Curriculum Vitae Dr. Charles B. Breckenridge

NAME Charles Breckenridge	POSITION/INSTITUTE/DATE Head, Inhalation & Reproductive Toxicology/Bio- Research Laboratories Ltd. (1980-1982) Manager/Senior Research and Technology Fellow, Syngenta Crop Protection LLC., (1983-2017) Principal and Manager, Quality Scientific Solutions, LLC, (2017 to present)		
EDUCATION			
INSTITUTION AND LOCATION	DEGREE (if applicable)	MM/YY	FIELD OF STUDY
University of Saskatchewan, Saskatoon, Canada	BA Honors	1971	Physiological Psychology
McMaster University, Hamilton, Ontario, Canada	PhD	1978	Electrophysiology/Sleep
Post-Doctoral Industrial Fellowship, Bio- Research Laboratories, Ltd, Montreal, PQ.		1978-1980	Inhalation & Reproduction Toxicology

A. Personal Statement

In my academic studies, I focused on the structure and function of the central nervous system with special emphasis on the role of the limbic system in memory and learning (Winocur and Breckenridge (1973), the neurophysiological mechanism regulating sleep and the organization of the visual system (Breckenridge and Heron, 1975; Ph.D. Thesis, 1978).

In my professional career as a toxicologist, beginning with an Industrial Postdoctoral Fellowship at Bioresearch Laboratories in Montreal, (now Charles River Laboratories), I have conducted the full spectrum of toxicological studies including inhalation (Breckenridge et al., 1982,1986; Levinski, et al., 1981), reproductive (De Sesso et al., 2015), developmental (Scialli et al., 2015), chronic toxicity (Breckenridge et al., 1983) and carcinogenicity (Stevens et al., 1994, 1999; Genter and Breckenridge, 2009) studies. I specialized in evaluating the effects of xenobiotics on the endocrine (Eldridge et al. 1994a, 1994b, 1996, 2008; Foradori et al, 2009a, 2009b, 2011, 2013, 2014, 2017; Simpkins et al., 2011; Breckenridge et al., 2015) and nervous systems (Breckenridge et al., 2009; 2013, Smeyne, et al, 2016).

My involvement with quantitative risk assessment began with leading an industry team in the creation of a software program to conduct cumulative and aggregated risk assessment (CARES) using stochastic probabilistic risk assessment tools (Breckenridge et al., 2002). More recently I have integrated physiological based pharmacokinetics (PBPK) models (Campbell et al., 2016) into such analyses (Breckenridge et al., 2016). I am currently involved in the development of approaches for integrating epidemiological research into hazard based weight-of-the-evidence risk assessments (Adami, et al., 2011; Breckenridge et al., 2016).



B. Positions and Honors

Head, Inhalation and Reproduction Toxicology, Bio-Research Lab. Ltd. Montreal, Canada (1978-82)
Manager of Toxicology, Ciba-Geigy, Ltd, Summit, NJ. (1983-85)
Senior Toxicologist, Ciba-Geigy, Ltd, Greensboro, NC (1985-1988)
Senior Group Leader, Ciba Geigy, Ltd., Greensboro, NC (1988-1989)
Manager, Toxicology, Ciba-Geigy Ltd, Greensboro, NC (1990-1996)
Manager, Human Safety Assessment, Novartis/Syngenta, Greensboro, NC (1997-2002)
Head, Global Human Risk Assessment Methodologies, Greensboro, NC (2002-2003)
Senior Syngenta Fellow, Human Safety Department, Greensboro, NC (2003 to June, 2017)
Principal and Manager, Quality Scientific Solutions, LLC, Reidsville, NC (2017 to present).

C. Other Experience and Professional Memberships

American Chemical Society (~2000 to present) Endocrine Society (2012, to present) International Society of Exposure Science (2012 to present) Society of Toxicology of Canada (~1980 to present) Society of Toxicology (USA; 2013 to present Society for Neurosciences (2012 to present) National Science & Engineering Council of Canada, 1984-85.

D. Honors

C. S Agri NOVA Award Winner, Ridomil Gold Development, Ciba Crop Protection, 1995. American Crop Protection Aggregate Exposure/Risk Task Force, 1996 – 1997 Head of CARES (Cumulative & Aggregate Exposure Evaluation System) (1999 - 2002) Novartis Leading Scientist Award, November,1999. Syngenta Fellow, January, 2002; Senior Syngenta Fellow, April, 2003 Adjunct Associate Professor, Wake Forest School of Medicine, Dept. of Physiology and Pharmacology, April, 2007 to present.

E. Theses

Breckenridge, C.B. Cue-dependent behavior of hippocampectomized rats in a spatial sequence task. Honors Thesis, University of Saskatchewan, 1971.

Breckenridge, C.B. The effects of sensory deprivation on sleep and other regulatory processes in the adult cat. Ph.D. Thesis, McMaster University, 1978.

F. Publications (Full Paper)

Adami, H-O., Berry, C., **Breckenridge, C.**, Smith, L.,Swenberg, J., Trichopoulos, D., Weiss, N., Pastoor, T., Toxicology and Epidemiology: Improving the Science with a Framework for Combining Toxicological and Epidemiological Evidence to Establish Causal Inference. *Tox. Sci.*, 2011, 122, 223-234.

Ashby, J., Tinwell, H., Stevens, J., Pastoor, T., **Breckenridge, C.B.** The effects of atrazine on the sexual maturation of female rats. Regulatory Toxicology and Pharmacology, 2002, 35, 468-473.



Breckenridge C.B., Berry C., Chang E.T., Sielken R.L., Jr., Mandel J.S. (2016) Association between Parkinson's Disease and Cigarette Smoking, Rural Living, Well-Water Consumption, Farming and Pesticide Use: Systematic Review and Meta-Analysis. PLoS ONE 11(4): e0151841. doi:10.1371/journal.pone.0151841

Breckenridge, C.B., Sawhey-Coder, P., Tisdel, M.O., Yi, K.D., Simpkins, J.W., Foradori, C.D. and Handa, R.J. Effect of age, duration of exposure and dose of atrazine on sexual maturation and the luteinizing hormone surge in female Sprague-Dawley rats. *Birth Defects Research, Part B; Developmental and Reproduction Toxicology, 2015, 104, 204-2017.*

Breckenridge, C.B., Campbell, J.L., Clewell III, H.J., Andersen, M.E., Valdez-Flores, C. and Sielken, R.L. Probabilistic risk assessment of total chlorotriazines in drinking water using a physiological-based pharmacokinetic model. *Tox Sci*, 2016, 150, 269-282.

Breckenridge, C.B., Foradori, C.D., Sawhney-Coder, P., Simpkins, J.W., Sielken Jr., R.L, and Handa, R.J. Changes in sensitivity to the effects of atrazine on the LH surge in female SD rats after repeated daily doses: Correlation with liver enzyme expression. Accepted: Birth Defects Research Part A: Clinical and Molecular *Teratology*, 2017.

Breckenridge, C.B., Holden, L., Sturgess, N., Weiner, M., Sheets, L., Sargent, D., Soderlund, D.M., Choi, J-S., Symington, S., Clark, J.M., Burr, S. & Ray, D. Evidence for a separate mechanism of toxicity for the Type I and the Type II pyrethroid insecticides. *Neurotox.*, 2009, 30S, S17-S31.

Breckenridge, C., Lulham, G., Hollomby, B, Bier, C., Losos, G., & Ecobichon, D.J. A subchronic inhalation toxicity study of a Matacil formulation in the albino rat. *Toxicology and Applied Pharmacology*, 1986, 82, 181-190.

Breckenridge, C.B., Pesant, M., Durham, H.D. and Ecobichon, D.J. A 30-day toxicity study of inhaled fenitrothion in the albino rat. *Toxicology and Applied Pharmacology*, 1982, 62, 32-43.

Breckenridge, C.B., Proctor, B.J., and Hardy, T.L. Chronic Toxicity of BRL 14151K and BRL 25000 in the beagle dog. *Chemotherapy*, 1983, 31, 203-237.

Breckenridge, C.B., Sturgess, N.C., Butt, M. Wolf, J.C., Zadory, D., Beck, M.; Mathews, J.M., Tisdel, M.O., Minnema, D., Travis, K.Z., Cook, A.R., Botham P.A. and Smith, L.L. Pharmacokinetic, neurochemical, stereological and neuropathological studies on the potential effect of paraquat in the substantia nigra pars compacta of male C57BI/6J mice. *Neurotoxicol.* 2013,37, 1-14.

Brown, R.J. and **Breckenridge, C.B.** A technique for long-term blood sampling or intravenous infusion in the freely moving rat. *Biochemical Medicine*, 1975, 13, 280-286.

Campbell Jr., J.L., Andersen, M.E., Hinderliter, P.M., Yi, K.D., Pastoor, T. P., **Breckenridge, C.B.** and Clewell III, H.J. PBPK model for atrazine and its chlorometabolites in rat and human. *Toxicol. Sci*, 2016, 150, 441-453.

DeSesso, J.M., Scialli, A.R., White, T.E.K. and **Breckenridge, C.B.** Multi-generation reproduction and male developmental toxicity studies on atrazine in rats. *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, 2014, 101, 237-253.

Eldridge, J.C., Fleenor-Heyser, D.G., Extrom, P.C., Wetzel, L.T., **Breckenridge, C.B.**, Gillis, J.H., Luempert, L.L., and Stevens, J.T., Short-term effects of chlorotriazines on estrus in female Sprague-Dawley and Fischer 344 rats. Journal of Toxicology and Environmental Health, 1994, 43, 155-167.

Eldridge, J.C., Stevens, J.T., Wetzel, L.T., Tisdel, M.O., **Breckenridge, C.B.**, McConnell, R.F., and Simpkins, J.W.: Atrazine: Mechanisms of Hormonal Imbalance in Female SD rats. *Fund. Appl. Toxicol.* 24(12): 2-5. 1996

Eldridge, J.C., Tennant, M.K., Wetzel, L.T., **Breckenridge, C.B.**, & Stevens, J.T. Factors affecting mammary tumor incidence in chlorotriazine-treated female rats: Hormonal properties, dosage, and animal strain. Environmental Health Perspectives, 1994, 102, Supplement 11, 29-36.

Eldridge, J.C., Stevens, J.T. and **Breckenridge, C.B.** Atrazine Interaction with Estrogen Expression Systems. Environmental Contaminant Toxicology, 2008, 196, 147-160.

Foradori, C.D., Hinds, L.R., Quihuis, A.M., Lacagnina, A.F., **Breckenridge, C.B.**, and Handa, R.J. The Differential Effects of Atrazine on Luteinizing Hormone Release in Adrenalectomized Adult Female Wistar Rats. *Biology of Reproduction*, 2011, 85, 684-689.

Foradori, C.D., Zimmerman, A.D., Hinds,L..R., Zuloaga, K.L., **Breckenridge, C.B.**, and Handa, R.J. Atrazine Inhibits Pulsatile Gonadotropin-Releasing Hormone (GnRH) Release Without Altering GnRH Messenger RNA or Protein Levels in the Female Rat *Biology of Reproduction*, 2013, 88, 1-7.

Foradori, C.D, Coder, P.S., Tisdel, M.O., Yi, K.D., James W. Simpkins, J.W., Handa, R.J. and **Breckenridge**, **C.B.** The effect of atrazine administered by gavage or in diet on the LH surge and reproductive performance in intact female Sprague Dawley and Long Evans rats *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, 2014, 101, 262-275.

Foradori, C.D., Zimmerman, A.D., Coder, P.S., Peachee, V.L., Handa, R.L., Kimber, I., Pruett, S.B., and **Breckenridge, C.B.** Lack of immunotoxic effects of repeated exposure to atrazine associated with the adaptation of adrenal gland activation. Reg. Toxicol. Pharmacol. 2017, 89, 200-214.

Hovey, R.C., Coder, P.S., Wolf, J.C., Sielken Jr., R.L., Tisdel, M.O., and **Breckenridge, C.B.** Quantitative Assessment of Mammary Gland Development in Female Long Evans Rats following In Utero Exposure to Atrazine. Tox. Sci., 2010; 119, 380-390.

Kimber, I., Pruett, S.B and Breckenridge, C.B. Atrazine and mammalian immunotoxicity: A review. Submitted Reg. Toxicol. Pharmacol. Submitted, September, 2017.

Levinsky, H.V., **Breckenridge, C**., Gonci, D.A. & McIlhenny, H.M. Six-month inhalation studies of pirbuterol acetate aerosol in the beagle dog and squirrel monkey. Fundamental and Applied Toxicology, 1981, 1, 426-431.

Minnema, D.J., Travis. K.Z., **Breckenridge, C.B.**, Sturgess, N.C., Butt, M., Wolf, J.C., Zadory, D., Beck, M.J., Mathews, J.M., Tisdel, M.O., Cook A.R., Botham, P.A. and Smith, L.L. Dietary administration of paraquat for 13 weeks does not result in a loss of dopaminergic neurons in the *substantia nigra* of C57BL/6J mice. J. Regulatory Toxicol. Pharmacol. 2014, 68, 250-258.

Minnema, D.J., Travis. K.Z., **Breckenridge, C.B.**, Sturgess, N.C., Butt, M., Wolf, J.C., Zadory, D., Herberth, M. Watson, S., Cook A.R., and Botham, P.A. Dietary administration of diquat for 13 weeks does not result in a

loss of dopaminergic neurons in the *substantia nigra* of C57BL/6J mice. Regulatory Toxicol & Pharmacol., 2016, 75, 81-88.

Scialli, A.R., DeSesso, J.M. and **Breckenridge, C.B**. Developmental toxicity studies with atrazine and its major metabolites in rats and rabbits *Birth Defects Research Part B: Developmental and Reproductive Toxicology*, 2014, 101,199–214.

Sielken, R.L., Jr., Valdez-Florez, C., Holden, L.R., **Breckenridge, C.B.**, and Stevens, J., Statistical inferences about the mechanism of action in carcinogenicity studies. *Scand J Work Environ Health* 2005;31 suppl 1:151-155.

Simpkins, J.W., Swenberg, J.S., Weiss, N., Brusick, D., Eldridge, J.C., Stevens, J.T., Handa, R.J., Hovey, R.C., Plant, T.M., Pastoor, T.P., and **Breckenridge, C.B**., Atrazine and breast cancer: A framework assessment of the toxicological and epidemiological evidence. *Tox. Sci.*, 2011, 123, 441-459.

Smeyne, R.J., **Breckenridge, C.B.**, Beck, M., Jiao, Y, Butt, M., Wolf, J.C, Zadory, D., Minnema, D, Sturgess, N.C., Cook, A.R., and Botham, P., (2016) Assessment of the effects of MPTP and paraquat on dopaminergic neurons and microglia in the substantia nigra pars compacta based upon 2-D and 3-D stereological methods. PLOS ONE, DOI:10.1371/journal.pone.o164094, October 27, 2016

Stevens, J.T., **Breckenridge, C.B.**, Wetzel, L.T., Gillis, J.H. Luempert, L.G., Eldridge, J.C. Hypothesis for mammary tumorigenesis in Sprague-Dawley rats exposed to certain triazine herbicides. *J. Toxicol Environ. Hlth.*, 1994, 43, 139-153.

Stevens, J.T., **Breckenridge, C.B.**, Wetzel, L.T., Thakur, A.K., Liu, C., Werner, C., Luempert III, L.C., and Eldridge, J.C. A Risk Characterization for Atrazine: Oncogenicity Profile. *J. Toxicol. Environ. Hlth.* Part A, 56: 69-109, 1999.

Tennant, M.K., Hill, D.S., Eldridge, J.C., Wetzel, L.T., **Breckenridge, C.B.**, & Stevens, J.T. Possible antiestrogenic properties of chloro-s-triazines in rat uterus. *J. Toxicol. Environ. Hlth*. 1994, 43, 183-196.

Tennant, M.K., Hill, D.S., Eldridge, J.C., Wetzel, L.T., **Breckenridge, C.B.**, & Stevens, J.T. Chloro-s-triazine antagonism of estrogen action: Limited interaction with estrogen receptor binding. *J. Toxicol. Environ. Hlth.*, 1994, 43, 197-211.

Trentacoste, S.V., Friedmann, A. S., Youker, R.T., **Breckenridge, C.B.**, & Zirkin, B.R., Atrazine effects on Testosterone levels and androgen-dependent reproductive organs in peripubertal male rats. J of Androl. 2001, 22, 142-148.

Wetzel, L., Luempert, L.G., **Breckenridge, C. B.**, Tisdel, M. O., Stevens, J. T., Thakur, A.K., Extrom, P. J. & Eldridge, J. C. Chronic effects of atrazine on estrus and mammary tumor formation in female Sprague-Dawley and Fischer 344 rats. *J. Toxicol. Environ. Hlth.* 1994, 43, 139-153.

Winocur, G. and **Breckenridge, C.** Cue-dependent behavior of hippocampally damaged rats in a complex maze. Journal of Comparative and Physiological Psychology, 1973, 82, 512-522.

Weiner, M., Nemic, M., Sheets, L., Sargent, D., and **Breckenridge, C.** Comparative functional observatory battery study of twelve commercial pryrethroid insecticides in male rats following acute oral exposure. Neurotox. 2009, 30S, S1-S16.



Yau, E. T., Amemiya, K., Lindsay, L. A., Wimbert, K. V., Giknis, Wetzel, L., Stevens, J., Traina, and **Breckenridge, C.** The effect of the triazine herbicide atrazine on embryonic and fetal development. *Teratology.* 39:409-438.1989.

G. Syngenta Sponsored Reviews and Publications – CBB Contractor

Alexander, D.D., Mink, P.J., Adami, H-O., Cole, P., Mandel, J.S., Oken, M.M., and Trichopoulos, D., (2007). The non-Hodgkin lymphomas: A review of the epidemiologic literature. Int. J. Cancer, 120, 1-39.

Alexander, D.D., Mink, P.J., Adami, H-O., Chang, E.T., Cole, P., Mandel, J.S. and Trichopoulos, D., (2007). Multiple myeloma: A review of the epidemiologic literature. Int. J. Cancer, 120, 40-61.

Boffetta, P., Adami, H-O., Berry, C. Mandel, J.S., (2013). Atrazine and cancer. A review of the epidemiology evidence. Eur. J. Canc Prev. 22, 169-180.

Brent, J. and Schaeffer, T.H., (2011). Systematic review of Parkinsonian syndromes in short and long-term survivors of paraquat poisoning. JOEM, 53, 1332-1336.

Chang, E.T., Adami, H-O., Bailey, W.H., Boffetta, P., Krieger, R.I., Suresh H. Moolgavkar, S.H, and Jack S. Mandel, J.S., (2014) Validity of geographically modeled environmental exposure estimates. Crit. Rev. Toxicol., 44, 450-466.

Foradori, C.D., Hinds, L.R., Hanneman, W.H., Legare, M.E., Clay, C.M., and Handa, R.J., (2009a). Atrazine inhibits pulsatile luteinizing hormone release without altering pituitary sensitivity to a gonadotropin-releasing hormone receptor agonist in female Wistar rats. Biology of Reproduction, 81, 40-45.

Foradori CD, Hinds LR, Hanneman WH, Handa RJ. (2009b). Effects of atrazine and its withdrawal on gonadotropin-releasing hormone neuroendocrine function in the adult female Wistar rat. Biol Reprod 81(6):1099–1105.

Goodman, M. Mandel, J.S., M., Scialli, A.R., and DeSesso, J., (2014). Atrazine and pregnancy outcomes: A systematic review of the epidemiology evidence. *Birth Defects Research, Part B. Developmental and Reproductive Toxicology*, 101, 215-236.

Mandel, J.S., Adami, H-O., and Cole, P. (2012) Paraquat and Parkinson's disease: An overview of the epidemiology and a review of two recent studies. Reg Tox Pharmacol, 62,385–392.

Sathiakumar, N., MacLennan, P.A., Mandel, J. and Delzell, E. (2011). A review of epidemiology studies of triazine herbicides and cancer. Crit. Rev Toxicol. 41, 1-34.

Wirdefeldt, K., Adami, H-O., Cole, P., Trichopoulos, D. and Mandel, J. (2011). Epidemiology and etiology of Parkinson's disease: A review of the evidence. Eur. J. Epidemiol., 26, S1-S58.

H. Letters to the Editor

Berry, C., Botham, P., **Breckenridge, C.** and Smith, L. Comments on Paths from Pesticides to Parkinson's Disease. Sci., 2013, 341, 722-723.

Cook, A.R, **Breckenridge, C.** Sturgess, N., Minnema, D., Travis, K., and Botham, P. (2014). Biochem Molec Toxicol., 28(7), 289-290.

Cook, A.R., Botham, P.A., **Breckenridge, C.B.**, Minnema, D.J., Sturgess, N.C., Travis, K.Z. (2016). Neurotoxicity of paraquat and paraqut-induced mechanisms of developing Parkinson's disease. Laboratory Investigations, 96, 1028-1089.

I. Book Chapters

Breckenridge, C.B., Simpkins, J., Eldridge, J.C., and Stevens, J.T., Symmetrical Triazine Herbicides: A Review of Regulatory Endpoints. Chapter 79, pp 1711-1723. In *Handbook of Pesticide Toxicology: Agents.* 3rd Edition, R. Kreiger (Ed.), Classes of Pesticides, Academic Press, Inc. New York. 2010.

Breckenridge, C.B. and Stevens, J.T. Crop Protection Chemicals: Mechanisms of Action and Hazard Profiles, Chapter 16. In: Principals and Methods of Toxicology. 5th Edition, A. Wallace Hayes (Ed.), Taylor and Francis Ltd, Philadelphia. pp. 727-840, 2007.

Breckenridge, C.B., Sielken, R.L., Jr., and Stevens, J. T. Aggregate and Cumulative Exposure and Risk Assessment. Chapter 5. In *Pesticides: Managing Risks and Optimizing Benefits*. N.N. Ragsdale and J.N. Seiber, Eds. ACS Symposium Series 734. Oxford University Press., Washington, pp. 38-67. 1999.

Breckenridge, C.B., Werner, C. Stevens, J.T., and Sumner, D.D.: Hazard Assessment for selected Symmetrical and Asymmetrical Triazine Herbicide. Chapter 25 In: <u>The Triazine Herbicides</u>, H. M. LeBaron, J. McFarland, O. Burnside, and R. Clark, Eds. Elsevier, San Diego, pp 387-398, 2008.

Genter, M.B. and **Breckenridge, C.B**. Chloroaceteamide-Induced Nasal Carcinogenesis in Rats. 2009. Chapter 17, pp 427-434. In: Nose and Viral Cancer: Etiology, Pathogenesis, Editors: A. Medeiros, C. Veloso, Nova Sciences Publishers, Inc.

Stevens, J.T. and **Breckenridge, C.B.** Agricultural Chemicals: Regulation, Risk Assessment, and Risk Management. In *Regulatory Toxicology*, S.C. Gad (Ed.), Taylor and Francis Books, London pp. 215- 243, 2001.

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Stevens, J.T. and **Breckenridge, C.B.** Crop Protection Chemicals. Chapter 13. In *Principles and Methods of Toxicology*, 4th Edition, A. Wallace Hayes (Ed.), Taylor and Francis Ltd, Philadelphia. pp. 565-648. 2001.

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J. Posters and Platform Presentations at Scientific Meetings

Bier, C., Collins, C., Breckenridge, C., Lulham, G., & Proctor, B. Acute toxicity (oral and inhalation) of methyl-DBCP. The Toxicologist, 1984, 4, 20.

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Minnema, D., Breckenridge, C., Eldridge, J.C., McFarland, J. and Stevens, J.: The Effect of 6-Months Feeding of Atrazine, Simazine, and A Common Metabolite, Diamino-Chloro-Triazine, on the Luteinizing Hormone Surge in Female Sprague-Dawley Rats. *The Toxicologist.* Abstract # 1524. 2001.

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