



PubH 6160

Principles of Toxicology II

Spring 2018

Credits:	3
Meeting Days:	Tuesdays and Thursdays
Meeting Time:	3:35 pm – 4:50 pm
Meeting Place:	Mayo 1260
Instructors:	Lisa Peterson and Irina Stepanov
Office Address:	2-126 CCRB
Office Phone:	612-626-0164
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E-mail:	peter431@umn.edu (LP); stepa011@umn.edu (IS)
Office Hours:	by appointment

I. Course Description

This second part of the Principles of Toxicology course is focused on toxicodynamics. In this course, students will learn to apply their knowledge of basic toxicokinetic principles and metabolic systems to elucidate mechanisms of toxicity induced by xenobiotic compounds. In addition, they will learn basic principles of omics-based approaches and methodologies, and how such data can be integrated to assess and predict adverse effects of chemical exposures across multiple levels of biological complexity. At the end of the course, students will give a scientific presentation on a published article of their choice (approved by instructors) that explores the mechanism of a toxicodynamic process.

Acknowledgments

The contents of PubH 6160 have been developed with the contributions of the Toxicology Advisory Board comprised of toxicology experts from Minnesota Department of Health, Environmental Protection Agency and various companies and organizations, including Cargill, Medtronic, 3M, Ecolab, Upsher-Smith, Covestro, and Proximagen. The Board members provided input on the conceptual development of the current course, and are acknowledged for their contributions.

II. Course Prerequisites

Biochemistry and PubH 6104 or permission of the instructor

III. Course Goals and Objectives

Students will: 1) learn basic principles of signaling pathways and mechanisms of cell death; 2) understand gene-environment interactions; 3) examine the application of genomics, proteomics, and metabolomics data in determining how xenobiotics disrupt normal cellular processes; 4) understand mechanisms of systemic and organ toxicity induced by xenobiotics; and 5) learn how to analyze and interpret complex data sets in toxicological research and deliver a scientific presentation.

IV. Methods of Instruction and Work Expectations

The primary method of instruction will be classroom lecture and discussions. 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.

V. Course Text and Readings

Books

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

Comprehensive Toxicology, Second Edition, Editor Charlene McQueen, 2010; available 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.

International Agency for Research on Cancer: IARC Monographs on the Evaluation of Carcinogenic Risk to Humans, available online through the IARC website.

Examples of journals for scientific presentation (online access through UMN library)

- Annual Reviews in Pharmacology and Toxicology
- Chemico-Biological Interactions
- Chemical Research in Toxicology
- Critical reviews in toxicology
- Regulatory Toxicology and Pharmacology
- Toxicology letters
- Environmental toxicology
- Food and chemical toxicology

VI. Course Outline/Weekly Schedule

Date	Topic and reading materials	Specific learning points or activities	Instructor
1/16	Lecture 1: Introduction to the course	<ul style="list-style-type: none">• Overview of toxicodynamics• Overview of the course structure and explanation of the course project (paper presentation) <p><u>Reading:</u> Chapter 3 Casarett & Doull's Toxicology.</p>	Irina Stepanov, Lisa Peterson
1/18	Lecture 2: Signaling pathways	<ul style="list-style-type: none">• Understand how signaling molecules bind to receptors• Understand how interaction of cell with its environment can influence cell morphology, behavior, division, or survival• Understand how exposure to chemicals may affect these interactions <p><u>Reading:</u> Chapter 3 Casarett & Doull's Toxicology.</p>	Carol Lange

1/23	Lecture 3: Mechanisms of cell death – apoptosis, necrosis, autophagy	<p>Compare and contrast discussion of assigned reviews</p> <ul style="list-style-type: none"> • Understand basic mechanisms of apoptosis, necrosis, and autophagy • For each cell death mechanism, understand: mediators of process; effects of environmental exposures; clinical implications <p><u>Readings:</u> 1) Comprehensive Toxicology 2nd Edition, Volume 1 Chapter 12 Cytolethality 2) Chapter 3 Casarett & Doull's Toxicology. 3) Chapter 16, Molecular and Biochemical Toxicology 4) https://www.sciencedirect.com/science/article/pii/B9780128029374000077</p>	Lisa Peterson
1/25	Lecture 4: Genomics	<ul style="list-style-type: none"> • Understand genetic variation and its impact on the toxic response • Methodologies: hybridization, molecular cloning, gene sequencing 	Colin Campbell
1/30	Lecture 5: Epigenomics	<ul style="list-style-type: none"> • Understand epigenetics and its importance in gene regulation and disease • Understand how chemical exposures and other environmental stressors affect DNA methylation • Methodologies for the analysis of DNA methylation and histone modifications <p><u>Reading:</u> Comprehensive Toxicology 2nd Edition, Volume 1 Chapter 18</p>	Lisa Peterson
2/1	Lecture 6: Transcriptomics	<ul style="list-style-type: none"> • Understand gene regulation and how chemical exposures affect gene expression • Methodologies: hybridization, PCR <p><u>Reading:</u> Comprehensive Toxicology 2nd Edition, Volume 1 Chapter 18</p>	Kevin Silverstein
2/6	Lecture 7: Paper discussion	<p>Paper on genomics, epigenetics, transcriptomics</p> <p><u>Paper for discussion:</u> http://toxsci.oxfordjournals.org/content/120/1/33.full.pdf+html http://toxsci.oxfordjournals.org/content/120/1/33/suppl/DC1</p>	Lisa Peterson
2/8	Lecture 8: Proteomics	<ul style="list-style-type: none"> • Chemical exposures and post-translational protein modifications • Analytical tools and platforms for studies of protein expression and modifications <p><u>Reading:</u> https://reader.elsevier.com/reader/sd/ED3FC33FE5C8CBB95268EB0BF3E6A7834D744B26285C188F51020D32142E7E9BE4F954C21E8A858D5B5FDCD2393BAABD Chapter 4, Molecular and Biochemical Toxicology</p>	Yue Chen
2/13	Lecture 9: Metabolomics	<ul style="list-style-type: none"> • The principles of metabolomics • Analytical tools and platforms for metabolomics studies • Selection of appropriate experimental designs 	Irina Stepanov

		<ul style="list-style-type: none"> Analysis and interpretation of metabolomics data <p>Reading: https://pdfs.semanticscholar.org/455e/1e21d2ab1dc844f73bccee5a749b28d4775a.pdf Chapter 5, Molecular and Biochemical Toxicology</p>	
2/15	Lecture 10: Systems Toxicology discussion	<ul style="list-style-type: none"> Discussion of genomics, proteomics and metabolomics data use in toxicology <p>Paper to discuss: http://pubs.acs.org/doi/pdf/10.1021/acs.chemrestox.6b00401</p>	Lisa Peterson
Deadline to provide instructor with 3 article options for the potential scientific presentation			
2/20	Lecture 11: Endocrine Disruption	<ul style="list-style-type: none"> Mechanisms and effects of endocrine disruption by environmental contaminants Complexities, knowledge gaps, and limitations in identifying the causes of endocrine disruption 	Bill Toscano
2/22	Lecture 12: Developmental Toxicology	<ul style="list-style-type: none"> Impact of environmental exposures on male and female reproductive capability. Impact of environmental exposures on in utero development and birth outcomes. <p>Reading: Chapter 10 Casarett & Doull's Toxicology. Chapter 34, Molecular and Biochemical Toxicology</p>	Bill Toscano
2/27	Lecture 13: Paper discussion	Developmental toxicology paper	Irina Stepanov
3/1	Lecture 14: Neurotoxicity	<ul style="list-style-type: none"> Mechanisms of neurotoxicity Environmental neurotoxicants Neurotoxicity assays <p>Reading: Chapter 16 Casarett & Doull's Toxicology. Chapters 30 and 31, Molecular and Biochemical Toxicology</p>	Lisa Peterson
3/6	Lecture 15: paper discussion	Neurotoxicity paper	Silvia Balbo
		<p>Paper to discuss: https://academic.oup.com/toxsci/article/88/1/193/1662975</p>	
3/8	Lecture 16 Midterm	Midterm assessment	
Deadline to select paper for the scientific presentation			
Spring break			
3/20	Lecture 17: Oxidative stress and inflammation	<ul style="list-style-type: none"> Mechanisms of oxidative stress and inflammation, and their interaction Environmental exposures and stressors contributing to oxidative stress and inflammation Biomarkers of oxidative damage, inflammation, and tools for their analyses 	Irina Stepanov
3/22	Lecture 18: Immunotoxicology – cytokine networks	<ul style="list-style-type: none"> The immune system, major functions, levels and types of immune regulation Immune pathologies and mechanisms of immunotoxicology by environmental agents Methodologies and tools for the assessment of immunotoxicological effects <p>Reading:</p>	Devarani Chatterjee

		Chapter 12 Casarett & Doull's Toxicology. Chapter 32, Molecular and Biochemical Toxicology	
3/27	Lecture 19: Paper discussion	Immunotoxicology paper	Irina Stepanov
3/29	Lecture 20: Carcinogenesis - DNA damage and mutagenesis	<ul style="list-style-type: none"> • Formation of DNA adducts and other DNA modifications by environmental agents • DNA repair mechanisms and impact of chemical exposures on DNA repair • Types and consequences of mutations • Methodologies for the analysis of DNA damage, repair, and mutagenesis <p><u>Reading:</u> Chapters 8 and 9 Casarett & Doull's Toxicology. Chapters 22-25, Molecular and Biochemical Toxicology</p>	Silvia Balbo
4/3	Lecture 21: Carcinogenesis – promotion/progression	<ul style="list-style-type: none"> • Multistage carcinogenesis model of cancer • Mechanisms of cancer promotion and progression • Environmental agents that facilitate cancer promotion and progression • In vitro and animal models 	Betsy Wattenberg
4/5	Lecture 22: Paper discussion	Carcinogenesis paper	Irina Stepanov
4/10	Lecture 23: In class workshop	Review of draft paper presentations	Lisa Peterson, Irina Stepanov
4/12	Lecture 24: Hepatotoxicity	<ul style="list-style-type: none"> • Mechanisms of hepatotoxicity • Hepatotoxic agents/metabolites • In vitro and animal models <p><u>Reading:</u> Chapter 13 Casarett & Doull's Toxicology. Chapter 28, Molecular and Biochemical Toxicology</p>	Rob Roy, Catherine Jacobson
4/17	Lecture 25: Nephrotoxicity	<ul style="list-style-type: none"> • Mechanisms of nephrotoxicity • Nephrotoxic agents/metabolites • In vitro and animal models <p><u>Reading:</u> Chapter 14 Casarett & Doull's Toxicology. Chapter 29, Molecular and Biochemical Toxicology</p>	Rob Roy, Catherine Jacobson
4/19	Lecture 26: Respiratory toxicity	<ul style="list-style-type: none"> • Mechanisms of respiratory toxicity • Respiratory irritants, inflammatory agents • In vitro and animal models <p><u>Reading:</u> Chapter 15 Casarett & Doull's Toxicology. Chapter 27, Molecular and Biochemical Toxicology</p>	Rob Roy, Catherine Jacobson
4/24	Lecture 27: Cardiovascular toxicity	<ul style="list-style-type: none"> • Mechanisms and stages of cardiovascular toxicity • Cardiovascular toxicants • In vitro and animal models <p><u>Reading:</u> Chapter 18 Casarett & Doull's Toxicology.</p>	Nicole Soucy
4/26	Lecture 28: Student presentations	Scientific presentation of the selected papers	Lisa Peterson, Irina Stepanov
5/1	Lecture 29: Toxicity testing	<ul style="list-style-type: none"> • Toxicity testing in regulatory and industry settings • Predictive capacity and limitations of in vitro and in vivo data • Novel alternative testing methods 	Kelly Coleman

5/3	Final exam	Final assessment	Lisa Peterson, Irina Stepanov
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Course project

Course project will consist of giving a 15-minute scientific presentation (plus 5 min Q&A) on a published article that explores the mechanism of a toxicodynamic process. Each student will be required to select three papers which will be evaluated by instructors so that at least one can be approved for presentation. If more than one paper is approved, the student will choose which one to present. If none of the papers is acceptable, student will have to select additional paper options for approval. At the end of the semester, students will give a scientific presentation of their selected papers as if this is their own research project. Specific guidelines and grading rubrics for presentations will be reviewed at the beginning of the course and posted on the Moodle site.

VII. Evaluation and Grading

Grading percentages will be based on points earned through the assignments and exams. A total of 400 points (100% of the total grade) can be earned as determined by the following:

- Classroom activities and evaluations (100 points, 25% of the grade)

The purpose of these activities is to involve students in active learning process and to apply the gained knowledge to the analysis of case studies.

Paper discussions (90 points). Students will read assigned research papers and prepare for class discussion, focusing on the critique of issues relevant to the specific course topic (as indicated by the instructor). Points will be awarded for active discussion in the class. A total of six papers will be discussed (15 points/paper). If a student is unable to attend the class, an opportunity will be offered to earn points by writing a summary of the assigned paper.

Lecture evaluations (10 points). Students will be required to evaluate lectures by using a provided template and upload the evaluations on Moodle site (<https://moodle.umn.edu/>). Points (0.5 point/evaluation) will be awarded for turning in the evaluation within 24 hours after the end of the class.

- Exams (200 points, 50% of the grade)

Students can earn a maximum of 100 points for each exam – midterm and final – to a total of 200 points.

- Paper presentation (100 points, 25% of the grade)

Each student will present their selected paper following guidelines provided by the instructors. Points will be awarded according to the rubric which will be provided by the instructors at the time when the paper selection is approved.

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

The University utilizes plus and minus grading on a 4.000 cumulative grade point scale in accordance with the following:

A	4.000 - Represents achievement that is outstanding relative to the level necessary to meet course requirements
A-	3.667
B+	3.333
B	3.000 - Represents achievement that is significantly above the level necessary to meet course requirements
B-	2.667
C+	2.333
C	2.000 - Represents achievement that meets the course requirements in every respect
C-	1.667
D+	1.333
D	1.000 - Represents achievement that is worthy of credit even though it fails to meet fully the course requirements

S Represents achievement that is satisfactory, which is equivalent to a C- or better.

For additional information, please refer to:

<http://policy.umn.edu/Policies/Education/Education/GRADINGTRANSCRIPTS.html>.

Course Evaluation

The SPH will collect student course evaluations electronically using a software system called CoursEval: www.sph.umn.edu/courseval. 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. The Disability Resource Center Student Services 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 DRC at 612-626-1333 or drc@umn.edu 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>.

The Office of Student Affairs at the University of Minnesota:

The Office for Student Affairs provides services, programs, and facilities that advance student success, inspire students to make life-long positive contributions to society, promote an inclusive environment, and enrich the University of Minnesota community.

Units within the Office for Student Affairs include, the Aurora Center for Advocacy & Education, Boynton Health Service, Central Career Initiatives (CCE, CDes, CFANS), Leadership Education and Development – Undergraduate Programs (LEAD-UP), the Office for Fraternity and Sorority Life, the Office for Student Conduct and Academic Integrity, the Office for Student Engagement, the Parent Program, Recreational Sports, Student and Community Relations, the Student Conflict Resolution Center, the Student Parent HELP Center, Student Unions & Activities, University Counseling & Consulting Services, and University Student Legal Service.

For more information, please see the Office of Student Affairs at <http://www.osa.umn.edu/index.html>.

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.*

OR:**Academic Freedom and Responsibility, for courses that 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 and conduct relevant research. 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.*

When conducting research, pertinent institutional approvals must be obtained and the research must be consistent with University policies.

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, (Dr Kristin Anderson, SPH Dean of Student Affairs), or the Vice Provost for Faculty and Academic Affairs in the Office of the Provost.

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

Student Academic Success Services (SASS): <http://www.sass.umn.edu>:

Students who wish to improve their academic performance may find assistance from Student Academic Support Services. While tutoring and advising are not offered, SASS provides resources such as individual consultations, workshops, and self-help materials.

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