCDD), reported birth defects, cancers, liver disease, and other illness. These concerns lead to improvement in the manufacturing process of 2,4,5-T to reduce TCDD contamination and ultimately lead to cancellation of 2,4,5-T and reduction in use of 2,4-D. However, some herbicides may cause cancer, reproductive or developmental

effects, or endocrine system effects.

There is also concern that some herbicides may affect wildlife, especially aquatic organisms. For example, atrazine, a persistent herbicide, may adversely affect frogs. Concerns about the effect of atrazine on amphibians resulted in its ban in the European Union, but atrazine remains one of the most widely used herbicides in the US (over 70 million pounds used per year). Persistent herbicides may also contaminate surface water and groundwater.

Integrated Pest Management

Integrated pest management (IPM) is an approach to pest management that can significantly reduce pesticide use. Widely used in agriculture, landscape maintenance, and structural pest control, it emphasizes prevention and monitoring of pest problems and considers pesticide applications only when non-chemical controls are ineffective or impractical.

IPM can be practiced by individuals in and around their homes. A home IPM approach stresses proper food-waste management, appropriate plant selection and landscape design, biological and cultural controls, and physical controls such as traps, barriers, and mechanical removal.

Regulatory Standards

In the United States, regulation initially focused on protecting the consumer from pesticide residue on food, but it became apparent that protection was needed for workers applying or working near pesticides. Congress passed the first federal act specifically dealing with pesticides in 1947. This act, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), allowed the US Department of Agriculture to regulate appropriate labeling of pesticides. Unfortunately, this law did not provide sufficient protection for consumers or workers. Rachel Carson's *Silent Spring*, published in 1962, explored the harmful effects of pesticides, especially DDT, on people, wildlife, and the environment and marked a turning point in our understanding of the effects of chemicals on human and environmental health.

In 1972 the US Environmental Protection Agency was formed and given authority to register pesticides based on evaluating and weighing estimated risks and benefits. Subsequent revisions to FIFRA greatly expanded the testing requirements companies must comply with before pesticides could be registered for use. Current requirements include acute toxicity testing of full formulations (including inert ingredients); however,

chronic and sub-chronic testing is only required for the active ingredients. Results of these tests, which are conducted by manufacturers and submitted to EPA, are used to estimate potential risks to human health and the environment. There is also an international effort to harmonize regulatory standards between the United States, Europe, and Japan.

In 1996 the Food Quality Protection Act passed by Congress required that special consideration be given to children's exposures and their special sensitivity to pesticides and other chemicals. This act requires an added safety factor when calculating risk to children.

Recommendations and Conclusions

Pesticides are widely used to help ensure an adequate food supply as well as to protect our health and safety from unwanted pests. But despite their benefits, these chemicals are not without their problems: they pose known and potential risks to human and environmental health. With estimates of 3 million people being overtly affected by pesticides each year, there is clearly much work to be done to reduce exposures. Many developing countries continue to use pesticides that have been banned in the United States and Europe.

Home use of pesticides is widespread, and unfortunately there are many incidents of home poisoning with pesticides. Consumers who use pesticides often apply them at much greater rates per acre than do farmers and professional pesticide applicators. Children are at particularly increased risk to pesticides that have been tracked in from outdoors as well as those used inside the home.

Individually and collectively we need to examine our use of all forms of pesticides and consider alternatives to their use. More research is needed to find and test less-toxic alternatives as well as to develop pesticides that do a better job targeting particular species.

Businesses, schools, institutions, and home gardeners that use pesticides should explore integrated pest management (IPM) methods to reduce pesticide use. Storage and proper disposal of pesticides also deserves special attention.

An ongoing problem is the lack of data on the use of pesticides in various sectors. States and nations should consider adopting pesticide use registries to determine the actual volume of pesticides used, and to assist in the study of pesticide-related health and environmental effects. Finally, farmworkers and other workers who apply pesticides should receive adequate training on proper handling, storage, and

protective equipment.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Pesticides presentation material and references. Website contains presentation material related to the health effects of pesticides.

European, Asian, and International Agencies

• European Commission. Chemical and Pesticide Information. Site contains policy and other information on the use of pesticides in agriculture. [accessed September 30, 2008]
• World Health Organization (WHO). WHO Pesticide Evaluation Scheme (WHOPES). WHOPES is an "international programme which promotes and coordinates the testing and evaluation of new pesticides proposed for public health use." [accessed September 30, 2008]
• International Programme on Chemical Safety (IPCS). IPCS's main roles are to establish the scientific basis for safe use of chemicals, and to strengthen national capabilities and capacities for chemical safety. [accessed September 30, 2008]

North American Agencies

• Health Canada. Pesticide Information. Health Canada provides a range of information on pesticides in English or
French. [accessed September 30, 2008]
• US Environmental Protection Agency (EPA). Office of Pesticides Programs (OPP). OPP's mission is "to protect public health and the environment from the risks posed by pesticides and to promote safer means of pest control." [accessed September 30, 2008]
• US Geological Survey (USGS). National Water-Quality Assessment (NAWQA) Program. NAWQA provides an assessment of water use in the US and of pesticides in the streams, rivers, and groundwater of the United States. [accessed September 30, 2008]
• California Department of Pesticide Regulation. The mission of this department is "to protect human health and the environment by regulating pesticide sales and use, and by fostering reduced-risk pest management." [accessed September 30, 2008]

Non-Government Organizations

• Pesticide Action Network North America (PANNA). "PANNA works to replace pesticide use with ecologically sound and socially just alternatives." [accessed September 30, 2008]
• Pesticide Action Network International (PANI). "PANI is a network of over 600 participating nongovernmental organizations, institutions and individuals in over 60 countries working to replace the use of hazardous pesticides with ecologically sound alternatives." (English, French, Spanish) [accessed September 30, 2008]
• Pesticide Action Network North America (PAN). PAN Pesticide Database. "The PAN Pesticide Database brings together a diverse array of information on pesticides from

many different sources, providing human toxicity (chronic and acute), ecotoxicity, and regulatory information for about 6,400 pesticide active ingredients and their transformation products, as well as adjuvants and solvents used in pesticide products." [accessed September 30, 2008]
• National Pesticide Information Center (NPIC). Call 1-800-858-7378. NPIC is based at Oregon State University and is cooperatively sponsored by the University and the EPA. NPIC serves as a source of objective, science-based pesticide information on a wide range of pesticide-related topics, such as recognition and management of pesticide poisonings, safety information, health and environmental effects, referrals for investigation of pesticide incidents and emergency treatment for both humans and animals, and cleanup and disposal procedures. [accessed September 30, 2008]
• Beyond Pesticides. "Beyond Pesticides is a national network committed to pesticide safety and the adoption of alternative pest management strategies which reduce or eliminate a dependency on toxic chemicals." [accessed September 30, 2008]
• EXTOXNET InfoBase. EXTOXNET provides a variety of information about pesticides, including the Pesticide Information Profiles (PIPs) for specific information on pesticides and the Toxicology Information Briefs (TIBs) contain a discussion of certain concepts in toxicology and environmental chemistry. [accessed September 30, 2008]
• Washington Toxics Coalition (WTC). WTC provides information on model pesticide policies, alternatives to home pesticides, and much more. [accessed September 30, 2008]

Integrated Pest Management (IPM)

• US Environmental Protection Agency. Integrated Pest Management (IPM) Principles. Defines IPM principles and provides additional resources. [accessed September 30, 2008]
• University of California. Statewide Integrated Pest Management Program (UC IPM). The UC IPM program "develops and promotes the use of integrated, ecologically sound pest management programs in California to serve agriculture, urban and community, and natural resources audiences." [accessed September 30, 2008]
• US Federal IPM Coordinating Committee. Provides information to/from the United States Federal IPM Coordinating Committee. [accessed September 30, 2008]
• IPM Institute of North America, Inc. "An independent nonprofit organization formed in 1998 to foster recognition and rewards in the marketplace for goods and service providers who practice Integrated Pest Management, or IPM." [accessed September 30, 2008]
• IPMopedia. IPM Education Project. Provides a wide range of information on IPM. [accessed September 30, 2008]

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US Environmental Protection Agency. 2008. "Carbofuran Cancellation Process". [accessed September 2, 2008]
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Dryden, M. W., and S.M. Gaafar. "Blood consumption by the cat flea, Ctenocephalides

felis (Siphonaptera: Pulicidae)". *J Med Entomol*, 28, 3 (1991): 394-400.
"Farm worker illness following exposure to carbofuran and other pesticides – Fresno County, California, 1998." *MMWR*, 48, 6 (1999): 113-116. [accessed September 2, 2008]

A Small Dose of Lead

or

An Introduction to the Health Effects of Lead

Lead: Quick Facts
Uses: batteries, old paint, stabilizer in PVC plastic, solder, toys, hobby materials, x-ray shielding, smelters, ammunition, wheel weights, and more. Previously used in gasoline and pesticides.
Source: home, paint, dust, toys, contaminated soil, workplace, ethnic health remedies
Recommended daily intake: none (not essential)
Absorption: intestine (50% kids, 10% adults), inhalation
Sensitive individuals: fetus, children, and women of childbearing age
Toxicity/symptoms: developmental and nervous system, lowered IQ, memory and learning difficulties, behavioral problems
Historical use: long history of use, major problem in paint of older housing, areas around old smelters can be contaminated
Global: widespread environmental contaminant
Recommendations: avoid, wash hands, wash children's hands and toys, phase out uses in PVC and children's products, remove old lead-based paint

Introduction

In the 2nd century BCE, Dioscorides noted, "Lead makes the mind give way." In

modern times, lead has been heavily used in paint and as a gasoline additive. Even low levels of lead exposure cause subtle brain damage in children; this was recognized and acted upon only in the last thirty years. It is now well documented that even blood lead levels below 10 µg/dL can harm the developing brain. Lead has no beneficial biological effects.

Lead is naturally present in soil and water at very low levels, but people have caused extensive distribution of lead in the environment. Lead's physical properties of low melting point, easy malleability, corrosion resistance, and easy availability make it well suited to applications both ancient and modern. It is found alongside gold and silver, making lead both a by-product and a contaminant during the smelting of these precious metals. The earliest recorded lead mine dates from 6500 BC, in Turkey.

History of Lead Use

Significant production of lead began about 3000 BC, and large mines in Spain and Greece contributed to the global atmospheric redistribution of lead. The Roman Empire was the first society to use lead widely; in fact, the word plumbing is derived from *plumbum*, Latin for lead, which also gave rise to the chemical symbol for lead, Pb. Lead is slightly sweet to taste, making it a good additive for fine Roman wine that was then shipped all over Europe. Even in those times, there were reports that lead caused severe colic, anemia, and gout. Some historians believe that lead poisoning hastened the fall of the Roman Empire.

Lead in Paint

In more modern times, the durability of lead made it an excellent paint additive, but the sweetness made it tempting to young children. Childhood lead poisoning was linked to lead-based paints in 1904. Several European countries banned the use of interior lead-based paints in 1909. At one time baby cribs were painted with lead-based paint, which resulted in infant illness and death. In 1922, the League of Nations banned lead-based paint but the United States declined to adopt this rule. In 1943, a report concluded that children eating lead paint chips could suffer from neurological disorders including behavior, learning, and intelligence problems. Finally, in 1971, lead-based house paint was phased out in the United States with the passage of the Lead-Based Paint Poisoning Prevention Act.

Homes built prior to 1978 may have lead-based paint either inside or outside, and homes and apartments built prior to 1950 are very likely to have lead-based paint both inside and outside and should be inspected carefully. This is a particularly serious problem for children living in older housing in large cities. A CDC report found that 35% of African-American children living in inner cities with more than 1 million people had blood lead levels greater that 10 µg/dL, which is the CDC action level established in 1991. In the 1990s, the EPA required that information on lead be disclosed when a

home or apartment is sold or rented. In addition, specific training is required for workers removing lead from homes or apartments. Lead-based paint continues to remain a serious problem for many children. The history of the use of lead-based paint is summarized in the table below.

Table 8.1 History of Lead-based Paint Usage

Year	Event
1887	US medical authorities diagnose childhood lead poisoning
1904	Child lead poisoning linked to lead-based paints
1909	France, Belgium and Austria ban white-lead interior paint
1914	Pediatric lead-paint poisoning death from eating crib paint is described
1921	National Lead Company admits lead is a poison
1922	League of Nations bans white-lead interior paint; US declines to adopt
1943	Report concludes eating lead paint chips causes physical and neurological disorders, behavior, learning and intelligence problems in children
1971	Lead-Based Paint Poisoning Prevention Act passed
1978	Lead-based house paint banned

Lead in Gasoline

The addition of lead to gasoline is one of the greatest public health failures of the 20th century. Tetraethyl lead (TEL) was discovered in 1854 by a German chemist and in 1921, Thomas Midgley of the US found that it reduces engine knock. This was a period of tremendous competition in the automobile industry and of growth in the oil, gas, and chemical industries in the United States. A year later the US Public Health Service issued a warning about the potential hazards associated with lead. In 1923 the DuPont Corporation began the first large-scale production of TEL and the first workers died from lead exposure. The same year, leaded gasoline went on sale in selected regions of the country. During this period DuPont acquired a 35% ownership of General Motors, and General Motors and Standard Oil formed a joint company, Ethyl Corporation, to produce TEL. In 1924 five workers died from lead poisoning at the Ethyl facility in New Jersey, although the total number of workers affected by lead exposure is unknown.

In 1925 sales of TEL were suspended while the US Surgeon General reviewed the safety of TEL. The next year, a committee approved the use of TEL in gasoline and sales were immediately resumed. By 1936, 90% of the gasoline sold in the US contained lead, and the Ethyl Corporation was expanding sales in Europe. In the early 1950s the US Justice Department investigated anticompetitive activities associated with DuPont, General Motors, Standard Oil, and Ethyl Corporation. Environmental concerns were highlighted in a 1965 report documenting that high levels of lead in the environment were caused by human use of lead. In 1972 the US EPA gave notice of an intended phase-out of lead in gasoline and was promptly sued by the Ethyl Corporation. Four years later the EPA standards were upheld in court and in 1980 the National Academy of Sciences reported that leaded gasoline was the greatest source of environmental lead contamination. In 1979, the effects of lead on the intellectual development of children were documented in a seminal paper written by Herbert Needleman and others.

The fight over phasing out leaded gasoline was far from over when, in 1981, then Vice President George Bush's task force proposed to relax or eliminate the lead phase-out program. The relationship between leaded gasoline and blood lead levels was demonstrated when the EPA reported that blood lead levels declined by 37% in association with a 50% drop in the use of leaded gasoline between 1976 and 1980. Subsequent studies showed a correlation between the increase in gasoline use during the summer and a rise in blood lead levels. By 1986 the primary phase-out of lead from gasoline was completed but in some areas of the country, such as Washington State, leaded gasoline was available until 1991. The World Bank called for a ban on leaded gasoline in 1996 and the European Union banned leaded gasoline in 2000.

It is estimated that 7 million tons of lead were released into the atmosphere from gasoline in the United States alone.

Occupational Exposures

Occupational exposure to lead has decreased from the overt cases of death and disability in the 1930s and 1940s, but, as case studies illustrate, it continues to occur. In the past, painters using lead-based paints suffered from health problems such as wrist and foot drop or as Ben Franklin reported, the "dangles." Lead paint removal from bridges and buildings is now regulated. Radiator repair and battery recycling continue to be sources of lead exposure. Battery recycling facilities in less-developed countries are a serious source of worker lead exposure and environmental contamination. Public safety officials that train at shooting ranges using lead ammunition may be exposed to elevated levels of lead. Occupational exposure is a potential hazard not only to the adults but also to their children as the lead may be brought home on clothing.

Other Uses

Home hobbies or businesses can also be a source of lead exposure. Lead is commonly used in painting and soldering and in making stained glass, jewelry, pottery, ammunition, or fishing sinkers. Exposure can also occur from stripping lead-based paint from furniture or wood work. Lead-glazed pottery has caused a number lead poisonings, particularly when high-acid foods, which leach lead from the glaze, are consumed from the pottery.

At one time canned foods were a significant source of lead because of poor-quality solder joints in the cans. High-acid foods, such as tomatoes, would leach lead from the cans. Finally, contamination of drinking water with lead occurs primarily from the use of lead solder joints or old fixtures, and occasionally, from the use of lead pipes. As with many metals, lead was used in a number of health remedies, some of which are still available and used by some ethnic groups.

Lead continues to show up in a range of products, many destined to be used by children. Because lead is cheap and easy to use it is found in jewelry and other trinkets. These products are used and handled by children, resulting in additional lead exposure. Lead is used as a stabilizer for PVC plastics and has been found in mini-blinds for windows and in school lunch boxes. Cosmetics such as lipstick were discovered to be contaminated with lead. Recently lead-based paint has been found on children's toys. Even candy and candy wrappers have been found to be contaminated with lead. State and national laws have been enacted to ban what seems to be obvious: the sale of children's products that contain lead.

Case Studies

Taking Lead Home (1998)

In 1998 a California mother requested a blood lead level determination for her 18-month-old child (MMWR, 2001). The result was a blood lead level (BLL) of 26 µg/dL,

which was well above the Center for Disease Control's (CDC) 10 µg/dL recommended criterion for clinical case management. It was subsequently found that the father had a BLL of 46 µg/dL; the Occupational Safety and Health Administration (OSHA) requires that workers with BLLs greater than 40 µg/dL receive additional medical examinations. Further testing found that his 4-month-old daughter had a BLL of 24 µg/dL. This worker was employed in a company that refinished antique furniture, some of which was covered with lead-based paint. Subsequent testing of co-workers found that two refinishers had BLLs of 29 and 54 µg/dL and four carpenters had BLLs of 46, 46, 47, and 56 µg/dL. A child in another family had a BLL of 16 µg/dL. What will be the long-term effects on the intellectual abilities of these children?

Lead-contaminated Town (2001)

The children and families of Herculaneum, Missouri have a lead problem (N.Y. Times, 2002). Herculaneum is home to Doe Run Company, one of the largest lead smelters in the United States, producing 160,000 tons of lead per year. A generation ago, over 800 tons of lead were released into the environment as part of the smelting process. This was reduced to 81 tons in 2001 and the target is 34 tons in 2002. There are signs on the main street informing people about the "high lead levels on streets" and warning children not to play in the streets or on curbs. One-fourth of children under age six were found to have lead poisoning. The US EPA is working to reduce childhood exposure to lead and the company has purchased a number of the most affected homes. How has lead affected the children of Herculaneum? Who is responsible for reducing this hazard?

Lead in Children's Toys, Candy, and Jewelry (2006)

Lead in children's products was highlighted by several serious incidents of lead poisoning, including one death, from ingestion of jewelry containing lead (MMWR 2004, 2006). Many of the jewelry pieces contained over 50% lead, and hundreds of thousands of items were recalled. A report from Los Angeles County estimated that 34% of the children with elevated blood lead levels were exposed to lead-containing products brought into the home, such as folk and traditional medications, candy, ceramic dinnerware, and metallic toys and jewelry. More recently, lead was discovered in vinyl lunch boxes, where it was used to stabilize the PVC (vinyl) plastic. Lead exceeding the CPSC standard (0.06% by weight, or 600 ppm) was also found in paint on imported children's toys. Many consider this to be an excessive amount and have advocated state and federal regulations to lower the amount of lead allowed in paint and to require the testing of children's toys for lead. Despite our knowledge about the effects of lead exposure on children's health, we continue to needlessly expose those who are most vulnerable.

Biological Properties

The absorption, distribution, and subsequent health effects of lead illustrate the basic

principles of toxicology. Foremost is the sensitivity of children to the adverse effects of even low levels of lead exposure. There are many reasons that children are more sensitive to lead. Children are much smaller than adults and will receive a much higher dose by weight given the same exposure. They also absorb lead at a higher rate: adults absorb only 5-10% of orally ingested lead, while children absorb approximately 50% and can absorb much more depending on nutrition. Both children and pregnant women absorb more lead because their bodies have a greater demand for calcium and iron. Lead substitutes for calcium and is thus readily absorbed, particularly if a diet is low in calcium and iron. Children in low-income families, who often have poor diets and live in older housing containing lead, are most vulnerable to the developmental effects of lead. The same is true for pregnant women, whose bodies need more calcium.

Lead distributes in several compartments within the body, each with a different half-life. When lead enters the bloodstream it attaches to red blood cells and has a half-life of about 25 days in blood. Lead readily crosses the placenta, thus exposing the developing fetus and fetal nervous system to lead. Lead is also stored in the muscle, where it has a longer half-life of about 40 days. Calcium requirements for children are high in part because of rapid bone growth. Lead readily substitutes for calcium and is stored in bone, which is visible in x-rays of children with very high lead exposure (fortunately this is very rare now, at least in the United States). In normal circumstances, bone turnover or half-life is very long, so the half-life of lead in the bone is about 20 years. However, if bone turnover is increased, the lead in the bone is mobilized into the blood. This can occur during pregnancy or in older women subject to osteoporosis.

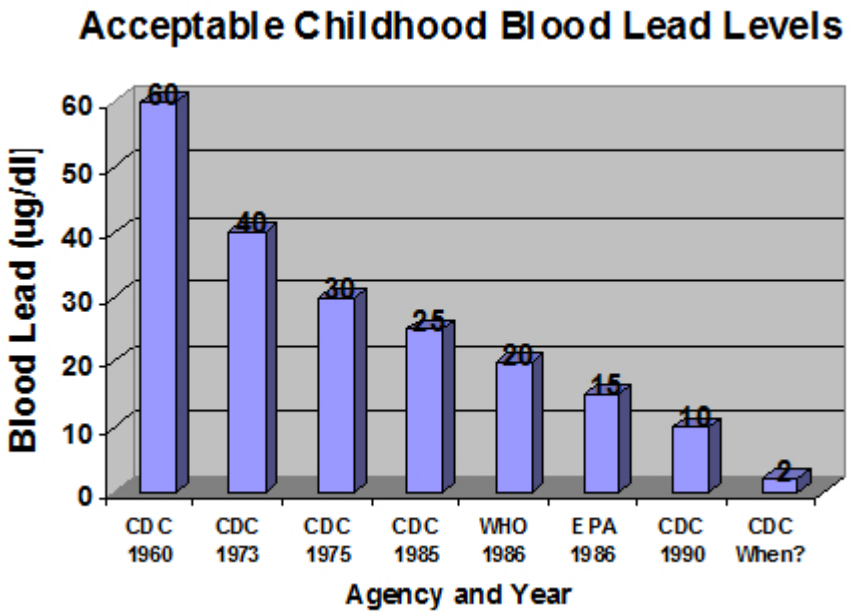
We accumulate lead over a lifetime, but particularly when we are young, so that as adults our bone and teeth contain approximately 95% of the total lead in the body. As we shall see, the short half-life of lead in the blood made tooth lead levels an important indicator of childhood lead exposure and a vital marker to use in correlating exposure with developmental effects.

Health Effects

Lead is one of the most intensively studied hazardous agents of the 20th century. The more toxicologists and other researchers investigated the health effects of lead, the more they realized that even very low levels of lead exposure were hazardous (Gilbert and Weiss, 2006). The most common biomarker of lead exposure is the blood lead level, usually measured in micrograms (µg) per one tenth of a liter of blood (dL) or µg/dL. For example, many regulatory agencies set 40 µg/dL as a level of concern for adult male workers. Typically, at this level workers would be removed from the environment responsible for the exposure and ideally some determination would be made as to the cause of the exposure.

The blood level of concern for children has dropped steadily as shown in the graph below, and some believe that there is sufficient data on the health effects below 10 µg/dL that the CDC should significantly lower the blood lead action level (Gilbert and Weiss, 2006).

Figure 8.1 Acceptable Blood Lead Levels for Children Over the Years



The decline in acceptable childhood blood levels was a function of research and of improved control of lead contamination, such as the removal of lead from gasoline. A blood lead level of 10 µg/dL does not represent a "safe" level, only one where it is prudent to take action to reduce exposure. But it must be noted that a level of 10 µg/dL is considered an action level and does not provide any margin of safety for a child's developing nervous system. Currently, there appears to be no safe level of lead exposure for the developing child.

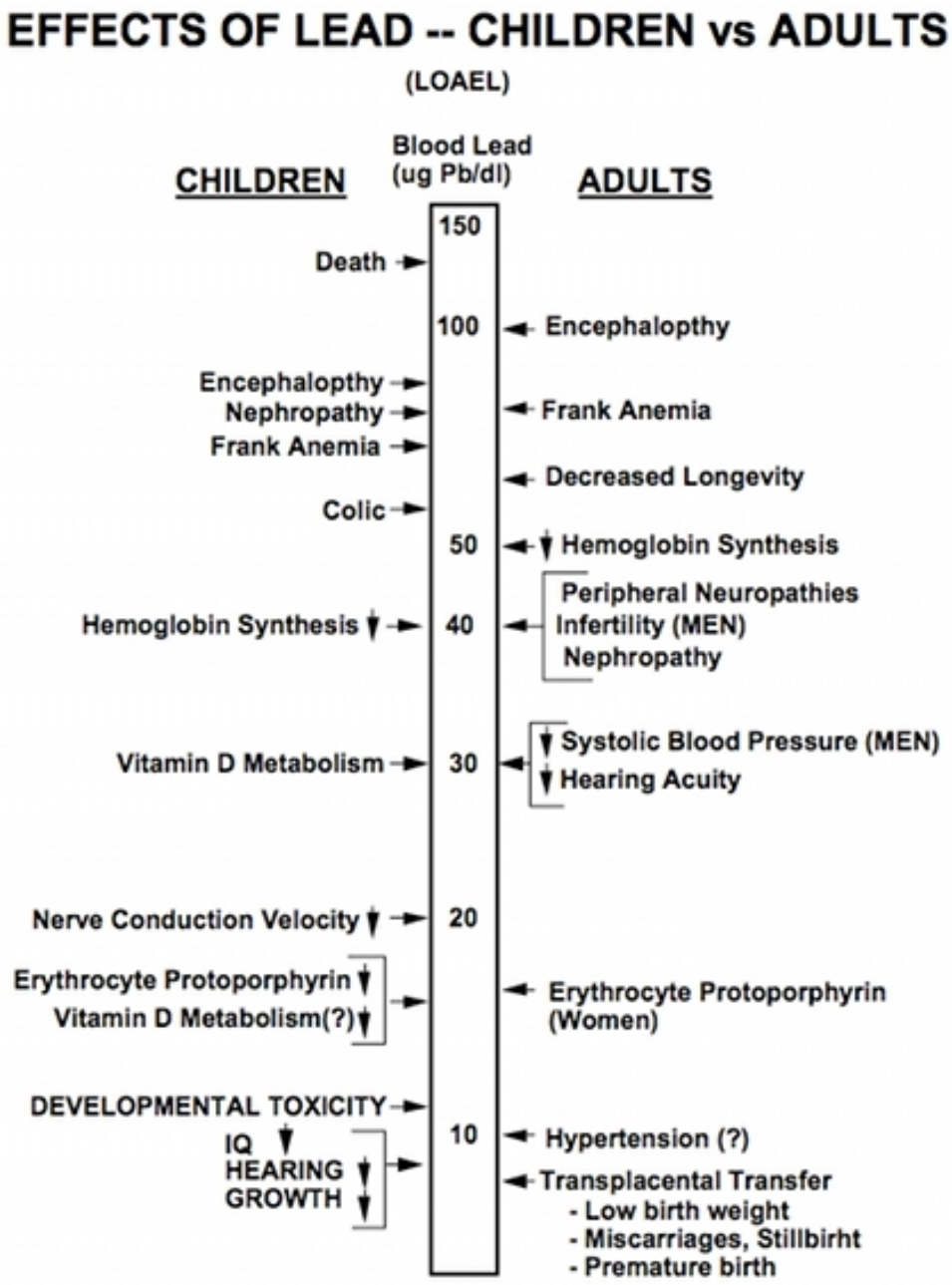
The nervous system is the most sensitive target of lead poisoning. Fetuses and young children are especially vulnerable to the neurological effects of lead because their brains and nervous systems are still developing. At high levels of lead exposure, the brain will swell (encephalopathy), possibly resulting in death. At one time it was thought that children who survived high levels of exposure would recover and have no adverse effects. However, in the 1940s, persistent learning and developmental effects were demonstrated in children exposed to high levels of lead. In 1979, a study by Needleman showed that even low levels of lead exposure would reduce the school performance of children. This study was one of the first to use tooth lead as marker of childhood exposure, which correctly classified early childhood exposure even if current blood lead levels were normal.

Numerous studies found similar results and it is now generally accepted that in every 10 µg/dL increase in blood lead levels, within the range of 5 to 35 µg/dL, there is a 2- to 4-point IQ deficit. Subsequent long-term studies of infants and young children exposed to lead showed that as they became older, there was an increased likelihood that they would experience decreased attention span, reading and learning disabilities, and failure to graduate from high school.

Adult nervous system effects are also apparent following lead exposure. In the past, painters using lead-based paint developed damage to the peripheral nervous system, which caused a wrist or foot drop. Nerve damage in the forearm could be evaluated by using an instrument to measure how fast the nerves conduct an electrical signal from one point to the next. But, as was the case with children, when more subtle effects were looked for, they were found. There is evidence of decreased cognitive performance in adults with blood levels greater that 25 µg/dL.

Lead exposure can produce a number of other effects. One of the most common effects is on the red blood cells: they become fragile and hemoglobin synthesis is impaired, which results in anemia. Similar to other metals, lead adversely affects kidney function, but this is now rare with reductions in occupational exposure. Several studies have demonstrated that elevated lead exposure is related to elevated blood pressure levels, particularly in men. There also appears to be a weak association between lead exposure and increased incidence of lung and brain cancer. Lead exposure is a reproductive hazard for both males and females. In males, lead affects sperm count and sperm motility, resulting in decreased offspring.

Figure 8.2 Effects of Blood Lead - Children vs. Adults



Reducing Exposure

While there are standards for lead exposure, at this time there is no level that is considered safe, so the best policy is to avoid lead exposure altogether. This is difficult because as a contaminant in food, water or dust, lead cannot be seen, tasted, or smelled. Be aware of potential sources of lead and take appropriate action.

If you are moving into an older home and have young children or are planning to start a family, have the paint and soil around the house tested for lead. If the house is old it

may contain pipes or solder joints with lead or with fixtures with high concentrations of lead. Test kits are available in some stores but these generally only indicate if lead is present, not how much. If you are renovating an old home, sanding or removing paint may create dust with high concentrations of lead. Young children exhibit hand-to-mouth behaviors and will ingest significant amounts of lead just from the dust. The EPA has information on safe home renovation.

If you work or come into contact with lead, wash your hands as soon as possible. If you handle lead and then eat, whatever you touch with your hands will contain a small amount of lead. Removing your shoes before coming into the house will reduce tracking in dust that contains lead. This is particularly important if there is indication of soil contamination, such as might occur near or downwind from a smelter.

Beware of any hobby using lead or products that might contain lead. Reduce or eliminate lead-based products whenever possible. Most states now ban lead pellets for hunting because the lead pellets are a hazard to birds and contaminate the environment with lead. Old cooking utensils, leaded crystal, and some pottery glaze may contain lead that will leach into foods, particularly those high in acid. Even some cosmetics contain lead, particularly haircoloring products that gradually hide gray hair. Tobacco contains a small amount of lead, which is another reason to avoid inhalation of tobacco smoke.

Regulatory Standards

US governmental agencies have set limits on lead in drinking water, plumbing, paint, and in occupational settings. State laws also exist and may be more stringent than those of the federal government.

- OSHA (Occupational Safety and Health Administration) standard for lead in air: 0.5 mg/m^3 (milligrams per cubic meter)
- EPA maximum level for lead in public drinking water systems: 15 µg/L
- EPA air lead standard 0.15 $µg/m^3$, rolling 3-month average
- Consumer Product Safety Commission standard for lead in paint: less than 0.06% by weight
- EPA standards for lead in new plumbing: less than 0.2% lead in solders and flux, less than 8% lead in pipes and pipe fittings (standards apply to public water systems and residential or nonresidential facilities connected to a public water system)

Recommendation and Conclusions

The developing nervous system of children is by far the most sensitive to lead

exposure. Because of a child's small size and greater absorption of lead, even a very low level of exposure results in a high dose of lead. The developing nervous system is exquisitely sensitive to the effects of even small amounts of lead, resulting in life-long learning deficits. Exposure to lead at an early age clearly deprives children of their ability to express their genetic potential. The optimal action is to avoid lead exposure and ensure children and pregnant women have an adequate diet with appropriate calcium and iron. Additional recommendations include washing hands frequently and taking off shoes to reduce dust in the home.

On a broader scale, we need to reduce the use of lead in a wide range of consumer products. Clearly this starts with products meant for children such as toys, vinyl plastics, jewelry, and candy. Large amounts of lead are distributed in the environment from a variety of sources such as lead fishing sinkers, car wheel weights, and bullets used in hunting and target practice. Most importantly, we must reduce the number of homes contaminated with lead-based paint. Many of these changes will require legislative or regulatory changes and acceptance that these changes benefit society. Finally, the CDC must review and lower the blood lead action level to send a clear message that no level of child lead exposure is acceptable.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Lead presentation material and references. Website contains presentation material related to the health effects of lead.

European, Asian, and International Agencies

• International Programme on Chemical Safety (IPCS). "The two main roles of the IPCS are to establish the scientific health and environmental risk assessment basis for safe use of chemicals (normative functions) and to strengthen national capabilities for chemical safety (technical cooperation)." [accessed April 4, 2009]
• Australian Department of Sustainability, Environment, Water, Population and Communities. Air Quality Fact Sheet. This site provides educational material about the sources of lead and strategies for living with lead. [accessed April 4, 2009]

North American Agencies

• Health Canada. Lead. Health Canada provides information on the health effects of lead and remediation programs. [accessed April 4, 2009]
• US Environmental Protection Agency (EPA). Lead in Paint, Dust, and Soil. Site has information on lead health effects and lead abatement. [accessed April 4, 2009]
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• US Environmental Protection Agency (EPA). Lead in Drinking Water. Safe Drinking Water Hotline: 1-800-426-4791. [accessed April 4, 2009]

• US Environmental Protection Agency The National Lead Information Center. Phone: 1-800-424-LEAD (424-5323)
• US Department of Labor Occupational Safety & Health Administration (OSHA). Lead. This site addresses workplace lead exposure. [accessed April 4, 2009]
• US Agency for Toxic Substance Disease Registry (ATSDR). Toxic Substances – Lead. [accessed April 4, 2003]
• Washington State Department of Ecology. PBT Initiative – Lead. Reviews the source and use of lead in Washington and offers recommendations on reducing lead exposure.

Non-Government Organizations

• Alliance for Healthy Homes. Works on many issues to prevent and eliminate household hazards that can harm the health of children, with a focus on reducing lead exposure. [accessed April 4, 2009]

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A Small Dose of Mercury

or

An Introduction to the Health Effects of Mercury

Inorganic Mercury (Hg): Quick Facts
Uses: consumer products, industry, dental amalgams, switches, thermometers
Source: mining, environment, workplace
Recommended daily intake: none (not essential)
Absorption: inhalation, poorly absorbed in intestine
Sensitive individuals: fetus, children, women of childbearing age
Toxicity/symptoms: nervous system, irritability tremor, drowsiness, depression, incoordination
Regulatory facts: ATSDR Minimal Risk Level by inhalation: 0.2 μg/m^3
General facts: long history of use, liquid silver evaporates at room temperature, bacteria converts to organic methyl mercury
Environmental concerns: global environmental contaminant
Recommendations: avoid, recycle mercury-containing devices

Organic Mercury (Methylmercury, Hg-CH_3): Quick Facts
Uses: limited laboratory use
Source: contaminates some fish (e.g. tuna, shark, pike)
Recommended daily intake: none (not essential)
Absorption: intestine (90%)
Sensitive individuals: fetus, children, women of childbearing age
Toxicity/symptoms: nervous system, developmental effects include cerebral palsy-like symptoms with involvement of the visual, sensory, and auditory systems, tingling around lips and mouth, tingling in fingers and toes, hearing loss, effects on vision
Regulatory facts: EPA RfD: 0.1 µg/kg/day, EPA: 0.3 ppm advised MeHg fish tissue level for human health (based upon water quality standards), FDA: 1 ppm in commercial fish, ATSDR Minimal Risk Level: 0.30 µg/kg/day, Canada: 0.5 ppm Hg for retail fish and seafood
General facts: bacteria convert inorganic mercury to methyl mercury then introduce to food supply (bioaccumulation)
Environmental concerns: global environmental contaminant, bioaccumulates in some fish
Recommendations: avoid, recycle mercury-containing devices

Introduction and History

Mercury exists in different forms with very different properties; thus each section of this chapter is divided into inorganic mercury, the common silvery liquid, and organic mercury (usually methyl mercury, Hg-CH_3), which is generated from inorganic mercury by bacteria and accumulates in some commonly consumed species of fish.

Mercury's dual nature of being both industrially useful and potentially harmful was recognized historically, but only in the last 20 years have we begun to appreciate its more subtle qualities and effects. The contradictory nature of mercury was recognized in Roman mythology, in which the winged messenger Mercury, who was noted for his cleverness, cunning and eloquence, was both the god of merchants and commerce as well as of thieves and vagabonds. The history of mercury's use by humans shows our struggle to balance and understand the usefulness of this compound with its harmful effects to humans and the environment. We now grapple with mercury as a global pollutant as we recognize its potential risks to children.

• • •

"For then she bare a son, of many shifts, blandly cunning, a robber, a cattle driver, a bringer of dreams, a watcher by night, a thief at the gates, one who was soon to show forth wonderful deeds among the deathless gods..."

- Description of the birth of the Greek god Mercury

• • •

Inorganic Mercury

Elemental mercury, also known as quicksilver or metallic mercury, is a silvery liquid at room temperature. It has a low boiling point, a high vapor pressure (e.g. evaporates) at room temperature, and a high density, weighing 13.6 times as much as water. Stone, iron, lead, and even humans can float on its surface (see Putman, 1972). Its toxicity has been recognized since Roman times when slaves mined it in Almaden, Spain; this mine remains active today as a major mercury source. While all rock types contain some mercury, cinnabar contains the greatest concentration of inorganic mercury (>80%). Elemental mercury is produced from cinnabar by condensing the vapor of heated ore. In the United States elemental mercury is produced primarily as a byproduct of mining.

Elemental mercury is used industrially in electric lamps and switches, gauges and controls (e.g., thermometers, barometers, thermostats), battery production, nuclear weapons production, and the specialty chemical industry, including the production of caustic soda. Because elemental mercury has a high affinity for gold and silver, it has been, and continues to be, used for precious metal extraction from ore. Elemental mercury has also been used for over one hundred years in mercury-silver amalgam preparations to repair dental caries. Mercury continues to be used in folk remedies and in certain cultural practices, with unknown public health implications.

The Chinese used cinnabar to make red ink before 1000 BC, and also used it in cosmetics, soaps and laxatives. Inorganic mercury (as an acid of mercury nitrate) was used in the felting industry to aid in matting felt; felting was a leading source of occupational mercury exposure in the United States into the 1940s. A 1937 Census of Manufacture of the US Census Bureau reported 5.2 million pounds of hatter's fur used in the production of over 30 million felt-hat bodies in 140 factories, and a study of 25 Connecticut hat factories demonstrated evidence of chronic mercurialism among 59 of 534 hatters.

Peruvian Incas used elemental mercury to wash gold-bearing gravel as early as 1557. The original extraction process took 20 to 30 days but was modified by the 1830s, leading to the ability to extract gold in a pan over a fire in less than six hours. A similar process continues to be used to this day, especially in Central and South America, Africa, and the Philippines, where approximately 3 to 5 kg of mercury are required to extract 1 kg of gold.

Dental amalgams were used as early as the 7th century, and the first commercial mercury dental amalgam was used in the 1830s in New York. Chronic mercury exposure among dentists and dental assistants is a well-recognized occupational hazard. Concerns over the public health risks of mercury amalgam fillings have also been raised in the scientific literature, though this is an area of significant controversy. Recent studies indicate that the amount of mercury in the urine is related to the number of dental amalgams and that a similar relationship exists for mercury excretion in human breast milk. Some countries are advising children and women of childbearing age not to use mercury-based dental amalgams. The US FDA, while taking no position on this issue, is requesting additional information and reviewing its advisory. Perhaps the most important aspect is that there is a very acceptable alternative to mercury amalgams, which from a precautionary principle perceptive would suggest that mercury amalgams should be avoided. Sweden prohibits the use of dental amalgam in ordinary dental care and bans its use in children and youth.

Mercury thermometers have been used for decades. In some instances their use has been discontinued, such as in infant incubators where it was found that significant mercury vapor concentrations could develop if the thermometers were broken. Disposal of thermometers and thermostats continues to add significantly to the toxicity of municipal waste. In 1995, discarded thermometers contributed 16.9 tons of mercury to the municipal solid waste stream in the US.

Organic Mercury

The first reported use of organic mercury compounds in chemical research occurred in 1863. Their synthesis immediately led to the recognition of their extremely high toxicity relative to inorganic mercury forms, and by 1866 two chemists had died from organic mercury poisoning. Therapeutic applications of organic mercurials in the treatment of CNS syphilis, which began in 1887, led to non-occupational poisoning; the use of organic mercury-based medicines ceased soon after because of their extremely high toxicity. The use of synthetic organic mercurials as antifungal dressings for agricultural seeds began in 1914. Their use in this industry has resulted in scattered case reports of acute poisoning associated with the chemical manufacture, application, and inadvertent consumption of either the treated grain or of animals fed with the treated grain. The use of organic mercurials in agriculture has resulted in large-scale poisoning episodes worldwide, such as occurred in Iraq.

Both elemental mercury and inorganic mercury are used in chemical manufacture, including vinyl chloride and acetaldehyde synthesis (inorganic mercury), and chlor-alkali production (elemental mercury). For example, the Minamata factory used mercuric oxide dissolved into sulfuric acid as a catalyst for the hydration of acetylene

to acetaldehyde. In addition, vinyl chloride production at the Minamata factory used mercuric chloride absorbed onto activated carbon for the production of vinyl chloride from acetylene and hydrogen chloride. These processes directly led to the contamination of Minamata Bay and the Agano River, Niigata with mercury effluent. This discharge caused large-scale human methyl mercury exposure and toxicity during the 1950s and 1960s and led to our present-day appreciation of mercury's environmental cycling, biomethylation, and food chain transfer.

Organic mercury compounds have also been used in latex paint to extend the shelf life, though such uses are currently restricted in the United States following the recognition of the potential hazard to children. Subsequent evaluation of interior rooms of homes painted with mercury-containing latex paint found that mercury vapor concentrations were elevated and in several cases were above the 0.5 $\mu g/m^3$ concentration recommended by the Agency for Toxic Substances and Disease Registry.

Case Studies

Minamata, Japan: Mercury and Fish

In the late 1950s the subtle and serious consequences of methyl mercury exposure became evident in Minamata, Japan. Initially, health experts were baffled by early signs of uncoordinated movement and numbness around the lips and extremities, followed by constriction in visual fields in fishermen and their families. Developmental effects were clearly evident in infants who exhibited subtle to severe disabilities. This spectrum of adverse effects was finally related to methyl mercury exposure from consumption of contaminated fish. Minamata Bay was contaminated with mercury and methyl mercury from a factory manufacturing the chemical acetaldehyde. Mercury was used in the manufacturing process, and both mercury and methyl mercury were discharged into Minamata Bay. The fish in the bay accumulated increasing amounts of methyl mercury, which was subsequently passed to the fish-consuming residents of the area. This was one of the first modern lessons of the consequences of the bioaccumulation of methyl mercury.

Mercury and Gold Mining

Environmental contamination from the use of mercury in gold mining started centuries ago and continues today. The Peruvian Incas first used elemental mercury in gold mining in the 1500s. The gold binds to the mercury and when the mercury is removed, the gold remains. Imagine heating a pan of a silvery substance (mercury-gold amalgam) and watching it turn to gold, a trick worthy of any alchemist: the mercury literally evaporates into the atmosphere, leaving the gold behind. This practice continues today in Central and South America, Africa, and the Philippines. It is estimated that it takes approximately 3 to 5 kg of mercury to extract 1 kg of gold. A large portion of this mercury contaminates the local environment, and by moving into the atmosphere it is rained down to earth many miles and even countries away, contributing to global mercury contamination. The elemental mercury is converted to methyl mercury by bacteria, then it moves up the food chain, often accumulating in fish that are consumed by a range of animals and humans. Local miners and their families, particularly children, suffer from mercury exposure.

Mercury-coated Seed Grain in Iraq

The toxic antifungal properties of organic mercury compounds were beneficial when applied to seed grain, but when humans consumed these seeds there were tragic consequences. During much of the 20th century, seeds were coated with organomercury compounds to reduce their destruction by fungus in the soil. Often these seeds were colored pink to indicate they were coated with an antifungal agent and were for planting only, not consumption. During the early 1970s, a severe drought in Iraq resulted in a loss of seed grain and people struggled with malnutrition. Pink-colored mercury-coated seed grain was shipped to Iraq for planting. Unfortunately, the local population could not read the foreign language on the seed bags nor recognize the pink seeds as hazardous. Bread made from these seeds was pink, tasty, and toxic, particularly to the developing child. Many people died or were tragically disabled for life, giving the world another lesson in communication and mercury toxicity.

Mercury in Paint

Prior to the 1990s, mercury compounds were routinely added to interior and exterior paint to prevent bacterial and fungal growth. The practice of adding mercury to paint was halted after the adverse effects of inhaled mercury were seen in a 4-year-old boy. The child's unventilated bedroom was painted with interior latex paint containing mercury. The boy was diagnosed with acrodynia, a rare disease caused by mercury exposure and characterized by flushed cheeks, pink, scaling palms and toes, profuse sweating, insomnia, and irritability. Manufacturers agreed to discontinue the use of mercury in paint in 1991 but because people often store paint for long periods of time, existing paint could still cause health problems.

Mercury Under Floorboards

Mercury is commonly used in many industrial applications and is a source of a nasty surprise when not adequately removed. In 1996 it was reported that six children and a number of adults were exposed to mercury vapor while living in condominiums in a converted manufacturing building. Prior to being converted, this building had been used to manufacture mercury vapor lamps. Pools of mercury were discovered beneath the floorboards of the condominiums.

Biological Properties

Inorganic Mercury

When mercury vapor from elemental mercury is inhaled, it is readily and rapidly absorbed into the blood stream, easily crossing the blood-brain barrier and the placenta. Ingestion of elemental mercury is far less hazardous than inhalation of mercury vapor due to its poor absorption in the gut. After entering the brain, mercury is oxidized and will not transfer back across the blood-brain barrier, thus continued exposure to mercury vapor results in the accumulation of mercury in the nervous system.

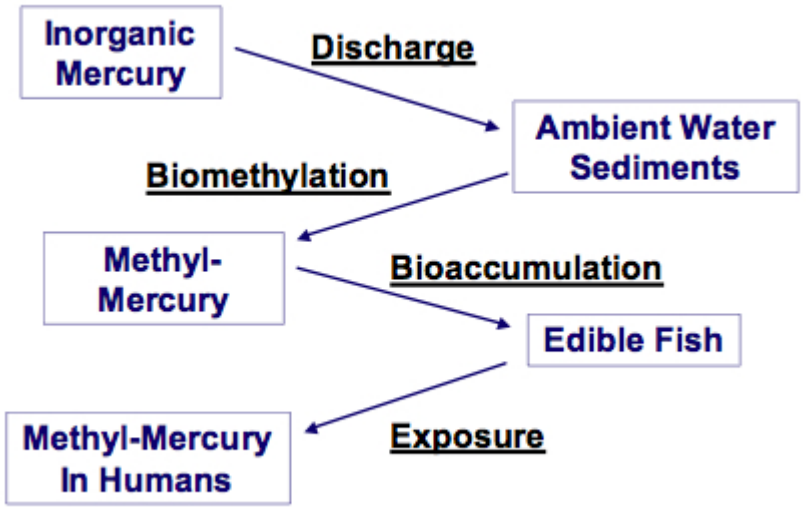
Inorganic mercury can also exist in the form of monovalent (Hg+, mercuric) or divalent (Hg2+, mercurous) salts. Two major mercury chloride salts, calomel (mercurous chloride) and sublimate (mercuric chloride) were first produced in the Middle Ages. Inorganic mercury-based skin creams were first used during this period

for the treatment of syphilis, and inorganic mercury was used as a clinical diuretic during the early 1900s.

Organic Mercury

While there are many synthetic organic mercury compounds, the most important organic mercury is the naturally occurring form methyl mercury (MeHg). In the environment, inorganic mercury is biotransformed to MeHg primarily through microbial methylation in sediments of fresh and ocean waters. Once produced, MeHg readily enters the aquatic food chain and bioaccumulates in tissues of aquatic organisms. Because MeHg is stored throughout the life of aquatic organisms, it is transferred up the food chain and results in the highest concentrations in larger, long-lived, predatory species such as swordfish, pike, and ocean tuna. The bulk of mercury in fish is stored in muscle, and almost all of the mercury in muscle is MeHg. The concentration of MeHg in fish depends on the age and trophic level of the particular fish, and can be quite substantial (> 1000 µg/kg (ppm)). For example, the total mercury in the edible tissues of shark and swordfish can average as high as 1200 µg/kg. The use of organomercurials as fungicides and paint preservatives and in medicinal applications has ceased; therefore, fish and marine mammal consumption is the primary source of human MeHg exposure.

Figure 9.1 Mercury to Methylmercury



Health Effects

Inorganic Mercury

Elemental mercury in the form of mercury vapor is readily and rapidly absorbed into the blood stream when inhaled and easily crosses the blood-brain barrier and the placenta. Oral ingestion of elemental mercury is far less hazardous than inhalation of mercury vapor due to its poor absorption in the gut. Acute, high level exposure to mercury vapor can result in respiratory, cardiovascular, neurological, and gastrointestinal effects, and even death.

Both acute, high-dose exposure and chronic, low-dose exposure to mercury vapor can

result in increasing and irreversible neurological effects. Symptoms include tremors and loss of feeling in the hands (paresthesia or stocking-glove sensory loss), emotional instability, insomnia, memory loss, and neuromuscular weakness. Exposure to mercury vapor may precipitate tremor, drowsiness, depression, and irritability; such symptoms form the basis for the expression "mad as a hatter" and the character the Mad Hatter in Lewis Carroll's *Alice's Adventures in Wonderland*. Decreased performance on memory tests and verbal concept formation have also been documented in industry workers exposed to mercury vapor. Neurotoxic effects such as dizziness, weakness, insomnia, numbness, and tremor were observed in a 12-year-old girl exposed to spilled mercury.

Organic Mercury

The devastating health consequences of methyl mercury (MeHg) exposure were well documented from several tragic incidents (see the case studies section). Historically, MeHg exposure played a very important role in drawing worldwide attention to the consequences of industrial pollution, not just for workers but also for the general public. In the 1950s, the consequences of MeHg exposure to the people of Minamata and Niigata, Japan were recognized. In both cases MeHg exposure resulted from consumption of fish from waters receiving industrial effluent discharge containing mercurials, which demonstrated conclusively that MeHg poisoning could occur through food-chain transfer of MeHg. By 1974 over 2,150 cases of what was then called Minamata disease had been established in the Minamata region alone. Observations of an abnormally high incidence of cerebral palsy-like symptoms with involvement of the visual, sensory, and auditory systems among children from the Minamata region also heralded a new concern over the potential developmental toxicity of industrially derived MeHg. However, as with the adult cases of MeHg poisoning, establishing a causal relationship between environmental MeHg and cases of observed infantile developmental toxicity was difficult because the affected children had not eaten fish and there were no identified neurological effects in their mothers, based on evaluations at that time. The susceptibility and the sensitivity of the fetus to MeHg-induced neurotoxicity were later documented in other studies.

A tragic incident in Iraq clearly documented the fetal effects of maternal methyl mercury exposure (see case study section). During the winter of 1971 some 73,000 tons of wheat and 22,000 tons of barley were imported into Iraq. This grain, intended for planting, was treated with various organic mercurials. Unfortunately, this grain was made into flour and consumed throughout the country, resulting in the hospitalization of some 6,530 people and the death of 459 at the time of the study (Table 9.1).

The accumulated evidence leaves no doubt that MeHg is a serious developmental toxicant in humans, especially to the nervous system. While the toxicological and behavioral outcomes resulting from high-concentration *in utero* exposures are not in debate, questions regarding risks and mechanisms of action following low-concentration, chronic *in utero* exposures remain.

A US National Research Council report states that "over 60,000 newborns annually might be at risk for adverse neurodevelopmental effects from in utero exposure to MeHg (methyl mercury)." This report clearly makes the point that many infants are

exposed to mercury above levels considered safe.

Table 9.1 Major Mercury Poisoning Incidents

Place	Year	Cases
Minamata, Japan	1953-60	1000
Niigata, Japan	1964-65	646
Guatemala	1963-65	45
Ghana	1967	144
Pakistan	1969	100
Iraq	1956	100
Iraq	1960	1,002
Iraq	1971	40,000

One of the complications with diagnosing MeHg exposure is that presentation of symptoms appears to occur after a latency period during which no effects are observed. The period of latency appears to be related to the level of exposure, with higher exposure concentrations resulting in a shorter latency period. The exact biological mechanisms underlying this latency period are unclear. Some researchers have suggested that latency not only reflects the time to reach accumulation of MeHg in the brain, but also reflects achievement of a threshold wherein enough tissue is destroyed that the capacity of the CNS to compensate for the damage is overwhelmed. Observation of long latencies following cessation of MeHg administration in animals and humans, however, may also derive from long-term demethylation of MeHg to inorganic mercury in the brain.

Reducing Exposure

Inorganic Mercury

There are numerous sources of metallic mercury in the home and workplace. The best advice is to properly dispose of any product with mercury and above all to avoid exposure, especially by inhalation, particularly for young children. In the past few years, many industries have worked to reduce the use of mercury in products. In

addition, some states have restricted the use of mercury or have developed programs to aid in the recycling and recovery of mercury. The average household fever thermometer contains about 3 grams of mercury, which does not seem like much until it is multiplied by the 105 million households in the United States. Even if only half of the households had a mercury thermometer, the total amount of mercury is very large. Additional sources of atmospheric mercury include coal-fueled electric generation facilities, hospital waste, fluorescent light bulbs, dental offices, and even crematoriums. Efforts are being made on a number of fronts to mandate reduction in mercury released into the atmosphere and to reduce the use of mercury in general. As individuals, we must also work to ensure mercury products are properly recycled and take action to reduce atmospheric mercury.

If a mercury spill occurs it is very important to ventilate the area and NOT use a vacuum cleaner to clean up the mercury. A vacuum cleaner will only warm and disperse the mercury. Collect all the mercury, place it in a sealed container, and take it to an appropriate disposal site. If it is a large spill, professionals must be called.

Common Sources of Metallic Mercury

- Switches in gas furnaces, heaters, etc.
- Major household appliances (tilt switches in freezers, dryers, etc.)
- Irons (tilt switches)
- Automobile switches
- Bilge pumps, sump pumps, etc. (float switches)
- Dental amalgam
- Measuring devices and lab equipment, such as barometers, manometers, etc.
- Medical equipment and supplies
- Fluorescent lights
- Batteries
- Computers
- Novelty items
- Film pack batteries

Organic Mercury

The primary concern with organic mercury is methyl mercury in fish. Children and women of childbearing age should be cautious about consuming fish known to accumulate mercury, such as tuna, shark, swordfish, and pike. Local fish consumption advisories should be followed.

Regulatory Standards

Inorganic Mercury

Below are some of the advisories on mercury vapor inhalation.

- ATSDR Minimal Risk Level (MRL): 0.2 µg/m^3
- OSHA Permissible Exposure Limits (PEL)-TWA: 0.05 mg/m^3
- ACGIH Threshold Limit Value (TLV)-TWA: 0.05 mg/m^3

Organic (Methyl Mercury)

The primary human exposure to methyl mercury is from consumption of contaminated fish. The most sensitive population is the developing fetus or infant due to the effects

of methyl mercury on the nervous system and on development. Exposure limits and fish consumption advisories are directed at pregnant women, women of childbearing age, and children. All agencies also recognize that fish has many nutritional benefits and is an important part of many people's diet. Below is a list of some of these recommendations, but it is very important to consult the local fish consumption advisories.

- FDA: 1 ppm in commercially harvested fish (i.e. tuna fish)
- FDA Action level: 0.47 µg/kg/day
- ATSDR Minimal Risk Levels (MRLs): 0.30 µg/kg/day
- Washington State Total Daily Intake: 0.035-0.08 µg/kg/day
- EPA Reference Dose (RfD): 0.1 µg/kg/day
- (In 1997 the EPA estimated that 7% of the women of childbearing age in the United States exceed the established RfD of 0.1 µg/kg/day.)
- 41 states have issued over 2,000 fish consumption advisories related to mercury

Recommendation from the State of Washington (US)

- Women of childbearing age should limit the amount of canned tuna they eat to about one can per week (six ounces.) A woman who weighs less than 135 pounds should eat less than one can of tuna per week.
- Children under six should eat less than one half a can of tuna (three ounces) per week. Specific weekly limits for children under six range from one ounce for a twenty pound child, to three ounces for a child weighing about sixty pounds.

Recommendation and Conclusions

Mercury is a potent toxicant and a global environmental pollutant. There is overwhelming data demonstrating that low levels of exposure to methyl mercury or mercury vapor damage the nervous system, particularly that of the sensitive developing fetus. Mercury vapor travels around the globe in the atmosphere. Once on the ground or in the water, it is converted to methyl mercury and accumulates in the food supply, contaminating fish, a main source of protein for many people. There needs to be a global effort to reduce human release of mercury into the environment. The production, sale and use of mercury must be restricted in recognition of the health effects of mercury. Mercury use in consumer products, such as thermostats, thermometers, and jewelry should be eliminated and replaced with already existing and cost-effective alternatives. Coal contains low levels of mercury that are released as the coal is burned. The discharge from coal-fired electric generating facilities can be greatly reduced with current technology. Finally, there must be ongoing monitoring of mercury contamination in fish and appropriate advisories to protect sensitive populations. This will involve education of the consumer about limiting the consumption of fish that accumulate mercury.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Mercury presentation material and references. Website contains presentation material related to the health effects of mercury.

European, Asian, and International Agencies

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North American Agencies

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A Small Dose of Arsenic

or

An Introduction to the Health Effects of Arsenic

Arsenic: Quick Facts
Uses: wood preservative, pesticides, semiconductor manufacturing
Source: coal combustion, drinking water, environment, medical drug, seafood
Recommended daily intake: none (not essential)
Absorption: inhalation, skin, intestine: inorganic low/organic high
Sensitive individuals: children
Toxicity/symptoms: peripheral nervous system (tingling in hands and feet), skin cancer (ingestion), lung cancer (inhalation); hyperpigmentation (keratosis) of palms and soles; vascular complications
Regulatory facts: EPA: Drinking water 10 µg/L (0.01 ppm, 10 ppb); EPA RfD: 0.3 µg/kg/day; OSHA: Workplace air 10 µg/m³; ATSDR MRL: 0.3 µg/kg/day
General facts: long history of use as medicine and poison
Environmental concerns: global environmental contaminant, bioaccumulates in fish and shellfish (mostly in a form that is not harmful)
Recommendations: avoid, do not use arsenic treated lumber, test drinking water

Overview

People long ago recognized that depending on the dose, arsenic could either treat an illness or be used as a poison to cause death. Its medicinal use to treat syphilis and amebic dysentery ended with the introduction of penicillin and other antibiotics in the 20th century. Arsenic-based compounds are currently used to treat some forms of cancer. As a poison, arsenic trioxide (As_2O_3) has several desirable qualities: it looks like sugar and is tasteless, and it only takes about a tenth of gram to kill someone. While its use as a human poison has greatly declined, arsenic is still used as an herbicide, particularly in growing cotton, and as a wood preservative. Arsenic poisoning from well water remains a serious worldwide human health concern.

Introduction and History

Arsenic is a versatile metal, forming various compounds, either inorganic or organic. Inorganic arsenic is widely distributed in nature, usually in the trivalent form (As_{3+}) but also as pentavalent arsenic (As_{5+}). Most rocks contain 1-5ppm of arsenic. The trivalent forms include arsenic trioxide, sodium arsenite, and arsenic trichloride. Organic arsenic, much less toxic than inorganic arsenic, is produced in a biomethylation process by many organisms including humans and shellfish. Though arsenic occurs naturally in rocks and soil, the majority of arsenic released into the environment is from industrial smelting.

Uses

Arsenic use and production has declined with recognition of its toxicity and the development of suitable replacements. It is not mined but produced as byproduct of smelting for copper, lead, and zinc. The last US smelter producing arsenic closed in 1985 in Tacoma, Washington. (See Tacoma Smelter.) Smelters typically released the trivalent arsenic trioxide and lead into the atmosphere, which contaminated the local environment and left an unwelcome legacy for local residents.

Arsenic is used in the manufacture of silicon-based computer chip technology and in glass manufacture to control color. Inorganic arsenic is no longer used as a pesticide in cotton fields and orchards, but some forms of organic arsenic continue to be applied to cotton fields. The wood preservative CCA, chromated copper arsenate, has been phased out for use residentially and in children's play areas by the US EPA. (See the next page, Case Studies, for more information on CCA.) Inorganic arsenic is also released from coal-fired electric generation facilities, and cigarette smokers inhale some arsenic from tobacco. Organic arsenic compounds are also used as a feed additive to enhance growth of poultry and swine. The import of arsenic into the US has declined from 20,000 metric tons in 2002 and 2003 to less that 8,000 metric tons in 2007.

Exposure

We are exposed to constant but low levels of arsenic, unless receiving greater exposure in an occupational setting or from arsenic-contaminated drinking water. Normally, the background air contains less than 0.1 µg/m3 and drinking water less than 5 µg/L, but water levels can be significantly higher. Food usually supplies less than 10 µg/day of arsenic but can be higher with the consumption of fish and particularly shellfish, which can have arsenic levels up to 30 µg/g.

The majority of arsenic in food is organic, a form that is generally less toxic than inorganic arsenic. The total average daily exposure to arsenic is about 20 µg/day from food and water (assuming 2000 mL/day average water consumption at 5 µg/L arsenic). Children have higher levels of exposure, particularly if drinking water concentrations of arsenic are elevated, because of their smaller size and greater consumption of water relative to their size. Several state health departments and public interest groups have expressed concern about children repeatedly exposed to arsenic form playing on arsenic-treated desk or play structures. Some exposure and associated risk calculations exceed EPA's acceptable risk levels. Arsenic exposure can also occur if arsenic-treated wood is burned or if sawdust from treated wood is inhaled.

Arsenic poisoning from well water remains a serious worldwide human health concern. In West Bengal and Bangladesh, more than 75 million people are exposed to arsenic-laden water that threatens their health. (See Arsenic Poisoning in Bangladesh.) People of Argentina, Chile, and Taiwan also have elevated arsenic in their drinking water. In the United States, federal agencies fiercely debate arsenic drinking water standards, which would limit the amount of arsenic in municipal wells. This is particularly relevant to areas of the western United States that have elevated levels of arsenic in drinking water.

Case Studies

Arsenic in Drinking Water

Arsenic in drinking water is a worldwide problem affecting the lives of millions of people. High levels of arsenic in local soil or rock contaminate the local water supply. In the United States, the federal government has struggled for many years to establish standards of arsenic in the drinking water. The US Environmental Protection Agency has recently lowered the standard from 50 ppm (50 µg/L) to 10 ppm. This standard will require additional treatment of a number of municipal water supplies, particularly in the western United States. The standard is being lowered because chronic exposure to low levels of arsenic can cause skin cancer and other illnesses. Even at the new standard of 10 ppm, there is a risk of cancer.

In other areas of the world, such as Bangladesh, elevated arsenic levels in drinking water is more acutely life threatening. People were encouraged to establish local wells to reduce exposure to bacteria-contaminated drinking water, but it was subsequently discovered that many of these wells have high levels of arsenic in the water. It is estimated that 75 million people in Bangladesh are exposed to arsenic-contaminated water, resulting in 200,000 to 270,000 deaths from cancer each year. In addition, people suffer from skin changes on the palms of hands and soles of feet. (See Arsenic Poisoning in Bangladesh.)

Pressure-treated Wood

By far the largest use of arsenic is in treating wood to prevent decay or insect damage. Several compounds are used, but the vast majority of wood is treated with a pesticide called chromated copper arsenate (CCA), first used in the 1940s. CCA is a water-based mixture of inorganic salts of chromium, copper, and arsenic that is forced into the wood under pressure. Wood treated with CCA is still found in decks, playground equipment, outdoor furniture, fences, construction lumber, utility poles, piers, and pilings. The amount of arsenic in treated wood can be quite large. A standard eight-foot length of treated 2" x 4" lumber contains as much as 15 grams of arsenic. To put this in perspective the lethal dose of arsenic in humans is 70 to 200 mg or about 1 mg/kg. Since December 31, 2003, CCA was no longer used in wood for most residential settings, including decks and play sets. There are a number of arsenic-free wood preservatives on the market that are registered for use in treated wood for residential use.

The health risks of exposure to arsenic-treated lumber have been debated for years, although it is well known that inhaling sawdust from construction with treated lumber can be quite dangerous. Ideally the arsenic-based wood preservative is "fixed" to the wood, but research has shown that arsenic leaches from the wood with rainfall and that arsenic can be rubbed off from the surface by hand contact. Arsenic contamination of soil under decks often exceeds hazardous waste cleanup standards. Children who play on decks or other treated surfaces pick up arsenic on their hands and later ingest some of the arsenic when they put their hands in their mouth or pick up food. Health professionals, the wood preserving industry, and public interest groups have hotly debated the hazards of these exposures. In 2002, producers of arsenic-treated wood reached an agreement with EPA to phase out the residential uses of arsenic treated lumber, including decks, play equipment, fences, etc. CCA will still be available for commercial uses such as utility poles. The alternative wood treatment most used to replace CCA is a copper-based preservative called ammoniacal copper quaternary, or ACQ. ACQ has a much lower toxicity to humans than CCA.

Biological Properties

Soluble inorganic arsenic compounds, such as arsenic trioxide, are readily absorbed

from the intestine (80-90%). Organic arsenic compounds found in seafood are not well absorbed. Arsenic can also be absorbed through the lungs and skin. Most of the arsenic in the blood is bound to red blood cells. Once ingested, inorganic arsenic is biotransformed by the liver to a methylated form of arsenic and excreted in the urine with a half-life of three to five days. Arsenic is also excreted in the outer layer of skin cells and in sweat. Arsenic binds to sulfhydryl-containing proteins and concentrates in the hair and fingernails. At higher levels of exposure, white bands, called Mees' lines, are visible in the nails.

Health Effects

The acute effects of inorganic arsenic poisoning are well known from the incidence of suicidal, homicidal, and accidental poisonings. Ingestion of 70 to 180 mg of arsenic trioxide can be fatal, but initial effects may be delayed for several hours. Symptoms following oral ingestion include constriction of the throat with difficulty in swallowing, severe intestinal pain, vomiting, diarrhea, muscle cramps, severe thirst, coma, and death. If the patient survives the acute symptoms there is often peripheral nervous system damage.

The symptoms of chronic arsenic exposure are most often associated with contaminated drinking water. Early signs of arsenic exposure are garlic odor on the breath, excessive perspiration, muscle tenderness and weakness, and changes in skin pigmentation. More advanced symptoms include anemia, reduced sensation in the hand and feet from damage to the peripheral sensory system (stocking and glove syndrome), peripheral vascular disease, skin changes on palms and soles, and liver and kidney involvement. Changes in circulation can lead to gangrene of extremities, especially of the feet, which has been referred to as blackfoot disease. Hyperpigmentation and hyperkeratosis of palms and soles occurs in three to six months with repeated ingestion of 0.4 mg/kg per day. Many of the symptoms are dose and time dependent. In other words, repeated low levels of exposure over an extend period of time can produce effects similar to a one-time, high level of exposure.

Arsenic causes both skin and lung cancer. Skin cancer was observed over 100 years ago in patients treated with arsenical compounds, and lung cancer was seen in smelter workers who chronically inhaled arsenic dust. Although arsenic is an established human carcinogen, it has been difficult to confirm and study in animal models. Arsenic readily crosses the placenta, but there appears to be increased methylation of arsenic to its organic form, which reduces its toxicity to the fetus.

Reducing Exposure

The toxicity of chronic exposure to arsenic is well established and the best

recommendation is to avoid arsenic exposure entirely. The most common home exposure is from contaminated drinking water and arsenic-treated lumber. Certain areas of the country have higher levels of arsenic in water. The EPA has lowered the arsenic drinking water standard to 10 ppb and required water providers to meet the new standard by January 2006.

Avoid inhalation of sawdust from arsenic-treated lumber, and never burn any treated lumber or sawdust. Families with decks, play equipment, furniture, or other structures made with arsenic-treated lumber should take steps to reduce exposure, especially to children. Home uses of arsenic-treated lumber have been phased out in the United States, but it is estimated that approximately 60 billion board feet of arsenic-treated lumber are still in use in the United States as of 2002. This is about enough to cover half the state of California with a deck two inches thick. Several state agencies have recommended that treated lumber on which children may play be coated periodically with paint or other sealer to reduce hand contact and subsequent ingestion of arsenic. Those who choose to remove arsenic-treated decks or other structures may want to test the soil underneath to see if levels exceed state standards. And always wash your hands after coming in contact with any arsenic-treated product.

Regulatory Standards

- EPA Drinking water: 10 µg/L (10 ppb)
- EPA RfD: 0.3 µg/kg/day (inorganic chronic exposure)
- OSHA Workplace air: 0.5 mg/m³
- ATSDR MRL: 0.3 µg/kg/day (chronic exposure)

Recommendation and Conclusion

Arsenic is an ancient and well-known hazard and, along with lead and mercury, is a significant environmental contaminant. The inorganic form is far more toxic than organic arsenic, which is commonly found in seafood. Arsenic-contaminated drinking water is a worldwide problem that affects millions of people. Human exposure also occurs from arsenic-treated lumber.

The best recommendation is to avoid or reduce exposure to inorganic arsenic.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Arsenic presentation material and references. Website contains presentation material related to the health effects of arsenic.

European, Asian, and International Agencies

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A Small Dose of Metals

or

An Introduction to the Health Effects of Metals

Introduction

• • •

"An excellent man, like precious metal, is in every way invariable; A villain, like the beams of a balance, is always varying, upwards and downwards."

- John Locke

• • •

Metals occupy a large part of the periodic table and are generally good conductors of electricity or heat. They form cations and ionic bonds with non-metals, which makes many of them essential for humans and indeed for all life, while some are very toxic.

We began using metals to build and shape our society over 4,000 years ago. The Greeks and Romans were some of the first to document both the toxic and potential healing effects of metals. Arsenic was well known both as a poison and treatment for disease.

The use of metals in our industrialized society has significantly altered the natural distribution of metals in the environment. Our progress and folly is well documented in Greenland ice. Lead in Greenland ice began increasing at about 800 BC and as civilizations flourished and declined, a dramatic increase occurred when lead was added to gasoline in the 1920s. Overall, there has been a 200-fold increase in lead in Greenland ice due to human use of lead.

Metals cannot be created or destroyed, but can change form, which alters their biological availability and toxicity. Metallic mercury evaporates and is redistributed globally in the atmosphere. When the mercury returns to land or water, bacteria form methyl mercury ($Hg\text{-}CH_3$), which is then taken up by increasingly larger organisms and ultimately ends up in fish, such as tuna, that humans and other animals consume.

The principles of toxicology, dose/response and individual sensitivity, are well illustrated by the metals. Historically, most interest and concern was with the obvious effects of metal toxicity such as colic from lead, or symptoms of the "Mad Hatter" from mercury. The emphasis has changed to the more subtle and long-term effects and concern for potentially sensitive individuals. It is now well documented that children exposed to even low levels of lead will have a lowered IQ and other learning difficulties. This knowledge has resulted in significant changes in our use of metals.

In this chapter, the metals are divided into three sections: 1) nutritionally important

metals or essential metals; 2) important toxic metals; and 3) medically useful metals. There is also a very brief section on chelating agents used to treat over-exposure to metals. Only selected metals are reviewed and the reviews are very brief, covering key points about their biological activity and toxic effects. The accompanying presentation material has one slide for each metal that highlights key facts. Three metals, arsenic, lead, and mercury are covered in more detail in separate chapters. These three metals are recognized as persistent environmental contaminants and are toxicologically important.

Nutritionally Important Metals

Introduction

Our very existence is dependent on a number of metals, the most common of which is iron. Because they are essential elements, the beneficial and adverse effects of these metals have been carefully studied and recommendations developed on daily intake. These recommendations are generally very broad and can vary depending on age and whether a woman is pregnant. The recommended daily intakes quoted below are for adults. These recommendations are actually oral exposure levels with intestinal absorption highly variable and dependent on the specific metal and other factors. A quick look at a typical cereal box will demonstrate the importance placed on these elements.

Since they are essential for life, the toxicity of these metals can result from either nutritional deficiency or excess exposure, but the focus will be on excess exposure. Depending on the route of exposure, metal toxicity can be very different. For example, metals like zinc and manganese can be very toxic when inhaled. As we have seen with many agents, there is a beneficial and a hazardous side depending on route of exposure and amount of exposure. Nutritional iron deficiency is worth mentioning, as it is a problem in the United States as well as worldwide, and lack of iron can contribute to lead toxicity.

Table 11.1 Summary of Nutritionally Important Metals

Metal	Function	Source	Toxicity (when in excess)	Recommended Daily Allowance
Chromium (Cr)	Associated with insulin	Food supply	Kidney damage, lung cancer (inhalation)	50 to 200 μg (Cr^{3+})
Copper (Cu)	Synthesis of hemoglobin	Food supply	Toxicity is very rare, deficiency: anemia; excess: liver and kidney	1.5-3.0 mg
Iron (Fe)	Hemoglobin	Food	Intestinal tract, liver	10 to 15 mg

		supply	damage	
Magnesium (Mg)	Associated with many enzymes	Food supply (grains and nuts)	Deficiency: neuromuscular weakness, convulsions	280 to 350 mg
Manganese (Mn)	Associated with many enzymes	Food supply, Inhalation in welding	Parkinson's-like syndrome	2 to 5 mg
Selenium (Se)	Anticancer	Food supply	Heart	55 to 70 µg
Zinc (Zn)	Associated with many enzymes	Food supply	Deficiency: impaired growth	12 to 15 mg

Chromium (Cr)

Chromium is an abundant essential element that exists in oxidation states from Cr^{2+} to Cr^{6+}, of which Cr^{3+} is biologically important and Cr^{6+} industrially important. Cr^{3+} is associated with insulin and regulation of glucose. Recommended daily intake is 50 to 200 µg. Chromium (Cr^{6+}) has a range of industrial uses including as an alloy in stainless steel and in tanning leather, but it is also highly toxic. The most serious industrial exposure is by inhalation and this exposure is most prominent in chrome production and plating industries. Acute chromium exposure causes kidney damage, skin contact can cause contact dermatitis, and inhalation irritates the nasal lining. It should also be considered a lung carcinogen.

Copper (Cu)

Copper is involved in hemoglobin synthesis and human toxicity from either deficiency or excess is rare. Recommended daily intake is 1.5-3.0 mg. It is widely used in a number of products including plumbing and electrical wire and is readily available in the food supply. Copper deficiency has been associated with anemia but is generally associated with broader nutritional problems. Grazing animals, for example cattle, can ingest too much copper, which affects the liver and kidney. Copper is much more toxic to aquatic life than to mammals and is a significant environmental contaminant in water. In humans, Wilson's disease, a genetic inability to metabolize copper, can be treated with the chelator penicillamine.

Iron (Fe)

There is 3 to 5 grams of iron in the body and two-thirds of that is associated with the

oxygen-carrying hemoglobin in red blood cells. Recommended daily intake is 10 to 15 mg, but this increases to 30 mg during pregnancy. Iron deficiency is the most common nutritional deficiency worldwide, affecting both children and adults. It results in anemia or a decrease in the oxygen-carrying capacity of the blood. The intestinal tract actively transports iron and if there is low iron in the diet, other metals such as lead will be absorbed, resulting in increased lead toxicity. Before the introduction of childproof caps for medicine, children were often treated for the acute effects of iron toxicity after ingesting iron supplements; effects include vomiting, liver damage, shock, kidney failure and possibly death. Chronic excess exposure to iron can result in ulceration of the intestinal tract, which in turn results in bloody vomit and black feces.

Magnesium (Mg)

Magnesium, a nutritionally essential metal, is found in grains, seafood, nuts, meats, and drinking water. Recommend daily intakes ranges from 280 to 350 mg per day for adult females and males, respectively. It is also used in a number of antacids and cathartics. Milk of magnesia or magnesium hydroxide is known as a universal antidote for poisoning. Magnesium is a cofactor in a number of essential enzymes and involved in several key metabolic reactions. It is primarily absorbed in the small intestine and is routinely excreted in the urine at about 12 mg/day. Magnesium blood levels are constant and are consistently regulated by the body.
Magnesium deficiency, usually the result of decreased absorption or excessive excretion, results in neuromuscular weakness and ultimately, convulsions. Dietary deficiency in cattle is known as the grass staggers. Magnesium toxicity from impaired excretion or excessive consumption of antacids results in nausea, vomiting, hypotension, and central nervous system effects.

Manganese (Mn)

Manganese is an essential element involved in numerous enzymatic reactions, particularly those associated with the fatty acids. Intestinal tract absorption is poor (less than 5%) but it is readily available in foods such as grains, fruits, nuts and tea. Recommended daily intake is 2 to 5 mg. There is increased interest in the toxicity of manganese because of its use in the gasoline additive MMT (methylcyclopentadienyl Mn tricarbonyl), which results in manganese salts being distributed into the environment from the tail pipes of cars. There is ongoing research on the potential adverse effects from use as a fuel additive.

Manganese is also an important alloy in steel. Inhalation of manganese dust during mining or steel production can cause respiratory disease. Manganese exposure can also result in a serious nervous system disease that resembles the movement disorders of Parkinson's disease, characterized by difficulty walking, irritability, and speech difficulties.

Selenium (Se)

Selenium is readily available in a variety of foods including shrimp, meat, dairy products and grains, with a recommended daily intake of 55 to 70 µg. Selenium occurs in a several forms, with Se^{+6} being biologically most important. Selenium is readily absorbed by the intestine and is widely distributed throughout the tissues of the body, with the highest levels in the liver and kidney. It is active in a variety of cellular

functions and interacts with vitamin E. Selenium appears to reduce the toxic effects of metals such as cadmium and mercury and to have anticarcinogenic activity. Selenium produces notable adverse effects both in deficiency and excess; thus recommended daily intake for adult is approximately 70 µg/day but should not exceed 200 µg/day.

Excess selenium intake can occur in both animals and humans living in areas with elevated selenium in the soil. Most grass and grains do not accumulate selenium, but when an animal consumes plants that do accumulate selenium (some up to 10,000 mg/kg) they can develop a condition called the "blind staggers." Symptoms include depressed appetite, impaired vision, and staggering in circles, and can ultimately lead to paralysis and death. Humans are susceptible to similar effects as well as additional neurological effects. Selenium deficiencies result in heart disorders, skeletal muscle effects, and liver damage.

Zinc (Zn)

Zinc plays a number of important roles in the body and deficiency results in serious adverse effects. Recommended daily intake is 12 to 15 mg. Zinc is very abundant in the environment and readily available in many foods, including grains, nuts, legumes, meats, seafood, and dairy products. Numerous enzymes require zinc, as do proteins that regulate gene expression. Zinc plays a role in the immune system and is also important in the development and function of the nervous system.

Zinc deficiency during fetal or infant development can lead to impaired growth, increased illness, impaired healing, loss of hair, and central nervous system disorders. Some studies have linked adult zinc deficiency with neurological disorders such as Alzheimer's disease. Diseases associated with zinc deficiency are linked to liver disorders from alcoholism. A number of drugs, particularly chelating agents and some antibiotics, affect zinc's homeostasis. Exposure to zinc and other metals during welding can cause metal fume fever, characterized by chills, fever, weakness, and sweating.

Toxicologically Important Metals

Introduction

While some metals are nutritionally important, others have no beneficial biological effects and in some cases cause serious toxic effects. Our complex relationship to metals is well illustrated by lead, which we have used for a variety of purposes since ancient times. In the last hundred years, lead was extensively used in paint and as a gasoline fuel additive. In the last 30 years, it was recognized that children exposed to even low levels of lead could suffer permanent brain damage and reduced intelligence. This worldwide use and distribution of lead has had significant effects on individuals as well as society as a whole. There is a somewhat similar story for mercury. The examples of lead and mercury clearly illustrate the fundamental principles of toxicology: dose/response and individual sensitivity.

Table 11.2 Summary of Toxic Metals

Metal	Toxic Effects	Source
Aluminum (Al)	Dialysis dementia	During dialysis, food, drinking water
Arsenic (As) (can exist in different forms)	Cancer (skin and lung) Neurotoxic (sensory effects) Liver and vascular	Drinking water, smelting of ore, used in pesticides, treated wood
Beryllium (Be)	Lung, hypersensitivity, delayed and progressive effects (berylliosis), contact dermatitis	Nuclear power plants, alloy in metals, coal combustion
Cadmium (Cd)	Lung, emphysema, kidney, calcium metabolism, possible lung carcinogen	Shellfish, cigarette smoke, taken up by plants, metal alloy - welding
Cobalt (Co)	Inhalation exposure "hard metal" pneumoconiosis	Alloy in metals, but also associated Vitamin B12
Lead (Pb)	Decreased learning and memory (children very sensitive)	Old paint, food, formerly used as a gasoline additive, auto batteries
Mercury, Inorganic (Hg)	Tremor, excitability, memory loss, the "Mad Hatter"	Thermometers, switches, fluorescent lights, some "button" batteries
Mercury, Organic ($Hg\text{-}CH_3$)	Tremor, developmental effects on nervous system	Fish
Nickel	Lung carcinogen, contact dermatitis	Jewelry, cooking utensils, other objects containing nickel
Tin (Sn)	Inorganic – low, lung Organic – central nervous system	Inorganic: food packaging, dust; Organic: rare

Aluminum (Al)

Aluminum was first isolated in 1825 and is now recognized as the most abundant metal in the environment. Historically, this abundance has not translated into biological availability because it is highly reactive and remains bound to a range of elements. However, acid rain has increased the bioavailability of aluminum in the environment. Aluminum is used in a wide range of products from airplanes, to beer and soda cans, to cooking pans. Human exposure to aluminum is from drinking water, food, and some drugs. Daily intake ranges from 1 to 10 mg, but it is poorly absorbed in the intestine. Aluminum does not appear to have any essential biological function.

The neurotoxic effects of aluminum were first observed in people undergoing dialysis for treatment of kidney failure. This syndrome, called dialysis dementia, starts with speech disorders and progresses to dementia and convulsions. Symptoms corresponded with elevated aluminum levels commonly found in bone, brain, and muscle following 3 to 7 years of treatment. Elevated levels of aluminum were also found in the brains of people suffering from Alzheimer's disease. Despite considerable research, it is not clear if the aluminum accumulation in the brain is a cause of Alzheimer's disease or a result of changes in the brain associated with the disease.

Arsenic (As)

Arsenic has a colorful history, having been used with great effect as a poison and also to treat a variety of ailments, including cancer. Its properties were first studied over 2000 years ago and contributed to some of the first theories on toxicology. Despite its toxicity, arsenic was still used in cosmetics into the 20th century. Prior to the recognition of the toxic properties of arsenic, it was widely used as a pesticide in orchards, which resulted in soil contamination. The vast majority of treated wood in residential decks and other structures contains arsenic. Workplace exposure occurs in the smelting of ore, and arsenic is also widely used in the electronics manufacturing industry. Of considerable public concern, which has resulted in several large studies by the government, is the presence of arsenic in drinking water. Some municipal or well waters can contain elevated arsenic levels.

Chemically, arsenic is complex in that it can exist in a variety of forms including trivalent, pentavalent, arsenic trioxide (computer chip manufacture), and arsenic acid. Arsenic is excreted in skin cells, sweat, hair, and fingernails, where it can be seen as white transverse bands. Acute exposure to arsenic results in gastrointestinal pain, sensory loss, cardiovascular failure, and death. Chronic exposure or survival of acute exposure can cause loss of peripheral sensory function and loss of central nervous system function. Chronic arsenic exposure can also cause cancer of the lung and skin.

Beryllium (Be)

Beryllium is an important metal used in the nuclear power industry and in combination with other metals. Its presence in coal and oil results in more than 1250 tons being released into the environment annually from fuel combustion at power plants. Exposure is primarily from inhalation, but skin contact can result in dermatitis. Cigarette smokers also inhale a little beryllium. Initially, beryllium distributes to the liver but ultimately is absorbed by bone.

Contact dermatitis and hypersensitivity to beryllium is the most common toxic reaction. Workplace inhalation of beryllium can be very serious. Acute exposure can result in an inflammatory reaction along the entire respiratory tract. Chronic beryllium disease (CBD) or berylliosis can result from chronic workplace exposure. This is a serious and progressive degenerative disease in which the lungs become increasingly fibrotic and dysfunctional. Long-term exposure can result in lung cancer, and beryllium is classified as a carcinogen by international regulatory agencies. Testing available for genetic susceptibility to CBD raises a number of ethical issues.

Cadmium (Cd)

Cadmium is a widely distributed metal used in manufacturing and is present in a number of consumer products. Dietary exposure to cadmium is possible from shellfish and plants grown on cadmium-contaminated soils. Absorption is increased when associated with low levels of iron or calcium in the diet. Some plants, such as tobacco, can concentrate cadmium from even low levels in the soil. The lung readily absorbs cadmium, thus cigarette smokers have elevated cadmium exposure. Cadmium is also used as a metal alloy, in paint, and in batteries (Ni-Cad, nickel-cadmium). Workplace exposure can occur in welding and battery manufacture.

Oral ingestion of cadmium results in less than 10% absorption, but inhalation exposure results in much higher absorption through the lungs. Cadmium accumulates in the liver and kidney, with the kidney being particularly important in binding cadmium and reducing its toxicity. Ingestion of high levels from acute exposure can result in abdominal pain, nausea, and vomiting, while inhalation exposure results in impaired breathing (pulmonary edema or accumulation of fluid in the lungs). Chronic exposure can result in obstructive lung disease, emphysema, and kidney disease. Cadmium may also be related to increases in blood pressure (hypertension) and is a possible lung carcinogen. Cadmium affects calcium metabolism and can result in bone loss. This condition has been referred to as "Itai-Itai" disease, which means "Ouch-Ouch" in Japanese and reflects the bone pain associated with cadmium's effects on calcium.

Cobalt (Co)

Cobalt in small amounts is an essential element associated with vitamin B12, but at high levels it can be toxic. There are no daily recommended intake levels for cobalt because intestinal bacteria use cobalt to produce cobalamin, which in turn is an essential component of vitamin B12. Industrially, cobalt is used in pigments and permanent magnets and as an alloy to harden metals in tungsten carbide blades or drills.

High chronic oral consumption of cobalt has been used to treat anemia but can also cause goiter. High acute consumption of cobalt can cause vomiting, diarrhea, a sensation of warmth, and heart failure. Heart failure was noted during a period when cobalt was added to beer to improve foaming. When inhaled, for example in metal grinding for sharpening, cobalt can cause "hard metal" pneumoconiosis, a progressive disease of the lungs.

Lead (Pb)

Lead was as important in the Roman Empire as it was in the 20th century, and its use has been almost equally as disastrous. In the Roman Empire lead's malleability and low melting point made it ideal for plumbing, not unlike its use in solder in household plumbing centuries later. The Romans also added lead to wine as a sweetener and preservative. In the 20th century lead was commonly added to paint, sometimes as much as 50%, which in fact created an excellent, long-lasting paint. But the sweetish taste of lead attracted children who readily consumed lead paint chips, a behavior referred to as pica. Due to its low melting point, lead was also used as solder in tin food cans and in plumbing. In what some refer to as the greatest public health disaster of the 20th century, lead was added to gasoline to improve car engine durability. Lead was emitted from the tail pipes of cars, contaminating both local and distant areas. Children absorb up to 50% of lead that is orally ingested, as it substitutes for the much-needed calcium. In contrast, adults absorb only about 10% of orally ingested lead. As the toxicity of lead at lower levels was recognized, it was banned from paint and from gasoline. Lead is still a serous concern in areas near smelters and in housing with lead-based paint.

The Greek Dioscorides recognized the health effects of lead in the 2nd century BC when he stated, "Lead makes the mind give way." In the 1700s, Benjamin Franklin noted that lead exposure caused the "dry gripes," or stomach upset. Painters who used lead-based paint suffered from "wrist drop" caused by the effects of lead on the peripheral nervous system. At the turn of the 20th century it was recognized that children seemed to be particularly sensitive to high levels of lead that resulted in a swelling of the brain, kidney disease, effects on hemoglobin, and possible death. In the 1970s, studies demonstrated that even low levels of lead exposure harmed the developing nervous system. It is now well accepted that lead is a very potent neurotoxicant. Australia banned the use of lead in paint in the 1920s but this step was not taken until 50 years later in the United States. On the average the biggest drop in the blood lead levels of children occurred following the phase-out of lead in gasoline in 1980s. The US Centers for Disease Prevention and Control (CDC) has established a blood lead level of 10 µg/dl or greater as an action level. There is no safety factor associated with this number and there are sufficient data to indicate that the nervous system of children is damaged at blood lead levels of 10 µg/dl and that the blood action level should be lowered (see chapter 8).

Inorganic Mercury (Hg)

Inorganic mercury is a silvery colored liquid at room temperature. Many people have had the opportunity to "play" with mercury, coating pennies and pushing it around on a flat surface. Now we know that the mercury was evaporating and that there are serious health consequences to the inhalation of mercury vapor. Due to its reactive properties and ability to combine with other metals, inorganic mercury was used at nuclear weapons facilities and in gold mining. In the gold mining process, the ore would be mixed with the mercury and the metallic mixture heated to evaporate the mercury, leaving the gold behind. This process results in a significant release of mercury into the atmosphere. The atmospheric circulation of mercury has made it an important worldwide contaminant. When returned to the earth or water, inorganic mercury is converted into an organic mercury compound (see below).

Although there are growing efforts to phase out the use of mercury in consumer products, it has been widely distributed in thermometers, switches (thermostats and car trunk lid switches), fluorescent light bulbs, and scientific instruments such as used in measuring blood pressure. Many of us have mercury in our mouths as a dental amalgam with silver. Dental fillings contain approximately 50% mercury. This use of mercury has resulted in crematoriums being an important source of atmospheric release. Dental offices are also an important source of mercury released into the waste stream and then into the environment. Mercury has also been used to treat a variety of diseases including syphilis. Coal contains mercury, and combustion of coal at power plant is a significant source of atmospheric mercury. While human activity has greatly contributed to the release of mercury, some release occurs naturally from soil containing mercury and from volcanic activity.

The toxic effects of mercury vapor have been well documented and even recorded in the literature as the "Mad Hatter" in Lewis Carroll's *Alice in Wonderland*. Mercury was used to cure the felt used in hats, and workers developed the characteristic signs of mercury vapor toxicity. Acute exposure to high concentrations of mercury vapor causes respiratory distress that can be fatal. The symptoms of chronic exposure to mercury vapor include personality changes such as excitability, depression, memory loss, fine motor tremors that can become progressively worse, gingivitis, and hallucination. There is some mercury inhalation exposure from dental amalgams but for most people there are no health-related effects. Metallic mercury is very poorly absorbed from the intestine, thus it is less hazardous to swallow the mercury from a thermometer than to inhale it (see chapter 9).

Organic Mercury (Primarily Hg-CH_3)

There are several different types of organic mercury, but by far the most important in terms of health effects is methyl mercury. When atmospheric mercury is deposited on the ground or in water it is converted to methyl mercury by bacteria. Mercury compounds are very toxic and converting the inorganic mercury to methyl mercury is the bacteria's way to reduce the toxicity of the mercury. Small animals then consume the bacteria along with the methyl mercury, and bigger animals in turn consume the smaller animals, thus increasing the concentrations of methyl mercury. Methyl mercury accumulates in the larger carnivorous animals, most important of which are fish such as tuna, pike, and shark. Mercury accumulates in the muscle of the fish, which makes it all but impossible to avoid consumption of the methyl mercury. Methyl mercury is readily absorbed from the intestine, and it crosses the blood-brain barrier and the placenta.

The devastating health effects were first documented in Minamata, Japan in the late 1950s, chiefly among fishermen and their families. A subsequent mercury-poisoning incident took place in Iraq when people consumed seed grain coated with organic mercury fungicides. Both of these incidents, as well as others, affected thousands of people and clearly demonstrated the most significant adverse developmental effects of mercury exposure. Early-stage effects include tingling and numbness around the mouth and lips and may extend to the fingers and toes. Continued exposure can result in difficulty walking, fatigue, inability to concentrate, loss of vision, tremors, and

eventually death. The developing fetus and young children are particularly sensitive to the effects of methyl mercury exposure. The serious health effects of mercury and its widespread distribution have resulted in numerous health advisories and restrictions on fish consumption. Typically, children and women of childbearing age are advised to limit their consumption of species of fish known to accumulate mercury. The US Food and Drug Administration limits the amount of mercury in canned tuna to 1 ppm (see chapter 9).

Nickel (Ni)

Nickel is widely used as a metal alloy component in stainless steel, where it increases hardness and corrosion resistance. Nickel is also used in nickel-metal hydride batteries found in some electronics and electric vehicles. It is generally present in the environment and appears to be an essential element for some plant life and bacteria. It is available in low concentrations in the food supply. The most serious workplace exposure is from inhalation. Exposure to the general population is from jewelry, cooking utensils, and other metals containing nickel.

For the general population the primary health concern is an allergic response from skin contact. In the workplace, inhalation of nickel compounds can cause respiratory tract cancer, particularly lung and nasal cancers. Nickel is one of the few proven human carcinogens. Contact dermatitis is also a common workplace hazard.

Tin (Sn)

Tin is anther ancient metal that continues to have a variety of uses. The inorganic form is used in food packaging, solder, brass, and in alloys with other metals. The organic forms of tin, triethyltin and trimethyltin are used as fungicides, bactericides, and antifouling agents for boats.

Inorganic tin is poorly absorbed by the intestine and toxicity is rare. Prolonged inhalation of tin dust can cause lung disease. Organic tins are readily absorbed by the intestine and are far more toxic. Exposure to organic tins can cause swelling of the brain and cell death in the nervous system.

Medically Important Metals

Introduction

The medical use of metals has declined with the advent of more-targeted drug therapies, but historically metals were used to treat a wide range of human diseases from diarrhea to syphilis to malaria. Currently, they are used to treat a limited number of diseases such as ovarian cancer and arthritis, but even these uses are in decline. The exception to this is fluorine, which, while technically a halogen, is covered in this section because of its widespread use in municipal water supplies to reduce dental caries. The therapeutic use of metals is generally limited by their toxicity. Metals illustrate well the need to balance the benefits of treatment with toxic side effects.

Table 11.3 Summary of Medically Important Metals

Metal	Function	Source	Toxicity (when in excess)
Bismuth (Bi)	Antacid (ulcers)	Medical, consumer products	Kidney damage
Fluoride (F)	Strengthens tooth enamel	Naturally occurring, added to drinking water	Mottled tooth enamel, increased bone density
Gallium (Ga)	Soft tissue visualization in x-rays	Mining, medical injection	Kidney damage
Gold (Au)	Treat rheumatoid arthritis	Mining, medical	Dermatitis, kidney damage
Lithium (Li)	Treat psychiatric disorders	Food supply	Tremor, seizures, cardiovascular effects, nausea
Platinum (Pt)	Anti-cancer agent (cisplatin), catalytic converters	Anti-cancer drug, mining	Kidney, hearing, nervous system effects

Bismuth (Bi)

Bismuth, discovered in 1753, has a long history of medical uses including treatment of diseases ranging from syphilis to malaria to diarrhea. More recently, the antibacterial properties of bismuth-containing antacids have been used to treat peptic ulcers. In general the medical use of bismuth has declined with the advent of new drug therapies.

Acute toxicity of high-level exposure to bismuth is kidney damage. Chronic low-level exposure to bismuth can result in weakness, joint pain, fever, mental confusion, and difficulty walking. Symptoms usually resolve when exposure is stopped but ongoing exposure can lead to death.

Fluoride (F)

Fluoride is widely distributed in soils and is present naturally in drinking water. Fluoride is the salt, such as sodium fluoride, of the element fluorine. It is readily absorbed by the intestine and incorporates into bone or tooth enamel. Fluoride is

commonly added to municipal drinking water across the United States based on strong data that it reduces dental decay. The current recommended level of fluoride in drinking water is 1 ppm. This practice is supported by the US Centers for Disease Control (CDC). In addition to drinking water, fluoride is also present in a range of consumer products, often at much higher levels, including toothpaste (1,000-1,500 parts per million or ppm), mouthwashes, and fluoride supplements. It also occurs in foods prepared with fluoridated water. The majority of the beneficial effects of dental fluoride are related to its topical application rather from ingestion.

Excess exposure to fluoride results in stained or mottled teeth, referred to as dental fluorosis. This is common in areas where fluoride water levels are above 4 ppm. Chronic elevated fluoride exposure can also result in increased bone density. Unresolved is what level of fluoride exposure results in harmful health effects to children. Children's small size means that per pound of body weight, they receive a greater dose of fluoride than adults. The CDC estimates that up to 33% of children may have dental fluorosis because of the excessive intake of fluoride either through drinking water or through other fluoride-containing products. This concern resulted in the CDC recommendation to limit fluoride exposure in children under eight years of age and to use fluoride-free water when preparing infant milk formula.

The EPA has a maximum contaminant level goal for fluoride in drinking water of four ppm. In 2006, the National Research Council of the National Academies issued a report that examined the appropriateness of EPA's 4 ppm maximum contaminant level goal for fluoride in drinking water in light of new evidence of the hazards of low level fluoride exposure. The NRC was not directed to conduct a risk assessment of the effects of low-level fluoride exposure nor to analyze other sources of exposure to fluoride. Referring to human and animal studies related to neurobehavioral effects, the NAS reports states "the consistency of the results appears significant enough to warrant additional research on the effects of fluoride on intelligence." The NRC suggested that 2 ppm might be a more appropriate maximum contaminant level. The primary question remains whether exposures to fluoride via multiple routes may result in a high enough cumulative exposure to contribute to developmental effects.

Gallium (Ga)

Gallium, like mercury, is a liquid at room temperature but unlike mercury is much less hazardous. Its most interesting use is that when ingested, it becomes a visualization tool for soft tissues and bone lesions while taking x-rays. Industrial applications include use in high-temperature thermometers, in metal alloys, and as a substitute for mercury in arc lamps.

Gallium's low toxicity and liquid state at room temperature make it an excellent diagnostic tool. Gallium has a half-life in the body of 4 to 5 days. Higher levels of exposure can cause kidney damage as well as nausea, vomiting, and anemia.

Gold (Au)

Gold's aesthetic and electrical properties make it highly desirable and widely used in a number of industrial applications. Medically, gold and gold complexes are used to treat rheumatoid arthritis, but due to its toxicity this use is declining as better treatments

become available. Gold has a long half-life in the body.

As with many metals, gold can damage the kidney. Lesions of the mouth and skin are seen following gold therapy to treat arthritis.

Lithium (Li)

Lithium was first used to treat manic-depressive illness in 1949 but was not used in the United States until 1970 due to concerns about its toxicity. When used as a therapeutic agent, lithium blood levels must be kept within a very narrow range (i.e. a narrow therapeutic index). Lithium appears to be nonessential but is readily absorbed by the intestine and is found in plants and meat. Normal daily intake is about 2 mg. Lithium is used in some manufacturing processes, as a lubricant, as an alloy, and most recently in batteries.

Outside its therapeutic range, lithium has a wide range of undesirable effects. Nervous system related effects include tremor, difficulty walking, seizures, slurred speech, and mental confusion. In addition there can be cardiovascular effects, nausea, vomiting, and kidney damage.

Platinum (Pt)

Platinum is a relatively rare earth metal usually found with related metals osmium and iridium. While it has a number of industrial applications, its common consumer application is in catalytic converters. This application has actually increased platinum concentrations in roadside dust. The ability of platinum and its derivatives to kill cells or inhibit cell division was discovered in 1965. Platinum-based drugs, such as cisplatin, are used to treat ovarian and testicular cancer, cancers of the head and neck, as well as other cancers. Unfortunately, the toxic side effects of these agents often limit their usefulness.

In the industrial setting, platinum is relatively harmless but a few people may be susceptible to developing an allergic skin response (contact dermatitis) and possibly a respiratory response. When used as anti-cancer agent it is typically administered intravenously. It kills cells or inhibits cell division by interfering with DNA synthesis. The most common toxic side effect is kidney damage, but hearing loss, muscular weakness, and peripheral nerve damage are also possible. Platinum is a good example of the benefits and hazards of using a highly toxic drug to treat the uncontrolled cell division of cancer.

Chelating Agents

The most obvious way to treat poisoning from excessive metal exposure is to remove the metal from the body, thus chelating agents were developed. While treatment may be necessary, it is far more desirable to prevent exposure. In fact, the best treatment for low-level exposure is often to identify the source of exposure and eliminate contact with the metal. An excellent example of this principle is lead, where the most important action is to reduce or eliminate exposure.

While the word chelate comes from the Greek word for "claw," the development of

chelating agents is not that old. The first chelating agent, BAL (British Anti Lewisite), was developed during World War II as a potential treatment for arsenic-based war gases. The ideal chelating agent would readily bind only with the target metal, forming a non-toxic complex that would be easily excreted from the body. Unfortunately, this is easier said than done. BAL, for example, binds with a range of metals but actually enhances the toxicity of cadmium.

A consistent undesirable property of all chelating agents is that they also combine with essential metals and increase their excretion from the body. The two most common essential metals adversely affected by chelating agents are calcium and zinc. Excessive lead exposure can be treated with the chelating agent calcium-EDTA and not with its related sodium salt, which greatly increases excretion of calcium, potentially having toxic side effects. Blood lead levels are reduced when the lead displaces the calcium to bind with EDTA; the complex is then excreted in the urine. This results in a movement of lead from the soft tissues such as muscle into the blood, which can result in a spike in blood lead levels that may elevate brain lead levels and cause subsequent neurological effects. The lead stored in bone is not affected and will remain until some event mobilizes calcium distribution from the bone. A recent study showed that lead chelation dropped blood lead levels, but did not protect against cognitive deficits.

In summary, while chelating agents can be an effective treatment in some circumstances, they must be approached cautiously. The most important action is to identify the source of exposure and reduce or eliminate it. It is also very important to consider what essential metals may be bound and excreted by the agent. The body tightly regulates most essential metals, and disruption of these levels can have serious undesirable (toxic) effects.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Metals presentation material and references. Website contains presentation material related to the health effects of metals.

European, Asian, and International Agencies

• UK Department of Health (DOH). Pregnancy and Early Years. The Department of Health provides information on nutritional requirements for children and mothers. [accessed April 9, 2009]
• World Health Organization (WHO). Nutrition. WHO information on nutrition. [accessed April 10, 2009]

North American Agencies

• Health Canada. Food and Nutrition. Health Canada provides information on nutritional issues. [accessed April 9, 2009]
• US Agency for Toxic Substance Disease Registry (ATSDR). See fact sheets and case studies in many metals and other agents. [accessed April 10, 2009]

Non-Government Organizations

• Dartmouth Toxic Metals Research Program. The site has general information on toxic metals. [accessed April 10, 2009]

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A Small Dose of Solvents

or

An Introduction to the Health Effects of Solvents

Solvents: Quick Facts
Uses: varied: recreational (alcohol) to industrial (gasoline, degreasers)
Source: synthetic chemistry, petroleum products; plant oils
Recommended daily intake: none (not essential)
Absorption: intestine, inhalation (major), skin
Sensitive individuals: fetus, children
Toxicity/symptoms: nervous system, reproductive system, and death
General facts: long history of use (alcohol), high volatility of solvent results in inhalation exposure of vapors
Environmental concerns: volatile organic compounds react with sunlight to produce smog; solvents may contaminate groundwater
Recommendations: avoid, use proper workplace protection

Introduction and History

Solvents are a broad class of compounds that we are commonly exposed to when we pump gas at the gas station, change the car oil, paint the house, glue something back together, drink alcohol, or use anesthetic when we undergo surgery. Solvents are highly volatile in air and are readily absorbed by the lungs when the vapors are

inhaled. The small molecular weight of most solvents and their high fat solubility means they are easily absorbed across the skin. Occupational exposure to solvents is common, with an estimated 10 million workers in the United States exposed either though inhalation or skin contact. Acute exposure can result in loss of coordination, reduced speed of response, and a general feeling of drunkenness. Long-term exposure can result in decreased learning and memory, reduced ability to concentrate, changes in personality, and even structural changes in the nervous system.

Some people find the effects of solvents on the nervous system desirable and purposely inhale (sniff) solvents to induce a form of intoxication. In the United States approximately 15% of high school students have tried solvent inhalation at least once. Solvents available for inhalation and abuse are common in the home. Home products that may contain solvents include paints, paint remover, varnishes, adhesives, glues, degreasing and cleaning agents, dyes, marker pens, printer inks, floor and shoe polishes, waxes, pesticides, drugs, cosmetics, and fuels, just to name a few.

In general there are few benefits to solvent exposure and it should be avoided. The one important exception is the use of solvents to induce unconsciousness prior to surgery. As mentioned above, the solvent ether was discovered centuries ago but not used in surgery until the 1840s. Some physicians and dentists first became aware of the effects of ether during "ether frolics" while attending school. Nitrous oxide was also experimented with around the same time but was not widely adopted by dentists and surgeons until the 1860s. Despite its liver toxicity, chloroform was also used as an anesthetic particularly in England and Scotland starting in the late 1840s. Anesthetic agents changed little until the accidental discovery of cyclopropane in 1929. With the increased use of electronic equipment in the surgery area, the flammability of the anesthetic agents became an important issue. In 1956, halothane was discovered by researchers in England, ushering in a new era in anesthesiology.

The use of solvents greatly expanded with the Industrial Revolution, which resulted in solvents' widespread release into the environment. Solvents such as volatile organic compounds (VOCs) readily evaporate into air, for example, when oil-based paint dries. Industrial release also occurs during manufacture or spills.

Solvent contamination of drinking water is not uncommon and is a public health issue. VOCs that enter groundwater become trapped until released during use. Human exposure occurs from drinking contaminated water or from bathing. Solvents such as benzene and trichloroethylene are commonly found at hazardous waste sites and may endanger nearby groundwater.

Biological Properties

From a biological perspective the most important properties of solvents are their volatility, high fat solubility (lipophilicity), and small molecule size. Solvents with these characteristics are termed volatile organic compounds (VOCs). Under normal working conditions solvents readily evaporate into the air, from where they enter the lungs. The high lipid solubility and small molecule size means they are quickly absorbed across lung membranes and enter the blood supply. Blood from the lung moves directly to the brain and other body organs before reaching the liver, where metabolism of the solvent occurs. With ongoing exposure, equilibrium is reached between the amount in the body and the concentration of the solvent in the air.

Solvents are also well absorbed following oral or skin exposure. Most solvents are quickly absorbed from the gut, although the presence of food may delay absorption. Alcohol is a good example of a solvent typically consumed orally. The skin offers little barrier to solvents. Skin exposure to solvents can result in local irritation and increased blood levels of the solvent.

Solvents are eliminated from the body by metabolism or exhalation. The more volatile and fat-soluble the solvent, the greater its concentration in exhaled air. Exhaled air can be used to estimate solvent concentrations in the blood, as in breath analysis for alcohol exposure. Metabolism of solvents occurs primarily in the liver by P450 enzymes. In most cases the metabolism results in reduced toxicity and increased elimination of the resulting products. For example, the toxicity of toluene is reduced when liver enzymes change the compound so that it does not readily cross cell membranes. However, the toxicity of benzene is increased when it is changed to a compound that can attack the blood-forming cells of the bone marrow, causing leukemia.

There is considerable variability in people's ability to metabolize solvents. Subtle genetic differences can increase or decrease an individual's ability to metabolize certain solvents, resulting in increased or decreased toxicity. The liver is also prone to damage by some solvents, such as carbon tetrachloride (CCl_4). This damage can actually be made worse by prior exposure to alcohol.

Products that are mostly solvent:

- Gasoline
- Diesel fuel
- Charcoal lighter fluid
- Lantern fuel

- Lubricating oils
- Degreasing agents
- Paint strippers
- Paint thinner
- Turpentine
- Nail polish remover
- Rubbing alcohol

Products that are partially solvent based:

- Glues
- Adhesives
- Oil-based paints
- Furniture polishes
- Floor polishes and waxes
- Spot removers
- Metal and wood cleaners
- Correction fluid
- Computer disk cleaner
- Varnishes and shellacs
- Wood and concrete stains

Case Studies

Anesthetics

• • •

"I also attended on two occasions the operating theatre in the hospital at Edinburgh, and saw two very bad operations, one on a child, but I rushed away before they were completed. Nor did I ever attend again, for hardly any inducement would have been strong enough to make me do so; this being long before the blessed days of chloroform. The two cases fairly haunted me for many a long year."

- Charles Darwin, Autobiography (1993)

• • •

An effective anesthetic agent must be easy to use, quickly render the patient unconscious, and not produce any toxicity. Dr. William T.G. Morton first publicly

demonstrated the use of ether as an effective anesthetic agent at the Massachusetts General Hospital on October 16, 1846 before a crowd of skeptical physicians. Ether $(CH_3CH_2)_2O$ was first discovered in 1275 by Raymundus Lullius, a Spanish chemist. Its hypnotic effects were soon appreciated (and enjoyed by some), but for many decades ether was only used occasionally to treat medical ailments. The success of surgical procedures did not improve until the introduction of antiseptic procedure and infection control some 20 years later. Ether was replaced by cyclopropane in 1929, which in turn was replaced by halothane in 1956. While anesthetic agents are desirable for the patient, exposure to hospital staff is highly undesirable and an important occupational consideration.

n-Hexane

n-Hexane is a simple and common hydrocarbon found in solvents, degreasing agents, glues, spray paints, gasoline, silicones, and other common substances. A common workplace exposure to n-hexane is from degreasing agents, which usually contain a mixture of solvents. In 1997 a 24-year-old male automotive technician went to his doctor complaining of numbness and tingling of the toes and fingers. Further neurological evaluation revealed reduced sensation in the forearms and diminished reflexes. For the previous 22 months this worker had used, on a daily basis, aerosol cans of brake cleaner that contained 50-60% hexane (composed of 20%-80% n-hexane), 20-30% toluene, and 1-10% methyl ethyl ketone. He used this degreasing agent to clean brakes, small tools, and even car engines, commonly using latex gloves while at work. His condition improved when exposure to the cleaning agent was stopped. 2,5-hexanedione, a urinary metabolite of n-hexane that is thought to be the toxic agent responsible for the nervous system effects, can be measured and used to estimate exposure to n-hexane. A subsequent study found that automotive technicians were indeed exposed to n-hexane. Degreasing products typically contain a mixture of solvents that are readily absorbed when inhaled or allowed to pass through the skin. The latex gloves used by this worker offered little protection. More information on this case study can be found at MMWR (2001).

Health Effects

The majority of us are exposed to low levels of solvents every day. Millions of workers around the world are exposed on a daily basis to high levels of solvents that can adversely affect health. Workers often come in contact with more than one solvent during a day's work. Health hazards from solvent exposure range from mild to life-threatening depending on the compound involved and the level and duration of exposure. It should also not be forgotten that many solvents are highly flammable.

Acute effects often involve the central nervous system because of the rapid absorption of the solvent from the lungs and direct distribution to the brain. The immediate effects may result in drowsiness or mild impairment of judgment. In most situations these effects are not serious and will end quickly once exposure stops. In some

circumstances a slight lapse of judgment could be disastrous. A person responding to a hazardous materials spill or perhaps a fire must take appropriate precautions to limit exposure to any solvents that could impair her or his judgment and thus increase risk of injury.

Chronic exposure to solvents can result in a range of organ-system effects. Damage to the peripheral nervous system results in a tingling sensation and loss of feeling in the hands and feet, increased reaction time, and decreased coordination. Reproductive effects included decreased and damaged sperm, which causes a loss in fertility. Liver and kidney damage is possible from a range of solvents. Cancer is also caused by a number of different solvents, such as benzene and carbon tetrachloride.

There is no doubt that repeated exposure to high levels of solvent can result in permanent damage to the nervous system. These changes may result in impaired learning and memory, decreased attention spans, and other psychological effects. There is also considerable data indicating that chronic low-level exposure to solvents can result in a cluster of symptoms variously referred to as painter's syndrome, organic solvent syndrome, or chronic solvent encephalopathy. The painter's syndrome was first described in Scandinavia in the late 1970s and became a recognized occupational disease in these countries. The cluster of symptoms includes headache, fatigue, sleep disorders, personality changes, and emotional instability, which progress to impaired intellectual function and ultimately, dementia. Early symptoms are often reversible if exposure is stopped.

Health Effects of Solvents

Table 12.1 Health Effects of Solvents

Reproductive hazard	methoxyethanol, 2-ethoxyethanol, methyl chloride
Developmental hazard	alcohol (Ethyl Alcohol)
Liver or kidney damage	Toluene, carbon tetrachloride, 1,1,2-2-tetrachloroethane, Chloroform
Nervous system damage	n-hexane, perchloroethylene, n-butyl mercaptan
Carcinogenic	carbon tetrachloride, Trichloroethylene, 1,1,2,2-tetrachloroethane,

	perchloroethylene, Methylene Chloride, Benzene
Visual system hazard	methanol

The easy availability of solvents in commercial and household products, combined with the rapid onset of nervous systems effects, encourages the use of solvents as an intoxicating drug. The recreational inhalation of solvents can produce euphoria, visual and auditory hallucinations, and sedation. As mentioned above, repeated exposure to high levels of solvents results in permanent brain damage. Children who accidentally drink furniture polish or other solvent-based household products are vulnerable to nervous system effects and possibly pneumonitis.

Reducing Exposure

From a health perspective there are few redeeming features of solvents except for their use as anesthetics. Clearly the simple recommendation is to avoid exposure unless administered for some medical reason. In the workplace, appropriate ventilation and personal safety equipment should be in place at all times. There are numerous national and international regulations on solvent exposure in the workplace. Substitution of less-toxic solvents in processes and products can reduce the risk of injury.

Regulatory Standards

In workplaces, standards and exposure recommendation are complex because they must address both level and duration of exposure. Below are some of the common terms used in establishing exposure recommendations.

STEL - Short term exposure limits (15 minute exposure): protects against loss of consciousness or loss of performance, allows short-term exposure in emergency situations

TLV - Threshold Limit Value

TWA - Time Weighted Average (acceptable for 8-hr day, 40-hr week)

TLV-C - Threshold Limit Value-C (ceiling not to be exceeded)

Recommendation and Conclusions

Solvents are common around the home and workplace. As with most toxic substances, the best policy is to substitute less-toxic products whenever possible, and to reduce exposure through ventilation or protective equipment when substitutes are not available. Inhalation of solvents is particularly dangerous because of the rapid exchange in the lungs and quick access to the nervous system. Solvent inhalation produces predictable short-term effects but the long effects of repeated solvent exposure are not well characterized.

Additional Resources

Slide Presentation and Online Material

- A Small Dose of Solvents presentation material and references. Website contains presentation material related to the health effects of solvents.

European, Asian, and International Agencies

- United Nations. Office on Drugs Control and Crime (UNODC). [accessed April 16, 2009]

North American Agencies

- US Department of Labor Occupational Safety & Health Administration (OSHA). Safety and Health Topics: Solvents. This site has extensive information on solvents in the workplace. [accessed April 16, 2009]
- US Agency for Toxic Substance Disease Registry (ATSDR). Hazardous Substance Fact Sheets. Site contains fact sheets and case studies on many common solvents. [accessed April 16, 2009]
- US National Institute on Drug Abuse (NIDA). Drugs of Abuse Information. Site contains information on inhalants and solvents as drugs of abuse. [accessed April 16, 2009]
- US Environmental Protection Agency (EPA). Ozone Layer Depletion - Alternatives / SNAP. Site has comprehensive information on alternatives to ozone and other solvents for products and processes. [accessed April 16, 2009]
- US National Library of Medicine. Tox Town: Solvents. Addresses various areas where solvents can be found including city, farm, and workplace. [accessed April 16, 2009]
- US National Institute for Occupational Safety and Health (NIOSH). Organic Solvents. Excellent information on a wide range of solvents. [accessed April 16, 2009]

Non-Government Organizations

- Anesthesia Nursing & Medicine. Site has in-depth information on the history and current practice of anesthesia. [accessed April 16, 2009]
- The Wood Library-Museum of Anesthesiology. The objective of the Wood Library-Museum of Anesthesiology is to collect and preserve literature and equipment pertaining to anesthesiology and to make available to the anesthesiology community, others in the medical profession and the public the most comprehensive educational, scientific and archival resources in anesthesiology. [accessed April 16, 2009]

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A Small Dose of Radiation

or

An Introduction to the Health Effects of Radiation

Nonionizing Radiation: Quick Facts
Description: lower-energy radiation found in UV and visible light, emitted by various devices, used in communications technology
Uses: power transmission, TV, radio, & satellite transmissions, radar, light bulbs, heating, cooking, microwave ovens, lasers, photosynthesis (sunlight), mobile phones, WiFi networks, and more (see chapter text)
Source: Ultraviolet light, visible light, infrared radiation, microwaves, radio & TV, mobile phones, power transmission
Recommended daily intake: different depending on source, i.e. sunlight can damage skin
Absorption: depends on source
Sensitive individuals: variable, e.g. fair-skinned children (sunburn)
Toxicity/symptoms: Depends on source. Solar radiation: sunburn, cataracts, cancer; microwave radiation: warming of skin or internal organs; controversy exists around exposure to low frequency energy such as AC power lines
Regulatory facts: government regulates exposure: FDA and FCC set a Specific Absorption Rate limit of 1.6 W/kg for mobile phones
General facts: long history of use

Environmental concerns: our dependency on energy results in a range of consequences; for example, burning coal to generate electricity releases mercury into the atmosphere

Recommendations: depending on individual sensitivity, limit exposure to solar radiation (ultraviolet radiation); reduce

Ionizing Radiation: Quick Facts
Description: higher-energy radiation, with enough energy to remove an electron from an atom and damage biological material
Uses: nuclear power, medical x-rays, medical diagnostics, scientific research, cancer treatment, cathode ray tube displays
Source: radon, x-rays, radioactive material producing alpha, beta, and gamma radiation, cosmic rays from the sun and space
Recommended daily intake: none (not essential)
Absorption: interaction with atoms of tissue
Sensitive individuals: children, developing organisms
Toxicity/symptoms: damages DNA, leading to cancer
Regulatory facts: heavily regulated
General facts: long history of exposure to low levels
Environmental concerns: many nuclear cleanup sites contain radioactive waste that must be moved off site to prevent possible leakage
Recommendations: limit exposure, monitor workplace exposure where applicable

Introduction and History

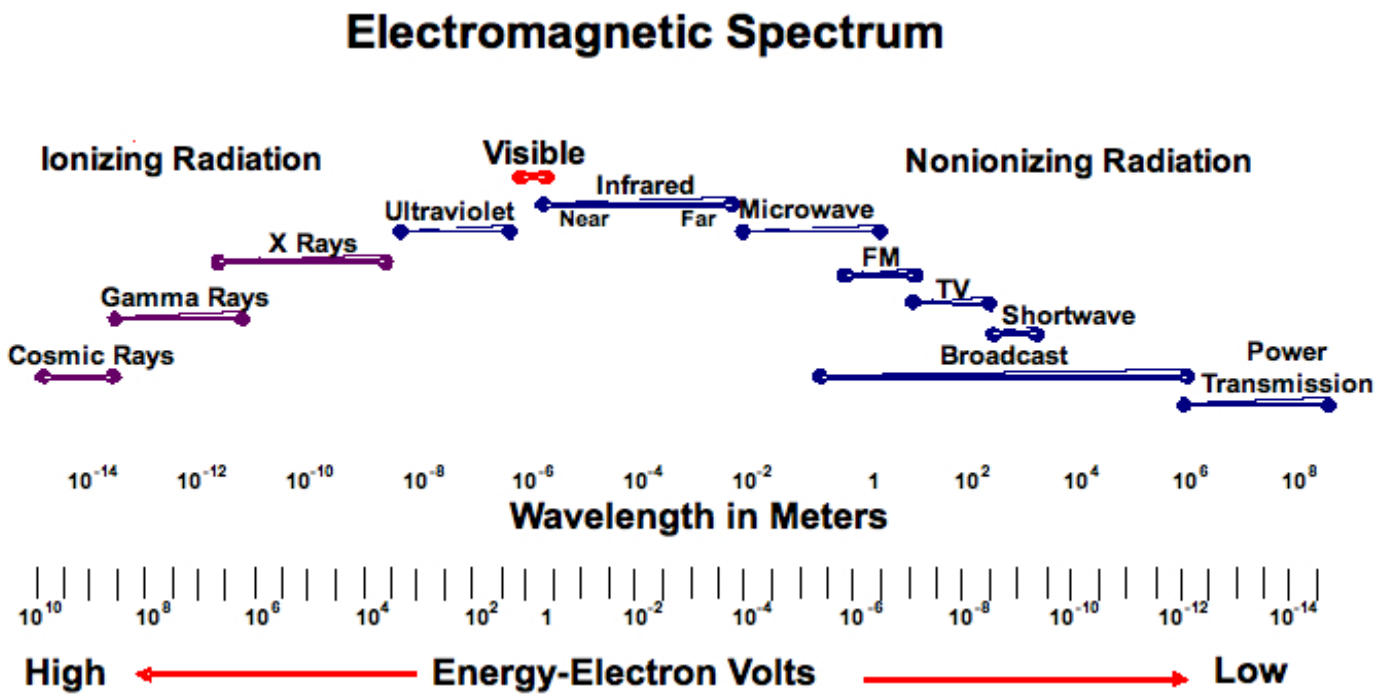
All life is dependent on small doses of electromagnetic radiation. Plants depend on small doses of radiation, living by converting this energy through photosynthesis to sustain them and in turn provide food for many of the earth's animals. We are surrounded by and depend on radiation-emitting devices, from the sun to our cell phones and radios, from medical x-rays to the electricity that powers our homes. Radiation-emitting devices have many benefits, but we are still learning about some of the health effects. To effectively explore the health effects of radiation exposure, it is first necessary to examine the physics of radiation.

The electromagnetic spectrum is roughly divided into ionizing and nonionizing radiation (Figure 13.1). The distinction depends on the amount of energy carried by the radiation, which is directly related to the vibration frequency of the electric and magnetic fields. When the frequency (and hence energy) is high enough, the radiation can separate electrons from atoms, ionizing the material it passes through. Nonionizing radiation includes ultraviolet, visible, infrared, radio and TV, and power transmission. We depend on the sun's radiation for photosynthesis and heat. Ionizing radiation includes high-energy radiation such as cosmic rays, x-rays, or gamma rays generated by nuclear decay. Ionizing radiation also includes several types of sub-atomic particles such as beta radiation (high energy electrons) and alpha radiation (helium ions). Medical x-rays are an example of a common beneficial exposure to ionizing radiation. Nuclear radiation is used to generate electricity and cure disease, but is also an important element in military weapons. Uses of nuclear radiation pose serious problems of human exposure and environmental contamination.

The understanding and subsequent use of various forms of radiation provide a fascinating window into human civilization. The cave dwellers were probably the first to manage radiation when they learned to control and use fire. The control and use of electricity was another huge step forward. But the turn of the 20th century really marked the beginning of rapid progress in the understanding and harnessing of the power of radiation. This period also ushered in a growing understanding of the potential adverse effects of radiation exposure. In 1903, Marie Curie and Pierre Curie, along with Henri Becquerel, were awarded the Nobel Prize in physics for their contributions to understanding radioactivity, including the properties of uranium. To this day, the "curie" and the "becquerel" are used as units of measure in radiation studies. In 1895, Wilhem Conrad Roentgen discovered x-rays, and in 1901 he was awarded the first nobel prize for physics. These discoveries led to significant advances in medicine.

Work by Enrico Fermi and others lead to the first sustained nuclear chain reaction in a laboratory beneath the University of Chicago football stadium on December 2, 1942. Subsequently, this knowledge was used to develop the atomic bombs that were dropped on Japan in an effort to end World War II. Much of our understanding of the effects of nuclear radiation exposure has come from the victims in Japan as well as the many workers in uranium mines.

Figure 13.1 Electromagnetic Spectrum



Case Studies

Radium Girls

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> "Not to worry," their bosses told them. "If you swallow any radium, it'll make your cheeks rosy." The women at Radium Dial sometimes painted their teeth and faces and then turned off the lights for a laugh.
>
> - From: 'Radium Girls' By Martha Irvine, Associated Press, *Buffalo News*, 1998

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Marie Curie discovered radium in her laboratory in Paris in 1898. The unique properties of this naturally occurring radioactive element suggested to many that it had therapeutic uses. In the early 1900s radium therapy was accepted by the American Medical Association: radium was thought to cure a range of illness including arthritis, stomach ailments, and cancer. Tonics of radium were available for oral consumption, to "bring the sun to your stomach," as well as by injection. In reality, the alpha particle emissions of radium caused rather than cured cancer.

This cancer-causing effect of radium was realized only after the tragic plight of young women working as radium-dial painters in watch factories came to the public's attention. The use of radium to illuminate watch dials began before World War I and continued during the 1920s. US Radium Corporation employed young women to paint radium on watch dials. The women used their lips to point the brushes: each time they pointed their brushes, they ingested a small amount of radium. The radium moved to the bone, where it continued to emit alpha radiation that damaged the cells near the radium particles. As a result of their exposure to radium, many of these women developed painfully debilitating bone decay and died of cancer. The long half-life of

radium combined with its sequestration in bone resulted in lifetime radiation exposure.

During the 1920s a group of these women sued Radium Corporation. Many of them were victorious in court and received a small amount of money, becoming the first to receive compensation for occupational injury. It is estimated that 4,000 people, mostly women, were occupationally exposed to radium as watch dial painters. This population formed the basis of several studies investigating the long-term effects of radiation. Their story was made into the movie "Radium City" (1987) and more recently, a play. There is also an excellent book entitled *Radium Girls: Women and Industrial Health Reform, 1910-1935* by Claudia Clark.

Solar Radiation: Sunlight from Warmth to Sunburn

Sunlight is essential for life but, as with most things, too much can be harmful. The World Health Organization estimates that 2 to 3 million non-malignant skin cancers and over 130,000 malignant melanomas occur globally each year. Ultraviolet (UV) radiation is the primary cause of skin cancer as well as many more acute cases of sunburn. Thinning of the atmospheric ozone layer, which filters much of the UV radiation, has increased the harmful effects of elevated UV exposure. UV exposure can increase the incidence of cataracts of the eye, reduce the effectiveness of the immune system, and accelerate the effects of aging. Skin damage is also common, particularly for fair skinned people exposed to too much UV radiation from the sun. Children need additional protection from the sun because their skin is more sensitive to the effects of UV radiation. Sunlight is necessary, however, because it stimulates the synthesis of Vitamin D, which is important in the metabolism of calcium.

Solar radiation is part of the electromagnetic spectrum of radiation. The wavelength of visible light is 400-760 nanometers (nm). Less than 400 nm is ultraviolet (UV) radiation and greater than 760 nm is infrared radiation, the heat of the sun. Our skin, the largest organ of the body, has naturally developed means to protect us from UV radiation. UV radiation stimulates the production of the pigment melanin, which absorbs UV radiation and protects skin cells from damage. People with darker-colored skin have ongoing production of melanin and are better protected from damage than people with lighter-colored skin, and there is considerable genetic variation in the production of melanin. Sunburn occurs when UV radiation damages a cell and the body responds by increasing blood flow, resulting in a reddish and hot presentation. UV radiation damages cellular DNA. Although the cells have built-in repair mechanisms, repeated DNA damage can result in skin cancer.

Chemicals in sunscreens work much like melanin to absorb UV radiation. The most common is para-aminobenzoic acid or PABA, but there are others. Most glass, but not clear plastic, will block UV radiation. Relatively simple measures, such as hats and clothing, will greatly reduce exposure. Snow reflects about 90% of UV radiation, making snow blindness a significant concern.

UV radiation illustrates the basic principles of toxicology in that individual sensitivity varies greatly and it is best to limit your dose (exposure) to control your response. The challenge is to understand and manage the risk and benefits of our individual exposure and the resulting acute and long-term effects.

Microwave Radiation, Communication, and Your Mobile Phone

Mobile phones or cell phones are now an almost essential device, with over 4 billion subscribers. The devices have become increasingly sophisticated: they are now powerful computers with wireless Internet access, global positioning, and many other features. From a toxicological perspective there are two primary concerns: 1) hazardous materials in the device that require proper disposal and 2) the potential health effects of the nonionizing radiation associated with data transmission. The billions of phones are now a major source of pollution from an array of hazardous materials such lead, mercury, cadmium, PBDEs, and other materials. While a minimal hazard to the user, these material are significant environmental contaminants and are hazardous to people if not properly recycled.

These devices use radio waves or microwaves to transmit and receive information (electromagnetic waves with wavelengths ranging from 1mm-1m, or frequencies between 0.3 GHz and 300 GHz). Nonionizing radiation is absorbed by the body and is standardized as the Specific Absorption Rate (SAR). In the United States, the Food and Drug Administration (FDA) and the Federal Communications Commission (FCC) share regulatory responsibilities related to mobile devices and set a SAR limit of 1.6 W/kg, averaged over a volume of 1 gram of tissue. In general, national and international governmental agencies do not believe that exposure to radiation from the use of mobile phones is related to any health effects. However, there is ongoing research on possible health effects, particularly those related to cancer. As a precaution, various devices can be used to keep the transmitter away from the head while using it for extended periods. There is also growing regulation regarding the use of mobile phones while operating a motor vehicle because the resulting distraction impairs concentration and reaction time.

Biological and Physical Properties

Nonionizing Radiation

Nonionizing radiation has less energy and is generally less interactive with biological material than ionizing radiation. We are surrounded by energy from devices and products that emit nonionizing radiation. For example, radio and TV transmissions surround us but do not significantly interact with our bodies. Light bulbs convert electrical energy into visible light and heat, all forms of nonionizing radiation.

However, a microwave oven is designed to interact with biological material to produce heat. The microwave energy readily passes through paper, glass, and plastic but is absorbed by water molecules in food, causing them to vibrate, which heats the food. The microwave oven generates enough energy to be potentially harmful without appropriate shielding; government regulations are in place to limit the amount of energy leakage permitted from a microwave oven. Note that the interaction of microwaves with human tissue is not through ionization but through heating.

We are exposed to a variety of different types of radiation around our homes. Appliances such as hair dryers emit electromagnetic radiation. Our TVs and computer monitors expose us to additional electromagnetic radiation, as do our cell phones and

radios.

Products that depend on nonionizing radiation:

- Mobile/cellular phones
- Mobile/cellular telephone base stations
- Radio towers
- Microwave towers
- Lasers (including laser pointers)
- Magnetic Resonance Imaging (MRI)
- Radio transmissions (AM or FM)
- TV transmissions
- Short-wave radio transmissions
- Satellite transmissions
- Electrical blankets
- Appliances
- Light bulbs
- Computer and TV monitors
- Microwave ovens
- Power lines (both large and small)
- Visible light
- Ultraviolet radiation
- Radar
- WiFi networks

Ionizing Radiation

Ionizing radiation has sufficient energy to produce ion pairs as it passes through matter, freeing electrons and leaving the rest of the atoms positively charged. In other words, there is enough energy to remove an electron from an atom. The energy released is also enough to break bonds in DNA, which can lead to significant cellular damage and cancer. The health effects and dose/response relationship for radiation exposure are well established from human exposures to radiation and from other research. The four main types of ionizing radiation are alpha particles, beta particles (electrons), gamma rays, and x-rays.

Alpha particles are heavyweight and relatively low-energy emissions from the nucleus of radioactive material. The transfer of energy occurs over a very short distance of about 10 cm in air. A piece of paper or layer of skin will stop an alpha particle. The primary hazard occurs in the case of internal exposure to an alpha-emitting material: cells close to the particle-emitting material will be damaged. Typical sites of accumulation include bone, kidney, liver, lung, and spleen. Radium is an alpha-particle emitter that accumulates in the bone following ingestion, causing a bone sarcoma.

Airplane travel increases our exposure to cosmic and solar radiation that is normally blocked by the atmosphere. Radiation intensity is greater across the poles and at higher altitudes, thus individual exposure varies depending on the route of travel. Storms on the sun can produce solar flares that release larger amounts of radiation than normal. For the occasional traveler this radiation exposure is well below recommended limits established by regulatory authorities. However, frequent fliers

and airline workers can be exposed to levels of radiation that exceed established guidelines.

Sources of ionizing radiation (and exposed populations):

- Medical x-ray devices (patients, medical workers)
- Radioactive material producing alpha, beta, and gamma radiation (laboratory workers, hospital workers, patients)
- Cosmic rays from the sun and space (airplane travelers)

Radiation Units

The units used to describe the exposure and dose of ionizing radiation to living material are confusing at best. First, the units have changed to an international system, SI, which stands for Systeme Internationale. We will use the SI system, but the table below compares the SI system with the older system.

The fundamental descriptive unit of ionizing radiation is the amount energy, expressed in Coulombs per kilogram of air, and is the unit of exposure in air. The absorbed dose is the amount of energy absorbed by a specific material such as the human body and is described as the Gray (Gy), previously the Rad. The energy transfer of the different particles and gamma rays is different. A weighting factor is used to allow comparison between these different energy transfers. The unit for the equivalent dose is the Sievert (Sv). A further possible refinement applies a weighting factor to each type of tissue. Recommended limits on radiation exposure are expressed in Sv (Table 13.1).

Table 13.1 Measures of Radiation Energy

Item	Previous Unit	SI Unit	Ratios
Activity (i.e. quantity rays or particles)	Curie (Ci)	Becquerel (Bq)	1 Ci = 3.7 x 10^{10} Bq 1 mCi = 37 MBq 1 μCi = 37 KBq
Exposure	Roentgen (R)	X (Coul/kg)	1 R= 2.58x10^{-4} Coul/kg
Absorbed Dose	Rad	Gray (Gy) Gy = 1 J/kg	1 Gy = 100 rad 1 rad = 10 mGy
Equivalent Dose	Rem	Sievert (Sv)	1 Sv = 100 Rem 1 rem = 10 mSv

m = milli = 1/1000
SI = international system of units (Systeme Internationale)

Health Effects

We are constantly exposed to ionizing and nonionizing radiation from natural occurring

sources as well as radiation generated and managed by our society. The challenge is to understand and manage the risks and benefits of our individual exposure.

Nonionizing Radiation

We are surrounded by nonionizing radiation, the majority of which does us no harm. The visible light from the sun, the in-house light bulbs, radio and TV transmissions, and electric appliances all contribute to our background exposure to nonionizing radiation. Most evidence indicates that this radiation is harmless, although some studies have found possible effects. However, at higher levels and longer durations of exposure, nonionizing radiation can be harmful.

The classic example is sunlight or solar radiation. Ultraviolet radiation from the sun, part of the electromagnetic spectrum with wavelengths less than 400 nm, can damage the skin. Sunburn (erythema) is the result of excessive exposure of our skin to UV radiation when we lack the protection of UV-absorbing melanin (see case study above). Acute cellular damage causes an inflammatory-type response and increased vascular circulation (vasodilation) close to the skin. The increased circulation cause the redness and hot feeling to the skin. Lightly pressing on the skin pushes the blood away and the spot appears white. Darker-skinned people have an ongoing production of melanin, which protects them to some extent from UV radiation. In lighter-skinned people, UV radiation stimulates the production of melanin, producing a tan and protection against UV radiation. Extreme exposure can result in blistering and severe skin damage. UV radiation can also damage cellular DNA, and repeated damage can overwhelm the DNA repair mechanism, resulting in skin cancer. Skin cancer accounts for approximately one-third of all cancers diagnosed each year. Thinning of the atmospheric ozone layer, which filters UV radiation, is suspected as being one cause of the increased incidence of skin cancer. Wearing protective clothing can reduce UV radiation exposure. Sunscreen locations contain chemicals that absorb the UV radiation, as does melanin. Solar radiation is a classic example of the principle of toxicology: beware of individual sensitivity and dose yourself in a way that limits any adverse response.

The use of microwave and radio-frequency (MW/RF) devices has grown dramatically in the past 20 years. The most popular consumer products are microwave ovens and cell or mobile phones. MW/RF radiation is also used in a wide range of commercial applications such as radar, solder machines, welders, heat sealers, drying equipment, and glue curing. In biological tissues microwave radiation produces heat: a warming sensation can be felt on the skin or even internal organs and body temperature can be raised.

Microwave ovens must comply with government standards to minimize exposure. Cell phones use low level radio-frequency energy that is well below a level that would warm tissue, but there is ongoing research on effects related to chronic exposure. In the United States, the Food and Drug Administration (FDA) is responsible for protecting the public from radiation from microwave ovens, television sets, computer monitors, and cell phones. The FDA and the Federal Communications Commission (FCC) share regulatory responsibilities related to mobile devices and set a SAR limit of 1.6 W/kg.

Ionizing Radiation

Ionizing radiation is more harmful than nonionizing radiation because it has enough energy to remove an electron from an atom and thus directly damage biological material. The energy is enough to damage DNA, which can result in cell death or cancer. The study of ionizing radiation is a large area of classical toxicology, which has produced a tremendous understanding of the dose/response relationship of exposure. The primary effect of ionizing radiation is cancer. It can also affect the developing fetus of mothers exposed during pregnancy. Radiation exposure has a direct dose/response relationship: the more radiation you receive, the greater your chance of developing cancer.

Our knowledge of the effects of radiation developed gradually from tragic experience over the last century. Early in the century, researchers such as Marie Curie died of cancer presumably related to her radiation exposure. At the time some writers even extolled the virtues of people dying to advance the cause of science. Occupational exposure was another tragic learning environment. Young women employed to paint radium on watch dials died from bone cancer in the 1920s and 1930s (see above case study). During this time radium was promoted as a cure of many maladies and even recognized by the American Medical Association. We had a lot to learn.

From uranium mineworkers we learned of the hazards of radon exposure. Radon is a radioactive gas that is present in uranium mines and can also be found in high concentration in soil in some places. Radon exposure results in lung and esophagus cancer. The actual carcinogens are daughter products of radon that adhere to the internal tissue and emit alpha particles. While excess cancer in mine workers is well established, there is considerable concern about the effects of lower-level chronic exposure that might be found in homes, particularly in the basement (see chapter on Cancer and Genetic Disease).

A great deal was learned from the atomic bomb survivors. The US military dropped the first atomic bomb on Hiroshima, Japan on August 6, 1945 and a second on Nagasaki, Japan, three days later. The bombs used two different types of radioactive material, ^{235}U in the first bomb and ^{239}Pu in the second. It is estimated that 64,000 people died from the initial blasts and radiation exposure. Approximately 100,000 survivors were enrolled in follow-up studies, which confirmed an increased incidence of cancer.

X-rays were also used to treat disease. From 1905 to 1960 x-rays were used to treat ringworm in children. Well into the 1950s x-rays were used to treat a degenerative bone disease called ankylosing spondylitis.

The primary lessoned learned in all these is that the greater the dose, the greater the likelihood of developing cancer. The second lesson was that there could be a very long delay in the onset of the cancer, from 10 to 40 years. It should be remembered that we evolved with a background exposure to naturally occurring ionizing radiation, and we continue be exposed to low levels of natural background radiation. Some have estimated that 1 in 100 cancers are the result of this background exposure.

Reducing Exposure

Three ways to reduce exposure to radiation are:

Time

Limit the amount of time you spend near the source of radiation. One of the easiest examples is that you avoid getting sunburned by limiting the amount of time in bright sunlight. This same principle applies to ionizing radiation, such as emitted by radioactive material.

Distance

Increase your distance from the source of radiation. Emissions from the source of radiation decrease in intensity rapidly.

Shielding

The effectiveness of shielding depends on the type of radiation and the shielding material itself, but in general placing absorbent shielding material between you and the radiation source reduces exposure. This can be as simple as wearing a hat to protect your face from the sun or using a lead apron in the dentist's chair to shield other parts of your body from the dental x-rays.

Regulatory Standards

The first organized effort to protect people from radiation exposure began in 1915 when the British Roentgen Society adopted a resolution to protect people from x-rays. In 1922 the United States adopted the British protection rules, and various government and nongovernmental groups were formed to protect people from radiation. In 1959, the Federal Radiation Council was formed to advise the president and recommend standards. In 1970 the US Environmental Protection Agency was formed and took over these responsibilities. Now several government agencies are responsible for protecting people from radiation-emitting devices.

Standards for Radiation Exposure

Recommended exposure limits are set by the US National Council on Radiation Protection (NCRP) and worldwide by the International Council on Radiation Protection (ICRP). The occupational exposure guidelines are 100 mSv in 5 years (average, 20 mSv per year) with a limit of 50 mSv in any single year. For the general public the standard is 1 mSv per year. This must be put in the context of natural background radiation, which is approximately 3 mSv/year depending upon location (such as elevation) as well as other variables.

Recommendation and Conclusions

We evolved in an environment containing natural radiation, from solar energy to radioactive elements. Radiation is described by the electromagnetic spectrum in terms of wavelength and frequency. A further division is made between ionizing and nonionizing radiation. Ionizing radiation has sufficient energy remove electrons, thus the ability to directly damage biological tissue. During the past century we have learned how to exploit the electromagnetic spectrum for many useful purposes (and some not so useful) and have also learned about some of the hazards of radiation

exposure.

Some radiation is helpful and necessary, as in the case of sunlight, which allows us to see. The nonionizing radiation of the sun warms us, but too much ultraviolet radiation can cause sunburn or cancer, depending on our individual sensitivity. There is clearly a dose/response relationship between exposure and effect, with individual sensitivity playing an important role. Microwave and radio-frequency radiation are incredibly useful in heating food and in transmitting information.

Ionizing radiation is far more dangerous than nonionizing radiation because it can directly damage cellular DNA and proteins, causing cell death or possibly cancer. Ionizing radiation occurs as alpha and beta particles, gamma rays, and x-rays. Each has its unique characteristics that require different safety approaches. In general, the more radiation exposure a person receives, the greater the likelihood of developing cancer. A precautionary approach that limits radiation exposure is best.

Additional Resources

Slide Presentation and Online Material

A Small Dose of Radiation presentation material and references. Website contains presentation material on the health effects of radiation.

European, Asian, and International Agencies

- Australian Radiation Protection and Nuclear Safety Agency (ARPANSA). ARPANSA is "charged with responsibility for protecting the health and safety of people, and the environment, from the harmful effects of ionizing and non-ionizing radiation". [accessed May 9, 2009]
- UK Health Protection Agency (HPA). Centre for Radiation, Chemical and Environmental Hazards. "CRCE provides advice, research and services to protect the public from hazards resulting from exposure to chemicals and poisons, radiation both ionising and non-ionising and ultrasound and infrasound." [accessed May 9, 2009]
- World Health Organization (WHO). Ultraviolet radiation. Site contains information on the global efforts to reduce UV (sunlight) radiation exposure. [accessed May 9, 2009]

North American Agencies

- Health Canada. Radiation Protection Bureau. Health Canada provides information on the health effects of radiation for consumer and clinical radiation protection. [accessed May 9, 2009]
- US Centers for Disease Control and Prevention (CDC). National Center for Environmental Health. This site contains information on health effects and emergency response to radiation exposure. [accessed May 9, 2009]
- US Environmental Protection Agency (EPA). Radiation Protection. This site has a tremendous amount of information on ionizing and nonionizing radiation and environmental contamination. [accessed May 9, 2009]
- US Environmental Protection Agency (EPA). Radiation Protection: Calculate Your Radiation Dose. This site shows you how to examine your current exposure to radiation. [accessed May 9, 2009]
- US Food and Drug Administration (FDA). Radiation-Emitting Products. This site

contains information on the health effects and regulation of radiation emitting devices and products. The mission of the radiological health program is to protect the public from hazardous or unnecessary radiation emissions from electronic products. [accessed May 9, 2009]
• US Food and Drug Administration (FDA). Cell Phones. Site contains general and regulatory information on cell phones and related technology. [accessed May 9, 2009]
• US Federal Communications Commission (FCC) Office of Engineering and Technology. Radio Frequency Safety. The FCC is required "to evaluate the effect of emissions from FCC-regulated transmitters on the quality of the human environment." [accessed May 9, 2009]
• US Department of Labor Occupational Safety & Health Administration. Radiofrequency and Microwave Radiation. The OSHA site contains information on microwave and radio-frequency devices. [accessed May 9, 2009]
• New Jersey Department of Environmental Protection. Radiation Protection & Release Prevention. New Jersey has an excellent site with a wide range of information on radiation. [accessed May 9, 2009]
• US Agency for Toxic Substance Disease Registry (ATSDR). See fact sheets and case studies in environmental health. [accessed May 9, 2009]
• National Oceanic and Atmospheric Administration (NOAA). Air Resources Laboratory. Site contains UV radiation monitoring information. [accessed May 9, 2009]
• US Nuclear Regulatory Commission (NRC). "The NRC regulates US commercial nuclear power plants and the civilian use of nuclear materials." [accessed May 9, 2009]

Non-Government Organizations

• National Council on Radiation Protection & Measurements (NCRP). "The NCRP seeks to formulate and widely disseminate information, guidance and recommendations on radiation protection and measurements which represent the consensus of leading scientific thinking." [accessed May 9, 2009]
• Health Physics Society. Site has extensive information about the health physics and radiation protection. [accessed May 9, 2009]
• University of Michigan. Radiation & Health Physics. Site contains information "written for three distinct groups: the general public, students and the health physics community at large." [accessed May 9, 2009]
• Washington Nuclear Museum and Educational Center (WANMEC). WANMEC provides information on the history of nuclear material use in the state of Washington. [accessed May 9, 2009]

References

Clark, Claudia. *Radium Girls: Women and Industrial Health Reform, 1910-1935*. New York: University of North Carolina: 1997.

A Small Dose of Persistent Environmental Contaminants

or

An Introduction to the Health Effects of Persistent Environmental Contaminants

Persistent Environmental Contaminants: Quick Facts
Terminology: has various names depending on agency, e.g. US EPA: Persistent Bioaccumulative and Toxic (PBT) or United Nations: Persistent Organic Pollutant (POP)
Uses: varies, often restricted or banned (but still present in the environment)
Source: industry, waste sites, food chain, and environment
Recommended daily intake: none (not essential)
Absorption: varies
Sensitive individuals: fetus, children, elderly, all species accumulate PBTs
Toxicity/symptoms: range of toxic effects: developmental, learning and memory, cancer, etc.
Regulatory facts: various local, national, and international agencies working to eliminate or greatly reduce
General facts: long history of use, bioaccumulates
Environmental concerns: global environmental contaminants

Recommendations: avoid, work towards phaseouts

Introduction and History

During the 1950s and 1960s there was an enormous increase in the use of chemicals in agriculture, industrial manufacturing, and around the home. We powdered our bodies with DDT to remove lice and spread DDT far and wide to control mosquitoes. We used other pesticides to kill insects and control weeds in an effort to improve crop yields. Lead was added to gasoline to make cars run better and added to house paint to make it last longer. At the same time we took advantage of the more sinister qualities of lead when we combined it with arsenic to spray on fruit trees to control pests. Pulp and paper mills used mercury to control fungi and molds to ensure that our paper remained white. Seeds were coated with mercury to stop soil fungi. Thermometers, thermostats, and switches brought mercury into everyone's home and school. Many will remember playing with a small silver ball of liquid mercury. Expansion of the electrical power system required chemicals that could withstand heat. For this purpose PCBs seemed to be the answer. All these chemicals appeared to be safe. A small dose did not seem harmful.

During the 1970s we began to appreciate that even a small dose can harm sensitive individuals. In *Silent Spring*, Rachel Carson sounded one of the first alarms about the effects of environmental contaminants. Evidence accumulated that a pesticide like DDT can cause very unexpected effects. The first and most obvious was the thinning of birds' eggshells, which caused a sharp decline in predator bird populations. Predatory birds are at the top of the food chain, where they accumulate and concentrate DDT. We then became aware of the potential of low-level exposures to persistent chemicals to cause diseases like cancer that appear only after many years. Humans, being at the top of the food chain, accumulate DDT in fat. Fat is mobilized during lactation, and mothers who breastfeed pass along the DDT to their infants, who receive a large dose because of their low weight. We also learned that mercury and lead cause developmental effects, harming the developing nervous system for a lifetime.

It turns out that most of these chemicals have similar characteristics that contribute to their toxicity to both humans and other species. First, the substances are environmentally persistent. Many of the early pesticides, and certainly the metals, do not break down in the environment, or do so only very slowly. If persistent chemicals are released continually to the environment, the levels tend to rise ever higher. Second, the early pesticides were toxic to many species, not just the target species, and often killed beneficial insects or plants. Third, many of these compounds bioaccumulate or concentrate in species as they move up the food chain. The chlorinated pesticides accumulate in the fat of animals, with animals higher in the food chain accumulating more and more of these pesticides. Most species cannot metabolize or break down the compounds: lead accumulates in bone and methylmercury in muscle. And finally, because of their persistence in the environment and accumulation in various species, the persistent toxicants spread around the world, even to places that never used them. Animals at the top of the food chain, such as

polar bears and beluga whales, routinely have fat PCB levels greater than 6 ppm even though these animals live far from where PCBs were used or produced.

To address the public and environmental health concerns caused by these and other compounds, government agencies have initiated various programs and regulations to control or restrict the use of the offending substances. Laws were passed to ensure more rigorous testing of compounds before widespread use, although this was not entirely effective. For example, the US Toxic Substances Control Act (TSCA) was passed in 1976 but has been largely ineffective for chemical management. The US Food Quality Protection Act (FQPA) of 1996 was more effective in implementing pesticide testing requirements. Researchers worked to develop new pesticides and other agents that were more specific in their toxicity and much less persistent. The use of many of the persistent chemical pesticides was restricted or even banned in some places. Individual countries are responsible for regulations, so there are some countries that still use pesticides that are banned elsewhere.

Lists of persistent chemical pollutants are created to help prioritize efforts to reduce exposure. There are many lists, and even lists of lists, that are often revised as new data become available. The United Nations Environment Programme (UNEP) created a list called Persistent Organic Pollutants (POPs) that focuses on "chemical substances that persist in the environment, bioaccumulate through the food web, and pose a risk of causing adverse effects to human health and the environment." The UNEP also created a list of Persistent Toxic Substances. The US EPA created a list of agents called Persistent Bioaccumulative and Toxic (PBT). Both lists included organic chemicals and metal.

Regional groups are also beginning to create lists of persistent chemical pollutants to emphasize and prioritize local issues. For example, Washington State Department of Ecology, in the United States, has created a list of Persistent, Bioaccumulative Toxins (PBTs), with 27 chemicals to be phased out in the state. It is instructive to look at the overlap of these lists. The table below compares the lists of persistent chemical pollutants from these agencies. Overall, there is considerable agreement on what chemicals are considered a priority. It is also obvious that pesticides are a major class of persistent chemicals, as are flame retardants.

Table 14.1 Classification of Persistent Chemicals

Chemical	EPA	WA State	UN (POPs)	UN (PTSs)	Class
Aldrin/Dieldrin	X	X	X	X	Pesticide
Benzo(a)pyrene	X	X			PAH (See below)

Cadmium		X			Metal
Chlordane	X	X	X	X	Pesticide
Chlordecone		X	X		Pesticide
DDT, DDD, DDE	X	X	X	X	Pesticide
Dicofol		X			Pesticide
Dioxins (TCDD) & Furans	X	X	X		Combustion byproducts
Endrin		X	X	X	Pesticide
Endosulfan		X			Pesticide
Hexachlorobenzene	X	X	X	X	Pesticide
Alpha- and beta-hexachlorocyclohexane			X		Pesticide
Heptachlor		X		X	Pesticide
Hexabromobiphenyl		X	X		Flame retardant
Hexabromodiphenyl ether			X		Flame retardant
alkyl-lead	X	X	X		Metal
Lindane		X	X	X	Pesticide
Mercury (methyl mercury)	X	X		X	Metal

Methoxychlor		X			Pesticide
Mirex	X	X	X	X	Pesticide
Octachlorostyrene	X				Byproduct
Pendimethalin		X			Pesticide
Pentabromo diphenyl ether (PBDEs)		X			Former flame retardant
Pentachlorobenzene			X		Fungicide, flame retardant
Pentachloronitrobenzene		X			Pesticide
Perfluorooctane sulfonic acid,		X	X		Widely used in many products
Polybrominated hydrocarbons (PBDEs)		X		X	Contaminant
Polychlorinated biphenyls (PCBs)	X	X	X	X	Heat-resistant industrial insulator and lubricant
Polycyclic aromatic hydrocarbons (PAHs)		X		X	Combustion byproducts
Tetrabromodiphenyl ether		X	X		Flame retardant
Tin (organotins)				X	Metal
Toxaphene	X	X	X	X	Pesticide

Trifluralin		X			Pesticide
1,2,4,5-tetrachlorobenzene		X			Pesticide

Case Studies

Lindane Dump Site

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From Advertisement for ORTHO Lindane, 1953
"Check These ORTHO Lindane Advantages:
High Safety Factor – Authorities have approved Lindane for lice and mange control on dairy cattle. Shows no contamination in milk when properly applied. … Even used by dermatologists for human itch, lice and scabies. Not cumulative and practically odorless. Any taken in by a warm-blooded animal is eliminated."
- *Entoma: A Directory of Insect and Plant Control 10th edition*, George S. Langford (ed.), published by The Entomological Society of America (1953-1954), page 165.

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Lindane (gamma-hexachlorocyclohexane) is one of the last of the old-style organochlorine pesticides still in use. Use of organochlorines such as DDT, aldrin, dieldrin, heptachlor, and toxaphene is restricted or banned in many countries because of their persistence in the environment, their bioaccumulation, and toxicity. Lindane was first isolated in 1825 along with other similar compounds, but its deadly effects on insects were not recognized until the 1940s.

Lindane was widely used because it killed a broad range of insects from fleas and tics to worms that damaged crops. For a time it was even used to kill rodents. Lindane was often applied as a spray on crops, where it would be either ingested or inhaled. Lindane attacks the nervous system, causing trembling, loss of coordination, paralysis, and ultimately, death. Initially its environmental persistence was considered an asset, but eventually that was seen as a liability and prompted restrictions in its use.

Lindane is stable in water and has an average half-life of 15 months in soil. It is also highly toxic to fish; trout are affected at levels as low as 1.7 µg of lindane per liter of water. The US EPA restricted its use in 1983, as have most European countries, and in 2006 the EPA cancelled its registration as a pesticide. However, it continues to be used in products to control head lice and scabies, under the jurisdiction of the US FDA in the United States, but even these uses are controversial and are being cancelled in some countries. The primary concern is not only lindane's toxicity, but also its persistence and environmental transport.

The US EPA set a drinking water limit of 0.2 parts per billion (ppb) of lindane. Industrial dumpsites such as the one in Allegheny County, Pennsylvania contain an estimated 400 tons of lindane waste and other waste dumped over a 50-year period on 30 acres of land. The runoff from this site as well as others have the potential to contaminate drinking water with lindane. Lindane is regularly detected in surface water in the United States (see US Geological Survey monitoring studies).

Health Effects

Table 14.2 provides a very brief description of the chemicals and their associated toxicity. Additional information on individual agents can be found elsewhere in this book as well as in many other sources.

Table 14.2 Chemicals and Toxicity

Chemical	Comment
Aldrin/Dieldrin	Pesticide; organochlorine; bioaccumulates; used to control mosquitoes and termites; importation and manufacture prohibited in the US in 1987
Benzo(a)pyrene	Polycyclic aromatic hydrocarbon (see below)
Cadmium	Metal; naturally occurring; used in steel, plastics, batteries; in cigarette smoke; lung carcinogen
Chlordane	Pesticide; organochlorine; bioaccumulates; used to control mosquitoes and termites; importation and manufacture prohibited in the US; use banned in 1988
DDT, DDD, DDE	Pesticide (DDT); breakdown product (DDD, DDE); organochlorine; bioaccumulates; used to control mosquitoes; importation and manufacture prohibited in the US in 1972; affects wildlife; found in breast milk and fat
Dicofol	Pesticide; organochlorine; bioaccumulates; insecticide on fruits; analog of DDT; degrades but very toxic to aquatic wildlife including fish
Dioxins (TCDD) & Furans	Byproduct of combustion in municipal and medical waste incinerators; bioaccumulates; human carcinogen
Endrin	Pesticide; organochlorine; bioaccumulates; insecticide used on many crops; most uses canceled in 1980
Endosulfan	Pesticide; organochlorine; bioaccumulates; currently used

	as an insecticide; US EPA ban to take effect by 2016, efforts to ban globally in progress
Heptachlor epoxide	Pesticide; organochlorine; bioaccumulates; breakdown product of heptachlor, an insecticide used from 1953 to 1974 in the US on a wide range of insects; most uses canceled in 1974; importation and manufacture prohibited in the US; all uses banned in 1988
Hexachlorobenzene	Pesticide; organochlorine; bioaccumulates; fungicide used on seeds; most uses ended in 1965 but is a byproduct of solvent manufacture
Lead	Metal; widely distributed in environment when used as a gasoline additive and in paint; now banned from use in gasoline and paint; potent child neurotoxicant
Lindane	Pesticide; organochlorine; bioaccumulates; insecticide widely used prior to 1983; regulated as drinking water contaminant by US EPA
Mercury	Metal; persistent; bioaccumulates; contaminates many species of fish; widely used in industrial processes; causes developmental neurotoxicity; children most susceptible
Methoxychlor	Pesticide; organochlorine; bioaccumulates; used as a replacement for DDT; in the US, 3.7 million pounds manufactured in 1978; use has declined significantly; regulated as a water contaminant
Mirex	Pesticide; organochlorine; bioaccumulates; extensively used in US from 1962-1978 to control fire ants; all uses canceled in US in 1978
Octachlorostyrene	Byproduct of electrolytic production of magnesium; listed by US EPA as persistent and bioaccumulative
Pendimethalin	Pesticide; herbicide used to control grasses and broadleaf weeds in cropfields and turf

Pentabromo diphenyl ether	Formerly used as flame retardant
Pentachlorobenzene	Pesticide; fungicide used for treatment of seeds and soil
Polybrominated hydrocarbons	Used in the manufacture of plastic products; bioaccumulate; highly persistent in the environment
Polychlorinated biphenyls (PCBs)	Heat and fire resistant; extensively used from 1929 to 1977 in electrical transformers; all manufacture banned; extensively regulated; very widespread global contaminant
Polycyclic aromatic hydrocarbons (PAHs)	Combustion byproducts; class of 100 chemicals; some of the first known carcinogens
Tin (organotins)	Used in a number of consumer products including paint; bioaccumulates and persistent; affects nervous system
Toxaphene	Pesticide; organochlorine; bioaccumulates; extensively used on US cotton crops from 1947 to 1980; manufacture and use prohibited in the US
Trifluralin	Pesticide; herbicide used to prevent emergence of weeds in cropfields and landscapes
1,2,4,5-tetrachlorobenzene	Pesticide; insecticide; intermediate in herbicide production; related to dioxin (TCDD)

Reducing Exposure

Exposure depends on various factors, such as location, diet, housing, occupation, and socioeconomic issues. For example, methylmercury bioaccumulates in certain fish and is particularly toxic to the developing fetus. Many government agencies advise that children and women of childbearing age reduce their consumption of certain species of fish known to bioaccumulate methylmercury, but this may be difficult for those dependent on high-fish diets. Reducing exposure to persistent chemical pollutants is difficult because they are so pervasive and continue to build up over time. While individuals can sometimes reduce exposure to particular PBTs, such as mercury, by regulating their diet, in general government agencies have found that the most

effective way of reducing exposure is by phasing out the uses of the products or processes that create these chemicals.

Many of the chemicals identified as persistent chemical pollutants are pesticides. Integrated Pest Management (IPM, see definition below) is an approach to pest control that can significantly reduce pesticide use while still providing adequate or even improved results. IPM programs are used in agriculture, landscaping, and indoor pest control. Typically, IPM programs maximize prevention of pest problems through non-chemical methods, and chemicals, when used, are selected for minimum risk to non-target species. Many institutions, such as schools, are adopting IPM protocols for pest management.

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"Integrated Pest Management (IPM) is a sustainable approach to managing pests by combining biological, cultural, physical and chemical tools in a way that minimizes economic, health and environmental risks."

- Integrated Pest Management Practices on 1991 Fruits and Nuts, RTD Updates: Pest Management, 1994, USDA-ERS, 8pp)

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Additional Resources

Slide Presentation and Online Material

• A Small Dose of Persistent Environmental Contaminants presentation material and references. Website contains presentation material on the health effects of Persistent Environmental Contaminants.

European, Asian, and International Agencies

• European Commission. Environment. Website deals with the registration, evaluation, authorization and restriction of chemical substances. [accessed May 11, 2009]
• United Nations Environment Programme (UNEP). Persistent Organic Pollutants. Information on international efforts to reduce persistent pollutants. [accessed May 11, 2009]
• Stockholm Convention on Persistent Organic Pollutants. "The Stockholm Convention on Persistent Organic Pollutants is a global treaty to protect human health and the environment from chemicals that remain intact in the environment for long periods, become widely distributed geographically, and accumulate in the fatty tissue of humans and wildlife." [accessed May 11, 2009]

North American Agencies

• Health Canada. Chemical Substances Online. Health Canada provides information on the health effects and environmental distribution of chemical substances in Canada. [accessed May 11, 2009]
• US Centers for Disease Control and Prevention (CDC). National Biomonitoring Program. [accessed May 9, 2009]
• US Environmental Protection Agency (EPA). Persistent Bioaccumulative and Toxic (PBT) Chemical Program. Information on the efforts of EPA to reduce PBT chemicals. [accessed May 9, 2009]
• US Geological Survey. This site contains information and maps on the use of

pesticides across the US both as contaminants and crop use. [accessed May 11, 2009]
• Washington State Department of Ecology. Persistent, Bioaccumulative Toxics Initiative. Information on Washington's approach to persistent, bioaccumulative toxins, and includes several chemical action plans. [accessed May 11, 2009]
• US Department of Agriculture National Institute of Food and Agriculture. Integrated Pest Management. Site provides information and other links on IPM. [accessed May 11, 2009]

Non-Government Organizations

• Environmental Health Research Foundation (EHRF). Biomonitoring Info. "A resource for policymakers, scientists, educators, workers, journalists and the public on the nature and promise of biomonitoring." [accessed May 11, 2009]
• Pesticide Action Network UK. PAN UK works to eliminate the dangers of toxic pesticides, exposure to them, and their presence in the environment in Europe. [accessed May 11, 2009]
• Pesticide Action Network North America (PANNA). "PANNA works to replace pesticide use with ecologically sound and socially just alternatives." [accessed May 11, 2009]
• Washington Toxics Coalition (WTC). WTC provides information on model pesticide policies, alternatives to home pesticides, information on persistent chemical pollutants, and much more. [accessed May 11, 2009]
• Beyond Pesticides. "Beyond Pesticides is a national network committed to pesticide safety and the adoption of alternative pest management strategies which reduce or eliminate a dependency on toxic chemicals." [accessed May 11, 2009]
• Northwest Coalition for Alternatives to Pesticides (NCAP). "NCAP works to protect people and the environment by advancing healthy solutions to pest problems." [accessed May 11, 2009]
• University of California. Statewide Integrated Pest Management Program (UC IPM). "UC - IPM develops and promotes the use of integrated, ecologically sound pest management programs in California." [accessed May 12, 2009]
• Environmental Defense Fund. The Arctic at Risk: A Circumpolar Atlas of Environmental Concerns. Site has maps and information on contaminants in the arctic. [accessed May 12, 2009]
• IPMopedia. Integrated Pest Management information. IPMopedia offers free and up-to-date integrated pest management advice from green gardening experts. [accessed May 21, 2009]

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Carson, Rachel. *Silent Spring*. Boston: Houghton Mifflin, 1994.
Atkin, J. and Klaus M. Leisinger (Editors). *Safe and Effective Use of Crop Protection Products in Developing Countries*. Wallingford: CABI Publishing, 2000.
Sexton, K., Needham, L., and J. Pirkle. "Human Biomonitoring of Environmental Chemicals". *American Scientist Classics* 92, 1 (2004): 38.
National Research Council. *Human Biomonitoring for Environmental Chemicals*. Washington, D.C.: National Academy Press, 2006.

A Small Dose of Endocrine Disruptors

or

An Introduction to the Health Effects of Endocrine Disruptors

Endocrine Disruptors: Quick Facts
Uses: wide range of chemicals, including pesticides, plastics, flame retardants, and pharmaceuticals
Source: synthetic chemistry, plants
Recommended daily intake: none (not essential)
Absorption: intestine, respiratory system (lungs), skin
Sensitive individuals: fetus and children
Toxicity/symptoms: endocrine system: mimics estrogen, anti-estrogenic; effects on hormone levels, sexual characteristics, reproduction, and development
Regulatory facts: FDA and EPA are reviewing
General facts: billions of pounds used every year in wide range of products
Environmental concerns: widely distributed in environment and can affect wildlife
Recommendations: minimize use, avoid exposure to children, and consider alternatives

Introduction and History

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"For example, recent work in the United States suggests that environmental levels of some EDCs are at least an order of magnitude greater in sewage sludge here than in Europe."

- Robert C. Hale, *Environmental Health Perspectives*, August 2003

• • •

Endocrine-disrupting chemicals (EDCs) constitute a broad variety of chemicals that interact with the endocrine system, sometimes at very low levels of exposure. Adverse effects include altered development (such as feminization), reproductive system changes, decreased fertility, changes in the brain and behavior, impaired immune systems, and the increased incidence of endometriosis and some forms of cancer. The primary concerns regarding EDCs are 1) that they can produce adverse health effects at very low levels of exposure, 2) we are exposed to multiple EDCs from conception and throughout our lives, and 3) the chemicals are widely distributed in the environment and affect both humans and animals. Below is a small list of common chemicals thought to interact with the endocrine system.

Table 15.1 Potential Endocrine Disruptors

Class	Chemical	Use
Pesticide	DDT	Insecticide (no longer allowed in US)
	2,4-D	Herbicide
	Atrazine	Herbicide
Plastics ingredients	Bisphenol-A	Hardener in plastics, building block for polycarbonate plastic
	Phthalates	Softener in plastics, solvent
Industrial chemical	Nonylphenol (breakdown product of nonylphenol ethoxylates)	Detergents, paints, pesticides
Fire retardant	Polybrominated diphenyl	Fire retardant

	ethers (PBDEs)	
Drug	Diethylstilbestrol (DES)	No longer used to prevent miscarriages
Contaminants	Dioxin	Byproduct PVC plastics, incineration byproduct, contaminant in certain chlorinated compounds
	Arsenic, Lead, Mercury	Widespread contaminants
	Polychlorinated biphenyls (PCBs)	Formerly used in transformer oils

Case Studies

Hormonal Contraceptives

Oral contraceptives, the most widely used form of birth control taken by millions of women throughout the world, are the ultimate endocrine disruptor. The search for a hormonal form of birth control began in the 1930s and was championed by women such as Margaret Sanger. An important breakthrough occurred in 1939, when Russell Marker discovered a way to synthesize progesterone from plants. Research on the use of hormones to disrupt female fertility accelerated in the 1950s and on May 9, 1960, the Food and Drug Administration approved "the Pill," a combination of an estrogen and a progesterone that inhibits female fertility by preventing ovulation. Potential toxicity related to oral contraceptives was first reported in late 1961 with patient reports of blood clots and pulmonary embolism. Further research confirmed these reports and found that smokers were at greater risk. It was subsequently found that the levels of estrogen and progesterone could be significantly decreased and still effectively disrupt female fertility. There is growing concern about the excretion of these synthetic hormones (as well as natural ones) in the urine and their movement from sewage treatment plants into the environment, where they affects wildlife, such as fish reproduction.

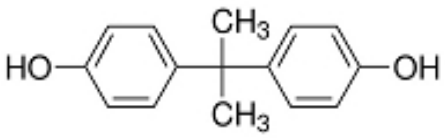
Synthetic Estrogens

The mildly estrogenic compound Bisphenol-A (BPA) was first created in 1891 by Aleksandr Dianin, a Russian, who named it "Dianin's Compound." In 1938, the much more potent synthetic estrogen diethylstilbestrol (DES) was synthesized by Leon Golberg, a graduate student at the University of Oxford in England. In 1941, the FDA approved DES's use for menopausal symptoms and in 1947, its use to prevent miscarriages. However, in 1953, the first study was published indicating that DES was not effective in preventing miscarriages. Manufacturers continued to market DES to

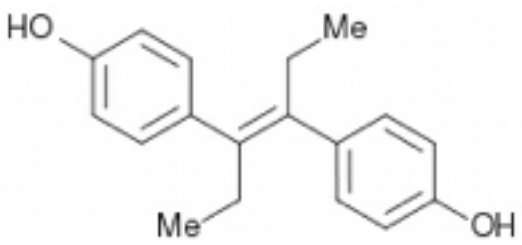
pregnant women until 1971, when the first study was published linking DES to vaginal cancer in female children of women taking DES. Between 1941 and 1971, millions of women and their children were exposed to DES.

Meanwhile, in the 1940s and 1950s, the chemical industry discovered that BPA was an excellent hardener for epoxy resins and the plastic polycarbonate. It is now used in a wide range of products, from plastics to linings of food cans, with an estimated use per year of 6 billion pounds. The CDC has found that over 90% of Americans have BPA in their urine, with the highest exposure occurring in infants and children. Overt toxicity from exposure to BPA occurs at only very high doses, but more subtle effects on the endocrine system occur at very low doses. Though animal studies and limited human studies have found endocrine-related health effects, government agencies have been reluctant to ban or restrict the use of BPA. Recently, local governments such as Washington State have moved to ban BPA from plastic baby bottles in an effort to reduce exposure to the most vulnerable.

Figure 15.1 Chemical Structure of Synthetic Estrogens



Bisphenol-A (BPA)



Diethylstilbestrol

Atrazine

Endocrine disruptors come in many forms, including herbicides like atrazine, used to kill broadleaf and grassy weeds. It was introduced in 1958 and eventually banned in the European Union as a persistent groundwater contaminant. In the United States, atrazine remains one of the most widely used herbicides. Several studies have found that atrazine feminizes male frogs by disrupting the endocrine system. Other pesticides such as organochlorines (including DDT) are also thought to be endocrine disruptors, even at very low levels of exposure.

Biological Properties

Endocrine System

The endocrine system is the body's chemical communication system, using blood vessels to move chemicals throughout the body that communicate with different cells. These naturally occurring chemicals, called hormones, are secreted by various glands throughout the body and signal specific sensitive cells to respond. Hormones regulate and influence almost all the basic functions of life, such as growth, metabolism, reproduction, sexuality, fear response, anger, and pregnancy. Many hormones

influence the secretion of other hormones in a complex feedback loop. Finally, hormones are produced, and can cause effects at, incredibly low levels. Major hormone-producing glands and examples of excreted hormones are listed in Table 15.2.

Table 15.2 Major Glands and Examples of Hormones and Function

Gland (location)	Example hormone	Function
Pineal gland (brain)	Melatonin	Sleep
Pituitary gland (brain)	Growth hormone	Growth, cell reproduction
	Prolactin	Milk production, sexual gratification
	Thyroid-stimulating hormone	Stimulates thyroid gland to secrete T3 and T4
	Luteinizing hormone	Female: ovulation Male: regulates testosterone
Thyroid gland (neck)	Thyroxine (T4)	Metabolism
	Triiodothyronine (T3)	Metabolism
Adrenal gland (above kidneys)	Glucocorticoids	Affects glucose uptake
	Adrenaline	Fight-or-flight response (range of effects)
Pancreas	Insulin	Regulates glucose
Ovary (female)	Progesterone	Pregnancy, muscle relaxation, range of effects

	Estrogens	Growth, sexual characteristics
Testes (male)	Testosterone (androgen)	Muscle mass, bone density, sexual maturation

Health Effects

Overview

There is growing evidence that exposure to EDCs during development is particularly hazardous. For example, early exposure to EDCs may result in cancer later in life (see Birnbaum and Fenton, 2003): prenatal exposure to the synthetic estrogenic compound DES can result in vaginal cancers. Animal and human studies indicate that natural and synthetic estrogens can cause breast and vaginal cancers. Animal studies also indicate that dioxin, an environmental contaminant, can interfere with breast tissue development and potentially lead to cancer.

Another organ vulnerable to endocrine disruptors is the thyroid and, by extension, the nervous system. The thyroid glands start to develop very early in gestation. A sensitive feedback system between the hypothalamus, pituitary, and thyroid gland regulates thyroid hormone production. Thyroid hormone is essential for normal brain development, influencing brain cell growth and migration, formation of connections between cells, development of supporting cells, and general functional development. Decreased thyroid hormone adversely affects all aspects of brain development. Normal thyroid function is also necessary for proper hearing development. A wide range of chemicals can adversely interact with thyroid hormone (for additional information see Howdeshell, 2002), and there is growing concern that fetal and early exposure to EDCs results in neurodevelopmental disorders such as autism, reduced IQ, and hyperactivity disorders (ADHD).

Anabolic Steroids for Sports Performance Enhancement

One of the many uses of anabolic steroids is to increase muscle mass, strength, and endurance for sports performance enhancement. The use of steroids is just one aspect of "doping" to enhance performance, which is defined as "the use of a drug or blood product to improve athletic performance." Doping also includes the injection of red blood cells to improve oxygen carrying capacity, which will not be covered in this chapter. The use of steroids to enhance performance began when ancient Olympic athletes ate sheep testicles to boost testosterone (the most basic anabolic steroid). Research on testosterone and other steroids progressed rapidly in the 1930s, with synthesis of testosterone from cholesterol accomplished in 1935. It was quickly recognized that testosterone increased muscle mass, appetite, bone growth, induced male puberty, and could be used to treat chronic wasting conditions. However, there are a number of hazards associated with its use, including growth of the vocal cords and body hair, changes in cholesterol levels, acne, high blood pressure, liver damage, and testicular atrophy. Testosterone and synthetic derivatives (now more than 100)

are used as performance-enhancing drugs but are now generally banned and are tested for in professional sports.

Reducing Exposure

While it is not possible to entirely avoid exposure to endocrine disrupting chemicals, some simple precautions can be taken. This is particularly important during fetal development and infancy. Avoid using plastic baby bottles or toys that contain BPA or phthalates. Reduce exposure to pesticides as much as possible by purchasing local organic foods or foods that contain lower levels of pesticide residue. Chemicals such as lead and pesticides can be tracked indoors on shoes, so it is always recommended to remove your shoes before coming indoors.

Regulatory Standards

In 1996, the US Food Quality Protection Act and the Safe Drinking Water Act directed the EPA to establish a program to test for endocrine-disruption chemicals. In 1998 the EPA established the Endocrine Disruptor Screening Program and took the first step to define and validate tests for endocrine-disrupting chemicals. The tests include cell-based (*in vitro*) screening tests suitable for rapidly assessing the potential toxicity of the approximately 85,000 chemicals currently in use. This data is then used to determine which chemicals require more sophisticated animal-based tests. The program has progressed very slowly and it was not until 2007 that testing began.

There has also been considerable controversy over the endocrine effects of bisphenol-A, which is used in plastics and to line food cans. The Food and Drug Administration is in the process of reviewing the many studies on the health effects of BPA.

Recommendation and Conclusions

There is an abundance of evidence that the endocrine system is very sensitive and essential for normal development. Adverse effects of EDCs include cancer and neurodevelopmental disorders such as reduced IQ. We are unavoidably exposed to a wide range of naturally occurring and synthetic EDCs.

The developing fetus and infant are especially sensitive to EDCs and exposure should reduced as much as possible. Unfortunately, many common products needlessly contain EDCs, such as baby bottles, plastic toys, and can linings. When possible avoid these products and urge manufacturers to use alternatives. Governments should also be encouraged to proceed with EDC screening and issue appropriate regulations to control exposure. A precautionary approach is warranted when a chemical is suspected of being an endocrine disruptor, especially if there is likely to be wide exposure to susceptible populations.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Endocrine Disruptors presentation material and references. Website contains presentation material related to the health effects of Endocrine Disruptors.

European, Asian, and International Agencies

• European Commission. Plant Protection Products. Site contains policy and other information on the use of pesticides in agriculture. [accessed September 30, 2008]
• World Health Organization (WHO). WHO Pesticide Evaluation Scheme (WHOPES). WHOPES is an "international programme which promotes and coordinates the testing and evaluation of new pesticides proposed for public health use." [accessed September 30, 2008]
• International Programme on Chemical Safety (IPCS). "Through the International Programme on Chemical Safety (IPCS), WHO works to establish the scientific basis for the sound management of chemicals, and to strengthen national capabilities and capacities for chemical safety." [accessed September 30, 2008]

North American Agencies

• National Toxicology Program. Selected Toxicity Information on Bisphenol-A. [accessed May 23, 2009]
• US Environmental Protection Agency (EPA). Endocrine Disruptor Screening Program (EDSP). Describes the program, efforts to develop the screening test, and prioritization of chemicals to be tested. [accessed June 15, 2009]
• US National Institutes of Environmental Health Sciences (NIEHS). Endocrine Disruptors. Provides an overview of endocrine disruptors and recent research. [accessed May 23, 2009]

Non-Government Organizations

• The Endocrine Disruption Exchange, Inc. (TEDX). A nonprofit organization that compiles and disseminates information on the health effects of endocrine disruptors. [accessed May 23, 2009]
• The Endocrine Disruption Exchange, Inc. (TEDX). Prenatal Origins of Endocrine Disruption: Critical Windows of Development. "Critical Windows of Development is a timeline of how the human body develops in the womb, with animal research showing when low-dose exposure to endocrine disrupting chemicals during development results in altered health outcomes." [accessed May 23, 2009]
• Natural Resources Defense Council. Endocrine Disruptors. General information on endocrine disruptors. [accessed June 9, 2009]

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Colborn, T., vom Saal, F. S., and A. M. Soto. (1993) "Developmental Effects of Endocrine-Disrupting Chemicals in Wildlife and Humans". *Environmental Health Perspectives* 101, 5 (1993): 378-384.
Birnbaum, L. S. and S. E. Fenton. "Cancer and Developmental Exposure to Endocrine Disruptors". *Environmental Health Perspectives* 111, 4 (2003): 389-396.
Howdeshell, KL. "A Model of the Development of the Brain as a Construct of the Thyroid System". *Environmental Health Perspectives Supplements* 110, 3 (2002). [accessed June 15, 2009]

A Small Dose of Animal and Plant Toxins

or

An Introduction to the Health Effects of Animal and Plant Toxins

Animal Toxins: Quick Facts
Uses: medicinal
Source: spiders, insects, snakes, lizards, fish, and frogs
Recommended daily intake: none (not essential)
Absorption: varies but can be very fast, e.g. bites
Sensitive individuals: children (small size), those previously sensitized
Toxicity/symptoms: varies
Regulatory facts: none
General facts: long history of use and desire to avoid, often accompanied by fear of the animal
Environmental concerns: global distribution, concern about expanding distribution to new areas
Recommendations: follow precautions for avoiding contact

Plant Toxins: Quick Facts
Uses: medicinal
Source: wide variety of plants
Recommended daily intake: none (not essential)
Absorption: intestine, skin
Sensitive individuals: children, previously sensitized individuals
Toxicity/symptoms: varies
Regulatory facts: none
General facts: long history of use and desire to avoid
Environmental concerns: global distribution, concern about expanding distribution to new areas
Recommendations: generally avoid; know the poisonous plants in area

Introduction and History

The creatures of the world, both animals and plants, produce a wide range of biologically active substances; these substances that cause an adverse effect are called toxins. Toxins refers only to toxic agents produced by animals and plants, not to toxic substances such as lead or pesticides. The classification of a substance as a toxin tends to be in the eye of the beholder. Is caffeine, a naturally occurring agent in many plants, a toxin, a pharmacologically active compound, or both?

The study of plant and animal toxins is truly fascinating. Toxins offer many lessons in dose/response as well as a window into the struggle for growth and survival in hostile environments. They are used offensively to aid in gathering food or defensively to ward off predators. To accomplish these tasks, toxins must interact with biological tissue. The study of their biological activity has provided us with important drugs and greatly improved our understanding of the mechanisms of biology. Much of this work

has advanced only since the 1970s, when the sensitive instrumentation necessary to separate these venomous mixtures became available.

The toxins of the world are really the medicine chest of nature. Pharmaceutical companies explore the world looking for new plants or animals that might be naturally producing a new drug. On the one hand, we have come to depend upon many of the substances produced by animals and plants. On the other hand, we all learn to avoid the sting of bees, and we know that even some of our houseplants are toxic. Mushrooms are a classic example of species that can be good to eat, be deadly poisons, or, when used judiciously, produce hallucinations that some find desirable. Foxglove and lily-of-the-valley contain a compound called digitalis that lowers blood pressure and prevents heart attacks. However, digitalis is quite toxic and the plants themselves are considered poisonous.

In the following sections we can only take a brief look at this fascinating subject.

Case Studies

Puffer Fish

About 100 species of puffer fish use the powerful tetrodotoxin to discourage consumption by predators. Tetrodotoxin is found in all organs of the fish but is highest in the liver, skin, and intestine. The origins of the toxin are not clear, but one possibility is that the fish come in contact with bacteria that produce tetrodotoxin. Puffer fish may also have elevated levels of saxitoxin, a neurotoxin responsible for paralytic shellfish poisoning. Saxitoxin is produced by dinoflagellates (algae) and most often contaminates mussels, clams, and scallops. Both saxitoxin and tetrodotoxin are heat stable so cooking does not reduce toxicity.

Tetrodotoxin causes paralysis by affecting the sodium ion transport in both the central and peripheral nervous systems. A low dose of tetrodotoxin produces tingling sensations and numbness around the mouth, fingers, and toes. Higher doses produce nausea, vomiting, respiratory failure, difficulty walking, extensive paralysis, and death. As little as 1 to 4 mg of the toxin can kill an adult. Saxitoxin has a very different chemical structure than tetrodotoxin but has similar effects on transport of cellular sodium and produces similar neurological effects. Saxitoxin is less toxic that tetrodotoxin. Some people, particularly in Asia, consider the puffer fish a fine delicacy, providing it is carefully prepared by experienced chefs. The trick is to get just a small dose to feel mild tingling effects but not the more serious symptoms of tetrodotoxin poisoning. In the United States tetrodotoxin poisoning is rare but a recent report by the US CDC described several case studies of people catching and consuming puffer fish containing elevated levels of these toxins and suffering the ill effects (MMWR, 2002).

Jimson Weed

Jimson weed is the common name of one plant in a family of plants recognized since ancient times for their interesting effects on the nervous system. The deadly nightshade plant (*Atropa belladonna*) was used in the Roman Empire and during the Middle Ages both as a cure and a poison. Women used preparations from this plant to

dilate their pupils as a sign of allure and beauty. Some say the name belladonna refers to beautiful Italian women with dilated pupils. The drug responsible for these effects is called atropine, from the other part of the scientific name for deadly nightshade. We are commonly given a form of atropine (homatropine) to dilate our pupils during eye examinations. This is a short-acting form of atropine that keeps your eyes dilated for a few hours rather than the seven or more days that results from atropine. Atropine is also the same drug taken to counteract the effects of pesticides and chemical warfare agents that act by inhibiting acetylcholinesterase. In addition to atropine, this family of plants contains scopolamine and other belladonna alkaloids. They act by inhibiting the actions of acetylcholine at central and peripheral nerves. Besides dilation of the pupils, exposure to the belladonna alkaloids stops salivation, causing a dry mouth, difficulty swallowing, and an irregular heart rate. A larger dose causes central nervous system effects such as hallucinations, loss of memory, and confusion. Jimson weed, part of the belladonna family of plants, is a common weed in North America. The easy availability of Jimson weed and its ability to alter the nervous system leads to youth experimenting with the plant. Unfortunately, the consequences, especially when combined with other drugs, can be very serious and even lead to death (MMWR, 1995).

Mushroom Poisoning

Worldwide, the most dangerous mushrooms are the "death cap" mushroom (*Amanita phalloides*) or the "death angel" (*Amanita ocreata*). The greatest number of deaths occurs in children less than 10 years of age, but adults are also susceptible. Often it is difficult to associate symptoms with eating the mushrooms because there is a 10-12 hour delay before symptoms become apparent. The initial symptoms are nausea, vomiting, diarrhea, and an irregular heart rate. Ultimately the toxin, amatoxin, damages liver cells causing liver and kidney failure and possibly death. The amatoxin binds to RNA and inhibits protein synthesis. Amatoxin is very potent: ingestion of only 0.1 to 0.3 mg/kg of body weight results in death. For a child weighing 10 kg (or about 22 lbs), only 1 mg of amatoxin can result in a fatal poisoning. In 1997 the US CDC reported that two out of four people who picked and consumed the "death angel" mushroom died of liver failure. This report clearly demonstrates that care is necessary in consuming wild mushrooms (MMWR, 1997).

Animal Toxins

Animal toxins are roughly divided into venoms and poisons. Venoms are offensive, used in the quest for food. Snakes produce toxins that can immobilize or kill prey for food. The venom of spiders paralyzes insects to allow the spider to feed on the victim's body fluids. While the venoms may also be used defensively, their primary purpose is to aid in the quest for food. Most venom is delivered from the mouth, but there are exceptions, like the scorpion that uses its tail.

Poisons are primarily defensive, designed as protection against predators. Poisons are often sprayed or delivered with a stinger to penetrate the skin. Some fishes have poisons in their spines. Toxins can also be on the skin or be part of the meat of the animal, thus making them poisonous to touch or eat. Some poisonous animals develop very colorful markings to advertise their undesirable qualities.

Venoms, either large or small molecules, are usually variants of essential biological molecules such as lipids, steroids, histamines, or other proteins. They are often mixtures with a specific mechanism of action such as paralysis of the nervous system. Poisons usually cause more localized pain to discourage predators, but depending on the dose and the sensitivity of the individual, the poison can be deadly.

There are some unique challenges for animals that produce toxins, particularly venoms. The toxin must be concentrated and stored in a large enough dose to be effective but without being toxic to the animal that produces it. After a quick delivery, the toxin must be rapidly absorbed and act quickly to defeat that prey's response. These properties, along with precise action, make toxins the envy of drug developers.

Arthropods

Insects, spiders, scorpions, crabs, centipedes, millipedes, and even plankton are all arthropods, the largest and most diverse animal phylum. Some are capable of producing very powerful toxins that aid in the quest for food. Humans come in contact with these toxins usually by accident or as a result of the animal defending itself. Some insects, mosquitoes and ticks for example, are capable of transmitting other organisms to humans that cause disease. While these organisms may be toxic to humans, they are not toxins and will not be discussed in this chapter.

Arachnids (Scorpions, Spiders, Ticks)

Scorpions

There are approximately 1000 species of scorpions but only around 75 are clinically important. In some parts of the world scorpion stings are common and for the most part treated like bee or wasp stings, producing no long-lasting effects. There are a few scorpions with venom potent enough to harm humans, particularly children. The most potent venoms are low-molecular-weight proteins that affect the nervous system. There is usually immediate pain at the site of the sting, with elevated or irregular heart rate being one of the first clinical signs. Most adults recover within 12 hours, but because of their low weight, children are vulnerable to more serious and long-lasting clinical effects.

Spiders

Spiders or arachnids use their venom to paralyze prey while they feast on the victim's body fluids. They primarily feed on insects and other spiders. The venom of about 200 out of the 30,000 species of spiders present a risk to humans. The venom of spiders is a complex mixture of neuroactive proteins and other chemicals. Researchers have studied venoms to understand the mechanism of their effects and to search for new drugs. If spiders were bigger they would be truly dangerous. Fortunately they are small, with only a very small amount of venom. Because of our much larger size we receive only a small dose, but when a spider bites another insect it delivers a very large dose indeed.

In the United States one of the infamous venomous spiders is the black widow spider, but there are many similar species found around the world in temperate or tropical climates. It has a number of common names depending on the region of the world and

ranges in color from brown to gray to black. The black widow species is shiny black and on the belly of the females is a red hourglass. Both the male and females are venomous, but only the female has fangs large enough to penetrate human skin. The venom of this species is made up of large proteins thought to affect the transmission of calcium ions of nervous system cells. The initial sting of the bite is followed by muscle cramps, sweating, and possibly decreased blood pressure. There is no adequate treatment but the bite is seldom fatal.

Another globally distributed venomous spider is the brown recluse or violin spider. It too comes in numerous varieties depending upon the region of the world. The spider has a range of colors but most unique are its six eyes. The venom of the brown recluse contains a range of proteins designed to dissolve the victim's cellular proteins, but the most active agent affects the red blood cells. The effects of the venom vary, but a in the worst case there is serious necrosis of tissue at the center of the bite, with the surrounding area becoming red and swollen. The venom literally dissolves the cells of the skin and surrounding tissue, which of course triggers the body's own defensive reactions. Significant tissue damage can occur particularly if the bite is on the face, but the bites are almost never fatal. There is no effective treatment for the venom other than supportive care.

The best protection is to avoid activities that may lead to spider bites, especially those of dangerous spiders. It is important to recognize which kinds of spiders are potentially dangerous, since most are harmless and shouldn't be needlessly killed.

Ticks

Ticks have a bad reputation for good reasons. Not only are they carriers of a number of diseases, the saliva of some can cause paralysis. North American natives were aware of tick paralysis, but the condition was officially noted as a disease of both animals and humans in 1912. The bites of at least 60 species of ticks can cause paralysis, which often does not appear until several days after the bite. The first indication is redness and swelling around the site of the bite. This is followed by neuromuscular weakness and difficulty in walking. If the tick is not removed, speech and breathing are affected, with eventual respiratory paralysis and death. Fortunately, removal of the tick results in a quick recovery of function. The exact mechanism of paralysis is not known but it appears to come from a substance the affects the neuromuscular junction. While not related to the venom of the tick saliva, the tick can also transmit diseases such as Lyme disease, Rocky Mountain spotted fever, Q fever, typhus, and others.

Table 16.1 Arachnids (Scorpions, Spiders, Ticks)

Class	Examples	Delivery & Venom	Comments
Arachnids (scorpions, spiders, ticks)	Scorpions	Stinger: neurotoxin, no enzymes	Localized pain, mostly dangerous to children

	Latrodectus: Widow spiders (black, brown, red-legged spider)	Bite: neurotoxin, large molecular proteins	Localized pain, sweating, muscle cramps, decreased blood pressure
	Loxosceles: Brown or Violin Spiders	Bite: complex mixture of enzymes	Serious tissue damage, attacks blood cells
	Ticks	Bite: saliva neurotoxin, transmits other diseases	Tick paralysis: causes weakness & difficulty walking (remove tick)

Insects

Some moths and caterpillars produce irritating substances to fend off predators with substances that do not taste good.

A much more aggressive group of insects, with great power for their size, is ants. Ants produce poisonous or irritating substances as a means of defense. Most ants have a stinger, and some can spray substances onto skin or onto the wound created by their powerful jaws. There are thousands of species of ants, and the poisonous substances they produce vary enormously. Some ants create substances with large amounts of proteins that can cause an allergic response. Others ants produce formic acid, which is very irritating to the skin. Fire ants, common in the United States, produce a substance rich in alkaloids that can cause localized tissue destruction and necrosis. Multiple bites can be dangerous and even life threatening for both humans and animals. Multiple stings can cause nausea, vomiting, difficulty breathing, coma, and death.

Bee Stings

- A honey bee has about 150µg of poison, but only a small fraction is typically injected. The faster the stinger is removed, the less the response.

The stings from bees, wasps, hornets, and related insects are well known to many people. Humans have collected honey for at least 6000 years. Honeybees sting when threatened and to protect their hive and honey from both humans and other predators, including yellow jackets. Yellow jackets, a type of wasp, are attracted to the smell of a hive's honey and will attempt to steal the honey. Watching the honeybees defend their hive from yellow jackets illustrates their need for a stinger. The stinger of a honeybee is barbed and usually left behind in the skin, literally ripped out of the bee, that will soon die. Also, left behind is a complex substance of many different proteins including histamine, dopamine, and a substance that breaks down tissue. When stung, it is advisable to remove the stinger as soon as possible to reduce exposure. Some people advise putting a meat tenderizer on the site of the sting. This may help because a meat tenderizer is designed to digest protein and soften meat. In

the event of a bee sting, the tenderizer is used to digest the bee protein. Response to bee stings varies enormously from almost nothing to life threatening. Usually there is localized swelling as the body rushes to wipe out the foreign protein that has invaded the body. Some people are highly allergic to bee stings (about 1 or 2 per 1000 people), and for them the response is not localized and results in a massive response that can lead to death. Even for those not allergic, multiple stings can cause breathing problems, decreased blood pressure, shock, and death.

Wasp stings tend to contain less protein and more of a substance related to formic acid that produces intense burning.

Table 16.2 Insects

Examples	Poison or Venom	Comments
Moths and caterpillars	Irritating substance	Designed so they do not taste good
Ants	Variable: proteins, formic acid, others	Variable response: irritation, allergic response, tissue damage
Honey bees	Complex proteins	Swelling, allergic reaction
Wasps	Formic acid	Irritating

Reptiles

Lizards

Humans are a far bigger threat to lizards than they are to us. Lizards are generally slow moving and nocturnal, with few enemies other than humans. The venom is a complex mixture that contains serotonin, a neurotransmitter, but lacks many of the other protein-degrading enzymes. Clinical effects are minor unless you are small and receive a large dose.

Snakes

Snakes occupy a unique place in our collective imagination. The primary function of snake venom is to immobilize or kill prey for food. A secondary function of the venom is defensive or protective, but clearly snakes are not capable of eating large animals such as humans. Often venomous snakes will strike but not release venom, which conserves a resource valuable to them. Approximately 400 of the more than 3,500 species of snake are sufficiently venomous to be a threat to humans and other large animals.

Worldwide, there are an estimated 300,000 to 400,000 venomous snakebites per year with about 10% (or 30,000) resulting in death. In the United States, there are

approximately 7,000 venomous bites per year but only 1 death per 500 bites, testifying to the value of prompt medical treatment.

The most common venomous snakebites in North America are from vipers. This class of snakes has the most advanced venom delivery system. The venom is quickly injected through hinged tubular fangs that can be folded into the snake's mouth. The pit vipers, such as rattlesnakes, have a head sensor located between their nostril and eyes, which is thought to guide the strike even in the dark. The venom from vipers is a very complex enzyme-based substance that quickly causes localized swelling and tissue destruction (necrosis). The protein-based venom causes an allergic-type reaction leading to hemorrhage of body fluids, decreased blood pressure, shock, fluid in the lungs, and death.

Table 16.3 Reptiles

Class	Examples	Venom & Delivery	Symptoms
Vipers (*Viperidae*)	Rattlesnakes Water moccasins Copperheads Bushmasters	Very complex enzyme-based venoms, Advanced delivery: hinged tubular fangs	Swelling & necrosis at site, effects blood cells, hemorrhage, decreased blood pressure, shock
Elapidae	Cobras Kraits Coral snakes	Neurotoxin (some very potent) Fixed fangs, usually low dose	Nervous system effects, paralysis, numbness, respiratory failure

The second most common venomous snakes are the *Elapidae*, of which cobras and coral snakes are well known. These snakes deliver their venom from fixed fangs and must hold on to the victim while the venom is released. These snakes tend to be smaller than vipers and deliver a smaller dose of poison. But what they lack in size they make up for in potency. The venom of these snakes predominately affects the nervous system, causing paralysis and numbness. Death is usually the result of respiratory failure from nervous system effects.

Marine Animals

Shellfish

Shellfish such as mussels, clams, oysters, and scallops are not naturally toxic but can become so after feeding on plankton contaminated with a toxin. When visible, the blooming of the plankton (dinoflagellate) is called red tide and can cause significant death among marine animals. There are several types of toxins, mostly affecting the nervous system. The newest, domoic acid, first appeared in 1987 off Prince Edward Island in Canada. This neurotoxin caused confusion and memory loss, particularly in the elderly. Several elderly people died following seizures and coma. Domoic acid is

heat stable, so cooking does not affect the toxin. Government agencies now monitor for contaminants of shellfish and move quickly to restrict harvesting. The domoic acid incident clearly indicates the importance of ongoing monitoring of the food supply.

The puffer fish is probably the best known neurotoxic fish. Several related species of fish, as well as other marine life, such as some frogs, starfish, octopus, and others, contain tetrodotoxin. Many people consider this fish a delicacy despite the occasional reported death from poor preparation. Tetrodotoxin is heat stable but water soluble, so careful preparation is necessary to limit neurological effects. Symptoms of poisoning include a rapid onset of numbness in the lips and mouth which then extends to the fingers and toes, followed by general weakness, dizziness and respiratory failure, and death. The mechanism of action is similar to that of saxitoxin and affects sodium channel permeability.

It should also be remembered that fish high in the food chain such as tuna, swordfish, and shark accumulate toxic substances like mercury or PCBs. Mercury affects the nervous system and is a proven reproductive hazard.

Table 16.4 Marine Animals

Animal Class	Examples	Toxin	Symptoms	Comment
Shellfish (filter-feeding mollusks)	Mussels, clams, oysters, scallops	Several kinds of toxin taken up from plankton (dinoflagellate)	See below	
	Paralytic Shellfish Poisoning (PSP)	Saxitoxin in their muscles	Numbness, respiratory paralysis	Sodium channel permeability
	Diarrheic Shellfish Poisoning (DSP)	High-molecular-weight polyethers	Nausea, vomiting, diarrhea	Usually mild but annoying
	Neurotoxic Shellfish Poisoning (NSP)	Brevetoxins	Numbness of mouth, muscular aches, dizziness	
	Amnesic Shellfish	Domoic acid	Confusion, memory loss,	Affects elderly

	Poisoning (ASP)		seizure, coma	
Coelenterates	Jellyfish, anemone, coral	Nematocyst	Sting, muscle cramps	
Fish	Sea Snail (cigua) and some fish, oysters and clams	Ciguatera, scaritoxin and maitotoxin	Numbness, salivation, cardiovascular effects, respiratory paralysis	Inhibits acetyl cholinesterase
Fish	Puffer Fish (fugu, blowfish, toadfish), some frogs, starfish, octopus	Tetrodotoxin	Numbness, paralysis, respiratory failure, death	Decreased sodium channel permeability
Fish	Tuna, shark, swordfish	Mercury (toxicant)	Neurotoxic, reproductive effects	Not produced by fish itself, concentrated in muscle

Plant Toxins

Introduction

Plants produce a range of chemicals designed to fend off predators or discourage consumption by insects or animals. For thousands of years humans have experimented with plants to search for food and treatment for illnesses, and even to alter one's perception of the world. Wide ranges of drugs are derived from plants, and the world's leading pharmaceutical companies continue the search. Others promote the use of plants, with varying degrees of processing, as herbal or natural medicine.

This section focuses only on the human toxicity of some of the better-known plants, organized by organ system affected. The tables below summarize the most important facts.

Effects on Skin

One of the best methods of protection for a plant is to make skin contact painful. This is done through either an allergic antibody-mediated response or through direct-acting chemicals. For an allergic-type response it is not the first contact that produces the reaction but rather the next contact. For example, poison ivy produces a class of chemicals called urushiol that cause a widely variable allergic response in about 70% of people exposed. Although not a direct protection for the plant, pollen of ragweed, mugwort, or grasses cause an allergic response in many people.

Dieffenbachia or dumb cane, a common houseplant, produces a juice that is released when a stem is broken or chewed and causes a painful, rapid swelling and inflammation of the tongue and mouth. The symptoms can take several days to resolve and are caused by oxalate crystals coated with an irritating protein. Stinging nettle (*Urtica*) releases histamine, acetylcholine, and serotonin from fine tubes with bulbs at the end that break off on the skin, causing an intense burning or stinging sensation.

Table 16.5 Skin Effects of Plant Toxins

Symptoms	Plant Examples	Toxin/Comment
Allergic dermatitis (plant itself): rashes, itchy skin	Philodendron, poison ivy, cashew, bulbs of daffodils, hyacinths, and tulips	Antibody mediated after initial sensitization, variable response. Allergens located on outer cells of plant.
Allergic rhinitis (pollen): sniffles and sneezing, runny eyes	Ragweed (North America), mugwort (Europe), grasses	Antibody mediated; pollen widely distributed in air. Very common, can be debilitating.
Contact dermatitis Oral: swelling and inflammation of mouth Skin: pain and stinging sensation	Dumb cane (*Dieffenbachia*) Nettles (*Urtica*)	Calcium oxalate crystals coated with inflammatory proteins. Fine tubes contain histamine, acetylcholine and serotonin.

Effects on the Gastrointestinal System

For the plant, another good way to stop consumption by an animal is to make the animal sick to the stomach. This approach is used by a number of plants, but the mechanism of action varies. The first approach is direct irritation of the stomach lining

to induce nausea and vomiting. The induction of mild vomiting is medically useful in some situations. The "sacred bark" of the California buckthorn produces cascara that is used as a purgative to induce mild vomiting.

Other approaches to induce gastrointestinal discomfort have far more serious toxic effects. The chemical colchicine stops cell division (an antimitotic), producing severe nausea, vomiting, and dehydration, which can lead to delirium, neuropathy, and kidney failure. However, colchicine is used in the treatment of gout and studied as an anticancer agent because it stops cell division. Most toxic of all are plants that produce lectins, and the most toxic of these is the chemical ricin produced by castor beans. Only 5 to 6 seeds are necessary to kill a small child. Fortunately, following oral consumption much of the ricin is destroyed in the stomach. Ricin is extremely effective at stopping protein synthesis, so much that direct exposure to only 0.1 µg/kg can be fatal.

Table 16.6 Gastrointestinal Effects of Plant Toxins

Symptoms	Plant Examples	Toxin/Comment
Direct stomach irritation: nausea, vomiting and diarrhea	California buckthorn (sacred bark), tung nut, horse chestnut, pokeweed	Emodin & esculine (toxins); oil from seeds, nuts; some medical uses; children are most often affected
Antimitotic (stops cell division): nausea, vomiting, confusion, delirium	Lily family, glory lily, crocus, may apple	Colchicine (gout treatment)
Lectin toxicity: nausea, diarrhea, headache, confusion, dehydration, death	Wisteria, castor bean (*Ricinus communis*)	Lectins bind to cell surfaces Ricin: blocks protein synthesis, very toxic: 5 to 6 castor bean seeds can kill a child

Effects on the Cardiovascular System

The medically important drug digitalis was derived from foxglove (*Digitalis purpurea*). At medically useful doses, digitalis slows and stabilizes the heart rate, but at high dose it produces an irregular heart rate and decreased blood pressure.

The Greeks first reported "mad honey poisoning" almost 2500 years ago, and honey poisoning still affects people around the world, when bees gather nectar from

rhododendrons and take it back to their hives. The cardiovascular effects are caused by grayanotoxin, which is produced in the leaves and nectar of rhododendrons and are concentrated in the honey by the bees. Goats and sheep are also affected when they consume the leaves of rhododendron or some lily plants.

The cardiovascular effects of consuming mistletoe contributed to some thinking it had either holy or demonic powers.

Table 16.7 Cardiovascular Effects of Plant Toxins

Symptoms	Plant Examples	Toxin/Comment
Digitalis-like glycosides: cardiac arrhythmias	Foxglove (*Digitalis purpurea*), squill, lily of the valley	Contain glycosides that are similar to digitalis: scillaren, convallatoxin
Heart nerves: decreased heart rate and blood pressure, general weakness	Lily, hellebore, death camas, heath family, monkshood, rhododendron	Alkaloids, aconitum, grayanotoxin (concentrated in honey)
Blood vessel constriction (vasoconstriction)	Mistletoe (berries contain toxin)	Holy or demonic effects on heart first described in 1597; toxin is called phoratoxin

Effects on the Nervous System

Table 16.8 Nervous System Effects of Plant Toxins

Symptoms	Plant Examples	Toxin/Comment
Seizures	Water hemlock (parsley family), mint family	Cicutoxin affects potassium channels; monoterpenes in mint oils
Stimulation from excitatory amino acids: headache, confusion, hallucinations	Red alga (red tide), green alga, mushrooms (*Amanita* family (fly agaric)), flat pea (*Lathyrus*)	Kainic acid, domoic acid: concentrated in shellfish Ibotenic acid: muscarinic (hallucinations) Lathyrism: motor neuron degeneration

Aberrant behavior, excitability, muscle weakness, death	Locoweed (Australian & Western US)	Swainsonine toxin: liver enzyme inhibitor, well known to affect cattle
Stimulation	Coffee bean, tea, cola nut	Caffeine: most widely consumed stimulant in the world
Death (neurotoxic)	Poison hemlock (*Conium maculatum*)	Coniine: neurotoxic alkaloid, used by Socrates
Paralysis (demyelination of peripheral nerves)	Buckthorn, coyotillo, tullidora (US, Mexico)	Anthracenones: attack the myelin that surrounds the peripheral nerves
Atropine-like effects: dry mouth, dilated pupils, confusion, hallucinations, memory loss	*Solanaceae* family: jimson weed, henbane, deadly nightshade (*Atropa belladonna*), angel's trumpet	Clinical effects of many of the plants recognized since ancient times. Deaths are rare but children vulnerable; hallucinations from muscarine & psilocybin; angel's trumpet contains atropine and scopolamine
Neuromuscular effects: mild stimulation to muscle paralysis, respiratory failure (curare), death	Tobacco, *Strychnos* family (curare), blue green algae (anatoxin-A)	Nicotine blocks acetylcholine receptors; curare used as a hunting poison (very potent receptor blocker)

Effects on the Liver

Fungi produce two of the most potent toxins affecting the liver. The "death cap" and "death angel" mushrooms from the *Amanita* family kill several people every year when mistakenly consumed. There are also a number of fungi and molds that grow on nuts or grain. High humidity and poor storage conditions encourage the growth of a fungus on nuts that produces aflatoxin, a very potent toxin that causes liver cancer. People with prior liver disease such as hepatitis are particularly susceptible.

Table 16.9 Liver Effects of Plant Toxins

Symptoms	Plant Examples	Toxin/Comment
Hepatitis and cirrhosis of liver from contaminated grain	Ragwort or groundsel	Pyrrolizidine alkaloids attack liver vessels: affects humans and cattle (but some species resistant)
Liver failure and death	Mushrooms: "Death cap" (*Amanita phalloides*)	Amatoxin and phalloidin affect RNA and protein synthesis
Liver cancer	Fungus that grows on peanuts, walnuts, etc.	Aflatoxins: produced by fungus in poorly stored grain

Effects on the Reproductive System

Reproductive and developmental toxins are primarily a concern for livestock. A high rate of fetal malformations in sheep offspring occurs following grazing on *Veratrum californicum* that grows in the mountains of North America. Plants that induce abortion, such as bitter melon seeds, have a long history of use of in humans.

Table 16.10 Reproductive Effects of Plant Toxins

Symptoms	Plant Examples	Toxin/Comment
Teratogen: malformations in offspring (sheep)	*Veratrum californicum* (native to North America)	Veratrum: blocks cholesterol synthesis, seen in offspring of mountain sheep
Abortifacients: cause fetal abortions	Legumes (*Astrogalus*); bitter melon seeds (*Momordica*)	Swainsonine toxin stops cell division; lectins halt protein synthesis (used by humans)

Regulatory Standards

Government regulatory agencies monitor some toxins as potential food contaminants. For example, agencies routinely monitor shellfish for several toxins and when

necessary issue restrictions on harvesting. Many of the naturally occurring toxins are unregulated and the consumer must be aware of the potential hazards. It is really up to you, for example, to know what mushroom you are consuming if you don't buy it at a store.

Note that some governments regulate noxious weeds, including some poisonous plants, but others are sold at garden stores.

Recommendation and Conclusions

Children, because of their small size, are often the most susceptible to many of the naturally occurring toxins, just as they are to other toxicants. The caffeine from a can of cola will have a much bigger effect on a small child than it will on an adult. Health status and age, both young and old, also influence the response. Aflatoxin from contaminated nuts has a greater likelihood of causing cancer in some with a liver disease such as hepatitis. It is important to develop a knowledge of which plants and animals can be dangerous and learn how to avoid dangerous contact with them.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Animal and Plant Toxins presentation material and references. Website contains presentation material related to the health effects of animals and plant toxins.

European, Asian, and International Agencies

• Amphibians and Reptiles of Europe. A large sample of European Amphibians and Reptiles. [accessed June 16, 2009]

North American Agencies

• Society For The Study Of Amphibians And Reptiles (SSAR). SSAR, a nonprofit organization established to advance research, conservation, and education concerning amphibians and reptiles. [accessed June 16, 2009]
• Health Canada. Drugs and Health Products. Natural Health Products Regulations work to "ensure that all Canadians have ready access to natural health products that are safe, effective, and of high quality, while respecting freedom of choice and philosophical and cultural diversity." [accessed June 16, 2009]
• US Food and Drug Administration (FDA). Seafood. Site has information on seafood health and safety issues. [accessed June 16, 2009]
• Northwest Fisheries Science Center (NWFSC). Harmful Algal Bloom Program. NWFSC Harmful Algal Bloom Program, part of the US National Oceanic and Atmospheric Administration, provides information related to algal blooms. [accessed June 16, 2009]
• US Food & Drug Administration (FDA). Foodborne Pathogenic Microorganisms and Natural Toxins Handbook The "Bad Bug Book." The "Bad Bug Book" contains extensive information on natural toxins. [accessed June 16, 2009]

Non-Government Organizations

• Texas A&M University System. Natural Toxins Research Center (NTRC). NTRC provides global research, training, and resources that will lead to the discovery of medically important toxins found in snake venoms. [accessed June 16, 2009]
• Cornell University. Plants Poisonous to Livestock. This site "includes plant images, pictures of affected animals and presentations concerning the botany, chemistry, toxicology, diagnosis and prevention of poisoning of animals by plants and other natural flora (fungi, etc.)" [accessed June 16, 2009]
• Alternative Medicine Foundation, Inc. HerbMed®. "HerbMed®—an interactive, electronic herbal database—provides hyperlinked access to the scientific data underlying the use of herbs for health. It is an evidence-based information resource for professionals, researchers, and general public." [accessed June 16, 2009]
• American Association of Poison Control Centers (AAPCC). The AAPCC is a US-based organization of poison centers and interested individuals who coordinate information on common poisons. [accessed June 16, 2009]
• The Vaults of Erowid. The Vaults of Erowid website contains information on a wide variety of natural plants and chemicals. [accessed June 16, 2009]

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Mebs, Dietrich. *Venomous and Poisonous Animals: A Handbook for Biologists, Toxicologists and Toxinologists, Physicians and Pharmacists*. Medpharm, 2002.
"Amanita phalloides Mushroom Poisoning – Northern California, June 6, 1997". MMWR 46, 22 (1997): 489-491. [accessed June 16, 2009].
"Neurologic Illness Associated with Eating Florida Pufferfish, 2002". *MMWR* 51, 15 (2002): 321-323. [accessed June 16, 2009].
"Epidemiologic Notes and Reports Jimson Weed Poisoning -- Texas, New York, and California, 1994". *MMWR* 44, 3 (1995): 41-44. [accessed June 16, 2009].

A Small Dose of Neurotoxicology

or

An Introduction to Toxicology of the Nervous System

Introduction

• • •

> "The upsurge of interest in recent years in academia, industry, and government on the effects of toxic chemicals on the nervous system has created a new discipline of neurotoxicology."
>
> - Peter S. Spencer & Herbert H. Schaumberg, in *Experimental and Clinical Neurotoxicology*, 1980

• • •

The human brain is the most complex structure ever developed. It is only in the last few decades that we have begun to truly appreciate its flexibility, its complexity, and its vulnerability. The flexibility of the human nervous system is remarkable: when our ancient ancestors struggled for survival they were dependent on fire, hunting, and caves for shelter, while we rely on electricity, the supermarket, and central heating and cooling. For most, our ability to process complex information is far more important than our strength and reflexes.

The brain's complexity is made evident by the billions of cells that form billions upon billions of connections, all in a remarkably small confined space. In turn these cells communicate using chemicals called neurotransmitters. Neurotransmitters are frequently the target of drugs and chemicals that affect the nervous system. Prozac, a drug used to treat mild depression, affects the neurotransmitter serotonin.

The vulnerability of the nervous system to both temporary changes and permanent damage from a wide variety of agents is increasingly evident. For thousands of years humans have searched out agents that affect the nervous system. Many people today are regular users of alcohol, caffeine, or other agents designed to affect the nervous system. Industrialization ushered in an era of rapid development of new chemicals, often accompanied by human exposure that we learned, sometimes through tragic experience, can irreparably damage the nervous system. No one can reach his or her full genetic potential with a damaged nervous system. As a consequence, neurotoxicology developed as a discipline in the 1970s to advance our understanding of the effects of chemicals on the nervous system.

What is Neurotoxicity?

> **Neurotoxicity or a neurotoxic effect:** an adverse change in the chemistry, structure, or function of the nervous system following exposure to a chemical

or physical agent

Voluntarily and involuntarily, we are exposed to a range of chemicals that affect the nervous system. We spend billions of dollars every year voluntarily purchasing chemicals such as caffeine, alcohol, and nicotine to influence our nervous system. Most stores and many industries are dependent on our desire to influence our nervous system. Many of us are familiar with the undesirable effects of too much caffeine or alcohol, which is a form of neurotoxicity. Fortunately, we quickly recover from the neurotoxic effects of caffeine or alcohol and learn to manage our consumption of these chemicals to minimize the undesirable effects and maximize the desirable effects. In this sense, many of us are experienced neurotoxicologists.

Voluntary consumption of drugs that our society has classified as illegal is also common. These drugs range from the active ingredient of the easily cultivated marijuana plant to chemicals produced in illicit laboratories. Billions of dollars are spent on the purchase of illegal drugs and in turn billions more are spent on trying to stop their manufacture and purchase. The direct and indirect costs to our society of the "war on drugs" are enormous.

A range of legal drugs is sold by the pharmaceutical industry to treat illnesses of the nervous system. Advances in our understanding of the structure and function of the nervous system has accelerated the development of chemicals for treating diseases such as Parkinson's syndrome, Alzheimer's disease, and mild depression. The treatment of mild depression with drugs like Prozac is a billion-dollar industry. However, some drugs may produce undesirable nervous system side effects that can limit their utility in disease treatment. The anticancer drugs vincristine and cisplatin damage sensory nerves in the fingers and the antibiotic gentomycin can affect hearing.

We are also involuntarily exposed to chemicals, compounds, or even physical agents that can damage the nervous system. The science of neurotoxicology has largely focused on understanding the adverse effects of agents on the nervous system. This research has shown that the nervous system, particularly the developing nervous system, is vulnerable to permanent damage by a number of agents. For example, even low levels of lead exposure will permanently damage the nervous system of young children, reducing their ability to learn and perform well in school, and ultimately affecting their performance and quality of life as adults. Alcohol, while having a predictable effect on the pregnant mother, can be disastrous for the nervous system of the developing infant. Many workers are exposed to agents such as solvents or pesticides that can transiently affect the nervous system or even cause permanent damage. Physical agents such as noise and heat can also adversely affect the nervous system or degrade performance. Many people, including construction workers who routinely use hearing protection devices, are a testament to the awareness that excessive exposure to loud noise will permanently damage hearing.

A more formal definition of neurotoxicity or a neurotoxic effect is as an adverse change in the chemistry, structure, or function of the nervous system following exposure to a chemical or physical agent. An important part of this definition is that

the effect may produce either structural change in the nervous system, such as gross cell loss, or functional changes that may be related to subtle changes in nerve cell communication. Even minor changes in the structure or function of the nervous system may have profound consequences for neurological, behavioral, and related body functions. Often the very young and elderly are more susceptible to neurotoxic effects. Lead is a good example of a compound that at high levels of exposure can cause actual nerve cell damage but at low levels, particularly in children, can cause functional losses such as decreased learning and memory.

Defining and testing for neurotoxicity is difficult because there is no one easy-to-define measure. Neurotoxicology effects can be divided into five areas (Table 17.1).

Table 17.1 Neurological and Behavioral Effects of Exposure to Toxic Substances

Motor effects	Convulsions, weakness, tremor, twitching, lack of coordination, unsteadiness, paralysis, reflex abnormalities, activity changes
Sensory effects	Equilibrium changes, vision disorders, pain disorders, tactile disorders, auditory disorders
Cognitive effects	Memory problems, confusion, speech impairment, learning impairment
Mood and personality effects	Sleep disturbances, excitability, depression, irritability, restlessness, nervousness, tension, delirium, hallucinations
General effects	Loss of appetite, depression of neuronal activity, narcosis, stupor, fatigue, nerve damage

Adapted from W.K. Anger (1986)

Case Studies

Caffeine

Caffeine is the most widely consumed stimulant drug in the world. It occurs naturally in coffee, tea, and the cola nut and is added to many soft drinks. Many of us consume coffee and soda drinks because of the desirable stimulatory effects produced by caffeine; many of us have consumed too much caffeine and felt the consequences. The undesirable effects of caffeine—the agitation, the inability to concentrate, the mild

tremors, and the general unpleasantness—are a form of neurotoxicity. Literally your brain, and more specifically, the adenosine receptors in your brain, has too much caffeine. These effects are a reversible form of neurotoxicity as we metabolize caffeine quickly. By experience we have learned how to moderate our caffeine consumption to avoid the unpleasant side effects. A great deal of money is made from the neuroactive and physiological effects of caffeine. You can learn more about this fascinating drug in the chapter on caffeine.

Lead

The decision to use lead as a gasoline additive resulted in one of the greatest public health disasters of the 20th century. Lead from the tail pipes of cars settled as dust over wide areas and was most prevalent in high-traffic areas along city streets. Going from hand to mouth, the lead from cars and some additional lead from old lead-based paint were ingested by young children. In the 1970s and 1980s, researchers demonstrated that even low levels of lead exposure damaged the nervous system of children, confirming what the Greeks knew 2000 years ago: that "Lead makes the mind give way" (Dioscorides). Exposure of the developing nervous system to lead causes irreversible harm, degrading the learning and memory capabilities of the child and resulting in a lifetime of deficit. While lead was banned from most paint and removed from gasoline, it still remains a threat to many children living in older homes with lead paint or near areas contaminated with lead. Lead is still turning up in children's toys, jewelry, PVC plastics (as a stabilizer), and other products accessible to children. Lead is an example of a neurotoxic agent that causes permanent, irreversible damage to the developing nervous system, robbing children of their genetic potential. You can learn more about developmental effects of lead in chapter 8.

Prozac (fluoxetine hydrochloride)

Prozac, produced by the pharmaceutical company Eli Lilly and Company, was first approved for the treatment of depression in Belgium in 1986. A year later, in 1987, it was approved for use in the United States. It is now approved for use in over 90 countries and used by more than 40 million people worldwide. Needless to say it is a very profitable drug.

Prozac is commonly prescribed for treatment of mild depression, which is not uncommon as we make our way through the dramas and disappointments of life. Prozac, similar to many neuroactive chemicals, has a remarkably specific effect on one neurotransmitter. Typically, a neurotransmitter is released from one cell to communicate across a very small gap and picked up by a neuroreceptor on another cell. Once the neurotransmitter has performed its function of communicating with the other, it is either degraded or taken back up by the releasing cell to be reused. Prozac functions by blocking this reuptake, thus leaving more neurotransmitter within the cell gap to continue stimulating the receiving cell. Prozac selectively inhibits the reuptake of the neurotransmitter serotonin. The increased availability of serotonin appears to reduce the symptoms of depression. A range of drugs, including the well-known hallucinogen LSD, acts through serotonin.

MPTP and Parkinson's disease

In the early 1980s, MPTP or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was

accidentally produced as a contaminant of a new compound that clandestine chemists created in their search for a synthetic heroine. Tragically, drug users exposed to MPTP developed tremors and a lack of muscle control that was very similar to symptoms of Parkinson's disease. Parkinson's disease is usually a slow-developing disease associated with the natural process of aging and the dying of cells in the brain. Further study revealed that MPTP attacked cells in a specific area of the brain that produces the neurotransmitter dopamine, the very same cells implicated in Parkinson's disease. This was the first time that a compound was clearly implicated in causing Parkinson's-like disease. Researchers immediately began searching for other compounds that might cause Parkinson's disease or interact with the aging processes to accelerate the onset of the disease. A number of studies have examined the association of exposure to some pesticides with an increase in Parkinson's disease. Researchers now use MPTP to develop animal models for finding new treatments for Parkinson's disease and to better understand the underlying progression of the disease.

Biology of the Nervous System

Overview

The nervous system can be divided into the central nervous system (CNS), which includes the brain and spinal cord, and the peripheral nervous system (PNS), which carries information to and from the CNS. The PNS is the information highway while the CNS is the coordinating center. Sensory information such as touch or pain is transmitted to the CNS by the nerves of the PNS. For example, if we touch something hot the CNS will then command, through the PNS, to move those muscles that will withdraw us from the pain, in the case of something hot. The CNS also communicates with a number of glands and organs through the PNS. In addition to the basic functions of keeping us alive, the brain is responsible for our thinking, reasoning, and emotions.

The brain is incredibly complex. It is estimated to contain between 10 billion and 100 billion cells that form approximately 10^{15} connections; this is a huge number, 100 million times more than the 42 million transistors on a state-of-the-art microprocessor chip. The information-processing capabilities of the brain are enormous. The nervous system starts developing early in gestation and continues to grow and change, particularly in the first few years of infancy and childhood. During development, the brain organizes into separate but interconnected areas that control different functions. For example, the area of the brain that processes visual information is located in the back of your head. During development, cells from the eyes must connect with cells of the optic nerve to move information to the visual processing center of the brain. This complex dance of one cell looking for a partner in another area of the brain is one reason the brain is so sensitive to disruption by a range of compounds.

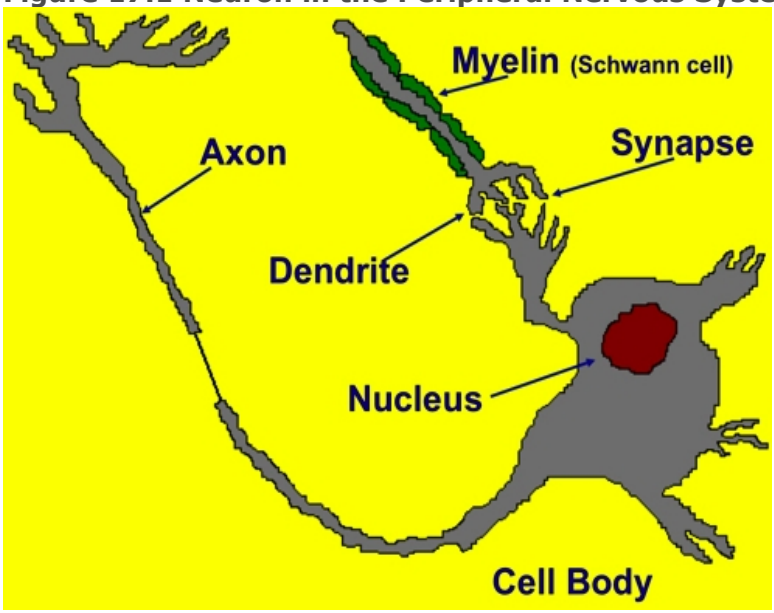
The peripheral nerves undergo many similar challenges. Think of the longest nerves in your body that run from the bottom of your spinal cord to your toes. These very long cells must be able to connect, grow, and communicate with the right cells of the spinal cord, which in turn must communicate with the cells of the brain.

Cells of the Nervous System

The nervous system consists of cells called neurons (Figure 17.1), that are responsible for the majority of information transfers in the central and peripheral nervous systems and supporting cells. In the PNS, the neurons can be very long. For example, consider the information that must be sent to and from your fingers or toes to sense touch or pain or move the muscles. The neurons have a cell body and a long connecting structure called an axon. To increase the transmission speed along the axon, another cell, a Schwann cell, wraps the axon to provide a form of insulation and facilitate the movement of electrical signals. The Schwann cells literally wrap themselves around the long axon, forming multiple layers similar to tree rings. As will be discussed below these cells are susceptible to damage because of the long axon and the energy requirements of the cell.

In the CNS, glial cells aid in the communication between densely packed neurons. These cells also play a big part in forming the blood-brain barrier. The blood-brain barrier keeps some classes of chemicals from entering the brain, which can make it very difficult to treat diseases of the brain. However, some chemicals, such as caffeine, readily enter the brain, as do many other neuroactive compounds. Compounds essential for function are actively transported across this barrier.

Figure 17.1 Neuron in the Peripheral Nervous System

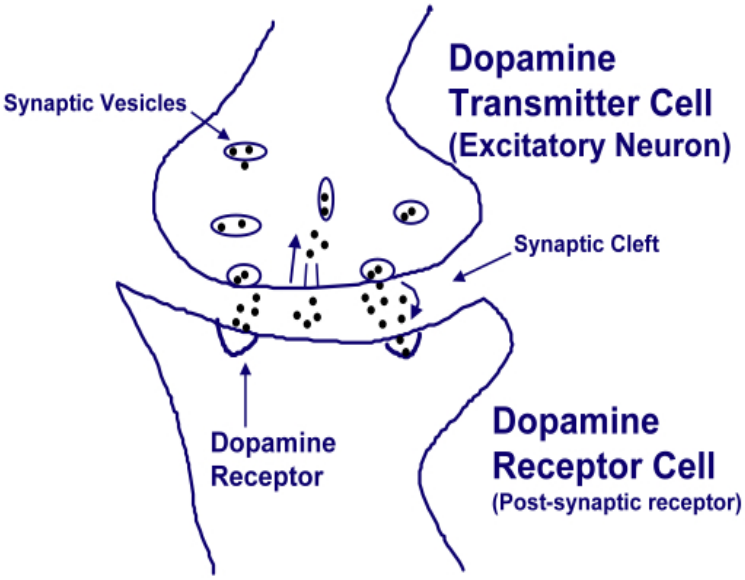


Transmission of Information in the Nervous System

Nerve cells communicate by the release of chemicals (neurotransmitters) into the space between the cells (Figure 17.2). The neurotransmitter is typically stored in a small packet (synaptic vesicle) and then released in response to a signal that is transmitted down the cell axon. In the example in Figure 17.2, dopamine, an important neurotransmitter involved in movement disorders related to Parkinson's disease, is released into the gap (synaptic cleft) and reacts with specific receptors on the adjacent cell. This in turn causes a reaction in the adjacent cell. Dopamine in the gap can either be broken down or absorbed into the releasing cell and repackaged for future use.

In Parkinson's disease the dopamine-releasing cells are damaged or die, thus reducing the release of dopamine. Loss of the dopamine neurotransmitter contributes to the movement disorders associated with Parkinson's disease. Typically, the loss of dopamine-producing cells in a very specific location in the brain does not become evident until old age, and for a long time Parkinson's disease was thought of as strictly age related. In the 1970s this concept was changed when chemists produced a designer drug meant to mimic common narcotics; the drug had an impurity that resulted in Parkinson's-like syndrome in young people never thought to be susceptible to Parkinson's disease. A specific compound, MPTP, was found to cause the death of the dopamine-producing cells in the same area of the brain. While the consequence to the individuals was tragic, MPTP has proven to be a very important research tool for understanding this disease as well as developing new treatments.

Figure 17.2. Nervous System Communication



What Causes Neurotoxicity?

There is no simple or correct way to examine the causes of neurotoxicity. I have divided them into three overlapping areas: neurotransmitter/receptor effects, which are often transient; damage to the peripheral nerves, which is often permanent; and damage to the developing nervous system, which is almost always permanent.

Nerve cells have unique structural and physiological features that often make them more susceptible to damage from chemical agents. Cells of the central nervous system have a high metabolic rate that makes them highly dependent on glucose and oxygen, much like computer chips need lots of electrical power. Anything that disrupts the flow of glucose or energy utilization within the cell causes a loss of function and potentially long-term damage. Nerve cells, unlike muscle cells, can only work for a very short time without oxygen. The most obvious indicator of this is that we quickly loose consciousness when our brain is deprived of well-oxygenated blood. Agents like carbon monoxide reduce the availability of oxygen to the brain, quickly causing unconsciousness or even death. Cyanide, working by a very different mechanism, inhibits a cell's ability to utilize oxygen, which produces the same results. In the

peripheral nervous system, the length of cells contributes to their increased susceptibility to damage from agents that disrupt the transfer of nutrients along the length of the cell. Acrylamide, for example, causes damage to the cell transport system, which results in paralysis that is first noticed in the legs.

In the majority of cases, the cells of the nervous system cannot divide and replace themselves, thus most damage is permanent. The developing nervous system exposed to lead will be damaged for a lifetime. However, peripheral nerves can grow, recovering some of the connections and functionality that results in some sensation and return of movement, usually most noticeable in the arms and legs.

Neurotransmitter/Receptor Effects

Many naturally occurring compounds and an increasing number of synthesized chemicals work by influencing the effectiveness of a specific neurotransmitter. Typically neurotransmitters are released from one neuronal cell and are picked up by specific receptors in the adjacent cell, which causes the receiving cell to react. The receptor then releases the neurotransmitter into the gap between the cells. At this time the neurotransmitter must be removed either by being broken down by a specific enzyme or be taken back up by the releasing cell to be reused. A compound can influence a neurotransmitter and thus the response of the receiving cell in several ways: 1) blocking the receptor so that the neurotransmitter cannot reach the receptor and thus the receiving cell is unable to respond; 2) mimicking the neurotransmitter so that the receiving cell responds even though there is no naturally occurring neurotransmitter; 3) blocking the degradation of the neurotransmitter, thus leaving the neurotransmitter to react with another receptor; or 4) blocking the reuptake of the neurotransmitter into the releasing cell, which leaves the neurotransmitter free to react again with the receptor.

Table 17.2 provides just a few examples of different neuroactive agents and their mechanism of action. Caffeine, the most widely consumed stimulant drug in the world, works by affecting the adenosine receptor. Adenosine is a naturally occurring depressant, so caffeine works by blocking the depressive actions of adenosine, causing stimulation.

Table 17.2 Mechanism of Action of Neuroactive Agents

Compound	Neurotransmitter	Action
Caffeine	Blocks the adenosine receptor	Stimulant
Organophosphate insecticides	Increase the neurotransmitter acetylcholine by blocking its degradation	Stimulant

Nicotine	Mimics acetylcholine, thus looks like increased acetylcholine	Stimulant
Fluoxetine (Prozac)	Increases serotonin by blocking its reuptake into neuronal cells	Stimulant
LSD (lysergic acid diethylamide)	Mimics serotonin, thus stimulating receptor	Hallucination
THC: Delta 9-tetrahydrocannabinol (Cannabis)	Cannabinoid receptor	Relaxation, euphoria, enhancement of senses, increase in appetite and sense of time
Cocaine	Blocks dopamine transporter, thus increasing dopaminergic stimulation	Increases alertness and energy, euphoria, insomnia, restlessness, fear, paranoia, hallucinations
Domoic acid (shellfish)	Glutamate, aspartate	Loss of memory

Agents acting through a specific neurotransmitter are often transient, and exposure must be repeated to continue the effect, an example is our repeated need for caffeine every morning. This is not always the case. Very potent (poisonous) nerve gases permanently block the agent responsible for degrading acetylcholine, causing death because the nervous system cannot recover.

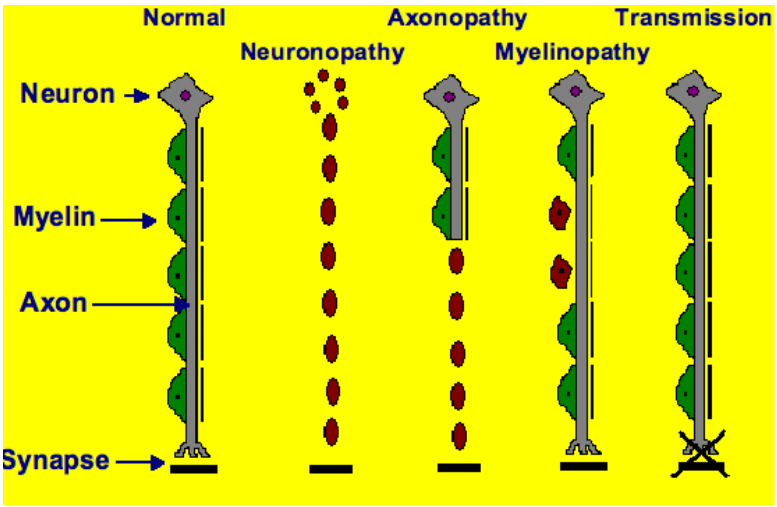
Damage to the Peripheral Nerves

The peripheral nerves of the body communicate sensation and deliver commands from the central nervous system to move muscles from our fingers to our toes—quite a distance. Peripheral nerves are wrapped by a specialized cell to form an insulation (myelin) that aids the transmission of electrical signals along the length of the nerve cell. Agents damage the peripheral nervous system either by killing the nerve cell (neuronopathy), attacking the axon (axonopathy), or attacking the insulation that surrounds the cells (myelinopathy) (Table 17.3 and Figure 17.3). Interfering with the neurotransmitter is a form of transmission toxicity, which was discussed in more detail above.

Table 17.3 Peripheral Nervous System Damage

Name	Type	Example
Neuronopathy	Nerve cell death	MPTP, trimethyltin
Axonopathy	Degeneration of axon	Hexane, acrylamide
Myelinopathy	Damage to myelin (e.g. Schwann cells)	Lead, hexachlorophene
Transmission toxicity	Disruption of neurotransmission	Organophosphate pesticides, cocaine, DDT

Figure 17.3 Peripheral Nervous System Damage



Damage to the Developing Nervous System

The developing nervous system is more vulnerable to damage than the mature nervous system for a number of reasons. The blood-brain barrier of the central nervous system is not well developed in the very young, which allows toxic agents easy access to the nervous system. The nervous system develops through our gestation and continues changing well into our teens with cells multiplying, growing in size or length, migrating to a new location, or forming connections with other cells. During this period toxic agents may kill cells, interfere with their migration, or interfere with the cell-forming connections. Different areas of the nervous system develop at different times, so exposure to an agent such as alcohol during the fourth month of gestation will have different effects than exposure during the sixth month.

Damage to the brain can range from the severe and obvious to the very subtle and undetectable. Exposure to high levels of alcohol during gestation can cause obvious

reductions the ability of a child to perform well in school and even contribute to society. More difficult to assess is the damage caused by very low levels of exposure. Low levels of exposure to alcohol or lead during development may reduce a child's IQ only slightly, by a degree that is within the normal range of variation. These more subtle changes can only be examined by comparing large groups of people, some of whom are exposed to the agent and some that are not. Group-based studies such as these were the first to show that even low levels of lead exposure during development can cause subtle decreases in IQ, thus depriving an individual of the ability to reach their full genetic potential. Any one individual would not know if their intellectual capabilities had been reduced, but on a large scale these changes have serious implications for society. Additional information is available in the lead and alcohol chapters.

Another area of concern is exposure to fat-soluble compounds such as PCBs or chlorinated pesticides. All cells contain lipids or fat; the high number of densely packed cells of the brain means that the brain is just a big ball of fat. The brain is a great storage site for fat soluble compounds can cross the blood-brain barrier. An additional concern is that these compounds can be mobilized from the fat of women breastfeeding their infants, resulting in exposure to the infant and, given the size of the infant, this exposure translates into a large dose.

Diseases of the Nervous System

Can toxic agents cause what have been classically defined as diseases of the nervous system, such as Parkinson's disease, Alzheimer's type dementia, multiple sclerosis, or amyotrophic lateral sclerosis (ALS)? The discovery that the chemical MPTP can cause a syndrome very similar to Parkinson's disease focused people's attention on the possibility that chemical agents may play a role in the onset of neurological disorders once exclusively associated with aging or just bad luck. MPTP selectively damaged the same neurons, in the same area of the brain, as those responsible for Parkinson's disease. Supporting the hypothesis that chemical agents may contribute to Parkinson's disease were data showing that the incidence of this disease was correlated with the increased use and exposure to chemicals. Additional research found that the active metabolite of MPTP that was really responsible for damaging the neurons, was very similar to the chemical structure of some pesticides. This immediately raised the question: Could pesticide exposure increase the incidence of Parkinson's disease or cause the disease to occur at an earlier age? In fact, researchers did find some correlation with pesticide exposure in farm workers and the onset of Parkinson's disease.

Exposure to metals is associated with a number of neurological disorders, so it was reasonable to ask: Could exposure to metals contribute to age-related neurological disorders? Researchers found that brain cells of many Alzheimer's patients has elevated levels of aluminum, and kidney dialysis patients could suffer from a neurological disorder related to elevated exposure to aluminum. Additional study has never found that aluminum exposure causes Alzheimer's disease; there is, however, some data supporting the possibility that exposure to mercury results in accelerated age-related decline of cognitive function.

Neurological and psychiatric disorders such as depression, hyperactivity, and manic depression have driven many pharmaceutical companies to develop neuroactive drugs to treat these conditions. This is an active area of research that will accelerate as we gain more knowledge of the underlying mechanisms of the nervous system. Early drugs used to treat psychiatric disorders often had highly undesirable side effects that often limited their long-term use or required additional drugs to manage the complications. Newer drugs are more specific and have fewer side effects.

The following table lists a few of the examples of neurotoxicology caused by a variety of agents.

Table 17.4 History of Neurotoxicology

Year(s)	Location	Substance	Comments
400 BC to now	Worldwide	Lead	Hippocrates recognizes lead toxicity in the mining industry; lead used to sweeten Roman wine; modern: lead used in paint and as a gasoline additive; low-level lead exposure shown to damage the nervous system of children
Ancient	Worldwide	Mercury	Mine workers poisoned; 1930s hat industry (the Mad Hatters); 1950s Japan mercury in fish; 1970s mercury in seed grain; acceptance of mercury as a developmental neurotoxicant; released from coal fired electrical plants; ongoing contamination of fish
1930s	United States (Southeast)	TOCP	Compound often added to lubricating oils contaminates "Ginger Jake," an alcoholic beverage; more than 5,000 paralyzed, 20,000 to 100,000 affected
1930s	Europe	Apiol (w/TOCP)	Abortion-inducing drug containing TOCP causes 60 cases of neuropathy
1932	United States (California)	Thallium	Barley laced with thallium sulfate, used as a rodenticide, is stolen and

			used to make tortillas; 13 family members hospitalized with neurological symptoms; 6 deaths
1937	South Africa	TOCP	60 South Africans develop paralysis after using contaminated cooking oil
1950s	France	Organotin	Contamination of Stalinon with triethyltin results in more than 100 deaths
1950s	Morocco	Manganese	150 ore miners suffer chronic manganese intoxication involving severe neurobehavioral problems
1950s-70s	United States	AETT	Component of fragrances found to be neurotoxic; withdrawn from market in 1978; human health effects unknown
1956	Wales	Endrin	59 people become ill after eating bakery foods prepared from flour contaminated with the insecticide endrin; convulsions resulted in some instances
1956	Turkey	HCB	Hexachlorobenzene, a seed grain fungicide, leads to poisoning of 3,000 to 4,000; 10 percent mortality rate
1956-77	Japan	Clioquinol	Drug used to treat travelers' diarrhea found to cause neuropathy; as many as 10,000 affected over two decades
1959	Morocco	TOCP	Cooking oil contaminated with lubricating oil affects some 10,000 individuals

1968	Japan	PCBs	Polychlorinated biphenyls leaked into rice oil, 1,665 people affected
1969	Japan	n-hexane	93 cases of neuropathy occur following exposure to n-hexane, used to make vinyl sandals
1971	United States	Hexachlorophene	After years of bathing infants in 3 percent hexachlorophene, the disinfectant is found to be toxic to the nervous system and other systems
1971	Iraq	Mercury	Mercury used as fungicide to treat seed grain is used in bread; more than 5,000 severely poisoned, 450 hospital deaths, effects on many infants exposed prenatally not documented
1973	United States (Ohio)	MnBK	Fabric production plant employees exposed to solvent; more than 80 workers suffer polyneuropathy, 180 have less severe effects
1974-75	United States (Hopewell, VA)	Chlordecone (Kepone)	Chemical plant employees exposed to insecticide; more than 20 suffer severe neurological problems, more than 40 have less severe problems
1976	United States (Texas)	Leptophos (Phosvel)	At least 9 employees suffer serious neurological problems following exposure to insecticide during manufacturing process
1977	United States (California)	Dichloropropene (Telone II)	24 individuals hospitalized after exposure to pesticide Telone following traffic accident
1979-80	United States (Lancaster,	BHMH (Lucel-7)	Seven employees at plastic bathtub manufacturing plant experience

	TX)		serious neurological problems following exposure to BHMH
1980s	United States	MPTP	Impurity in synthesis of illicit drug found to cause symptoms identical to those of Parkinson's disease
1981	Spain	Toxic oil	20,000 people poisoned by toxic substance in oil, resulting in more than 500 deaths; many suffer severe neuropathy
1985	United States	Aldicarb	More than 1,000 individuals in California and other Western States and British Columbia experience neuromuscular and cardiac problems following ingestion of melons contaminated with the pesticide aldicarb
1987	Canada	Domoic acid	Ingestion of mussels contaminated with domoic acid causes 129 illness and 2 deaths; symptoms include memory loss, disorientation, and seizures
1991	United States	Domoic acid	Shellfish contaminated with domoic acid found in the Northwest
2001	United States	Chlorpyrifos	Powerful insecticide phased out for home use

Adapted from: *Neurotoxicity: Identifying and Controlling Poisons of the Nervous System* US Congress, Office of Technology Assessment (1990)

Who Is Vulnerable?

Without a doubt the developing fetus and child are the most vulnerable to the effects of chemicals on the nervous system. Children have no control over these exposures, which can result in a lifetime of disability. The nervous system of adults is clearly affected by a range of chemicals, both those we voluntarily expose ourselves to and those in our environment.

The home, workplace, and general environment each represent unique places of possible exposure to neuroactive agents. The home contains a range of compounds that affect the nervous system: caffeine in coffee and tea, alcohol, medicines, pesticides, cleaning agents, paints, and solvents, to name just a few. Compounds such as lead or pesticides can be tracked into the home on shoes or bare feet. Working family members may bring agents such as lead home on clothing. Probably the greatest concern in workplaces is solvent exposure from cleaning agents or chemical processes. Farmers and pesticide workers can also be exposed to compounds clearly designed to affect the nervous system. The outdoor environment can contain elevated levels of a number of persistent chemicals that can adversely affect the nervous system, such as lead, mercury, and chlorinated pesticides.

Table 17.5 Exposure to Neurotoxic Compounds

Home	children: during development from maternal exposure children: lead in the home cleaning agents solvents
Workplace	solvents pesticides
Environment	lead mercury (in fish) pesticides persistent environmental pollutants

Regulatory Standards

As our appreciation for the subtle neurological effects and long-term consequences of exposure to compounds has increased, there has been a gradual increase in the testing requirements for new compounds. Government agencies can now require additional testing for the neurotoxic effects of a compound. However, for many compounds we know very little about their potential to cause neurotoxicity or affect the developing nervous system. In the case of lead, there is no safety factor included in the levels of concern indicated by the Center for Disease Control; the standard was based on a low level found in the general population when lead was removed from gasoline. In general, the government struggles to keep up with the ever-growing list of new chemicals and struggles to assess their potential to cause neurotoxic injury.

Recommendation and Conclusions

Many of us regularly consume compounds that affect our nervous system and are well aware of chemicals that cause neurotoxicity, so the recommendation is simple: be aware. The developing nervous system is very sensitive to neurotoxicity and exposure

to the wrong chemical at the wrong time can cause a lifetime of disability. From an ethical and social perspective this vulnerability of the developing nervous represents unique challenges and responsibilities. Many of the persistent bioaccumulative toxicants are neurotoxic, which is a compelling reason for these compounds to be phased out or banned. Our expanding understanding of the nervous system, combined with the knowledge of the subtle harm that can be done, is one of the most important contributions of the toxicological sciences.

Additional Resources

Slide Presentation and Online Material

A Small Dose of Neurotoxicology presentation material and references. Website contains presentation material related to the neurotoxic effects of chemicals.

European, Asian, and International Agencies

- Organization For Economic Co-Operation And Development (OECD). Chemical Safety. This OECD Site contains general information on chemical safety as well as specific testing guidelines for neurotoxic effects of chemicals. [accessed June 20, 2009]
- International Neurotoxicology Association (INA). Site provides links to neurotoxicology testing guidelines and other information on neurotoxicology. [accessed June 20, 2009]
- International Brain Research Organization (IBRO). "IBRO is a nonprofit international organization for neuroscientists." [accessed June 20, 2009]

North American Agencies

- US Food and Drug Administration (FDA). Neurotoxicology. Information on FDA and neurotoxicology. [accessed June 20, 2009]
- US National Institute of Health. National Institute of Neurological Disorders and Stroke (NINDS). NINDS is works to shape "the future of research and its relationship to brain diseases". [accessed June 20, 2009]
- US National Research Council. Environmental Neurotoxicology. Publication available on the web at this site. [accessed June 20, 2009]

Non-Government Organizations

- Society for Neuroscience (SFN). "SFN is a nonprofit membership organization of basic scientists and physicians who study the brain and nervous system." [accessed June 20, 2009]
- ALS Association (ALSA). The mission of The ALS Association is to find a cure for and improve the quality of life for those afflicted with ALS. [accessed June 20, 2009]
- Institute of Neurotoxicology & Neurological Disorders (INND). INND was founded in 1999 and focuses on education and policy issues related to neurotoxicology. [accessed June 20, 2009]
- Neurobehavioral Teratology Society (NBTS). The NBTS mission is to understand how the environment affects the health of infants and children. [accessed June 20, 2009]

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Spencer, Peter S. and Herbert H. Schaumburg (Eds). *Experimental and Clinical Neurotoxicology 2nd edition*. New York: Oxford University Press, 2000.

Dobbs, Michael R. *Clinical Neurotoxicology: Syndromes, Substances, Environments*. Philadelphia: Saunders, 2009.
Harry, G. Jean, and Hugh A. Tilson. *Neurotoxicology, Third Edition (Target Organ Toxicology Series)*. New York: Informa HealthCare 2009.
US Environmental Protection Agency "Guidelines for Neurotoxicity Risk Assessment". *Federal Register* 63, 93 (1998):26926-26954.

A Small Dose of Cancer

or

An Introduction to the Health Effects of Cancer

Introduction

Cancer is the uncontrolled growth of cells that have damaged DNA expression. The cancerous cells repeatedly divide, displacing normal tissue. The cancer or neoplasm may be either benign or malignant: a benign cancer stays confined to the tissue of origin, while malignant cancer can spread to other organs. The secondary growths or metastases are a serious complication to any treatment of the cancerous cells. A tumor is any space-filling group of cells that may or may not be cancerous.

Benign growths or tumors are usually noted by adding the ending "-oma." For example, adenoma would be a benign growth of the adrenal cortex, a hormone-producing group of cells near the kidney. Malignant tumors are noted by adding "sarcoma" or "carcinoma". A malignance of the adrenal cortex would be an adenocarcinoma. Bone cancer would be osteosarcoma.

Toxicology informs us about cancer on two accounts. First, toxicology research provided insight into the causes of cancer and likelihood of developing cancer. Second, many cancer treatments have serious toxicological side effects. Cancer treatment must often balance the need to kill the cancerous cells and the need to protect healthy cells.

Cancer: A Short History

The oldest descriptions of cancer date back to Egypt, at about 1600 BC. The so-called Edwin Smith Papyrus describes eight cases of what appears to be breast cancer. The tumors of the breast were treated by cauterization, with a tool called "the fire drill."

The first occupational association with cancer was noted in 1700 with the observation that nuns had an elevated incidence of breast cancer. In 1775, the English physician and surgeon Percivall Pott made the observation that exposure to soot might explain

the high incidence of scrotum cancer in chimney sweeps. This was the first indication that exposure to chemicals, in this case a complex mixture, could cause cancer. However, this new knowledge did not immediately translate into improved working conditions for chimney sweeps. Over 100 years later it was observed that cancer of the scrotum was rare in continental Europe but still high in England, possibly due to better hygiene practices in Europe. We still have not taken to heart the cancerous consequences of exposure to smoke and tar, as ongoing consumption of tobacco products clearly shows. (Photo: chimney sweep in the 1850s.)

The industrial revolution of the late 19th and early 20th centuries brought clear confirmation that occupational exposure to chemicals could cause cancer. The first indication came from increases in skin and bladder cancers associated with cutting oils and dyes. In 1895, bladder cancer was associated with workers in the aniline dye industry. Further worker-based studies found that exposure to specific chemicals could be responsible for the cancer. In 1915, Japanese researchers reported that they could induce skin tumors in animals by repeatedly applying a coal tar solution to the skin of rabbits. These early studies, subsequently repeated with mice, ushered in the scientific investigation of the chemical causes of cancer. These studies also initiated the systematic investigation of the adverse health effects of chemicals, which in many ways laid the foundation for the toxicological sciences.

But chemicals are not the only cause of cancer. Marie Curie, awarded Nobel Prizes in both physics and chemistry, discovered radium in 1898. The green glow of radium fascinated people, and many thought it was a cure for many diseases, including cancer. The carcinogenicity of radium became tragically apparent when young women developed bone cancer from painting watch dials with radium. The use of nuclear weapons by the US military in World War II, and subsequent development of the defense and nuclear industries in various countries, have raised public awareness of the health consequences of radiation exposure. Naturally occurring background radiation, as well as our many medical and industrial exposures to radiation, is responsible for some cancers.

More recent research has broadened our understanding of cancer's causes. Epidemiology studies of various human populations indicated that inorganic metals such as arsenic and nickel could cause cancer; this was subsequently confirmed in animal studies. Various hormones are implicated in organ-specific cancer, such as breast cancer. Nutrition and diet also appear to be related to cancer, specifically high caloric intake. The grain contaminant aflatoxin B1 is known to cause liver cancer.

Chemical mixtures or exposure to multiple agents can increase the incidence of cancer; for example, smoking and asbestos exposure increase the likelihood of lung cancer. And finally, we are now learning that our genetic makeup increases the likelihood that certain cancers will develop. For example, breast cancer is linked to specific genes.

Table 18.1 Selected History of Cancer

Year	Cancer Type	Cause
1775	Scrotal Cancer	Soot
1822	Skin Cancer	Arsenic
1879	Lung Cancer	Uranium Mining
1895	Bladder Cancer	Aniline Dyes
1902	Skin Cancer	X-rays
1908	Leukemia	Filterable Agents
1914	Experimental induction of skin cancers	Coal Tar
1928	Experimental induction of skin cancers	UV Light

Cancer Case Studies

Soot

In 1775, Percivall Pott observed that there was an increased incidence of scrotum cancer in chimney sweeps and suggested that soot might be the cause. This was the first linking of occupational chemical exposure to cancer. Unfortunately this understanding was not translated into action and prevention. By the late 1890s, scrotal cancer was relatively rare on the European content but still high in England, which some suggested was due to poor hygiene: failure to remove the soot from the skin resulted in chronic exposure to the chemicals in soot, which resulted in cancer. This example recalls the most basic tenets of public health: wash your hands (or other body parts).

Scientific investigation of the cancer-causing properties of soot took a step forward when Japanese research found that skin tumors developed if coal tar was repeatedly

applied to the skin of rabbits. In the 1930s polycyclic aromatic hydrocarbons were isolated from coal tar and demonstrated to be carcinogenic. Despite this evidence, millions of people continue to expose themselves to the soot from tobacco and suffer from the resulting lung cancer.

Benzene

Benzene, C_6H_6, is a clear, colorless liquid at room temperature that readily evaporates. It is derived from petroleum and is widely used in the production of other products such as rubber, nylon, synthetic fiber, lubricants, glues, detergents, dyes, drugs, and pesticides, to name just a few. Worldwide, benzene use and production are measured in the billions of pounds, making it one of the top twenty chemicals in use. In the United States, benzene is present in gasoline at about 2%, but in other countries the amount may be up to 5%.

Benzene is classified as a human carcinogen. Liver enzymes convert benzene to more toxic metabolites; this mechanism is thought to be what causes its carcinogenicity. Benzene is readily absorbed by inhalation, and acute exposure can result in central nervous system effects such as dizziness, drowsiness, and eventual unconsciousness. Chronic exposure to benzene affects the bone marrow by crippling blood cell production, causing anemia, which can ultimately result in leukemia.

At one time benzene was widely used as a solvent, resulting in excessive worker exposure; it continues to be a significant workplace contaminant. Benzene is present in the indoor environment from offgassing of glues, synthetic materials, and tobacco smoke. Smokers can have benzene body burdens ten times that of nonsmokers. Because of its widespread use in industry, benzene is a common contaminant of hazardous waste and old industrial sites. The US EPA recommends the benzene not exceed 5 ppb (parts per billion or 0.005 mg/L) in drinking water. The US Occupational Health and Safety Administration set a standard of 1 ppm of benzene in the air over an 8-hour period with an action level set at 0.5 ppm in an effort to encourage reductions in the workplace environment. Other agencies have established even lower standards down to 0.1 ppm benzene in the air.

Asbestos

Asbestos, a recognized human carcinogen, has a long and curious history. Asbestos continues to cause serious human health effects and continues to be the subject of legal action against companies that used or produced it.

Asbestos is the common name given to a group of six different naturally occurring fibrous minerals that can be separated into long fibers that can be spun and woven. The material is strong, flexible, resistant to heat and most solvents and acids, making it a very useful industrial product. Knowledge of asbestos goes back to the 2nd

century BC, but the first recorded use of the word asbestos was in the 1st century AD by Pliny the Elder.

The fire-resistant properties of asbestos were recognized early and contributed to its derivation from the Greek *sbestos* or "extinguishable," thus a-sbestos or inextinguishable. The Romans used asbestos to make cremation cloths and lamp wicks and in the Middle Ages, knights used asbestos to insulate their suits of armor. The use of asbestos increased with the Industrial Revolution and the need for a material to insulate steam boilers, such as those in locomotives. The first asbestos mine opened in 1879 in Quebec, Canada. Canada continues to be the world's largest producer of asbestos, followed by Russia, China, Brazil and several other countries. In the United States, California produces a small amount but the majority of the asbestos used in the United States is imported from Canada.

Serious lung disease associated with asbestos inhalation was first described in the early 1900s in England. This disease became known as asbestosis and was fully described in British medical journals in 1924 as young workers died from asbestos exposure. By the early 1930s, dose-related injury, length of time exposed, and the latency of response were being well characterized in both Europe and the United States. By the mid and late 1930s the first associations with lung cancer were documented. In the 1960s the consequences of asbestos exposure for many workers in World War II started to become evident. Mesothelioma, a cancer of the lining of the lung, was found to be almost exclusively associated with asbestos exposure.

In the United States, regulation of asbestos exposure started in the early 1970s, with exposure limits rapidly decreasing as the serious and latent consequences of asbestos exposure became apparent. White asbestos or chrysotile was used in thousands of consumer products and is common in many older homes. The serious health effects of asbestos exposure have resulted in both regulatory and legal action, and many countries have instituted complete bans on asbestos use.

Radon

Radon is another example of a very curious and toxic compound that many of us regularly inhale, one hopes in small amounts. For those regularly exposed to radon, there is an increased risk for lung cancer and for those who smoke, radon exposure results in a three-fold increase in the incidence of lung cancer. In the United States it is estimated that indoor radon exposure causes between 7,000 and 30,000 lung cancer related deaths each year, second only to tobacco smoking.

Radon-222 is a colorless and odorless radioactive gas that results from the decay of Radium-226, which is widely distributed in the earth's crust. Radon decays with a half-life of 3.8 days into solid particles of polonium. It is actually the breakdown of

polonium that causes cancer: polonium sticks to the tissues of the lung, and when it decays it releases an alpha particle, which damages the DNA of the closest cell.

Lung diseases, possibly related to radon, were first reported in the 1400s, and in 1879 lung cancer was seen in European miners. Radon was discovered several years later in 1900 by the German chemist Friedrich Ernst Dorn. Regulation of workplace exposure began in the 1950s and subsequent studies of underground mine workers in Canada, Czechoslovakia, France, Australia, Sweden and the United States have allowed researchers to develop very sophisticated models of the cancer-causing effects of radon.

It is difficult to translate these results into the effects of radon on indoor home exposure. The United States EPA sets an action level of four picocuries per liter (pCi/l). There are some areas of the United States and Europe with high levels of radon that can enter homes, schools or public buildings, particularly underground levels. In the United States, it is estimated that 1 in 15 (6%) of homes have elevated levels of radon. A number of public and private organizations provide information on reducing indoor radon exposure.

Genetic Toxicology and the Biology of Cancer

Genetic toxicology is the study of the effects of chemical and physical agents on genetic material. It includes the study of DNA damage in living cells that leads to cancer, but it also examines changes in DNA that can be inherited from one generation to the next. Genetic toxicology, although not called that at the time, got its start in 1927 when American geneticist Hermann J. Muller (1890-1967) demonstrated that x-rays increased the rate of gene mutations and chromosome changes in fruit flies.

The relevance of genetic toxicology is clearly evident from inheritable diseases such as phenylketonuria (an inability to metabolize phenylalanine), cystic fibrosis (lung disease), sickle cell anemia, and Tay-Sachs disease. Recent advances in molecular biology and genomic sciences are leading to a far greater understanding of the genetic cause of disease and even pointing the way to treatments.

DNA Mutations

To understand cancer it is necessary to explore the cellular changes that turn a normal cell into a malignant cell that repeatedly and uncontrollably divides. This transformation occurs when there is genetic damage or an alteration in the structure of a cell's DNA.

DNA, short for deoxyribonucleic acid, is the coding machinery of life. The beauty of DNA is its simplicity. The double helix of DNA is made of the compounds adenine (A), guanine (G), thymine (T), and cytosine (C). These chemicals are bound in long stretches as AT and CG pairs, and wrapped in sugar molecules that hold them together. Long stretches of these AT and CG combinations form genes which when "read" produce the proteins that drive our cells.

Ideally the DNA sequence would not change except in the recombining that occurs during reproduction. However, DNA damage occurs regularly as part of the cell process, and from interaction with both normal cellular chemicals and with toxic chemicals. A very robust repair mechanism rapidly and very accurately repairs the DNA damage, but if for some reason the DNA is repaired incorrectly, a mutation occurs. The mutation is a subtle or not-so-subtle change in the A, G, C, or T that make up the DNA.

Many of the mutations have no effect, some have minor effects, and a small number have life-threatening effects. If a mutation occurs in the wrong place, a cell can start to divide uncontrollably, becoming a malignant cell and causing a cancer. If a mutation occurs in our germ line cells, the mutation can be passed on to our offspring.

Mutagens

Chemicals that induce mutations in the DNA are called mutagens, and when these changes lead to cancer the chemical is called a carcinogen. Not all mutagens are carcinogens, and not all carcinogens are mutagens. In 1946 it was shown that nitrogen mustards (derived from mustard gas first used by the military in 1917 during WWI) could induce mutations in the fruit fly and reduce tumor growth in mice. Genetic toxicology developed ways to test chemical and physical agents for their mutagenic properties, and in the 1970s, Bruce Ames and others developed a cellular-based test for genetic mutations. This test became known as the Ames assay. Sophisticated variations of these tests are now required by many government regulatory agencies to test chemicals for mutagenicity before they are of approved for use.

Often it is a metabolite (breakdown product) of the compound that causes cancer, not the original compound. Ideally, a foreign chemical is made less toxic when metabolized, but sometimes a chemical can be made more toxic. This more-toxic chemical can then interact with cellular DNA or proteins and produce malignant cells. This process is called bioactivation. It is also possible for a chemical to encourage bioactivation or to accelerate the development of a cancer. Many variations of the Ames test that include liver cells were developed to simulate the metabolism of the chemical in the liver and determine if bioactivation would result in mutations.

Efforts to understand the underlying biology of cancer are ongoing. The genomic sciences are helping to explain why some people are more susceptible to cancer than

others. We also know that there are many causes of cancer and that we can reduce the likelihood of developing cancer.

What Causes Cancer?

We are continuously exposed to a wide range of chemical and physical agents, both natural and human-generated, that may cause cancer. Exposure to sunlight, background radiation, natural and manufactured chemicals, even oxygen can damage our DNA and result in cancer.

Because our knowledge is imperfect, there is a great deal of conflicting information on the causes of cancer and what can be done to reduce the risk of developing cancer. And we are just beginning to understand how our individual genetic makeup influences the possibility of developing cancer and other genetic-based disease.

Table 18.2 Some Known Causes of Cancer

Cause	Example
Lifestyle	Tobacco and alcohol consumption, diet
Ambient environmental exposures	Air, drinking water
Organic chemicals	Benzo(a)pyrene (in coal tar), Benzene
Inorganic chemicals and metals	Arsenic, cadmium, nickel
Fibers	Asbestos
Radiation	Sunlight (ultraviolet), radioactive material
Drugs	Diethylstilbestrol (DES)
Viruses	Epstein-Barr, AIDS, papilloma
Genetic	Increased likelihood (ex. breast cancer)

Lifestyle choices are the cause of many cancers. Tobacco consumption probably accounts for between 25 to 40% of all cancer deaths. The other major lifestyle choices associated with cancer are alcohol consumption and diet. Alcohol increases the incidence of liver disease and liver cancer. Diet has a broad range of effects, some good and some not so good. Some cooked meats have a higher concentrations of agents that appear to cause cancer; however, a diet rich in vegetables may reduce the incidence of cancer. High caloric intake and high fat consumption may encourage the onset of cancer from other agents.

Numerous organic chemicals are known or likely carcinogens. In the 1930s, benzo(a)pyrene was isolated from coal tar and shown to cause skin cancer. Further investigation revealed an entire class of carcinogenic compounds called polycyclic aromatic hydrocarbons (PAHs). Shortly after World War II, it was discovered that azo dyes could also cause cancer. In the 1960s, naturally occurring contaminants from a grain fungus (aflatoxin) were found to be a potent liver carcinogen.

Inorganic chemicals and fibers are also carcinogenic. Arsenic is the most serious human carcinogen because of exposure from drinking water. Cadmium, chromium, and nickel are all lung carcinogens. The most common lung carcinogen is asbestos, which has unique properties making it ideal for many industrial and even home insulation applications. It was also used in shipyards and in car brake pads. This widespread use resulted in thousands of workers being exposed to asbestos and suffering from a range of lung diseases, including cancer. Asbestos exposure produces a very unique form of lung cancer called mesothelioma. Mesothelioma is caused in part by asbestos fibers inducing a chronic irritation of the lung, resulting in an inflammatory response that ultimately causes some cells to become cancerous.

Hormones, which regulate many important bodily functions, are also associated with cancer. One of the first hints of the relationship between hormones and cancers was the observation that nuns had a greater incidence of breast cancer. This was due to the nuns not having children. Since that time there have been numerous studies on the association of birth control, childbirth, and most recently, hormone replacement, with cancer. In males there is ongoing study of hormones and prostate cancer. While it is clear that hormones and cancer are related, the exact characterization of this relationship is still unclear.

We are becoming increasingly aware of the importance of diet and nutrition in reducing the risk of cancer. From a toxicological perspective, it is important to reduce exposure to agents that increase the risk of cancer. Cancer, like declining physical and mental ability, is related to old age and may even be a natural consequence of the

aging process. However, exposure to cancer-causing agents increases the risk or likelihood of developing cancer.

Regulatory Standards

National and international agencies have established systems to classify agents according to the likelihood that the agent may cause cancer. This is often a difficult process because the information on an agent may be incomplete or inconclusive. Data from any human epidemiology studies are evaluated first, followed by information from animal studies. The International Agency for Research on Cancer (IARC) has developed one of the most comprehensive classification schemes. In this scheme an agent is rated from 1 to 4 based on human and animal data (see table 18.3). Other classification schemes are in use by the US EPA, National Toxicology Program, National Institute of Occupational Health Sciences (NIOSH), and the State of California.

Table 18.3 IARC Classification Scheme for Carcinogenicity of Chemical and Physical Agents

Group	Evidence	Example
1. Carcinogenic to humans	Sufficient human data	Aflatoxin, benzene, arsenic, formaldehyde
2A. Probably carcinogenic to humans	Limited human data Sufficient animal data	PCBs, styrene oxide, creosotes
2B. Possibly carcinogenic to humans	Limited or inadequate human data Sufficient animal data	Styrene, TCDD-dioxins, lead, mirex
3. Not classifiable as to its carcinogenicity to humans	No enough human or animal data	Diazepam, melamine, phenol
4. Probably not carcinogenic to humans	Inadequate human data Inadequate animal data	

(Source: IARC: Preamble to the IARC Monographs, 2006)

Government regulatory agencies do not always agree on the classification of cancer-causing compounds and there are several different schemes, used by different agencies. Elaborate animal study protocols are used to determine if an agent may

cause cancer.

Recommendation and Conclusions

While scientists have made great strides in understanding the causes of cancer and developing treatments, there will always be a risk for developing cancer. The likelihood of developing cancer is related to our individual sensitivity and our dose/response curve. As individuals, we can try to be aware of the risks of exposure to suspected carcinogens and take appropriate actions to reduce our exposure, but this can be difficult due to a lack of ingredient labeling. There must be better labeling of ingredients and easier access to information about chemicals that may be carcinogenic.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Cancer presentation material and references. Website contains presentation material related to the health effects of cancer.

European, Asian, and International Agencies

• International Agency for Research on Cancer (IARC). IARC's mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. [accessed July 7, 2009]

• World Health Organization (WHO). Cancer. Site has information on international exposure to a wide range of compounds that cause cancer. [accessed July 7, 2009]

• Australia SunSmart. An Australian site that focuses on skin cancer and its primary cause, the sun. [accessed July 7, 2009]

• Australia: Cancer Council Victoria. "The Cancer Council Victoria is an independent, volunteer-based charity whose mission is to lead, coordinate, implement, and evaluate action to minimize the human cost of cancer for all Victorians." [accessed July 7, 2009]

• Chrysotile Institute. The Chrysotile Institute is dedicated to promoting the safe use of asbestos in Canada and throughout the world. (French and English.) [accessed July 7, 2009]

• CancerHelp UK. Provides a free information service about cancer and cancer care for people with cancer and their families. [accessed July 7, 2009]

• Japan: National Cancer Center. Site has information on the treatment and cause of cancer for Japan. (Japanese or English versions available.) [accessed July 7, 2009]

North American Agencies

General Information on Cancer

• US Centers for Disease Control and Prevention (CDC). Cancer Prevention and Control. The CDC monitors cancer incidence and promotes cancer prevention and control. [accessed July 7, 2009]

• US National Cancer Institute (NCI). Cancer Information Service (CSI). A service of the US National Cancer Institute, CSI is a "source for the latest, most accurate cancer information for patients, their families, the general public,and health professionals." [accessed July 7, 2009]

• US Environmental Protection Agency (EPA). Guidelines for Carcinogen Risk Assessment. EPA cancer risk assessment guidelines. [accessed July 7, 2009]

• US Environmental Protection Agency (EPA). National Center for Environmental Assessment (NCEA). Applying science to improve risk assessment and environmental decision making. [accessed July 7, 2009]

• US National Cancer Institute (NCI). The NCI, established under the National Cancer Act of 1937, is the Federal Government's principal agency for cancer research and training. [accessed July 7, 2009]

• US National Cancer Institute (NCI). The Cancer Mortality Maps & Graph Website. This site provides interactive maps, graphs (which are accessible to the visually-impaired), text, tables, and figures showing geographic patterns and time trends of cancer death rates for the time period 1950-1994 for more than 40 cancers. [accessed July 7, 2009]

Benzene Information

• US Agency for Toxic Substance Disease Registry (ATSDR). See fact sheets and case studies in environmental benzene. [accessed July 7, 2009]

• US Environmental Protection Agency (EPA). Benzene. Hazard fact sheet on benzene. [accessed July 7, 2009]

Asbestos Information

• US Agency for Toxic Substance Disease Registry (ATSDR). See fact sheets and case studies in environmental asbestos. [accessed July 7, 2009]

• US National Cancer Institute (NCI) Asbestos Exposure and Cancer Risk. Extensive information on asbestos. [accessed July 7, 2009]

• US Environmental Protection Agency (EPA). Asbestos. Extensive information on asbestos. [accessed July 7, 2009]

Radon Information

• US Environmental Protection Agency (EPA). Radon. US EPA has extensive information

on radon exposure in the US. [accessed July 7, 2009]

• US Geological Survey (USGS). Radon in Earth, Air, and Water. Maps and supply information on radon in the US. Archival information; no longer updated. [accessed July 7, 2009]

Non-Government Organizations

• American Association for Cancer Research (AACR). "AACR accelerates progress toward the prevention and cure of cancer by promoting research, education, communication, and collaboration." [accessed July 7, 2009]

• The American Cancer Society (ACS). The ACS is a nationwide community-based voluntary health organization dedicated to eliminating cancer as a major health problem by preventing cancer, saving lives, and diminishing suffering from cancer through research, education, advocacy, and service. [accessed July 7, 2009]

• American Lung Association (ALA). Site has information on radon in the home environment as well as tobacco and asthma. [accessed July 7, 2009]

• Children's Cancer Association (CCA). Provides information and resources regarding childhood cancer. [accessed July 7, 2009]

• Environmental Mutagen Society (EMS). EMS fosters research on the basic mechanisms of mutagenesis as well as on the application of this knowledge in the field of genetic toxicology. [accessed July 7, 2009]

• National Radon Safety Board (NRSB). "The NRSB seeks to encourage the highest standards of practice and integrity in radon services through the development of independent standards and procedures for certifying, approving and accrediting radon testers, mitigators, measurement devices, chambers and laboratories." [accessed July 7, 2009]

• Roswell Park Cancer Institute (RPCI). PRCI is a comprehensive treatment center with a focus on prevention and education. [accessed July 7, 2009]

• The White Lung Association. Nonprofit organization focused on asbestos exposure. [accessed July 7, 2009]

A Small Dose of Developmental Toxicology

or

An Introduction to Pregnancy and Developmental Toxicology

Introduction and History

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"Nature creates monsters for the purpose of astonishing us and amusing herself."
- Pliny (61–105 AD)

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Many organisms, including humans, evolve through sexual reproduction and the sometimes prolonged development of the resulting offspring. It is truly astonishing that male and female germ cells (a sperm and an egg) can merge and develop into an independent organism. In order to facilitate the discussion of this enormous and complex subject, it will be divided into three areas: reproduction, issues associated with the egg and sperm; pregnancy, the critical environment of early development; and development of the infant. The focus will be primarily on humans, but the development of all organisms can be adversely affected by chemical or physical agents. This chapter provides only the briefest examination of the disorders and adverse effects of various agents on reproduction and development. Harmful agents affect the developing organism in dramatic and subtle ways and can harm a person for a lifetime at enormous cost to the individual and society.

Only in the last 100 years have we begun to understand the mysteries of reproduction and development. Prior to advances in the biological sciences, ancient civilizations invoked fertility goddesses to oversee reproduction. Many thought malformed or abnormal infants were a message or warning of future events. A small statue of conjoined twins dating from 6500 BC was discovered in Turkey. A clay tablet (2000 BC) found along the Tigris River described 62 malformations and related the abnormalities to future events. In the 15th and 16th centuries, malformed infants were thought to be a product of the devil and both mother and child were killed. Some thought that the development of the child was influenced by what the mother was viewing. Thus, Aristotle recommended that a mother view beautiful statuary to increase her child's beauty. One definition of the word monster is an abnormal animal or plant. Monster is derived from the Latin *monstrum omen*, and from *monere* to warn, reflecting the notion that abnormal infants told of the future. Greek for monster is *teras*, which is the route of teratology, the study of malformations or monsters.

The more scientific investigation of abnormal development began in the 1830s when Etienne Geoffroy Saint-Hilaire studied the effects of different conditions on the development of chicken eggs. But it was not until the late 1800s and early 1900s that

it was more widely recognized that genetics played an important role in development. In the 1930s and 1940s, experiments by Josef Warkany and others clearly demonstrated that a wide range of agents such as vitamin A deficiency, nitrogen mustard, alkylating agents, hypoxia, and x-rays could cause malformation in rodents. In 1941, the rubella virus infection was linked to malformed infants. However, many thought that the placental environment protected the infant during pregnancy. This understanding changed dramatically with the discoveries that methylmercury was a developmental toxicant and that thalidomide caused severe abnormalities (see below).

While the knowledge that toxic agents can dramatically affect the developing fetus has only developed relatively recently, there is a long and curious history of toxicology and reproduction. Since ancient times, people have sought ways to stop the onset of reproduction by killing sperm before it meets the egg. A variety of natural products were used with varying degrees of success. Now, more modern chemicals specifically designed to be toxic to sperm, such as nonoxynol-9, are used as a spermicides. There are ongoing efforts to develop compounds that are not toxic to people but are toxic to the viruses and bacteria that cause sexually transmitted diseases.

Continuing advances in the biological sciences and technology provided greater insight into the reproductive process. This research led to a detailed understanding of the hormones that control the female reproductive process. In the 1950s scientists developed "the pill," which manipulated the natural estrogen and progesterone hormones and thus the onset of the reproductive process. Early versions of "the pill" had a number of undesirable side effects that decreased when the drug dosage levels were lowered. In essence, "the pill" is an endocrine disruptor and a desirable one. It was subsequently discovered that many different chemicals could affect or disrupt the endocrine system (see Chapter 15). Some of these chemicals, such as DDT, dioxin, and phthalates, were widely distributed in the environment and began to reduce the fertility of wildlife.

We will now examine in more detail some of the physiological and toxicological aspects of reproduction, pregnancy, and development.

Reproduction

For all species, reproduction is essential and usually starts with the merging of the egg and sperm cells. In humans, it is estimated that 50% of all pregnancies end in miscarriage or spontaneous abortion, often before the woman realizes that she is pregnant. The most common reason for failed pregnancy is chromosomal abnormality. Human cells have 46 chromosomes, which are the genes that control cell function and make us unique. The egg and the sperm cells each contain only 23 chromosomes that must correctly combine during reproduction to create a cell with 46 chromosomes and start the development process. Failures in this process and the early stages of cell division are thought to be the primary reason for early loss of pregnancy.

Successful reproduction (and sex) involves many complex chemical processes that can be disrupted at various points and reduce fertility and conception. Part of this process is under the control of the endocrine system, and chemicals that affect the endocrine

system are termed endocrine disruptors. Following the development of "the pill" in the 1950s, it was discovered that a number of chemicals released into the environment could disrupt the endocrine system and reduce the fertility of wildlife. Some are concerned that exposure to these chemicals, such as DDT and dioxin (TCDD), at current levels may also affect human fertility. Approximately 15% of couples of reproductive age are infertile. Endocrine disruptors may also affect fetal development, causing demasculationization and feminization of the offspring, which in turn cause reduced fertility in the next generation.

Chemicals can also directly affect male reproductive organs or sperm. Decreased sperm count or motility or sperm abnormalities can result in male sterility or reduced fertility. For example, occupational exposure to lead can result in infertility due to sperm abnormalities. Male sterility can also result from exposure from the fungicide dibromochloropropane (DBCP). Drugs or chemicals, such as alcohol and narcotics that affect the central nervous system, can also reduce sexual activity and thus fertility.

Female reproductive organs are also vulnerable to the effects of chemicals, including changes in ovulation or menstrual cycle, decreased implantation of the fertilized egg, or inability to maintain pregnancy.

Table 19.1 Examples of Chemicals That Affect Reproduction

Class of Chemical	Examples
Endocrine disruptors	DDT, dioxin, phthalates
Heavy metals	Lead (decreased or abnormal sperm)
Organic solvents	Toluene, benzene, n-hexane
Drugs	Alcohol, narcotics, hypotensive drugs, chemotherapeutic agents, steroids, diethylstilbestrol
Pesticides	Dibromochloropropane (DBCP), methoxychlor, linuron (herbicide)
Disease	Diabetes

Pregnancy

The female body undergoes a number of significant changes during pregnancy; some of these changes can increase vulnerability to toxic compounds. A healthy woman

readily adapts to the changes of pregnancy, but it is important to be aware of the consequences of some of these changes. As the pregnancy progresses, the heart rate increases and the amount of blood volume circulated increases, and blood pressure increases. The expanded blood volume results in increased urinary output. Antibiotic prescriptions may need to be altered to accommodate the changes in blood volume and urinary excretion. Respiration is also affected as oxygen consumption increases by 15 to 20%. Increased intake of nutrients such as iron and calcium are required during pregnancy, and the gastrointestinal tract changes to increase absorption of selected nutrients. An unintended consequence of this change is an increased absorption of lead during pregnancy. Normally, the adult absorbs 10% of lead following oral exposure, but because lead substitutes for calcium, lead absorption during pregnancy is increased to levels similar to that of a child. Liver function decreases, resulting in the decreased metabolism of certain drugs (an increase in half-life). For example, the metabolism of caffeine decreases during the second and third trimesters of pregnancy, resulting in higher blood caffeine levels for longer periods of time. The half-life of caffeine in a woman approximately doubles during pregnancy. Caffeine and its metabolites readily cross the placenta, exposing the infant to these chemicals.

Table 19.2 Physiological Changes During Pregnancy

Cardiovascular	Increases in cardiac output, heart rate, blood pressure; blood volume expands
Respiration	Oxygen consumption increases 15 to 20%
Urinary output	Increases
Gut absorption	Greater absorption of iron and calcium (or toxic compounds such as lead)
Liver metabolism	Decreases for some drugs or chemicals, e.g. caffeine (longer half-life)

Development

One of the great lessons learned in the past 50 years is that the developing organism is more vulnerable than the adult to the effects of many chemicals. This sensitivity begins at the time of fertilization and continues throughout childhood. This knowledge has been reinforced multiple times through tragic experiences with thalidomide, alcohol, methylmercury, lead, and many other agents. Our knowledge has progressed from concern over chemicals that cause physical fetal malformation to recognition that chemicals can cause much more subtle but still harmful effects.

A primary reason for the sensitivity of the developing fetus is the rapidly multiplying number of cells. Not only are the cells rapidly dividing, they are changing into organ-specific cells. The nervous system alone ultimately has over 100 billion nerve cells responsible for transmitting information, as well as over 1 trillion glial or connecting cells. Many of these cells will undergo migration to different regions of the brain and form synaptic connections with other cells, and some will even die off in a programmed manner. Throughout gestation, different organs or cells within an organ are going through various growth and development phases. Chemicals can interfere with this process in very unexpected and unpredictable ways.

The infant remains vulnerable to exposure to chemicals following birth. The infant's liver only gradually begins to function after about six months of age. This delay has important implications if the infant is exposed to drugs dependent on liver metabolism. For example, an infant cannot metabolize caffeine. The infant can only excrete the caffeine in the urine, resulting in the half-life of caffeine being measured in days rather than hours, as it would be for an adult. Infants are also growing rapidly and require nutrients such as calcium and iron, which are readily absorbed from the gastrointestinal tract. Lead, a well-established neurotoxicant, is absorbed along with the calcium, making the infant more vulnerable to any lead exposure. Infants will absorb 50% of lead from oral exposure while adults only absorb 10%. Infants are also much smaller than adults, so that even a small amount of exposure represents a large dose. The hand-to-mouth behavior of an infant increases exposure to contaminants that may be in house dust or on toys. In addition, infants have a higher respiratory rate and consume more food relative to their body weight. All these and other factors combine to increase an infant's vulnerability to harmful chemicals. The following table lists just a few of the compounds known to affect fetal and infant development.

Table 19.3 Agents and Chemicals That Affect the Developing Infant

Metals	Lead, methylmercury, arsenic (in animals)
Chemicals	Chlorobiphenyls, solvents (toluene), endocrine disruptors (DDT, TCDD)
Radiation	X-rays (therapeutic), atomic fallout
Infections	Rubella virus, herpes simplex virus, toxoplasmosis, syphilis
Medical Drugs	Antibiotics (tetracyclines), anticancer drugs, anticonvulsants (valproic acid), lithium, retinoids (vitamin A), thalidomide, diethylstilbestrol (DES), anticoagulants (warfarin)
Recreational Drugs	Alcohol (ethanol), tobacco, cocaine, solvent abuse

Plants	Many herbs, skunk cabbage (*Veratrum californicum*), sheep & cattle, parasites (frogs)

Thalidomide

Thalidomide was introduced in 1956 as a sedative (sleeping pill) and to reduce nausea and vomiting during pregnancy. It was withdrawn in 1961 after it was found to be a human teratogen. In 1960 researchers in Australia and Germany observed an unusual increase in rare human malformations of missing limbs (amelia) or shortened long bones (phocomelia), particularly of the arms. It was soon realized that these unusual malformations were associated with the consumption of thalidomide by the mother during early pregnancy. Over 5000 infants were affected by thalidomide, primarily in Europe, Canada, and Australia. There were very few cases in the United States because a reviewer at the US Food and Drug Administration, Frances Kelsey, MD, PhD, demanded additional safety data prior to approval. The routine animal safety studies of that period had failed to predict the adverse effects of thalidomide. This event resulted in significant changes to the animal testing requirements to evaluate the possible teratogenic and developmental effects of drugs. Recently, thalidomide was approved to treat multiple myeloma and leprosy but with extraordinary precautions being taken because of its developmental effects.

Ethanol (Alcohol)

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"You will conceive and bear a son…now then be careful to take no wine or strong drink and to eat nothing unclean".

- Judges 13:3-4

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The Bible (Judges 13:3-4) cautioned against the consumption of alcohol during pregnancy, but it was not until the 1970s that tragic fetal effects of alcohol were described in detail. Fetal Alcohol Syndrome (FAS), characterized by facial malformations, growth retardation, small head size, and greatly reduced intelligence, results from maternal consumption of alcohol. FAS affects 4,000 to 12,000 newborn infants in the United States and 1 to 3 births per 1000 worldwide per year. A milder form of the developmental effects of alcohol is Fetal Alcohol Effect (FAE). FAE infants are slow to develop and have learning disabilities. FAE affects up to 36,000 infants in the United States, while the number of infants affected worldwide is not known. Alcohol consumption during pregnancy is the most common preventable cause of adverse nervous system development. Alcohol should not be consumed during pregnancy in any amounts.

Methylmercury

Bacteria convert inorganic mercury (quicksilver) to methylmercury ($Hg\text{-}CH_3$) in an effort to detoxify the mercury. Other organisms including fish consume the bacteria along with the methylmercury; larger fish consume the smaller fish and accumulate

methylmercury in fish muscle. Humans and other animals consume the fish and can be poisoned by the mercury. The developing fetus is particularly sensitive to the adverse developmental effects of methylmercury. The tragic effects of fetal methylmercury exposure were first observed in the 1950s in Minamata, Japan. High exposure and severe developmental effects were also observed in other unfortunate incidents including the consumption in Iraq of seed grain coated with organic mercury. Further study revealed that even low levels of methylmercury exposure harm the developing fetus. Across the globe there are advisories on fish consumption due to methylmercury contamination for children and women of childbearing age. This is an unfortunate development because fish are an excellent source of protein and essential fats.

Lead

The use of lead in paint and as a gasoline additive was one of the greatest public health disasters of the 20th century. The Greek physician Dioscorides reported in the 2nd century BC that "Lead makes the mind give way." In 1922 the League of Nations banned white-lead interior paint, a move the United States declined to follow, and a year later leaded gasoline went on sale in the United States. Our experience with lead emphasizes the sensitivity and vulnerability of the developing nervous system. Not only is the developing nervous system more sensitive to lead, but children absorb more lead than adults following oral exposure and their small size means they receive a larger dose of lead. It is now well accepted that even low levels of lead exposure harm the developing nervous system, reducing the IQ for a lifetime. Regulatory authorities around the world are working to reduce lead exposure by removing lead from gasoline and paint.

Endocrine-disrupting Chemicals

Depending upon the circumstance and desired effects, endocrine-disrupting chemicals can be either good or bad. The endocrine system is a finely balanced system responsible for fertility and for many of the feminine and masculine traits we are all familiar with. Endocrine disruptors are used by millions of women in the form of "the pill" to control fertility. Chemicals in birth control pills subtly manipulate the endocrine system to reduce fertility. Unfortunately, we now know that many chemicals are capable of influencing the endocrine systems. When these chemicals, such as DDT and TCDD, are released into the environment, they reduce the fertility of wildlife. Exposure to endocrine disruptors is linked to decreased fertility in shellfish, fish, birds and mammals. Endocrine disruptors such as nonylphenol have been shown to feminize male fish, interfering with reproduction. Some studies have also linked exposure to endocrine disruptors to decreases in human male sperm count. Ironically, urinary metabolites of the birth control pill, as well as the female hormone estrogen, pass through waste treatment plants and are released into the aquatic environment, where even small concentrations cause feminization of male fish.

Herbal Medicines During Pregnancy

Herbal or "natural" remedies are a multibillion-dollar business that is largely unregulated by government agencies. Herbal products are readily available and are often claimed to improve health, but they also contain many physiologically active chemicals. The ingredients have not undergone the rigorous testing required of

medical drugs to determine if there are any undesirable effects on the developing fetus or infant. There is a long history of herbal remedies being used as contraceptives, to induce abortions, or to delay or increase uterine contractions. Any of these possible effects indicate that the herbal product should not be consumed during pregnancy. Manufacturers are not required to demonstrate safety of herbal or "natural" products. Given the sensitivity of the developing fetus, consumption of herbal products during pregnancy should be approached very cautiously.

Regulatory Standards

Government regulatory authorities in Europe, North America, and Asia require extensive testing of food additives and new drugs for reproductive and developmental effects. A significant expansion of drug testing occurred following the tragic experience with thalidomide. Testing requirements have gradually evolved, becoming more sophisticated as our understanding of potential effects on the nervous system increased. Reproductive and developmental testing is also required of some pesticides and other chemicals that may be released into the environment or have significant human exposure.

A variety of cell-based and animal-based studies can be performed to ensure that a new chemical does not cause reproductive or developmental effects. A battery of tests is done to ensure that there are no harmful effects on fertility. Teratogenicity studies are performed to ensure that the chemical does not cause physical malformations in the offspring from exposure during pregnancy. Multiple generations of animals may be continuously exposed to ensure that a compound is safe.

There are an estimated 50,000 to 60,000 industrial chemicals in common use. We know very little about the reproductive and developmental effects of the majority of these chemicals. In addition, there are no safety testing requirements for "natural" products. In 1986, the voters of the State of California passed a law requiring the governor of the state "to publish, at least annually, a list of chemicals known to the state to cause cancer or reproductive toxicity." This effort is an excellent source of information on chemicals that can cause birth defects or reproductive harm.

Recommendations and Conclusions

Awareness about the potential effects of chemicals on reproduction, pregnancy, and development needs increased attention from individuals as well as society. A growing body of knowledge indicates that the developing organism is more vulnerable to the adverse effects of chemical exposure. Planning for a healthy baby is best started preconception and should continue throughout pregnancy and after birth. Exposure to hazardous chemicals should be reduced or eliminated to prevent adverse developmental effects.

Additional Resources

Slide Presentation and Online Material

• Pregnancy and Developmental Toxicology presentation material and references. Website contains presentation material related to this book for each chapter.

European, Asian, and International Agencies

• European Teratology Society (ETS). The ETS is dedicated to the prevention of adverse effects on reproduction and development. [accessed July 26, 2009]
• Thalidomide Victims Association of Canada. Information on thalidomide in English or French. [accessed July 26, 2009]
• World Health Organization (WHO). Pregnancy. Information from World Health Organization on efforts to improve pregnancy outcome. [accessed July 26, 2009]

North American Agencies

• US National Library of Medicine. Thalidomide: Potential Benefits and Risks. The NLM site contains an extensive bibliography on thalidomide. [accessed July 26, 2009]
• US Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition. Education Campaigns for Pregnant Women. This FDA website offers information on food safety for pregnant women. [accessed July 26, 2009]
• US Department of Health and Human Services. Information for Pregnant Women. Site contains general information and links on pregnancy and fetal development for men and women. [accessed July 26, 2009]
• US Centers for Disease Control and Prevention (CDC). Pregnancy Homepage. Site contains information and links on pregnancy and fetal development. [accessed July 26, 2009]
• US National Children's Study. "The National Children's Study will examine the effects of environmental influences on the health and development of 100,000 children across the United States, following them from before birth until age 21. The goal of the study is to improve the health and well-being of children." [accessed July 26, 2009]
• California Office of Environmental Health Hazard Assessment (OEHHA). Proposition 65. Passed in 1986 by the voters of California, Proposition 65 "requires the Governor to publish, at least annually, a list of chemicals known to the state to cause cancer or reproductive toxicity". [accessed July 26, 2009]

Non-Government Organizations

• Teratology Society. "The Teratology Society is a multidisciplinary scientific society founded in 1960, the members of which study the causes and biological processes leading to abnormal development and birth defects at the fundamental and clinical level, and appropriate measures for prevention." [accessed July 26, 2009]
• Society for Developmental Biology. "The purpose of the society is to further the study of development in all organisms." [accessed July 26, 2009]
• March of Dimes. March of Dimes works to "give all babies a fighting chance against the threats to their health: prematurity, birth defects, low birth weight." [accessed July 26, 2009]

References

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World Health Organization. "Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals". *Environmental Health Criteria* 237 (2007). This volume addresses the unique vulnerability of children to social economic factors, nutrition, environmental chemicals and other hazards. [accessed July 26, 2009]

Hood, R.D. *Developmental and Reproductive Toxicology: A Practical Approach, 2nd edition*. Boca Raton: CRC Press, 2005.

A Small Dose of Toxics in the Home

or

An Introduction to Toxics in the Home

Toxics at Home: Quick Facts
Uses: various uses in household products (medicines, pesticides, cleaning agents, paint, mercury thermometers, plastics)
Source: naturally occurring (mold, radon) and purchased household products
Recommended daily intake: usually not recommended
Absorption: skin, oral, inhalation
Sensitive individuals: children (account for majority of poisoning incidents around the home)
Toxicity/symptoms: varies greatly (acute and long-term effects)
Regulatory facts: EPA, FDA, Consumer Product Safety Commission
General facts: many home products are necessary, but often less toxic alternatives are available
Environmental concerns: serious environmental concern (i.e. mercury, detergents)
Recommendations: use less toxic alternatives, dispose of hazardous wastes properly

Introduction

The home is a complex environment that contains many hazards and toxic materials,

some naturally occurring and many others that we bring into the home. A common naturally occurring hazard is radon, a radioactive material that is released from the soil and bedrock. In a humid environment, mold and mildew can grow, releasing spores and toxins into the indoor air. Dust mites, invisible to the human eye, roam our home and in the right circumstances cause health problems.

Some of the greatest hazards are from what we bring into the home. The toxicology of household products is fascinating because we are all familiar with the products and because so many different kinds of products are involved. A typical home may contain cleaning products, cosmetics and personal care products, paints, medications, pesticides, fuels, and various solvents. Thermometers and thermostats may contain mercury, a well-known neurotoxicant. Older homes were often painted with lead-based paint, which when consumed causes serious developmental effects. Building materials may contain toxic solvents that are released into the home. The toxicity and ingredients of household products vary widely, but highly toxic products are found in most homes.

Toxics in the Home

- Radon
- Lead in paint
- Indoor air pollutants
- Second-hand smoke
- Mold and mildew
- Household hazardous waste
- Dust from inside and tracked in from outside
- Consumer products, e.g. old foam mattresses or cushions
- Household products
- Cleaning products, cosmetics and personal care products, paints, medications, pesticides, fuels and various solvents, mercury thermometers

Both the general environment and individuals in the home can suffer the consequences of products used in and around the home. Many household products contain chemicals that contaminate our air and water when used. Consumers in the United States use about 8.3 billion pounds of dry laundry detergent and about a billion gallons of liquid detergent per year. Some of these laundry and dishwashing detergents contain phosphate. High phosphate levels in water encourage the growth of algae, which can suffocate other marine life. Mercury from broken thermometers can harm the individual but also moves into the atmosphere, into surface waters, and ultimately into the fish we eat. Paints, varnishes, motor oil, pesticides, antifreeze, and fluorescent lights are clearly hazardous wastes that when improperly disposed of harm the environment. Consumers in the United States generate 1.6 million tons of household hazardous waste each year. How many pounds of hazardous waste do you have in your home?

Many countries and regions have poison centers that provide information for people exposed to toxic substances. It is estimated that there are over 17,000 chemicals found in the home, many which have only limited toxicity information. The centers maintain large databases on products and substances as well as the appropriate

response following exposure. Every day there are many household exposure incidents, some resulting in immediate and serious consequences (see below). By far the most vulnerable population is children. In the United States more than 50% of the poisoning incidents involve children less than six years of age. The poison centers primarily focus on acute or immediate response to an incident. The poison centers also respond to calls related to animal poisoning.

Poisoning events in United States, 2007

- 2.5 million reported exposures
- 1.6 million information calls
- 51% involved children under age 6
- 93% occurred in the home
- 423,290 treated in a health care facility
- 1,597 deaths reported in 2007

Source: National Poison Centers, 2007 data (Bronstein et al, 2008)

Exposure to hazardous substances in the home can also have long-term health implications. Children and the elderly spend a great amount of time in the home, increasing their exposure to any toxic substances found there. Over 15 million people in the United States suffer from asthma, including 5 million children. The number of children with asthma continues to increase despite ongoing research into the possible causes. The causes may include household dust, droppings from dust mites, and mold. Asthma-related illness results in over 100,000 hospital visits by children and the loss of over 10 million school days per year. A very different kind of long-term disability results from childhood lead exposure. The US Centers for Disease Control and Prevention estimated that over one million US children have elevated blood lead levels due to household exposures.

Exposure

Routes of Exposure

Residents can be exposed to household products by accidental ingestion, skin contact, splashing into the eyes, and by inhalation of vapors or airborne particles. Exposures can be short-term, resulting from a single product use or spill, to long-term, from frequent product use or offgassing of volatile components.

Ingestion

- Direct ingestion of product
- Hand to mouth contact

Inhalation

- Acute inhalation of product during use
- Chronic inhalation of indoor air

Skin/eye contact

- Splashing/spilling during use
- Violent chemical reactions
- Contact with treated surfaces

Acute Exposures

In the year 2009, poison centers in the United States responded to nearly 2.5 million

incidents, mostly home exposures to chemical products, animal bites, and poisonous plants. Over 50% percent involved children under the age of six. In all, over 25,000 incidents resulted in medical outcomes deemed "major," and there were 1,544 deaths. Almost half of the incidents stemmed from exposure to pharmaceutical products. Of the remaining exposures, the largest groups resulted from cosmetics and personal care products and household cleaners. Although the large number of incidents says more about the ubiquity of potentially hazardous products in the home than about their toxicity, the numbers also point out the extent of the potential dangers if products are toxic or if medical aid is not rapidly received. Many more deaths and serious injuries would occur if not for the rapid intervention of poison centers.

Several groups of household products can have serious and rapid acute health impacts:

Corrosives

Strong acids, bases, or oxidizers can cause permanent eye damage, skin burns, and, if swallowed, severe gastrointestinal damage. Examples of corrosive products include alkaline drain cleaners and oven cleaners, acid-based toilet bowl cleaners and rust removers, concentrated disinfectants, and some concentrated pesticides, especially fungicides.

Solvents

Products with a high percentage of solvents, such as oil-based paints, paint removers, fuels, lighter fluids, furniture polishes, and some pesticides can cause potentially fatal pneumonia if aspirated into the lungs as a result of accidental ingestion. If used in an unventilated space, they can also cause symptoms of acute intoxication, including dizziness, nausea, and in some cases nerve damage or other effects.

Medications

Useful as prescribed, many medications are toxic and can be very dangerous if taken by someone other than the intended patient—especially a child—or if taken in too high a dose.

Pesticides

Although many household pesticides are rather dilute, some are concentrated enough to be acutely toxic. These include concentrates of insecticides, fungicides, and some herbicides.

Chronic Exposures and Effects

Chronic or long-term exposures can occur through repeated use of a product or through contact with long-lasting residues in the air, soil, household surfaces, or dust. EPA's TEAM (Total Exposure Assessment Methodology) studies found that levels of a dozen volatile organic compounds were two to five times higher indoors than outdoors, regardless of the geographic location of the home. When volatile products are used indoors, levels of chemicals in the air can exceed background levels by 1000 times or more and persist for a long time.

Contaminated soil can also be a major source of exposure, especially for children who play in it or mouth their hands. In addition to isolated, elevated levels of contaminants

from industrial sources, studies show consistently elevated levels of lead near the foundation of homes once painted with lead-based paint. Wooden decks built from treated lumber containing arsenic typically contaminate the soil beneath to levels far above background levels. Lead and other contaminants are tracked into the home on shoes, where they are stored in house dust. Carpets can contain large reservoirs of dust that elude all but the most diligent vacuuming. House dust also can contain elevated levels of pesticides, combustion soot, nicotine, and allergens.

Products containing volatile ingredients, such as solvents, cause a general decline in indoor air quality when used inside the home. Volatile solvents often found in household products include those shown in the table below. The last column shows permissible air concentrations of these solvents in occupational settings. The higher the number is, the less toxic the material.

Volatile Toxic Chemicals

Table 20.1 Volatile Toxic Chemicals

Ingredient	Product	Occupational Exposure Limits (ppm)
Ethanol	Alcoholic beverages	1000
Acetone	Nail polish remover	750
Ethyl acetate	Nail polish remover, marker pens	400
Isopropanol	Rubbing alcohol, personal care products	400
Gasoline	Motor fuel	300
Methanol	Paint remover	200
Turpentine	Paint thinner	100
Xylene	Spray paint, marker pens, adhesives	100
Hexane	Adhesives	50

Methylene chloride	Paint remover	50
Toluene	Paint remover, spray paints	50
Carbon monoxide	Auto exhaust, burning charcoal	10
Naphthalene	Mothballs	10
Paradichlorobenzene	Mothballs	10
Formaldehyde	Particleboard, plywood	0.30
Chlorpyrifos	Insecticide (discontinued for household use in the US after the end of 2001)	0.014

Certain household products contain ingredients that can cause long-term or delayed chronic health effects such as cancer, reproductive effects, nervous system effects, and developmental effects. The table below lists some examples of types of products, ingredients, and the health effects that overexposure may lead to.

Chronic Health Effects

Table 20.2 Chronic Health Effects

Ingredient	Found in*	Cancer	Reproductive	Developmental	Nervous system
Chlorothalonil	Fungicide	X			
Triforine	Fungicide			X	
Carbaryl	Insecticide	X			X
Arsenic	Treated wood	X			X

Lindane	Lice treatment	X			X
Paradichlorobenzene (PDCB) or naphthalene	Mothballs	X			
Hexane	Adhesive				X
Lead	Hair dye, toys, paint	X	X	X	X
Benzene	Gasoline	X		X	
Aspirin	Pain relievers		X	X	
Ethyl alcohol	Beverages			X	X
Methylene chloride	Paint remover	X			X
Polybrominated diphenyl ethers (PBDEs)	Mattresses, cushions, plastics		X	X	X
Bisphenol-A (BPA)	Baby bottles, can liners		X	X	X

*Potential for listed ingredient to be found in product or category varies depending on product formulations.

Risk

One of the greatest difficulties in estimating the toxicity of household products is the fact that most of the ingredients are not disclosed on product labels or other documents. Household pesticides, for example, often contain well over 90% so-called inert ingredients, more recently referred to as "other" ingredients. The terminology relates to their function in the product rather than their toxicological characteristics,

and these ingredients, with few exceptions, are not listed on product labels. Although product labeling regulations in the United States do allow one to deduce certain acute toxicity characteristics from careful reading of required label warnings, the conclusions one can draw are limited. Frequently, the Material Safety Data Sheet (MSDS), a document required by the U. S. Occupational Safety and Health Administration, contains LD50 (the amount of a substance causing death in half the exposed test population) or other toxicity data. Unfortunately, many MSDSs contain incomplete and apparently inaccurate information, making them a flawed tool for toxicity assessment. In other countries, labels are quite different, and even less information may be available.

The risk of adverse effects from exposure to household products is difficult to estimate because of the wide variety of products available, the many ingredients they contain, the presence of many "trade-secret" ingredients, and the wide variety of exposure scenarios. It is worth noting that the highest exposures to household products are typically to those most likely to be particularly susceptible: children, the elderly, and the chronically ill. These groups tend to spend, on average, more time in the home than adults aged 20 to 60, who are more likely to work outside the home and to be in good health. Children also exhibit behaviors that increase their exposure to toxic agents in the home: they play on the floor, they put their hands in their mouth, and they are curious about their surroundings. Combined with their low body weight, proportionately higher intake of food and water, and their developmental stage, these behavioral factors contribute to elevated risks.

Risks are undoubtedly increased when products are not used as directed. Examples might include using concentrates at full strength, mixing products with incompatible chemicals, using products with inadequate ventilation, or deliberately inhaling solvents to get high. Reasons for "misusing" products are many:

- Label too difficult to read (e.g. too small, not in native language, poorly written)
- Consumer doesn't bother to read label
- Directions too difficult or inconvenient (what is "adequate" ventilation?)

Nevertheless, even when used as directed, some products may cause significant health risks. Estimates of health risks are often controversial because they involve various assumptions about exposure that are difficult to measure and because the risk assessor may have a financial stake in the outcome. There are many examples of consumer products that have been banned or taken off of the market because of unacceptable health or environmental risks: the pesticides chlorpyrifos, diazinon, and DDT; the wood preservatives pentachlorophenol and creosote; arsenic-treated lumber; carbon tetrachloride; and lead-based paint. Since the risk of using these products didn't change on the day they were taken off the market, one can infer that the products were unsafe before removal. More recently, extensive testing has found lead in many children's toys. Brominated flame retardants (polybrominated diphenyl ethers or PBDEs) are used in foam rubber and plastics, leach out, and end up in house dust. In addition, Bisphenol-A, an endocrine disruptor, is used in baby bottles and food-can liners. Given the huge number of consumer products already on the market and entering the market every year, regulatory agencies will typically be delayed in identifying unsafe products.

Risk Reduction

The risk from using household products can be reduced by reducing the hazard level (toxicity), by reducing exposure, or both. Reducing the toxicity—choosing less-toxic products—is arguably the best strategy because safer product choices can do more than reduce risk in the home. Safer products may also use fewer toxic chemicals in their manufacture and may be safer for the environment when disposed of.

When no safer alternatives are available, reducing exposure becomes especially important. Usually, product labels will explain the recommended safety equipment and procedures appropriate for a particular product. In addition to safety gear, ventilation, and mixing precautions, labels may also mention storage requirements. Unfortunately, some label directions are not specific enough to guarantee that following them will guarantee safe use.

Label-directed or common sense precautions should always be taken, even when using relatively low-toxicity products. For example, all chemical products should be kept out of children's reach.

Innovative programs are also available to help home residents reduce exposure to toxic substances. The Master Home Environmentalist™ program of the American Lung Association trains volunteers to visit homes and conduct a Home Environmental Assessment. Home residents are encouraged to make changes to reduce exposures to toxic substances. A major focus of this program is on reducing asthma in children.

Safer Alternatives

Avoiding the use of toxic products can take the form of avoiding chemical products altogether for certain jobs, choosing products made from safer ingredients, and buying ready-to-use dilutions rather than concentrates. The table below shows some examples of less-toxic alternatives for common products.

Less-toxic Alternatives

Table 20.3 Less-Toxic Alternatives

Alternative	Instead of Using	Toxic Ingredient Avoided
Latex paint	Oil-based paint	Solvents
Snake, plunger	Caustic drain opener	Corrosive lye
Scouring powder	Acid toilet cleaner	Corrosive hydrochloric acid
Beneficial nematodes	Insecticide for soil grubs	Diazinon, carbaryl, or other

		insecticide
Weed puller, mulch	Herbicide	2,4-D, dichlobenil, etc.

A few additional comments are necessary regarding alternatives to pesticides. Pest control is a complex process involving living organisms that can often be difficult to control using a single method. Integrated Pest Management (IPM) is a decision-making process that utilizes preventative strategies, careful monitoring, realistic pest tolerances, and natural enemies to reduce the need for chemical pesticides. Although chemical pesticides may be used in IPM, a good IPM program typically reduces chemical use considerably and attempts to use only those chemicals that will minimize human and environmental impacts. Household pest control can follow the same strategies, using non-chemical methods whenever possible and choosing lower-impact pesticides if chemicals are necessary.

Recommendations

Although the risks of household products are difficult to estimate, taking common-sense precautions can easily reduce them:

- Minimize purchase of toxic or otherwise hazardous products.
- Store all chemical products out of children's reach.
- Read and follow label directions.
- Dispose of hazardous products in accordance with local regulations.

It is difficult for consumers to identify least-toxic products by comparing product labels. Government agencies could do much more to assist and protect consumers:

- Government agencies should require that all product ingredients be listed on product labels. This practice would allow product users to better understand product hazards and to avoid ingredients they are allergic to or don't wish to purchase.
- Government agencies in the United States that regulate product labels should harmonize their labeling systems to avoid inconsistencies between products that are regulated by different agencies.
- Ultimately a more precautionary approach needs to be adopted to protect human and environmental health.

Additional Resources

Slide Presentation and Online Material

A Small Dose of Toxics at Home presentation material and references. Website contains presentation material related toxics in the home.

European, Asian, and International Agencies

• UK Department of Health (DOH). Healthy Schools. Healthy Schools is a wonderful site with information for students, parents, and teachers on creating a healthy indoor environment. [accessed August 16, 2009]
• World Health Organization (WHO). Child Health. Site has information on global child health issues. [accessed August 16, 2009]

North American Agencies

• US Department of Health and Human Services National Institutes of Health, National Library of Medicine. Household Products Database. Site has a range of information about household products including their potential health threats. [accessed August 16, 2009]
• US Environmental Protection Agency (EPA). Household Hazardous Waste. Site has general information on household hazardous waste. [accessed August 16, 2009]
• US Environmental Protection Agency (EPA). Office of Pollution Prevention & Toxics (OPPT). The site promotes safer chemicals and risk education. [accessed August 16, 2009]
• US Environmental Protection Agency (EPA). Indoor Air Quality (IAQ). This site contains information on indoor air and related health issues. [accessed August 16, 2009]
• California Office of Environmental Health Hazard Assessment. Art Hazards Program. Site has information on hazardous art/craft supplies and alternatives. [accessed August 16, 2009]
• Seattle Office of Sustainability and Environment. Site covers information on encouraging a sustainable environment including purchasing less toxic products. [accessed August 16, 2009]
• King County Household Hazardous Waste. Site contains information on managing and disposing of household hazardous products and waste. [accessed August 16, 2009]

Non-Government Organizations

• American Association of Poison Control Centers (AAPCC). The AAPCC is a US-based organization of poison centers and interested individuals who coordinate information on common poisons. [accessed August 16, 2009]
• California Poison Control System (CPCS). Site has wide range of information on poisons in and around the home. [accessed August 16, 2009]
• Environmental Working Group (EWG). This organization provides information on a range of consumer products including databases on sunscreens and cosmetics. [accessed August 16, 2009]
• Center for Health, Environment and Justice. ChildProofing our Communities Campaign. Site is "geared to protect children from exposures to environmental health hazards." [accessed August 16, 2009]
• Washington Toxics Coalition (WTC). WTC provides databases of toxic-free toys, alternatives to home pesticides, and information on persistent chemical pollutants, model pesticide policies, and much more. [accessed August 16, 2009]
• Green Seal. Green Seal encourages the purchasing of products and services that cause less toxic pollution and waste. [accessed August 16, 2009]
• Women's Voices for the Earth. WVE has information on green clean products and household hazards. [accessed August 16, 2009]

• Clean Production Action. Sick of Dust Chemicals in Common Products. CPA's report on chemicals in dust and other green products. [accessed August 16, 2009]

References

A Guide to Health Risk Assessment. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. [accessed August 16, 2009].
Bronstein, A.C., et al. "2007 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th Annual Report". *Clinical Toxicology* 46, 10 (2008): 927-1057.
Ott, Wayne R., and John Roberts. "Everyday Exposure to Toxic Pollutants". *Scientific American* February 1998.
Steinemann, Anne C. "Fragranced consumer products and undisclosed ingredients". *Environmental Impact Assessment Review* 29, 1 (2009): 32-38.

A Small Dose of Risk Assessment

or

An Introduction to Risk Assessment

Introduction and History

Risk assessment is both old and new. It is old in the sense that humans and animals survive by evaluating the risk of harm verses the benefits of action. For early humans hunting for food or eating a new plant involved risk of harm, but doing nothing risked starvation. In our current society, this kind of informal risk assessment is directed more towards the risks of eating undercooked hamburger or riding a bicycle without a helmet. More formally, risk assessment now refers to a mathematical calculation of risk based on toxicity and exposure.

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"If someone had evaluated the risk of fire right after it was invented they may well have decided to eat their food raw."

- Julian Morris, Institute of Economic Affairs in London

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Concern about the risk of chemical exposures also has a long history. For a period of time, food poisons were a concern for those in power.

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"What is food to one man may be fierce poison to others."

- Lucretius (c. 99 BC–55 BC)

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Percivall Pott made one of the first observations of a health risk related to occupational exposure. In 1775, he noted that chimney sweeps had an elevated incidence of cancer of the scrotum. A century later, in 1895, it was observed that workers in the aniline dye industry were more likely to develop bladder cancer.

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"We should remember that risk assessment data can be like the captured spy: If you torture it long enough, it will tell you anything you want to know."

- William Ruckelshaus, first administrator of US EPA, 1984

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The number of workers exposed to chemicals grew rapidly with the onset of the Industrial Revolution and advances in chemical engineering. One the first efforts to systematically evaluate the risk of exposure to chemicals was started in 1938 by a group convened in Washington, D.C. that subsequently became the American Conference of Governmental Industrial Hygienists (ACGIH). In 1941 the Chemical Substances Committee of the ACGIH was established and charged with investigating

and recommending exposure limits for chemical substances. They established exposure limits or Threshold Limit Values (TLVs) for 148 chemicals. ACGIH now publishes a list of TLVs for 642 chemical substances and physical agents and 38 Biological Exposure Indices for selected chemicals.

In 1958, in response to the increased awareness that chemicals can cause cancer, the US Congress passed the Delaney clause, which prohibited the addition to the food supply of any substance known to cause cancer in animals or humans. Compared to today's standards, the analytical methods used to detect a potentially harmful substance were very poor. As the analytical methods improved, it became apparent that the food supply contained low levels of substances that were known to cause cancer in either animals or humans. The obvious question was: Is a small amount of a substance "safe" to consume? This question in turn raised many others about how to interpret data or extrapolate data to very low doses.

The 1970s saw a flourishing of activity to develop and refine risk assessment methodologies. The initial focus was to develop risk assessment procedures to establish exposure limits for cancer-causing substances, the primary concerns being the food supply and the workplace. These efforts were gradually expanded to include non-cancer endpoints such as nervous system development, reproductive effects, and effects on the immune system. Researchers at national and international agencies are developing better approaches to dealing with uncertainty in health effects data and applying judgment in interpreting the results. The area of judgment is a critical aspect of risk assessment. The process of interpreting and communicating risk assessment results requires full understanding and disclosure of the assumptions, data gaps, and possible financial interests that may play a role.

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> "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."
>
> - Principle 15: Rio Declaration, 1992

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Concerned by the shortcomings of risk assessment, a growing body of scientists is advocating a precautionary approach to risks that are not fully understood. The precautionary principle has been applied to issues related to toxicology, public health and sustainable development, and use of the environment (Cairns (2003; Goldstein (2001), and is an established global principle (Rio Declaration, 1992).

Risk Assessment

Hazard x Exposure x Individual Sensitivity = Risk

Risk assessment is the process of estimating association between an exposure to a

chemical or physical agent and the incidence of some adverse outcome. The relationship between hazard, exposure, and individual sensitivity is never exact. For example, understanding the hazard depends on the end point such as cancer or immune or nervous system effects. Exposure depends on the route and duration. Individual sensitivity can be influenced by genetics, age, gender, or other variables. Initially the focus was human health, but now it has broadened to include wider environmental and ecological concerns. Risk management is a more overtly political process directed at determining an action based on relevant public and environmental health goals, cost, societal issues, and other related or even unrelated issues. An important part of risk management is balancing the risks, costs, and benefits—never an easy task.

Hazard Identification

The first step in risk assessment is to gather health-related information associated with an exposure. Ideally, hazard identification starts before there is significant use of the agent. The structure of the compound is compared to that of compounds with known toxicity profiles, and cell-based studies are often performed to screen for toxicity. Finally, animal bioassays and human studies are performed to characterize and develop a toxicity profile. Multiple health-related endpoints are evaluated to determine if the compound is associated with adverse effects. Advantages of animal studies include experimental control and accurate knowledge of the dose.

Using knowledge gained from animal studies or observations from human populations, a more formal human epidemiology study may be performed. Human studies have the obvious advantage of being conducted on the subject of most interest, but they are time consuming and expensive, and often have many variables that are difficult to control.

Common Toxicity Endpoints for Hazard Identification

- Carcinogenicity
- Mutations
- Altered immune function
- Teratogenicity
- Altered reproductive function
- Neurobehavioral toxicity
- Organ-specific effects
- Ecological effects (wildlife, environmental persistence)

Exposure Assessment

If the hazard assessment indicates that the compound is potentially hazardous, the next step is to evaluate the various possibilities for exposure. What is the most likely route of exposure: oral, inhalation, or skin? How much absorption is expected from the different routes of exposure? Information is also needed on amount, duration, and frequency of exposure. Is exposure occurring in the home, workplace, school, or other areas? This information helps to define the population of concern. Exposure information may also be important for designing appropriate studies on hazard assessment and certainly for the next step of establishing dose/response relationships.

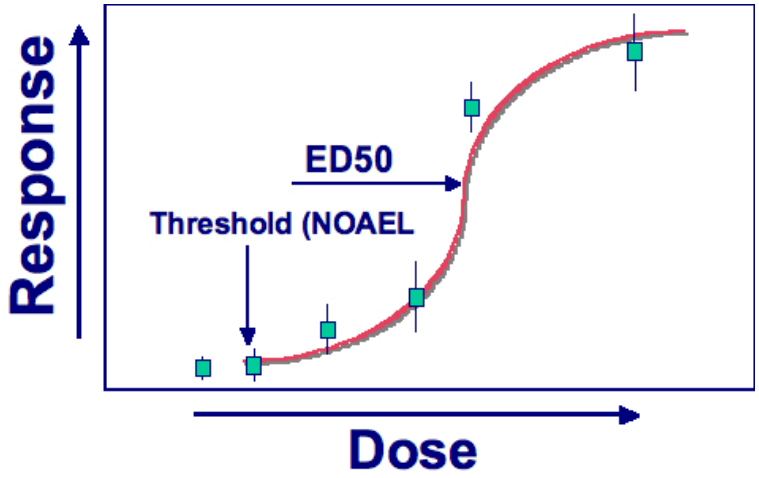
Dose/Response Assessment

To characterize the dose/response relationship for the agent, data from the initial hazard assessment, combined with exposure assessment information, are used determine the most sensitive endpoint. Available data are then used to define the dose at which there is no observed effect (NOEL, no observed effect level) and the shape of the dose/response curve. It may be necessary to perform additional studies to define the dose/response curve. The ED50 is defined as the effective dose at which 50% of the subjects respond.

Risk Characterization

The final step is to take all the information from hazard assessment, exposure assessment, and dose/response assessment and summarize it in a risk characterization for the chemical substance. Any uncertainties in the data set or missing information must be evaluated. While all efforts are made to minimize professional judgment by having robust data, it is often the case that not enough of the right information is available. Recommendations must still be made as to an acceptable level of exposure for a given population, the goal being to ensure the even the most sensitive individuals are protected from any adverse effects. The dose thought to insure protection is called a reference dose (RfD) or acceptable daily intake (ADI). Note the word safe is NOT used, only the avoidance of adverse effects.

Figure 21.1 Dose Response



Acceptable Daily Intake

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"The daily intake of a chemical, which during an entire lifetime appears to be without appreciable risk on the basis of all known facts at the time."

- World Health Organization, 1962

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There are of course many mathematically complex ways to perform a risk assessment but first, key questions about the biological data must be resolved. The most sensitive endpoint must be defined along with relevant toxicity and dose/response data. A standard risk assessment approach that is often used is the so-called divide by 10 rule. Dividing the dose by 10 applies a safety factor to ensure that even the most

sensitive individuals are protected. Animal studies are typically used to establish a dose/response curve and the most sensitive endpoint. From the dose/response curve a NOAEL dose, or no observed adverse effect level, is derived. This the dose at which there appears to be no adverse affects in the animals studies at a particular endpoint which could be cancer, liver damage, or a neurobehavioral effect. This dose is then divided by 10 if the animal data is in any way thought to be inadequate. For example, there may be a great deal of variability, there were adverse effects at the lowest dose, or only tests of short-term exposure to the chemical were conducted. An additional factor of 10 is used when extrapolating from animals to humans. Last, a factor of 10 is used to account for variability in the human population or to account for sensitive individual such as children or the elderly. The final number is the reference dose (RfD) or acceptable daily intake (ADI). This process is summarized below.

Animal Dose Response Data: NOAEL (No Observed Adverse Effect Level)
↓
Divide by 10 (Account for inadequate animal data)
↓
Divide by 10 (Animal-to-human extrapolation)
↓
Divide by 10 (Human variability or individual sensitivity)
↓
Reference Dose (RfD) or Acceptable Daily Intake (ADI)

Safety factors are typically used in a risk assessment to define an acceptable dose for food additives and pesticides. It is very important to ensure that an artificial sweetener such as aspartame, which is commonly consumed by all age groups as well as pregnant women, have a large margin of safety. In contrast, consider a compound such as lead. The risk of lead exposure to the developing child is well known but there has been no safety factor applied to blood lead levels of concern.

Table 21.1 Factors to Consider

Route of Exposure	Pertinent Factors
Ingestion	Concentration of toxicant in ingested material, amount consumed, frequency of ingestion, absorption factor
Skin	Concentration of toxicant in applied material, skin area exposed, absorption factor
Inhalation	Concentration of toxicant in air, breathing rate, exposure time, absorption factor

Risk Management

Risk management is the process if deciding what to do to reduce a known or suspected risk. It balances various community demands with scientific information generated from the risk assessment. Public perception of risk is also considered. The following table characterizes some of the factors that influence perception of risk.

Table 21.2 Characteristic of Risk

Characteristic	Level	Examples
Knowledge	Little known	Food additives
	Much known	Alcoholic drinks
Newness	Old	Guns
	New	Space travel
Voluntariness	Not voluntary	Crime
	Voluntary	Rock climbing
Control	Uncontrollable	Natural disasters
	Controllable	Smoking
Dreadedness	Little dread	Vaccination
	Great dread	Nerve gas
Catastrophic Potential	Unlikely	Sunbathing
	Likely	War
Equity	Distributed	Skiing
	Undistributed	Hazardous dump

(Adapted from Kraus and Slovic (1988))

An individual's perception of risk is sometimes very different from a risk assessment

based on a more objective analysis of the data. For example, individuals often rank nuclear power as a high risk but most experts give it a low risk rank.

Early risk evaluation often looked only at death as the main endpoint, asking if a particular action or exposure lead to increases in death or reduced the number of working years. Advances in the biological sciences have required that more complex risk analysis be undertaken to evaluate quality of life issues, not just death as an endpoint. The challenge for both risk assessment and risk management will be to incorporate quality of life and individual values into the decision-making process.

Precautionary Principle

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"When an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."

- Wingspread Statement on the Precautionary Principle, Jan. 1998

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Another approach to risk-based decision-making is the precautionary principle. The risk assessment and risk management approach used in United States places a heavy reliance on the certainty of the data. The precautionary principle emphasizes that there is always some uncertainty and that decisions should be based on recognizing the possibility of harm. When in doubt, a cautious approach should be taken until adequate data are available to show that there is little potential for harm. Action to reduce exposure to hazardous agents should begin even if there is some uncertainty in the data. In other words, some uncertainty in the data should not be used as an excuse for inaction. This approach is being given more consideration in Europe than in the United States. The approach gains credibility when one considers how its application years ago would have prevented the tragic effects of lead in gasoline and paint.

Precautionary Assessment

The goal of precautionary assessment (PA) is to move beyond risk assessment and allow communities and individual to incorporate their knowledge, values, and ethics into a more comprehensive evaluation of a hazardous condition. The PA combines the philosophy and ethics of the precautionary principle with the standard scientific evaluation of the hazards. Precautionary assessment contains three basic elements: a) community and social issues, b) exposure, and c) hazard and toxicity. Each element is broken down into a series of questions that are scored numerically and summed to produce a summary score for each element. The PA is designed to help place the knowledge available within the context of the community. In contrast to the traditional risk assessment, the PA is a more comprehensive approach to evaluating the human and environmental health risks. Overall, the PA can be considered a more reasonable, rational, and responsible approach to evaluating risk of chemicals. A detailed discussion of the PA and spreadsheet are available online (Gilbert, 2006). Other authors have also discussed alternative decision-making approaches to risk assessment, for example O'Brien (2000).

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Risk Assessment presentation material and references. Website contains presentation material related risk assessment.

European, Asian, and International Agencies

• UK Department of Health (DOH). Guidance on a strategy for the risk assessment of chemical carcinogens. [accessed August 24, 2009] The Department of Health has published information and research outcomes on risk and public health. [accessed August 24, 2009]
• International Programme on Chemical Safety (IPCS). Health Impacts of Chemicals. Information on global risk assessment issues. [accessed August 24, 2009]
• EnviroLink: The Online Environmental Community. "The EnviroLink Network is a nonprofit organization founded in 1991. EnviroLink maintains a database of thousands of environmental resources and provides internet services to nonprofit organizations. [accessed August 24, 2009]
• World Health Organization (WHO) Organization for Economic Co-operation and Development. Chemicals Assessment. "OECD assists member countries developing in and harmonizing methods for assessing such risk." [accessed August 24, 2009]
• National Institute for Environmental Studies. Center for Environmental Risk Research. The center aims to provide policy responsive research on improving assessment methods for environmental risk. (English and Japanese) [accessed August 24, 2009]

North American Agencies

• US Environmental Protection Agency (EPA). National Center for Environmental Assessment (NCEA). NCEA goals are to apply "science to improve risk assessment and environmental decision making." [accessed August 24, 2009]
• US Environmental Protection Agency (EPA). Risk Assessment. NCEA goals are to apply "science to improve risk assessment and environmental decision making." [accessed August 24, 2009]
• US National Cancer Institute (NCI). Breast Cancer Risk Assessment Tool. An interactive tool designed by scientists at the National Cancer Institute (NCI) to estimate a woman's risk of developing invasive breast cancer. [accessed August 24, 2009]
• California Office of Environmental Health Hazard Assessment (OEHHA). Risk Assessment. "OEHHA is responsible for developing and providing risk managers in state and local government agencies with toxicological and medical information relevant to decisions involving public health." [accessed August 24, 2009]

Non-Government Organizations

• American Conference of Governmental Industrial Hygienists (ACGIH). "The ACGIS community of professionals advances worker health and safety through education and the development and dissemination of scientific and technical knowledge. [accessed August 24, 2009]
• Toxicology Excellence for Risk Assessment (TERA). TERA is a nonprofit [501(c)(3)] corporation that works to "protect public health developing, reviewing, and

communicating risk assessment values and analyses." [accessed August 24, 2009]
• Society for Risk Analysis (SRA). "SRA provides an open forum for all those who are interested in risk analysis. Risk analysis is broadly defined to include risk assessment, risk characterization, risk communication, risk management, and policy relating to risk." [accessed August 24, 2009]
• Harvard Center for Risk Analysis (HCRA). HCRA focuses on "using decision science to empower informed choices about risks to health, safety, and the environment." [accessed August 24, 2009]
• The Science & Environmental Health Network. Precautionary Principle. SEHN advocates the wise application of science to protecting the environment and public health. [accessed August 24, 2009]

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Goldstein, Bernard D. (2001). "The Precautionary Principle Also Applies to Public Health Actions". *American Journal of Public Health* 91, 9 (2001): 1358-1361.
Rio Declaration on Environment and Development. Stockholm, Sweden: United Nations, 1992.
Nielsen, E., Ostergaard, G. and J. C. Larsen. *Toxicological Risk Assessment of Chemicals: A Practical Guide*. New York: Informa HealthCare, 2008.
O'Brien, M. *Making Better Environmental Decisions: An Alternative to Risk Assessment*. Cambridge: MIT Press, 2000.
Gilbert, S.G. (2006) Precautionary Assessment: Getting Out of the Risk Assessment Box.

A Small Dose of Ethics

or

An Introduction to Ethical, Legal, Social, and Social Issues in Toxicology

Introduction

Rapid advances in science and technology have produced enormous benefits but have also created undesirable hazardous side-effects that impact human health and the environment. The toxicological sciences strive to understand and evaluate the health and environmental effects of chemical and physical agents. The impact of this expanding body of science on society has grown enormously in the last 100 years, and with that have arisen corresponding financial, legal, and individual implications. Despite the increased scientific data and understanding, decision making has become more difficult and complex. It is thus increasingly important to consider the ethical, legal, and social issues that confront toxicologists, public health professionals, and decision makers.

The fundamental principles that an ethical toxicologist should consider can be summarized as: 1) dignity, which includes respect for the autonomy of human and animal subjects; 2) veracity, an adherence to transparency and presentation of all the facts so all parties can discover the truth; 3) justice, which includes an equitable distribution of the costs, hazards, and gains; 4) integrity, an honest and forthright approach; 5) responsibility, an acknowledgment of accountability to all parties involved; and 6) sustainability, consideration that actions can be maintained over a long period of time (Gilbert and Eaton, 2009).

Beyond these basic principles it is important to have a vision of environmental health that is grounded in ethical considerations.

Historical Perspective

Looking back, it is easy to see the beginnings of an ethical framework for decision making in the Greek physician Hippocrates (460-377 BC), who studied the effects of food, occupation, and climate on causation of disease and is credited with the basic medical tenet of "do no harm." Bernardo Ramazzini (1633-1714), an Italian physician, examined the health hazards of chemicals, dust, metals, and other agents

encountered by workers in 52 occupations, which he documented in his book *De Morbis Artificum Diatriba* (Diseases of Workers).

Aldo Leopold, considered by many to be America's first bioethicist, summarized ethical responsibilities in a simple statement in 1949. "A thing is right when it tends to preserve the integrity, stability, and beauty of the biotic community. It is wrong when it tends otherwise." It can be extrapolated from this ethical statement that exposing people, particularly children, to harmful agents robs them of their "integrity, stability, and beauty," indeed their potential, and is therefore wrong. Health, ecological, and ethical concerns about chemical exposures were highlighted by Rachel Carson in *Silent Spring*, first published in 1962. Carson sounded one of the first alarms about the effects of environmental contaminants and catalyzed numerous regulatory changes related to chemical use. Her writings include the following statements: "It is the public that is being asked to assume the risks ... the public must decide whether it wishes to continue on the present road and it can only do so when in full possession of the facts..." "Only within the moment of time represented by the present century has one species—man—acquired significant power to alter the nature of his world."

The next major book to capture public attention on this subject was *Our Stolen Future* by Theo Colborn, Dianne Dumanoski, and John Peter Meyers, first published in 1996. This book focused on the reproductive and developmental effects of synthetic chemicals and raised awareness and concern about endocrine disruptors.

At the same time, there were ongoing efforts to define a more philosophical and ethical approach to managing the chemicals we have grown dependent upon. The idea for an Earth Charter was first proposed in 1987 as an approach to creating a broad ethical statement with the goal of establishing a global civil society. The Earth Charter took a step forward in 1992 at The Earth Summit in Rio de Janeiro, also known as the Rio Summit or Rio Conference, which produced the 27 Principles of the Rio Declaration. Principle 15 defined the precautionary principle as an approach to protect human health and the environment. In January 1998, the Wingspread Conference on the Precautionary Principle was held in Racine, Wisconsin to define the precautionary principle.

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"When an activity raises threats of harm to the environment or human health, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."

- Wingspread Statement on the Precautionary Principle, January 1998

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The Earth Charter was being developed during this period and was ultimately adopted by many countries, states, and organizations. Relevant to toxicologists is one the principles which states: "Prevent harm as the best method of environmental protection and, when knowledge is limited, apply a precautionary approach." The Precautionary

Principle as a base for decisions is more readily accepted in Europe, but there are ongoing efforts in the United States to adopt a more precautionary approach in the management of chemicals.

Legal Issues

There is a wide range of laws and regulations that shape the role of toxicology in society. One of the first laws dealing with toxicology, passed in 82 BCE by the Roman Emperor Sulla, was intended to deter intentional poisonings because women were poisoning men to acquire their wealth. In 1880, food poisonings spurred Peter Collier, chief chemist, US Department of Agriculture, to recommend passage of a national food and drug law. In 1938, the Federal Food, Drug, and Cosmetic Act was adopted following an incident in which Elixir Sulfanilamide, containing the poisonous solvent diethylene glycol, killed 107 people, many of whom were children. The need to control chemical contamination was recognized in the 1976 when the US Congress passed the Toxic Substances Control Act (TSCA) to "prevent unreasonable risks of injury to health or the environment associated with the manufacture, processing, distribution in commerce, use, or disposal of chemical substances." TSCA became largely ineffective following court decisions and there is now an effort to pass chemical policy reform legislation. Mean while Europe has moved forward with REACH, Registration Evaluation and Authorization of Chemicals, a system that requires testing and evaluation of chemicals before their introduction into commerce.

Social Considerations

Toxicologists and public health professionals play an important role in society in protecting and promoting public health. There has been an extra focus on ethical and social issues related to children's health. The US Society of Toxicology code of ethics indicates that toxicologists should be thoughtful public health advocates. While seldom explicitly stated, professional codes of ethics such as those for SOT are often based on the following social responsibilities: 1) to share and use knowledge, 2) to promote the health and well-being of children, and 3) to maintain the right of all species to reach and maintain their full potential.

Additional Ethical Considerations

A toxicologist is also concerned with issues of integrity and honesty in the conduct and interpretation of toxicological studies. It is important to examine and acknowledge conflicts of interest. Toxicology associations as well state and federal agencies, nonprofits, and universities have statements and guidelines on conflict of interest and disclosure. In addition, toxicologists must adhere to rules and regulations regarding the use of animals and humans in scientific studies. The conduct of studies involving

humans has a rich history that has become increasingly well defined and regulated to ensure adequate knowledge and consent of subjects involved.

Summary

The purest of ethical behavior and decision making requires the thoughtful development and articulation of fundamental principles upon which to base any action. The ethical toxicologist must consider and integrate basic ethical principles into the decision making process. This approach moves beyond what is legally required: an ethical approach requires ongoing discussion and considerations as the toxicological sciences and society evolve. Toxicologists must not only be familiar with the rules and regulations regarding the ethical conduct of research, but also with the underlying ethical principles. The challenge is to move beyond a purely legal adherence to the rules but toward an ethical approach grounded in carefully considered and articulated ethical principles that drive the responsible conduct and application of research in modern societies.

Additional Resources

Slide Presentation and Online Material

• A Small Dose of Ethics presentation material and references. Website contains presentation material related ethics.

European, Asian, and International Agencies

• European Commission. European Group on Ethics in Science and New Technologies (EGE). The EGE aims to coordinate actions and communications on ethics across the European Commission. [accessed January 22, 2010]
• Anscombe Bioethics Centre. "The Anscombe Centre is a Roman Catholic academic institute that engages with the moral questions arising in clinical practice and biomedical research." [accessed January 22, 2010]

North American Agencies

• US Environmental Protection Agency Office of Science Advisor. Program in Human Research Ethics (PHRE). PHRE supports "the ethical conduct and regulatory compliance of human subjects research (HSR) conducted, supported, or regulated by EPA." [accessed January 23, 2010]
• US Department of Health & Human Services. Office for Human Research Protections (OHRP). OHRP "provides leadership in the protection of the rights, welfare, and well-being of subjects involved in research". [accessed January 23, 2010]
• US National Institutes of Health. Bioethics Resources on the Web. Provides a broad range of resources related to ethics. [accessed January 23, 2010]

Non-Government Organizations

• Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International). AAALAC is a "private, nonprofit organization that promotes the humane treatment of animals in science through voluntary accreditation and

assessment programs." [accessed January 23, 2010]
• American Board of Industrial Hygiene (ABIH). Code of Ethics. Applies to all ABIH-certified professionals, applicants, and examinees. ACGIH®, the American Industrial Hygiene Association (AIHA), and AIHA's Academy of Industrial Hygiene (AIH). [accessed August 24, 2009]
• Society of Toxicology. Code of Ethics. Example of professional code of ethics. [accessed August 24, 2009]

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Carson, Rachel. *Silent Spring*. Boston: Houghton Mifflin, 1994.
Colborn, T., Dumanoski, D., and Meyers, J.P. *Our Stolen Future: Are We Threatening Our Fertility, Intelligence and Survival? A Scientific Detective Story.* New York: Dutton, 1996.
Gilbert, S. G. (2005) "Ethical, legal, and social issues: our children's future". *Neurotoxicology* 26, 4 (2004): 521-530.
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Gilbert, S.G. and D. L. Eaton. "Ethical, Legal, Social, and Professional Issues in Toxicology". *General and Applied Toxicology. Third edition*. Bryan Ballantyne, Dr Timothy C. Marrs, Tore Syversen (eds). New York: Wiley, 2009.
Leopold, A. *A Sand County Almanac*. Oxford: Oxford University Press, 1949.
Maurissen, J. P., et al. "Workshop Proceedings: Managing Conflict of Interest in Science. A Little Consensus and A Lot of Controversy". *Toxicol Sci* 87, 1 (2005).

Glossary

Term	Definition	Example
Absorption	The process by which an agent is taken into an organism's cells or blood supply	Absorption of nicotine by the lungs
Acute exposure	Exposure of a single or very limited number of doses	One alcoholic drink
Acute response	The response associated with acute exposure	Drunk from an evening drinking alcohol
Acute toxicity	Undesirable effects of an acute exposure	Hangover from drinking alcohol
Anemia	Decreased ability of blood to transport oxygen	Fewer or damaged red blood cells (can be caused by lead)
Asbestosis	A progressive, non-cancerous disease due to asbestos exposure that causes shortness of breath from scarring of the lung	Asbestos workers
Bioaccumulate	The ability of some organisms to accumulate specific compounds	Fish accumulate methyl mercury in muscle; DDT and PCBs accumulate in fat (among other compounds)
Biotransformation	The changing of one substance into another by an organism, often to increase excretion or reduce toxicity	Bacteria changing mercury into methyl mercury
Carcinogen or carcinogenic	Any substance that causes cancer	Asbestos
Chelating Agent	An agent that binds to other agents to	Used to treat elevated

	facilitate their excretion	lead or mercury levels
Chromosome	Parts of cells responsible for heredity characteristics (DNA)	Most humans have 46 chromosomes
Chronic Toxicity	Health effects from long-term exposure	Smoking cigarettes
Corrosive	Causes burns to the skin or other body tissue	Lye, strong cleaning agents
Detoxification	The biochemical process to neutralize (i.e. metabolize) or excrete a toxicant	The metabolism of alcohol
Distribution	How a chemical agent distributes throughout the body	PCBs and pesticides accumulate in fat
Dose	A measured amount of exposure, usually in terms of body weight or sometimes surface area	10 mg/kg
Dose/response	The effect or response of an agent is related to the dose or amount of exposure	One cup of coffee is ok but two or three results in unpleasant effects
Erythema	Sunburn and skin inflammation; dilation of the blood vessels causes redness and heat	UV radiation
Excretion	How the body removes agents from its cells or the entire body	Mercury excreted in the urine
Exposure	Duration and type of contact with an agent	
Route of exposure	How the agent gains access to the organism: dermal (skin), inhalation (lung), or stomach (ingestion)	Cigarette smoke: lung Lead: ingestion
Frequency of exposure	How often the exposure occurs, and the time between exposures	Consider four beers in an hour vs. four beers over four days

Duration	How long the exposure occurs (see acute and chronic exposure)	Acute exposure to gas fumes at a gas station, or lifetime exposure to food additives
Fetal Alcohol Syndrome (FAS)	Pattern of physical, developmental, and nervous system disabilities seen in babies born to mothers who consumed alcohol during pregnancy	Affects 1 to 3 per 1000 infants worldwide
Fetal Alcohol Effect (FAE)	Similar to FAS: learning and nervous system disabilities without the obvious physical deformities	Incidence unknown
Half-life	A measure of the time taken to reduce the amount of agent by one half	The half-life of caffeine in the blood is three to four hours
Hazard	An agent or situation capable of causing an adverse effect or harm	Loud noise (can cause deafness) Lead (can reduce IQ)
LD-50	Lethal dose that will kill 50% of a group of animals	The LD-50 of nicotine is 1mg/kg
Leukemia	Cancer of the blood-forming organs of the bone marrow	Caused by benzene
Mesothelioma	A rare cancer of the thin membranes lining the lungs, almost always related to asbestos exposure	Asbestos workers (increases with smoking)
Metabolism	The change of one substance in another, usually to aid excretion or reduce toxicity	Caffeine being changed to less active compounds
Milligram (mg)	One thousandth of a gram	1 mg
Minimal Risk Levels (MRLs)	ATSDR definition: "An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of	Inorganic mercury in air; MRL by inhalation: 0.2 $\mu g/m^3$

	adverse noncancer health effects over a specified duration of exposure."	
Mutagen or Mutagenic	Any substance that causes alterations in cellular DNA	Ionizing radiation
Neurotoxicity	Production of an adverse change in the structure or function of the nervous system following exposure to a chemical or physical agent	Neurotoxic agents include mercury, lead, pesticides, heroin, and alcohol
Neurotransmitter	A chemical used to communicate between cells of the nervous system	Dopamine, serotonin
PCBs	Polychlorinated biphenyls: used as cooling agent in transformers because of their low flammability; now banned because of their environmental persistence and bioaccumulation in the fat of many species, including whales and humans	
Pesticide	"… any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any insects, rodents, nematodes, fungi, or weeds or any other form of life declared to be pests … and any substance or mixture of substances intended for use as a plant regulator, defoliant or desiccant." - Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA, 1947)	DDT, atrazine, carbofuran
Pharmacology	The study of the beneficial and adverse effects of drugs	Benefits of aspirin or caffeine
Pollutant	An agent, often released by human activity, that adversely affects the environment	DDT, PCBs, mercury, lead
Reference Dose (RfD)	A daily exposure level (dose) that is not expected to cause any adverse health	EPA's RfD for methyl

	effects in humans	mercury: 0.1 µg/kg/day
Response	The reaction to an exposure to, or dose of, an agent	Stomachache from eating too many green apples
Risk	The probability of injury, disease, loss of function, or death for an individual or population exposed to a hazardous substance (Risk = Hazard X Exposure)	
Risk assessment	The process by which the nature and magnitude of risks are identified	
Risk Communication	Strategies for effectively communicating information about hazards and risk	
Risk management	The process of determining whether or how much to reduce risk through our actions	
Susceptibility	Factors that can increase or decrease the adverse effects of an agent	
Su-Age	The young and elderly are often more susceptible to the effects of an agent	Lead is far more toxic to infants than adults
Su-Health	Disease can increase susceptibility to an agent	Liver disease can increase susceptibility
Su-Pregnancy	The many physiological changes that occur during pregnancy alter susceptibility	Greater absorption of lead, longer half-life of caffeine
Su-Sex	Man and women differ in their response to agents due to hormonal influences	Female birth control pill is the most obvious
Teratogen or Teratogenic	Any substance that causes defects in the developing embryo or fetus (birth	Alcohol can cause facial deformities (FAS)

	defects)	
Teratology	The branch of science that deals with the causes, mechanisms, manifestations and prevention of congenital defects; from the Greek *teras*, meaning abnormal form	
Therapeutic index	Measure of a drug's benefit and safety; a wide index indicates that a drug has few toxic effects at high dose levels	Wide index: antibiotics Narrow index: lithium
Toxic substance (regulatory term)	Any substance that can cause acute or chronic injury to the human body or is suspected to do so	US NIOSH publishes a list of toxic substances
Toxicant (poison)	An agent cable of causing toxicity; a poison	DDT, lead, noise, solvents, food additives, ozone
Toxic effect	The adverse reaction to an agent	Soft egg shells, reduced IQ, cancer
Toxicokinetics or Pharmacokinetics	The study of the absorption, distribution, and excretion of agents	The period of time alcohol stays in the body
Toxicology	The study of the adverse effects of chemical and physical agents on living organisms	Study of lead's effects on the developing nervous system
Toxin	A natural biological agent (from plants, animals, bacteria, or fungi) that causes toxicity	Domoic acid in shellfish, caffeine in plants
Xenobiotic	A foreign compound, i.e. one that is not naturally found in an organism	Caffeine in humans

Abbreviations Used in the Text

Abbreviation	Definition
ARND	Alcohol-Related Neurodevelopmental Disorder
CNS	Central Nervous System
BLL	Blood Lead Level
FAS	Fetal Alcohol Syndrome
FAE	Fetal Alcohol Effect
IARC	International Agency for Research on Cancer
MSDS	Material Safety Data Sheet
MRLs	Minimal Risk Levels (ATSDR)
PEL	Permissible Exposure Limits (OSHA)
Ppm	Parts Per Million
RfD	Reference Dose
TLV	Threshold Limit Value
TWA	Time-Weighted Average

Units of Measure

Abbreviation	Definition
µg	Microgram (.000001 gram, one millionth of a gram)
mg	Milligram (0.001 grams, one thousandth of a gram)
Kg	Kilogram (1000 grams, 2.2 lbs)
ml	Milliliter (0.001 liter, one thousandth of a liter)
dL	One tenth of a liter (100 ml)
L	Liter (1.056 liquid quart)
Lbs	Pounds (0.45 kg)

US Government Agencies

Abbreviation	Definition
ACGIH	American Conference of Governmental Industrial Hygienists
ATSDR	Agency for Toxic Substances and Disease Registry
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
NIOSH	National Institute for Occupational Safety and Health
OSHA	Occupational Safety and Health Administration
USGS	US Geological Survey

Appendix: Demonstration of the Principles of Dose/Response

Definitions:
Dose is the amount of exposure to an agent.
Response is the reaction to the dose.
Materials Required:
Four large drinking glasses (wine glasses work very well)
One small drinking glass
Food color (blue is best, in a container to dispense drops)
One pitcher of water
a) Demonstration of the importance of the dose amount (see first figure)
Fill about three-fourths of three large glasses with water. This represents the approximate water content in individuals. I usually ask the class how much water is in each of them, which makes for a fun discussion.
Put one drop of blue food color in the first glass, three drops in the second glass, and six to nine drops in the last glass. Ask the class to count with you and also ask how many drops they would like to have in the last glass.
Stir with a pencil or pen and discuss the change in color as a response to the increased dose of food color in each glass. Discuss how some chemicals, caffeine being one, distribute throughout total body water.
b) Demonstration of the importance of size (see second figure)
Fill about three-fourths of one large glass and about three-fourths of the small glass with water. The large glass represents an adult and the small glass represents a small child.
Put one drop of food color in each glass. The small glass will be much darker and will usually look like the high-dose glass from the first demonstration.
Discuss the importance of size and the impact weight has on dose, depending on sophistication of the group. A small child that drinks one can of caffeinated soda will have a very different response than an adult because of the difference in the dose of caffeine relative to body size.
Discussion
For exposure to a chemical agent, dose is usually expressed in relation to body weight. This is because for a fixed amount of toxic agent, the dose, and likewise the effect, depends directly on weight. We know, for example, that one shot of alcohol would have a very big effect on a child weighing 10 lbs and a much smaller effect on an adult weighing 200 lbs. To take this into account, dose is measured in units of milligrams of toxicant per kilogram of body weight, abbreviated mg/kg. If someone consumed 100 mg of caffeine, approximately the amount in a cup of coffee or two cans of caffeinated soda, and if they weighed 70 kg (about 155 lbs), the dose would be 100 mg per 70 kg of body weight or 1.4 mg/kg. On the other hand, if a child weighing only 10 kg (about 22 lbs) consumed the same 100 mg of caffeine, the dose would 10 mg/kg, seven times as large because the body weight is one seventh. Thus size and amount of exposure determine the dose and are critical factors in toxicology. This principle can be an extremely important factor in home lead or pesticide exposures, where the dose a child receives is far greater than the adult due to the child's small size and extra sensitivity.

Effects of Amount on Response

The Greater the Dose, The Greater the Effect.

Effects of Size on Response

The Smaller the Size, The Greater the Effect.