Australian Government
National Health and Medical Research Council

NHMRC

Consultation paper

Biotoxin-related illnesses in Australia – Health and medical research needs

November 2020

1. Introduction

In 2018, the House of Representatives Standing Committee on Health, Aged Care and Sport (the Committee) conducted an Inquiry into Biotoxin-related Illnesses in Australia (the Inquiry). The Committee received submissions about the ill-effects suffered by people exposed to contaminated indoor environments, most commonly water-damaged buildings[1].

Biotoxins in the context of the Inquiry largely refer to moulds and their spores, but could also include other biotoxic agents that may be present in damp indoor environments. Moulds are naturally-occurring types of fungi that can be found throughout the environment, both indoors and outdoors. Mould produces airborne spores, which have the potential to cause health issues if inhaled by susceptible individuals[2, 3] such as people with allergies, asthma, weakened immune systems and/or other health conditions[4, 5]. In addition to these known health impacts of mould biotoxins, a complex syndrome of chronic, multisystem and multi-symptom illness, referred to as Chronic Inflammatory Response Syndrome (CIRS) or dampness and mould hypersensitivity syndrome (DMHS)[6], has been described in Australia and internationally as a biotoxin-related illness[7-9]. CIRS and biotoxin-related illnesses have been reported following exposure to mould biotoxins in buildings arising from excessive moisture build-up from water damage. Buildings can become water-damaged after events such as leaks, heavy rain and flooding. Moisture can also enter a building through incoming air or through a build-up of condensation[9-11].

As CIRS and biotoxin-related illnesses are not captured within the National Notifiable Diseases Surveillance system[12], it is difficult to estimate the number of people who are exposed to indoor mould and experiencing health conditions related to biotoxins.

The Committee received evidence that there is no general consensus on the potential health impacts of biotoxins associated with mould and water damaged buildings. Further, it heard there is some uncertainty regarding the level at which mould may begin to pose a health risk. As a result, the Inquiry recommended – and the Australian Government accepted – that further research into CIRS-like syndromes and any links with mould and biotoxins be undertaken, with a view to assisting in the diagnosis, treatment and management of patients.

The purpose of this paper is to consult experts, professional groups, research end-users and patient support groups on the health and medical research gaps identified by the Inquiry. The consultation will inform the development of an NHMRC Targeted Call for Research into Biotoxin-related Illnesses in Australia (Biotoxins TCR).

2. NHMRC's role

The National Health and Medical Research Council (NHMRC) is the Australian Government's lead agency for funding health and medical research that contributes to improvements in individual and population health. NHMRC awards research funding based on rigorous, competitive peer review that identifies the best science and most significant research.

One of NHMRC's grant schemes, Targeted Calls for Research (TCR), has a small annual budget allocation to allow for a one-time solicitation of grant applications to address a specific or emerging health issue. The scope, objectives and selection criteria of a TCR are highly specified to ensure successful applications fulfil the desired outcomes of the call and address a specific research gap.

As part of the Australian Government's response to the Inquiry, NHMRC will allocate $2 million to conduct a TCR into Biotoxin-related Illnesses in Australia.

This grant opportunity aligns with NHMRC's strategic priority of "Integrated and coordinated approaches to chronic conditions" as identified in the *NHMRC Corporate Plan 2020-21*. It also complements other funding opportunities available through NHMRC's grant program, which welcome applications for research on all aspects of human health.

2.1. Analysis of NHMRC research funding and activities

Between 1999 and 2019, NHMRC awarded approximately $28 million for research related to biotoxins (Table 1). Application numbers and success rates over the same period are shown in Figure 1.

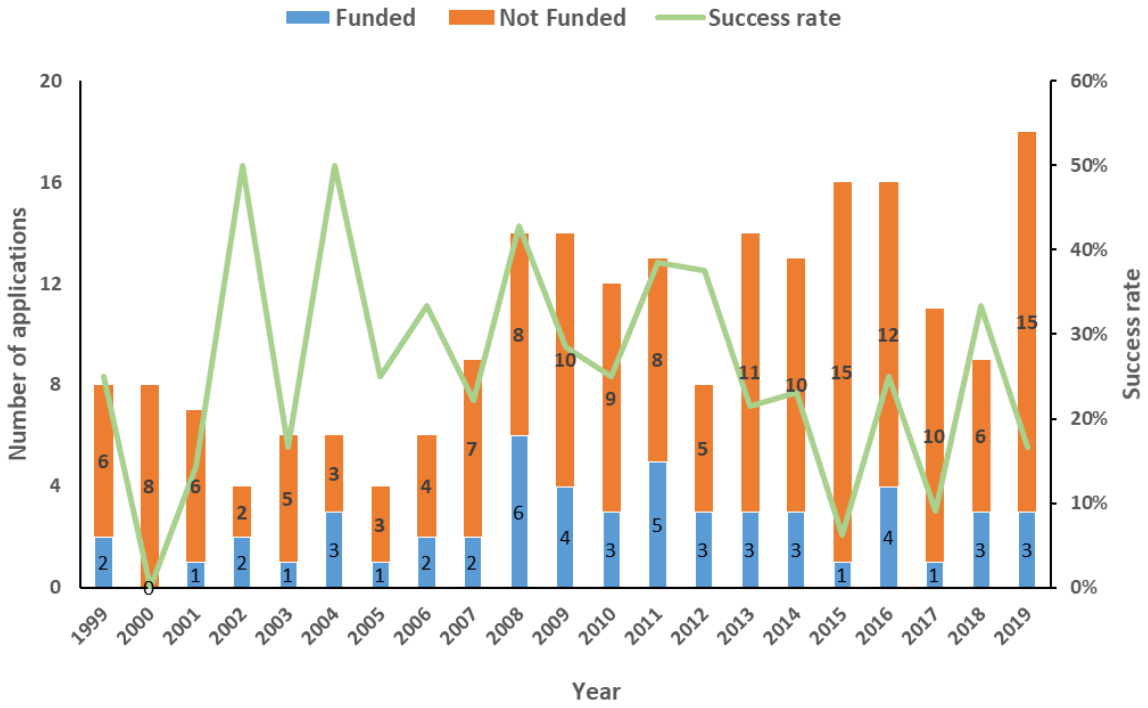

Figure 1: Number and success rate of NHMRC-funded research applications related to biotoxins between 1999 and 2019.

As shown in Table 2, most of the funded projects studied the health impacts of mould biotoxins in vulnerable (e.g. immunocompromised) population groups or involved testing new drugs. Only a small number of projects have specifically addressed the health implications of mould in indoor built environments.

These funding data suggest that there is an opportunity to expand the current knowledge of biotoxin-related illnesses and CIRS in Australia by capitalising on existing national capacity and capability and building international linkages.

In addition, in October 2020, NHMRC announced $2.5 million in funding over five years to support a new Centre of Research Excellence (CRE) in Healthy Housing. While not specifically focused on the health effects of household mould, the Centre aims to support healthy housing policy and housing-focussed interventions that will provide positive impacts

for population health. Further information on the Healthy Housing CRE, including areas of research focus, can be found on the Healthy Housing CRE website.

3. Adverse health effects of mould biotoxins

While the Committee heard there was insufficient evidence and a lack of consensus in Australia on the potential health impacts of biotoxins associated with mould and water damaged buildings, a number of predominately international studies have reported a range of possible health effects[13-16] and point to a growing body of evidence in this area[6, 17-19].

For example:

- Reviews[13, 20-22] and meta-analyses[23, 24] of epidemiological evidence from multiple countries with various climatic conditions have reported an association between indoor dampness-related factors and various respiratory health effects such as asthma exacerbation, asthma development, respiratory infections, hypersensitivity pneumonitis, coughing, wheezing and dyspnoea.
- Several studies[18, 25, 26] and a recent review of the literature (2020)[15] have found associations between living in water-damaged buildings and adverse health effects including CIRS-like symptoms. These symptoms can include ongoing fatigue, headaches, pain, eye problems, gastrointestinal tract problems, cognitive symptoms such as 'brain fog', skin issues and muscle cramps, amongst others[27, 28].
- Some research suggests that certain groups of the population including immunocompromised people (e.g. undergoing cancer therapy), those with an immature immune system (e.g. children) or others with genetic susceptibility or allergy to mould are more vulnerable to living in water-damage buildings and may display CIRS-like symptoms more than other groups[16, 18, 19, 22, 24].
- Recent research has highlighted the growing issue of unhealthy housing in Australia. It was estimated that in 2016, around 2.5 million Australians occupied housing likely to adversely impact their health, with unhealthy housing vulnerability often intersecting with other forms of disadvantage[29].

4. Research gaps and challenges

The Inquiry received submissions from many individuals, professionals and organisations from across Australia regarding the need for further research to support effective diagnosis, treatment and management of CIRS-like syndromes[1].

Areas of particular need identified through the Inquiry were:

- Determining the prevalence of CIRS in the population, including whether predictive testing could be used and the prevalence of susceptible gene types.
- Determining the most effective methods for the identification and treatment of CIRS.
- Developing a better understanding of the nature of biotoxin-related illness, including the health effects of exposure to mould and biotoxins and any links between exposure and complex symptoms most commonly reported as typifying CIRS.
- Broader research into potential overlaps between groups of patients who have very similar symptoms such as those associated with CIRS, Lyme disease and/or chronic fatigue syndrome (e.g. whether there is a common background in the biology of people so that different triggers might produce similar symptoms).

Other research needs mentioned in the literature include, but are not limited to:

- Better methods and guidelines to address current difficulties in diagnosing patients [18] and to assist with identifying vulnerable and at-risk population groups, such as the identification of specific biomarkers associated with displaying the symptoms in susceptible, vulnerable and even tolerant individuals[6, 30-32].
- High quality, consistent evidence to support treatment options and management methods for CIRS-like symptoms in subjects exposed to biotoxins in water-damaged buildings[18, 19, 28].
- Reliable metrics and an understanding of dose-response relationships to understand the health risks[33-35].

The Committee noted that options to improve the diagnosis and treatment of complex illness and unexplained symptoms may help to reduce the social and financial burden for individuals, ensure doctors are provided with adequate support and training, and reduce the resulting impact on the health system.

5. The way forward

Your views are sought on the following questions:

1. What are the gaps in evidence for biotoxin-related illnesses and CIRS-like symptoms caused by indoor mould that most urgently need to be addressed in Australia?
2. How would addressing these gaps benefit the diagnosis, treatment and/or management of patients?
3. What research, if any, is already underway or planned to address these gaps and how could a TCR best complement these activities?
4. What are the challenges in addressing the need for research into these conditions?
5. What research areas are likely to:
    a. reduce the impact of biotoxin-related illnesses on affected individuals and communities
    b. assist health services to manage these health issues, and/or
    c. enable policy makers to make informed decisions?

This feedback will assist NHMRC in identifying the specific areas of research most needed to understand how people with complex symptoms associated with exposure to biotoxins can be more effectively diagnosed, treated and managed in the health system, and how these needs can be best addressed through a TCR.

Deadline and format of submissions

Responses should be recorded using the provided Consultation Response Form and submitted via email to targeted.research@nhmrc.gov.au no later than 18 January 2021.

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Table 1: NHMRC funding of biotoxin research between 1999 and 2019 grouped by funding scheme

Year	Career Development Fellowships	Early Career Fellowships	Ideas Grants	Postgraduate Scholarships	Project Grants	Research Fellowships	Total
1999				$26,889	$242,563		$269,452
2000							
2001					$511,650		$511,650
2002					$515,875		$515,875
2003						$658,750	$658,750
2004					$2,023,750		$2,023,750
2005					$588,679		$588,679
2006					$787,238		$787,238
2007					$1,798,363		$1,798,363
2008	$387,490				$2,203,486		$2,590,975
2009		$324,387			$1,521,801		$1,846,188
2010					$1,539,714		$1,539,714
2011					$2,931,497		$2,931,497
2012				$141,559	$1,291,833		$1,433,392
2013					$1,713,450		$1,713,450
2014		$246,922			$1,191,006		$1,437,928
2015					$598,270		$598,270
2016				$128,539	$2,421,598		$2,550,137
2017					$720,717		$720,717
2018				$132,126	$641,174	$736,188	$1,509,488
2019			$1,448,827	$132,742			$1,581,568
Grand total	**$387,490**	**$571,309**	**$1,448,827**	**$561,855**	**$23,242,664**	**$1,394,938**	**$27,607,083**

Table 2: Details of applications funded by NHMRC between 1999 and 2019 on health implications of biotoxins

Application Year	CIA Name	Title	Administering Institution	Budget Total	Broad Research Area	Field Of Research
1999	Dr Ann Koehler	Studies on dimorphism in Penicillium marneffei	James Cook University	$26,889.00	Basic Science	Microbiology not elsewhere classified
1999	Prof Peter Gibson	Airway inflammation in allergic aspergillosis	University of Newcastle	$242,562.73	Clinical Medicine and Science	Respiratory Diseases
2001	Lesley Wright	An enzyme from a pathogenic fungus which may be used as a target for anti-fungal drug development	University of Sydney	$511,650.00	Basic Science	Medical Microbiology not elsewhere classified
2002	A/Pr Euan Tovey	Exposure to Fungi in Asthma	University of Sydney	$200,500.00	Clinical Medicine and Science	Allergy
2002	Prof Alex Andrianopoulos	How fungi cause disease in man	University of Melbourne	$315,375.00	Basic Science	Medical Microbiology not elsewhere classified
2003	A/Pr Euan Tovey	Uncoupled Research Fellowship	University of Sydney	$658,750.00	Basic Science	Allergy
2004	Prof Monica Slavin	Can we improve the treatment of fungal infections in hematology patients by using new diagnostic tests?	Burnet Institute	$1,095,500.00	Clinical Medicine and Science	Infectious Diseases
2004	Prof Wieland Meyer	Phylogeny of pathogenic fungi	University of Sydney	$440,750.00	Basic Science	Medical Microbiology not elsewhere classified
2004	Lesley Wright	How does phospholipase B get out of pathogenic fungal cells?	University of Sydney	$487,500.00	Basic Science	Medical Microbiology not elsewhere classified
2005	Prof Katrina Jolliffe	Fungal Phospholipases: A Novel Drug Discovery Platform	University of Sydney	$588,679.35	Basic Science	Medical Microbiology not elsewhere classified
2006	Prof James Fraser	Microevolution of the fungal pathogen Cryptococcus during human infection	University of Queensland	$322,028.39	Basic Science	Medical Microbiology not elsewhere classified
2006	A/Pr Robert Ashman	How phagocytic cells recognise yeast	University of Queensland	$465,210.05	Basic Science	Biochemistry and Cell Biology not elsewhere classified
2007	Prof Alex Andrianopoulos	Discovering unique pathways in pathogens which can be used to control them.	University of Melbourne	$540,075.08	Basic Science	Medical Microbiology not elsewhere classified
2007	Prof Tania Sorrell	Predicting the risk of invasive candidiasis in critically ill patients	University of Sydney	$1,258,287.42	Clinical Medicine and Science	Epidemiology
2008	Prof Bircan Erbas	Outdoor aeroallergen exposure and asthma exacerbations	La Trobe University	$473,924.87	Public Health	Epidemiology
2008	Prof Alex Andrianopoulos	Understanding how pathogens infect their hosts and cause disease.	University of Melbourne	$342,735.34	Basic Science	Medical Microbiology not elsewhere classified
2008	Prof James Fraser	Evolution of virulence in a pathogenic fungus	University of Queensland	$387,489.51	Basic Science	Medical Microbiology not elsewhere classified
2008	Mr Carl Morrow	Evolution of a fungal pathogen of humans	University of Queensland	*	Basic Science	Medical Microbiology NEC
2008	Prof Katrina Jolliffe	Targeting Fungal Phospholipid Metabolism for Antifungal Drug Discovery	University of Sydney	$828,557.78	Basic Science	Medical Microbiology not elsewhere classified
2008	A/Pr Deidre Carter	Fungal proteins important in animal infection	University of Sydney	$558,267.64	Basic Science	Medical Microbiology not elsewhere classified
2009	Prof Christine Wells	Understanding susceptibility to fungal infection	Griffith University	$581,427.84	Basic Science	Gene Expression (incl. Microarray and other genome-wide approaches)
2009	Prof Anton Peleg	Understanding the interactions between bacteria and fungi; the potential to uncover new targets for antibiotics	Monash University	$324,386.90	Basic Science	Infectious Diseases
2009	A/Pr Julianne Djordjevic	How do host invading factors get released by pathogenic fungi	University of Sydney	$536,304.35	Basic Science	Medical Microbiology not elsewhere classified

Application Year	CIA Name	Title	Administering Institution	Budget Total	Broad Research Area	Field Of Research
2009	Prof Graham Lieschke	Understanding a fungal infection and looking for new treatment approaches	Walter and Eliza Hall Institute of Medical Research	$404,068.71	Basic Science	Infectious Diseases
2010	Prof Alex Andrianopoulos	Investigating the interactions between host and pathogen	University of Melbourne	$578,085.75	Basic Science	Medical Microbiology not elsewhere classified
2010	Prof Luke Guddat	Discovery of new antifungal agents.	University of Queensland	$481,135.86	Basic Science	Enzymes
2010	Prof Anton Peleg	Interactions between bacteria and fungi; the potential to uncover new targets for antibiotics	Monash University	$480,492.68	Basic Science	Medical Bacteriology
2011	A/Pr Deidre Carter	New drug strategies for fungal diseases	University of Sydney	$484,420.45	Basic Science	Medical Microbiology not elsewhere classified
2011	A/Pr Ana Traven	Characterization of new targets for antifungal drug development	Monash University	$337,614.21	Basic Science	Cellular Interactions (incl. Adhesion, Matrix, Cell Wall)
2011	Prof David Gottlieb	Cell therapy to prevent and treat fungal infections in transplant patients	University of Sydney	$987,873.31	Clinical Medicine and Science	Haematological Tumours
2011	Prof Wieland Meyer	Discovering the genetic basis of fungal virulence	University of Sydney	$561,189.91	Clinical Medicine and Science	Medical Infection Agents (incl. Prions)
2011	Prof Wieland Meyer	DNA barcoding of pathogenic fungi	University of Sydney	$560,398.86	Clinical Medicine and Science	Medical Infection Agents (incl. Prions)
2012	Prof James Fraser	Purine metabolism as an antifungal drug target	University of Queensland	$704,198.62	Basic Science	Medical Microbiology not elsewhere classified
2012	Prof Tania Sorrell	Pathogenesis of cryptococcal meningoencephalitis	University of Sydney	$587,634.77	Clinical Medicine and Science	Medical Microbiology not elsewhere classified
2012	Dr Rachel Tham	The contribution of outdoor fungi, air pollution and respiratory viruses on child asthma hospitalisations	University of Melbourne	$141,558.88	Public Health	Epidemiology
2013	A/Pr Julianne Djordjevic	The inositol polyphosphate kinase pathway in Cryptococcus neoformans	University of Sydney	$545,189.80	Basic Science	Medical Microbiology not elsewhere classified
2013	Prof Graham Lieschke	Understanding the causes of fungal infection in order to treat them better	Monash University	$561,028.33	Basic Science	Haematology
2013	Prof Anton Peleg	Prevention of Hospital-acquired Infections	Monash University	$607,231.92	Basic Science	Medical Microbiology not elsewhere classified
2014	Dr Thomas Naderer	Fungal determinants and host cell death signals in fatal Candida infections	Monash University	$654,091.81	Basic Science	Medical Microbiology not elsewhere classified
2014	Prof Luke Guddat	Acetohydroxyacid synthase: A new drug target for human fungal pathogens	University of Queensland	$536,914.53	Basic Science	Structural Biology (incl. Macromolecular Modelling)
2014	Dr Sandeep Chhabra	New strategies to target multiple drug resistance in clinically relevant fungal infections.	Monash University	$246,922.08	Basic Science	Structural Biology (incl. Macromolecular Modelling)
2015	A/Pr Ana Traven	An investigation into mitochondrial dynamics in the human pathogen Candida albicans	Monash University	$598,270.38	Basic Science	Medical Infection Agents (incl. Prions)
2016	Prof Alex Andrianopoulos	Dissecting virulence attributes in a human pathogenic fungus	University of Melbourne	$843,929.51	Basic Science	Medical Microbiology not elsewhere classified
2016	Prof James Fraser	Microevolution of Cryptococcus neoformans	University of Queensland	$802,450.02	Basic Science	Medical Microbiology not elsewhere classified
2016	Ms Karen Urbancic	Defining targets for antifungal stewardship in immunocompromised patients: optimising care and safety	University of Melbourne	$128,539.35	Clinical Medicine and Science	Infectious Diseases

Application Year	CIA Name	Title	Administering Institution	Budget Total	Broad Research Area	Field Of Research
2016	Prof Wieland Meyer	Closing the gap in early diagnostic capabilities for mycoses - DNA barcoding to combat an emerging global health problem	University of Sydney	$775,218.42	Clinical Medicine and Science	Medical Microbiology not elsewhere classified
2017	A/Pr Ana Traven	An investigation into chromatin dynamics in host-pathogen interactions and fungal virulence	Monash University	$720,716.60	Basic Science	Medical Infection Agents (incl. Prions)
2018	Dr Hayley Barnes	Clinical and biological approaches to improving diagnostic confidence of Chronic Hypersensitivity Pneumonitis	Monash University	$132,126.09	Clinical Medicine and Science	Respiratory Diseases
2018	A/Pr Ana Traven	Control of host-pathogen interactions and fungal virulence by short chain fatty acids	Monash University	$641,174.17	Basic Science	Medical Infection Agents (incl. Prions)
2018	Prof Benjamin Marsland	Harnessing the microbiome to protect against chronic lung diseases	Monash University	$736,188.15	Clinical Medicine and Science	Allergy
2019	A/Pr Julianne Djordjevic	Fungal IP7-protein interaction and invasive fungal disease: a dangerous liaison.	University of Sydney	$744,154.32	Basic Science	Signal Transduction
2019	Prof Avril Robertson	Novel Broad Spectrum Antifungals Active Against Drug Resistant Candida Auris	University of Queensland	$704,672.20	Clinical Medicine and Science	Biologically Active Molecules
2019	Dr Olivia Smibert	Defining the role of the host microbiome and transplantation	University of Melbourne	$132,741.92	Clinical Medicine and Science	Infectious Diseases

*This grant was offered but declined by the applicant and so no funding amount is recorded.