

Chadwick M. Thompson, Ph.D., M.B.A.

SENIOR MANAGING SCIENTIST MECHANISTIC AND COMPUTATIONAL BIOLOGY

CONTACT INFORMATION

ToxStrategies LLC 23501 Cinco Ranch Blvd, Suite H210 Katy, TX 77494 Phone (281) 712-2062, x2002 Fax (832) 218-2756 cthompson@toxstrategies.com

PROFESSIONAL PROFILE

Dr. Chad M. Thompson holds a doctoral degree in Biomedical Sciences and specializes in mechanistic and quantitative aspects of risk assessment. He has written extensively on the mode of action (MOA) of high-profile compounds such as formaldehyde, hexavalent chromium, and dioxin. He has also helped design, conduct, and analyze multimillion-dollar research projects with a focus on understanding the toxicity of environmental contaminants and application of such information to risk assessment. Dr. Thompson has extensive experience in dose-response modeling (including benchmark dose modeling), and he helped develop dose-response packages for the R statistical language (www.r-project.org). Dr. Thompson specializes in the integration of dose-response, toxicological, and mechanistic information in human health risk assessment. As a former health scientist at the U.S. Environmental Protection Agency (EPA), he is a co-author of multiple IRIS chemical risk assessments, as well as several agency documents on risk assessment practices and policies, including the application of physiologically based pharmacokinetic (PBPK) models, toxicogenomic data, and lifestage susceptibility information in risk assessment. Dr. Thompson is a coauthor of more than 50 publications in the peer-reviewed literature, many of which pertain directly to human health risk assessment. He is a former Risk Policy Fellow with the American Association for the Advancement of Science (AAAS).

EDUCATION AND DEGREES EARNED

2001 MBA, Virginia Commonwealth University, Richmond, VA

1999 Ph.D. in Biomedical Sciences, University of Texas Health Science Center, Houston

1994 BS in Psychology (cum laude), Old Dominion University, Norfolk, VA









PROFESSIONAL HONORS/AWARDS

2013	Society of Toxicology Risk Assessment Specially Session (RASS) top 10 papers of 2012
2012	Society of Toxicology Risk Assessment Specially Session (RASS) top 10 papers of 2011
2010	Society of Toxicology Risk Assessment Specially Session (RASS) top 10 abstracts of the year award
2009	Level II Scientific and Technological Achievement Awards (STAA): Developing Guidelines for Physiologically Based Pharmacokinetic (PBPK) Modeling in Quantitative Risk Assessment
2009	Level III Scientific and Technological Achievement Awards (STAA): Outlining the Sensitivity of Inferences on Mode-of-Action and Cancer Risk Estimates using Clonal Growth Models
2009	Honorable Mention: A Groundbreaking Lifestage-Specific Approach to Health Risk Assessment of Environmental Exposures
2008	Superior Performance Award, cash award from U.S. EPA
2007	U.S. EPA Bronze Medal Award for preparing A Framework for Assessing Health Risk of Environmental Exposures to Children
2007	Superior Performance Award, cash award from U.S. EPA
2006	U.S. EPA Bronze Medal Award for preparing Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment
2006	Superior Performance Award, cash award from U.S. EPA
2004	2004–2005 AAAS Science & Technology Policy Fellowship
2003	2003–2004 AAAS Science & Technology Policy Fellowship

2003 Ruth L. Kirschstein National Research Service Awards for Individual Postdoctoral Fellows (declined in order

PROFESSIONAL ASSOCIATIONS

American Association for the Advancement of Science

to accept the AAAS Science & Technology Policy Fellowship)

Society of Toxicology, RASS Specialty Section, Mechanisms Specialty Section, LSSOT Regional Chapter

SERVICE/PEER REVIEW

Biomedical and Environmental Sciences
Cell Biology & Toxicology
Chemical Research in Toxicology
Chemosphere
Drug & Chemical Toxicology
Environmental Research
Environmental Toxicology & Pharmacology
Expert Opinion on Drug Metabolism & Toxicology

Food & Chemical Toxicology
Human and Ecological Risk Assessment
International Journal of Medical Sciences
Journal of Toxicology and Environmental Health
Journal of Applied Toxicology
Regulatory Toxicology and Pharmacology
Toxicology and Applied Pharmacology
Toxicology Letters



SELECTED PROFESSIONAL EXPERIENCE

Toxicological Risk Assessment

Evaluated and interpreted toxicology data on a variety of environmental contaminants, including formaldehyde, methanol, chromium, nickel, dioxin and dioxin-like compounds (DLCs), brominated flame retardants, and various VOCs. Areas of expertise include hazard characterization, and dose-response analysis, pharmacokinetics, and developments of toxicity and safety values.

Conducted toxicological evaluations of chemical substances present or potentially present in vaccines, and also derived safe levels for excipients, detergents, surfactants, and other chemicals used in the production or inactivation of vaccine products.

Conducted comprehensive literature reviews on the toxicology of nickel compounds in support of registration under the Registration, Evaluation & Authorisation of Chemicals (REACH) initiative. Populated an International Uniform Chemical Information Database (IUCLID) for each substance. Evaluated key studies for reliability and relevance, synthesized large volumes of data, and generated integrative reports.

Developed, managed, analyzed, and published research into the mode of action (MOA) of intestinal tumors in mice exposed to hexavalent chromium [Cr(VI)] in drinking water. Analyzed *in vivo* and *in vitro* toxicological responses, including toxicogenomic and genotoxic endpoints.

Analyzed dose-response data pertinent to the development of safety values for oral exposure to Cr(VI) using benchmark dose and constrained nonlinear regression modeling techniques.

Communicated toxicological study findings on Cr(VI) to regulatory authorities across North America.

Collaborated with international researchers to develop methods for assessing the presence or absence of potential thresholds in the dose response of genotoxic endpoints both *in vitro* and *in vivo*.

Assisted in the development of an R language script (*viz.*, drsmooth) for using smoothing splines to determine point-of-departure values in toxicological dose-response data sets.

Explored techniques for deriving relative potency estimates for DLCs using toxicogenomics and dose-response modeling methods.

Prepared comments on several external review drafts developed by regulatory agencies, including draft risk assessments, toxicological bioassays, and risk assessment practices and policy documents.

Coordinated and co-wrote portions of U.S. EPA IRIS chemical risk assessments, including reactive gases (e.g., formaldehyde) and systematically distributing compounds (methanol).

Evaluated Provisional Peer-Reviewed Toxicity Values (PPRTVs) for benzene and propene derivatives for U.S. EPA's Superfund program.

Served as a member of the U.S. EPA Pharmacokinetic Workgroup that provides expert consultation to EPA chemical managers regarding the application of PBPK models for ongoing assessments.

Regulatory Toxicology

Coordinated the completion and review of several risk assessment documents—including those related to the use of PBPK models for application in risk assessment, qualitative and quantitative approaches to considering children's susceptibility, and the exploration of the use of "omics" data in hazard characterization and doseresponse in risk assessment. Co-author of:



- Approaches for the Application of Physiologically Based Pharmacokinetic Models and Supporting Data in Risk Assessment (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=157668)
- A Framework for Assessing Health Risks of Environmental Exposures to Children (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363)
- An Approach to Using Toxicogenomics Data in EPA Risk Assessments (http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=213405)

Research & Development

Managed the development of Access databases containing physiological data for supporting PBPK model development for humans of various life stages and health conditions, as well as laboratory species.

Collaborated and published with national and international academic scientists on the collection, characterization, and analysis of lifestage-specific physiological data and their application in PBPK modeling and risk assessment.

Collaborated and, with scientists at Karolinska Institute and the VTT Technical Research Centre of Finland, published on mechanisms of formaldehyde toxicity—including potential respiratory effects relating to the dual function of alcohol dehydrogenase 3 in the oxidation of formaldehyde and reduction of the endogenous bronchodilator S-nitrosoglutathione (GSNO).

Project Management

Assisted in the oversight of a multimillion-dollar research project on the mode of action of hexavalent chromium. Responsibilities included direct interaction with contract laboratories regarding aspects of final study design, contract review, schedule oversight, managing and authorizing payments to contractors, providing scientific consultation and judgment on technical issues, and providing final approval on delivered work products.

Served as the Technical Project Officer on several contracts with outside vendors. Responsibilities included developing cost estimates for bid proposals, managing and approving payments to contractors, writing statements of work, reviewing and selecting bid contracts providing scientific consultation and judgment on technical issues related to contracts, and providing final approval on delivered contract products.

Litigation Support

Prepared (and rebutted) expert reports for formaldehyde litigation relating to alleged adverse health effects from formaldehyde and mobile home exposures.

Taught CLE course related to causation and Havner guidelines.

COMPUTER & LANGUAGE SKILLS

Ingenuity Pathways Analysis (IPA), IUCLID 5, U.S. EPA's Benchmark Dose Modeling Software (BMDS); PROAST, BMDExpress, U.S. EPA's Regional Deposited Dose Ratio (RDDR) software v. 2.3, Multi-Path Model of Particle Deposition (MPPD) v. 2.1, Berkeley Madonna (ordinary differential equation solver); GraphPad Prism, @RISK Monte Carlo Software, Microsoft Office (including Access); Minitab Statistical Package, R statistical language.



MANUSCRIPTS

Vincent M, Fitch S, Bylsma L, **Thompson CM**, Rogers S, Britt J, Wikoff D. 2024. Assessment of associations between inhaled formaldehyde and lymphohematopoietic cancer through integration of epidemiological and toxicological evidence with biological plausibility. Toxicol Sci, in press, <u>accepted ms. ahead of publication</u>.

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 kfae045. doi: 10.1093/toxsci/kfae045. Online ahead of print. 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 kfae044. doi: 10.1093/toxsci/kfae044. Online ahead of print. PMID: 38574381

Thompson CM, Brorby G, Keig-Shevlin Z, Smith R, Franzen A, Ulrich K, Blanchette AD, Doepker C. 2023. Assessment of the in vivo genotoxic potential of three smoke flavoring primary product mixtures. Environ Mol Mutagen 64(8–9):420–431; doi: 10.1002/em.22576.

Thompson CM, Kirman C, Harris MA. 2023. Derivation of oral cancer slope factors for hexavalent chromium informed by pharmacokinetic models and *in vivo* genotoxicity data. Regul Toxicol Pharmacol 145:105521, doi: 10.1016/j.yrtph.2023.105521.

Thompson CM, Proctor DM, Harris MA. 2023. Letter to "Chepelev et al. Establishing a quantitative framework for regulatory interpretation of genetic toxicity dose-response data: Margin of exposure case study of 48 compounds with both in vivo mutagenicity and carcinogenicity dose-response data." Environ Mol Mutagen 64(4):259–260; doi: 10.1002/em.22537.

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 J, 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. 1926233231159078, doi: 10.1177/01926233231159078. Epub ahead of print. PMID: 36987989.

Rogers JM, Heintz MM, **Thompson CM**, Haws LC. 2023. A putative adverse outcome network for neonatal mortality and lower birth weight in rodents: Applicability to per- and polyfluoroalkyl substances and relevance to human health. Birth Def Res 115:1011–1062.

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 4:937168, https://doi.org/10.3389/ftox.2022.937168.

Lea IA, Pham LL, Antonijevic T, **Thompson C**, Borghoff SJ. 2022. Assessment of the applicability of the threshold of toxicological concern for per- and polyfluoroalkyl substances. Regul Toxicol Pharmacol 133:105190, <u>open access</u>.

Chappell GA, Wolf JC, **Thompson CM**. 2021. Crypt and villus transcriptomic responses in mouse small intestine following oral exposure to hexavalent chromium. Toxicol Sci, kfab152, doi: 10.1093/toxsci/kfab152. Epub ahead of print. PMID: 34935971.



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 Rev Toxicol 51(2), https://doi.org/10.1080/10408444.2021.2000934.

Thompson CM, Bhat VS, Brorby GP, Haws LC. 2021. Development of updated RfD and RfC values for medium carbon range aromatic and aliphatic total petroleum hydrocarbon fractions. J Air Waste Manag Assoc 71(12):1555–1567, doi: 10.1080/10962247.2021.1974123.

Proctor DM, Bhat V, Suh M, Reichert H, Jiang X, **Thompson CM**. 2021. Inhalation cancer risk assessment for environmental exposure to hexavalent chromium: Comparison of margin-of-of exposure and linear extrapolation approaches. Regul Toxicol Pharmacol 124:104969, https://doi.org/10.1016/j.yrtph.2021.104969.

Felter SP, Zhang X, **Thompson C**. 2021. Butylated hydroxyanisole: Carcinogenic food additive to be avoided or harmless antioxidant important to protect food supply? Regul Toxicol Pharmacol 121:104887.

Chappell GA, Wikoff DS, **Thompson CM**. 2021. Assessment of mechanistic data for hexavalent chromium-induced rodent intestinal cancer using the key characteristics of carcinogens. Toxicol Sci 180(1):38-50, https://doi.org/10.1093/toxsci/kfaa187.

Gentry R, **Thompson CM**, Franzen A, Salley J, Albertini R, Lu K, Greene T. 2020. Using mechanistic information to support evidence integration and synthesis: A case study with inhaled formaldehyde and leukemia. Crit Rev Toxicol 50(10):885–918, https://doi.org/10.1080/10408444.2020.1854678.

Thompson CM, Gentry R, Fitch S, Lu K, Clewell HJ. 2020. An updated mode of action and human relevance framework evaluation for formaldehyde-related nasal tumors. Crit Rev Toxicol 50(10):919–952, https://doi.org/10.1080/10408444.2020.1854679.

Thompson CM, Donahue DA, Hobbs C, Costecalde Y, Franzen A, Suh M, Proctor DM, Harris MA. 2020. Exposure to environmentally-relevant concentrations of hexavalent chromium does not induce ovarian toxicity in mice. Regul Toxicol Pharmacol 116, open access: https://doi.org/10.1016/j.yrtph.2020.104729.

Chappell GA, **Thompson CM**, Wolf JC, Cullen JM, Klaunig JE, Haws LC. 2020. Assessment of the mode of action underlying the effects of GenX in mouse liver and implications for assessing human health risks. Toxicol Pathol 48(3):494–508, doi: 10.1177/0192623320905803. PMID: 32138627.

Pham LL, Borghoff SJ, **Thompson CM**. 2020. Comparison of threshold of toxicological concern (TTC) values to oral reference dose (RfD) values. Regul Toxicol Pharmacol 113:104651 [open access], https://doi.org/10.1016/j.yrtph.2020.104651.

Bhat VS, Cohen SM, Gordon EB, Wood CE, Cullen JM, Harris MA, Proctor DM, **Thompson CM**. 2020. An adverse outcome pathway for small intestinal tumors in mice involving chronic cytotoxicity and regenerative hyperplasia: A case study with hexavalent chromium, captan, and folpet. Crit Rev Toxicol (open access), https://doi.org/10.1080/10408444.2020.1823934.

Chappell G, Rager J, Wolf J, Babic M, Leblanc, Ring C, Harris MA, **Thompson CM**. 2019. Comparison of gene expression responses in the small intestine of mice following exposure to three carcinogens using the S1500+ gene set informs a potential common adverse outcome pathway. Toxicol Pathol 47(7):851–864, https://doi.org/10.1177/0192623319873882.

Thompson CM, Fitch SE, Ring C, Rish W, Cullen JM, Haws LC. 2019. Development of an oral reference dose for the perfluorinated compound GenX. J Appl Toxicol 39:1267–1282; open access: https://onlinelibrary.wiley.com/doi/full/10.1002/jat.3812.



Rager JE, Suh M, Chappell G, **Thompson CM**, Proctor DM. 2019. Review of transcriptomic responses to hexavalent chromium exposure in lung cells supports a role of epigenetic mediators in carcinogenesis. Toxicol Lett 305:40–50.

Clewell RA, **Thompson CM**, Clewell HJ. 2019. Dose-dependence of chemical carcinogenicity: Biological mechanisms for thresholds and implications for risk assessment. Chem Biol Interact 301:112–127.

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Klaren WD, Ring C, Harris MA, **Thompson CM**, Borghoff S, Sipes NS, Hsieh J-H, Auerbach SS, Rager JE. 2018. Identifying attributes that influence *in vitro*-to-*in vivo* concordance by comparing *in vitro* Tox21 bioactivity versus *in vivo* DrugMatrix transcriptomic responses across 130 chemicals. Toxicol Sci 120:709–723, available at https://doi.org/10.1093/toxsci/kfy220.

Wikoff DS, **Thompson C**, Rager J, Chappell G, Fitch S, Doepker C. 2018. Benefit-risk analysis for foods (BRAFO): Evaluation of exposure to dietary nitrates. Food Chem Toxicol (in press). https://doi.org/10.1016/j.fct.2018.08.031.

Moffat I, Martinova N, Seidel C, **Thompson CM.** 2018. Hexavalent chromium in drinking water. Journal AWWA 110:5.

Thompson CT, Suh M, Chappell G, Borghoff S, Ellis-Hutchings R, Wiench K, Finch L, Proctor DM. 2018. Assessment of the mode of action underlying development of forestomach tumors in rodents following oral exposure to ethyl acrylate and relevance to humans. Regul Toxicol Pharmacol 96:178–189 doi: 10.1016/j.yrtph.2018.05.006.

Proctor DM, Suh M, Chappell G, Borghoff SJ, **Thompson CM**, Wiench K, Finch L, Ellis-Hutchings R. 2018. An adverse outcome pathway (AOP) for forestomach tumors induced by non-genotoxic initiating events. Regul Toxicol Pharmacol 96:30–40, doi: 10.1016/j.yrtph.2018.04.016.

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Thompson CM, Kirman CR, Hays SM, Suh M, Harvey SE, Proctor DM, Rager JE, Haws LC, Harris MA. 2018. Integration of mechanistic and pharmacokinetic information to derive oral reference dose and margin-of-exposure values for hexavalent chromium. J Appl Toxicol 38:351–365. doi: 10.1002/jat.3545.

Thompson CM, Wlolf, JC, McCoy A, Suh M, Proctor DM, Kirman CR, Haws LC, Harris MA. 2017. Comparison of toxicity and recovery in the duodenum of B6C3F1 mice following treatment with intestinal carcinogens captan, folpet, and hexavalent chromium. Toxicol Pathol 45(8):1091–1101. DOI: 10.1177/019262331yy4324.

Rager JE, Auerbach SS, Chappell GA, Martin E, **Thompson CM**, Fry RC. 2017. Benchmark dose modeling estimates of the concentrations of inorganic arsenic that induce changes to the neonatal transcriptome, proteome, and epigenome in a pregnancy cohort. Chem Res Toxicol 30(10):1911–1920; DOI: 10.1021/acs.chemrestox.7b00221.

Thompson CM, Suh M, Proctor DM, Haws LC, Harris MA. 2017. Ten factors for considering the mode of action of Cr(VI)-induced gastrointestinal tumors in rodents. Mut Res/Genetic Toxicol Environ Mutagen 823:45–57.

Thompson CM, Young RR, Dinesdurage H, Suh M, Harris MA, Rohr AC, Proctor DM. 2017. Assessment of the mutagenic potential of hexavalent chromium in the duodenum of Big Blue® rats. Toxicol Appl Pharmacol 330(1):48-52.



Rager JE, Ring CL, Fry RC, Suh M, Proctor DM, Haws LC, Harris MA, **Thompson CM**. 2017. High-throughput screening data interpretation in the context of *in vivo* transcriptomic responses to oral Cr(VI) exposure. Toxicol Sci kfx085. doi: 10.1093/toxsci/kfx085.

Thompson CM, Rager JE, Suh M, Ring CL, Proctor DM, Haws LC, Fry RC, Harris MA. 2016. Transcriptomic responses in the oral cavity of F344 rats and B6C3F1 mice: Implications for risk assessment. Environ Mol Mutagen 57:706–716.

Thompson CM, Bichteler A, Rager JE, Suh M, Proctor DM, Haws LC, Harris MA. 2016. Comparison of in vivo genotoxic and carcinogenic potency to augment mode of action analysis: Case study with hexavalent chromium. Mutat Res 800:28-34.

Thompson CM, Suh M, Mittal L, Wikoff D, Welsh B, Proctor DM. 2016. Development of linear and threshold no significant risk levels for inhalation exposure to titanium dioxide using systematic review and mode of action considerations. Regul Toxicol Pharmacol 80:60–70.

Suh M, **Thompson CM**, Brorby GP, Mittal L, Proctor DM. 2016. Inhalation cancer risk assessment of cobalt metal. Regul Toxicol Pharmacol 79:74–82.

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Thompson CM, Wolf JC, Elbekai RH, Paranjpe MG, Seiter JM, Chappell MA, Tappero RV, Suh M, Proctor DM, Bichteler A, Haws LC, Harris MA. 2015. Duodenal crypt health following exposure to Cr(VI): Micronucleus scoring, y-H2AX immunostaining, and synchrotron x-ray fluorescence microscopy. Mutat Res 789–790:61–66.

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ABSTRACTS, PRESENTATIONS, POSTERS

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.

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