PENNSTATE 1855

eTOXIC
Environmental Toxicology Inquiry Curriculum

Module 1: Everyday Toxicology
Lesson 4: How Are Toxic Effects Different over Different Time Scales?

Lesson Overview

Summary:

In this lesson, students extend, contextualize, and connect the concepts of acute and chronic doses and effects. In order to connect these concepts tangibly, and to refine their research skills, students will work in groups to design mock human clinical trials to test the safety and effectiveness of a hypothetical new drug. This exercise will reveal the contrast in cost, logistics, and reliability of studies of acute and chronic effects of drugs and environmental toxins.

Students will make the further connections between acute and chronic doses to mutagenesis and carcinogenesis (anticipating more detailed material in subsequent modules). Finally, students will consider the extreme case of a single exposure of a persistent, fat-soluble toxin giving rise to chronic effects. This case introduces concepts of persistence that will be greatly expanded upon in the next lesson's treatment of kinetics.

Pedagogically speaking, designing human clinical trials will give students the opportunity to think very rigorously, deliberately, critically, and creatively about large-scale experiments. As such, the bulk of the lesson is devoted to group activities and discussion, where this thinking takes place.

The homework assignment applies the distinction between acute and chronic mechanisms to cigarettes. Students read a news article about a recently-published study, as well as the primary journal article. In the assignment, students connect concepts from the lesson and the articles, and observe the contrasts between the popular press and scholarly publications.

Objectives:

By the end of the lesson, students will be able to:

1. distinguish between acute and chronic effects of substances on human health.
2. design human studies that evaluate drug safety and effectiveness to instructor satisfaction.
3. determine the relationship of mutagenesis and carcinogenesis to long-term health risks to instructor satisfaction.
4. explain the time course of physiological effects based on

the solubility of substances to instructor satisfaction.
5. contrast news articles and scholarly publications to instructor satisfaction.

Grades: 9th through 12th

Prepping the Lesson

Instructions:

Materials/Technical Resources:

It is our recommendation that you walk through the teacher and student materials for this lesson to ensure that students will be able to receive the information through the modes of delivery that we intended prior to using the material in the classroom. If you or your school does not have the resources needed, you may need to make some modifications depending on the resources you have available.

The following materials/technical resources will be needed to complete the lesson. We recommend using Option #1 to provide the materials to your students in the manner in which they were intended to be delivered.

Option #1 (Preferred Technology Requirement)
You will need to have access to a computer, the Internet, and a projection device during the entire lesson. Your students will need to have access to computers and the Internet. You and your students will simultaneously step through the module while using their given computers. You may have to make special arrangements for all of your students to have a computer. Be sure you and your students will not be blocked from Google Documents, YouTube, and your selected online collaborative tool. You may be currently using an online collaborative tool but if not, we recommend Facebook groups, Edmodo, or eChalk.

Option #2 (Minimum Technology Requirement)
If you do not have a way for your students to access the Internet individually, then you will need to facilitate their access to the information. You will need access to a computer, the Internet, and a projection device during the entire lesson. You will step through the module as your students watch and complete the presented activities. There may be modifications to the delivery of the materials that you will need to make, depending upon the resources you have available. Be sure you have access to Google Documents, You Tube, and your selected online collaborative tool. You may be currently using an online collaborative tool but if not, we recommend Facebook groups, Edmodo, or eChalk.

Lesson Time and Supply List:

This document will provide you with information on prep time needed, a list of supplies, and total lesson time for this particular lesson. See appendix for the Lesson, Time and Supply List document.

Student Homework:

Prior to starting this module, it is important to determine which online collaborative tool you and your students will be using. Once you have had an opportunity to review all of the lessons, decide how you will facilitate the homework discussions and submissions using your selected online collaborative tool. Be sure to give your students clear directions and objectives on your expectations of the use of this tool and their participation in their homework activities. We highly encourage you to participate with your students in their homework discussions to enhance the quality of the experience.

Essential Vocabulary:

assay, carcinogenesis, clinical trial, controlled clinical studies, dioxin, double-blind, experimental drug, fat cells, fat soluble, fatty acids, hypothetical aspirin derivative, informed consent, metabolism, molecules, mutagenesis, placebo effect, polycyclic aromatic hydrocarbons, preclinical trials, safe drug, teratogenesis, tetrachlorodibenzo-p-dioxin (TCDD), triglycerides, U.S. Food and Drug Administration (FDA), water soluble (See Lesson 1, 2, and 3 for additional vocabulary words.)

Student Notebook:

Laboratory notebooks are arguably the most useful tool at an experimenter's bench. Remind students of the critical importance of recording all experimental observations, and especially recording all experimental conditions (e.g., the type of chemical treatment, the range of concentrations, number and species of seeds, etc.) when starting an experiment so that they can maintain comprehensive, unambiguous control over those variables when they follow up with subsequent experiments.

Implementing the Lesson

Instructions:

1. Guided Discussion (5 Minutes)

Pharmaceutical Company Scenario

At the beginning of class, present two or three selected examples from the dose/response curves that students posted in the previous homework assignment.

Review these responses in a group discussion with the entire class. Select examples that:

- illustrate well the distinction between acute and chronic effects.
- illustrate well the distinction between beneficial and harmful effects.
- prompted insightful comments from other students.
- make "good guesses" about relative doses. In general, "good guesses" will fit the following patterns:
    - acute effects appear at higher **single** doses; **chronic effects appear at lower repeated doses.**
    - beneficial effects **should—in the case of a safe drug**—appear at lower doses than harmful effects.

You might share with students (or simply use as a guide to a complete answer) the example answer of the ficitional drug Xanadin. A link to this video is located in the online lesson plan.

2. Group Activity (20 Minutes)

Teacher Tip: *For more information, share the summaries of phased clinical trials on the path to drug approval by the U.S. Food and Drug Administration (FDA) at clinicaltrials.gov and wikipedia.org. (See appendix for full web addresses.)*

Teacher Tip: *(This can be an optional discussion if you feel it will work with your class and you have the extra class time.)*

Obviously, toxicologists cannot measure lethality in human subjects, so they measure median lethal dose in lab animals—usually rats *(continued on next page)*

Clinical Trial Study

Students will now work in their groups to extend the homework activity to a more realistic and detailed scenario. They will design (but obviously not carry out!) one of two clinical trial studies in human subjects that will test the safety and effectiveness of a hypothetical aspirin derivative.

Provide students with the Clinical Trial Study worksheet and randomly assign one of the following two studies to each group:

1. Clinical Trial Study: Pain Relief and Stomach Upset
2. Clincial Trial Study: Lowered Heart Attack Risk

Clinical Trial Study worksheets are located in the appendix.

One key insight students should gain from this activity and the discussion that follows it is that, by the very nature of drugs and toxins, it is much more difficult to study their chronic effects.

The following reminders and prompts may be useful before the activity:

- Remember that a phase III trial is mainly designed to **confirm and strengthen** confidence in the results previously collected in preclinical experiments and phase I and phase II clinical studies.

(continued from previous page) and mice, as rodent physiology is usually similar to human physiology. Ultimately, though, in order for a drug to be approved, its median effective dose must be measured directly in humans, and evidence must be presented that supports the assumption that median lethal dose in humans is comparable to that measured in lab animals.

However, before median effective dose is measured in humans, it must be measured in lab animals. Sometimes these observations require clever experiments: how can you tell when a rat's headache gets better? In short, rodents display certain behavior when they are in pain, like licking or scratching their extremities. An observer can count the number of times test animals exhibit these habits in an hour, and the frequency of these behaviors is taken as a measure of pain, and thus a readout of the efficacy of a pain relief drug. With human subjects, of course, an investigator can simply ask them to rate their pain on a standardized scale.

- **Median lethal dose** will have been measured in preclinical trials in laboratory animals—it is **never directly measured in humans!**

- An **assay** is a **laboratory test** (like measuring protein concentration or counting the number of times a mouse licks its paw per minute) or clinical test (like asking subjects to rate on a scale of 1 to 10 how jittery they feel). It is the **consistent method by which an experimenter collects data.**

- You learned about positive and negative **controls**. What would serve as the positive control in a clinical trial for an aspirin substitute?
  *(**Answer**: aspirin.)*

  What would serve as a negative control in a clinical trial?
  *(**Answer**: in general, it is not considered ethical to include negative controls—i.e., no treatment—in clinical trials.)*

- Control subjects (given aspirin) and experimental subjects (given the experimental drug) must be **assigned randomly** in order to maximize the chances that the results will be valid.

- Control subjects and experimental subjects must be assigned in a **double-blind** manner—neither subject nor experimenter can know which group the subject is assigned to—in order to avoid increasing the **placebo effect**.

- An absolutely crucial and carefully scrutinized step in human studies is obtaining **informed consent** from each subject. Subjects must be provided, in writing, very clear and detailed information about the nature of the study, the possible risks and benefits, the control groups to which they may be randomly assigned, and so forth. Each subject must affirm in writing that he or she understands this material and consents to participate in the study.

3. Post-Activity Discussion (10 Minutes)

Experimental Design

After each group has come up with a design and entered it into their notebooks, have a volunteer from a group that designed an acute study (**"Pain Relief and Stomach Upset"**) summarize their design. Other groups can comment on and critique that design based on their own ideas.

Next, have a volunteer from a chronic study group (**"Lowered Heart Attack Risk"**) share their design, and solicit feedback from other groups.

In a whole class discussion, ask students to articulate the contrasts between these two types of studies. Consider the amount of personnel and money required for such a study, and how long it would take to complete, for example.

Ideal answers to the above questions might look something like the following:

> ***The Assay: Pain Relief and Stomach Upset.*** *This study's key assay might be a questionnaire, to record subjects' subjective report of pain on a scale of 1 to 10, as well as their subjective report of stomach upset on a scale of 1 to 10 (as well as qualitative assessments of pain and stomach upset). These questions might be asked immediately before and 30 minutes after administration of the drugs.*
>
> ***The Assay: Lowered Heart Attack Risk.*** *This study's apparently simple assay might be counting the number of subjects who suffer a second heart attack, and recording other side effects. However, the method of collecting data in order to observe a chronic effect (see below) requires that each subject be followed over a long time period.*
>
> ***The Subjects: Pain Relief and Stomach Upset.*** *It is necessary to have access to subjects who report pain. So the study might recruit certain hospital patients who are otherwise healthy and not taking other drugs who have minor pain and would normally be given aspirin.*
>
> ***The Subjects: Lowered Heart Attack Risk.*** *It is necessary to have access to subjects who have had one heart attack. So the study might recruit patients who are being discharged after a hospitalization for their first heart attack and who would have been prescribed low daily doses of aspirin.*
>
> ***Data Collection and Follow-Up: Pain Relief and Stomach Upset.*** *One person (a nurse or physician's assistant) could, during one visit, identify an eligible subject, obtain informed consent, administer the drug, and collect the complete data set from the*

questionnaire. No follow-up would be required. Consider the amount of personnel and money required for such a study, and how long it would take to complete—perhaps six months to a year?

Data Collection and Follow-Up: Lowered Heart Attack Risk. *Subjects would be identified and give informed consent during preparation for discharge from the hospital. They would have to commit—for years!—to a daily low-dose regimen of a drug, and in order for the study's results to be valid, their consistent participation in this regimen would have to be verified (e.g., by weekly reminder telephone calls). Moreover, in order to obtain statistically significant results, this regimen, with consistent tracking and follow-up, would have to be maintained for many years! [In actual aspirin trials, the average length of follow-up has in fact been about four years—up to ten years in some studies (Baigent et al. 2009).] Meanwhile, each subject would have to be monitored regularly for overall health, indicators of cardiac risk, and long-term side effects.*

At some point in the discussion, you may also note that it is not simply chronic drug effectiveness that is difficult to measure. The effects of environmental toxins can be much more difficult to evaluate over the long term—if not more so, because it can be difficult or impossible to definitively identify victims, much less follow them clinically over the long term.

For instance, after the 2011 earthquake and tsunami in Japan, there has been great alarm about the long-term health effects from the release of radioactive material from the Fukushima nuclear reactors. One comparable incident is the disaster at Chernobyl in 1986. The acute death toll was easy to measure: 31 people died in the disaster itself. However, in order to evaluate the chronic effects for the rest of the population of the northern hemisphere, indeed the world, who were exposed to elevated levels of radiation after the event, scientists and public health specialists can only make estimates. These estimates range from 4,000 to 200,000 to over a million deaths from cancer and other causes in the years since the accident. Needless to say, these results are controversial.

4. Guided Discussion (5 Minutes)

<u>How Can an Acute Exposure Give Rise to a Chronic Effect?</u>
We will discuss two mechanisms by which the time course of an acute effect can be extended to a more chronic effect.

1. by permanently altering DNA through mutation

2. by storing persistent substances in fat tissue

These two concepts help to extend, contextualize, and connect the concepts of acute and chronic doses and effects. In addition, they are key concepts themselves in toxicology.

We mention the first mechanism only briefly. Below we provide some external resources for an optional discussion of mutagenesis and Module 2 extends the discussion in considerable detail.

Storage in fat tissues, on the other hand, is the basis of the activities that take up the remainder of this lesson. Moreover, the concepts of **storage and elimination** form the foundation of a sophisticated quantitative exploration of toxicokinetics and pharmacokinetics in the next lesson of this module.

Ask the class to brainstorm a list of mechanisms by which a single exposure to a substance could cause a lasting effect. They might have ideas like permanent organ damage, sensitization to subsequent exposures, synergistic effects (like drug interactions) that cause long-term effects, etc.

If the group doesn't think of **mutation and fat storage**, prompt them with hints (e.g., "What about DNA?" "What about vitamins? Aren't some of them fat soluble?").

Collect all the responses and highlight mutation and fat storage. We will explore fat storage (and, optionally, mutagenesis, teratogenesis, and carcinogenesis) in more detail in the following activities.

5. Guided Discussion (5 Minutes) *Additional Time Not Included in Overall Day Estimation*

Mutagenesis *(Optional Discussion)*
Use the following points to guide a discussion of the means by which mutations can give rise to lasting effects of toxic exposures. The level of detail can be adjusted based upon the background of the particular audience.

- **Mutation** simply means a change in genetic information, which is synonymous with a change in DNA sequence. **Mutagenesis** simply means causing mutations, in the toxicological context by chemical action. (In practice, the two terms are often used synonymously.)

- There are many types of mutation, including **deletion or insertion of relatively large sequences**, but here we will consider **single-nucleotide changes in DNA sequence** caused by errors in DNA replication that precede mitosis (or meiosis).

- A given mutation may be **harmless** (sometimes, including silent and neutral mutations), **beneficial** (very rarely, and serving as the basis of evolution by natural selection), or **harmful** (almost always).

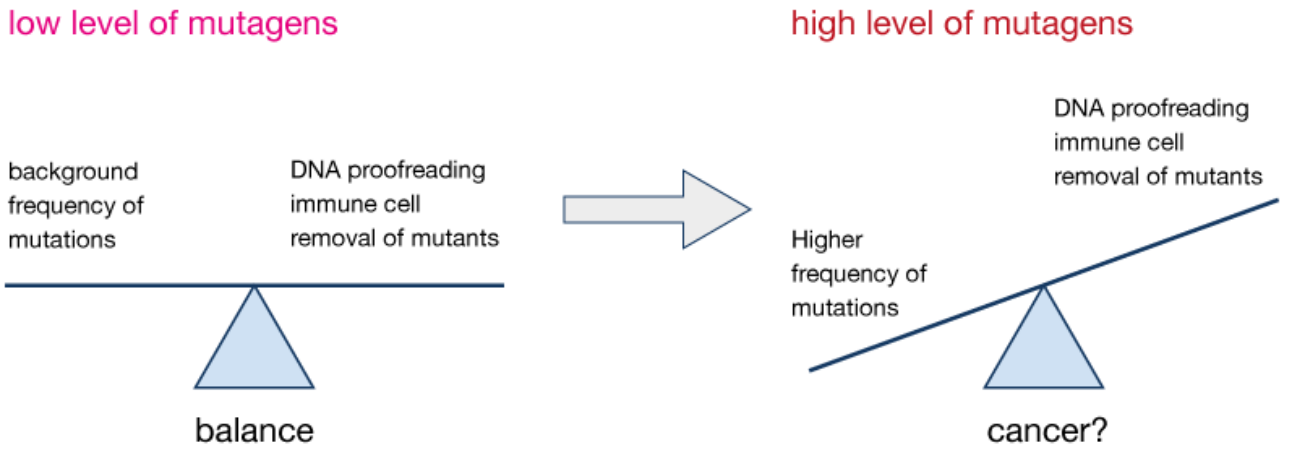
- Mutations can and do arise spontaneously, as a result of very low-frequency DNA replication errors.

- Toxins that chemically modify DNA (via covalent attachment or noncovalent interactions like intercalating between base-pairs) will interfere with the **DNA polymerase enzyme** complex that replicates DNA, thus raising the frequency of mutations caused by replication errors.

- There are two important defenses against mutation:
    1. so-called **proofreading enzymes** in the nucleus can detect replication errors and correct them.

    2. certain cells of the **immune system** detect and eliminate body cells that exhibit mutant proteins.

- The body seeks to maintain a balance between the background frequency of mutations on one side, and cells' proofreading activity and the capacity of the immune system to remove mutant cells on the other side.



Thus low-level chronic doses of mutagens below a certain threshold can be rendered harmless, depending on individual sensitivity and other variables. But higher levels of mutagens can lead to mutant cells escaping both defense mechanisms, and lead to cancer.

- However, the consequences of mutation can vary greatly depending on the cellular context. Students may be able to think of these two examples (and many more):

    1. **Embryonic cells**, which divide rapidly and give rise to huge numbers of subsequent cells that may be critical to embryonic development. Disruption of development by mutagenesis is one mechanism of **teratogenesis**.

    2. During **germ cell development**, certain cells undergo **meiosis** and ultimately give rise to sperm and egg cells. If these cells suffer mutations, those mutations are passed on to the next generation.

- **Cancer is a disease of mutation.** Chronic mutagenesis can lead to **carcinogenesis**. Cells that accumulate a few mutations in key genes can become **precancerous**. Precancerous cells can subsequently progress, following accumulation of a few more mutations in other key genes, through the stages of **dysplasia**, **carcinoma**, and **metastasis**.

To sum up: mutation—which can lead to genetic changes in germ cells (sperm and egg), teratogenesis (disruption of embryonic development), and carcinogenesis (emergence of cancer cells)—is one mechanism by which a relatively short exposure could lead to chronic effects.

6. Group Activity (5 Minutes)

Teacher Tip: *If students have a year or so of chemistry background, they ought to be able to make an explanation using the following sorts of vocabulary and concepts:*

- *polar vs. nonpolar molecules*
- *hydrophobic vs. hydrophilic interactions*
- *mechanism of water separating from oil in salad dressing because charged and polar (partially charged) molecules attract each other very strongly, thus excluding uncharged and nonpolar molecules.*

<u>Fat Soluble vs. Water Soluble</u>

Another mechanism by which an acute exposure could lead to longer-term effects is the storage of persistent substances in fat cells.

Prompt students to divide the vitamins into two categories based on their solubility. Also ask them to explain what these properties mean for retention in body tissues. This may be common knowledge for them, or it might require some help from the instructor. You may want to use the vitamin cards located in the appendix to help depict the chemical structure of the vitamins in order to divide them into "water soluble" (hydro**philic**) and "fat soluble" (hydro**phobic**). Identify the prominent chemical groups that determine these properties, and what their fate is in the body.

Prompt and collect a table of responses, which might look like the following:

	Water Soluble hydroPHILIC	Fat Soluble hydroPHOBIC
prominent determining chemical groups	hydroxyl groups (-OH) carboxyl groups (-COOH) amine groups (-N-) aldehyde groups (=O)	hydrocarbon chains aromatic hydrocarbon rings
examples	B vitamins C	A D E K
fat in the body	excess eliminated, mostly in urine	excess trapped in fat cells

Using the structural formulas of fatty acids, triglycerides, and the vitamins, prompt students to explain the chemical properties of the vitamins in terms of their physical structures.

7. Article (2 Minutes)

Case Study

Share the following case study with students:

> One notorious case was recently in the news that illustrates a single dose that had a chronic—many years long—effect.
>
> In 2004, Viktor Yushchenko was a candidate in the Ukrainian presidential election. He was deliberately poisoned with a very high dose of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), a very potent form of dioxin.
>
> The effects of such a high-dose dioxin poisoning, like in similar accidental exposures, are characterized by a severe acne and other lesions on the face (along with other severe health effects). Apparently, the aim of the poisoning was to disfigure candidate Yushchenko. Nevertheless, he eventually won the election.
>
> Gradually Mr. Yushchenko has made a recovery, but even today his appearance reflects the high levels of TCDD that remain in his body—thousands of times higher than normal.

8. Guided Discussion (4 Minutes)

Case Study:

After you have shared the case study with your students, ask them "Why do victims of TCDD poisoning still carry such high levels of the toxin even years after one large exposure?"

You may want to give them a minute or so to reflect in their laboratory notebooks first, then ask them to volunteer to answer the question.

> ***Ideal Answer:*** *The structure of TCDD has two important consequences for its persistence in body tissues—as well as in the environment.*
>
> *First, the molecule is very fat soluble and very insoluble in water. Virtually all of the TCDD that an organism ingests will end up in fat stores.*
>
> *Moreover, TCDD and other dioxins are in a category of molecules that simply did not exist in the biosphere before the Industrial Revolution (except perhaps in the smallest trace amounts). Thus there is no organism that produces an enzyme that breaks down this molecule. In addition, the molecule itself is quite stable and breaks down spontaneously only very slowly.*
>
> *Therefore, high levels of TCDD in the body accumulate in fat—and in the environment, accumulate in soil and sediment—and remain for years or even decades.*

9. Guided Discussion (2 Minutes)

Conclusion

The following points will help wrap up the lesson, connect to another module in this curriculum, and anticipate the next lesson.
Former Ukrainian President Viktor Yushchenko's case, in which his body still carries a high level of dioxin nearly a decade after a single large deliberate exposure, is an extreme example of very slow metabolism and elimination of a toxin or drug. The next lesson will greatly expand upon these concepts and provide students tools for quantifying them.

Homework

10. Video (3 Minutes)

Teacher Tip: *Post the reflective questions for "Addiction and Carcinogensis from Smoking" to your class's online collaborative tool. Separately, post the question under "How Can the Body Get Rid of Toxins and Drugs?" to your class's online collaborative tool.*

Addiction and Carcinogenesis from Smoking

Remind students to complete the homework assignment.

There are three parts to the assignment: **"Addiction and Carcinogenesis from Smoking"** video, **"Addiction and Carcinogenesis from Smoking"** reflective questions, and **"How Can the Body Get Rid of Toxins and Drugs?"** reflective questions.

11. Reflective Questions (15 Minutes)

Addiction and Carcinogenesis from Smoking

Read the news article **"Smoking Causes Gene Damage in Minutes"** featured on *Discovery News*. Then look at the **"Immediate Consequences of Cigarette Smoking: Rapid Formation of Polycyclic Aromatic Hydrocarbon Diol Epoxides"** peer-reviewed article in the journal *Chemical Research in Toxicology*. **(Information on these articles are located in the appendix.)**

Answer these questions using your online collaborative tool:

1. How do these experimental results connect acute dose with chronic effect?

2. Do you think that a single cigarette could cause cancer? Why or why not?

3. What are some of the differences between a news article about the results of a study written by a journalist and a journal article about the study written by the scientists who carried out the study?

12. Reflective Questions (5 Minutes)

How Can the Body Get Rid of Toxins and Drugs?

Answer this question, separately, using your online collaborative tool:

- What are the ways by which a drug or toxin can be eliminated from the body? In other words, how does the body get rid of foreign molecules?

Appendix

Prep Time, Supply List, and Total Lesson Time

Prep Time:

We recommend 30-45 minutes, depending on your expertise level with the content. Each module will vary depending on your previous experience with the content and technology.

Materials:

Each student will need

- a copy of the Clinical Trial Study worksheet that you decide to give each group.
- to be part of a group that will complete the “Fat Soluble vs. Water Soluble” activity in which they will need a copy of the “Vitamin Card Game” sheet.
- access to a computer to view the “Xanadin” video (unless you decide to show the video through the class projector unit) or you may choose not to show it at all.
- their homework added to the online collaborative tool.

You will need

- to identify two or three student examples from the dose/response curves that students posted within last night’s homework assignment on their online collaborative tool.
- access to a computer to view the example answer of the fictional drug Xanadin, if you choose to share it with your students.
- to make copies of the Clinical Trial Study worksheets and decide which student groups receive which worksheet.
- to decide if you would like to complete the optional discussion on mutagenesis.
- to print and cut the “Vitamin Card Game” pieces in order to hand them out to your students.
- to detemine how you will share a case study about Viktor Yushchenko with your students.
- to post your students’ homework to your class’s online collaborative tool.

Total Lesson Time:

Lesson Activity	**Amount of Time in Class**
Guided Discussion: Pharmaceutical Company Scenario	5 Minutes
Group Activity: Clinical Trial Study	20 Minutes
Post-Activity Discussion: Experimental Design	10 Minute
Guided Discussion: How Can an Acute Exposure Give Rise to a Chronic Effect?	5 Minutes
Guided Discussion: Mutagensis *(Optional Activity)*	15 Minutes (Time not caculated in total time)
Group Activity: Fat Soluble vs. Water Soluble	5 Mintues
Article: Case Study	2 Minutes
Guided Discussion: Case Study	4 Minutes
Guided Discussion: Conclusion	2 Minutes
Total Time	**53 Minutes**

Lesson Activity	**Amount of Time out of Class**
Video: Addiction and Carcinogenesis from Smoking	3 Minutes
Reflective Questions: Addiction and Carcinogenesis from Smoking	15 Minutes
Reflective Questions: How Can the Body Get Rid of Toxins and Drugs?	5 Minutes
Total Time	**23 Minutes**

Resources - Web Addresses

Clinical Trial Study

For more information, share the following summary of phased clinical trials on the path to drug approval by the U.S. Food and Drug Administration (FDA): (sources: Clinicaltrials.gov and wikipedia.org)

Clinicaltrials.gov: http://clinicaltrials.gov/ct2/info/understand#Q19
Wikipedia.org: http://en.wikipedia.org/wiki/Clinical_trial#Phases

Addiction and Carcinogenesis from Smoking

"Smoking Causes Gene Damage in Minutes" (http://news.discovery.com/human/smoking-cigarettes-genetic-damage-110115.html)

"Immediate Consequences of Cigarette Smoking: Rapid Formation of Polycyclic Aromatic Hydrocarbon Diol Epoxides" article in the *Chemical Research in Toxicology* journal (http://pubs.acs.org/doi/full/10.1021/tx100345x)

Clinical Trial Study: Pain Relief and Stomach Upset

Background: How a New Drug Gets Approved

An experimental drug is tested first in test tubes and petri dishes, then in live animals. These studies are called **preclinical trials**. Only after it appears that a drug is both safe and effective in animals is it allowed to proceed to clinical (or human) trials.

Clinical trials are conducted in **phases**. The studies in each phase address different questions:

In **phase I trials**, researchers test an experimental drug for the first time in a small group of people (20-80) in order to evaluate its safety, determine a safe dosage range, and identify side effects. Note that phase I trials make no determination about the drug's effectiveness in human subjects.

In **phase II trials**, the experimental drug is given to a larger group of people (100-300) to see whether it is effective and to further evaluate its safety. Note that these studies are designed to evaluate the effectiveness of the drug for only one particular use ("indication") in patients with the disease or condition under study and to determine the common short-term side effects and risks.

In **phase III trials**, the experimental drug is given to a large group of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare its effectiveness to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

Scenario

You and your group are executives in a major pharmaceutical company. Together you are responsible for the introduction to market of a new aspirin derivative. The company's scientists have developed a promising new drug called Spiron. It is closely related to aspirin, and **it is hoped** that it will have **fewer of the harmful effects** of aspirin (stomach upset) but **still have the same therapeutic effects** of aspirin, both acute (pain relief) and chronic (lower risk of second heart attack).

Spiron has showed great promise in animal testing as well as in human studies up through phase II clinical trials. You are now preparing to launch phase III human trials, the final experiments required to submit a new drug to the U.S. Food and Drug Administration (FDA) for final approval. If Spiron is successful in these studies, it can be prescribed to patients.

Your task is to design a study to evaluate the **acute effects** of Spiron, in particular, **pain relief and stomach upset**.

Assignment

Your task is to design a study to evaluate the **acute effects** of Spiron, in particular, **pain relief and stomach upset**.

Use the space provided below and the "Questions for Thought" to brainstorm ideas about how you will design this study. When you have an experimental design that you think is complete, **record it in your laboratory notebook.**

Questions for Thought

Focus on the following questions when considering your experimental design. These need not be done in any particular order, and in fact should be considered together.

1. What are you going to measure, and how are you going to measure it? In other words, what will be the assay in your study?

2. Who will you recruit as subjects for your study?

3. In detail, describe how you will collect data from your subjects. Will you need to follow up with your subjects? Why and how?

Clinical Trial Study: Lowered Heart Attack Risk

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Your task is to design a study to evaluate the **chronic effects** of Spiron, in particular, **lowered heart attack risk, as well as any harmful side effects**.

Assignment

Your task is to design a study to evaluate the **chronic effects** of Spiron, in particular, **lowered heart attack risk**, as well as any harmful side effects.

Use the space provided below and the "Questions for Thought" to brainstorm ideas about how you will design this study. When you have an experimental design that you think is complete, **record it in your laboratory notebook.**

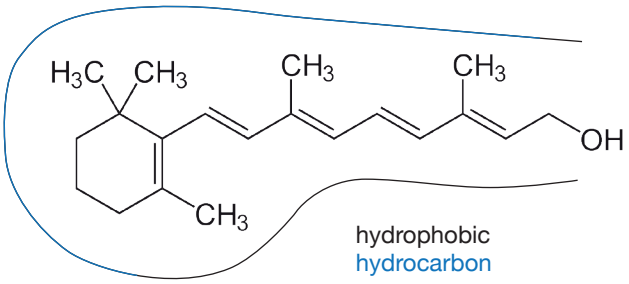
Questions for Thought

Focus on the following questions when considering your experimental design. These need not be done in any particular order, and in fact should be considered together.

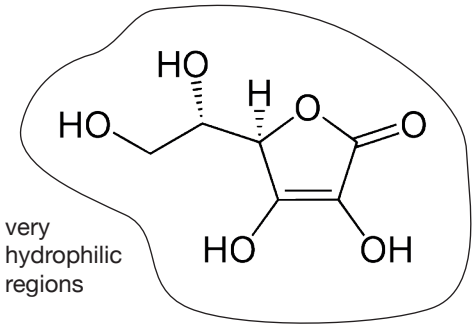
1. What are you going to measure, and how are you going to measure it? In other words, what will be the assay in your study?

2. Who will you recruit as subjects for your study?

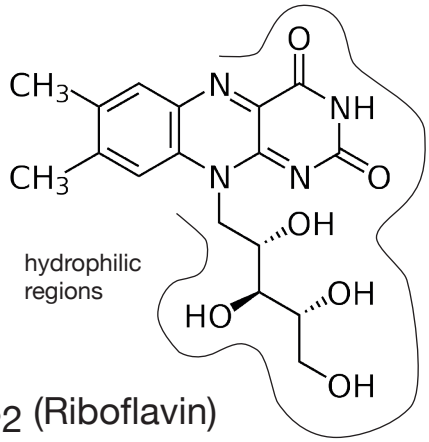
3. In detail, describe how you will collect data from your subjects. Will you need to follow up with your subjects? Why and how?



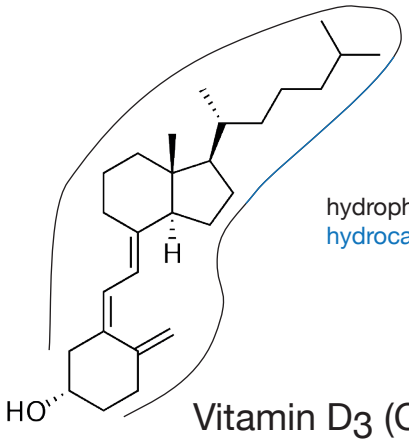
Vitamin A (Retinol)



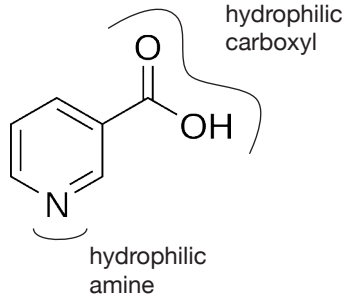
Vitamin C (Ascorbate)



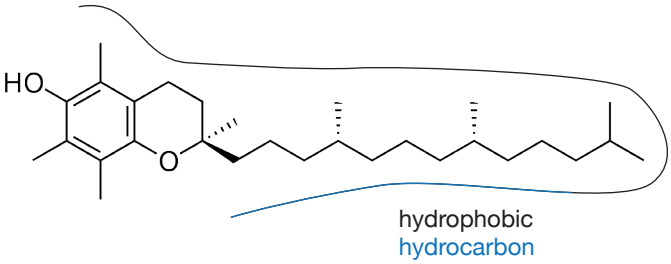
Vitamin B_2 (Riboflavin)



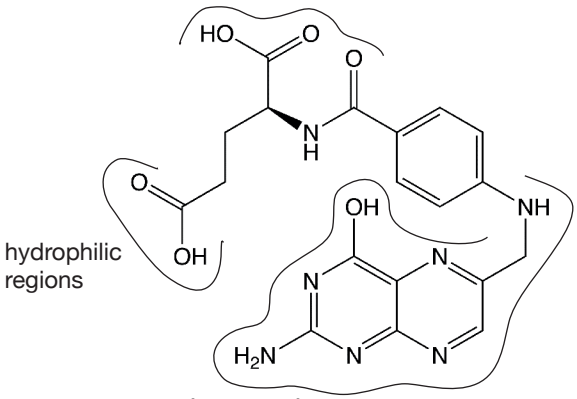
Vitamin D_3 (Cholecalciferol)



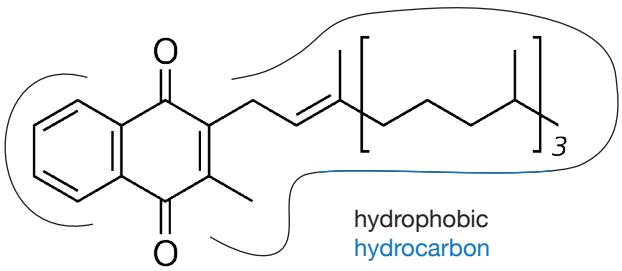
Vitamin B_3 (Niacin)



Vitamin E (Tocopherol)



Vitamin B_9 (Folate)



Vitamin K (Phylloquinone)