

PubH 6160-01
Systems Toxicology
Spring 2016

Credits:	3
Meeting Days:	Mondays and Wednesdays
Meeting Time:	4:25 pm – 5:40 pm
Meeting Place:	Mayo 1155
Instructor:	Lisa Peterson
Office Address:	MCRB 760D
Office Phone:	612-626-0164
Fax:	612-626-5135
E-mail:	peter431@umn.edu
Office Hours:	by appointment

I. Course Description

In this course, students will learn to apply information regarding basic pharmacokinetic principles and metabolic systems to elucidate mechanisms of toxicity induced by xenobiotic compounds. In addition, they will learn basic principles of metabolomic methods and their application to determine how environmental chemicals disrupt normal cellular processes.

II. Course Prerequisites

Biochemistry and PubH 6104 or permission of the instructor

III. Course Goals and Objectives

Students will: 1) learn basic pharmacokinetic principles of absorption, distribution, and elimination; 2) investigate biochemical mechanisms by which xenobiotics are bioactivated and detoxified by Phase I and Phase II enzymes; 3) examine genetic and environmental factors that affect these enzymes and influence the biochemical fate of xenobiotics; 4) learn how xenobiotics can influence endogenous pathways; and 5) formulate logical hypotheses about the biochemical basis of toxicity of xenobiotics.

IV. Methods of Instruction and Work Expectations

The primary method of instruction will be classroom lecture. The students are expected to attend each class and participate in classroom discussions. It is expected that the students have read and are capable of discussing any assigned readings in class.

Exams: There will be a midterm (100 points).

Participation points: participation in the discussion of papers (20 points per paper)

Research Paper:

There will be one research paper on this chemical. The final paper (double spaced, 12 point) should have the following parts:

Part 1. The physical chemical properties of the compound

Part 2. The toxicological and/or pharmacological properties of the compound

Part 3. A description of the known pharmacokinetic parameters for the compound, which includes major sites of how the compound is absorbed, distributed and excreted. Include in this description, how the physical chemical properties of the compound influence these parameters and how they relate to the toxicology and/or pharmacology of the compound. This section should include a scheme showing a physiologically based pharmacokinetic model for the compound along with a paragraph describing the model.

Part 4. A description of the major routes of metabolism including a discussion of enzymes involved. Compare what is known about human versus animal models.

Part 5. A discussion of factors (endogenous, environmental, chemical and genetic) that affect the toxicological and/or pharmacological properties of the compound.

Part 6. A discussion of 'omic studies performed with the chemical and how those studies advance our knowledge of how the chemical causes its toxic and/or pharmacological effects.

The maximum page limit for each part is as follows:

Parts 1 and 2: 2 pages total.

Part 3: 2 pages plus one additional page which includes a picture of a physiologically based pharmacokinetic model with 1-2 paragraph description of that model.

Part 4: 2 pages

Part 5: 4 pages

Part 6: 2 pages

Subsequent pages may be used for references. All resources should be appropriately referenced – references should include all authors, title of journal article, journal name, volume, inclusive pages, year. Websites are not acceptable sources. The information should be pulled from the primary scientific literature.

Key components of each part:

1. Physical Chemical Properties

- a. Chemical name
- b. Chemical Structure
- c. Color/form (Solid, liquid or gas at room temperature)
- d. Melting point, boiling point, vapor pressure if known
- e. Lipid/water solubility (logP value if known)
- f. State if it is an acid or base
- g. Name any ionizable groups and provide the pKa for each group
- h. State whether the molecule is charged or uncharged at physiological pH
- i. List any other properties that you think are important to its biological activity

2. Toxicological/Pharmacological Properties.

- a. Toxicological/pharmacological properties of the chemical (e.g. carcinogen, endocrine disruptor, etc)
- b. Site(s) of toxicity/pharmacological activity
- c. Molecular targets of the chemical
- d. Molecular mechanism of toxicity/pharmacological action

3. Pharmacokinetic Characteristics

For each characteristic, indicate the following:

- i. The role the physical chemical properties play in determining that characteristic.
 - ii. The relationship of the pharmacokinetic characteristic to the toxicology/pharmacology of the chemical
- b. Major sites of exposure

- c. Major mechanism of absorption (passive diffusion, active and/or passive transport, etc.)
- d. Absorption parameters such as bioavailability
- e. Major distribution sites
- f. Distribution parameters such as volume of distribution
- g. Major pathways of clearance (metabolism and/or excretion)
- h. Clearance parameters such as clearance rate and elimination half-life
- i. A physiological based pharmacokinetic model for your chemical
 - i. Must incorporate all sites of absorption, clearance, toxicological/pharmacological targets

4. Metabolic Pathways

- a. List the major routes of metabolism
- b. Name the enzymes involved in these routes

5. Factors Affecting Toxicological/Pharmacological Properties

- a. Species
- b. Genetics
- c. Sex
- d. Age
- e. Nutrition
- f. Other xenobiotics
- g. Health/pathological conditions
- h. Other factors?

6. System Toxicological Studies

- a. Summarize several toxic studies reported for your chemical
- b. For each study, indicate how that study advanced our knowledge of how the chemical causes its toxic and/or pharmacological effects

Timeline for submission of parts (electronic submission is ok):

Monday, January 25, 2016: Let Dr. Peterson know the topic of your paper.

Wednesday, February 10, 2016: Turn in a draft of Parts 1 and 2 (no more than 2 pages total).

Monday, February 29, 2016: Turn in draft of Part 3 plus the physiologically based pharmacokinetic model (no more than 2 pages for part 3)

Wednesday, March 30, 2016: Turn in draft of Part 4 (no more than 2 pages).

Wednesday, April 20, 2016: Turn in draft of Part 5 (no more than 4 pages).

Friday, May 13, 2016: Turn in final document containing parts 1-6 to Dr. Peterson's office by 12 noon. This document will contain all requested changes to parts 1-5 and part 6.

Each draft will be graded with a total of 25 points (total points: 100). To receive full credit for drafts, the student must turn in a draft that demonstrates serious effort towards completion of the section. The final product will also be graded with a total of 100 points possible.

Oral Presentation:

On the last day of class, each student will make a 20 min oral presentation of their research report. This is worth 50 points.

V. Course Text and Readings

The following books are on reserve at the Biomedical Library

Casarett & Doull's Toxicology. Available at the Biomedical Library Reserve Desk as well as online through the biomedical library website.

Molecular and Biochemical Toxicology, Fourth Edition, Editors: R.C. Smart and E. Hodgson, 2008; available online through the biomedical library website

Resources for the research paper:

Books in the Library:

International Agency for Research on Cancer (1972) IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, Vol 1-77.

Journals:

Annual Reviews in Pharmacology and Toxicology <http://pharmtox.annualreviews.org/>

Cancer, Epidemiology, and Biomarkers-ejournal accessible through MNCAT

Chemico-Biological Interactions

<http://ej.lib.umn.edu/url=http://www.sciencedirect.com/science/journal/00092797>

Chemical Research in Toxicology <http://pubs.acs.org/journals/crtoec/index.htm>

Drug Metabolism and Disposition <http://dmd.aspetjournals.org/>

Drug Metabolism Reviews: in Biomed Library

Online Resources:

Links to Metabolism journals and sites: <http://www.issx.org>.

Scifinder, link to gaining access: <https://www.lib.umn.edu/indexes/s>

PubChem: <http://pubchem.ncbi.nlm.nih.gov/>

VI. Course Outline/Weekly Schedule

Lecture Schedule.		
Date	Topic	Lecturer
January 20, 2016	Introduction	Lisa Peterson
January 25, 2016	Let Dr. Peterson know your chemical How to search the literature Absorption: Reading: Unit 2, Section 1 Casarett & Doull's Toxicology: http://www.r2library.com/Resource/Title/0071470514	Frank Sayre Lisa Peterson
January 27, 2016	Distribution/Elimination	Lisa Peterson
February 1, 2016	Toxicokinetics Reading: Unit 2, Section 3 Casarett & Doull's Toxicology: http://www.r2library.com/Resource/Title/0071470514	Lisa Peterson
February 3, 2016	Introduction to Physiologically based Pharmacokinetic Models	Lisa Peterson
February 8, 2016	Physiologically based Pharmacokinetic Model	Lisa Peterson
February 10, 2016	Regulation of xenobiotic enzyme activity Draft of Parts 1 and 2 due at class time	Linda von Weymarn
February 15, 2016	Introduction to metabolism and its role in toxicology Reading: Unit 2, Section 2 Casarett & Doull's Toxicology http://www.r2library.com/Resource/Title/0071470514	Lisa Peterson

February 17, 2016	Xenobiotic metabolism: cytochrome P450	Lisa Peterson
February 22, 2016	Xenobiotic metabolism: Other Phase I enzymes	Lisa Peterson
February 24, 2016	Xenobiotic metabolism: Phase II metabolism	Lisa Peterson
February 29, 2016	Xenobiotic metabolism continued Draft of Part 3 and PBPK model due at class time	Lisa Peterson
March 2, 2016	Factors that influence toxicity	Lisa Peterson
March 7, 2016	Factors that influence toxicity	Lisa Peterson
March 9, 2016	Transgenic animal models Get take home mid-term exam	Lisa Peterson
March 14-18, 2016	Spring Break	
March 21, 2016	Transporters Take home exam due at class time	William Elmquist
March 23, 2016	Systems Toxicology	Lisa Peterson
March 28, 2016	Genomics	Lisa Peterson
March 30, 2016	Epigenomics Draft of Part 4 due at class time	Heather Nelson
April 4, 2016	In class paper discussion Toxicol. Sci. 120: 33-41, 2011. http://toxsci.oxfordjournals.org/content/120/1/33.full.pdf+html http://toxsci.oxfordjournals.org/content/120/1/33/suppl/DC1	Lisa Peterson
April 6, 2016	Transcriptomics	Kevin Silverstein
April 11, 2016	In class paper discussion Chem. Res. Toxicology 19: 223-233, 2006. http://pubs.acs.org/doi/pdf/10.1021/tx050285z	Lisa Peterson
April 13, 2016	Proteomics	Yue Chen
April 18, 2016	In class paper discussion PLOS ONE 7 e49524 2012. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0049524	Lisa Peterson
April 20, 2016	Metabolomics Draft of Part 5 due at class time	Lisa Peterson
April 25, 2016	In class paper discussion PNAS 106: 14728-14733, 2009 http://www.pnas.org/content/106/34/14728.full.pdf+html?with-ds=yes	Lisa Peterson
April 27, 2016	Networks/models and In class paper discussion The Pharmacogenomics Journal 14: 208–216, 2014. http://www.nature.com/tpj/journal/vaop/ncurrent/full/tpj201339a.html	Lisa Peterson

May 2, 2016	Student Presentations	
May 4, 2016	Student Presentations	
Friday, May 13, 2016: Turn in final paper to Dr. Peterson's office by 12 noon. Electronic submissions are ok.		

VII. Evaluation and Grading

Grading Criteria - Letter grades and associated points are awarded in this course as follows below, and will appear on the student's official transcript.

A --	93 - 100 %
A- --	90-92 %
B+ --	87-89 %
B --	83-86%
B- --	80-82 %
C+--	77-79 %
C --	73-77 %
C- --	70-72 %
D+--	67-69 %
D --	63-66 %
D- --	60-62 %
F --	0 - 60 %

F (or N) – Represents failure (or no credit) and signifies that the work was either (1) completed but at a level of achievement that is not worthy of credit or (2) was not completed and there was no agreement between the instructor and the student that the student would be awarded an I.

S – Achievement that is satisfactory will be expected to complete all assignments and receive a minimum of 70% to receive a passing score (achievement required for an S is at the discretion of the instructor but may be no lower than a 70%).

Procedure for contesting a grade:

If you disagree with the way an answer to an exam question has been graded, please do the following:

- a. Make a photocopy of the exam question and your answer.
- b. Write an explanation of why you disagree with the way your answer was graded.
- c. Deliver the items mentioned in 1 and 2 to the office of the instructor within one week of receiving the grade from your exam.
- d. Make an appointment with the instructor to discuss your question regarding the grading of the exam question.

Late work will be penalized by reduction in points: 5% of the total points for every late day.

Course Evaluation

Beginning in fall 2008, the SPH will collect student course evaluations electronically using a software system called CourseEval: www.sph.umn.edu/courseeval. The system will send email notifications to students when they can access and complete their course evaluations. Students who complete their course evaluations promptly will be able to access their final grades just as soon as the faculty member renders the grade in SPHGrades: www.sph.umn.edu/grades. All students will have access to their final grades through OneStop two weeks after the last day of the semester regardless of whether they completed their course evaluation or not. Student feedback on course content and faculty teaching skills are an important means for improving our

work. Please take the time to complete a course evaluation for each of the courses for which you are registered.

Incomplete Contracts

A grade of incomplete "I" shall be assigned at the discretion of the instructor when, due to extraordinary circumstances (e.g., documented illness or hospitalization, death in family, etc.), the student was prevented from completing the work of the course on time. The assignment of an "I" requires that a contract be initiated and completed by the student before the last official day of class, and signed by both the student and instructor. If an incomplete is deemed appropriate by the instructor, the student in consultation with the instructor, will specify the time and manner in which the student will complete course requirements. Extension for completion of the work will not exceed one year (or earlier if designated by the student's college). For more information and to initiate an incomplete contract, students should go to SPHGrades at: www.sph.umn.edu/grades.

University of Minnesota Uniform Grading and Transcript Policy - A link to the policy can be found at onestop.umn.edu.

VIII. Other Course Information and Policies

Grade Option Change (if applicable)

For full-semester courses, students may change their grade option, if applicable, through the second week of the semester. Grade option change deadlines for other terms (i.e. summer and half-semester courses) can be found at onestop.umn.edu.

Course Withdrawal

Students should refer to the Refund and Drop/Add Deadlines for the particular term at onestop.umn.edu for information and deadlines for withdrawing from a course. As a courtesy, students should notify their instructor and, if applicable, advisor of their intent to withdraw.

Students wishing to withdraw from a course after the noted final deadline for a particular term must contact the School of Public Health Office of Admissions and Student Resources at sph-ssc@umn.edu for further information.

Student Conduct Code

The University seeks an environment that promotes academic achievement and integrity, that is protective of free inquiry, and that serves the educational mission of the University. Similarly, the University seeks a community that is free from violence, threats, and intimidation; that is respectful of the rights, opportunities, and welfare of students, faculty, staff, and guests of the University; and that does not threaten the physical or mental health or safety of members of the University community.

As a student at the University you are expected adhere to Board of Regents Policy: *Student Conduct Code*. To review the Student Conduct Code, please see: http://regents.umn.edu/sites/default/files/policies/Student_Conduct_Code.pdf.

Note that the conduct code specifically addresses disruptive classroom conduct, which means "engaging in behavior that substantially or repeatedly interrupts either the instructor's ability to teach or student learning. The classroom extends to any setting where a student is engaged in work toward academic credit or satisfaction of program-based requirements or related activities."

Use of Personal Electronic Devices in the Classroom

Using personal electronic devices in the classroom setting can hinder instruction and learning, not only for the student using the device but also for other students in the class. To this end, the University establishes the right of each faculty member to determine if and how personal electronic devices are allowed to be used in the classroom. For complete information, please reference: <http://policy.umn.edu/Policies/Education/Education/STUDENTRESP.html>.

Scholastic Dishonesty

You are expected to do your own academic work and cite sources as necessary. Failing to do so is scholastic dishonesty. Scholastic dishonesty means plagiarizing; cheating on assignments or examinations; engaging in unauthorized collaboration on academic work; taking, acquiring, or using test materials without faculty permission; submitting false or incomplete records of academic achievement; acting alone or in

cooperation with another to falsify records or to obtain dishonestly grades, honors, awards, or professional endorsement; altering, forging, or misusing a University academic record; or fabricating or falsifying data, research procedures, or data analysis. (Student Conduct Code:

http://regents.umn.edu/sites/default/files/policies/Student_Conduct_Code.pdf) If it is determined that a student has cheated, he or she may be given an "F" or an "N" for the course, and may face additional sanctions from the University. For additional information, please see: <http://policy.umn.edu/Policies/Education/Education/INSTRUCTORRESP.html>.

The Office for Student Conduct and Academic Integrity has compiled a useful list of Frequently Asked Questions pertaining to scholastic dishonesty: <http://www1.umn.edu/oscai/integrity/student/index.html>. If you have additional questions, please clarify with your instructor for the course. Your instructor can respond to your specific questions regarding what would constitute scholastic dishonesty in the context of a particular class-e.g., whether collaboration on assignments is permitted, requirements and methods for citing sources, if electronic aids are permitted or prohibited during an exam.

Makeup Work for Legitimate Absences

Students will not be penalized for absence during the semester due to unavoidable or legitimate circumstances. Such circumstances include verified illness, participation in intercollegiate athletic events, subpoenas, jury duty, military service, bereavement, and religious observances. Such circumstances do not include voting in local, state, or national elections. For complete information, please see: <http://policy.umn.edu/Policies/Education/Education/MAKEUPWORK.html>.

Appropriate Student Use of Class Notes and Course Materials

Taking notes is a means of recording information but more importantly of personally absorbing and integrating the educational experience. However, broadly disseminating class notes beyond the classroom community or accepting compensation for taking and distributing classroom notes undermines instructor interests in their intellectual work product while not substantially furthering instructor and student interests in effective learning. Such actions violate shared norms and standards of the academic community. For additional information, please see: <http://policy.umn.edu/Policies/Education/Education/STUDENTRESP.html>.

Sexual Harassment

"Sexual harassment" means unwelcome sexual advances, requests for sexual favors, and/or other verbal or physical conduct of a sexual nature. Such conduct has the purpose or effect of unreasonably interfering with an individual's work or academic performance or creating an intimidating, hostile, or offensive working or academic environment in any University activity or program. Such behavior is not acceptable in the University setting. For additional information, please consult Board of Regents Policy: <http://regents.umn.edu/sites/default/files/policies/SexHarassment.pdf>

Equity, Diversity, Equal Opportunity, and Affirmative Action

The University will provide equal access to and opportunity in its programs and facilities, without regard to race, color, creed, religion, national origin, gender, age, marital status, disability, public assistance status, veteran status, sexual orientation, gender identity, or gender expression. For more information, please consult Board of Regents Policy: http://regents.umn.edu/sites/default/files/policies/Equity_Diversity_EO_AA.pdf.

Disability Accommodations

The University of Minnesota is committed to providing equitable access to learning opportunities for all students. Disability Services (DS) is the campus office that collaborates with students who have disabilities to provide and/or arrange reasonable accommodations.

If you have, or think you may have, a disability (e.g., mental health, attentional, learning, chronic health, sensory, or physical), please contact DS at 612-626-1333 to arrange a confidential discussion regarding equitable access and reasonable accommodations.

If you are registered with DS and have a current letter requesting reasonable accommodations, please contact your instructor as early in the semester as possible to discuss how the accommodations will be applied in the course.

For more information, please see the DS website, <https://diversity.umn.edu/disability/>.

Mental Health and Stress Management

As a student you may experience a range of issues that can cause barriers to learning, such as strained relationships, increased anxiety, alcohol/drug problems, feeling down, difficulty concentrating and/or lack of motivation. These mental health concerns or stressful events may lead to diminished academic performance and may reduce your ability to participate in daily activities. University of Minnesota services are available to assist you. You can learn more about the broad range of confidential mental health services available on campus via the Student Mental Health Website: <http://www.mentalhealth.umn.edu>.

Academic Freedom and Responsibility: *for courses that do not involve students in research*

Academic freedom is a cornerstone of the University. Within the scope and content of the course as defined by the instructor, it includes the freedom to discuss relevant matters in the classroom. Along with this freedom comes responsibility. Students are encouraged to develop the capacity for critical judgment and to engage in a sustained and independent search for truth. Students are free to take reasoned exception to the views offered in any course of study and to reserve judgment about matters of opinion, but they are responsible for learning the content of any course of study for which they are enrolled.*

Reports of concerns about academic freedom are taken seriously, and there are individuals and offices available for help. Contact the instructor, the Department Chair, your adviser, the associate dean of the college, or the Vice Provost for Faculty and Academic Affairs in the Office of the Provost. *[Customize with names and contact information as appropriate for the course/college/campus.]*

** Language adapted from the American Association of University Professors "Joint Statement on Rights and Freedoms of Students".*

Template update 9/2013