THE UNIVERSITY OF NEWCASTLE AUSTRALIA

# The Consequences of Acrylamide Exposure on the Male Germ Line

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B. Biotech. (Hons) Class I

*A thesis submitted to the Faculty of Science and Information Technology, The University of Newcastle, Australia, in fulfilment of the requirements of the degree of Doctor of Philosophy.*

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# Declarations

*Statement of Originality*

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Belinda Jean Nixon

Date: 21st December 2013

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I hereby certify that the work embodied in this thesis contains a published paper of which I am a joint author. I have included as part of the thesis a written statement, endorsed by my supervisor, attesting to my contribution to the joint publications.

Belinda Jean Nixon

Date: 21st December 2013

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(Signature of Primary Supervisor)
Dr. Shaun D. Roman

Date: 21st December 2013

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(Signature of Co-Supervisor)
A/Prof. Brett Nixon

Date: 21st December 2013

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# Manuscripts Included as Part of this Thesis

- Nixon, B. J., Stanger, S., Nixon, B. and Roman, S. (2012). *Chronic exposure to acrylamide induces DNA damage in male germ cells of mice.* Toxicological Sciences: An official journal of the Society of Toxicology. 129: 135-145.

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# List of Additional Publications

- Nixon, B. J., Nixon, B. and Roman, S. D. (2012) *The Consequences of Acrylamide Exposure on the Male Germ Line.* Society for Reproductive Biology, Brisbane, QLD, Australia. Oral presentation.

- Nixon, B. J., Nixon, B. and Roman, S. D. (2011) *The Consequences of Chronic Exposure to Acrylamide on the Male Germ Line.* Biology RHD Conference, University House, University of Newcastle, Australia. Oral presentation.

- Nixon, B. J., Nixon, B. and Roman, S. D. (2011) *The Consequences of Acrylamide Exposure on the Male Germ Line.* Joint World Congress on Reproductive Biology and Society for Reproductive Biology, Cairns, QLD, Australia. Oral presentation.

- Nixon, B. J., Nixon, B. and Roman, S. D. (2011) *The Response of Early Male germ Cells to Acrylamide Exposure.* Joint World Congress on Reproductive Biology and Society for Reproductive Biology, Cairns, QLD, Australia. Poster presentation.

- Nixon, B. J., Nixon, B. and Roman, S. D. (2010) *The Consequences of Acrylamide Exposure on the Male Germ Line.* Society for Reproductive Biology, Sydney Exhibition and Convention Centre, Australia (2010) Oral presentation.

- Nixon, B. J., Nixon, B. and Roman, S. D. (2010) *The Consequences of Acrylamide Exposure on Early Male Germ Cells.* OzBio, Melbourne Convention and Exhibition Centre, Australia. Poster presentation.

- Nixon, B. J., Nixon, B. and Roman, S. D. (2009) *The Consequences of Chronic Exposure to Acrylamide on the Male Germ Line.* ARC Centre of Excellence for Biotechnology and Development Conference, Melbourne, Australia. Oral presentation.

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An electronic version of this thesis, together with all associated files and data, are included on disc found on the inside back cover of this thesis.

# Abstract

Acrylamide is a commonly used industrial compound; however it is also naturally occurring in cooked foods such as potatoes, breads and coffee. Since the discovery of acrylamide formation in food, significant research has been carried out to determine the consequences of human dietary exposure to acrylamide. The reproductive toxicity of acrylamide was the focus of this thesis; however the compound is also known to cause neurotoxicity, carcinogenicity and genotoxicity. In rodent studies, acrylamide reproductive toxicity is primarily mediated through paternal exposure, and has been observed to induce DNA damage, male infertility, dominant lethality, heritable translocations and embryo resorptions. Thus, prolonged exposure to acrylamide in males not only has implications within the individual, but may have consequences for future offspring.

The aims of this thesis were to examine the nature of DNA damage induced by acrylamide in male germ cells, and to investigate whether this damage could be induced at levels equivalent to human estimates. These aims were addressed using a series of experiments in isolated mouse germ cells, as well as a chronic exposure study in which acrylamide was administered to male mice via the drinking water for one year. Genome-wide microarray analyses were subsequently used to explore the molecular mechanisms that mediate the damage induced in the testis of acrylamide exposed mice.

The results of this study indicated that acrylamide-mediated DNA damage was likely due to the presence of both DNA adducts as well as oxidative damage in mouse male germ cells. Furthermore, chronic exposure to acrylamide in male mice led to significant dose and time-dependent increases in DNA damage in male germ cells. Microarray analyses offered insight into the mechanisms that generate deleterious effects in the testes of mice following acrylamide exposure, and identified several potential biomarkers of exposure. The outcomes of this research will provide better understanding of acrylamide toxicity and shed light on the consequences of xenobiotic exposure in the male.