

**ENV H 593 A: Current Topics in Risk Assessment**  
**Winter Quarter 2020: Biomarkers for Risk Assessment**  
**Credits: 2**

**Instructors:**

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**Course Times and Locations:**

Day/Time: Tuesday, 1:30 pm - 3:20 pm

Location: 4225 Roosevelt Way NE in Roosevelt 2228

**Course Description:**

This journal club is designed to present a risk based introduction to state-of-the-art biomarkers and their use and abuse in public health, personalized medicine, as well as environmental and occupational assessment. The course will provide fundamentals of designing biomarkers including classical characterization using sensitivity and specificity and then quickly move to a series of biomarkers that will illustrate issues of design, application (including issues of timing, multiple assessments and targeted and untargeted approaches), multiple complex responses across omics (e.g. transcriptomics, metagenomics and metabolomics), and complex health endpoints (stress and epigenetics). Interesting recent abuses with Olympic athletes and race horses will provide interesting current controversies in biomarker applications and identify needs for future uses. Developing appropriate biomarkers for emerging drugs of abuse will be the final discussion topic for this course. Based on student interest we will have case studies designed to assist students in their own research to be informed by biomarkers.

**Winter 2020 Learning Objectives:**

- Identify biomarkers used in four disciplines of health (environmental, occupational, clinical, and pharmacology)
- Learn fundamentals of designing biomarkers
- Discuss and evaluate applications of biomarkers for complex mixtures and endpoints
- Learn how to characterize sensitivity and specificity of biomarkers

## ENV H 593 Syllabus, Winter Quarter 2020

- Assess state-of-the-art biomarkers for *omic* responses
- Identify how biomarkers are used in risk assessment and management

### 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 (i.e. slides) of key points from your readings and reports. Respectful engagement is an important component of this class.
- **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 each week before class starts. You will need to submit five Article Reports throughout the quarter.
- **25% Research Relevancy Report and Presentation** - 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

## ENV H 593 Syllabus, Winter Quarter 2020

research relevancy report for the quarter. In addition to the report, please prepare a brief presentation (i.e. slides) (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](mailto:uwdrs@uw.edu) or [disability.uw.edu](http://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](mailto: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.

## ENV H 593 Syllabus, Winter Quarter 2020

- 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

## ENV H 593 Syllabus, Winter Quarter 2020

### Draft Course Schedule *(Subject to student interest and involvement)*

<u>Session #</u>	<u>Date</u>	<u>Topic</u>	<u>Readings</u>
Session 1	01/07/20	Introduction and Definition of Biomarkers and Biological Exposure Indices (BEIs)	No Required Readings
Session 2	01/14/20	Occupational and Environmental Biomarkers	Pesticides Industrial agents (e.g. acrylamide)
Session 3	01/21/20	Types of Biomarkers	Protein and DNA adducts
Session 4	01/28/20	Dried Blood Spots and Other Tissue Biomarkers (e.g. buccal cells, urine)	
Session 5	02/04/20	Temporal Considerations in Biomarkers: Cases in Metals and Solvents	
Session 6	02/11/20	Cortisol (hair), Stress Biomarkers, and Markers of Social Economic Status (SES)	
Session 7	02/18/20	Risk Assessment Tools for Biomarkers	BAP example
Session 8	02/25/20	Targeted and Untargeted Metabolomics	
Session 9	03/03/20	Toxic Algae	
Session 10	03/10/20	Presentation of Research Relevancy and Summary	

**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.

## Topics and References

### ***DNA adducts, Protein adducts (types in blood and serum)***

#### Protein Adducts:

- Marsillach J, Hsieh EJ, Richter RJ, MacCoss MJ, Furlong CE. Proteomic analysis of adducted butyrylcholinesterase for biomonitoring organophosphorus exposures. *Chem Biol Interact.* 2013 Mar 25;203(1):85-90. PMID: 23123252; PMCID: PMC4108156.
- Marsillach J, Richter RJ, Kim JH, Stevens RC, MacCoss MJ, Tomazela D, Suzuki SM, Schopfer LM, Lockridge O, Furlong CE. Biomarkers of organophosphorus (OP) exposures in humans. *Neurotoxicology.* 2011 Oct;32(5):656-60. PMID: 21767566; PMCID: PMC3279568.
- Costa LG, Deng H, Gregotti C, Manzo L, Faustman EM, Bergmark E, Calleman CJ. Comparative studies on the neuro- and reproductive toxicity of acrylamide and its epoxide metabolite glycidamide in the rat. *Neurotoxicology.* 1992 Spring;13(1):219-24. PMID: 1508423.
- Preston GW, Dagnino S, Ponzi E, Sozeri O, van Veldhoven K, Barratt B, Liu S, Grigoryan H, Lu SS, Rappaport SM, Chung KF, Cullinan P, Sinharay R, Kelly FJ, Chadeau-Hyam M, Vineis P, Phillips DH. Relationships between airborne pollutants, serum albumin adducts and short-term health outcomes in an experimental crossover study. *Chemosphere.* 2020 Jan;239:124667. PMID: 31499299.
- Lu SS, Grigoryan H, Edmands WM, Hu W, Iavarone AT, Hubbard A, Rothman N, Vermeulen R, Lan Q, Rappaport SM. Profiling the Serum Albumin Cys34 Adductome of Solid Fuel Users in Xuanwei and Fuyuan, China. *Environ Sci Technol.* 2017 Jan 3;51(1):46-57 PMID: 27936627; PMCID: PMC5567851.
- Riutta A. Occupational Determinants of Chlorpyrifos Adducts to Plasma Cholinesterase in Chlorpyrifos Exposed Agricultural Workers in Washington State. 2012 MS Thesis, University of Washington.
- Carlsson H, Rappaport SM, Törnqvist M. Protein Adductomics: Methodologies for Untargeted Screening of Adducts to Serum Albumin and Hemoglobin in Human Blood Samples. *High Throughput.* 2019;8(1). PMID: 30857166; PMCID: PMC6473736

#### DNA Adducts:

- Ewa B, Danuta MŠ. Polycyclic aromatic hydrocarbons and PAH-related DNA adducts. *J Appl Genet.* 2017 Aug;58(3):321-330. PMID: 27943120; PMCID: PMC5509823.
- Pampanin DM, Brooks SJ, Grøsvik BE, Le Goff J, Meier S, Sydnnes MO. DNA adducts in marine fish as biological marker of genotoxicity in environmental monitoring: The way forward. *Mar Environ Res.* 2017 Apr;125:49-62. PMID: 28167386. (Review)
- Segerbäck D, Calleman CJ, Schroeder JL, Costa LG, Faustman EM. Formation of N-7-(2-carbamoyl-2-hydroxyethyl)guanine in DNA of the mouse and the rat following intraperitoneal administration of [<sup>14</sup>C]acrylamide. *Carcinogenesis.* 1995 May;16(5):1161-5. PMID: 7767980.

### ***Dried Blood Spots***

- Yano Y, Schiffman C, Grigoryan H, Hayes J, Edmands W, Petrick L, Whitehead T, Metayer C, Dudoit S, Rappaport S. Untargeted adductomics of newborn dried blood spots identifies

## ENV H 593 Syllabus, Winter Quarter 2020

- modifications to human serum albumin associated with childhood leukemia. *Leuk Res.* 2019 Nov 6;88:106268. PMID: 31760269.
- Yano Y, Grigoryan H, Schiffman C, Edmands W, Petrick L, Hall K, Whitehead T, Metayer C, Dudoit S, Rappaport S. Untargeted adductomics of Cys34 modifications to human serum albumin in newborn dried blood spots. *Anal Bioanal Chem.* 2019 Apr;411(11):2351-2362. PMID: 30783713; PMCID: PMC6461474.
  - Petrick L, Edmands W, Schiffman C, Grigoryan H, Perttula K, Yano Y, Dudoit S, Whitehead T, Metayer C, Rappaport S. An untargeted metabolomics method for archived newborn dried blood spots in epidemiologic studies. *Metabolomics.* 2017 Mar;13(3). pii: 27. PMID: 29706849; PMCID: PMC5918689.
  - Funk WE, Waidyanatha S, Chaing SH, Rappaport SM. Hemoglobin adducts of benzene oxide in neonatal and adult dried blood spots. *Cancer Epidemiol Biomarkers Prev.* 2008 Aug;17(8):1896-901. PMID: 18708378; PMCID: PMC2821034.
  - Barr DB, Kannan K, Cui Y, Merrill L, Petrick LM, Meeker JD, Fennell TR, Faustman EM. The use of dried blood spots for characterizing children's exposure to organic environmental chemicals. Submitted to *Environmental Research*.

### ***Buccal cell collection/epithelial cells?***

REFERENCES TO BE ADDED

### ***Cortisol (hair), stress biomarkers, and markers of social economic status (SES)***

- Sternthall MJ, Ciull BA, Chiu YH, Cohen S, Wright RJ. Associations among maternal childhood socioeconomic status, cord blood IgE levels, and repeated wheeze in urban children. *J Allergy Clin Immunol* 2011; 128: 337–345.

### ***Temporal considerations in biomarkers: cases in metals and solvents -in hair, nails, and teeth***

- Luderer U<sup>++</sup>, Bushley A, Stover BD, Bremner WJ, Faustman EM, Takaro TK, Checkoway H and Brodtkin CA. *Effects of occupational solvent exposure on reproductive hormone concentrations and fecundability in men.* *American Journal of Industrial Medicine.* 2004; 46(6): 614-626.
- Ponce RA<sup>++</sup>, Bartell SM<sup>+</sup>, Kavanagh TJ, Woods JS, Griffith WC, Lee RC, Takaro TK and Faustman EM<sup>+++</sup>. Uncertainty analysis methods for comparing predictive models and biomarkers: A case study of dietary methyl mercury exposure. *Regulatory Toxicology and Pharmacology.* 1998; 28(2): 96-105.
- Bartell S<sup>+</sup>, Ponce R<sup>++</sup>, Takaro T, Zerbe R, Omenn G and Faustman E<sup>+++</sup>. Risk estimation and value-of-information analysis for three proposed genetic screening programs for chronic beryllium disease prevention. *Risk Analysis.* 2000; 20(1): 87-99.
- Bartell S<sup>+</sup>, Takaro T, Ponce R<sup>++</sup>, Hill J<sup>+</sup>, Faustman E and Omenn G. Risk assessment and screening strategies for beryllium exposure. *Technology.* 2000; 7: 241-9.
- Bartell SM<sup>+</sup>, Ponce RA<sup>++</sup>, Sanga RN<sup>+</sup> and Faustman EM<sup>+++</sup>. Human variability in mercury toxicokinetics and steady state biomarker ratios. *Environ Res.* 2000; 84(2): 127-32.



## ENV H 593 Syllabus, Winter Quarter 2020

- Sanga R+, Bartell S+, Ponce R++, Boischio A, Joiris C, Pierce C and Faustman E+++. Effects of uncertainties on exposure estimates to methylmercury: a Monte Carlo analysis of exposure biomarkers versus dietary recall estimation. *Risk Analysis*. 2001; 21(5): 859-68.
- Bartell SM+, Griffith WC and Faustman EM+++. Temporal error in biomarker-based mean exposure estimates for individuals. *Journal of Exposure Analysis and Environmental Epidemiology*. 2004; 14(2): 173-179.
- Funk WE, McGee JK, Olshan AF, Ghio AJ. Quantification of arsenic, lead, mercury and cadmium in newborn dried blood spots. *Biomarkers*. 2013;18(2):174-7. PMID: 23311290; PMCID: PMC3687773.
- Baker MG, Stover B, Simpson CD, Sheppard L, Seixas NS. Using exposure windows to explore an elusive biomarker: blood manganese. *Int Arch Occup Environ Health*. 2016;89(4):679-87. PMID: 26589320; PMCID: PMC4829443.
- Reiss B, Simpson CD, Baker MG, Stover B, Sheppard L, Seixas NS. Hair Manganese as an Exposure Biomarker among Welders. *Ann Occup Hyg*. 2016;60(2):139-49. PMID: 26409267; PMCID: PMC4834832.

### ***Targeted and untargeted metabolomics***

- Baker MG, Simpson CD, Lin YS, Shireman LM, Seixas N. The Use of Metabolomics to Identify Biological Signatures of Manganese Exposure. *Ann Work Expo Health*. 2017;61(4):406-415. PMID: 28355443; PMCID: PMC6075188.
- Wang M, Rang O, Liu F, Xia W, Li Y, Zhang Y, Lu S, Xu S. A systematic review of metabolomics biomarkers for Bisphenol A exposure. *Metabolomics*. 2018;14(4):45. PMID: 30830327.

### ***BELs (benchmark techniques for quantifying in a regulatory setting)***

REFERENCES TO BE ADDED

### ***Toxic algae***

- Lefebvre KA, Yakes BJ, Frame E, Kendrick P, Shum S, Isoherranen N, Ferriss BE, Robertson A, Hendrix A, Marcinek DJ, Grattan L. Discovery of a Potential Human Serum Biomarker for Chronic Seafood Toxin Exposure Using an SPR Biosensor. *Toxins (Basel)*. 2019 May 23;11(5). pii: E293. PMID: 31126088; PMCID: PMC6563296.
- Lefebvre KA, Frame ER, Gulland F, Hansen JD, Kendrick PS, Beyer RP, Bammler TK, Farin FM, Hiolski EM, Smith DR, Marcinek DJ. A novel antibody-based biomarker for chronic algal toxin exposure and sub-acute neurotoxicity. *PLoS One*. 2012;7(5):e36213. PMID: 22567140; PMCID: PMC3342169.
- Cao R, Wang D, Wei Q, Wang Q, Yang D, Liu H, Dong Z, Zhang X, Zhang Q, Zhao J. Integrative Biomarker Assessment of the Influence of Saxitoxin on Marine Bivalves: A Comparative Study of the Two Bivalve Species Oysters, *Crassostrea gigas*, and Scallops, *Chlamys farreri*. *Front Physiol*. 2018;9:1173. PMID: 30246779; PMCID: PMC6110902.

### ***UELs (cells out of urine?) –interest in microRNAs – whether they are predictive or not***

- Weldon BA, Shubin SP, Smith MN, Workman T, Artemenko A, Griffith WC, Thompson B,

## ENV H 593 Syllabus, Winter Quarter 2020

Faustman EM. *Urinary microRNAs as potential biomarkers of pesticide exposure*. Toxicol Appl Pharmacol. 2016 Jan 27. 2016 Dec 1;312:19-25.

### ***Epigenetics***

REFERENCES TO BE ADDED

### ***Proteins relevant in aging or biomarkers for disease***

- Lehallier B, Gate D, Schaum N, Nanasi T, Lee SE, Yousef H, Moran Losada P, Berdnik D, Keller A, Verghese J, Sathyan S, Franceschi C, Milman S, Barzilai N, Wyss-Coray T. Undulating changes in human plasma proteome profiles across the lifespan. Nat Med. 2019 Dec;25(12):1843-1850. PMID: 31806903.
- Fonseca FL, da Costa Aguiar Alves B, Azzalis LA, Belardo TM. Matrix Metalloproteases as Biomarkers of Disease. Methods Mol Biol. 2017;1579:299-311. PMID: 28299745.