

LAB Notes

Toxicology

LAB Notes

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IN THIS ISSUE:

Toxicology: Our Vital Link to Health & Safety	1
A Primer in Toxicology	1
Chemical Toxicity is NOT a Simple Picture	2
RISK vs. BENEFIT: You Decide...	2
Poison Control Facts	3
CONNECTIONS: Environmental Toxicity	3
Risk Assessment	4
CONNECTIONS: Risk vs. Benefit	4
Materials Order Form	4
The Use of Animals in Toxicology	5
Alternatives: Pursuing the "3R's"	5
"Cruelty-Free"	5
The Ames Assay: 3R's Pioneer	5
Assessing Personal & Public Health Risks	6
Science vs. Perception	6
Perceived vs. Actual Risk	7
Selected Resources	8

TOXICOLOGY: Our Vital Link to Health & Safety

Personal health and safety is a priority for each of us. Many of us take for granted the safety of our medications and con-

sumer products, highlighting how safe these have become for their intended use. When they are accidentally misused, we have confidence that our poison control centers can help us prevent tragedy.



Each day we come into contact with a variety of consumer products. How do you know they are really safe?

How the safety of the products and drugs we use is determined is the business of the science of toxicology. As with other fields of biomedical and biological science, the use of animal models is a critical tool in the experimental armament of a toxicologist for assessing the risks associated with

TOXICOLOGY... is the study of the qualitative and quantitative effects of chemicals on living systems.

the chemicals we use. And like other areas of biomedicine and biology, the pursuit of alternatives to animal research is a priority for toxicology professionals.

This MSMR special topic newsletter offers an introduction to this complex and fascinating field of science.

A Primer in Toxicology

Each of us is concerned to some degree about the effects of chemicals on people, animals, and the environment. We know that some chemicals can have severely adverse impacts — for example, the many deaths from methyl isocyanate expo-

sure in Bhopal, India a number of years ago, or the birth defects in children whose mothers took thalidomide during pregnancy. We are also aware of chemicals in the environment that affect public health, such as the effects on our children of

lead in soil and drinking water. How concerned should we be about the countless small exposures to chemicals we experience each day? This is the business of **toxicology**.

...continued on page 2

Continued from cover page...

What substances are toxic?

Any substance can be toxic. The higher the exposure to a substance, the greater the chance of an adverse effect. One example is sodium chloride, or table salt. Although essential to life, children have died from eating salt and many adults suffer from hypertension, which is associated with too much salt in the diet.

All substances are poisons...
The right dose differentiates
a poison and a remedy.

- Paracelsus

A number of vitamins are toxic at high doses. Vitamin D, in fact, is classed as a highly toxic substance and only tiny amounts are needed for proper nutrition. Many foods and beverages actually contain chemicals that could be toxic if you ate very large quantities. Carrots, for example, contain arsenic. Many plants produce toxins and many spiders, snakes, and insects produce venoms that contain powerful toxins. Certain bacteria also produce toxins, e.g., the *botulinus* toxin found in improperly preserved foods.

How does a substance exert a toxic effect?

The mechanisms for toxicity vary widely. Some chemicals disrupt the body's ability to use oxygen. In cyanide poisoning, for example, oxygen can get to tissue cells, but cannot be used once it arrives. The *botulinus* toxin interferes with the transmission of nerve impulses, which can lead to paralysis of respiration.

How does exposure occur?

Before a toxic effect can occur, there must be *exposure*. A toxic substance may enter the body through the mouth, lung, or skin.

Once ingested, a chemical may be absorbed across the wall of the gastrointestinal tract into the bloodstream. Most of a chemical absorbed in this way is carried first to the liver. The liver biotransforms the chemical into a less — or sometimes more — toxic form.

Unless a substance is injected directly into the body, the lung is usually the most rapid means of entry into the bloodstream. For example, gaseous anesthetics act very rapidly. And inhaled toxins, such as the fumes released by burning plastics, can have rapid and catastrophic effects.

Skin is usually a defense against toxic substances, but it can also be a point of entry. For example, the pesticide parathion is absorbed through the skin into the bloodstream. In a recent case, a scientist was poisoned by mercury absorbed through laboratory gloves.

The effects of a toxin will depend on the dose and how the body responds to the dose. Some substances are poorly absorbed by the body and may be excreted rapidly, while others may be stored and built up in tissues over time. Dioxin is an example of an environmental chemical in the latter category.

Why and how are animals used in toxicology?

Animals are used as models to predict the effects of human exposure to a chemical. Once toxicity is determined in animals, low-risk products may receive approval by regulatory agencies for consumer purchase. Many chemicals or chemical formulations (e.g.,

Chemical toxicity is NOT a simple picture...

Atropine... is a supertoxic chemical produced in the deadly nightshade plant. It is also an antidote for organophosphate pesticides and for nerve gas poisoning.

Botulinus toxin... is the most acutely toxic chemical known. It has also been used to treat muscle spasms.

Thalidomide... produces serious birth defects in humans. Yet it is also a potent immune response modifying drug, and is being studied for use as an immunosuppressant in organ transplant recipients and as a drug for ameliorating some AIDS-related conditions.

Vitamin A... is an essential nutrient. It is also a human teratogen (causes birth

herbicides, veterinary drugs, and animal feed additives) are not tested in people, but animal (*in vivo*) test results are used to predict the effect of accidental human exposure or misuse.

At the early stages of drug development, *pharmacokinetic* studies in animal models determine the **A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion (**ADME**) of a potential new drug. These studies can only be conducted in intact, living organisms and yield information critical for designing further toxicology studies and human clinical trials.

Other animal studies used in toxicology include lifetime toxicity and carcinogenicity studies, which determine toxicity and cancer-causing potential of a chemical over the lifetime of an animal. Developmental toxicity studies determine the effects of chemicals on a developing fetus. And neurotoxicity studies determine the effects on the nervous system. Most of these studies are conducted in rodent species.

In general, animal-based toxicology studies help determine the hazard potential of a chemical by defining how it might injure people and other animals. These studies, in combination with non-animal tests and other related information, are used by regulatory

RISK vs. BENEFIT: You Decide...

Aspirin is a drug with many beneficial uses. It is generally regarded as quite safe. However, it is not without side effects. Aspirin has a complex range of effects. It is a pain reliever, and reduces fever and inflammation. It is also an acidic compound and may act as a stomach irritant in some people. It may also have adverse effects on pregnant women in the third trimester. With prolonged use of the drug also comes a risk of some hearing loss.

Doctors often prescribe 4-8 aspirin each day for patients suffering from arthritis, a painful and debilitating disease. Imagine that your joints ached constantly, limiting your activity. Aspirin could help relieve your pain. *Would you take the aspirin? In other words, would you prefer to live with the pain or with the possible side effects of the treatment?*

agencies to perform risk assessment to determine whether the benefit of a particular drug or product is worth the potential risk.

What factors influence how toxic a chemical will be?

A wide variety of factors influences chemical toxicity. A chemical may be very toxic to one species but have little effect on another. The toxicity of dioxin, for example, varies greatly among species, being highly toxic in guinea pigs and only slightly toxic to hamsters.

Within a single species, *individual differences* make some individuals more resistant and some more susceptible to chemical toxicity. Some people, for example, may react to food additives such as sulfites or MSG. The *gender* of the animal can affect sensitivity as well. Women are more susceptible to alcohol than men. Age can also affect toxicity. Babies and small children have less well developed immune systems and higher respiration rates than adults, making them generally more susceptible. *Nutrition* can also affect susceptibility. Mice fed a well-balanced, but low-calorie diet have been shown to develop fewer cancers and other diseases than do overweight mice.

How the body metabolizes a chemical also affects toxicity. The liver typically metabolizes substances into less toxic forms, but it can sometimes make a chemical more toxic. This is true of some environmental carcinogens, which are not carcinogenic in and of themselves, but become so when processed by the liver.

Many other factors also affect toxicity. Elemental mercury (such as that found in thermometers) is less toxic than

CONNECTIONS: Environmental Toxicity

Toxic chemicals can build up through the food chain. When chemicals do not break down easily, they may be ingested at safe levels by organisms low on the food chain, but build up in higher feeders. A rodent may not be harmed by an insecticide, but a bird of prey that feeds on the rodent may accumulate the chemical in

mercury in compound form. By the same token, barium is a toxic heavy metal, yet barium sulfate, which is used in x-ray diagnosis, is fairly innocuous because it is so insoluble that it is not absorbed across the wall of the gastrointestinal tract.

How do combinations of chemicals interact in the body?

This is an area of ongoing concern and study by toxicologists because we are typically exposed to many chemicals rather than just one. Most commonly, the effects of multiple exposures is *additive*. Sometimes, a second chemical can *antagonize* (or diminish) the action of another — such an antagonist may be an appropriate *antidote*. One example is the use of excess oxygen as a treatment for carbon monoxide poisoning.

The interaction of most concern is *synergism*, in which one chemical enhances the toxicity of another. An example is radon exposure and smoking. A smoker exposed to radon is much more susceptible to lung cancer than a non-smoker.

The major problem with exposure to many chemicals at the same time is predicting the net effect. This is a subject toxicologists will be struggling with for many years to come. ■

Frequently, information about the toxicity of a product in humans is unavailable. When that is the case, poison specialists must rely on previous **ANIMAL TOXICITY TESTING** in order to make a decision as to how severe an injury is likely to be from such an exposure, what the appropriate triage should be, and how a patient should be managed.

its body. And products such as mercuric compounds in water systems can build up in fish and then accumulate to even higher levels in birds and mammals (including people) that then eat the fish.



Toxic chemicals can build up through the food chain.

POISON CONTROL FACTS

- There are some 3,000,000 hazardous substances in the environment. About 470,000 drugs, chemicals and organic toxins (from plants) are categorized in the Poisindex, a common information source for poison control centers.
- The average American family brings some 400 toxic compounds into the household annually.
- The Massachusetts Poison Control Center responds to more than 70,000 phone calls in Massachusetts each year -- 1 poisoning call every 15 seconds. About 60% of these calls involve children under the age of 5.
- Nationally, poison control centers receive almost 1.6 million calls related to poisoning each year. Again, more than 60% of these reported poisonings involve young children.
- For exposure to non-pharmaceutical products, most common are: (1) cleaning products and deodorizers, (2) cosmetics and personal care products, and (3) poisonous plants. These account for more than half of poisonings among children under 6 years of age.
- For exposure to pharmaceuticals, most common are: (1) analgesics, (2) cold and cough preparations, and (3) topical medications. These account for about half of the exposures for children under 6 years of age.
- Animals are also victims of accidental poisoning. Over 40,000 cases of poisoning in animals are reported to poison control centers each year, most of these in companion animals. Insecticides account for most animal poisonings with household products.

RISK ASSESSMENT

There is no way to eliminate the risk involved with exposure to synthetic and natural chemicals. However, toxicologists working with government regulators have developed means to assess risk.

Risk assessment is a process in which the toxicity of chemicals in animals and other models, as well as the level of human exposure, is examined. From this evaluation is calculated a "safe dose" of the compound. Risk assessment is used to set **standards** (levels that should not

be exceeded) -- for example, the level of pesticide residue on fresh fruits and vegetables.

The risk assessment process is deliberately conservative. When definite answers are not known, worst case assumptions are made to ensure that even very sensitive people would not be harmed by a standard exposure.



Scientists seek to minimize risks associated with use of consumer products and other chemicals.

CONNECTIONS: Risk vs. Benefit

Toxicity can vary from species to species, and even among individuals of the same species. This causes a problem, for example, when strains of bacteria develop resistance to certain antibiotics or when some people develop side effects to drugs. Drug side effects demonstrate the evaluation of **risk vs. benefit**. In other words, *do the benefits of disease control outweigh the disadvantage of adverse side effects in some people?* Similar risk-benefit analysis is used in many of our daily personal decisions.

Toxicology-Related Classroom Materials from MSMR

BioRAP... a topical student newsletter, including *Product Safety Testing* and *Risk Assessment* issues. Up to 10 copies FREE.

Casey's Awakening... a storybook/workbook on biomedical research & testing. Single copies FREE to NE teachers. \$5.50 for additional copies.

Consumer Product Safety... a booklet describing issues in consumer product safety. From *Join Hands*. Up to 10 copies FREE.

The Importance of Animals in the Science of Toxicology... a fact sheet from the Society of Toxicology. Single copies FREE.

People & Animals: United for Health... an interactive, poster-sized health and science calendar/activity sheets for K-8 classrooms. In perpetual calendar format. \$15 per calendar, FREE to MA teachers.

People & Animals: United for Health... a comprehensive curriculum resource on issues in biomedical research and testing. Includes text, set of 169 slides, discussion guide and poster. \$100 per package.

PERIL... a CD-ROM game on risk perception. Up to 5 copies FREE.

Risky Business... curriculum guidelines for skills, awareness and understanding of risk assessment. FREE.

Toxicology: An Educator's Resource Guide... a 7-lesson study unit with teacher notes, student worksheets, and classroom exercises. Single copies FREE.

Classroom Materials Order Form

Item	Qty.	Price	Subtotal

Subtotal: _____

Shipping: _____

Total: _____

PAYMENT & SHIPPING

Pre-payment by check, money order, or purchase order is required.

Shipping and handling rates are as follows:

Order Total	Shipping
\$ 0—25	\$ 5
\$ 25—50	\$ 10
\$ 50—100	\$ 15
Over \$ 100	Call the MSMR.

Name _____

Address (Street address required.) _____

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The Use of Animals in Toxicology*

Many interrelated processes operate within the human and animal body. An example involves the absorption, metabolism, distribution, and excretion of food and drugs. These normal processes can be affected by exposure to chemicals, and the body can modify the effects of such substances by making them either less or more toxic. The complex interrelationships of organ and chemical systems make it impossible to determine the safety of chemicals unless they have been studied in living animals.

The most direct way to determine the effects of people of a new drug or chemical in the air, in food or water, would be to study the consequences of exposure in humans. Although limited testing is performed in human volunteers, scientific and social ethics dictate that it is unacceptable to test drugs or other chemicals in people before their adverse effects have been extensively studied in multiple animal species. By using animals that are biologically similar to humans, toxicologists can predict effects that could occur in people. Because studies in laboratory animals are currently the only reliable alternative to human testing, the use of experimental animals is an essential part of toxicological research.

Most importantly, the use of laboratory animals has been indispensable for almost every medical breakthrough of this century.

More than 99 percent of all animals used in biomedical research and testing are bred specifically for that purpose by licensed breeders. Rats, mice and other rodents comprise 85-90 percent of the animals used in research and testing.

While the use of animals in research and testing is clearly directed toward the advancement of human health and welfare, toxicologists like other scientists are concerned about the welfare of the animals for ethical, scientific and economic reasons. Humane and appropriate care and use of research animals is critical to the success of safety studies and other toxicological research. Valid research requires that stress or pain to the animals be reduced to the absolute minimum.

Toxicologists use the fewest number of animals that they can in studies to produce valid results. Individual researchers design their studies to minimize the use of animals and ensure their well-being.

Adapted from *The Importance of Animals in the Science of Toxicology*, produced by the Society of Toxicology, (703) 438-3115.

Alternatives: Pursuing the "3R's"

The development and validation of alternatives to animal models and the refinement of existing methods are a priority in toxicology for scientific, humane, and economic reasons. Although some methods currently exist that could replace animals, few are suitable and reliable for use in toxicology to assess risk to humans and other animals. Therefore, the use of animals will be essential in safety research for the foreseeable future.

When speaking of "alternatives," we are referring to the "3R's" concept, which was first presented in a 1959 publication entitled *Principles of Humane Experimental Technique*, by W.M.S. Russell and R.L. Burch. It is the definition used by government agencies when referring to "alternatives," and is generally accepted by both scientists and the animal protection community. The "3R's" are:

REPLACEMENT refers to the use of methods that do not involve whole, living animals. Computer models or cell and tissue culture are examples.

REDUCTION refers to the use of fewer animals to obtain the same amount or more information. Improving statistical methods to allow use of fewer animals is an example.

REFINEMENT means alteration of existing procedures to minimize the discomfort they cause to the animals. Use of new, more effective analgesics or closer monitoring for signs of pain are

"CRUELTY-FREE"

Some companies promote their products as "Cruelty-Free" or "Not Tested on Animals." The use of these phrases is possible because there are no **legal definitions** for these terms.

Some companies apply these claims to finished products only, although they may rely on raw material suppliers or contract laboratories to perform the animal testing necessary to ensure safety.

Many raw materials used in consumer products were tested on animals years ago. A manufacturer might only use those raw materials and base its "Cruelty-Free" claims on the fact that the materials or products are not **currently** tested on animals.

The Ames Assay: 3R's Pioneer

Bruce Ames of the University of California at Berkeley was the first scientist to substitute single cells for animals in toxicology. In the 1960s, he developed a strain of *Salmonella typhimurium* to test for **mutagenicity** (*ability of a compound to change an organism's genetic material*). The strain carried a mutation in one of its histidine synthesis genes that could be repaired by any of several mutations.

In exposing those bacteria to chemicals, Ames found that the number of bacteria then able to make histidine was proportional to the ability of the chemicals to induce mutations in animal models.

ASSESSING PERSONAL & PUBLIC HEALTH RISKS: SCIENCE *is the Key*



How can you help yourself live out your natural life span? What can our society do to help each of us as individuals live full, healthy lives?

First, we need to know what causes illness and premature death. Second, we need to know the factors that are most responsible. These are not necessarily the same as the direct causes. Cancer causes death, for example, but it is not clear which factor(s) — environmental pollution, diet, or other factors — are most responsible for causing cancer. Similar questions surround other causes of illness and premature death, creating healthy scientific debate.

Identifying key underlying causes of illness and early death and assessing the risk to individuals which arise from these factors is an important step in improving our chances of living out our natural life span.

Advocates for a given position sometimes make misleading statements that one event causes another. In fact, other events may cause both. When people start wearing overcoats, for example, home heating bills generally go up. But overcoats do not cause heating bills to increase. The onset of cold weather is the direct cause of both the appearance of overcoats and the increased heating bills.

These and other misperceptions can lead us to make personal and public health decisions that put ourselves and others at risk. It is important to base our decisions on good solid science. Only **science** can come close to determining the actual risks associated with the lifestyles we pursue. ■

SCIENCE versus PERCEPTION

Below is a partial list of activities or technologies that are known to increase the average risk of premature death. Look over the list and rank these activities in terms of your perception of their risk (“1” being highest risk). See page 7 and discuss the responses in class.

- _____ Motor vehicles
- _____ Smoking
- _____ Alcoholic beverages
- _____ Hand guns
- _____ Surgery
- _____ Motorcycles
- _____ X-rays
- _____ Pesticides
- _____ Electrical power
- _____ Swimming
- _____ Oral contraceptives
- _____ Private aviation
- _____ Heavy construction
- _____ Food preservatives
- _____ Bicycles
- _____ Aviation (commercial)
- _____ Police work
- _____ Firefighting
- _____ Railroads
- _____ Nuclear power
- _____ Food coloring
- _____ Home appliances
- _____ Hunting
- _____ Antibiotics
- _____ Vaccinations
- _____ Spray cans
- _____ High school football
- _____ Power mowers
- _____ Mountain climbing
- _____ Skiing

PERCEIVED vs. ACTUAL RISK

How do your perceptions of risk compare with the perceptions of others? How do all of these perceptions compare with the scientific data?

ACTIVITY/TECHNOLOGY	LEAGUE OF WOMEN VOTERS RESPONSES	COLLEGE STUDENTS RESPONSES	SCIENTIFIC DATA
Motor vehicles	2	5	1
Smoking	4	3	2
Alcoholic beverages	6	7	3
Hand guns	3	2	4
Surgery	10	11	5
Motorcycles	5	6	6
X-rays	22	17	7
Pesticides	9	4	8
Electrical power	18	19	9
Swimming	19	30	10
Oral contraceptives	20	22	11
Private aviation	7	15	12
Heavy construction	12	14	13
Food preservatives	25	12	14
Bicycles	16	14	15
Aviation (commercial)	17	18	16
Police work	8	8	17
Firefighting	11	10	18
Railroads	24	23	19
Nuclear power	1	1	20
Food coloring	26	20	21
Home appliances	29	27	22
Hunting	13	18	23
Antibiotics	28	21	24
Vaccinations	30	29	25
Spray cans	14	13	26
High school football	23	21	27
Power mowers	27	25	28
Mountain climbing	15	22	29
Skiing	21	25	30



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The mission of the Massachusetts Society for Medical Research, Inc. is to promote and enhance biomedical and biological research, including the proper care and use of animals, for the improved health and well-being of people, animals, and the environment. In furtherance of this mission, the goal of the MSMR is to improve basic literacy in and enthusiasm for life science among the public, the media, and especially future generations of citizens and scientists.



In service to its mission, the MSMR develops and supports programs and materials for classrooms and for the public that foster better understanding of science and the nature of research and testing.

DISCUSSION: *What's in a Label?*

- All consumer products must have labels. What kinds of information do we obtain from product labels?
- Where does the information on product labels come from?

Invite an MSMR speaker to your classroom to help you answer these questions. Call the MSMR at 978.251.1556.

SELECTED TOXICOLOGY RESOURCES

WEB SITES

AltWeb, at the Johns Hopkins Center for Alternatives to Animal Testing. <http://www.sph.jhu.edu/~altweb/cgi/websearch.cgi>

Canadian Network of Toxicology Centres. <http://www.uoguelph.ca/cntc/>

American Association of Poison Control Centers, directory of poison control centers in the U.S. <http://www.aapcc.org/findyour.htm>

Arizona Poison and Drug Information Center, a resource for information on natural and human-made poisonous chemicals. http://www.pharmacy.arizona.edu/centers/poison_center/

Chemicals and Human Health, a Web site designed to help high school students and teachers learn the basic principles of toxicology and scientific research, and to provide real-world applications of textbook concepts. <http://www.biology.arizona.edu/chh>

Household Chemical Agency Web Site for Children, a new interactive site by EPA to teach children about household products that may contain harmful chemicals. Includes information about toxic substances stored in different rooms in the house, and educational games. <http://www.epa.gov/opptintr/kids/hometour/index.htm>

JOIN HANDS. <http://www.joinhand.org/>

National Institute of Environmental Health Sciences Kids' Page, lots of fun activities for kids. <http://www.niehs.nih.gov/kids/kids.htm>

Phytochemical and Ethnobotanical Databases, searchable databases for chemicals in plants and herbs and their biological activities. <http://www.ars-grin.gov/duke/>

Poison Center Answer Book, information about common poisons. http://wellness.ucdavis.edu/safety_info/poison_prevention/poison_book/

Society of Toxicology. <http://www.toxicology.org/>

Toxicology/Environmental Health Information. <http://sis.nlm.nih.gov/tehip1.htm>

BOOKS / CURRICULA / CD-ROMS

Essentials of Cell Biology: Toxicology in Action CD-rom. FREE. Contact: Health & Environmental Resources for Educators, University of Washington, 4225 Roosevelt Way NW, Ste. 100, Seattle WA 98105-6099.

PERIL CD-rom. FREE. Contact: <http://www.uoguelph.ca/cntc/>.

Risky Business Curriculum. Contact: <http://weber.u.washington.edu/~k12/cgi-bin/back.cgi?122>.

Bloomfield, Molly. Challenge Problems for High School Students: Environmental Health Science Curricula. Contact: bloomfm@smile.orst.edu.

Dereski, Mary. Chemicals in My World Curriculum (grades K-12). FREE. Contact: m.dereski@wayne.edu.

Moreno, Nancy. My Health, My World Curriculum. Contact: nmoreno@bcm.tmc.edu.

Ottoboni, M. Alice. The Dose Makes the Poison: A Plain Language Guide to Toxicology (2nd ed.), John Riley & Sons, 1997.