

MAMMALIAN TOXICOLOGY

(Biology 666, 3 credit, Spring 2016; WISER class #7680)

Campbell website:

<http://kcampbell.bio.umb.edu>

SCHEDULE FOR MAMMALIAN TOXICOLOGY

Biology 666, Spring 2016, Weekly Sessions

Mondays 2:00PM - 5:00PM

Room: M01-0318

Topic; Text Readings (Casarett and Doull, *Toxicology: The Basic Science of Poisons* = C)

1. Organization, e-mail addresses, student/instructor introductions, overview of course, projects. Definition and derivation of toxicology and sister sciences endocrinology and pharmacology; definition of toxins and toxicants; Key features of toxicology and study of toxicants; Modes of exposure, elimination, bioavailability, partition; C 1-3, 5, 7 (January 25, 2016)
2. Toxicant targets; Physiologic dose-response; C 2, 21; The role of intercellular chemical communication: hormone, receptor, transducer, effector; agonist, antagonist; Interconnections of transduction mechanisms; Classical toxicological testing; C 3; End of Drop (February 1, 2016)
3. Organismal regulation, feedback circuits; C 20, 21; Cell cycle controls: current models; Bioinformatics in toxicology, new paradigms; C 3, 8; articles (February 8, 2016)
4. **President's Day (February 15, 2014)**
5. Project Discussion; Toxicogenomics, metabolomics, organ simulations; articles (February 22, 2016)
6. Cell death: necrosis, apoptosis; C 3, 13, 18, 20; Neural and immune function overview; C 3, 12, 16, 19; Introduction of regulatory issues (February 29, 2016)
7. Finalization of Project Choices; Biochemistry of toxicant metabolism, enterohepatic circulation; Toxicodynamics and toxicokinetics C 5, 6, 7, 13 (March 7, 2016)
8. **Spring Break (March 13-20, 2016)**
9. Project Drafts Due. Gamete production in mammals; Gestation in mammals; Modeling reproductive toxicants; C 9, 10, 20 (March 21, 2016)
10. Mammalian toxicity testing II: *in vivo*, *in vitro*, multi-generation, and modeling risk assessment; C 2, 8, 9, 10, 20; Molecular methods, high throughput testing; C 9, 31 (March 28, 2016)
11. Stress and dose interactions; Diet as modulator or mode of exposure; Developmental status/age and toxicity; C 10, 29, 30 (April 4, 2016)
12. Predispositions to toxic risk; Moderators of toxic risk; C 4, 9; Carcinogenesis : Are the toxicity models correct?; C 8, 9, 25 (April 11, 2016)
13. **Patriot's Day (April 18, 2016)**
14. Discussion of Draft Projects; Adequacy of models for developmental toxicity; C 10, 29; Steroid disruptors: estrogen, androgen, progestin, corticoid; C 20, 21, 29; Thyroid, retinoid and other disruptors; C 10, 20, 21 (April 25, 2016)
15. The work of FDA, EPA, NIEHS, OSHA, history & key regulations; Implications of new work; C 1, 28-33 (May 2, 2016)
16. Final Project Presentations and Copies Due. Summary Discussion (May 9, 2016)
17. Final Exam Period/ Final Exam (May 16-20, 2016; Grades posted by May 23, 2016)

Prerequisites:

General and Organic Chemistry + General Biology & at least one advanced course in Cell Biology, Biochemistry, or Physiology; or Permission of the Instructor.

Course Description:

Mammalian Toxicology (Biology 666) is a 3 credit graduate course offered to students with appropriate prerequisites in chemistry and biology.

This course provides a background in principles of toxicology as they are applied to mammalian systems. Coverage will include: basic concepts in evaluation of poisons and their commonalities with evaluations of drugs and hormones; toxicant exposure routes, uptake, sites and mechanisms of action, storage, metabolism, activation, and clearance; toxicant roles in carcinogenesis, development, endocrine, and reproductive functions; exploration of the role of diet, lifestyle, and concurrent exposures; methods of toxicant evaluation with emphasis on multigeneration and high throughput testing; and environmental and medical implications of toxicant or toxin exposures on individual and ecological health.

The course will cover basic tenets of toxicology but will also underline the similarities and commonalities of this science with those of endocrinology and pharmacology. It will emphasize the integrative nature of these disciplines and will feature the applied nature of toxicology as an investigative and regulatory science.

Course resources will include a major text but will also draw heavily on Internet resources and original papers. Case studies may be used to cover parts of the material and active discussion will be encouraged through the use of key questions and one or more writing assignments. Development of Web-based resources will be an aim in projects associated with this class.

Specific Objectives:

- 1. Learn the basic framework of testing and evaluation that forms the foundation of toxicology.**
- 2. Explore the commonalities and links between toxicology, endocrinology, and pharmacology.**
- 3. Demonstrate how toxicology integrates and synthesizes the knowledge gleaned from a spectrum of other disciplines and applies it to investigating the nature of and risks associated with exposure to toxicants and toxins.**
- 4. Investigate the problems of health and the environment encountered in mammalian systems as a result of exposure to xenobiotics.**
- 5. Apply the knowledge base to help uncover the existing gaps in knowledge of mammalian toxicology.**

Method of Evaluation:

Students will be graded on one in-class, closed book exam given as a final (25%). Participation in class, discussion, and peer critiquing of student projects will constitute 35% of the grade. A group writing project involving exploration of a topic jointly chosen with the instructor will constitute 40% of the grade. The project will be submitted as a Web-compatible document that explores a gap or questionable aspect of current toxicological practice or a topic that will not be covered fully within the context of the course, *e.g.*, appropriateness for classifying toxicants as initiators, promoters, or progressors of carcinogenesis; current knowledge of the impact of phytoestrogens on apoptosis within the rat endometrium; or the molecular relatedness of P450 enzymes involved in Type I metabolism across multiple species as ascertained using online molecular databases. This year I suggest work as a group on the following question for a mutually agreed compound:

Q: How well does the existing toxicogenomic and modeled toxicity data fit the known *in vivo* results for a GRAS compound?

1. Probable exposure/dosage?
2. Cumulative exposure/dosage?
3. Route and modes of exposure?
4. Metabolic peculiarities or commonalities to be considered?
5. Anticipated distribution and clearance?
6. Anticipated toxicant mechanisms and physiological responses?
7. Relatedness of target molecules (*e.g.*, proteins) among species and probability of similar targeting?
8. Recommendations on testing for toxicant exposure?
9. Recommendations on acute and chronic toxicity testing?
10. Legal rules and regulations governing the toxicant in the US and elsewhere?
11. Recommendations on toxicant use/non-use?

The project document can use figures, models, and tables as well as a narrative argument to make or illustrate points. It should incorporate standard references for all texts and journal articles cited as well as complete URLs for Internet or Web resources. No materials should be copied or reproduced without alteration or permission from the original author in production of this document. The penultimate version of the project should be submitted electronically one month prior to the end of the term. This will be critiqued by the instructor and at least two student peers. The final version of the project will be due at the time of the final and must be submitted electronically. The documents may be added to the course Website at the end of the term including appropriate information on their authorship. Communications with the instructor may occur in person or via e-mail.

Students are expected to take the in-class exam on the date scheduled. Should there be an unavoidable problem, the Instructor may, at his discretion, provide a makeup exam. Prior reading of assigned materials and familiarity with linked Internet sites is expected prior to any scheduled meeting times.

Readings:

Chapters in the assigned text are indicated above. These provide some background for the lectures or weekly meetings. These will be supplemented by readings in other texts, journal articles, or Web documents. Whenever possible, these will be drawn from sources that are accessible through the Internet or in every science library. In other instances, I will have a copy in my office or available in the Biology Offices.

The textbook or supplemental texts are readily available through Internet book services, many have new, used, or rental volumes for less than suggested retail prices. **Note: I have not requested these texts in the bookstore this year because of the limited number of students in the class and the usual pricing policies.**

Required Text:

Casarett & Doull's Toxicology: The Basic Science of Poisons, 7th Ed. C.D. Klaassen. McGraw-Hill Professional: New York, NY. 2007. 1280 pp. ISBN-13: 978-0071470513 (~\$80 full price new; hardcover)

Or

Casarett & Doull's Toxicology: The Basic Science of Poisons, 8th Ed. C.D. Klaassen. McGraw-Hill Professional: New York, NY. 2013. 1454 pp. ISBN-10: 0071769234 | ISBN-13: 978-0071769235 (~\$108 full price new; hardcover)

Alternatively,

Casarett & Doull's Essentials of Toxicology, Second Edition. [Curtis Klaassen](#), [John B. Watkins III](#). McGraw-Hill Professional: New York, NY. 2010. 472 pp. ISBN-10: 0071622403 | ISBN-13: 978-0071622400 (~\$58 full price new, paperback) [Note this is not quite as complete as the hardcover, but is still a good option]

Or

A Textbook of Modern Toxicology, Fourth Edition, Ernest Hodgson. 2013 ISBN-10: 047046206X | ISBN-13: 978-0470462065 (~\$91 full price new, hardback) [This is an excellent option that may be used in future offerings of this course.]

Supplemental Texts:

(Readings may be drawn from these. However, they are listed here as a source for more extended reading, not necessarily for acquisition in association with this course.)

Silent Spring. R. Carson. Fawcett Crest: New York, NY. 1970. [Many other editions are available.]

Our Stolen Future. T. Colburn, D. Dumanoski, J.P. Myers. Penguin Books: New York, NY. 1997.

The Biological Basis of Cancer, 2nd Ed. R.G. McKinnell, R. E. Parchment, A.O. Perantoni, I. Damjanov, G.B. Pierce. Cambridge University Press: New York, NY. 2006. ISBN-13: 978521606332.

Goodman and Gilman's Manual of Pharmacology and Therapeutics. L. Brunton, K. Parker, D.

Blumenthal, I. Buxton (eds), McGraw-Hill Medical: New York, NY, 2008, ISBN-13: 9780071443432.

Hormonally Active Agents in the Environment. Committee on Hormonally Active Agents in the Environment, Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council. National Academy Press: Washington, D.C. 1999.

Endocrine and Hormonal Toxicology. P.W. Harvey, K.C. Rush, A. Cockburn. John Wiley & Sons Ltd.: Chichester, UK. 1999.

Generations at Risk: Reproductive Health and the Environment. T. Schettler, G. Solomon, M. Valenti, A. Huddle. The MIT Press: Cambridge, MA. 1999.

Toxicology for the Next Millennium. R.J. Isfort, J. Lederberg. Annals of the New York Academy of Sciences, Volume 919. New York Academy of Sciences: New York, NY. 2000.

Hormonal Chaos: The Scientific and Social Origins of the Environmental Endocrine Hypothesis. S. Krimsky. Johns Hopkins University Press: Baltimore, MD. 2000.

Pills, Potions, Poisons: How Drugs Work. T. Stone, G. Darlington. Oxford University Press: Oxford, UK. 2000.

Introduction to Biochemical Toxicology, 3rd Ed. E. Hodgson, R.C. Smart. John Wiley & Sons, Inc.: New York, NY. 2001.

Molecular and Biochemical Toxicology, 4th Ed. R.C. Smart, E. Hodgson. John Wiley & Sons, Inc.: New York, NY. 2008. ISBN-13: 9780470102114.

Toxicology Secrets: Questions You Will Be Asked ... on Rounds, in the Ed, on Bedside Oral Exams. L.J. Ling, R.F. Clark, T.B. Erickson, J.H. Trestrail III. Hanley and Belfus, Inc.: Philadelphia, PA. 2001.

Toxicology and Risk Assessment: A Comprehensive Introduction. H. Greim & R. Snyder. John Wiley & Sons, Inc.: The Atrium, Southern Gate, Chichester, West Sussex, England. 2008. ISBN 978-0-470-86893-5.

Academic Regulations:

All student performance and conduct will be governed by University policies and regulations on the University Website:

https://www.umb.edu/life_on_campus/policies/community/code/purpose

These include policies on attendance, conduct in the classroom, and plagiarism. If you are not already familiar with these policies please read them so misunderstandings and problems are minimized.

Disabilities:

If you have a disability and feel you will need accommodations in order to complete course requirements, please contact the Ross Center for Disability Services (Campus Center, UL, Room 211) at (617) 287-7430 or navigate to:

<https://www.umb.edu/academics/vpass/disability/students/accommodations>