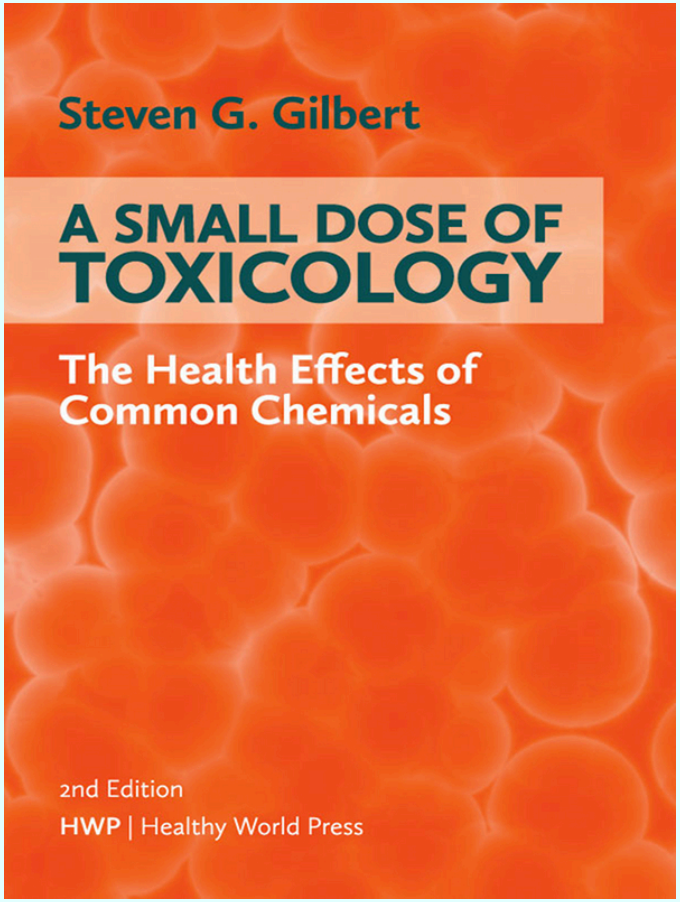
A Small Dose of Toxicology 3rd Edition



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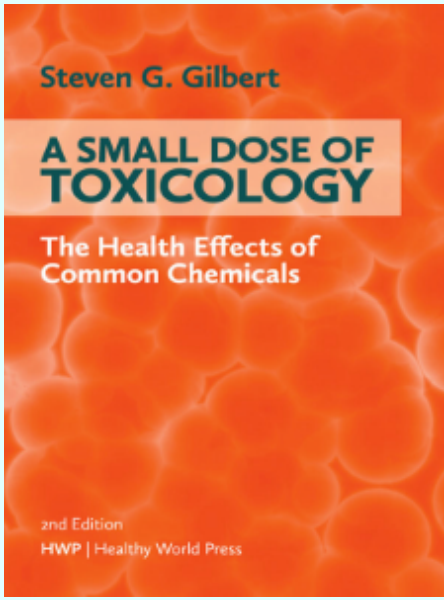

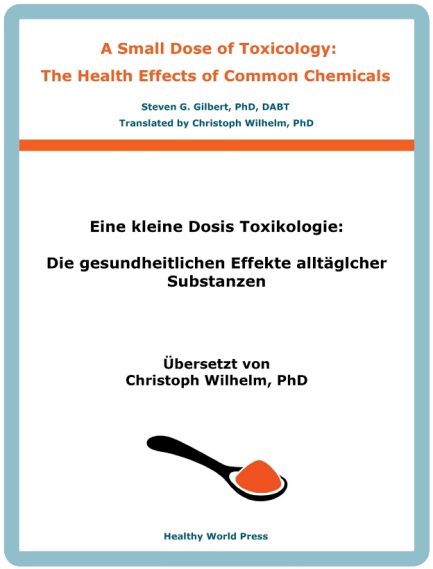

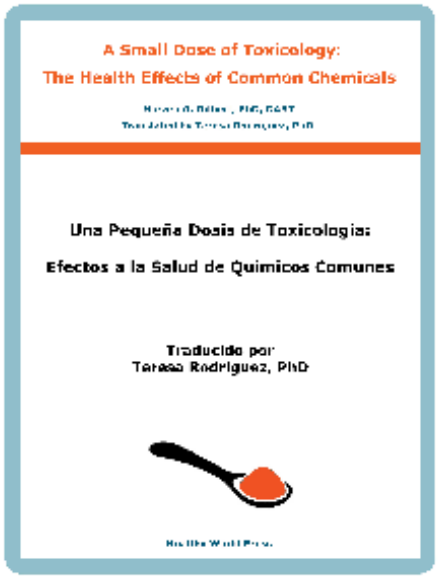

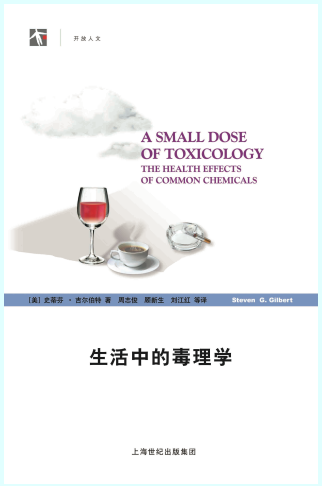

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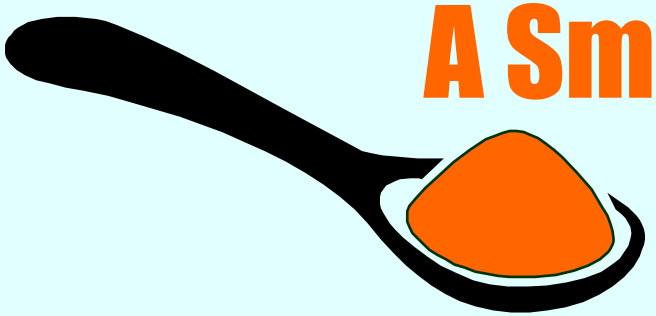

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- Learn about the effects of nicotine, alcohol, lead, mercury, pesticides ….
- Learn about toxic chemicals around the home & workplace
- Learn about risk assessment & the precautionary principle

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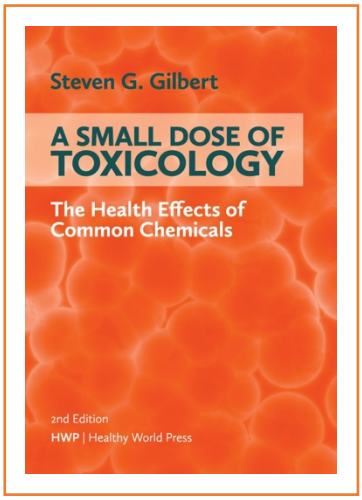

A Small Dose of Toxicology
3rd Edition
Released as a FREE E-book
November 14, 2020

Seattle, WA -- A Small Dose of Toxicology: The Health Effects of Common Chemicals, 3rd Edition, by Steven G. Gilbert, PhD, DABT, was released as a free e-book November 14, 2020. This new Edition added several new chapters and updated all chapters. The good news is that you can download each chapter as a PDF file and PowerPoint files can be used for teaching of that particular chapter material. It's free, try it out at www.asmalldoseoftoxicology.org.

A Small Dose of Toxicology is an introductory toxicology textbook that examines the health effects of common chemical agents and places toxicology within the framework of everyday life. Agents covered include not only obvious candidates such as lead, mercury, and solvents, but familiar compounds such as caffeine, alcohol, nicotine, cannabis, and fluoride. Additional chapters cover basic toxicology, targets of toxic agents, risk assessment, history, and ethics.

This revised and expanded Third edition is available only as a free e-book and contains numerous hyperlinks to articles and PowerPoint presentations on the "A Small Dose of Toxicology" web site at (www.asmalldoseoftoxicology.org). Links to references and other informational websites are also included. Free copies can be downloaded as individual chapters or as a full book in PDF format. A Small Dose of Toxicology is designed for students of all ages who are interested in learning about how common everyday chemicals affect their health. Teachers and students can freely access PowerPoint slides and links to current references for each chapter from the web site. The book strives to engage students and readers by placing scientific information in the context of history, society, and culture.
In keeping with desire to share its efforts to foster a more peaceful, healthy, and sustainable world, A Small Dose of Toxicology is offered for free as an ebook.

Donations are encouraged to support the work of INND (The Institute of Neurotoxicology and Neurological Disorders). INND is a 501(c)(3) corporation so all donations are tax deductible. Contact: Steven G. Gilbert, 206-605-6536, sgilbert@innd.org.

Toxicology and You
Or
An Introduction to A Small Dose of Toxicology

Chapter 1 of Third Edition of
A Small Dose of Toxicology - The Health Effects of Common Chemicals

By
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Toxicology and You

Toxicology is about the chemicals that adversely affect the health and well-being of life on the earth we inhabit. Chemicals are not all bad, after all we are made up of chemicals, indeed life is made up of a vast array of chemicals working together in an intricate synchrony. Chemicals are life and we depend on them to live. Unfortunately, some naturally occurring or human created chemicals can upset the balance that we depend on to lead a healthy life. This is toxicology, the understanding of how a small distortion in the chemical balance can adversely affect health of even result in death.

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 as 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 future chapter, caffeine provides an excellent example of how we apply knowingly or unknowingly the principles of toxicology. Understanding how caffeine interacts with the body can even explain why the 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, historical, and personal events.

The purpose of *A Small Dose of Toxicology* is to build upon our intuitive understanding of toxicology into knowledgeable and comfortable application of the principles of toxicology. Placing some form and structure around what we already intuitively know about toxicology will allow more critical analysis of not only our immediate environment but many of the current events that shape our local and global society. Toxicological considerations shape directly or indirectly many decisions about our home, play, school, or work environments. As citizens in a democratic society, we must be able to meaningfully engage decision makers in industry, government, and the news media to influence the development of our local environment as well as society. 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 effect on our lives, ask insightful questions, and ultimately influence the decision makers.

Historically, toxicology was most often concerned with how much of a substance it took to kill you. Literature has some splendid examples of the awareness of naturally occurring poisons. The ancient Greeks were very knowledgeable about the properties of the plant, 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 a well-known playwright, Shakespeare:

From Romeo and Juliet - act 5
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.


Shakespeare ?

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, which was really about the toxic and additive properties of opium. 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 to make money. Opium was not made illegal in the United States until 1924. The popularity of drug use continues and governments are engaged in a variety of efforts to curb their use including "drug wars" with neighboring countries.

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. Life has many examples of toxicology, if one only thinks or sees in terms of a toxicologist.

Every Day Examples of Toxicology
Or

What do these have in common?

Below are a few examples (Table 1.1), there are many more and they occur everyday in the news. Can you add to this list? What toxicology related or biology related issues have been in the news recently?

Table 1.1 Every Day Examples of Toxicology

What Aspect of Toxicology?	Comment
Thalidomide	Developed as a sedative in the early 60's but found to cause a rare birth defect, phocomelia. In 1962 legislation was passed that new drugs must undergo sufficient animal and human testing prior to approval for use by the FDA.
Hong Kong	a) Many chickens and birds in Hong Kong were killed to stop the spread of a potentially deadly avian virus that could move to humans b) 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 to Chinese population. Consider our own current "war on drugs".
Princess Diana	At the time of death her driver may have had too much alcohol to drink.
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 Helm 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 demands on and is 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

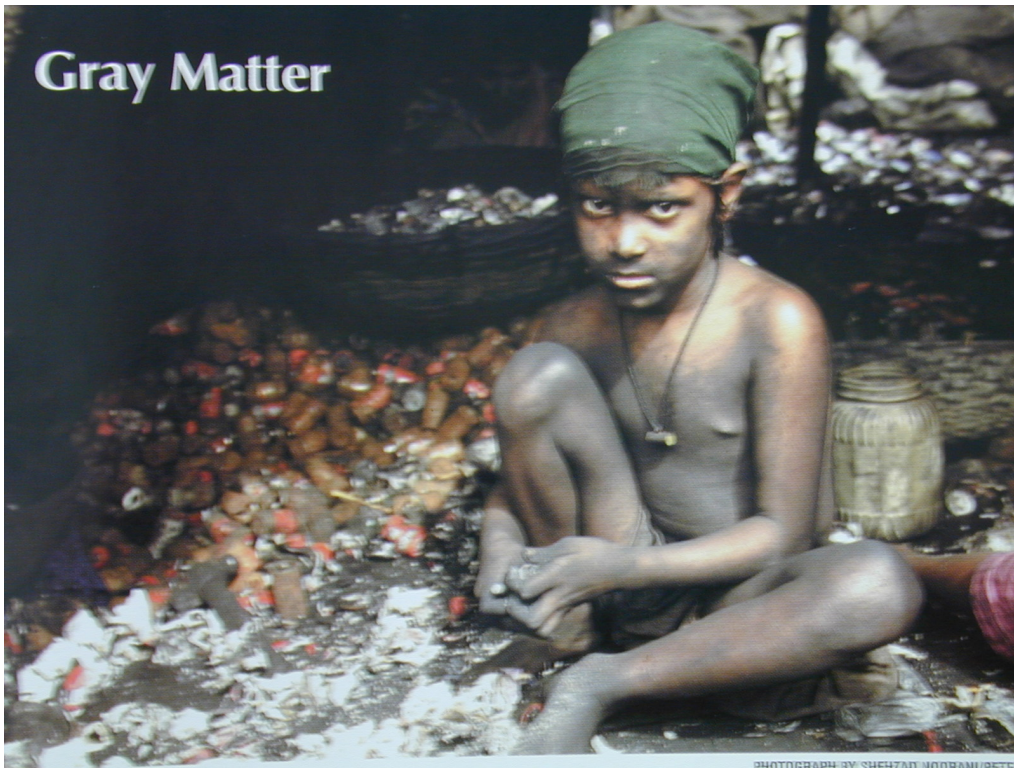
	be tracked in the home on shoes or by pets. Removing shoes can reduce contamination in the home.
12,000 Children	Estimated number of children with Fetal Alcohol Syndrome
Coeur d'Alene, Silver Valley, ID	Town contaminated by lead
Solar Radiation (ultraviolet light)	Sunburn, cancer
Arsenic	Found in drinking water, and old smelter and mining sites, coal ash, cause skin disease and cancer

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 side 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 both the pharmacological or beneficial aspects of caffeine and at the same time be looking at 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 easily recognizable and undesirable side-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 (undesired or harmful) 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 the consumption of or exposure to the agent. As our understanding of toxicology has increased, there has been a shift in focus by recognizing the unique sensitivity of individuals and to more subtle 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 the changing perspective on toxicology. 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 to lead. Harming the learning and memory of 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 live time and well 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. (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 workplace 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 numerous 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. Changes in stream temperature can affect the ability of fish to live and reproduce. 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 just an annoying 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, greater focus on the subtle responses of the organism, and recognition of the sensitivity of individuals. Thus toxicology has moved away from death as an endpoint to a focus on performance and quality of life. Expose to hazardous vapor may result in 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 systems such as consideration of global warming or the effects of logging on the rain forest. Increased atmospheric carbon dioxide is a toxic event which results in a response of global warming. What dose of logging can a rain forest sustain? The basic principles of toxicology are a framework for considering the small local events to large global events or entire biosystems, which moves us into

ecological considerations. Application of the principles of toxicology to even very large events where there is an action or exposure or a reaction and a response results in a simplification that can lead to unique perspective. However, 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.

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 have learning disabilities. These 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 to 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 changes in performance and function.

Ensuring environmental health is a complex interaction of the individual as well as society and ranges from the local to the global. 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 mercury is also going into the atmosphere. The wind may take the mercury in the atmosphere far away but eventually it comes 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. It was subsequently found to weaken bird shell eggs, causing serious declines in predatory birds. An interesting property of DDT and a number of related pesticides is that they can be stored in fat. As the DDT moves up the food chain from smaller to larger animals more and more accumulates in the fat. During breast feeding fat is mobilized and along with it the DDT, which appears in the breast milk, consumed by the infant. These are two of the many

examples that we must confront as we begin to appreciate the global implication of toxicology and environmental health and impacts on individuals

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 it was determined that a new sleeping pill, thalidomide, was shown to cause birth defects. Infants in Europe and Australia were born with birth defects when their pregnant women used thalidomide. 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 the use of pesticides, industrial chemicals, hazardous waste, drinking water, air pollutants and other environmental hazards. These two agencies, as well as other federal and state agencies, spend a lot of money based on principles of toxicology.

The title of this book, "A Small Dose of Toxicology", identifies a primary aim, 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 the consumption of other recreational drugs? Why are some individuals more sensitive than others? Was food cooked long enough to insure that all bacteria are killed? My focus is on the practical application of toxicology in our day-to-day lives, but I want to keep a perspective on applying the principles of toxicology to bigger issues. I omitted some of the details on the chemistry and mechanism of action 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 the chemistry and mechanisms of action of both common and obscure toxic agents. It is 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.

Understanding the principles of toxicology can provide the power to discover new insights into decision-making. The principles of toxicology can then be applied to ever-changing circumstances as we search for some understanding of the issues. The power is in having the knowledge to evaluate a new situation.

> "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

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

The "Principles of Toxicology" chapter provides an overview of the principles of toxicology while subsequent chapters explore specific topics in great depth. The reader is encouraged to pick and choose specific areas 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. A teacher can use this material for classroom presentation or the student can use the presentation material as class notes or for review of the chapter material. As a teacher myself, I have always wondered how many times the same material has been reproduced to accommodate a lecture.

This third edition of "A Small Dose of Toxicology" is designed to take advantage of the extensive information on numerous web sites that are designed to grow as our understanding of toxicology expands. The grand mission of this edition 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.

Toxicological Resources

There is a large and ever-growing body of information on toxicology, particularly on the World Wide Web. Many national government, international organization and non-government agencies have excellent web sites with detailed information on the issues discussed in this book. I urge you to consult these sites for more in-depth information. Your local bookstore, particularly a large university bookstore or an ecologically oriented store may have additional information. Unfortunately much of the in-depth medically or highly scientific information is not very accessible. There are also many non-

governmental organizations that can provide additional information and a different perspective. Computer networks and local public and university libraries also contain a wealth of information. Teaching aids, including, material directly related to this book are also available on-line or from a variety of organizations.

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 is online: www.asmalldoseoftoxicology.org (accessed: 14 October 2019).
  Web site contains presentation material related to this book for each chapter and other related odds and ends.

- Interdisciplinary Center for Exposures, Diseases, Genomics and Environment, Department of Occupational and Environmental Health Sciences, School of Public Health, University of Washington. Online: https://deohs.washington.edu/edge/ (accessed: 14 October 2019).
  Organized into Collaborative Research Teams (CRTs) around thematic, environmental disease-focused topics..

U.S. National Library of Medicine (accessed: 14 October 2019).

- **Toxicology and Environmental Health Information Portal**
  https://envirotoxinfo.nlm.nih.gov/
- **TOXMAP**— U.S. maps showing amounts and locations of toxic chemicals released into the environment
  https://toxmap.nlm.nih.gov/
- **TOXNET**— Network of databases on toxicology, hazardous chemicals and environmental health
  https://toxnet.nlm.nih.gov/

Toxicology Education Foundation (TEF). Online: http://www.toxedfoundation.org/ (accessed: 14 October 2019)..

TEF provides grants and resources for education in toxicology.

Society of Toxicology (SOT) – K-12 Resources. Online: https://www.toxicology.org/education/k12/k12.asp (accessed: 14 October 2019).

U.S. national toxicology organization site has a variety of useful information and links to educational resources on toxicology and related biological sciences.

European, Asian, and International Agencies

- Organization For Economic Co-Operation And Development (OECD) – **Chemical safety and biosafety**. Online: https://www.oecd.org/chemicalsafety/ (accessed: 14 October 2019).
  This OECD Site contains general information on environmental and chemical health and safety, along with a variety of tools.

- European Union - Public Health. Online: http://www.ec.europa.eu/health (accessed: 14 October 2019).
  European Union has extensive health related information in many languages.

- European Environment Agency. Online: https://www.eea.europa.euc (accessed: 14 October 2019).
  European Environment Agency has extensive environmental health related information in many languages.

- England – The National Institute for Health and Care Excellence (NICE). Online: http://www.nice.org.uk/ (accessed: 14 October 2019).
  NICE was set up as a Special Health Authority for England and Wales and its role is to improve health and social care through evidence-based guidance.

- England – Department of Health (DOH). Online: <http://www.doh.gov.uk/> (accessed: 14 October 2019).
  The aim of DOH is to improve the health and well-being of people in England.

- International Chemical Safety Cards. Online: https://www.cdc.gov/niosh/ipcs/ (accessed: 14 October 2019).
  "The International Chemical Safety Cards (ICSC) are data sheets that provide essential safety and health information in a clear and concise way."

- International Toxicity Estimates for Risk (ITER). Online: http://www.tera.org/iter/ (accessed: 14 October 2019).
  "ITER is a compilation of human health risk values from a number of international health organizations and independent groups."

- Chemical Safety Information from Intergovernmental Organizations. Online: <http://www.inchem.org/ (accessed: 14 October 2019).
  Rapid access to internationally peer reviewed information on chemicals published through the International Programme on Chemical Safety (IPCS).

- International Agency for Research on Cancer (IARC). Online: http://www.iarc.fr/ (accessed: 14 October 2019).

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.

- World Health Organization (WHO). Online: http://www.who.int/en/ (accessed: 14 October 2019).
  The World Health Organization, the United Nations specialized agency for health, was established on 7 April 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.

- International Programme on Chemical Safety (IPCS). Online: https://www.who.int/ipcs/en/ (accessed: 14 October 2019).
  "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."

- Encyclopaedia of Occupational Health and Safety. Online: http://www.ilocis.org/ (accessed: 14 October 2019).
  Published by the International Labour Organization's Constitution to promote "the protection of the worker from sickness, disease and injury arising out of employment".

- Human and Environmental Risk Assessment (HERA). Online: http://www.heraproject.com/ (accessed: 14 October 2019).
  HERA, on ingredients of household cleaning projects is a voluntary industry program to carry out Human and Environmental Risk Assessments on ingredients of household cleaning products. HERA 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.

- Japan - National Institute of Health Sciences (NIHS). Online: http://www.nihs.go.jp/index.html (accessed: 14 October 2019).
  Japan's NIHS regulates drugs and chemicals.

North American Agencies

- Health Canada. Online: http://www.hc-sc.gc.ca/index-eng.php (accessed: 14 October 2019).
  Health Canada provides extensive health related information in English or French.

- The Canadian Centre for Occupational Health and Safety (CCOHS). Online: http://www.ccohs.ca/ (accessed: 14 October 2019).

CCOHS promotes a safe and healthy working environment by providing information and advice about occupational health and safety.

- Canadian CHEMINDEX database. Online: <http://ccinfoweb.ccohs.ca/chemindex/search.html> (accessed: 14 October 2019).
  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.

- Canadian MSDS Database. Online: <http://ccinfoweb.ccohs.ca/msds/search.html> (accessed: 14 October 2019).
  Material Safety Data Sheets on over 120,000 compounds from 600 North American manufacturers and suppliers.

- U.S. National Library of Medicine. Online: http://www.nlm.nih.gov/nlmhome.html (accessed: 14 October 2019).
  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 other searchable databases.

- U.S. Environmental Protection Agency (EPA). Online: <http://www.epa.gov/> (accessed: 14 October 2019).
  Contains a wealth of information on many common environmental pollutants such as lead, mercury and pesticides as well as regulatory information. The site also has a great kids section.

- U.S. Environmental Protection Agency (EPA) – Integrated Risk Information System (IRIS). Online: http://www.epa.gov/iris/ (accessed: 14 October 2019).
  "IRIS is a database of human health effects that may result from exposure to various substances found in the environment." An excellent souse of information about many compounds – a great starting place.

- U.S. Environmental Protection Agency (EPA) - Toxics Release Inventory (TRI) Program. Online: <http://www.epa.gov/tri/> (accessed: 14 October 2019).
  "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."

- U.S. Food and Drug Administration (FDA). Online: <http://www.fda.gov/> (accessed: 14 October 2019).

All you would ever want to know about the drug approval process as well as basic information on diseases and current event topics.

- U.S. Food and Drug Administration (FDA) - Milestones in U.S. Food and Drug Law History. Online: <http://www.fda.gov/opacom/backgrounders/miles.html> (accessed: 14 October 2019).
  Site contains an interesting historical perspective and time line on the U.S. FDA.

- U.S. Occupational Safety and Health Administration (OSHA). Online: <http://www.osha.gov> (accessed: 14 October 2019).
  OSHA is responsible for regulating the work place environment. The site has information on current standards and business requirements.

- U.S. National Institute for Occupational Safety and Health (NIOSH). Online: <http://www.cdc.gov/niosh/> (accessed: 14 October 2019).
  NIOSH is responsible for conducting research and making recommendations for the prevention of work-related disease and injury.

- U.S. Centers for Disease Control and Prevention (CDC). Online: <http://www.cdc.gov/> (accessed: 14 October 2019).
  CDC is recognized as the lead federal agency for protecting the health and safety of people of the United States.

- U.S. Consumer Product Safety Commission (CPSC). Online: <http://www.cpsc.gov/> (accessed: 14 October 2019).
  CPSC works to save lives and keep families safe by reducing the risk of injuries and deaths associated with consumer products.

- U.S. National Toxicology Program (NTP). Online: https://ntp.niehs.nih.gov (accessed: 14 October 2019).
  NTP exists to develop the information and the tools that both agencies of government and industry need so that we can all live together safely in the same world. David P. Rall, M.D., Ph.D., Director, 1978–1990

- U.S. National Institute of Environmental Health Sciences (NIEHS). Online: <http://www.niehs.nih.gov/> (accessed: 14 October 2019).
  Wide range of information linking the environment, toxicology and health.

- California Environmental Protection Agency (CalEPA). Online: <http://www.calepa.ca.gov/> (accessed: 14 October 2019).
  "The CalEPA mission is to restore, protect and enhance the environment, to ensure public health, environmental quality and economic vitality."

- California Office of Environmental Health Hazard Assessment (OEHHA). Online: <http://www.oehha.ca.gov/> (accessed: 14 October 2019).
  "The OEHHA mission is to protect and enhance public health and the environment by objective scientific evaluation of risks posed by hazardous substances."

Non-government Organizations

- Environmental Defense. Online: <http://www.environmentaldefense.org/> (accessed: 14 October 2019).
  "Environmental Defense 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."

- Environmental Defense – Scorecard. Online: <http://www.scorecard.org/> (accessed: 14 October 2019).
  Site has information on health effects and state exposure issues.

- Toxicology Excellence For Risk Assessment. Online: <http://www.tera.org/> (accessed: 14 October 2019).
  "Our mission is to support the protection of public health by developing, reviewing and communicating risk assessment values and analyses; improving risk methods through research; and, educating risk assessors, managers, and the public on risk assessment issues."

- North American Association for Environmental Education (NAAEE). Online: <http://www.naaee.org/> (accessed: 14 October 2019).
  NAAEE mission is to bring the brightest minds together to accelerate environmental literacy and civic engagement through the power of education. Since 1971, the Association has promoted environmental education and supported the work of environmental educators.

- American Lung Association (ALA). Online: http://www.lungusa.org/ (accessed: 14 October 2019).
  ALA fights lung disease in all its forms, with special emphasis on asthma, tobacco control and environmental health.

- Society of Toxicology (SOT). Online: <www.toxicology.org> (accessed: 14 October 2019).
  U.S. based international professional organization for toxicologists.

- International Union of Toxicology (IUTOX). Online: <www.iutox.org> (accessed: 14 October 2019).

Mission is to improve human health through the science and practice of toxicology world-wide.

- Schaffer Library of Drug Policy. Online: <http://www.druglibrary.org> (accessed: 14 October 2019).
  Offers an incredible history and information on commonly used recreational drugs.

Library References

- TOXNET – National Library of Medicine. Online: <http://toxnet.nlm.nih.gov/> (accessed: 14 October 2019).
  TOXNET is a resource for searching databases on toxicology, hazardous chemicals, environmental health, and toxic releases.

- Toxicology and Environmental Health Information Portal- National Library of Medicine. Online: <https://envirotoxinfo.nlm.nih.gov/> (accessed: 14 October 2019).
  Site has links to many sites on a variety of toxicology information.

- TOXMAP— National Library of Medicine. Online: https://toxmap.nlm.nih.gov/ (accessed: 14 October 2019).
  U.S. maps showing amounts and locations of toxic chemicals released into the environment

- U.S. National Library of Medicine. Online: <http://www.nlm.nih.gov/> (accessed: 14 October 2019).
  Site provides easy access to medical and scientific literature and numerous databases.

- IUPAC Glossary of Terms Used in Toxicology — National Library of Medicine. Online: https://envirotoxinfo.nlm.nih.gov/toxicology-glossary.html (accessed: 14 October 2019).

Reference Books (lots of good information, but costly)

Principles and Methods of Toxicology, (6th Edition), ed by A. Wallace Hayes and Claire L. Kruger, 2014. Taylor & Francis, London, P. 2184. (An important book on the principles of toxicology with a emphasis on testing and safety assessment in toxicology.)

Casarett & Doull's Toxicology, The Basic Science of Poisons (9th Edition), ed Curtis D. Klaassen, 2018. McGraw-Hill, New York. P. 1648. (One of the classic toxicology textbooks that contains more than anyone wants to know about toxicology.)

Goodman and Gilman's The Pharmacological Basis of Therapeutics (13th Edition), ed. Laurence Brunton, Bjorn Knollmann, Randa Hilal-Dandan, 2017, McGraw-Hill Education, New York, p 1808. (A detailed book on the pharmacological (i.e. beneficial) and toxicological (i.e. adverse) effects of drugs. Also considerable basic physiological information.)

U.S. Congress, Office of Technology Assessment, Neurotoxicity: Identifying and Controlling Poisons of the Nervous System, OTA-BA-436 (Washington, DC: U.S. Government Printing Office, April 1990.) (An excellent overview of toxicology with an obvious emphasis on chemical agents that affect the nervous system.)

Principles of Toxicology
Or
A Small Dose of Toxicology

Chapter 2 of Third Edition of
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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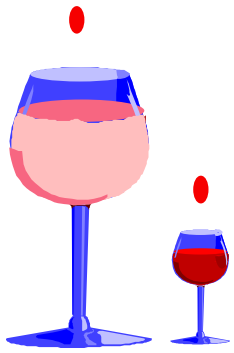


Introduction

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 while 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.

Basic Principles of Toxicology

Dose-Response

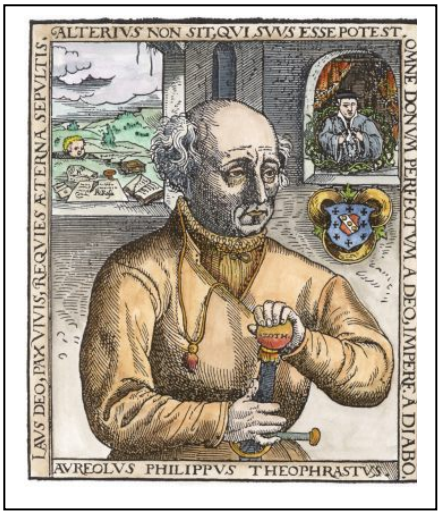
Risk = Hazard X Exposure

Individual Sensitivity

Our ancient ancestors worried about being poisoned ether 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 was born in Switzerland (Figure 2.1), a year after Columbus sailed 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 (cAD3-64), 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, such as water.)

What Paracelsus failed to emphasize is the variation in sensitivity of the individual. A bee sting or a peanut can be deadly for some individual while only annoying or even tasty for most people. There are now numerous examples demonstrating that the developing infant is very sensitive to the poisonous effects of a substance that does 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 only useful when linked to the sensitivity of the individual to a particular substance.

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 web site http://beckerexhibits.wustl.edu/rare/collections/schlueter.html

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. Age is important factor for the very young or the elderly for very different reasons. 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 that other people because of their genetics. All these factors are important as we judge our susceptibility to a particular hazard.

There are many familiar hazards in our lives, some easier to evaluate than others. 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 or 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 to the nervous system or of causing cancer 10 years after exposure is clearly not obvious. The formal process of determining the potential of agent to cause harm is called risk assessment. The risk assessment process is in itself complicated and often controversial because needed data may not be available or there is conflicting information. Risk assessment is the process of combining all the known information about the hazard of and exposure to an agent and making a determination of the potential for harm to people, animals or the environment. The next step is risk management.

Risk management combines the risk assessment with economic, political, public opinion and other consideration 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 that 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 of 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) consuming this one-cup of coffee would receive a dose of 100 mg divided by 70 kg, or about 1.4 mg/kg of caffeine. The importance of including body weight becomes clear if you consider a child that 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.

The difficult part of calculating the dose is often determining the exact amount of exposure to the agent. The amount of caffeine in a cup of coffee varies depending on the bean and brewing method, to say nothing of the size of the cup. Very sensitive instrumentation is now available to analytical chemists 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 easily calculated by weighing the material. Package labeling usually indicates how many milligrams of the drug each pill contains, so the dose can be calculated. An infant formulation contains much less drug per pill, but because of the difference in weight between the infant and the adult the dose may be 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. For example, to determine a dose of sunlight requires knowing the number of hours of exposure, the intensity of the light as well as the skin surface area.

Workplace and environmental exposures are often repeated and ongoing 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. A*cute 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. For many drugs, we are looking for the immediate or acute response following exposure. 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 and effect or 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 response that occurs will vary with the dose, the duration of exposure, and the individual. 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. An emergency response worker that 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. On the other hand, long-term exposure to coal dust can lead to black lung and severe disability. 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 is illustrated in Figure 1 and 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. It is important to know if a substance distributes into body water because we made up of approximately 75% water. 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 50/100 mg/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. Because caffeine distributes evenly throughout total body water you can almost imagine the change in shade depicted in Figure 2.2 as the concentration of the caffeine in the blood. 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 that weighs only 10 kg receives a dose of 5 mg/kg after one can of cola. An adult that weights 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.

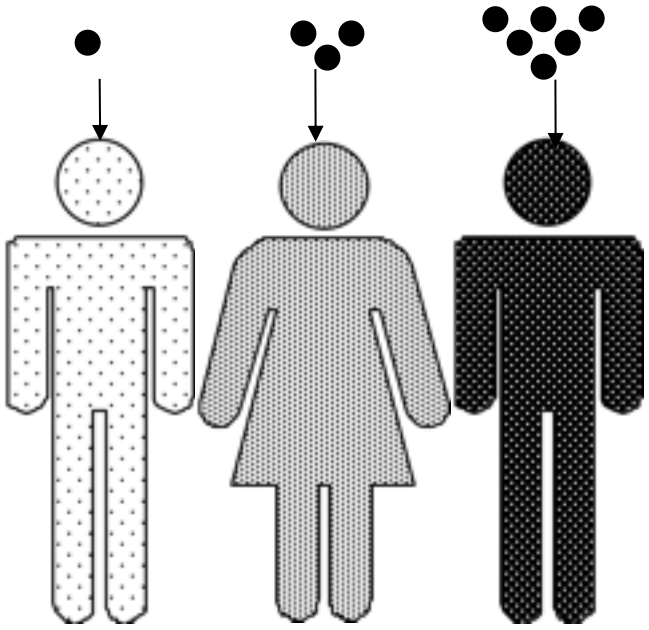
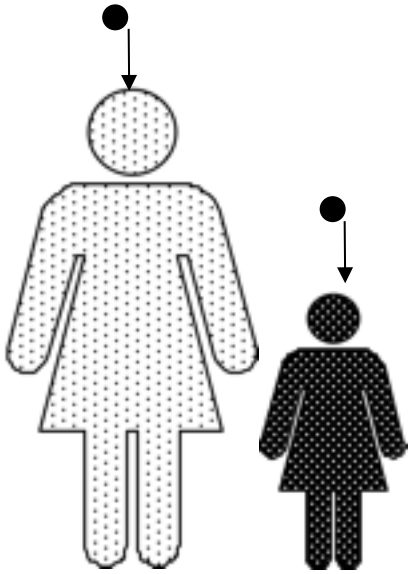
The importance of dose	**The Importance of size**
	
The larger the dose, the greater the effect	The smaller the size, the greater the effect

Figure 2.2 The Effect of Dose and Body Size on Response
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) graphically illustrates the critical relationship between dose and response. In this case, we define the response as difficulty in walking and the dose of

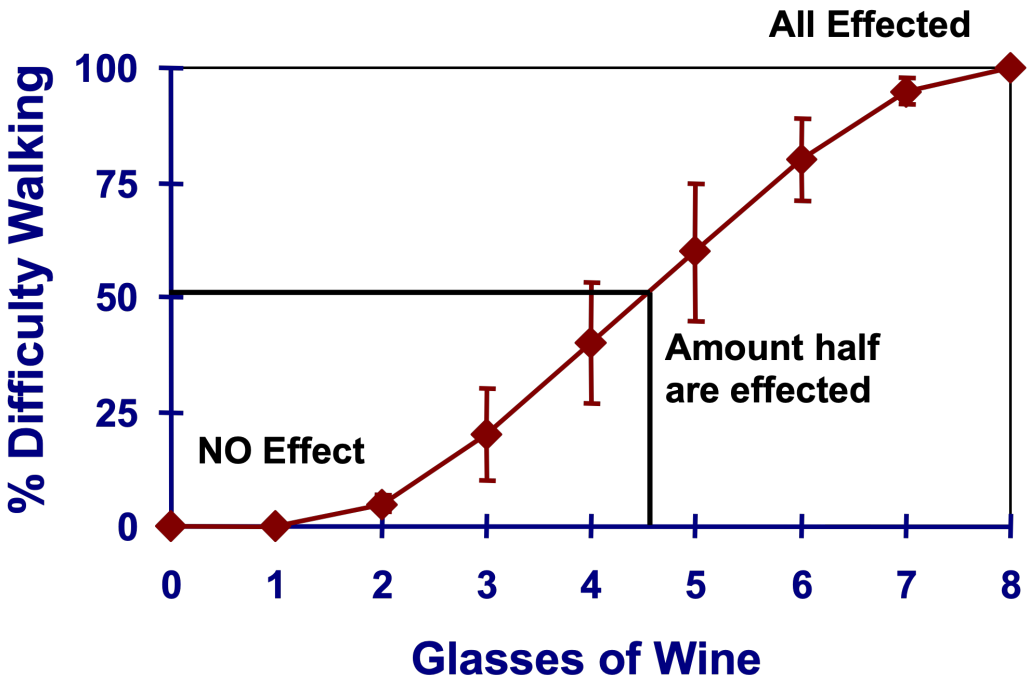


Figure 2.3: Dose Response Graph for Drinking Wine

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. 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).

or exposure to alcohol as a glass of wine. To change from exposure to dose we would need to know the body weight and amount of alcohol in the 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 difficulty walking until finally everyone was affected.

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, gender, as well as others. 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.

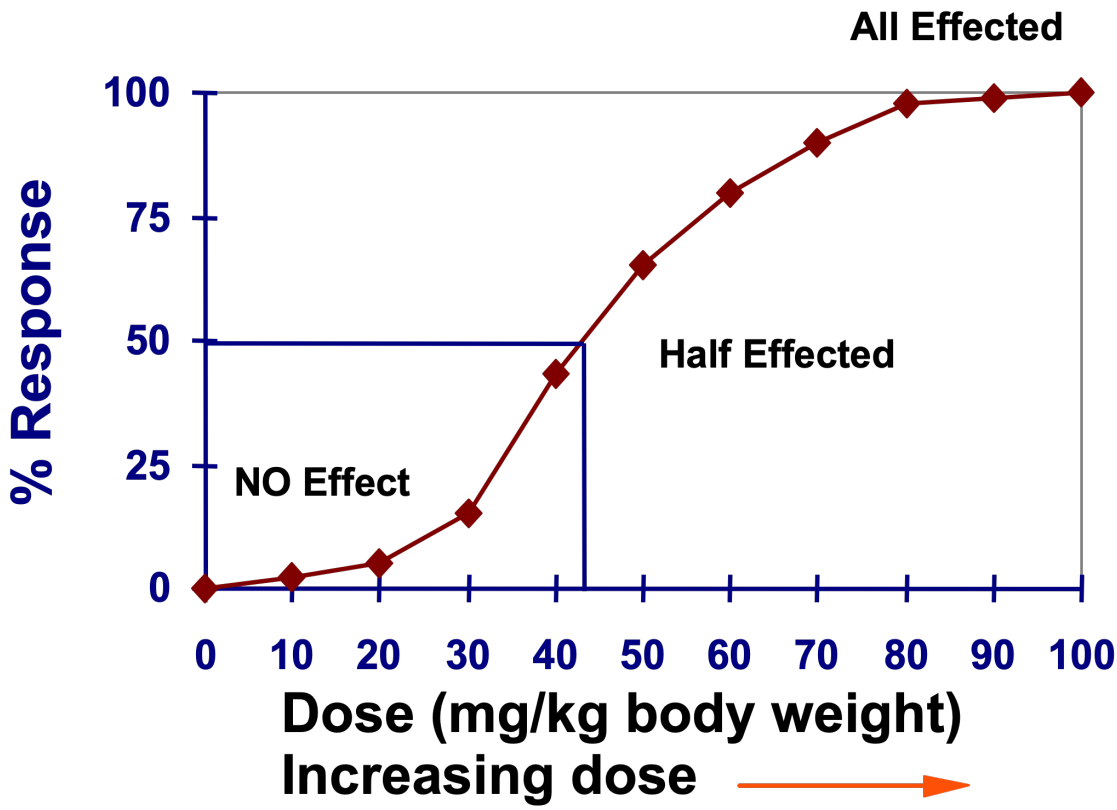


Figure 2.4: An Idealized Dose / Response Graph

The horizontal axis indicates the dose in mg/kg of body weight, while the vertical axis is the percent of maximum response. For 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 cure 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% responses 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 responded 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 between individuals. 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

The biological effects of an agent often span a broad range from beneficial to harmful, depending on the dose and individual sensitivity. The scientific discipline of toxicology developed in an effort to understand and characterize the potentially harmful or hazardous properties of an agent. *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 *Hazard*. 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 used for cleaning, the chemicals that run our cars, 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 for birds consuming animals. Still later we learned that DDT was a very persistent chemical and highly soluble in fat. DDT thus accumulated up the food chain and in this case birds at the top of the food chain were 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 breast-feeding, fat and DDT are mobilized and become the food of nursing

infants, which represents a large dose to a small infant. 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 lead 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 as well as 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 Products Safety Commission (CPSC) works to reduce injury from consumer products. The U.S. Environmental Protection Agency (EPA) governs the release of chemicals into the environment to protect the 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 and considerable cost to society. It was only recently that the government forced the tobacco industry into acknowledging the addictive properties of nicotine and began to recover health costs through litigation. While the adverse effects of excessive alcohol consumption have been recognized for a long time, it was only in the 1970's that birth defects related to alcohol consumption during pregnancy were recognized. In contrast, the U.S. 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 the 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 a subsequent chapter.

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 on populations of test animals such as rats and mice. Determination of an LD50 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 pass out at high blood alcohol levels and die not due directly to 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	LD-50 (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. A variety of tests are performed to evaluate the potential harmful effects 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. Moderate consumption of alcohol can present few hazards for an adult, but this same amount of alcohol can harm the developing fetus. Lead has many beneficial uses and has long been recognized as a hazard, but it is only relatively recently that harmful effects on the developing nervous system have been characterized. At what point does caffeine produce an undesirable effect and another cup of coffee become something to avoid? How much of a hazard is caffeine? To answer these questions, we need to know more about how the body metabolizes or breaks down chemical agents.

Routes of Exposure and Absorption

An agent exerts its effects when it enters or comes into contact with the body, 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 difference 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 the urine, feces, and sweat or through 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 reaction, 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 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. Carbon monoxide 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 the 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 pregnant women. 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. In this situation, the intestines are able to absorb increased amounts of calcium and iron but will take lead as a poor substitute (more on this in the lead chapter). 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. It is also a good idea to wash your hand before eating or touching food so that what may be on your skin does not ride along on the food you eat.

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 stimulator effect. It takes approximately 30 minutes to absorb the caffeine from a cup of coffee and reach your 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. 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 seen by an alcoholic, are very different: specifically, cirrhosis of the liver. The chronic effect of childhood lead exposure can be impaired learning that will be a 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 of 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. The fluid surrounding the infant (amniotic fluid) will have the same level of drug as the mother's blood for compounds that readily distribute throughout body water, such as caffeine. Thus, the infant is literally swimming in caffeine and its metabolites. Fetal methylmercury can actually be higher than that of the mother, because the developing infant acts as a storage site for maternal mercury. The brain, on the other hand, 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 and producing its stimulatory effect. While there are obviously many good aspects of 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, we primarily work with single exposures to chemicals 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 effect 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 against toxic agents. *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 my 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 quickly eliminated in the urine.

Chelators bind 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. 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 3 or 4 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 7 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 corresponding long half-live 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.

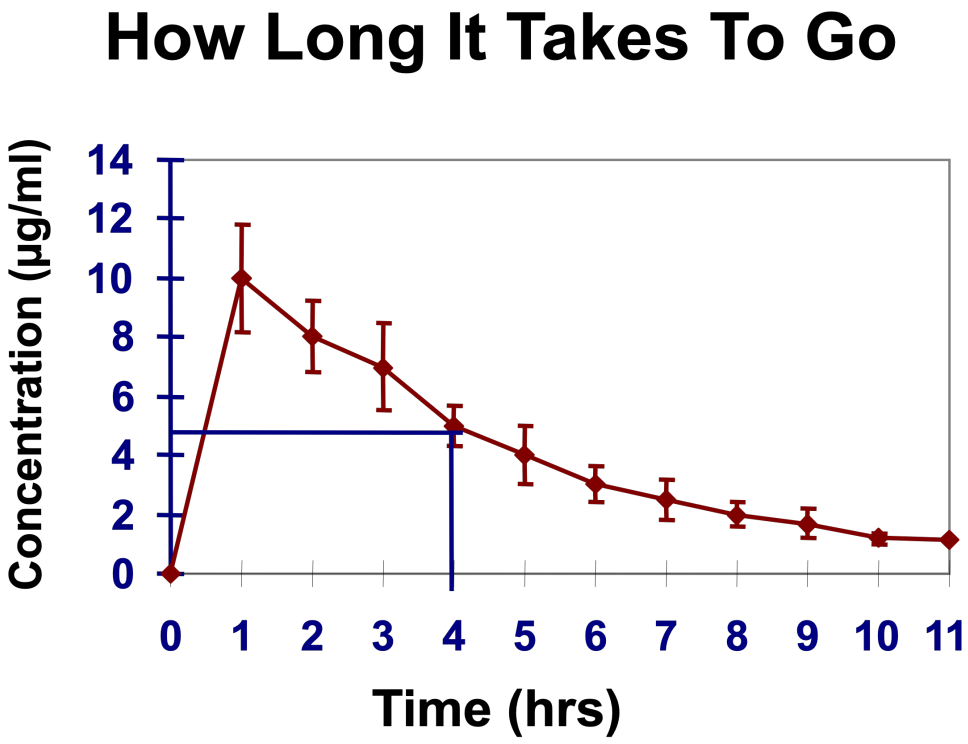


Figure 2.5. A characterization of Half-life
A substance is consumed at time zero (for example, drink a cup of coffee and we could measure blood caffeine concentrations) and blood samples are collected at every hour. Concentration of the agent is plotted against time. The black line represents the half-life when the blood concentration as dropped by one half its maximum. Thus, in this example, the half-life is 4 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 of 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 effects than others from the same exposure. 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 7 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 decreased ability to metabolize them and decreased ability 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. Pregnancy 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. This means that a pregnant woman will maintain higher blood caffeine levels for a longer period of time than when not pregnant, resulting in increased caffeine exposure to the developing infant. Agents stored in the fat, such as pesticides and PCBs can be mobilized during lactation and thus passed on to a nursing infant. 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 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 include headaches, fatigue, lack of concentration, memory loss, asthma and other often subjective responses following exposure. 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 the immune system responses and, more recently, on involvement of the nervous system. Others investigators, while respecting the symptomatology, postulate that the responses are due to some form of psychological illnesses. Whatever the mechanism of action, it is important to attempt to associate cause and effect relationships and apply the principles of toxicology. Identification of what agents 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 persons 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 the 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
Individual Control	Uncontrollable
Familiar	Unfamiliar
Low Dread	High Dread
Affects Everybody	Affects Children
Naturally Occurring	Human Origin (synthetic)
Little Media Attention	High Media Attention
Understood	Not Understood
High Trust	Low Trust

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

In the past, much of the 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 those 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 will 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 this benefits of removing lead from gasoline was greater than the costs. A program was then developed to gradually phase out lead from gasoline in line with the engines of new cars not requiring lead and the replacement of old cars.

Summary

The principles of toxicology are summarized in 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. Around our home, we must decide which cleaning products to use or whether to apply pesticides to our lawn or garden. 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? On what basis do we make this

decision? Advances in the toxicological sciences along with general advances in the biological sciences provide new knowledge and understanding upon which to make these and other decisions. And finally, I hope that beyond the principles of toxicology that you will find that toxicology is both fun and informative.

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A Small Dose of Risk Assessment
Or
An Introduction to Risk Assessment

Chapter 3 in Third Edition of
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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Introduction and History

Risk assessment is both old and new. Old in the sense that humans and animals survive by evaluating the risk of harm verses the benefits of action. For early humans, the hunt 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 now more directed 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.

> "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 of the Institute of Economic Affairs in London

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.

> “What is food to one man may be fierce poison to others.”
>
> Lucretius (c. 99 B.C.–c. 55 B.C.)

Percivall Pott made one of the first observations of a health risk related to occupational exposure. In 1775, he noted that chimney sweeps had 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.

> "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 -1st administrator of U.S. EPA 1984.)

The number of workers exposed to chemicals grew rapidly with onset of the industrial revolution and advances in chemical engineering. One the first efforts to systematically

evaluate the risk of exposure to chemicals began in 1938 when 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 U.S. 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 to detect a potentially harmful substance were very poor. As the analytical methods improved, it became apparent that the food supply had low levels of substances there 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 flourish 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 work place. 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 the resulting need to apply 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.

> " 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

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 a multi-step process to relate the association of exposure to a chemical or physical agent with 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 system or nervous system effects. Exposure depends on the route and duration. Individual sensitivity could be influenced by genetics, age (young or old), 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.

Risk assessment is the process of estimating association between an exposure to a chemical or physical agent and the incidence of some adverse outcome.

Steps in risk assessment

- Hazard Identification
- Exposure Assessment
- Dose-Response Assessment
- Risk Characterization

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. 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 done 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
- Neuro-behavioral toxicity
- Organ-specific effects
- Ecological effects (wildlife, environmental persistence)

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.

Exposure Assessment

- Route of exposure (skin, oral, inhalation)
- Amount of exposure (dose)
- Duration and frequency of exposure
- To whom (animals, humans, environment)

Next it is important 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 used to define 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.

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.

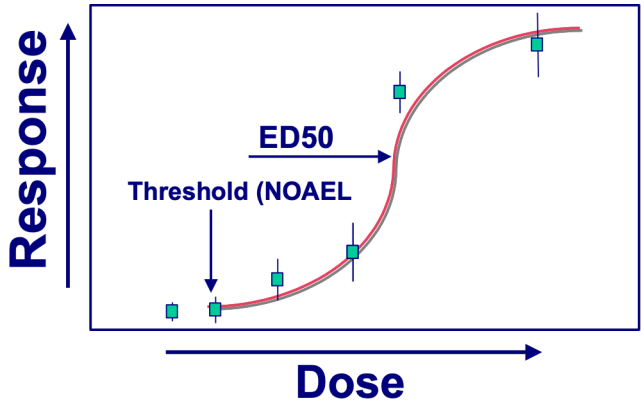

Figure 22.1 Dose Response

Acceptable Daily Intake (ADI)

"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."
WHO (1962)

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 insure the 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 animal 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, or there were adverse effects at the lowest dose, or there were only tests of

short-term exposure to the chemical. 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.

Safety factors are typically used in a risk assessment to define an acceptable dose for food additive and pesticides. It is obviously very important to ensure that an artificial sweetener such as aspartame, which is commonly used in artificially sweetened sodas, has a large margin of safety. All age groups as well as pregnant women consume artificial sweeteners so it must have a large margin of safety. On the other hand, 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 level of concern.

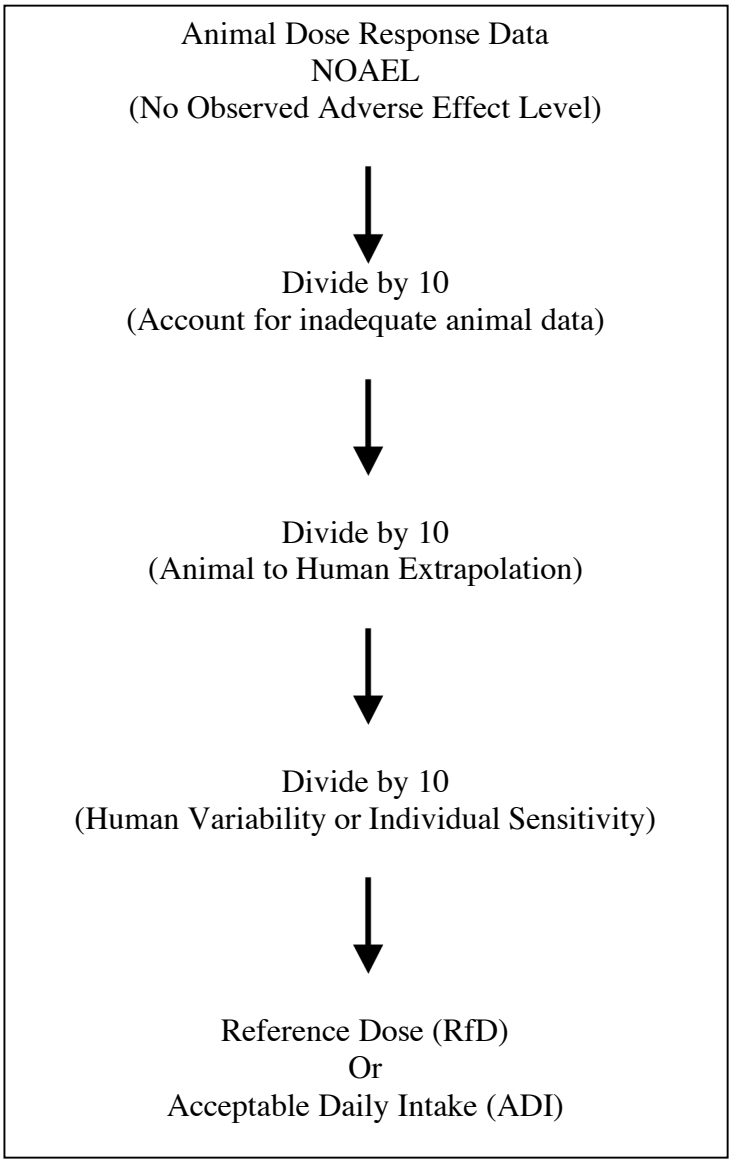

Table 22.1 Factors to consider

Route of exposure	
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 of deciding what to do to reduce a known or suspected risk. Risk management balances the various community demands with the 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 22.2 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	Not controllable	Natural disasters
	Controllable	Smoking
Dreadedness	Little dread	Vaccination
	Great dread	Nerve gas
Catastrophic potential	Not likely	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 just looked at death as the main endpoint, asking if a particular action or exposure lead to increases in death or reduced number of working years. Advances in the biological sciences have required that more complex risk analysis be undertaken to evaluate quality of life issues and not just death as an endpoint. The challenge for both risk assessment and risk management will be to take into consideration quality of life and individual values into the decision-making process.

Precautionary Principle

> "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

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, be cautious 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 on line (Gilbert, 2006). Other authors have also discussed alternative decision-making approaches to risk assessment, for example O'Brien (2000).

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A Small Dose of Ethics
Or
An Introduction to Ethical, Legal, and Social Issues in Toxicology

Chapter 4 in Third Edition of
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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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 professional, decision makers, and indeed everyone.

The fundamental principles that an ethical toxicologist should consider can be summarized as: 1) dignity, which includes the 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 distributions of the costs, hazards, and gains; 4) integrity, an honest and forthright approach; 5) responsibility, an acknowledgement 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 grounded in ethical considerations.

> One vision or ethical perspective is that we have "an environment in which all living things have the best opportunity to reach and maintain their full genetic potential"
>
> S.G. Gilbert (2005)

An Historical Perspective

An ethical and philosophical perspective on our work has a rich and evolving history. Looking back, it is easy to 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". Bernardino 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." (Leopold, 1949).

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* (Carson, 1994), 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.

> "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. "
>
> Rachel Carson

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 really 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 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 Wingspread Conference on the Precautionary Principle was held in Racine, Wisconsin to define the precautionary principle.

"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

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, U.S. Department of Agriculture, to recommend passage of a national food and drug law. The Federal Food, Drug, and Cosmetic Act was adopted in 1938, following an incident in which the Elixir Sulfanilamide, containing the poisonous solvent diethylene glycol, killed 107 persons, many of whom were children. The need to control chemical contamination was recognized in the 1976 when the U.S. 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. In 2016 Congress passed the Frank R. Lautenberg Chemical Safety for the 21st Century Act which was the first major overhaul in many years. In essence this bill did not go into affect because of changes in the administration and the EPA. Meanwhile, 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 U.S. 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 that for SOT are often based on the

following social responsibilities: 1) a responsibility to share and use knowledge, 2) a duty to promote the health and well-being of children, and 3) that all species have a right to reach and maintain their full potential.

Other 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 interests. Toxicology associations as well state, federal, nonprofit organizations, 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 purist 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 their 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 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 and decision making in modern societies.

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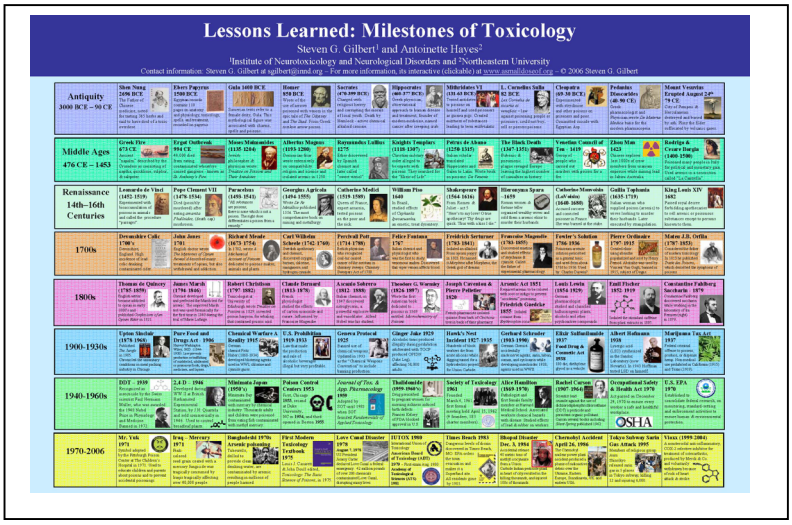
A Small Dose of Toxicology History
Or
An Introduction to the History of Toxicology and Lessons Learned



Chapter 5 in Third Edition of
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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History of Toxicology – Lessons Learned

Introduction - Antiquity

Milestones of Toxicology – interactive poster https://www.asmalldoseoftoxicology.org/milestones-posters

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 encountered. Early experimentation with plants was driven by an interest in food as well as 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 as it changed hands and was lost and found again since 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 were used for assassinations throughout history. Mithridates VI, who was the King of Pontus in Asia Minor 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, as well as making it illegal to buy, sell, or purchase poisons.

In the 1400s arsenic became a common poison, sometimes used by women to assassinate an inconvenient husband for his 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 exotic radioactive alpha-particle emitter polonium 210. There is also increasing concern for the potential use of bio-weapons to kill people or disrupt society. A strain of anthrax, the bacterium *Bacillus anthracis*, killed several people in the US in 1991. Anthrax has an interesting history and was well known as potentially fatal to farm animals and humans. Louis Pasteur developed a vaccine of 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 that “the dose makes the poison”. The first association of an occupational exposure to cancer was made in 1775 by Percival 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. This trend accelerated during the 1900s. The Germany military, supported by a robust chemical industry, were the first to use chemical weapons in World War I. On April 22, 1915, the German military released chlorine gas over the battlefield at Ypres Salient in Belgium, killing an estimated 5,000 French and Algerian troops. The start of the chemical revolution was stimulated by World War II, which included the development of very powerful nerve gases. Chemical weaponry stockpiling was an integral part of the

arms race throughout the Cold War, and their destruction has proved challenging, costly, and time consuming. The Chemical Weapons Convention of 1993 outlaws the production, stockpiling, and use of chemical weapons by all signatories. The aftermath of WWII stimulated the development of an array of pesticides and an enormous global chemical industry.

Recognizing Hazards

With the widespread use of chemicals and other agents such as metals, 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 lead 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, 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 resulted in tragic effects on the developing fetus and even some of the adults that lived in the area and depended on fish in their diet. The publication of Rachael Carson's *Silent Spring* in 1962 marked a turning point in the management of chemicals in the United States and ultimately lead to the banning of the pesticide DDT. In 1978, the contamination of Love Canal in upstate New York vividly demonstrated the consequences of not appropriately 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. All of these events produced obvious and disastrous to many people and the environment, effecting future generations. The challenge now is to recognize the subtler effects of chemical exposures that might cause cancer or affect the nervous system of children and 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 sometimes leading to polices 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, which contained diethylene glycol as a vehicle. Over 100 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 as the European Union embraced 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 were translated into regulatory standards to protect human health and the environment.

History of Toxicology Resources

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

Web-based References

- Milestones of Toxicology – Interactive Poster – PDF file available online at: < https://www.asmalldoseoftoxicology.org/milestones-posters> (accessed: 4 August 2008).
  The Milestones of Toxicology interactive poster is a clickable pdf file that presents a colorful review of toxicology that allows the user to click on a topic for

additional information. A high-resolution version suitable for printing is also available.

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Chapter 6 - Connecting the Dots:
Third Edition - New: 07/05/20

A Small Dose of Connecting the Dots
or
Connecting the Dots:
Toxicological Decision-Making and Communication in 21st century

Chapter 6 in Third Edition of
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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Abstract
This book, "A Small Dose of Toxicology", provides a science based introduction to the principals of toxicology and the health effects common chemicals. But there are other aspects that are important to consider such as history, ethics, and regulation. A subtext of this book is to turn knowledge into action. A new approach is needed for the process of problem solving and policy decision-making when protecting human and environmental health from hazardous chemicals. Often when communities or organizations are working to undertake chemical policy reform, they are hampered by challenges of communicating the problem(s) and desired actions to policy makers. On the other hand, policy makers may fall back on old formulaic approaches to addressing community concerns about chemical exposures, not taking into account the historic issues related to the use of a chemical or even ethical guidance with regard to protecting vulnerable populations. Communications are often at cross-purposes and confusing. We are proposing a new, standardized way to collect, collate, and communicate the background science, history, and ethical principles that address a chemical exposure problem and the desired action needed for chemical policy reform.

The hazard evaluations and risk assessment typically used for decision-making and regulations involves consideration of standard dose-response studies (mostly in animals) and assumptions about probabilities and safety factors. But risk assessment is only part of the answer. The challenge is not only to continue to generate more data to refine our understanding of dose-response, but also to use the knowledge we already have to make decisions to protect human and environmental health today. This new framework, called Connecting the Dots (CtD), broadens the decision-making framework to provide a more nuanced approach to policy making. CtD takes the concerns of the impacted individual, community, and environment into account and does not focus only on dose-response studies. The proposed alternative approach links existing science with ethical principles and a review of historical decisions and uses of the chemical(s) in question. The framework is designed to help all parties, those desiring action, and those tasked with policy development, to better communicate and make sensitive and equitable decisions about actions that need to be taken to address exposure problems.

Key Words
Communication
Risk assessment needs improvement
Transparency, veracity
Community-based ethics
Connecting the dots

Introduction

> **"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."**
> **Richard Lewontin** (New York Review of Books, Jan 7, 1997)

Scientists, public health professionals, and policy makers are in the business of exploring, developing, and communicating facts, and making decisions and even policies. But often the greatest challenge for those who use this information is not in identifying the scientific facts, but rather in effectively communicating and acting on those facts in a way that puts information in context with the past and within the expectations of a civil society. This chapter describes a new strategy: "Connecting the Dots" (CtD), which takes an identified problem, develops a framework of scientific facts, history, and ethics that supports and guides suggested action(s) to address the problem (Figure 1). Putting scientific facts within this framework provides concerned citizens, communities, organizations, scientists, and policy makers with the tools to understand and use information. The goal is to provide a tool to help organize information to address a problem and persuade policy makers or others to make changes and take action. Ultimately this can enhance everyone's ability to carefully explore an approach to a problem, concisely communicate that information, and ultimately direct and take action.

Problem Identification:

Figure 1 – Connecting the Dots (CtD)

Advances in science and technology have produced enormous benefits, but have also created undesirable hazardous effects that impact human and environmental health. Despite the increased scientific data and understanding, decision-making has become more difficult and complex. It is also important to consider the ethical, historical, legal, economic, and social issues that confront toxicologists, public health professional, and decision makers. It is with these considerations in mind that developing a method to connecting the facts of science, historical analysis, and ethics together to promote or discourage a specific action. Developing a CtD story is a multi-step effort starting with identifying the problem, doing research on the science, history, and related ethical principles, then developing an action designed to address the identified problem and finally crafting it all into a succinct story. The CtD is a tool to present fact-based information in transparent manner that is designed to support an action to address a specific problem.

The 'Connecting the Dots' tool consists of four primary "dots": science, ethics, and history that surround a desired action. The dots may be augmented, depending on the topic or need to delve deeper into a specific area. The four areas are discussed in more detail below. The three dots (science, ethics, and history) were chosen because they represent general areas of content that are helpful, if not necessary, to consider with developing an approach to a problem. Legal considerations were not included because laws and regulations are often captured in a review of history and may be further address and explored once an action is identified. Another topic, or dot, that might be considered, may be economics, which is often an important consideration in developing approaches to problems. While economics is not specifically included in the proposed CtD framework, the model is meant to be flexible and the inclusion of additional dots is encouraged while maintaining a concise presentation of the most relevant issues. The information collected should address the identified problem, be supportive of a suggested action, and should be parsimoniously presented in no more than four written pages (two pages back to back) in order to recognize the limited time policy makers, have to review information. If this compiled information is used in testimony in front of a government committee, it needs to brief but as complete as possible.

The Connecting the Dots (CtD) Process:

The Connecting the Dots (CtD) process is designed to apply a standardized approach to address an identified problem and support a specific action. The four pages of a CtD fact sheet include: a cover page with overview points followed by three pages that provide supporting details for action goal, including sections on the science, history (including relevant regulatory standards), and ethics. The CtD process really starts with acknowledge that there is a problem that need to addressed. Typically, this requires research into the scientific facts, history, and ethics. This generally leads to a first draft of action statement and the CtD fact sheets. The first page is meant to provide a very brief summary of the stated problem and an introduction to key points. In developing and using a CtD fact sheets, users can specifically educate decision-makers, policy-makers, and the public, which may help lead to a consensus for action to address an environmental of human health challenge. The front-page bullet points are meant to provide highlights of the issue, identifies a specific action goal, and a brief justification for the

specified action. The remaining three pages provide information on the science, ethics, and history, including current regulatory standards if applicable, and references. It may be further tailored to meet the needs of particular audiences, such as regulators, public interest groups, members of the public, academics, legislators, or legislative staff (Legislature, 2019).

The process of developing and using the CtD process is also meant to stimulate critical thinking about a problem and proposed approach to addressing the issue. The process starts with clearly articulating the problem, doing research on the science, history, and ethics, which leads to formulation of the action. Developing an action is really an evolving and iterative process. Some of the questions that might arise by undertaking this process might include: what are the underling scientific findings? what were some of the precipitating events that lead to the problem? who are the vulnerable populations? who is or has benefited from the current status? and why should that be changed? How the information, past positions, values of stakeholders, vested interests interact and connect is integral to decision making.

It is also important to consider that audience of the CtD fact sheet. Once the general structure of science, history, and ethics are addressed the CtD fact sheet can be modified to suite a specific audience or presentation. For example, a CtD fact sheet directed toward the general public may have slightly different language than a CtD fact sheet directed toward legislative policy makers. For example, the ethics or history dot may be expanded to include more information on policy approaches over the last few decades. The CtD process is meant to be flexible and easily adaptable to different situations or audiences.

The author of a CtD fact sheet has several important responsibilities. One of the most important considerations is to know the audience. For example, the knowledge base of students is very different from a group of scientists. One should also consider and acknowledge the personal biases and conflicts of interest or relevant financial relationships of the authors (Maurissen et al., 2005).

Three example CtD fact sheets are included in the appendix (childhood lead exposure, lead shooting ranges, and fluoride). CtD fact sheets also are being developed for many of the chapters of the book “A Small Dose of Toxicology” and will be available on the web site www.asmalldoseoftoxicology.org.

First a word about Risk Assessment and Risk Communication

Risk assessment and risk management has been around for 1000’s of years, after all it was important to judge the probability of becoming a meal of the resident saber tooth tiger (Aven, 2016). The last 100 years has seen risk assessment and risk management become a recognized science (Hansson & Aven, 2014) (Hansson & Aven, 2014). The US Environmental Protection Agency (EPA) has been using risk assessment modeling since the mid 1970s as a process to estimate the human health risk of cancer from exposure to pesticides and other chemicals (Embry et al., 2014; Faustman & Omenn, 2013). Risk assessment methods and related risk communication strategies are increasingly being pushed to evaluate and discuss very low level

effects (Gwinn et al., 2017). Risk assessment has been touted as the gold standard for setting regulatory limits to protect human health and is widely used in the US and elsewhere. The process involves four basic steps: 1. Hazard Identification, 2. Dose-Response Assessment, 3. Exposure Assessment, and 4. Risk Characterization (Faustman & Omenn, 2013).

> **Hazard Identification** Examines whether a stressor has the potential to cause harm to humans and/or ecological systems, and if so, under what circumstances. **Dose-Response Assessment** considers the numerical relationship between exposure and effects. **Exposure Assessment** looks at data related to frequency, duration, and concentration of exposure. And, **Risk Characterization** examines how well data support conclusions about the nature of the health risk from exposure. This process involves making assumptions about the probability of various conditions or characteristics being present with little or no relationship to the actual people or communities who are trying to use the guidance. (NRC, 1983).

While this approach is laudable and better than not considering these basic conditions at all, it is incomplete and outdated. What are not considered in this process are health outcomes other than cancer, such as reproductive, neurotoxic, developmental, and immunologic. Nor are individual susceptibilities, pre-existing conditions, gender, or genetic predisposition considered in this process. The unique susceptibilities of the very young or fragile elderly are not considered. The interactive effects of exposure to several compounds or environmental stressors are not considered. Nor are the health effects of chemical mixtures considered. Unfortunately, the US EPA risk assessment process often is a permission to pollute with the implication that exposures at the level assigned by risk assessment are 'safe' regardless of the unique exposures or underlying health issues of the individual or communities exposed. And equally important is the fact that the assumptions and incomplete data upon which a risk assessment is based are poorly or not communicated at all to the public. As William Ruckelshaus (the first administrator of the EAP) once said, "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". A new approach is needed. Risk assessment asks "How much harm can we tolerate." Instead of focusing on the actions should we take to reduce human and ecological harm (Gilbert, 2005).

Beyond Risk Assessment

Current biological and toxicological knowledge now allows us to look beyond basic risk assessment in our effort to protect human and environmental health. It is time to consider whether or not risk assessment, as it is currently applied, meets the needs of the community and the new demands of chemical regulation. One demand that must be met concerns Environmental Justice (EJ) define by the EPA as the "fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation and enforcement of environmental laws, regulations and policies" (Eaton & Gilbert, 2013). Given the uncertainties surrounding the EPA risk assessment models and the possible adverse, non-cancerous, consequences of exposures to harmful

compounds, a more precautionary approach is needed. The foundation of Connecting the Dots was built with a desire to strengthen the fundamental of the toxicological sciences, risk assessment, ethics, and other essential elements of how we define harm. (Eaton & Gilbert, 2013).

When chemical exposures yield non-cancerous outcomes that are sometime subtle or differentially affect vulnerable populations, the precautionary principle should be incorporated in the review of the science. The most widely accepted definition of the precautionary principle is from the Wingspread Conference of 1998: "When an activity raises threats of harm to human health or the environment, precautionary measures should be take even if some cause and effect relationships are not fully established scientifically" (Raffensperger & Tickner, 1999). Central components of the precautionary principle can by stated as: establish public health goals; taking preventive action in the face of uncertainty; shifting the burden of responsibility (proof) to the; proponents of an activity; exploring a wide range of alternatives to possibly harmful actions; increasing public participation in decision making (Gilbert, 2005).

Broadly defined, the goal of a precautionary assessment is to allow communities and individuals to incorporate the unique needs and challenges of specific communities, and to include their values into a more comprehensive evaluation of a hazardous condition. It combines the philosophy and ethics of the precautionary principle with a standard scientific evaluation of the hazards. A 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. In contrast to the traditional risk assessment, a precautionary approach is a more comprehensive and contextual way to evaluate the human and environmental health risks

Recent scientific advances in our understanding of how DNA expression can be modified by environmental conditions, such as diet or stress, indicates that subtle changes in health outcomes. This is known as "epigenetics". In keeping with the acknowledgement of the interactive and combined effect of genetics and environment, we suggest that a precautionary approach to risk assessment is a tool to implement the ethics of "epiprecaution". A precautionary assessment moves beyond the usual risk assessment approach to include the ethical construct to not only reduce risk by "doing no harm" or "minimize harm", but to move to "doing good". We have an ethical responsibility to our children to have an environment that is supportive and nurturing and one in which they can reach and maintain their full potential, not just one that is free from exposure to chemicals (Gilbert, 2015).

Developing a 'Connecting the Dots' Fact Sheet

Science – the bedrock of knowledge

Science is an ongoing and continual process that builds knowledge and facts following a systematic study of testable predictions. The scientific method is well described and agreed upon by the scientific community; it is the systematic observation and experimentation to test a prediction of hypothesis. The Oxford Dictionaries Online define the scientific method as "a method or procedure that has characterized natural science since the 17th century, consisting in systematic observation, measurement, and experiment, and the formulation, testing, and modification of hypotheses". Scientific findings are divided into many categories and subcategories as knowledge has expanded and continues to evolve. To this list can be added the life sciences such as biology and then toxicology. Disciplines such as medicine and toxicology are often considered to be applied sciences that use the scientific method. When there is controversy, regarding the interpretation of scientific findings, it is important to develop an agreed upon process for examining the scientific information or at the very least understand why there is disagreement.

Over the past few years the “sciences” have been used to justify a variety of personal opinions. Some have focused on the uncertainty inherent in science as a strategy to discount science or deflect the use of science in policy decisions. While it is true that the very nature of the scientific method includes the recognition of uncertainty, in fact, one of the beauties of science is that quest for knowledge is always evolving. Scientific findings, like most human endeavors, are influenced to some degree by the biases of the scientists conducting the research and the individuals interpreting published findings. More effort is needed to transparently acknowledge individual biases, conflicts of interest, and research funding sources. The toxicological science were not immune from labeling and there developed a branch called evidence-based toxicology (Stephens et al., 2013) (Silbergeld & Scherer, 2013) (Faustman & Omenn, 2013) (Eaton & Gilbert, 2013). The toxicological sciences are particular susceptible to controversy about particular findings because of the money that can be made, or lost, from the way scientific findings are interpreted and used by profitmaking companies (Maurissen et al., 2005).

Typically, any scientific discipline can be broken down to a common set of studies with defined methodology. It should be noted that toxicology is one of the few scientific disciplines that have developed a large and vibrant for profit business that supports data development and report generation. Toxicology has both studies with defined methodology and studies with far more flexible methods that allow the exploration of mechanism of action and effective dose. These laboratories conduct contract a prescribed set of studies with primary variable being the dose of the test compound. The studies are done to determine at what dose an adverse effect is apparent. As a general rule the greater the exposure to humans or distribution of a compound the more well studied the compound and the larger number of ecological reports produced. The focus of the scientific dot is to summarize the scientific information that is accessible. Data or certain reports may not be accessible because they are not publically available and considered to be confidential information. There are a number of examples were scientific information has been hidden or distorted to facilitate advantage conclusions about a product’s safety (EEA, 2002, 2013). It may also be a situation were on side of dispute focuses on uncertainty in the scientific process instead of taking a more precautionary approach as

documented in Late lessons from early warnings (EEA, 2002, 2013). These two EEA reports examine in detail the human life consequences of failing to take a precautionary approach in chemical management.

The last 10 to 15 years have seen many scientist working to summarize the scientific literature related to childhood exposure to an array of chemical compounds. These review papers can serve as examples of supporting literature for a CtD process. A particularly good example is the consensus statement on the neurotoxic effects of chemical exposure in childhood (Bennett et al., 2016). In addition, there are several authors who have a long track record of publications on the health effects of chemicals (Lanphear, 2015) and (Axelrad, Bellinger, Ryan, & Woodruff, 2007).

Using the Science Dot

The Science Dot focuses on scientific data and reported findings of research related to the identified problem and possible policy or action efforts. For example, one scientific fact around childhood lead exposure is that children absorb more lead than adults and because they are smaller than adults, they receive a bigger dose for the same exposure (Gilbert & Weiss, 2006). This information can be used as part of the Science Dot and leads to an Action to establish policy to reduce childhood lead exposures. Ironically the Science Dot can be the most difficult and complex to write because of the range of scientific research findings and the ongoing evolution of the science. It will typically take the most room and require the most referenced information. It is important to remember that you are building a story so that people can understand the scientific facts within the context of ethics and history and understand how this information addresses the stated problem and leads to possible action alternatives.

History – Looking back to go forward

Understanding the historical perspective on an issue is a critical part of making good decisions. History helps us to understand how humans have shaped the environment and how the environment has shaped humans. But is also gives us a chance to learn from our mistakes and apply the knowledge and experiences that can inform current circumstances. The thoughts and arguments that went into current regulatory approaches to protecting human health and the environment are by nature historical and as time, culture, expectations, and science evolve we can use these historical records to help make better decisions and take better actions.

Why study history?

History provides a framework upon which we can better understand current issues, rules, regulations, and behaviors (Stearns, 1998). Understanding and using historical discoveries, reports, and experiences is an important, even necessary, element of implementing toxicological information in the present day. Historical references can help provide a foundation for current practices and policies, help predict future experiences, explain the evolution of scientific thought, and help us learn from mistakes of the past. Toxicological history

goes back hundreds of years (Gilbert, 2011), (Gilbert & Hayes, 2006), (Hayes & Gilbert, 2009) (Gallo, 2013). It helps us predict and even anticipate the future by reflecting on and learning from the ideas, and mistakes, of researchers, teachers, and advocates who have gone before. Understanding how things have changed, why they changed, and what stayed the same despite the efforts at change helps anticipate and even predict how future actions and activities will play out.

Often people from the past inspire us with their ideas, their work, and their thoughts about how they addressed challenges similar to our own. Reviewing historical activities for lessons learned, or for ways humans have faced difficulty situations, or for examples of things that worked well can inspire us to continue along similar paths and may even provide guidance in an increasingly complex world (EEA, 2002, 2013).

History is a study in trial and error and a view on what worked, and what did not. Science too is a process of continual exploration and evolution of information and observations. Science and history both build on the work of the past to help understand the present day and even the future. Even research conducted 50 years ago can make important contributions to addressing current problems. Science incrementally approaches a better understanding of why things are the way they are and how things work. From this standpoint history and science go hand-in-hand to help decision-makers continually progress towards better solutions to problems we face (Shaffer & Gilbert, 2017).

Relevance of historical toxicology

Humans have long been interested in how plants and minerals affected the human body, long before there was an actual scientific discipline called 'toxicology'. Human reactions to ingesting herbs, spices, fermented liquids, and various concoctions were often closely observed and reactions, positive and negative, were noted and passed on to ensuing generations. Experimentation and trial and error became the foundation for future advances as those historical experiences were passed on by oral tradition or eventually in writing. Even fatal effects informed future users; the father of Chinese medicine and pharmacology Shen Nung (2696 BCE) (Gilbert & Hayes, 2006) (Hayes & Gilbert, 2009) died sampling an herbal remedy – a great lesson for his followers.

One example of how history informs and impacts the present day is the use of the metal lead. The human health consequences of exposure to lead dust and fume were recognized more than 2000 years ago with observers noting that ''lead makes the mind give way'' (Gilbert & Weiss, 2006). Despite this 'scientific' observation, future users of lead in metal-working, roofing, cooking, paint, gasoline, and ammunition often ignored this historical knowledge regarding the adverse health effects of exposure to lead, to the detriment of the lives of many. However, this evolution of scientific knowledge eventually influenced the regulation of the use of lead in a variety of products, though regulatory and policy decisions were often based more on economics and practicalities than health effects. It wasn't until the 1920s that lead-based paint was banned in Europe and not until 1978 in the United States. Lead exposure was found

to be particularly worrisome for children as research increasingly demonstrated that lead exposure had a highly negative impact on early childhood intellectual development (Gilbert & Weiss, 2006). Unfortunately, leaded gasoline is still used in most parts of the world, as are many other lead-based products. Even historic uses of lead that are seemly in a 'safe' form can have health impacts in present day. The recent fire at the ancient Notre Dame cathedral in Paris vaporized the lead-based roof of the structure, resulting in deposits of exceedingly high levels of lead fume and dust across the city and beyond.

One of the early practitioners of what is now called 'toxicology' is Paracelsus (1493-1541), a physician, alchemist, and astrologer. The classic (and historic) principle of toxicology, 'the dose makes the poison', has been attributed to Paracelsus. This quote reflects the historic evolution of scientific observations that all substances have the potential to be poisonous, depending on the amount of exposure. In the 1700's the understanding of the link between exposure and effect was advanced by Percivall Pott (1714-1788) who documented and reported that chimney sweeps, who were regularly and frequently cleaning the inside of Victorian England chimneys full of coal dust and soot, were susceptible to scrotal cancer due to their regular and cumulative exposure to the fireplace soot, or as the causative agent was later identified, polycyclic aromatic hydrocarbons (Hayes & Gilbert, 2009).

The scientific process and scientific understanding is one of building on a history of observations, discoveries, successes, and failures, it also puts current problems within a context of years of evolution of scientific of thought.

Using the History Dot

Reading and understanding history gives us a chance to learn from past mistakes and apply the knowledge and experiences that can inform current circumstances (EEA, 2002, 2013). The thoughts and arguments that went into current regulatory approaches to protecting human health and the environment are by nature historical and as time, culture, expectations, and science evolves, we can use these historical records to help make better decisions and take better actions (Gross & Birnbaum, 2017) .

History is an important part of making ethical decisions. History provides an opportunity to see how past decisions may have unfairly or disproportionately affected certain groups of people. The perspective of history provides a clearer view of who benefited and who was harmed and what information were people given when it came to making decisions. If people did not obtain sufficient, or correct, information or if information was withheld, then decisions may have been poorly made and harm was done needs to be addressed and changed with present day decisions and actions. Without the perspective of history, many of these injustices cannot be recognized or modified (Lane et al., 2008).

It is important that we look back to go forward and consolidate our experiences into useful practices that allows use to learn from our mistakes. Using the opportunity to review the

history of past actions, research, successes, and failures and incorporate those things into present day thinking is a critical part of educating decision-makers and moving towards better practices and actions for everyone.

Ethics – A framework for Decision Making

Ethics is a philosophical approach to considering concepts of right and wrong. As such ethics can provide a framework or guide to decision-making so that actions or policy approaches incorporate the values of the recipients, the proponents, and other concerned parties to an action. The Ethics Dot section provides an opportunity to explicitly explore the perspective, values, interests, environmental justice, and concerns (Gilbert, 2015) of impacted populations and individuals, identify who is at greatest risk, who benefits from the action, and at what costs.

<Photograph about here>

Why include ethics?

Consideration of ethics includes principles of conduct and how we choose to live. It identifies ideal activities or behaviors and includes discussions and consideration of justice and fairness. There are several approaches to ethics such as utilitarianism (a proper course of action is one that maximizes a positive effect), deontology (goodness determined by examining actions), consequentialism (rightness based on consequences), or pragmatism (moral correctness evolves) for the purposes of this chapter ethics is considered to be a thought process that includes identification of values and how they related to the action goal. Governments use laws and regulations to motivate 'good' behavior; ethics implicitly addresses behavior that lies beyond governmental control. Some have refined the ethical approach to addressing environmental issues (Environmental Ethics; Brennan & Lo, 2016) or through combining ethics with legal and social issues into ELSI – Ethical, Legal, and Social Implications (Figure 2).

Figure 2. Dots around ethics.

The fundamental ethical principles with regard to toxicology may be summarized as: 1) dignity and respect for the autonomy of human and animal subjects; 2) veracity, an adherence to transparency and presentation of all the facts; 3) justice, an equitable distributions of the costs, hazards, and gains; 4) integrity, an honesty and forthrightness; 5) responsibility, an acknowledgement of the accountability of all parties involved; and 6) sustainability, consideration that actions should be maintained over a long period of time (Gilbert & Eaton, 2009).

The more explicit use of ethical principles increasingly entered into policy discussions. 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." (Leopold, 1949).

Some believe that this ethical statement suggests 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 (Carson, 1994)*, first published in 1962. Carson sounded one of the first alarm about the effects of environmental contaminants and catalyzed numerous regulatory changes related to chemical use.

> "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. “
>
> Rachel Carson (Carson, 1994)

The idea for an Earth Charter (*Earth Charter*, 1997) 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, which produced the 27 Principles of the Rio Declaration. Principle 15 defined the Precautionary Principle as an approach, some would say an approach based in the ethical principle of ‘do no harm’ to protect human health and the environment. In January 1998 Wingspread Conference on the Precautionary Principle was held in Racine, Wisconsin to further define the Precautionary Principle (Gilbert, 2005; Kriebel et al., 2001). Many countries, states, and organization have since adopted the Earth Charter. Lessons can be learned from this approach when it comes to addressing problems and identifying actions related to human health.

> "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

The concept of epigenetics also provides the scientific and biological foundation for the importance of “doing good”. This concept could be called “epiprotection” or “epiprevention” to signify the need to move above and beyond preventing exposures to harmful material to one that is nurturing and supportive (Gilbert, 2015). We have an ethical responsibility to ensure that our children have an environment in which they can reach and maintain their full potential, not just free of exposure to chemicals but an environment that is supportive and nurturing.

Using the Ethics Dot

A consideration of ethics and ethical principles when constructing the Ethics section of a CtD document encourages an evaluation of available information from the framework of values, identifying possible harms or costs, and obtaining input from all concerned parties with a goal of doing no harm to achieve the best possible outcome.

Incorporating an ethical component into the CtD document will require thoughtful development and articulation of fundamental ethical principles upon which the suggested action should be based. This approach may be time consuming when working with stakeholders to articulate their values and goals, some of which may not be transparent even to them. It requires a move beyond what is legally required toward an exploration, discussion, and incorporation of the values of all parties.

Action – Addressing the Problem

A desired action is at the center around which to rotate the supporting information of science, history, and ethics, and other 'dots' such as economics. The Action dot works to address the stated problems and is the conclusion of the research and effort that went into understanding and linking the relevant science, history, and ethics. The Action is a desired effort to address or resolve the problem. A good example of this is the Action of crafting a bill to be considered through the legislative process and hopefully will ultimately lead to a vote of approval. In this situation, the goal and audience are well defined. Another approach, perhaps a little more forthright, would to conduct organized and structured research on the content of the three dots, science, history and ethics, to explore what might be possible actions to take to meet a specific goal or to determine whether a goal needs to be narrowed. The CtD approach is a tool for linking, organizing, evaluating, and communicating existing knowledge. The CtD can be used as a tool support advocacy for the action.

The desired Action can be big or small, but should be stated as simply and specific as possible. For example, according to the Occupational Safety and Health Administration (OSHA) a worker's occupational lead exposure can reach 60 ug/dL before the worker is removed from the work place (Shaffer & Gilbert, 2017). A CtD Action may be "Reduce worker lead exposure so that blood lead levels are less than 5 µg/dL". Other CtD Actions may be stated in the form of protecting children from lead-based paint or passing a bill to reduce the use a pesticide. See the action dot in the three examples in the appendix.

Conclusion

The Connecting the Dots (CtD) paradigm is designed to facilitate systematic exploration of an identified problem and to communicate with and between the public and decision makers. The CtD approach encourages people to think more deeply abut the relationship between science, history, and ethics while supporting an Action to address a specific problem. The CtD approach was developed with the understanding that there is tremendous amount of information available on a given topic, but it is not often presented in a concise format neither does it regularly capture the values of parties involved nor does it provide clear rationale for a suggested Action. By selecting highly specific examples from science, history, and ethics relevant to support the desired action, the author can keep the CtD document to four pages

(two pages front to back), which increase the likelihood that the information will be read and used by target audience. We need more time and effort placed in realm of scientific communication and education.

The CtD approach was developed with the acknowledgement that despite the complexity of the many issues, there is a real need to give people at all levels concise, methodical, and well supported information to help them make effective policy decisions and take action to ensure a safe and healthy environment. The CtD approach puts scientific information in the context of history, society, culture, and values to help people connect the dots to collectively make better decisions.

Garrett Hardin in his paper "The Tragedy of the Commons" (Hardin, 1968) concluded that "It is our considered professional judgment that this dilemma has no technical solution." The vast majority of our problems in the complex world we have created must be managed or prevented. The Connecting the Dots (CtDs) is meant to help us move forward to create a healthier world for all of our children.

Appendix – Three Examples of Connecting the Dots (CtD) in Separate Document

Childhood Lead

Shooting Ranges
ß
Fluoride

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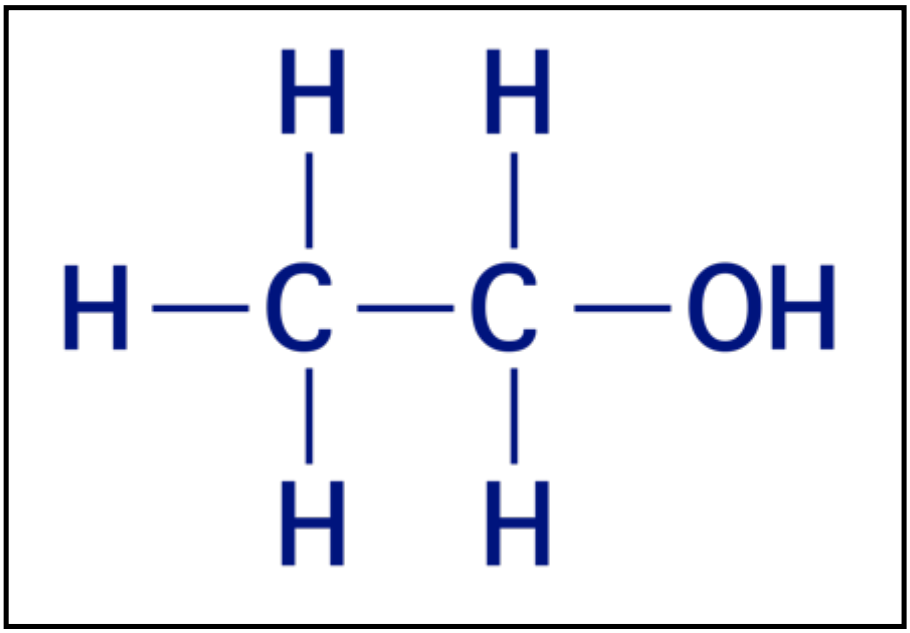
A Small Dose of Alcohol

Or

An Introduction to the Health Effects of Alcohol

By Steven G. Gilbert, PhD, DABT



Ethanol - C_2H_5OH

Dossier

Name: Ethyl Alcohol (CH_3-CH_2-OH)
Use: 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; kids – lowered IQ, learning and behavioral problems; adults – memory loss, inebriation, liver disease, cancer
Regulatory facts: government agencies recommend women not consume alcohol during pregnancy; blood alcohol regulated by local governments when operating a motor vehicle
General facts: long history of use, consumed world wide, 9.1 infants per 1000 affected by FASD worldwide
Environmental: voluntarily consumed
Recommendations: do not consume alcohol during pregnancy, otherwise limit consumption and do not drive a motor vehicle after drinking

Case Studies

> "Alcohol is the number one drug of choice among our Nation's youth. Yet the seriousness of this issue does not register with the general public or policymakers."
>
> Enoch Gordis, M.D. Past Director, National Institute on Alcohol Abuse and Alcoholism.

> "You will conceive and bear a son…now then be careful to take no wine or strong drink and to eat nothing unclean".
>
> –13 Judges 3-4

Fetal alcohol syndrome disorder

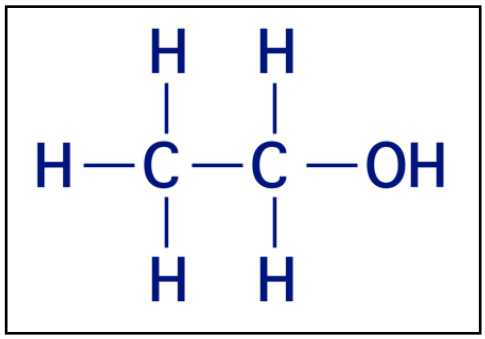
Despite its long history of use, the effects of alcohol on the developing fetus were not recognized until the early 1970s. Fetal Alcohol Syndrome Disorder (FASD) is the result of maternal consumption of alcohol during pregnancy and is one of the leading causes of permanent learning disabilities and physical growth deficiency. Some believe that 1% of the U.S. population may be affected and more worldwide (see below CDC website Fetal Alcohol Spectrum Disorders (FASDs) Prevalence of FASDs). FAS is identified by characteristic changes in facial features particularly around the mouth and eyes. A milder form without the facial deformities, but with associated with leaning disabilities and CNS dysfunction is called Fetal Alcohol Effect (FAE) or Alcohol-Related Neurodevelopmental Disorder (ARND). In the U.S., it is estimated that 4 million infants are born each year with an estimated between 1,300 and 8,000 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. Some believe that some European countries might number as high as 1 to 5 per 100 school children (or 1% to 5% of the population.) The effects of alcohol on the infant illustrate the sensitivity of the developing fetus to the chemical exposure. The tragedy is twofold: 1) the effects of alcohol on the fetus are preventable and 2) the effects last a lifetime, robbing the individual of the opportunity to express their full genetic potential.

Alcohol and the Liver

Alcohol has a range of effects in addition 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 U.S., 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. Some heavy drinkers develop an inflammation (alcoholic hepatitis) of the liver. Metabolites of alcohol, produced by the liver, are toxic to the liver cells. 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.

Introduction and History

> 'T is not the drinking that is to be blamed, but the excess.
>
> John Selden (1584–1654) In "Table Talk" 1689



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 love/hate relationship with alcoholic beverages began over 10,000 years ago with the accidental fermentation of beer. The production of wine soon followed and cultivation of vineyards is documented by about 3,000 BC. The ancient ruler of Babylon, Hammurabi, commented on the purchase and sale of wine in rules set down in 2,000 BC. Followers of the Greek god of wine, Dionysus, taught the cultivation of vines and frolic in 1,500 BC. The unfortunate combination of lead and wine may have helped hasten the end of the Roman Empire where wine was stored and served in lead containing vessels. Being slightly sweet, lead was even added to the wine. The use of alcoholic beverages is shaped by the technology of the era and various attempts by society to regulate its consumption. 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.

Whiskey – Water of life (Gaelic uisge beatha) – Alcohol was once thought to be a cure for many illnesses, including the common cold.

The word alcohol comes from the Arabic, *al-kuhul*, originally referring to a white powder of antimony used as eye makeup. Alchemist of the 16th century began referring to alcohol as the essence from distillation, thus the essences of wine. 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.

Alcohols are a large class of chemical compounds characterized by an OH (oxygen and hydrogen) group attached to a carbon atom. The simplest alcohol is methanol or wood alcohol (CH_3-OH). Methanol is highly toxic and an undesirable contaminant of some homemade alcoholic beverages. Ethyl alcohol, the intoxicating form of alcohol, a product of fermentation and found in many beverages, is CH_3-CH_2-OH.

Fermentation – Sugar ferments to Alcohol and Carbon dioxide

$$C_6H_{12}O_6 \rightarrow 2C_2H_5OH + 2CO_2$$

The accidental fermentation of grain probably produced the first beer. Fermentation occurs when microorganisms such as yeast, fungi, or bacteria break down complex molecules to produce energy in the absence of oxygen. Most often, fermentation produces unpleasant acids, but fermentation can produce useful products such as yogurt, cheese, sauerkraut, and black tea. During fermentation, certain strains of yeast produce ethyl alcohol and carbon dioxide in their quest for energy from available sugars. Below is a list of common fermentation starting points and the end products either as a direct result of fermentation of from further distillation.

- Cereal grains –> Beers and whiskeys
- Honey –> Mead
- Grapes –> Wine and brandy
- Root vegetables –> Vodka
- Sugar cane –> Rum

Beer fact – The dark porter beers were first developed in London, England in 1722 to nourish potters and heavy laborers.
An Irish brewer named Guinness refined this process in the late 1700's to produce a beer that still bears his name.

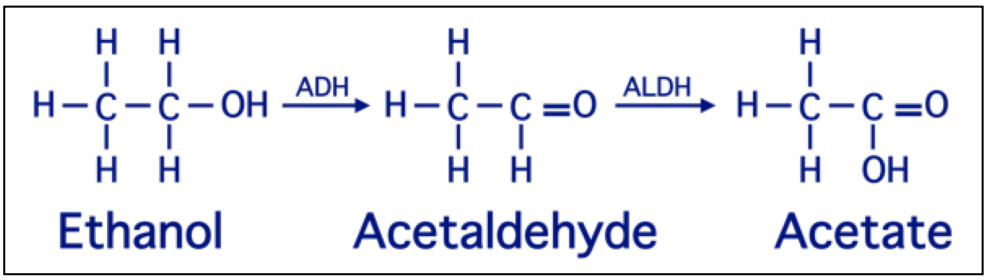
Biological Properties

Alcohol is an excellent and widely used solvent, appearing in many products from gasoline to drugs and of course common alcoholic beverages. 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, the annual corn ethanol production for use in fuel has grown from 175 million gallons in 1980 to nearly 9.3 billion gallons in 2008. World wide production is estimated at over 16 billion gallons and is expected to continue to grow. Approximately 25% of U.S. corn croplands are used for ethanol production. According to the U.S. Department of Energy in 2018, out of 14.62 billions of bushels of corn produced, 5.60 billions of bushels were used to produce corn based ethanol. The use of food based products for ethanol fuel production is contributing to increased food costs world wide.

Alcohol is readily absorbed from the stomach and the intestine. Elapsed time from the last drink of alcohol to the highest blood level is about 30 minutes. As direct experience will bear out, 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 industrial hazard were alcohols are used in commercially.

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 3.1).

Figure 3.1 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, which makes alcohol consumption very unpleasant. Antabuse (disulfiram), a common drug prescribed to discourage alcohol consumption, blocks ALDH causing blood levels of acetaldehyde to rise and 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 limit of 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 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 the percent alcohol in the drink.

How alcohol effects 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 dissolving the cells lipid membranes and disrupting the function of various proteins. More recently, researches have focused on specific receptors such as

glutamate (excitatory) and GABA (inhibitory). Despite intensive research, the mechanism by which alcohol effects 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 with economic costs estimated to be over $275 billion a year, including medical expenses, lost worker productivity, automobile accidents, crime, and other costs. 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.

A drink is defined as - 0.5 oz (15 ml) of ethanol.

One 12-oz (360 ml) bottle of beer

One 5-oz (150 ml) glass of wine

1.5 oz (45 ml) of 80-proof distilled spirits

Because the percent ethanol in a beverage varies, the volume to achieve 0.5 oz of ethanol also varies. For example, wine can range from approximately 8 to 15 % ethanol.

Children

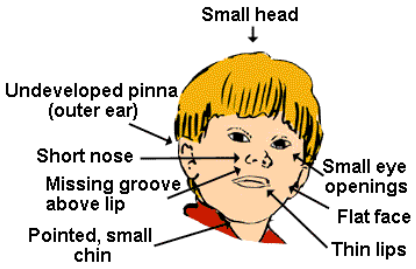


Figure 3.2 Effects of in utero alcohol exposure

Despite alcohol's long history of use, the association of adverse effects of maternal alcohol consumption on the developing fetus was only first described in 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, Seattle, WA, U.S. FAS is characterized by physical and facial abnormalities (Figure 3.2), 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 life long impacts. Another form of alcohol related effects is Fetal Alcohol Effect (FAE) which designates children born with learning or memory disabilities, but without the characteristic physical abnormalities. The disabilities associated with fetal alcohol exposure are not described as Fetal Alcohol Spectrum Disorder (FASD) which recognizes the range of effects alcohol has on development. In addition, alcohol consumption during pregnancy also 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.

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 with minor disabilities. Recent studies in the United States estimate that from 14 to 22.5 percent of women report drinking some alcohol during pregnancy. An additional concern is that a woman is often not aware they are pregnant during the first few vey 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" unable to find the shore.

Adults

Alcohol, a toxic solvent, flows freely in our society. Because it is heavily advertised, easy to make, easier to purchase, 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. This has not always been the law when I grew up the drinking age was 18 years old. In Europe and other parts of the world the legal drinking age is generally 18 and sometimes 16 years of age.

The main acute effect is inebriation, which in turn spawns violence, spousal and child abuse, crime, motor vehicle accidents, workplace and home accidents, drowning, suicide, and accidental death.

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 in 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.

Alcohol Withdrawal Effects

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

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 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 scaring or hardening of the liver called cirrhosis. All these changes to the liver result in decreased ability to metabolize alcohol as well other drugs or will even enhance the toxicity of some drugs, such as the pain reliever Tylenol (acetaminophen).

The International Agency for Research on Cancer (IARC) classifies "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.

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 are pregnant should not consume alcohol. Men need to support and encourage no 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.

Regulatory Standards

Advice or regulation related to alcohol consumption during pregnancy was slow to arrive even after the fetal works were well documented and more still needs to done to discourage alcohol consumption during pregnancy.

- 1981 - U.S. Surgeon General first advised that women should not drink alcoholic beverages during pregnancy.

- 1988 - U.S. requires warning labels on all alcoholic beverages sold in the United States.

- 1990 - U.S. Dietary Guidelines state that women who are pregnant or planning to become pregnant should not drink alcohol.

- 1998 - 19 states require the posting of alcohol health warning signs where alcoholic beverages are sold.

Recommendation and Conclusions

Alcohol is readily available a 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 gave 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.

More Information and References

Slide presentation and online material

A Small Dose of Alcohol slide presentation material and references are online:

European, Asian, and international Agencies

- England – Department of Health (DOH). Alcohol and drug misuse prevention and treatment guidance. Online: < https://www.gov.uk/government/collections/alcohol-and-drug-misuse-prevention-and-treatment-guidance> (accessed: 03 March 2020).
  The DOH England provides extensive information on the health alcohol and drug misuse prevention and treatment guidance effects of alcohol

- International Council on Alcohol and Addictions (ICAA). Online: <http://www.icaa.ch/> (accessed: 03 March 2020). Lausanne, Switzerland
  "ICAA is dedicated to preventing and reducing the harmful use and effects of alcohol, tobacco, other drugs and addictive behaviours on individuals, families, communities and society."

North American Agencies

- Health Canada – Fetal Alcohol Spectrum Disorder (FASD). Online: <https://www.canada.ca/en/public-health/services/diseases/fetal-alcohol-spectrum-disorder.html> (accessed: 04 March 2020).
  About FASD, its cause, signs and symptoms, health effects, prevention, support and information for professionals.

- U.S. Centers for Disease Control's "Fetal Alcohol Syndrome Disorders". Online: < https://www.cdc.gov/ncbddd/fasd/> (accessed: 04 March 2020).

- U.S. The Bureau of Alcohol, Tobacco, Firearms and Explosive (ATF), Department of Justice. Online: <http://www.atf.gov/> (accessed: 04 March 2020).
  ATF's unique responsibilities include protecting the public and reducing violent crime and enforce the Federal laws and regulations relating to alcohol and tobacco diversion, firearms, explosives, and arson.

- U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA). Online: http://www.niaaa.nih.gov (accessed: 04 March 2020).
  "The NIAAA supports and conducts biomedical and behavioral research on the causes, consequences, treatment, and prevention of alcoholism and alcohol-related problems."

- U.S. National Institute of Health – National Institute on Drug Abuse – Alcohol. Online: https://www.drugabuse.gov/drugs-abuse/alcohol (accessed: 04 March 2020).
  The NIDA has extensive information on a range of drugs including alcohol.

Non-Government Organizations

- Alcoholics Anonymous (AA). Online: <http://www.aa.org/> (accessed: 04 March 2020)
  An international organization dedicated to helping people with alcohol consumptions concerns.

- Center for Science in the Public Interest (CSPI). Online: <http://www.cspinet.org/> (accessed: 04 March 2020).
  "CSPI is an advocate for nutrition and health, food safety, alcohol policy, and sound science."

- Mothers Against Drunk Driving (MADD). Online: <http://www.madd.org/> (accessed: 04 March 2020).

"MADD's mission is to stop drunk driving, support the victims of this violent crime, and prevent underage drinking."

- Nordic Studies on Alcohol and Drugs | SAGE Publications Ltd https://uk.sagepub.com/en-gb/eur/nordic-studies-on-alcohol-and-drugs/journal202614 (accessed: 03 March 2020).
  Nordic Studies on Alcohol and Drugs is a fully peer-reviewed, open access journal for social science research on alcohol and drugs.

- Rutgers, The State University of New Jersey Center of Alcohol & Substance Use Studies. Online: http://alcoholstudies.rutgers.edu (accessed: 04 March 2020).
  The Center of Alcohol & Substance Use Studies (CAS) is a multidisciplinary institute dedicated to addiction research, education and training. We are a center in the Graduate School of Applied and Professional Psychology (GSAPP).

- National Organization on Fetal Alcohol Syndrome. Online: <http://www.nofas.org/> (accessed: 04 March 2020).
  "NOFAS works to prevent prenatal exposure to alcohol, drugs, and other substances known to harm fetal development by raising awareness and supporting women before and during their pregnancy, and supports individuals, families, and communities living with Fetal Alcohol Spectrum Disorders (FASDs) and other preventable intellectual/developmental disabilities."

- Alcohol and Drug History Society (ADHS). Online: https://alcoholanddrugshistorysociety.org (accessed: 04 March 2020).
  ADHS mission is to promote scholarship and discussions about the history of alcohol and drug use, abuse, production, trade and regulation across time and space.

- Fetal alcohol syndrome - Symptoms and causes - Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/fetal-alcohol-syndrome/symptoms-causes/syc-20352901 (accessed: 03 March 2020).
  Provides detailed description of FAS. States: "There is no amount of alcohol that's known to be safe to consume during pregnancy. If you drink during pregnancy, you place your baby at risk of fetal alcohol syndrome."

References

Astley, S.J. (2004). Diagnostic Guide for Fetal Alcohol Spectrum Disorders: The 4-Digit Diagnostic Code. Seattle: University of Washington. PDF available at FAS Diagnostic and Prevention Network. Ranks the four key features of FASD on a Likert scale of one to

four. Available: https://depts.washington.edu/fasdpn/pdfs/guide2004.pdf > (accessed: 05 March 2020).

Fetal Alcohol Syndrome – Diagnosis, Epidemiology, Prevention, and Treatment. Kathleen Stratton, Cynthia Howe, and Frederick C. Battaglia, Editors; Committee to Study Fetal Alcohol Syndrome, Institute of Medicine, Washington, DC. 1996. The National Academy Press. Online: <http://www.nap.edu/catalog.php?record_id=4991> (accessed: 05 March 2020).

WHO Global Status Report on Alcohol 2018. World Health Organization, Released September 21, 2018. Online: < https://communitymedicine4asses.com/2018/09/22/global-status-report-on-alcohol-and-health-2018/ > (accessed: 05 March 2020).

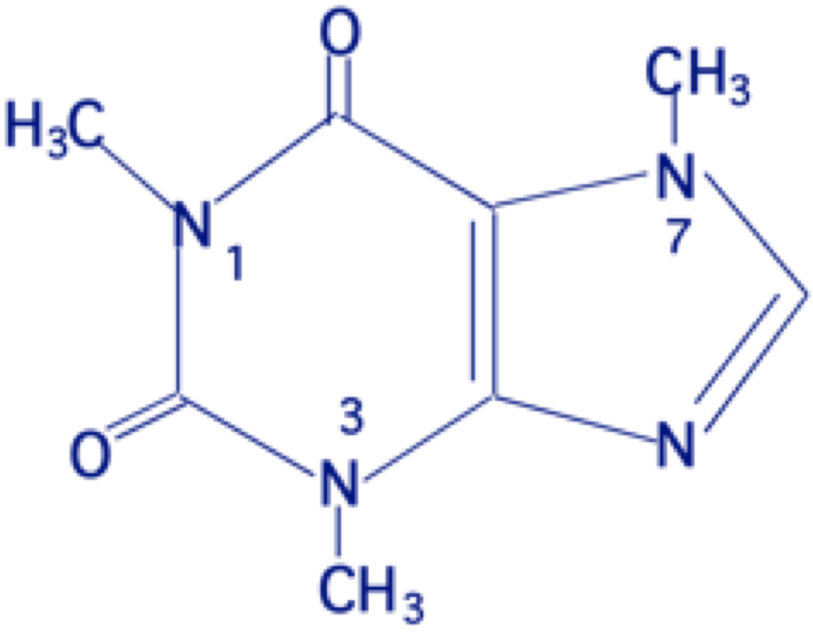
Wattendorf, D. J., and Muenke, M. (2005). Fetal alcohol spectrum disorders. American family physician 72, 279-82, 285. Open access: http://www.aafp.org/afp/20050715/279.html (accessed; 05 March 2020).

Riley, E.P., Infantem M.A. and Warren, K.R. (2011) Fetal Alcohol Spectrum Disorders: An Overview Neuropsychology Review volume 21, Article number: 73 (2011).

Cook, JL, Green, CR, CM Lilley, SM Anderson etal… (2016) Fetal alcohol spectrum disorder: a guideline for diagnosis across the lifespan. Canadian Medical Association CMAJ February 16, 2016 188 (3) 191-197; DOI: https://doi.org/10.1503/cmaj.141593 Online: < https://www.cmaj.ca/content/188/3/191.short> (accessed; 05 March 2020).

A Small Dose of Caffeine
Or
An Introduction to the Health Effects of Caffeine

By Steven G. Gilbert, PhD, DABT



Caffeine or 1,3,7-trimethylxanthine

Caffeine Industry
The coffee and cola industries owe their wealth to the physiological and pharmacological properties of the drug caffeine.
S.G. Gilbert (2001)

Dossier

Name: Caffeine (1,3,7-trimethylxanthine)
Use: most widely used stimulant in the world
Source: coffee, tea, cola and other soft drinks, chocolate, stimulant pills, some analgesics
Recommended daily intake: the U.S. Food and Drug Administration (FDA) advised 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: contaminates sewage discharge
Recommendations: be thoughtful about consumption

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), U.S. 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), U.S. 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).

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 that can be called a form of neurotoxicology and you are on your way to becoming a neurotoxicologists.

An additional question related to the nervous system effects of caffeine is 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 drug for many large corporations and small businesses to make large amounts of money.

The 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 and allow a number of international corporations to make vast sums of money?

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

Introduction and History

> If Christianity is wine, and Islam coffee, Buddhism is most certainly tea. – Alan Watts, The Way of Zen, 1957

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 and compared to alcohol and nicotine to become 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. Caffeine, even more than alcohol and nicotine, demonstrates the human interest and capacity to consume drugs that affect our nervous system.

In this chapter, we will explore why we so readily consume caffeine. There are sound physiological and pharmacological reasons why so many companies make so much money from caffeine. The economics are staggering. Coffee alone is one of the largest cash crops in the world and produced all over the world. It is estimated that in 2019 coffee production was approximately that 10 million kilograms (more that 2.2 billion pounds – a huge amount), which would translate in to over a trillion cups of coffee and literally tons of caffeine. This does not even take into consideration the caffeine consumed from cola beverages, tea (approximately 6 million tones), 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 inquires, many scientific papers and conference, and many books and articles. Perhaps the best book to combine both 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 of caffeine and society from its ancient roots to present times, as well as a look at the health effects. A book devoted almost entirely to the health effects of caffeine is *Caffeine and Health* by Jack E. James, published in 1991. There is no lack of information on caffeine.

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 caffeine drinks. The first documented use is in China by its first great emperor, Shen Nung, in about 2700 B.C. Throughout Chinese history there are many references to tea and its many benefits. The earliest written record

of tea consumption is from a Chinese document from 350 B.C. 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 aspect of trade on the Silk Road to China. About 800 A.D. tea was introduced to Japan. In Japan the consumption of tea, more specifically a green powdered 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, the 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. Tea bags were accidentally invented in 1908. In more recent times, we are treated to a great many fragrant varieties of tea from around the world.

Coffee's history is equally rich and savory. According to the legends 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 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. By the 1700s there were coffee shops throughout Europe, and coffee was fast becoming part of the culture. Coffee trees were introduced into the Americas in 1723. 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 Starbuck's coffee shop was 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 but by people all over the world consume not so much for the caffeine but for the taste. Archeological 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 it names from Theobroma. The Spanish explore Hernando Cortés brought cocoa to Spain in 1528, were it was kept secret from the rest Europe until 1600 when it quickly became very popular, so popular that the Pope had to declare that chocolate drink did not break a fast. The first English chocolate houses opened up in 1657. 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 it was a staple of solders at war and just about everyone else.

A glance at the table 5.1 illiterates how caffeine cuts across society, trade, politics, and industry to become the drug of choice for billions of people. The amount caffeine in a particular product, as well as the amount consumed, can vary enormously. The amount of caffeine in a cup of coffee varies with the type of bean, the roasting, and the type of brewing method employed. The cup size adds another variable. Tea actually has a higher concentration of caffeine than coffee, but the extraction of the caffeine from coffee is more efficient than that of tea. If you want more caffeine in your tea, however, you only need to brew it for a longer period of time. By weight coca has the least amount of caffeine, but it also has the structurally similar compound theobromine. Caffeine is added to many cola and other soda-like beverages. Some are known for their high caffeine concentration. It is now possible to buy water-based drinks fortified with caffeine. Over the counter pills of caffeine are available, and many analgesic medications contain caffeine as well, in part to alleviate the headache due to lack of caffeine.

Table 5.1 Common products and caffeine concentration

Product	Caffeine	Size
Coffee	50-150 mg	Cup about 8 ounce or 225 ml
Tea	20-100 mg	Cup about 8 ounce or 225 ml
Cola drink	20-100	8 ounce or 225 ml
Energy Drinks	120-300	12 ounce
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 B.C.	T	Tea discovered in China or introduced form India
350 B.C.	T	First written description of Tea drinking in China.
400 B.C.	Ch	Olmec people of Mexico made chocolate drinks
250 A.D.	Ch	Mayans of Mexico were cultivating cocoa crops
450	T	Turkish traders bargain for Tea and the Silk road is born.
800	T	Tea introduced to Japan.
850 (about)	Co	Coffee beans discovered - The fable says that an Ethiopian goat or sheepherder noticed that the goats were more alter after eating the wild berries. He then sampled this new delicacy.
1100 (about)	Co	First coffee trees and roasting of coffee beans.
1450	T	Japanese Tea ceremony created and popularized
1475	Co	Constantinople – the world's first coffee house.
1528	Ch	Cocoa was brought to Spain by Hernando Cortés
1600s	Co	Coffee enters Europe and moves quickly to the Americas
1600s	Ch	Chocolate drinks introduced into Europe
1610	T	Dutch bring Tea to Europe

1657	Ch	First English chocolate houses open
1700s	Co	Coffee house open throughout Europe.
1723	Co	First coffee plants are introduced into the Americas.
1773	T	Boston Tea party, rebellion against England's tea tax
1776	T	England sends first Opium to China to help pay for tea.
1822	Co	First espresso machine is created in France.
1828	Ch	Screw press that extracted the cocoa butter from the beans invented in Holland
1835	T	First experimental tea plantations 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 opens its first location in Seattle, Washington's Pike Place Market.

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 cocoa beans—or the leaves—as in tea. The common use of caffeine-bearing substances throughout the world 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.

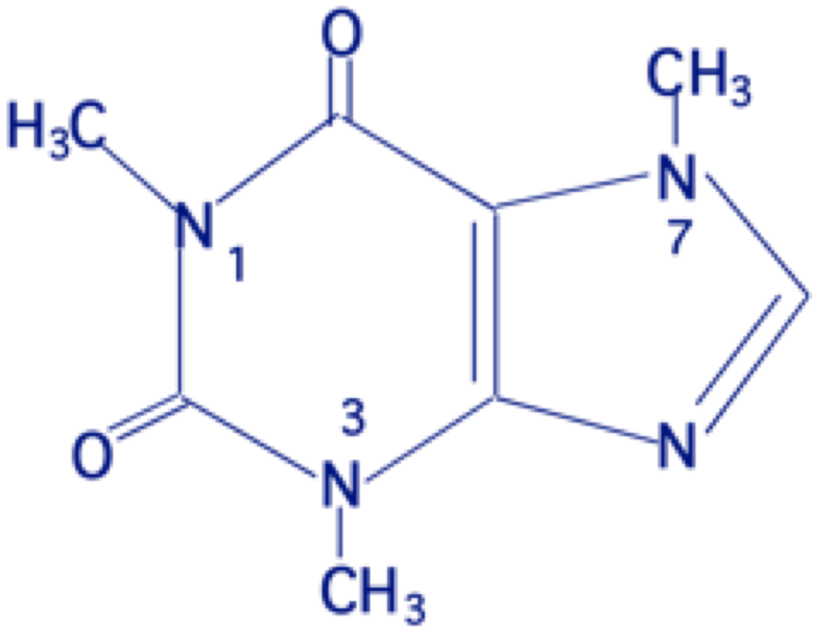


Figure 5.1 Caffeine or 1,3,7-trimethylxanthine

Purified, caffeine (Figure 5.1) is a white crystalline powder with a bitter taste. While caffeine is not particularly soluble in water, it 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. From an insects perspective the caffeine family on chemicals are insecticides. But with humans it has clearly has the opposite effect of encouraging consumption of the plant.

The chemical name of caffeine is 1,3,7-trimethylxanthine, and it is part of the purine family derivatives of methylxanthines (Figure 5.2). 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.

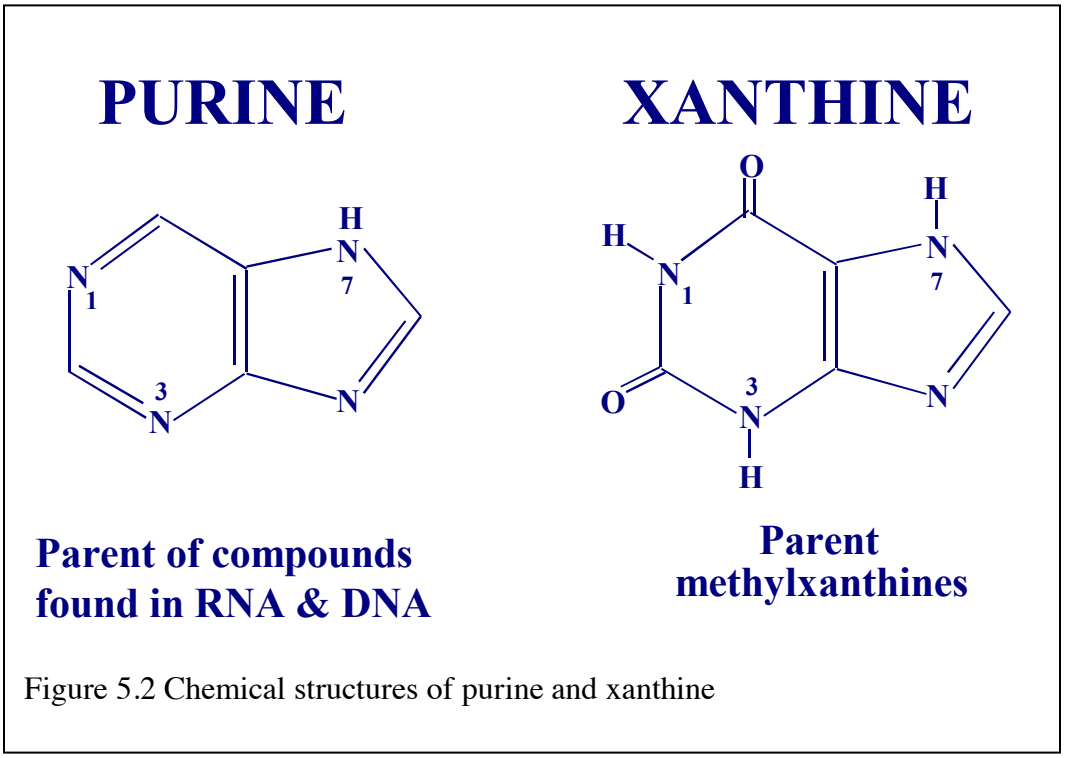


Figure 5.2 Chemical structures of purine and xanthine

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 the common metabolites of caffeine.

Caffeine is readily and completely absorbed from the intestine following oral ingestion. It distributes throughout body water, so that blood, urine or breast milk will all have about the same concentration of caffeine. Metabolism varies between individuals, but on average he 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. If you are a smoker, you will metabolize caffeine more quickly, usually with a half-life of about three hours. During pregnancy, the half-life of caffeine increases to 8-10 hours. The newborn cannot metabolize caffeine and must 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 (CH3) groups to make di- or mon-methylxanthines, which are excreted in the urine. The relatively short half-life of caffeine is an important property of the drug and accounts for its for its repeated consumption. The half-life of theophylline is about twice that of caffeine.

Caffeine and the related dimethylxanthines have similar pharmacological or therapeutic effects and similar 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 or up-regulating the number of adenosine receptors.

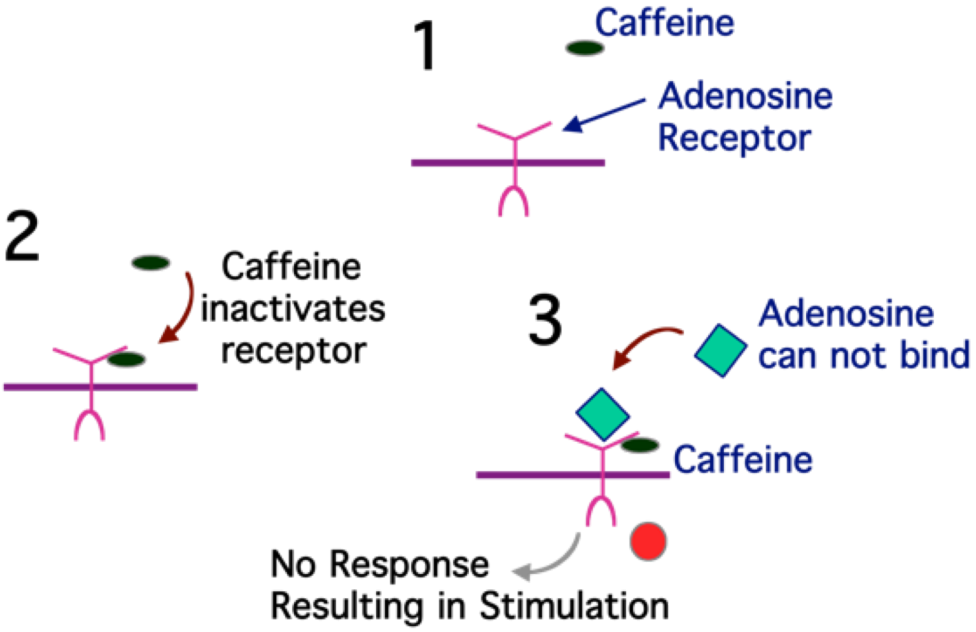


Figure 5.3 Mechanism of action of caffeine

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 the treatment of infants that stop breathing for extend periods of time (sleep apnea), which can lead to sudden infant death.

Methylxanthines have a number of other effects, including effects on smooth muscles and the cardiovascular system. The most notable effect on smooth muscles is relaxing the bronchi of the lungs. 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.

The caffeine naïve individual 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 the ability to stay awake. Long-term consumption of caffeine does not seem to lessen the desirable effects of caffeine. In other words, long-term consumption of caffeine does not result in tolerance to the stimulatory effects. This is important for the caffeine industry because if we developed tolerance to this drug we would stop consuming because it lost its 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 to most caffeine consumers. Too much caffeine results in uncomfortable to adverse central nervous system effects, or neurotoxicity. The 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, but for other people consumption of caffeine late in the day affects sleep. It is important to understand your own individual response to caffeine.

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, a classic sign of drug dependence. Awareness of your individual potential to suffer from withdrawal effects of caffeine is important. This knowledge can often explain the onset of a headache when there is a sudden or unexpected cessation of caffeine consumption.

Chocolate contains theobromine, which can be toxic to dogs.

Most of the overt toxicity of the methyl xanthines, 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 as 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 a dog 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 are 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 U.S. 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. The half-life increases to about twice normal, or 8-10 hours. This means that after caffeine consumption the material 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 U.S. FDA advises pregnant women avoid or limit caffeine consumption in an effort to address these concerns.

People who drink caffeine have learned from experience how much to consume and thus to avoid the adverse behavioral effects of *too much* caffeine. Excessive consumption of caffeine is an almost perfect example of the fundamental dose / response principle of toxicology. A 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 not agreement 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 there be easily available caffeinated products in high schools? What the consequences of caffeine exposure to high school students?

Regulatory Standards

The U.S. 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.

More Information and References

Slide Presentation

- A Small Dose of Caffeine slide presentation material and references are online: Web site contains presentation material related to the health effects of caffeine.

European, Asian, and International Agencies

- International Food Information Council (IFIC) Foundation. Online: https://foodinsight.org (accessed: 07 March 2020).
  The International Food Information Council (IFIC) Foundation is dedicated to the mission of effectively communicating science-based information on health, nutrition and food safety for the public good. IFIC is supported primarily by the broad-based food, beverage and agricultural industries.

- England – The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) is an independent scientific committee that provides advice to the Food Standards Agency, the Department of Health and other Government Departments and Agencies on matters concerning the toxicity of chemicals.
  –Reproductive Effects of Caffeine 2008. Online: https://cot.food.gov.uk (accessed: 07 March 2020).
  Excellent report on the reproductive effects of caffeine.

North American Agencies

- U.S. MEDLINEplus Health Information. Online: <http://www.nlm.nih.gov/medlineplus/caffeine.html> (accessed: 07 March 2020).
  Medline has multiple references on caffeine, including a number of useful web based links.

- U.S. PubMed - https://pubmed.ncbi.nlm.nih.gov/?term=caffeine A search for recent research on caffeine. (accessed: 07 March 2020).

- U.S. Food and Drug Administration (FDA) Spilling the Beans: How Much Caffeine is Too Much?. Online: https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much (accessed: 07 March 2020).
  This FDA wed site provides general information on caffeine.

Non-Government Organizations

- Center for Science in the Public Interest – Caffeine – The Good, the Bad, the Maybe (March 2008). Online: < https://cspinet.org/eating-healthy/ingredients-of-concern/caffeine-chart > (accessed: 09 March 2020).
  Chart of amount of caffeine in various drinks. General information on the health effects of caffeine is also available at this site. For example: Beware of These

Effects of Caffeine on the Body - https://cspinet.org/tip/beware-these-effects-caffeine-body . (accessed: 09 March 2020).

- March of Dimes – Caffeine in Pregnancy Fact Sheet. Online: https://www.marchofdimes.org/pregnancy/caffeine-in-pregnancy.aspx (accessed: 09 March 2020).
  March of Dimes has a number of fact sheets including this one on caffeine.

- In Pursuit of Tea. Online: <http://www.inpursuitoftea.com/> (accessed: 09 March 2020).
  Company web site dedicated to "Exploring remote regions of the world to supply the finest Teas".

- Caffeine – The Vaults of Erowid. Online: <http://www.erowid.org/chemicals/caffeine/caffeine.shtml> (accessed: 09 March 2020).
  The Erowid web site has a wide range of information on caffeine.

- Caffeine and Pregnancy. Organization of Teratology Information Specialists (OTIS) - MotherToBaby. Online: < https://mothertobaby.org/fact-sheets/caffeine-pregnancy/pdf/ > Numerous fact sheets on wide range of medicines. (accessed: 09 March 2020),
  Advices women to limit caffeine consumption during pregnancy.

References Books

There are many books on caffeine. I have picked just a few – see below. A quick scan through Amazon or Google search will provide you with lots of reading. To look into caffeine in further detail, I would recommend Wikipedia, which has an extensive and will referenced article on caffeine.

Caffeine: How Caffeine Created the Modern World Audible Audiobook – Original recording by: Michael Pollan Caffeine: How Caffeine Created the Modern World Audible Audiobook – Original recording

The Truth About Caffeine Audible Audiobook – Unabridged
Marina Kushner (Author), Timothy McKean (Narrator), SCR, LLC (Publisher). The book *The Truth About Caffeine* exposes caffeine's darker side that scientists know. New and updated third edition. ©2010 Al Kushner

The World of Caffeine – The Science and Culture of the World's Most Popular Drug. By: Bennett Alan Weinberg and Bonnie K. Bealer. Routledge, New York and London 2001. ISBN-13: 978-0415927239

Reference Papers

Caffeine is popular research subject. I have selected a small sampling some new some older. There is also a wide selection of animal studies that I did not reference.

Caffeine & Health. By Jack E. James. Academic Press – Harcourt Brace Jovanovish, Publishers. New York, 1991.

Robert L. Brent, Mildred S. Christian, and Robert M. Diener. (2011) Evaluation of the Reproductive and Developmental Risks of Caffeine. Birth Defects Res (Part B) 92:152–187, 2011. © 2011 Wiley-Liss, Inc.

Kolahdouzan, M., & Hamadeh, M. J. (2017). The neuroprotective effects of caffeine in neurodegenerative diseases. CNS neuroscience & therapeutics, 23(4), 272–290. https://doi.org/10.1111/cns.12684

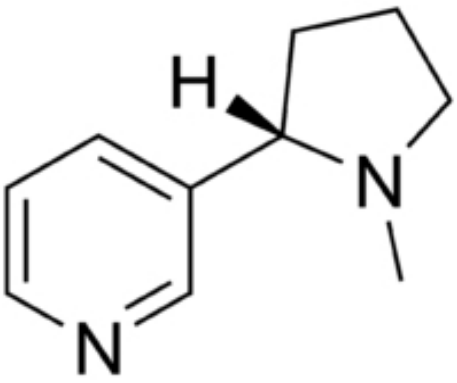
Doepker, C., Franke, K., Myers, E., Goldberger, J. J., Lieberman, H. R., O'Brien, C., Peck, J., Tenenbein, M., Weaver, C., & Wikoff, D. (2018). Key Findings and Implications of a Recent Systematic Review of the Potential Adverse Effects of Caffeine Consumption in Healthy Adults, Pregnant Women, Adolescents, and Children. Nutrients, 10(10), 1536. https://doi.org/10.3390/nu10101536

dePaula, J. and Farah, A. (2019) Caffeine Consumption through Coffee: Content in the Beverage, Metabolism, Health Benefits and Risks. Beverages 2019, 5, 37; doi:10.3390/beverages5020037. www.mdpi.com/journal/beverages

Gaelle Gourmelon. (2017). What You Should Know About The Chocolate You're Eating. http://blogs.worldwatch.org/chocolate-ethical-sustainable/. Gaelle Gourmelon is the Director of Communications and Marketing at the Worldwatch Institute. Her work aims to connect people with their environment to empower them to make informed decisions.

A Small Dose of Nicotine
Or
An Introduction to the Health Effects of Nicotine

By Steven G. Gilbert, PhD, DABT



Nicotine.
((*S*)-3-(1-Methyl-2-pyrrolidinyl)pyridine)

Dossier

Name: Nicotine
Use: pesticide, drug in tobacco, chewing, smoking
Source: tobacco contains nicotine
Recommended daily intake: none (not essential)
Absorption: lung, skin, stomach (poor), intestine (better), (poor absorption in the stomach because nicotine is a strong base)
Sensitive individuals: fetus, children
Toxicity/symptoms: dependency producing, acute effects: nausea, vomiting, salivation, diarrhea, dizziness, mental confusion, weakness
Regulatory facts: RfD (none), LD50 10 mg/kg, not currently regulated but legislation is being considered to allow regulation by FDA. In 1964, the U.S. Surgeon General issued a report linking smoking with lung cancer and heart disease. In 1994 that the US FDA determined that nicotine was a dependency-producing drug.
General facts: long history of use; produces dependency in user
Environmental: growing demand for cigarettes in developing countries and vaping becomes popular
Recommendations: avoid

Case Studies

"The Divine Origin of Tobacco"

Tobacco was a powerful medicine for the first people of the Americas. The indigenous peoples in California tribal legend, trace 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 shaman relied upon tobacco for guidance, a source of strength, and part of the 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)

1000 BC

Figure 6.1 Mayan priest with smoking tobacco
Ancient temple carvings depict Mayan priests in Central America smoking tobacco through a pipe. Tobacco leaves become widespread in medicine for use on wounds as a means of reducing pain. Later the Aztecs incorporate smoke inhalation into religious rituals.

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 required hospital treatment. In the fields, the worker's clothes became wet from moisture on the tobacco leaves, and most workers did not use gloves or protective clothing. 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. Appropriate worker education about the absorption of nicotine through the skin and the use of protective clothing would reduce the incidence of GTS. For more information see Morbidity Mortality Weekly Report on GTS (reference below).

Second and Third Hand Smoke

First hand smoke is the particulate matter that is directly inhaled into a smokers lungs. Second hand smoke is particulate matter that is inhaled into a by standers lungs. While

Third hand smoke referees to the toxicants that linger on the surfaces of material after the original smoke has cleared. Second hand smoke is particularly hazardous to children in a home environment but extends to all enclosed environments. In 2020 it is hard to imagine smoking on air planes or even in airports. The health effects of second hand smoke are essentially identical to first hand smoke such lung cancer, cardiovascular, other associated diseases. The acceptance of the health effects of second hand smoke was radically changed the regulatory rules that governed smoking. Smoking in the workplace ended as well as smoking in the public except in designated areas. Recognizing that rules governing second hand smoke would broadly reduce smoking the cigarette industry fought the science of the health effects of second and third hand smoke, fortunately industry lost several of the legal cases. The tobacco was make for excellent reading with nicotine at the heart of the story.

Facts on cigarettes
During 2017, about 249 billion cigarettes were sold in the United States—a 3.5% decrease from the 258 billion sold in 2016.
Four companies—Philip Morris USA, Reynolds American Inc., ITG Brands, and Liggett—accounted for about 92% of U.S. cigarette sales.

Introduction and History

Nicotine is a potent and addictive drug with a long history of use with enormous effects on our society. From a toxicology perspective, nicotine is a pesticide that naturally occurs in tobacco, and is a powerful drug with multiple nervous system effects. Thus, cigarettes or vaping devices are highly effective drug delivery devices.

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 to part of the healing arts and sacred rituals of many of the native peoples of the Americas.

There are various theories of how tobacco was introduced to Europe, but undoubtedly (see above box) Christopher Columbus and his crews sampled this native weed and succumbed to its spell. Once introduced into Europe at about 1528, 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.

"We found a man in a canoe going from Santa Maria to Fernandia. He had with him…some dried leaves which are in high value among them, for a quantity of it was brought to me at San Salvador".

Christopher Columbus' Journal, 15 October 1492

The habit of tobacco use is directly related to the biological effects of nicotine. While people in the 1500s did not understand the mechanisms behind the complex physiological effects of nicotine, they certainly felt and appreciated its stimulating and relaxing properties. The desire to consume nicotine is encouraged not only by these seemingly pleasant effects, but also by the need to avoid the unpleasant effects of no longer having nicotine in your blood.

The societal effects of tobacco and nicotine started early and continues today. By the early 1600s tobacco farming had become an important cash crop for export 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 along with slavery. 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 capturing 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 physiological effects of tobacco consumption, largely related to nicotine, helped it became a powerful habit that has influenced society in countless ways. It is only relatively recently that society has looked at the true cost of tobacco consumption.

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 much 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 bowl full of tobacco.

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 U.S. Surgeon General issued a report linking smoking with lung cancer and heart disease, which started a slow recognition among policy makers of the true cost of smoking and began efforts to reduce consumption. It was not until 1994 that the U.S. Food and Drug Administration officially determined that nicotine was a dependency-producing drug. The U.S. 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. While tobacco consumption is declining in North America and parts of Europe, it continues to increase in many parts of the world that have yet to recognize the costs both to the individual and ultimately to society.

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 (see below). 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.

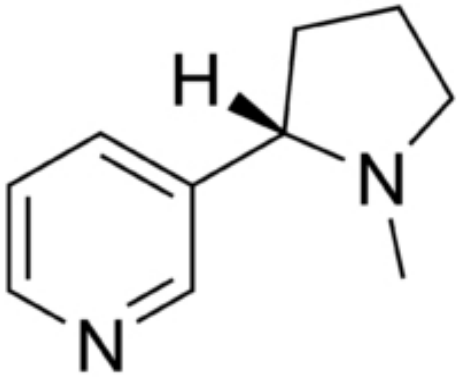


Figure 2. Nicotine.
((*S*)-3-(1-Methyl-2-pyrrolidinyl)pyridine)

Nicotine based insecticides were first developed by Henry Feuer, a chemist at Purdue University, in 1970. Shell chemists later refined and developed it as nithiazine postsynaptic acetylcholine receptor agonist. In 1985, Bayer patented imidacloprid as a neonicotinoid. This class of compounds called neonicotinoids were commercially very successful and by mid 2010 were generating over $1 billion in revenue. Unfortunately, neonicotinoids were not powerful against

Nicotine based pesticides are no longer registered by the U.S. (EPA, 2008).

Biological Properties

Nicotine (Figure 2) has a range of physiological effects and has provided researchers with an opportunity to learn about 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 central and peripheral nervous systems that trigger 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 exposure to nicotine (a smoke) in an effort to restore the blood nicotine levels. The primary metabolite of nicotine is cotinine, which has a much longer half-life than nicotine. Nicotine and its metabolites are readily excreted in the urine. 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 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

> 1604: "A Counterblaste to Tobacco"
>
> "Smoking is a custom loathsome to the eye, hateful to the nose, harmful to the brain, dangerous to the lungs, and in the black, stinking fume thereof nearest resembling the horrible Stygian smoke of the pit that is bottomless." -- James I of England, "A Counterblaste to Tobacco."

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.

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

E-cigarette (Electronic cigarette)

An e-cigarette (electronic cigarette) is a battery powered device that simulates tobacco smoking, often called vaping. It consists of a power source such as a battery, an atomizer and a container such as a cartridge or tank which contains a liquid. Instead of smoke, the user inhales vapor, thus called vaping. The liquid which becomes the vapor, varies in composition varies but is commonly made up of propylene glycol, glycerin, nicotine, flavors, and traces of toxicants, carcinogens, heavy metals, and metal nanoparticles. The toxicity of the inhaled vapor is unknown but is often considered to be less that regular tobacco smoking. In reality the vaping devise is really just a drug, most often nicotine, delivery device along with a range of other toxic byproducts. Most importantly don't start, which according to some is already increasing independently of regular smoking,

Reducing Exposure

> "To cease smoking is the easiest thing I ever did. I ought to know, I've done it a thousand times."
> Mark Twain

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. Second hand smoke should be avoided, particularly for children, and laws limiting second hand smoke exposure encouraged.

Regulatory Standards

On March 21, 2000, the U.S. Supreme Court ruled that the U.S. Food and Drug Administration did not have the authority to regulate tobacco. New laws are being considered by the US congress that would give the FDA expanded authority to regulate nicotine and tobacco products. As of 2018, 169 states have signed the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC), which governs international tobacco control.

Recommendation and Conclusions

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 second and third hand smoke exposure should be encouraged. Most importantly don't use a product the internally puta toxicparticles in your lungs.

More Information and References

Slide Presentation

- A Small Dose of Nicotine presentation material and references online:
  Power point slides contains presentation material related to the health effects of nicotine.

European, Asian, and International Agencies

- England – Department of Health - Health matters: smoking and quitting in England. Online: https://www.gov.uk/government/publications/health-matters-smoking-and-quitting-in-england/smoking-and-quitting-in-england (accessed: 15 March 2020).

- Society for Research on Nicotine and Tobacco. Online: <http://www.srnt.org/> (accessed: 15 March 2020).
  "he Society for Research on Nicotine & Tobacco (SRNT) is the only professional association dedicated exclusively to the support of researchers, academics, treatment professionals, government employees, and the many others working across disciplines in the field of nicotine and tobacco research."

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  Covers tobacco and international efforts to track and reduce use of tobacco.

- Global Information System on Tobacco Control (GISTOC) . Online. Available HTTP: https://www.who.int/tobacco/global_data/en/ (accessed: 15 March 2020). "Tobacco Free Initiative (TFI) is working to set up a global information system on tobacco control."

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- Health Canada – Tobacco. Online: < https://www.canada.ca/en/health-canada/services/health-concerns/tobacco.html > (accessed: 15 March 2020). Heath Canada information on the health effects of tobacco products.

- US Centers for Disease Control and Prevention (CDC). Online: <http://www.cdc.gov/tobacco/> (accessed: 15 March 2020). US CDC site has multiple listing on health, tobacco and nicotine.

- US National Institute on Drug Abuse (NIDA). Online: https://www.drugabuse.gov/drugs-abuse/tobacconicotine-vaping (accessed: 15 March 2020). US NIDA site has general information on Tobacco, Nicotine, and E-Cigarettes.

- US Medline plus – Smoking Tobacco. Online: https://medlineplus.gov/smoking.html (accessed: 15 March 2020). Site has many good reference on smoking tobacco.

- Odani S, Armour BS, Graffunder CM, Willis G, Hartman AM, Agaku IT. State-Specific Prevalence of Tobacco Product Use Among Adults — United States, 2014–2015. MMWR Morb Mortal Wkly Rep 2018;67:97–102. DOI: http://dx.doi.org/10.15585/mmwr.mm6703a3external icon

Non-Government Organizations

- Neuroscience for Kids – Nicotine. Online: http://faculty.washington.edu/chudler/nic.html. (accessed: 15 March 2020). Addresses the health effects of smoking tobacco and nicotine.

- Tobacco and Nicotine – The Vaults of Erowid. Online: <http://www.erowid.org/plants/tobacco/tobacco.shtml> (accessed: 15 March 2020).
- Site has a wide range of information on tobacco and nicotine.

- Tobacco Portal - https://tobacco.publichealth.gsu.edu/resources/data (accessed: 15 March 2020) A resource center providing links to tobacco related data, reports, scientific information and publications.

- e-cigarettes. Wikipedia https://en.wikipedia.org/wiki/Electronic_cigarette - (accessed: 18 July, 2020).

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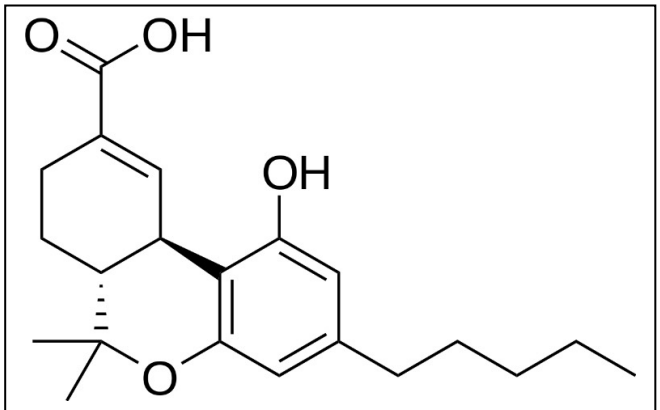
A Small Dose of Marijuana
Or
An Introduction to the Health Effects of Cannabis (or Marijuana)

By Steven G. Gilbert, PhD, DABT



Tetrahydrocannabinol
(Active chemical in Marijuana)

Dossier

Name: Marijuana (THC, CBD)
Use: drug in leaves, smoke, or chewing
Source: Planted many varieties
Recommended daily intake: none (not essential)
Absorption: lung – quick route to the brain - seconds, skin, stomach much slower 30+ minutes
Sensitive individuals: fetus, children
Toxicity/symptoms: dependency producing, acute effects: nausea, vomiting, salivation, diarrhea, dizziness, mental confusion, weakness
Regulatory facts: Federal vs State regulations

- Federal: classified as Schedule I drug, with a high potential for abuse and no accepted medical use
- Many states have decriminalized cannabis and openly allow the sale of THC and various CBD products

General facts: long history of use; most widely used drug, over 100 chemicals in typical plant
Environmental: growing demand
Recommendations: use with caution, avoid if considering pregnancy

In prospective

“If we are going to live so intimately with these chemicals eating and drinking them, taking them into the very marrow of our bones-we had better know something about their nature and their power.”
Rachel Carson, *Silent Spring*

Ten Dollar Bill Made From Hemp

Hemp farming

In 1914 the first Federal Reserve Bank note were issued after being printed on hemp paper. The front side depicted Andrew Jackson, slave owner and president (1829-1837) above the signature of Andrew Mellon, the Secretary of the Treasury under multiple presidential administrations. Mellon was one of the richest people in the US and head of several banks and oil companies, including Standard Oil, which is today Exxon Mobile, one of the the world’s largest oil companies. He was also the uncle of Harry Anslinger, the first leader of the Federal Bureau of Narcotics, 1931-1961. Anslinger champing of Cannabis and Hemp Prohibition was a great cheerleader of the Reefer Madness misinformation campaign and the primary person responsible for marijuana prohibition. The back of the bill depicted a farming scene on the left half and an early industry scene complete with smoke pollution pouring out of smoke stacks. The hemp *Farming*, a scene in Manchester Township, York County, Pennsylvania, was engraved by Marcus W Baldwin. Hemp was a useful and important commodity.

Introduction to Cannabis / Marijuana

The Cannabis plant, often referred to as Marijuana, is truly a marvel, a natural wonder, which has made it very hard to control or regulate. It also provides a fascinating look into humans as the attempt to regulate the use of a recreational substances. The plant fiber, used for rope, and cloth about 10,000 years ago is usually called hemp. The age a

first use makes hemp one of the first plants purposefully cultivated by humans. The use as a recreational occurred about 2,700 BCE by the Chinese. The use of Cannabis as a medicine and mind altering plant attacked a wide range interests from religious and government officials. Acceptance of cannabis by the rulers of society and the general people varied enormously depending on location and culture.

History Cannabis

A quick search of the web on marijuana or cannabis produce all kinds of information on the use and misuse of the cannabis plant. Below lists just a few of the highlights from a far more extensive events involving cannabis.

Time line

- 8000 BCE: used to make cloth and rope
- 2700 BCE: first Medicinal or ritual purposes by Shen Nung a father of Chinese medicine
- 1484: Pope Innocent VIII labels cannabis as an unholy sacrament of the satanic mass and issues a papal ban on cannabis medicines
- 1563: Queen Elizabeth I ordered land owners with 60 acres or more to grow cannabis or face a fine
- 1500s: mandatory cultivation of Hemp ordered throughout the New World, ordered all families to plant one teaspoon of hemp seed.
- In preparation of war, mandatory cultivation laws were passed, and colonist increased their production of Hemp, for paper and clothes
- 1911: variety of states ban cannabis/Marijuana – effectively setting up the drug wars
- 1914: harvesting of hemp depicted on ten dollar bill hat was oriented on hemp paper
- 1937:The Marihuana Tax Act of 1937 affectively outlawed marijuana on the national levels
- 1970: The Controlled Substances Act is enacted. Cannabis is classified as a Schedule I drug, with a high potential for abuse and no accepted medical use, thereby prohibiting its use for any purpose.
- 1973: Oregon became the first state to decriminalize cannabis, variety of states follow this lead
- 1996: California became the first state to legalize medical cannabis with the approval of a voter Proposition 215
- 2012: Colorado and Washington become the first two states to legalize the recreational use of cannabis, many states follow these examples
- 2018: The 2018 farm bill legalizes low-THC hemp nationwide and effectively releases hemp-derived cannabidiol (CBD) from the Controlled Substances Act
- 1972: President Richard Nixon opposes the policy of cannabis decriminalization.

- 1977: President Jimmy Carter endorses legislation to federally decriminalize cannabis, declaring that "Penalties against possession of a drug should not be more damaging to an individual than the use of the drug itself."
- 1980: Presidential candidate Ronald Reagan warns that "Leading medical researchers are coming to the conclusion that marijuana ... is probably the most dangerous drug in the United States."

(Some of the historical timeline markers were taken from Wikipedia "Timeline of cannabis laws in the United States". https://en.wikipedia.org/wiki/Timeline_of_cannabis_laws_in_the_United_States)

Mechanism of Action

The primary neuroactive compound in Cannabis is Tetrahydrocannabinol (THC). THC is one of over 100 cannabinoids produced by cannabis. Depending on the stain of cannabis the plan may have approximately 3 to 20% of THC. There is some evidence that THC can reduce nausea and vomiting during anticancer drugs, improve appetite in people with HIV/AIDS, or to treat chronic pain and muscle spasms. Treatment of other condition have been proposed but there has been on limited studies do to restrictions applied by many governments.

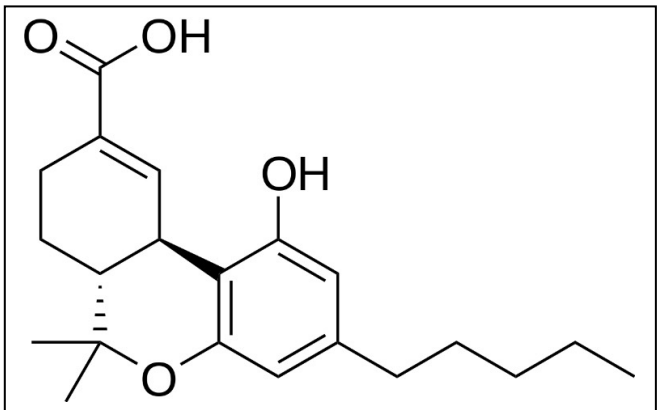


Figure 2. Nicotine.
((*S*)-3-(1-Methyl-2-pyrrolidinyl)pyridine)

The recreational effects of Cannabis are well know to 100s of million people around the world. US Federal lists THC as a Schedule I by US federal law under the Controlled Substances Act for having "no accepted medical use" and "lack of accepted safety". However, dronabinol, a manufactured pharmaceutical form of THC, has been approved by the FDA as an appetite stimulant for people with AIDS and an antiemetic for people receiving chemotherapy. This controversy between legal vs illegal Cannabis has been going for centuries. Schedule I by US federal law[15] under the Controlled Substances Act for having "no accepted medical use" and "lack of accepted safety". However, dronabinol, a pharmaceutical form of THC, has been approved by the FDA as an appetite stimulant for people with AIDS and an antiemetic for people receiving chemotherapy.

There is no lethal dose of THC. Dogs and monkeys were given 9,000 mg/kg with no lethal effects.

The mechanism of action of THC and other cannabinolds depends on the cannabinold receptors CB1 and CB2. Both of these receptors are agonist to THC and CBDs, which means that THC and CBD stimulate the activity of the receptors. CB2 is mainly expressed in cells of the immune system. The mechanism of action of THC and indeed the whole

class of these compounds is complex and not well understood. THC is metabolized primarily in the liver by the cytochrome P450 enzyme system. Approximately 100 metabolites have been identified with many still psychoactive. THC is excreted primarily in the feces (about 50%) and about 29% in the urine.

Consumption of Cannabis

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The consumptions usually by inhalation(smoking or vaporizing) or by ingestion (food or drink). All consumption involves heating the plants Tetrahydrocannabinolic acid (THCA, 2-COOH-THC) which is a precursor of tetrahydrocannabinol (THC), the main active component of cannabis. It is important to consider the different methods of consumption and the effects it has on absorption of the THC and neuroactive experience. The acute effects of Cannabis or THC are best experienced through smoking the Cannabis leaves. In this more the Cannabis is delivered directly to the brain the CB1 and CB2 receptors. You quickly receive a "rush" or "high". Cannabis can also be consumed by ingestion typically in a cookie or brownie. The Cannabis absorption through the gut is slower thus producing a more gradual "high" and subsequently raked more time to decline. No matter what properties are being considered it must be remembered that there is tremendous variability in the cannabis being consumed such as the amount of THC or other CBDs in the product.

Health or General Effects

The effects of any preparation of Marijuana varies tremendously depending in plant. The study of the medicinal or positive health effects of Cannabis has been hampered by the having a consistent stain to study as well as leg al issues. Despite these imitations some studies have shown that appetite can be improved, reduce nausea and vomiting, treat chronic pain, and quite muscle spasms. Over 30 states have medically prescribed cannabis such as dronabinol and nabilone. The ability to prescribe THC or other cannabinoids as greatly increased its medical uses.

The adverse effects that have been attributed to Cannabis have been many and often motivated by some other issue such as religion or other prejudice. Many of the medical issues associated with Cannabis may also be the result of multiple drug exposure.

Regulatory Standards

Cannabis is most commonly illegal but the rules its procession are not enforced or is illegal except for medical reasons which requires a physician's prescription. However, there are still large parts of the world where Cannabis is illegal. In the United States, the federal rules are in tension with the state rules.

Recommendation and Conclusions

The most important action is legalize Cannabis and to the needed studies to assess the both beneficial and adverse health effects. Similar to alcohol it is to easy for individuals to grow and use Cannabis.

More Information and References

Slide Presentation

- A Small Dose of Cannabis presentation material and references online:
  Power point slides contains presentation material related to the health effects of Cannabis.

European, Asian, and International Agencies

- WHO – World Health Organization – Cannabis Online :
  https://www.who.int/substance_abuse/facts/cannabis/en/ (accessed: 01 August 2020).
  Summarizes worldwide consumption of Cannabis.

North American Agencies

- Government of Canada – Cannabis in Canada-Get the facts – Online:
  https://www.canada.ca/en/services/health/campaigns/cannabis.html (accessed: 01 August 2020).

- Marijuana and Public Health - US Centers for Disease Control and Prevention (CDC). Online: https://www.cdc.gov/marijuana/health-effects.html (accessed: 01 August 2020).
  US CDC site has multiple listing on health and cannabis. (The US also uses Marijuana and Cannabis interchangeably)

  Marijuana intoxication: MedlinePlus Medical Encyclopedia. US NLM
  Online: https://medlineplus.gov/ency/article/000952.htm
- Marijuana ("pot") intoxication is the euphoria, relaxation, and sometimes undesirable side effects that can occur when people use marijuana.. Some states in the Unites States permit marijuana to be used legally to treat certain medical problems. Other states have also legalized its use. (accessed: 01 August 2020).

Resources from Washington State Department of Agriculture

- **Hemp & CBD in food** –
  - https://agr.wa.gov/departments/food-safety/food-safety/hemp-cbd-in-food
- **Recreational Marijuana**
  - https://agr.wa.gov/departments/marijuana
- **Pesticide and fertilizer use for the production of marijuana in Washington**
    - https://agr.wa.gov/departments/marijuana/pesticide-use

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Non-Government Organizations

Wikipedia resources – excellent well referenced resources

The Cannabis Portal – Online: https://en.wikipedia.org/wiki/Portal:Cannabis (accessed: 01 August 2020)
Comprehensive list of resources on Cannabis.

Cannabis (drug) – Online: https://en.wikipedia.org/wiki/Cannabis_(drug) (accessed: 01 August 2020)
Well referenced review of Cannabis from history, legal, and health effects.

Legal history of cannabis in Canada – Wikipedia Canada – Online: https://en.wikipedia.org/wiki/Legal_history_of_cannabis_in_Canada (accessed: 01 August 2020)

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Lauren M. Jansson, Chloe J. Jordan, Martha L. Velez. Perinatal Marijuana Use and the Developing. JAMA - Published Online: July 16, 2018. doi:10.1001/jama.2018.8401

A Small Dose of Pesticide
Or
An Introduction to the Health Effects of Pesticides

By Steven G. Gilbert, PhD, DABT

Dossier

Insecticides

Name: Insecticides
Use: kill insects
Source: synthetic chemistry, plants
Recommended daily intake: none (not essential)
Absorption: intestine, respiratory system (lungs), skin
Sensitive individuals: fetus, children, and elderly
Toxicity/symptoms: nervous system, range of problems depending on chemical
Regulatory facts: RfDs exist for many insecticides. Regulated by EPA.
General facts: billions of pounds used every year in agriculture, golf courses, around the home, and by commercial real estate
Environmental: pesticides are used globally; some are very persistent in the environment
Recommendations: minimize use, avoid exposure to children, and consider alternatives including Integrated Pest Management practices

Herbicides

Name: Herbicides
Use: kill or damage plants
Source: synthetic chemistry, manufactured by industry
Recommended daily intake: none (not essential)
Absorption: intestine, respiratory system (lungs), skin
Sensitive individuals: fetus, children, and elderly
Toxicity/symptoms: varies
Regulatory facts: References Doses (RfDs) exist for some herbicides. Regulated by the EPA.
General facts: long history of use; often used in combination with genetically modified plants
Environmental: widespread global use and contamination
Recommendations: minimize use, avoid exposure to children, and consider alternatives including Integrated Pest Management practices

Case Studies

Cats, dogs and fleas

Fleas are very small and annoying blood-sucking pests, capable of spreading serious human diseases. We come in contact with fleas, primarily through our cat and dog pets. 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 sucking 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 over stimulation of acetylcholine nicotinic nerves, resulting in the insect's paralysis and death. When used to control fleas, it is typically applied to the back of the animal's neck. *Imidacloprid* is absorbed through the skin and circulates in the blood. Fleas get exposed when biting and consuming the insecticide-infused blood. The average flea weighs between 0.5 mg and 1 mg, though they can double their body weight when feeding. It takes only a very small amount of the pesticide in the blood of the cat or dog to kill the flea. The flea, because of its very small size, receives a large dose relative to its body weight. 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 over exposed, 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, of that 1.2 billion pounds is used in agriculture. Worldwide agricultural pesticide use is an additional 5 billion pounds of active ingredient each year. The active pesticide chemical is often less that 1% of the material applied, so these estimates do not include other chemicals used to dissolve or apply the active pesticide chemical. These additional chemical, sometimes call 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. Commercial agriculture uses approximately 60% of pesticides and the rest is used by homeowners, commercial real estate managers, government, and industry use the rest on lawns, gardens, golf courses, and inside buildings.

The use of pesticides in large agricultural applications requires special training and knowledge to ensure that farm worker and crop picker's 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 of the insect, and can have similar effects on wildlife such as birds, and humans. Farm workers come into contact with pesticides during pesticide application or when entering the fields too soon after an application. Due to its toxicity to humans and mammals, the US EPA moved to ban all use of *carbofuran* in 2008.

Here is an example of some of the problems with *carbofuran*. *Carbofuran* pesticide is used on cotton; however there is an EPA –required 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 the worker exposure to the active ingredient. In 1998, there was an aerial application of carbofuran 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 pesticides than adults and are very vulnerable to this type of take home exposures from the workplace. For more information on this incident see the U.S. Centers for Disease Control report (MMWR, 1999).

Introduction and History

> "Chlordane: America's leading lawn and garden insecticide. Used extensively by pest control operators for termite control, because of its long lasting effectiveness." Velsicol Chemical Corporation – Advertisement – 1959
>
> U.S. EPA lists chlordane as a persistent bioaccumulative toxic chemical. In 1978, EPA cancelled use of chlordane on food crops and in 1988 all use was banned.

The function of a pesticide is usually to destroy some form of life. Many plants and animals have evolved to develop their own sophisticated natural pest resistance as protection from other plants, insects, or animals bent on doing them harm. For example, both caffeine and nicotine are naturally produced chemicals manufactured by the plants to discourage pests. Humans have learned to use these naturally occurring pesticides, such as nicotine, to protect their crops In the twentieth century new discoveries in chemical synthesis lead to a remarkable array of deadly synthetic pesticides designed to kill bacteria, fungi, plants, animals, and even other humans. The development and use of pesticides is a large and complex subject that includes chemistry, biology, environmental

fate, and governmental regulations. This chapter will provide a brief overview of this complicated group of compounds.

The two largest classes of synthetic pesticides are insecticides, which are designed to kill insects, and herbicides, which are designed to kill plants. Other major groups of pesticide compounds include fungicides, rodenticides, and antimicrobials. A word about antimicrobials, although many medications and antimicrobial products work by killing organisms such as parasitic worms, bacteria, or viruses, pharmaceuticals are not defined as pesticides and are regulated through a different mechanisms. For example, antibiotics are pesticides directed at bacteria. They are generally safe for humans and animals to consume at dosages prescribed by physicians or veterinarians. But as with many pesticides, antibiotics can cause problems. They are generally not specific to only one kind of bacteria and thus may kill helpful bacteria. Even more serious, bacteria adapt to the antibiotic and become resistant to its effects. In this chapter we will focus on the more traditional pesticides.

One of the first pesticides was sulfur, which was initially used by the Chinese in 1000 BC to control bacteria and mold (fungus). Sulfur is still widely used today. For example, 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 then as medicine (see chapter on arsenic). Arsenic trioxide was used as a weed killer in the late 1800s and lead arsenate 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. To this day some orchard soils remain contaminated with lead and arsenic. Arsenic in the form of chromated copper arsenate is used today to prevent wood that is in contact with soil from rotting.

Plants have provided several other important ‘natural’ pesticides. In the late 1600s nicotine, an extract from tobacco leaves was recognized as a potent insecticide and continues to be in limited use as a pesticide. Another group of ‘natural’ insecticides are pyrethrums, which are harvested and refined from chrysanthemums. The Strychnine tree, *nux vomica*, contains strychnine, which is used to kill rodents. Rotenone, another important insecticide and fish poison was extracted from the root of *Derris eliptica*, a climbing plant from Southeast Asia. Plant extracts are useful ways to control pests, but they are often difficult to purify and produce in large quantities. Consequently, it wasn’t until advances in synthetic chemistry and a better understanding of pest biology, did a significant increase in the use of pesticides occur.

Ready For Immediate Delivery! D.D.T., The Wonder Chemical In My-T-Kil Spray—49¢ quart – Bloomingdale's Housewares, 6th Floor

My-T-Kil spray's chief ingredient is the miraculous chemical called D.D.T. that's fronts page news. The army has already proven its success in killing mosquitoes, bedbugs, cockroaches, etc., and seeing that they stay killed! Now you can use this wonder spray containing D.D.T. to combat bugs and insects. Warning: follow directions carefully.

From a 1945 advertisement in the New York Herald Tribune

Synthetic chemistry advanced rapidly in the 1930s and by the early 40s a range of new pesticides had been developed, including organochlorines like DDT. In 1937 the first organophosphorus 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, this class of compounds was re-purposed after some additional research and development into the insecticides we would recognize today.

Along with the development of insecticides was an effort to develop new herbicides to increase food production and to use as possible warfare agents. In 1946, the first commercially available chlorine-based herbicides were marketed to kill broad-leaf 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 that disrupt plant growth. These herbicides have been extensively utilized in agriculture, to clear roadsides and rights of way. Herbicides, notably 2,4,5-T was extensively used during the warfare to clear enemy hiding places, such as the jungles of Vietnam. 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 such as DDT, bioaccumulate in the fat and will persist for a long time. Dioxin are classified as carcinogens and are known also effect the reproductive and immune systems. Dioxin contamination ultimately lead to the cancellation of 2,4,5-T by the U.S. EPA, but 2,4-D is still one of the most widely used herbicides.

We have learned through bitter experience that we need to regulate the manufacture and use of pesticides. In the United States, regulation initially focused on protecting the consumer from pesticide residue on food, but it was also apparent that protection was need for the 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), was the first attempt to require pesticides be both safe and effective. Unfortunately, this law did not provide sufficient protection for

consumers or workers. Rachel Carson's *Silent Spring*, published in 1962, explored the continued problematic use of pesticides and marks a turning point in our appreciation of the effects of chemicals on human and environmental health. In 1972 the U.S. Environmental Protection Agency was formed and given authority to register pesticides based on evaluating and weighing estimated risks and benefits. 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 acts requires an added safety factor when calculating risk to children

Both the volume of use and the amount of money spent on pesticides demonstrates our dependency on these chemicals. The EPA reported that 4.9 billion pounds of pesticide were used in the United States in 2001, which is equivalent to 4.5 pounds per person. Approximately 888 million pounds of active ingredient with 600 different compounds are included in these pesticides. In 2001, the agricultural industry used about 675 million pounds of pesticide active ingredient and another 102 million pounds were used by homeowners and by government and general industry on lawns and gardens. This use alone amounted to an expenditure of $11.09 billion, of which $7.4 billion was spent by the agricultural industry. Another 0.80 billion pounds was used for wood preservatives and 2.6 billion pounds were used in disinfectants (Table 7.1). Worldwide about 5.05 billion pounds of pesticide active ingredient was used as agricultural-based pesticides in 2001 at a cost of $31.8 billion.

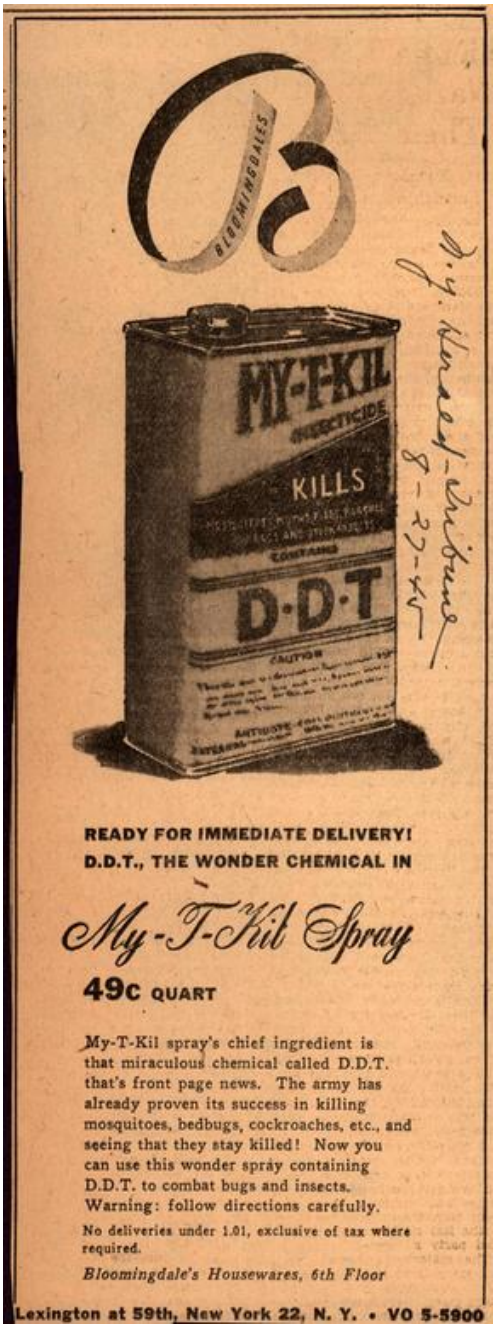


Figure 7.1 DDT advertisement

Table 7.1 Pesticide Use in the United States (2012 estimates)

	Agriculture	Industry/ Gov	Home & Garden
Herbicides	564	26	28
Insecticides	34	12	14
Fungicides	53	10	2
Fumigant	111	-	-
Sulfur & oil	122	-	-
Other	15		15

(Chlorine and hypochlorites are used in water purification)
Source: EPA Pesticides Industry Sales and Usage 2005 and 2012 Market Estiments

The history, development, toxicology, use, and regulation of pesticides make a fascinating story on many different levels. From a toxicology perspective, the principle of dose-response and individual sensitivity is demonstrated by unique sensitivity if small insects and children. The unique sensitivities of children and the subtle effects of pesticide exposure is driving the demand for more tightly regulated pesticides use and motivating efforts to reduce unintended exposures. Some communities are moving to ban the use of pesticides on lawns and landscaping and to ban the use of roadside herbicide spraying to control unwanted plant growth. People worldwide are recognizing the residual impact of pesticides on the environment. While pesticides may be needed to help protect crops and enable us to feed the world's expanding population; the challenge is to use these agents 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

Introduction

Exposures to pesticides can occur through foods, drinking water, home use of pesticides, indoor insect control, or through occupational exposure. Pesticides take advantage of two basic principles of toxicology: dose/response and individual sensitivity. They are designed to kill — and for insecticides this usually means toxicity to the nervous system – but size is important. A small amount of pesticide can be fatal to an insect, primarily

because the insect's small size and high rate of metabolism. For an insect a small exposure represents a very large dose on a body weight basis. The same small amount is relatively less harmful to an animal of much larger size because it is a small dose for the animal based on body weight. It is this same principle that makes children more vulnerable than adults to pesticides as well as their develop nervous systems. Table 6.2 illustrates how much of a chemical is need to achieve the same dose for an adult, a child, and insect. While a single exposure can be deadly, repetitive exposures to even small amounts of pesticides can cause adverse health effects.

Table 7.2 Comparison of body weight and dose

	Body Weight	Amount of chemical need for a dose of 10 mg/kg
Adult	70 kg (150 lbs)	700 mg
Child	10 kg (22 lbs)	100 mg
Insect	1 mg	0.00001 mg (1/100,000 mg)

mg = milligram, kg = kilogram

There is no perfect pesticide from the standpoint of the target organism and the unintended victims. Pesticides work by interfering with some basic biological function that is essential for life, and because all living organisms share many common biological mechanisms, pesticides are never specific to just one species. While killing a true pest, pesticides also kill other organisms that are either desirable or at least not undesirable, and we have a far from perfect understanding of what is undesirable. The ideal pesticide would be highly specific to only the target organism, be quick acting, and would degrade rapidly to non-toxic materials in the environment.

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. This means that given a sufficient exposure, insecticides will adversely affect human health. Insecticides are lethal to insects because of the high dose (exposure relative to body size). The similarities of nervous system structure make it nearly impossible to design insecticides that are highly specific for this mode of action; consequently, there are always a number of non-target organisms that may be affected by exposure. The newer insecticides are designed to be more specific and have the least amount of persistence in the environmental. We will discuss the most prominent classes of insecticides, organochlorines, pyrethroids, organophosphates, and carbamates in more detail.

Organochlorines, which include DDT, illustrate many of the challenges of insecticides. While they have the advantage of being cheap to manufacture and effective against serious target species, they have some serious unintended consequences. The chemical structure of organochlorines is diverse, but they all contain chlorine, which places them

in a larger class of compounds called chlorinated hydrocarbons. From the perspective of the nervous system, organochlorines disrupt the movement of ions such as calcium, chloride, sodium and potassium into and out of the nerve cells. Depending on the structure of the chemical, it may also have other effects on the nervous system as well. At one time organochlorines were thought to be ideal because they are very stable, persistent and slow to degrade in the environment, lipid soluble (therefore readily taken up by insects), and apparently harmless to mammals. Unfortunately it eventually became clear that the attributes of persistence and fat solubility were actually very undesirable for the environment and for mammals. Their persistence and solubility caused them to be passed up the food chain where they bioaccumulate in fat of large animals and humans and are passed on to nursing young. The global transport and use of these chemicals resulted in the contamination of wild life 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 that came in contact with these chemicals was one of the first signs of the unintended consequences of DDT. Unexpectedly, DDT caused a thinning of the birds' eggshells and resulted in the death of their developing young. Organochlorines like DDT are largely banned now in North America and Europe, but are still manufactured and used in developing countries. Organochlorine insecticides provide many important lessons about the desirable and undesirable properties of pesticides.

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 ones that would target selected species and would be less toxic to mammals. When the organophosphate parathion was first used as replacement for DDT it was believed to be an improvement as it was more specific. Unfortunately there were a number of human deaths because workers failed to appreciate parathion's greater toxicity after working with much less acutely toxic DDT.

The problem with organophosphates and carbamates is that they affect an important neurotransmitter common to both insects and mammals. This neurotransmitter, acetylcholine, is essential to the way nerve cells communicate with each other. The acetylcholine that is released by one nerve cell initiates communication with another nerve cell, but that stimulation must eventually be stopped. To stop the communication, acetylcholine must be removed from the area around the nerve cells. This class of insecticides blocks an enzyme specifically designed to remove (break down) the no-longer-needed acetylcholine. The enzyme that breaks down acetylcholine is called acetylcholinesterase and this class of insecticides is commonly referred to as acetylcholinesterase inhibitors to acknowledge that they block this enzyme. Structural differences between the various organophosphates and carbamates affect the efficiency and degree to which the acetylcholinesterase is blocked. For example, nerve gases are

highly efficient and permanently block acetylcholinesterase, while the commonly used pesticides block acetylcholinesterase only temporarily. The human toxicity of these pesticides presents significant health hazards, and researchers continue to work to develop new insecticides that have fewer unintended consequences.

One of the newer class of insecticide, pyrethroids, is loosely based upon the naturally occurring pyrethrum that is 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 organochlorines and organophosphates, 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 the sunlight.

Herbicides

Herbicides are used to kill or damage a plant and are the most rapidly growing type of pesticide. Prior to the 1930s, herbicides were non-specific and often very toxic to humans as well as other animals. In the 1930s when they were developing new insecticides, researchers discovered several chemicals that selectively killed plants. These chemicals are now widely used to increase food production by killing weeds that choke out or compete with food crops and they have been used in warfare as defoliants. Herbicides have a variety of chemical structures and mechanisms of action, so they will be discussed in only general terms here. Interested readers are referred to the many web sites and the extensive research literature on herbicides (see below and the presentation).

The most famous (or infamous) of herbicides are the chlorophenoxy compounds that include 2,4-D and 2,4,5-T and its contaminant TCDD. This herbicide mixture, sometimes called Agent Orange in the 1960s, was widely used to kill broad-leaved plants in agriculture fields, along roadsides, and 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 they appear to interact with plant growth hormones. Improvements in the manufacturing possess of chlorophenoxy compounds and the cancellation of 2,4,5-T registration has reduced the amount of its related contaminants, such as dioxin, in the environment.

Paraquat and the related chemical diquat are nonselective herbicides that are also toxic to mammals. Occupational or accidental exposure to paraquat can occur with 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 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, that have a range of actions on plants and animals . Herbicides have become an essential part of the agriculture business and thought by some to be necessary to have the crop yields needed to feed the world's growing population. However, a serious limitation of many herbicides is their lack of specificity; in other words, herbicides can damage the crops of interest. The manufacturer of herbicides are working to address this problem and are increasingly turning to biotechnology to creategenetically modify crops that are herbicide resistant. For example, the Monsanto company produces the glyphosate-based herbicide called 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.

Fungicides, rodenticides, molluscicides

Fungicides were developed to control the fungi and mold that in various forms are all around and on us. Early fungicides were sulfur, copper sulfate, and mercury based compounds. Chemical fungicides are now available for both medical treatment of human fungal disease and for use in agricultural applications. Control of plant fungus is important not only because they can damage the plant but also because some fungi produce toxic chemicals (mycotoxins) that are equally or more harmful. One of the more interesting fungi, *Aspergillus flavus*, often contaminates nuts (e.g. peanuts) and grains (e.g. corn). This fungus produces aflatoxin, which can cause liver disease and in some situations liver cancer. Another naturally occurring grain fungus produces an ergot alkaloid, which can cause hallucinations.

The chemical fungicide hexachlorobenzene was widely used in the 1940s and 1950s 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 tragic human suffering when hungry people ate the treated grains rather than planting them for crops. The use of such potentially dangerous fungicides as these can be avoided through seed harvest and storage procedures that limit contamination or by modifying environmental conditions, such as controlling humidity and temperature.

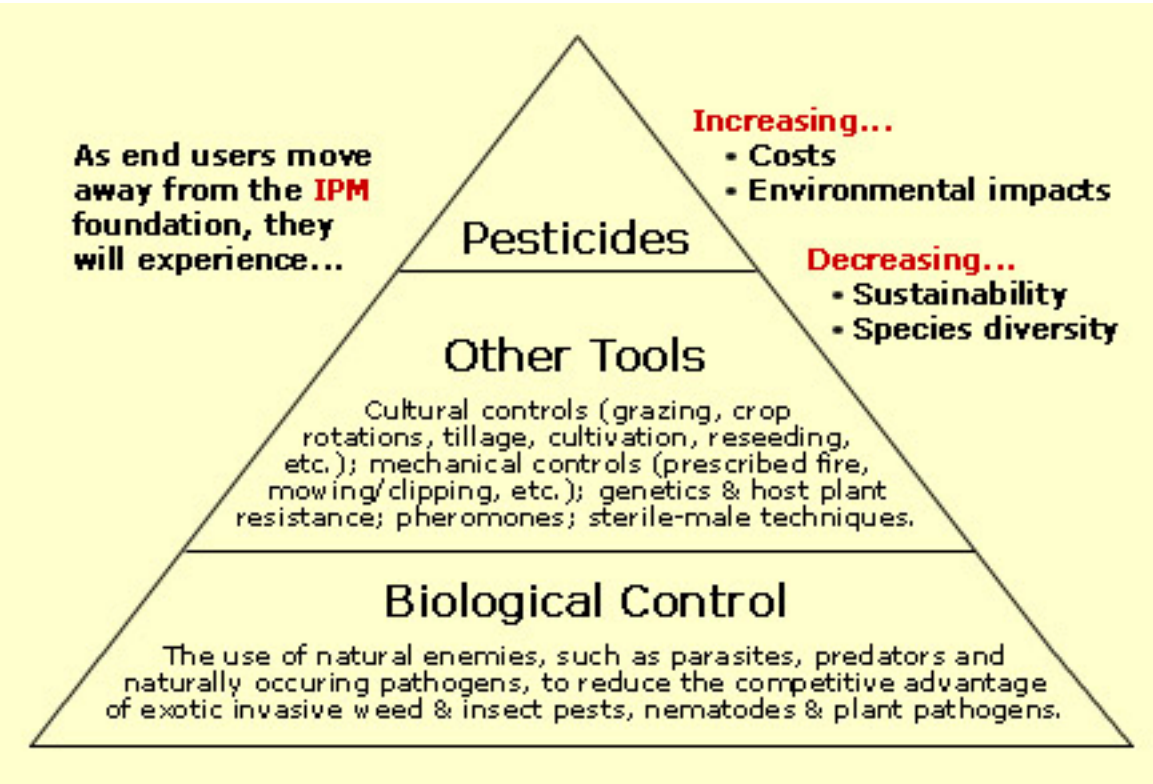
Rodenticides are a broad class of chemicals designed to kill small mammals such as rats and mice. Some rodenticides are anticoagulants and work by inhibiting blood-clotting; these are often used to control rat populations. One of the first anticoagulant rodenticides was warfarin, which is related to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

(very toxic), and thiourea based compounds. The primary alternative to using chemical rodenticides is trapping.

Molluscicides are used to control slugs and snails. Mollus are closely related to shellfish. The most common used active ingredient in molluscicides is metaldehyde, which disrupts the gastric organs of the mollus causing death. This product is often manufactured in the form of brightly colored pellets, which has the unfortunate unintended consequence of being attractive (and toxic) to children. The pellets are also attractive to other wildlife, such as dogs, cats, and birds. Some manufacturers have added a bitter agent to make the products unpalatable to children or other animals. Alternatives to using chemical molluscicides include trapping, barriers, or by designing gardens that is less attractive to slugs. Slug bait that is based on iron phosphate as the active ingredient is also available and appears to be somewhat less toxic.

Integrated Pest Management (IPM)

Integrated Pest Management (IPM) is an alternative and environmentally sensitive strategy for pest management. IPM uses the natural defense mechanisms of plants to combat pests and if necessary, uses pesticides in a highly selective manner. IPM also takes advantage of the life cycles of pests and relies careful planting of crops that are appropriate for the specific environment where they are planted. One of the goals of IPM is to minimize pesticide use and when pesticide use is necessary to use the least toxic pesticide. Pesticides can kill beneficial insects. IPM works to protect the overall ecological community, reduce human exposure to pesticides while maintaining crop productivity and plant beauty.



From: TEAM Leafy Spurge project, USDA, http://www.team.ars.usda.gov/index.html

Health Effects

Introduction

Three of the most important health related issues with regard to pesticide use are 1) worker safety, 2) effects on children, and 3) unintended effects on other species and the environment. It is also important to remember some of the basic principles of toxicology: the differences between high-dose acute exposures and chronic exposure at lower levels and the potential impact on health related to the different routes of exposure (review Chapter 1).

All species have certain fundamental biological similarities and no matter how hard we try, pesticides cannot be designed to target just one species. Pesticides are designed to kill and because they are non-specific, they often kill or harm non target organisms, including humans. The World Health Organization estimates that there are 3 million cases of pesticide poisoning each year with up to 220,000 deaths, largely in developing countries.

Often the application of pesticides is not very precise and unintended exposures occur to other organisms in the general area of the pesticide application. Children, and indeed any young and developing organisms, are particularly vulnerable to the harmful effects of a pesticide. The consequence of even low levels of exposure during development is not well understood but may have adverse health effects.

Pesticide exposure can result in 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. Pesticide exposure also can result in asthma, allergies and hypersensitivity. Chronic exposure to pesticides is another problem. It can result in neurological effects as well as the possibility of an increased risk of cancer. In addition, the ingredients other than the specific active ingredients (sometimes referred to as inert ingredients) in many pesticide formulations include solvents that are toxic if inhaled or can be absorbed by the skin. These 'inert' ingredients may not be tested as thoroughly as active pesticide ingredient and are seldom disclosed on product labels. Thus, workers who apply pesticides and those who may be exposed do not know all the chemicals they are exposed to.

The Natural Resources Defense Council (NRDC) report, "Intolerable Risk: Pesticides in Our Children's Food" focused on the possible adverse effects of pesticides on children. The report notes that the smaller size of children relative to adults and different food consumption practices can result in the greater risk to children. 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. The use and regulation of pesticides illustrates the complexities of risk analysis and risk management and the difficulties in determining an acceptable level of exposure with acceptable risks, particularly for the wide range of populations that come in contact with these products.

Human Health Effects of Insecticides

All the major insecticides affect the nervous system so the health effects of human exposure can appear similar. Acute ingestion of organochlorines insecticides can results in a loss of sensation around the mouth; hypersensitivity to light, sound, and touch; dizziness; tremor; nausea; vomiting; apprehension; and confusion. Chronic exposure to insecticides can cause weight loss, muscle weakness, headache, anxiety and a range of other neurological complaints. DDT is an example of an insecticide that was thought to be relatively safe for humans because it was poorly absorbed through the skin. It is not uncommon to see pictures from the 1950s of people being dusted with DDT to kill insects and demonstrate its safety. Acute poisoning by oral ingestion of DDT can occur at a level of approximately 10 mg/kg which is a relatively large amount. But it was the environmental persistence, the accumulation of the insecticide in human and animal

tissue, and the effect on birds that caused DDT to be banned, along with most of the organochlorines,.

Another organochlorine insecticide worthy of individual mention is Kepone or chlordecone. In 1975, over 70 workers manufacturing Kepone in Hopewell, Virginia, developed a variety of neurological symptoms the most prominent of which became know as the "Kepone shakes". Their symptoms started about 30 days after their first exposure to Kepone. Subsequent testing also revealed a decrease in sperm count and motility. Kepone was later found to be too environmentally toxic and its use was discontinued in favor of organophosphates.

Organophosphates, while environmentally less hazardous than the organochlorines, present their own challenges. Foremost, they are toxic to mammals. Unlike DDT, organophosphates are absorbed through the skin, which can lead to problems protecting workers from exposure. Acute organophosphate 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. Usually (if the exposure is not too great) the symptoms of acute exposure decline within days after cessation of exposure as acetylcholine levels return to normal. Some organophosphates also have a delayed neurological reaction characterized by muscle weakness in the legs and arms. One example of the human health effects of organophosphates occurred during Prohibition when people consumed a homemade alcoholic drink made out of Jamacian ginger that was contaminated with the organophosphate triorthocresyl phosphate (TOCP). More than 20,000 people were affected by the condition called "ginger jake paralysis. Later research found that these effects could be reproduced in animals and the US government required testing for delayed effects as part of the registration of organophosphates. The human toxicity of organophosphates resulted in a steady decline in their use as new alternatives were developed.

Among the most promising alternatives were synthetic pyrethroids. However, pyrethroids, cause hyper-excitation, aggressiveness, uncoordination, whole-body tremor, and seizures. Acute exposure in humans, usually resulting from skin exposure due to poor handling procedures, usually resolve within 24 hours. While not particularly toxic to mammals, they can cause an allergic skin response in humans. Some pyrethroids may cause cancer, reproductive or developmental effects, or endocrine system effects.

Human Health Effects of Herbicides

Herbicides are designed to kill plants, not animals, and in general are 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 contaminants in the active chemical ingredient. There is an enormous amount of animal and some human toxicity data on 2,4-D and 2,4,5-T, but it

now appears that much of this toxicity was caused by the contaminant dioxin (or TCDD). Military personnel and others exposed to Agent Orange, which was often contaminated with TCDD, reported birth defects, cancers, liver disease, and other illness. These concerns lead to improvement in the manufacturing process to reduce TCDD contamination and ultimately lead to a reduction in use of 2,4-D herbicides.

There is also concern that some herbicides may affect wildlife. 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 at over 70 million pounds per year. Persistence of herbicides may also contaminate surface and ground water. There is an ongoing need for more alternatives to the use of herbicides.

Human Health Effects of Other Pesticides

Fungicides have caused a number of human health disasters. In the late 1950s, approximately 4,000 people in Turkey were poisoned by hexachlorobenzene that had been applied to seed grain to protect against soil fungus. Adults and particularly children who inadvertently ate the treated seed grain developed diseases of the skin and bone. In Iraq, a similar incident occurred when people consumed grain coated with a mercury based fungicide.

Rodenticides are clearly designed to kill mammals and thus (with the exception of thiourea compounds) are toxic to humans. Contact with these compounds should be avoided as much as possible. Environmental concerns occur when other animals consume a poisoned rodent and are in turn poisoned. Eagles, wolves, and other animals that eat rodents and are high in the food chain are particularly vulnerable.

Reducing Exposure

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.

Individually and collectively we need to examine our use of all forms of pesticides and consider alternatives to the 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. Storage and proper disposal of pesticides also deserves special attention. Pesticide use around the home should be avoided as much as possible and consideration given to non-chemical methods of pest control. Integrated pest management (IPM) is an approach

that can significantly reduce pesticide use through prevention, monitoring, and less-toxic choices. Widely used in agriculture, landscape maintenance, and structural pest control, IPM can also be practiced by individuals in and around their homes. An IPM approach stresses proper food-waste management, landscape design, plant selection, natural pest controls, and physical controls such as traps, barriers, and mechanical removal.

Regulatory Standards

Experience has clearly demonstrated to the need to regulate pesticide use. In the United States, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) was passed in 1947 and allowed the U.S. Department of Agriculture to regulate appropriate labeling of pesticides. Later the U.S. Food and Drug Administration was given responsibility to ensure that food supply was safe from pesticides. In 1972, the administration of FIFRA was transferred to the U.S. Environmental Protection Agency. 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.

Recommendation 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 attributes, these chemicals are not without their problems. There are several known and potential risks with the use of pesticides and more research needs to be done to find and test alternatives as well as to develop pesticides that do a better job targeting particularly species. Work also needs to be done to develop pesticides that cause the least amount of environmental damage. Businesses, schools, institutions, and the home gardeners that use pesticides should explore integrated pest management (IPM) methods to reduce pesticide use. An ongoing problem is the lack of data on the use of pesticides in agriculture, business or home. 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 effects and the unintended effects on the environment.

More Information and References

Slide Presentation

- A Small Dose of Pesticide presentation material and references online:
- www.asmalldoseoftoxicology.org
- Web site contains presentation material related to the health effects of pesticides.

European, Asian, and International Agencies

- European Union – Chemical and Pesticide Information. Online: <https://ec.europa.eu/food/plant/pesticides_en > (accessed: 02 September 2020). European site contains policy and other information on the use of pesticides in agriculture.

- World Health Organization - WHO Pesticide Evaluation Scheme (WHOPES). Online: <https://www.who.int/whopes/resources/en//> (accessed: 02 September 2020).
  WHOPES is an "international programme which promotes and coordinates the testing and evaluation of new pesticides proposed for public health use."

  World Health Organization - WHO Pesticide Information Online: < https://www.who.int/topics/pesticides/en> (accessed: 02 September 2020).
  WHO high level information on international use and health related to pesticides.

- International Programme on Chemical Safety (IPCS). Online: <http://www.who.int/pcs/index.htm> (accessed: 02 September 2020).
  "IPSC main roles are to establish the scientific basis for safe use of chemicals, and to strengthen national capabilities and capacities for chemical safety."

North American Agencies

- Health Canada – Pesticides and Pest Management. Online: <https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management.html> (accessed: 02 September 2020). Health Canada provided a range of information on pesticides in English and French.

- U.S. Environmental Protection Agency (EPA) - Office of Pesticides Programs (OPP). Online: <http://www.epa.gov/pesticides/> (accessed: 02 September 2020).
  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." (2008).

- U.S. Geological Survey – National Water-Quality Assessment (NAWQA) Program. Pesticides and Water Quality Online: <http://water.usgs.gov/nawqa/pnsp/> (accessed: 02 September 2020).
  NAWQA provides an assessment water use in the U.S. and of pesticides in the streams, rivers, and ground water of the United States.
  Also - Estimated Annual Agricultural Pesticide Use – maps and graphs https://water.usgs.gov/nawqa/pnsp/usage/maps/ (accessed: 02 September 2020).

- California Department of Pesticide Regulation. Online: <http://www.cdpr.ca.gov/> (accessed: 02 September 2020).
  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."

Non-Government Organizations

- Pesticide Action Network North America (PANNA). Online: <http://www.panna.org> (accessed: 04 September 2020).
  "PANNA works to replace pesticide use with ecologically sound and socially just alternatives."

- Pesticide Action Network International (PANI). Online: <http://www.pan-international.org/> (accessed: 04 September 2020).
  "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)."

- Pesticide Database site – by Pesticide Action Network North America (PAN). Online: <http://www.pesticideinfo.org/> (accessed: 04 September 2020).
  "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."

- National Pesticide Information Center (NPIC) Call 1-800-858-7378. Online: <http://npic.orst.edu> (accessed: 04 September 2020).
  NPIC provides objective, science-based information about pesticides and pesticide-related topics to enable people to make informed decisions about pesticides and their use. NPIC is a cooperative agreement between Oregon State University and the U.S. Environmental Protection Agency.

- Beyond Pesticides. Online: <http://www.beyondpesticides.org/> (accessed: 04 September 2020).
  Beyond Pesticides is a national network works with allies in protecting public health and the environment to lead the transition to a world free of toxic pesticides

- EXTOXNET InfoBase. Online: <http://ace.orst.edu/info/extoxnet/> (accessed: 04 September 2020).
  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.

Integrated Pest Management (IPM) Principles

- U.S. Environmental Protection Agency (EPA) - Integrated Pest Management (IPM) Principles. Online: <https://www.epa.gov/safepestcontrol/integrated-pest-management-ipm-principles> (accessed: 04 September 2020).
  Defines IPM principles and provides additional resources.

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A Small Dose of Lead

Or

An Introduction to the Health Effects of Lead

By Steven G. Gilbert, PhD, DABT

Dossier

Name: Lead (Pb)
Use: batteries, old paint, stabilizer in PVC, hobbies, solder, toys, X-ray shielding, smelters, and previously in gasoline and pesticides
Source: home, paint, dust, toys, children hands to mouth, workplace, ethnic health remedies
Recommended daily intake: none (not essential)
Absorption: intestine (50% children, 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
Regulatory facts: air - 0.5 mg/m^3, drinking water 15 μg/L, not allowed in paint or automobile gasoline, 0.15 μg/m^3 air standard
General facts: long history of use, major problem in paint of older housing, areas around old smelters can be contaminated
Environmental: global environmental contaminant
Recommendations: avoid, wash hands, wash kids hands and toys, phase out uses in PVC plastics, child products, remove old lead-based paint

Case Studies

In the 2nd century BC, Dioscorides noted, "Lead makes the mind give way". Despite this warning, the seemingly endless uses of lead have repeatedly brought it into daily use and widespread distribution. In modern times, lead was heavily used in paint and as a gasoline additive. The subtle brain damage that even low levels of lead exposure causes in children was recognized and acted upon only in the last 30 years. It is now well documented that even blood levels below 10 μg/dL can harm the developing brain, robbing children of their intellectual potential. As the following case studies demonstrate lead remains a serious concern.

Take home lead - 1998

In 1998 a California (MMWR, 2001) mother requested a blood lead level determination for her 18-month-old child. The result was a blood lead level (BLL) of 26 μg/dL, which was well above the Center for Disease Control's (CDC) recommended criterion for clinical case management. It was subsequently found that the father had a BLL of 46 μg/dL, which was above the Occupational Safety and Health Administration (OSHA) requirement that worker with BLLs great 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 intellectually abilities of these children?

Lead contaminated town - 2001

The children and families of Herculaneum, Missouri have a lead problem (N.Y. Times, 2002), a big lead problem. 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 was 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 the children under 6 were found to have lead poisoning. The U.S. 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 products meant for children were highlighted by several serious incidents of lead poisoning, including one death, from ingestion of jewelry containing lead (MMWR 2004, 2006). Many of these products contain over 50% lead. These incidents resulted in the recall of hundreds of thousands of items. A report from Los Angeles County estimated that 34% of the children with elevated blood lead levels were exposed to lead-based 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 were it was used to stabilize PVC plastics. Lead was also found in the paint on imported children's toys that exceeded the standard of 0.06% lead by weight (600 ppm). 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 require the testing of children's toys for lead. Despite allow of our knowledge about the childhood health effects of lead we continue to needless exposure those most vulnerable.

Introduction and History

> If we were to judge of the interest excited by any medical subject by the number of writings to which it has given birth, we could not but regard the poisoning by lead as the most important to be known of all those that have been treated of, up to the present time.
> M.P. Orfila, *A General system of Toxicology*, 1817

Lead provides many insightful lessons for a student of toxicology, history and society. During over 8000 years of using lead, we have relearned forgotten and ignored lessons on the health effects of lead. Lead is naturally presence at very low levels in the soil and water prior to the extensive environmental distribution by people but has no beneficial biological effects. Its 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 along side 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.

Pb Lead

Atomic Number: 82
Atomic Mass 207.20

Significant production of lead began about 3000 BC and lead was first widely used by the Roman Empire. Large mines in Spain and Greece contributed to the global atmospheric redistribution of lead. Easily manipulated, lead was used by the Roman's in plumbing. 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 these 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. For thousands of years, Greenland ice has faithfully recorded the rise and fall of lead use by civilizations that came and went.

In more modern times, the durability of lead made it an excellent paint additive but the sweetness made it a tempting edible item for 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 deaths and other illness. 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 will very likely 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 the 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 was being 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 in for many children. The history of the use of lead based paint is summarized in table 8.1.

Table 8.1 - History of Lead-Based Paint

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

Adapted from Gilbert and Weiss, 2006.

> "Therefore, in contrast to popularized reports, there is no persuasive evidence that low level lead exposure is responsible for any neurobehavioral or intelligence defects. In fact, the bulk of the evidence suggests that there is no adverse impact of low level lead exposure."
> International Lead Zinc Research Organization, October 1982
>
> "Lead Poisoning remains the most common and societal devastating environmental disease of young children."
> Public Health Service - L. Sullivan, 1991

The addition of lead to gasoline is one of the greatest public health failures of the 20th century. It is a fascinating story of the intersection of big business, government and societal interests. Tetraethyl lead (TEL) was discovered in 1854 by a German chemist and in 1921 shown to reduce car engine knock by Thomas Midgley of the United States. This was a period of tremendous competition in the automobile industry and growth in the oil, gas and chemical industries in the United States. A year latter the U.S. Public Health Service issued a warning about the potential hazards associated with lead. In 1923 the Du Pont 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 Du Pont 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 die from lead poisoning at the Ethyl facility in New Jersey, although the number affected by lead exposure is unknown. In 1925 sales of TEL were suspended while the U.S. 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 U.S. contained lead, and the Ethyl Corporation was expanding sales in Europe. In the early 1950s the U.S. Justice Department investigated anticompetitive activities associated with Du Pont, 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 U.S. 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 Science 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 lead from 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. We are still living with the decisions made in the 1920s to add lead to gasoline. It is estimated that 7 million tons of lead were released into the atmosphere from gasoline in the United States alone.

Occupational exposure to lead has decreased from the overt cases of death and disability in the 1930s and 1940s, but, as the 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.

Home hobbies or business can also be a source of lead exposure. Lead is commonly used in stained glass, jewelry making, glazes on pottery, painting, soldering, making ammunition or fishing sinkers, and exposure can occur from stripping 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 goods, such as tomatoes, would leach lead from the cans. Finally, contamination of drinking water with lead occurs primarily from lead solder joints or old fixtures and occasionally lead pipe was used to bring water to a home. As with many metals, lead was used in a number of 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 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 pails. Cosmetics, such as lipstick were discovered to be contaminated with lead. Recently lead based paint was used on children's toys. Even candy and candy wrappers were found to be contaminated with lead. State and national laws were enacted to ban what seems to obvious, the sale of products meant for children that contain lead.

Biological Properties

The absorption, distribution and subsequent health effects of lead illustrate the basic principles of toxicology. Foremost is the sensitivity of the children to the adverse effects of even low levels of lead exposure and second is dose. There are many reasons why children are more sensitive to lead. Children are much smaller than adults and by weight will receive a much higher dose given the same exposure. Differences in absorption of lead also increase the sensitivity of children. Adults absorb only 5-10% of orally ingested lead while children absorb approximately 50% and can absorbed much more depending on nutrition. Children and pregnant women will absorb more lead because their bodies have a greater demand for calcium and iron, and the intestine responds by favoring their absorption. Lead substitutes for calcium and is thus readily absorbed, particularly if a diet is low in calcium and iron. Children in families of low income are often in older housing that contains lead and with a poor diet 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 blood stream it attaches to red blood cells and in the blood has a half-life of about 25 days. Lead readily cross 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 was actually 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, which can be caused by decreasing estrogen levels. 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 maker to use in correlating with developmental effects.

Health Effects

"How long a useful truth may be known and exist, befor it is generally receiv'd and practis'd on"
Benjamin Franklin - 1763

Lead is one of the most intensively studied hazardous agents of the twentieth 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 ideal 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 Figure 8.1 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).

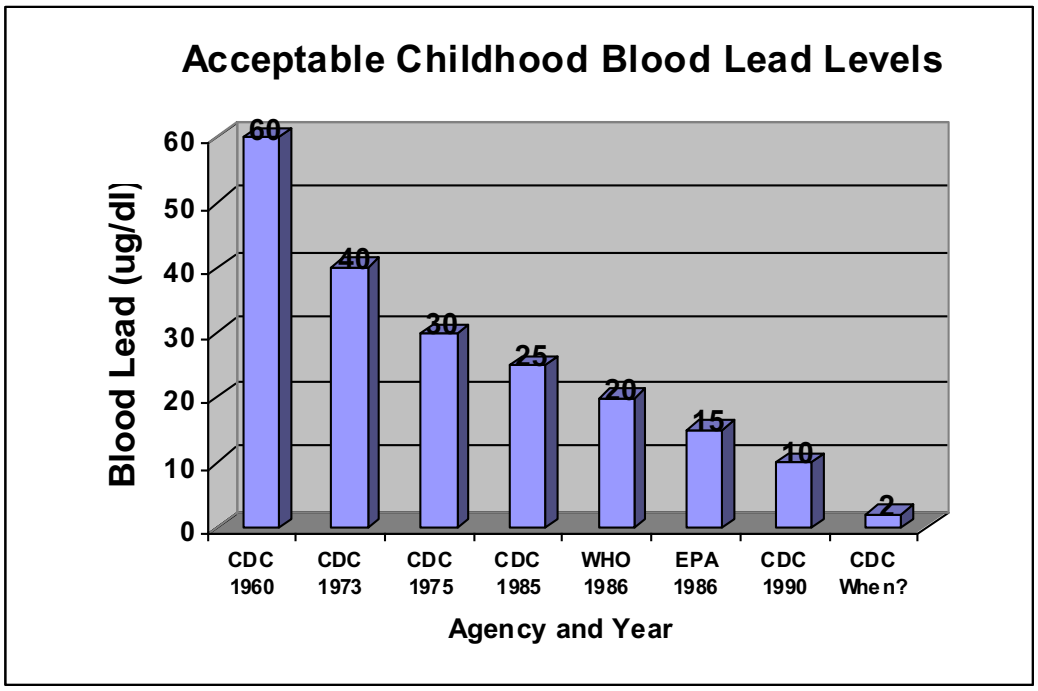


Figure 8.1 Acceptable Childhood Blood Lead Levels

The decline in acceptable childhood blood levels was a function of research and 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 (encephalophathy), possibly resulting in death. At one time it was thought the children that survived high levels of exposure would recover and have no adverse effects. 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 every 10 μg/dL increase in blood lead levels there is a 2 to 4 point IQ deficit within the range of 5 to 35 μg/dL. While a few point IQ drop my not seem like much over the entire population it is very serious and even more serious for the individuals affected. Subsequent long-term studies of infants and young children exposed to lead showed that as they became older that was an increased likelihood that they would suffer from 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 could be evaluated in the forearm 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. In adults with blood levels greater that 25 μg/dL there is evidence of decreased cognitive performance.

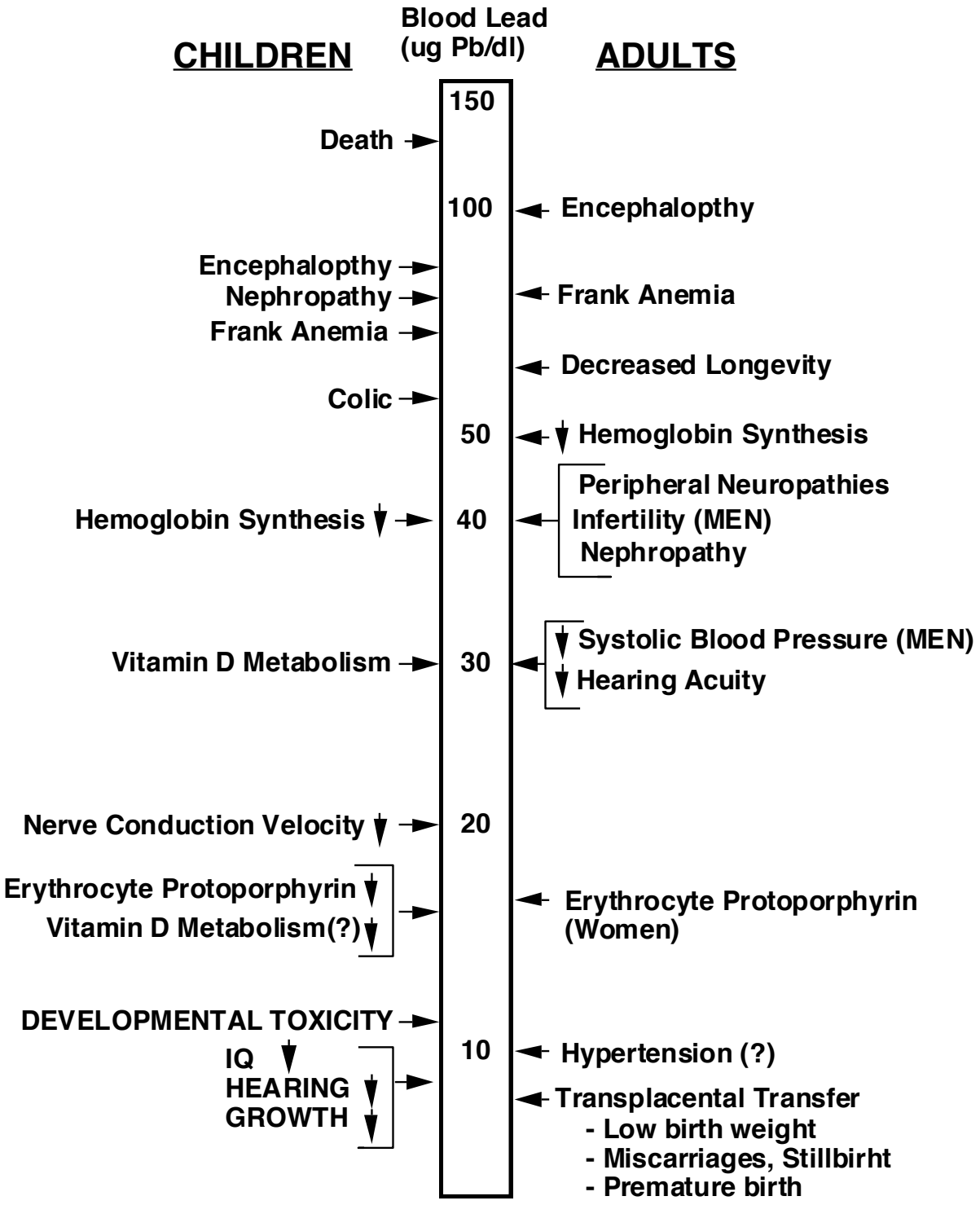
Lead exposure can produce a number of other effects. One of the most common effects is on the red blood cells. The red blood cells become fragile and hemoglobin synthesis is impaired, which results in anemia. Changes in the red blood cells and some enzymatic changes were used as a maker for lead exposure. Similar to other metals, lead adversely effects 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 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.

The fact that children are more sensitive to the effects of lead exposure is illustrated in the Figure 8.2. It is clear that amount of lead it takes to kill someone is not nearly as important as the lifetime effects on the quality of life.

Figure 8.2 Effects of Blood Lead – Children vs. Adults

EFFECTS OF LEAD -- CHILDREN vs ADULTS

(LOAEL)



Adapted from: ATSDR, 1989, by S.G. Gilbert

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. The next best thing is to be aware of potential sources of lead and take appropriate action. For example, if you are moving into an older home with young children or you 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 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. Home renovation is an important source of lead exposure. 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 down wind 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 hair coloring products that gradually hide gray hair. Tobacco contains a small amount of lead, another reason to avoid inhalation of tobacco smoke.

Regulatory Standards

Governmental agencies have set limits on lead in the drinking water and in occupational settings. State laws also exist and may be more stringent than the U.S. Federal government.

OSHA – lead in air – 0.5 mg/m^3 (milligrams per cubic meter) The OSHA standards are under review. See Shaffer & Gilbert review.
EPA maximum level for lead in public drinking water systems is 15 $\mu g/L$; EPA
EPA air lead standard 0.15 $\mu g/m^3$ rolling 3-month average

From CDC (September 7, 2020
“CDC now uses a blood lead reference value of 5 micrograms per deciliter to identify children with blood lead levels that are much higher than most children’s levels. This new level is based on the U.S. population of children ages 1-5 years who are in the highest 2.5% of children when tested for lead in their blood.

This reference value is based on the 97.5th percentile of the National Health and Nutrition Examination Survey (NHANES)'s blood lead distribution in children. The current reference value is based on NHANES data from 2007-2008 and 2009-2010."

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 a child of his or her 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 your hands frequently and taking off your shoes to reduce dust in the home.

On 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 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.

More Information and References

Slide Presentation

- A Small Dose of Lead presentation material and references online: www.asmalldoseoftoxicology.org
  Web site contains presentation material related to the health effects of lead.

European, Asian, and International Agencies

- International Programme on Chemical Safety (IPCS) - Upcoming International Lead Poisoning Prevention Week. Online: <https://www.who.int/campaigns/international-lead-poisoning-prevention-week> (accessed: 6 September 2020).

"The aim of International Lead Poisoning Prevention Week is to draw attention to the health impacts of lead exposure, highlight efforts by countries and partners to prevent childhood lead exposure, and accelerate efforts to phase out the use of lead in paint."

- Australia – Australian Government Department of the Environment, Water, Heritage and the Arts. Online: <http://www.environment.gov.au/protection/chemicals-management/lead> (accessed: 06 September 2020).
  This site provides educational material about the sources of lead and strategies for living with lead.

North American Agencies

- Health Canada - Lead. Online: < https://www.canada.ca/en/health-canada/services/environmental-workplace-health/environmental-contaminants/lead.html> (accessed: 06 September 2020).
  Health Canada provides information on the health effects of lead and remediation programs.

- U.S. Environmental Protection Agency (EPA) Office of Pollution Prevention and Toxics - Lead Program. Online: <https://www.epa.gov/lead> (accessed: 06 September 2020).
  Site has information on lead health effects and lead abatement.

- U.S. Centers for Disease Control and Prevention (CDC). Online. <https://www.cdc.gov/nceh/lead/> (accessed: 06 September 2020).
  Site has information on CDC Childhood Lead Poisoning Prevention Program.

- U.S. Department of Housing and Urban Development (HUD) - The Office of Lead Hazard Control and Healthy Homes (OLHCHH). Online: < https://www.hud.gov/program_offices/healthy_homes> (accessed: 6 September 2020).
  Site contains information on lead paint in English and Spanish.

- U.S. EPA Safe Drinking Water – Final "lead free" rule - Online: http://www.epa.gov/safewater/lead/index.html. (accessed: 06 September 2020).

- U.S. EPA The Lead Hotline - The National Lead Information Center - Phone: 1-800-424-LEAD (424-5323) - https://www.epa.gov/lead/forms/lead-hotline-national-lead-information-center (accessed: 06 September 2020).

- U.S. Department of Labor Occupational Safety & Health Administration. Online: < http://www.osha.gov/SLTC/lead/index.html> (accessed: 06 September 2020). This site addresses work place lead exposure.

- U.S. Agency for Toxic Substance Disease Registry (ATSDR). Online: < http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=22 > (accessed: 06 September 2020).
  Toxicology Profile Series – Lead - The Lead Poisoning Prevention Outreach Program funded by the Environmental Health Center (EHC).

- Washington State, Department of Ecology – Lead Chemical Action Plan. Online: http://www.ecy.wa.gov/programs/swfa/pbt/lead.html.
- Reviews the source and use of lead in Washington and make recommendation on the reduction of lead exposure. (accessed: 06 September 2020).

Non-Government Organizations

- Washington Swan Working Group - an Affiliate of The Trumpeter Swan Society - Lead Poisoning. Online: <http://www.swansociety.org/> (accessed: 07 September 2020).
  Site has information on the lead poisoning of swans.

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A Small Dose of Mercury
Or
An Introduction to the Health Effects of Mercury

By Steven G. Gilbert, PhD, DABT

Dossier

Name: Mercury (Hg) (inorganic)
Use: consumer products, industry, dental amalgams, switches, thermometers
Source: mining, environment, workplace
Recommended daily intake: none (not essential)
Absorption: inhalation, intestine poor
Sensitive individuals: fetus, children, women of childbearing age
Toxicity/symptoms: nervous system, irritability tremor, drowsiness, depression, incoordination, and tremors, (mad as a hatter)
Regulatory facts: ATSDR – MRL – Inhalation 0.2 $\mu g/m^3$
General facts: long history of use, liquid silver evaporates at room temperature, bacteria convert to organic methyl mercury
Environmental: global environmental contaminate
Recommendations: avoid, recycle mercury-containing devices

Name: Mercury (organic) (methyl mercury - $Hg\text{-}CH_3$)
Use: 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 child bearing age
Toxicity/symptoms: nervous system, developmental effects include cerebral palsy-like symptoms with involvement of the visual, sensory, and auditory systems, tingling around lips & mouth, tingling in fingers & toes, vision, hearing loss
Regulatory facts: EPA – RfD – 0.1 $\mu g/kg/day$
later – EPA 0.3 ppm advised MeHg fish tissue level for human health based upon water quality standards
FDA – 1 ppm in commercial fish
ATSDR – MRL – 0.30 $\mu g/kg/day$
Canada - 0.5 ppm Hg for retail fish and seafood

General facts: bacteria convert inorganic mercury to methyl mercury then in to food supply (bioaccumulation)

Case Studies

> *"Well, Mr. Baldwin this is a pretty kettle of fish."*
> Queen Mary of England

Minamata, Japan – Mercury and Fish

In the late 1950s the subtle and serious consequences of methyl mercury exposure became evident in Minamata, Japan. Initially, early sings of uncoordinated movement and numbness around the lips and extremities followed by constriction in visual fields in fishermen and their families baffled health experts. Developmental effects were clearly evident in infants that 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 form from a factory manufacturing the chemical acetaldehyde. Mercury was used in the manufacturing process, which also resulted both mercury and methyl mercury being 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 is left behind. 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 can be rained down to earth many miles and even counties away contributing to the global mercury contamination. The elemental mercury is converted to methyl mercury by bacteria after which it moves up the food chain, often in fish that are consumed by a range of animals and humans. Local miners, their families and particularly children suffer from mercury exposure.

Mercury coated seed grain in Iraq

The toxic anti-fungal 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 twentieth century, seeds were coated with organo-mercury compounds to reduce their destruction by fungus in the soil. Often these seeds were pink colored to indicate they were coated with an anti-fungal agent and were for planting only, not consumption. During the early 70s, a severe drought in Iraq resulted in a loss of seed grain as people struggled with malnutrition. Pink-colored mercury-coated seed grain was shipped to Iraq to 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 mercury containing interior latex paint. 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 this 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 6 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.

Introduction and History

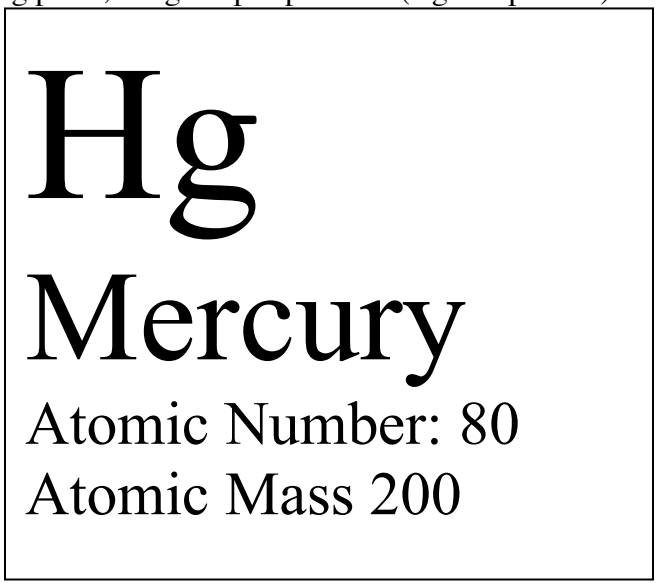
Mercury exists in different forms with very different properties; thus each section of this chapter is divided into inorganic mercury – the common silvery liquid – and organic mercury (usually methyl mercury – $Hg\text{-}CH_3$) that is generated from mercury and accumulates in some commonly consumed 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 and 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, with 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, in precious metal extraction from ore. Elemental mercury has 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 in red ink before 1000 BC, and 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 U.S. Census Bureau reported 5.2 million pounds of hatter's fur used in the production of over 30 million felt-hat bodies among 140 factories in the United States, and a study of 25 Connecticut hat factories demonstrated evidence of chronic mercurialism among 59 of 534 hatters.

Figure 9.1 The Mad Hatter

Peruvian Incas used elemental mercury to wash gold-bearing gravel as early as 1557. The original extraction process, which took place over 20 to 30 days, underwent subsequent modification, leading to the ability to extract gold in a pan over a fire in less than 6 hours by the 1830s. With some modifications this process continues to be used to this day, especially in Central and South America, Africa, and the Philippines, where it requires approximately 3 to 5 kg of mercury 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 1830's 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 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 women of child bearing and children not to use mercury based dental amalgams. The U.S. FDA while taking no position on this

> Wipe off this glass three times.
> There is arsenic in it.
> I hear messages from God
> through the fillings in my teeth.
>
> Anne Sexton (1928–1974)

issue is requesting additional information and is 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 be achieved if the thermometers were broken in this enclosed environment. 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 municipal solid waste stream.

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 scales 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 Minamata Factory used mercuric chloride absorbed onto activated carbon for the production of vinyl chloride from acetylene and hydrogen chloride. It is these processes that directly led to the contamination of Minamata Bay and the Agano River, and Niigata by mercury effluent. This discharge resulted in the 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 this 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 microgram per m3 concentration recommended by the Agency for Toxic Substances and Disease Registry.

Biological Properties

Inorganic Mercury

Inorganic mercury can also be in the form of salts as either monovalent (Hg+, mercuric) or divalent (Hg2+, mercurous). 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.

When mercury vapor from elemental mercury is inhaled, it is readily and rapidly absorbed into the blood stream, easily crosses 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, will result in mercury accumulation in the nervous system.

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. Organomercurials have been used as fungicides, as paint preservatives, and in medicinal applications, though these uses have ceased as a result of their recognized neurotoxicity. Therefore, fish and marine mammal consumption are the primary sources of human MeHg exposure, and to a lesser degree research applications of MeHg and other organomercurials.

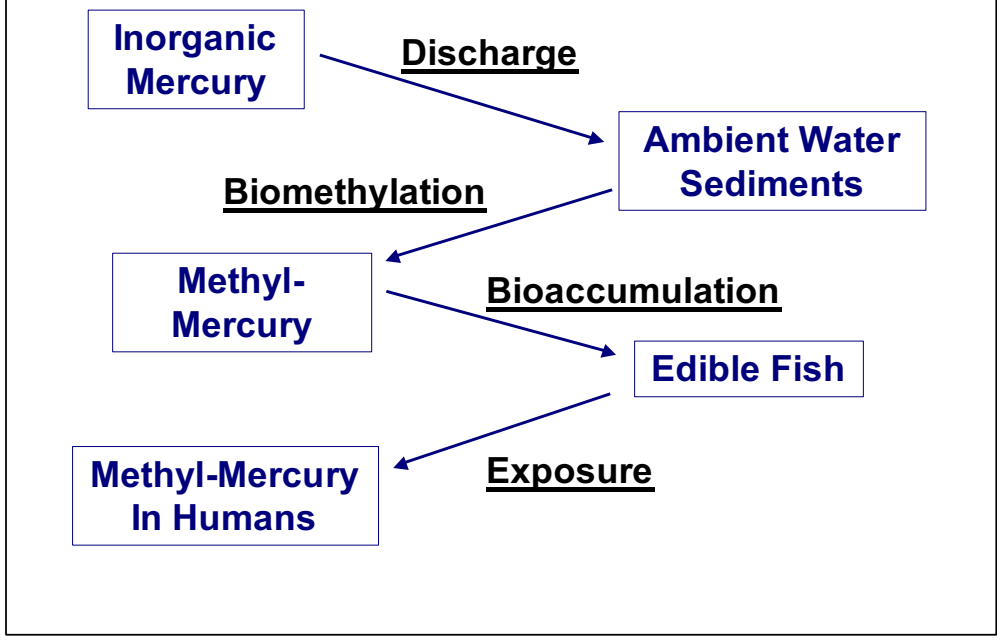


Figure 9.2 Mercury to Methylmercury

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.

Either acute, high dose or 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 Mad Hatter in Lewis Carol’s, “Alice’s Adventures in Wonderland.” Decreased performance on memory tests and verbal concept formation has 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 1950's, 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 2150 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 to establish. Difficulties in making an association arose 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, relative to adults, 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 was 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 death of 459 at the time of the study (Table 9.1).

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

A U.S. National Research Council report states "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	1953-60	1000
Nigata	1964-65	646
Guatemala	1963-65	45
Ghana	1967	144
Pakistan	1969	100
Iraq	1956	100
Iraq	1960	1,002
Iraq	1971	40,000
On-going	2001	???

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 avoid exposure, especially 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 also 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 is does not seem like much until it is multiplied by the 105 million house holds 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 in general reduce the use of mercury. As individuals, we must also work to insure 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 do NOT use a vacuum cleaner to clean up the mercury. A vacuum cleaner will only warm and disperse the mercury in the room. Collect all the mercury and place in a sealed container and take to an appropriate disposal site. If it is large spill professionals must be called.

Table 9.2 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 child bearing age should be cautious about consuming fish know to accumulate mercury such as tuna, shark, swordfish, and pike. Local fish consumption advisories should be followed

Regulatory Standards

Inorganic –Mercury

The liquid silver inorganic mercury evaporates into the atmosphere. When inhaled, mercury cross move easily into the blood and then to the brain, thus the primary hazard concern is from inhalation. Metallic mercury is poorly absorbed after oral ingestion, thus much less hazardous than inhalation. Below are some of the advisories on mercury vapor inhalation.

- ATSDR – Minimal Risk Level (MRL) – 0.2 $\mu g/m^3$
- 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 (neurotoxic) and developmental effects. Exposure limits and fish consumption advisory are directed at pregnant women, women of childbearing age and children. All agencies also recognize the fish consumption has many nutritional benefits and is an important part of many peoples diet. Nevertheless, the widespread distribution of mercury and subsequent bioaccumulation of methyl mercury requires that many agencies have developed recommendation for levels of mercury in fish. 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 the 7% of the women of child bearing 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 (U.S.)

- 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.

See: http://www.doh.wa.gov/fish/FishAdvMercury.htm

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 the sensitive developing nervous system. 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 mercury. Mercury use in consumer products, such as thermostats, thermometers and jewelry should be eliminated and replaced with already well-established 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 on going monitoring of mercury contamination in fish and appropriate advisories issued to protect sensitive populations. This will involve education of the consumer about limiting the consumption of fish that accumulate mercury.

Summary of Recommendations on Mercury

- Reduce global environmental release
- Restrict global production and sale and use
- Clean up contaminated sites
- Reduce mercury emission from coal fired electric power facilities
- Reduce or eliminate use in consumer products (cars, thermometers, thermostats, jewelry)
- Advise women of childbearing age on fish consumption
- Monitor mercury levels in fish

More Information and References

Slide Presentation

- A Small Dose of Mercury presentation material and references online: www.asmalldoseoftoxicology.org
  Web site contains presentation material related to the health effects of mercury.

European, Asian, and International Agencies

- United Nations Environment Program's Global Mercury Assessment 2018. Online: <https://www.unenvironment.org/resources/publication/global-mercury-assessment-2018> (accessed: 08 September 2020).

This program aims to develop a global assessment of mercury and its compounds, including an outline of options for addressing any significant global adverse impacts of mercury.

- World Health Organization – Elemental Mercury and Inorganic Mercury: Human Health Aspects. Online: http://www.inchem.org/documents/cicads/cicads/cicad50.htm (accessed: 08 September 2020).
  Document on human health aspects of inorganic and organic mercury.

North American Agencies

- Health Canada - Mercury. Online: < https://www.canada.ca/en/health-canada/services/healthy-living/your-health/environment/mercury-human-health.html > (accessed: 08 September 2020).
  Health Canada provides information on the health effects and environmental distribution of mercury.

- Health Canada - Mercury - information sheet < https://www.canada.ca/en/health-canada/services/chemical-substances/fact-sheets/chemicals-glance/mercury-compounds-public-summary.html > (accessed: 08 September 2020).
  Health Canada provides information on the health effects of mercury..

- U.S. Food and Drug Administration (FDA) – Mercury and Methylmercury. Online: https://www.fda.gov/food/metals-and-your-food/mercury-and-methylmercury (accessed: 08 September 2020).
  Site has recent FDA consumer information on Mercury and Methylmercury.

- U.S. Environmental Protection Agency (EPA)

  1. EPA – Main site on Mercury. Online: <http://www.epa.gov/mercury/> (accessed: 08 September 2020).

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  3. EPA (1997). Mercury Study Report to Congress. Office of Air Quality Planning and Standards and Office of Research and Development. EPA-452-R-97 –003 through –010 (Volumes I-VIII0. Online: <https://www.epa.gov/mercury/mercury-study-report-congress> (accessed: 08 September 2020).

4. EPA Integrated Risk Information System. Online: <https://www.epa.gov/iris> (accessed: 08 September 2020)

- U.S. Agency for Toxic Substance Disease Registry (ATSDR) – Toxicology Profile Series on Mercury. Online: http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=24 (accessed: 08 September 2020).
  ATSDR produces toxicology profile documents on many compounds including mercury.

- U.S. Department of Labor - Occupational Safety & Health Administration (OSHA). Online: <http://www.osha.gov/> (accessed: 08 September 2020).

- U.S. Geological Survey (USGS). Online: https://www.usgs.gov/science-explorer-results?es=mercury (accessed: 08 September 2020).
  Site has maps and supply information on mercury.

- U.S. National Research Council (NRC) – EPAs Methylmercury Guideline Is Scientifically Justifiable For Protecting Most Americans But Some May Be at Risk. Online: <http://www.nationalacademies.org/publications/> (accessed: 08 September 2020).
  The full NRC report on mercury can be read on the web, search on methylmercury.

- Washington State Department of Health – Fish Facts for Health Nutrition. Online: <http://www.doh.wa.gov/fish/> (accessed: 08 September 2020).
  Site has information on Washington State's advisory of fish consumption and mercury.

- Washington State Department of Ecology – Mercury Reduction in Washington – Including the Mercury Chemical Action Plan. Online: http://www.ecy.wa.gov/mercury/ (accessed: 08 September 2020).
  Comprehensive information on uses and release of mercury in Washington and efforts to reduce mercury use and release. .

Non-Government Organizations

- The Mercury Policy Project (MPP). Online: <http://www.mercurypolicy.org/> (accessed: 13 September 2020).
  "MPP works to raise awareness about the threat of mercury contamination and promote policies to eliminate mercury uses, reduce the export and trafficking of mercury, and significantly reduce mercury exposures at the local, national, and

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Methylmercury – organic mercury

- General overview - https://en.wikipedia.org/wiki/Methylmercury
- Mercury poisoning - https://en.wikipedia.org/wiki/Mercury_poisoning
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Mercury – inorganic

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- Mercury poisoning - https://en.wikipedia.org/wiki/Mercury_poisoning

A Small Dose of Arsenic

Or

An Introduction to the Health Effects of Arsenic

By Steven G. Gilbert, PhD, DABT

From Wikipedia - Elemental arsenic — mineral specimen
https://en.wikipedia.org/wiki/Arsenic

Dossier

Name: Arsenic
Use: wood preservative, pesticides, semiconductor manufacturing
Source: coal combustion, drinking water, environment, medical drug, seafood
Recommended daily intake: none (not essential)
Absorption: inhalation, intestine – inorganic high, organic low, skin
Sensitive individuals: children
Toxicity/symptoms: Peripheral nervous system (tingling in hands in 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/m^3
ATSDR - MRL - 0.3 μg/kg/day
General facts: long history of use as medicine and poison
Environmental: global environmental contaminate, bioaccumulates in fish and shellfish (mostly in a form that is not harmful)
Recommendations: avoid, do not use arsenic treated lumber, test drinking water

Case Studies

> (Henry Adams)….he found himself invariably taking for granted, as a political instinct, with out waiting further experiment—as he took for granted that arsenic poisoned—the rule that a friend in power is a friend lost.
>
> Henry Adams (1838–1918). The Education of Henry Adams. 1918

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 U.S. 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 (see map in presentation). The standard is being lowered because chronic exposure to low levels of arsenic can cause skin cancer and others 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 the drinking water is more acutely life threatening. People were encouraged to establish local wells to reduce exposure to bacteria-contaminated drinking water. It was subsequently discovered that many of these wells have high levels of arsenic in the water. It is estimated that 75 million people of Bangladesh are exposed to arsenic-contaminated water that will result 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. (for additional information see presentation).

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 use in treated wood for domestic 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.

Introduction and History

> I pray my companion, if he wishes for bread, to ask me for bread, and if he wishes for sassafras or arsenic, to ask me for them, and not to hold out his plate, as if I knew already.
>
> Ralph Waldo Emerson (1803–1882).

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 twentieth 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, it is tasteless, and it only takes about a tenth of gram to kill

As Arsenic
Atomic Number: 33
Atomic Mass 74.92

someone. While its use as a human poison has greatly declined, arsenic is still used as a pesticide particularly in growing cotton, as an herbicide and as a wood preservative.

Arsenic poisoning from well water remains a serious world wide human health concern. Internationally, in West Bengal and Bangladesh more than 75 million people are exposed to arsenic-laden water that threatens their health. 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 arsenic their drinking water.

Arsenic is a versatile metal, forming various compounds, either inorganic or organic, with a complex chemistry. Inorganic arsenic is widely distributed in nature usually in the trivalent form (As^{3+}) but also as pentavalent arsenic (As^{5+}). 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.

Arsenic use and production has declined with recognition of its toxicity and the development of suitable replacements. It is not mined but produced as by product of smelting for copper, lead and zinc. The last U.S. smelter producing arsenic in Tacoma, Washington closed in 1985. Smelters typically released the trivalent arsenic trioxide and lead into the atmosphere which contaminated the local environment leaving an unwelcome legacy for local residents. This use of arsenic is also being phased out, such as its use as a wood preservative in CCA, as reflected by a decline in imported arsenic from 20,000 metric tons in 2002 and 2003 to less that 8,000 metric tons in 2007. 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. 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.

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 $\mu g/m^3$ and drinking water less than 5 $\mu g/L$, 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 $\mu g/g$. 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 $\mu g/L$ 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 from breathing sawdust from treated wood.

Biological Properties

> Wipe off this glass three times.
> There is arsenic in it.
> I hear messages from God
> through the fillings in my teeth.
>
> Anne Sexton (1928–1974)

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 3 to 5 days. Arsenic is also excreted in the outer layer of skin cells and 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

> They put arsenic in his meat
> And stared aghast to watch him eat;
> They poured strychnine in his cup
> And shook to see him drink it up
>
> A.E. (Alfred Edward) Housman (1859–1936)

The acute effects of inorganic arsenic poisoning are well known from 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 have been

referred to as blackfoot disease. Hyperpigmentation and hyperkeratosis of palms and soles occurs in 6 to 3 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 cause 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 only supernatural agents, which can in any manner be allowed to us moderns, are ghosts; but of these I would advise an author to be extremely sparing. These are indeed, like arsenic, and other dangerous drugs in physic, to be used with the utmost caution …..
>
> Henry Fielding, 1917

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 arsenic drinking water standard to 10 ppb and required water providers until January 2006 to meet the new standard.

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 has 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, 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 should 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/m^3
ATSDR – MRL – 0.3 μg/kg/day (chronic exposure)

Recommendation and Conclusions

Arsenic is an ancient and well-known hazard and, along with lead and mercury, is an important 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.

More Information and References

Slide Presentation

- A Small Dose of Arsenic presentation material and references online: www.asmalldoseoftoxicology.org
  Web site contains presentation material related to the health effects of arsenic.

European, Asian, and International Agencies

- World Health Organization (WHO). Online: < https://www.who.int/news-room/fact-sheets/detail/arsenic > (accessed: 16 September 2020).
  WHO arsenic in drinking water fact sheet. Inorganic arsenic is very toxic, can contaminate drinking water.

- World Health Organization (WHO). Arsenic in Drinking Water and Resulting Arsenic Toxicity in India & Bangladesh. Online: <https://www.who.int/ipcs/assessment/public_health/arsenic/en/> (accessed: 16 September 2020).
  WHO report on arsenic in drinking water.

North American Agencies

- Health Canada – Arsenic in Drinking Water. Online: < https://www.canada.ca/en/health-canada/services/healthy-living/your-health/environment/arsenic-drinking-water.html > (accessed: 16 September 2020).
  Health Canada provides information on the health effects arsenic in drinking water.

- U.S. Food and Drug Administration (FDA). "Arsenic in Food and Dietary Supplements" Online: < https://www.fda.gov/food/metals-and-your-food/arsenic-food-and-dietary-supplements > (accessed: 16 September 2020).
  FDA Guidance Document for Arsenic in Food and Dietary Supplements.

- U.S. Environmental Protection Agency (EPA) - Arsenic Compounds. Online: < https://cfpub.epa.gov/si/si_public_record_report.cfm?Lab=ORD&count=10000&dirEntryId=42498&searchall=&showcriteria=2&simplesearch=0&timstype= html > (accessed: 16 September 2020).
  EPA site has general information and research on arsenic.

- U.S. Environmental Protection Agency (EPA) – Integrated Risk Information System – Inorganic Arsenic. Online: <https://www.epa.gov/iris/inorganic-arsenic-meetings-webinars#:~:text=The%20IRIS%20Program%20has%20been%20utilizing%20webinars%20in,the%20inorganic%20arsenic%20assessment%20can%20be%20found%20below%3A > (accessed: 16 September 2020).
  Site contains EPA's risk assessment evaluation of inorganic arsenic.

- U.S. Environmental Protection Agency (EPA) – Toxics Release Inventory (TRI) Program. Online: <http://www.epa.gov/tri/> (accessed: 16 September 2020).
  Site has information on arsenic release in the United States.

- U.S. ATSDR – Agency for Toxic Substance Disease Registry – Toxicology Profile Series Arsenic. Online: <https://emergency.cdc.gov/agent/arsenic/> (accessed: accessed: 16 September 2020).

- U.S. National Research Council (NRC) - Arsenic in Drinking Water: 2001 Update. Online: < http://www.nap.edu/catalog.php?record_id=10194 > (accessed: 16 September 2020).
  The NRC report on arsenic can be accessed from the their web site.

- U.S. Geological Services (USGS). Online: < https://www.usgs.gov/mission-areas/water-resources/science/arsenic-and-drinking-water?qt-science_center_objects=0#qt-science_center_objects> (accessed: 16 September 2020).
  Site contains a map of United States showing arsenic in water.

Non-Government Organizations

- SOS Arsenic Poisoning In Bangladesh / India. Online: http://www.sos-arsenic.net/. (accessed: 17 September 2020).
  Information in English, German, Spanish, and French on arsenic poisoning in Bangladesh and India.

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- Arsenic poisoning – map arsenic in ground water - https://en.wikipedia.org/wiki/Arsenic_poisoning https://en.wikipedia.org/wiki/Arsenic_contamination_of_groundwater
- Arsenic biochemistry - https://en.wikipedia.org/wiki/Arsenic_biochemistry

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A Small Dose of Fluoride

Or

An Introduction to the Health Effects of Fluoride

Fluorite Crystal – Wikipedia
https://en.wikipedia.org/wiki/Fluoride

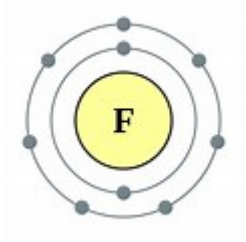
Dossier

Name: Fluoride
Uses: dental carries prevention, add to dinking water, additive in toothpaste and other dental products
Source: additive in drinking water, toothpaste, medication
Recommended daily intake: drinking water concentrations 0.7 mg/Kg
Absorption intestine
Sensitive individuals: children
Toxicity/symptoms: considerable controversy surrounding benefits' vs health effects, benefits reduced dental carries, hazards causes dental fluorosis increases hypothyroidism neurotoxic – can decrease IQ's and increase ADHD in children, acts mostly topically, not systemically
No use and not produced until WW II – used to separate isotopes of uranium
Regulatory facts:
EPA – The maximum contaminant level (MCL) for fluoride in drinking water is 4.0 ppm (4 mg/L)
CDC – The recommended level for fluoridating drinking water is 0.7 ppm (0.7 mg/L)
NSF – Maximum concentration allowed for fluoride is 1.2 ppm.
Ethical issues: no informed consent on fluoride ingestions, standard risk/benefit studies not done
Environmental: widely used in the US but in not Europe or rest of world
Recommendations: avoid, particular for young children

Case Studies

> "Fluoride seems to fit in with lead, mercury and other poisons that cause chemical brain drain. The effect of each toxicant may seem small, but the combined damage on a population scale may be serious, especially because the brain power of the next generation is crucial to all of us."
> **— Philippe Grandjean, PhD**
>
> "I am appalled at the prospect of using water as a vehicle for drugs. Fluoride is a corrosive poison that will produce serious effect on a long-range basis. Any attempt to use the water this way is deplorable."
> **--- Charles Gordon Heyd, MD, Past President, American Medical Association.**

Introduction



To add or not to add fluoride to community drinking water – that is the question. Currently, about 74% of the U.S. population, often without their knowledge or consent, drinks fluoridated water. There has been a 70-year controversy over the efficacy, safety and ethics of the consumption of fluoridated water. The American Dental Association (ADA, 2019) (ADA) and the Center for Disease Control and Prevention (CDC, 2019) (CDC) as well as others maintain that consumption of fluoridated water is safe, reduces dental caries in children and adults, and therefore has significant public health benefits. Others claim that adding fluoride to drinking water causes significant benefits that are greatly overstated, and is, moreover, unethical. Risks from fluoride ingestion include lowered IQs and increased rates of ADHD and hypothyroidism. Since the 1960s, fluoride toothpaste has become widespread, a topical use generally acknowledged to be more effective in preventing cavities than ingestion through water. This societal trend is thought to be a major reason why tooth decay rates have decreased, rather than because of water fluoridation (see graph – Tooth Decay Trends: Fluoridated vs. Unfluoridated Countries). Given the growing evidence of risks and uncertain evidence of benefits, many public health professionals are recommending that fluoridation of drinking water be discontinued.

The fluoridation vs the anti- fluoridation discussion has been going on since the 1940's. While "A Small Dose of Toxicology" strives a balanced view of Fluoride science there is a tilt toward the anti-fluoridation view. Information in favor of fluoridation is easily found at the CDC's web site and ADA (American Dental Association) web site.

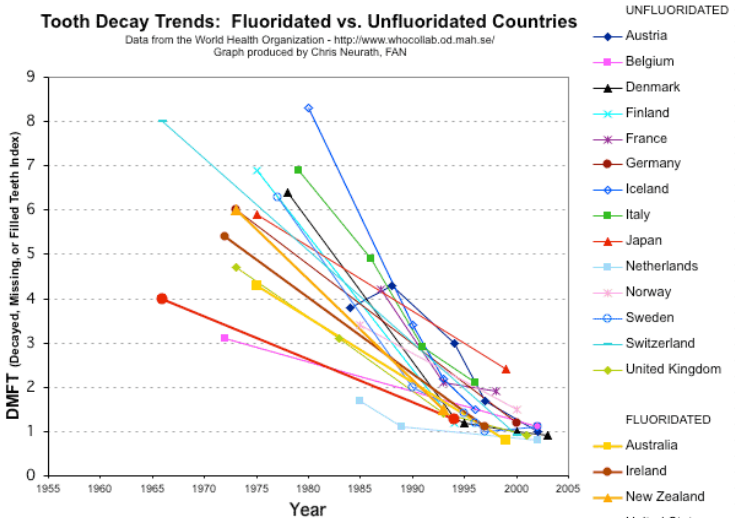
Science & Facts: Fluoride

- Neurotoxic – can decrease IQ and increase ADHD in children
- May increase hypothyroidism
- Causes dental fluorosis
- Dental benefits from contact with teeth, not ingestion

Health Effects

Science & Facts

There are several important aspects to the science surrounding fluoridation: 1) are there significant hazards at expected human exposure levels? 2) do the potential societal benefits outweigh the hazards?; and 3) are some people more vulnerable than others to the harmful effects of fluoride?



There is no question that ingested fluoride can be detrimental to human health. The challenge is determining if there is a level of exposure to fluoride that is safe and improves dental health.

Dental fluorosis, which damages tooth enamel, is caused by an excess of ingested fluoride by young children. At a very mild or mild level, it causes white splotches or stripes on teeth. At moderate or severe levels, the mottling is more pronounced and can cause yellow or brown stains and pitting of the enamel, which can increase cavities. A 2019 study (Neurath et al., 2019) found that both prevalence and severity of fluorosis have jumped. Nearly 65% of 12-15 year-olds in the U.S. are afflicted, with 27.9% moderate and 2.6% severe levels, reinforcing a 2018 study (Wiener, Shen, Findley, Tan, & Sambamoorthi, 2018) that found similar increases in 16-17 year-olds. Fluoridated water is a major contributor to all levels.

Fluoride has been identified as an endocrine disruptor. In fact, fluoride has been known to lower thyroid function since the 1950's, when it was used to treat hyperthyroid patients. In 2006, the National Academy of Science (NAS) (Council., 2011) stated unequivocally that it **"decreased thyroid function."** Studies in Canada (Malin & Till, 2015) and England (Peckham, Lowery, & Spencer, 2015) have added further evidence that increases fluoride exposure contributes to hypothyroidism.

The 2006 NAS review also determined **"fluoride has the ability to interfere with the functions of the brain."** Since then, hundreds of studies in animals and humans have further validated that conclusion. In

2012, a meta-analysis (Choi, Sun, Zhang, & Grandjean, 2012) found that children ingesting higher levels of fluoride tested an average 7 IQ points lower, with supporting evidence from 26 of 27 studies. Most of the children in these studies were exposed to fluoride at higher concentrations than in typical U.S. water, but in many the total exposure to fluoride was similar to what millions of Americans receive.

In 2017, an NIH-funded prospective study (Bashash et al., 2017) found that every one part per million increase in fluoride in pregnant women's urine was associated with a reduction of their children's IQ by 5-6 points. By 2018, out of 60 studies, 53 had linked higher fluoride levels with lower IQ levels in children (Network, 2019).

Of additional concern is that the chemical typically used to fluoridate water, fluorosilicic acid, can be contaminated with lead and/or arsenic. (International, 2019) Both are known to be neurotoxic, and there are no safe levels for either.

Since the 1950s, the Public Health Service (PHS) recommendation for the concentration of fluoridated water has been 1.0 mg/L (milligrams per liter or ppm) for most of the U.S., with a range of 0.7 to 1.2 mg/L. In 2015, this recommendation was lowered to 0.7 mg/L to reduce the toxic side effects of fluoride ingestion while attempting to maintain its beneficial effects. For toxicological assessments, ingested doses are typically adjusted by body weight. Children eat more, breathe more, and drink more than adults on a body weight basis, so they will have higher fluoride doses than adults. Moreover, child organ systems such as the brain and bones are still developing, making them more vulnerable to the toxic effects of fluoride. Typically, when managing risk and benefits of a compound, standard toxicological protocols are applied, including safety factors, to ensure safety for the most vulnerable individuals.

History

History

- 1950: U.S. Public Health Service endorses fluoridation, despite few safety studies
- 2006: NAS *Fluoride in Drinking Water* identifies fluoride as endocrine disruptor and links to multiple health risks
- 2012: Meta-analysis shows higher fluoride levels linked to lower IQ's in 26 of 27 studies
- 2017–2019: High quality studies confirm lowering IQ at common exposure levels

The history of community water fluoridation is a reflection of the post WWII era of the 1950's, when many thought chemicals could solve almost any problem. Our gaze was focused on the beneficial properties of the chemicals, not on the potential hazards. A classic example is DDT, which, in addition to being a potent pesticide, almost killed off predatory birds and more recently was found to be harmful to humans.

Since the 1930's, fluoride has been known to have two opposing qualities for oral health: decreasing cavities but increasing dental fluorosis. There was also early evidence it could weaken bones and lower thyroid function.

In the 1940's, discussions began on the question of fluoridating water at levels that would maximize the benefit but minimize the harm. In 1945, two studies began, comparing one fluoridated city (Grand Rapids/Muskegon, MI, at 1 ppm) with a similar unfluoridated one

(Newburgh/Kingston, NY). They were designed to run for at least ten years, but early promising from Grand Rapids on cavity reduction and pressure from Wisconsin dentists, who had already persuaded at least 50 cities in that state to start fluoridating, led the PHS to approve fluoridation in 1950, after only five years. This was quickly followed by endorsements from the American Dental Association, American Public Health Association and American Medical Association.

All asserted fluoridation was safe, even though no long-term safety studies had ever been done on any diseases, and there were no studies on endocrine disruption, neurotoxicity, cancer, diabetes or chemical sensitivities. Their statements on the certainty of no health risks have continued to the present day, even after the 2006 NAS review cited numerous health risks and the need for more research on several harmful medical conditions, including cancer, diabetes, kidney disease, neurotoxicity and others.

Today, the endorsement of fluoridation by the U.S. government and much of the medical establishment is in stark contrast to most of the rest of the world. Approximately 95% of the world's population drinks unfluoridated water. Out of 196 nations, only 24 have any artificial fluoridation and of those, only 10 for more than half their population. Over 98% of Europe's population drinks unfluoridated water, where only five out of 48 nations have any at all. Some nations have fluoridated salt, but it is always sold as a consumer choice.

In 1999, the CDC included fluoridation as one of its top ten public health achievements of the 20th century. It is revealing that of all ten, this is the only one that has been rejected or not even considered by most nations, cities and health organizations in the world. It's also important that much of the most authoritative scientific evidence against fluoridation has come out since 1999, and the CDC has not changed its position.

Ethics

- Fluoride in water is used as a drug
- No informed consent for ingestion
- Most families cannot avoid intake through water supply
- Kids should be able to reach and maintain their full potential

Ethics

A drug is defined by the FDA as any substance used in the diagnosis, treatment or prevention of disease. For example, the FDA requires a label on fluoridated toothpaste that says, for children under 6, "If more than used for brushing is accidentally swallowed, get medical help or contact a Poison Control Center right away." But when fluoride is added to drinking water, the FDA has looked the other way and refuses to regulate it. Unlike other drugs, fluoridated water has never undergone clinical trials to establish its safety and effectiveness. Fluoridated water is in a "black hole" without any regulation. The EPA regulates it as a contaminant when it occurs naturally, but has stated they will not even consider health risks when fluoride is intentionally added to drinking water (Cross & Carton, 2003).

Physicians prescribe drugs on an individual's needs, ensuring that they are pharmaceutical grade (not contaminated) and recommending a specific dose for a specific length

of time. They also must inform their patients of potential harmful side effects. However, the final decision on whether to take the drugs rests with the patient. With fluoridation, all these safety and ethical protocols are violated, taking away the individual's right of informed consent.

European nations, including France, Germany, Belgium, the Netherlands and Czech Republic, cite the ethical problem of putting a drug in drinking water as a reason they disallow fluoridation (Network, 2019).

Fluoridation is also an environmental and social justice issue. Health conditions that render people more vulnerable to fluoride exposure, such as kidney disease and diabetes, are more prevalent among low-income populations, as are nutrient deficiencies. Moreover, low-income families cannot afford expensive filters or bottled water to avoid fluoridated water. They have no choice.

Finally, the "Precautionary Principle" says that whenever there is evidence that a substance is causing health or environmental harm, preventive measures should be taken, even if the evidence isn't 100% conclusive. The burden of proof should be to show beyond a reasonable doubt that the substance is safe, not absolute proof that it is harmful. Numerous scientific studies, from the 1950's to present day, suggest harm from fluoridation. Discontinuing this practice is the prudent and ethical preventive measure to take.

Regulatory Standards

Current Regulations (USA)

EPA – The maximum contaminant level (MCL) for fluoride in drinking water is 4.0 ppm (4 mg/L)
CDC – The recommended level for fluoridating drinking water is 0.7 ppm (0.7 mg/L)
NSF – Maximum concentration allowed for fluoride is 1.2 ppm; maximum allowable concentration of arsenic is 1.0 ppb; maximum allowable concentration of lead is 1.5 ppb
OSHA – Workplace air - 0.5 mg/m^3
ATSDR – MRL – 0.3 $\mu g/kg/day$ (chronic exposure)

Recommendation and Conclusions

More Information and References

Slide Presentation

- A Small Dose of Fluoride presentation material and references online:
  - www.asmalldoseoftoxicology.org

  Web site contains presentation material related to the health effects of arsenic.

European, Asian, and International Agencies

European Commission - The Scientific Committee on Health and Environmental Risks (SCHER) Fluoride – Online: https://ec.europa.eu/health/scientific_committees/opinions_layman/fluoridation/en/about.htm#content (accessed: 01 October 2020). Extensive information on fluoride from European view

North American Agencies

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> On January 7, 2011, EPA announced its intent to review the national primary and secondary drinking water regulations for fluoride.

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Water fluoridation - https://en.wikipedia.org/wiki/Water_fluoridation
Water fluoridation controversy - https://en.wikipedia.org/wiki/Water_fluoridation_controversy
Fluoridation by country - https://en.wikipedia.org/wiki/Fluoridation_by_country

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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 periodic table and are generally good conductors of electricity or heat. Metals forms cations and ionic bonds with non-metals which makes many of them essential for humans and indeed for all life, while making others very toxic. We began using metals to build and shape our society over 4000 years ago. The Greeks and Romans were some of the first 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 the Greenland ice. Lead in the Greenland ice began increasing about 800 BC, documenting its use and redistribution 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 the Greenland ice due to human use of lead.

Metals cannot be created or destroyed, but can change form, altering their biological availability and toxicity. Metallic mercury evaporates and is redistributed from the atmosphere across the globe. When the mercury is retuned 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 of the 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 highlighting 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. Some of the more important ones are described below. 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 – child or adult, young or old – or during pregnancy. 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 metal and other variables. 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. However, 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. Depending on the route of exposure, metal toxicity can be very different. 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.

Summary Table - Nutritionally Important metals

Table 7.1 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 – anima; excess – liver and kidney	1.5-3.0 mg
Iron (Fe)	Hemoglobin	Food supply	Intestinal tract, liver damage	10 to 15 mg
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 is most prominent in chrome production and plating industries. Acute chromium exposure causes kidney damage and skin contact can cause contact dermatitis and when inhaled irritate the nasal lining. It should also be considered a lung carcinogen.

Copper (Cu)

Copper is involved in hemoglobin synthesis and human toxicity is rare either from deficiency or excess. 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, affecting the liver and kidney. Copper is much more toxic to aquatic life than to mammals and is an important 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 of the 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. Iron deficiency 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 metal 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, suffering 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. Magnesium 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 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 systems 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 the 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, as MMT (methylcyclopentadienyl Mn tricarbonyl), which results in manganese salts being distributed into the environment from the tail pipes of cars. 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. There is ongoing research on the potential adverse effects from use as a fuel additive.

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. Selenium 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 results 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, there is another group with no beneficial biological effects and in some cases 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.

Summary Table – Toxic Metals

Table 7.2 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 B_{12}
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 lose, the “Mad Hatter”	Thermometers, switches, fluorescent lights, some “button” batteries
Mercury - Organic (Hg-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 or 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 variety of aliments, 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 found 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 and pentavalent or as arsenic trioxide (computer chip manufacture) and arsenic acid. Arsenic is excreted in skin cells, sweat, hair and fingernails, which 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 component used in the nuclear power industry and combined with other metals. Its presence in coal and oil results in more than 1250 tons being released in to 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 increasing 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 CBDraises 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 effects 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 effects on calcium.

Cobalt (Co)

Cobalt in small amounts is an essential element associated with vitamin B12 but at high levels 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, permanent magnets and as an alloy to harden metals as 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 and a sensation of warmth, and heart failure. The latter 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 plumbing centuries later that can be found in many households. 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 used as solder in tin cans containing food 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. Lead is still a serous concern in areas near smelters and in housing with lead-based paint. As the toxicity of lead at lower levels was recognized it was banned from paint and from gasoline.

The Greek Dioscerides 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 that 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 U.S. 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 on Lead).

The BLL for children was changed in 2012, affectively making it 5.0 μg/dl While acknowledging that there is no safe level of lead exposure. "CDC now uses a blood lead reference value of 5 micrograms per deciliter to identify children with blood lead levels that are much higher than most children's levels. This new level is based on the U.S. population of children ages 1-5 years who are in the highest 2.5% of children when tested for lead in their blood.
This reference value is based on the 97.5th percentile of the National Health and Nutrition Examination Survey (NHANES)'s blood lead distribution in children. The current reference value is based on NHANES data from 2007-2008 and 2009-2010."

Mercury – Inorganic (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 the use of mercury out of 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 entering 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 Louis Carol'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 tremor 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 on Mercury).

Mercury – Organic (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 the 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 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, tremor and eventually death. The developing fetus and young children are particularly sensitive the effects of methyl mercury exposure. The serious health effects of mercury combined with its widespread distribution have resulted in numerous health advisories and restriction 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 U.S. Food and Drug Administration limits the amount of mercury in canned tuna to 1 ppm. (see chapter on Mercury)

Nickel (Ni)

Nickel is widely used as a metal alloy component in stainless steel, where it increases hardness and corrosion resistance. Nickel is 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 generally as antifouling agents for boats.

Inorganic tin is poorly absorbed 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.

Medical 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 and malaria. Currently, they are used to treat a limited number of diseases such as ovarian cancer and arthritis, but even this use is in decline. The exception to this is fluorine, which, while technically a halogen, is covered in this section because of its widespread use as in municipal water supplies to reduce dental caries. The therapeutic use of metals is generally limited by their toxicity. Metals illustrate well balancing the benefits of treatment against toxic side effects.

Summary Table - Medically Important Metals (and Fluoride)

Table 7.3 Summary of Medically Important Metals

Metal	Function	Source	Toxicity (when in excess)

Bismuth (Bi)	Antacid (ulcers)	Medial, consumer products	Kidney damage
Fluoride (F)	Strengths teeth enamel	Naturally occurring, added to drinking water	Mottled tooth enamel, increased bone density, more?
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, seizers, heart, nausea
Platinum (Pt)	Anti-cancer agent (cisplatin), catalytic converters	Anti-cancer drug, mining	Kidney, hearing, nervous system

Bismuth (Bi)

Bismuth, discovered in 1753, has a long history of medical uses including treatment of diseases ranging from syphilis and 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 can lead to death with ongoing exposure.

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 recommend level of fluoride in the drinking water is 1 ppm. This practice is supported by the U.S. 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 at 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, pound-for-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 as to whether exposures to fluoride via multiple routes of exposure, from drinking water, food and dental-care products, 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 tat when ingested it becomes a visualization tool of soft tissues and bone lesions during an x-ray. Industrial applications include use in high temperature thermometers, metal alloys and as a substitute for mercury in arc lamps.

Gallium's low toxicity and liquid state at room 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 for its toxicity. When used as a therapeutic agent, lithium blood levels must kept within a very narrow range (i.e. a narrow therapeutic index). Lithium appears to be non-essential 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 systems related effects include tremor, difficulty walking, seizures, slurred speech, mental confusion, as well as others. 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, and cancers of the head and neck, as well as others. Unfortunately, the toxic side effects of these agents often limit their usefulness.

In the industrial setting, the platinum metal 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 treatment of poisoning from excessive metal exposure is to remove the metal from the body, thus the development of chelating agents. 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 complex with essential metals and increases 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, not its related sodium salt because this would greatly increase excretion of calcium, potentially having toxic side effects. Blood lead levels are reduced when the lead displaces the calcium to bind with EDTA and 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 resent study showed that lead chelation dropped blood lead levels, but did not protect against cognitive deficits (Rogan et al., 2001).

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.

More Information and References

Slide Presentation

- A Small Dose of Metals presentation material and references online: www.asmalldoseoftoxicology.org .
  Web site contains presentation material related to the health effects of the various metals.

European, Asian, and International Agencies

- England – Department of Health - Maternal and child nutrition. Online: <https://www.nice.org.uk/Guidance/PH11> (accessed: 02 October 2020).
  The Department of Health provides information on nutritional requirements for children and mothers.

- World Health Organization. Online.: < https://www.who.int/health-topics/nutrition> (accessed: 02 October 2020).
  Who information on nutrition, also search the health topics section for a specific metal.

North American Agencies

- Health Canada – Food and Nutrition. Online: <https://www.canada.ca/en/health-canada/services/food-nutrition.html> (accessed: 02 October 2020).
  Health Canada provides information on nutritional issues.

- U.S. Agency for Toxic Substance Disease Registry (ATSDR). Online: <http://www.atsdr.cdc.gov/> (accessed: 02 October 2020).
  See fact sheets and case studies in many metals and other agents.

- Centers for Disease Control and Prevention (CDC Maternal, Infant & Toddler Nutrition, Physical Activity & Healthy Growth. Online: https://www.cdc.gov/nccdphp/dnpao/resources/maternal-infant-toddler-resources.html (accessed: 02 October 2020).

Non-Government Organizations

- Dartmouth Toxic Metals Research Program. Online.
  <https://sites.dartmouth.edu/toxmetal/> (accessed: 02 October 2020).
  The site has general information on toxic metals.

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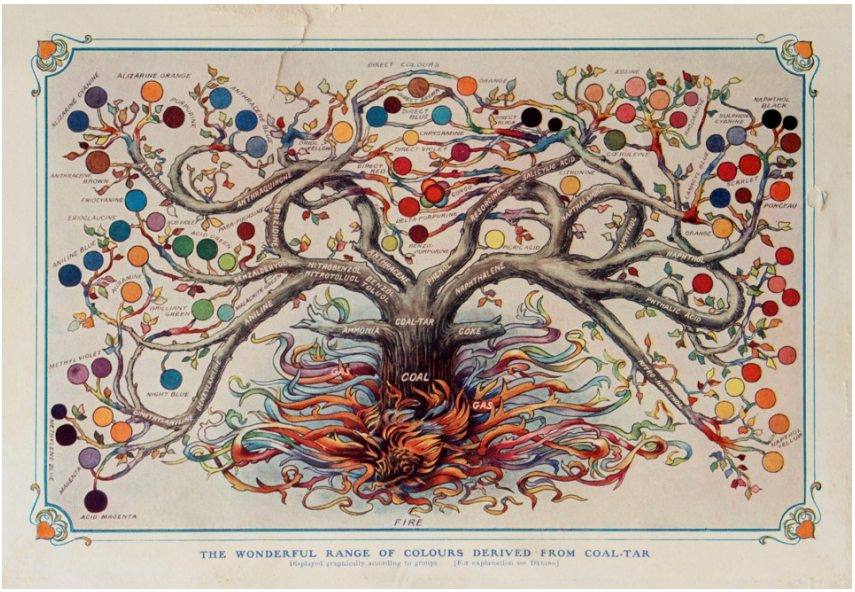
Michael C. Byrns and Trevor M. Penning (2018). Environmental Toxicology: Carcinogens and Heavy Metals. Chapter in Laurence Brunton, Bjorn Knollmann, Randa Hilal-Dandan. Goodman & Gilman's The Pharmacological Basis of Therapeutics. 13th edition. McGraw-Hill, New York, 2018, pp. 1297-1316.

Rogan, W.J., Dietrich, K.N., Ware, J.H., Dockery, D.W., Salganik, M., Radcliffe, J., Jones, R.L., Ragan, N.B., Chisolm, J.J., Jr. & Rhoads, G.G. (2001). The Effect of Chelation Therapy with Succimer on Neuropsychological Development in Children Exposed to Lead. N Engl J Med, 344, 1421-1426.

National Research Council. Fluoride in Drinking Water: A Scientific Review of EPA's Standards. In: National Research Council of the National Academies. Available at http://books.nap.edu/openbook.php?record_id=11571&page=R1; 2006.

A Small Dose of Solvents
Or
An Introduction to the Health Effects of Solvents



Benzene Tree

Dossier

Name: Solvent (broad class of chemicals)
Use: 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), highly volatility of solvent results in inhalation exposure of vapors
Environmental: volatile organic compounds react with sunlight to produce smog
Recommendations: avoid, use proper workplace protection

Case Studies

Anesthetic Agents

> "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. Raymundus Lullius, a Spanish chemist, discovered ether $(CH_3CH_2)_2O$ in 1275. Its hypnotic effects were soon appreciated (and enjoyed by some), but for many decades ether was only used to treat the occasional medical ailments. Even with ether, the success of surgical procedures did not improve until the introduction of anapestic procedure and infection control some 20 years latter. Ether was replaced by cyclopropane in 1929, which was replace by halothane 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 a 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. He commonly used 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 and 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).

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 as an anesthetic when we undergo surgery. Solvents are highly volatile in air and are readily absorbed by the lung 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 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.

Robert Hinckley's (1880's) "The First Operation with Ether"

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 included 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 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 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 their widespread release into the environmental. 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 the groundwater become trapped until released during use. Human exposure occurs from drinking water or from exposure during 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 which they enter the lungs. The high lipid solubility and small 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 body burden and concentration of the solvent in the air.

Solvents are 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 concentration 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. The toxicity of toluene is reduced when liver enzymes change the compound so that it does not readily cross cell membranes. On the other hand, 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 from one person to another in their ability to metabolize solvents. Subtle genetic difference can increase or decrease an individual's ability to metabolize certain solvents, resulting in more or less toxicity. The liver is also prone to damage by some solvents, for example, carbon tetrachloride (CCl_4). This damage can actually be made worse by prior exposure to alcohol.

Table 11.1 Products that contain solvents

Products that are mostly solvent	Partially solvent based
Gasoline	Glues
Diesel fuel	Adhesives
Charcoal lighter fluid	Oil based paints
Lantern fuel	Furniture polishes
Grease	Floor polishes and waxes
Lubricating oils	Spot removers
Degreasing agents	Metal and wood cleaners
Paint strippers	Correction fluid
Paint thinner	Computer disk cleaner
Turpentine	Varnishes and shellacs
Nail polish remover	Wood and concrete stains
Rubbing alcohol	

Health Effects

The majority of us are exposed to low levels of solvents every day. Millions of workers around the world are exposed to high levels of solvents on a daily basis 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 and that fire is also a significant health hazard.

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 their 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 tingling sensation and loss of feeling in the hands and feet, increased reaction time, and decreased coordination. Reproductive effects included decreased and damaged sperm causing 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 span and other psychological effects. There is also considerable data to 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 encephalophathy. 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, emotional liability, progressing to impaired intellectual function and ultimately dementia. Early symptoms are often reversible if exposure is stopped.

Table 11.2 Health Effects of Solvents

Effects of Solvents	**Examples**
Reproductive hazard	methoxyethanol, 2-ethoxyethanol, methyl chloride
Developmental hazard	alcohol (ethanol)
Liver or kidney damage	toluene, and carbon tetrachloride, 1,1,2-2-tetrachloroethane, chloroform
Nervous system damage	n-hexane, perchloroethylene, n-butyl mercaptan
Cause cancer	carbon tetrachloride, trichloroethylene, 1,1,2,2-tetrachloroethane, perchloroethylene, methylene chloride, benzene

Visual system	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. Beyond purposeful inhalation for the direct nervous system effects there is accidental exposure. Children that 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 when used 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) – protect on acute effects --- protect against loss of consciousness or loss of performance – allow need for short term exposure in emergency situation
TLV – Threshold Limit Value
TWA – Time Waited 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 reduce exposure via ventilation or protective equipment if 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.

More Information and References

Slide Presentation

- A Small Dose of Solvents presentation material and references online: www.asmalldoseoftoxicology.org
  Web site contains presentation material related to the health effects of solvents.

Specific solvents

For information on specific solvents, the Agency for Toxic Substances and Disease Registry (ATSDR) provides the following fact sheets:

- Benzene (258 KB, PDF)
- Acetone (140 KB, PDF)
- Tetrachloroethylene (PCE or PERC) (259 KB, PDF)
- Trichloroethylene (TCE) (259 KB, PDF)
- Xylenes (72 KB, PDF)

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A Small Dose of Radiation
Or
An Introduction to the Health Effects of Radiation

Chapter 18
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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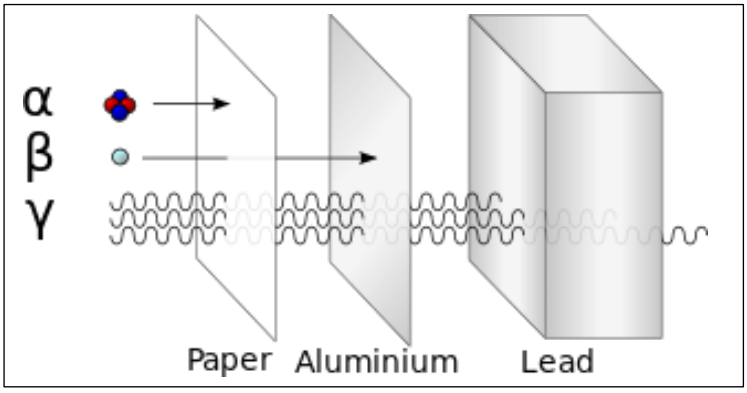
Supporting web site
web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"



Dossier

Name: Nonionizing Radiation
Use: power transmission, communication, LEDs, light bullbs, heating, cooking, microwave ovens, vision, lasers, photosynthesis (sunlight), mobile phones, WiFi, etc.
Source: Ultraviolet light, visible light, infrared radiation, microwaves, radio & TV, mobile phones, power transmission
Recommended exposure: 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 SAR limit of 1.6 W/kg for mobile phones.
General facts: long history of use
Environmental: Our dependency on energy results in a range of consequences, for example drilling for oil and mining coal to run power plants to generate electricity, in turn mercury is released in the atmosphere from burning coal.
Recommendations: depending on individual sensitivity; limit exposure to solar radiation (ultraviolet radiation); reduce energy consumption

Name: Ionizing Radiation
Use: nuclear power, medical x-rays, medical diagnostics, scientific research, cancer treatment, cathode ray tube displays
Source: Radon, x-rays, radioactive material produce 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: 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

Case Studies

Radium Girls

> "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

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. U.S. 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. The alpha radiation damaged the cells near the radium particle. As a result of their exposure to radium, many of these women develop painfully debilitating bone decay and died of cancer. The long half-life of radium combined with its sequestration in the 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 into 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 melanin pigment, which absorbs UV radiation and protects the skin cells from damage. People with darker-colored skin have ongoing production of melanin and are better protected from damage than people with less skin color. 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. About 90% of UV radiation is reflected by snow, making snow blindness a significant concern.

UV radiation illustrates the basic the 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 resulting acute and long-term effects.

Microwave radiation, communication and your mobile phone

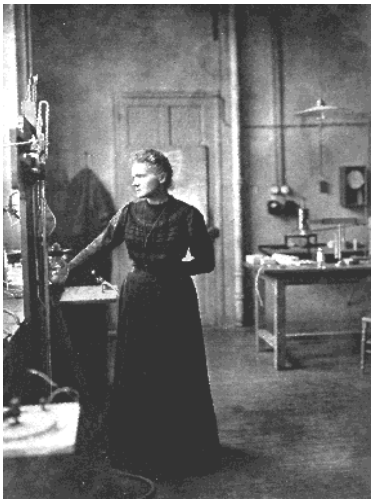
Mobile phones or cell phones are now an almost essential device with over 4 billion subscribers. The devices have become increasingly sophisticated with capabilities well beyond the simple phone call. These devices are now powerful computers with wireless internet access, global positioning, and many 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 serious 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.

The direct use-related health concern with mobile phones is associated with the nonionizing radiation used to transmit data to and from the device. 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.

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. There are many benefits from radiation-emitting devices, 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.


Marie Curie

The electromagnetic spectrum is roughly divided into ionizing and nonionizing radiation (Figure 12.1). The distinction depends on the amount of energy carried by the radiation, which is directly related to the frequency of vibration 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, microwaves, radio & 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) and others. 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 issues 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 twentieth 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 lead 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.

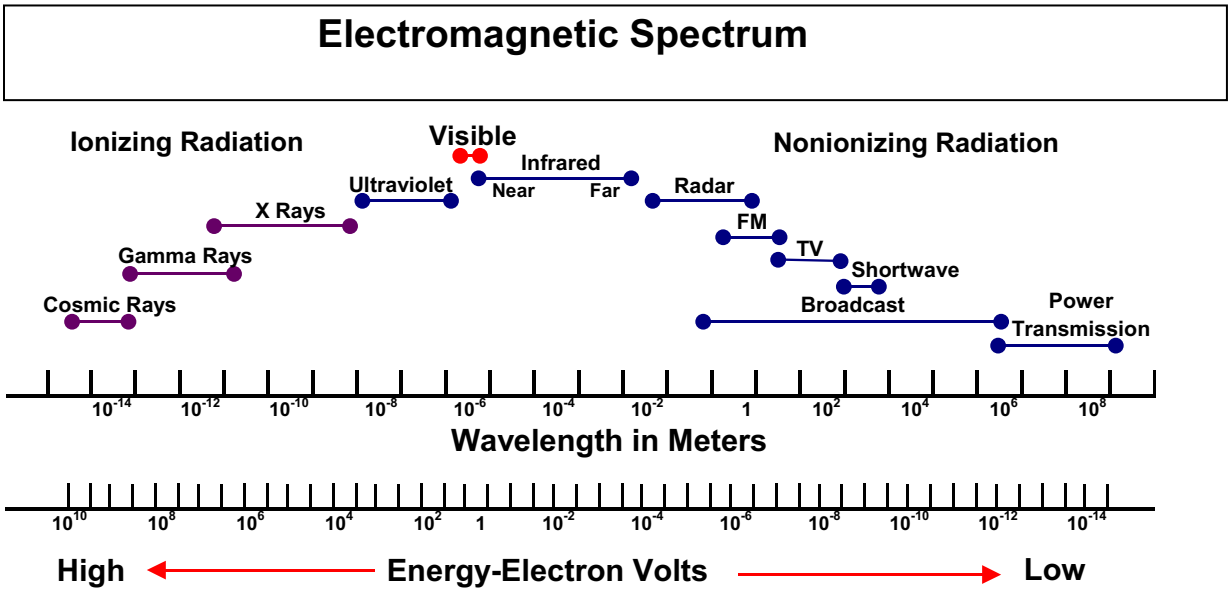


Figure 12.1 Electromagnetic Spectrum

Biological and Physical Properties

Nonionizing radiation

Nonionizing radiation has less energy and in general is 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 transmission 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.

On the other hand, 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 material. 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 rather heating.

Table 12.1 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

Around our home we are exposed to a variety of different types of radiation. Home 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.

Ionizing radiation

Ionizing radiation has sufficient energy to produce ion pairs as it passes through matter that is it frees electrons and leaves 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 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 alpha-particle-emitting material will be damaged. Typical sites of accumulation include bone, kidney, liver, lung, and spleen. Radium is an alpha-particle emitter that when ingested accumulates in the bone, 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 various depending on the route of travel. Storms on the sun can produce solar flares that can 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 levels of radiation that exceed established guidelines.

Sources of ionizing radiation or 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 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 refinement is possible that applies a weighting factor to each type of tissue. Recommended limits on radiation exposure are expressed in Sv (Table 12.2).

Table 12.2 Measures of Radiation Energy

Item	Previous Unit	SI Unit	Ratios
Activity (i.e. quantity rays or particles)	Curie (Ci)	Bequerel(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 risk 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. 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 application such as radar, solder machines, welders, heat sealers, drying equipment, glue curing and others. In biological tissues microwave radiation produce 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 that 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 the uranium mines, as well as in high concentration in the 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 U.S. military dropped the first atomic bomb on Hiroshima, Japan on August 6, 1945 and a second on Nagasaki, Japan, three days latter. 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 a 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 U.S. 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 U.S. 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 of natural radiation from the solar energy of the sun 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 radiations. 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 along the way 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 world. 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 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 is divided into alpha and beta particles and gamma rays. Each has its unique characteristics, which require different safety approaches. In general, the more

radiation exposure a person receives, the greater the likelihood of cancer. Thus a precautionary approach that limits radiation exposure is best.

More Information and References

Slide Presentation

A Small Dose of Radiation presentation material and references online: www.asmalldoseoftoxicology.org

Web site contains presentation material on the health effects of radiation.

European, Asian, and International Agencies

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- World Health Organization (WHO) - Radiation. Online: https://www.who.int/health-topics/radiation (accessed: 06 October 2020).
  Site contains information on the global efforts to reduce radiation exposure.

North American Agencies

- Health Canada – Radiation and Your Health. Online: https://www.canada.ca/en/services/health/health-risks-safety/radiation.html (accessed: 06 October 2020).
  Health Canada provides information on the health effects radiation for consumer and clinical radiation protection.

- US Centers for Disease Control and Prevention (CDC) Radiation and Your Health. Online: <https://www.cdc.gov/nceh/radiation/default.htm (accessed: 06 October 2020).
  This site contains information on health effects and emergency response to radiation exposure.

- US Environmental Protection Agency (EPA) - Radiation Protection. Online: <http://www.epa.gov/radiation/> (accessed: 06 October 2020).

This site has a tremendous amount of information on ionizing and nonionizing radiation and environmental contamination.

- US Environmental Protection Agency (EPA) - Radiation Protection - Calculate Your Radiation Dose. Online: https://www.epa.gov/radiation/calculate-your-radiation-dose (accessed: 06 October 2020).
  This site shows you how to examine your current exposure to radiation.

- US Food and Drug Administration – Center for Devices and Radiological Health. Onlinehttps://www.fda.gov/training-and-continuing-education/cdrh-learn (accessed: 5 May 2009).
  This site contains information on the health effects and regulation of radiation emitting devices and products. The mission of the CDRH radiological health program is to protect the public from hazardous or unnecessary radiation emissions from electronic products.

- U.S. Food and Drug Administration – Cell Phones. Online: https://www.fda.gov/radiation-emitting-products/cell-phones/scientific-evidence-cell-phone-safety/ (accessed: 06 October 2020).
  Site contains general and regulatory information on cell phones and their safety.

- US Federal Communications Commission (FCC) – Office of Engineering and Technology – Radio Frequency Safety. Online: https://www.fcc.gov/general/radio-frequency-safety-0 (accessed: 06 October 2020).
  The FCC is required "to evaluate the effect of emissions from FCC-regulated transmitters on the quality of the human environment".

- US Department of Labor, Occupational Safety & Health Administration (OSHA), Radiofrequency and Microwave Radiation. Online: https://www.osha.gov/radiofrequency-and-microwave-radiation (accessed: 06 October 2020).
  The OSHA site contains information on microwave and radio-frequency devices.

- US Nuclear Regulatory Commission (NRC). Online: <http://www.nrc.gov/> (accessed: 5 May 2009).
  "The NRC regulates U.S. commercial nuclear power plants and the civilian use of nuclear materials."

Non-Government Organizations

- National Council on Radiation Protection and Measurements (NCRP). Online: <http://www.ncrp.com/> (accessed: 06 October 2020).
  "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."

- Health Physics Society. Online: <http://www.hps.org/> (accessed: 06 October 2020).
  Site has extensive information about the health physics and radiation protection.

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by Claudia Clark, Publisher: University of North Carolina Pr; ISBN: 0807823317; (June 1997). 384 pages.

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A Small Dose of Persistent Environmental Contaminants
Or
An Introduction to the Health Effects of Persistent Environmental Contaminants

Chapter 19
A Small Dose of Toxicology - The Health Effects of Common Chemicals

ED3 – Revised October 2020

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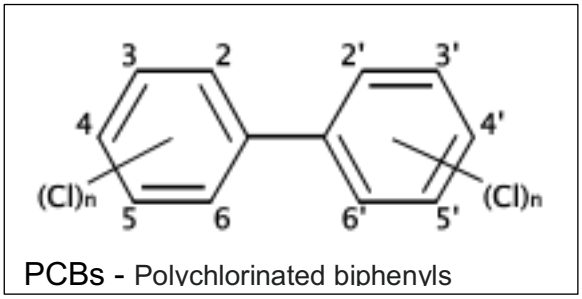
Supporting web site:
web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"



PCBs - Polychlorinated biphenyls

Dossier

Name: Persistent Environmental Contaminants has various names depending on agency – e.g. U.S. EPA Persistent Bioaccumulative and Toxic (PBT) or United Nations Persistent Organic Pollutant (POP) or forever chemicals
Use: 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: global environmental contaminants
Recommendations: avoid, work towards phaseouts

Case Studies

Lindane Dump site

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, George S. Langford (ed), published by The entomological Society of America. – 10th edition 1953-1954, page – 165.

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 environmentand 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 attacks the nervous system causing trembling, loss of coordination, paralysis, and ultimately death. Lindane was often applied as a spray on crops, where it would be either ingested or inhaled. Initially its environmental persistence was considered an asset, but eventually that was seen as a liability and lead to restrictions in it 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 ug of lindane per liter of water. The US EPA restricted its use in 1983, as have most European countries and in 2006 its registration as a pesticide was cancelled. 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 U.S. 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 runoffs 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 U.S. Geological Survey monitoring studies).

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 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 a small dose can harm sensitive individuals. Thirty years ago in *Silent Spring*, Rachael Carson, sounded one of the first alarms about the effects of environmental contaminants. Toxicity does come in small doses to sensitive individuals (including animals). Evidence accumulated that a pesticide like DDT can cause very unexpected effects. The first and most obvious was the thinning of birds' eggshells, causing a sharp decline in predator bird populations. Predatory birds are at the top of the food chain, where they accumulate and concentrate DDT. Next we became aware of the potential of low-level exposures to these agents to cause diseases like cancer that appears only after many years. Humans at the top of the food chain accumulate DDT in fat. Fat is mobilized during lactation, and breast-feed mothers pass along the DDT to their infant. The small infant actually receives 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 substances have similar characteristics that contribute to their toxicity to both humans and other species of plants and animals. 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. This means they are available to cause harm to other organisms, often not even the target

of the pesticide. Second, the early pesticides were broadly acting and toxic to many species, not just the target species. These poisons often killed beneficial insects or plants. Third, many of these compounds would bioaccumulate or concentrate in species as they moved up the food chain. The chlorinated pesticides accumulate in the fat of animals. Animals that consumed other animals would accumulate more and more of these pesticides. Most species could not 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 Substance 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 of persistent chemicals, which 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 U.S. EPA crated a list of agents called Persistent Bioaccumulative and Toxic (PBT). Both these lists included organic chemicals and metals. 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 as 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).

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			A 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 by products
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				By product
Polychlorinated biophenyl's (PCBs)	X	X	X	X	Heat resistant
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	Contaminate

Polycyclic aromatic hydrocarbons (PAHs)		X		X	Combustion by products
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

Health Effects

Table 14.2 provides a very brief description of the chemicals and 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 U.S. in 1987.
Benzo(a)pyrene	A PAH (see below under PAH)
Cadmium	Metal – naturally occurring – used in steel and plastics, batteries, cigarette smoke – lung carcinogen
Chlordane	Pesticide – Organochlorine – Bioaccumulates – Used to control mosquitoes and termites Importation and manufacture prohibited in the U.S., 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 U.S. 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 Bioaccumulates – municipal and medical waste incinerators – human carcinogen
Endrin	Pesticide – Organochlorine – Bioaccumulates – Insecticide used on many crops – Most use canceled in 1980
Endosulfan	Pesticide – Organochlorine – Bioaccumulates – Currently used as an insecticide

Heptachlor epoxide	Pesticide – Organochlorine – Bioaccumulates – Heptachlor epoxide is a breakdown product of heptachlor, an Insecticide from 1953 to 1974 in U.S. on wide range of insects. Most use canceled in 1974 and importation and manufacture prohibited in the U.S., use banned in 1988.
Hexachlorobenzene	Pesticide – Organochlorine – Bioaccumulates – Fungicide used in seeds, most use ended in 1965 but is a by-product in 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 U.S.EPA
Mercury	Metal – Persistent – Bioaccumulates – Contaminates many species of fish. Widely used in industrial processes. Cause developmental neurotoxicity – children most susceptible.
Methoxychlor	Pesticide – Organochlorine – Bioaccumulates – Used as a replacement for DDT. In the U.S., 3.7 million pounds manufactured in 1978. Use has declined significantly – regulated as a water contaminant.
Mirex	Pesticide – Organochlorine – Bioaccumulates – Extensively used in U.S. from 1962-1978 to control fire ants. All use canceled in U.S. in 1978.
Octachlorostyrene	By product of electrolytic production of magnesium. List by U.S. EPA as persistent and Bioaccumulative.
Pendimethalin	Pesticide – Herbicide used to control grasses and broadleaf weeds in crop fields 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 and are highly persistent in the environment.
Polychlorinated biophenyl's (PCBs)	Heat and fire resistant – extensively used from 1929 and 1977 in electrical transformers – all manufacture banned – extensively regulated – very widespread global contaminant.
Polycyclic aromatic hydrocarbons (PAHs)	Combustion byproducts – class of 100 chemicals – combustionby products from oil to tobacco. Some of the first known carcinogens.
Tin (organotins)	Organotins are used in a number of consumer products including paint as a pesticide. Bioaccumulates and persistent, affects nervous system.

Toxaphene	Pesticide – Organochlorine – Bioaccumulates – Extensively used on U.S. cotton crops from 1947 to 1980. Manufacture and use prohibited in the U.S.
Trifluralin	Pesticide – Herbicide used to prevent emergence of weeds in crop fields and landscapes
1,2,4,5-tetrachlorobenzene	Pesticide – insecticide and intermediate in herbicide production – related to Dioxin (TCDD)

Reducing Exposure

Exposure depends on region of the world, diet, housing, occupation, socioeconomic issues, and other factors. For example, methylmercury bioaccumulates in certain fish and is particularly toxic to the developing fetus. Many government agencies advise that women of childbearing age or children 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-targeted species. Many institutions, such as schools, are adapting IPM protocols for pest management.

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

More Information and References

Slide Presentation

- A Small Dose of Persistent Environmental Contaminants presentation material and references online: www.asmalldoseoftoxicology.org .
  Web site contains presentation material on the health effects of Persistent Environmental Contaminants.

European, Asian, and International Agencies

- European Commission on the Environment -). Online: < https://ec.europa.eu/environment/index_en > (accessed: 8 October 2020).
  REACH is a new European Community Regulation on chemicals and their safe use (EC 1907/2006). It deals with the Registration, Evaluation, Authorization and Restriction of Chemical substances. The new law entered into force on 1 June 2007.

- United Nations Environment Programme (UNEP) – Persistent Organic Pollutants (POP). Online: < http://www.chem.unep.ch/pops/ > (accessed: 8 October 2020)
  UNEP is the global champion for the environment with programs focusing on sustainable development, climate, biodiversity and more.

- Stockholm Convention on Persistent Organic Pollutants (POP). Online: < http://chm.pops.int/ > (accessed: 8 October 2020).
  "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."

North American Agencies

- Health Canada - Chemical Substances Online: < https://www.canada.ca/en/health-canada/topics/chemicals-your-health.html> (accessed: 9 October 2020).
- Health Canada provides information on the health effects and environmental distribution of chemical substances in Canada.

- US Centers for Disease Control and Prevention (CDC). Environmental Health Laboratory, National Biomonitoring Program (NBP). Available: http://www.cdc.gov/biomonitoring/. (accessed: 9 October 2020).
  CDC's Division of Laboratory Sciences coordinates the National Biomonitoring Program (NBP) which offers an assessment of nutritional status and the exposure of the U.S. population to environmental chemicals and toxic substances.

- US Environmental Protection Agency Persistent Organic Pollutants: A Global Issue, A Global Response Online: https://www.epa.gov/international-cooperation/persistent-organic-pollutants-global-issue-global-response. (accessed: 8 October 2020).
  A global effort.

- US Environmental Protection Agency – Persistent Bioaccumulative Toxic (PBT) Chemicals Rules Under the TRI Program. Online: < https://www.epa.gov/toxics-release-inventory-tri-program/persistent-bioaccumulative-toxic-pbt-chemicals-rules-under-tri> (accessed: 9 October 2020).
  Information of the efforts of U.S. EPA to reduce PBT chemicals.

- US Geological Survey. Online: < https://www.usgs.gov/science-explorer-results?es=chemicals> (accessed: 9 October 2020).
  This site contains information and maps on the use of chemicals across the US both as contaminants, use, and distribution.

- Washington State Department of Ecology – Addressing priority toxic chemicalsPersistent, Bioaccumulative Toxins. Online: < https://ecology.wa.gov/Waste-Toxics/Reducing-toxic-chemicals/Addressing-priority-toxic-chemicals> (accessed: 9 October 2020).
  Information on Washington's approach to persistent, bioaccumulative toxins, and includes several chemical action plans.

- US Department of Agriculture – Integrated Pest Management (IPM). Online: <https://www.ers.usda.gov/topics/farm-practices-management/fertilizers-pesticides/ > (accessed: 9 October 2020).
  Site provides information and other links on pest management.

Non-Government Organizations

- Pesticide Action Network UK. Online: < http://www.pan-uk.org/ > (accessed: 08 October 2020).
  PAN-UK works to eliminate the dangers of toxic pesticides, exposure to them, and their presence in the environment in Europe.

- Pesticide Action Network North America (PANNA). Online: <http://www.panna.org> (accessed: 08 October 2020).
  "PANNA works to replace pesticide use with ecologically sound and socially just alternatives."

- Toxic Free Futures (TFF). Online: <https://toxicfreefuture.org> (accessed: 08 October 2020).

Our mission: Toxic-Free Future advocates for the use of safer products, chemicals, and practices through advanced research, advocacy, grassroots organizing, and consumer engagement to ensure a healthier tomorrow.

- Beyond Pesticides. Online: <http://www.beyondpesticides.org/> (accessed: 08 October 2020).
  "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."

- Northwest Coalition for Alternatives to Pesticides (NCAP). Online: <http://www.pesticide.org/> (accessed: 08 October 2020).
  "NCAP works to protect people and the environment by advancing healthy solutions to pest problems."

- University of California Statewide Integrated Pest Management Program (UC IPM). Online: <http://www.ipm.ucdavis.edu/> (accessed: 08 October 2020).
  "UC - IPM develops and promotes the use of integrated, ecologically sound pest management programs in California."

- Environmental Working Group – Developed a list of Fruits and vegetables "dirty dozen" with the most toxic chemicals Online: https://www.ewg.org/foodnews/dirty-dozen.php (accessed: 08 October 2020).

Wikipedia

- Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH). Online: https://en.wikipedia.org/wiki/Registration,_Evaluation,_Authorisation_and_Restriction_of_Chemicals . (accessed: 8 October 2020).

- United Nations Environment Programme. Online: https://en.wikipedia.org/wiki/United_Nations_Environment_Programme . (accessed: 8 October 2020).
- The United Nations Environment Programme (UNEP or UN Environment[1]) is responsible for coordinating the UN's environmental activities and assisting developing countries in implementing environmentally sound policies and practices.

- Persistent organic pollutant (POPs). Online: https://en.wikipedia.org/wiki/Persistent_organic_pollutant - (accessed: 8 October 2020).

- Stockholm Convention on Persistent Organic Pollutants. Online: https://en.wikipedia.org/wiki/Stockholm_Convention_on_Persistent_Organic_Pollutants - (accessed: 8 October 2020).

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National Research Council (2006). Human Biomonitoring for Environmental Chemicals - Committee on Human Biomonitoring for Environmental Toxicants, National Academy Press Available: http://www.nap.edu/catalog.php?record_id=11700 (accessed: 8 October 2020).

A Small Dose of Endocrine Disruptors
Or
An Introduction to the Health Effects of Endocrine Disruptors

Chapter 20
A Small Dose of Toxicology - The Health Effects of Common Chemicals

ED3 – Revised October 2020

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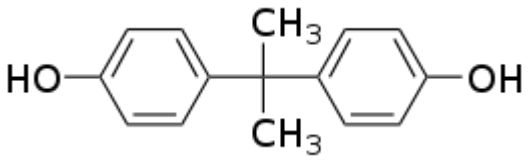
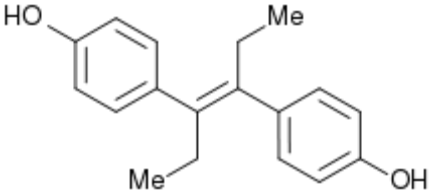
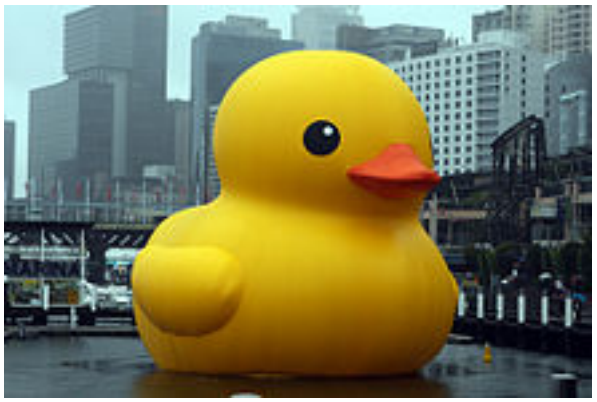
Supporting web sites
web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"

	
Bisphenol-A (BPA)	diethylstilbestrol

Dossier

Endocrine Disruptors Chemicals (EDCs)

Name: Endocrine Disruptors
Use: wide range of chemicals, pesticides, plastics, flame retardants, medicine
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, mimic estrogen, anti-estrogenic, effects on hormone levels, sexual characteristics, reproduction, developmental effects
Regulatory facts: FDA and EPA are reviewing
General facts: billions of pounds used every year in wide range of products
Environmental: widely distributed in environment and can affect wild life
Recommendations: minimize use, avoid exposure to children, and consider alternatives, avoid any rubber ducks



From Wikipedia - https://en.wikipedia.org/wiki/Rubber_duck

Case Studies

Hormonal Contraceptives

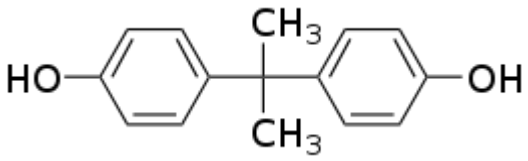
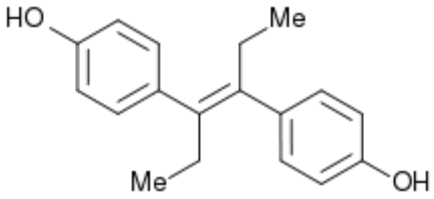
Oral contraceptives, the most widely used form of birth control, are used by millions of women throughout the world, are actually the ultimate endocrine disruptor. The search for a hormonal form of birth control began in the 1930s and was championed by women such as Margaret Sanger. An important breakthrough 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. On May 9, 1960, the Food and Drug Administration approved "the Pill", a combination of an estrogen and a progesterone, taken by mouth to inhibit 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, affecting wildlife, such as fish reproduction.

Synthetic Estrogens

A 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 its use for menopausal symptoms and in 1947 to prevent miscarriages. In 1953 the first study was published indicating that DES was not effective in preventing miscarriages. The manufacturers continued to markete DES for pregnant women until 1971, when the first study was published linking DES to vaginal cancer in female offspring. Between 1941 and 1971, millions of women and their offspring 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 lining of food cans, with estimated use per year of 6 billion pounds. The CDC found that over 90% of people had 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. Animal studies and limited human studies have found endocrine-related health effects but government agencies have been reluctant to ban or

restrict the use of BPA. Recently local governments [examples] have moved to ban BPA from plastic baby bottles in an effort to reduce exposure to the most vulnerable.

	
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 ground water contaminant. Atrazine remains one of the most widely used herbicides in the United States. Several studies have found that Atrazine feminizes male frogs by disrupting the endocrine system. Other pesticides such DDT and organochlorines are also thought to be endocrine disruptors even at very low levels of exposure.

Introduction and History

> 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, brain and behavior, impaired immune system, 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 EDC from conception and then throughout our lives, and 3) the

chemicals are widely distributed in the environment affecting both humans and animals. Below is a small list of common chemicals thought to interact with the endocrine system.

Potential Endocrine Disruptors

Class	Chemical	Use
Pesticide	DDT	Insecticide (no longer allowed in US
	2,4-D	Herbicide
	Atrazine	Herbicide
Plastics additives	Bisphenol A	Harden in plastics
	Phthalates	Softener in plastics, solvent
Industrial chemical	Nonylphenol (breakdown product of nonylphenol ethoxylates	Detergents, paints, pesticides
Fire retardant	Polybrominated diphenyl ethers (PBDE)	Fire retardant
Drug	Diethylstilbesterol (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 (PCB)	Formerly used in transformer oils

Biological Properties

Endocrine System

The endocrine system is the body's chemical communication system, using the blood vessels to move chemicals throughout the body to communicate with different cells of the body. These naturally occurring chemicals, called hormones, are secreted by the by various glands throughout the body (see table below). Hormones move throughout the body, signaling specifically sensitive cells to respond. These chemicals regulate and influence almost all the basic functions of life such as growth, metabolism, reproduction, sexuality, fear response, anger, pregnancy, and many other big and small functions. In a complex feedback loop many hormones influence the secretion of other hormones. 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 2. However, many organs can secrete hormones as well, including kidneys, placenta, stomach, liver, and others.

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 (kidney)	Glucocorticoids	Effects glucose uptake
	Adrenaline	Fight-or-flight response (range of effects)
Pancreas (kidney)	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

Introduction

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). For example, 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 indicate that dioxin, an environmental contaminant, can interfere with breast tissue developmental and potentially lead to cancer.

Another organ vulnerable to endocrine disruptors is the thyroid and, by extension, the nervous system. The thyroid glands start development 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, migration, formation of connections between cells, development of supporting cells, and general functional development. Decreased thyroid hormone adversely affects all aspects of brain development. A wide range of chemicals can adversely interact with thyroid hormone (for additional information see Howdeshell, 2002). Normal thyroid function is also necessary for proper hearing development. 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 Steroid – Performance Enhancement

One of the many uses of anabolic steroids is for sports performance enhancement to increase muscle mass, strength, and endurance. 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 covers the blood products such as injecting red blood cells to improve oxygen carrying capacity, which will not be covered in this chapter.

> **Ancient Greek Athletes -** "The Greek physician Galen is reputed to have prescribed 'the rear hooves of an Abyssinian ass, ground up, boiled in oil, and flavored with rose hips and rose petals' to improve performance."

The use of steroids to enhance performance started a long time ago 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 use less pesticides. Chemicals such as lead and pesticides can be tracked indoors on shoes, so it is always recommended to remove your shoes before coming indoors.
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Regulatory Standards

In 1996, the U.S. 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 to rapidly examine the approximately 85,000 chemicals in use prior to more sophisticated animal-based tests. The program has progressed very slowly and it was not until 2007 that testing began.

There has also be 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 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 chemicals, such as baby bottles, plastic toys and can lining. When possible avoid these products and urge manufacture to use alternatives. The government 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 and especially if there is likely to be wide exposure to susceptible populations.

More Information and References

Slide Presentation

- A Small Dose of Endocrine Disruptors presentation material and references online: http://www.asmalldoseoftoxicology.org or Web site contains presentation material related to the health effects of Endocrine Disruptors.

European, Asian, and International Agencies

- European Union – Chemicals and Pesticides Information. Online: < https://www.europarl.europa.eu/factsheets/en/sheet/78/chemicals-and-pesticides > (accessed: 12 October 2020).
  Site contains policy and other information on the use of pesticides in agriculture.

- World Health Organization - WHO Pesticide Evaluation Scheme (WHOPES). Online: < https://www.who.int/whopes/resources > (accessed: 12 October 2020).
  WHOPES is an "international programme which promotes and coordinates the testing and evaluation of new pesticides proposed for public health use."

- International Programme on Chemical Safety (IPCS). Online: http://www.ilo.org/safework/info/WCMS_111391/lang--en/index.htm (accessed: 12 October 2020).
  WHO is the Executing Agency of the IPCS, whose main roles are to establish the scientific basis for safe use of chemicals, and to strengthen national capabilities and capacities for chemical safety.

North American Agencies

- NTP-CERHR Monograph on the Potential Human Reproductive and Development al Effects of Bisphenol-A (2008) Online: < https://pubmed.ncbi.nlm.nih.gov/19407859 > (accessed: 12 October 2020).

- US EPA Endocrine Disruption and Endocrine Disruptor Screening Program (EDSP). Online: http://www.epa.gov/endo/ (accessed: 12 October 2020).
  Describes the program, efforts to develop the screening test, and prioritization of chemicals to be tested.

- US National Institutes of Environmental Health Sciences (NIEHS), National Institutes of Health - Endocrine Disruptors. Online: http://www.niehs.nih.gov/health/topics/agents/endocrine/index.cfm. (accessed: 12 October 2020).
  Provides an overview of endocrine disruptors and recent research.

Non-Government Organizations

- The Endocrine Disruption Exchange, Inc. (TEDX). Online: < http://www.endocrinedisruption.com/> (accessed: 12 October 2020).

A non-profit organization that compiles and disseminates information on the health effects of endocrine disruptors. Now closed but still a source o f very relevant information.

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A Small Dose of Nanotoxicology
Or
An Introduction to the Health Effects of Nanomaterials

Chapter 21
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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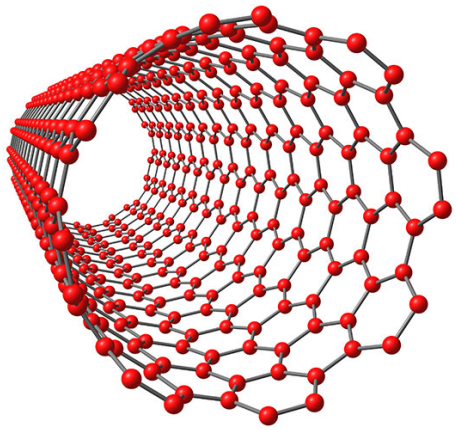
Supporting web sites
web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"



Carbon Nanotube – from NIOSH

Dossier

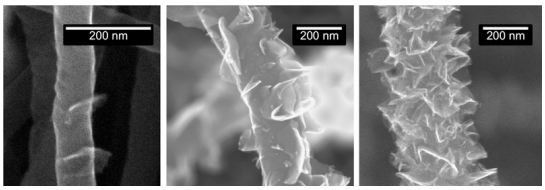
Toxicology of Nanomaterials

Name: Nanotoxicology
Definition of nanomaterials: materials sized from 1 to 100 nanometres (a nanometer is one billionth of a meter)
Use: wide range of chemicals, pesticides, plastics, flame retardants, medicine, paints, cosmetics, sunscreens, clothing, baby toys, and much more
Source: synthetic chemistry, plants
Recommended daily intake: none (not essential)
Absorption: intestine, respiratory system (lungs), skin
Sensitive individuals: fetus and children, workers
Toxicity/symptoms: endocrine system, mimic estrogen, anti-estrogenic, effects on hormone levels, sexual characteristics, reproduction, developmental effects
Regulatory facts: FDA and EPA are reviewing the use and potential hazards of nanomaterials
General facts: billions of pounds used every year in wide range of products
Environmental: widely distributed in environment and can affect wild life
Recommendations: minimize use, avoid exposure to children, and consider alternatives, expand research into toxicity, adopt precautionary approach

Case Studies

Carbon Nanotubes – Health Concerns?

Carbon nanotubes (CNTs) are typically created from one-atom-thick sheets of carbon, called graphene, that is rolled to form a hollow structure. Nanotubes can be either single-walled nanotubes or multi-walled nanotubes with a typical single-walled tube having a diameter of about 1 nanometer. CNTs are attractive to industry because they have multiple extraordinary properties including great hardness and strength, thermal and electrical conductivity, and optical properties as well as other capabilities depending on manufacture and other chemicals or elements that are added. CNTs are now common in industry processes as well consumer products such as skis, baseball bats, golf clubs, car parts, paints and others. There is a concern that CNTs may be hazardous to human and environmental health. The physical structure of nanotubes appears similar to that of asbestos fibers which appear to be long and sharp when magnified. Inhalation of asbestos can cause malignant mesothelioma a fatal lung cancer following a latency period of 20-40 years. Approximately 18,000 people died from malignant mesothelioma between 1999 and 2005. Animal studies using rodents have reported lung damage from CNTs similar to that caused by asbestos. This has important implications for people working with CNTs. The great variety in their ```size, shape, surface area, chemical coating make toxicology studies difficult to design and replicate. Some studies indicate that CNTs can cross cell walls and result in cell death.



Nanosilver

Nanosilver has many interesting characteristics but it was added to consumer products because of its antibacterial properties. Over two thousand years ago, Hippocrates (460 BC – 370 BC) acknowledged the antimicrobial and healing properties of silver. By the early 1900s the antimicrobial properties of silver were well known and used in a number of medical treatments. For example, people placed silver coins in milk to preserve its freshness. Silver sulfadiazine was used successfully to treat external infections and as an antiseptic in the treatment of burns but is now being replaced by nanosilver products. The use of silver in medicine declined with the introduction of antibiotics. Recently, the use of silver-impregnated wound dressing has increased particularly for burn patients. The ability to more easily manufacture nanosilver particles has stimulated a range of applications in consumer products to take advantage of its antibacterial properties. The products range from nanosilver-impregnated socks to baby toys, kitchen tools, paint, sunscreen, cosmetics, and water treatment, to name just a few. While nanosilver is increasingly used in industrial and consumer applications, there has not been a systematic evaluation of environmental or human health hazards. Cell-based studies clearly demonstrate that nanosilver can be toxic to a variety of organ cells, such as lung, liver,

kidney, and brain. There is also evidence that nanosilver particles are readily absorbed through inhalation or skin contact. In addition, there are concerns about environmental release of nanosilver when it is washed down the drain from consumer products. The toxic properties of silver are typical of heavy metals, but the advantage was that silver appeared to minimally toxic to humans, unlike other metals such as mercury, lead, or arsenic. Silver solutions, sometimes called colloidal silver, are marketed as alternative medicines with a variety of unsubstantiated beneficial effects.

Bear toy with nanosilver

Nanomaterials in Sunscreens

The ultraviolet radiation of the sun provides an excellent lesson in dose response in which a small dose is beneficial while a larger dose (exposure) to sunlight is hazardous. A small dose of or exposure to sunlight (ultraviolet UVB wavelength of 290-315 nanometers) is important for the production of vitamin D. The result of too much exposure of unprotected skin to the ultraviolet radiation of the sun is sunburn and is also associated with skin cancer, premature skin aging, and cataracts of the eyes. Sun exposure is mutagenic, causing damage to the cellular DNA, which can lead to cancer. To protect against the undesirable aspects of sunlight you can limit exposure, wear protective clothing, or apply sunscreens to unprotected skin. Sunscreens are made up of chemicals that absorb the UV radiation or of inorganic particles such as zinc oxide or titanium dioxide or a combination that reflect the UV radiation. Typical sunscreens block the UVB that causes sunburn but do not always block UVA ultraviolet light so it is recommended to use broad-spectrum sunscreens that block both UVA and UVB. Many sunscreens use nanosized zinc or titanium in part because the material becomes transparent at the nanoscale. Thus the white titanium appears clear instead of white. Chemicals can also be applied to the small particles, to enhance their effectiveness. The concern is that the nanosized particles may be absorbed through the skin or swallowed with unknown consequences. There is also concern that the material is washed off into the environment with unknown effects on the biotic community.

Introduction and History

Nanometer one billionth of a meter (10^{-9})
From the Greek nanos or 'dwarf'
Nanoparticle 1 – 100 nanometers

"Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications."
(see www.nano.gov)

Nanomaterials or nanoparticles are generally defined as being between 1 to 100 nanometers. At this scale, the physical and chemical properties of a material can change. For example, titanium, which is usually white, becomes clear at the nanoscale. The small size of nanoparticles means that there is a much greater surface area to volume ratio, which makes the material potentially more reactive. Nanoparticles can also be coated with chemicals that can react with the environment.

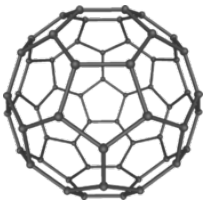
A nanometer in perspective

- Sheet of paper is about 100,000 nm thick.
- A strand of human DNA is 2.5 nanometers in diameter
- A human hair is approximately 80,000-100,000 nanometers in diameter
- There are 25,400,000 nm in an inch.
- A single gold atom is about a third of a nanometer in diameter
- A nanometer is a millionth (10^{-9}) of a millimeter

The use of nanomaterials dates back many centuries, when people unknowingly used them a variety of objects (see table below). For example, colloidal gold and silver was used to change the color of the glass in the Roman Lycurgus Cup, which looks opaque green but turns red when light shines from the inside. The famous steel of the Damascus swords was strengthened by carbon nanotubes that appeared during the rigorous shaping of the steel blade.

The understanding of these interesting phenomena and the emergence of the new field of nanotechnology was only possible be steady advances in technology. In 1936 the field-emission microscope, allowing the experimentally observation of atoms, was invented by Erwin Müller (1911-1977). The next major advance was in 1981 when Gerd Binnig and Heinrich Rohrer at IBM's Zurich lab invented the scanning tunneling microscope, which allowed imaging surfaces at the atomic level, resulting in the ability to "see" individual atoms. In the intervening years nanotechnology was predicted by the physicist Richard Feynman in a lecture in titled "There's Plenty of Room at the Bottom," in 1959 (reference below). He predicated that someday there would be the technology to manipulate individual atoms and molecules, something that did in fact happen. In 1985 the "buckyball" was discovered. It is a structure of carbon atoms that resembles a soccer ball in shape, though much smaller, of course (see illustration). Shortly thereafter, in 1991 carbon nanotubes were discovered, tubular in shape, very strong and with a range of interesting properties. In the late 1990s nanomaterials begin to appear in consumer products. The U.S. government took noticed and established the National Nanotechnology Initiative (NNI) to coordinate federal research and development efforts and to promote nanotechnology (http://nano.gov/). Gradually, authoritative reports advocating the need to address potential health, environmental, social, ethical, and regulatory issues associated with nanotechnology began to appear. The challenge now is to assess the consequences of human and ecological exposure to nanomaterials and balance these against the benefits.

Roman Lycurgus Cup



Milestones in Nanotechnology *

Year	Event
~300 AD	Lycurgus Cup (Rome), dichroic glass, looks opaque green but turns red when light shines from inside, the result of colloidal gold and silver in the glass. http://www.nano.gov/timeline
~600-1500	Stained glass windows in European cathedrals contained nanoparticles of gold chloride and other metal oxides
~1200-1800	"Damascus" saber blades contained carbon nanotubes and cementite nanowires
1857	Nanogold solutions can appear as different colors depending on the lighting – demonstrated by Michael Faraday (1791-1867)

1936	Field emission microscope, allowed the experimental observation of atoms - invented by Erwin Müller (1911-1977)
1959	"There's Plenty of Room at the Bottom" - first lecture on technology and engineering at the atomic scale by Richard Feynman (1918-1988) of the California Institute of Technology
1981	Scanning tunneling microscope - allowed imaging surfaces at the atomic level permitting scientists to "see" individual atoms, invented by Gerd Binnig and Heinrich Rohrer at IBM's Zurich lab.
1985	Buckminsterfullerene (C60) or buckyball was discovered by researchers at Rice University, soccer ball in shape and composed entirely of carbon.
1986	Atomic force microscope invented – provided the ability to view, measure, and manipulate materials down to fractions of a nanometer in size
1991	Carbon nanotube (CNT) – very strong, with electrical and thermal conductivity, entirely composed of carbon but in a tubular shape
1999-to?	Consumer products appeared employing nanotechnology, from cars to golf balls to paint to clothing and more
2000	National Nanotechnology Initiative (NNI) – started by President Clinton to coordinate Federal R&D efforts and promote nanotechnology (http://nano.gov/)
2004	Nanoscience and Nanotechnologies: Opportunities and Uncertainties published by Britain's Royal Society and the Royal Academy of Engineering, advocating the need to address potential health, environmental, social, ethical, and regulatory issues associated with nanotechnology
2008 updated 2011	Nanotechnology-Related Environmental, Health, and Safety (EHS) Research published by the US NNI (http://nano.gov/node/681)`
	*For a more detailed list see http://www.nano.gov/timeline

Nanomaterials in Use

There are over 1,300 identified consumer products employing nanomaterials, according to a list compiled by the Project on Emerging Nanotechnologies (see http://www.nanotechproject.org/). The products include baby toys such as a baby bear and baby blanket impregnated with nanosilver, sun screens and cosmetics, kitchen utensils, socks and shirts, paint, computer products, golf clubs and much more. Silver nanoparticles are being used in a wide variety of products to kill bacteria. Nanosilver is touted as being natural and "clinically

proven to fight against harmful bacteria, molds and mites". Nanoparticles in paint are advertised to improve adhesion and provide anti-mildew properties.

Nanomaterials are also widely used in university and industry research labs studying the properties of nanoparticles and trying to find new applications.

A basic issue is determining what products or facilities are using nanoparticles, the type of nanoparticles, and the quantity. As noted by the US EPA "Currently, tracking products that contain nanosilver is getting to be difficult because the products are almost always packaged under numerous brand names, and current labeling regulations do not require that the nanomaterials be listed as an ingredient." Maps that detail nanomaterials use and consumer product information are available (see http://www.nanotechproject.org/inventories/map/). Some organizations are working on a cradle-to-grave cost / risk evaluation for products using nanoparticles, that would access potential hazards across manufacture, use, and disposal (see U.S. EPA State of the Science Literature Review: Everything Nanosilver and More – August 2010 - https://www.epa.gov/chemical-research/research-nanomaterials). The European Union is implementing a new approach to nanomaterials called Classification, Labeling and Packaging (CLP) Regulation. CLP stipulates that if the form or physical state of a substance is changed, an evaluation must be done to determine if the hazard classification should be changed.

Health and Environmental Effects of Nanomaterials

Introduction

A basic principle of toxicology is that risk of harm is related to hazard, exposure, and individual sensitivity. The assessment of any of these parameters is complicated by the large variety of nanoparticles and nonmaterials, and the unique characteristics related to a nanoparticles small size and large surface area, which changes physical properties, as well as other applied chemicals. In addition, procedures for the analytical measurement of specific nanoparticles must be developed and validated for a variety of media such air, water, soil, tissue, blood or urine. Consideration must be given to other characteristics of the nanoparticles beyond just concentration to include size, shape, surface charge, crystal structure, surface chemistry, surface transformations, and chemical coatings. Most importantly the small size and the large surface area to volume ratio means that nanomaterials have unique physiochemical properties compared to materials of the same kind only larger. The challenge is determining how the nanomaterials interact with biological systems. The classic questions of persistence and bioaccumulation in animals, humans, or the environment must also be addressed. The development of a standard set

of procedures to assess the potential hazards of nanoparticles is urgently needed (see papers by Maynard et al. 2006 and 2011). Below are examples of the challenges associated with addressing the nanotoxicology of specific nanoparticles.

Distribution, exposure, and absorption

Given the wide range of products using or incorporating nanomaterials there is a growing distribution and potential for exposure to nanomaterials. In some products the nanomaterials are tightly bound or are a structural part of the product and thus not bioavailable. In products such as sun screens, however, the nanosized titanium dioxide or zinc oxide are applied to the skin where there is the potential for dermal absorption or oral ingestion. A variety of cosmetics are now employing nanomaterials, which increases the possibility of absorption through the skin. Breaks in the skin, sunburn, eczema, rashes, condition of skin, cut or scrape, or age of skin can accelerate absorption of the nanoparticles into the blood stream. There is also concern that these materials can be washed off the skin into the environment. There are similar concerns with nanosilver when used a bactericide because the nanomaterials must be bioavailable to be affective. Nanosilver particles may turn up in the water waste-stream and affect sewage treatment.

The manufacture of nanomaterials or their use in product manufacture presents important challenges for occupational exposure. For example, the inhalation of carbon nanotubes my result in damage to lung tissue and possibly lead to lung cancer as occurs with the inhalation of asbestos fibers. There have been calls for greater monitoring and control of potential exposure to nanotube materials. The unintended production of nanomaterials in diesel exhaust or soot (combustion-derived nanoparticles) can be a serious hazard to workers or those near the source of the exhaust, such as trucks, trains, or ships. The small size of these nanomaterials means that they can move deep into the lungs, resulting in acute effects such as asthma or long term damage. The nanoparticles can carry other chemical contaminants on their surface, such polycyclic aromatic hydrocarbons (PAHs), deep into the lungs.

Ultimately, there must be more information on the manufacture, use, fate, and transport of nanomaterials to better assess human exposure and ecological distribution of nanomaterials.

Health Effects

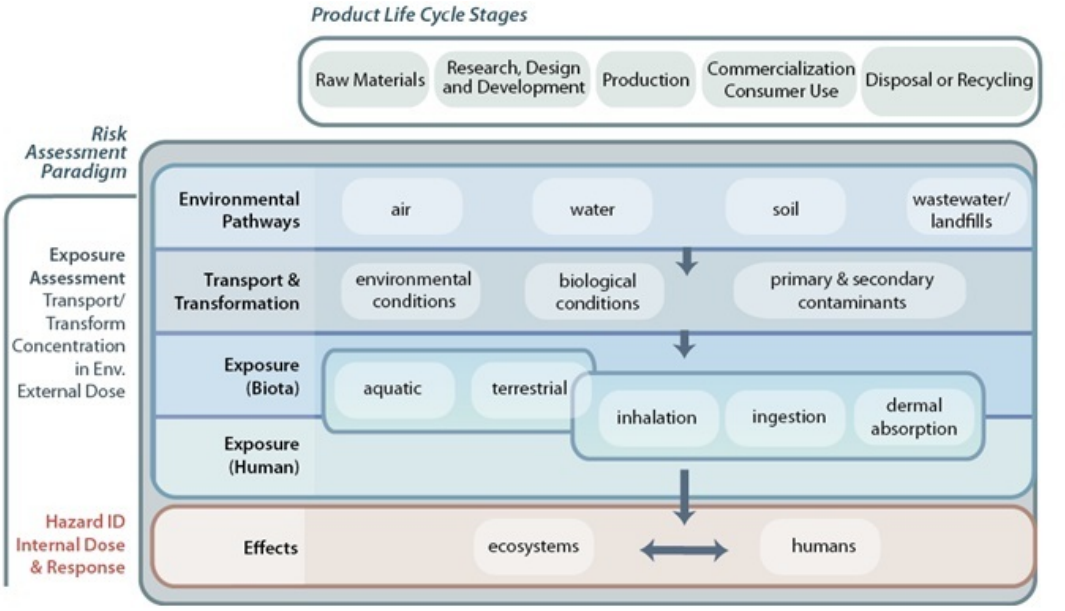
The potential health effects of nanoparticle exposure to humans or other organisms are just beginning. Studying the toxicity of nanoparticles is complicated by a host of factors such as the variety of substances, variation in size and surface area, chemical charge, chemical coating and other factors. An additional challenge is developing the analytical methodology for measuring the amount of nanomaterials in the tissue or biological fluid, to permit the assessment of tissue distribution or even cellular exposure. There are similar problems in evaluating distribution of the nanoparticles in the environmental

media of air, water, or soil. It is known, that once in the body, nanoparticles can distribute into all organs and cross cell boundaries. Once inside the cell, the nanoparticles may interact with cellular DNA or cell proteins, thus interfering with normal cell function or resulting in an inflammatory response. An area of some study is the ability of nanoparticles to increase the production of reactive oxygen species (ROS), including free radicals, which can result in oxidative stress, inflammation and other cellular damage. It should be remembered that nanosilver is useful precisely because it kills bacterial cells. Little is known about potential immunological effects of nanoparticles other than some reports of allergic response to nanosilver particles. Studies in fish exposed to nanoparticles in the water indicated that the nanoparticles were readily absorbed and caused brain damage and affected the liver. The consequences of ecological exposure to small organisms is poorly studied and could be significant because for a small organism a small exposure represents a big dose and potential serious consequences.

Persistence and bioaccumulation of the various nanomaterials in their many forms, shapes, and coating is not well understood. There has been very little study on the potential developmental effects of nanomaterial exposure. In summary, there are many challenges to assessing the risks of nanomaterials to human health or the environment and a lot more research needs to be done. The history of toxicology is replete with examples in which the application of technology got ahead of the understanding and/or regulation of its health and environmental effects. The results of some of these cases have been devastating.

Evaluation summary

The chart below from nano.gov provides a good summary of the challenges and areas of concern.



from: http://nano.gov/you/environmental-health-safety. The risk assessment paradigm (on left) integrated with nanomaterial life cycle stages (across top). (Design credit: N.R. Fuller of Sayo-Art.)

Reducing Exposure

Reducing exposure is predicated on knowing if there is exposure. It is currently very difficult even to know if there are nonmaterials in a given product. When they are present, their potential bioavailability may be unknown. As a result, exposure cannot be predicted or quantitively evaluated.

Regulation of nanotechnology

Currently there is no comprehensive regulation that addresses industrial process or consumer products that use nanomaterials or nanotechnology. Despite the rapid increase in the use nanoparticles in consumer products from socks to sunscreens and the potential for human and ecological exposure there is no consistent approach or requirement to evaluate potential hazardous effects. The US EPA is struggling to adapt the 1976 Toxic Substances Control Act (TSCA) to address the potential hazards of nanoparticles. The U.S. Food and Drug Administration (FDA) is challenged to address the use of nanomaterials in products it regulates, such as foods, cosmetics, drugs, devices, and veterinary products. The FDA has released draft guidance related to nanotechnology applications in cosmetics and food substances (see reference below). The laws governing

the Consumer Product Safety Commission do not mandate pre-marketing product approval, thus the CPSC can only address potential risk after public distribution of the product. The statement below is a good reminder of the problems faced by regulatory agencies as they try to address the use of nanomaterials. The workplace is an area of potentially high exposure to nanomaterials through inhalation, ingestion, or dermal exposure. The US Occupational Safety & Health Administration (OSHA) and National Institute for Occupational Safety and Health (NIOSH), that regulate and research occupational health and safety issues, attempt to address workplace exposures. For agencies and consumers, the failure to require adequate labeling of the use nanomaterials makes health assessments very difficult.

Consumer Product Safety Commission

Evaluation of Consumer Products
The potential safety and health risks of nanomaterials, as with other compounds that are incorporated into consumer products, can be assessed under existing CPSC statutes, regulations and guidelines. Neither the Consumer Product Safety Act (CPSA) nor the Federal Hazardous Substances Act (FHSA) requires the pre-market registration or approval of products. Thus, it is usually not until a product has been distributed in commerce that the CPSC would evaluate a product's potential risk to the public.

CPSC Nanomaterial Statement -
http://www.cpsc.gov/LIBRARY/CPSCNanoStatement.pdf

A basic issue is determining what products or facilities are using nanoparticles, the type of nanoparticles, and the quantity. As noted by the U.S. EPA "Currently, tracking products that contain nanosilver is getting to be difficult because the products are almost always packaged under numerous brand names, and current labeling regulations do not require that the nanomaterials be listed as an ingredient." Maps that detail nanomaterials use and consumer product information are available Some organizations are working on a cradle to grave cost / risk evaluation for products using nanoparticles that would access potential hazards across manufacture, use, and disposal (see US EPA State of the Science Literature Review: Everything Nanosilver and More – August 2010 - https://www.epa.gov/chemical-research/research-nanomaterials). The European Union is implementing a new approach to nanomaterials called Classification, Labeling and Packaging (CLP) Regulation. CLP stipulates that if the form or physical state of a substance is changed, an evaluation must be done to determine if the hazard classification should be changed.

Recommendation and Conclusions

Nanomaterials have interesting properties and have tremendous potential in many areas. Their use in industrials processes and consumer products is expanding rapidly. The huge challenge is making sure we understand the potential risks and that we properly balance the risks and the benefits. More research is needed on the potential human and ecological effects of nanomaterials. It is critical that our understanding and mitigation of potential adverse effects does not fall substantially behind the use of these materials.

More Information and References

Slide Presentation

- A Small Dose of Nanotoxicology presentation material and references online: www.asmalldoseoftoxicology.org
  Web site contains presentation material related to the health effects of nanomaterials.

European, Asian, and International Agencies

- Nanowerk - http://www.nanowerk.com/ (accessed 10 October 2020) – Food Safety - http://www.nanowerk.com/spotlight/spotid=25256.php
  Committed to educate, inform and inspire about nanosciences and nanotechnologies..

- World Health Organization - WHO Food Safety – Nanotechnology – "State of the art on the initiatives and activities relevant to risk assessment and risk management of nanotechnologies in the food and agriculture sectors". FAO/WHO technical paper 9 September 2013. Report Online: (accessed 14 October 2020)

North American Agencies

- The National Nanotechnology Initiative (NNI) Online at http://nano.gov/ (accessed: 14 October 2020)
  U.S. Government Initiative on Nanotechnology is a federal R&D program established to coordinate the multiagency efforts in nanoscale science, engineering, and technology.

- The National Nanotechnology Initiative (NNI) Timeline Online at http://www.nano.gov/timeline (accessed: 14 October 2020)
  U.S. Government Initiative on Nanotechnology time line of milestones in the development of nanotechnology.

- NASA Ames Center for Nanotechnology. Online at https://www.nasa.gov/centers/ames/research/technology-onepagers/ames_nanotech.html (accessed: 14 October 2020)
  Started in early 1996 the research work focuses on experimental research and development in nano and bio technologies (also great images).

- Nanotechnology at PNNL. The Pacific Northwest National Laboratory (PNNL), operated by Battelle for the U.S. Department of Energy. Online at http://www.pnl.gov/nano/ (accessed: 14 October 2020).
  Overview of nanoscience, nanoengineering and nanotechnology.

- Understanding Nanotechnology - http://www.understandingnano.com/ (accessed: 14 October 2020) also Regulation of Nanotechnology Materials and Productshttp://www.understandingnano.com/nanotechnology-regulation.html
  Web site dedicated to making nanotechnology concepts and applications understandable by anyone. Website is owned and published by Hawk's Perch Technical Writing, LLC.

- US EPA State of the Science Literature Review: Everything Nanosilver and More – August 2010Online: https://www.epa.gov/chemical-research/research-nanomaterials (accessed: 14 October 2020).

- US FDA Nanotechnology: Science and Research. Online: https://www.fda.gov/science-research/science-and-research-special-topics/nanotechnology-programs-fda (accessed: 14 October 2020).

- US OSHA Nanotechnology - Department of Labor - Occupational Safety & Health Administration (OSHA) - Online at http://www.osha.gov/dsg/nanotechnology/nanotechnology.html (accessed: 14 October 2020).
  Address worker safety and health issues related to the use or production of nanomaterials.

- US NIOSH Nanotechnology - Centers for Disease Control and Prevention - The National Institute for Occupational Safety and Health (NIOSH) - : http://www.cdc.gov/niosh/topics/nanotech/ (accessed: 14 October, 2020).

Does research on worker safety and issues related to the use or production of nanomaterials.

- The Center for Integrated Nanotechnologies (CINT) at Sandia National Laboratories is a Department of Energy/Office of Science Nanoscale Science Research Center (NSRC). Online at http://cint.lanl.gov (accessed: 14 October, 2020).
  "Our vision is to become a world leader in nanoscale science by developing the scientific principles that govern the design, performance, and integration of nanoscale materials."

Commercial / For profit Organizations

- Nanotechnology Now (NN) http://www.nanotech-now.com/ (accessed: 14 October, 2020) Nanotechnology Glossary http://www.nanotech-now.com/nanotechnology-glossary-N.htm
  NN was created to serve the information needs of business, government, academic, and public communities. And with the intention of becoming the most informative and current free collection of "nano" reference material.

Non-Government Organizations

- Nano-silver policy failure puts public health at risk by Friends of the Earth. Sept. 2011. Online at http://www.foe.org/news/archives/2011-09-nano-silver-and-bacterial-resistance (accessed: 14 October, 2020).
  A critical look at the use of nanosilver materials in a consumer products.

Wikipedia

Nanotoxicology – Online: https://en.wikipedia.org/wiki/Nanotoxicology. (accessed: 14 October 2020).
Nice summary of the intersection of nanomaterials and toxicology.

Nanotechnology – Online: https://en.wikipedia.org/wiki/Nanotechnology. (accessed: 14 October 2020).
Overview of nanotechnology and access to many wiki based articles on Nanotechnology.

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- Nanosilver: Weighing the Risks and Benefits. Environmental Health Perspectives. volume 121 | number 7 | July 2013. http://dx.doi.org/10.1289/ehp.121-a220.

A Small Dose of Animal and Plant Toxins
or
An Introduction to the Health Effects of Animal and Plant Toxins

Chapter 22
A Small Dose of Toxicology - The Health Effects of Common Chemicals

ED3 – Revised October 2020

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web: www.asmalldoseof.org - "A Small Dose of Toxicology"

The toxic mushroom *Amanita muscari*

Dossier – Animal Toxin

Name: Animal Venoms and Poisons
Use: medicinal uses
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), 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: global distribution, concern about expanding distribution to new areas
Recommendations: follow precautions for avoiding contact

Dossier – Pant Toxin

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

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 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 system. 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 similar effects on transport of cellular sodium, and produces similar neurological effects but 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 U.S. 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 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 our eye examination. 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 you take 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 and difficulty swallowing and 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 combined with its ability to alter the nervous system leads to youth experimentation 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 irregular heart rate. Ultimately the toxin, amatoxin, damages the liver cells resulting in 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 weighting 10 kg (or about 22 lbs) only 1 mg of amatoxin could result in a fatal poisoning. In 1997 the U.S. CDC reported that 2 out of 4 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).

Introduction and History

The creatures of the world, both animals and plants, produce a wide range of biologically active substances. Biologically active substances produced by animals or plants that cause an adverse effect are called toxins. Toxins refers only to toxic agents produced by animals and plants, not toxic substances such a 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 or just 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 predictors. 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 as 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. 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, 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. On the other hand, digitalis is quite toxic and the plants themselves are considered poisonous.

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

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 in the quest for food. Most venom is delivered from the mouth, as in snakes and spiders, 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 for example have poisons 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 marking to advertise their undesirable qualities.

The purpose of the venom is offensive while that of a poison is defensive, which in turn influences the characteristics of the toxin. 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 paralyzing the nervous system. Poisons are designed to teach a predator that this is not a good meal. They usually cause more localized pain to discourage a predator but depending on the dose and sensitivity of the individual the poison can be deadly.

There are some unique challenges for the animal that produces toxin, particularly venoms. The toxin must be concentrated and stored in 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 the drug developers.

Arthropods

Insects, spiders, scorpions, craps, centipedes, millipedes, and even plankton are all arthropods, the largest and most diverse animal phylum. Some are capable of producing very powerful toxins as an 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 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 represent a risk to humans. The venom of spiders is a complex mixture of neuroactive proteins and other chemicals. Researchers have studied venoms both to understand the mechanism of their effects but also in search of new drugs. If spiders were bigger they would be truly dangerous. Fortunately they are small, with only a very small about 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 a surrounding area becoming red and swollen. The venom has literally dissolved 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 17.1 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 (back, 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 – transmit other diseases	Tick paralysis – weakness & difficulty walking – Remove tick

Insects

Some moths and caterpillars produce irritating substances or fend off predators with substances that do not taste good and are thus avoided.

A much more aggressive group of insects, with great power for their size, that almost all of us have come in contact with, are 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 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 on the skin. Fire ants, common in the United States, produce a substance rich in alkaloids, which 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 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 a bee that will soon die. Left behind also 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 formic acid related substance that produces an intense burning.

Table 17.2 Insects

Examples	Poison or Venom	Comments
Moths and caterpillars	Irritating substance	Designed so they do not taste good
Ants	Variable - proteins, formic acid and other	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 in 500 deaths, 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 delivered through hinged tubular fangs that can be folded into the snake's mouth. The venom is quickly injected into the victim. 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 enzymatic-based substance, which 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 17.3 Reptiles

Class	Examples	Venom & Delivery	Symptoms
Vipers (Viperidae)	Rattlesnakes Water moccasins Copperheads Bushmasters	Very complex enzymatic based, advanced delivery – hinged tubular fangs	Swelling & necrosis at site, affects 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 onto 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 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 the 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 the 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, leading to 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 17.4 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	Na 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 Poisoning (ASP)	domoic acid	Confusion, memory loss, seizure, coma	Affects elderly
Coelenterates	Jelly fish, anemona, 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	Nervous system Numbness, paralysis, respiratory failure, death	Decreased Na channel permeability
Fish	Tuna, shark, sword fish	Mercury (toxicant)	Neurotoxic, reproductive effects	Not produced by fish itself, concentrated in muscle

Plant Toxins

In the battle to survive, plants have developed a wide array of defensive measures. Plants produce a range of chemicals designed to fend off predators or discourage consumption by insects or animals. We will look at the chemicals that plants produce from a human prospective, that is, how they affect us when we eat or come in contact with the plant. For thousands of years humans have experimented with plants in a search for food, as treatment for illness, and even to alter one perception of the world. Wide ranges of drugs are derived from plants, and the search continues by the world's leading pharmaceutical

companies. Others promote the use of plants as herbal or natural medicine. This section will focus only on the toxicity of some of the better-known plants, organized by organ system affected.

The tables below summarize the most important facts. The text provides additional information only if necessary to clarify a particular point. We can only scratch the surface of this fascinating area of biology.

Skin

One of the best protections 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. Poison ivy produces a class of chemicals called urushiol that cause a very 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 nettles (*Urtica*) releases histamine, acetylcholine, and serotonin from fine tubes with bulbs at the end that break off in the skin causing an intense burning or stinging sensation.

Table 17.5 Effects on Skin

Organ System	Symptoms	Plant Examples	Toxin / Comment
Skin	Allergic Dermatitis – Plant Rashes, itchy skin	Philodendron, poison ivy, cashew, bulbs of daffodils, hyacinths, tulips,	Antibody mediated after initial sensitization, very variable response. Allergens located on outer cells of plant
	Allergic Dermatitis – Pollen Sniffles & 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 & stinging sensation	Dumb cane (Dieffenbachia) Nettles (Urtica)	Calcium oxalate crystals coated with inflammatory proteins Fine tubes contain histamine, acetylcholine and serotonin

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 useful in some situations. The "sacred bark" of the California buckthorn produces cascara that is used to induce mild vomiting (a purgative).

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. On the other hand, 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 17.6 Gastrointestinal System

Organ System	**Symptoms**	**Plant Examples**	**Toxin / Comment**
Gastrointestinal	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 – block protein synthesis, very toxic: 5 to 6 beans can kill a child

Cardiovascular system

The medically important drug cardiovascular 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. The bees concentrate the toxin in the honey. 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. The first more scientific observations on the cardiovascular effects of consuming mistletoe berries were in 1597.

Table 17.7 Cardiovascular System

Organ System	**Symptoms**	**Plant Examples**	**Toxin / Comment**
Cardiovascular	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.

Nervous system

There are many plants that produce a wide variety of substances that can affect the nervous system. We have exploited the nervous system effects of plants for thousands of years and we continue to derive great value from some plants. In 399 B.C. Socrates died from a dose of the Greek state poison extracted from hemlock. An interesting story possibly about a poison found in hemlock is found in the Bible, Book of Numbers, 11:31-33. Hungry Israelites died after eating quail blown in from the sea. Some have speculated that the quail had consumed seeds from hemlock that contained coniine. The quail are not affected by coniine, but it is stored in their tissue making them deadly for humans to eat. The production and sale of coffee is a large international business solely designed to satisfy the demand for caffeine (see Chapter 4), the most widely consumed stimulant in the world. Mushrooms present another interesting challenge. Every year people are sickened and even die from eating poisonous mushrooms, while others consume them for their hallucinogenic effects.

Below is a brief look at some of the plants produce neuroactive substances.

Table 17.8 Nervous system

Organ System	**Symptoms**	**Plant Examples**	**Toxin / Comment**
Nervous System	Seizures	Water hemlock, (parsley family), mint family	Cicutoxin – affects potassium channels. Monoterpenes in mint oils
	Stimulation – 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 shell fish, Ibotenic acid, muscarinic, (hallucinations) Latthyrism – motor neuron degeneration
	Aberrant behavior, very excitable, muscle weakness, death	Locoweed - Australian & Western U.S. plant	Swainsonine toxin – liver enzyme inhibitor - well known to affect cattle
	Stimulation	Coffee bean, tea, cola nut,	Caffeine, most widely consumed stimulant in the world
	Neurotoxic – death	Poison hemlock (*Conium maculatum*)	Coniine – neurotoxic alkaloid – Poison used by Socrates
	Paralysis – demyelination of peripheral nerves	Buckthorn, coyotillo, tullidora (U.S., Mexico)	Anthracenones – attack the myelin that surrounds the peripheral nerves
	Atropine-like effects – dry mouth, dilated pupils, confusion, hallucinations, memory lose	*Solanaceae* family – jimsonweed, henbane, deadly nightshade (*Atropa belladonna*), angles trumpet (atropine and scopolamine)	Clinical effects of many of the plants recognized since ancient times. Deaths are rare but children vulnerable. Hallucinations from muscarine & psilocybin
	Neuromuscular – mild stimulation to muscle paralysis,	Tobacco – South American – *Strychnos* family (curare)	Nicotine –blocks acetylcholine receptors

	respiratory failure (curare), death	Blue green alga (anatonin A)	Curare – used as a hunting poison very potent receptor blocker

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 consume these mushrooms (see case study example). 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 17.9 Liver

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

Reproductive Effects

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* growing 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 17.10 Reproductive Effects

Organ System	**Symptoms**	**Plant Examples**	**Toxin / Comment**
Reproductive Effects	Teratogen – malformations in offspring (sheep)	*Veratrum californicum* – native to North America	Veratrum – blocks cholesterol synthesis – seen 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 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.

More Information and References

Slide Presentation

- A Small Dose of Animal and Plant Toxins presentation material and references. www.asmalldoseoftoxicology.org
  Web site contains presentation material related to the health effects of animals and plant toxins.

European, Asian, and International Agencies

- Amphibians and Reptiles of Europe. Online: < http://www.herp.it/> (accessed: 15 October 2020).
  A large sample of European Amphibians and Reptiles.

North American Agencies

- Society For The Study Of Amphibians And Reptiles (SSAR). Online: < http://www.ssarherps.org/> (accessed: 15 October 2020).).
  SSAR, a not-for-profit organization established to advance research, conservation, and education concerning amphibians and reptiles.

- Health Canada - Natural Health Products Directorate. Online: < https://www.canada.ca/en/health-canada/services/drugs-health-products/natural-non-prescription.html > (accessed: 15 October 2020).
  Natural Health Products Directorate works 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".

- U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition. Online: < https://www.fda.gov/about-fda/fda-organization/center-food-safety-and-applied-nutrition-cfsan > (accessed: 15 October 2020).
  Site has information on seafood health and safety issues.

- Northwest Fisheries Science Center's (NWFSC) Harmful Algal Bloom Program . Online: < https://www.fisheries.noaa.gov/region/west-coast#northwest-science > (accessed: 1 September 2020).
  NWFSC Harmful Algal Bloom Program, part of the U.S. National Oceanic and Atmospheric Administration, provides information related to algal blooms.

- U.S. Food & Drug Administration Center for Food Safety & Applied Nutrition Foodborne Pathogenic Microorganisms and Natural Toxins Handbook – The "Bad Bug Book". Online: < https://www.fda.gov/food/foodborne-pathogens/bad-bug-book-second-edition > (accessed: 15 September 2020).
  The "Bad Bug Book" contains extensive information on natural toxins either on the web or book can be downloaded.

Non-Government Organizations

- Natural Toxins Research Center (NTRC) - Texas A&M University System. Online: < http://www.tamuk.edu/artsci/departments/nntrc/index.html > (accessed: 16 June 2009).
  NTRC provides global research, training, and resources that will lead to the discovery of medically important toxins found in snake venoms.

- Cornell University Plants Poisonous to Livestock. Online: <http://www.ansci.cornell.edu/plants/index.html> (accessed: 15 September 2020).

This is "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.)".

- American Association of Poison Control Centers (AAPCC). Online: <http://www.aapcc.org/> (accessed: 15 September 2020).
  The AAPCC is a United States based organization of poison centers and interested individuals that coordinates information on common poisons.

- The Vaults of Erowid. Online: <http://www.erowid.org/ > (accessed: 15 September 2020).
  The Vaults of Erowid web site contains information on wide variety of natural plants and chemicals.

Wikipedia – a great library

- Mushroom poisoning. Online: https://en.wikipedia.org/wiki/Mushroom_poisoning (accessed: 15 September 2020).

- List of poisonous plants. Online: https://en.wikipedia.org/wiki/List_of_poisonous_plants (accessed: 15 September 2020).

- List of poisonous animals. Online: https://en.wikipedia.org/wiki/List_of_poisonous_animals (accessed: 15 September 2020).

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Venomous and Poisonous Animals: A Handbook for Biologists, Toxicologists and Toxinologists, Physicians and Pharmacists. by Dietrich Mebs, Medpharm 360 pages, 2002.

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A Small Dose of Neurotoxicology
Or
An Introduction to Toxicology of the Nervous System

Chapter 23
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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Introduction

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 evident by the billons of cells that form more billions upon billions of connections and all this taking place in a remarkably small confined space. In turn these cells communicate using different 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. Lastly, the vulnerability of the nervous system to both transient affects 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 are regular users of alcohol or caffeine as well as many other agents designed to affect the nervous system. Industrialization ushered in an era of rapid development of new chemicals with every expanding use in our society often accompanied by human exposure that we then learned, through sometimes 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 in the 1970s to advance our understanding of the effects of chemicals on the nervous system.

> "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

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 from these experiences we learn to manage our consumption of these chemicals to minimize any undesirable effects and maximize the desirable effects. In this sense, many of us are experienced neurotoxicologists.

Voluntary consumption of chemicals (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. On the hand, some drugs may produce undesirable nervous system side affects 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 affect 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 works that routinely use hearing protection devices a test 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 function 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 function 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 15.1).

Table 15.1 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. Fortunately, we metabolize caffeine quickly and the undesirable effects end. 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 twentieth 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 2nd BC). 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. However, lead is still turning up in children's toys, jewelry, as a stabilizer in PVC plastics, 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 a child of their genetic potential. You can learn more about developmental effects of lead from the lead chapter.

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 used 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 form one cell to communicate across a very small gap to be 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 produce 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. 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; a huge number when compared to

the 42 million transistors on a state of the art microprocessor chip, 100 million times more. The information processing capabilities of the brain is 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.

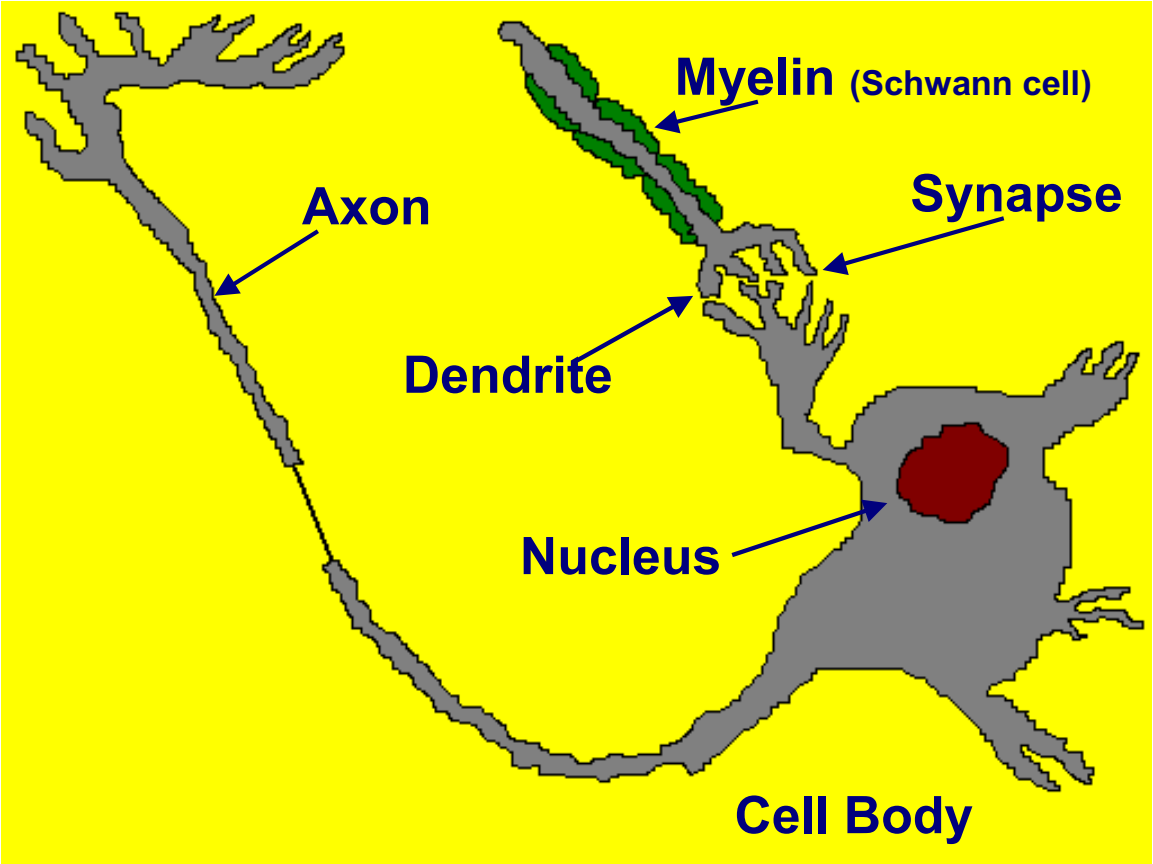
The peripheral nerves are undergoing many similar challenges. Think of the longest nerves in your body that run form the bottom of your spinal cord to your toes. These very long cells must be able to connect, grow and communicate with the right cells of the spinal cord, which in turns must communicate, with the cells of the brain.

Cells of the Nervous System

The nervous system consists of cells, called neurons (Figure 15.1), which are responsible for the majority of information transfers in the central and peripheral nerves 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 either 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 to 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, glia cells aid in the communication between the densely packed neurons of the CNS. 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 15.1 Neuron in the peripheral nervous system.



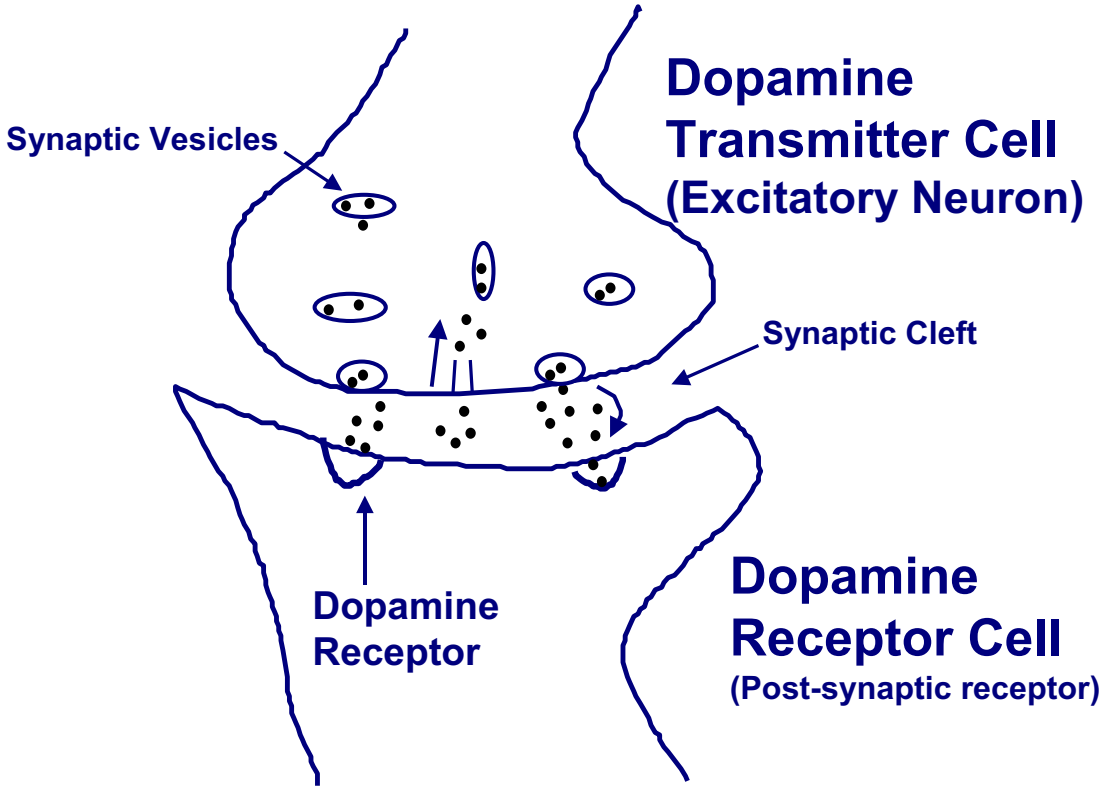
Transmission of information in the Nervous System

Nerve cells communicate by the release of chemicals (neurotransmitters) into the space between the cells (Figure 15.2). 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 15.2, 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 taken back up into the cell that released it and repackaged for future use.

In Parkinson's disease the dopamine-releasing cells are damaged or die, thus reducing the release of dopamine. Lose 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 along time Parkinson's disease was thought of as strictly aged related. In the 1970s this concept was changed when chemists produced a designer drug meant to mimic common narcotics that 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 15.2. 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 resulting quickly in 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 it can 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 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 release cell, which leaves the neurotransmitter free to again react with the receptor.

Table 15.2 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 15.2 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, and enhancement of senses, increase in appetite, sense of time
Cocaine	Blocks dopamine transporter, thus increasing dopaminergic stimulation	Increases alterness & energy, euphoria, insomnia, restlessness, fear, paranoia, hallucinations
Domoic Acid (shell fish)	Glutamate, aspartate	Loss of memory

Agents acting through a specific neurotransmitter are often transient, and exposure must be repeated to continue the effect, witness 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 thus 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 signal up 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 by attacking the insulation that surrounds the cells (myelinopathy) (Table 15.3 and Figure 15.3). Interfering with the neurotransmitter is a form of transmission toxicity, which was discussed in more detail above.

Table 15.3 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

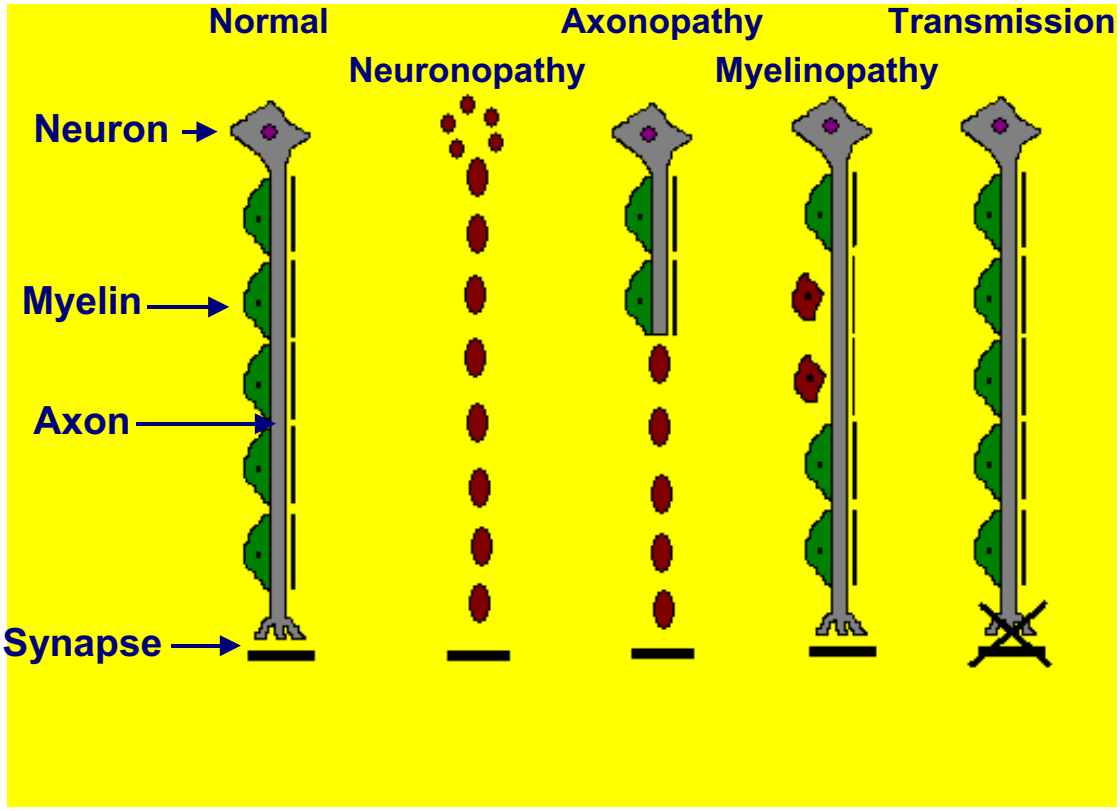


Figure 15.3 Peripheral Nervous System Damage

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 really 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 the that incidence of this disease had increased when compared to historical patterns, which correlated with the increased use and exposure to chemicals. Additional research 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, but much additional study has never found that aluminum exposure cause Alzheimer's disease. There is, however, some data supporting the possibility that exposure to mercury could result in accelerated age-related decline of cognitive function.

Neurological and psychiatric disorders such as depression, hyperactivity, and manic depression have driven many pharmaceutical companies and research 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 mange 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 15.4 History of Neurotoxicology

Year(s)	Location	Substance	Comments
400 BC to now	World wide	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	World wide	Mercury	Mine workers poisoned; 1930's hat industry (the Mad Hatters); 1950's Japan mercury in fish; 1970's 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 Stallinon 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	—	endrin	49 persons 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 severe poisoning, 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, TX)	BHMH(Lucel-7)	Seven employees at plastic bathtub manufacturing plant experience serious neurological problems following exposure to BHMH
1980s	United States	MPTP	Impurity in synthesis of illicit drug found to cause symptoms identical t those of Parkinson's disease
1981	Spain	toxic oil	20,000 persons poisoned by toxic substance in oil, resulting in more than 500 deaths; many suffer severe neuropathy
1984	Bhopal, India	Methyl isocyanate	December 2, 1984, an accident at the Union Carbide pesticide plant in Bhopal, India, released at least 30 tons of a highly toxic gas called methyl isocyanate,
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 phase 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 the chemicals on the nervous system. As children they have no control over these exposures that can result in a lifetime of disability. The nervous system of adults is clearly affected by a range of chemicals both those sought after and 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 a 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 the 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 15.5 Exposure to Neurotoxic Compounds

Home	a) children during development form maternal exposure b) children – lead in the home c) cleaning agents d) solvents
Workplace	a) solvents b) pesticides
Environment	a) lead b) mercury (in fish) c) pesticides d) 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 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 indicted by the Center for Disease Control but rather the standard was set based on a low level found in the general population as 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 an important augment for these compounds to be phased our 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.

More Information and References

Slide Presentation

A Small Dose of Neurotoxicology presentation material from INND Online: www.asmalldoseoftoxicology.org

Web site 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. Online: < https://www.oecd.org/chemicalsafety/> (accessed: 16 October 2020).
  This OECD Site contains general information on chemical safety as well as specific testing guidelines for neurotoxic effects of chemicals.

- International Neurotoxicology Association (INA). Online: <http://www.neurotoxicology.org/> (accessed: 16 October 2020).

Site provides links to neurotoxicology testing guidelines and other information on neurotoxicology.

- International Brain Research Organization (IBRO). Online: <http://www.ibro.org/> (accessed: 16 October 2020).
  "IBRO is a non-profit international organization for neuroscientists."

North American Agencies

- US Food and Drug Administration (FDA) – Neurotoxicology Division Access: Online: https://www.fda.gov/about-fda/nctr-research-offices-and-divisions/division-neurotoxicology > (accessed: 16 October 2020).
  The Division focuses on increasing FDA's understanding of the processes associated with neurotoxic outcomes—harmful effects associated with the brain and nervous system.

- US Environmental Protection Agency (EPA) Guidelines for Neurotoxicity Risk Assessment Online: < https://www.epa.gov/risk/guidelines-neurotoxicity-risk-assessment > (accessed: 16 October 2020).
  This EPA site provides information on neurotoxicity risk assessment.

- US National Institute of Health - National Institute of Neurological Disorders and Stroke (NINDS). Online: <http://www.ninds.nih.gov/> (accessed: 16 October 2020).
  NINDS is works to shape "the future of research and its relationship to brain diseases".

Non-Government Organizations

- Society for Neuroscience (SFN). Online: <www.sfn.org/> (accessed: 16 October 2020).
  "SFN is a nonprofit membership organization of basic scientists and physicians who study the brain and nervous system."

- ALS Association (ALSA) (amyotrophic lateral sclerosis). Online: <http://www.alsa.org/> (accessed: 16 October 2020).
  The mission of The ALS Association is to find a cure for and improve living with ALS.

- Developmental Neurotoxicology Society (DNTS; formerly known as the Neurobehavioral Teratology Society (NBTS). Online: http://www.dntshome.org/ (accessed: 16 October 2020).
  DNTS mission is to understand how the environment affects the health of infants and children.

Journal

NeuroToxicology is a peer-reviewed scientific journal covering research on the toxicology of the nervous system.

Wikipedia

Neurotoxicology - https://en.wikipedia.org/wiki/Neurotoxin

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Djai B. Heyer, Rhiannon M. Meredith Environmental toxicology: Sensitive periods of development and neurodevelopmental disorders. NeuroToxicology 58 (2017) 23–41.

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A Small Dose of Cancer and Genetic Toxicology
Or
An Introduction to Cancer and Genetic Toxicology

Chapter 24
A Small Dose of Toxicology - The Health Effects of Common Chemicals

ED3 – Revised October 2020

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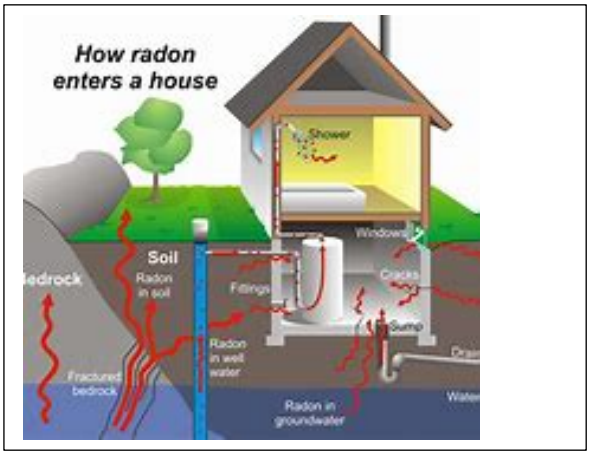


What is cancer?

Caner is an unwelcome, potentially life-threatening diagnosis that one third of us will experience. The oldest descriptions of cancer date back to Egypt 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." Clearly there was a desire and need to treat this treaded disease but the conclusion was "There is no treatment." It is only in the last 100 years that we have developed more sophisticated tools to treat cancer.

We now know much more about cancer, its causes and treatment. Technically 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 cancers 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 of the treatments of cancer have serious toxicological side effects. Cancer treatment must often balance the need to kill the cancerous cells without harming the normal cells of the body.

Initially, our understanding of cancer was advanced entirely by humans, the ultimate experimental subject. 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 very astute observation that exposure to soot might explain the high incidence of cancer of the scrotum in chimney sweeps. This was the first indication that exposure to chemicals, in this case a complex mixture, could cause cancer. 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.

The industrial revolution of the late 19th and early 20th century 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 cause of cancer. These early animals studies initiated the systematic investigation of the adverse effects of chemicals, which in many ways laid the foundation for the toxicological sciences.

But chemicals are not the only cause of cancer. During this incredible period of time, researchers such as Marie Curie (1867-1934) were discovering radioactivity, and in 1895 Wilhem Conrad Roentgen discovered X-rays. Marie Curie was ultimately awarded Nobel Prizes in both physics and chemistry, the only person ever so honored. One of her discoveries was 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 (for more details see the radiation chapter). The use of nuclear weapons by the U.S. military and subsequent development of the defense and nuclear industries has made us all well aware of the consequence of radiation exposure. Naturally occurring background radiation combined with our many medical and industrial exposures to radiation is responsible for some cancers.

Table 19.1 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 Dye
1902	Skin Cancer	X-rays
1908	Leukemia	Filterable Agent
1914	Experimental Induction of Skin Cancers (rabbit)	Coal Tar
1928	Experimental Induction of Skin Cancers	UV Light

As our observational powers improved so did our appreciation of what causes cancer. Epidemiology studies of various human populations indicated that inorganic metals such as arsenic and nickel could cause cancer. This was subsequently confirmed in laboratory studies with animals. 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 B_1 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.

Our cells and bodies have evolved to fight off cancer. Specific DNA repair mechanisms work to correct damaged DNA. Our immune system works to isolate and kill rogue cancer cells. Cancer appears to be part of life, an aspect of the aging process, even bad luck. Clearly, however, we have learned that reducing our exposure to certain chemical and physical agents can decrease the likelihood of developing cancer or at least delay its onset.

Causes of cancer

- **Organic chemicals (alcohol, tars, dyes, solvents ….)**
- **Inorganic agents (metals – arsenic, nickel …)**
- **Hormones**
- **Nutrition (diet, fat, high calories)**
- **Tobacco products**
- **Chemical mixtures**
- **Genetics**

Case Studies

Soot

In 1775, Percivall Pott observed that there was an increased incidence of cancer of the scrotum 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 hydrocarbon was isolated from coal tar and demonstrated to be carcinogenic. Despite this evidence, millions of people continue to exposure themselves to the soot from tobacco and suffer from the resulting lung cancer.

Benzene

Benzene, C6H6, is a clear, colorless liquid at room temperature and readily evaporates into the air. 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 20 chemicals in use. In the United States, benzene is present in gasoline at about 2% but in other countries may be up to 5%. It is readily absorbed by inhalation. Acute exposure can result in central nervous system effects such as dizziness, drowsiness and eventual unconscious. Liver enzymes convert benzene to more toxic metabolites, which is thought to be the mechanism for the carcinogenic effects of benzene. It is one of the few compounds classified as a human carcinogen. 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 out-gassing of glues, synthetic materials, and tobacco smoke. Smokers can have benzene body burdens 10 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 B.C., but the first recorded use of the word asbestos was in the 1st century A.D. 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 along 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 1900's 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 in many countries the total banning of the use of asbestos.

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 that smoke radon exposure results in a 3-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 break down of polonium that causes cancer. Polonium sticks to the tissues of the lung, and when it decays an alpha particle is released which damages the DNA of the closest cell, ultimate causing lung cancer. 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 a home, schools or public building, particularly the below ground 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.

Biology of Cancer and Genetic Toxicology

Cancer is the result of a cell's machinery going horribly out of control. In its simplest form, there is a permanent change a cell's DNA that allows that cell to repeatedly divide, passing this change along to the next cell. 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.

Genetic toxicology is the study of the effects of chemical and physical agents on genetic material. Genetic toxicology includes the study of DNA damage in living cells that leads to cancer but also changes in DNA that can be inherited from one generation to the next. The relevance of genetic toxicology is clearly evident from inheritable diseases such as phenylketonuria (an ability to metabolize phenylalanine), cystic fibrosis (lung disease), cycle cell anemia, or Tay-Sachs disease. Recent advances in the molecular biology and genomic sciences are leading to a far greater understanding of the genetic cause of the disease and even pointing the way to treatments.

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. At that time Muller and others were investigating how naturally occurring changes in the genes related to structural changes in the fruit fly. The rapidly reproducing and short-lived fruit fly was an excellent subject, but waiting for the spontaneous changes to occur in their genes—at that time they did not yet know about DNA—was slow. Muller used X-rays to increase the rate of change in genes, thus furthering his research efforts but also demonstrating an important toxicological property of X-rays. As our knowledge of biology deepened, it was discovered how the energy of X-rays caused changes in the DNA.

DNA, short for deoxyribonucleic acid, is the coding machinery of life. The beauty of DNA is in its simplicity that results in the complexity of life. The double helix of DNA is made of the compounds adenine (A), guanine (G), thymine (T), and cytosine (C). These chemical are bound in long stretches as AT and CG pairs, and wrapped in sugar molecules to hold them together. Long stretches of these AT and CG combinations form genes which when "read" produce the proteins that drive our cells.

Typical short strand of DNA

G C A G C A T
C G T C G T A

When sequences of G, C A, and T are read (by RNA), they are translated into other chemicals that eventually become proteins. Ideally the DNA sequence would not change except in the recombining that occurs during reproduction. However, a cell's DNA is

located in the very dynamic and demanding environment of the cell, where damage can occur. DNA damage occurs regularly as part of the cell process and from interaction with normal cellular chemicals as well as toxic chemicals. Fortunately, there is a very robust repair mechanism that rapidly and very accurately repairs the DNA damage. However, if for some reason the DNA is repaired incorrectly, a mutation occurs. The mutation is a subtle or even not-so-subtle change in the A, G, C, or T that make up the DNA.

Normal strand of DNA	---	Mutated Strand
G C A G C A T		**G C A A C A T**
C G T C G T A		**C G T T G T A**

Many of the mutations have no effect, some have minor effects, and even a smaller 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 it can be passed on to our offspring. Muller used X-rays to induce many mutations, some of which would be in the germ line cells of fruit fly and thus passed on to the next generation, which he could study.

Chemicals can damage the DNA and induce mutations. 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, but in general it is best to avoid 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 reduces tumor growth in mice. As the relationship of gene mutations to cancer become evident, genetic toxicology developed ways to test chemical and physical agents for their mutagenic properties. In the 1970s these tests were greatly simplified when Bruce Ames and others developed a cellular-based test for genetic mutations. This test became know as the Ames assay. Sophisticated variations of these tests are now required by many government regulatory agencies to test for the mutagenicity of a chemical before approval for use. For example, you would not want an artificial sweetener to cause mutations even at a very low rate.

Often it is not the parent compound that causes the cancer but instead a metabolite of the original compound. Ideally, a foreign chemical is made less toxic by metabolism, 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 that another chemical may encourage bioactivation or possibly interact to accelerate the development of a cancer. This knowledge influences the test required of chemicals because some were not mutagens until metabolized by liver enzymes. Many variations of the Ames test were developed that include liver cells to simulate the metabolism of 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?

The causes of cancer are varied: many known, most likely multiple, many unknown, and just a random event of no specific cause. We are continuously exposed to a wide range of chemical and physical agents, from both natural- and human-generated sources that may cause cancer. Because our knowledge is not perfect 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. We are just beginning to understand how our individual genetic makeup influences the possibility of our developing cancer and other genetic-based disease. In the future we will have even more knowledge about how the environment will interact with our genetics to cause cancer. We will briefly examine some of the known causes of cancer (Table 19.2).

Table 19.2 Exposure to Cancer Causing Agents

Cause	Example
Lifestyle	Tobacco consumption – drinking alcohol – diet
Environmental exposures	Air, drinking water
Organic chemicals	Benzo(a)pyrene (in coal tar), benzene
Inorganic chemicals and metals	Arsenic, cadmium, nickel
Fibers	Asbestos
Radiation	Sun (ultraviolet), radioactive material
Drugs	DES (diethylstilbestrol)
Viruses	Epstein-Barr virus, AIDS, papillomavirus
Genetic	Increased likelihood (breast cancer)

Lifestyle choices are the cause of many cancers. This is obvious from even a quick look at the correlation between tobacco consumption and lung cancer. The age-adjusted incidence of lung cancer for males peaked in the late 1980s and then started to decline with the decline in smoking. But for females, the increase in lung cancer appears to be peaking in the late 1990s and has yet to start declining. These data testify to the delayed onset of cancer and the relationship with tobacco consumption. Tobacco consumption probably accounts for between 25 to 40% of all cancer deaths.

The other major lifestyle choices associated with cancer are diet and alcohol consumption. Alcohol increases the incidence of liver disease and 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. On the other hand 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. As with most things, a high dose results in a greater response. In the most cases a high dose of calories, fat, alcohol or tobacco increases the likelihood of cancer.

Numerous organic chemical agents are known or highly likely to cause cancer. In the 1930s benzo(a)pyrene was isolated from coal tar and shown to cause skin cancer. Further investigation discovered an entire class of carcinogenic compounds called polycyclic aromatic hydrocarbons (PAHs) that caused cancer. Prior to World War II was a rich period of chemical synthesis. It was soon discovered that the azo dyes could also cause cancer. Naturally occurring contaminants from a grain fungus (aflatoxin) was found to be a potent liver carcinogen. A high incidence of liver cancer occurred when grain was poorly stored and people had liver disease such as hepatitis. People from hot and humid areas of Africa were particularly at risk for liver cancer from this grain fungus.

Inorganic chemicals and fibers are also carcinogenic. Arsenic is the most serious human carcinogen because of exposure from drinking water (see arsenic chapter). Cadmium, chromium and nickel are all lung carcinogens. The most common lung carcinogen is asbestos. The unique properties of asbestos made it ideal for many industrial and even home insulation applications. It was used in shipyards and in car brake pads. This widespread use resulted in thousand 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 the fibers inducing a chronic irritation of the lung resulting in an inflammatory response that ultimate results in some cells becoming cancerous.

Hormones regulate many important bodily functions and are also associated with cancer. One of the first hints of the relationship of hormones to cancers was the observation that nuns had a greater incidence of breast cancer. This was naturally related to the nuns not having children and now we know that may be hormone related. 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.

Who Is Vulnerable?

We are all vulnerable to cancer. Exposure to sunlight, background radiation, natural and manufactured chemicals, even oxygen can damage our DNA and result in cancer. We know that exposure to certain chemical or physical agents can increase the risk of developing cancer. There are many examples of workplace exposures resulting in cancer. Radon gas in coal and uranium mines can cause lung cancer. Asbestos exposure has affected thousand of workers and resulted in compensation claims from the companies. Of course, not smoking would result in the greatest reduction in cancers and other health related effects of tobacco.

The figures below illustrate the U.S. male and female cancer death rates from 1938 to 1998. The most striking changes, for both male and female are for lung cancer deaths, which also reflects the changes in cigarette smoking. The peaks in lung cancer correspond to the delay in onset of lung cancer after the start of smoking. The incidence of lung cancer in males is declining with the drop in tobacco consumption while that of females is just peaking.

Figure 19.1 Female Age Adjusted Caner Death Rates

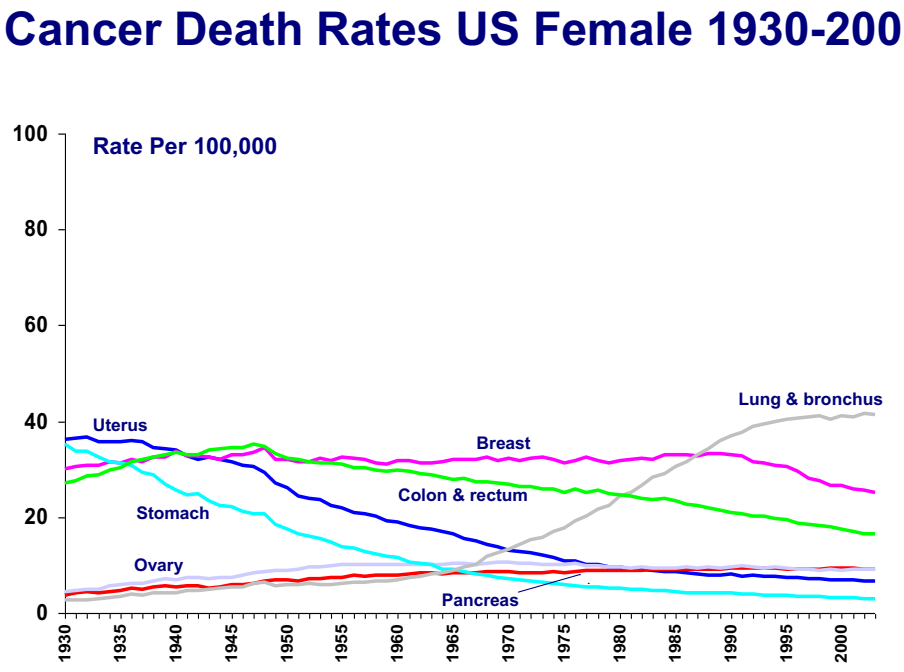
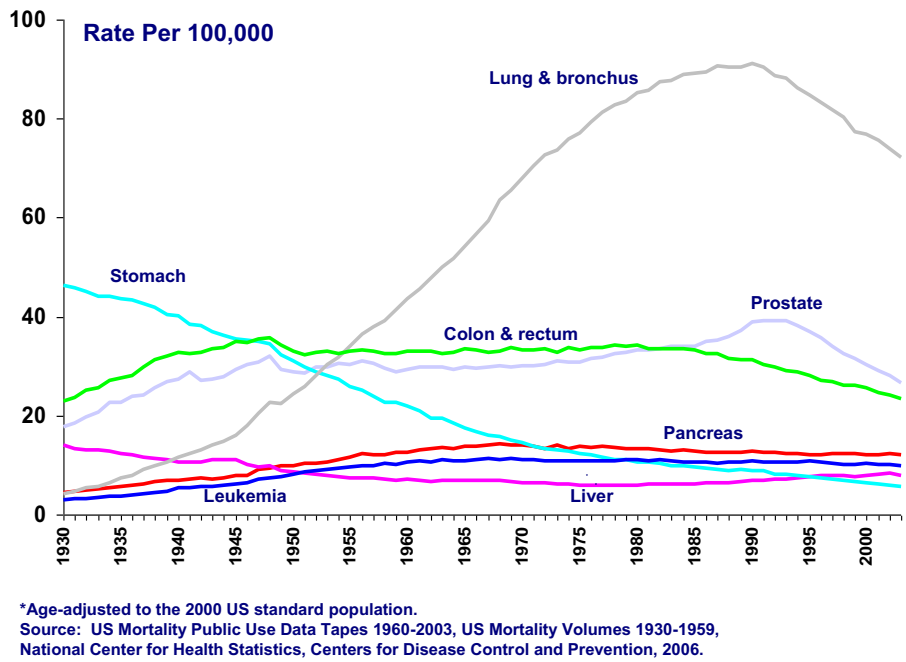


Figure 19.2 Male Age Adjusted Caner Death Rates



Advances in the genomic sciences will ultimately provide us with individual knowledge of our vulnerability to cancer. Some of these cancers are triggered by interaction of genes and environmental exposures. This knowledge will provide even more incentive to reduce or control exposure to specific agents.

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 and then 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 (Table 19.3). Other classification schemes are in use by the U.S. EPA, National Toxicology Program, NIOSH, and the State of California.

Table 19.3 IARC Classification Scheme for Human Carcinogenicity

Group	Evidence	Examples
1. Agent is human carcinogen	Sufficient human data	Aflatoxin, benzene, Arsenic
2A. Agent is probably a human carcinogen	Limited human data Sufficient animal data	PCBs, styrene oxide
2B. Agent is possibly a human carcinogen	Limited or inadequate human data Sufficient animal data	Styrene, TCDD
3. Agent is not classifiable as to a human carcinogen	Not enough human or animal data	Diazepam
4. Agent is probably not a human carcinogen	Inadequate human data Inadequate animal data	

Government regulatory agencies do not always agree on the classification of cancer-causing compounds and there are several different scheme used by different agencies. Elaborate animal study protocols are used to determine if an agent may cause cancer. As part of the approval process, government agencies require animal testing for carcinogenicity for new compounds entering the food supply. We want to be sure that the latest artificial sweetener will not cause cancer.

Recommendation and Conclusions

The war on cancer is really a long and never ending battle. While scientist have made great strides in understanding the causes of cancer and developing treatments, there will always be a risk for developing cancer. 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. The likelihood of developing cancer is related to our individual sensitivity and our dose / response curve. Less exposure means you will be less likely to develop cancer. Most importantly, there must be better labeling of ingredients and easier access to information about chemicals that may be carcinogenic.

More Information and References

Cancer & Genetic Toxicology presentation material and references online is available at www.asmalldoseoftoxicology.org

<u>European, Asian, and International Agencies</u>

- IARC - International Agency for Research on Cancer (IARC) - World Health Organization (WHO). Online: <http://www.iarc.fr/> (accessed: 18 October 2020).

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.

- World Health Organization (WHO) - Cancer. Online: < https://www.who.int/news-room/fact-sheets/detail/cancer > (accessed: 18 October 2020).
  Site has information on international exposure to a wide range of compounds that cause cancer.

- Japan – National Cancer Center (English). Online: < https://www.ncc.go.jp/en/ncch/index.html > (accessed: 18 October 2020).
  Site has information on the treatment and cause of cancer for Japan (Japanese or English version available).

- Cancer Research UK. Online: < https://www.cancerresearchuk.org/about-cancer/type > (accessed: 18 October 2020).
  Provide a free information service about cancer and cancer care for people with cancer and their families.

North American Agencies

General Information on Cancer

- US Environmental Protection Agency (EPA) - National Center for Environmental Assessment (NECA). Online: <http://cfpub.epa.gov/ncea/> (accessed: 19 October 2020).
  Applying science to improve risk assessment and environmental decision making.

- US National Cancer Institute (NCI). Online: <http://www.cancer.gov/> (accessed: 19 October 2020).
  The NCI, established under the National Cancer Act of 1937, is the Federal Government's principal agency for cancer research and training

- US Centers for Disease Control and Prevention (CDC). Online: <http://www.cdc.gov/cancer/> (accessed: 19 October 2020).
  The CDC monitors cancer incidence and promotes cancer prevention and control.

- US National Cancer Institute - NCI Cancer Atlas. Online: < https://gis.cancer.gov/canceratlas/ > (accessed: 19 October 2020).
  This site provides interactive maps, graphs (which are accessible to the blind and 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.

Benzene Information

- US Environmental Protection Agency (EPA). Online: nothing

- US Agency for Toxic Substance Disease Registry (ATSDR). Online: < https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14> (accessed: 19 October 2020).
  See fact sheets and case studies in environmental benzene.

Asbestos Information

- US Environmental Protection Agency (EPA). Online: nothing

- U.S. Cancer Information Service (CSI) - Asbestos Exposure and Cancer Risk. Online: < https://www.cancer.gov/about-cancer/causes-prevention/risk/substances/asbestos/asbestos-fact-sheet> (accessed: 19 October 2020).
  Extensive information on asbestos.

- US Agency for Toxic Substance Disease Registry (ATSDR). Online: < https://www.atsdr.cdc.gov/asbestos/health_effects_asbestos.html> (accessed: 19 October 2020).
  See fact sheets and case studies in environmental asbestos.

Radon Information

- US Environmental Protection Agency (EPA). Online: <http://www.epa.gov/radon/> (accessed: 19 October 2020).
  USEPA has extensive information on radon exposure in the U.S.

- U.S. Geological Survey (USGS). Online: < https://www.usgs.gov/faqs/what-radon?qt-news_science_products=0#qt-news_science_products> (accessed: 19 October 2020).
  Maps and supply information on radon in the United States

Non-Government Organizations

- The American Cancer Society (ACS). Online: <http://www.cancer.org/> (accessed: 19 October 2020).
  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.

- American Association for Cancer Research (AACR). Online: < http://www.aacr.org/ > (accessed: 19 October 2020).
  "AACR accelerates progress toward the prevention and cure of cancer by promoting research, education, communication, and collaboration."

- American Lung Association (ALA). Online: < https://www.lung.org > (accessed: 19 October 2020).
  Site has information on radon in the home environment as well as tobacco and asthma.

- Roswell Park Cancer Institute (PRCI). Online: < http://www.roswellpark.org/ > (accessed: 19 October 2020).
  PRCI is a comprehensive treatment center with a focus on prevention and education.

- Fred Hutchinson Cancer Research Center (FHCRC) Online: https://www.fredhutch.org (accessed: 19 October 2020).
  The mission of Fred Hutch is the elimination of cancer and related diseases as causes of human suffering and death.

Wikipedia

Cancer - https://en.wikipedia.org/wiki/Cancer - (accessed: 19 October 2020). Provides an overview with a list of cancer causes.

Cancer research - https://en.wikipedia.org/wiki/Cancer_research - (accessed: 19 October 2020).

Carcinogen - https://en.wikipedia.org/wiki/Carcinogen - (accessed: 19 October 2020).

Seminal papers-

The Hallmarks of Cancer, published in 2000, and Hallmarks of Cancer: The Next Generation, published in 2011, by Douglas Hanahan and Robert Weinberg. Together, these articles have been cited in over 30,000 published papers.

A Small Dose of Developmental Toxicology
Or
An Introduction to Pregnancy and Developmental Toxicology

Chapter 25
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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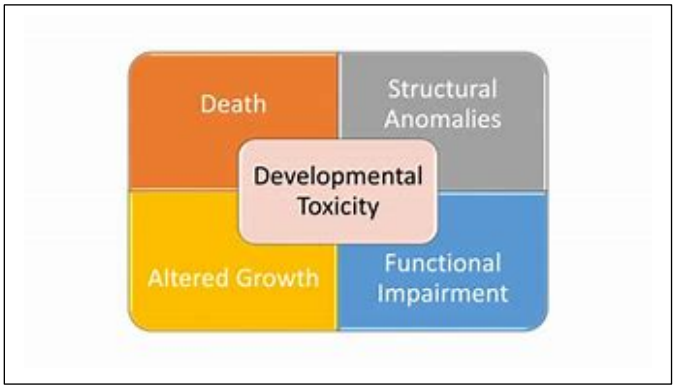
Supporting web sites
web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"



Introduction and History

> "Nature creates monsters for the purpose of astonishing us and amusing herself".
>
> Pliny (61–105 AD)

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 affects by chemical or physical agents. The 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 that 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 civilization invoked a fertility goddess 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 century, 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 increases 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 discovery that methylmercury was a developmental toxicant and in the 1960s when 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 the sperm before they meet 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 is ongoing effort 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 as well as technology provided greater insight into the reproductive process. This research developed into a detailed understanding of the hormones that control the female reproductive process. In the 1950s and 1960s 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, which 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 most cases start 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 women realizes that she is pregnant. The most common reason for a pregnancy to fail 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 contain only 23 chromosomes each and 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 to 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. In the 1950s understanding of the endocrine system lead to the development of birth control pills as a way to reduce fertility in humans. This is a desirable and planned use of endocrine disruptors. Subsequently, it was discovered that a

number of chemicals released into the environment could disrupt the endocrine system and reduce fertility of wildlife. Some are concerned that exposure to these chemicals at current levels, such as DDT and dioxin (TCDD), 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, decreased sperm motility, or 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.

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, diethylstibestrol
Pesticides	dibromochloropropane (DBCP), methoxychlor, linuron (herbicide)
Disease	Diabetes

Pregnancy

The female body undergoes a number of significant changes during pregnancy, some of which can increase vulnerability to toxic compounds. A healthy woman readily adapts to the chances 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 affected as oxygen consumption increases by 15 to 20%. Increased nutrients such as iron and calcium are required during pregnancy, and the gastrointestinal tract changes to increases 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, the 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 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.

Physiological changes during pregnancy

Cardiovascular	Increased - cardiac output heart rate, blood pressure, blood volume expands
Respiration	Oxygen consumption increases 15 to 20%
Urinary output	Increases
Gut absorption changes	Great absorption of iron and calcium (or toxic compounds such as lead)
Liver metabolism	Decreases for some drugs or chemicals – i.e. 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 experience with thalidomide, alcohol, methylmercury, lead and many other agents. Our knowledge has progressed from concern only 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, formation of 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 hold 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 list just a few of the compounds know to affect fetal and infant development.

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 (tetracylines), 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)

Examples

Thalidomide

Thalidomide was introduced in 1956 as 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 malformation 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 U.S. Food and Drug Administration, Frances Kelsey, MD, PhD, demanded additional safety data prior to approval of thalidomide. 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)

> "You will conceive and bear a son…now then be careful to take no wine or strong drink and to eat nothing unclean".
> Bible - Judges 13:3-4

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, and greatly reduced intelligence, results from maternal consumption of alcohol. FAS affects 4,000 to 12,000 newborn infants in the United States and from 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 (quick silver) to methylmercury (CH_3-Hg) 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 observed in other unfortunate incidents including the consumption of seed grain coated with organic mercury in Iraq. Further study revealed that even low levels of methylmercury exposure harm the developing fetus. Across the globe there are advisories on fish consumption related to methylmercury 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 Dioscerides 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 which 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 removing lead-based 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 subtle 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 Issues

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 with our increased understanding of potential effects on the nervous system. 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 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, the there are no safety testing requirements for "natural" products. In 1986, the voters of the State of California passed a law requiring that 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, continue throughout pregnancy and subsequent fetal development. Exposure to hazardous chemicals should be reduced or eliminated to prevent adverse developmental effects.

More Information and References

Slide Presentation

- Pregnancy and Developmental Toxicology presentation material and references online is available at Toxipedia. Online: www.asmalldoseoftoxicology.org
  Web site contains presentation material related to this book for each chapter.

European, Asian, and International Agencies

- European Teratology Society (ETS). Online: < http://www.etsoc.com/> (accessed: 19 October 2020).
  The society is dedicated to the prevention of adverse effects on reproduction and development.

- The Thalidomide Victims Association of Canada. Online: <http://www.thalidomide.ca> (accessed: 19 October 2020). Information on thalidomide in English or French.

- WHO Pregnancy. Online: < https://www.who.int/health-topics/maternal-health > (accessed: 19 October 2020). Information from World Health Organization on efforts to improve pregnancy outcome.

North American Agencies

- American College of Obstetricians and Gynecologists (ACOG) https://www.acog.org (accessed: 19 October 2020). The scientific evidence over the last 15 years shows that exposure to toxic environmental agents before conception and during pregnancy can have significant and long-lasting effects on reproductive health'

- Center for the Evaluation of Risks to Human Reproduction (CERHR) - The National Toxicology Program. Online: < https://pubmed.ncbi.nlm.nih.gov/15729732/ > (accessed: 19 October 2020). CERHR web site has "information about potentially hazardous effects of chemicals on human reproduction and development."

- Developmental & Reproductive Toxicity NTP is located at the National Institute of Environmental Health Sciences, part of the National Institutes of Health. Online: https://ntp.niehs.nih.gov/whatwestudy/testpgm/devrepro/index.html - (accessed: 19 October 2020).

- National Agricultural Library - Nutrition During Pregnancy Online: <http://vm.cfsan.fda.gov/~dms/wh-preg.html> (accessed: 19 October 2020) This web site contains an extensive for pregnant women.

- US Centers for Disease Control and Prevention (CDC) – Health Topic: Pregnancy. Online: <http://www.cdc.gov/pregnancy/ (accessed: 19 October 2020) Site contains information and links on pregnancy and fetal development.

- California – Office of Environmental Health Hazard Assessment – Proposition 65. Online: <http://www.oehha.ca.gov/prop65.html> (accessed: 19 2009) 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".

Non-Government Organizations

- The Society for Birth Defects Research and Prevention (BDRP) (was the Teratology Society). Online: < https://birthdefectsresearch.org/ > Accessed: 19 October 2020).
  BDRP is the premier source for cutting-edge research and authoritative information related to birth defects and other disorders of developmental origin.

- Society for Developmental Biology. Online: < http://www.sdbonline.org/> (accessed: 19 October 2020).
  "The purpose of the Society is to further the study of development in all organisms."

- March of Dimes. Online: <http://www.modimes.org> (accessed: 19 October 2020).
  "March of Dimes leads the fight for the health of all moms and babies. We believe that every baby deserves the best possible start. Unfortunately, not all babies get one. We are changing that."

Wikipedia

- Developmental toxicity – Online: https://en.wikipedia.org/wiki/Developmental_toxicity. (accessed: 19 October 2020).

References

- Riddle, John M. Eve's Herbs: A History of Contraception and Abortion in the West., Harvard University Press; Cambridge, Mass 1999, 352 pages.

- World Health Organization, Geneva Switzerland. Principles for Evaluating Health Risks in Children Associated with Exposure to Chemicals. Environmental Health Criteria 237 (2007). http://www.who.int/ipcs/publications/ehc/ehc237.pdf. (accessed: 26 July 2009).
- This volume addresses the unique vulnerability of children to social economic factors, nutrition, environmental chemicals and other hazards.

- Hood, R.D. (2005) Developmental and Reproductive Toxicology: A Practical Approach, 2nd edition CRC Press, Boca Raton, FL

A Small Dose of Air Pollution
or
An Introduction to the Health Effects of Air Pollution

Chapter 26
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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Air pollution new and old

Dossier

Toxicology of Air Pollution

Name: Air Pollutants
Definition of air pollution: contamination of the indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere. Includes a wide range of chemicals and contaminants but six pollutants of noted concern are ozone, particulate matter, carbon monoxide, nitrogen oxides, sulfur dioxide, and lead
Use: Major pollutants do not have uses themselves but are byproducts of combustion and other processes in transportation, energy generation, etc.
Recommended daily intake: none (not essential)
Absorption: respiratory system (lungs)
Sensitive individuals: fetus and children, elderly, people with chronic respiratory problems
Toxicity/symptoms: irritation of the respiratory tract, dizziness, headache, neurological disorders, cancer, and reproductive effects
Regulatory facts: in the US the EPA sets some standards for air pollutants
General facts: emissions of billions of pounds of chemicals and particulate matter every year from a wide range of products and industries, and from combustion of fossil fuels such as coal and gasoline
Environmental effects: widely distributed in environment, linked with climate change and acid rain, and can affect wildlife and ecological health
Recommendations: minimize air pollution on a global scale, avoid exposure to children and other sensitive groups, expand research on toxicity and alternative sources of energy, adopt precautionary approach, reduce the use of fossil fuels, support international treaties

Case Studies

> "As soon as I had gotten out of the heavy air of Rome, and from the stink of the chimneys thereof, which being stirred, poured forth whatever pestilential vapors and soot they had enclosed in them, I felt an alteration to my disposition"
> 61 C.E., Seneca, Roman philosopher and noted essayist

Donora Smog

The Donora Smog occurred in Donora, Pennsylvania, USA, starting on October 27, 1948 and lasting until it rained on October 31. The five days of severe air pollution caused the death of at least 20 people and respiratory illness (coughing and other signs of respiratory distress) in approximately 7000 people, half the population of Donora. Donora was a mill town on the Monongahela River, 24 miles southeast of Pittsburgh, PA, built to take advantage of inexpensive Pennsylvania coal. US Steel's Donora Zinc Works and American Steel and Wire plant released hydrogen fluoride, sulfur dioxide, and other poisonous emissions, which winds typically diluted and dispersed. . This severe smog occurred when warmer air trapped a layer of colder air beneath it, concentrating the industrial pollutants and forming yellowish acid smog. The air was so dirty that emergency responders reported great difficulty in reaching sickened families. In addition, smog and other emissions killed much of the vegetation within a half-mile radius of the plants. There are reports that even ten years after this event, mortality rates in the community remained elevated. This event was a major stimulus for enactment of the US Clean Air Act and the creation of the Environmental Protection Agency. Devra Davis documented this event in her 2002 book *When Smoke Ran Like Water: Tales of Environmental Deception and the Battle Against Pollution* (see reference below).

Great Smog of London

The great smog of London, also referred to as the Big Smoke, started on December 5, 1952, and lasted until December 9, 1952. Initial reports stated that 4,000 people died

prematurely due to the smog, but this toll was raised to as many as 12,000 people, with over 100,000 suffering a variety of illnesses. Many of the deaths were the result of respiratory infections, with the young and elderly being the most vulnerable. This event was the worst of a series of deadly smog events in London caused by the population growth and the Industrial Revolution. The Great Smog was caused by a cold spell that resulted in the increased burning of coal to keep warm as well as emissions from several coal burning power plants located in the city. The type of coal used, low-grade with high sulfurous content, increased the amount of sulfur dioxide in the smoke and contributed to the severity of the smog. In addition, diesel buses had replaced electric trams, adding to the air pollution. The word "smog" was derived by combining of the words smoke and fog. The yellow-black color of the London smog resulted from chimney smoke and particles of soot from the burning of coal. The large number of deaths and illnesses resulted in the passage of the Clean Air Act of 1956 by an Act of the Parliament of the United Kingdom. Overall this event was an significant impetus to the development of the modern environmental and human health movement.


London Smog 1952

Diesel Exhaust

Diesel exhaust produced from a wide range of equipment including trucks, ships, trains, construction equipment, farm vehicles, and buses is a serious human health and environmental hazard. It is a very significant contributor to air pollution particularly in high population areas, especially when high-sulfur fuel is used. Air pollutants in diesel exhaust include nitrogen oxides and fine-particle material, sometimes referred to as diesel particulate matter (DPM). In addition, the unintended production of nanomaterials in diesel exhaust or soot (combustion-derived nanoparticles) can be a serious hazard to workers and others near the source of the exhaust, such as trucks, trains, or ships. The small size of these nanomaterials allows them to move deep into the lungs, resulting in acute effects such as asthma, or long-term damage. The nanoparticles can also carry chemical contaminants on their surface, such polycyclic aromatic hydrocarbons (PAHs), deep into the lungs (see nanotoxicology chapter). Diesel exhaust exposure can adversely affect health, resulting in increased asthma attacks, cardiopulmonary disease such as heart attack and stroke, respiratory disease such as pneumonia and lung cancer, adverse birth outcomes, and premature death.

Air Pollution Defined
Air pollution is contamination of the indoor or outdoor environment by any chemical, physical or biological agent that modifies the natural characteristics of the atmosphere. (WHO - http://www.who.int/topics/air_pollution/en/)

Introduction and History

"the smell of burning coal was disagreeable and troublesome".
Theophrastus (a student of Aristotle) Ancient Greece (3rd century BCE)

Air pollution is not new but the volume and concentration of contaminants has steadily increased with the development of modern civilization and can be very harmful to human health, even deadly. The Greeks and Romans noted the polluted air millennia ago, as documented in writings of Theophrastus and Seneca. The source of this foul air was stoves, home heating, and smelting of ore for lead and silver, and more generally from the growing population and concentration of people in cities. Evidence of the global distribution of lead air pollution from this period is found in the elevated lead concentrations preserved in Greenland ice sheets.

The unrestrained use of fossil fuels and subsequent air pollution was much worse in the Industrial Revolution. The use coal- and wood-burning stoves for heating and cooking, combined with industrial burning of fossil fuels, created massive air pollution events, especially when weather inversions occurred (see table of some notable events). One of the first people to take note of the air pollution in London was John Evelyn, who wrote the pamphlet *Fumifugium*, or, *The inconveniencie of the aer and smoak of London dissipated together with some remedies humbly proposed* in 1661. He recommended that polluting industries such as cement kilns and brewers be relocated outside the city. Part of the problem was that usage of high-sulfur sea coal increased as wood became scarce.

In 1663 Evelyn's pamphlet was summarized in stanza 23 of "Ballad of Gresham College," given here in modern English.

[...] shows that 'tis the sea-coal smoke
That always London does environ,
Which does our lungs and spirits choke,
Our hanging spoil, and rust our iron.
Let none at Fumifuge be scoffing
Who heard at Church our Sunday's coughing.

As deadly air pollution events occurred with greater frequency in countries undergoing rapid industrialization, people became less tolerant and demanded that governments take action to improve air quality. In developed countries, changing fuel sources and installing pollution control devices have substantially improved air quality. However, developing countries such as India and China have struggled to balance rapid industrial growth with air pollution control. The use of coal-fired electric power plants with limited pollution control devices, often near cities, has created very serious air pollution problems. While there are ways to reduce air pollution from large point sources like power plants, non-point sources such as automobiles and trucks are increasing dramatically as economies develop. Ongoing research documents the serious health problems associated with air pollution, particularly for children.

Air pollutants can distribute widely in the environment and cause significant ecological harm. For example, toxaphene, a pesticide used in the corn belt of the United States, and flame retardants, used widely in industry and commercial products, can be found in the fatty tissues of animals in the Arctic, like the polar bear. Airborne nitrogen oxides deposited in water bodies cause increased algae growth, which depletes oxygen in the water and kills fish. Power plants emit sulfur dioxide, which is carried thousands of miles from the source and contributes to acid rain. Coal contains a wide range of contaminants such as mercury that are released as air pollution if not trapped during the combustion process. When the mercury falls out of the air into water, it is converted to methylmercury and bioaccumulates up the food chain, contaminating fish, an important food source for both people and wildlife.

Notable Air Pollution Events

> "Fly the city, shun its turbid air
> Breathe not the chaos of eternal smoke"
> British medical poet John Armstrong, The Art of Preserving Health, 1744

Date	Place	Description
500 BC - 300 AD	Greek and Roman empires	Mining and smelting of lead and silver caused pollution preserved in the Greenland Ice Sheets
300 BC	Athens	Theophrastus stated, "smell of burning coal was disagreeable and troublesome."
61 AD	Rome	Seneca noted oppressive conditions of the Roman air

		Roman's used "beach houses" to escape city pollution and installed chimneys 8 meters tall to dissipate smoke.
1200	London	Middle ages – burning of oak wood and then "sea coal" (often high sulfur) in kilns for cement, heating, and brewing.
1285	London	Commission established to address severe air pollution.
1661	London	John Evelyn published one of the first pamphlets on air pollution.
1698	England / World	First crude steam engines, start of Industrial Revolution, centralized industrial manufacturing powered by coal.
1306	England	Edward I bans coal use in kilns, to no effect, sea coal use increases.
1869	Pittsburgh, PA	Burning of soft coal in locomotives in the city outlawed, but ban not enforced
1930	Meuse Valley, Belgium	Meuse Valley fog/smog from industrial air pollution and climatic conditions killed 60 people and sickened 1000s.
1948	Donora, Pennsylvania, USA	Five days of severe air pollution from coal-fired steel plants resulted in the death of at least 20 people and illness in 7000, half the population.
1952	London, England	The Big Smoke: smog from coal burning lasted four days; initial reports of 4,000 deaths, but toll was raised to as many as 12,000 people, with over 100,000 suffering a variety of illnesses
1962	Silent Spring	Rachel Carson's book Silent Spring published, credited with launching the global environmental movement.
1966	New York City	Elevated SO_2 levels during Thanksgiving (November 23-25) blamed for excess deaths
1970	Earth Day	Environmental teach-in called Earth Day was held for the first time on April 22, 1970.
1984	Bhopal, India	Accidental release of 40 metric tons of methyl isocyanate from a Union Carbide pesticide plant, approximately 15,000 people died and 150,000-600,000 injured
1986	Lake Nyos, Cameroon	Carbon dioxide released from the lake, suffocated 1800 people and livestock from nearby villages.

Indoor Air Pollution / Air Quality

Indoor air quality is critically important because many people, particularly the young and the elderly, spend a great amount of time inside homes or schools. The workplace, either the office building or manufacturing facility, is also a potential setting for hazardous chemical exposure. The table below lists some sources of indoor air pollutants; inadequate ventilation of the indoor environment can cause chemicals released from consumer products to build up. Smoke from wood-burning stoves and fireplaces can also significantly contribute to outdoor air pollution in the local community.

The health effects from indoor air pollutants vary widely depending on the pollutants involved and the age and medical condition of those exposed. Children are vulnerable because they have small airways and respiration rates higher than adults'. Acute effects can include fatigue, headache, dizziness, sore throat, irritation of the eyes and nose, asthma, and anxiety. Chronic or repeated exposure can result in chronic obstructive respiratory disease (COPD), asthma, heart disease, and cancer. This cluster of health symptoms has been associated with "sick-building" syndrome, where poor building ventilation leads to adverse health effects.

It is estimated that 3 billion people, mostly in poor and developing countries, use wood, animal dung, crop waste, or coal for cooking and for heating their homes. This exposes men, women, and children to excessive levels of particulate matter, which increases the likelihood of COPD and pneumonia; children are particularly susceptible and premature death may result.

Table X – Sources of Indoor Air Pollutants

Combustion products	Wood-burning stove or fireplace, tobacco products (second-hand smoke), oil, gas, kerosene, coal, charcoal, cooking fuels
Building materials	Asbestos-containing insulation or tiles, lead based paint, new carpet (off gassing of glues/solvents), old carpet (mold, dust containing tracked-in contaminants), furniture or cabinetry containing pressed wood products (off gas formaldehyde), paint, sealants
Consumer products	Cleaning products, bathroom curtains, personal care products, glues and maintenance products, hobby materials, cars in attached garages, paints, art supplies, perfumes, air fresheners, dryer sheets (Read chapter on Toxics in the Home for more information.)
Other items	Radon, pesticides, lead, asbestos, carbon monoxide, pets, mold

Air Pollutants

In the United States the first federal legislation addressing air pollution was the Air Pollution Control Act of 1955, which that primarily called for research. The first effort to control air pollution was the Clean Air Act of 1963. This act was significantly amended and strengthened in 1970, and established the National Ambient Air Quality Standards (NAAQS) for six priority pollutants. The Clean Air Act has since been amended several times, most recently in 1990 with the inclusion of actions to address acid rain. Concerns about the six air pollutants addressed by the National Ambient Air Quality Standards are briefly summarized below.

Ozone (O_3)

Ozone consists of three oxygen atoms and was first recognized by Christian Friedrich Schönbein in 1840 as part of the odor from lightning storms. It is beneficial in the upper layer of earth's atmosphere (stratosphere) as it blocks the sun's harmful ultraviolet rays, but in the breathing zone of the lower atmosphere (troposphere), ozone is a pervasive and harmful outdoor air pollutant. Ozone is created when sunlight reacts with pollutants such as volatile organic compounds (VOCs) and nitrogen oxides (NO_x) that are released from the burning of fossil fuels by cars, trucks, electrical power plants, and chemical plants. While low levels of ozone occur naturally, exposure to elevated levels of ozone are harmful to the lungs. Acute exposure can cause difficulty breathing, coughing, pain while breathing, and asthma attacks, while chronic exposure can cause asthma and permanent damage to the lungs, aggravating chronic lung diseases like emphysema and bronchitis, generally reducing lung function, and increasing susceptibility to respiratory illness. Tangible efforts to reduce ozone levels, such as reducing the use of motor vehicles, have been taken for Olympic sporting events so the performance of athletes is not impaired. In the United States ground-level ozone is one of six major air pollutants regulated by National Ambient Air Quality Standards (NAAQS) under the US Clean Air Act.

Nitrogen Oxides (NO_x)

The two most significant sources of nitrogen oxides, particularly the highly reactive nitrogen dioxide (NO_2), are motor vehicles and the burning of coal for electric power generation or industrial boilers. Additional sources include forest fires, the burning of wood for home heating and cooking, and tobacco smoke. Low levels of exposure to NO_x cause respiratory tract irritation of the nose, throat and lungs, coughing, asthma attacks, and difficulty breathing; high levels of chronic exposure cause permanent damage to the tissues of the respiratory tract, resulting in emphysema and bronchitis. The health effects are of particular concern for people living near sources of NO_2 such as busy roadways. Nitrogen oxides also contribute to acid rain and interact with other pollutants and sunlight to catalyze the formation of ozone. In the United States nitrogen oxides are one of six

major air pollutants regulated by National Ambient Air Quality Standards (NAAQS) under the US Clean Air Act.

Sulfur Dioxide (SO_2)

The primary source of atmospheric sulfur dioxide is the burning of coal and oil to generate electricity or to facilitate other industrial process such as smelting for metallic ores. Burning high-sulfur fuels on trucks, locomotives, and ships is also a significant source. Sulfur dioxide is also an important precursor, along with nitrogen dioxide, to sulfuric acid or acid rain (H_2SO_4), and it reacts with other pollutants in the atmosphere to form small particulates. Most people are familiar with the strong rotten-egg odor of sulfur dioxide. Even low-level exposures can trigger a constriction of the bronchi, difficulty breathing, and an asthma attack. Long-term exposure can cause lung damage leading to emphysema, bronchitis, and cardiovascular disease. Technology is available to remove sulfur from coal-burning effluent and produce low-sulfur fuels. In the United States sulfur dioxide is regulated as an occupational hazard and is one of six major air pollutants regulated by National Ambient Air Quality Standards (NAAQS) under the U.S. Clean Air Act. Sulfur dioxide is useful in wine making, where it is used as an antimicrobial to control bacteria and natural yeasts and as an antioxidant to protect the wine from oxygen.

Particulate Matter

Particulate matter is a mixture of liquid droplets and small particles including metals, organic chemicals, acids, dust, soil, and combustion byproducts. It is produced by the combustion of fossil fuels, wood, and almost anything that is burned. Regulatory agencies are particularly concerned with particles smaller than 10 micrometers (PM_{10}) because they can move deep into the lungs and can carry a variety of chemicals. Particles less than 2.5 micrometers $PM_{2.5}$ are considered even more hazardous because they not only move deep into the lungs but also can cross into the bloodstream. Inhalation of particulate matter is associated with asthma attacks, heart attacks, stroke, respiratory disease, increased risk of cardiovascular disease, and premature death. In the United States both PM_{10} and $PM_{2.5}$ are regulated as one of six major air pollutants under the National Ambient Air Quality Standards (NAAQS).

Carbon Monoxide (CO)

Carbon monoxide poisoning is a distressingly common form of fatal air pollution. When combustion occurs in a low oxygen environment, carbon monoxide is formed instead of carbon dioxide. Aristotle (384–322 BCE) was one of the first to note that burning coals emanated toxic fumes; as a form of execution, criminals were shut in a bathing room with smoldering coals. It was not until 1800 that the structure of CO was identified. Carbon monoxide is colorless, odorless, and tasteless, and readily combines with hemoglobin, inhibiting its function of carrying oxygen to organs and tissues. Carbon monoxide poisoning can present as flu-like symptoms of headache, nausea, vomiting, dizziness, and fatigue, sometimes going unrecognized. A failing furnace or indoor use of charcoal fires or generators can lead to the production of CO and subsequent death. In the United States

carbon monoxide is regulated as one of six major air pollutants under the National Ambient Air Quality Standards (NAAQS).

Lead

Lead air pollution was a global issue millenniums ago. Greenland ice sheets reveal a rise in airborne lead pollution due to the smelting and use of lead during Greek and Roman times from 500 BCE to 300 CE. The use of lead, and its worldwide distribution, increased dramatically during the Industrial Revolution. Perhaps the worst public health decision ever made was the addition of lead to motor fuel, which markedly increased the average child's blood lead level. After the US ban on leaded gasoline for motor vehicles, levels of lead in the air decreased by 94 percent between 1980 and 1999 and childhood blood lead levels declined significantly. Leaded gasoline for use in racecars was banned only recently, and leaded gasoline is still used in piston-driven airplanes. An ongoing concern, particularly for developing countries, is airborne lead contamination from ore smelting, battery recycling, and electronic waste. In the last few years, lead contamination from gold mining in Nigeria has killed over 400 children and harmed thousands. In addition, several developing countries continue to use leaded motor fuel.

Volatile Organic Compounds (VOCs)

Volatile organic compounds are organic chemicals with a low boiling point that readily evaporate into the air. VOCs occur naturally but are generated by a wide variety of human activities and form a significant component of both indoor and outdoor air pollution. Common examples are formaldehyde, used in paints, glues, and pressed wood, and benzene, a solvent found in gasoline. Short-term exposure to VOCs can irritate the respiratory tract and eyes while long-term exposure can cause neurological disorders, cancer, and other effects. VOCs can also interact with nitrogen dioxide and sunlight to form ozone or particulate matter.

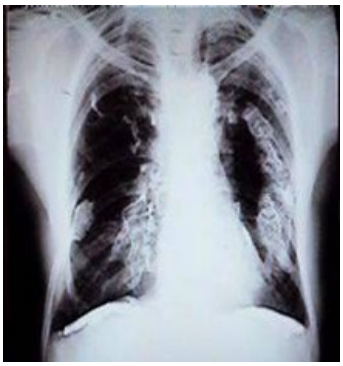
Asbestos

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 B.C., but the first recorded use of the word asbestos was in the 1st century A.D. 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.

Phthalates

Phthalates are a class of high-volume chemicals that are ubiquitous in the environment. They are plasticizers that, when added to plastics, impart a softening characteristic lending flexibility to the plastic. These water-insoluble, synthetic organic chemicals are usually added to polyvinyl chloride (PVC) plastics and have a wide expanse of uses, including in many common household items, cosmetics, and medical devices. As phthalates are not chemically bound to the plastics in which they are used, they can leach out into the environment.

Human exposure to phthalates begins in utero, and some levels of exposure are nearly unavoidable. Each year, more than 18 billion pounds of phthalates are used worldwide. Phthalates are used as plasticizing agents to make rigid plastics into flexible vinyl. They are ubiquitously found in the environment. They are also listed as "inert" ingredients in many sprays including pesticides, cosmetics, and wood finishes.

NAAQS standards

National Ambient Air Quality Standards (NAAQS) are standards established by the United States Environmental Protection Agency under authority of the Clean Air Act as of October 2011 (see EPA - http://www.epa.gov/air/criteria.html)

Pollutant		Type	Standard	Averaging Time
Sulfur Dioxide	SO_2	Primary[1]	0.075 ppm	1-hour
	SO_2	Secondary[2]	0.5 ppm (1,300 μg/m³)	3-hour
Particle Pollution	PM_{10}	Primary and Secondary	150 μg/m³	24-hour
	$PM_{2.5}$	Primary	12 μg/m³	annual
	$PM_{2.5}$	Secondary	15 μg/m³	annual
	$PM_{2.5}$	Primary and Secondary	35 μg/m³	24-hour
Carbon Monoxide	CO	Primary	35 ppm (40 mg/m³)	1-hour
	CO	Primary	9 ppm (10 mg/m³)	8-hour
Ozone	O_3	Primary and Secondary	0.075 ppm (150 μg/m³)	8-hour
Nitrogen Dioxide	NO_2	Primary	0.100 ppm	1-hour
	NO_2	Primary and Secondary	0.053 ppm (100 μg/m³)	annual
Lead	Pb	Primary and Secondary	0.15 μg/m³	Rolling 3 months

[1]**Primary standards** provide public health protection, including protecting the health of "sensitive" populations such as asthmatics, children, and the elderly.
[2]**Secondary standards** provide public welfare protection, including protection against decreased visibility and damage to animals, crops, vegetation, and buildings.

Child Health and Air Pollution

Children are small but eat more, drink more, and breathe more than adults, based on body weight. Thus a small exposure is a big dose for a child because of their low body weight. Recent papers describing research on children and air pollution document the vulnerability of children to air pollution. Perera et al. (2007) describe how airborne polycyclic aromatic hydrocarbons (PAH) from fossil fuel burning adversely affects child behavior. Millman et al. (2008) describe the negative impact of air pollution related to coal burning in China on child development. Finally, Becerra et al. (2013) describe an association between air pollution from traffic in Los Angeles, California and childhood

autism. Taken together, these studies and other research clearly document the vulnerability of children to air pollution and the importance of clean air during development.

Reducing Exposure

Reducing exposure to air pollution can be challenging, depending upon location and societal commitment. Indoor air pollution can be somewhat controlled by purchasing consumer products that emit fewer chemicals. Outdoor air pollution or work place exposures are far more difficult for individuals to control, but society can make improvements. Cars engines have been greatly improved to reduce air pollution and increase gas millage. Pollution from trucks and other diesel engines has also been greatly reduced through improved engine design and using low sulfur fuel. Individuals can make a difference by using mass transit, walking, or riding a bike. Some states are requiring more energy efficient appliances. In addition solar panels and other forms of alternative energy are becoming more practical and cost effective.

Regulation of Air Pollution

Following incidents where people suffered from the harmful effects of air pollution, it was recognized that the regulation of air pollution was essential to the well-being of humans and ecosystems. Regulation started locally and gradually expanded to national and international efforts to control air pollution and reduce the worldwide distribution of harmful chemicals. It is important to note the possible overlaps between local and international issues: for example, contaminants from coal burned in the United States or China cause local air pollution but also contribute to international pollution. International treaties have successfully contributed to reducing specific air pollutants such as CFCs, but great effort will be necessary to control pollutants such as mercury and greenhouse gases, which contribute to global warming. Below are some of the notable regulatory events.

Regulations Related to Air Pollution

Year	Name	Comment
1955	Air Pollution Control Act	Provided for research and declared that air pollution was a danger to public health and welfare, but preserved the "primary responsibilities and rights of the states and local government in controlling air pollution"
1963	Clean Air Act	Acknowledged that air pollution was a national problem that crossed state lines, published national air quality standards
1965	Motor Vehicle Air Pollution Control Act	Acknowledged that autos were a significant source of national air pollution, and national standards were needed

1970	National Environmental Policy Act (NEPA)	Stated that it was the duty of the U.S. government to "encourage productive and enjoyable harmony between man and his environment", and established the Environmental Protection Agency (EPA), to take responsibility for environmental regulation and protection.
1970	Clean Air Act Amendments	Significantly strengthened the Clean Air Act, setting National Ambient Air Quality Standards (NAAQS) for six criteria pollutants
1986-1989	Montreal Protocol	Montreal Protocol on Substances that Deplete the Ozone Layer: international treaty to phase out chemicals like Chlorofluorocarbons, adopted 1986 and entered into force in 1989
1997-2005	Kyoto Protocol	United Nations Framework Convention on Climate Change (UNFCCC) - an international treaty to reduce emissions of greenhouse gases, adopted 1997 and entered into force in 2005

Recommendation and Conclusions

Air pollution knows no boundaries and is thus a regional, national, and international issue. The unrestrained burning of fossil fuels such as coal, oil, and, gasoline for electrical power generation, transportation, cement kilns, and chemical production are the major contributors of air pollution, greenhouse gases, and global warming. More research into alternative forms of energy and a reduction in the use of fossil fuels is essential to maintain a sustainable world and protect human health. Coal-burning power plants and boilers are significant point sources of air pollution and should have pollution control technology devices installed. The availability and use of mass transit and alternative forms of transportation must be developed to reduce the use of non-point sources of air pollution such as cars and trucks. Consumer products should be designed to reduce contributions to air pollution during manufacture and use. While outdoor air pollution is important, more attention must be given to the air quality indoors. As a global society we must work towards regulation that protects people locally as well as globally, preserving human and ecological health for current and future generations. We all, and especially our children, have a right to an environment in which we can reach and maintain our full potential, free of harmful air pollutants.

More Information and References

Slide Presentation

- A Small Dose of Air Pollution presentation material and references online: www.asmalldoseoftoxicology.org
  Web site contains presentation material related to the health effects of Air Pollution.

European, Asian, and International Agencies

- World Health Organization (WHO) Air pollution. Online at http://www.who.int/topics/air_pollution/en/ (accessed: 28 October 2020)
  Overview of indoor and outdoor air pollution as well as health related information.

- World Health Organization (WHO) Household air pollution and health. Online: https://www.who.int/en/news-room/fact-sheets/detail/household-air-pollution-and-health (accessed: 28 October 2020)

- England – Department for Environment Food and Rural Affairs – Air Pollution. Online at http://uk-air.defra.gov.uk (accessed: 28 October 2020)

- England - Air Quality England. Online at http://www.airqualityengland.co.uk (accessed: 28 October 2020)
  "This website shows the latest near-real time air quality data for UK Government, local authorities and the private sector across England."

North American Agencies

- AIRNow – supported by U.S. EPA, NOAA, NPS, tribal, state, and local agencies Online at http://airnow.gov/ (accessed: 19 October 2020)
  Provide U.S. national air quality information, daily AQI forecasts and real-time AQI conditions for over 300 cities across the U.S.

- Health Canada - Health Effects Of Air Pollution - Online https://www.canada.ca/en/health-canada/services/air-quality/health-effects-indoor-air-pollution.html (accessed: 19 October 2020)
  Overview of air pollution and health related issues.

- EPA Air Page – Online at http://www2.epa.gov/learn-issues/air-resources#air-pollution (accessed: 19 October 2020)
  EPA provides a wealth of information on air pollution regulations, air quality, emissions monitoring, and health and environmental impacts.

- US Clean Air Act – this page no longer exits
  EPA provides a brief introduction (in plain English) Guide to the 1990 Clean Air Act

- US EPA - Air Quality Criteria for Ozone and Related Photochemical Oxidants (2006 Final) – Online at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923 (accessed: 19 October 2020)

- US EPA Indoor Air Pollution – Online at http://www.epa.gov/iaq/index.html (accessed: 19 October 2020).
  EPA provides excellent overview and references related to indoor air quality.

- US EPA – Sulfur Dioxide – Online at http://www.epa.gov/airquality/sulfurdioxide/index.html (accessed: 19 October 2020)

- US EPA – Nitrogen Oxides – Online at http://www.epa.gov/airquality/nitrogenoxides/ (accessed: 19 October 2020)

- US EPA – Particulate matter – Online at http://www.epa.gov/airquality/particlepollution/ (accessed: 19 October 2020)

- US EPA – Carbon monoxide – Online at http://www.epa.gov/airquality/carbonmonoxide/ (accessed: 19 October 2020)

- US Occupational Safety & Health Administration - Indoor Air Quality – Online at http://www.osha.gov/SLTC/indoorairquality/index.html (accessed: 19 October 2020)

Non-Government Organizations

- American Lung Association (ALA) - - Online at http://www.lung.org (accessed: 19 October).
  The American Lung Association works to "save lives by improving lung health and preventing lung disease through Education, Advocacy and Research".

- The National Association of Clean Air Agencies (NACAA) – Online at http://www.4cleanair.org/ (accessed: 19 October 2020)
  Provides information on air pollution and represents air pollution control agencies in 45 states and territories and over 116 major metropolitan areas across the United States.

- Natural Resources Defense Council – AIR – Online: https://www.nrdc.org/stories/air-pollution-everything-you-need-know (accessed: 28 October 2020)
  A basic introduction to air and its pollution.

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A Small Dose of Water Pollution
Or
An Introduction to the Health Effects of Water Pollution

Chapter 27
A Small Dose of Toxicology - The Health Effects of Common Chemicals
ED3 – Revised November 2020

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Supporting web sites
web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"


Water from flint MI

Dossier

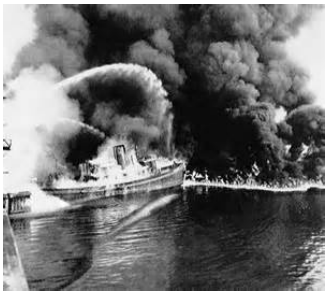
Toxicology of Water Pollution

Name: Water Pollutants
Definition of water pollution: contamination of indoor or outdoor water by any chemical, physical or biological agent that modifies the natural characteristics of the water, reducing its beneficial usability for people and/or ecosystems
Use: avoid use of polluted water but drink plenty of clean water
Recommended daily intake: none (but water is essential)
Absorption: Skin and gastrointestinal system
Sensitive individuals: fetus and children, elderly, people with chronic health problems
Toxicity/symptoms: depends upon pollutant / contamination
Regulatory facts: in the US the EPA sets some standards for water pollutants
General facts: caused by emissions of billions of pounds of chemicals and particulate matter every year from a wide range of products and industries, combustion of fossil fuels such as coal and gasoline, and bacterial contamination
Environmental effects: widely distributed in environment, affects wildlife and ecological health, and human health
Recommendations: minimize water pollution on a global scale, avoid exposure by children and other sensitive groups, expand research on toxicity and alternative sources of energy, adopt precautionary approach, reduce the use of fossil fuels, support international treaties

Case Studies

The Cuyahoga River: Pollution Burns

Strange as it may seem, the Cuyahoga River in Ohio has caught fire at least 13 times, with the first fire occurring in 1868. The Cuyahoga River is located in northeastern Ohio and drains into Lake Erie, one of the freshwater Great Lakes of the US/Canada. In 1969 the river was considered one of the most polluted rivers in the US. It had thick sticky masses of oil several inches thick floating along, often full of garbage, which is a perfect feed for fires. In 1952 a river fire caused $1 million in damages. A fire in 1969 was reported in *Time* magazine and received widespread attention. The pollution and fires helped spur efforts to clean up the river, and some credit the fires with encouraging the passage of the Clean Water Act and the Great Lakes Water Quality Agreement, and the creation of the federal Environmental Protection Agency (EPA) and the Ohio Environmental Protection Agency (OEPA). These new rules and regulations significantly improved water quality by controlling point source pollution from industry.

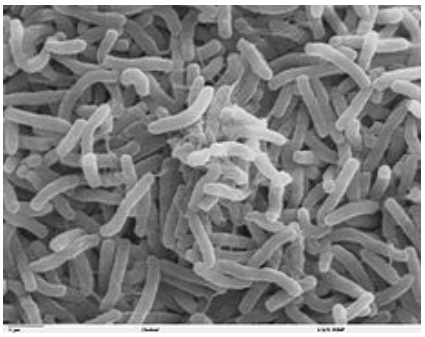


Flint River Disaster: Lead in Drinking Water

On April 25, 2014 the city of Flint, Michigan switched its source of drinking water from Lake Huron, supplied by Detroit Water and Sewerage Department, to the Flint River. However, Flint failed to add appropriate corrosion inhibitor chemicals to the water, which resulted in lead and other contaminants from the aging pipes leaching into the water. Water from one Flint home was tested and found to contain lead at 13,200 parts per billion (ppb); the maximum contaminant level (MCL) set by the EPA is 15 ppb. Following the change in water sources, the number of children with elevated blood lead levels increased dramatically, particularly in poor neighborhoods. It was estimated that between 6,000 and 12,000 children were exposed to drinking water with elevated levels of lead. The US CDC states that there is no safe level of lead exposure to lead, especially for children. The Flint disaster is particularly tragic because we have known for years that lead exposure has a devastating impact on developing brains. Flint is a poor city with a large number of African American residents, which prompted a concern that the disaster was a case of environmental racism. The simple step of adding corrosion inhibitors to the water would

have prevented the suffering inflicted on the people of Flint. (see Chapter 8 – A Small Dose of Lead)

London Well Water: Cholera Outbreak, 1854



Water can also be contaminated with bacteria that when ingested make people very ill or even cause death. A classic example is the bacterium *Vibrio cholera* (see image) that causes cholera, an infection of the small intestine. The main symptoms are profuse watery diarrhea and vomiting, which rapidly lead to death. Transmission is primarily through consuming contaminated drinking water or food. The severity of the diarrhea and vomiting can lead to rapid dehydration and electrolyte imbalance. Primary treatment is with oral rehydration solution and if these are not tolerated, intravenous fluids. Worldwide, cholera affects 3-5 million people and causes 100,000-130,000 deaths a year as of 2010. About one hundred million bacteria must typically be ingested to cause cholera in a normal healthy adult. This dose, however, is smaller in those with lower gastric acidity. Children are also more susceptible, with two to four year olds having the highest rates of infection. The last major outbreak of cholera in the United States occurred in 1910-1911. Effective sanitation practices, if instituted and adhered to in time, are usually sufficient to stop an epidemic.

A major contribution to fighting cholera was made by the physician and medical scientist John Snow (1813-1858), who in 1854 found a link between cholera and contaminated drinking water in London. He is considered to be one of the fathers of epidemiology, because of his work in tracing the source of a cholera outbreak in Soho, England. Dr. Snow proposed a microbial origin for epidemic cholera in 1849; he famously removed a pump handle from a pump that served an area of London, stopping the cholera epidemic. In his major "state of the art" review of 1855, he proposed a substantially complete and correct model for the etiology of the disease. In two pioneering epidemiological field studies, he was able to demonstrate that human sewage contamination was the most probable disease vector in two major epidemics in London in 1854. His model was not immediately accepted, but it was seen to be the more plausible, as medical microbiology developed over the next thirty years or so.

This incident demonstrates the importance of safe drinking water and public health infrastructure for maintaining the health and well-being of communities.

Water: An Introduction

Clean water (H_2O) is essential for life as we know it, and clean water is relatively scarce and becoming more so. Some astonishing facts about water: 1) by body weight we are about two-thirds water; 2) about two-thirds of the Earth's surface is covered with water but most of this is saltwater; 3) about 3% of this water is freshwater and 2% of that is frozen; 4) therefore only 1% of the Earth's water is available for use to drink, bathe in, grow food and cook with, and use in manufacturing. The water cycle describes how water circulates between the atmosphere, surface water such as rivers, plants, oceans, and soil. The natural circulation of water is essential for ensuring clean drinking water. In 2016 approximately 1 billion people, out of a global population of 7.4 billion, do not have access to clean water.

What Causes Water Pollution?

Of primary concern are the contaminants added to water by people that can cause undesirable health effects in humans or wildlife. There is the old adage that "the solution to pollution is dilution," but is this really true? To a small extent yes, but in a larger context it is not. One person can use a river or even a stream as his or her personal sewage dump, but managing the volume of waste from a city of 1 million people requires an entirely different approach. Similar to our bodies, rivers and other bodies of water have a limited ability to metabolize or excrete undesirable contaminants.

It is important to distinguish between point and non-point sources of pollution. Point sources such as a pipe dumping material into a river can often be readily identified and stopped, while non-point sources of pollution are diffuse and difficult to address. For example, agricultural runoff or water contaminated by roads does not have one easily identifiable owner or source. Below are different examples of water pollution. It is also important to distinguish between cause and sources of water quality that make it unfit for consumption or use. Chief causes of water pollution include pathogens, mercury, PCBs, nutrients, and organic enrichment/low dissolved oxygen. The op sources of impairment include atmospheric deposition, agriculture, hydrologic modifications, and old mines, to name only a few.

Chemical Pollutants Overview

Chemical pollutants represent a wide variety of substances that can be categorized in different ways. In addition to the distinction between point and non-point sources mentioned above, we can also consider water pollution as micro vs. macro. Micro-pollution is what we have control over in our homes, workplaces, or schools. For example, flushing used oil down the storm drain or flushing unneeded drugs down the toilet would be micro-pollution that we as individuals could stop. However, as a community the oil or

drugs might be thought of as nonpoint source pollution. Macro-pollution is generally only addressed by community policy decisions such as cleaning up a river and affects a broad area. We have little individual control over macro-pollution. We as stewards of the Earth have the task of thinking four dimensionally: point source vs. non-point source, and macro vs. micro water pollution.

Volatile Organic Compounds (VOCs)

Volatile Organic Compounds (VOCs) are a broad classification of chemicals that include fuel products such as gasoline, kerosene, heating oil, benzene, and toluene, as well as chlorinated solvents such as carbon tetrachloride, trichloroethylene, and vinyl chloride. The fuel products have obviously been widely used in the transportation and heating industries. There are a variety of regulations that address VOCs from home oil tanks and gasoline filling station tanks over fears of contamination of groundwater. The chlorinated solvents have been widely used as industrial cleaning and degreasing agents and the leaching of these compounds through the soil has resulted in a variety of efforts to clean up industrial sites. For example, the water near a number of old military sites has been contaminated with solvents. This includes the US Marine Corp's Camp Lejeune where excess levels of perchloroethylene (PCE), a dry cleaning solvent, trichloroethylene (TCE), a degreaser, and other contaminants were found. VOCs often are present near older industrial sites or landfills.

The health effects of VOCs ingested from water are often complicated by inhalation but can produce neurological disorders and cancers such as lymphomas or leukemia. Usually these VOCs stay in the body for relatively short times (short half-lives) but chronic exposure can be serious, with children being especially vulnerable to exposure and effects. Maximum Contaminant Levels (MCLs) for VOCs in drinking water have been established by many states and the United States Environmental Protection Agency (USEPA) but may not incorporate recent toxicological information.

Chlorinated Solvents	**Fuel Products and Components**
carbon tetrachloride	gasoline
1,2-dichloroethane	kerosene
1,1-dichloroethylene	heating oil
cis-1,2-dichloroethylene	benzene
trans-1,2-dichloroethylene	airplane and jet fuel
methylene chloride	motor oils
tetrachloroethylene	methyl tert-butyl ether (MTBE)
1,1,1-trichloroethane	toluene
trichloroethylene	xylenes
vinyl chloride	n-hexane

Waterborne Organisms
Water often contains a wide array of living organisms including viruses, bacteria, and parasites, some of which can cause health effects if ingested. A recent example is the outbreak of cholera in Haiti after the 2010 earthquake: over 700,000 Haitians were affected and over 9,000 died. Typhoid fever is another disease spread by contaminated water. Toxic algal blooms can produce shellfish contaminated with domoic acid, which is a neurotoxin that causes amnesic shellfish poisoning (ASP). Drinking water contaminated with harmful organisms is more likely to be encountered in developing countries, and travelers should be cautious. Industrialized countries need to invest in water systems in countries around the world where people lack access to clean and safe water. The WHO states: "Globally, an estimated 1.9 billion people rely on water supplies that are contaminated with feces. This requires many to use household water treatment (HWT) technologies to help prevent disease and make water safe for drinking." This is an ongoing global issue that requires attention.

Radioactive Contamination
The hazard from radioactive contamination of water is complex because it depends on a number of variables. Ionizing radiation emits alpha particles, beta particles, or gamma rays, which have varying amounts of energy. The potential hazard is usually greater if the contamination is ingested, which means cells are close to the emitting contaminant. The Fukushima Daiichi nuclear disaster has highlighted water contamination and subsequent contamination of the food supply, primarily by radioactive strontium or cesium. There is also concern about tritium, which is radioactive hydrogen that easily becomes like water, in essence radioactive water, that can leak from operating nuclear power plants. In addition there are contaminated sites, used during the Cold War to create plutonium, that were usually set next to rivers, such as the Hanford Nuclear Reservation. Naturally occurring radioactive elements such as uranium can be disturbed during mining and become part of the mine tailings. The most relevant radioactive contaminant levels set by the EPA are:

Alpha particles (low energy) 15 picocuries per liter (pCi/L)
Beta particles 4 millirems per year (tritium emits beta particles)
Uranium 30 ug/L (30 ppb)

The general idea is to keep exposure to radioactive contaminants in water below 4 millirems per year. (See Chapter 13, A Small Dose of Radiation.)

Pharmaceuticals in Drinking Water
An increasingly important source of water contamination is pharmaceutical drugs, which can be prescription medicines, supplements or over-the-counter therapeutic drugs, illegal drugs, or veterinary drugs. These are sometimes called environmentally persistent pharmaceutical pollutants. Pharmaceuticals reach water bodies through sewage, which contains active ingredients or metabolites from human excrement as well as unneeded

drugs disposed in toilets, animal waste, personal care products, or landfill runoff. Caffeine from coffee and tea and birth control hormones are commonly found in wastewater. The small size of the pharmaceutical molecules can make them difficult and expensive to remove during the sewage treatment process, and they may enter bodies of water or be recycled back into treated drinking water. The best way to keep unwanted drugs out of the water supply is to implement drug take-back programs where unwanted drugs can be dropped off at specific sites, often drug stores, for proper disposal. Currently there are only four counties in the US–Alameda, King, San Francisco, and San Mateo–that have such programs (more information is at www.takebackyourmeds.org).

Water Fluoridation

The addition of fluoride to drinking water to control or prevent tooth decay remains controversial from a scientific and ethical perspective. On January 25, 1945 Grand Rapids, Michigan became the first municipality to add fluoride to drinking water in an effort to prevent tooth decay. Nearby Muskegon's drinking water was left fluoridated as the experiment's control city for comparison purposes. Following this trial there was no scientific consensus that fluoridation reduced tooth decay in children, yet it was hailed a public health victory. This practice is still supported by the US Centers for Disease Control (CDC) and approximately 70% of municipal drinking water in the United States is currently fluoridated. Fluoride is also present in a range of consumer products including toothpaste (1,000-1,500 parts per million or ppm), mouthwash, and fluoride supplements, and food products made with fluoridated water (such as beverages and canned soups) also contain fluoride. The US EPA has set 4 mg/L, or 4ppm, as the maximum contaminant level (MCL). In some water systems it is a natural contaminant.

Ecological Concerns

Chemical Pollution / Toxicity

Chemical contaminants often end up in our global oceans or rivers. Fish and shellfish can take up these contaminants from the water directly, or by eating other creatures. One toxic chemical that contaminates water bodies worldwide is mercury, emitted from coal-burning power plants. Released as inorganic mercury, bacteria then convert this inorganic mercury into methylmercury, or organic mercury, which is then passed up the food chain where it biomagnifies (increases in concentration) and bioaccumulates (increases in total amount). While mercury accumulates in the muscle, other compounds, such as PCBs, are stored in fat. This process that starts with contaminated water has a profound effect on wildlife as well as humans that consume fish and shellfish. This has prompted state and federal agencies to issue fish consumption advisories. The concern about fish contamination has in turn driven water cleanup efforts to reduce pollutant levels in the water and thus in the fish.

Thermal Pollution / Toxicity

Thermal pollution refers to the effects of raising or lowering the water temperature. The most common and frequent concern is rising water temperatures in a river or lake after water taken from the river or lake is used to cool an industrial process. The most common use is in nuclear or coal-fired electrical power generation plants. In the initial design these plants ran single base operations, where river water was heated to generate steam and then sent back to the river at a relatively high temperature. More modern designs have closed systems that use giant cooling towers to significantly cool the water. The warmer water decreases the water's oxygen levels and also kills fish and other wildlife that cannot tolerate the high water temperature.

Mining Contamination and Waste

Mining is one of the greatest contributors to surface and groundwater contamination. Contamination from mine tailings as well as the ore processing can include high concentrations of chemicals and metals, such as arsenic, mercury, lead, cadmium, and sulfuric acid. For example mercury is commonly used in the extraction of gold and the gold ore can have high concentrations of lead. Acid mine drainage, or the outflow of acidic water, is also a serious problem in metal or coal mines that expose sulfate soils (see picture to the right). Acid mine drainage may also contain elevated levels of nickel and copper. It is also important to acknowledge the disruption of surface water caused by dumping soil from open pits or from mountaintop removal.

Indoor Water Pollution / Water Quality

Indoor water or tap water is supplied to most homes in developed countries but is often lacking in developing countries. Public drinking water is regulated by the US EPA under the Safe Drinking Water Act (SDWA) but about 10% of drinking water is from private wells and is not regulated. A great amount is known about managing water to reduce pollutants but in the case of Flint, Michigan, the lack of proper treatment resulted in lead-contaminated water. Groundwater and hence drinking water can also become contaminated with metals such as arsenic from coal ash.

Control of Water Pollution

Control of water pollution requires vigilance in controlling all pollution sources, including air and soil contaminants. The easiest to control are point sources such as sewage treatment facilities. Large industrial facilities may operate their own pretreatment facilities or a more complete waste treatment facility designed to deal with particular chemicals. However, even more responsible is designing and using processes that use less hazardous materials. Agricultural and home use of pesticides and fertilizers can be reduced as farms and homes move more toward organic plant management.

Child Health and Water Pollution
Children are small but eat more, drink more, and breathe more than adults, based on body weight. Thus a small exposure is a big dose for a child because of their low body weight. Contaminant-free water is vital for healthy children.

Reducing Exposure
Reducing exposure to polluted water can be challenging, depending upon location and societal commitment.

Regulation of Water Pollution

There are a wide range of laws and regulations that govern water quality, which testifies to the importance of clean water for all of life. Below is a brief summary of some of the most important laws in the United States and internationally.

US Clean Water Act
The Clean Water Act (CWA) was first passed by the US Congress in 1948 and was known as the Federal Water Pollution Control Act. It was completely rewritten and expanded in 1972 in part due to incidences such at the Cuyahoga River repeatedly catching fire, most recently in 1968. Additional major changes were made in 1977 and 1987. The CWA addressed surface waters but not groundwater. Several national laws, notably the Safe Drinking Water Act, Resource Conservation and Recovery Act, and the Superfund act, addressed the contamination of groundwater. (ref. US EPA Summary of the Clean Water Act)

US Safe Drinking Water Act
The Safe Drinking Water Act (SDWA), which became effective December 16, 1974, is administered by the US EPA and intended "to assure that the public is provided with safe drinking water." The EPA has set water quality standards for microorganisms, organic and inorganic chemicals, and radionuclides. These standards apply to the approximately 155,000 public water systems but not to private wells. Bottled water is regulated by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act.

EPA Lead and Copper Rule
Acknowledging the adverse health effects of lead and copper, the US EPA issued the first lead and copper rule on June 7, 1991 and followed up with subsequent revisions. This rule not only set the action level for lead at 0.015 mg/L (15 ppb) and for copper at 1.3 mg/L but required monitoring, set standards for allowed lead in pipe and fixtures, and required corrosion control technology. There is considerable controversy over the water sampling procedures. Despite these efforts, incidents like that in Flint, MI continue to occur.

Recommendation and Conclusions

Water pollution knows no boundaries and is thus a regional, national, and international issue. Contaminant-free water requires investment and planning. Municipal water is tested at the source and can be treated, while managing private wells is the responsibility of the user. It should always be remembered that children are more vulnerable and thrive on clean, fresh water.

More Information and References

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- Wikipedia: Clean Water Act Online: https://en.wikipedia.org/wiki/Clean_Water_Act - (accessed: 06 November 2020)

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A Small Dose of Soil Pollution
Or
An Introduction to the Health Effects of Soil Pollution

Chapter 28
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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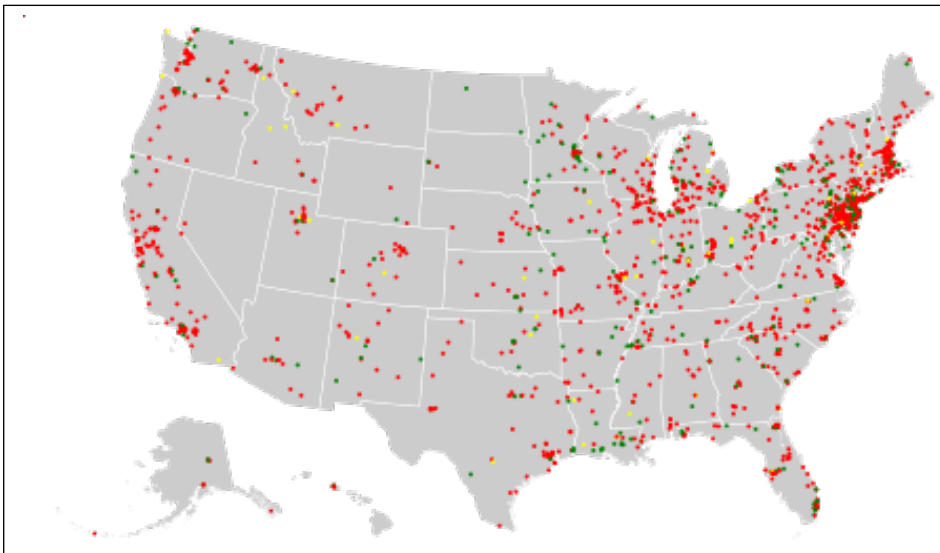
Supporting web sites
web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"



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Dossier

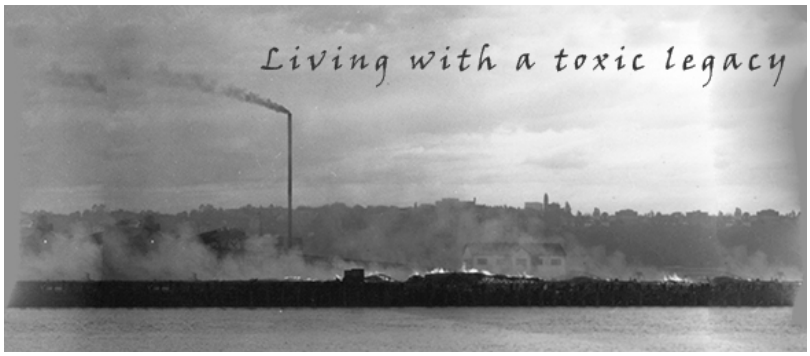
Toxicology of Soil Pollution

Name: Soil Pollutants
Definition of soil pollution: contamination of the indoor or outdoor soil by any chemical, physical, or biological agent that modifies the natural characteristics of the soil, reducing its beneficial usability for people and/or ecosystems
Use: no desired use unless mining of pollutants
Recommended daily intake: none (not essential)
Absorption: skin, inhalation, and gut system
Sensitive individuals: fetus and children, women of childbearing age, the elderly, people with chronic health problems
Toxicity/symptoms: varies depending on the chemicals
Regulatory facts: in the US the EPA sets some standards for soil pollutants
General facts: emissions of billions of pounds of chemicals and particulate matter every year from a wide range of products and industries including agriculture, and from combustion of fossil fuels such as coal and gasoline
Environmental effects: widely distributed in environment, linked with climate change and acid rain, and can affect wildlife and ecological health
Recommendations: minimize soil pollution on a global scale, avoid exposure by children and other sensitive groups, expand research on toxicity and alternative sources of energy, adopt precautionary approach, reduce the use of fossil fuels and pesticides, support international treaties, reduce use of all materials that generate waste

Notable Soil Pollution Events

Tacoma Smelter

The Tacoma Smelter furnace was fired up on September 12, 1889 and began melting metal ores to extract copper, lead, and arsenic that were easily shipped by water and rail but contaminated the surrounding area. The smelter was known for its tall 562-foot smokestack, which sent pollutants up and away from the smelter into surrounding communities. They were following the tried but true dictum that the solution to pollution is dilution. While the smelter was permanently closed in 1986 and the stack demolished in 1993, the environmental damage was already complete. The American Smelting and Refining Company (ASARCO) operated a copper smelter on the shores of Commencement Bay in Ruston, near Tacoma, Washington for almost 100 years. The facility began its life as a lead smelter in 1889, and was converted to a copper smelter in 1902. It was sold to ASARCO in 1905. The soil around the immediate area and up into Vashon Island was polluted with lead and arsenic.

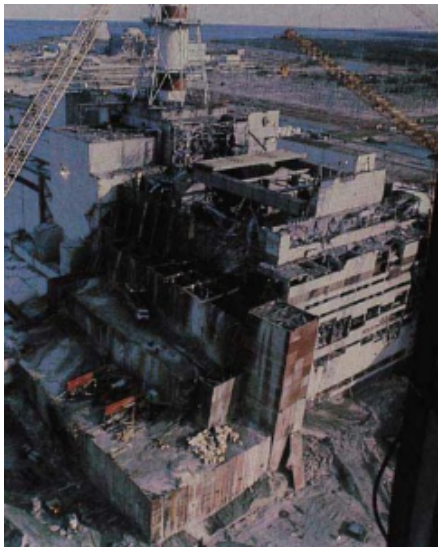


Coal Ash

Coal ash is the material that is left after burning coal. The makeup of the ash varies depending on the type of the coal but it typically includes substantial amounts of silicon dioxide (SiO_2), aluminum oxide (Al_2O_3), and calcium oxide (CaO), as well as varying amounts of arsenic, lead, beryllium, cadmium, chromium, mercury, selenium, and small concentrations of dioxins and PAH (Polyaromatic hydro carbons) compounds. The challenge is finding something to do with the large volume of waste. Some of the ash is recycled into other products such as concrete, and the unused ash is often stored in large ponds. On December 22, 2008, the largest release of coal ash occurred when a dyke broke on the Tennessee Valley Authority's Kingston Fossil Plant in Roane County, Tennessee, USA and released 1.1 billion US gallons of coal ash slurry into the surrounding environment. This spill of muddy ash covered over 300 acres and destroyed several houses. The sludge and contaminants were dredged from the local

river. Many fish were killed and the river was blocked for over a year. In other words contaminated soil was every where.

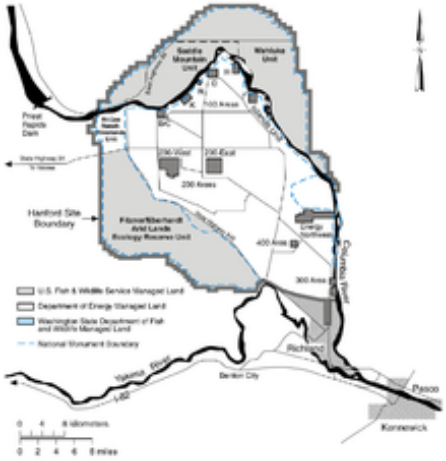
Radiation Pollution



Chernobyl Exclusion Zones

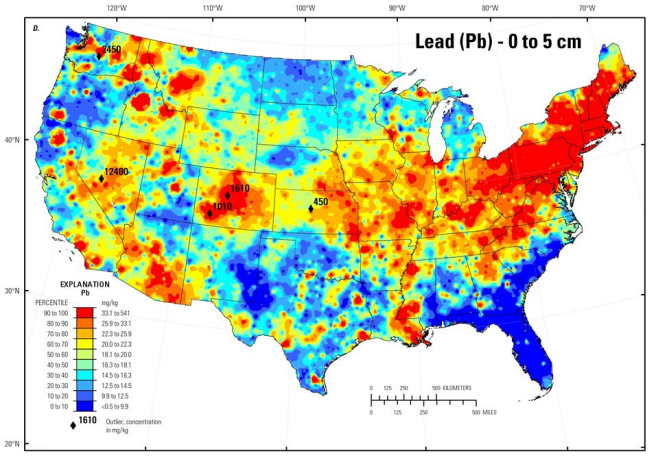
A nuclear reactor at the Chernobyl Nuclear Power Plant in the city of Pripyat, Ukraine exploded and caught fire on April 26, 1986, releasing enormous amounts of radiation into western USSR and Europe and contaminating the soil and vegetation. Following the expulsion and release of radioactive cesium and strontium an exclusion area of approximately 1000 square miles was established to significantly limit human use. Radioactive cesium-137 has a half-life of about 30 years and is readily taken up by animals and plants. Radioactive strontium-90 has a half-live of about 28 years, substitutes for calcium, and also bioaccumulates. Similar exclusion zones were also established near Fukushima, Japan following the nuclear disaster there on March 11, 2011. Radioactive soil at this scale is extremely difficult to deal with, only leaving the option of waiting for the natural decline in radioactivity.

Hanford Nuclear Reservation



Hanford Nuclear Reservation near Richland, WA is the most contaminated waste site in the Western Hemisphere. About two-thirds of the plutonium used during the Cold War to make and test nuclear weapons was created and extracted at Hanford, creating enormous contamination. Waste that contained a variety of compounds and radioactive materials would often be allowed to leak into soil or deliberately placed in trenches or ponds. The largest legacy that is already haunting future generations is 177 tanks that collectively hold 53 million gallons of hazardous waste. The tanks contain a witch's brew of chemicals and radiological compounds, some in tanks that have leaked, or are leaking, into the soil.

Lead in Soil



Lead is probably one of the most serious and widespread soil contaminants. Lead exposure, particularly for children, is so serious that the US Centers for Disease Control and Prevention (CDC) lowered the blood lead action level to essentially 5 µg/dl and declared that there is no safe level of lead exposure. Lead exposure is common because lead is useful in a variety of applications and is relatively easy to mine. Soil near lead mines or other mining operations for other valuable metals such as silver or gold is often contaminated with lead. Lead ore is usually smelted, which can release large quantities of lead through smokestacks, distributing it over large areas. Children play in the dirt in their yards or neighborhood and then inhale or ingest the lead-laden dust. The lead- contaminated soil and dust are then tracked into the home, magnifying the family's exposure. Children are not little adults in that not only are their developing organs more susceptible, they eat more, dink more, and breathe more per body weight than adults. In addition, lead was added to paint and gasoline. Lead-based paint can contaminate the soil around the home including in the garden and backyard. Lead from gasoline can also contaminate the soil along busy roadways. Fortunately, most uses of lead-based paint and gasoline have ended, but the contamination continues. The Bunker Hill Mine and Smelting Complex, was a large smelter located in Kellogg, Idaho, in the Coeur d'Alene Basin and when built, it was the largest smelting facility in the world. It was an area used for a century for the extraction silver and other metal mining and processing. In the 1970s the hazard of lead in soil was finally recognized and millions of dollars was invested removing the lead in the soil.

Introduction to Soil Contamination

In general soil is easily contaminated but it is far more difficult to clean up. Soil pollution or contamination is any change or addition to the soil that makes it harmful to plants or animals, including humans. Soil pollution is often difficult to separate from air and water pollution as there can be movement of the contaminant between these different media. Soil pollution is often associated with industrial activity or any intensive human activity.

Soil contamination can occur from spills of oil directly into the soil, from a smelter releasing contaminants such as lead and arsenic into the air which ultimately contaminate

the soil, from a leaking home heating oil tank, from the waste from nuclear reactors, landfills, and illegal dumping of waste or industrial by products, and many other situations. Contaminated soil can act as a reservoir that gradually releases contaminants into the air or groundwater. Soil can also be tracked in to a car or home from a contaminated area, increasing exposure to the contaminants, particularly by children. This had been well documented for lead and pesticides.

Ever since humans have started living in large communities, we have struggled with what to do with our waste. Improper disposal of human waste products can cause water contamination and lead to cholera. Sewage treatment plants combined with elaborate waste piping systems have largely solved this problem, but animal waste from large intensive farms remains a problem.

Tanks are another source of soil pollution. Tanks buried in the soil seem like a good idea until they start leaking. For example, there are thousands of home heating oil tanks buried in homeowners' yards. Eventually these tanks leak and contaminate the soil and generate a costly cleanup bill. Larger commercial tanks, such as those at gas stations, have similar problems. Very large tanks were used at the Hanford Nuclear Reservation in Washington State to hold chemicals and radioactive material left after the extraction of plutonium. These tanks have leaked over a million gallons of contaminated waste into the soil but the material does not stop as it heads toward the Columbia River.

The point is that soil contamination can come from a wide variety of sources. It can be very difficult to characterize what chemicals are in the soil, and if they are migrating to a different place. Soil exposure also occurs in a wide variety of ways: kids eat it, our skin absorbs it, our shoes track soil indoors, and we are exposed to dirt in the home or the car.

Examples of Soil Pollution

Radiological Contamination

Soil contains radioactive elements that occur naturally or are released from human activities. Radon gas, for example, is a product of the natural radioactive decay of uranium. Radon particles can be inhaled into the lungs, where they undergo further decay, emitting energy that can damage DNA and cause lung cancer. Uranium is a naturally occurring element found in rocks and soil at varying concentrations. In the open, environment radon gas radially disperses so is of little concern, but hazardous levels can be reached in indoor environments of homes, schools, and workplaces, particularly in unventilated areas such as basements. (For more information on ionizing radiation see Chapter 18, A Small Dose of Radiation.)

About 2000 years ago uranium was used by the Romans to produce a yellow-colored glass but uranium became highly desirable during WW II as fuel for nuclear weapons. Uranium was mined around the world for generating plutonium and for fueling nuclear

power reactors. The mining of uranium generated incredible amounts of radioactive contaminated soil. Despite the knowledge of the hazards of uranium and its daughter product radon, workers were not informed about the potential for lung cancer. The tailings and other contaminated soil were often left behind as the mines were abandoned. Cleanup was left to others, including federal agencies. The Uranium Mill Tailings Radiation Control Act of 1978 was passed by the US Congress to address some of the cleanup. In 1990 the US Congress passed the Radiation Exposure Compensation Act, to compensate workers exposed to the hazards of mining uranium. The waste tailings from mining uranium if just one example of the mining waste that is produced and not properly disposed of.

Pesticides

Soil is essential for life and has a very complex ecosystem all its own. A healthy soil promotes the growth of plant life and enhances the growth of food crops. Pesticides have long been used to manage seemingly undesirable plants, animals, insects, and fungi, and can be applied to the plant or to the soil. Pesticides become a problem or a pollutant when they harm humans or upset the ecological balance by harming desirable insects or wildlife. Some pesticides are highly persistent and accumulate in the environment and soil. From the soil the pesticide can be tracked into a worker's home and expose family members. Soil fumigants are applied directly into the soil where they typically form a gas that can kill insects, fungi, or plants. The problem with pesticides and soil pollutants in general is that they can be blown by the wind and contaminate neighboring areas. Consideration must also be given to the entire pesticide product, which includes the active ingredient as well as other agents. These other ingredients are usually considered confidential business information but can include preservatives, petroleum products, and chemicals to aid distribution and absorption of the active ingredient. Lead arsenate were used in apple orchards prior WWII when farmers switched to chemical based pesticides such as organophosphate based chemicals.

Lead Pollution

Lead has been a well-known hazard for over 2000 years; Dioscorides first noted that "Lead makes the mind give way" in the 2nd century BC (see Chapter 12 on the health effects of lead). It is now acknowledged that there is no safe level of lead exposure for children. After 20 years, in 2011, the US CDC lowered the blood lead action level for children to effectively 5 µg/dL from 10 µg/dL. Prior to this the US EPA set lead soil contamination levels of 400 ppm for bare soil in residential areas and 1,200 ppm for industrial areas in an effort to provide children with a great level of protection. For uncontaminated or "natural" soil the level found was about 50 ppm. These numbers are difficult to establish because they are based on estimates of children's soil consumption or exposure to contaminated soil. Ideally as the CDC lowered the blood lead level, the EPA would have lowered the acceptable soil lead level to less than 400 ppm.

Lead arsenate was widely used as a pesticide in apple orchards to control a variety of insects. The pesticide accumulated in the soil or was tracked indoors, exposing

farmworkers' family members. While the use of lead arsenate pesticides declined significantly after WW II, it was not banned by the EPA until 1988. Lead in soil became a problem as orchards were subsequently used for locating housing or schools.

Lead can also contaminate the soil of local gardens. The lead can come from airborne deposits from the past use of leaded gasoline or from flaking of lead-based paint. Vegetables that fruit above the ground generally do not accumulate lead, such as tomatoes or squash. Vegetables that fruit in the ground, such as carrots or potatoes, tend to have higher concentrations of lead, and are also covered in the lead-contaminated dirt.

Regulation of Soil Pollution

Water and air pollution were usually the first to impact the health of people to a significant enough extent to provoke regulation. Soil pollution was not a priority because no one eats or breathes soil to survive. The increase in population, along with the Industrial Revolution and the development of radiological sciences, have generated large quantities of solid waste that contaminate soil. To address these issues the United States Congress passed a series of laws to regulate, manage, and reduce the amount of waste generated.

The US The Environmental Protection Agency (EPA) is responsible for enforcing all the solid waste laws. The first law to address solid waste was the Solid Waste Disposal Act (SWDA), an Act of Congress passed in 1965. This act was in response to the large volume of solid waste generated by businesses; it was common practice to dump waste in nearby landfills. SWDA was quickly recognized as not being strong enough as it was repeatedly amended. The Resource Recovery Act (RRA) of 1970 was the first to increase government involvement in waste management. Major revisions occurred when Congress enacted the Resource Conservation and Recovery Act (RCRA) of 1976. The primary goal of RCRA was to protect human health and the natural environment from the hazards of industrial chemical radiological waste.

As the map on the opening page of this chapters makes clear is that there is a very large number of chemical and radiological waste sites. Often now abandoned and because contaminated soil makes the site and even surrounding area unusable. For example, old and abandoned smelters leave behind a very large foot print that must maintained or remediated. To solve this and other problems in 1980 Congress, by passing the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA) (Superfund), that allowed the EPA authority to start the clean-up and the determine whom are the responsible parties.

Regulations Related to Soil Pollution

Year	Name	Comment
1936	Soil Conservation and Domestic Allotment Act of 1936	Paid farmers to reduce production so as to conserve soil and prevent erosion
1965	Solid Waste Disposal Act (SWDA)	First federal effort to improve waste disposal technology
1970	Resource Recovery Act (RRA)	Increased government involvement in waste management
1976	Resource Conservation and Recovery Act (RCRA)	Regulated disposal of solid waste and hazardous waste
1984	The Hazardous and Solid Waste Amendments (HSWA)	Increased EPA involvement with hazardous waste and storage tanks
1980	Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA)	Identified polluters and recovered natural resource damages caused by hazardous substances (cleanup with Superfund)

Recommendation and Conclusions

Soil pollution comes in many forms, knows no boundaries, and is thus a regional, national, and international issue. Clean productive soil is an essential part of life as we know it. Like air and water, we must consider soil as an essential resource that needs to be protected and not spoiled with hazardous chemicals or exploited for short-term gain.

More Information and References

Slide Presentation

A Small Dose of Soil Pollution presentation material and references online:
http://www.asmalldoseoftoxicology.org.
Website contains presentation material related to the health effects of soil pollution.

European, Asian, and International Agencies

- World Health Organization (WHO). Radon and health. Online at http://www.who.int/mediacentre/factsheets/fs291/en/
  Overview of indoor and outdoor radon pollution as well as health-related information. [accessed January 1, 2021]

- European Commission. Soil. Online at http://ec.europa.eu/environment/soil/ The importance of soil to ecosystem. [accessed January 1, 2021]

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North American Agencies

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- U.S. Environmental Protection Agency. Soil Fumigant. Online at https://www.epa.gov/soil-fumigants. [accessed January 1, 2021]

Non-Government Organizations

- National Pesticide Information Center - a cooperative agreement between Oregon State University and the U.S. Environmental Protection Agency. Soil and Pesticides. Online at http://npic.orst.edu/envir/soil.html [accessed January 1, 2021]
  NPIC provides objective, science-based information about pesticides and pesticide-related topics to enable people to make informed decisions.

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A Small Dose of Toxics in the Home
Or
An Introduction To Toxics In The Home

Chapter 29
A Small Dose of Toxicology - The Health Effects of Common Chemicals

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web: www.asmalldoseoftoxicology.org - "A Small Dose of Toxicology"

Dossier

Name: Toxics at Home
Use: 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: 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 to 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 it deals with products that we are all familiar with 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 a 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.

Table 18.1 Toxics in the Home

Toxics in the Home

- Radon
- Asbestos – pipe insulation, linoleum, celling tile
- Lead in paint
- Indoor air pollutants
- Second-hand smoke
- Mold & mildew
- Household hazardous waste
- Dust from inside and tracked in from out side
- 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-based thermometers

Both the general environment and individuals in the home can suffer the consequences of the produces used in and around the home. Many household products contain chemicals that when used contaminate our air and water. 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 home, many with 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 handle information and animal poisoning related calls.

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 result in over 100,000 children visiting a hospital and losing over 10 million school days per year. A very different kind of long-term disability results from childhood lead exposure. The U.S. Centers for Disease Control and Prevention estimated that over one million U.S. 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 off gassing 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, 0ver 25,000 incidents resulted in medical outcomes deemed "major", and there were 1,544 deaths. Almost half 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.

I also believe home is where the children are. This could mean a day care, grandmothers home, a school, a play ground, a friends house, as the kids get older a car, just think of all the places a kid might be. The multiple by all the exposures a child might receive. For example radiation from the sun could cause a sunburn before one is even aware there is a problem. In this very real senesce, I have only covered small amount of the ground,

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, sever 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. They include concentrates of insecticides, fungicides, and some herbicides.

Chronic Exposures/Chronic 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 by 1000 times or more and persist for a long time. Contaminated soil can 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. 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 eludes 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 18.2 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, market 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	Particle board, plywood	0.30
Chlorpyrifos	Insecticide*	0.014

* Chlorpyrifos was discontinued in U.S. for household use after the end of 2001.

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 18.3 Chronic Health Effects

Ingredient	Found in*	Cancer	Reproductive	Developmental	Nervous
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 or (PBDE)	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 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 with inadequate ventilation, or deliberately inhaling solvents to get high. Reasons for "misusing" products are many:

1. Label too difficult to read (e.g. too small, not in native language, poorly written)
2. Consumer doesn't bother to read label
3. 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 and diazinon, DDT; the wood preservatives pentachlorphenol 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 turned up lead in many childrens' toys. Brominated flame retardants (polybrominated diphenyl ethers or PBDE) are used in foam rubber and plastics, where they 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 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 residence reduce exposure to toxic substances. The Master Home Environmentalist™ program of the American Lung Association trains volunteers to visit home and contact 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 17.4 Least-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 words 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:

1. Minimize purchase of toxic or otherwise hazardous products.
2. Store all chemical products out of children's reach.

3. Read and follow label directions.

4. 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:

1. 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.

2. 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.

3. Ultimately a more precautionary approach needs to be adapted to protect human and environmental health.

More Information and References

Slide Presentation

A Small Dose of Toxics at Home presentation material and references online: specific information including a PowerPoint presentation at:
www.asmalldoseoftoxicology.org
Web site contains presentation material related toxics in the home.

European, Asian, and International Agencies

- England – Department of Health – Healthy Schools. Online: < http://www.healthyschools.org.uk/ > (accessed: 23 October 2020).
  Healthy Schools, while focusing on schools is wonderful site with information of students, parents, and teachers on creating a healthy in door environment.

- World Health Organization – WHO | Children's environmental health indicators. Online: <https://www.who.int/activities/monitoring-progress-on-children-s-environmental-health > (accessed: 23 October 2020).
  Site has information on global child health issues.

North American Agencies

- U.S. Household Products Database – National Institutes of Health, National Library of Medicine. Online: <https://medlineplus.gov/householdproducts.html > (accessed: 23 October 2020).

Site has a range of information about household products including their potential health threats.

- U.S. Environmental Protection Agency - Household Waste. Online: https://www.epa.gov/hw/household-hazardous-waste - (accessed: 23 October 2020).
  Site has a self-directed educational program on managing household waste.

- U.S. Environmental Protection Agency - Chemicals under the Toxic Substances Control Act (TSCA Online: < https://www.epa.gov/chemicals-under-tsca > (accessed: 23 October 2020).
  The site promotes safer chemicals and risk education.

- U.S. Environmental Protection Agency – Indoor Air Quality (IAQ). Online: < https://www.epa.gov/report-environment/indoor-air-quality .
  This site contains information on indoor air and related health issues.

California

- California Environmental Protection Agency, or CalEPA – Online: < https://calepa.ca.gov > (accessed: 23 August 2020).
  Led California in creating and implementing some of the most progressive environmental policies in America

- California – Office of Environmental Health Hazard Assessment (OEHHA). Online: < https://oehha.ca.gov > (accessed: 23 October 2020).

Non-Government Organizations

- American Lung Association of Washington (ALA). Online: < https://www.lung.org > (accessed: 23 October 2020).
  Seeks to improve lung health and prevent lung disease

- American Association of Poison Control Centers (AAPCC). Online: <http://www.aapcc.org/> (accessed: 23 October 2020).
  "AAPCC is a nationwide organization of poison centers and interested individuals."

- California Poison Control System (CPCS). Online: <http://www.calpoison.org/> (accessed: 25 October 2020.
  Site has wide range of information on poisons in and around the home.

- CR Consumer Reports is an independent, nonprofit member organization that works side by side with consumers for truth, transparency, and fairness in the

marketplace. Online: https://www.consumerreports.org/ (accessed: 23 October 2020).

- Environmental Working Group (EWG). Online: < http://www.ewg.org/ > (accessed: 23 October 2020).
  This organization provides information on a range of consumer products including data bases on sunscreens and cosmetics.

- Center for Health, Environment and Justice - Online: < http://chej.org > (accessed: 25 October 2020).
  Site is "geared to protect children from exposures to environmental health hazards."

- ·Toxic-Free Future (formally Washington Toxics Coalition (WTC)). Online: < https://toxicfreefuture.org > (accessed: 25 October 2020).
  Toxic-Free Future advocates for the use of safer products, chemicals, and practices through advanced research, advocacy, grassroots organizing, and consumer engagement to ensure a healthier tomorrow.

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  The Office of Sustainability & Environment (OSE) collaborates with a wide range of stakeholders to develop innovative environmental solutions that foster equity, vibrant communities, and shared prosperity.

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  Green Seal encourages the purchasing of products and services that cause less toxic pollution and waste.

- Washington State, King County – Household Hazardous Waste. Online: < https://kingcountyhazwastewa.gov > (accessed: 25 October 2020).
  Site contains information on managing and disposing of household hazardous products and waste.

- Women's Voices for the Earth. Online: < https://www.womensvoices.org > (accessed: 25 October 2020).
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