Melissa M. Heintz, Ph.D.

ASSOCIATE DIRECTOR, HEALTH SCIENCES
SUPERVISING SCIENTIST

CONTACT INFORMATION

ToxStrategies LLC
31 College Place, Suite B118
Asheville, NC 28801
Phone (828) 393-0389 x8007
mheintz@toxstrategies.com

PROFESSIONAL PROFILE

Dr. Melissa Heintz is a toxicologist in ToxStrategies' Asheville, North Carolina, office. She received her Ph.D. in Environmental Toxicology from Clemson University, where her dissertation research investigated the potential for environmental toxicant inhibition of the detoxification enzyme subfamily, CYP2B, and the subsequent effects on lipid metabolism, allocation, and development of fatty liver disease. Dr. Heintz has experience conducting safety and exposure assessments for various environmental contaminants, especially per- and polyfluoroalkyl substances (PFAS), using methods that include both *in vitro* and *in vivo* experimental models, prediction models, systematic literature review and meta-analysis, and whole transcriptome analyses. She has designed and carried out several *in vitro* and *in vivo* studies that utilize 'omic applications to answer either screening-level or specific mechanistic toxicity questions.

Dr. Heintz has experience in both collecting and reviewing mechanistic data to evaluate human health and ecological hazards from exposure to toxic substances. As a mechanistic toxicologist, Dr. Heintz has examined the effects of environmental toxicant exposure on lipid metabolism and gene expression in *Daphnia magna*. In addition, she used neuron and fibroblast cell lines from patients with autism spectrum disorder (ASD) to study differential gene expression and genomic variants in response to toxic stressors. She has also screened and analyzed numerous clinical drugs, industrial chemicals, and endogenous compounds for induction or inhibition activity in cytochrome p540-transfected baculosomes and HepG2 cell lines using metabolic activity assays. Furthermore, she has used statistical analysis programs, including R and GraphPad Prism, to analyze and create data visualizations of these toxicological data sets.

She has conducted several systematic reviews of the scientific literature to investigate the evidence available on the potential hazards and toxicity of various substances present in foods and consumer products, as well as the environment. Her role in conducting systematic reviews includes initial scoping and problem formulation, development of search strategy, literature screening and full-text review using literature review tools (e.g., SWIFT, DistillerSR), analyzing the reliability and strength of evidence, and reporting findings. She has applied systematic review approaches to the benefit/risk analysis of food ingredients and contaminants, GRAS dossier submissions, and development of adverse outcome pathways (AOPs).

In addition to her expertise in mechanistic toxicology, Dr. Heintz has also conducted ecotoxicology studies on estuarine fish populations to assess transgenerational effects of endocrine-disrupting compounds from anthropogenic sources such as paper mill and wastewater effluents and livestock feedlot runoff. Estrogenic and androgenic chemicals were used singly and in mixtures to identify exposure effects on reproductive success, sex characteristics, and behavioral endpoints in freshwater and estuarine fish models.

Dr. Heintz has presented her research at national and international scientific meetings and reported her results in peer-reviewed scientific journals. She also has more than 10 years of experience in science communication and has disseminated scientific research findings to students at all education levels, including K-12 and college students, as well as the general public.

EDUCATION AND DEGREES EARNED

2020 Ph.D., Environmental Toxicology, Clemson University, Clemson, SC

2013 M.S., Marine Biology, University of North Carolina, Wilmington, NC

2011 B.S., Biology (marine biology concentration), Saint Francis University, Loretto, PA

PROFESSIONAL ASSOCIATIONS

2017–present Society of Toxicology

- Computational Toxicology Specialty Section
- Risk Assessment Specialty Section
- Women in Toxicology Specialty Section
- Southeastern Regional Chapter (2016–2019)

2021–present Society of Environmental Toxicology and Chemistry

- OMIC Special Interest Group
- Endocrine Disrupter Testing and Risk Assessment
- Carolinas Regional Chapter (2011–2013, 2018–2020)

2021-present The Toxicology Forum

2021-present ICCF Expert Working Group member for the Environmental Safety Assessment of Animal Feed Ingredients

PROFESSIONAL ACTIVITIES, SERVICE, HONORS, AND AWARDS

2022 Toxicology Forum 2023 Program Planning Committee Member

2022 SETAC 2022 Scientific Program Committee Member

2022 Women in Toxicology Awards Committee Volunteer

2020 Student Ambassador for PRIMO20 conference, Charleston, SC

2020 Clemson Biological Sciences Commitment to Service Award

2020 Department of Biological Sciences Engagement Award

2020	Society of Toxicology Graduate Student Travel Award
2020	Clemson Graduate Travel Grant (spring)
2019	Organizing committee member for Clemson Biological Sciences Annual Student Symposium
2019	Clemson Graduate Travel Grant (summer)
2019	Clemson Biological Sciences Commitment to Service Award
2018–2021	Save Our Saluda (nonprofit to protect and restore the Upper Saluda Watershed): Board member and secretary
2018	American College of Toxicology North American Travel Grant
2018	Clemson Graduate Travel Grant (spring and fall)
2017	NIH grant to fund participation in Mount Desert Island Biological Laboratory's Environmental Genomics course
2013	UNCW Making a Difference in North Carolina Award

PROFESSIONAL EXPERIENCE

Mechanistic Toxicology

Conduct whole transcriptome analyses and data visualization of sample data from *in vitro* and *in vivo* studies using an established bioinformatic workflow including quality control assessment of samples, data normalization, identification of differentially expressed genes using DESeq, gene set enrichment analyses, Ingenuity Pathway Analysis (IPA), and benchmark dose analysis using BMDExpress.

Interpreted large sets of *in vitro* high-throughput screening (HTS) assay data available through the ToxCast/Tox21 screening programs in support of safety and hazard assessments.

Examined the role of human and murine CYP2B in diet-induced obesity *in vivo* using two novel mouse models—a Cyp2b9/10/13-null mouse model, created using sgRNA and CRISPR/Cas9 systems, and a humanized-CYP2B6-transgenic (TG) mouse model using CYP2B6-TG mice (previously generated) bred with Cyp2b9/10/13-null mice. Utilized various 'omic applications to identify potential mechanistic role of CYP2B in development of obesity and metabolic disease, including RNA-sequencing and RT-qPCR, as well as targeted and non-targeted LC-MS/MS lipidomics.

Used humanized-CYP2B6-TG and Cyp2b-null mouse models to investigate sensitivity to development of non-alcoholic fatty liver disease (NAFLD) following exposure to perfluorooctane sulfonate (PFOS) via oral gavage.

Examined effects of exposure to the environmental toxicants atrazine and triclosan on development, and studied sphingomyelin metabolism in *Daphnia magna*. In addition, determined the putative role of nuclear receptor HR96 by assessing changes in gene expression using RNA sequencing.

Neuron and fibroblast cell lines from patients with autism spectrum disorder (ASD) were used to study deficiencies in mitochondrial responses to toxic stressors. Differential gene expression and genomic variants (i.e., SNPs and INDELs) were identified within these cell lines to determine a potential mechanism for increased oxidative stress.

Screened and analyzed numerous clinical drugs (e.g., bupropion, artemisinin, statins), agricultural chemicals (e.g., atrazine, chlorpyrifos, endosulfan, parathion), industrial chemicals (e.g., bisphenol A, jet fuel, nonylphenol, ticlopidine, triclosan), and endogenous compounds (e.g., estradiol, testosterone, lithocholic acid, DHA, linoleic acid) for their ability to induce or inhibit crucial detoxification enzymes (i.e., CYP3A, CYP2B) in cytochrome p450-transfected baculosome enzymatic activity assays.

HepG2 and CYP2B6-HepG2 cell lines were used in metabolic activity assays (e.g., MTS, MTT) and lipid accumulation assays (Nile Red) to investigate effects of exposure to various n-6 and n-3 polyunsaturated fatty acids (PUFAs) and their oxylipin metabolites, as well as environmental toxicants (e.g., nonylphenol, ticlopidine, chlorpyrifos).

Systematic Review

Conducted several systematic reviews for toxicants with large literature data sets, investigating a variety of endpoints and outcomes of interest. Responsible for initial scoping and problem formulation, development of search syntax, literature screening and full text review using literature review tools (e.g., SWIFT, DistillerSR), analyzing reliability and strength of evidence, and reporting findings.

Developed standardized search syntax for classification and identification of relevant literature for various toxicological endpoints and exposure (e.g., genotoxicity, nephrotoxicity, cancer, acute or chronic) using various search engines (e.g., PubMed, Embase).

Used systematic review to conduct a benefit/risk analysis for foods, where the hazards and safety of flavoring methods for consumer foods were compared and evaluated in a tiered assessment.

Conducted safety and exposure assessment for multiple GRAS dossiers, including literature searches and interpreting and summarizing toxicity, safety, and exposure data from publicly available literature and regulatory bodies, in both animal feed- and human-food-relevant contexts.

Utilized systematic review approaches to develop an Adverse Outcome Pathway for neonatal mortality in rodents.

Ecotoxicology

Investigated endocrine disruption effects in *Menidia menidia* populations in the Lower Cape Fear River region of North Carolina. Sampled fish populations near paper mill and wastewater effluents, and livestock feedlot runoff, and examined exposure effects on endpoints that included vitellogenin, fecundity, gonad histology, and secondary sex characteristics.

Conducted transgenerational studies on subpopulations of fish sampled from various effluent discharge sites to identify potential endocrine-disrupting compound (EDC) exposure effects on reproductive success and sex ratios of subsequent F1 and F2 generations.

Studied effects of EDC exposure on risk-taking and foraging behavior in freshwater fish (*Poecilia reticulata*) after exposure to the estrogenic compound, 17α-ethinylestradiol (EE2), and the androgenic compounds, 17α/β-trenbolone, individually and in mixtures.

Involved with restoration of Carolina oyster reefs, specifically the eastern oyster (*Crassostrea virginica*)— assessed how differing reef designs and placement can facilitate colonization and long-term success of the restoration effort.

Investigated conditional effects of larval bluehead wrasse based on their solitary or group emergence behavior on Caribbean coral reefs.

MANUSCRIPTS

Wikoff DS, Vincent MJ, **Heintz MM**, Pastula ST, Reichert H, Klaren WD, Haws LC. 2025. Application of a quantitative uncertainty assessment to develop ranges of plausible toxicity values when using observational data in risk assessment: A case study examining associations between PFOA and PFOS exposures and vaccine response. Toxicol Sci; doi: 10.1093/toxsci/kfae152. Online ahead of print 10 Jan 2025. PMID: 39792025.

Thompson CM, **Heintz MM**, Cullen JM, Haws LC. 2024. Letter to the Editor of Environmental Pollution: In regard to Wan et al. (2024), "GenX caused liver injury and potential hepatocellular carcinoma of mice via drinking water even at environmental concentration." Environ Pollut, May 20:124171; doi: 10.1016/j.envpol.2024.1241741.

Heintz MM, Klaren WD, East AW, Haws LC, McGreal SR, Campbell RR, Thompson CM. 2024. Comparison of transcriptomic profiles between HFPO-DA and prototypical PPARα, PPARγ, and cytotoxic agents in wild-type and PPARα knockout mouse hepatocytes. Toxicol Sci 200(1):183–198; doi: 10.1093/toxsci/kfae045. PMID: 38574385.

Heintz MM, Klaren WD, East AW, Haws LC, McGreal SR, Campbell RR, Thompson CM. 2024. Comparison of transcriptomic profiles between HFPO-DA and prototypical PPARα, PPARγ, and cytotoxic agents in mouse, rat, and pooled human hepatocytes. Toxicol Sci 200(1):165–182; doi: 10.1093/toxsci/kfae044. PMID: 38574381

Racz L, Gauthier A, Bare J, **Heintz M**, Feifarek D, Kennedy S, Panko J. 2024. Assessment of perfluorocarboxylic acids in fluorinated high-density polyethylene containers and estimation of potential non-cancer risks associated with anticipated use scenarios. Reg Tox Pharm 147:105560.

Henderson RG, Lefever TW, **Heintz MM**, Trexler KR, Borghoff SJ, Bonn-Miller MO. 2023. Oral toxicity evaluation of cannabidiol. Food Chem Toxicol 113778; https://doi.org/10.1016/j.fct.2023.113778.

Heintz MM, Haws LC, Klaunig JE, Cullen JM, Thompson CM. 2023. Assessment of the mode of action underlying development of liver lesions in mice following oral exposure to HFPO-DA and relevance to humans. Toxicol Sci. 192(1):15–29, doi: 10.1093/toxsci/kfad004. PMID: 36629480; PMCID: PMC10025879.

Thompson CM, **Heintz MM,** Wolf JC, Cheru R, Haws LC, Cullen JM. 2023. Assessment of mouse liver histopathology following exposure to HFPO-DA with emphasis on understanding mechanisms of hepatocellular death. Toxicol Pathol 51(1–2):4–14; doi: 10.1177/01926233231159078. Epub ahead of print. PMID: 36987989.

Heintz MM, Chappell GA, Thompson CM, Haws LC. 2022. Evaluation of transcriptomic responses in livers of mice exposed to the short-chain PFAS compound HFPO-DA. Front Toxicol, https://doi.org/10.3389/ftox.2022.937168.

Godfrey G, Laplaca SB, **Heintz MM**. 2022. Developing young watershed citizen scientists through professional partnerships in the classroom. Am Biol Teacher, https://doi.org/10.1525/abt.2022.84.4.202.

Heintz MM, Kumar R, Maner-Smith KM, Ortlund EA, Baldwin WS. 2022. Age- and diet-dependent changes in hepatic lipidomic profiles of phospholipids in male mice: Age acceleration in Cyp2b-null mice. J Lipids, https://doi.org/10.1155/2022/7122738.

Olack EM, **Heintz MM**, Baldwin WS. 2022. Dataset of endo-and xenobiotic inhibition of CYP2B6: Comparison to CYP3A4. Data in Brief, https://doi.org/10.1016/j.dib.2022.108013.

Thompson CM, Aardema MJ, **Heintz MM**, MacGregor JT, Young RR. 2021. A review of mammalian in vivo genotoxicity of hexavalent chromium: implications for oral carcinogenicity risk assessment. Crit Rve Toxicol. https://doi.org/10.1080/10408444.2021.2000934.

Doepker CL, **Heintz MM**, van de Ligt J, Wikoff DS. 2021. Review of potential risks associated with supplemental dietary exposure to nitrate-containing compounds in swine—A paradox in light of emerging benefits. Transl Anim Sci, https://doi.org/10.1093/tas/txab203.

Heintz MM, Doepker CL, Wikoff DS, Hawks SE. 2021. Assessing the food safety risk of ochratoxin A in coffee: A toxicology-based approach to food safety planning. J Food Sci (open access).

Hamilton MC, **Heintz MM**, Pfohl M, Marques E, Ford L, Slitt AL, Baldwin WS. 2021. Increased toxicity and retention of perflourooctane sulfonate (PFOS) in humanized CYP2B6-Transgenic mice compared to Cyp2b-null mice is relieved by a high-fat diet (HFD). Food Chem Toxicol 152:112175, https://doi.org/10.1016/j.fct.2021.112175.

Chappell GA, **Heintz MM**, Borghoff SJ, Doepker CL, Wikoff DS. 2021. Lack of potential carcinogenicity for steviol glycosides — Systematic evaluation and integration of mechanistic data into the totality of evidence. Food Chem Toxicol 150:112045, https://doi.org/10.1016/j.fct.2021.112045.

Chappell GA, **Heintz MM**, Haws LC. 2021. Transcriptomic analyses of livers from mice exposed to 1,4-dioxane for up to 90 days to assess potential mode(s) of action underlying liver tumor development. Curr Res Toxicol 2:30–41; https://doi.org/10.1016/j.crtox.2021.01.003.

Heintz MM, Haws LC. 2021. Correspondence to the Editor Regarding Guillette et al. 2020, Elevated levels of per- and polyfluoroalkyl substances in Cape Fear River Striped Bass (Morone saxatilis) are associated with biomarkers of altered immune and liver function. Environ Int 146:106299, https://doi.org/10.1016/j.envint.2020.106299.

Heintz, MM, McRee, R, Kumar, R, Baldwin, WS. 2020. Gender differences in diet-induced steatotic disease in Cyp2b-null mice. PLoS ONE 15(3):e0229896.

Heintz MM, Kumar R, Rutledge M, Baldwin WS. 2019. Cyp2b-null male mice are susceptible to diet-induced obesity and perturbations in lipid homeostasis. J Nutr Biochem 70:125–137.

Heintz MM, Brander SM, White JW. 2015. Endocrine disrupting compounds alter risk-taking behavior in guppies (*Poecilia reticulata*). Ethology 121:480–491.

PRESENTATONS

Reátegui-Zirena EG, Lange SS, Jenkins A, **Heintz MM**, Franke K, Perry CS, Thompson C, et al. Acute health-based screening level derivation for cyanotoxins (microcystin, cylindrospermopsin and anatoxins). Abstract 7.05P-Th-197, Society of Environmental Toxicology and Chemistry, 45th Annual Meeting, Fort Worth, TX, October 2024.

Heintz M, Klaren W, East A, Haws L, Thompson C. Delayed transcriptomic responses in PPARa knockout mouse hepatocytes compared to wild-type hepatocytes exposed to HFPO-DA or PPARa agonist GW7647: Support for a PPARa-dependent mode of action for HFPO-DA in mouse hepatocytes. Abstract 4100, Society of Toxicology Annual Meeting, Salt Lake City, UT, March 2024.

Thompson CM, **Heintz MM**, Rogers SI, Fitch SE, Rivera BN, Klaren WD, Vincent MJ, Wikoff DS, Haws LC. Evidence identification and appraisal supporting development of an updated toxicity value for HFPO-DA. Abstract 3654, Society of Toxicology Annual Meeting, Salt Lake City, UT, March 2024.

Lea IA, Feifarek D, Mihalchik A, **Heintz M**, Haws L, Nyambego H, Goyak K, Borghoff SJ. Evaluation of the endocrine disrupting potential of di-isodecyl phthalate. Abstract 3930, Society of Toxicology Annual Meeting, Salt Lake City, UT, March 2024.

Borghoff SJ, Feifarek D, Mihalchik A, **Heintz M**, Haws L, Nyambego H, Goyak K, Lea IA. Evaluation of the endocrine disrupting potential of di-isodecyl phthalate. Abstract 3931, Society of Toxicology Annual Meeting, Salt Lake City, UT, March 2024.

Lynn SG, Lea IA, Urban J, Borghoff SJ, Wikoff D, Fitch S, Perry C, Choksi N, Britt J, **Heintz M**, Klaren W, et al. Development and application of systematic approach to inventory and interrogate thyroid hormone network information. Abstract 4357, Society of Toxicology Annual Meeting, Salt Lake City, UT, March 2024.

Haws LC, **Heintz MM**, Thompson CM. Updated mode of action information informing the risk assessment of HFPO-DA (GenX). Poster presented at Society of Toxicology Annual Meeting, Nashville, TN, March 2023.

Heintz MM, Haws LC, Thompson CM. Assessment of the mode of action underlying development of liver lesions in mice following oral exposure to HFPO-DA (GenX) and relevance to humans. Poster presented at Society of Toxicology Annual Meeting, Nashville, TN, March 2023.

Klaren WD, **Heintz MM**, East AW, Thompson CM, Haws LC. *In vitro* transcriptomic analyses informing the mode of action of HFPO-DA (GenX) in the liver. Poster presented at Society of Toxicology Annual Meeting, Nashville, TN, March 2023.

Lea IA, **Heintz MM**, Feifarek D, Haws LC, Borghoff SJ. Weight-of-evidence evaluation of endocrine activity for di-isodecyl phthalate (DIDP) and di-isononyl phthalate (DINP). Poster presented at Society of Toxicology Annual Meeting, Nashville, TN, March 2023.

Heintz MM, LaPlaca SB, Haws LC. Application of an integrated ecotoxicological study reliability tool in the derivation of predicted no-effect concentrations for short chain and ultrashort chain per- and polyfluoroalkyl substances. Poster presented at Society of Environmental Toxicology and Chemistry (SETAC), Philadelphia, PA, November 2022.

LaPlaca SB, **Heintz MM**, Wikoff D, Haws LC. Multi-step integration of ecotoxicological study reliability in ecological risk assessment. Poster presented at Society of Environmental Toxicology and Chemistry (SETAC), Philadelphia, PA, November 2022.

Heintz MM, Chappell GA, Thompson CM, Wolf JC, Rogers JM, Haws LC. HFPO-DA (GenX) transcriptomic responses in pregnant and non-pregnant rat livers: Analyses to inform the role of maternal effects on neonatal toxicity. Poster presented at Society of Toxicology Annual Meeting, San Diego, CA, March 2022.

Rogers JM, **Heintz MM**, Thompson CM, Haws LC. Development of a putative adverse outcome pathway for neonatal mortality in rodents: Implications for human health risk assessments of PFAS. Poster presented at Society of Toxicology Annual Meeting, San Diego, CA, March 2022.

Heintz MM, Olack EM, Baldwin WS. Human CYP2B6 is an anti-obesity enzyme that produces active α-linolenic acid metabolites. Society of Toxicology meeting, Anaheim, CA, March 2020.

Heintz MM, McRee R, Kumar R, Baldwin WS. Gender differences in diet-induced nonalcoholic steatohepatitis (NASH) in Cyp2b-null mice. Society of Toxicology meeting, Anaheim, CA, March 2020.

Heintz MM, Kumar R, Baldwin WS. Cyp2b-null male mice are susceptible to high-fat diet-induced obesity due to changes in PUFA metabolism and response to hepatic lipids as measured by RNAseq. International Congress on Toxicology (ICTXV), Honolulu, HI, July 2019.

Olack E, **Heintz MM**, Baldwin WS. Human CYP2B6 is an anti-obesity enzyme involved in unsaturated fatty acid metabolism. International Congress on Toxicology (ICTXV), Honolulu, HI, July 2019.

Heintz MM, Sengupta N, Noorai R, Baldwin WS. Triclosan exposure represses development and alters sphingomyelin metabolism in Daphnia magna as determined by RNA-seq and lipidomics. 20th Pollutant Responses in Marine Organisms (PRIMO20, Charleston, SC, May 2019.

Heintz MM, McRee R, Baldwin WS. The role of Cyp2b in diet-induced nonalcoholic steatohepatitis. Invited speaker: Clemson University Environmental Toxicology program seminar, Clemson, SC, April 2019.

Heintz MM, Kumar R, Baldwin WS. Cyp2b-null male mice are susceptible to high-fat diet-induced obesity due to changes in PUFA metabolism and response to hepatic lipids as measured by RNAseq. American College of Toxicology, 39th Annual Meeting, West Palm Beach, FL, November 2018.

Heintz MM, Kumar R, Baldwin WS. Cyp2b-null male mice are susceptible to high-fat diet-induced obesity due to changes in PUFA metabolism and response to hepatic lipids as measured by RNAseq. Southeastern Society of Toxicology meeting, Gainesville, FL, October 2018.

Williams TL, **Heintz MM**, Baldwin WS. Several toxicants increase retention of triglycerides in Daphnia magna and human liver cells. Annual Biomedical Research Conference for Minority Students (ABRCMS), Indianapolis, IN, November 2018.

Williams TL, **Heintz MM**, Baldwin WS. Several toxicants increase retention of triglycerides in *Daphnia magna* and human liver cells. Research Experiences for Undergraduates (REUs), Alexandria, VA, October 2018.

Williams TL, **Heintz MM**, Baldwin WS. Several toxicants increase retention of triglycerides in Daphnia magna and human liver cells. Clemson Summer Research Symposium, July 2018.

Heintz MM, Kumar R, Baldwin WS. The role of Cyp2b in the metabolism of unsaturated fatty acids. #1291, Society of Toxicology meeting, San Antonio, TX, March 2018.

McRee R, **Heintz MM**, Baldwin WS. Inhibition of CYP2B6 does not necessarily alter toxicity except in the case of chemicals with known active metabolites. #1292, Society of Toxicology meeting, San Antonio, TX, March 2018.