ENV H 593 A: Current Topics in Risk Assessment

Spring Quarter 2020

3 R’s – Using Systems-Based Approaches to Identify Alternatives for In Vivo Animal Experiments

Credits: 2

Instructor:

Elaine M. Faustman, PhD, DABT
Professor, Department of Environmental and Occupational Health Sciences and Director, Institute for Risk Analysis and Risk Communication (IRARC)

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Phone: 206-685-2269
E-mail: faustman@uw.edu
Office Hours: By appointment

Course Times and Locations:

Day/Time: Tuesday, 3:00 pm - 4:50 pm
Location: 4225 Roosevelt Way NE in Roosevelt 212

Course Description:

This journal club will introduce participants to the current actions within the US and around the world to reduce animal use in experiments. A systems-based approach to answering “when, where and how” will be used to frame the readings and case studies. Case studies designed to illustrate how replacement, reduction, and refinement (3R) approaches can affect basic research design, chemical discovery (new drugs and green chemistry), and facilitate translation for regulation will be explored. Lessons learned from early activities with Cosmetics and “Read Across” will be emphasized as model cases for other regulatory and industrial applications.

Spring 2020 Learning Objectives:

- Learn what the 3 R’s mean for animal-based experimental approaches
- Identify databases that inform experimental design and enhance use of in vitro systems
- Evaluate “in Silico” and QSAR methodologies
- Identify pathway specific considerations for use of invertebrate model organisms
- Identify new in vitro disease models
- Assess how alternative models can inform green chemistry
- Assess how new methodological approaches, such as organs on a chip, can incorporate systemic response to drugs or environmental chemicals
- Learn how to incorporate considerations of species extrapolation, genetic variability, and developmental timing into new approach methodologies
- Assess Human on a Chip to evaluate “fit for purpose” for clinical as well as regulatory assessments
- Learn about the regulatory statutes for using mammalian animals in research

Additional Generic Learning Objectives:

1. Think critically about risk assessment by completing reading assignments and participating in class discussions.
2. Communicate the concept of integrated risk assessment and risk communication.
3. Explain the risk assessment framework as it relates specifically to the current quarter topic.
4. Analyze assigned readings and interpret their relevance to not only the quarter topic but also their applicability and generalizability to risk assessment topics at large.
5. Summarize key points from assigned journal articles or other required readings.
6. Prepare and deliver an oral presentation(s) discussing the required reading.
7. Critique risk assessment applications as they relate to the current quarter topic.
8. Identify risk assessment strengths and challenges, as well as the role of uncertainty.
9. Develop skills to think critically about the methods and tools used for assessment, management, and communication of risk.

Course Requirements

Reminder this class is a journal club so please come to each session prepared to share your articles or sections with your colleagues. Please use the “Article Report Form Template” to structure your review. Please feel free to share a few slides that share these highlights in a manner you wish to share. We will always be able to pull up the original article but sometimes your tailored slides facilitate the discussion.

You will be requested to review two articles for each class and to complete 5 of the article report forms. If you will be missing class, please send your review by email.

You will also, by the end of the class, be requested to complete one “Research Relevancy Report Form Template”. Note that this report can cover more than one article and be more of a summary of lessons learned from the sessions. Total page limits for this assignment is 3 pages double spaced. We will discuss further in class the purpose and intent of this report.

Grading:

- **50% Weekly Discussion Participation and Related Assignments:** Weekly summations and presentation of key points from readings and respectful engagement in substantive in-class discussions.
- **25% Five Article Reports** - See the template at the end of the syllabus and limit your responses to 2 pages double spaced. Reports will be graded for completeness and thoughtfulness. Reports should be submitted on Canvas each week before class starts. Please post the article you selected on the Canvas Discussions Page. You will need to submit five Article Reports throughout the quarter.
- **25% In-Class Presentation and Report** - Presentation or demonstration of the applications to your own research or interest area. Please use the Research Relevancy Report Template at the end of this syllabus and limit your response to 3 pages double spaced. You will be required to submit ONE research relevancy report on Canvas for the quarter. In addition to the report, please prepare a brief presentation (about 10 minutes) with 2-3 figures/tables to support your observations.

Academic Integrity Statement:

Students at the University of Washington (UW) are expected to maintain the highest standards of academic conduct, professional honesty, and personal integrity.

The UW School of Public Health (SPH) is committed to upholding standards of academic integrity consistent with the academic and professional communities of which it is a part. Plagiarism, cheating, and other misconduct are serious violations of the University of Washington Student Conduct Code (WAC 478-120). We expect you to know and follow the university's policies on cheating and plagiarism, and the SPH Academic Integrity Policy. Any suspected cases of academic misconduct will be handled according to University of Washington regulations. For more information, see the University of Washington Community Standards and Student Conduct website.

Access and Accommodations:

Your experience in this class is important to me. If you have already established accommodations with Disability Resources for Students (DRS), please communicate your approved accommodations to me at your earliest convenience so we can discuss your needs in this course. If you have not yet established services through DRS, but have a temporary health condition or permanent disability that requires accommodations (conditions include but not limited to: mental health, attention-related, learning, vision, hearing, physical or health impacts), you are welcome to contact DRS at 206-543-8924 or uwdrs@uw.edu, or disability.uw.edu. DRS offers resources and coordinates reasonable accommodations for students with disabilities and/or temporary health conditions. Reasonable accommodations are established through an interactive process between you, your instructor(s) and DRS. It is the policy and practice of the University of Washington to create inclusive and accessible learning environments consistent with federal and state law.

Multi-cultural Inclusion Commitment from Environmental Health:

The UW School of Public Health seeks to ensure all students are fully included in each course. We strive to create an environment that reflects community and mutual caring. We encourage students with concerns about classroom climate to talk to your instructor, your advisor, a member of the departmental or SPH Diversity Committee and/or the program director. DCInfo@uw.edu is a resource for students with classroom climate concerns.
We have the privilege of learning together and we have a responsibility to engage in dialogue in a way that supports learning for all of us. Many of the issues we will discuss in this course may concern issues of disproportionate risks, sensitivities, and impacts due to age, gender, race, and/or social inequalities. This is what public health hopes to address, however we know that these can be difficult topics to address, hence we thus feel it is even more important to be sensitive to our colleagues’ experiences and ideas. Here are some practices we as learning community members can strive to use in our learning process:

- My own viewpoint is important—share it. It will enrich others.
- My students’ and colleagues’ viewpoints are important—listen to them. Do not judge them.
- Extend the same listening respect to others I would wish them to extend to me. We all have room to grow to become better listeners in non-judgmental ways.
- Recognize that I might miss things others see and see things others might miss.
- Raise my views in such a way that I encourage others to raise theirs.
- Inquire into others’ views while inviting them to inquire into mine.
- Ask questions when I don’t understand something.
- Surface my feelings in such a way that we make it easier for others to surface theirs.
- Test my assumptions about how and why people say or do things.
- Challenge what was said or done, rather than make assumptions about the individual.
- Beware of either-or thinking.
- Be willing to take risks in moving outside my comfort zones.
- Affirm others

**Article Report Form Template:**

*PLEASE LIMIT RESPONSES TO 2 PAGES DOUBLE SPACED*

Date:

Reviewer Name:

Title, Author, and Date of Paper:

- What was the purpose of this paper?
- What methods did the author use?
- What were the key results?
- What key issues does the author(s) cite in the discussion?
- How does this article contribute to today’s discussion topic?

**Research Relevancy Report Form Template:**

*PLEASE LIMIT RESPONSES TO 3 PAGES DOUBLE SPACED*

Date:

Reviewer Name:

Title, Authors, and Date of Paper:

- What was the purpose of this paper?
- What were the key results?
- Describe the most surprising findings from this quarter.
- How can you relate your research expertise to addressing these findings?
- Identify critical data gaps.

**Course Schedule:**

<table>
<thead>
<tr>
<th>Session #</th>
<th>Date</th>
<th>Topic</th>
<th>Readings</th>
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<tr>
<td></td>
<td>03/31/20</td>
<td>Orientation to the course</td>
<td>No Required</td>
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<tr>
<td>Session 1</td>
<td>03/31/20</td>
<td>History of 3Rs (Replacement, Reduction, and Refinement): Providing context for our current actions and state of science</td>
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Regulatory Context for National and International Efforts on 3Rs

Session 2  04/07/20

Conduct Guidelines Available for In Vitro and Alternative Tests

Artificial Intelligence, In Silico, and Quantitative Structure-Activity Relationship (QSAR)

Session 3  04/14/20

Modelling: Httk, In Vivo to In Vitro Extrapolation (IVIVE)

Extrapolation Across Species and Disease Using Structured Ontologies

Session 4  04/21/20 Single Cell Transcriptomics

Epigenetic Signals (ENCODE Databases)

Stem Cells

Mutagenesis and Carcinogenesis Assays

Session 5  04/28/20 Yeast, C.elegans, and Drosophila Models

Ecotoxicity and Fish Models

Session 6  05/05/20 One Health Concepts in 3Rs

AOP Applications

Session 7  05/12/20 Organ Specific Models (Liver, Kidney, Lung, Reproductive, Brain, Skin)

Human on a chip

Session 8  05/19/20

Microphysiological Models

Session 9  05/26/20 Example Applications to Research

Session 10  06/02/20 Example Applications to Research

Topics and References

Session 1: Orientation and History of 3Rs
No Readings Required


Session 2: Regulatory Context, Conduct Guidelines


Session 3: Artificial Intelligence, In Silico, httk, IVIVE, QSAR

7. Cherkasov Artem et al. Qsar Modeling: Where have you been? Where are you going to? https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4074254/
15. US EPA. ComTox Website. https://comptox.epa.gov/dashboard
17. **ADD IVIVE REFS**

Session 4: Ontologies, Single Cell Transcriptomics, Epigenetic Signals (ENCODe Databases), Stem Cells

3. **ADD SINGLE CELL TRANSCRIPTOMIC REFS**
4. **ADD EPIGENETIC SIGNAL REFS**
5. O’Connor Michael. The 3R principle: advancing clinical application of human pluripotent stem cells (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3706962/)
Session 5: Mutagenesis, Carcinogenesis, Yeast, C. Elegans, Drosophila

1. Fernandes Kimberly. Using Genetic Mouse Models to Gain Insight into Glaucoma: Past Results and Future Possibilities (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4628899/)
2. Bae Harold et al. Bayesian Polynomial Regression Models to Fit Multiple Genetic Models for Quantitative Traits (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4446790/)
4. Brouwer Andrew. A systematic approach to determining the identifiability of multistage carcinogenesis models (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5472511/)
5. Moolgavkar SH. Cell proliferation and carcinogenesis models: general principles with illustrations from the rodent liver system. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1519428/)
8. Taskova K et al. Literature optimized integration of gene expression for organ-specific evaluation of toxicogenomics datasets. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6331104/)
17. Buy Mutant C Elegans. (https://invivobiosystems.com/transgenics/c-elegans-services/?utm_medium=ppc&utm_source=adwords&utm_term=%2BElegans%20%2BBuy&utm_campaign=&hsa_src=g&hsa_kw=%2BElegans%20%2BBuy 812954995904&hsa_net=adwords&hsa_ver=3&gclid=CjwKCAjwguzzBRBiEiwAgU0FT77IXhDZAqMy6Zt_mDzOpr-IM24ZloAAvzxnI49zUnnHwd3TfbU2BoCnx4QAvD_BwE) (https://invivobiosystems.com/transgenics/c-elegans-services/?utm_medium=ppc&utm_source=adwords&utm_term=%2BElegans%20%2BBuy&utm_campaign=&hsa_src=g&hsa_kw=%2BElegans%20%2BBuy 812954995904&hsa_net=adwords&hsa_ver=3&gclid=CjwKCAjwguzzBRBiEiwAgU0FT77IXhDZAqMy6Zt_mDzOpr-IM24ZloAAvzxnI49zUnnHwd3TfbU2BoCnx4QAvD_BwE)
18. (https://invivobiosystems.com/transgenics/c-elegans-services/?utm_medium=ppc&utm_source=adwords&utm_term=%2BElegans%20%2BBuy&utm_campaign=&hsa_src=g&hsa_kw=%2BElegans%20%2BBuy 812954995904&hsa_net=adwords&hsa_ver=3&gclid=CjwKCAjwguzzBRBiEiwAgU0FT77IXhDZAqMy6Zt_mDzOpr-IM24ZloAAvzxnI49zUnnHwd3TfbU2BoCnx4QAvD_BwE) Koon Alex et al. Drosophila melanogaster As a Model Organism to Study RNA Toxicity of Repeat Expansion-Associated Neurodegenerative and Neuromuscular Diseases (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5359753/)
19. Wang Lihui et al. Drosophila as a model to study the role of blood cells in inflammation, innate immunity and cancer  

Session 6: Ecotoxicity, Fish, One Health, AOP

2. Handy, Richard et al. Practical considerations for conducting ecotoxicity test methods with manufactured nanomaterials: what have we learnt so far?  
4. Chakraborty Chiranjib et al. Zebrasfish: A complete animal model to enumerate the nanoparticle toxicity  
6. Leme, Daniela. UFPR Laboratory of In Vitro Ecotoxicology. 
10. Fernandez I et al. Fish as a model to assess chemical toxicity in bone. 
11. Ortiz-Santaliestra ME et al. Validity of fish, birds and mammals as surrogates for amphibians and reptiles in pesticide toxicity assessment. 

Session 7: Organ Specific Models (Liver, Kidney, Lung, Reproductive, Brain, Skin)

1. Godoy, Patricio et al. Recent advances in 2D and 3D in vitro systems using primary hepatocytes, alternative hepatocyte sources and non-parenchymal liver cells and their use in investigating mechanisms of hepatotoxicity, cell signaling and ADME  
2. Bajaj Piyush et al. Emerging Kidney Models to Investigate Metabolism, Transport, and Toxicity of Drugs and Xenobiotics  
4. Kim, Yong et al. Comparative lung toxicity of engineered nanomaterials utilizing in vitro, ex vivo and in vivo approaches  

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC555947/
5. The presence of macrophages and inflammatory responses in an in vitro testicular co-culture model of male reproductive development enhance relevance to in vivo conditions.  


7. Wu, Qi et al. Organ-on-a-chip: recent breakthroughs and future prospects  
   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7017614/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7017614/)


10. Nicholas TP et al. The Effects of Gene × Environment Interactions on Silver Nanoparticle Toxicity in the Respiratory System.  


    [http://dmd.aspetjournals.org/content/46/11/1692](http://dmd.aspetjournals.org/content/46/11/1692)


Session 8: Human-on-a-chip, Microphysiological Models

1. Abaci Hasan et al. Human-on-a-chip design strategies and principles for physiologically based pharmacokinetics/pharmacodynamics modeling.  

   [https://link.springer.com/article/10.1007/s12015-017-9738-0](https://link.springer.com/article/10.1007/s12015-017-9738-0)

   [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4156579/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4156579/)


Session 9: Example Applications to Research

Session 10: Example Applications to Research

Course Summary:

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<th>Date</th>
<th>Details</th>
<th>Time</th>
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<td>Tue Mar 31, 2020</td>
<td>ENV H 593 A Sp 20: Current Topics In Risk Assessment (<a href="https://canvas.uw.edu/calendar?event_id=1425030&amp;include_contexts=course_1372468">https://canvas.uw.edu/calendar?event_id=1425030&amp;include_contexts=course_1372468</a>)</td>
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