SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science and Increasing the Impact of Toxicology

Society of Toxicology—Undergraduate Toxicology Course Learning Framework

Approved by SOT Council November 2018; updated May 2020.

This Learning Framework was created by the Learning Objectives Work Group, a group appointed by the Education Committee with the charge of creating a guide to facilitate the creation or modification of undergraduate courses in toxicology. The group included Joshua Gray (chair), Chris Curran, Vanessa Fitsanakis, Sid Ray, and Karen Stine with significant contributions from Betty Eidemiller. For more background see "Society of Toxicology Develops Learning Framework for Undergraduate Toxicology Courses Following the Vision and Change Core Concepts Model," *Toxicological Sciences*, Volume 170, Issue 1, July 2019, Pages 20–24, https://doi.org/10.1093/toxsci/kfz090.

The objectives were modeled after the Core Concepts of the Vision and Change report and are aligned with similar Core Concepts which have been developed for other life science courses by their professional scientific societies and which are published at CourseSource. The Learning Framework was developed following an analysis of undergraduate toxicology syllabi submitted to the SOT's teaching resource collection as well as an analysis of undergraduate toxicology texts of all genres. We endorse the Vision and Change Core Competencies and Disciplinary Practices as analytical, experimental, and technical skills are desired course outcomes.

Design and Usage

The Level One Core Concepts build on the foundation of the five Core Concepts first developed for Undergraduate Biology by Vision and Change and used in the subsequent development of objectives for courses such as Biochemistry and Molecular Biology. Level Two Toxicology Concepts are broad disciplinary categories, beneath which Level Three Learning Objectives discuss particular learning goals. Level Four Example Learning Objectives and Case Studies illustrate how the Level Three Learning Objectives might be taught and are not intended to be comprehensive. Many Level Four examples are case studies and include references to associated articles, such as links to a case study's website, PubMed unique identifier (PMID), or PubMed Central reference number (PMCID) which might be useful in teaching an objective.

A faculty member developing a course would be likely to select a subset of these Toxicology Concepts and Learning Objectives depending on the emphasis of that course, such as pharmacology, industrial hygiene, ecological toxicology, etc. It is not anticipated that a faculty member would attempt to teach all the concepts or objectives in a single semester; rather, a faculty member would use this Learning Framework as a tool to help create a course that meets the needs of their institution.

Level One Core Concepts

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Evolution

Evolution drives the interplay between toxicants/toxins and xenobiotic defense mechanisms and justifies the use of model organisms.

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How is the use of model organisms fundamental to toxicology?	Describe features of ideal model systems.	• Explain why low cost of maintenance, large number of offspring, and simplicity are characteristics of ideal model systems. • Describe how use of a common model system contributes to reproducibility across laboratories. • Explain how some model organisms are selected for organ-specific similarity to humans, for example, eyes of rabbits or skin of pigs. • Explain how some model organisms are selected based on metabolic or genetic similarity to humans.
	Describe common model systems, including *Drosophila, C. elegans*, mouse, rat, and non-human primate.	• Describe the historical importance of each common model system. • Describe which model systems have similar xenobiotic metabolic pathways to humans. PMID28931683 • Describe the advantages of simple animal model systems compared with cell culture or other *in vitro* approaches. • Describe how genetic similarities between *Drosophila* and humans make it a valuable model system. PMID29056683 • Describe how *Drosophila* models metal toxicity in humans. PMID28684721 • Describe the use of *C. elegans* as a model for viral host interactions. PMID28931683 • Discuss the history of the development of *C. elegans* as a model organism. PMID28326696 • Explain the importance of using multiple animal models when testing toxicity due to species differences. • Case study: Explain how thalidomide validates the importance of testing multiple animals when testing for toxicity. • Describe the use of laboratory animals (mouse, rat, guinea pig, rabbits, dogs, and non-human primates) as models for disease pathogenesis and toxicity testing. Ernest Hodgson Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
	Describe how evolution is fundamental to the use of model systems in toxicology.	• Describe the relationship between genetic phylogeny and similarity in physiology in terms of model systems for toxicology. • Describe the role of evolution in comparisons of genes across species. • Describe how evolution provides the rationale that animal studies are translatable to humans.

Evolution

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How is the use of model organisms fundamental to toxicology?, *continued*	Describe ethical reasons for using model organisms	• Describe how ethical issues impact the types of experiments that can be performed on humans. • Describe how lack of data in humans supports the use of animals in research. • Describe how reduction, refinement, and replacement (the three R's) ensure the best ethical treatment of animals used in research. • Describe the role of the Institutional Animal Care and Use Committee (IACUC) in guiding research at local institutions, ensuring the ethical treatment of animals. • Describe the increasing importance of *in vitro* and *in silico* models such as QSAR in supplanting studies involving model organisms. Yves Alarie Eminent Toxicologist Lecture http://www.toxicology.org/education/edu/Evolution of Toxins eminent.asp • Describe ethical and other considerations for the replacement of model organisms with in vitro assays. Alan M. Goldberg Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
How have toxins evolved?	Contrast toxins and toxicants.	• Contrast a toxin from a toxicant. • Describe historical uses of toxins. • Describe the structure of toxins as peptides or with functional groups similar to amino acids. • List and describe common toxins to which people are exposed on a regular basis. • Describe common uses for compounds classified as toxins.
	Explain the role of toxins in organismal defense.	• Contrast poisons and venoms. • Describe the various ways animals and plants use toxins. PMID12179963 • Describe common treatments used by clinical toxicologists to treat people exposed to various toxins. • Distinguish between primary and secondary metabolites as defense molecules for various plants. • Discuss how animals and plants prevent intoxicating themselves with their own toxins. • Describe how quorum sensing affects the production of toxins in infectious microorganisms. • Case study: Describe how quorum sensing by *Vibrio cholerae* affects expression of GI tract toxins and impacts the symptoms of "rice water diarrhea."

Evolution

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How have toxins evolved?, *continued*	Explain mechanisms of avoidance of poisoning by toxins.	• Describe how prey detect toxins present in predators. • Discuss the role that taste and smell may have in avoidance. • Identify protective mechanisms (physical and chemical) used to prevent intoxication. • List common mechanisms associated with degradation/detoxification of toxins. For example, many toxins are amino acid chains. • Evaluate the success of various protective mechanisms. • Describe one example of how seed lectin exhibits a toxin activity and a structural activity. PMID16441240
	Explain the importance of secondary metabolites.	• Define the difference between a primary and secondary (or secondary and tertiary) metabolite. • Describe what additional protection and cost the production of a secondary metabolite may provide the organism. • Compare and contrast the difference in toxicity caused by secondary metabolites. • List organisms that use secondary metabolites as deterrents (non-lethal chemicals) to predators. • List organisms that use secondary metabolites as lethal defenses against predators. • Case study: Describe the additional protection and cost incurred in oak trees responding to infestations with gypsy moths by induction of secondary metabolites in New York in the 1980s. PMID17770257
	Discuss how important toxins have been helpful in characterizing basic biological properties.	• List important toxins that are used in toxicology, pharmacology, neuroscience, and other disciplines. • Describe the major advances in science associated with each toxin. • Describe how toxins used in research alter physiology of the system being studied. • Case study: Describe how tetrodotoxin is used to investigate the role of sodium channels by inhibiting the channel. • Case study: Describe how nicotine is used to investigate the role of nicotinic acetylcholine receptors.
How have xenobiotic defense mechanisms evolved?	Discuss the role of xenobiotic defense mechanisms in protection of organisms from toxicants and toxins.	• List common mechanisms of detoxification. • Discuss the difference between general defense mechanisms and detoxication pathways. • Describe key enzymes that aid metabolism of toxic substances. • List common toxins and toxicants and how they are specifically detoxicated. • Provide examples of how specific organisms deal with specific insults with which they come into contact. • Case study: Selenium-accumulating plants. http://irri.org/news/hot-topics/pesticides-in-rice-production

Evolution

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How have xenobiotic defense mechanisms evolved?, *continued*	Explain how evolution informs the development of the cytochrome P450 superfamily of genes.	• Discuss hypotheses regarding differences in the number of P450 enzymes in different species. http://drnelson.uthsc.edu/P450.evolution.2000.html • Describe the hypothesis that the cytochrome P450 gene superfamily evolved from a single common ancestor. PMID22687468 • Describe the evolution of transcription factors that regulate the cytochrome P450 genes from the nuclear receptor family and bHLH-PAS family. PMID22687468 • Case study: Describe how exposure to polycyclic aromatic hydrocarbons in the Elizabeth River system of southeastern Virginia selected for resistance in Atlantic killifish. PMID26505693
	Explain how evolution drives resistance to toxicants, toxins, metals, and radiation.	• Describe how toxins and toxicants (such as pesticides or antibiotics) are sources of selective pressure that drive evolutionary change. • Describe the micro-evolution of resistance to DDT. PMID21416112 • Describe the example of evolution of sulfide spring fishes in response to environments rich in H_2S. PMID29368386 • Describe how application of low levels of pesticides can increase mutation rates by inducing stress that leads to resistance. PMID21308950 • Case study: Rice plant hopper resistance to common pesticides. PMID18803329 http://irri.org/news/hot-topics/pesticides-in-rice-production
	Describe how knowledge of genetic information can predict function of similar genes within the same organism or in other organisms.	• Describe the evolution of myoglobin and hemoglobin from a primordial globin gene. • Describe how the Basic Local Alignment Search Tool (BLAST) is used to provide regions of local similarity between protein or nucleotide sequences. https://www.ncbi.nlm.nih.gov/books/NBK1734/ • Analyze evolutionary trees to determine the relatedness of genes or protein sequences. https://evolution.berkeley.edu/evolibrary/article/0_0_0/evotrees_interpretations_02 • Case study: Using Next Generation Sequencing techniques and evolutionary toxicology to assess ecological risks. www.mdpi.com/2073-4441/10/4/490/pdf
How do toxicants exert selection pressures?	Describe, using examples, the role that toxicants can play in exerting selection pressures on populations.	• Explain the fundamental concepts behind the process of natural selection. • Describe the effects of pesticides on both pest populations and nontarget populations. PMCID5533829 • Describe the effects of antibiotics on bacterial populations. PMCID4567305

Biological Information

Differences in genomes and environmental exposure drive differences in susceptibility and responses to toxicants.

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How does carcinogenesis occur in response to genotoxic and nongenotoxic carcinogens?	Describe the general characteristics of cells that have undergone neoplastic conversion.	• Explain the development of genetic instability in cells undergoing neoplastic conversion. PMCID4274643 • Describe the changes in the cell cycle which are typically seen in neoplastic cells. • Describe how neoplastic cells alter their apoptotic pathway for their survival. PMCID4091735 • Explain the factors behind the tendency for local invasiveness in neoplastic cells. • Explain metastasis and describe the molecular changes behind the development of metastatic potential in neoplastic cells. PMCID4071451, PMCID3910084 • Describe how matrix metalloproteinases facilitate metastasis of neoplastic cells. PMCID4564058
	Describe the mutational theory of carcinogenesis and explain the evidence that supports it.	• Describe the multistage model of carcinogenesis and the roles of initiation, promotion, and progression. PMID8334671 • Describe the evidence for the link between mutagenesis and carcinogenesis as generated by laboratory studies. • Describe the evidence for the role of mutagenesis which derives from observations of inheritability at both the cellular and organismal levels. • Describe the discovery of oncogenes and tumor suppressor genes and explain how this influenced the mutational theory. • Explain how evidence from DNA repair mechanism deficits supports the mutational theory. • Explain how missense, nonsense, insertion, deletion, frameshift, and repeat expansion mutations can affect proto-oncogenes and tumor suppressors. • Explain the relationship between DNA damage and cell division in the emergence of cancer. Samuel M. Cohen Eminent Toxicologist lecture. http://www.toxicology.org/education/edu
	Explain the roles that proto-oncogenes can play in normal cell function; then relate these, using specific examples, to the role of proto-oncogenes in carcinogenesis.	• Explain how missense, nonsense, insertion, deletion, frameshift, and repeat expansion mutations can affect proto-oncogenes. • Explain and give examples of proto-oncogene products (ras, PDGF, and others) with roles in ligand-receptor interactions and signal transduction. PMID26892781, PMCID4382731 • Explain and give examples of proto-oncogene products (fos, jun, myc, and others) with roles in regulation of gene expression (transcription factors).

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How does carcinogenesis occur in response to genotoxic and nongenotoxic carcinogens?, *continued*	Describe the role of tumor suppressor genes; using specific examples, explain how they can play a role in preventing and/or genetically predisposing to cancer.	• Explain how missense, nonsense, insertion, deletion, frameshift, and repeat expansion mutations can affect proto-oncogenes. • Describe the roles of tumor suppressor gene products (p53, Rb-1, and others) in regulation of the cell growth cycle. PMCID2773645 • Describe the roles of tumor suppressor gene products (BRCA-1 and others) in DNA repair. • Explain how drugs/therapies can be custom designed to target specific tissues that have genetic predispositions to cancer. • Describe the role of monoclonal antibodies used in treating cancer. PMID29061772 • Case study: Describe how mutation in the tumor suppressor gene BRCA increases the risk for ovarian and breast cancers. • Case study: Describe how polymorphisms in the APC gene increase the risk for colorectal neoplasia. PMID23896379 • Case study: Describe how imatinib targets the bcr-abl fusion protein. PMID10619854
	Compare and contrast the effects of point and frameshift mutations on a gene.	• Describe the potential consequences of point mutations in various regions of DNA including genes (both exons and introns) and promoter regions. • Describe the relationship between the position of a point mutation within a codon and consequences for amino acid substitutions • Explain why a point mutation might or might not result in an alteration in protein structure and/or function. • Describe the significance of point mutations in terms of specific amino acid substitutions (e.g., nonpolar for polar, etc.). • Describe the significance of the location of point mutations/amino acid alterations in terms of primary structure of the protein. • Explain why frameshift mutations are often more severe than point mutations in terms of functional consequences. • Explain how either a point mutation or frameshift mutation could produce a “stop” codon and the consequences of that on protein structure and function.

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How does carcinogenesis occur in response to genotoxic and nongenotoxic carcinogens?, *continued*	Identify the parts of the DNA molecule which are most vulnerable to damage by physical and chemical agents and describe the mechanisms through which the damage occurs.	• Describe oxidative deamination of nucleotides. • Describe the alkylation of bases, including the discussion of "hot spots" in the genome. PMCID5217664, PMCID1856827 • Explain the process of formation of DNA adducts, using examples (including nitrogen mustards, PAH). PMCID5509823 • Describe cross-linking and other mechanisms of damage to DNA. PMCID3755464 • Explain how alkylating chemotherapeutic agents induce genomic injury to normal and transformed cells. • List examples of monoalkylating and polyalkylating agents. • Case study: Describe how UV-induced DNA damage affects DNA at the molecular level.
	Explain the differences between pro-carcinogens and carcinogens and name examples of each.	• Describe the metabolic activation of pro-carcinogens, including examples such as nitrosamines, cyclophosphamide, and polycyclic aromatic hydrocarbons. PMID26652254, PMCID4408964 • Describe how cytochrome P450 enzymes play a prominent role in the bioactivation of procarcinogens to create ultimate carcinogens. PMID9685642
	Explain the concept of promotion and discuss the various mechanisms through which toxicants can act as promoters.	• Explain stimulation of cell division as a mechanism of promotion. • Explain how free radicals are produced. • List different types of free radicals that are produced during xenobiotic metabolism. • Explain how alterations in biotransformation reactions serve as a mechanism of promotion of toxic reactions or toxicity. • Explain inhibition of DNA repair as a mechanism of promotion of toxicity. • Explain how hormones (including estrogen, adipokines, and others) can mediate promotion of cytotoxic reactions. PMID25781552
	Describe the excision repair and mismatch repair systems for repairing DNA damage.	• Describe the molecular mechanism of the excision repair systems. PMID28798238 • Describe the molecular mechanism of the mismatch repair system. PMID28927527 • Describe the relationship between excision repair defects and xeroderma pigmentosum. PMCID5556200 • Describe the relationship between mismatch repair and hereditary nonpolyposis colon cancer. PMID27315067

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How does carcinogenesis occur in response to genotoxic and nongenotoxic carcinogens?, *continued*	Compare and contrast the threshold versus the non-threshold models for risk following exposure to carcinogens and be able to discuss the public policy implications of both.	• Discuss the difficulties involved in generating data applicable to low level exposure to humans. • Provide examples of policy decisions (including institution of the Delaney Clause by the FDA) relating to the debate over cancer risk. • Discuss how thresholds relate to regulatory definitions such as the "threshold of toxicological concern" (TTC). PMID15829616 • Describe the assessments done to pharmaceuticals, pesticides, and chemicals to evaluate carcinogenic and mutagenic potential. PMCID4382620
	Explain the concepts behind *in vitro* tests for mutagenic potential of toxicants and compare and contrast the strengths and weaknesses of these test versus animal bioassay studies.	• Explain how the Ames test is used to identify potential carcinogens and list the limitations of the Ames assay. • Compare and contrast the major *in vitro* bacterial testing systems with *in vitro* mammalian systems. PMID22147568 • Explain the rationale for the addition of microsomes to *in vitro* tests in terms of identifying pro-carcinogens. • Explain why *in vitro* tests are problematic in testing for epigenetic carcinogens and promotion. • Explain why animal bioassay studies for carcinogenesis typically utilize high dose levels.
What effects can the environment have on gene expression?	Discuss the role that nutrition plays in regulating transcription factors.	• Describe how SREBP-1c/SREBF regulate lipogenic genes as they relate to non-alcoholic fatty liver disease. PMID23545492 • Describe the role of inflammatory transcription factors and cytokines in lipogenesis. PMID16952562 • Describe the role of PPARγ in high-fat diet induced obesity and insulin resistance. PMID1872365 • Explain the role of folic acid in preventing developmental toxicity. • Identify dietary factors that alter gene regulation.

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What effects can the environment have on gene expression?, *continued*	List the changes that toxicants may induce in the protein structure, nucleic acid sequence, and/or fatty acid metabolites.	• Describe how aflatoxin reacts with DNA to induce mutations. • Describe how ultraviolet light induces thymidine dimers in DNA. • Explain how various free radicals (reactive oxygen species and biological reactive intermediates) cause damage to cellular organelles. • Describe how free radicals cause membrane lipid peroxidation. • Describe how 4-hydroxynonenal is produced by lipid peroxidation and induces a lipid peroxidation chain reaction in the plasma membrane. • Describe how prions induce changes in protein structure that result in prion disease. • Describe the effects of oxidizing agents on proteins and nucleic acids. • Describe the effects of metals on protein structure and function. • Identify the common DNA changes induced by different toxicants. • Identify compounds associated with fatty acid oxidation.
	Describe mechanisms of epigenetic transfer of information.	• Describe how DNA methylation, histone modification, and non-coding RNA (ncRNA)-associated gene silencing transmit epigenetic information. PMID15164071 • Describe the role of CpG islands in promoters in regulating gene expression. • Describe how cancerous cells have altered DNA methylation patterns that result in altered gene expression. • Describe epigenetic mechanisms that increase or reduce gene expression. • Explain how chromatin remodeling can affect gene expression. • Case study: Describe how epigenetic factors might be altered during surrogate pregnancy. PMCID5485514 • Case study: Describe how DNA methylation, transcription factor activity, and histone modification affect LINE-1 reactivation as an example of toxicants regulating the genome via epigenetics. Kenneth Ramos Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp • Describe genetic imprinting and the importance of developmental timing in the inheritance of epigenetic information. Cheryl Lyn Walker Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What effects can the environment have on gene expression?, *continued*	Describe how toxicants can induce changes in epigenetic information that can be transferred to subsequent generations.	• Describe environmental factors that can influence epigenetic mechanisms or epigenetic marks. • Identify toxicants and dietary factors (vitamins and dietary supplements) that can affect DNA methylation. • Identify toxicants that can affect chromatin remodeling. • Describe how benzene exposure affects methylation. PMID29370017 • Describe how aflatoxin B1, air pollution, arsenic, bisphenol A, cadmium, chromium, lead, mercury, polycyclic aromatic hydrocarbons, persistent organic pollutants, tobacco smoke, and nutritional factors influence DNA methylation in humans. PMID29328878
	Describe how gene/environment/time interactions affect developmental disorders and disorders of aging.	• Identify critical windows of susceptibility to toxicant exposure. • Identify allelic differences that affect susceptibility to developmental toxicant exposure. • List agents that have the potential to cause developmental defects. • Describe how developmental exposures can lead to adult disease. • Interpret graphs of functional changes over the lifespan before/after toxicant exposure to predict onset of disease/dysfunction.
	Describe features of model systems used to examine gene/environment interactions.	• Justify why transgenerational studies must include the F3 generation at a minimum. • Describe the development of primordial germ cells and potential impacts of toxicant exposures. • Describe the transgenerational effects of insulin resistance. • Case study: Describe transgenerational effects of diethylstilbestrol. PMID12902917 • Case study: Describe transgenerational effects of high fat diet. PMID25059803
	Describe toxicant/toxin effects on gene expression.	• Compare patterns of gene expression associated with toxicant exposure. • Identify tissue-specific patterns of gene expression based on routes of exposure. • Describe how dioxin and other polycyclic aromatic hydrocarbons regulate transcription through the aryl hydrocarbon receptor (AhR). • Describe how fibrates regulate gene expression through the peroxisome proliferator-activated receptor alpha (PPARα). • Describe how phytoestrogens regulate gene expression through the estrogen receptor. • Describe how partial antagonists like tamoxifen alter gene expression through the estrogen receptor.

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What effects can the environment have on gene expression?, *continued*	Describe genetic polymorphisms that affect toxicokinetics and risk.	• Identify allelic differences associated with increased cancer risk following toxicant exposure. • Identify allelic differences associated with decreased antioxidant response. • Identify allelic differences that alter the response to metals. • Identify allelic differences that alter susceptibility to arsenic. • Identify allelic differences that alter susceptibility to morphine. • Case study: Describe how polymorphisms in alcohol dehydrogenase ADH1B result in higher sensitivity to ethanol toxicity in some populations. PMID17718397 • Case study: Describe why polymorphisms of CYP2D6, 2C19, and 2C9 account for variations in phase 1 drug metabolism. PMID19514967
How do biomarkers indicate exposure to toxicants?	Describe how biomarkers can be used to indicate exposure to a toxicant.	• Describe how blood tests/panels may be used to assess a wide variety of toxicities. • Provide examples of the different kinds of biomarkers, such as direct measurements (weight, body temperature, number of offspring), chemical product, protein, mRNA, and DNA sequence. • Describe how the comprehensive metabolic panel is used to provide a medical screen for organ function (kidney, liver, heart, etc.), diabetic and parathyroid status, and electrolyte and fluid balance. • Describe how biomarkers can be used in occupational health and safety when monitoring for drug or chemical exposures.
	List the types of biomarkers that are currently used.	• Describe how serum levels of aspartate transaminase (AST), alanine transaminase (ALT), and gamma-glutamyltransferase are used to quantify organ toxicity. • Describe how the ratio of AST to ALT can be used to differentiate specific organ injuries. • Describe how cardiac troponin is used as a biomarker for cardiac function and health. • Describe how kidney injury is assessed by quantifying blood urea nitrogen and creatinine and their ratios. • Case study: Describe how N-acetyl-beta-glucosaminidase is used as a biomarker for tubular injury of the kidney. PMCID2742480 • Case study: Describe neurotoxicity biomarkers. PMCID4659531

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do biomarkers indicate exposure to toxicants?, *continued*	Describe the role of validation in evaluating biomarkers of epigenetic changes.	• Describe the important role of biomarkers in pharmaceutical development. PMID12364809 • Describe the importance of validation in determining the usefulness of a biomarker. PMID12364809 • Describe some features of biomarker validation, including: sensitivity, specificity, ease of bioanalytical assessment, rate of false negatives and false positives, and establishment of toxicokinetic parameters for the biomarker. PMID12364809 • Case study: Describe the process and challenges of biomarkers for cancer. PMCID4511498 • Case study: Review ongoing efforts in developing biomarkers for cancer. PMID25458054 • Case study: Review ongoing efforts in developing biomarkers for neurotoxicity. PMCID4659531
What differences occur in how individuals or populations are affected by exposure to different doses of a toxicant?	Explain how differences in individuals result in differences in susceptibility of a population to toxicants.	• Describe how polymorphisms in cytochrome P450 enzymes (CYP2A6, 2B6, 2C9, 2C19, and 2D6) relate to differences in risks upon exposure to drugs. PMID21149643 • Contrast genetic, epigenetic, environmental, and pathophysiological reasons for individual's differences in response to toxicants. • Contrast the various P450 phenotypes, including poor metabolizers (two defective alleles), intermediate metabolizers (heterozygous for a defective allele or carrying two alleles with decreased activity), extensive metabolizers (carrying two functional alleles), or ultra-rapid metabolizers (carrying more than two active gene copies). PMID21149643 • Case study: Describe how a rare defective allele in CYP1B1 results in elevated risk of glaucoma. PMID12624268 • Case study: Describe how a defective allele in CYP2C9 resulted in neurological signs of phenytoin intoxication. PMID11673755

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What differences occur in how individuals or populations are affected by exposure to different doses of a toxicant?, *continued*	Explain why inbred animals are used in many toxicological tests.	• Describe how inbreeding is performed to generate an inbred, or isogenic, strain. • Define the scientific term "inbred" and explain why most laboratory animal strains are inbred. • Contrast the benefits and risks of using inbred versus outbred strains of laboratory animals. Explain why studies using inbred strains are more reproducible due to less genetic variability, but why inbred studies might not translate to outbred strains. • Explain how mutations carried by inbred strains alter their susceptibility to toxicants when compared with wild type animals. • Explain why generating a hybrid of two inbred strains reduces issues caused by mutations in recessive genes. • Provide the name of a first-generation cross of two inbred strains. For example, the name of a first-generation cross of a female C57/BL6 and a male DBA/2 mouse is B6D2F1. PMID20562325 • Explain why the number of animals used in an experiment using outbred mice must be higher than an experiment using inbred mice. • Case study: Summarize the argument for using multiple inbred strains in place of outbred strains in toxicology, safety testing, and drug development. PMID20562325
	Contrast idiosyncratic reactions with other kinds of variation in a population's response to a toxicant.	• Contrast Type 1-4 hypersensitivity reactions. • Compare an immune reaction versus other types of idiosyncratic response reactions. • Describe how a drug or its reactive metabolite may act as a hapten to induce an idiosyncratic adverse drug reaction. PMID18052104 • Contrast intrinsic versus idiosyncratic toxicities. PMID20019161 • Case study: Describe the idiosyncratic reaction to penicillin. PMID16879083 • Case study: Describe the idiosyncratic hepatotoxic reaction to halothane. PMID8989020
	Contrast Margin of Safety with Therapeutic Index with regards to prediction of drug safety in a population.	• Contrast the formulas for Margin of Safety and Therapeutic Index. • Describe a situation in which Therapeutic Index may be less useful than Margin of Safety in determining the safety of a drug for a population. • Explain why cancer drugs often have a lower Therapeutic Index than other approved drugs.

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What differences occur in how individuals or populations are affected by exposure to different doses of a toxicant?, *continued*	Explain the concept of dose spacing in terms of toxicity.	• Describe the interplay between exposure and rates of elimination. • Describe how a slow excretion rate can contribute to cumulative toxicity. • Explain the rationale behind the FDA's recommendation that pregnant women limit their intake of fish to a certain number of days per week, and why type of fish matters. https://www.fda.gov/downloads/food/foodborneillnesscontaminants/metals/ucm537120.pdf
	Describe the concept of hormesis as it applies to toxicology.	• Describe why a hormetic dose-response curve is called "U-shaped" or "biphasic." PMCID2248601 • Contrast a typical dose-response curve with a biphasic dose-response curve. • Describe the role of different mechanisms of action at different doses in hormetic responses. • Case study: Describe how preconditioning ischemia protects cells against a subsequent more severe ischemia. PMID3769170 • Case study: Review the history of hormesis and explain the controversy surrounding this topic. PMID2669125, PMID8523095, http://pubs.acs.org/doi/pdf/10.1021/es072436l • Case study: Describe how nutritional deficiency and excess of Vitamin A is an example of hormesis.
How do predisposing factors such as variations in health, gender, and age affect the response of a population to a toxicant?	Describe how endocrine disruptors affect the development and function of the reproductive system.	• Describe how endocrine disruptors exhibit different toxicities depending on the time of exposure during development. • Describe the use of laboratory animals as surrogates for developmental toxicants. PMID2653734 • Describe how exposure to endocrine disruptors causes permanent changes due to alteration of development. • Case study: Describe how DDT administered to neonatal rats induces persistent estrus syndrome. PMID5105675 • Case study: Describe how diethylstilbestrol affects the development and function of female reproductive tissues depending on the timing of exposure during development. PMID11252812, PMID7024873 • Case study: Describe how the anti-androgens flutamide and finasteride affect male sex organ differentiation during *in utero* development. PMID1324152
	Describe how partial agonists such as tamoxifen function to block hormone signaling pathways.	• Compare and contrast agonists, antagonists, and partial antagonists. • Describe how partial agonists can act as antagonists under some circumstances. • Case study: Describe how the thyroid hormone receptor antagonist NH3 affects thyroid signaling in rats. PMID17440037 • Case study: Describe how tamoxifen is used to treat estrogen-sensitive cancers.

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do predisposing factors such as variations in health, gender, and age affect the response of a population to a toxicant?, *continued*	Describe the effects of sex hormones on adolescents and adults.	• Describe the masculinizing effects of anabolic steroids, including testosterone. http://www.pbs.org/wnet/secrets/the-state-sponsored-doping-program/52/ • Describe the effects of anti-estrogen treatment on the female reproductive system. • Describe the benefits and risks of hormone replacement therapy treatment. • List the effects of phytoestrogens on males and females.
	Relate the sequence of human development to time periods in which teratogen exposure results in developmental toxicity.	• Define teratogen, contrasting the toxicity of the dose to the fetus versus the mother. PMID20563928 • Describe the critical windows concept: that certain stages of development offer heightened sensitivity to teratogenesis by a toxicant depending on its mechanism of action. • Case study: Describe fetal alcohol syndrome. • Case study: Describe how consumption of *Veratrum californicum* (Liliaceae) causes differential teratogenesis depending on the timing of exposure during pregnancy. PMID2218940 • Case study: Describe how diethylstilbestrol affects the development and function of female and male reproductive tissues depending on the timing of exposure during development. PMID11252812, PMID7024873 • Case study: Describe how exposure to thalidomide during fetal development causes different teratological abnormalities depending on the timing of exposure. 3067417
	Explain why children may be more susceptible to toxicants than adults.	• Contrast the expression of biotransformational enzymes in children and adults. • Explain why the smaller size of children increases the toxicity of a fixed dose of toxicant due to a higher mg/kg dose. • Describe how differences in pH in the digestive system contribute to differential toxicities in children versus adults. • Describe why features of the developing organism are more susceptible to perturbation by chemicals. • Describe the threshold theory of toxicology and how it applies to some chemicals but not others, particularly during development. • Case study: Describe the effect of lead exposure on neurological development. • Case study: Describe why neurotoxicants are more harmful to newborns than adults.

Biological Information

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do predisposing factors such as variations in health, gender, and age affect the response of a population to a toxicant?, *continued*	Describe the effect of pregnancy on susceptibility of females to toxicants.	• Explain how decreased gastrointestinal mobility during pregnancy results in higher blood concentrations and increased absorption of slowly absorbed drugs. • Explain how decreased plasma albumin results in an altered bound/unbound toxicant fraction. • Explain how increased renal elimination during pregnancy affects toxicokinetics. • Explain how metabolic inactivation in the liver late in pregnancy affects the susceptibility of females to toxicants.
	Explain how epigenetic mechanisms can play a role in DNA gene expression and carcinogenesis.	• Describe the mechanisms by which alteration in histones, methylation patterns, and other epigenetic mechanisms can alter gene expression. PMCID2802667 • Explain the role of microRNAs in regulation of gene expression; also explain their potential role in carcinogenesis. PMID2844907, PMCID3724248

Risk Assessment and Risk Management

Epidemiology and historical events together with science drive regulatory responses to risk for individuals and the environment.

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What is the connection between toxicology and epidemiology?	Compare the strengths and weaknesses of different epidemiological study designs.	• Compare the strengths and weaknesses of epidemiological study designs, including prospective, retrospective, cross-sectional, and case-control study versus cohort study. http://sphweb.bumc.bu.edu/otlt/mph-modules/ph/outbreak/outbreak7.html • Contrast prospective cohort studies, retrospective cohort studies, and ambidirectional studies. • Contrast internal, external, and general population comparison groups.
	Differentiate correlation and causation and incidence versus prevalence.	• Describe how dose-response studies are important in differentiating correlation and causation. • Describe the difficulties in using epidemiological data to differentiate correlation and causation. • Contrast incidence and prevalence for a given disease or toxic effect.
	Interpret relative risk and odd ratios.	• Given a sample set of data, calculate "relative risk" for an epidemiological study. PMID26231012 • Given a sample set of data, calculate the "odds ratio" for an epidemiological study. PMID26231012

Risk Assessment and Risk Management

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What is the connection between toxicology and epidemiology?, *continued*	Differentiate statistical significance and biological significance.	• Contrast "biological significance" and "statistical significance." • Describe why a measured, statistically significant difference in an experiment may not be biologically significant. • Describe possible reasons why an observation in one species or population may not be translatable to the population in which hazard is ultimately being assessed. Examples include genetic differences or environmental differences.
	Compare and contrast the various forms of bias and how to control for them.	• Contrast selection bias, prevalence-incidence bias, Berkson's bias, and verification bias. • Contrast positive and negative types of confounding bias. • Define a confounder variable in epidemiology. • Case study: Describe how smoking is a confounding risk factor with alcohol consumption for coronary heart disease. https://www.healthknowledge.org.uk/e-learning/epidemiology/practitioners/chance-bias-confounding
Why are certain populations at greater risk from exposure to toxicants?	Describe causes for the major at-risk populations: infants and young children, pregnant women, older adults, people with weakened immune systems, people with inflammatory conditions, and elderly.	• Describe how young children are at higher risk for toxicant exposure due to the developmental state of their xenobiotic defense mechanisms. • Describe features of aging populations that cause higher risk from acute kidney injury. PMID25257519 • Define the healthy worker effect. PMCID2847330 • Describe occupational-related hazards to workers. • Describe how sensitive subpopulations (due to medical conditions or medications, for example) in the worker population need to be considered when establishing an acceptable exposure limit. • Describe how lung disease such as asthma, COPD, and fibrosis, contribute to increased risk. • Describe how inflammatory conditions are associated with increased risk from exposure to toxicants. • Case study: Describe how aging reduces xenobiotic defense in the mouse model system. PMID17521389

Risk Assessment and Risk Management

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are organisms living in the natural environment affected by natural and anthropogenic toxicants?	Describe the effects of exposure to gaseous environmental pollutants to organisms and to the environment.	• Describe the distribution and toxic effects of inhaled gases and particulates (such as carbon oxides, sulfur oxides, and nitrogen oxides) in the human respiratory system. • Compare and contrast the types of physiological effects seen following acute exposure to airborne toxicants with the effects seen following chronic exposures. • Explain the mechanisms of the greenhouse effect. • Discuss models of global warming. PMID24480426, PMCID3601420 • Describe the mechanism of contribution of carbon oxides to global warming. • Describe the mechanism of contribution of sulfur and nitrogen oxides to acid rain. • Explain the mechanisms behind acid rain; describe the effects of acid rain on aquatic and terrestrial communities; also describe the role of environmental buffering capacity in terms of effects. • Case study: Describe the Bohr effect and amino acid charge state equilibrium on hemoglobin/myoglobin oxygen binding and distribution of oxygen throughout the body.
	Explain the environmental consequences of incomplete combustion of organic material such as hydrocarbon fuels.	• Describe the origin and composition of photochemical smog. • Describe how particular matter pollution is created. • Describe the mechanism of action of particulate matter pollution by incomplete combustion of organic material. • Contrast the formation of ozone in the upper atmosphere versus lower atmosphere.
	Discuss the findings linking exposure to particulate matter to adverse effects on human health.	• Explain the effects of particulate matter on pulmonary function. PMCID5343780, PMCID4922809 • Explain the effects of particulate matter on neurological function. PMCID5544553, PMCID4974252 • Discuss the link between exposure to particulate matter and developmental toxicology. PMCID4917489 • Discuss the link between exposure to ultrafine/nanosized particles and blood clots leading to cardiovascular disease. • Case study: Describe the toxicity of nanoparticles in the skin. Nancy Monteiro-Riviere Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
	Compare and contrast point and nonpoint source water pollution in terms of sources, typical content, and options for control.	• Provide examples of pollution by organic substances, including petroleum products, solvents, pesticides, polymers, and pharmaceuticals. • Provide examples of pollution by inorganic substances, including metals, nitrates, and phosphates.

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are organisms living in the natural environment affected by natural and anthropogenic toxicants?, *continued*	Describe the environmental impacts of oil spills and the remediation processes used to combat them.	• Discuss effects of major oil spills including the Exxon Valdez and the Deepwater Horizon. PMID14684812, 27301686 • Describe the risks and benefits of bioremediation, including use of genetically-modified organisms. PMID28511936 • Describe the risks and benefits of chemical dispersants. PMID25938731
	Explain the mechanisms behind the process of eutrophication, as well as the consequences for aquatic life.	• Describe the role of fertilizers and waste in eutrophication. • Explain the consequences of eutrophication on ecological community structure. • Case study: Describe the link between eutrophication and harmful algal blooms. PMID28781587
	Compare and contrast the major categories of pesticides in terms of their mechanisms of action, persistence in the environment, and risks to human health and the ecosystem.	• Summarize the effects of organochlorine insecticides (DDT, chlordane, aldrin, and others). PMID26563787 • Summarize the effects of organophosphate and carbamate insecticides. PMID26563788 • Summarize the effects of pyrethroid insecticides. PMID26563787 • Summarize the effects of chlorphenoxy acid herbicides (2,4-D and 2,4,5-T). PMID15578861 • Summarize the effects of bipyridyl herbicides (paraquat and diquat). PMID18161502
	Describe some of the sources of metal pollution in water and give examples of effects of environmental exposure to metals on human health and/or ecological function.	• Describe the effects of lead on human health, including neurological and hematological effects. • Describe the physiological and ecological effects of cadmium. • Describe the physiological and ecological effects of arsenic. • Describe the physiological and ecological effects of mercury, including discussion of differences between different species of mercury. PMID28889024 • Case study: Describe the impact of prenatal exposure to methylmercury in the context of the Minamata, Japan, pollution incident. PMID30081479
	Describe the hazards associated with the presence of plastics in the environment.	• Describe the effects of microplastics in the environment. PMCID5044952 • Describe the effects of macroplastics in the environment. PMID27232963 • Describe the release of dioxins caused by trash burning. • Describe the effects of microwaving plastics.

Risk Assessment and Risk Management

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are organisms living in the natural environment affected by natural and anthropogenic toxicants?, *continued*	Compare and contrast the options of incineration, detoxication, biodegradation, and burial of hazardous waste in terms of the risks and benefits of each.	• Evaluate the use of UV and chemical treatments for detoxification. • Evaluate the use of high temperature combustion and pyrolysis; discuss the problem of the disposal of ash. • Describe strategies for landfill design and protection against leaching of toxicants into the water supply. • Describe the three steps in a modern waste water treatment plant. • Case study: Describe issues associated with water re-use following treatment in water treatment plants.
	Discuss the natural radioactive sources that contribute to toxicology and current issues involving safe long-term disposal of radioactive wastes.	• Compare and contrast the risks and benefits of on-site storage versus reprocessing versus central storage. • Describe radiation and radon-related hazards. • Case study: Explore the debate over Yucca Mountain as a long-term solution for US spent nuclear fuel and high-level radioactive waste. PMID22569220
How is the science of toxicology applied to government regulations to ensure the protection of individuals and the environment?	Describe the controversy of threshold versus non-threshold assumptions with regard to regulatory policy regarding toxicants.	• Contrast hazard and risk. • Contrast threshold and no-threshold responses to toxicants. • Describe the controversy of the no-threshold relationship with regard to ionizing radiation. PMID19332842 • Case study: Describe the rationale behind a no-threshold relationship for lead exposure. PMID27837574
	Describe the major environmental laws of the United States (and/or other nations).	• Describe major historical events that led to the evolution of environmental laws, such as patent medicines, "The Jungle," and the "Crying Indian Commercial." • Describe the Clean Air Act and Clean Water Act. • Describe the Safe Drinking Water Act. • Describe the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and its amendments: aka Superfund Act.

Risk Assessment and Risk Management

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How is the science of toxicology applied to government regulations to ensure the protection of individuals and the environment?, *continued*	Discuss the importance of regulatory harmonization across various markets	• Describe how Good Laboratory Practices provide harmonization of laboratory technique and information reported across markets. • Describe the role of the Organization for Economic Cooperation and Development in harmonization of study design, interpretation of data, and reporting. • Describe the role of the United Nations "Globally Harmonized System of Classification and Labelling of Chemicals." • Case studies: The Organisation for Economic Cooperation and Development (OECD), International Council for Harmonisation (ICH), Veterinary International Council for Harmonisation (VICH), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA). • Describe the role of the International Council for Harmonisation in terms of drug development. Ruth A. Roberts Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
	Describe how toxicology testing is used to inform regulatory policy.	• Describe the National Toxicology Program and how it informs regulatory policy. • Describe the role of contract research organizations in producing toxicology data to inform regulatory policy. • Consider how regulatory decisions are made for the many chemicals that are in commerce with limited data. William Benson Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
	Describe efforts to reduce the use of animals in research.	• Describe how the 3Rs (reduce, refine, and replace) are used to minimize the use of animals in scientific research. • Describe the Guiding Principles for the Use of Animals in Toxicology, as defined by the Society of Toxicology https://www.toxicology.org/pubs/statements/Guiding_Principles_in_the_Use_of_Animals_%20in_Toxicology.pdf • Describe how refinement of experimental design results in reduction of animal suffering and improves animal welfare. • Describe how reduction balances reducing the number of animals used in an experiment with having enough animals for sufficient experimental statistical power. • Describe how models and tools replace the use of animals. https://www.nc3rs.org.uk/the-3rs
	Contrast risk assessment and risk management.	• Contrast risk assessment and risk management. • Describe how risk management uses information from risk assessment to make informed decisions. • Identify risk assessment examples under the classic paradigm of Hazard Identification, Exposure Assessment, Dose-Response, and Risk Characterization.

Risk Assessment and Risk Management

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How does poison management protect human health through a knowledge of poisons and their antidotes?	List various ways that poisons enter the body.	• Identify the portals of entry for toxicants into the body. • Case study: Contrast absorption of the metal lead via each major portal of entry into the body. • Case study: Contrast absorption of the metal mercury via each major portal of entry into the body.
	List signs and symptoms associated with poisoning.	• Describe the relationship between the patient suffering from poisoning or overdose and airway management. • Delineate the need for medical direction in caring for the patient with poisoning or overdose. • Case study: Describe the signs of organophosphate exposure using the SLUDGE acronym.
	Describe the general treatment of drug overdose.	• Contrast the following strategies for treatment of drug overdose: gastric lavage, emesis, activated charcoal, charcoal-resin hemoperfusion, hemodialysis, peritoneal dialysis, cathartics, pressor agents, cardiac monitoring, and support of the airway.
	Discuss the emergency medical care for the patient with possible overdose and/or suspected poisoning.	• Explain the rationale for having medical direction early in the prehospital management of the poisoning or overdose patient. • Describe the role of Poison Control Centers in reducing morbidity and mortality from exposure to toxicants. • Case study: Describe the mechanism of N-acetylcysteine as an antidote for acetaminophen overdose. • Case study: Describe the mechanism of antivenoms for snake bites.
	Describe the importance of poisoning and overdose, their manifestations, and prevention strategies utilized in the management of a few prototype toxins.	• Describe aflatoxin poisoning in terms of overdose, manifestation, and prevention strategies. • Describe saxitoxin poisoning in terms of overdose, manifestation, and prevention strategies. • Describe domoic acid (anemic shellfish poisoning) in terms of overdose, manifestation, and prevention strategies. • Describe botulinum in terms of overdose, manifestation, and prevention strategies.
	Explain the role and function of Poison Control Centers and TESS (Toxic Exposure Surveillance System).	• Describe federal, state, and other governmental Poison Control Centers and how they function at each level of government. • Outline the history of the Poison Control Center. https://www.wnycstudios.org/story/poison-control/

Risk Assessment and Risk Management

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How have historical incidents impacted the development of the regulatory laws concerning toxicology?	Describe the impact of historical events in workplace toxicology on the development of regulatory law.	• Define "industrial hygiene." • Enumerate worker safety practices designed to prevent injury to workers. • Describe "permissible exposure limits" as they relate to chemical substances as defined by the Occupational Safety and Health Administration. • Describe the role of the Occupational Safety and Health Administration or equivalent governmental body in your country of residence. • Describe how time-weighted averages are used with both short-term exposure limits and ceiling limits. • Case study: Describe the various categorizations that are used by NIOSH to categorize toxicants, such as "skin notations" and "sensitization notations." https://www.cdc.gov/niosh/topics/skin/skin-notation_profiles.html, PMID23851069
	Describe the history of key events in toxicology, including the mechanism of toxicity of the toxicant behind the event and the related public policy.	• Describe the history of the Love Canal as it relates to toxicology and public policy. • Describe the history of the Bhopal disaster (methyl isocyanate) as it relates to toxicology and public policy. • Describe the history of the Minamata disease disaster as it relates to toxicology and public policy. • Describe the history of the Seveso disaster as it relates to toxicology and public policy. • Describe the history of Rachel Carson's publication of "Silent Spring" (DDT) as it relates to toxicology and public policy. • Describe the history of "the radium girls" as it relates to toxicology and public policy. • Describe the history of Agent Orange (dioxin) as it relates to toxicology and public policy. • Describe the history of Times Beach, MO, and how it relates to toxicology and public policy. • Describe the history of the cleanup of the Hudson River by General Electric Corporation as it relates to toxicology and public policy. • Describe how toxicology became an academic discipline. John Doull Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp • Review the major historical events in the history of toxicology. Michael A. Gallo Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
	Describe what brownfields are.	• Articulate the legal definition of a brownfield. • Describe government's role in brownfield remediation. • Outline the Superfund program's history and current function.

Systems Toxicology

Toxicants affect cellular, organ, individual, and ecological systems.

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do cells respond to exposure to toxicants?	Describe the types of chemical bonds that can characterize the interaction of toxicants with the major classes of cellular macromolecules.	• Explain the differences between hydrogen bonding, ionic attraction, and covalent bonding in terms of stability of a non-covalent versus covalent bond. • Describe how suicide inhibitors function. • Case study: Describe how nerve agents can undergo aging to prevent reaction of acetylcholinesterase by oximes.
	Explain the interaction of toxicants with enzymes in terms of sites of action and enzyme kinetics, including the differences between competitive and noncompetitive inhibition.	• Review the concepts of V_{max} and K_M. • Explain the use of Michaelis-Menten kinetics for making experimental determination of competitive versus noncompetitive binding of toxicants. • Cite examples of enzyme inhibition, including inhibition of acetylcholinesterase by organophosphates and role of aging in reversibility of inhibition. PMID28869561
	Describe the major categories of receptors found in cells and differentiate between toxicants classified as agonists, antagonists, and partial agonists in terms of their interactions with those receptors.	• Describe the action of G protein-coupled receptors (including beta adrenergic and muscarinic acetylcholine receptors), along with examples of drugs and toxicants which interact with them (including beta blockers and atropine). • Describe the action of receptor tyrosine kinases, along with examples of drugs and toxicants which interact with them. • Describe the action of ligand-gated ion channels (including the nicotinic acetylcholine receptor and NMDA receptors), along with examples of drugs and toxicants which interact with them (including curare). • Describe the action of intracellular receptors (including steroidal hormone receptors), along with examples of drugs and toxicants which interact with them. • Contrast the mechanism of action of botulinum toxin and tetanus toxin; explain why very similar mechanisms of action have opposite physiological effects.
	Explain the potential impact of toxicants on ion channels in terms of membrane potentials.	• Describe how TRPV1 is affected by capsaicin and resinaferatoxin. • Describe how tetrodotoxin functions at the molecular level. • Describe how saxitoxin functions at the molecular level.

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do cells respond to exposure to toxicants?, *continued*	Describe the sources and characteristics of free radicals and explain the mechanisms behind the process of lipid peroxidation.	• Explain the concept and give examples of free radicals. • Describe the formation of free radicals from biotransformation processes (chlorinated hydrocarbons). • Describe the formation of free radicals (superoxide and hydrogen peroxide) as byproducts of oxidative phosphorylation. • Describe the structure of biological membranes, noting the presence of vulnerable unsaturated fatty acids, and describe the action of free radicals on those membranes.
	Explain what alkylating agents are and discuss how they interact with DNA.	• Explain the alkylation of bases, including discussion of "hot spots" for adduct formation. • Describe examples of alkylating agents. • Case study: Describe the mechanism of action of DNA alkylation by nitrogen mustard.
	Explain the circumstances under which cells produce stress proteins and describe examples of some of their protective mechanisms and effects (including the role of several stress proteins as chaperones).	• Describe the mechanism for induction of stress proteins (including discussion of the heat shock factor and heat shock element). PMID28852220 • Describe some examples and general roles of stress proteins in cellular protection (chaperones, regulation of receptor function). • Describe examples of the roles of protein misfolding and stress proteins in disease. PMCID5433227
	Compare and contrast the mechanisms behind cell death, including apoptosis, necrosis, and autophagy.	• Describe the fundamental steps in apoptosis, including discussion of extrinsic and intrinsic pathways. • Explain the roles of mitochondria, cytochrome c, and the mitochondrial permeability transition in apoptosis. PMID28325213 • Describe the effects of the regulators of apoptosis, including Bax, Bid, Bad, Bcl-2, Bcl-XL. • Compare and contrast apoptosis and necrosis and discuss hypotheses concerning what determines which path a cell will take. • Discuss the concept of autophagy as it relates to cell survival and cell death. PMID28866100

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are organs affected by exposure to toxicants?	Identify and describe organ toxicity emanating from therapeutic and nontherapeutic (intentional and unintentional) drug/chemical exposures.	• Provide examples of prototype therapeutics (acetaminophen, doxorubicin, bleomycin, caffeine) and non-therapeutic toxins (aflatoxin, botulinum toxin, snake venom toxin, *E. coli* toxin, etc.). • Explain how these toxins produce toxicity. • Describe how a specific bioactivation pathway may lead to a specific form of toxicity. • Explain specific changes (biochemical, morphological, molecular) associated with toxicity. • Make correlations between biochemical, morphological, and molecular changes during development of toxicity. • Describe some of the parameters that can be measured in order to demonstrate toxicity.
	Recognize system-specific and organ-specific toxic effects on humans and other experimental models.	• Provide examples of organ specific hepatotoxins, neurotoxins, pulmonary toxins, nephrotoxins, etc. • Identify unique ways in which therapeutic agents cause specific organ toxicity. • Discuss how specific bioactivation products (free radicals, biological reactive intermediates, etc.) produce specific forms of toxicity to specific types of cells. • Provide examples of organ specific parameters that are used to determine specific organ toxicity (ALT/AST for liver toxicity; BUN/Creatinine for nephrotoxicity; CK/Troponins for cardiotoxicity, etc.). • Discuss specific morphological changes in specific areas of organs during toxicity. • Correlate biochemical (serum chemistry) parameters with histopathological changes.
	Predict/explain possible toxicological consequences after exposure to one or more drugs/chemicals within safe limits.	• Provide examples of pharmacogenetic options and pre-existing conditions that can lead to the appearance of toxicity, even within normally safe exposure limits. • Define possible toxicological interactions and drug interactions even within nominally safe short-term exposures. • Describe the potential for toxicity after long-term exposures at nominally safe levels. • Compare and contrast synergism, antagonism, potentiation, and additive reactions in toxicology and be able to provide examples of each. • Explain the biological mechanisms that might lead to "greater than additive" and "less than additive" pharmacokinetic and pharmacodynamic effects for chemical mixtures. • Explain how human microbiota can contribute to drug interactions and adverse drug reactions.

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are organs affected by exposure to toxicants?, *continued*	Describe the importance of the bioactivation process for prodrugs.	• Provide specific examples of Phase I and Phase II bioactivation reactions. • Explain how these reactions can lead to the production of useful (from a prodrug) free radical species and/or toxic free radical species and/or other Biological Reactive Intermediates (BRIs). • Discuss cellular targets of these reactive species, such as plasma membranes, mitochondria, DNA, RNA, etc. • Discuss consequences of the interaction between BRIs and macromolecules (lipids, DNA, enzymes). • Discuss quantitative methods to determine toxic end points generated via free radicals (lipid peroxidation, oxidative damage to DNA, etc.).
	Decipher the mechanisms for drug- and chemical-induced toxicity in *in vivo* and *in vitro* models and appropriately design and interpret drug screenings.	• Explain differences in drug metabolism (biotransformation reactions) between *in vivo* and *in vitro* models. • Discuss the mechanism behind differences (such as the presence or absence of CYP450 isozymes) in drug metabolism. • Explain the advantages and disadvantages of using *in vivo* and *in vitro* models for toxicity screenings. • Explain LD_{50}, LC_{50}, LD_{20}, and related items for *in vivo* and *in vitro* systems. • Provide examples of different types of clinical trials and delineate how *in vivo* and *in vitro* models are used in various phases of clinical trials.
	Discuss the important role the liver plays in xenobiotic metabolism.	• Describe liver anatomy and lobule zonation. Provide examples of the types of cells found in the liver. • Explain which cells are responsible for xenobiotic metabolism and why. • Explain how detoxification pathways operate in liver cells. • Discuss the different types of liver injuries (cirrhosis, necrosis, fatty liver, steatosis, etc.) which are initiated by different types of xenobiotics. • Explain morphological, biochemical, and molecular changes associated with different types of liver injuries. • Correlate biochemical changes (serum chemistry and tissue biochemistry) with morphological changes. • Provide examples of various biomarkers of different types of liver injuries.

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are organs affected by exposure to toxicants?, *continued*	List the characteristics that enable the kidney to efficiently excrete xenobiotics.	• Describe kidney anatomy and provide examples of the types of cells found in kidneys. • Outline the mechanism of excretion and how different kidney structures coordinate fluid regulation. • Describe the interactions between the cardiovascular system and renal system and how they affect kidney function. • Explain how kidneys can be vulnerable to toxicity at therapeutic doses of drugs. • Provide examples of the different types of kidney injuries (acute kidney injury, chronic kidney injury, kidney stone formation, etc.) initiated by different types of xenobiotics. • Explain morphological, biochemical, and molecular changes associated with different types of kidney injuries. • Correlate biochemical changes (serum chemistry and tissue biochemistry) with morphological changes. • Describe the differences between acute and chronic renal failure, as well as treatment options. • List various biomarkers of different types of kidney injuries.
	Recognize system-specific and organ-specific toxic effects on humans and other experimental models.	• Describe the anatomy, physiology, and pathophysiology of organ systems. • Provide examples of prototypical neurotoxicants, reproductive toxicants, cardiotoxicants, nephrotoxicants, pneumotoxicants, etc. • Provide examples of signs, symptoms, and assessment tools of neurotoxicity, reproductive toxicity, nephrotoxicity, pulmonary toxicity, etc. • Outline the similarities and differences between humans and experimental models while assessing organ-specific toxicities. • Describe how data from animal studies can be extrapolated to humans. • Describe the role of the immune system in toxicology. Jack Dean Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are organs affected by exposure to toxicants?, *continued*	Describe the characteristics of the nervous system that make it vulnerable to many toxicants.	• Describe the complex anatomy of both branches of the nervous system (CNS and PNS). • Contrast the structure and function of various cells of the CNS and PNS. • Discuss the complexity of the structural and functional integration of the nervous system. • Explain how ion channels, axonal transport, and synaptic transmission are subjected to toxic effects by drugs and chemicals. • Describe the structure and function of the blood brain barrier as well as the protective role that it plays. • Explain the susceptibility of the nervous system to lipid-soluble toxicants. • Describe how the limited repair ability of neurons makes the nervous system vulnerable to injury. • Explain how heavy dependence on glucose makes the nervous system more vulnerable to toxicants. • Describe how pesticides function as neurotoxicants. Marion Ehrich Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
How are body systems affected by exposure to toxicants?	Discuss the role that the circulatory system plays in exacerbating or limiting toxicity.	• Describe the anatomy, physiology, and pathophysiology of the cardiovascular system. • Explain how the cardiovascular system plays a role in the systemic distribution of toxicants. • Describe the differential distribution of toxicants in the body due to differences in lipid solubility and plasma distribution. • Explain how numerous factors found in the blood (different types of cells, glutathione, detoxifying enzymes) detoxify and facilitate elimination of toxicants from the body. • Discuss how the cardiovascular system works in coordination with the excretory system (renal) to exacerbate toxicity.
	Explain adverse reactions originating from toxic exposures in any setting and medication errors in a healthcare setting.	• Explain the types of adverse drug reactions and types of medication errors. • Provide examples of the manifestations of adverse drug reactions and outcomes of medication errors. • Explain irreversible and reversible drug reactions. • Discuss possible corrective actions after onset of adverse reactions. • Describe how medication errors can be minimized at every level of healthcare (doctors, pharmacists, nurses and other healthcare workers).

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are body systems affected by exposure to toxicants?, *continued*	Predict/explain possible toxicological consequences after exposure to drugs/ chemicals below and above safe limits.	• Provide examples of pharmacogenetic options and pre-existing conditions that can lead to the appearance of toxicity, even within nominally safe exposure limits. • Define possible toxicological interactions and drug interactions even within nominally safe short-term exposures. • Describe the potential for toxicity after long-term exposures at nominally safe levels. • Contrast synergism, antagonism, potentiation, and additive reactions in toxicology and be able to provide examples of each. • Explain the biological mechanisms that might lead to "greater than additive" and "less than additive" pharmacokinetic and pharmacodynamic effects for chemical mixtures • Explain how human microbiota can contribute to drug interactions and adverse drug reactions.
	Evaluate and interpret relevant information from the toxicology literature, explain toxicological interactions, and identify preventable causes.	• Name examples of toxicology literature sources (such as Medline, PubMed, and NLM drug interaction databases) that describe toxicological interactions and provide information that can be used to prevent future exposures. • Describe how data from animal studies can be extrapolated to humans using toxicology literature sources, dose-response, cause and effect, and time-course relationships. • Outline the importance of dose-response, cause and effect, and time-course relationships in toxicology. • Explain how the above relationships can be extrapolated to determine safe and toxic levels of exposure. • Explain drug interactions from perspectives of LD_{50}, LC_{50}, LD_{20} doses for *in vivo* and *in vitro* models. • Differentiate the relationships in toxicology (additive, synergistic, antagonistic, and potentiation). • Explain mortality, lethality, acute, and chronic toxicity. • Delineate how the above principles can be applied in various phases of clinical trials. • Describe various steps which can be taken to prevent toxicity, including removing the exposure source, reducing the exposure, dividing the exposure, boosting antioxidants, pharmacogenetics factors, and cellular protective mechanisms.

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How are body systems affected by exposure to toxicants?, *continued*	Describe various analytical, molecular, and computational tools used to interpret information from toxicology studies to understand toxicological interactions and to describe preventable causes.	• Describe analytical tools used in toxicology, such as chromatographic procedures, including liquid, ion-exchange, size exclusion, thin layer, and affinity chromatography. • Describe molecular techniques used in toxicology, such as PCR, microarrays, MiRNA profiling, Western blot, Northern blot, Southern blot, electrophoresis, ELISA, metabolomics, next generation sequencing, and chromatin immunoprecipitation. • Describe how instrumental techniques (including ESR, NMR, and IR) are used to detect free radicals or their biological derivatives in biological fluids. • Discuss how computational tools such as QSAR, Toxtree, Toxmatch, DART, CRAFT, and PBPK models are frequently used to predict toxicity or fate of toxic drugs and chemicals. • Describe how modification of the chemical structure based on results from physiologically-based pharmacokinetic modeling can reduce toxicological effects.
	Describe and interpret the general principles of clinical toxicology and discuss factors that influence toxicity.	• Describe the kinds of studies used to evaluate toxicity (acute, sub-acute). • Describe safety pharmacology-related end points (cardiovascular, respiratory, and neurological systems). • Describe how genetic factors (pharmacogenetics) can influence xenobiotic metabolism in the body. • Analyze how genetic factors can be used to customize drug exposure to individuals with certain ethnic backgrounds. • Explain how nutritional factors (high fat/low fat diet, diets with insufficient or excessive antioxidants or vitamins, diets rich in sugars, diets deficient in proteins, etc.) can considerably influence xenobiotic metabolism in the body. • Describe how diet and nutrition are linked to body's defense system (antioxidant imbalance oxidized/reduced glutathione ratios, ascorbate level, alpha-tocopherol level, etc.) or cytoprotection mechanisms. • Outline how environmental factors are linked to diseases (exposure to high levels of CO, CO_2, drinking water contaminants, air pollutants, radiation, etc.).
How do toxicants affect an organism's development and reproduction?	Contrast the four reproductive endpoints: fertility, menstrual cycle, sperm count and viability, and sexual behavior.	• Describe how the menstrual cycle can be affected through altered corpus luteum function, fertilization, maintenance of implantation, or alteration of the hypothalamus/pituitary system. • Describe how the testis can be affected by modification of CNS function, pituitary, testicular vasculature, nutrition, pineal, fertilization, or paternal development. • Case study: Describe the effect of m-dinitrobenzene on rat testis. PMID3341027 • Case study: Describe the mechanism of action of abortifacients that induce pregnancy loss through reduction of progesterone. PMID2886593 • Case study: Describe how busulfan affects germ line development in rats. PMID26973761

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do toxicants affect an organism's development and reproduction?, *continued*	Contrast the primary developmental toxicological endpoints.	• Contrast teratology, birth weight, growth, and neurobehavioral changes as primary developmental toxicological endpoints. • Describe how susceptibility of a fetus to teratogens differs depending on the stage of development of the fetus. • Describe mechanisms of toxicants affecting onset of puberty. • Describe mechanisms of pheromones on affecting the onset of puberty.
	Discuss the downstream effects that occur from exposure to an endocrine disrupting compound.	• Describe mechanisms of pheromones on affecting onset of puberty. • Describe how DES exposure at particular development points in development has different effects. • Case study: Describe how DES exposure results in adenocarcinoma in daughters. PMID5549830 • Case study: Describe how sewage effluent containing birth control medications causes feminization of male fish. PMID16818251
How do toxicants move through the environment to affect ecosystems?	Contrast the effects of environmental toxicants on r strategists versus K strategists.	• Define r strategists and K strategists. • Contrast the relationships between population numbers and carrying capacity for r strategists and K strategists. • Differentiate between density-dependent and density-independent action of toxicants. PMCID4921107
	Describe, using examples, the role that toxicants can play in exerting selection pressures on populations.	• Explain the fundamental concepts behind the process of natural selection. • Describe the effects of pesticides on both pest populations and nontarget populations. PMCID5533829 • Describe the effects of antibiotics on bacterial populations. PMCID4567305
	Contrast the effects of toxicants on predator populations, prey populations, and the interactions between them.	• Describe the characteristics of predator-prey kinetics. • Provide examples of the impact of toxicants on predator-prey interactions. PMCID4935736
	Discuss how toxicants can alter ecosystem structure in terms of effects on energy flow and the trophic pyramid.	• Provide examples of effects of toxicants on producers, potentially leading to decreases in productivity. PMCID5009500 • Provide examples of effects of toxicants on detritivores, potentially leading to decreases in release of nutrients. PMCID5420384

Systems Toxicology

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do toxicants move through the environment to affect ecosystems?, *continued*	Explain the concept of residence times for toxicants in the environment and compare and contrast the ways in which toxicants move through soil, atmosphere, and water.	• Compare average residence times for toxicants moving through ecological compartments. • Describe the factors that influence residence times for toxicants.
	Explain the concepts of bioavailability and bioconcentration.	• Describe the chemical factors that influence the tendency for toxicants to bioaccumulate. PMCID5044975 • Provide specific quantitative examples of bioconcentration of toxicants, such as DDT or PCBs. • Provide specific examples of biotransformation affecting bioconcentration (mercury, for example). PMCID1797140
	Discuss examples of typical species used in ecotoxicological single-species testing.	• Discuss the use of daphnids, fathead minnows, quail, and other species as models for ecotoxicology. PMCID3764090, PMCID4490443, PMCID3744572, PMCID4388576
	Compare and contrast the strengths and limitations of the most common methods of ecotoxicological testing including microcosms, mesocosms, field studies, and mathematical modeling.	• Describe the strengths and weaknesses of microcosms and mesocosms in measuring toxic effects. • Compare and contrast flow-through versus static testing aquatic systems. • Discuss the issues with locating appropriate control areas for comparison in assessing ecological disasters. • Discuss the complexity of ecological models using examples of assumptions and trade-offs made in ecological modeling.
	Identify important concepts in ecotoxicological risk assessment	• Explain some of the complexities involved in assessing risk at population, community, and ecosystem levels. PMCID5141515 • Define the concept of adverse outcome pathways in ecotoxicology. PMID25439131, PMCID3478868

Pathways and Transformations of Energy and Matter

Interaction of toxicants with organisms is described through paradigms in dose-response, Absorption, Distribution, Metabolism, and Excretion (ADME), and toxico-/pharmacokinetics.

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do toxicants affect homeostasis for exposed organisms?	Describe how toxicants disrupt homeostasis.	• Identify physiological functions that may be targets of toxic insult. • Explain how a toxicant disrupts homeostasis in a specific target tissue or organ. • Describe how organisms respond to toxicant exposure and attempt to restore homeostasis. • Describe how the inability to restore homeostasis leads to pathology. • Describe how organisms handle allostasis differently after toxicant exposure.
	Describe the role of xenobiotic defense mechanisms in maintaining homeostasis.	• Characterize proteins involved in general toxicant and toxin protection (e.g., albumin, transferrin, peroxidases, macrophages, etc.). • Describe the function of Phase I and Phase II enzymes in detoxication pathways. • Describe the function of antioxidant response systems in redox balance. • Identify key proteins involved in sequestration and excretion of metals.
	Contrast a physiological versus a pathological adaptation to a stimulus.	• Compare and contrast physiological apoptosis, necroptosis, and necrosis versus toxicant or toxin-induced apoptosis, necroptosis, and necrosis. • Describe an antioxidant pathway that could lead to detoxication or DNA/protein damage and how that pathway is used under normal conditions (e.g., protein misfiling and chaperones versus ER stress). • Describe a metabolic pathway that could lead to detoxication or DNA adducts. • Case study suggestion: Describe how chronic exposure to testosterone causes pathological adaptations that result in dysfunction.
	Contrast physiological and pathological cellular adaptations.	• Contrast the physiological and pathological adaptations of atrophy, hypertrophy, hyperplasia, metaplasia, dysplasia, anaplasia, and neoplasia. • Compare cellular and tissue changes following toxicant exposure. • Case study: Describe how growth hormone induces physiological or pathological adaptations depending on the timing of exposure. • Case study: Describe how opioids induce pathological adaptations (e.g., receptor removal or endocytosis)

Pathways and Transformations of Energy and Matter

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How does the concept of dose-response relate to toxicology?	Describe the different protocols for dosing: exposure time, administration, absorbance, internal, and delivered.	• Compare and contrast acute, subacute, subchronic, and chronic paradigms. • Describe how route of exposure affects dose. • Define absorption specific to the discipline of toxicology. • Describe the importance of modeling exposure so that it represents human (or animal) exposures in the environment or industrial setting. • Describe the influence of age, nutrition, and genetic background on dose.
	Describe a dose-response curve, labeling the axes and identifying important regions of the plot.	• Describe the assumptions made if the curve is based on the mean of a population. • Describe the difference between individual response and population response for a dose-response curve. • Describe the importance of the linear portion of the dose-response curve and the margin of error associated with it. • Compare and contrast lethality, effect, and inhibition, and the shapes of those dose-response curves. • Distinguish between efficacy and potency. • Describe the importance of defining an appropriate end point/response. • Describe the difference between nutrient dose-response curves and toxicant dose-response curves. • Describe the importance of inflection points in the dose-response curve. • Describe the importance of outliers or hypersensitive individuals to a dose-response curve. • Describe how a dose-response curve can help determine a causal relationship between exposure and effect. • Apply the Henderson-Hasselbach equation to dose-response curves in the presence and absence of inhibitors. • Application: Explain the statement "Dose-response curves do not allow determination of mechanism." • Case study: Describe the controversy surrounding the linear no-threshold hypothesis. • Case study: Apply the dose-response concept to homeopathic medicine.

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How does the concept of dose-response relate to toxicology?, *continued*	Describe the features of a dose-response curve.	• Define threshold dose. • Describe the quantitative relationship between dose and response. • Describe whether a cause/effect relationship can be determined from a dose-response curve. • Describe how comparison of dose-response curves allows interpretation of the relative toxicity of two compounds in a population. » Focus on the importance of matching parameters (route, time, age, etc.). • Compare and contrast threshold values and NOAELs in a dose-response curve. • Compare and contrast efficacy and potency. • Describe uncertainty factors, and safety factors (interspecies, chronic studies) used for extrapolation of data to humans.
	Explain differences in dose-responses in a population of individuals.	• Apply population dose-response curves to individuals. • Characterize allelic variations that alter response following toxicant exposure. • Compare and contrast the roles that non-genetic factors such as age, sex, weight, and diet have on individual responses to toxicant exposures.
	Describe why individuals who have idiosyncratic responses (either hypersensitivity or hyperresistance to toxicants) are outliers and propose mechanisms for their differences.	• Describe the role of the immune system in generating idiosyncratic responses. • Discuss how polymorphisms in cytochrome P450 enzymes can cause hypersensitivity or hyperresistance to toxicants. • Identify and characterize how differences in epigenetic methylation/acetylation can cause idiosyncratic responses • Describe why it is important to perform toxicology tests in both males and females.
	Describe how alterations in homeostasis can affect an individual's dose-response.	• Describe the role of mitochondria and other organelles in normal cellular homeostasis. • Describe how pre-exposure to low doses of a toxicant may protect against a subsequent exposure to that or other toxicants. • Describe the effect of nutritional status (e.g., lack of vitamins for enzyme cofactors) on homeostasis and response to xenobiotics. • Describe how age affects metabolism and homeostasis. • Describe how disease states affect homeostasis. • Describe how drugs of abuse alter homeostasis. • Case study: Describe how a low dose of testosterone can protect against toxicity of CCl_4.

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Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do concepts of administration, distribution, metabolism, and elimination (ADME) help characterize the mechanism of action of toxicants?	Describe the fundamental basis of xenobiotic defense through ADME.	• Characterize each step of ADME. • Describe how vascularization affects xenobiotic defense. • Describe the primary importance of the liver and kidney in xenobiotic defense. • Explain the role of Phase I and II enzymes in ADME. • Describe how vehicles affect ADME. • Contrast lipophilicity and hydrophilicity and how they affect ADME. • Define bioavailability as it relates to ADME. • Explain how storage in the lipid or bone as one route of elimination affects ADME at the time of toxic exposure and later during weight loss or bone remodeling. • Describe how remobilization of toxicants from lipids in times of starvation stress can cause toxicity. • Case study: Describe toxicant remobilization from lipid tissues during starvation of Sarasota Bay dolphins during red tide in the 1990s.
	Explain why LD_{50} is commonly used as a measure of toxicity of a compound.	• Explain the importance in choosing an appropriate animal model to make useful comparisons to humans. » Discuss what it means to use an "appropriate animal model." • Explain how LD_{50} is affected by route of exposure. • Explain the importance of length of exposure in determining LD_{50}. • Compare and contrast LD_{50} and LC_{50}. • Consider differences in EC_{50} and IC_{50}. • Describe the use of uncertainty factors when extrapolating animal-derived LD_{50} data to humans.
	Describe the concept of ADME as it relates to toxicant exposure.	• Define the words that make up the acronym ADME: absorption, distribution (or disposition), metabolism, and excretion. • Describe how characteristics of ADME change with dose. • Contrast unsaturated with saturated elimination. • Explain the five major processes of elimination: renal, fecal, pulmonary, biotransformation, and other means (sweat, milk, hair, nails). • Define biotransformation. • Apply the Henderson-Hasselbach equation to ADME . • Case study: Describe the ADME of ethanol. • Case study: Describe the ADME of acetaminophen.

Pathways and Transformations of Energy and Matter

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do concepts of administration, distribution, metabolism, and elimination (ADME) help characterize the mechanism of action of toxicants?, *continued*	Contrast the major sites of entry for toxicants and how site of entry affects dose and risk.	• Describe the three major portals of entry to the body: gastrointestinal, inhalational, and dermal. • Contrast the major sites of entry for toxicants and their surface areas in humans: respiratory system (100 m^2), gastrointestinal system (300 m^2), and integumentary system (2 m^2). • Describe percutaneous absorption and the effects of skin conditions (cuts, scratches, inflammation, sunburn, and hair follicles) on penetration. • Describe how route of exposure affects the toxicity of a toxicant or toxin.
	Describe features of chemicals and barriers that affect absorption of compounds.	• Differentiate simple diffusion, active transport, facilitated diffusion, phagocytosis, and pinocytosis. • Compare and contrast how the characteristics of chemicals affect diffusion: size, molecular charge, ionization, water solubility, and concentration differences across membranes. • Discuss how particle size affects and determines which regions of the respiratory system are targeted. • Contrast the efficacy of capture of different kinds of gases by the turbinates of the nose and explain how this affects exposure to the lung. • List the chemical disposition features of importance, including: duration and concentration at site of entry, rate of absorption, total amount of toxicant absorbed, distribution within the body and presence at specific sites, efficiency of biotransformation, toxicity of metabolites, storage of the toxicant and metabolites in the body, and rate and sites of elimination. • Case study: Contrast aspirin and aniline for their relative absorbance in the stomach or intestines due to pH. • Case study: Describe the elimination of iron. • Case study: Explain why a dose of a chemical given intravenously often results in a higher body burden than a chemical given orally.

Pathways and Transformations of Energy and Matter

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How do concepts of administration, distribution, metabolism, and elimination (ADME) help characterize the mechanism of action of toxicants?, *continued*	Contrast the mechanisms of elimination, including excretion, storage, and biotransformation.	• Compare and contrast Phase I and Phase II metabolism. • Describe the role of the skin and bone as a route of elimination. • Describe how defects in excretory pathways modify the toxicity of compounds in sensitive populations (e.g., infants, pubescent adolescents, elderly). • List examples of where storage of toxicants can occur and the types of toxicants that get stored there: plasma proteins, adipose tissues, bones, liver. • Explain why renal excretion is good at eliminating molecules smaller than 60,000 MW and water-soluble compounds. • Identify chemicals eliminated via the feces including bile, which is good at eliminating organic acids and bases, metals, and nonionized chemicals. • Describe enterohepatic circulation. • Explain why lipophilic gases are primarily eliminated via exhalation.
How can ADME be quantified using toxicodynamics and toxicokinetics (TDTK)?	Define toxicokinetics, pharmacokinetics, toxicodynamics, and pharmacodynamics.	• Define body burden. • Describe how the volume of distribution (VD) is used to help quantify exposure and body burden. • Describe the three compartments of water in the body (plasma, interstitial, and intracellular) and their role in toxicant distribution. • Compare and contrast toxicokinetics and toxicodynamics. Melvin Andersen Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
	Explain how toxicokinetic studies are used to determine changes in concentration of a chemical and its metabolites over time in blood and other tissues.	• Interpret data on area under the curve (AUC), clearance, and half-life. • Identify standard tests that can be used to estimate the concentrations of the parent compound and metabolites. • Explain the limitation of animal studies and computer models in predicting an individual human's response.
	Explain several methods of toxicokinetic analysis.	• Describe the use of radiolabeled chemicals in toxicokinetic studies. • Describe how toxicokinetics is used to identify persistence, half-life ($t_{1/2}$), and the bioaccumulation of toxicants.

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How can ADME be quantified using toxicodynamics and toxicokinetics (TDTK)?, *continued*	Describe how one-, two-, or multi-compartment models are used to approximate toxicokinetics.	• Explain the assumptions of the one-compartment model. » Explain why a one-compartment model is often sufficient despite its simplicity. • Explain the difference between one-compartment and two-compartment models. • Describe how binding to plasma proteins can affect the distribution of a toxicant. • Describe how the nervous system acts as a separate compartment from the rest of the body.
	Describe how saturation affects the elimination of a compound.	• Case study: Describe how ethanol is eliminated from the body. • Case study: Describe the mechanism by which ethanol protects against methanol toxicity. • Case study: Describe how elevation in CYP2E1 affects the rate of metabolism of ethanol and the synergy of this pathway with acetaminophen bioactivation.
	Contrast zero-order versus first-order kinetics of elimination.	• Describe the first-order manner in which one-compartment model systems typically eliminate a chemical. » Describe the relationship between first-order elimination and half-life. • Create a graph showing elimination of a chemical using one-compartment model kinetics (time is x axis, log of concentration is y axis). • Explain why saturable systems exhibit zero-order kinetics. • Draw a two-compartment model illustrating rates of entry, metabolism, and excretion. • Case study: Describe how ethanol is eliminated from the body primarily via zero-order kinetics.
	Describe how barriers (e.g., blood-brain barrier or placenta) alter toxicokinetics.	• Describe why the placenta as a barrier to toxicants is controversial. • Describe the structure of the blood-brain barrier and how active transport is used to prevent diffusion of lipophilic compounds into the CSF. • Explain why most toxic chemicals pass the placenta via passive diffusion. • Explain how the blood-brain barrier slows the rate of diffusion of drugs. • Case study: Describe characteristics of P-gp null mice such as their increased susceptibility to ivermectin and vinblastin. PMID 7910522, PMID 9717696
	Apply mathematical and computation methods to toxicokinetics.	• Describe methods that can be used to quantify the biodistribution of xenobiotics in a living organisms. • Identify mathematical models that extrapolate from one route of exposure to another for the determination of internal dose. • Compare and contrast experimental and computational methods for assessing xenobiotic disposition. • Demonstrate how computational methods can be used to quantify the amount of toxicant at a site of action. • List ways in which mathematical models are used along the source-to-outcome continuum for risk assessment.

Pathways and Transformations of Energy and Matter

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What is the relationship between toxicology and pharmacology?	Contrast measurements of drug safety.	• Define the maximum tolerated dose • Compare and contrast margin of safety and therapeutic index for a drug. • Describe why chemotherapeutics have a smaller therapeutic index and margin of safety than other drugs.
	Explain the concept of dose spacing.	• Describe how slow rates of excretion or metabolism can cause accumulation of a toxicant over time through frequent low-dose exposures. • Case study: Describe the effect of large doses of acetaminophen given at once versus over time on phase two metabolic pathways. • Case study: Describe how limitations on dietary fish consumption relate to fractional dosing and mercury exposure.
	Describe the role of toxicology in the drug development process, including preclinical studies and clinical trials.	• Describe the process of drug development. • Describe the Ames assay and its use in determining potential mutagens. • Describe resorufin-based cellular viability assays. • Describe how high-throughput screens using high content data are used to screen drug candidates for toxicity. • Describe the process of drug development. Ruth A. Roberts Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
How does oxidative stress contribute to toxicology?	Describe free radical forms of oxygen and nitrogen.	• List the major reactive oxygen and nitrogen species. • Show the interrelationship among the various reactive oxygen and nitrogen species. • Describe how free radicals can serve as signaling molecules. • Describe the role of free radicals in the immune system. • Describe the role of nitric oxide in neurotransmission. • Describe how free radicals are produced by mitochondria. • Compare and contrast the toxicity of the various reactive oxygen and nitrogen species. • Discuss why the hydroxyl radical is so toxic.

Pathways and Transformations of Energy and Matter

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
How does oxidative stress contribute to toxicology?, *continued*	Describe the mechanism of lipid peroxidation.	• Describe the role of the cell membrane in lipid peroxidation. • Describe how lipid peroxidation products act as signaling molecules. • Describe how lipid peroxidation is used as a strategy for killing bacteria. • Describe how lipid peroxidation can affect mitochondria and the nucleus. • Describe how homeostasis is disrupted by loss of membrane integrity. • Describe membrane repair. • Contrast lipid peroxidation repair and protein/DNA repair mechanisms.
	Describe the defenses organisms have against free radicals.	• Describe the role of vitamins and essential metals in defense against oxidative stress. • Describe the role of melanin in defense from oxidative stress. • Describe how antioxidant molecules defend against oxidative stress. • Compare and contrast mitochondrial versus cytosolic defense pathways against free radicals. • Describe the balance between oxidants and antioxidants in defense against free radicals. • Case study: Describe the mechanism of action of paraquat toxicity.
	Describe the nrf2 pathway and how it signals defense against oxidative stress.	• Describe the role of transcription factors in the nrf2 signaling pathway. • Contrast the roles of nrf2 in different tissues. • Contrast inducible versus constitutively active enzymes. • Explain how antioxidant enzymes are controlled by multiple transcription and signaling pathways. • Case study: Describe the double-edged sword nature of nrf2 in protection of the cell from toxicants. PMID16543142 • Describe the discovery of the nrf2 pathway and its role in protection against a variety of toxicants. Curtis D. Klaassen Eminent Toxicologist lecture. http://www.toxicology.org/education/edu/eminent.asp
What effects can toxicants have on energy metabolism?	Discuss the role that glycolysis plays in energy production.	• Contrast aerobic and anaerobic metabolism. • Describe the importance of metabolic phosphorylation for sequestering molecules in the cell. • Describe the implications of cytoplasmic acidification. • Describe the long-term effects of shifting to glycolysis for energy production. • Contrast respiratory capacity of model organisms versus humans.

Pathways and Transformations of Energy and Matter

Toxicology Concepts	Learning Objectives	Example Learning Objectives and Case Studies
What effects can toxicants have on energy metabolism?, *continued*	Describe the importance of ATP in cellular homeostasis.	• Describe the role of phosphorylation in production of ATP. • Describe the importance of ATP in cell cycle control. • Contrast how kinase and phosphatase activity are balanced. • Explain how the maintenance of concentration gradients requires energy. • Describe how mitochondrial inhibitors affect cellular function. • Explain how apoptosis requires energy.
	List the implications of a high-fat/high-energy diet.	• Describe the importance of carbohydrates in metabolism. • Describe the role of Krebs cycle anabolism in carbohydrate catabolism. • Contrast catabolism of polyunsaturated fatty acids and saturated fatty acids. • Describe the role of cholesterol in membrane integrity. • Describe the necessity of cholesterol in steroid synthesis. • Explain how high-fat/high-energy diets disrupt cellular metabolism. • Discuss the importance of omega-3 fatty acids in health.
	Describe the central role of oxidative phosphorylation in energy generation.	• Discuss the importance of mitochondrial energy coupling. • Contrast the proton (electrical) gradient and pH gradient across the mitochondrial inner membrane. • Explain mechanisms for monitoring redox potential in the cell. • Describe the importance of the NAD^+/NADH balance. • Discuss the implications of inhibiting Complex I in the electron transport chain. • Discuss implications of inhibiting Complex IV in the electron transport chain. • Describe diseases associated with mitochondrial inhibitors. • Case study: Describe the mechanism of action of inhibitors of oxidative phosphorylation, such as rotenone and cyanide. • Case study: Describe how the mitochondrial uncoupler 2,4-dinitrophenol causes toxicity. • Case study: Describe how redox-cycling toxicants such as menadione can disrupt the NAD(P)H/$NAD(P)^+$ balance.

Vision and Change Core Competencies and Disciplinary Practice

A competency-based approach to undergraduate biology ducat ion focuses on demonstrating analytical, experimental, and technical skills as measurable outcomes of student learning. Biology literacy is defined primarily in terms of acquired competencies, demonstrated with in the context of fundamental biology concepts.
Vision and Change Report 2011 www.visionandchange.org

Core Competency	Instantiation of Ability in Disciplinary Practice	Demonstration of Competency in Practice	Examples of Core Competencies Applied to Biology Practice
Ability to apply the process of science	Biology is an evidence-based discipline	Design scientific process to understand living systems	• Observational strategies • Hypothesis testing • Experimental design • Evaluation of experimental evidence • Developing problem-solving strategies
Ability to use quantitative reasoning	Biology relies on applications of quantitative analysis and mathematical reasoning	Apply quantitative analyses to interpret biological data	• Developing and interpreting graphs • Applying statistical methods to diverse data • Mathematical modeling • Managing and analyzing large data sets
Ability to use modeling and simulation	Biology focuses on the study of complex systems	Use mathematical modeling and simulation tools to describe living systems	• Computational modeling of dynamic systems • Applying informatics tools • Managing and analyzing large data sets • Incorporating stochasticity into biological models

Vision and Change Core Competencies and Disciplinary Practice, *continued*

Core Competency	Instantiation of Ability in Disciplinary Practice	Demonstration of Competency in Practice	Examples of Core Competencies Applied to Biology Practice
Ability to tap into the interdisciplinary nature of science	Biology is an interdisciplinary science	Apply concepts from other sciences to interpret biological phenomena	• Applying physical laws to biological dynamics • Chemistry of molecules and biological systems • Applying imaging technologies
Ability to communicate and collaborate with other disciplines	Biology is a collaborative scientific discipline	Communicate biological concepts and interpretations to scientists in other disciplines	• Scientific writing • Explaining scientific concepts to different audiences • Team participation • Collaborating across disciplines • Cross-cultural awareness
Ability to understand the relationship of science and society	Biology is conducted in a societal context	Identify social and historical dimensions of biology practice	• Evaluating the relevance of social contexts to biological problems • Developing biological applications to solve societal problems • Evaluating ethical implications of biological research