THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Assessing Exposure of Young Australian Children to Toxicants in the Home Environment using a Web-Based Questionnaire

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Bachelor of Medicine Bachelor of Surgery, Bachelor of Science

A thesis submitted for the degree of Doctor of Philosophy at

The University of Queensland in 2018

Faculty of Medicine

Abstract

The presence of endocrine disrupting chemicals (EDCs) in the home environment is ubiquitous and is a major contributor to the exposure of young children to these chemicals. EDCs are found throughout the domestic environment, including in consumer goods, dust, air and food. Whilst the term EDCs refers to chemicals that have been demonstrated to disrupt the normal homeostasis of the endocrine system, they also affect a variety of other systems.

Epidemiological evidence suggests that exposure to EDCs during the foetal period and childhood may be contributing to the increasing incidence of non-communicable diseases, such as obesity, during childhood and possibly later in life. However, to date, little research has been conducted in Australia to assess exposure of young (less than three years old) children to EDCs and associated health outcomes. The current 'gold standard' of assessing human exposure to these chemicals is biomonitoring. Biomonitoring in environmental epidemiology studies of children is ethically and practically challenging. There is a pressing need to develop alternative practical and accurate exposure assessment methods for use in large-scale children's environmental epidemiology studies.

The aim of this PhD was to explore the feasibility of online questionnaires as an alternative method of exposure assessment – by designing a household-level exposure-assessment questionnaire and then administering it in conjunction with human biomonitoring. The feasibility testing was conducted for two selected groups of EDCs, insecticides, with the pyrethroids and organophosphates as the chemicals of interest, and polybrominated diphenyl ether flame retardants (PBDEs). Plastics, with bisphenol A and phthalates as the focus, were included in the questionnaire design phase of this thesis, but were then excluded from the questionnaire in the human biomonitoring study to reduce its length.

To identify potential determinants of exposure to be included in the exposure-assessment questionnaire extensive literature reviews were conducted. However, the information obtained from literature reviews alone was insufficient to ensure the content validity of the questionnaire, since data on EDC exposure pathways in Australian households were scarce and international data is not necessarily generalisable to the Australian context. Additional primary research was therefore undertaken in Queensland, Australia, to obtain more information on insecticide exposures. A more extensive literature review was also undertaken with a specific focus on the flame-retardant BDE-209.

The questionnaire was then designed and pre-tested. After this phase, plastics were removed from the questionnaire to reduce its total length. To assess the feasibility of the approach, the questionnaire was administered in a questionnaire-biomonitoring study of 61 families with children

aged <2 years (at the time of recruitment) from Brisbane and Toowoomba, QLD. Practical aspects of questionnaire administration were assessed and the content validity of the questionnaire was examined by assessing the association between questionnaire data and human biomonitoring data via linear regression modelling.

The PBDE flame retardants as a group failed to meet many of the criteria important for effective exposure-assessment questionnaires during the design phase of the questionnaire. Despite the extensive literature reviews conducted in this PhD, many gaps in our knowledge of PBDE sources and exposure pathways exist for young children. Of the known possible sources, many of these cannot be confidently identified via a questionnaire. Since there are multiple sources and exposure pathways (including historical and maternal exposures) that contribute to PBDE body burdens in children, it is not feasible to measure all of these in a questionnaire. Finally, in the questionnaire-biomonitoring study, associations between questionnaire data and PBDE biomonitoring concentrations were not consistent with exposure determinants that had previously been identified. Biomonitoring therefore remains the exposure assessment method of choice for PBDEs.

There was a relatively greater body of work examining young children's exposure to insecticides and more Australian data about likely sources were identified via the literature reviews and the analysis of calls to the Queensland Poisons Information Centre. In contrast to PBDEs, the major pathways of exposure to insecticides, including diet and domestic pest-control product use, were readily assessable via the questionnaire. In the questionnaire-biomonitoring study, the associations between biomonitoring data of insecticide concentrations and questionnaire data were generally consistent with determinants that were identified in the questionnaire design phase. These findings suggest that questionnaires may be a feasible method of insecticide exposure assessment in young children. Based on this assessment, a formal validation study for the insecticide component of the questionnaire is indicated.

In summary, the questionnaire-based approach to exposure assessment may be feasible when comprehensive exposure pathway data for the chemical of interest are available, when the total number and complexity of exposure pathways is limited, and when sources are readily identifiable via a questionnaire.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

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Publications during candidature

Peer Reviewed Papers

He C., Wang X., Thai P., Baduel C., Gallen C., Banks A., Bainton P., English K., Mueller J.F.: *Organophosphate and brominated flame retardants in Australian indoor environments: Levels, sources, and preliminary assessment of human exposure*. Environ Poll 01/2018; 235:670-679., DOI:10.1016/j.envpol.2017.12.017

Chen Y., Sjodin A., McLachlan M.S., English K., Aylward L.L., Toms L.M., Varghese J., Sly P.D., Mueller J.F.: *Persistent organic pollutants in infants and toddlers: Relationship between concentrations in matched plasma and faecal samples*. Environ Int 10/2017; 107., DOI:10.1016/j.envint.2017.06.019

English K., Chen Y., Toms L.M., Jagals P., Ware R.S., Mueller J.F., Sly P.D.: *Polybrominated diphenyl ether flame retardant concentrations in faeces from young children in Queensland, Australia and associations with environmental and behavioural factors*. Environ Res 10/2017; 158:669-676., DOI:10.1016/j.envres.2017.07.022

Heffernan A.L., English K., Toms L.M., Calafat A.M., Valentin-Blasini L., Hobson P., Broomhall S., Ware R.S., Jagals P., Sly P.D., Mueller J.F.: *Cross-sectional biomonitoring study of pesticide exposures in Queensland, Australia, using pooled urine samples*. Environ Sci Poll Res 09/2016; 23(23)., DOI:10.1007/s11356-016-7571-7

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English K., Jagals P., Ware R.S., Wylie C., Sly P.D.: *Unintentional insecticide poisoning by age: An analysis of Queensland Poisons Information Centre calls*. Aust N Z J Public Health 08/2016; 40(5)., DOI:10.1111/1753-6405.12551

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Reports

Gallen, C.; Banks, A.; Wang, X.; He, C.; English, K.; Gallen, M.; Hearn, L.; Toms, L.M.; Mueller, J. (2015) *Indoor Exposure to Brominated Flame Retardants: Report for Australian Department of Environment*, UniQuest, Brisbane

Publications included in this thesis

English K., Healy B., Jagals P., Sly P.D: *Assessing exposure of young children to common endocrine-disrupting chemicals in the home environment: A review and commentary of the questionnaire-based approach.* Rev Environ Health 02/2015; DOI:10.1515/reveh-2014-0069

– incorporated in Chapter 3

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Karin English (Candidate)	Conception and design (60%) Analysis and interpretation (80%) Drafting and production (50%)
Bridget Healy	Conception and design (5%) Analysis and interpretation (5%) Drafting and production (10%)
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Peter Sly	Conception and design (15%) Analysis and interpretation (5%) Drafting and production (20%)

English K., Jagals P., Ware R.S., Wylie C., Sly P.D.: *Unintentional insecticide poisoning by age: An analysis of Queensland Poisons Information Centre calls*. Aust N Z J Public Health 08/2016; 40(5)., DOI:10.1111/1753-6405.12551

– incorporated in Chapter 6

Contributor	Statement of contribution
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English K., Toms L.M., Gallen C., Mueller J.F.: *BDE-209 in the Australian Environment: Desktop review*. J Hazard Mater 08/2016; 320., DOI:10.1016/j.jhazmat.2016.08.032

– incorporated in Chapter 5

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	Drafting and production (40%)
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English K., Chen Y., Toms L.M., Jagals P., Ware R.S., Mueller J.F., Sly P.D.: *Polybrominated diphenyl ether flame retardant concentrations in faeces from young children in Queensland, Australia and associations with environmental and behavioural factors.* Environ Res 10/2017; 158:669-676., DOI:10.1016/j.envres.2017.07.022

– incorporated in Chapter 8

Contributor	**Statement of contribution**
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Leisa-Maree L. Toms	Conception and design (0%) Analysis and interpretation (5%) Drafting and production (5%)
Paul Jagals	Conception and design (0%) Analysis and interpretation (5%) Drafting and production (5%)
Robert S. Ware	Conception and design (0%)

	Analysis and interpretation (10%)
	Drafting and production (5%)
Jochen Mueller	Conception and design (10%)
	Analysis and interpretation (5%)
	Drafting and production (5%)
Peter D. Sly	Conception and design (10%)
	Analysis and interpretation (5%)
	Drafting and production (5%)

Contributions by others to the thesis

Bridget Healy assisted in drafting the exposure-assessment questionnaire, particularly the questions about plasticisers, and some materials used in the questionnaire-biomonitoring study, such as sample collection instructions, were provided by Bridget. Yiqin Chen completed the methods development and analysis for PBDEs in faeces. Yan Li completed the methods development and analysis for insecticides in urine.

Chapter 9 is a paper that is being prepared for publication. Chang He, Geoff Eaglesham, Jochen Mueller and Xianyu Wang assisted Yan Li with the methods development for the insecticides urinalysis. This paper was drafted by me, with the exception of the parts of the paper that describe the methods for the urinalysis, which were drafted by Yan Li. An earlier version of the paper was proof-read by Chang He, Xianyu Wang, Peter Sly, Rob Ware, Yan Li, and Jochen Mueller with minor edits (grammar, formatting etc.) suggested. Rob Ware reviewed the statistical methods that I used in this paper and provided feedback about the reporting of the statistical methods and results.

Statement of parts of the thesis submitted to qualify for the award of another degree

"None"

Research Involving Human or Animal Subjects

Ethical approval was obtained from:

The University of Queensland (2015000397 & 2015000153), Australia

The Children's Health Queensland Human Research Ethics Committee (HREC 13QRCH207 & HREC15QRCH40).

Approval letters are in the appendix.

Acknowledgements

I would like to acknowledge the assistance of Julie Varghese, Sally Galbraith and Dori Czovek with their assistance with participant recruitment. I would like to acknowledge Bridget Healy for her input regarding the initial questionnaire design, particularly the plastics questions.

I am grateful to the donors of the School of Medicine Scholarships that I received during my candidature, including the donors of the William Nathaniel Robertson Scholarship and Charles Ferdinand Marks and Elizabeth Gray Marks Prize 2016.

I would also like to acknowledge my supervisors, Peter Sly, Paul Jagals, and Rob Ware and other members of the University of Queensland, Jochen Mueller and Gita Mishra, who offered me additional research opportunities during my candidature and provided me with guidance throughout the PhD process.

I would like to thank my father, Dallas English, for teaching me where to find answers without ever giving them away in the process.

I would like to thank my 'thesis support team', Robert Looke, Korinne Northwood, Claire Shackleton, Jo Schagen, Kate and David Looke and my parents Virginia and Dallas English.

Finally, I would like to thank the numerous teachers and mentors I have had over the years who have inspired me to pursue research in the field of toxicology and public health.

Financial support

This research was supported by an Australian Government Research Training Program Scholarship.

I was the recipient of three scholarships from the University of Queensland School of Medicine:

- Charles Ferdinand Marks and Elizabeth Gray Marks Prize 2016
- Willian Nathaniel Robertson Scholarship 2014 & 2016

Keywords

Exposure assessment, flame retardants, pesticides, plasticisers, questionnaire-based exposure assessment, biomonitoring, children's exposure assessment

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 111706, Epidemiology, 30%

ANZSRC code: 111506 Toxicology (incl. Clinical Toxicology), 10%

ANZSRC code: 111705 Environmental and Occupational Health and Safety, 60%

Fields of Research (FoR) Classification

FoR code: 1117, Public Health and Health Services 90%

FoR code: 1115 Pharmacology and Pharmaceutical Sciences, 10%

Dedications

In memory of Dr William von Witt

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List of Abbreviations used in the Thesis

2-Methyl-3-phenylbenzoic acid (MPA)

3,5,6-Trichloropyridinol (TCPy)

3-Methyl-4-nitrophenol

3-Phenoxybenzoic acid (PBA)

Australian Competition and Consumer Commission (ACCC)

Australian Pesticides and Veterinary Medicines Authority (APVMA)

Benzyl butyl phthalate (BzBP)

Benzyl butyl phthalate(BzBP)

Bisphenol A (BPA)

Body mass index (BMI)

Brominated diphenyl ether (BDE-100)

Brominated diphenyl ether (BDE-153)

Brominated diphenyl ether (BDE-209)

Brominated diphenyl ether 28 (BDE-28)

Brominated diphenyl ether 47 (BDE-47)

Brominated diphenyl ether 99 (BDE-99)

Building Code of Australia (BCA)

cis 3-(2,2-Dibromovinyl)-2,2-dimethyl-cyclopropane-1-carboxylic acid (DBCA)

cis- and trans-3-(2,2-dichlorovinyl)-2, 2-dimethyl-cyclopropane-1-carboxylic acid (DCCA)

Cytochrome P450 (CYP 450)

Di-2-ethyl hexyl phthalate (DEHP)

Dialkylphosphates (DAPs)

Dibutyl phthalate (DBP)

Diethyl dithiophosphate (DEDTP)

Diethyl phosphate (DEP)

Diethyl phthalate (DEP)

Diethyl thiophosphate (DETP)

Di-isobutyl phthalate(DiBP)

Dimethyl dithiophosphate (DMDTP)

Dimethyl phosphate (DMP)

Dimethyl thiophosphate (DMTP)

Endocrine disrupting chemicals (EDCs)

Food frequency questionnaires (FFQs)

Food Standards Australia New Zealand (FSANZ)

Hexabromocyclododecane (HBCDD)

High impact polystyrene (HIPS)

Intra-class coefficient (ICC)

Maximum permitted concentrations (MPC)

Method limit of detection (mLOD)

Method limit of quantification (mLOQ)

Mono-(2-ethyl-5-carboxypentyl)phthalate (MECPP)

Mono-(2-ethyl-5-hydroxyhexyl)phthalate (MEHHP)

Mono-(2-ethyl-5-oxohexyl)phthalate (MEOHP)

Mono-2-ethyl hexyl phthalate (MEHP)

Monobenzyl phthalate (MzBP)

Monoethyl phthalate (MEP)

Monoisobutyl phthalate (MiBP)

Mono-*n*-butyl phthalate (MnBP)

National Industrial Chemical Notification and Assessment Scheme (NICNAS)

National Registration Scheme for Agricultural and Veterinary Chemicals (NRS)

Peroxisome proliferator-activated receptors (PPaR)

Personal-care products (PCPs)

Polyamides/nylon (PA)

Polybrominated diphenyl ethers (PBDEs)

Polybutylene terephthalate (PBT)

Polyethylene (PE)

Polyphenyl ether (PPE)

Polypropylene (PP)

Polyvinyl chloride (PVC)

Public Chemical Registration Information Search (PUBCRIS)

Queensland Poisons Information Centre (QPIC)

Questionnaire-based approach to exposure assessment (questionnaire-based approach to exposure assessment)

Restriction of Hazardous Substances (RoHS)

Scenario-based exposure modelling (SBEM)

Semivolatile organic compounds (SVOC)

Standard deviation (STD)

Therapeutic Goods Administration (TGA)

United Nations Environment Program (UNEP)

United States Environmental Protection Agency (EPA)

United States National Health and Nutrition Examination Survey (NHANES)

Waste electronics and electrical appliances (WEEE)

World Health Organisation (WHO)

X-Ray Fluorescence (XRF)

CHAPTER 1 INTRODUCTION

1.1 Context of the study

The exposure of young children to endocrine disrupting chemicals (EDCs), including in Australia, is likely to be widespread and there is mounting concern that early life exposure to these chemicals is contributing to increasing rates of non-communicable diseases (1-4). Chemicals with endocrine disrupting properties are found in a multitude of consumer products in the home, posing widespread hazard potential throughout the home environment. EDCs are detectable in dust, soil, air, food, water, and breast milk (5-9). Young children are particularly vulnerable to EDC exposure in the home because they spend much of their time indoors, have unique behaviour and physiology that leads to greater exposure, and may be more sensitive to a given exposure level, particularly when exposure occurs during critical windows of development (10).

In humans, EDCs may disrupt the endocrine system through binding to cell receptors, as well as altering the synthesis, metabolism and excretion of natural hormones and receptors (11). In adults, the endocrine system helps to maintain homeostasis, while in children the endocrine system tightly regulates normal growth and development. Therefore, disruptions to this tight control during early life can lead to health effects that are irreversible (12).

Although the magnitude of exposure to EDCs in the general population may be relatively small, many EDCs do not follow the traditional toxicological idiom that 'the dose makes the poison'. The dose-response association for many EDCs is non-monotonic, which means that, despite low magnitudes of exposure, there may be a human health risk associated with these low-dose environmental exposures. Low-dose effects in toxicology refer to effects that may be observed at a level of exposure that occurs in the general human population or at a level of exposure lower than that typically used in experimental toxicology studies (13). Exposure to individual EDCs does not occur in isolation; exposure to multiple EDCs concurrently has been shown to result in additive as well as synergistic effects (14).

Many of the exposure-outcome associations reported to date for the sentinel EDCs are relatively weak. Weak exposure-outcome associations occur because the hormonal mediators of these associations are also affected by a multitude of other intrinsic and extrinsic factors, because many of the associated outcomes operate on a continuous spectrum, as opposed to a clear dichotomy and because of exposure measurement error (15). However, when co-exposure to multiple EDCs is accounted for, as well as the fact that exposure is widespread, the estimated total burden of disease attributable to EDCs is significant. Elsewhere, EDC exposure has been estimated to account for a

1-2% loss of Gross Domestic Product (16, 17). EDCs have been classified as an emerging issue under the Strategic Approach to International Chemical Management, a joint initiative between the World Health Organisation (WHO) and the United Nations Environment Program (UNEP); Multiple agencies have called for preventative measures to minimise the harm of EDCs (18). Despite the fact that EDCs are a public health priority, EDC exposure assessment studies and epidemiological studies, which are dependent on accurate exposure assessment, are limited, particularly in Australia. Exposure assessment is the determination of the "concentration or amount of a particular agent that reaches a target organism, system or (sub)population in a specific frequency for a defined duration" and is conducted through three main methods, biological assessment, environmental assessment and indirect assessment, such as questionnaires or modelling (19).

1.2 The research problem

The ability to quantify human exposure to these chemicals through biomonitoring, the determination of a toxicant, its metabolite or other marker of exposure in human samples, is a relatively recent innovation. Biomonitoring is now typically seen as the 'gold standard' of exposure assessment (20). However, there are several limitations to this method, particularly when assessing exposure of young children to EDCs:

- Collection of biological samples from young children is practically and ethically difficult
- Multiple biological samples are required to characterise exposure to chemicals that have intermittent exposure patterns and short half-lives, making sample collection even more challenging
- Special sampling methods and sample processing/analytical methods need to be employed to avoid contamination of the sample since EDCs are widespread in the environment

Biological monitoring is therefore not typically used in large cohort studies of children, presumably because of these limitations (21). Alternative methods to biomonitoring include exposure assessment methods based on environmental monitoring, modelling as well as exposure-assessment questionnaires.

Questionnaire-based approaches to exposure assessment have historically been used for exposure assessment, particularly in epidemiological studies, because they avoid the practical and ethics challenges of collecting biological samples and are less costly than more direct biomonitoring methods (22). The questionnaire-based approach to exposure assessment can also be used to characterise retrospective exposures. Exposure-assessment questionnaires have been extensively

employed in combination with other methods of exposure assessment to explore determinants of exposure to the chemicals in this thesis, see Chapter 3. They have also been used in conjunction with other methods of exposure-assessment, to improve the accuracy of the exposure estimates, see section 2.5 (23).

Despite the widespread use of exposure-assessment questionnaires, there is limited discussion in the literature about the feasibility of using a questionnaire-based approach alone for EDC-exposure assessment (24). What is not clear, is whether the questionnaire-based approach alone can be used to assess EDC-exposure in children in place of biomonitoring, given the challenges of the latter approach.

1.3 Aim and objectives

The aim of this thesis is to assess the feasability of using the questionnaire-based approach to assess exposure.

To achieve this aim, the following objectives will be met in two parts;

Part 1: Identify what information is required to characterise exposure and evaluate whether this information can be obtained via an exposure-assessment questionnaire

- Establish the background, context and methods of exposure assessment
- Determine what items (exposure determinants) are required within the exposure-assessment questionnaire

Part 2: Design and assess the practicalities of administering exposure-assessment questionnaires; assess the content validity of the exposure-assessment questionnaire.

- Design and pre-test an exposure-assessment questionnaire
- Apply the questionnaire in a human biomonitoring study to assess to the practicalities of administering an exposure-assessment questionnaire and to assess to what extent the questionnaire data correlates with the human biomonitoring data

1.4 Significance of the study

If the questionnaire-based approach to exposure assessment could be used in place of biomonitoring, then the cost of conducting exposure assessment and participant burden could be reduced. These benefits would translate to more numerous EDC exposure-outcome studies as well as larger sample sizes within those studies. Given the relative scarcity of research in this area to

date, particularly in Australia, our understanding of EDC exposure-outcome associations could be greatly improved.

This study on the feasibility of the questionnaire-based approach to exposure assessment will provide guidance as to whether production and validation of an exposure-assessment tool based on the exposure-assessment questionnaire is indicated, and for what specific environmental toxicant groups it may be most suited. While in this study I will examine the feasibility of the questionnaire-based approach to exposure assessment for three selected and important groups of EDCs, these are not the only groups of EDCs for which there are human health concerns. I aimed to assess the feasibility of using the questionnaire-based approach to assess exposure to these specific chemicals – the conclusions, however, can be applied to other EDCs.

1.5 Scope

1.5.1 Study population

For part two of this thesis, the administration of the questionnaire in conjunction with human biomonitoring, the study population was restricted to families with children under the age of 2-years at the time of recruitment from urban areas of South East Queensland. The age range was selected to represent children who are likely to be exposed to the highest concentrations of environmental toxicants because of their unique physiology and behaviour.

1.5.2 Hazard selection

The study focused on three groups of important environmental contaminants, each consisting of one or more selected chemicals: 1) polybrominated diphenyl ether (PBDE) flame retardants, in particular BDE-209, 2) the insecticides, particularly pyrethroid and organophosphate insecticides and 3) plastics/plasticisers, specifically bisphenol A and phthalates. The three groups of contaminants were chosen using the following criteria:

- Known or highly suspected health risk associated with exposure during pregnancy or childhood
- Widespread exposure of Australian children to the specific chemical is likely or known to be the case
- The chemical (or its metabolite) is measurable in biological samples

1.6 Overview of the study

This thesis consists of 11 chapters. After Chapter 1 (Introduction), follows two parts, consisting of Chapters 2-6 (Part 1) and then Chapters 7-9 (Part 2). Part 1 includes all aspects up until the design

of the exposure-assessment questionnaire. Part 2 includes the design, pre-testing and analysis of the use of the questionnaire in the human biomonitoring study. The thesis concludes with the final discussion and conclusion, Chapter 10. The structure of the thesis is summarised in the figure below.

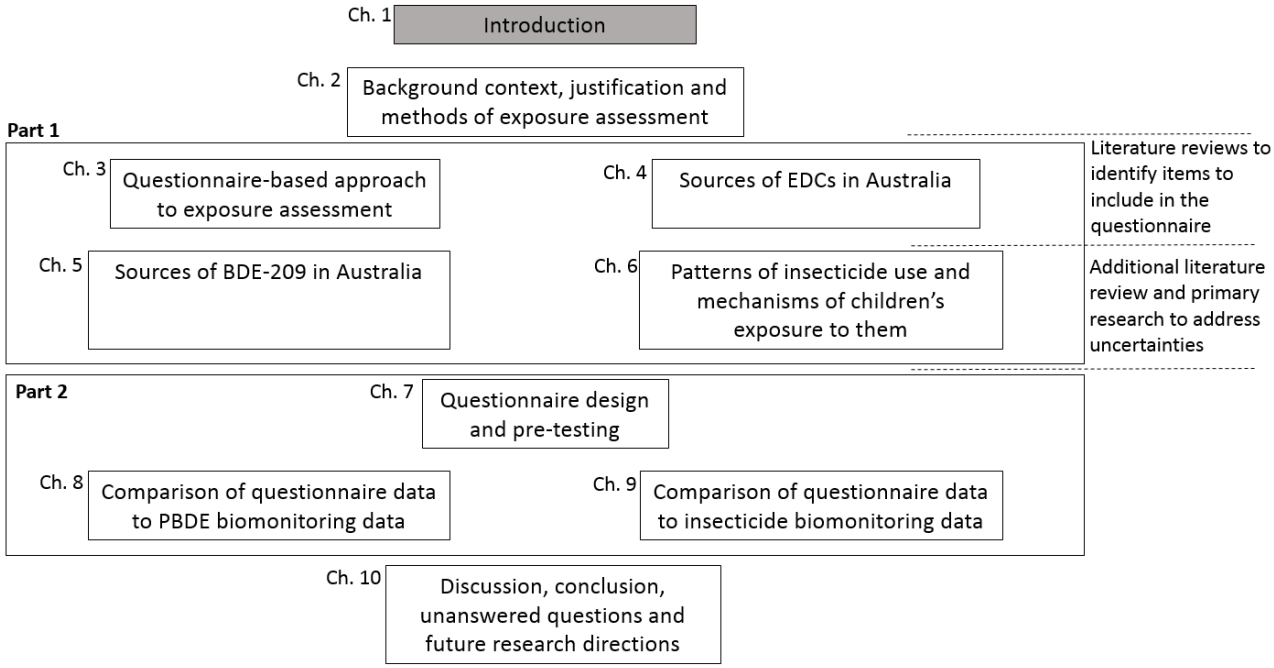

Figure 1-1 Thesis structure: Introduction

1.6.1 Part One

Part one describes a combination of narrative literature reviews and primary research necessary to characterise the exposure pathways of young Australian children to the EDCs. In Chapter 2 the context of the study is described. It provides the justification for why children are the focus of the study and discusses methods of exposure-assessment. Chapter 2 argues for the need to establish an alternative exposure-assessment tool for young children.

Chapter 3 includes a critical appraisal of the questionnaire-based approach to exposure assessment. In this chapter, the strengths and limitations of this approach are discussed. The steps necessary for the design and validation of questionnaire-based exposure-assessment instruments are described. Based on these findings, methods for the design of the exposure-assessment questionnaire in this thesis and its administration in a human biomonitoring study were developed accordingly. Chapter 3 also includes a review of studies that have combined biomonitoring and EDC-exposure-assessment questionnaires. This review is the first of several conducted to obtain the exposure

pathway information necessary to design the exposure-assessment questionnaire. Because the studies analysed in Chapter 3 were not specific to the Australian context, a review of exposure pathways specific to the Australian context was conducted, as presented in Chapter 4.

Based on the findings of Chapter 3 and 4, the pathways of young children's exposure to EDCs were identified, and gaps in the literature were noted. No data were available in Australia on patterns of insecticide use in Australian homes and there were limited data on the sources of BDE-209, the main PBDE congener found in dust in Australian homes. To obtain more information about sources of BDE-209 in Australian homes, a more thorough review of the literature including Government and technical reports was completed (Chapter 5). The only available data that could be analysed to provide more information about insecticides was via the Queensland Poisons Information Centre QPIC (Chapter 6). The aim of Chapter 6 was to determine which insecticides are likely to be used in Australian homes and explore exposure pathways of young children to these insecticides.

1.6.2 Part Two

In Part 2 of this thesis, the design of the questionnaire, its pre-testing and application into a questionnaire-biomonitoring study are described. Chapter 7 provides a more in-depth discussion of the methods and results for the design of the exposure-assessment questionnaire, including pre-testing. Based on the findings from pre-testing, BPA and phthalates were removed from the questionnaire to reduce its overall length. In Chapters 8 and 9, the results from administration of the questionnaire in a human biomonitoring study are presented in the form of two manuscripts, the first for PBDEs and the second for the insecticides. These results provide information about the content validity of individual questions within the questionnaire and additional information about the feasibility of the questionnaire-based approach, including practical aspects, such as acceptability of the questionnaire and participant burden.

The interpretation of the results from the questionnaire-biomonitoring study, with specific regard to the aim and objectives of this thesis are discussed in Chapter 10. In particular, this includes a more thorough discussion of the criteria for evaluating whether the questionnaire-based approach to exposure assessment is suitable for a particular chemical. Chapter 10 also includes a critical evaluation of the strengths and limitations of the study, with particular emphasis on how they affected to interpretation of the assessment of the feasibility of the questionnaire-based approach to exposure assessment. Finally, the main conclusions of the thesis are presented, and opportunities for further research are discussed.

PART ONE

CHAPTER 2 BACKGROUND, JUSTIFICATION AND METHODS OF EXPOSURE ASSESSMENT

This chapter provides the context for this thesis and the motivation behind assessing the feasibility of the questionnaire-based approach to exposure assessment. It begins by providing the evidence for why exposure of young children, including Australian children, to EDCs is of public health concern. This includes an overview of endocrine disruption, a discussion about why children are most affected by exposure to EDCs, a summary of the hazards selected for this thesis, an overview of the exposure-outcome associations for each group of EDCs in this thesis and summary of what is currently known about young Australian children's exposure to these chemicals.

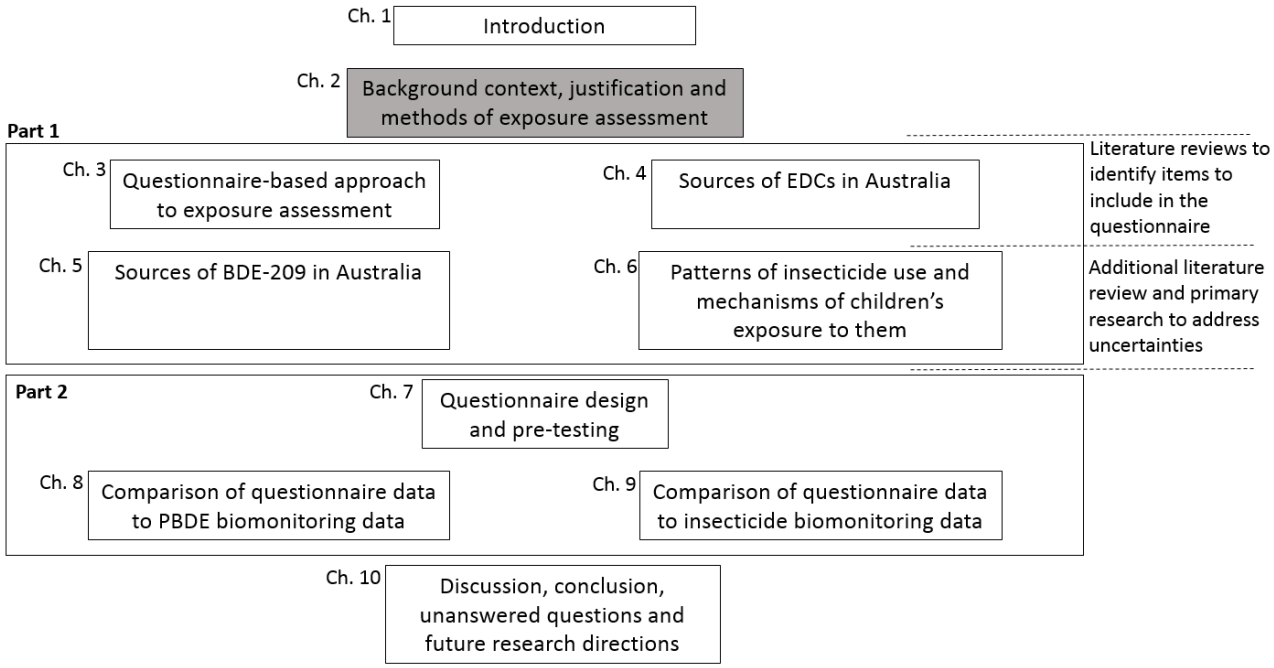

Figure 2-1 Thesis structure: Chapter 2

The second part of this chapter focuses on methods that are used to assess exposure, including environmental and biological monitoring, and scenario-based exposure modelling (SBEM). An overview of the methods of exposure assessment provides a basis for understanding techniques to characterise exposure, including how these techniques can be integrated with exposure-assessment questionnaires, as well as understanding the strengths and limitations of each exposure-assessment method. The findings from this discussion are also informative to the design of the questionnaire-biomonitoring study presented in Part 2 of this thesis. By comparing and contrasting the strengths and limitations of various methods of exposure assessment, I demonstrate how a questionnaire-based approach to exposure assessment could be a useful tool for researching the effect of EDCs on

young children's health. The next chapter, Chapter 3, provides a more detailed discussion of the questionnaire-based approach to exposure assessment, with particular reference to PBDEs, BPA and phthalates and organophosphate and pyrethroid insecticides.

2.1 Why are children most affected by exposure to endocrine disrupting chemicals?

EDCs may disrupt the endocrine system through interactions with receptors and by altering the function of natural hormones and receptors by influencing their synthesis, metabolism and excretion, as well as via other mechanisms, including epigenetics (11, 25, 26). While the endocrine system has a functional role in adults, regulating homeostasis, in children the endocrine system also has an organisational role, regulating normal organ development and maturation. Children are therefore particularly sensitive to the effects of endocrine disrupting chemicals, as exposure during these critical periods can lead to or contribute to the development of irreversible adverse health effects (18). In exposure risk assessment, s*usceptibility* is a term used to describe sub-groups where risk is different due to both differences in exposure and differences in response to exposure (27). *Sensitivity* describes increased risk due to differences in response. *Vulnerabilit*y is used to describe differences in exposure risk due to differences in susceptibility and differences in social factors, such as socioeconomic status.

Children are also more susceptible to EDCs because they are also at higher risk of exposure. Young children typically spend the majority of their day inside the home, where the concentration of toxicants is higher than outdoors (28). Infants occupy different microenvironments than adults and often for prolonged periods of time, which can lead to different or longer durations of exposure. Of these zones, the floor is a critical zone for very young children (<3 years of age, i.e. infants and toddlers). This is particularly relevant for products that result in widespread contamination of the floor, such as semi-volatile organic compounds (SVOC), as seen in Figure 9-2 on page 142.

The increased 'floor-time' of young children, combined with additional behavioural characteristics, such as mouthing, putting fingers and other objects in their mouth, may act as exposure synergists. At about four months of age infants begin to grasp objects and, in conjunction with mouthing objects, this can lead to increased exposure (10). The use of products specific to young children, including baby personal-care products and baby bottles, may also increase their exposure to EDCs (29, 30). Play activities may also lead to greater dermal and non-dietary exposures to environmental toxicants (31, 32). For example, toys and other baby products may contain EDCs or EDCs may distribute to them from other sources, which may lead to increased exposure through ingestion, inhalation or dermal uptake (33-35). Plush toys act as sinks for semi-volatile toxicants in

much the same way that other items that contain poly-foam, such as sofas, act as reservoirs for toxicants (36).

Physiological differences in infants compared to adults can modify not only the external exposure of young children to contaminants but also the internal exposure and biological response (37). Observational and experimental evidence suggests that the metabolism of toxicants during foetal development and early infancy differs from metabolism observed in adults. Decreased metabolism may lead to higher internal exposure, as well as exposure to a higher active dose. For example, children may be more susceptible to the effects of EDC exposure because the expression and activity of enzymes important for EDC metabolism, such as paraoxonase 1, members of the cytochrome P450 group of enzymes, and uridine diphosphonate glucuronosyltransferase (sub-family 2B) and sulfotransferase, are reduced during early development (38-43). Infant body composition also changes dramatically during the first year of life, with body mass index (BMI) typically peaking before the age of one, which alters body distribution and burden of toxicants (44).

2.2 Identifying the hazard

The following section provides a summary of the EDCs in this thesis. Formal reviews to characterise pathways of exposure to these chemicals are described in more detail in the following chapters. Organophosphate and pyrethroid insecticides, polybrominated diphenyl ether (PBDE) flame retardants, and BPA and phthalates are common additives in a variety of household items. Applications include insecticides, food packaging materials, food storage containers, children's toys, electronics and electrical equipment, building and construction materials, paints, furniture, carpets, mattresses, textiles and personal care products, see Table 2-1 (45, 46). Primary sources of EDCs are thus widely varied and found throughout the indoor environment.

Table 2-1 Major sources of EDCs in the home

Endocrine disrupting chemical class(es)	Sources in the home
Pyrethroid and organophosphate insecticides	Aerosol sprays, automatic dispensers, termite control, lawn/garden treatments, animal flea/tick treatments, head lice and scabies treatment, food, breast milk
BPA and phthalates (plasticisers)	Canned food, fresh food, drinking water, bottles, plastic storage containers, plastic food wrap, plastic dishware and utensils, personal care products, thermal receipts, toys, dental sealants, textiles, leather, epoxy resin, inks, home décor, food, breast milk
Polybrominated diphenyl ethers	Textiles, foam, electronics, food, breast milk

Polybrominated diphenyl ethers are semi-volatile organic compounds that can have up to 10 bromines attached to the carbons in the phenyl rings, Figure 2-2. Including isomers, there are 209 different possible types of brominated diphenyl ethers, called congeners. There were three common commercially available mixes of PBDEs, known as penta-BDE, octa-BDE and deca-BDE, named for the average number of bromines on the congeners within the mixture. Octa and penta-BDE have not been imported into Australia in pure chemical form since 2005 and global restrictions have curtailed their use in manufacturing (47). However, the persistence of PBDEs in the environment and the continued use of products in the home that have been treated with PBDEs likely contributes to ongoing exposure (46).

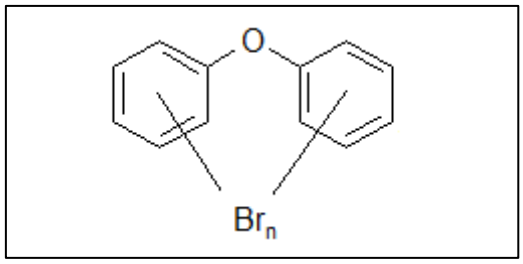

Figure 2-2 General structure of polybrominated diphenyl ethers (n=1 to 10)

Unlike the other sentinel EDCs, pyrethroid and organophosphate (OP) insecticides are designed for their toxic effects and are therefore widely used in both domestic and commercial settings for "preventing, destroying, repelling, or mitigating" unwanted pests (48). Pyrethroid esters are synthetic chemicals that have structures closely related to the botanical insecticide pyrethrum. There are two groups of synthetic pyrethroids, which are differentiated by the inclusion of a cyano group (type II only), see Figure 2-3. Pyrethroids disrupt the functioning of the nervous system through interactions with voltage-sensitive sodium channels, as reviewed by Soderlund, Clark (49). Piperonly butoxide is a cytochrome P450 monooxygenases (CYP 450) that acts as a synergist with pyrethroids and is therefore added to many pyrethroid containing products. Like pyrethroids, OPs are also neurotoxins, inhibiting the action of the enzyme acetylcholinesterase in the nerve synapses of both insects and mammals, which leads to prolonged and excessive acetylcholine signalling, as reviewed by Androutsopoulos, Hernandez (14).

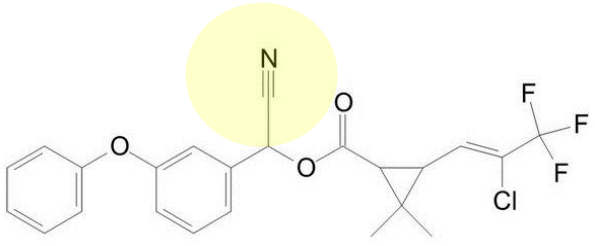

Figure 2-3 Chemical structure of pyrethroid esters with cyano group highlighted indicating that this is a type II pyrethroid ester

BPA is one of the most widely used chemicals. The most abundant uses of BPA are in the production of polycarbonate plastic[1], epoxy resins (bisphenol A diglyceride ether, known as BADGE), and in non-polymerised form, as seen in Figure 2-4, in thermal inks and polyvinyl chloride (PVC) (50). The use of BPA has been regulated in several countries and classified as a toxic agent by the Canadian Environmental Protection Agency (51). There is no restriction on the use of BPA in Australia, although some companies have voluntarily removed it from consumer goods and food packaging. Of note, as a result of the phase out of BPA, there has been increasing use of alternatives forms of BPA, such as BPS, which are also endocrine disruptors (52).

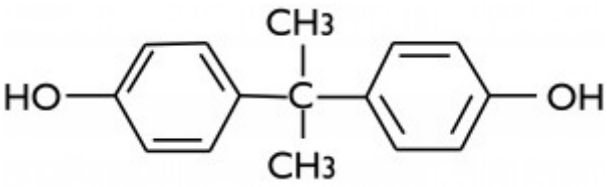

Figure 2-4 Chemical structure of bisphenol A

Like BPA, phthalates are also used for a variety of purposes, including as a plasticiser[2] for PVC and other plastic polymers, to impart flexibility and durability upon the final product, as surfactants, as lubricants, and in inks. Phthalates are divided into two groups, low and high molecular weight phthalates, based on the number of carbons in the carbon backbone, represented by R and R' in Figure 2-5. Several phthalates, including DEHP, DBP, BBP, DINP, DIDP and DNOP have been classified as toxic or are under review by international regulatory bodies and their use in children's products, medical products and some food contact products is regulated (53). In Australia, restrictions are in place on the high molecular weight DEHP, with a maximum permissible concentration of 1% in baby products that infants may mouth, such as toys (54).

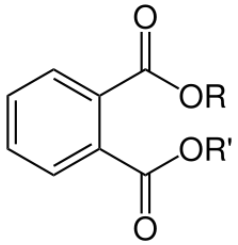

Figure 2-5 General structure of phthalates

[1] Plastics are polymers; polycarbonate plastic is made through polymerisation of the monomer bisphenol A.
[2] Plasticiser refers to chemicals that are additives during the polymerisation process. Unlike the monomers used to create the polymer, additives are not covalently bonded within the plastic.

2.3 Mechanism of action and exposure-outcome associations

Historically, chemicals were classified as endocrine disruptors if they interacted directly with nuclear hormonal receptors, including thyroid receptors, oestrogen receptors and androgen receptors. Although the sentinel EDCs in this review have been demonstrated to interact directly with these receptors, there are many additional mechanisms of actions by which EDCs can disrupt the normal functioning of the endocrine system (1, 55, 56). Because of these varied effects, the definition of an endocrine disrupting chemical has been updated to 'an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action' (57).

PBDEs are known to affect the metabolism of thyroid hormones, are suspected carcinogens, and can affect additional receptor and cellular pathways, including the aryl hydrocarbon receptors and oxidative stress pathways (58-64). PBDEs may be metabolised in the body via a process of debromination (to form lower congener PBDEs) or via hydroxylation (65). PBDEs and their metabolites are structurally very similar to endogenous thyroid hormones, as seen in Figure 2-6. This similarity permits PBDE metabolites to displace thyroid hormone from serum transporters and to interfere with endogenous thyroid hormone binding to thyroid hormone receptors (63, 66, 67).

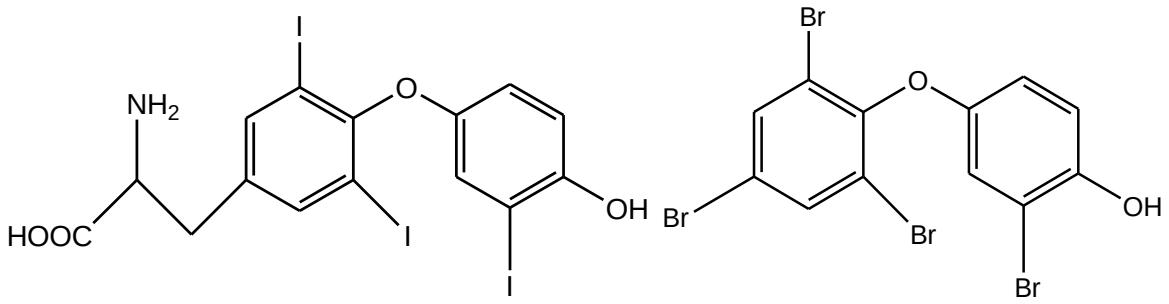

Figure 2-6 Structure of triiodothyronine (T3) versus structure of PBDE metabolite

OPs and pyrethroids disrupt cellular pathways involved in regulation of the cell cycle, cell differentiation, and apoptosis, as well as disrupting normal cellular signalling and metabolic processes (14, 68). Permethrin has been classified as 'likely to be carcinogenic' by the United States Environmental Protection Agency (69).

The suspected mechanisms of action of BPA are also diverse. In addition to demonstrated affinity for oestrogen receptors, BPA also shows affinity for other receptors, including the aryl hydrocarbon receptor and peroxisome proliferator-activated receptors (PPaR) α and γ (70-72). BPA is implicated in alterations to cellular signalling pathways involved in carcinogenesis, immune system regulation, inflammation, male and female reproductive system development and regulation, nervous system development, and metabolism (73). Phthalates, on the other hand, are best known for their antagonism of androgen receptors, but may also elicit effects through additional

mechanisms, including binding to PPaR-γ, disruption to normal thyroid hormone levels, oxidative stress and epigenetics (72, 74).

Human exposure to EDCs is associated with a wide range of chronic health outcomes, many of which overlap, see Table 2-2. Of the numerous reviews that have been conducted on EDC exposure-outcome studies, I direct the reader to two of the most comprehensive, including the "Endocrine Society's Second Statement on Endocrine-Disrupting Chemicals" and the World Health Organisation's "State of the Science on Endocrine Disrupting Chemicals" (18, 67). The main exposure-outcome associations that have been reported for the EDCs in this thesis are summarised in Table 2-2. Of note, the vast majority of these exposure-outcome associations have relied upon biomonitoring, with the exception of insecticides, for which exposure-assessment questionnaires have been used more extensively (75). The lack of specificity between contaminants and health outcomes may be attributable to the fact that the endocrine system can affect multiple body systems (15). Therefore, disruption to one component of the endocrine system by a specific contaminant can produce a variety of effects that are distantly related.

To date, the findings from exposure-outcome studies for the sentinel EDCs have been varied, often presenting conflicting results, provoking intense debate over the health effects of EDC exposure (76). Several factors are considered to have contributed to the variability in results from exposure-outcome studies (67). Biological mechanisms, such as genetic variations between populations, explains part of this discordance, as well as the fact that different effects may be observed depending on temporal patterns of exposure during early development (67, 77). Confounding is a problem for several EDC-exposure outcome associations, since several exposures and outcomes have a common cause. For example, studies assessing BPA exposure and health outcomes, particularly obesity, have been criticised because the association may be confounded by higher concentrations of BPA in energy-dense foods (78). Although confounding is undoubtedly an issue, it is likely that the effect of exposure measurement error is higher than the effect of confounding (79). Because the capacity to measure many of these chemicals in human biological samples is relatively new, extensive validation and reliability data are unavailable. Alternative methods that could be employed to account for measurement error, such as uncertainty analysis, are not routinely used in this field of epidemiology. Spiegelman et al. suggest that there may be insufficient human technical skill in this area to perform this analysis (79). Additionally, many of the exposure-outcome associations are expected to be weak, and therefore large sample sizes are required for adequate power (15). Many of the studies on EDCs to date have been relatively small, because of the practical and financial constraints associated with biomonitoring. Although meta-analysis can be used to assess exposure-outcome associations by combining studies, the number of studies for

each exposure-outcome combination is still too small (i.e. less than five) in many cases to make this approach effective or suitable (75).

To date, most epidemiological studies investigating exposure-outcome associations for the chemicals in this thesis have examined individual chemicals and exposure. However, it is likely that co-exposure to multiple EDCs can have complex interactions, including additive, synergistic and in some cases antagonistic effects (80). Since the mid-2000s, disease outcomes are increasingly understood as the interplay between the exposome, a concept that encapsulates cumulative exposure to biological/physical, psychological and social determinants of disease, as well as individual genetic (and epigenetic) factors (81). Although analytical methods to characterise the genome have made genome-wide association studies feasible, methods to study the exposome are lagging behind (82). Established laboratory methods to quantitatively measure environmental chemicals and or their metabolites in human biological samples are limited to approximately 300 chemicals, although this number is expanding (82).

Several of the adverse health impacts that occur from exposure during early development to the sentinel EDCs are also risk factors for the development of other diseases later in life. These include altered gestational duration, male reproductive tract abnormalities (hypospadias, cryptorchidism, and decreased anogenital distance), atopy, obesity, diabetes, and precocious puberty (1, 3, 83). Low-birth weight and prematurity predispose children to increased risk of neurodevelopmental deficits, diabetes, obesity, and respiratory dysfunction later in life (18). Hypospadias, decreased anogenital distance and cryptorchidism occur within a constellation of symptoms known as testicular dysgenesis syndrome; infants born with this syndrome are at increased risk of testicular cancer (18). Because of the time-lag between exposure during early life and the development of disease in adulthood, the full implications of EDC exposure remain to be understood (26). Finally, exposure to EDCs may be associated with multigenerational adverse health effects, via epigenetic mechanisms (84).

Table 2-2 Possible early-life EDC exposure-outcome associations in children; examples of EDC exposure outcome studies, including systematic reviews.

EDC group	Gestational outcomes	Neurobehavioural and neurodevelopmental outcomes	Reproductive or congenital disorders	Respiratory	Other	Cancer
Polybrominated diphenyl ethers	Low birth weight (85).	Decrease in IQ, reduction in fine motor skills, attention deficits, impaired perceptual reasoning and poorer verbal comprehension, anxiety and poorer social competence (55, 86-89).	Testicular dysgenesis syndrome, delayed onset of puberty (90).	No association (91).	Alterations in thyroid hormones (92).	High-molecular weight PBDE congener concentrations in household dust and childhood leukaemia (93).
Organophosphate insecticides	Decreased birth weight, length, gestational duration (3).	Neurodevelopmental disorders and delay, including abnormal neonatal reflexes, attention deficits, delay in normal motor development, cognitive deficits, disruption to normal sexual brain dimorphism (3, 94-96).	Hypospadias (97).	Wheeze (98).	Increased insulin levels (99).	Non-specific household insecticide use associated with leukaemia and brain tumours (100, 101).
Pyrethroids	No consistent association (102).	Neurodevelopmental disorders, such as autism, attention deficits/ hyperactivity disorder and neurodevelopmental delays (3, 94, 103).	Congenital heart disease (104).	Respiratory dysfunction (105, 106).		
Phthalates	Altered gestational duration (2).	Neurodevelopmental disorders and delay, more autistics and attention deficit behaviours, less masculine play among boys (2).	Testicular dysgenesis syndrome (2).	Asthma and atopic diseases such as eczema (2).	Increased obesity/overweight (inconsistent findings), delayed onset of pubarche, altered thyroid hormone levels (2, 107).	No studies identified examining early-life exposure and childhood cancers
Bisphenol A	Decreased birth weight, gestational duration (83).	Disruptions to neurobehavioural development, including internalising and externalising behaviours, attention deficit hyperactivity disorder (74, 108, 109)	Testicular dysgenesis syndrome (83).	Wheeze and asthma (83).	Increased obesity/overweight (inconsistent findings) (74, 83).	No studies identified examining early-life exposure and childhood cancers

2.4 Australia specific biomonitoring data

As the epidemiological evidence linking early-life EDC exposure to adverse health outcomes grows, there has been increasing discussion regarding the design and use of exposure assessment methods for these studies, particularly biomonitoring methods appropriate for use in children's environmental epidemiology studies (24). In Australia, researchers at The Queensland Alliance for Environmental Health Sciences have been instrumental in designing and validating both invasive and non-invasive biomonitoring methods to assess chemical exposure in young children over the past few years, which has dramatically expanded our research capabilities in this field. The number of published studies conducting biomonitoring in young children for the EDCs in this thesis has doubled during the period of this PhD research. However, the need for more biomonitoring data becomes apparent in the following paragraphs. In this section, the biomonitoring data for young Australian children from the beginning of this PhD, and then the progress made to date in this field are summarised.

Despite these advances, biomonitoring data for Australian children are still insufficient, as Australia has no Government funded nationwide biomonitoring program. Biomonitoring, discussed in more detail in the next section, is difficult in very young children. Biomonitoring for the EDCs in this thesis occurs via the blood for PBDEs or urine for the insecticides and plasticisers. In young children, it is an ethics challenge to obtain blood samples from young children for biomonitoring and it is practically tricky to collect both blood and urine samples in this population (110). In addition to sampling challenges, the analysis of samples is time-intensive and expensive. Therefore, studies in this field in Australia are typically limited to either a small number of samples from individual children or pooled samples from multiple individuals. Pooled samples are sourced from pathology laboratories when sample volumes provided by patients (for medical purposes) exceed the required amount.

In 2012 there were only two studies, using pooled samples, directly assessing PBDE body burdens in Australian children, the results of which demonstrated that the magnitude of exposure of Australian children under the age of five to PBDEs was likely to be several times greater than that of adults (111, 112). Children aged between 2.6 – 3 years had the highest mean levels of BDE-47 in their serum, at 51 ng g^{-1} lipid weight (lw) adjusted, whereas most adults had levels below 10 ng g^{-1} lw (111, 113). The serum concentrations from Australian children were in the middle of global levels, as Australian children had higher serum PBDE concentrations than children in Europe and lower levels than children in the USA, see Table 2-3 (111). Reassuringly, biomonitoring concentrations of the lower PBDEs from children's samples appears to have peaked and now be

declining, which suggests that exposure has decreased as a result of the changes to PBDE regulations and usage (113). In 2015, Chen published the first pilot-study in Australia assessing young children's PBDE body burdens via assessment of faeces concentrations, but the approach has not been applied to larger sample sizes (114).

In 2012, the only study that had conducted insecticide biomonitoring in Australian children (n=340, conducted in South Australia), found that concentrations of some metabolites, particularly the chlorpyrifos metabolite TCPy, were similar or higher than levels reported in other developed countries, see Table 2-4 (7, 115, 116). This finding was confirmed in 2016, in a cross-sectional biomonitoring study of pooled urine samples from children in South East Queensland (117).

In 2012, no studies had conducted biomonitoring for phthalates and BPA in Australian children, as such, no tables for international comparison are provided. Current tables for comparison are available from Heffernan et al. (118) and Ramos et al. (119). In 2013 Heffernan et al. published a paper assessing urinary excretion of BPA in Australian children, reporting similar levels to those found overseas (118). In a 2016 study of pooled urine samples, young Australian children (0-4 years) had higher concentrations of the metabolites of some phthalates (i.e. DEHP, BBzP, DiNP) than those reported in adults (119). Overall, the Australian study population had higher phthalate metabolite concentrations than those reported in the US and several European countries, as summarised by Ramos et al. (119).

In summary, the results from biomonitoring studies conducted to date suggest that the level of exposure of Australian children may be comparable and is sometimes higher than the level of exposure of children overseas to EDCs. However, because of the small number of studies, their small sample sizes, and the limited geographical area covered by the studies discussed, the results cannot be assumed to reflect exposure levels of all Australian children to EDCs.

Table 2-3 Biomonitoring data for children (<5 years) to BDE-47 (published data up to 2012)

Reference	Location	Age (years)	Number	Mean BDE – 47 concentration ng g-1 lipid weight adjusted (Standard deviation in brackets)
Carrizo and Grimalt (120).	Menorca Island, Spain	Children: 4	244	2.9 (10)
Chen, Chen (121).	Dalian, China	0-11	29	6.74
Fischer, Hooper (122).	California, U.S.A.	Children: one 1.5-year-old and one 5-year-old from the same family	2	1.5 years: 245 5 years: 137
Hertz-Picciotto, Bergman (123).	California, U.S.A.	2-5	94	89.76
Lunder, Hovander (124).	11 states, U.S.A.	Children 1.5 – 4	20	31 (14.9)
O'Brien, Blanchet (125).	Nunavik, Canada	1-5	126	34.6
Rose, Bennett (126).	California, U.S.A.	Children: 2-5	100	89.8 (78)
Stapleton, Eagle (127).	North Carolina, U.S.A.	Children: 1 to 3	83	23.3 (<3-350)*
Thomsen, Lundanes (128). **Thomsen, Liane (129).**	Norway (samples from 1998) Norway (samples from 2002)	Children: 0-4 Children: 0-4	Pooled samples; 14 per pool individuals Pooled samples; 29 individuals	6.2 4.8

Reference	Location	Age (years)	Number	Mean BDE – 47 concentration ng g-1 lipid weight adjusted (Standard deviation in brackets)
Toms, Harden (112)	Queensland, Australia (samples from 2004-2005)	Children: 0-4	Pooled samples; 100 per pool	25 (5.6)
Toms, Sjodin (111).	Queensland, Australia (samples from 2006-2007)	Children: newborns (cord blood), 0-0.5, .6-1, 1.1-1.5, 1.6-2, 2.1-2.5, 2.6-3, 3.1-3.5, 3.6-4, 4.1-6	Pooled samples; 30 per pool	2.6-3 years: 51 (36)

*range

Table 2-4 Insecticide biomonitoring studies of children (<5 years). Includes common pyrethroid and organophosphate insecticides, as measured by mean ug/g creatinine adjusted metabolites in urine (SD)

Reference	Location	Ages (years)	Number	Pyrethroid metabolites		Organophosphate metabolites				
				DCCA	3-PBA	TCPy	DMTP	DMDTP	DEP	DETP
				(metabolite of permethrin, cypermethrin and cyfluthrin)	(metabolite non-specific to pyrethroids)	(metabolite of chlorpyrifos)	(non-specific organophosphate metabolites)			
Babina, Dollard (115).	South Australia, Australia	2.5-6	340	8.1 (22.0)	1.2 (3.2)	21.5 (28.8)	20.2 (48.2)	12.4 (14.9)	7.4 (9.5)	8.3 (23.5)
Morgan, Sheldon (130).	Ohio, U.S.A.	1.7-5.6	127	-	1.5 (6.4) -	-	-	-	-	-
Morgan, Sheldon (131).	North Carolina, U.S.A.	2.0-5.5	129	-		11.9[a] (16)	-	-	-	-
Lu, Toepel (132).	Washington State, U.S.A.	3-11	23	*cis*-DCCA: 0.33 (1) *trans*-DCCA: 1.24 (2.6)	1.22[b] (2.4)	7.2[b] (5.8)	-	-	-	-
Naeher, Tulve (133).	Florida, U.S.A.	4-6	203	*Cis* –DCCA: 2.9 (7.9) *trans*-DCCA: 4.6 (10.4)	6.5 (13.9)	-	27.4 (61.6)	4.4 (11.6)	8.1 (9.2)	1.8 (3.6)
Becker, Seiwert (116).	Germany	2-5[c]	60	*Cis* –DCCA: 0.12 *trans*-DCCA: 0.21	0.34	-	9.2	-	3.4	1.2
Quiros-Alcala, Bradman (134).	California, U.S.A.	3-5[d]	20	-	-	-	5	<LOQ[e]	2.77[e]	<1[f]
Ding, Wang (135).	Shanghai, China	2	301	-	-	-	6.99	-	7.96	14.19

a. Median B. Median c.The study also included older children d. Only results for urban children are reported, results converted from nmol/L, not adjusted for creatinine (ug/L).
e. mean below LOQ

2.5 Approaches to exposure assessment

The limited biomonitoring studies to date, summarised in the previous section, demonstrate that exposure of young Australian children to EDCs is widespread. Moreover, as previously described, low-level chronic exposure of children to EDCs in countries elsewhere has been associated with a variety of adverse health outcomes. This then raises the question why aren't we monitoring children's exposure to EDCs in Australia to better understand the health risk and identify ways to minimise exposure? The following section describes the main approaches to exposure assessment, including the strengths and limitations of each approach, see Table 2-5 Summary of exposure assessment methods. From this discussion, the current barriers to studying EDC exposure-outcomes in large-scale studies become apparent. The approaches to exposure assessment described in this section are not mutually exclusive; exposure assessment is often conducted using a combination of biomonitoring data, environmental data, and modelling, as well as using information that can be obtained via questionnaires (136). In the next chapter, the questionnaire-based approach to exposure assessment is described in more detail.

This discussion of the main methods of exposure assessment provides a basis for:

- Understanding how knowledge of relevant EDC sources and exposure pathways is obtained, which is the focus of the next chapters.
- Assessing the practically and feasibility of using exposure-assessment questionnaires compared to other exposure-assessment methods
- Guiding the development of methods to assess the association of questionnaire data with biomonitoring data

2.5.1 Definitions

2.5.1.1 Exposure

Before beginning this discussion, it is important to clarify the terminology used in this field. Exposure assessment is formally defined as "The process of estimating or measuring the magnitude, frequency, and duration of exposure to an agent" (19). There are several ways to interpret the term exposure:

- External exposure refers to the total amount of toxicant that an individual encounters before the toxicant crosses a biological membrane
- Internal exposure is the amount of toxicant absorbed across the biological membrane

- The active dose is the amount of toxicant or its bioactive metabolites at relevant biological tissues – the amount of active dose for a given external or internal exposure can vary between individuals due to factors that affect toxicokinetics (absorption, distribution, metabolism and elimination)

The figure below summarises this concept. The distinction between external and internal exposure is important, as not all external exposure leads to internal exposure. Therefore, the purpose and interpretation of the results from different exposure assessment methods vary. For example, in the field of environmental epidemiology, biomonitoring is typically the method of choice because it is seen to most closely relate to internal exposure and therefore the biologically relevant dose. In the field of public health policy, biomonitoring results may be used to estimate aggregate external exposure, through the process of exposure reconstruction (79). Conversion between external and internal exposure can be performed via the use of toxicokinetic modelling (137).

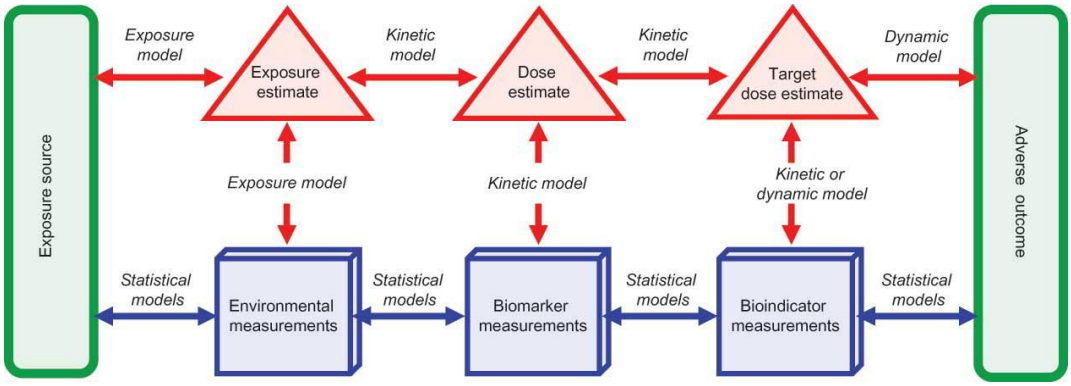

Figure 2-7 Exposure assessment diagram. Reproduced with permission from Tan, Sobus (115)

2.5.1.2 Exposure-assessment questionnaires and the questionnaire-based approach to exposure assessment

Finally, the questionnaire-based approach to exposure assessment has not yet been formally defined. In this thesis a distinction is made between the term exposure-assessment questionnaire and 'questionnaire-based approach to exposure assessment'. For the purposes of this thesis, the definitions are as follows

- The exposure-assessment questionnaire is a questionnaire that has been specifically designed to assess items that are important in the EDC-exposure pathway
- The term questionnaire-based approach to exposure assessment is used to describe an exposure-assessment instrument that includes an exposure-assessment questionnaire and *can be used to classify or predict exposure.*

- A validated instrument is one in which the predictive capacity of the instrument has been compared to the gold standard of exposure assessment for that hazard

For example, an exposure-assessment questionnaire may be used to measure an individual's intake of oranges or apples, but the instrument is what is used to predict the effect that eating these oranges or apples has on insecticide exposure. The *instrument* consists of qualitative data (obtained via the questionnaire) and quantitative data; modelling is used to derive exposure estimates from these data (23). A validated instrument is one in which the predictive capacity of the instrument has been assessed by administering it in conjunction with the gold standard for exposure assessment, which is biomonitoring for the EDCs in this thesis, but may be different exposure assessment methods for other hazards or chemicals (136).

Table 2-5 Summary of exposure assessment methods

Method	Description	Ideal application settings	Strengths	Limitations	Opportunities for integration with exposure-assessment questionnaires	Opportunities for integration with the questionnaire-based approach to exposure assessment
Environmental monitoring	Quantitative measure of the magnitude of the concentration of a toxicant in media (food, air, water, and dust) Environmental monitoring data can be used in models to estimate the exposure of a population, sub-population or even an individual	Exposure routes to an environmental chemical are well characterised Physiological and behavioural patterns concerning that exposure route are well characterised and consistent	Relatively non-invasive, although may require extensive sampling of homes or other private locations Can be used to identify sources and relevant pathways of exposure to chemicals of interest	Labour intensive, particularly when repeat sampling (i.e. to account for short-term variation in concentrations) or sampling of multiple media is required to adequately assess all relevant exposure pathways (i.e. food, dust, air, breast milk)	Can be used in conjunction with questionnaires to better characterise exposure pathways	Individual exposure estimates based on environmental monitoring data are improved by integrating them with information obtained from questionnaires and vice versa
Biological monitoring	Biomonitoring may be conducted on various samples, including urine, blood, hair and faeces, depending on the properties of the toxicant being investigated.	Exposure pathways are not known and sampling all relevant environmental media is not feasible Average, peak exposure or aggregate exposure can be assessed through an acceptable sampling protocol – i.e. relatively non-invasive, does not place undue burden on participants or researchers	Aggregate exposure to environmental chemicals is assessable even when some (or all) exposure pathways are unknown Biological monitoring can be relatively non-intrusive for some media, i.e. hair	Contamination of samples with environmentally ubiquitous chemicals may result in falsely elevated concentrations Can be costly and time-consuming, particularly when the use of alternative sample collection materials, laboratory equipment, reagents and methods is required to minimise contamination (138, 139) Multiple samples may be required when characterising exposure to chemicals that have substantial short-term intra-	Can be used in conjunction with questionnaires to better characterise exposure pathways	Can be used to validate the questionnaire-based approach

Method	Description	Ideal application settings	Strengths	Limitations	Opportunities for integration with exposure-assessment questionnaires	Opportunities for integration with the questionnaire-based approach to exposure assessment
				individual variation due to intermittent exposure and short half-lives		
Scenario-based exposure modelling (SBEM)	SBEM uses a conceptual or mathematical process to represent the exposure pathway. The output of exposure modelling may be an estimate of external or internal dose.	Estimating macro-scale exposure for risk assessment purposes	Non-invasive and cost-effective	May be inaccurate since SBEM relies on accurate data or modelling of the concentration of the environmental chemical in the relevant media, rates of contact of the individual with that media, transfer rates of the environmental chemical, uptake rates and pharmacokinetics (140). These parameters are frequently unavailable for young children. Time-consuming and costly if modelling is focused at the residential or individual level	Many exposure factors used in SBEM have been obtained from exposure assessment studies that include questionnaires	-
Questionnaire-based approach	An exposure-assessment questionnaire combined with a database that contains information about the effect of different exposure-scenarios on exposure. Exposure estimates are calculated from this data via statistical modelling.	See the discussion in the next chapter	Once-off administration of the instrument may collect data sufficient to accurately classify long-term exposure to toxicants with short half-lives and variable exposure patterns.	Validation of the instrument to assess long-term exposure to toxicants with short half-lives requires extensive, repetitive biological monitoring which is expensive, time-consuming, burdensome and biomonitoring techniques may not be available for all toxicants of concern. Comprehensive repetitive exposure-assessment questionnaires may be time	-	-

Method	Description	Ideal application settings	Strengths	Limitations	Opportunities for integration with exposure-assessment questionnaires	Opportunities for integration with the questionnaire-based approach to exposure assessment
			Relatively non-intrusive for participants. Inexpensive, particularly when questionnaires are administered online. Can be used to capture exposure events that occur too infrequently to be reliably characterised by typical biomonitoring protocols. May be combined with other validated questionnaires to improve health risk assessment.	consuming for participants to complete. Validation needs to be repeated for each population. Unable to directly quantify internal exposure to toxicants – this is a major limitation when toxicokinetic differences result in markedly different active doses between individuals for the same internal dose Cannot definitively identify all potential sources of exposure to EDCs in the home as EDC content and labelling practices vary greatly between goods. Some exposure pathways that have a small impact on toxicant body burden may not be detectable through the questionnaire-based approach when other exposure pathways are unaccounted for.		

2.5.2 Scenario-based exposure modelling

We begin the discussion of exposure assessment methods with scenario-based exposure modelling, because the data obtained from environmental and biological monitoring is often interpreted through the use of modelling. The strengths and limitations of SBEM are outline in Table 2-5. Scenario-based exposure modelling is used to guide exposure assessment, particularly population-level exposure assessment. The data obtained from SBEM is often used in the process of exposure risk assessment and to guide policy decisions. However, the process can also be used to estimate individual level exposure. An exposure model is "a conceptual or mathematical representation of the exposure process" (19). To aid in exposure assessment, the exposure process is best characterised by an exposure scenario or scenarios. The definition of an exposure scenario is "a combination of facts, assumptions and inferences that define a discrete situation where potential exposure may occur. These may include the source, the exposed population, the time frame of exposure, microenvironment(s) and activities" (19). For an example, an exposure scenario specific to this PhD, ingestion of PBDE contaminated dust, is displayed below.

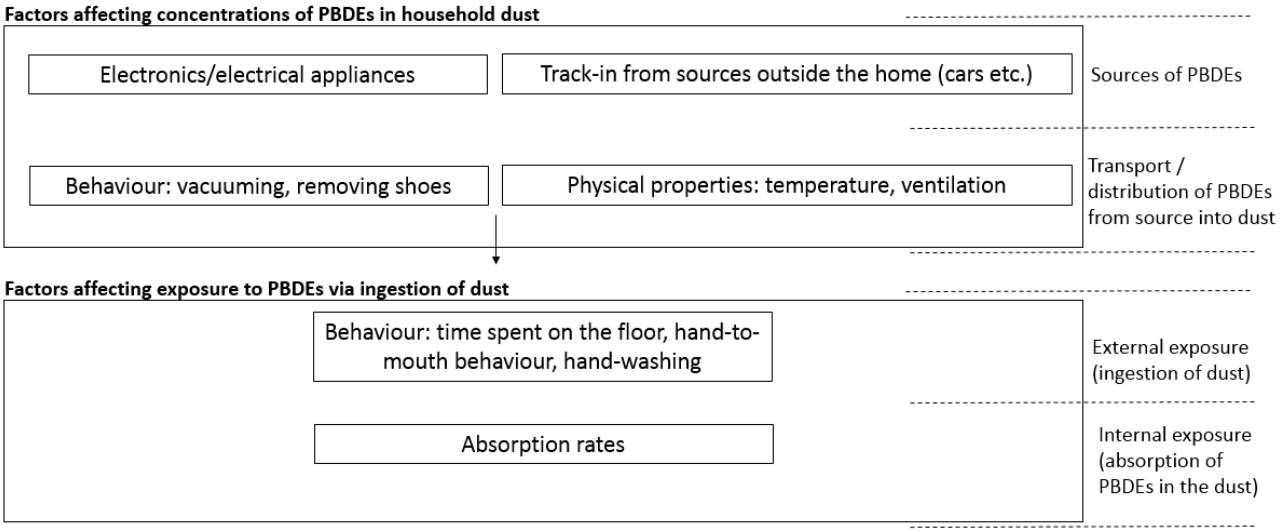

Figure 2-8 Example exposure scenario: Ingestion of PBDE contaminated household dust

The steps taken in SBEM are highly relevant to the design of exposure-assessment questionnaires and the methodologies for SBEM are well established. The first step of SBEM is division of the population into sub-groups or life stages based on age and specific lifestyle characteristics that may affect exposure. For this study, the population would be defined as children under the age of 3. The limitations of SBEM are most pronounced for children this age, because behavioural and physiological factors that affect exposure vary greatly between young children, and also between adults and children. Identifying appropriate sub-groups for SBEM is complex because of this

variation. The United States Environmental Protection Agency (EPA) has proposed a series of age groups for classifying children when studying exposure;[3] they are designed to take into account biological and behavioural factors that influence exposure (142). However, these groupings do not adequately account for the fact that individual exposure determining behaviours vary significantly amongst young children of the same age (140). On the other hand, grouping purely by developmental stages, i.e. whether infants are crawling or not, is also error-prone, as there may be variation between when an infant first performs an activity to when they do that activity regularly.

Once the population is defined, external exposure is estimated in SBEM by accounting for the exposure factors that affect exposure to the contaminant. To begin this process, the concentration of the toxicant in the media first has to be defined. Sometimes this data can be obtained from environmental monitoring data that has previously been collected, in other instances concentrations can be estimated using statistical modelling. In the case of the example above, the input for the concentration of PBDEs in household dust could either be from environmental monitoring studies that have measured PBDE concentrations in dust, or it could be modelled, using data on the likely sources of the PBDEs, such as electronics or sources outside of the home, and the factors that affect distribution of PBDEs from their sources into household dust, including the physical properties of the chemical, temperature, ventilation and behaviours of the residents in the household (143).

The receptors contact with the media is then modelled, accounting for factors that affect the frequency, duration and intensity of contact that the subpopulation may have with a given media or source containing the toxicant of interest. Modelling the receptor populations contact with a media is done by the use of quantitative values, for example, as outline in the US EPA's 'Exposure Factors Handbook' children under the age of 3 would be estimated to consume between 20 – 50 mg of dust per day (142, 144). Since there remain many gaps in our knowledge regarding the specific behaviours and physiology of young children, the accuracy of the parameters used to model children's exposure is often unknown. For example, for hand-to-mouth behaviour there is still relative large uncertainty about rates of dust ingestion attributable to this behaviour (145).

As previously described, exposure assessment methods are not mutually exclusive. Although scenario-based exposure assessment is typically applied at the population level, for the methods described below, the importance of defining the exposure scenario is still paramount and some

[3] For infants these age groups are as follows: birth to <1 month, 1 to <3 months, 3 to <6 months, and 6 to <12 months 141. Firestone M, Moya J, Cohen-Hubal E, Zartarian V. Selecting age groups for assessing & monitoring childhood exposure to environmental contaminants. Epidemiology. 2006;17(Suppl):S401..

amount of modelling is often still necessary to interpret the data obtained from environmental monitoring, biological monitoring or questionnaire data.

2.5.3 Environmental assessment

Environmental monitoring data is used to identify sources of environmental hazards and quantify the concentrations of hazards in various media, such as air, food and water. The scale of environmental monitoring extends from media that whole populations are exposed to, down to micro-environments that are specific to an individual, see Table 2-6 below. Environmental monitoring data can be used for several purposes, including

- Identifying sources of hazards and characterising exposure pathways
- Classifying exposure in health outcome studies (using raw environmental data alone or in combination with other methods, such as questionnaires or modelling) or for exposure risk assessment

Table 2-6 Scales of environmental monitoring

Environmental monitoring scale	Example
City-wide	Analysis of phthalate concentrations in food, water, air and dust to estimate aggregate average exposure of Delhi residents to phthalates and compare estimates to reference doses (146).
Neighbourhood/Sub-city	Monitoring air concentrations of BPA in different manufacturing facilities to compare health outcomes of workers with different levels of occupational BPA exposure (147).
Residential	Measurement of radon concentrations in individual homes (148).
Individual	Silicon bands worn by individuals to track exposure to EDCs across all the microenvironments they encounter (149).

In some cases, raw environmental monitoring data is used in exposure-outcome studies, under the assumption that the majority of exposure is attributable to contact with that one media, and that individual level variations in behaviour and physiology have minimal impact on contact with the media. As an example, household dust concentrations of the EDCs in this thesis have been used in exposure-outcome studies to classify exposure to these chemicals (91). However, in many cases, more refined exposure estimates that account for exposure via multiple environmental media, as well as individual exposure factors, are needed (150).

Similar to the requirements for SBEM, accurate exposure classification derived from environmental monitoring data requires that 1) environmental monitoring data or accurate estimates are available

for all relevant media 2) temporal and spatial variations in hazard concentrations/intensity are accounted for 3) accurate time-activity data are available and 4) the exposure that occurs in specific scenarios is well characterised, see Table 2-5. When these data are available, environmental monitoring can be an efficient and accurate method of exposure assessment, including at the individual level in some instances. Since the most common way to assess time-activity data for an individual is via questionnaires, environmental monitoring and questionnaires are clearly complementary.

The most extensive use of the questionnaire-based approach to exposure assessment, using environmental monitoring data and modelling to derive exposure estimates, has been in the field of occupational health (23). In epidemiological research this approach has also been used most extensively to estimate air pollution exposure and the same principle has been applied to estimate nutrient intake via the diet. For example, the accuracy and efficiency of assessment of occupational exposure to environmental hazards has been improved by the creation of job exposure matrices or job-specific surveys that are combined with environmental monitoring data (151, 152). In this approach, the questionnaire data, as well as modelling, are used to define the receptor's contact with the exposure media and environmental data provides the estimate of the concentration or intensity of the hazard specific to that exposure scenario, as described by the formula below.

$$QE_{exposure\ estimate} = \sum contact\ with\ media \times concentration\ in\ media$$

Where $QE_{exposure\ estimates}$ is the exposure estimate derived from the tool that combines questionnaire data and environmental data. Contact with media is determined via an exposure-assessment questionnaire and modelling. The concentration of the toxicant in the media is determined via environmental data.

This approach, of linking qualitative with quantitative data by way of modelling, has also been applied in non-occupational settings to improve the accuracy of exposure estimates. For example, Field et al. demonstrated that the strength of the association between residential radon exposure and lung cancer was increased by integrating extensive environmental monitoring data from the whole home with detailed time-activity data about time spent in each area of the home, as compared to using measurements of radon in one area of the home as a proxy for total radon exposure (148). Similarly, Dons et al. demonstrated how individual time-activity data can be combined with modelling and environmental data to provide more accurate estimates of individual-level air pollution exposure, compared to ambient air pollution data alone (153). In the field of nutrition, questionnaire-based approaches to assessing nutrient intake are often built by combining exposure-assessment questionnaires, particularly food frequency questionnaires, with data about the

concentration of nutrients within food (154). These instruments, some of which have been validated against nutrient biomarkers, are able to estimate intake of some nutrients with a relatively high level of accuracy (154).

The main advantage of techniques such as these, other than the improvement in the accuracy of the exposure estimates derived from the instrument, is that no analysis of biological samples is required and frequently environmental monitoring data estimates can be made from modelling and the literature or other publically available databases. This greatly reduces the cost and burden of this approach. However, this is only the case if there is sufficient pre-existing environmental monitoring data available that is generalisable to the study population of interest and the instrument would still be need to validated, usually against biomonitoring data.

Unlike the examples given above, which were based on hazard exposure via one media only, there are multiple relevant exposure media and sources that contribute to young children's aggregate exposure to each of the EDCs in this thesis. To build an EDC exposure assessment instrument using exposure-assessment questionnaires combined with environmental monitoring data would require data for the following media:

- Food
- Breast milk
- Water
- Dust
- Air
- Specific sources (i.e. personal-care products)

These data for the Australian context are not currently available for the EDCs in this thesis, as discussed in more detail in Chapter 4. While it would be possible to obtain this data, it is particularly resource intensive. For example, the comprehensive exposure assessment study undertaken by the Norwegian Institute of Public Health study employed 12 PhD students and 3 post-doctoral students for just 62 participants (155). Therefore, although the approach of combining environmental data with questionnaires has been applied with good effect to produce exposure instruments for a variety of hazards, it is not currently suitable for the EDCs in this thesis.

2.5.4 Biological assessment

Compared to environmental monitoring, biological monitoring can provide an aggregate measure of exposure to environmental toxicants, without requiring extensive sampling of multiple environmental media and knowledge of individual time-activity data. Biomonitoring can be used to monitor population-level exposure and establish reference ranges, detect unique exposure pathways

or identify individuals with high levels of exposure, monitor patterns of exposure temporally and geographically, examine associations with health outcomes in epidemiological research and, finally, to validate exposure-assessment questionnaires (156). In this section, I describe the main strengths and limitations of exposure assessment using biomonitoring. The use of biomonitoring for the development of questionnaire-based approaches to exposure assessment is described in detail in the following chapter.

Recently LaKind et al. published a proposed set of criteria to judge the quality of exposure-outcome studies in the field of environmental health reliant upon biomonitoring for exposure assessment. According to LaKind et al., the quality of biomonitoring exposure estimates are determined by factors that include how relevant the biomarker analysed is to chemical exposure, the precision and accuracy of analytical methods used to quantify it and how it is affected/interpreted with regards to inter-individual variation in factors that affect the sampling media (156). Also, one should consider the practicalities of collecting the media required for the biomarker measurement when evaluating the suitability of a biomarker for use in epidemiological research. The following sections summarises each of these criteria, as they have important implications for the design of the questionnaire-biomonitoring study in this thesis.

2.5.4.1 Relevance of biomarker to actual exposure

Biomarkers include parent compounds, their metabolites, as well as endogenous compounds whose concentration or other aspects are altered by interaction with the chemical of interest (82). Metabolites are the most common biomarker of exposure to chemicals with short half-lives that are renally excreted, including plasticisers and the insecticides in this study. Not all chemical metabolites are specific to one parent compound, as is the case for the majority of organophosphate and pyrethroid metabolites. This may be an important consideration when conducting exposure-outcome studies, particularly when experimental evidence suggests that parent compounds with the same metabolites have different mechanisms of action. The concentrations of chemical metabolites in biological samples does not always directly correlate to the concentrations of parent compound that an individual is exposed to. Metabolites of some toxicants, such as insecticides, are found throughout the domestic environment and children may be exposed to the metabolites in addition to parent compounds (131). This is important as there may be differences in the biological effect of parent compounds versus their metabolites. Therefore, in both these scenarios, environmental monitoring may also be required to confirm exposure to a specific parent compound. Also, since many EDCs are ubiquitous in the environment, they can contaminate samples and laboratory equipment and additional quality control measures are required to ensure that this is minimised (138, 139).

Before conducting biomonitoring studies, researchers must clarify the window of exposure that they intend to capture, as different biomonitoring approaches may be required. Multiple samples need to be collected and analysed to determine average exposure to rapidly metabolised chemicals (i.e. plasticisers and pyrethroid and organophosphate insecticides) with short-term variations in exposure. For example, in infants the intra-class coefficient (ICC) for BPA measured in urine samples collected over a period of 48 hours is 0.51; one-spot sample correctly classifies exposure tertile 70% of the time, but the ICC for a more extended period in infants is unknown (157). Frederiksen et al. reported an ICC for phthalates measured in spot urine samples collected a month apart from ages 1 month to 6 months in full-term infants of 0.31 for metabolites of MiBP and DiNP, 0.37 for metabolites of MnBP, 0.39 for metabolites of DEHP, 0.48 for MEP and 0.53 for BBzP (158). In these cases, the ability of the biomarker to measure 'actual' exposure is mainly dependent on the time-frame that the researchers are aiming to capture and the number of biological samples collected, as illustrated in the figure below (159, 160). Unlike the other sentinel chemicals, PBDEs are persistent lipophilic pollutants, with low variability in biomarkers concentrations over a long time frame (i.e. months) in adults and children; cumulative long-term exposure is characterised through the collection of just one biological (typically serum) sample (161, 162).

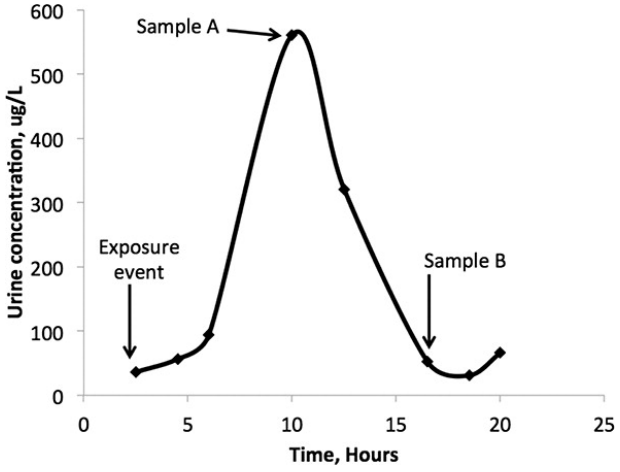

Figure 2-9 Time versus concentration for a chemical with a short half-life. although individual a and b have the same exposure, the measured concentrations differ due to differences in the time of sampling since the exposure event, reprinted with permission from Aylward, Hays (163).

2.5.4.2 Precision and accuracy of analytical methods for biomonitoring

The precision and accuracy of analytical methods is also an essential determinant of the suitability of a specific biomarker for use in exposure assessment. The importance of this to the current PhD cannot be overstated, however, an in-depth discussion of analytical methods for biomonitoring is beyond the scope of this PhD. Briefly, low-level environmental exposures present unique analytical challenges, particularly in children. Concentrations of chemicals of interest are frequently below the limit of detection of current laboratory methods, particularly when only small sample volumes

are available. For example, PBDEs have been found to be frequently below the limit of detection in serum samples from young children in Queensland (164). In the absence of more sensitive analytical methods, alternative methods of exposure assessment, including environmental monitoring or the questionnaire-based approach to exposure assessment may be required.

2.5.4.3 Inter-individual variation in factors that affect the sampling media

Physiological differences between individuals can also affect the interpretation of biomarkers. To compare concentrations of EDCs in urine between individuals, it is usually necessary to make adjustments based on each individual's urine production, however, there is no one method that is suitable in all scenarios (156). In adults, creatinine concentrations in urine are used to standardise concentrations between individuals. However, creatinine production in children varies greatly, and other methods to standardise concentrations may also be used, including urine-flow adjustment or specific gravity adjustment (118). The recommended approach currently is to present both unadjusted and adjusted findings for all biomonitoring and exposure-outcome research.

Finally, as suggested, the collection methods to obtain biological samples should also be a determining factor in the quality or suitability of biomonitoring methods. While adult participants may be able to produce urine samples readily at study visits, in infants and toddlers collection of urine samples is challenging, requiring additional materials and effort on behalf of the child's guardians. This leads to additional burden on the study participants and researchers. The additional cost and the possibility of reduced participation and retention rates are factors to be considered when using biological monitoring for exposure assessment, particularly in children who are not yet toilet trained.

In summary, biological monitoring is considered the 'gold standard' of exposure assessment. It is most useful or ideal when the biomarker, as measured in the specific matrix, meets the following criteria: the measured concentrations accurately reflect exposure to one specific parent chemical, analytical methods are sensitive enough to reliably detect the biomarker, the biomarker is stable in the matrix, samples can be collected and analysed without contamination and matrix effects (such as urine dilution) can be standardised to enable comparison between individuals (156). Compared to environmental monitoring, biomonitoring is particularly useful in situations where the relevant pathways of exposure are not known, or it is not feasible or possible to measure all the environmental media that may be relevant for exposure.

2.6 Summary

Exposure to EDCs during the critical periods of development (foetal development and childhood) can lead to more significant health effects compared to exposure during adulthood. EDCs,

including the sentinel EDCs in this PhD, are widely distributed throughout the home environment, and exposure of young Australian children to these chemicals is practically universal. Since the majority of EDCs found in consumer products have had no human health risk evaluation before their use, regulations to limit their use often occur once exposure to these chemicals is ubiquitous and human health risks have been identified. Regulatory bodies depend on not only on experimental evidence but also on human epidemiological research to guide their decision making. The accuracy of exposure assessment is one of the primary determinants of high-quality epidemiological studies. EDC-exposure-outcome studies that have been conducted to date, particularly in the past two decades, have relied mainly on biomonitoring. Biomonitoring is advantageous in that it can capture aggregate exposure to environmental toxicants even when exposure sources or pathways are unknown. However, biomonitoring often limits study sample sizes because of the burden associated with collecting and analysing samples. Furthermore, the typical sampling methodologies (limited numbers of biological samples) employed in exposure-outcome studies introduce substantial error into the exposure-outcome estimates. Environmental monitoring is particularly useful for assessing sources and identifying likely exposure pathways of humans to environmental toxicants. It can also be combined with modelling and questionnaires to estimate population or individual exposure. However, when the sources and exposure pathways to EDCs are numerous, extensive environmental monitoring is necessary, which can also be costly and burdensome. Furthermore, modelling may introduce error into exposure estimates, since the parameters that influence exposure, including behaviour and physiology, are not always well known, particularly for young children.

From the discussion in this chapter, it is apparent that there is no one ideal method of assessing children's environmental toxicant exposure. When choosing an exposure assessment tool, some of the leading features to be counterbalanced are: 1) accuracy 2) cost 3) burden to participants 4) burden to researchers and 5) suitability for the study population, including ethical and practical considerations. The next chapter contains an overview of the questionnaire-based approach to exposure assessment and further justification of its applicability to children's environmental epidemiology.

CHAPTER 3 THE QUESTIONNAIRE-BASED APPROACH TO EXPOSURE ASSESSMENT

Citation: English, K; Healy B; Jagals P; Sly PD (2015) Assessing exposure of young children to common endocrine-disrupting chemicals in the home environment: a review and commentary of the questionnaire-based approach, Rev Environ Health, 30(1):25-49

In the previous chapter, the need for an accurate, non-invasive, cost-effective exposure assessment tool to assess exposure of young children to EDCs was demonstrated. To date, there has been no review of the suitability and effectiveness of the questionnaire-based approach for this application. The following chapter contains an abridged and amended[4] published review paper on the questionnaire-based approach to exposure assessment. In the review, no studies were identified that set out to design and validate an EDC-exposure assessment questionnaire. Therefore, the focus of the review is predominantly on the assessment of studies that have previously used a questionnaire-biomonitoring approach to explore determinants of exposure of young children to the sentinel EDCs. The results and discussion provide an overview of the important exposure pathways with regards to young children's exposure to the sentinel EDCs, which is important information for the design of the exposure-assessment questionnaire that occurs in Chapter 7.

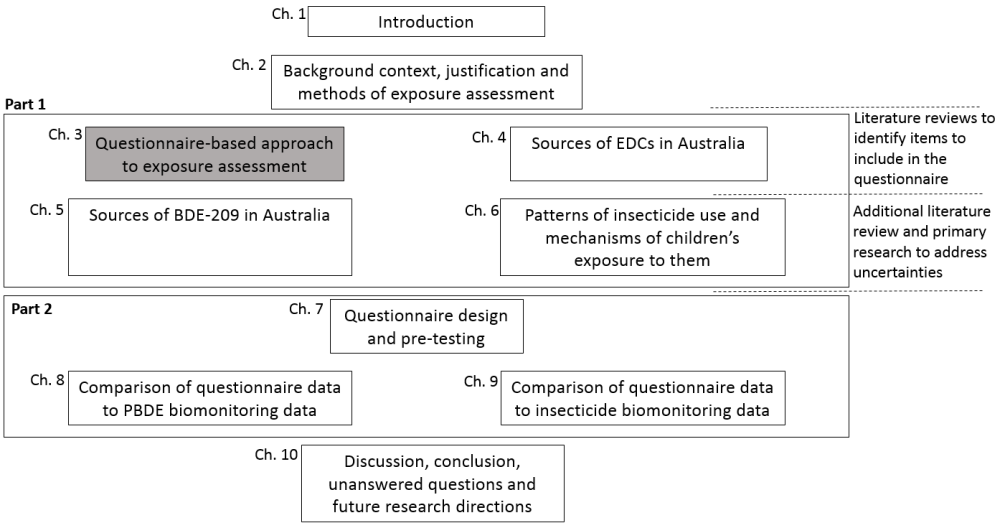

Figure 3-1 Thesis Structure: Chapter 3

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4 Much of the introduction from the paper has been removed to reduce repetition. The terminology throughout the paper has been altered to ensure consistency with the rest of the thesis.

3.1 Design of exposure-assessment questionnaires and development of questionnaire-based exposure assessment tools

In the following discussion, we provide a description of the steps for exposure-assessment questionnaire design and the design of questionnaire-based exposure assessment tools using biomonitoring. The design of a validated questionnaire-based exposure-assessment instrument can be described with four steps

1) Initial exposure-assessment questionnaire design

2) Questionnaire pre-testing and revisions

3) Design of the questionnaire-based exposure assessment instrument: including integrating the exposure-assessment questionnaire via software or statistical modelling with a database that describes the effect of specific exposure-scenarios on exposure

4) Test the predictive capacity of the instrument in an additional questionnaire-biomonitoring study

In the first step, the hazard(s) is identified, see section 2.2 on page 10. The pathways of exposure relevant to the hazard(s) are analysed – this step is important to ensure the content validity of the questionnaire - that all relevant pathways of exposure are identified and accounted for. This analysis informs the development of questions, with subsequent development of the questionnaire as a whole following. The questionnaire is designed so that individual questions, or combinations of questions can be used to adequately describe specific exposure scenarios that are relevant for the receptor population of interest and the hazard of interest.

For a comprehensive description of question design and holistic design of questionnaires we refer the reader to Dillman et al (165) and Chapter 7 of this thesis. The next crucial step in questionnaire design is pre-testing - this process may involve methods such as administering the questionnaire to focus groups or to volunteers under cognitive interviewing conditions, followed by revisions. This step aims to ensure that measurement error attributable to issues such as question misinterpretation and recall error are absent or minimised.

Design of the exposure-assessment *instrument* then begins. Since the literature regarding design of exposure-assessment questionnaires for this specific context is limited, the recommended steps draw upon the general principles of designing and evaluating exposure assessment methods, see White, Armstrong (136), as well as from other fields, including occupational health (23), and the design of dietary instruments to assess nutrient intake, for example see Serra-Majem, Frost Andersen (166).

As described previously, in section 2.5.1, the *instrument* uses modelling to predict exposure from qualitative data, obtained via the exposure-assessment questionnaire, and quantitative data. The quantitative data is necessary to determine the effect that exposure determinants, measured via the questionnaire, are likely to have on exposure. As previously described, in section 2.5.3 on page 30, environmental monitoring data may be appropriate for this. However, in some circumstances, as is the case for the groups of EDCs in this thesis, environmental monitoring data are unavailable and may not be able to be obtained readily. For example, the toxicant may not be measurable in the environmental media, or the toxicant may occur in a large number of media, at varying concentrations, which means that extensive environmental monitoring data would be required. In these circumstances, biomonitoring data may be more appropriate. Where possible, data describing the association between exposure determinants and biomonitoring can be obtained from the literature (166, 167). However, if these data are unavailable, then these data could be obtained by administering the exposure-assessment questionnaire and conducting biomonitoring in a study group representative of the population for which the instrument is intended to be used with (136). These data are then used to construct a database that describes the expected effect on exposure associated with each exposure determinant to be measured via the questionnaire. The final exposure assessment instrument can then be designed using software or statistical modelling methods to derive the exposure estimates from the questionnaire data and the exposure database.

Finally, the validity, or what is formally called the inter-method reliability, of the final questionnaire-based exposure assessment tool is assessed. This is done by administering the instrument in conjunction with the gold standard for exposure assessment and then analysing how well the exposure predictions from the instrument correlate with the biomonitoring results (136, 168). Validating exposure-assessment tools for epidemiological studies is important because measurement error in exposure-assessment instruments affects the exposure-outcome estimates in epidemiological studies (79, 169). When the error in the exposure-instrument has been quantified, statistical methods, such as regression calibration, can be employed to adjust for this error (79).

In the following review, no formal validation studies for EDC exposure-assessment questionnaires were identified. We assessed studies in which exposure-assessment questionnaire have been applied in combination with biomonitoring for the EDCs in this thesis. From this review we aimed to obtain information about the feasibility of administering exposure-assessment questionnaires, to identify possible sources of error that may be encountered in this approach, as well as to identify items to include in the exposure-assessment questionnaire for this thesis. We have divided these items into scenarios of common sources and modifiers of exposure, including diet, general features of the home and goods in the home, product use and consumer application behaviour.

3.2 Search methods

The aim of our literature search was to locate studies that assessed exposure of children to at least one of the toxicants of interest and collected questionnaire data. We conducted three separate searches via PubMed and Web of Knowledge for each of the three groups of toxicants. The primary terms were the toxicant(s) of interest, including: "BPA" "bisphenol A" "phthalate" "plasticiser" "polybrominated diphenyl ether(s)" "PBDE" "polybrominated biphenyl ether(s)" "brominated flame retardant" "pyrethrins" "pyrethroid" "organophosphates" "insecticides". Secondary terms included terms relating to children, behaviour, questionnaire, biomonitoring, the home environment and potential sources of exposure in the home. The inclusion criteria were 1) primary scientific reports from peer-reviewed journals 2) sample group including children under the age of ten years 3) exposure assessment to at least one of the toxicants of interest through the use of biomonitoring and 4) at least one question pertaining to possible exposure through the home environment. Some studies that assessed human exposure pathways to the toxicants of interest, but not necessarily in children <10 years of age or in the home environment were also included. Studies were excluded if they only assessed human health, were animal studies or did not address any of the toxicants of interest.

3.3 Association between questionnaire responses and biomonitoring data

We were unable to perform a systematic search of the literature using 'questionnaire' or 'survey' as keywords, as most of the relevant studies which reported on questionnaire data did not list these as keywords or discuss the use of questionnaires within the abstract. In other cases, the administration of a questionnaire was discussed, but no findings or results from questionnaire data were reported. We therefore conducted a broad search of full-text articles, as well as assessing the reference list of studies to ensure we identified as many relevant studies as possible. We assessed over 3 000 reports in total. A total of 8 papers for PBDEs, 13 papers for phthalates and BPA, and 16 papers for pesticides were assessed as highly relevant, these reports are found in the tables below. No studies designed to validate EDC-exposure-assessment questionnaires were identified. All identified studies used the exposure-assessment questionnaire combined with biomonitoring data to explore how young children are exposed to these chemicals. There is increasing recognition that in real life exposure occurs not to individual chemicals, but mixtures of chemicals. We therefore present results from the identified studies in scenarios of common sources and modifiers of exposure, including diet, general features of the home and goods in the home, product use and consumer application behaviour.

Table 3-1 Association between questionnaire responses and PBDEs. Biomonitoring estimates of internal exposure of young children (<10 years) to PBDEs.

	Media	Study name and location[1]	Age (years)	N[2]	Units	Features of the home	consumer goods	Diet and breastfeeding	Behaviour/time activity
Bradman, Castorina (170).	Blood	CHAMACOS U.S.A.	7	272	ng/g lipid;	Number of rooms with wall-to-wall carpeting in the home and ΣBDE[3] (β: 1.07, p-value 0.16), BDE-47 (β: 1.10, p-value 0.11)	NA[4] number of TVs	NA daily servings of dairy or meat, total daily fat intake or fish consumption at 5 years and internal exposure at 7 years Duration of exclusive breastfeeding and ΣBDE[3] (β: 1.05, p-value 0.04), BDE-47 (β: 1.06, p-value 0.03), BDE-153 (β: 1.03, 0.11)	Lack of safe places to play in neighbourhood and ΣBDE[3] (β: 1.42, p-value 0.003), BDE-47 (β: 1.44, p-value 0.005), BDE-153 (β: 1.34, 0.006)
Carrizo and Grimalt (120).	Blood	Spain	4	244				Average concentration of PBDE congeners and breastfeeding vs. formula feeding; BDE-47 (3.4, 0.73, p-value <0.01), BDE-99 (1.4, 0.26, p-value <0.01), ΣBDE[5] (3.6, 1.30, p-value <0.05)	
Eskenazi, Fenster (171).	Blood	Proyecto Mariposa, Mexico	5	283	-			Percent change in PBDE congener concentration per month breast feeding; BDE-47 (0.5% , p-value 0.62), BDE-99 (0.8%, p-value 0.42), BDE-100 (0.7%, p-value 0.41), BDE-153 (2.0%, p-value 0.004)	
Link, Gabrio (172).	Blood	Germany	9-11	1537 (66 pooled samples)				NA breast feeding and PBDEs	
Lunder, Hovander (124).	Blood	U.S.A.	1.5-4	20	-	NR[6]			
Rose, Bennett (126).	Blood	CHARGE, U.S.A.	2-5	94	pmol/g lipid;	Home size (m^2) and ΣBDE-197-209 (β: -0.18, p-value:0.11)	Purchase of a new mattress or upholstered furniture and ΣBDE-197-209	Frequency of pork consumption per week and ΣBDE-197-209 (β: 0.25 , p-value: 0.02); Frequency of poultry consumption per week and	NA age of car and time spent in cars

	Media	Study name and location[1]	Age (years)	N[2]	Units	Features of the home	consumer goods	Diet and breastfeeding	Behaviour/time activity
						Carpet or upholstered furniture and ΣBDE NR	(β:0.20, p-value: 0.05) NA number of electronics in the home	ΣBDE-28-153 (β: 0.10 , p-value: 0.06), Frequency of processed meat consumption per week and ΣBDE-28-153 (β: 0.06 , p-value: 0.39) ΣBDE 28 -153 concentrations and age in breast fed children (β: 0.20, p-value: 0.14)	
Stapleton, Eagle (127).	Blood	U.S.A.	1-3	83	ng/g			Months of breast-feeding Σ-BDE-47,-49 and -100 (β: 0.99 p-value: 0.41); BDE-153 (β: 1.07, p-value: <0.0001)	Hours away from home each week and Σ-BDE-47,-49 and -100 (β: 1.00, p-value 0.50), BDE-153 (β: 1.00, p-value 0.95)
Windham, Pinney (173)	Blood	BCERC, U.S.A.	6-9	599				NA breastfeeding and PBDEs	

1.CHAMACOS (The Center for the Health Assessment of Mothers and Children of Salinas); CHARGE (Childhood Autism Risks from Genetics and the Environment). BCERC (Breast Cancer and the Environment Research Centers) 2. N = Number of Participants 3. ΣBDE-17, -47, -66, -85, -99, -100, -153, -154, -183 4. NA = No Association 5. ΣBDE-17, -28, -47, -66, -71, -85, -99, -100, -138, -153, -154, -183, -190 6. NR = Not Reported.

Table 3-2 Association between questionnaire responses and plastics. Biomonitoring estimates of internal exposure of young children (<10 years) to BPA and phthalates.

Reference	Media	Study name[1] and location	Age (years)	N[2]	Units	Features of the home	Consumer goods and personal care products (PCP)	Behaviour/time activity	Diet and breastfeeding
Becker, Seiwert (174).	Morning urine sample	GerES IV, Germany	3-14	254	-	NA[3] plastic/vinyl home décor or furniture and DEHP		NA time spent playing on the floor and DEHP NA time spent indoors and DEHP NA time spent in cars and DEHP	NA consumption of meat, milk products, and fish and DEHP
Brock, Caudill (175).	Two spot urine samples	US	1-1.5	19	-		NA plastic toy use and MEP, MEHP, MBzP and MBP NA Primary caregiver's PCP use and MEP, MEHP, MBzP and MBP in children		NA consumption of solid food and MEP, MEHP, MBzP and MBP NA breastfeeding and MEP, MEHP, MBzP and MBP
Carlstedt, Jonsson (176).	Overnight urine sample	Sweden	0-1	83	ng/mol; creatinine-adjusted	NA size of the home and DEHP, BBzP, DBP and DEP vinyl flooring in infants room (presence vs. absence) and MBzP (GM: 10.3, 6.0, p-value <0.01)			Formula fed (yes vs. no) and MEHHP (5.6, 2.4, p-value < 0.001) MEOHP (7.7, 3.8, p-value <0.001)

Reference	Media	Study name[1] and location	Age (years)	N[2]	Units	Features of the home	Consumer goods and personal care products (PCP)	Behaviour/time activity	Diet and breastfeeding
						vinyl flooring in parents room (presence vs. absence) and MBzP (GM: 10., 6.0, p-value <0.01) Single-family home vs. apartment and MBzP (GM: 5.9, 6.4, p-value < 0.05)			
Casas, Valvi (78).	Spot urine sample	Sabadell birth cohort, Spain	4	130					NA consumption of meals stored in plastic containers, canned food and food in plastic containers and BPA
Hoepner, Whyatt (177).	Spot urine sample	CCCEH, US	3-7	306-398	-				NA breastfeeding and BPA
Koch, Preuss (178).	First-morning void urine sample	Germany	2.6-6.5	36	ug/L		Skin/body care product use (often or occasional use vs. seldom or never used) and MnBP (182, 89.7, p-value 0.047) NA MBzP	NA mouthing behaviour and MnBP or MBzP	
Lakind and Naiman (179).	Spot urine sample	NHANES 2005-2006, US	8-18	1054					Frequency of consumption of school lunches significantly positively associated with BPA exposure (CC[4] not reported)

Reference	Media	Study name[1] and location	Age (years)	N[2]	Units	Features of the home	Consumer goods and personal care products (PCP)	Behaviour/time activity	Diet and breastfeeding
									Frequency of consumption of soda significantly positively associated with BPA exposure (CC not reported) NA canned tuna consumption and BPA
Lewis, Meeker (180).	Spot urine sample	ELEMENT, Mexico	8-13	108	ng/mL	NA plastic/vinyl floor and BPA or phthalates	NA reported PCP use in previous 48 hours and BPA or MBzP Median concentrations (use vs. non use) in the previous 48 hours with reported PCP use: Boys; cologne and MEP (135, 49.5, p-value 0.007), MCPP (2.6, 1.7, p-value 0.009), MEHHP (57.1, 38.4, p-value 0.03), MEOHP (25.7, 16.5, p-value 0.01) Boys, lotion and MEHP (9.8, 6.7, p-value 0.02) Girls; coloured cosmetics and MBP (246, 101, p-value 0.02), MEHP (17.3, 7.2, p-value 0.001), MEHHP (102, 46.0, p-value 0.005),		NA primary water source (tap water, bottled water, purified, other) and BPA or phthalates NA consuming food microwaved on or in plastic containers or wrappers and phthalates or BPA NA consumption of canned food and beverages and BPA or phthalates

Reference	Media	Study name[1] and location	Age (years)	N[2]	Units	Features of the home	Consumer goods and personal care products (PCP)	Behaviour/time activity	Diet and breastfeeding
							MEOHP (40.0, 21.9, p-value 0.01), MECPP (141, 71.9, p-value 0.009) Girls; conditioner and MEP (276, 51.8, p-value 0.001) Girls, deodorant and MEP (147, 46.4, p-value 0.003) Girls and other hair products and MBP (293, 101, p-value 0.02), MIBP (22.0, 12.0, p-value 0.008), MCPP (4.5, 2.3, p-value 0.03)		
Li (181)	Morning urine sample	China	3-24	287	ug/L				Reported preferred use of plastic versus ceramic drinking vessel associated with significantly higher BPA concentration (p-value 0.037)
Mendonca, Hauser (182).	Urine sample collected from wet diaper	EARtH, U.S.A.	.25-1.5	31	-				NA breastfeeding or formula consumption and BPA
Sathyanarayana, Karr (29).	Urine sample collected	SFFI, U.S.A.	<2.5	163	Adjusted for square root creatinine		NA time spent playing with a plastic toy and phthalates[13]		

Reference	Media	Study name[1] and location	Age (years)	N[2]	Units	Features of the home	Consumer goods and personal care products (PCP)	Behaviour/time activity	Diet and breastfeeding
	from wet diaper						Ratio of phthalate metabolite concentrations (use vs. non-use in the previous 24 hours): Baby lotion and MEP (1.8, p-value <0.05), MMP (1.4, p-value <0.05) Baby shampoo and MMP (1.4, p-value <0.05) Baby powder and MiBP (1.6, p-value < 0.05) NA use of the above Personal care products and other phthalates[5] NA diaper cream or baby wipes and phthalates[5]		
Trasande, Sathyanarayana (183).	Spot urine	NHANES 2003-2008, US	6-19	2743					Percent change in phthalate concentration with each additional unit reported consumed via 24-hour dietary recall: kcal and DEHP (+0.007%, p-value <0.05); g grain intake and low-molecular weight phthalates[6] (-0.04%, p-value <0.05), g fruit intake and low-molecular weight phthalates[6] (-0.02%, p-value <0.05); g vegetable intake (0.01%, p-value <0.05); g non-whole grain and DEHP

Reference	Media	Study name[1] and location	Age (years)	N[2]	Units	Features of the home	Consumer goods and personal care products (PCP)	Behaviour/time activity	Diet and breastfeeding
									(0.08%, p-value <0.05), g dairy intake and DEHP (0.02%, p-value <0.05), g poultry and DEHP (0.22%, p-value <0.05), g soy and DEHP (-0.37%, p-value <0.05)
Volkel, Kiranoglu (30).	Urine collected in urine bags	Germany	0-0.5	47	ug/L				Median BPA concentration and reported use of baby bottle vs. non-use (2.11, 0.81)

1.GerES IV (German Environmental Survey on Children 2001/2002); CCCEH (Columbia Centre for Children's Environmental Health); NHANES (National Health and Nutrition Examination Survey);ELEMENT (Early Life Exposure in Mexico to Environmental Toxicants); EARtH (Environment and Reproductive Health); SSFI (Study for Future Families) 2. N = number of participants 3. NA = No Association 4. CC = Correlation Coefficient 5. BBzP, DBP, DEP, DEHP, DnOP, DMP 6. DEP, DBP, DnOP, DiBP

Table 3-3 Association between questionnaire responses and insecticides. Biomonitoring estimates of internal exposure of young children (<10 years) to organophosphates and pyrethroids,

	Media	Study name[1] and location	Age (years)	Units	N[2]	Diet	Insecticide use in the home	Behaviour/time activity	Other
Aprea, Strambi (184).	Spot urine sample	Italy	6-7	nmol/g creatinine	195	Consumption of meals at the school cafeteria (yes vs. no) and concentration of Σ organophosphate metabolites[3] (376.9, 327.3, p-value >0.05)	Use of pesticides in the home (yes vs no) and concentration of Σ organophosphate metabolites[3] (451.0, 329.0, p-value < 0.05)		Presence of a vegetable garden at the home (yes vs. no) and concentration of Σ organophosphate metabolites[3] (362.1, 321.4, p-value > 0.05) Presence of domestic animals at the residence (yes vs no) and concentration of Σ organophosphate metabolites[3] (301.9, 359.3, p-value >0.05)
Babina, Dollard (115).	First-morning void urine	Australia	2.5-6		340		NR[3]		
Becker, Seiwert (116).	First morning void urine	GerES IV, Germany,	2-5	ug/g	60	Consumption of fruit juice[4] and DMP (β: 0.14. p-value 0.011), DMTP (β: 0.11, p-value 0.029), DEP (β: 0.16, p-value 0.004), NA[5] DETP Consumption of fresh fruit per day[6] and DETP (β: 0.20. p-value <0.001), NA DMP, DMTP or DEP	Use of biocides indoors at home (vs. no use) and exposure to pyrethroids; *Cis*-DCCA (β: 0.10 p-value 0.049), *Trans*-DCCA (β: 0.10 p-value 0.040), NA 3-PBA		NA presence of garden at homes of children and exposure to organophosphates

	Media	Study name[1] and location	Age (years)	Units	N[2]	Diet	Insecticide use in the home	Behaviour/time activity	Other
						Consumption of boiled vegetables[7] and 3-PBA (β: 0.16 p-value 0.023), *Cis*-DCCA (β: 0.11 p-value 0.043), *Trans*-DCCA (β: 0.15 p-value 0.004)			
Bradman, Castorina (185).	Spot urine sample	CHAMACOS (rural population)	0.5-2	Log	~400	Daily servings of fruits and vegetables (more than one or one or less) and organophosphate metabolites; Σ DMAP metabolites[8] (β: 1.60. p-value <0.05), Σ DEAP[9] (β: 1.25, p-value >0.05)	NA use of insecticides in the home and organophosphate metabolites[10]	NA time spent mouthing fingers and toes and organophosphate metabolites[10]	NA any dogs and cats in the home and organophosphate metabolites[10]
Bradman, Whitaker (186).	Spot and overnight urine samples	Planning for the NCS, U.S.A.	0.5-1 and 2		20	NR	NR		
Lu, Toepel (132), Lu, Barr (187).	Daily first morning voids for 15 days	CPES-WA 2003, U.S.A.	3-11	ug/L	23		Residential Pesticide Use (yes vs no) and DVWA[11] 3-PBA (1.84, 0.94, p-value <0.001), *trans*-DCCA (1.91, 0.94, p-value <0.001)		
Morgan and Jones (188).	Up to six spot urine samples over 48 hours	CTEPP NC and OH, U.S.A.	2-5	ng/mL	135	Food type consumption (low vs. high) and TCP; apples (5.76, 9.40, p-value 0.04), fruit juice (8.41, 4.11, p-value 0.040), NA other food types	NR		

	Media	Study name[1] and location	Age (years)	Units	N[2]	Diet	Insecticide use in the home	Behaviour/time activity	Other
						Food type consumption (low vs. high) and 3-PBA; chicken/turkey (0.7, 0.41, p-value 0.013)			
Morgan, Sheldon (130).	Urine	CTEPP-OH 2000-2001, U.S.A.	1.7-5.6		127		NR		
Munoz-Quezada, Iglesias (189).	Two spot urine samples, one in summer and one in autumn	Chile	6-12		190	Consumption of foods found to typically contain residues of the organophosphate phosmet and Σ DMAP[8] metabolites (β: 4.12 p-value <0.0001)	Use of the organophosphate pesticide fenitrothion at the home and Σ DMAP[8] metabolites (β: 1.44 p-value 0.009)		
Naeher, Barr (190).	Urine; baseline and following head lice treatment	U.S.A.	6-10	ug/g creatinine	78				Permethrin exposure significantly higher following self-reported head lice treatment (CC[12] not reported)
Naeher, Tulve (133), Tulve, Egeghy (191), Tulve, Egeghy (192).	Spot urine	JAX-EXP	4-6	ug/g creatinine	203		Insecticide use in the home in the last 4 weeks (yes vs no) and 3-PBA (4.1, 2.8, p-value <0.05), *cis*-DCCA (1.6, 1.0, p-value <0.05), *trans*-DCCA (2.7, 1.7, p-value <0.05); DMP (3.9, 5.6, p-value >0.1), DMTP (5.2, 7.7, p-value >0.1), DMDTP (0.8, 1.2, p-value <0.1), DEP (4.8, 5.3, p-value >0.1) DETP (1.0, 1.0, p-value		

	Media	Study name[1] and location	Age (years)	Units	N[2]	Diet	Insecticide use in the home	Behaviour/time activity	Other
							>0.1) , DEDTP (0.2, 0.2, p-value >0.1)		
Riederer, Bartell (193).	Spot urine	NHANES 1999-2002, U.S.A.	6-10		179	3-PBA concentrations and consumption of food types (by bootstrap analysis); ground beef (3.3×10^{-2}, p-value <0.0001), toasted white bread (2.4×10^{-2}, p-value 0.0332) , ice cream (6.6×10^{-3}, p-value 0.0288), tortilla chips (-2.1×10^{-2}, p-value 0.0158), cheese (-$2.5\times10^{-}$2, p-value 0.0154) and cookies(-3.4×10^{-2}, p-value 0.0046), NA other foods and 3-PBA	NA reported domestic insecticide use and 3-PBA	NA time spent playing games and pyrethroid metabolites[13]	
Sexton, Adgate (194).	Three first morning void urine samples over one week	MNCPES, U.S.A.	3-13		102		Malathion exposure given insecticide use reported in the home vs. insecticide use not reported in the home (Odds Ratio: 0.550, p-value >0.05)		
Trunnelle, Bennett (195).	End of day spot urine sample	SUPERB, U.S.A.	2-8		83	NR	NR		
Trunnelle, Bennett (196).	End of day spot urine sample	MICASA, U.S.A.	2-8		103	Consumption of food items (yes vs. no) in the previous 24 hours and 3-PBA; apple (t value: -1.5, p-value 0.13), milk total (t value -1.2, p-value 0.22), all meat total (1.7, 0 .1), cereal total (t value -1.7, p-value 0.08)	Outdoor spray use and 3-PBA (t value 1.8, p-value 0.10)		Home Disrepair Score (water damage, water leaks, carpet damage, counter damage and rotten wood) and 3-PBA (t value 1.7, p-value 0.10)

	Media	Study name[1] and location	Age (years)	Units	N[2]	Diet	Insecticide use in the home	Behaviour/time activity	Other
Wilson, Strauss (197).	First-morning urine void	PEPCOT, U.S.A.	0-6		100		NR		

1.GerES IV (German Environmental Survey on Children 2001/2002; planning for NCS (National Children's Study); CPES (Children's Pesticide Exposure Study); CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas Quantitative Exposure Assessment Study); CTEPP (Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants); JAX-EXP (Biological and Environmental Monitoring for Organophosphate and Pyrethroid Pesticide Exposures in Children Living in Jacksonville, Florida Study); NHANES (National Health and Nutritional Examination Survey); MNCPES (Minnesota Children's Pesticide Exposure Study); SUPERB (Study of Use of Products and Exposure Related Behavior); MICASA (Mexican Immigration to California: Agricultural Safety and Acculturation Study); PEPCOT (Pesticide Exposure of Preschool Children Over Time) 2. N = number 3. NR = Not Reported 4. less than one glass-one glass-more than one glass 5. NA = No Association 6. >once day – once per day – less than once per day 7. once a week or less frequently – several times a week – daily 8. Dimethyl alkyl phosphate metabolites (DMAP): DMP, DMTP, DMDTP 9. Diethyl alkyl phosphate metabolites (DEAP): DEP, DEDTP, DETP 10. DMP, DMTP, DMDTP, DEP, DEDTP, DETP 11. DVWA (Daily Volume Weighted Average) 12. CC = correlation coefficient 13. 3-PBA, *trans*-DCCA, *cis*-DCCA

3.3.1 Diet

Dietary diaries, recalls and food frequency questionnaires (FFQs) have the potential to provide a wealth of data on dietary exposures in epidemiological studies. The less-varied diet of young children - compared to adults and older children - and their relatively larger food intake may lead to greater or different EDC exposures (10, 31). In infants, their diet is even more restricted, often to a singular source. Numerous EDCs occur in both breast milk and infant formula samples; thus dietary sources of exposure would be expected to be an important exposure pathway (198-202). If the primary dietary source is contaminated, this may result in increased exposure in infants. However, when considering EDCs, food-preparation practices that may increase or decrease the risk of chemical contamination also need to be considered. In the following section, we review the findings from studies that have assessed dietary determinants of young children's exposure to BPA and phthalates, PBDEs and organophosphate and pyrethroid insecticides.

More than a dozen studies have reported associations between dietary habits, including consumption of particular foods or liquids (including breast milk and formula) and consumption of foods that come into contact with plastic materials containing BPA and phthalates, see Table 3-2 on page 43. Trasande et al., controlling only for urinary creatinine, reported a positive association between total dietary energy intake and exposure to the high-molecular-weight phthalate DEHP, recorded in a 24-hour dietary recall from children enrolled in the United States National Health and Nutrition Examination Survey (NHANES) 2003-2008 (183). Positive associations between phthalate concentrations and increasing consumption of vegetables, dairy and poultry were reported. In contrast, consumption of fruit and grains were negatively associated with concentrations of low-molecular-weight phthalates, while consumption of soy was negatively associated with concentrations of DEHP. LaKind et al. reported that frequency of soda consumption, as measured through the NHANES questionnaire, was significantly associated with urine concentrations of BPA in children (179). Consumption of canned foods has been found to significantly increase exposure of adults to BPA but this association has not been adequately investigated in children (179, 203-205). A Spanish cohort of 4-year old children showed that consumption of canned fish and canned beverages, assessed through an FFQ, correlated with higher levels of BPA measured in spot urine samples, although the association was not statistically significant (78). The lack of significance may be in part explained by exposure misclassification from collecting only one spot urine sample, as well as the lack of accounting for recent dietary exposure and the time of day that the sample was collected.

Due to the short half-lives of BPA and phthalates, spot samples reflect only very recent exposure, which is not readily captured by an FFQ designed to assess longer-term exposure. In this scenario, it may be easier to validate a 24-hour recall or a prospective food diary to assess short-term exposure of children to plasticisers. If an FFQ is being designed for use to assess long-term exposure to plasticisers in epidemiological studies, it would be necessary to first validate such an FFQ against regular biological samples throughout the period to be assessed by the FFQ.

In infants, the mode and delivery of feeding appear to be an important cause of plasticiser exposure. Infants who are not exclusively breastfed have higher concentrations of DEHP metabolites in their urine than infants who are exclusively breastfed, which may indicate either contamination of infant formula or leaching of phthalates from baby bottles used to administer the infant formula (176). As several studies have reported varying concentrations of BPA and phthalates in infant formula, a questionnaire-based approach may be useful as it can capture information about factors that may indicate the presence and concentration of EDC's in infant formula (206, 207). These may include the brand of infant formula used, the water supply used to prepare the formula, the brand of baby bottle, and the length of time the formula is stored in a plastic bottle before administration and whether the formula is heated in the bottle or whether hot liquid is put into the plastic bottle. The way the bottle is cleaned between uses may also influence contaminant levels in the formula.

A limited number of studies have assessed whether breastfeeding is associated with biomonitoring concentrations of BPA or phthalates in children, of which none reported any significant associations (175, 177, 182). Although BPA and phthalates partition into breast milk, unlike PBDEs they do not accumulate in breast milk (182, 208, 209). Concentrations of plasticisers in breast-milk are therefore generally low and may vary according to recent maternal exposure. More research is required to understand how recent maternal exposure influences the variability of BPA and phthalate breast milk concentrations, as well as the relative contribution of breast milk to total body burden in infants. However, it is reasonable to expect that any questionnaire-based approach attempting to predict infant exposure to plasticisers through breast-milk needs to account for maternal exposure, as well as any plastic-based aides used in the collection and storage of breast milk, such as breast pumps, baby bottles or plastic freezer storage containers.

In school-aged children, the frequency of consumption of school lunches outside of the home, which may be a proxy for consumption of food prepared or stored in packaging, has also been found to be associated with BPA biomonitoring concentrations (179). The leaching of plasticisers from food-contact materials is facilitated under several conditions, including heating, exposure to alkaline conditions (i.e. dishwashing soap), and exposure to lipid-rich foods (210). Therefore,

when assessing exposure to plasticisers from food contact material through a questionnaire-based approach, it is pertinent to consider the conditions that the food contact materials are subject to and whether the materials come into contact with fatty foods in particular.

The persistent, lipophilic properties of PBDEs enable them to bioaccumulate and biomagnify in the food web. As such, lipid-rich foods and foods that originate from higher trophic levels contain the highest concentrations of PBDEs (202). PBDEs also persist in humans. Because of this property, unlike plasticisers, validation of an FFQ assessing average PBDE dietary intake over a given developmental period may be successfully achieved by comparison with spot-samples.

Only two studies, both from the US, have assessed whether the results of FFQs are associated with PBDE biomonitoring concentrations, see Table 2 (126, 170). Rose et al. found consumption of poultry, pork, and processed meat to be positively associated with PBDE concentrations in serum from children (126, 170). Neither study found an association between children's consumption of dairy products or fish and PBDE body burden (126, 170). PBDEs are known to vary greatly between different food items, which may be attributable to differences in lipid content or trophic levels. Therefore, the lack of association may be a result of collecting insufficiently detailed data regarding consumption of specific types of fish or dairy (202). Because of this marked variation in concentrations and the long half-lives of PBDEs the FFQ has advantages over a 2-day diary or 24-hour recall study approach in assessing cumulative exposure of children to PBDEs; The FFQ can capture rare events that may contribute significantly to dietary exposure that may otherwise be missed with a 2-day diary, such as consumption of seafood, which may only occur rarely in some populations.

Breastfeeding duration, as assessed through questionnaires, is a significant predictor of increased PBDE biomonitoring concentrations in infants and toddlers, Table 3-1 on page 41. The strength of the association tends to decrease with time since weaning and the association with specific PBDEs may vary according to maternal exposure, maternal age, and the half-life of the specific BDE congener (120, 124, 126, 127, 170, 171, 173).

The impact of diet on children's exposure to insecticides has been assessed through more than half a dozen studies that have used both questionnaires and biomonitoring, see Table 3-3 on page 49. Frequency of consumption, as assessed through questionnaires, of fruit, fruit juice, chicken/turkey, ground beef, toasted white bread, ice cream, tortilla chips, cheese, cookies and boiled vegetables has been found to be associated with insecticide biomarker concentrations; Consumption of fruit (as a broad category and also the sub-category of apples) was found to be a consistent significant predictor of increased organophosphate, but not pyrethroid, metabolite concentrations (116, 185,

188, 189, 193). A longitudinal intervention study also observed that switching to an organic diet significantly reduced organophosphate biomarker concentrations in urine, although the impact of consuming an organic diet on insecticide exposure in children has not been adequately investigated (132, 184). Insecticide residues may vary greatly in concentration between regions and between seasons (211). Therefore, insecticide exposure questionnaires designed to predict dietary exposure need to be specifically validated for each region that they are to be used in, across seasons and also for other factors that may modify exposure, such as washing or peeling fruits and vegetables before consumption.

3.3.2 General features of the home and goods in the home

Flooring may be a significant cause of exposure of young children to toxins in the home (212). Carlstedt et al. reported that the presence of vinyl flooring in infant's (n=88) bedrooms in Sweden, as assessed through a self-administered questionnaire completed by parents, was significantly and positively associated with phthalate metabolites concentrations in urine (176). In contrast, in a similarly sized cohort of children aged 8-13 (n=108) no association was reported between the presence of vinyl flooring in the home and phthalate metabolite concentrations in urine, as assessed through a nurse-administered questionnaire completed by the children with assistance from their parents (176, 180). The difference in findings may be attributable to a difference in exposure risk among young children (infants) as compared to older children. Phthalates in vinyl flooring can disperse into dust, which may explain the greater exposure risk that vinyl flooring poses to young children, as they ingest more dust than older children (213). Moreover, these differences could also be explained by the greater relative surface area of young children, the increased amount of time that they spend on the floor and the increased amount of time they spend in the home environment.

Several studies from the US have observed a weak positive association between questions relating to the presence of carpet in homes and BDE-47 (a specific PDBE congener) concentrations in biomonitoring samples from children and adults, which may be explained by the foam underlay of carpets containing PBDEs, the carpet itself, or the collection of PBDE contaminated dust within the carpet (170, 214, 215). As young children spend more time on the floor than adults, assessing the type of flooring in homes, the time spent on flooring by children, and the frequency of floor cleaning/vacuuming are important considerations for the content validity of a comprehensive EDC-exposure-assessment questionnaire for children.

Based on experimental evidence, features of the home such as ventilation, house size and cleaning practises alter the concentrations of toxins in dust, and may thus have the potential to modify exposure (216). Indeed, dust concentrations of BDE-209 are inversely correlated with house size

(217). Rose et al. reported a significant negative association between the size of their homes and BDE-209 concentrations in serum of Californian children (126). In contrast, Carlstedt et al. reported no significant association between the size of the home and phthalate metabolite concentrations in children's urine (176).

PBDEs have historically been used in foam-based materials to ensure they meet fire safety standards. Abrasion of the foam releases foam particles containing PBDEs that young children could then ingest either directly or in dust (218). No studies have assessed whether home furniture with exposed or crumbling foam is associated with PBDE biomonitoring concentrations, despite the fact that crumbling foam in the homes is positively associated with PBDE concentrations in house dust (219). Although baby-car seats and foam toys may contain PBDEs, we found no studies that assessed whether the presence or use of these products by children is associated with PBDE biomonitoring concentrations (220). Whilst the Californian study by Rose et al. did not focus on baby products per se, they did find a positive correlation between ΣBDE-197-209 in serum and the purchase of new mattresses, which in most cases was meant for the child (126). It has been suggested that baby and toddler products are sources of exposure inadequately accounted for, since human exposure to PBDEs peaks at approximately three years of age (34, 111).

The concentration of PBDEs in electronic appliances and equipment varies greatly (221, 222). This poses a significant challenge to the ability of the questionnaire-based approach to predict PBDE exposure. Two studies from California, US, have used questionnaires to assess whether electronics in the home are associated with children's PBDE biomonitoring concentrations (126, 170). Neither study found a significant association between the number or hours of use of electronics in the home and the concentration of any PBDEs in children's serum (126, 170). In contrast, significant associations between the presence of electronics in the home and PBDE body burden in adults has been reported for pregnant women living in New York, US, and North Carolina, US (214, 223). It is possible that the difference in findings is explained by the dominance of alternative exposure pathways, such as breastfeeding, attenuating any associations that may exist between the presence of electronics in the home and PBDE exposure in children.

To date, no studies have assessed the association between reported portable electronic device use, such as tablets, gaming devices and mobile phones, and exposure to PBDEs in children. With the growing use of electronic devices by children, including very young children, this is an important consideration. In cohorts of infants and toddlers, questions regarding mouthing (sucking or chewing on) of electronic devices may also need to be included.

While plasticisers are found extensively in the home environment, items containing plasticisers that young children may suck or chew on are of particular concern. Sathyanarayana found that maternally-reported time that their infants spent playing with plastic toys and using dummies was not predictive of exposure to DBP, DiBP, DEP, DEHP, DnOP or DMP, as measured in urine (29). Exposure to DiNP, which may be found in these products, was not assessed. Since the concentration of phthalates may vary between toys and the way that children play with the toys may also vary, it may be necessary to include questions that explore which toys are played with most often and how they are played with, including whether the child sucks or chews on the toy.

3.3.3 Products in the home: personal-care products and insecticides

Personal care products (PCPs) including shampoo, sunscreen, moisturising lotion and soap, are a major source of phthalates (29, 224, 225). Studies conducted in both the US and in Mexico have demonstrated that reported PCP use in the previous 24-48 hours by children is associated with urinary concentrations of phthalate metabolites (29, 180). In particular, the total number of reported PCPs used on infants or by children is significantly associated with DEP metabolite concentrations (29, 180). To our knowledge, no questionnaire-based approach has assessed whether selecting conventional versus eco-friendly or chemical-free products modifies exposure in children. Serrano et al. found that adult women in the US who reported always purchasing eco-friendly, chemical-free and environmentally household products had lower levels of exposure to phthalates than women who reported rarely or never purchasing these types of products (202, 226).

Questionnaires that have been used in conjunction with biomonitoring to assess children's exposure to insecticides have predominantly focused on assessing whether dietary factors or residential insecticide use modify exposure, see Table 3-3. As reported by Trunnelle et al., urinary insecticide metabolite concentrations are higher in children who live in homes that are in poor condition (196). Homes that are in a poorer condition may be difficult to clean, with a higher incidence of pest infestations leading to more frequent domestic insecticide use (227).

Self-reported insecticide use in the home has not been consistently associated with children's exposure to insecticides when organophosphates and pyrethroids are considered together. Findings are more consistent for studies examining the association between reported use of insecticides in the home and exposure to pyrethroids but not organophosphates. Of the four studies reporting the association between self-reported insecticide use and pyrethroid exposure, a significant positive association between self-reported insecticide use and pyrethroid exposure was reported by Becker et al. in Germany and by Lu et al. in the US and a non-significant positive association between self-reported use of outdoor spray and pyrethroid exposure was reported by Trunnelle et al., also in the

US (116, 187, 193, 195). Naeher et al. reported the association between self-reported insecticide use and exposure to both pyrethroids and organophosphates in the US and found a significant association only for pyrethroids. (133). It is likely that the association between domestic insecticide use and pyrethroid exposure from studies in the US is more consistent than the association with organophosphate exposure because, since the implementation of stricter regulations on the sale of organophosphates for domestic use, the use of pyrethroid active ingredients in domestic insecticides has increased (197).

Of the three studies that assessed whether the presence of a vegetable garden or time reportedly spent in the garden was associated with biomonitoring concentrations, only Aprea et al. reported a non-significant association between the presence of a vegetable garden and organophosphate metabolite concentrations in an Italian cohort of 6-7 year-old children (116, 184, 193). Both variables may act as proxies for exposure to insecticides due to their use in the garden. The strength of the association between insecticide exposure and the presence of a garden may vary according to location due to differences in patterns of use of insecticides in the garden as well as differences in children's behaviour, including how much time they spend in the garden.

A study assessing the association between head lice treatment and exposure to insecticides found that insecticide metabolites in urine were significantly elevated in a sub-group of children following medicated treatment for head-lice (190). The children who underwent lice treatment also had higher pre-exposure concentrations of insecticide metabolites than the control children. The authors concluded that this may be due to repeat treatments that are often required for head lice, but no data regarding the frequency of prior treatments were available.

3.3.4 Behaviour: a major knowledge gap

Several behaviours of children lead to increased EDC exposure relative to adults (112, 228). Within the home, infants and toddlers occupy different microenvironments than adults, which may lead to different pathways and durations of exposure (229, 230). Young children exhibit frequent hand and object-to-mouth behaviour (10). while certain play activities may lead to increased non-dietary EDC exposure (31-33, 35). Toys in themselves can be an important source of exposure to some EDCs (34). Collecting questionnaire data on individual behaviours in children can be particularly informative for exposure assessment since there is marked intra and inter-individual variation in these behaviours during developmental stages of childhood (140).

Questionnaires have the potential to provide valuable information on individual behaviour in children and on whether their behaviour modifies their exposure to toxicants in the home; however, this has only been tested through a limited number of studies. Bradman et al. and Koch et al. did

not find any association between questionnaire-reported hand-to-mouth behaviour in children and biomonitoring concentrations of organophosphate or phthalate metabolites (95, 178). Hand-to-mouth behaviours are believed to be a major contributor to children's exposure to many chemicals - an absence of association is therefore unexpected. However, there are multiple possible explanations for the absence of association, including the small sample size (n=36) in study by Koch et al., limitations of the biological monitoring (limited numbers of samples), and attenuation due to the dominance of alternative exposure pathways, including diet (particularly for DnBP and organophosphate insecticides), personal care product use (phthalates) and inhalation (particularly for BBzP and some organophosphates) (178, 185). In contrast, hand-to-mouth behaviours in adults as assessed through questionnaires has been associated with PBDE concentrations in serum (223, 231). Furthermore, Stapleton et al. demonstrated that reported hand-washing behaviour is associated with reduced PBDE concentrations in children's hand-wipe samples, which would be expected to lead to decreased exposure to PDBEs via non-dietary ingestion or trans-dermal absorption, since they have previously demonstrated that hand-wipe concentrations of PBDEs are correlated with PBDE body burden (127). Young children may also ingest toxicants through excess dietary exposure that occurs when toxicants transfer from their hands or other surfaces in the home to foods that they then consume (232). No studies have assessed - through questionnaires - whether exposure of children to EDCs may be modified by variables that could reduce excess dietary exposure, such as washing hands before eating.

Of the few studies that have assessed - through questionnaires - whether additional physical behaviours, such as crawling and playing on the floor modify exposure, none reported any significant associations between these behaviours and EDC biomonitoring concentrations (174, 193). In both studies only spot urine samples were collected. These variables have been found to modify exposure of children to toxicants in the home through alternative assessment methods, such as analysing toxicant concentrations on children's clothes (186, 233). In addition, although time-and-place activity diaries have been used in conjunction with exposure assessment in young children, few studies have assessed behaviour or time-activity patterns through the questionnaire-based approach (127, 174). In one study conducted in the US, children whose mothers reported having no safe places to play in their neighbourhood as 'a big problem' had elevated PBDE body burden, presumably from spending more time indoors (170). In contrast, Stapleton et al. found no association between time spent away from the home and PBDE biomonitoring concentrations (127). It may be necessary to collect more detailed time-and-place activity data than this to determine more accurately the time spent indoors, particularly in the home. Although more detailed time-activity data can be collected through 24-hour recalls, including online based surveys, these recalls

can be burdensome for parents of young children who may have other family and work responsibilities (234). The use of monitors, such as Global Positioning Systems and accelerometers, provides more accurate data and may be potentially less burdensome for study participants (235, 236). However, there are also issues with this approach, including the cost, possibility of technological issues and data analysis issues, privacy invasion and the impracticality of having very young children wear these devices (236).

3.4 Discussion

Few questionnaires have been adequately validated as to whether they may accurately assess exposure of children to toxicants in the home. Although some studies have demonstrated that responses to some questions are associated with EDC biomonitoring concentrations, there is typically marked variation between the studies which cause uncertainty in the use of this approach.

However, significant correlations between questionnaire responses and biomonitoring data have been reported for toxicants for which the exposure is relatively consistent - including benzyl butyl phthalate (BBzP) and vinyl flooring in the home, DEP and personal care product use and PBDEs and breastfeeding (29, 120, 127, 159, 170, 171, 176, 180). The association between breastfeeding and PBDEs appears strong not only because exposure is consistent, but also because PBDEs have half-lives on the order of weeks to years, as compared to hours, which means that biomonitoring measurement error attributable to short term-variation is low (237, 238). The feasibility of using the questionnaire-based approach to assess exposure to toxicants for which long-term exposure is not accurately classified characterised by one biological sample may be underestimated if the effect of measurement error is not accounted for (159, 239).

There are two key areas that introduced error into the studies presented in this review. These are a) factors associated with the design of the questionnaires and b) factors associated with the design of the questionnaire-biomonitoring studies. These errors could have contributed significantly to the variation in findings.

3.4.1 Error in the exposure-assessment questionnaire

Failing to account for all sources and causes of exposure can introduce error into the questionnaire (22). If all the pathways of exposure to a specific toxicant or groups of toxicants are not accounted for, the precision of the instrument will be reduced, as unaccounted for exposure pathways may obscure associations. Where exposure through one pathway dominates over all others, then small but significant associations between other pathways and exposure will be obscured, particularly when these pathways are inadequately characterised. For example, fewer associations between

questionnaire responses and PBDE biomonitoring concentrations have been reported for children compared to adults, which may be due to the greater contribution of non-dietary dust ingestion to children's exposure, which has been inadequately characterised through exposure-assessment questionnaires (240, 241). Throughout this review, we have alluded to pathways of exposure that need to be considered when designing an EDC-exposure-assessment questionnaire for young children at home.

Failing to account for unknown pathways of exposure can also attenuate true associations. For example, although it is assumed that the majority of exposure to BPA occurs through the diet, studies on individuals who have fasted have indicated that alternative exposure routes, such as dermal exposure, may also contribute substantially to exposure (242). More research is needed to better characterise exposure pathways of young children to flame retardants, plastics and insecticides in the home environment, particularly for children living in domestic and other settings associated with mainly poverty in developing countries, as the majority of the studies we have reviewed originated from developed countries. While children in developing countries may experience some of the same exposure pathways as children in developed countries, they may well have additional and different exposure pathways. For example, a Nicaraguan study found that children aged 11-15 who not only lived but also worked at a waste disposal site had PBDE exposures that exceeded - by 20-50 times - those of a reference group of children who lived in urban Managua, away from the waste site (243). Exposure levels of the reference children were similar to exposure levels in the US and higher than exposure levels of children in Europe.

In cases where exposure pathways are known, but the EDC sources cannot be definitively identified through a questionnaire, then a questionnaire-based approach alone cannot predict exposure with limited uncertainty. For many consumer goods, companies are not required to indicate on the label whether these contain EDCs. Moreover, the concentration may vary greatly between goods of the same type, making it difficult to identify sources of EDCs in the home environment (45, 222). Additional direct or on-site observation would be required to identify goods that contain EDCs.

Poor wording or phrasing of questions lead to misinterpretation of questions. This can lead to measurement error and obscure any true associations between questionnaire responses and exposure. In the Australian study conducted by Babina et al., many parents reported the use of "domestic disinfectants, dishwashing detergents and even air fresheners [to the question] 'Do you/your partner use pesticides in the house?'", when the authors were really interested in the use of insecticides (244). Misinterpretation of questions may be limited by ensuring that questionnaires

undergo pre-testing with a population representative of the study population prior to actual use (165).

Poor recall may also introduce error. For example, respondents can typically only infrequently recall specific product use, particularly when the recall time frame of use is long (194, 245-247). Additional methods, such as visual aids accompanying each question, have been used to help minimise recall error and improve comprehension (248). Also, it is difficult, if not impossible, to assess the average use of some products through questionnaires, particularly when their use is intermittent, and when the questionnaire is not answered by all adult residents in the home (249, 250). Alternative monitoring approaches, such as the use of bar-code scanners and taking an inventory, have been shown to be acceptable by participants in longitudinal studies, but require more resources and may be more intrusive (250, 251).

Use of proxy-respondents, which is necessary when assessing young children's exposure, may introduce error into the questionnaire-based approach. For example, Riederer et al. compared the reporting of pesticide use in NHANES by adults self-reporting and adults who were proxy-respondents for children (193). Although the reporting of household insecticide use was the same, adults tended to under-report the use of insecticides in the yard when they were the proxy-respondent for children (16% vs. 9%).

There are also additional challenges associated with the questionnaire-based approach specific to particular exposure pathways. Investigating the contribution of diet to exposure in children is made challenging by the fact that questionnaires to collect dietary information are typically burdensome, and it is difficult to portray frequency and quantity of intake of specific items accurately. Parents in the study conducted by Rose et al. had difficulty assigning portion sizes to the foods eaten (126). The authors, therefore, used only data regarding the frequency of food consumption. Frequency of food consumption is a reasonable approach in young children, for whom estimating portion sizes is also made difficult by frequent food spillages.

An additional issue that may arise when using a questionnaire-based approach to assess exposure to EDCs through the use of FFQs is that a high level of resolution, which introduces more burden, is required to accurately determine which foods in particular are associated with increased exposure and to determine whether there are any interactions between food types (193). In children, excess dietary exposure - that is ingestion of toxicants that have transferred to foods from contaminated hands or surfaces - may contribute substantially to total exposure (232). Additionally, as discussed earlier, exposure through the diet to plasticisers may be modified by how plastic food contact materials are used, what foods they come into contact with and how the food is prepared. Heating

foods in plastic containers may increase exposure but is rarely assessed in FFQs. When assessing children's exposure to EDCs via FFQs, it is necessary to ask about other factors that may modify exposure through the diet, other than just frequency of intake of specific food types.

3.4.2 Error in the design of questionnaire-biomonitoring studies

Multiple sources of error may be associated with the biomonitoring methods used in questionnaire-biomonitoring studies. The choice of sampling medium, the time of sampling and the number of samples to be taken may affect the accuracy of the exposure measurement. According to Barr et al. "differences between biomarker measurements made multiple times in the same child over a defined period or once in numerous children at approximately the same time can be because of dissimilarities in actual exposures, variations in pharmacokinetics, or both" (239). A major source of error is due to collecting only one spot-sample, particularly when attempting to measure exposure to toxicants with short half-lives (252). Most studies included in this review collected one biological sample. A minority collected two or more samples (175, 187-189, 194). Therefore, the potential for measurement error in the studies that have been reviewed is high.

3.4.3 Strengths and applications of the questionnaire-based approach

Up to this point of the discussion, we have suggested how the limitations of the questionnaire-based approach can be addressed. We now address the strengths and suggest potential applications of the questionnaire-based approach, as summarised in Table 2-5 on page 25. Questionnaires are usually less intrusive and less costly than direct methods of exposure assessment, particularly when questionnaires are administered online, which may allow researchers to increase the number of study participants. Questionnaires are the "most efficient data collection method, allowing a larger study size and greater statistical power", provided that limitations with the questionnaire-based approach can be sufficiently minimised (24). The questionnaire-based approach to exposure assessment may prove to be particularly useful when it comes to characterising long-term exposure to toxicants with short half-lives. In these cases, researchers would otherwise have to collect multiple biological samples at several time-points throughout the exposure period that they were trying to capture. Furthermore, data obtained from questionnaires can be used to complement direct monitoring data and provides useful insights into the contribution of particular exposure pathways to total exposure. The questionnaire-based approach to exposure assessment may also be combined with other questionnaires, such as the validated Home Observation for the Measurement of the Environment, to assess additional impacts of the home environment that may modify the health risks associated with children's exposure to toxicants (253).

It is worth noting that an initial search strategy using the terms of ‘questionnaire’ and ‘survey’ failed to detect many of the relevant articles, as those studies matching questionnaire data with bio-monitoring rarely listed ‘questionnaire’ as a keyword, and many studies did not mention in the abstract that questionnaires were administered. In addition, no EDC-exposure-assessment questionnaire validation studies were identified. This may be an indication that the potential benefits of questionnaires as a valuable tool for EDC exposure assessment is being under-recognised.

3.5 Conclusion

Despite the number of biomonitoring-questionnaire studies reviewed in this chapter, the true predictive capacity of the exposure-assessment questionnaire remains unknown, as no formal study to design and validate an EDC-exposure-assessment questionnaire has been conducted. However, biomonitoring studies conducted in conjunction with exposure-assessment questionnaires have provided a wealth of information on important determinants of children’s EDC exposure. Not only is this knowledge important information for the design of an exposure-assessment questionnaire, an important component of this thesis, it also suggests that if a sufficient number of these determinants are adequately captured by an exposure-assessment questionnaire, then theoretically the questionnaire-based approach should be able to be used to measure children’s EDC exposure. Since the findings in this review on children’s EDC exposure pathways were not specific to the Australian context, different exposure determinants may be important in Australia. To design an EDC-exposure-assessment questionnaire specific to Australia this information is needed, which is the focus of the next chapter.

CHAPTER 4 SOURCES OF ENDOCRINE DISRUPTING CHEMICALS IN AUSTRALIAN HOMES

As outlined in the previous chapter, the first step of questionnaire design is the identification of the hazard and analysis of the relevant pathways of exposure. It is crucial to identify and characterise all relevant pathways of exposure. The thorough review of previous questionnaire-biomonitoring studies presented in the previous chapter was not specific to Australia. Therefore, the next three chapters are composed of research that was conducted to identify relevant sources of EDCs in Australia, as well as potential exposure pathways. The first chapter is an unpublished review of primary research, as well as national databases and reports. It encompasses all three EDCs and is specific to Australia. This review identified significant knowledge gaps that would affect the content validity of the questionnaire. The following two chapters address these knowledge gaps, see the figure below for an overview. Chapter 5 is a more detailed review of sources of BDE-209 in the Australian environment. Chapter 6 is a published paper on an analysis of insecticide-related calls to the Queensland Poisons Information Centre (QPIC).

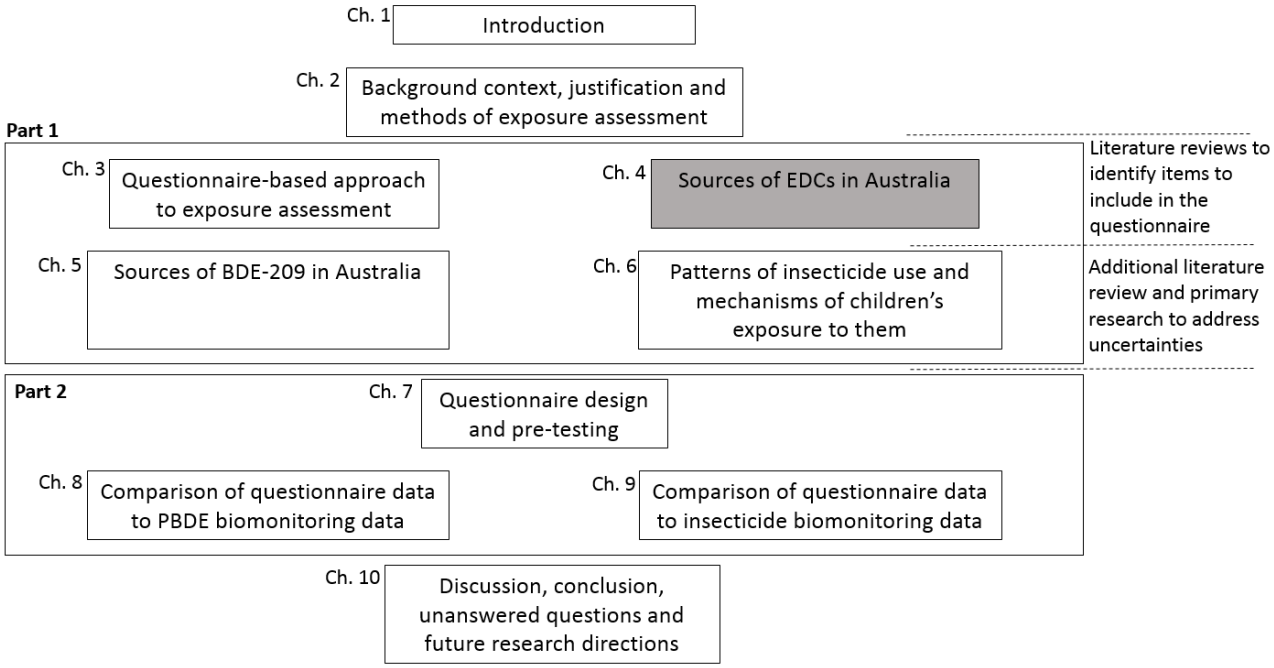


Figure 4-1 Thesis structure: Chapter 4

4.1 Introduction

Exposure of children to EDCs is attributable primarily to the presence of EDCs in the home environment, where young children spend much of their time (28, 254). Data from Australia on

sources of EDCs, children's exposure levels, and subsequent health outcomes are lacking. The aim of this review is, therefore, to assess the occurrence of the sentinel EDCs for this thesis in the Australian home environment to understand the exposure potential. We first review the unique sources of these chemicals and then discuss common sources, including breast milk and dust.

4.2 Review methods

A narrative overview, following the principles described by Green et al., of science and grey literature was conducted (255). Systematic searches of the Pubmed, Embase, Web of Knowledge and Toxnet databases were conducted to locate scientific papers published from 1980 to April 2014; these papers were then screened for relevancy. The primary search terms were the toxicant(s) of interest, secondary search terms included "child(ren)", "paediatric(s)", "pre-schoolers", "toddler", "infant", "baby", "home", "house", "indoor (air) pollutant", "exposure", "biomonitoring", "packaging", "food", "fish", "diet", "ingestion", "breast milk", "air", "dust", "hand-wipe" "personal care products", "baby bottles" and "car". Grey literature was obtained by searching online published reports and databases from Australian government agencies including Food Standards Australia New Zealand (FSANZ), Australian Pesticides and Veterinary Medicines Authority (APVMA), Australian Competition and Consumer Commission (ACCC), and National Industrial Chemical Notification and Assessment Scheme (NICNAS) for the toxicants of interest. All studies and reports from Australia that included laboratory analysis for at least one of the target chemicals in food, biological samples, consumer goods or house dust or discussion of the use of sources known to contain the target chemicals were deemed highly relevant and reviewed. Papers deemed relevant contained information about potential exposure pathways or biomonitoring but were not necessarily specific to the Australian context or exposure of children to toxicants in the home environment and were therefore not necessarily reviewed. Papers deemed not very relevant included human epidemiological studies and animal studies. Excluded papers provided no information on potential exposure pathways of children to the toxicants of interest.

4.3 Sources of endocrine disrupting chemicals in the home environment

4.3.1 Bisphenol A and Phthalates

Leaching of BPA from baby bottles has received much public attention in Australia and has been studied explicitly by the ACCC (256). The ACCC found no detectable BPA leaching from any of the bottles they analysed. However, the report's summary, that "typical infant feeding bottles and infant sip cups that are currently available on the Australian market do not expose infants to detectable amounts of Bisphenol A" must be interpreted with reference to the relatively high limit

of detection of their analytical method (10 ug L^{-1}). This limit of detection is higher than the average concentration of BPA that leaches into water or food simulant from polycarbonate materials under similar testing conditions (257). These testing conditions did not take into account the fact that leaching of BPA from bottles increases under real-life use scenarios (258, 259). For instance, the bottles tested by FSANZ were new, were only subject to one dishwashing episode before testing and were not subject to any sunlight exposure. In response to public demand, the use of BPA in baby bottles has been voluntarily phased out by most major suppliers of baby bottles, including in Australia (260). Since this phase-out, chemical alternatives to BPA, such as Bisphenol-S and others, have been used in the manufacture of polycarbonate plastics. There is concern that some of these replacements may also pose a health risk since BPA-free bottles have been shown to leach chemicals that can bind and activate oestrogen receptors in cells (259).

BPA in the diet has been the subject of two food surveys in Australia (261, 262). FSANZ detected BPA in 31% of 70 foods analysed, with a range of BPA concentrations from 1 ug kg^{-1} to 290 ug kg^{-1} (263). The concentrations detected were similar to concentrations reported overseas, while the frequency of detection was about half that reported in overseas studies (257). The sample with the highest concentration of BPA was a canned infant dairy dessert. CHOICE, a consumer advocacy group in Australia, assessed BPA in a selection of 38 canned foods, of which 33 had detectable levels of BPA (262). The highest concentrations occurred in canned corn, tuna and three baby food products. Since the CHOICE report was published a major supplier of baby food in Australia has reportedly phased BPA out of all baby products (264).

Although studies overseas have indicated that foods are a significant pathway of phthalate exposure, particularly to DEHP, the 2010 FSANZ study that surveyed phthalate contamination in Australian foods detected no phthalates in any of the five foods sampled (261, 265). It is possible that phthalates were present in the foods surveyed, but were not detected. The detection limit of the test technique varied between 30 to 1000 ug kg^{-1} according to the specific phthalate and food type being analysed. In many cases, the limit of quantification exceeded the average concentration of phthalates in similar food types analysed elsewhere. For example, although poultry typically has high levels of DEHP contamination (>300 ug kg^{-1}) relative to other food types, of the 19 studies that have assessed DEHP concentrations in poultry overseas, only one has reported a mean concentration above 1000 ug kg^{-1}, which was the limit of quantification for DEHP in poultry in the FSANZ study (265). The FSANZ 24th Total Dietary Survey will re-examine plasticisers in food.

In addition to food and toys, phthalates are also reportedly used in personal care products and cleaning products in Australia, although no data are available regarding the absolute concentrations

in these items (266). BPA and phthalates also have multiple applications in home building and decorating materials, including in flooring, furniture and sealants (266). Finally, a significant application of BPA is in the production of thermal ink, which changes colour when heat is applied. Thermal ink is used on receipts in major supermarkets in Australia (267). Contact with receipts may lead to direct exposure via the dermal route or indirect exposure via hand-to-mouth behaviour with hands or other surfaces contaminated with BPA from receipts (257).

4.3.2 Polybrominated diphenyl ethers

At the time of completing this review, no published data were available regarding specific consumer goods containing PBDEs in Australia, including children's goods, despite the fact that exposure of Australian children to PBDEs peaks in childhood (111). New Zealand, which has a smaller economy than Australia, imported about 12 tonnes of Deca-BDE in 2010 (46). PBDEs are lipophilic pollutants which are known to accumulate and persist in higher trophic levels and foods with high lipid content, such as dairy, meat and particularly fish (202). Results of an FSANZ study assessing PBDE content in Australian foods indicate that infant foods contain relatively low levels of PBDEs compared to other sources that are relevant to young children's exposure to PBDEs, such as breast milk. For instance, infant formula on average contained PBDEs at a level of 0.095 ng g^{-1} (268). Boiled eggs, grilled pork chops, bacon and cream contained the highest concentrations of PBDEs. Seafood contains some of the highest levels of PBDEs of any foods (269). Concentrations of PBDEs in seafood from a South Australian market had higher concentrations than the foods analysed in the FSANZ study, with the concentrations in the seafood ranging from 1.01 to 45 ng g^{-1} lipid weight adjusted (270). Fish collected from Moreton Bay in South East Queensland had similar concentrations, while fish samples collected from estuarine environments in Victoria had a larger range of PBDE concentrations, with the maximum concentration at 250 ng g^{-1} lipid weight adjusted (271, 272).

4.3.3 Organophosphate and pyrethroid insecticides

Of the insecticides selected for inclusion in this review, pyrethroids are by far the most prevalent on the Australian market. Pyrethroids occur in a vast array of pest-control products including aerosol products, medical treatments, garden and veterinary products (273). There are also six organophosphates, including omethoate, diazinon, dichlorvos, fenthion, maldison, and chlorpyrifos available for public use in Australia. Organophosphates occur in pest-control products for use around the home and garden, including lawn treatments, medical and veterinary products (273).

In Australia, all registered insecticide products are searchable via the online database of registered chemicals, Public Chemical Registration Information System Search (274). Based on an extensive

search and analyses of the database, more than 500 insecticide products are available for public domestic use in Australia, see Table 4-1. The number of pyrethroid and particularly organophosphate insecticides available for public use in Australia dramatically exceeds that in other countries, including the US, Germany and the United Kingdom (115).

Table 4-1 Insecticides available in Australia by product type (APVMA 39)

Type of application	Approximate number of commercial products available	Active ingredients	% of product types containing active ingredient
Aerosol	>100	Allethrin/Bioallethrin	40
		Tetramethrin	40
		Phenothrin	36
		Permethrin	27
		Esbiothrin	20
		Resmethrin	19
Barrier/surface sprays	>160	Imiprothin	47
		Permethrin	38
		Cypermethrin	30
		Tetramethrin	19
		Deltamethrin	17
Automatic sprayers	50	Pyrethrins	87
		Tetramethrin	21
		Allethrin	21
		Permethrin	13
		Transfluthrin	13
Bombs/fumigators	20	Permethrin	85
		Fenoxycarb	50
Ant baits or powder	>20	Permethrin	6a
		Boron	3
		Thiamethoxam	3
		Pyrethrins	2
		Indoxacarb	2
		Diazinon	1
Cockroach baits or powder	>30	Fipronil	25
		Indoxacarb	18
		Abamectin	18
		Boron	10
		Permethrin	9
Lawn treatments	>40	Chlorpyrifos	34
		Imidacloprid	25
		Bifenthrin	20
		Diazinon	4
Garden/outside	>25	Imidacloprid	46
		Pyrethroids	27
		Esfenvalerate	15

		Omethoate	4
Cat parasiticides (fleas/ticks)	>90	Pyrethrins	54
		Diazinon	11
		Fipronil	9
		Pyriproxyfen	9
Dog parasiticides (fleas/ticks)	>170	Pyrethrin	43
		Permethrin	22
		Fipronil	12
		Imidacloprid	7
		diazinon	6
		Maldison	2
Insecticides available for professional use in homes	Not determined	Commonly available active ingredients for professional use: bifenthrin, chlorpyrifos, fipronil, imidacloprid, permethrin	Not determined
Insecticides available/recommended for medical treatment by the australian therapeutic guidelines (head lice and scabies)	Not determined	Maldison Permethrin Pyrethrins plus piperonyl butoxide	Not determined

a. total number of products with active ingredient given for products used as ant baits or powders (not percentage) b. bifenthrin, pyrethrins, permethrin

More than 250 aerosol sprays and more than 50 automatic sprayers all containing pyrethroids are available for use inside and outside the home. Insecticide products for use in home gardens in Australia commonly contain the active ingredient imidacloprid, with the next most commonly available active ingredients being the organophosphate insecticide chlorpyrifos and various pyrethroids. Pyrethroids and pyrethrins are the most commonly found active ingredients available in veterinary products to treat pets but organophosphates, including diazinon and maldison, are also found in products that are used to treat pests on domestic animals, including cats and dogs. Professional pest control treatments, commonly containing pyrethroid or organophosphate insecticides, are also employed for treatment of termites, as well as other pests, in Australian homes (115). Despite the high number of available insecticide products in Australia, there is an absence of data regarding domestic and professional insecticide use patterns in Australian homes, including the typical amount of insecticides that are used, their frequency of use, as well as information regarding their handling, storage and the method of application.

Products used to treat pediculosis (including head lice) and scabies also contain insecticides. Unlike household insecticides, products registered as treatments for head lice are registered by the Therapeutic Goods Association. There is an absence of data regarding the prevalence of scabies in urban Australian populations, but in the indigenous rural community in Australia the prevalence of scabies has been recorded as high as 80% and is a significant contributor to the burden of disease

(275). In both Queensland and the Australian Capital Territory approximately 10% of the primary school population is estimated to receive regular (six-yearly or more) applications of insecticides for head lice, in some cases, the treatments are prophylactic (276, 277). The currently recommended treatments for head lice are maldison, an organophosphate, or permethrin or pyrethrins plus piperonyl butoxide (278). The current recommended treatment for scabies in Australia is 5% permethrin cream, applied topically (279).

Diet is also a potential pathway of exposure to pesticides for Australian children. Some foods that infants may potentially consume more than adults, such as non-organic fruit juice or fresh fruit and vegetables, may be relatively high in insecticides, leading to increased exposure (116). The 23rd FSANZ Australian Total Dietary Survey surveyed 92 foods and beverages for the presence of a range of pesticides, including organophosphate insecticides and pyrethroids insecticides (280). The results of foods that were found to contain insecticides are displayed in the table below.

Table 4-2 Insecticide residue concentrations for foods that tested above the limit of detection in the 23rd FSANZ study

Chemical	Food type	mg/kg
Allethrin	Mushrooms	0.0038
	Sausages, beef	0.0028
Bifenthrin	Nectarine	0.018
Chlorpyrifos	Apples	0.065
	Breakfast cereal, mixed grain	0.004
	Cucumber	0.0034
Chlorpyrifos-methyl	Biscuits, savoury	0.02
	Bread, fancy	0.01
	Bread, multigrain	0.024
	Bread, white	0.023
	Hamburger	0.013
	Pie, meat	0.015
	Pizza, meat and vegetable topping	0.016
Dimethoate	Capsicum	0.11
	Grapes	0.01
	Lettuce	0.028
	Nectarine	0.0068
	Strawberries	0.015
Fenitrothion	Biscuits, sweet, plain	0.038
Methamidophos	Capsicum	0.059
Omethoate	Capsicum	0.0069
Permethrin	Lettuce	0.14

The survey found no detectable insecticides in any of the baby foods analysed. However, based on the residue concentrations in other foods tested, exposure at the 90th percentile for 2-5-year-old children to chlorpyrifos was estimated to be at 20% of the allowable daily intake.

4.3.4 Breast milk

The concentrations of phthalates, BPA and insecticides in breast milk from Australian women are not known. In breastfeeding infants, breast milk can be a major source of toxicants, particularly for persistent lipophilic chemicals, such as PBDEs. In Australia, breast milk concentrations of PBDEs have been found to be around 10 ng g-1 lipid weight adjusted, which is higher than the typical concentrations of PBDEs in food (198, 268). Apart from BDE-209, breast milk is estimated to be the major contributor to PBDE exposure in breast-fed Australian infants (198).

4.3.5 Dust

No studies have assessed the concentration of BPA, phthalates or insecticides in dust in Australian homes. The results from studies conducted overseas have generally found that concentrations of BPA in dust are typically below 2 mg kg^{-1}, concentrations of DEP are below <10 mg kg^{-1}, concentrations of DEHP are between 200-800 mg kg^{-1} and concentrations of *cis* and *trans*-permethrin (common pyrethroid insecticides) are below 800 ng g^{-1} (5, 7, 281). Three studies have examined the levels of PBDEs in dust in Australian homes, one in Western Australia and two in Queensland (219, 240, 282). All studies found that BDE-209 was the dominant congener in dust, with a median concentration of BDE-209 of 415 ng g^{-1} reported in the Western Australian study (219). Sjodin et al. compared the concentration of PBDEs in dust collected from Queensland to dust collected in other countries, including Germany, Great Britain and the United States, and found the concentrations were higher than those in Germany, but lower than those collected in Great Britain and the USA (282).

4.4 Discussion

The review presented in this chapter was conducted to identify sources and exposure pathways specific to the Australian context. EDCs occur in food, dust, breast milk and a variety of household items in Australia. Similar to elsewhere, breast milk, dust and lipid-rich foods, including seafood, are likely to be significant sources of PBDE exposure. At the time of the review, data were scarce regarding the application of PBDEs to consumer goods. The most commonly found insecticides in domestic aerosolised pest-control products in Australia were pyrethroids, and the total number of these products registered for use was higher than other countries, indicating that these products may be important sources of young children's pyrethroid exposure. The contribution of other domestic pest control products to both organophosphate and pyrethroid exposure is more uncertain, since these products contained both types of insecticides. Since there is no data on actual usage patterns of these products it is difficult to determine the relevance of these products to children's insecticide

exposure. Published studies on insecticide residues on foods in Australia were too scarce and limited in their scope to assess dietary determinants of insecticide exposure in Australia adequately. Of all the chemicals, the least amount of data on exposure as well as exposure pathways was available for the plasticisers. Studies that were available on plasticisers in Australia were scarce and subject to methodological errors.

Because of the paucity of data on this subject to date, our knowledge of exposure pathways of young Australian children to EDCs remains far from comprehensive. As previously described, this is one of the main criteria that needs to be met to ensure that exposure-assessment questionnaires are effective. Without this knowledge, the content validity of the exposure-assessment questionnaire cannot be guaranteed. The review in this chapter therefore raises the first key findings of this thesis, the questionnaire-based approach to exposure assessment may not be suitable for chemicals for which exposure pathways have not been well described, a point that will be discussed in more detail later.

4.5 Conclusion

To ensure the content validity of the exposure-assessment questionnaire, more data are needed to assess dietary determinants of plasticiser exposure and sources of EDCs in Australian homes. Elsewhere, PBDEs have been reported to occur in a variety of household items, but at the time of this review, no studies had been conducted in Australia to assess the occurrence of PBDEs in goods within Australian homes. With regards to insecticides, more data are needed to assess usage patterns of insecticide products in Australian homes, exposure pathways of Australian children to these chemicals as well as dietary contributors to insecticide exposure. For PBDEs, it was possible to obtain more detailed information about potential sources in the Australian domestic environment, which is discussed in the following chapter. For the insecticides, data about usage patterns and exposure pathways could be obtained through primary research utilising a database recording calls to the Queensland Poisons Information Centre. No additional information about dietary sources of insecticides, the plastics or PBDEs could be obtained, as this would have required analytical testing of these items, which was not possible within the scope of this PhD.

CHAPTER 5 SOURCES OF BDE-209 IN THE AUSTRALIAN DOMESTIC ENVIRONMENT

Karin English, Leisa-Maree L. Toms, Christie Gallen, Jochen F. Mueller: *BDE-209 in the Australian Environment: Desktop review*. Journal of hazardous materials 08/2016; 320., DOI:10.1016/j.jhazmat.2016.08.032

As described in the previous chapter, see Figure 5-1, there are a limited number of published research studies in Australia regarding PBDE content in consumer goods and media relevant to exposure, despite the fact that at the commencement of this PhD peak exposure to PBDEs in Australia was shown to occur during early childhood (111). This made it particularly difficult to design a PBDE exposure-assessment questionnaire specific to Australia. For this reason, additional search methods were required to obtain information that would inform the design of the PBDE component of the exposure-assessment questionnaire.

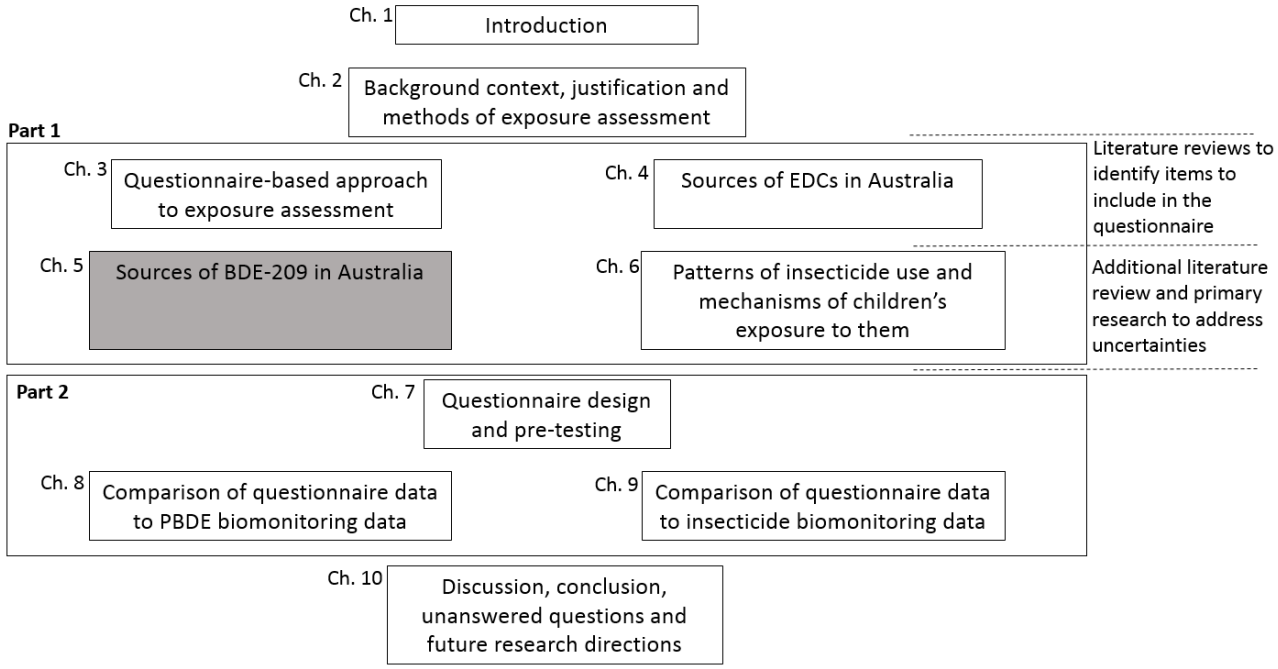


Figure 5-1 Thesis structure: Chapter 5

This additional research was undertaken as a part of a larger study conducted to assess BDE-209 in the Australian environment. Although the scope of this PhD includes a wider array of PBDEs, there are several reasons why it was appropriate to conduct a more thorough investigation specifically focused on BDE-209. BDE-209 is the main congener in the commercial PBDE mixture called decaBDE. This mixture, decaBDE, was the last to be listed on the Stockholm convention. In

Australia, concentrations of BDE-209 in household dust now greatly exceed concentrations of other lower molecular weight PBDEs and exposure is likely to be ongoing even after the use of decaBDE is restricted, since consumer goods containing BDE-209 will remain in homes for some time (283). To date, BDE-209 has been difficult to measure in environmental and particularly biological monitoring studies. Unlike the lower congener PBDEs, BDE-209 is relatively rapidly excreted and concentrations in blood are low as BDE-209 does not bioaccumulate to the same extent as lower PBDE congeners (284). Exposure pathway data and human health data are therefore much more limited than for lower molecular weight PBDEs. For these reasons a detailed assessment of BDE-209 was undertaken, which resulted in a published paper, presented (in abridged form) below. Several of the findings reported are from a report that was published in Australia following the completion of the review presented in Chapter 4.

5.1 Introduction

Since the 1970's flame retardants have been used in a diverse array of petroleum-based consumer products, including textiles, foam, electronics and electrical equipment, see Table 5-1 (285). Historically, three commercial mixtures of PBDEs have been or still are used, known as c-octaBDE, c-pentaBDE and c-decaBDE. Concerns over the bioaccumulation potential, persistence, long-range transport and toxicity of the congeners found in c-octaBDE and c-pentaBDE resulted in their addition to the Annexes of Stockholm Convention in 2009; Now c-decaBDE is being considered for listing on the Stockholm Convention (286). This review forms the first part in a larger study that will include quantitative testing of BDE-209 in goods. We aim to provide a best estimate of which goods are likely to contain BDE-209 in Australia and also identify areas of uncertainty.

Table 5-1 Industry reported uses of BDE-209 by product type (285, 287, 288).

Electronic and Electrical Equipment	Soft Furnishings	Construction materials	Automotive / Transportation
Housing of TVs and computers	Upholstery backing in some domestic settings (dependent on flammability standards)	Pipes	Fabric coatings (i.e. textiles in cars, planes, public transportation)
Mobile phones	Upholstery backing in public places (theatres, schools, hotels etc.)	Pillars for telephone and communications cables	Electrical wiring and cables
Fax machines, Scanners, Printers and Photocopiers	Carpets and curtains/drapes in domestic settings (dependent on flammability standards)	Air ducts	Interior components (predominantly housing of electrical components)
Audio and video equipment	Carpets and curtains/drapes in public places	Switches and connectors	Housing of entertainment

			units, audio-visual equipment
Remote controls	Camping equipment	Reinforced plastics	
Wire and cables	Military applications (clothing, equipment etc.)	Insulation	
Capacitor films		Solar panels	
Printed circuit boards			
Connectors in electrical and electronic equipment			
Circuit breakers			
Transformers			
Small household appliances (i.e. hair dryers, vacuum cleaners)			
Large household appliances (i.e. washing machines)			

5.2 Methods

To provide a best estimate of products likely to contain BDE-209 in Australia we undertook the following:

- A review of standards and codes pertaining to flammability in Australia, to identify products that may require treatment with flame retardants, we did not search for flammability standards pertaining to electronics and electrical appliances, as it has previously demonstrated that BDE-209 is likely to be found in these products (289).
- A review of grey-literature (industry, government and technical) reports regarding reported uses of BDE-209
- A review of scientific reports assessing products for their BDE-209 content, to identify any further items that may contain BDE-209, as well as to provide a best estimate for likely concentrations of BDE-209 in treated items

We initially sought to clarify some uses of BDE-209 by contacting major Australian manufacturers or organisations in the relevant areas of uncertainty. Attempts to obtain information through this approach proved extremely difficult and the information obtained (if available) was neither specific nor informative to the Australian context. We were therefore unable to pursue this aspect of the approach further.

Using the information obtained, we then provided an estimate of the likelihood of specific goods containing BDE-209 in Australia.

5.3 Results

Despite the dearth of primary scientific reports, we identified a variety of other sources of information regarding potential applications of BDE-209 in Australia. We identified several standards and one code, the Building Code of Australia (BCA), pertaining to flammability of items being manufactured, sold or used in construction within Australia (Figure 5-2), which we believe may be important drivers of the use of flame retardants in these materials.

Section C of the Building Code Australia (BCA) sets performance criteria for the fire resistance requirements of buildings types 2-9 (i.e. generally buildings other than single-dwelling homes). Under specification C1.10 of the BCA the following components of buildings must meet minimum fire hazard standards: floor linings and floor coverings, wall linings and ceiling linings, air-handling ductwork, lift cars, sarking (reflective foil), attachments to floors, ceilings, internal walls and the internal linings of external walls (curtains, drapes and blinds are generally exempt from this specification), and other insulation materials other than sarking materials.

Fire standards related to consumer goods include: children's nightclothes AS/NZS 1249:2014, protective clothing AS/NZS ISO 2801:2008 , floor coverings AS/NZS 2111.18:1997 (R2013), curtains – health care facilities and institutions AS 3789.9-1998 , upholstery materials AS/NZS 4088.1:1996 (R2013), tarpaulin fabric AS 2930-1987, child-restraint systems used in motor vehicles AS/NZS 1754:2013

Australian standards also cover a wide range of additional items, such as plastics and electrical equipment, as summarised in the Handbook of Australian Flammability Standards.

Legislation in other regions that certainly affects products in Australia include stringent flammability standards for commercial aircrafts that fly in European or US air space, as well as automotive standards for vehicles produced for the European and US market, which may also enter the Australian market, as well as other imported goods that are manufactured to meet flammability standards in other markets.

Figure 5-2 Flammability codes, standards and legislation in Australia (290-292).

Several informative grey literature reports were identified. The most comprehensive industry report of BDE-209 applications is provided by the Bromine Science and Environmental Forum (288). The reference text "Flame Retardant Materials", provided a technical description of BDE-209 applications. (293). Several government and other institutional reports were identified that were informative regarding potential applications of BDE-209 (46, 294-299). We failed to identify any scientific papers that discussed the use of BDE-209 in goods specific to the Australian market; although our group has previously conducted a study quantifying the presence of PBDEs in products imported into Australia in 2012 (289). We identified testing studies from elsewhere that assessed the concentration of BDE-209 in consumer goods and may be informative to the situation in Australia. In the following sections, we discuss pertinent findings for each of electronics and electrical appliances, textiles, construction materials, automotive/transport applications and toys.

5.3.1 Electronics and electrical equipment

A major use of BDE-209, including in Australia, is in high impact polystyrene (HIPS) for computer and TV housings and rear covers (297). As of the late 2000's, BDE-209 was the most commonly

used flame retardant in HIPS (300). To reach US flammability standards for TV sets (a likely major driver of BDE-209 content in TVs also destined for the Australian market), at least 10% total weight BDE-209 is required in HIPS (300). Flammability standards pertaining to specific states, territories or countries affect the flame retardant content of goods outside that jurisdiction, because of globalisation of markets (34). The reported use of BDE-209 in TV sets is confirmed in testing studies, which consistently find the highest BDE-209 concentrations in the rear covers of TVs, see Appendix Table 1. In composite samples from waste TVs in Europe, the maximum permitted concentrations (MPC) of BDE-209 specified in the European Union's (EU's) Restriction of Hazardous Substances (RoHS) Directive (0.1% total weight) are regularly exceeded (298). The inclusion of substantial concentrations of BDE-209 into TV rear covers is not exclusive to older, cathode ray TVs. In Australia, testing of nine new LCD and LED TVs found five contained BDE-209 concentrations in the rear cover between 4.9% - 9.1% total weight (all five televisions were manufactured in China) (289).

The concentration of BDE-209 in HIPS in the housing of computers and TVs, excluding rear covers, is consistently lower than that found in rear TV covers. Average concentrations are almost always less than <1% total weight of the polymer, but frequently greater than 0.1% (see Table 2). The highest concentration for a computer housing composite sample was reported at 0.48% by Morf et al., in Switzerland in 2003 (301). In Australia, one computer housing unit that was tested contained BDE-209 at 0.14% (289).

BDE-209 may also be incorporated into most other commercial polymers, including ABS, polypropylene (PP), polyethylene (PE), polybutylene terephthalate (PBT), polyamides/nylon (PA), polycarbonates, PVC or polyphenyl ether (PPE), for applications where heat is a concern; including light fittings, electrical plugs and connectors, and other components within electrical goods (287, 299, 300). Electronic and electrical items in Australia that have previously been found to contain BDE-209 include plugs of electrical appliances and power boards (~1% total product weight), an A4 laminator (0.52%), a tower fan (0.08%), deep fryer (0.08%), and a microwave (0.01%) (289). Results from swipe testing in Australia also indicated that BDE-209 can be found in various small household appliances, including bread makers, ice cream makers, milk frothers, hair dryers, high pressure cleaners, slow cookers, toasters, vacuum cleaners, hair straighteners, and various audio visual systems. This finding is supported by the international literature. In particular, the broad survey of waste electronics and electrical appliances (WEEE) in Europe by Wager et al. (2012) reported that BDE-209 concentrations in waste from small household items with high-temperature applications approached 0.1% (298).

BDE-209 is also incorporated into ABS, which is the major source of the flame retardant in larger household appliances, including cooling devices such as refrigerators, dishwashers, and washing machines (298). However, in the previous testing by our group, BDE-209 was infrequently detected in these items and at concentrations generally lower than in other electronic items (289). It is not known if older models of refrigerators in Australia contain BDE-209, as the focus of the earlier study was on newly imported products (289). Internationally, concentrations of close to 0.1% BDE-209 have been reported from WEEE composite samples from large household appliances without cooling, while composite samples from cooling devices are around 0.01-0.03% (298).

BDE-209 has also been reported by the Bromine Science Environmental Forum to have been used in electrical wires/cables and connectors/plugs (288). Data on the content of BDE-209 in plugs and particularly wires/cables in Australia are limited. In the earlier research our group undertook, BDE-209 was found in plugs of small electrical appliances, but wiring and cables were not examined using quantitative assessment (289). Only very low or non-detectable levels of bromine were found in cabling products using x-ray fluorescence analysis (289). Elsewhere, the concentration of BDE-209 has been reported to be low (0.017%) in telecommunications cabling waste samples (301).

5.3.2 Soft furnishings

The main application of BDE-209 for textiles is for the transport industry, including in motor vehicles, planes, and trains, with additional textile applications including upholstered furniture and curtains/drapes (302). The use of flame retardant treated textiles are likely to be more common in public locations (hospitals, schools etc.) or regions where flammability standards are stricter.

The main application of BDE-209 to textiles is in the form of a back-coating. A brominated flame retardant with antimony III oxide was first patented for back-coating application to textiles in 1982 (303). Since then, BDE-209 and hexabromocyclododecane (HBCDD), in combination with antimony III oxide, have been the two most commonly used brominated flame retardants for back-coating of textiles. Textiles commonly back-coated with these chemicals include cottons, cotton-polyester blends, acrylics, nylon, polypropylene and polyester (302, 304). These flame retardants are applied to the textile with a resin binder, for example an acrylic copolymer or ethylene-vinyl acetate copolymer (305). Although the actual application amount may vary depending on the weight of the textile, a typical application amount is approximately 50 grams of BDE-209 per square metre of textile, or 10-25% of the total weight of the textile (300, 305). The use of BDE-209 back-coatings on textiles is dependent on the inherent flammability of the textile, and the standards/codes affecting its end use.

The BCA excludes curtains from mandatory flammability testing; however this exclusion is subject to some uncertainty with regards to interpretation. Although the BCA sets minimum codes for construction in Australia, it is not uncommon for additional performance criteria to be specified by individual entities such as hospitals, institutions or commercial buildings. Therefore, major manufacturers of curtains in Australia may subject their textiles to flammability testing methods described in AS 1530 parts 2 and 3. However, besides hospitals and institutions, there are actually no standards pertaining to the flammability of curtains in Australia. The majority of curtains available for non-domestic purposes in Australia are manufactured from inherently flame retarded polyester (i.e. Trevira CS®), which means that the use of BDE-209 on these materials would be unlikely. In hospitals, disposable polypropylene curtains are commonly used, and these may be treated with organophosphorus flame retardants. Curtains that are not inherently flame retardant may be treated with BDE-209 back-coatings or with HBCDD (306), another bromine containing flame retardant that is listed in the Stockholm Convention.

Upholstery fabrics represent another major use of BDE-209 back-coatings in the textile industry, particularly for transport applications. The use of back-coating of upholstery textiles is relatively common, particularly if the fabric is not otherwise inherently flame retardant or is otherwise unable to meet flammability standards (302).

Application of BDE-209 to tents and tarpaulins has also been reported by industry (288), and a recent study in North Carolina found BDE-209 in the majority of tents tested (307). No data are available on tents in Australia.

Although flammability standards apply to protective clothing in Australia, the use of BDE-209 back-coating is not appropriate for protective clothing applications. Protective clothing items are generally manufactured from inherently flame resistant textiles, including polyaramides and polybenzimidazole.

5.3.3 Building and construction

Despite the wide variety of building materials that are reported to be treated with BDE-209, data are limited regarding actual concentrations of flame retardants in these materials, particularly in Australia (288). A wide variety of building materials are subject to the BCA. The major application of BDE-209 (by sheer volume) in building materials is likely to be to extruded polystyrene insulation, although HBCDD is also used for this purpose (308). Low levels of BDE-209 have been detected in polyurethane foam insulation (0.002% by weight), however extruded polystyrene insulation was not specifically tested (289). Other applications of BDE-209 include hot melt adhesives (these are used in lamination processes, including laminated wood), air-handling

ductwork, and lift cars, although more research is needed to assess the proportion of these products containing BDE-209 in Australia (308).

Most carpets available in Australia are either wool, nylon, polyester or polypropylene. Of these carpet types, for technical reasons, nylon is probably the most likely to be back-coated with BDE-209 (292). Wool is commonly treated with ammonium based or other flame retardants, while polyester and polypropylene may be manufactured with organophosphate flame retardants (302). It is likely that some carpets that are back-coated with BDE-209 are being used in Australia for flooring in buildings. However, carpets used for both domestic and commercial uses in Australia have previously been tested, using both XRF and swipe testing, and the use of brominated flame retardants does not appear to be widespread (289).

5.3.4 Automotive/transportation

Carpets and other interior upholstery from cars, but not other forms of transport, have been tested using both XRF and destructive testing in Australia (289). Only 2 of 47 automotive carpets tested through XRF were positive for bromine (maximum concentration 2.7%), 8 of 12 car seats tested were positive for bromine (maximum concentration 2.7%), while only one sample (back-seat lining) was found to contain BDE-209, and at a concentration of less than 0.0001%.

Much higher concentrations of BDE-209 are likely to be found in planes, commercial vehicles and public transport vehicles, for which the flammability standards are very stringent (309). Almost all items within planes are subject to flammability standards, including floor and floor coverings, panelling, light covers, storage bins, passenger seats, stowage bins, insulation, windows, hoses, and air ducting (309). Scientific studies have reported elevated dust and air concentrations of BDE-209 in planes and elevated BDE-209 body burden in aircraft maintenance workers (310).

5.3.5 Toys

We have included toys in this review because hard plastic toys may be a significant source of exposure to BDE-209, particularly to young children who may suck on these items. In the study by Chen et al. (2009), hard plastic toys were found to contain BDE-209 up to concentrations of 0.4% total weight (220). Although BDE-209 was also detected in other toy types, the highest concentrations were two orders of magnitude lower. In Australia, of two plastic toys that were tested (a remote control train and slot car race track), BDE-209 was not detected in either, however TBBPA was found to contribute 14.4% of the total weight of plastic used in the slot car race track (289). Testing using XRF of 109 toys in the same study, found that bromine was detected in typically very low levels (<0.1% bromine by weight) (289).

5.4 Discussion: estimate of goods likely to contain BDE-209 in Australia

Items that were estimated to have the highest likelihood of containing BDE-209 were electronics and electrical appliances and items used in transport modes including planes and public transport. Electronic goods that were most likely to contain very high concentrations of BDE-209 (>10% total weight) included TVs and power boards. Although the concentration of BDE-209 varies between individual TVs, there were no specific trends, in terms of age or specific type of TV, that were associated with higher or lower concentrations of BDE-209. The implications of this for waste management are profound.

Although much consumer concern has focused on the presence of PBDEs in soft furnishings and textiles, including couches, carpets, curtains and clothing (particularly for children), the findings of our review indicate that it is unlikely that BDE-209 is widespread in these applications in Australia, particularly in the domestic environment. However, further research is required to quantify the distribution of BDE-209 in these applications in the non-domestic setting in Australia, including in offices and institutions.

The use of BDE-209 in textiles intended for the transport industry has been documented overseas and in Australia. While the application of BDE-209 in carpets in private vehicles in Australia appears to be relatively uncommon, its application to textiles covering transport seats may be more common. However, no data were available regarding the use of BDE-209 in public or commercial transport vehicles and planes in Australia. It is likely that the use of BDE-209 in these applications is widespread, given the strict flammability standards and findings from studies elsewhere (310). Testing of transport vehicles for BDE-209 should be a priority for future research.

One of the greatest areas of uncertainty that may have important implications for waste management and human exposure, given the bulky nature of these items and their long life-span in the built environment, is the use of BDE-209 in building materials. The use of BDE-209 in insulation materials, including polystyrene insulation and other building materials (ducting, piping, hot melt adhesives), is likely, but data specific to Australia were not available. As such, quantitative testing of building materials for BDE-209 presence is a priority for future studies.

This work highlights the fundamental difficulties in analysing where and in what quantities BDE-209, has been used in Australia. The lack of information in Australia highlights the difficulty of monitoring toxic substances in consumer goods and in the environment. In particular, no specific information on the use of BDE-209, particularly in building materials, could be obtained from manufacturers or distributors and material safety data sheets were not commonly available online.

5.5 Conclusion

The aim of this review was to assess sources of BDE-209 in the Australian environment, including homes, given that this was identified as an area of uncertainty in the reviews presented in Chapter 3 and Chapter 4 of this thesis. However, despite completing the thorough review presented in this chapter, which included technical, government and newly published research, our estimates were still accompanied by a high level of uncertainty. As previously described, this is likely to affect the content validity of the exposure-assessment questionnaire.

Products that were estimated most likely to contain the highest levels of BDE-209 included:

- Computers and TVs
- Small household appliances
- Large household appliances: refrigerators
- Large household appliances: dryers and dishwashers
- Power cords and connectors
- Power boards
- Tents/tarpaulins
- Extruded polystyrene insulation
- Carpets (in various transport modes but not in homes)

Although the BDE-209 content of some household items remains to be characterised, this more extensive review on BDE-209, specific to the Australian context was informative for the design of certain aspects of the exposure-assessment questionnaire for this thesis, as well as the design of exposure-assessment questionnaires in general.

With regards to the questionnaire for this thesis, the most useful information obtained from this review was related to PBDE content in foam and soft furnishings. As described earlier, in Chapter 4, foam is an important source of PBDEs in the indoor environment in the US (219). However, in Australia, PBDEs are most likely to be found in relatively high concentrations in electronic appliances, but not in household soft furnishings or furniture. Therefore, more attention could be given in the questionnaire to assessing the presence of electronics and electrical appliances in the home, compared to foam containing items.

In terms of exposure-assessment questionnaires in general, this review again highlighted that the questionnaire may not be suitable to chemicals for which exposure pathways have not been comprehensively described, as it is impossible to ensure the content validity of a questionnaire when the sources of exposure and exposure routes are unknown. Furthermore, the questionnaire-based approach to exposure assessment may not be suited to assessing exposure to chemicals for which the sources cannot be confidently identified through the use of questions. For example, since goods are not labelled with their PBDE content but the PBDE content varies markedly between

goods of the same type (i.e. televisions), it may not be possible to assess sources of PBDEs in the home environment via a questionnaire.

CHAPTER 6 PATTERNS OF INSECTICIDE-PRODUCT USE AND CHILDREN'S EXPOSURE PATHWAYS IN THE AUSTRALIAN DOMESTIC ENVIRONMENT: AN ANALYSIS OF CALLS TO THE QUEENSLAND POISONS INFORMATION CENTRE

Karin English, Paul Jagals, Robert S. Ware, Carol Wylie, Peter D. Sly: *Unintentional insecticide poisoning by age: An analysis of Queensland Poisons Information Centre calls*. Australian and New Zealand Journal of Public Health 08/2016;, DOI:10.1111/1753-6405.12551

As described in Chapter 4, despite the relatively high number of available insecticide products in Australia, there is an absence of data regarding domestic and professional insecticide use patterns in Australian homes. For example, there is no data regarding the typical amounts of insecticides that are used, their frequency of use, as well as information regarding their handling, storage and the method of application. The aim of this study was therefore to understand the types of pest-control products that are being used in homes in Australia and to identify exposure pathways that may not have been previously identified in the literature. This was achieved by analysing insecticide-related calls to the Queensland Poisons Information Centre (QPIC).

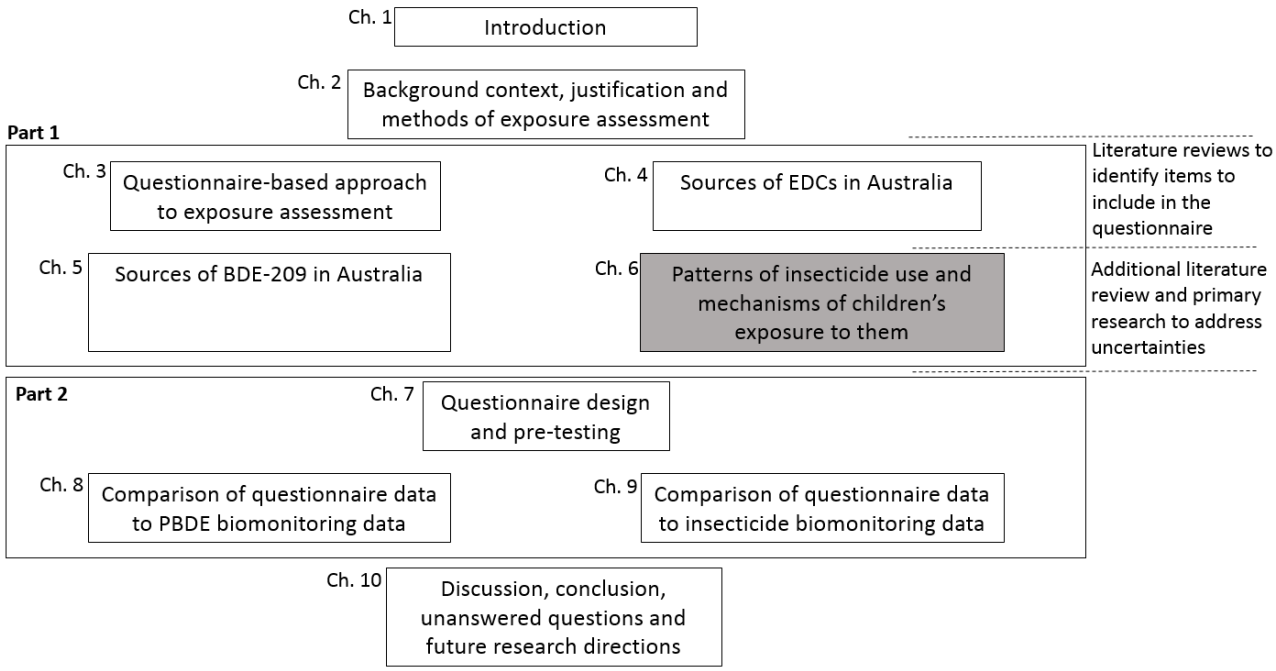


Figure 6-1 Thesis structure: Chapter 6

For the audience of the published paper presented in this chapter, the introduction and discussion were framed with reference to acute-insecticide exposure. Whilst some of the calls to the QPIC may have led to acute exposure events, in reality the majority of scenarios did not lead to acute exposure. Therefore, the behaviours and pest control product use practices that were identified in the exposure scenarios are informative not just to understanding acute exposure risk of young children to insecticides but also chronic exposure risk.

6.1 Introduction

Insecticides are chemicals that are widely used in both domestic and commercial settings for preventing, destroying, repelling, or mitigating unwanted pests (48). While agricultural and public health applications of insecticides have positive economic and health benefits, there are also adverse effects of insecticides on the environment and health. Early childhood is a period of pronounced vulnerability to insecticides, as young children are not only at increased risk of insecticide exposure, due to their unique behaviours and physiology, but are also more sensitive to the adverse health effects of insecticides (311, 312). Acute exposure to insecticides may result in local dermal irritation following skin contact, abdominal cramps, vomiting, diarrhoea, bronchospasm, dyspnoea, coughing, headaches, miosis, seizures, muscle twitching, paralysis and in severe cases death or long-term adverse health effects, although no studies in Australia have specifically investigated the association of young children's acute insecticide exposure and health outcomes (100). Rates of acute poisoning events in young children can only be inferred by hospital admission data and calls to poison information centres, as there is no comprehensive poisoning monitoring system in Australia. Over a one-year period from mid-2009 there were 26 hospitalisations of children aged 0-4 as a result of acute organophosphate and carbamate poisoning in Australia (other specific insecticide poisonings were not reported) (313). In 2014, the 6th most commonly cited poison in calls to Queensland Poisons Information Centre (QPIC) was pyrethrins/pyrethroids and children were involved in 57.6% of all calls received by QPIC during this period, however data specific to the insecticides involved in calls for children were not available in the public report (314).

The true extent of acute insecticide poisoning events and the burden on young children's health remains uncharacterised in Australia. Despite this, insecticides are widely available in Australia for applications in the domestic environment, including for indoor and outdoor pest control, veterinary treatments, and medical treatments, such as treatment of head lice (274). Compared to other countries, Australia has more insecticide products registered for use (115). One study in Australia has assessed chronic exposure of Australian children to insecticides, reporting that exposure is similar if not higher than exposure of children in other developed countries, but acute exposure

(high-dose exposure over a period of <24 hours) was not assessed (115). In this study, we examined all insecticide-related calls received by the Queensland Poisons Information Centre (QPIC) in 2014 to determine what insecticides are most commonly involved in insecticide poisoning events in young children, whether insecticide poisoning patterns vary by age and product type, and symptoms associated with exposure.

6.2 Methods

Australia has four poisons information centres, which are available on 13 11 26 to receive calls from both lay persons and health care professionals regarding actual and potential poisonings. In 2014 QPIC covered poisoning calls from the entire state of Queensland (population approximately 5 million) from 8.30am to 9pm Monday to Friday and 8.30am to 7pm Saturday and Sunday. When calls are received, the poisons information specialist routinely collects a history from each caller, including information regarding the exposure mechanism, chemical(s) or the chemical class involved, age and symptoms.

Call data in this study were obtained from the QPIC for the 2014 calendar year. Irrelevant calls, intentional exposures and duplicate entries were excluded. Calls were included if QPIC staff had classified them as relating to one of the following: pyrethroids/pyrethrins, organophosphates, fipronil, imidacloprid, carbamate insecticides, borates/boric acid, insecticide: other/unknown. Calls regarding rodenticides were excluded.

Information concerning age, product type, insecticide class and specific insecticide(s), recommended management, and mechanisms and routes for exposure was extracted from call records. The specific insecticide was identified where possible through the call record. If the insecticide content was not listed but the product name was given, the product and its active ingredients were searched for through the Public Chemical Registration Information Search (PUBCRIS) tool: https://portal.apvma.gov.au/pubcris (274). Information regarding data extraction are provided in the supplementary materials.

We examined call numbers by age (<1, 1, 2, 3, 4), product type, insecticide and insecticide class and mechanism and route of exposure. We also examined the type/specific insecticide in each specific product type received by QPIC in 2014. All calls (calls for children and adults) were included in the analysis of insecticides in each product type, due to the relatively small sample size. Summary statistics are reported as frequencies and percentages. Data analysis was conducted using Stata statistical software v12.0 (StataCorp, College Station, TX, USA). Ethical approval for this study was obtained from the University of Queensland, Australia.

6.3 Results

A total of 1023 entries were obtained from QPIC representing insecticide-related calls between 01 January and 31 December 2014 for both adults and children. Of these, 280 were identified as either duplicate entries (i.e., calls related to the same exposure event), calls unrelated to insecticides, or intentional exposures, leaving a total of 743 unique calls that met our criteria. Most calls to the QPIC were placed by lay persons, with a minority of calls placed by medical or other health care professionals seeking specific advice. During the study period 364 (49.0%) of the insecticide-related calls to the QPIC were regarding young children (< 5 years), correlating to an incidence of 115 calls per 100,000 children under the age of 5 in Queensland (315). The peak number of calls (143 calls) occurred in the 1 year old age group Figure 6-2, at 223 calls per 100 000 children (315).

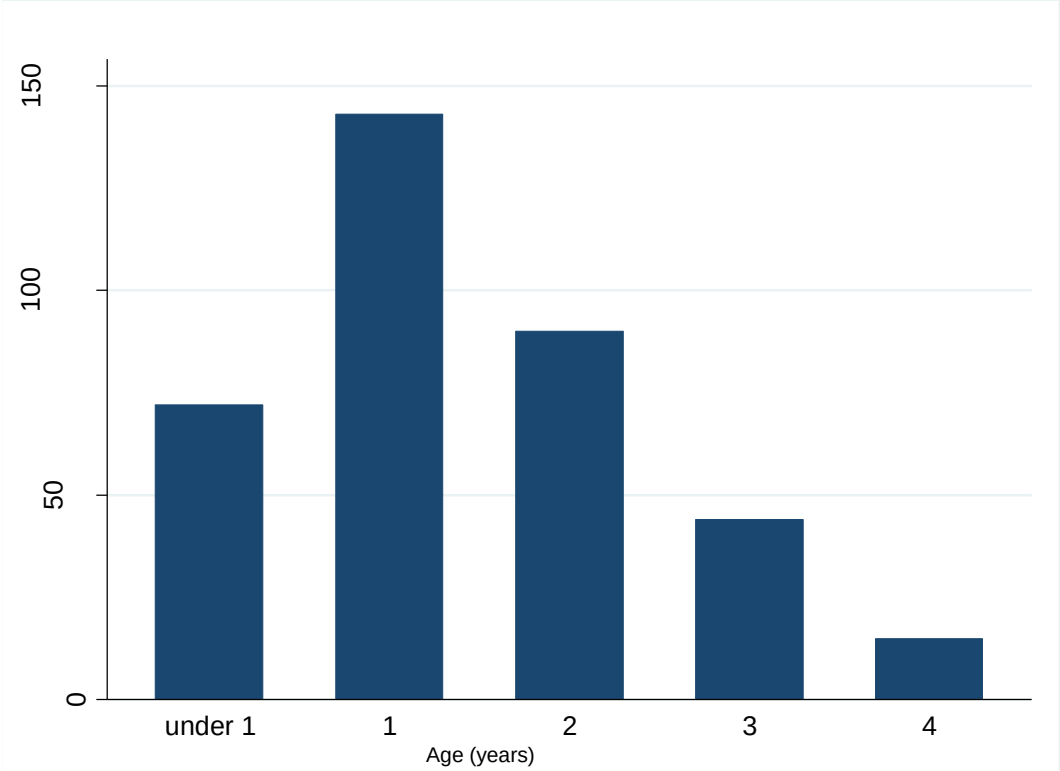


Figure 6-2 Insecticide-related calls to the Queensland Poisons Information Centre in 2014 by age

6.3.1 Calls by product type and insecticide type

The products most commonly identified in insecticide-related calls involving young children were baits/ant liquid and spray products (Table 6-1). Baits and ant liquid accounted for 142 (39.0%) of the calls that were received for young children. The age groups with the highest proportion of calls regarding baits/ant liquid were children aged under one and children aged one, 58.3% and 41.3% of all calls in these age groups were regarding these specific product types, respectively (

Table 6-2). The active ingredients identified in calls for ant/cockroach baits and ant liquid were most commonly borates/boric acid (48.8%), followed by indoxacarb (23.2%) and fipronil (17.1%) (

Table 6-3).

Table 6-1 Insecticide-related calls to the Queensland Poisons Information Centre in 2014 by product type for children <5 years

	Product type	Number of calls (percentage)
Household insecticides	Ant and cockroach baits and ant liquid	142 (39.0%)
	Sprays (fly sprays and other aerosol products requiring no dilution prior to use)	94 (25.8%)
	Mosquito coils	20 (5.5%)
	Granular products (ant or lawn treatments)/dust products (poultry powders)/ ant sand	16 (4.4%)
	Fumigators (i.e., flea bombs)	*
	Automatic aerosol dispensers	*
Animal and Veterinary Products	Other veterinary treatments (including animal husbandry applications and topical flea treatments)	29 (8.0%)
	Domestic animal flea shampoo	20 (5.5%)
	Animal flea/tick collars	*
Medicinal	Head lice treatments	*
Other products	Concentrated products[a] intended for dilution	14 (3.9%)
	Insecticide: other or unknown	14 (3.9%)
	Professional pest control	*
	Total	364

a.concentrated products are available for both household and professional use in Australia. NA: not applicable; no calls regarding this product type in specific age category. *Number withheld to prevent identification (n < 5)

Table 6-2 Insecticide-related calls to the Queensland Poisons Information Centre in 2014 by product type and age

		Age (years)					
		Under 1	1	2	3	4	Total Number of Calls for Young Children (0 to <5)
Household insecticides	Ant and cockroach baits and ant liquid N(%)	42 (29.6 %)	59 (41.6 %)	25 (17.6 %)	16 (11.3 %)	NA	142
	Sprays (fly sprays and other aerosol products requiring no dilution prior to use) N(%)	13 (13.8 %)	29 (30.9 %)	32 (34.0 %)	13 (13.8 %)	7 (7.5 %)	94
	Mosquito coils N(%)	6 (30 %)	13 (65 %)	*	NA	NA	20
	Granular products (ant or lawn treatments)/dust products (poultry powders)/ ant sand N(%)	*	7 (43.8 %)	5 (31.3 %)	*	*	16
	Fumigators (i.e. flea bombs) N(%)	*	NA	*	*	NA	*
	Automatic aerosol dispensers N(%)	NA	NA	*	NA	NA	*
Animal/veterinary products	Other veterinary treatments (including animal husbandry applications and topical flea treatments) N(%)	*	11 (37.9 %)	8 (27.6 %)	*	*	29
	Domestic animal flea shampoo N(%)	*	9 (45.0 %)	*	*	*	20
	Animal flea/tick collars N(%)	NA	*	*	NA	NA	*
Medicinal	Head lice treatments N(%)	NA	*	NA	*	*	*
Other products	Concentrated productsa intended for dilution N(%)	NA	6 (42.9 %)	5 (35.7 %)	*	*	14
	Insecticide: other or unknown N(%)	*	5 (35.7 %)	6 (42.9 %)	*	NA	14
	Professional pest control N(%)	*	*	NA	*	NA	*
	Total	72 (19.8 %)	143 (39.3 %)	90 (24.7 %)	44 (12.1 %)	15 (4.1)	364

Concentrated products are available for both household and professional use in Australia. NA: not applicable; no calls regarding this product type in specific age category.
*Number withheld to prevent identification (n < 5)

Table 6-3 Insecticides or insecticide classes in major product types identified in insecticide-related calls for all ages

	Insecticide Class: number and percentage (in brackets) per product type								
	Other	Borate/boric acid	Carbamates	Fipronil	Organophosphates	Pyrethrins and Pyrethroids	Indoxacarb	Imidacloprid	Total
Animal/Veterinary Products									
Animal flea/tick collars	NA	NA	*	NA	*	5 (55.6%)	NA	NA	9
Other veterinary treatments (including animal husbandry applications such as cattle tags, sprays etc.)	*	*	NA	9 (15.3%)	5 (8.5%)	16 (27.1%)	NA	26 (44.1%)	59
Domestic animal flea shampoos	NA	NA	NA	NA	5 (15.6%)	27 (84.4%)	NA	NA	32
Medicinal									
Head lice shampoos	*	NA	NA	NA	*	*	NA	NA	5
Household Insecticides									
Ant/Cockroach baits and ant liquid	NA	80 (48.8%)	NA	28 (17.1%)	*	NA	38 (23.2%)	*	164
Sprays (i.e. fly sprays and other aerosol products requiring no dilution prior to use)	*	NA	NA	NA	28 (12.3%)	194 (85.1%)	NA	*	228
Granular products	*	*	*	NA	5 (15.6%)	19 (59.4%)	NA	NA	32
Mosquito coils	NA	NA	NA	NA	NA	20 (100%)	NA	NA	20
Fumigators (i.e. flea bombs)	NA	NA	NA	NA	NA	20 (100%)	NA	NA	20
Automatic aerosol dispensers	NA	NA	NA	NA	NA	7 (100%)	NA	NA	7
Other Products									
Professional pest control	*	NA	NA	*	NA	6 (54.5%)	NA	NA	11
Concentrated products[a]	*	NA	8 (7.8%)	*	55 (53.9%)	34 (33.3%)	NA	*	102
Insecticide: other/uncertain	15 (27.8%)	*	*	*	12 (2.2%)	17 (31.5%)	NA	*	54
Total	41 (5.5%)	89 (12.0%)	13 (1.8%)	41 (5.5%)	115 (15.5%)	367 (49.4%)	38 (5.1%)	39 (5.3%)	743

Concentrated products are available for both household and professional use in Australia. Concentrated products are not placed under the category of 'household insecticides' as we did not differentiate between calls related to concentrated products for occupational or domestic use. NA: not applicable; no calls regarding this product type in specific age category. *Number withheld to prevent identification (n < 5)

Sprays (i.e., products not requiring dilution) accounted for 25.8% of all calls in young children. Most (85.1%) sprays contained a combination of one or more of 12 different pyrethroids, pyrethrins and/or piperonyl butoxide (Table 6-4). One organophosphate containing spray, "Crawly Cruncher household insecticide surface spray" (diazinon 38.0 g/L), was named in 12.3% of all calls for sprays. Additional product types reported in young children's organophosphate-related calls included granules/dust/ant sand containing maldison, head lice shampoos containing maldison, animal flea/tick collars containing diazinon, and a bait product containing chlorpyrifos - although chlorpyrifos containing baits are no longer registered in Australia.

Table 6-4 Insecticides identified in spray products in insecticide-related calls for all ages (children and adults) received by the Queensland Poisons Information Centre in 2014

Insecticide	Number of spray products in which specific insecticide was identified (percentage of all spray-product related calls containing specific insecticide)
Pyrethroids/pyrethrins	
Imiprothrin	65 (39.6%)
Cypermethrin	41 (25.0%)
Deltamethrin	27 (16.4%)
Tetramethrin	18 (11.0%)
Bifenthrin	13 (7.9%)
Permethrin	15 (9.2%)
Pyrethrins	13 (7.9%)
Allethrin	11 (6.7%)
Phenothrin	8 (4.9%)
Esbiothrin	6 (3.7%)
Bioresmethrin	4 (2.5%)
Pyrethrum	3 (1.8%)
Esfenvalerate	2 (1.2%)
Organophosphates	
Diazinon	23 (14.0%)

Other product types, including concentrated products, animal flea/tick collars, mosquito coils and animal flea shampoos each accounted for 5.5% or less of all calls for young children, while other veterinary products accounted for 8.0% of all calls for young children. Veterinary products, including animal collars, animal shampoo and other veterinary products, were found to contain a variety of insecticide active ingredients, including pyrethroids and pyrethrins, organophosphates (diazinon and maldison), fipronil, imidacloprid, and carbamates (propoxur). All mosquito coils contained the pyrethroid allethrin. Concentrated products reported in calls to QPIC in 2014 contained organophosphates (52.9%), pyrethroids (33.3%) and less commonly carbamates (7.8%) (

Table 6-2 and Table 6-5).

Table 6-5 Calls for children and adults related to concentrated products received by the Queensland Poisons Information Centre in 2014

Insecticide	Number of calls related to concentrated products in which specific insecticide was identified (percentage of all concentrated product related calls containing specific insecticide)
Pyrethroids	
Permethrin	11 (12.6%)
Bifenthrin	8 (9.2%)
Deltamethrin	6 (6.9%)
Pyrethrins	3 (3.5%)
Tetramethrin	1 (1.2%)
Cyalothrin	1 (1.1%)
Cypermethrin	1 (1.2%)
Flumethrin	1 (1.2%)
Carbamates	
Carbaryl	3 (3.5%)
Methomyl	3 (3.5%)
Propoxur	1 (1.2%)
Organophosphates	
Chlorpyrifos	29 (33.3%)
Maldison	6 (6.9%)
Diazinon	3 (3.5%)
Dimethoate	4 (4.6%)
Fenamphos	2 (2.3%)
Mevinphos	2 (2.3%)
Chlorfenvinphos	1 (1.2%)
Dichlorvos	1 (1.2%)
Ethion	1 (1.2%)
Prothiofos	1 (1.2%)
Malathion	1 (1.2%)

6.3.2 Mechanisms and routes of exposure

The oral route of exposure was the dominant route of exposure to insecticides for all common product types, Table 6-6. The topical route of exposure (dermal and eye) was a key route for exposure to concentrated products and sprays; accounting for 50.0% and 33.0% of exposures to these products, respectively. The most common mechanism for exposure via the oral route was the child accessing the product and mouthing or ingesting the product or its packaging. Some additional mechanisms of exposure were also identified that were specific to common product types (Table 6-6). These included: mouthing or ingesting an item or insects/animals (i.e., cockroaches and geckos/lizards) previously treated with a spray, direct application of a spray by the child or a

sibling, accessing and/or ingesting a concentrated product from a secondary container (i.e., following dilution), and contact with a veterinary product via a previously treated pet. The incidence of exposure to sprays via direct application peaked in children aged two (Table 6-6 and Table 6-7). This was unlike other exposure mechanisms that typically led to exposure via the oral route and peaked in children aged one and under.

Table 6-6 Exposure routes commonly involved in insecticide-related calls for children (<5 years) received by the Queensland Poisons Information Centre in 2014

	Oral			**Inhalational**	**Topical**		**Other**	
Product Type	Hand to mouth N(%)	Mouthing/ingestion of product or packaging N(%)	Mouthing/ingestion of item treated with product N(%)	Inhalational N(%)	Dermal N(%)	Eye N(%)	Unknown/not specified N(%)	Total
Ant/Cockroach baits and ant liquid	6 (4.2%)	133 (93.7%)	*	NA	*	NA	NA	142
Sprays (i.e. fly sprays and other aerosol products requiring no dilution prior to use)	5 (5.3%)	34 (36.0%)	19 (20.2%)	5 (5.3%)	15 (16.0%)	16 (17.0%)	NA	94
Other veterinary treatments (including animal husbandry applications such as cattle tags, sprays etc.)	NA	16 (55.2%)	*	NA	*	*	*	29
Mosquito coils	*	19 (95.0%)	NA	NA	NA	NA	NA	20
Domestic animal flea shampoos	*	16 (84.2%)	NA	NA	*	NA	NA	19
Granular products (i.e. ant treatments or lawn treatments)/dust products (i.e. poultry powders)/ant sand	*	8 (50.0%)	*	*	*	*	NA	16
Concentrated products	*	5 (35.7%)	NA	NA	7 (50.0)	NA	NA	14

NA: not applicable; no calls regarding this product type in specific age category. *Number withheld to prevent identification (n < 5)

Table 6-7 Exposure mechanisms by age to common insecticide products involved in insecticide-related calls received by Queensland Poisons Information Centre in 2014

	Exposure mechanism	Age (years)					
		<1	1	2	3	4	Total
Ant/cockroach baits and ant liquid	Child accessed product on the floor/accessible surface	40 (33.3%)	52 (43.4%)	18 (15.0%)	10 (8.3%)	NA	120
	Child accessed product in its original packaging	*	7 (36.8%)	6 (31.6%)	*	NA	19
	Insecticide included in a craft product	NA	NA	*	*	NA	*
	Total	42 (29.6%)	59 (41.5%)	25 (17.6%)	16 (11.3%)	NA	142
Sprays (i.e., fly sprays and other aerosol products requiring no dilution prior to use)	Accidental direct application of product to child	*	11 (26.8%)	18 (43.9%)	6 (14.6%)	5 (12.2%)	41
	Child accessed product in its original packaging	*	9 (42.9%)	6 (28.6%)	*	*	21
	Child in close vicinity of treatment	NA	*	*	*	*	9
	Leakage/accident	NA	*	*	NA	NA	*
	Child accessed product on the floor/accessible surface	NA	*	NA	NA	NA	NA
	Item/insect sprayed prior to child accessing item/insect	10 (50%)	*	*	*	NA	20
	Total	13 (13.8%)	29 (30.9%)	32 (34.0%)	13 (13.8%)	7 (7.5%)	94

NA: not applicable; no calls regarding this product type in specific age category. *Number withheld to prevent identification (n < 5)

6.3.3 Management of exposure

In the majority of insecticide-related calls for young children in 2014, the extent of the exposure was nil or minimal and this exposure was uncertain or unlikely to cause an adverse health effect. As appropriate to the situation, callers (75.6% of all of young children's calls) were given advice on possible symptoms to be aware of and when to seek medical assistance or reassurance (8.5% of all calls) that exposure was unlikely to result in adverse health outcomes. In 6.0% of calls advice was given to seek medical attention and a further 6.3% of calls were received from doctors or nursing staff, indicating that medical attention for the young child had already been sought. Spray products (45.5%) and baits/ant liquid (30.0%) accounted for the majority of calls for which medical attention was recommended. However, medical attention was also recommended for exposures involving animal flea/tick collars, concentrated products, granular/sand products and other veterinary products. Insecticides involved in the 22 calls for which medical attention for the young child was recommended included pyrethroids and or pyrethrins (22.7%), borate (22.7%), organophosphates (36.4%), fipronil (4.6%), carbamates (9.1%) and other/unknown (4.6%). Half of all spray product calls for which medical attention was recommended involved the organophosphate spray product "Crawly Cruncher household insecticide surface spray". Due to the small sample size, inconsistencies in symptom reporting and the inclusion of both confirmed and unconfirmed exposure incidents it was not possible to accurately assess associations between exposure and symptoms.

6.4 Discussion

6.4.1 Key findings

In this study we observed that exposure to insecticides peaked in children aged one. This pattern is similar to the pattern of exposure of young children in New South Wales, Australia, to non-medicinal products, which includes insecticides, reported by Schmertmann et al. (316). There is a growing body of literature suggesting that peak exposure of young children to non-medicinal chemicals occurs earlier than exposure to medicinal chemicals and that the difference may be attributable to storage patterns and the child's developmental stage (316, 317). We found that the intended method of use of the product, not just how it is stored, affected exposure patterns. We confirmed that normal behaviours associated with child developmental stage were a major determinant of exposure patterns; in this current study the majority of exposures were attributable to children accessing and mouthing products that were intentionally used on the floor, including bait stations, mosquito coils and ant liquid, as well as items or pest products that were non-intentionally

located on the floor or within reach. While it is widely known that young children put 'everything' into their mouths, the numerous cases of young children mouthing insects/animals that were observed in this study highlight the fact that the extent of this behaviour should not be underestimated.

Bait stations and ant liquids were the most common product category involved in calls for young children. The exposure potential associated with these product types is low, particularly in the case of baits, which are designed to be child-resistant and are generally effective in this regard. The exposure potential for insecticides in ant liquid may be higher as young children come into direct contact with the active ingredient. However in the majority of these cases poisoning is unlikely given the low strength of active ingredient found in these proprietary products (274). As suggested in Table 6-8, baits represent a safer pest control option to use in homes with young children, although they should not be placed on the floor within reach of young children.

Table 6-8 Common exposure scenarios in insecticide-related calls Received by Queensland Poisons Information Centre for young children (<5 years) and actions to prevent poisoning

Product Type	Insecticides or Insecticide Classes	Exposure Scenarios Reported	Frequency of Exposure Scenario[a]	Actions to Prevent Insecticide Poisoning in Young Children
Ant and Cockroach Baits and Ant liquid	Borates/boric acid Fipronil Indoxacarb	Child accesses product in use on the floor and mouths the product	84.5%	Place baits in locations that are out of reach of young children. Store ant liquid in a child-proof location. Consider use of baits in place of ant liquid in homes with young children.
		Child accesses the product when not in use and contacts product or packaging	13.4%	
Sprays[b]	Pyrethroids Pyrethrins Diazinon	Child or sibling access product and sprays self/sibling	43.6%	Remove and dispose of treated insects or other items immediately post-treatment. Store sprays out of reach of children. Avoid purchasing sprays that are not in child-proof packaging or that contain organophosphates.
		Child accesses the product when not in use and contacts product or packaging	22.3%	
		Child contacts or mouths an item or insect/animal treated with the spray	21.3%	

a. Determined by proportion of calls to QPIC for young children relating to this scenario for each product type. Uncommon scenarios are withheld to prevent identification b. see Table 6-4 for a complete list of insecticides in this product type.

With increasing age, the proportion of calls regarding other scenarios, including those involving direct application of sprays, increased, while exposures due to mouthing behaviours decreased. This pattern of exposure mimics that of exposure of NSW children to medicinal products (316). In most calls regarding sprays the exposure mechanism was direct application – either by the exposed child or a sibling. As children gain mobility they may be able to access locations where sprays are stored (particularly if the product is stored in an easy-to-access location) and, as young children's motor skills develop, they may be more readily able to activate the spray mechanism on these products. The majority of sprays contain pyrethroids. Acute pyrethroid exposures are rarely lethal, with most pyrethroid exposures resulting in no or minor symptoms (318, 319). In contrast, organophosphates, such as diazinon, are highly toxic to young children (320). While the majority of insecticide sprays are sold in propellant driven aerosol cans, the organophosphate containing spray available in Australia is sold in a plastic spray bottle with a trigger handle that activates a pump mechanism to dispense liquid through a nozzle, which can be placed in an on/off position. These bottles pose an unacceptably high exposure risk to young children, as they are not sufficiently child resistant (321). Given the disproportionately high number of calls for all age groups regarding this product type (there are hundreds of registered pyrethroid containing aerosol spray cans in Australia and only one registered organophosphate containing spray) and the relatively high number of referrals to seek medical attention regarding this product, it is clear that this product type poses as unacceptably high exposure and health risk not just to young children but also to adults (274). In some other developed countries, such as the US, diazinon containing pest products are no longer available for domestic use because they are deemed to pose an unacceptable risk to human health (322). Consideration by the Australian Pesticides and Veterinary Medicines Authority should be given to removing the registration for this product, as well as other organophosphate and carbamate containing products that young children may be exposed to.

Although relatively few calls involved exposure of young children to products containing organophosphates and carbamates, including sprays, veterinary products and concentrated products, the health risks associated with these products are likely to be substantially greater. Organophosphate and carbamate insecticides are highly toxic to young children, any ingestion is potentially lethal without medical treatment, and they are found in relatively high concentrations within some products available publically in Australia (100, 320, 323). Concentrations of organophosphates in concentrated products are in the order of hundreds of grams/L (274).

The limited data on acute insecticide exposures in Australia suggests that the symptoms from most accidental organophosphate and carbamate exposures in children are mild (due to the ingestion of relatively small amounts of active ingredient) (324). However, there has been no comprehensive

assessment of the acute or the chronic health effects associated with exposure of young children to these chemicals in Australia.

The relatively small number of calls received for young children related to exposure to concentrated products is reassuring. This pattern indicates that use of these product types may be infrequent in homes with young children or that they are being stored in locations or packaging that is effectively child-resistant. Concentrated products are typically sold in metal tins with tight sealing lids. In contrast, the number of calls for the other liquid pest control products, such as ant liquids and animal shampoo, were higher. The higher frequency of calls regarding these product types compared to concentrated products could be attributable to a greater frequency of use in homes with small children or differences in their packaging. These products typically come in plastic containers with lids that screw or pop on and off. Exposures of young children to liquid product types may be minimised by 1) avoiding their use in homes with young children 2) ensuring that these products are sold in child resistant packaging, which may require government review, and 3) ensuring that these products are stored or deployed out of reach of young children.

6.4.2 Limitations and future research directions

Our analysis provides an indication of the main mechanisms of poisoning of children from Queensland to insecticides, but it does not provide a full picture of patterns of insecticide use or poisoning risk throughout Australia. Firstly, calls to the poisons centres only represent scenarios in which families are concerned about potential exposure. Therefore, a full picture of insecticide-use patterns is not likely to be obtained via this analysis. Additional research is required to fully understand insecticide-use patterns in homes. This could include surveys of products in homes, as well as monitoring of their use. This is the approach that is being taken in the Californian Study of Use of Products and Exposure-Related Behaviours, but was beyond the scope of this PhD (325). It is also likely that poisoning patterns vary greatly between the states and territories, due to the influence of climate and associated pest burden on insecticide use. Future research should extend to include all areas of Australia. Our ability to detect rare but important exposure scenarios was limited by our small sample size and also by the fact that calls out-of-hours that may have been received by other poisons information centres were not included in this analysis. In addition, the data assessed does not contain all exposures in QLD. Some children may be taken directly to their GP and/or emergency department and, unless the QPIC was subsequently called, these exposures are not recorded in the current data set. Although we were able to distinguish between veterinary and domestic insecticides, we were not able to distinguish between garden insecticides and domestic insecticides. Future research should attempt to clarify the different routes of exposure and

health risk between these two types of insecticides. Although a history of symptoms is collected by QPIC, we were unable to systematically code this data. An accurate assessment of the association between specific exposures and health outcomes would require collection of additional data, including hospital records and confirmation of exposure. Although collecting additional health data was beyond the scope of this study, we believe that a comprehensive examination of the health risk associated with Australian children's exposure to insecticides is needed.

6.5 Conclusion

The primary research conducted in this chapter was completed to address uncertainties in our knowledge of patterns of insecticide use in Australia, as well as gaps in our knowledge of exposure pathways of young Australian to insecticides. This study confirmed that several unique behaviours of young children, particularly mouthing behaviours, combined with typical pest product use, predisposed them to increased contact with insecticides. Children aged one were at the greatest risk because of mouthing behaviours and increased time spent on the floor. The most common insecticide product involved in calls to the QPIC were baits, which contained borates/boric acid (48.8%), followed by indoxacarb (23.2%) and fipronil (17.1%). None of these chemicals were selected for inclusion as the EDCs in this PhD. However, the information obtained in this study suggests that further research to better characterise exposure of young Australian children to these insecticides is warranted.

Pest sprays were the next most common product involved in calls relating to young children, accounting for 25.8% of calls. Most (85.1%) sprays contained a combination of one or more of 12 different pyrethroids, pyrethrins and/or piperonyl butoxide. Based on the findings presented in Chapter 4, this confirmed the fact that domestic pest-spray products are likely contributors to children's pyrethroid exposure. However, surprisingly, one spray product involved in 12.3% of all calls relating to spray products contained the organophosphate diazinon. This was informative to the questionnaire design, as prior to this study, the pest-spray product question data would not have been compared to organophosphate biomonitoring results, since no organophosphates were identified in pest-spray products in the review presented in Chapter 4. The finding of a very wide number of insecticide products within spray-products also highlights another issue with the use of the questionnaire-based approach to exposure assessment, which is that it may not always be possible to assess exposure to specific chemicals when a large variety of chemicals are found in the same product type. Whilst participants may be able to recall use of specific pest-products, they may not be able to recall the specific ingredients within those products.

CONCLUSION OF PART ONE

Chapter 6 comprised the last part of the 'information gathering' necessary to design the exposure-assessment questionnaire. In Chapter 6, and previous chapters, it was clearly demonstrated that there are still many major gaps in our knowledge of Australian children's exposure to EDCs. Without a comprehensive understanding of chemical exposure pathways, the questionnaire-based approach to exposure assessment approach may not be a suitable instrument to assess exposure to those chemicals.

Despite this, key domains that are anticipated to be the most important determinants of Australian children's exposure to EDCs are:

1. Intake of lipid rich food and PBDEs

PBDEs are found in the greatest concentrations in lipid-rich foods from high trophic levels. Therefore, dietary variables, such as duration of breastfeeding and intake of meat/dairy/seafood, are predicted to be associated with PBDE biomonitoring concentrations.

2. Consumption of fresh fruit and vegetables and organic versus non-organic food

Insecticide biomonitoring results will be associated with frequency of consumption of non-organic fresh fruit and vegetables and frequency of consumption of fruit juice, as these food types generally contain higher concentrations of insecticides, particularly organophosphates. It is also possible that some dietary variables will be associated with pyrethroid exposure, since pyrethroids have also been detected on food samples in Australia, although this association may be obscured by domestic exposures.

3. Domestic insecticide use and pyrethroid exposure

Domestic insecticide use is predicted to be associated with pyrethroid exposure. Some domestic pest-control products contain organophosphates, but they are much less prevalent than pyrethroids. Organophosphates are also contained in products that pyrethroids are found in (i.e. flea/tick collars, insecticide sprays, garden treatments). Unless study participants provide exact product names, it may be impossible to determine whether the pest-product use is associated with organophosphate or pyrethroid exposure.

4. Flooring type and various EDCs

Several elements of flooring type may be associated with children's' exposure to various EDCs, including carpet floorings and several EDCs that are found in high concentrations in dust.

5. Features of the home and various EDCs

Additional factors are anticipated to be associated or modifiers of exposure include factors that affect the concentration of contaminants in dust, including the age of the home, its size, ventilation rates and frequency of cleaning.

6. Hand-to-mouth behaviour and various EDCs

Exposure will be modified by factors that affect hand-to-mouth exposures, including frequency of hand-washing, nail-biting and hand/thumb sucking).

PART TWO

CHAPTER 7 QUESTIONNAIRE DESIGN AND PRE-TESTING

Karin English, Yiqin Chen, Leisa-Maree Toms, Paul Jagals, Robert S. Ware, Jochen F. Mueller, Peter D. Sly: Polybrominated diphenyl ether flame retardant concentrations in faeces from young children in Queensland, Australia and associations with environmental and behavioural factors. Environmental Research 10/2017; 158:669-676., DOI:10.1016/j.envres.2017.07.022

This chapter justifies and describes the methods chosen to design and pre-test the questionnaire. The aim of this chapter is to

- Address methodological considerations in questionnaire design that have yet to be discussed
- Provide a description and justification of the methods selected for the design of the questionnaire and design of the exposure-questionnaire pre-testing study
- Describe the results of the questionnaire pre-testing study

The first section of this chapter describes in more detail the principles of rigorous questionnaire design. It describes the application of rigorous questionnaire design to the information obtained in Part One of this thesis to produce the exposure-assessment questionnaire (Online Survey).

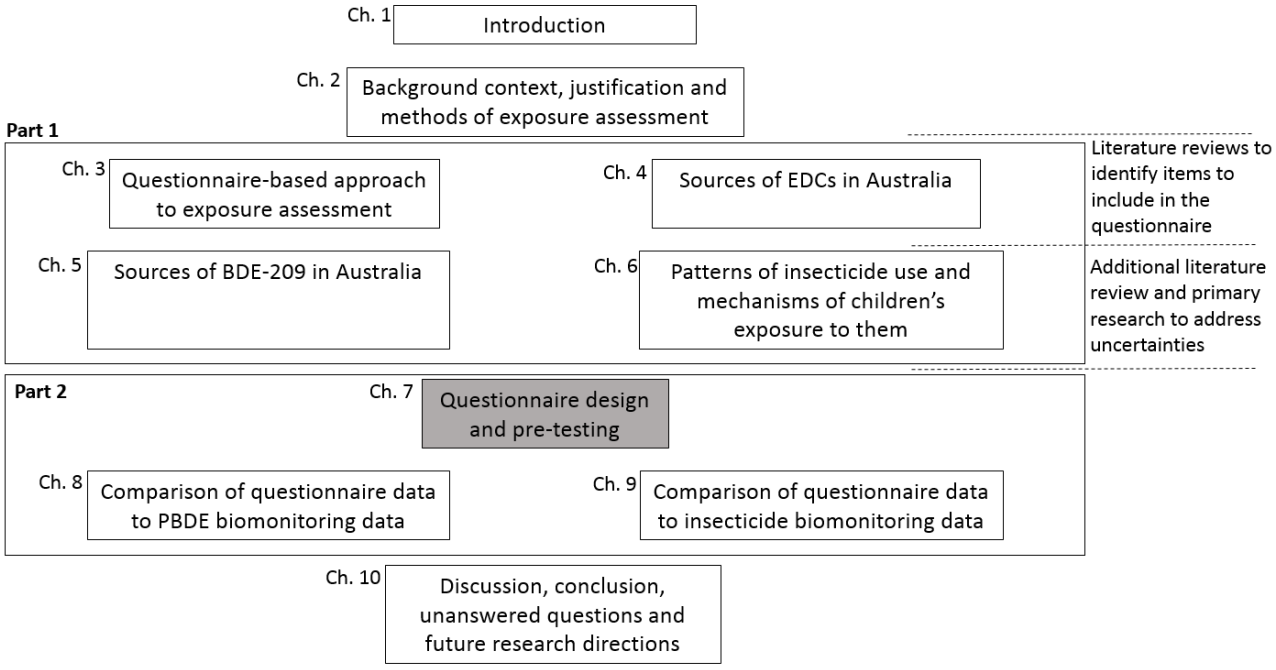


Figure 7-1 Thesis structure: Chapter 7

Once the initial design of the questionnaire was complete, it was pre-tested with a small convenience sample (n=5) of mothers in Brisbane. The questionnaires were pre-tested in a paper-format and online format. The questionnaires were then converted to an online format. The methods employed for pre-testing were qualitative, including verbal feedback on each question as well as the overall questionnaire. The description of this process, in section 7.1.5, is a small excerpt from the published paper, above. The rest of this paper is presented in the following chapter.

The design and methods for the questionnaire-biomonitoring study are provided in the subsequent chapters, which present the results from this study, first for PBDEs, and then for the insecticides.

7.1 Questionnaire design

As previously described, the core steps to consider in the design of *any* exposure-assessment questionnaires are:

- Hazard identification and analysis of the pathway of exposure
- Development of questions targeting critical elements in the exposure pathway
- Development of the questionnaire as a whole.
- Administration considerations

The steps employed in the design of the specific exposure-assessment questionnaire in this thesis followed these principles. Two questionnaires were designed, one predominantly to assess exposure to plastics (BPA and phthalates) as well as flame retardants (questionnaire 1) and one to assess exposure predominantly to insecticides (questionnaire 2). The full step-by-step process was as follows:

1. Hazard identification. Hazards were selected based on set criteria[5] described in Chapter 1 of this thesis.
2. Analysis of the pathways of exposure relevant to the hazard(s) and identification of domains to be assessed in the questionnaire. Domains that had previously been shown to be associated with exposure, as described in Chapter 3, were flagged for inclusion in the questionnaire. Additional domains were identified based on known sources of the contaminant and factors that were identified as potential modifiers of the exposure pathway, as identified in Chapters 4-6.

[5] Known or highly suspected health risk associated with exposure during pregnancy or childhood. Widespread exposure of Australian children to the specific toxicant is likely or known to be the case. The toxicant can be measured in environmental and biological samples. Exposure data for Australian children is currently insufficient

3. Individual question stems and responses were then designed to assess these domains.
4. Question stems and responses were revised to ensure maximum clarity of each question.
5. Individual questions were compiled into two questionnaires (due to the number of questions designed). Plastics and flame retardant questions were initially in the first questionnaire. Questions pertaining mainly to insecticides were compiled into the second questionnaire.
6. Editing of the overall layout and design of the questionnaire. During this process, consideration was given to the length of the questionnaire, the order of question placement - including questions with visual cues, and other aspects such as aesthetics and for the online questionnaires skip-logic and other programming were implemented and tested.
7. The questions and the format of the questionnaire were then informally reviewed by colleagues (Dr Bridget Maher, Dr Peter Sly) and experts (Dr Heather Stapleton, Dr Leisa-Maree Toms) in the area.
8. The questionnaire then underwent pre-testing (described in the next section)

The following section describes in more detail the methodological factors considered at each of these steps and provides specific examples.

7.1.1 Hazard identification

It is necessary to decide, before designing an exposure-assessment questionnaire, 'whether a small number of substances or many substances will be investigated and what the desired exposure-outcome variable is (for example, presence/absence of a substance, or quantitative estimates)' (22). The initial chemical groups considered for inclusion were as follows:

- Plasticisers (BPA, phthalates),
- Flame retardants (PBDEs only were considered. Although organophosphates are now widely used as flame retardants, at the beginning of this study there were scarce published data regarding organophosphate flame retardants)
- Pesticides (including insecticides, herbicides)
- Bioaerosols (moulds, allergens, bacterial products), and
- Combustion-related pollutants (particulates, nitrous oxide, carbon monoxide, polycyclic aromatic hydrocarbons, tobacco smokes).

The final group selected for inclusion, PBDEs, plastics and insecticides (pyrethroids and organophosphates), met all the criteria described earlier: measurable in biological samples, likely widespread human exposure and known/suspected health risk. To limit the total length

questionnaire, the plastics were excluded from the questionnaire-biomonitoring study because the total number of pathways, and therefore the number of questions required, was very large.

7.1.2 Question design

Questionnaire design commences once the hazards and their exposure pathways are identified and characterised. Questionnaire design should occur after this thorough review, to ensure that all important exposure pathways are included. In most cases, it is important to design questions that will collect information on the three determinants of aggregate dose; frequency, intensity, and duration, as well as questions regarding exposure route and ideally questions should be designed based on questions for which the content validity has previously been established (136). The particular type of exposure (i.e. average or peak), that is to be measured may depend on what the final epidemiological research question is. In some cases, all three factors of aggregate dose may not be needed. For example, the frequency of breastfeeding is independent of total daily intake (326). For this thesis, the questionnaire was designed to assess average long-term exposure to the sentinel EDCs.

Once all the critical variables for the questionnaire are identified, construction of individual questions and the questionnaire as a whole begins. There are multiple factors to consider in the overall design of the questionnaire, of which minimising error is paramount. As Biemer and Lyberg write,

> "A reduction in nonsampling errors requires thoughtful planning and careful survey design, incorporating the knowledge and theories of a number of disciplines, including statistics, sociology, psychology, and linguistics."(327).

The type of question, the question wording, response-options and visual cues can all affect question interpretation. Multiple choice questions are common in questionnaires, as they enable more efficient coding than open-ended responses, and they can also aid in recall (328). However, multiple-choice questions can also introduce inaccuracies. For example, multiple-choice questions that require respondents to classify activities into frequency per week may result in inaccuracies if the categories are not appropriate. Despite this, the questionnaire contained only closed-ended multiple choice questions to minimise data cleaning and coding. Participants were provided with multiple comment boxes throughout the questionnaire to provide feedback about individual questions if they were unsure about a particular question or if they wanted to provide additional comments to clarify their responses. In this way, ongoing feedback about the questionnaire was obtained, questions that are difficult for participants to answer were identified, and participant frustration was minimised.

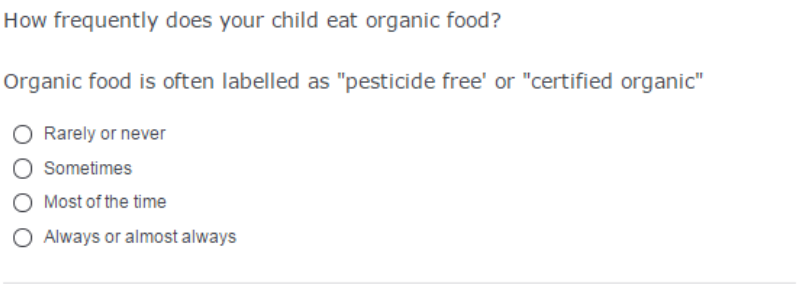
When multiple-choice questions are used, all respondents should have a category that is relevant to them, and the categories should be distinct enough to draw significant differences between respondents, where they exist. This was a particularly tricky aspect of the questionnaire design since behaviours vary significantly between individuals, particularly infants. To include all possible options for each question may result in a questionnaire that is too specific. For example, 'never' was not included as an option in dietary frequency questions, since some children may have tried a food type but then decided not to eat it again or may not have ever tried a food type. 'My baby does not eat this food at the moment' was a more appropriate response to reflect the variations in eating habits of infants and toddlers.


Please indicate how frequently your baby eats the following types of store bought/take-away foods:

	About once a day or more frequently	Several times a week but not every day	About once a week	Less than weekly	My baby does not eat this food at the moment
Lollies	○	○	○	○	○
Chocolate	○	○	○	○	○
Fries/Hot chips	○	○	○	○	○
Sausage rolls	○	○	○	○	○
Pizza	○	○	○	○	○
Burger	○	○	○	○	○

Figure 7-2 Question example: Take away food

Similarly, it is vital to provide question stems that are non-judgemental to prevent bias due to socially desirable reporting. For example, rather than asking the respondent how frequently *they* feed their child organic food (which implies an action or lack of action on the part of the respondent) the question was written without specifying who feeds the child:


How frequently does your child eat organic food?

Organic food is often labelled as "pesticide free' or "certified organic"

- ○ Rarely or never
- ○ Sometimes
- ○ Most of the time
- ○ Always or almost always

Figure 7-3 Question example: Organic food consumption

It was also essential to normalise behaviours associated with chemical exposure as much as possible, to minimise parental distress. This often equated to adding extreme categories of exposure or carefully presenting question responses so that options resulting in exposure came first. For this

reason, the same question (above) was also carefully considered to normalise children 'not' eating organic food.

As previously discussed, in Chapter 3, to minimise misinterpretation question stems must be clear and concise but not so specific as to make recall difficult. Ensuring that the wording is exact and objective may reduce problems associated with incorrect interpretation but can also make it difficult for the participant to answer the question. In the next example, participants were about factors that affect ventilation in the home. Ventilation modifies EDC exposure, as increased ventilation decreases the concentration of some airborne pollutants. Several factors affect patterns of window opening, including the weather, season and whether the participants are at home and at what time of day they are home. These factors are highly variable. Participants were asked about window opening only over the past week so that the information would be easier to recall. The following question regarding window opening also included several words in the question stem to make it easier for participants to answer the question. The word *approximately* and *any* were included to make it easier for participants to generalise, and reduce ambiguity (i.e. participants may have more than one living area, or they were unsure about what counted as a window). The broad categories for the responses also made it easier for participants to find an appropriate response.

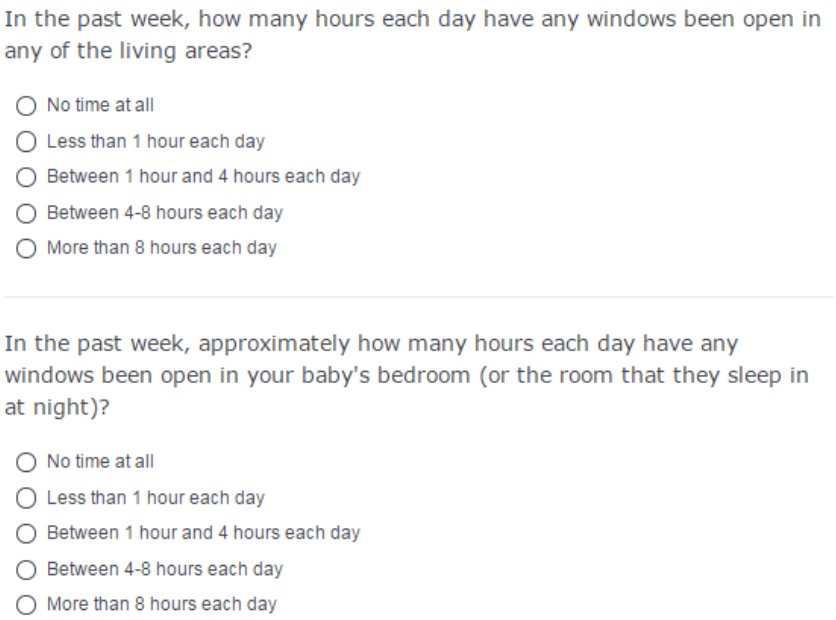


Figure 7-4 Question example: Ventilation

It is also best to avoid questions that ask about relatively insignificant events, particularly if they are in the past, and questions that include calculations, as discussed in the next section of this chapter (165). Respondents may have difficulty recalling insignificant events, thus increasing the burden of the questionnaire, particularly if these events are historical (136). This is particularly problematic

for assessing exposure to toxicants where the exposure route occurs through every day, insignificant event, such as microwaving food in a plastic container, which is important for plasticiser exposure, or when these everyday events occurred several years ago, for example historical seafood intake and maternal PBDE exposure.

7.1.3 Development of the questionnaire as a whole

Beyond the design of specific questions, there are broader factors that are important for questionnaire design. One of the first factors to consider is obtaining questionnaire respondents in the first place and then maximising retention of participants. Dillman advocates that the interaction between researchers and research participants is a 'social exchange' (165). Like any social exchange, acknowledging and rewarding the effort of others can foster goodwill, which can help with recruitment and retention. For example, below is the prompt presented to participants before beginning the questionnaire. The introduction provides instructions on how to complete the questionnaire. It also sets up the context for why we are asking these questions. The phrasing was specifically designed to mimic a typical 'social exchange' (165). 'Your information could really help us' acknowledges the effort of the participant and the importance of the information that they are sharing.

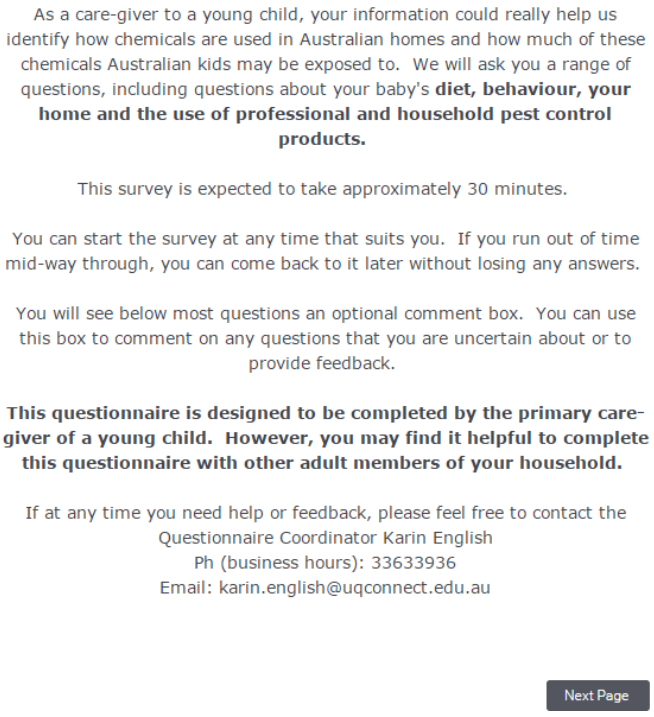


Figure 7-5 Questionnaire example: Introduction

Following the introduction to the questionnaire, participants were immediately asked relatively easy questions about their baby's behaviour, including some questions that were not relevant to exposure

assessment. However, these questions were likely to be interesting to respondents and similar to topics that they may talk about in a typical social exchange, such as whether their baby was talking yet. This question block was placed at the beginning of the questionnaire to engage the participants. More tedious or mundane questions occurred at the end of the questionnaire.

Another critical term described by Dillman et al. is *holistic* questionnaire design, which is an "approach [that] considers what type of question structures best measure the concept of interest, how questions are composed of multiple parts that work together, and how both the words and the visual presentations of questions are important."(165). 'Four types of visual design *elements* communicate meaning to respondents: words, numbers, symbols and graphics.'(165). With the use of a web-based questionnaire, cost does not limit the use of visual elements to enhance the questionnaire. Many basic visual design features aid questionnaire interpretation and information recall. The use of pictures, symbols and grouping of questions can also be used to aid in correct interpretation of questions and recall (165). In the final exposure-assessment questionnaire, questions were broken up into discrete blocks about similar subject matter. The mains blocks included: behaviour, diet and the home environment. Each time the block changed, participants were given a visual cue and introduction to the fact that the topic of questions had changed.

7.1.4 Administration of questionnaires

Other factors to consider in the design of a questionnaire include who is going to administer the questionnaire, the method of administering the questionnaire, how the data is to be collected and collated, and how long the questionnaire is.

An interviewer can administer questionnaires or the questionnaire can be self-administered, including proxy-administered, which was previously discussed in Chapter 3 (328). Questionnaires that are administered by an interviewer may be administered in-person or over the telephone. Questionnaires that are self-administered may be mailed out to the participant, given to the respondent in person (for example at a doctor's office), or conducted online. Self-administered questionnaires are typically the cheapest and easiest. It abdicates the need for interviewer training and for an appointment between the interviewer and respondent to be scheduled and completed. It also frees up the respondent to complete the questionnaire at a time and place that best suits them, for example at home with records that may be helpful for filling out the questionnaire, or with another family member who may help recall specific exposure events. However, completion rates for mailed out questionnaires tend to be lower (328).

One of the advantages of in-person interviews is that they are typically able to go for longer, between 1-2 hours, than either a self-administered questionnaire, maximum of 30 minutes to 45

minutes, or questionnaires administered over the telephone (22). In-person interviews or over the telephone interviews also allows the interviewer to prompt the respondent and help clarify any misunderstandings (328). However, this can also introduce error, since different interviewers themselves may interpret questions differently. An additional advantage of interviewer-administered questionnaires is that they can typically be more complex, with skip patterns that the interviewer is familiar with.

Web-based questionnaires offer the benefits of being faster and cheaper to administer and more efficient and accurate at data collection than either paper-based or interviewer-administered questionnaires. Web-based surveys also enable increased use of sophisticated skip-logic, visual aids, and multiple question types. For these reasons, a web-based platform was selected for this study.

While complex skip patterns may lead to errors in completion of self-administered paper questionnaires, a computer-assisted self-administered questionnaire overcomes this problem. For example, when Ryan et al. compared a computer-based version of the SE-36 General Health Questionnaire to the standard paper-based version, they found that participants completed the electronic version faster, with no errors, which was a significant improvement to the paper-based version, where 44% of the participants had at least one missing response or problematic question (329).

However, there are also drawbacks to web-based surveys. There may be an increased potential for selection bias, particularly where internet access and ability to use the internet is related to potential confounders, such as lower socioeconomic status. However, this issue can be overcome by offering all respondents assistance/training to complete the online survey or offering loan devices (234). With the increased use of web-based surveys respondent 'questionnaire fatigue', particularly in families with young children completing web surveys, has been observed (325). However, careful consideration of potential survey design and implementation to minimise burden may increase response rates (165, 234). In addition, automatic emails, including reminder emails or thank you emails, can be programmed to help reduce non-response rates.

An additional concern with regards to web-based questionnaires is data security. For this specific thesis, a secure online survey platform was selected for administration of the online questionnaires, Qualtrics. Qualtrics was selected for several reasons:

1. Easy to use
2. Wide-range of available question types
3. Advanced, sophisticated programming improves the flow of the survey for participants

4. The availability of an offline application (for iPads) which could be used in areas without wireless internet (or any internet) and taken to study visits
5. Highest level data security

Data from questionnaires administered via Qualtrics is exportable directly to excel, where it can then be stored or imported into statistical software packages. Pre-testing of the exposure-assessment questionnaire

Pre-testing of questionnaires is conducted to ensure that questions are not misunderstood or misinterpreted, that recall error and burden are minimised, and that methods of questionnaire administration are appropriate, user-friendly and reliable (327). During pre-testing a useful exercise is to ask respondents how confidently they can recall the information that is being asked of them. The respondent's self-reported confidence in answering questions may be able to guide the questionnaire design process. If particular questions consistently result in low confidence in recall, then their inclusion should be reconsidered or they should be redesigned to improve recall ability. This has been supported by the findings of Cust et al. - when their study participants reported that they could recall their physical activity with a high level of confidence over the past year, their questionnaire responses correlated better to their accelerometer data (330).

The questionnaire was pre-tested with a convenience sample of women (n=5) with infants under the age of 15 months, residing in urban areas of South East Brisbane, with English as a first language. It was not possible to administer both questionnaires to each study participant, given the length of the questionnaires and one participant was unable to complete the questionnaire at all, giving a final sample size of 4. Participants were provided with the following example prior to the interview:

The aim of my study is to design a questionnaire that can be used to predict exposure to babies to toxins in the home. I am in the early phases at the moment where I am ensuring that the questions are all understood, that all the respondents interpret the questions in the same manner, and that all the closed-ended questions have answers that respondents find applicable to them and that the questionnaire is not too long. The aim of this pretesting is to identify issues with the questionnaire so that the final questionnaire can be made as short and accurate as possible.

You are here today to help me identify problems! As we go through the questionnaire I am going to ask you to talk out loud to explain how you arrive at answers for each question. I will prompt you to explain:

- **What the question is asking**
- **How you are calculating an answer**
- **How you are selecting an answer**
- **How hard you find the question to answer**

An example is displayed below:

Participants question:

15 On an average day, how much time does your baby spend outside?

- Less than 20 minutes
- Between 20 minutes and 1 hour
- Between 1-2 hours
- Between 2 – 3 hours
- More than three hours

Example participants reasoning:

"This question is asking about the amount of time my baby spends NOT in the house. I'm calculating an answer based on the regular activities we do outside. Usually we eat breakfast and lunch outside, which takes about half an hour each. We also hang out the washing almost every day, which takes about fifteen minutes. In the afternoon we play outside for an hour or two. I'm selecting 2-3 hours because some days we don't play outside at all. This question is slightly tricky to answer because some days we spend lots of time outside and sometimes we spend very little time outside"

Figure 7-6 Example prompt for pre-testing of the questionnaire

Participants then completed only one of the questionnaires, see below. Information about individual questions was collected during the interview using the following checklist as well as written notes, where needed:

Table 7-1 Pre-testing of the questionnaire: Cognitive interviewing checklist

	Poor	Medium	Good
Question comprehension			X
Question interpretation			X
Suitability of answer choices		X	
Ease of recall	X		

Table 7-2 Pre-testing questionnaires: Results of general feedback

Participant number	Questionnaires administered	Interviewer remarks	General feedback
1085	Questionnaire 2	This participant was highly educated. The feedback provided was detailed and well-thought out.	Participant liked online questionnaire format. The participant highlighted that some of the questions could not be answered without the partner also present. The questions regarding behaviour needed to be situational (i.e. when does baby suck thumb instead of how long does baby spend sucking thumb each day). The responses to each question needed to be fewer. The responses would be easier if they did not require any calculations and were related to specific activities.
1009	Questionnaire 1	This participant was highly motivated due to an intense interest in reducing chemical exposure	The questionnaire is too long (it was unable to be completed during the study visit). Responses needed to be situational, with less reliance on calculations. Some of the questions were misinterpreted by the participant due to a lack of clarity.
1096	Questionnaire 1		The font was described as too small. There were issues with the skip-logic of the questionnaire (one section was

Participant number	Questionnaires administered	Interviewer remarks	General feedback
			skipped when it shouldn't have been). Some questions lacked clarity. Some questions raised alarm with the participant/were interpreted as being judgemental (organic food consumption). Some of the response options for the frequency of certain behaviours were inappropriate/not ideal for the participant.
1024	(attempted) questionnaire 1		This interview (home-visit) could not take place because the Qualtrics server crashed
1016	Questionnaire 1		Some of the response options for the frequency of specific behaviours were inappropriate/not ideal for the participant. Some of the question stems lacked clarity. Identified that some question banks (i.e. diet) were inappropriate for some children

7.1.5 Revisions following pre-testing

Following pre-testing, the questionnaire was revised to address identified issues. The pre-testing and revision of the questionnaire was carried out in repeated cycles. As Biemer and Lyberg describe, this process needs to be conducted with careful attention paid not to introduce more issues; "For example, modifications to the questionnaire to enhance concept clarity could create additional burdens on the respondent which also increase nonresponse."(327).

Several question types were consolidated into a matrix format (online) to reduce the number of pages of the questionnaire and the perceived number of questions, as participants stated the questionnaire was long. For example, questions about flooring type were consolidated into a matrix. Several questions that may have resulted in excess burden on participants, possibly resulting in recall error, were identified, particularly questions requiring multi-step calculations and estimations. For example, parents were initially asked how much time their baby spent outdoors with categories of times (i.e. 30 minutes to 1 hour/day) for responses, requiring a multistep calculation (all activities their child did outdoors multiplied by the average time for each activity). To reduce the burden, the question was changed to frequency of specific activities that may be done outdoors (i.e. walks taken outdoors, time outside while hanging washing etc.). During pre-testing, the online questionnaire platform was not always accessible - due to local issues with internet connectivity and one instance of the online server being unavailable. Subsequent to this, access to the questionnaire software off-line on a tablet device was obtained at an additional cost of $2000, so that the questionnaire could be administered on this device during study visits if the family elected for this option.

As suggested by participant 1085, a caveat was provided at the beginning of the online pesticide questionnaire to complete the questionnaire with the partner or other adult residents of the home, if needed. The wording of the questionnaire was also changed to ensure that the question stems did

not specifically refer to the 'mother'. This was done to ensure that any adult resident of guardian of the child would interpret the questionnaire as being relevant to them.

Visual stimuli were introduced into the pesticide questionnaire to improve the participants understanding of the question related to insect phobias, see below:

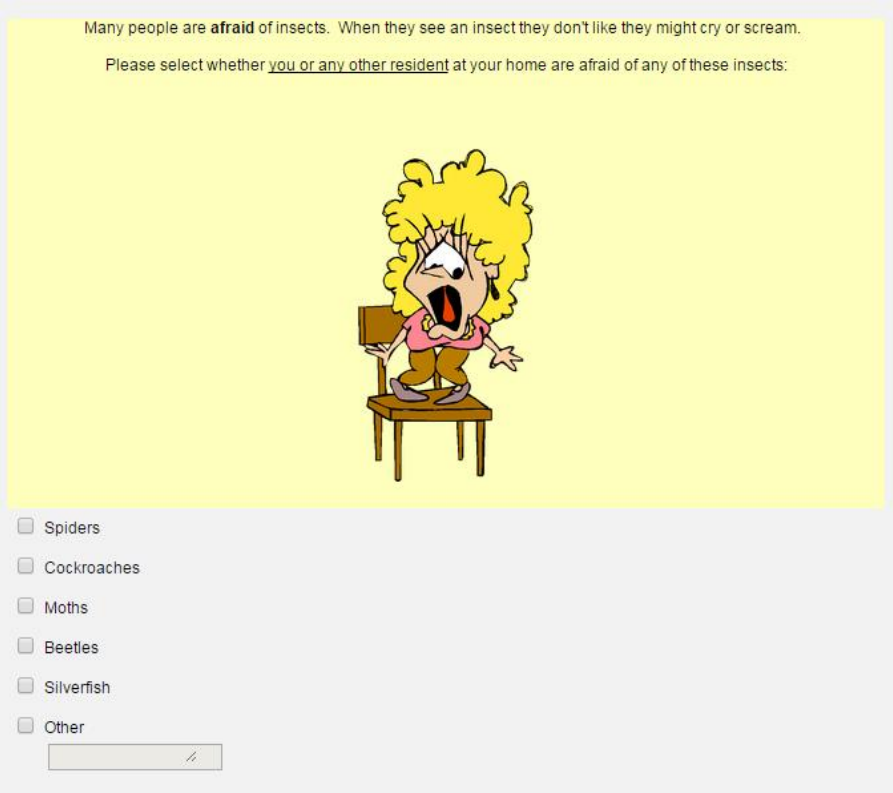


Figure 7-7 Visual stimuli to improve question clarity

Following interviews with participants 1096 and 1016 changes were made to several questions to improve clarity. Changes were made to ensure that participants only had to answer questions relating to diet if their child was eating solid foods regularly.

7.2 Discussion

One of the major issues encountered with the questionnaire was that the total number of questions required to assess the exposure determinants to each of the three groups of chemicals selected in this PhD was very large, resulting in a questionnaire that was excessively long. Therefore, just two groups of chemicals, the PBDEs and insecticides were included in the questionnaire-biomonitoring study. Although questionnaires have been used in both EDC exposure-outcome studies and exposure monitoring studies, there were relatively few questionnaires publically available to aid in the design of the questionnaire for use in this thesis. Additionally, although certain factors, such as hand-to-mouth behaviour are well-known to influence young children's chemical exposure, there was relatively little information available about how best to assess these factors via a questionnaire.

Therefore, almost all of the questions included in the final questionnaire were designed based on the theory and findings presented in phase 1 of this questionnaire, but not necessarily specific questions that have previously been used in exposure-assessment questionnaires. Therefore, the validity of these individual questions, as well as the validity of the compilation of questions that were designed to assessed specific exposure pathways, is unknown.

7.3 Conclusion

Although the questionnaire was designed following a systematic protocol, described in this chapter, since the majority of questions included in the questionnaire were designed *de novo* and based on the limited exposure pathway data available in Australia, the content validity of the questionnaire in this thesis is uncertain. The questionnaire-based approach is likely to be more accurate if

- Exposure pathways have been comprehensively described and are able to be assessed via a questionnaire (as described in the previous chapters of this thesis)
- Numerous questionnaire-biomonitoring studies are available to provide guidance on the validity of specific question types, as was the case with insecticide-related questions.
- The number of relevant exposure pathways to each chemical and the total number of chemicals are not too copious to require a questionnaire that is onerously long. In the case of this thesis, not all chemicals could be included in the final questionnaire because of this issue.

In the following chapters, the results from the questionnaire-biomonitoring study are presented. These findings provide information not only about the content validity of individual questions within the questionnaire, but also additional information about the feasibility of the questionnaire-based approach, including practical aspects, such as acceptability of the instrument and participant burden.

CHAPTER 8 COMPARISON BETWEEN PBDE EXPOSURE-ASSESSMENT QUESTIONNAIRE DATA TO FAECES PBDE CONCENTRATIONS

Karin English, Yiqin Chen, Leisa-Maree Toms, Paul Jagals, Robert S. Ware, Jochen F. Mueller, Peter D. Sly: Polybrominated diphenyl ether flame retardant concentrations in faeces from young children in Queensland, Australia and associations with environmental and behavioural factors. Environmental Research 10/2017; 158:669-676., DOI:10.1016/j.envres.2017.07.022

The following chapter includes the first results for the questionnaire-biomonitoring study, with specific regards to PBDEs. There were two main aims of the questionnaire-biomonitoring studies, including to assess the content validity of the questionnaire and to assess the practicalities of implementing the questionnaire. Descriptive modelling using linear regression was conducted to assess the content validity of the questionnaires (168). The advantage of this approach is for future studies in this area: as question variables that should be retained in the final questionnaire can be identified and the suitability of the questionnaire-based approach to exposure assessment can be compared between the insecticides and PBDEs. However, one of the major limitations of the use of linear regression modelling in this case is that the outcome variable (biomonitoring) is measured with significant error. Whilst statistical methods to address errors in covariates are readily available for regression analysis, statistical methods to account for error in the outcome are less accessible (79). Random error in the outcome variable is expected to increase the imprecision in biomonitoring-questionnaire estimates. In this study, faeces were selected as the biological monitoring medium. Unlike blood, faeces are non-invasive to collect and prior to toilet training, collection of faecal samples via nappies is relatively easy. Although this approach has been studied and compared to serum biomonitoring studies elsewhere, it is relatively new and there were some limitations, which are discussed in more detail in the chapter.

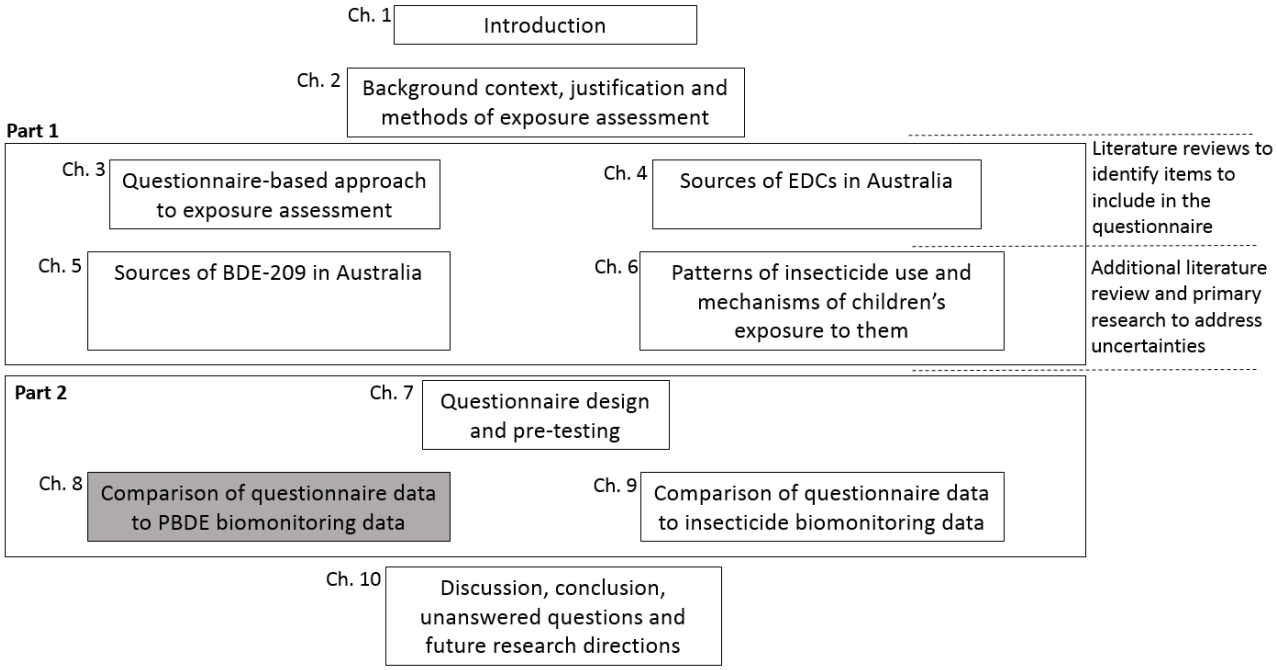


Figure 8-1 Thesis structure: Chapter 8

8.1 Introduction

PBDEs are persistent chemicals that have been used globally in a wide array of goods as flame retardants, particularly electronics, furniture and textiles, and transport applications, although the uses varying considerably by region (331). Historically, PBDEs were available as three major commercial mixtures, c-pentaBDE, c-octaBDE and c-decaBDE, named for the average number of bromines on each molecule. PBDEs are semi-volatile organic compounds that are added to polymers, such as acrylonitrile butadiene styrene and high impact polystyrene, which are used in the manufacturing of a variety of household items (292). PBDEs can migrate from these materials to the indoor environment and the broader environment through direct partitioning, volatilisation (off-gasing) and abrasion of polymers (218, 332, 333). PBDEs are consistently found in dust collected from homes, schools and offices, as well as lipid-dense foods, including dairy, meat and fish (113, 219, 334, 335). In Australia, as well as elsewhere, human exposure is ubiquitous (336).

In 2009, c-octaBDE and c-pentaBDE were added to the Stockholm Convention, over concerns regarding their bioaccumulation potential, persistence, long-range transport and toxicity (337). In contrast, c-decaBDE was initially thought to be relatively stable in the environment and pose minimal risk to human or ecological health, due to low bioavailability, low bioaccumulation and low bioactivity (338). However, BDE-209, the main component of c-decaBDE, has been observed

to undergo photolysis, resulting in the production of multiple lower BDE congeners, and animal and *in vitro* studies demonstrate that BDE-209 itself also exhibits toxic properties, similar to lower PBDE congeners (332, 339-342). Although epidemiological studies assessing the association of BDE-209 with human health are scarce, BDE-209 exposure during infancy has been associated with adverse neurodevelopmental outcomes (343, 344). Proceedings to add c-decaBDE to Annex A of the Stockholm Convention, which will require signatories to eliminate the production and use of c-decaBDE, are now underway (337).

Although the concentrations of some c-octaBDE and c-pentaBDE congeners in human serum and breast milk samples are decreasing, human exposure to PBDEs, particularly c-decaBDE, will continue to occur for decades to come, due to their continued presence in homes and the environment (345, 346). Despite ubiquitous human exposure to PDBEs, there are still many data gaps about how exposure to these chemicals occurs, particularly for young children (347). While several studies elsewhere have assessed PBDE exposure pathways in children through a combined biomonitoring-survey approach to assess potential exposure pathways, the data internationally with regards to BDE-209 are limited, with no such data available in Australia (120, 126, 171, 348-350). Long-term biomonitoring programs are also required for continued health risk assessment and to monitor the effect of regulations and other interventions on human PBDE exposure. However, the 'gold standard' of PBDE biomonitoring, using serum samples, is practically and ethically challenging in young children, therefore limiting the feasibility of this approach.

Our research group has been developing alternative, non-invasive methods, of assessing exposure of individual young children to PBDEs, including through measurement of toxicant concentrations in faeces and survey-based approaches (351). Analysis of PBDEs in faeces and meconium as a marker of internal PBDE body burden in toddlers and newborns has previously been validated by Sahlstrom et al and Jeong et al (350, 352). Significant correlations between congener-specific concentrations in faeces and serum for PBDEs were reported by Sahlstrom et al., including for BDE-209, which was the most abundant congener in faeces. Because of reduced absorption and short half-life of BDE-209, concentrations of BDE-209 in faeces are relatively high compared to serum; Moreover, concentrations of BDE-209 in serum are frequently below the limit of detection, particularly since only small volumes of serum can be obtained from young children (237, 238, 338). Therefore, the use of faecal samples in place of serum samples may overcome some of the analytical challenges associated with monitoring BDE-209 exposure in young children (353, 354). Our group has previously measured PBDE congeners BDE-47, 99, 100, 153 and 154, but not BDE-

209, in faeces, with reproducible results (114). Recently our group published an instrumental method for measuring BDE-209, which we can now apply to faecal samples (283). In this study, we aim to quantitatively assess young Australian children's exposure to PBDEs, including BDE-209, using faeces, and assess biomonitoring-questionnaire associations.

8.2 Methods

8.2.1 Recruitment

A convenience sample of families with children under the age of 2 years at the time of recruitment from South East Queensland, Australia, were recruited to participate in the biomonitoring (provide faeces) and complete an online survey regarding the home environment, diet, and behaviour. Recruitment occurred from April 2015 until April 2016. Participants were recruited from the general public, including via posters in public places and email lists, as well as from enrolled participants in other studies undertaken by our group. After participants consented, they were provided with a sample pack for stool collection, which consisted of a bamboo nappy liner for collection of stool samples and aluminium foil, as well as urine collection packs (for future research purposes), and biological sample bags for secure sample storage. Methods for sample collection and transportation, as well as an analysis of the potential for contamination during sample collection (i.e. from the nappy), which was found to be negligible, have previously been reported in depth by Chen et al (114). Participants were instructed to complete the questionnaire within two days of providing the sample. Samples were stored in secure biological sample storage packs in participant's home freezers prior to collection by the study team and stored at -20^{o} C prior to analysis. Ethics approval for this study was obtained from the University of Queensland, Australia, and the Children's Health Queensland Human Research Ethics Committee.

8.2.2 Analytical analysis

At the laboratory samples were freeze dried faeces and aliquots extracted and purified in a one-step method using 100 mL dionium^{TM} pressurised liquid extraction (PLE) cells and an accelerated solvent extractor (ASE 350, Dionex, Sunnyvale, CA, USA). The following BDE congeners: BDE-28, BDE-47, BDE-99, BDE-100, BDE-153, and BDE-154 were analysed for using a Thermo Fisher 1310 gas chromatography/high resolution mass spectrometer (GCMS), as previously described (114). BDE-209 was analysed using a gas chromatography mass spectrometer (Shimadzu GCMS-QP2010) using a newly published method (164).

In every batch of eight faecal samples, one diatomaceous earth sample was included as a blank and one pooled faeces sample was included to monitor the repeatability of the faecal sample analysis. All concentrations reported were blank-corrected using the median analyte amount in the blank samples. The method limit of detection (mLOD) was defined as three times the standard deviation (STD) of blank samples, while the method limit of quantification (mLOQ) was defined as 10 times the STD of blank samples. All chromatographic peaks were confirmed to have a signal-to-noise ratio greater than 3. The LOD and LOQ for each faecal sample was then calculated by dividing the mLOD and mLOQ by the sample amount. Measures below LOD were imputed as LOD/$\sqrt{2}$; measures between LOD and the mLOQ were imputed as the measured concentrations.

The average recoveries of the labelled standards ranged from 59% - 80% for all chemicals, see table below.

Table 8-1 Quality assurance and quality control for PBDE faeces analysis

Faeces	Internal standard (IS)	Recovery of internal standards (%) (n=40)	Repeatability of quality control samples[1] (n=5)
		Mean ± SD	CV[2]
PBDE28	^{13}C-PBDE28	59 ± 15	51%
PBDE47	^{13}C-PBDE47	63 ± 14	8.5%
PBDE99	^{13}C-PBDE99	80 ± 19	52%
PBDE100	^{13}C-PBDE100	66 ± 23	19%
PBDE153	^{13}C-PBDE153	67 ± 18	26%
PBDE154	^{13}C-PBDE154	77 ± 26	28%
PBDE183	^{13}C-PBDE183	62 ± 28	22%
PBDE209	^{13}C-PBDE209	75 ± 24	27%

[1]: A aliquot of a pooled faecal sample was analysed for each batch for quality control
[2:] CV: Coefficient of variation

All results were adjusted for dry weight (dw) faeces only, as we have previously found higher correlations between dw adjusted concentrations than lipid weight (lw) adjusted concentrations from samples collected from the same children five months apart (164). Serum PBDE concentrations were predicted from measured concentrations in faeces, using the ratio of faeces dw to serum lw concentrations (K_{fb}) reported by Salhstrom et al. (350). The following formula was applied to estimate serum concentrations:

$$Estimated\ mean\ serum\ PBDE\ concentration = faeces\ concentration / k_{fb}$$

8.2.3 Questionnaire

The questionnaire was completed online using a secure online questionnaire software platform (Qualtrics, Provo, UT). Domains of questions included child and maternal behaviour, including hand-washing and hand-to-mouth behaviour (maternal and child), diet (frequency of consumption of individual food items under the following categories: fruits and vegetables, dry snack, dry foods such as grains and cereals, dairy, baked goods, take-away food, and meat and fish), consumer attitudes, features and quality of the home environment, car usage, number of electronics in the home, and type and number of pets in the home. Family sociodemographic (i.e. income, education etc.) information was not collected. The online exposure assessment tool was designed following an extensive literature review of sources of PBDEs in Australia and previous studies that have utilised a combined biomonitoring-survey approach, and is available online (Online Survey) (351, 355). The questionnaire was pre-tested with a convenience sample of women (n=5) with infants under the age of 15 months.

8.2.4 Statistics

Data are described as geometric mean (with standard deviation). Because concentrations of PBDEs in faecal samples were consistently right skewed, data was transformed using the natural logarithm. Congeners reported were restricted to BDE47, BDE153 and BDE209, as the detection frequency for these congeners was >60 % whilst all other congeners had detection frequencies <30%. Correlation between congeners was assessed using pair-wise Pearson's correlation.

The response rate for each variable from the questionnaire was assessed, and variables with a poor response rate (>30% non-response) were candidates for elimination. The distribution of each variable was examined and if there were <5 participants in at least one category the variable's categories were consolidated. The variable 'interested in mouthing any objects' was a composite of two questions, which were designed after extensive feedback during pre-testing of the questionnaire 1) does your baby mouth (suck or chew on) a variety of objects (including hands) or just a few and 2) does your baby like to suck their thumb or fingers.

Bivariate associations were examined between age, behaviour and features of the home with log adjusted faeces dry weight PBDE concentrations using linear regression models. In the initial analysis we wanted to ensure that we did not exclude any potentially significant variables, so we retained variables with significant associations (p-values <0.1) and variables that were *a priori* selected, due to previously identified associations with congener concentrations. The final

multivariable models included variables where p-values remained at <0.05, using the likelihood ratio test. Results were exponentiated to represent the multiplicative per unit change in congener concentrations in faeces for continuous variables, or the change in mean faeces concentrations relative to the reference group for categorical variables. All data analysis was conducted using Stata statistical software v12.0 (StataCorp, College Station, TX, USA).

8.3 Results

8.3.1 Biomonitoring-survey study recruitment

Subsequent to pre-testing of the questionnaire, 61 parent-child pairs were recruited for the biomonitoring/questionnaire study, see Table 8-2. Stool samples were collected from 58 children, but sufficient volumes were only obtained from 46 participants, including 20 (43.5%) girls and 26 (56.5%) boys, and the questionnaire was completed for 60 participants. Participants who were excluded due to insufficient sample volumes were on average significantly younger than included participants (mean age 9.1 months versus 14.4 months; p=0.01) and more likely to be consuming only breast milk (87% versus 43%, p=0.00).

Table 8-2 Age and breast feeding status for study participants

Age	Number	Number with sufficient sample volume (%)	Currently breast feeding (%) *all participants*	Currently breast feeding (%) participants with biomonitoring results only
0 months	24	14 (58.3)	21 (91.3)	11 (84.6)
10 - 18 months	24	19 (79.2)	9 (39.1)	6 (33.3)
>18 month	13	13 (100)	2 (15.4)	2 (15.4)
Total	61	46 (75.4)	32 (52.5)	19 (31.1)

8.3.2 Concentrations in faeces and predicted concentrations in serum

The most abundant congener in faeces was BDE-209, followed by BDE-47, and BDE-153, see Table 8-3. All other congeners were detected in <21% of samples. There was no statistically significant correlation between the concentration of congeners BDE-47, BDE-153 and BDE-209 in faeces. Concentrations of BDE-47 were ten times higher on average in our sample population than those reported by Sahlstrom et al., while concentrations of BDE-153 were similar (350). Average concentrations of BDE-209 were similar between studies, although in the current study the maximum reported concentration was ten times greater. Serum concentrations of PBDEs in the study population were estimated from the faeces concentrations from this study using the faeces : serum concentrations from Salhstrom et al. and the formula described in the methods. The estimated serum concentrations were then compared to the findings from a separate study, which assessed serum PBDE concentrations in pooled samples from children <2 years of age in South East Queensland during the same time period. The derived concentration of BDE-47 in serum was 5 ng/g lw, which is approximately double the actual level that has been reported.

Table 8-3 Summary data PBDE concentrations in faeces (ng/g dry weight adjusted)

	Percent > LOD (%)	LOD range GM[1] (95% CI)	LOQ range GM[1] (95% CI)	Minimum	10th	25th	50th	75th	90th	Maximum	Mean (SD)	Skew
BDE-28	12.5	0.0095 (0.0086-0.010)	0.032 (0.029-0.035)	<LOD	0.0048	0.006	0.011	0.019	0.037	0.074	0.016 (0.015)	2.2
BDE-47	62.5	0.030(0.028-0.033)	0.10 (0.092-0.11)	<LOD	0.032	0.064	0.14	0.33	0.56	1.3	0.23 (0.24)	2.2
BDE-99	20.8	0.027 (0.025-0.030)	0.092 (0.083-0.10)	<LOD	0.018	0.025	0.05	0.071	0.11	0.30	0.061 (0.052)	2.6
BDE-100	2.1	0.065 0.059-0.071)	0.22 (0.20-0.24)	<LOD	0.032	0.040	0.049	0.075	0.120	0.97	0.080 (0.13)	6.4
BDE-153	60.4	0.0011 0.0010-0.0012)	0.0038 (0.0034-0.0041)	<LOD	0.00057	0.0013	0.010	0.028	0.078	0.53	0.031 (0.078)	5.8
BDE-154	0	0.0014 0.0013-0.0015)	0.0046 (0.0042-0.0051)	<LOD	0.00069	0.0008	0.010	0.0012	0.0016	0.0028	0.001(0.0004)	2.1
BDE-183	4.2	0.0014 0.0013-0.0015)	0.0046 (0.0042-0.051)	<LOD	0.00069	0.0008	0.001	0.0015	0.0028	0.11	0.0036 (0.016)	6.9
BDE-209	83.3	0.014 0.013-0.015)	0.046 (0.0042-0.051)	<LOD	0.0079	0.41	1.5	2.4	4.1	320	8.7 (46)	6.9

GM: Geometric mean

Table 8-4 Comparison of PBDE biomonitoring data from the current study n = 46 (ng/g dry weight faeces) to previous studies. Results from Sahlstrom et al. (350). and estimates of serum PBDE concentrations using previously derived faeces:serum ratios (Fc:Bc) compared to results from Toms et al. (unpublished data)

	Faeces PBDE concentrations this study (n=46), prior to log adjustment				**Faeces PBDE concentrations from Sahlstrom et al. (n=22)**					**Predicted serum PBDE concentrations this study (ng/g lw)**	**Pooled serum sample concentrations from 0-2 year olds, 2015 Toms et al. (ng/g lw)**
	% > LOD (%)	Median	Mean	Max	% > LOD (%)	Median	Mean	Max	Fc:Bc	-	-
BDE-28	12.5	0.01	0.02	0.07	0	-	-	<0.01	-	-	-
BDE-47	62.5	0.14	0.23	1.30	100	0.04	0.037	0.14	0.03	5.00	2.3
BDE-99	20.8	0.05	0.06	0.30	0	-	-	< 0.01	-	-	-
BDE-100	2.1	0.05	0.08	0.97	0	-	-	< 0.01	-	-	-
BDE-153	60.4	0.01	0.03	0.53	77	0.02	0.02	0.37	0.03	0.40	1.0
BDE-154	0	0.01	0.00	0.03	NA	NA	NA	NA	-	-	-
BDE-183	4.2	0.00	0.00	0.11	NA	NA	NA	NA	-	-	-
BDE-209	83.3	1.50	8.70	320	100	1.60	2.1	35.0	0.95	1.58	NA

NA: not measured

8.3.3 Association between concentrations in faeces and questionnaire data

Bivariable analysis of concentrations of BDE-47, BDE-153 and BDE-209 in faeces and questionnaire responses yielded numerous associations ($p < 0.1$), which are reported in full in Appendix C. For BDE-47 and BDE-153 as age in months increased concentrations in faeces decreased. Duration of breastfeeding, which has previously been associated with PBDE body burdens, could not be adequately analysed, because of the small size of the cohort and the varied age distribution of the cohort, which included children who were both pre and post-weaning, see Table 8-2 (350). For both BDE-47 and BDE-153, mobility was significantly associated with congener concentrations. In particular, children who were crawling and walking had lower concentrations of congeners in their faeces compared to children who were not mobile (BDE-47 e^{β}: 0.45 CI: 0.19-1.05, BDE-153 e^{β}: 0.15 CI: 0.04-0.63).

The majority of the behavioral and dietary predictor variables associated with BDE-47 and BDE-153 concentrations were also found to be negatively associated with age. Once adjusted for age, the majority of these variables became non-significant. For example, for BDE-47 no variables other than age remained significant in multivariable analysis, see Table 8-5. For BDE-153, the only variable, other than age, retained in the model was the presence of a cat in the home, although the association was of borderline significance ($p=0.05$). Mouthing behavior was also borderline significant in the BDE-153 multi variable model ($p=0.06$), but not retained.

In contrast to BDE-47 and BDE-153, age was not associated with BDE-209 concentrations in faeces. In addition, unlike BDE-47 and BDE-153, BDE-209 concentrations were positively associated with increased mobility, although the associations were not significant. Children who were crawling (e^{β}: 4.96 CI: 0.68-35.92), crawling and walking (e^{β}: 3.45 CI: 0.58-20.57), and walking only (e^{β}: 4.49 CI: 0.71-28.44) had higher concentrations of BDE-209 than children who were not yet mobile. Other variables that were found to be associated with lower BDE-209 concentrations included removing shoes before entering the home, owning the home versus renting, and taking more frequent walks outdoors. However, the use of a sunshade in the car when the weather was hot and owning versus renting the home were the only variables that retained statistical significance in the multi variable model for BDE-209.

Table 8-5 Multivariable analysis for each of BDE-47, BDE-153 and BDE-209. Variables significant at p< 0.05 were retained in the multivariable analysis. P-values are shown for entire categorical variables adjacent to the variable heading.

Congener	Parameter	P-value	e^{β}(CI)
BDE-47	Age in months	0.01	0.93 (0.90-0.97)
R2 = 0.17			
BDE-153	Age in months	0.00	0.88 (0.82-0.95)
	Pet cat in home	0.05	
	No		Reference
R2 = 0.30	Yes		0.34 (0.12-0.99)
BDE-209	Home	0.05	
	Owned		Reference
	Rented		3.91 (1.02 – 14.94)
	Sunshade use in car when weather hot	0.03	
	Yes		Reference
R2 = 0.19	No		4.21 (1.15 – 15.39)

8.4 Discussion

8.4.1 Concentrations of PBDEs in faeces from young children in South East Queensland and a comparison to literature values

In this study sample of young children from South East Queensland, Australia, the most abundant PBDE congener in faeces was BDE-209, with a mean concentration of 8.7 ng/g dw, which accounted for 95.4% of the total concentration of PBDEs in faeces. Similar high proportions of BDE-209 were observed in the study by Sahlstrom et al. (350). BDE-47 and BDE-153 were the next most abundant concentrations, each with average concentrations a magnitude smaller than the previous. Previous studies of PBDEs in faeces conducted in South East Queensland have not measured BDE-209, but have reported similar detection frequencies and concentrations of BDE-153 and BDE-47 (164). In contrast, Sahlstrom et al. reported average concentrations of BDE-47 in faeces from toddlers 11-15 months in Sweden an order of magnitude lower than the levels reported in this study (0.23 ng/dw versus 0.04 ng/dw), but similar concentrations of BDE-153 (0.03 ng/dw versus 0.02 ng/dw) and BDE-209 (8.7 ng/dw versus 2.1 ng/dw) (350). BDE-47 has also been reported as the dominant congener in adult human serum from Australia (i.e. 8.4 ng/g BDE-47 versus 3.3 ng/g BDE-153 in Australia), while in Sweden BDE-153 is more abundant than BDE-47 (i.e. 0.49 ng/g BDE-47 versus 1.52 ng/g BDE-153 in Sweden) (356, 357). Difference in the relative abundance of BDE-47 and BDE-153 in human biomonitoring samples between Australia and European countries may be due to greater use of the penta-BDE mixture in Australia, compared to European countries (356).

8.4.2 Interpretation of estimated serum PBDE concentrations

Faeces PBDE biomonitoring has only recently been described in the literature. Validation studies comparing this novel non-invasive PBDE biomonitoring technique to the traditional method of serum PBDE biomonitoring are scarce. As paired faeces-serum samples were not available in this study, we were unable to directly assess validity in this cohort. Instead, we conducted an indirect assessment, by estimated serum concentrations for the participants in this study and then comparing them to measured serum concentrations from a similar cohort. For both BDE-47 and BDE-153, the predicted serum concentrations were a factor of two from actual concentrations measured in serum pooled from children <2 years of age in South East Queensland during the same period of time. Several variables may have affected the accuracy of predicted serum concentrations, including the small sample size, analytical and sampling error, and the use of a generic Kfb for all participants, regardless of age or weaning status. These variables should be carefully considered in future studies aiming to calibrate faecal PBDE biomonitoring with serum PBDE biomonitoring. The partitioning of persistent pollutants between faeces and blood in infants and toddlers has previously been found to exhibit substantial short-term (i.e. day to day) and long-term intra-individual (across months) variation (164). Previously our group reported that modelled partitioning of BDE-47 between faeces and blood varies considerably during infancy, with the greatest faeces to serum concentrations occurring just prior to the introduction of solid food (i.e. Kfb =1 at 3 months compared to < 0.1 at 10 to 12 months of age) (358). After a peak at 3 months of age, faeces BDE-47 concentrations were found to then decrease with age, which we also reported for BDE-47 and BDE-153 in this present study (358). This finding may be attributable to decreasing PBDE intake via breast milk combined with the effect of dilution of internal PBDE body burdens as the child grows. In contrast, a previous study conducted in Australia in 2006-2007 on pooled serum samples demonstrated that peak PBDE exposure occurs between the ages of two and three years, however, it must be noted that this study was conducted a decade prior to the current study, during which time serum PBDE concentrations from young Australian children have been rapidly declining (113, 347).

As BDE-209 has not been assessed in Australian children, we were unable to assess whether our estimated BDE-209 serum concentration was similar to actual reported concentrations. Because of the low bioavailability of BDE-209 (4-14%), a larger proportion of BDE-209 in faeces may represent recently ingested BDE-209 that has been directly excreted (i.e. external exposure as compared to internal exposure) (338, 359). In comparison, a higher proportion of lower congener PBDEs are expected to reach equilibrium between the intra-luminal intestinal compartment and the

lipid compartment of the body within typical gut transit times, because of their higher bioavailability (~70% for BDE-47 and BDE-153) (338, 359). Furthermore, because of the bioaccumulation of these lower congeners a relatively greater proportion represents long-term body burdens compared to BDE-209. BDE-209 also behaves differently with regards to its transfer to dust compared to other PBDE congeners, as well as being found in higher concentrations in dust than lower congeners (331). Given its low volatility, a major transfer mechanism of BDE-209 to dust is via abrasion of polymers (218). These highly-concentrated particles are heterogeneously distributed, which means that day-to-day exposure to BDE-209 may be highly variable (360). Indeed, Sahlstrom et al. reported that the correlation between faeces:serum concentrations was highest for BDE-153 (0.90), followed by BDE-47 (0.77) and BDE-208 (0.77) and then BDE-209 (0.71) (350). Furthermore, concentrations in serum have been shown to be highly variable in adults over a 6-month period (360). Thus, compared to BDE-47 and BDE-153, BDE-209 faeces concentrations collected from a limited number of samples collected over a short time period (days) may not be an accurate measure of long-term PBDE internal exposure.

8.4.3 Concentrations in faeces and association with conditions and behaviours as reflected in our questionnaires

The dominance of BDE-209 in faeces in this study is expected, as BDE-209 is the most abundant congener in household dust in Australia and ingestion of contaminated dust is the major pathway of exposure of young children to BDE-209 (127, 361). Two studies have previously reported an association between BDE-209 in dust and corresponding concentrations in human adult matrices (362, 363), although others have found no association (335, 364). In this study, we found associations between four variables and BDE-209 concentrations in faeces, which may be acting to modify exposure to BDE-209 via dust. Children who were taken on daily walks had lower BDE-209 concentrations ($p < 0.1$) than those taken on walks once or twice a week or less. Concentrations of PBDEs are greater in indoor media (including dust and air), so time spent outdoors (thus time away from concentrated point sources) may reduce exposure by reducing contact (28). BDE-209 concentrations were also lower in samples from children whose mothers reported removing their own shoes before entering the home ($p<0.1$). Track-in of contaminants from the outdoor to the indoor environment has previously been described as an important contributor to children's exposure to chemicals, such as agricultural insecticides and lead, and is an important source of indoor PBDE contamination in e-waste recycling areas (365, 366). For track-in on shoes to result in relevant increases in household dust contamination, a primary or secondary source proximal to the home is required (367). As previously described, concentrations of BDE-209 can be several fold

higher in dust from cars than in homes (368). Cars, particularly when parked within the home (i.e. in an attached garage) or close to the home could therefore theoretically result in track-in of BDE-209 to the indoor environment.

BDE-209 concentrations were significantly lower in children whose mother's reported regularly using a sunshade beneath the front windscreen to keep the car cooler when the weather is hot, which is a common practice in Australia. PBDE concentrations in cars have previously been found to be associated with temperature and outdoor parking, which suggests that sunshade use may reduce airborne or dust BDE-209 concentrations in cars (369, 370). Previous combined biomonitoring-environmental monitoring studies have shown PBDE concentrations in dust from cars correlates with concentrations of PBDEs in their owner's serum (221, 371). However, biomonitoring-questionnaire studies have previously found no association between factors related to cars (including time spent in the car and age of car) and human exposure (126, 348). In this study, there was a lack of variability with regards to time spent in the car, with the majority of participants reporting that their children spent less than one hour per day in the car. Concentrations of PBDEs in cars are found to vary greatly, even between cars of the same manufacturer and age, making it difficult to account for PBDE concentrations in cars from survey questions alone (368, 372, 373). Exposure to BDE-209 contaminated car dust may also continue after leaving the car, via non-dietary ingestion of dust on contaminated hands and/or other objects or possibly track-in, as discussed above, making total PBDE exposure attributable to travelling in the car potentially independent of time spent in the car. The relative contribution of PBDE contaminated dust from cars to human PBDE exposure could be further assessed by analysing matched house, hand-wipe, car dust and faecal samples using X-Ray Fluorescence microscopy techniques (374).

BDE-209 concentrations were significantly higher in faeces from children who lived in rental homes. Previous reported associations between characteristics of the home environment and BDE-209 concentrations in biological matrices or dust that may also be related to rental homes include: an inverse association between the size of the home and BDE-209 body burden, a positive association between carpet in the home (and its age) and BDE-209 concentrations in dust, as well as an inverse association between increasing frequency of cleaning and BDE-209 body burdens (126, 348). Although we assessed these factors, none were associated with BDE-209 concentrations in faeces. South East Queensland has a diverse housing stock. This heterogeneity and the small sample size meant that we were underpowered to adequately assess the various features of the home environment – particularly those that were rented by participants - that may affect PBDE concentrations in faeces in this cohort. We also considered that rental homes may be more likely to

contain older appliances or electronics, containing decaBDE (355). However, we found no association between the number of appliances in the home and levels of BDE-209 in faeces, but did not take into account the age of the appliances. This absence of association is similar to the findings in other biomonitoring-questionnaires studies, with the exception of the study by Buttke et al., where an association between reported large-screen TV ownership was significantly associated with PBDE body burden (223, 360, 375). Since concentrations of PBDEs in household dust have been shown to correlate with bromine concentrations (a marker of likely PBDE presence) the importance of electronic goods to BDE-209 exposure should not be discounted (222). However, using a questionnaire-biomonitoring approach to assess the association is difficult, given that concentrations of bromine vary greatly between similar goods. Use of additional non-invasive monitoring, such as X-Ray Fluorescence, to account for the concentrations of PBDEs in household goods may be necessary to accurately assess the association between household electronic goods and human exposure through the biomonitoring-questionnaire approach.

For BDE-47, we found that older carpets or carpets of unknown age in the parent's bedroom were associated with higher concentrations in infant faeces. Two studies have previously reported lower PBDE concentrations in house dust when carpets have recently been purchased (143, 376), and several studies have reported positive associations between the presence and extent of carpeting in the home and PBDE body burdens in the home's residents, which may be due to the accumulation of PBDEs in carpets or from PBDE containing carpet underlays (170, 215, 348). In addition, of all PBDE congeners, BDE-47 concentrations in household dust have been most consistently and strongly correlated with markers (i.e. concentrations in hand-wipe, breast milk and serum samples) of children and adults exposure (356). Our group has also previously shown that faeces BDE-47 concentrations correlate closely with matched maternal breast milk samples (114). Therefore, both major routes of exposure of young children to PBDEs (breast milk and dust ingestion) may be affected by carpeting and the accumulation of dust in the home. BDE-153 concentrations in dust have also been correlated with residents exposure markers, but the association tends to be less strong than for BDE-47; Bramwell et al. attributed this to the long half-life of BDE-153 and the greater influence of historic exposures (356). We also found no association between carpeting presence and/or age in any area of the home and BDE-209 concentrations, despite the fact that BDE-209 is the most abundant PBDE congener in indoor dust in Australian homes (BDE-209 0.95 ug/g, BDE-47 0.05 ug/g, BDE-153 0.004 ug/g) and concentrations in dust have previously been found to be associated with carpet age (283, 377). It is possible that our sample size was underpowered to assess this association, but we also hypothesise that the relative importance of

carpet age may be greater for BDE-47 as, once products containing BDE-47 are removed from the home, their major source in the indoor environment may be older carpets. In contrast, BDE-209 is still frequently found in household items in Australia, presenting an ongoing primary source of release to the indoor environment (355).

Mouthing behaviour (interested in mouthing any objects – including fingers - versus not interested) was significantly associated with increased BDE-153 concentrations in faeces in this study (e^{β}: 3.68 CI: 0.96-14.04). Hoffman et al. recently reported higher BDE-47, -99 and -100 serum concentrations in young children who frequently lick their hands while eating, with the effect being modified by the concentrations of corresponding congeners measured from matching hand-wipe samples (348). However, the effect was only significant for BDE-99. Given the relatively small sample sizes of both studies, further research is warranted to assess the role of hand-to-mouth behaviour in PBDE exposure in young children. Finally, for BDE-153 only, we found that having a pet cat in the home was associated with lower concentrations in faeces. This novel finding requires further investigation for confirmation and/or assessment of how this association may be occurring.

8.4.4 Strengths and limitations

This study was the first in Australia to non-invasively assess determinants of children's PBDE exposure via a combined biomonitoring-questionnaire approach, and the first to characterise BDE-209 in biomonitoring samples from young children. Almost all (95%) participants provided stool samples in this study, which suggests that the sampling method was feasible and acceptable in this population. This may be attributable to the study being conducted in children who are not yet toilet trained and are therefore still wearing nappies, which makes sample collection relatively easy. However, 25% of samples were of insufficient volume for analysis, particularly in infants pre-weaning, suggesting that multiple samples are required in this population. This may increase participant burden and may need to be considered if this approach is to be used in the future with children who are not yet weaned. The completion of the questionnaire online by study participants minimised the cost and burden typically associated with administering paper questionnaires to study cohorts. Additionally, error associated with comprehension of the questions and recall burden was minimised by pre-testing the questionnaire. Missing questionnaire data was minimal, despite the length of the questionnaire, as the online questionnaire automatically applied skip logics that participants may have found difficult to follow in paper questionnaires.

Although several unique exposure pathways were presented in this study, which may promote further research and help identify possible interventions to limit PBDE exposure, overall the power

of the study to assess associations between questionnaire data and exposure data was limited. In particular, the study was limited by the small sample size, the sampling protocol (one faecal sample only) and the age range of the study participants, which spanned the period of weaning. There is significant uncertainty surrounding the physiological factors that affect PBDE toxicokinetics during infancy. Metabolism of PBDEs during this period of development has not been well characterised. To better understand metabolism of PBDEs in infancy future studies should analyse PBDEs and their hydroxylated metabolites in both faeces and serum. Given that the questionnaire-biomonitoring approach in this study was novel, it was not possible to conduct an adequate power analysis to determine the ideal sample size. However, this should be considered in future studies.

The questionnaire was designed to assess long-term (i.e. weeks-months) behavioural and dietary trends. While serum concentrations of lower PBDEs remain relatively consistent over this time period, faecal concentrations of PBDEs vary from day to day and the variability in both serum and faeces is even greater for BDE-209 (164, 360). The exposure classification error that would result from only collecting and analysing one faecal sample would affect the accuracy of estimated serum concentrations, as well as the questionnaire-validation process (351). Therefore, to adequately assess the association of questionnaire variables with PBDE exposure, the study should be repeated with a larger sample size, providing pooled samples from several days, and should be restricted to children at the same stage of weaning. Additionally, error could be further reduced by applying newer methods to deal with the issue of concentrations below the LOD. For example, instead of replacing concentrations with the LOD/$\sqrt{2}$, other methods, such as the β-substitution method could be applied (378, 379).

8.5 Conclusion

In the paper presented in this chapter we reported for the first time BDE-209 concentrations in biological samples from Australian children and associations between PBDE concentrations in faeces with behaviour, diet and features of the home. Unlike BDE-47 and BDE-153, BDE-209 was not associated with age. This may be due to the collinearity between age and breastfeeding, a major source of exposure to BDE-47 and BDE-153 but not BDE-209, as well as the child's growth resulting in a dilution of the body burdens of the more persistent (i.e. BDE-47 and BDE-153) PBDEs. Variables that were previously predicted to be associated with PBDE concentrations were not found to be associated with PBDE concentrations in this study. For example, breastfeeding and lipid-dense food consumption were not associated with concentrations of the lower PBDEs and electronic goods in the home were not associated with BDE-209 concentrations. The lack of

association may be due to the small sample size of the study, which made assessing age-related contributors to exposure difficult, as well as error in the biomonitoring approach, which may not accurately represent long-term internal exposure, as well as limitations of using a questionnaire to characterise exposure sources. As previously described, the faeces biomonitoring approach was relatively new. The biological sampling protocol was incorrect for this biomonitoring method and the method, when used as a means of estimating long-term internal exposure, is prone to measurement error. The sampling protocol was designed following the characteristics of serum PBDE concentrations, which is that concentrations are stable over a long-time period. However, compared to serum, concentrations of PBDEs in faeces are relatively variable. Therefore, more faeces samples should have been collected to reduce this measurement error. Furthermore, there still remains a relative paucity of data on the correlation of PBDEs in faeces and serum. Whilst BDE-209 was also affected by these issues, the findings may also have been affected by the design of the questionnaire. As described previously, the major sources of BDE-209 in Australian homes are electronics and electrical appliances, but concentrations vary greatly between similar items. As others have previously found, identifying BDE-209 exposure sources through a questionnaire may not be possible (360). There are no PBDE labelling requirements, so it is impossible to confirm that household items contain PBDEs without additional environmental monitoring. These approaches were not applied in the study, as they were not feasible with the limited resources and time available. In summary, we identified that the questionnaire-based-approach may not be suitable to assessing exposure to PBDEs, particularly BDE-209, primarily because it is difficult to confidently identify sources of PBDEs in the home environment. However, one must also keep in mind that our assessment was limited by the biomonitoring approach that was selected to assess the questionnaire.

CHAPTER 9 COMPARISON BETWEEN INSECTICIDE EXPOSURE-ASSESSMENT QUESTIONNAIRE DATA AND INSECTICIDE URINALYSIS DATA

In the following chapter the results from the analysis of the questionnaire and insecticide biomonitoring data are presented in the form of a paper that is being prepared for publication. This is the first study in Australia to report behavioural and dietary factors associated with biomarkers of insecticide exposure in young children. Unlike PBDEs, methods to measure insecticides in urine samples are more established and there is relatively more known about exposure pathways of young children to insecticides. Prior to commencing the study, it was known that multiple urine samples would be required to accurately assess exposure. Families were asked to collect two urine samples from their child over a 48-hour period. These samples were pooled prior to laboratory analysis, therefore reducing some of the effect of short-term variation. Additionally, although no validated insecticide exposure-assessment questionnaire exists, there have been more studies assessing insecticide exposure via questionnaires compared to PBDEs. Therefore, the design of the insecticide portion of the questionnaire was more sophisticated, as it could draw upon techniques that have previously aided in these studies and also minimise error by avoiding questions that have previously been problematic.

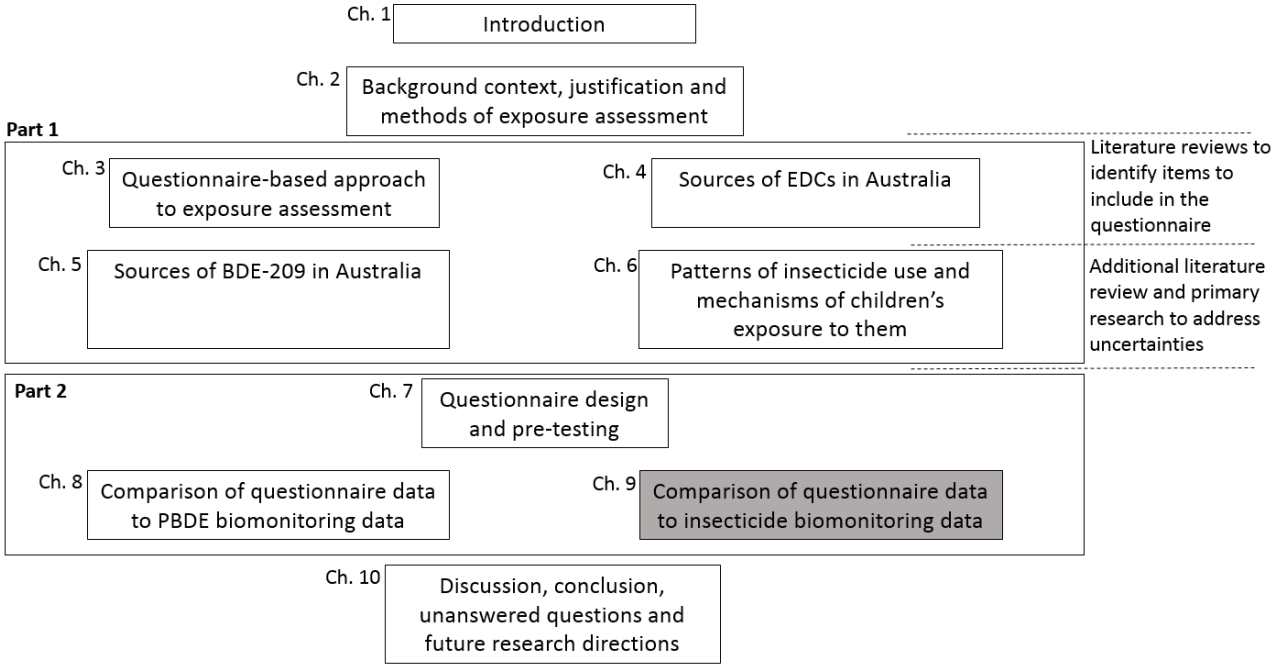


Figure 9-1 Thesis structure: Chapter 9

9.1 Introduction

Young children (infants and toddlers) are at greater risk of both acute (high-dose) and chronic (low-dose) exposure to insecticides than adults. Their different physiological characteristics and behavioural patterns lead to relatively greater exposure; Young children are also more sensitive to toxicant exposure, as their organ systems are immature and still developing (380). The main exposure pathways of young children are shown in Figure 1 below:

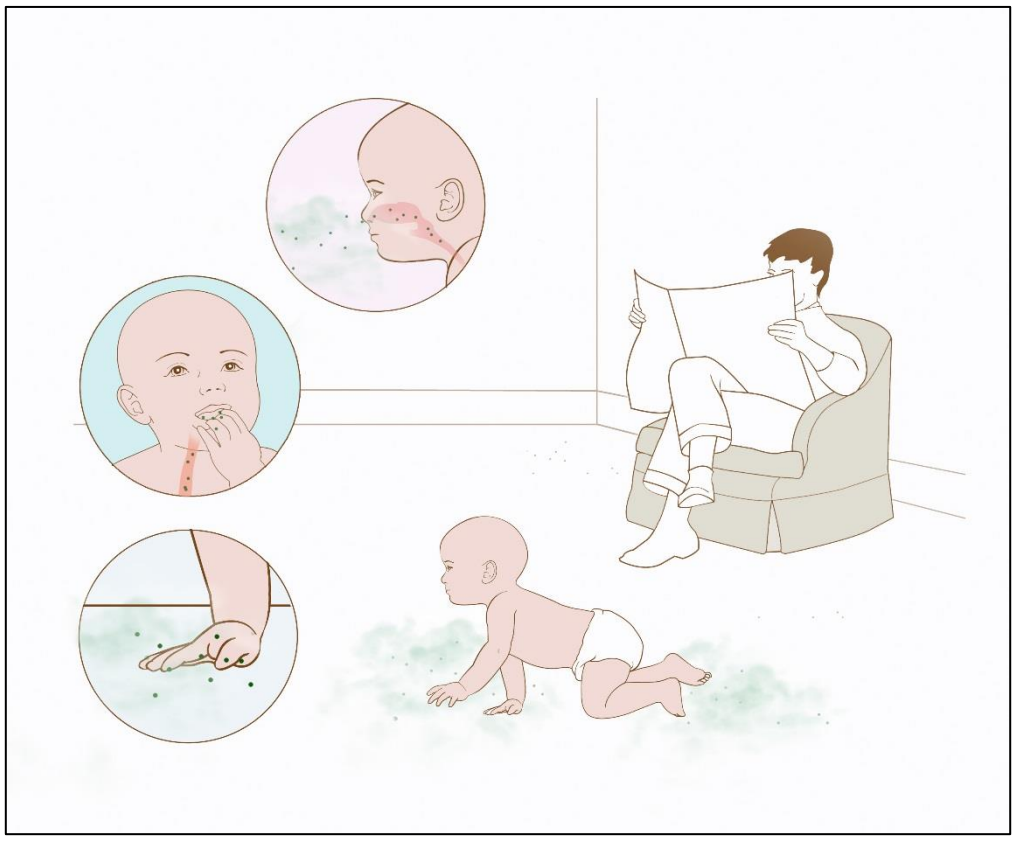


Figure 9-2 Major exposure pathways of young children to insecticides: mechanisms for increased exposure risk relative to adults. Increased exposure via inhalation is attributable to higher concentrations of insecticides found in the infant breathing zone, compared to the adult breathing zone, and the relatively greater intake of air by infants (381). Frequent hand-to-mouth behaviour predisposes infants to greater non-dietary insecticide exposure (232), and the relatively greater consumption of food by infants compared to adults also contributes to greater dietary intake (100). Increased contact with contaminants found on the floor in dust, as well as the greater relative surface area of infants, predisposes to greater levels of dermal absorption (10).

Previous studies have indicated that chronic low-level exposure of Australian children to both OP and pyrethroid insecticides is widespread (115, 117). Although a growing body of evidence implicates low-level exposure to insecticides during early life associated with a variety of adverse health outcomes, particularly adverse neurodevelopmental outcomes (3, 94-96, 100, 382), relatively little is known about how young Australian children are exposed to insecticides. More data are

needed to assess Australian children's exposure to insecticides to characterise the health risk and to identify ways to minimise relevant exposure.

Biomonitoring, the analysis of insecticide metabolite concentrations in urine as a measure of insecticide exposure, has been used with increasing frequency to measure exposure to non-persistent chemicals, including pyrethroid and OP insecticides (137). Biomonitoring has many advantages, of which the most notable is that aggregate exposure to environmental chemicals may be estimated, even when the sources or pathways of exposure to the parent chemical have not been characterised (20). However, multiple urine samples are required to accurately classify long-term exposure to chemicals with short half-lives, including insecticides (159). Although analytical methods for measuring these chemicals in biological samples are well established, sampling methodology to account for this short-term variation in exposure are not (156). In young children, prior to toilet training, special methods for urine collection are required (i.e. paediatric urine bags), which is burdensome to participants, as well as being logistically challenging and resource intensive (137).

As recently reviewed by our research group, exposure-assessment questionnaires could have several applications, particularly to epidemiological studies in young children where biomonitoring is practically challenging, for the reasons described above (351). When administered in conjunction with biomonitoring or environmental monitoring, they may also provide important information about potentially modifiable pathways of exposure to environmental toxicants. Although questionnaires have been used extensively to assess pesticide exposure, to our knowledge, there is no questionnaire that has been specifically designed and validated to assess exposure of young children to insecticides (247). The aim of this study was to assess the feasibility of an insecticide-exposure-assessment questionnaire for assessing young Australian children's exposure to insecticides. Since data regarding children's insecticide exposure are scarce in Australia, a secondary aim was to characterise individual levels of exposure of young Australian children (<3 years) to insecticides and examine how exposure may be occurring.

9.2 Methods

9.2.1 Study Design and Sampling

Participants were recruited from the general public, including via posters in public places and email lists, as well as from studies undertaken by our group. The study was conducted from April 2015 to May 2016 and conducted in urban areas of Brisbane and Toowoomba, located in South East Queensland, Australia. Families with children <2 years of age at recruitment were asked to collect

samples during a 48-hour period using paediatric urine collection bags (U-bag® MABIS Healthcare, Waukegan IL USA), from their enrolled child. Samples were stored in secure biological sample storage packs in participant's home freezers prior to collection by the study team and stored at -20^{o}C at the laboratory prior to analysis. The two urine samples from each individual were pooled prior to analysis. Ethical approval was obtained from the University of Queensland (2015000397), Australia, and the Children's Health Queensland Human Research Ethics Committee (HREC15QRCH40).

The following insecticide metabolites were included in the analysis:

Table 9-1 Insecticide metabolites measured in this study

Abbreviation	Full name	Parent chemical	Chemical class
DMP	Dimethylphosphate	Organophosphate insecticides	Organophosphate
DMTP	Dimethylthiophosphate	Organophosphate insecticides	Organophosphate
DMDTP	Dimethyldithiophosphate	Organophosphate insecticides	Organophosphate
DEP	Diethylphosphate	Organophosphate insecticides	Organophosphate
DETP	Diethylthiophosphate	Organophosphate insecticides	Organophosphate
DEDTP	Diethyldithiophosphate	Organophosphate insecticides	Organophosphate
TCPY	3,5,6-trichloro-2-pyridinol	Chlorpyrifos, chlorpyrifos-methyl	Organophosphate
MDA	Malathion dicarboxylic acid	Malathion	Organophosphate
IMPY	2-isopropyl-4-methyl-6-hydroxypyrimidine	Diazinon	Organophosphate
PNP	*para*-nitrophenol	Parathion; methyl parathion	Organophosphate
4F3-PBA	4-fluoro-3-phenoxybenzoic acid	Cyfluthrin	Pyrethroid
DBCA	*cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid	Deltamethrin	Pyrethroid
3-PBA	3-phenoxybenzoic acid	Cyhalothrin, cypermethrin, deltamethrin, fenpropathrin, permethrin, tralomethrin	Pyrethroid
***trans*-DCCA**	*trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid	Permethrin; cypermethrin; cyfluthrin	Pyrethroid

9.2.2 Urinary metabolites

The method used in this study is modified from Angerer and Hartwig (383) and Olsson et al. (384). The method in full detail is under preparation for publication. Briefly, for the six DAP metabolites

of OP insecticides, 2 mL of samples was spiked with 5 ng of isotopically labelled standards. The samples were then extracted with dried acetonitrile (ACN) and diethyl ether after being freeze-dried overnight. Subsequently, potassium carbonate and pentafluorobenzyl bromide (PFBBr) solution were added into the samples before they were derivatised overnight at 40°C. MilliQ water and *n*-hexane were then added to the derivatised samples before they were mixed on a shaker and centrifuged. The samples were then evaporated under a gentle nitrogen stream to near dryness. After being spiked with the instrument standard ($^{13}C_{12}$-polychlorinated biphenyl 141 in isooctane), the finalised samples were then analysed using a TRACE GC Ultra coupled to a TSQ Quantum XLS triple quadrupole mass spectrometer (Thermo Fisher Scientific).

For the other metabolites, 2 mL of each sample was spiked with 5 ng of isotopically labelled standards. To hydrolyse glucuronide or sulphate conjugated metabolites, β-glucuronidase solution was added into the samples. The samples were then mixed and incubated at 37°C overnight. The extraction process was accomplished via solid phase extraction (SPE) using hydrophilic-lipophilic balance (HLB) cartridges. After filtration, the filtrates were evaporated to near dryness and spiked with the instrument standard. Target compounds were analysed using liquid chromatography (Shimadzu, Nexera UHPLC system, Kyoto, Japan) coupled with tandem mass spectrometry (AB SCIEX QTRAP® 6500+, Ontario, Canada).

9.2.3 Creatinine

Creatinine was analysed using liquid chromatography (Shimadzu, Nexera UHPLC system, Kyoto, Japan) coupled with tandem mass spectrometry (AB SCIEX QTRAP® 5500, Ontario, Canada). Details of creatinine analysis have been published elsewhere (385).

9.2.4 Quality control procedures

Synthetic urine was prepared for use in a quality control (QC) assessment. Low, medium, and high-concentration QC samples (QCL, QCM and QCH) were prepared by fortifying the synthetic urine with target metabolites at three different levels. Non-fortified synthetic urine was used as blank sample. Within each batch of samples that were analysed, one each of QCL, QCM, QCH, and blank samples were also included. Intra-day variability was assessed by processing and analysing duplicate samples within the same batch and inter-day variability of the method was assessed by analysing duplicated QC samples as mentioned above within different batches.

9.2.5 Questionnaire

The design and pre-testing of the online questionnaire has been previously reported and is available online (Online Survey) (386). The questionnaire was pretested with a separate sample of families (n = 5) prior to administration, to minimise error in question interpretation or response. The online exposure tool was self-administered by respondents using Qualtrics (Qualtrics, Provo, UT). The tool included questions pertaining to child-related domains of behaviour, maternal behaviour, consumer attitudes, diet, characteristics of the home, cleaning practices and pets in the home. For mouthing behaviours of the child, the respondent was asked two questions, the first was "does your baby mouth (suck or chew on) a variety of objects (including hands) or just a few?" with responses "1. My baby mouths a wide variety of objects 2. My baby doesn't really mouth objects 3. My baby mouths just a few objects." The second was "does your baby like to suck their thumb or fingers?" and the responses were "1. My baby constantly or frequently sucks their thumb or fingers across any given day 2. My baby will usually suck their thumb or fingers at some point during the day, but not constantly 3. My baby only occasionally or rarely sucks their thumb or fingers, but not on a daily basis 4. My baby does not currently show any interest in sucking their thumb or fingers." In addition, respondents were asked to describe their child's consumption of organic foods "How frequently does your child eat organic food? Organic food is often labelled as "pesticide free' or "certified organic". Parents were then asked pest-control related domains of questions. To minimise difficulty recalling previous pest-control product use participants were provided with visual aids to recall pests (ants, cockroaches etc.) that may have been treated. Furthermore, questions about specific pest products were associated with pictures representative of the product type, to minimise misinterpretation. Due to the large number of questions included in the questionnaire, questions with poor response rates and or poor distribution of responses were eliminated or condensed, as previously described (386).

9.2.6 Statistical Analysis

Summary statistics are presented as median and mean and are presented unadjusted (µg/L) and adjusted for creatinine (ng/g). The distribution of the data were assessed using the skew test and histogram plots. Data were transformed using $\log_e$, after which data were approximately normally distributed. For analysis of insecticide concentrations, measures below the limit of detection (LOD) were replaced with ½ LOD. Pearson's correlation coefficient (with $\log_e$ adjusted concentrations) was used to assess correlations between metabolites from the same and different classes. We assessed whether metabolite concentrations were associated in a linear or quadratic fashion with age using a regression model with the following formula

$$Log\ Concentration = A + \beta_1 * Age + \beta_2 * (Age - Mean\ Age)^2 + \beta_3 * creatinine$$

Associations between biomonitoring and questionnaire data were assessed using linear regression. The analysis was restricted to metabolites with detection frequencies greater than 70%. Age in months and creatinine were included as covariates, as per the recommendation of Barr et al (239). Given the small sample size, exploratory multivariable models were only constructed for PBA. All data analysis was conducted using Stata statistical software v12.0 (StataCorp, College Station, TX, USA).

9.3 Results

9.3.1 Recruitment

A total of 61 parent-child pairs were recruited from suburban Brisbane (n=59) and suburban Toowoomba (n=2). Sufficient sample volumes for analysis and complete questionnaires were obtained from 56 of the participants. There was no difference in age or sex of excluded versus included participants (mean age included 12.9 months, excluded 14.0 months). 85.7% of the participants were consuming solid food regularly. Sociodemographic data were not collected.

9.3.2 Metabolite concentrations and detection frequencies

The metabolites with the greatest detection frequencies were PNP (92.9%), TCPy (89.3%), DMTP (76.8%), DCCA (76.8%), PBA (76.8%) and DMP (75.0%). The highest median concentrations were recorded for TCPy (4.86 ug/L), DMP (2.32 ug/L), PNP (2.07 ug/L) and DMTP (1.20 ug/L). The median concentrations of the pyrethroid metabolites PBA and DCCA were 0.46 and 0.35 ug/L, respectively. Results are shown unadjusted and adjusted for creatinine in the tables below.

Table 9-2 Summary results of insecticide metabolite concentrations in urine (ug/L)

	%LOD	Mean	Min	P5	P25	P50	P75	P95	Max
DMP	75.0%	7.03	0.16	0.16	0.76	2.32	7.80	37.00	50.00
DMTP	76.8%	4.73	0.06	0.06	0.11	1.20	3.10	33.00	56.00
DMDTP	14.3%	0.77	0.48	0.48	0.48	0.48	0.48	3.70	4.87
DEP	37.5%	2.23	0.75	0.75	0.75	0.75	2.72	8.60	11.22
DETP	28.6%	1.41	0.50	0.50	0.50	0.50	1.00	7.05	11.00
DEDTP	7.14%	0.30	0.29	0.29	0.29	0.29	0.29	0.55	0.55
TCPy	89.3%	9.86	0.03	0.03	0.57	4.86	13.64	43.36	48.95
IMPY	19.6%	1.11	0.11	0.11	0.11	0.11	0.11	7.43	15.80
MDA	14.3%	0.06	0.03	0.03	0.03	0.03	0.03	0.26	0.65
PNP	92.9%	2.50	0.15	0.15	1.22	2.07	3.34	6.30	13.67
PBA	76.8	1.30	0.04	0.04	0.10	0.46	0.93	6.27	15.20
F3PBA	7.1%	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
DBCA	7.1%	0.70	0.65	0.65	0.65	0.65	0.65	1.30	1.30
DCCA	76.8%	1.50	0.04	0.04	0.07	0.35	0.87	10.01	17.85

LOD: limit of detection. P5-p95: percentile.

Table 9-3 Summary results of insecticide metabolite concentrations in urine (ug/g creatinine).

	%LOD	Mean	Min	P5	P25	P50	P75	P95	Max
DMP	75.0	12.19	0.30	0.30	0.64	5.99	15.77	45.65	105.71
DMTP	76.8	6.78	0.10	0.10	0.10	2.48	5.64	50.91	53.23
DMDTP	14.3	1.26	0.88	0.88	0.88	0.88	0.88	3.77	8.40
DEP	37.5	4.68	1.39	1.39	1.39	1.39	4.93	18.10	31.85
DETP	28.6	2.50	0.93	0.93	0.93	0.93	1.76	11.37	32.35
DEDTP	7.14	0.56	0.53	0.53	0.53	0.53	0.53	1.02	1.02
TCPy	89.3	15.90	0.05	0.05	1.70	8.68	24.52	70.39	78.95
IMPY	19.6	2.21	0.20	0.20	0.20	0.20	0.20	13.50	24.77
MDA	14.3	0.09	0.05	0.05	0.05	0.05	0.05	0.51	0.92
PNP	92.9	5.62	0.27	0.27	3.18	4.72	6.49	14.04	25.32
PBA	76.8	2.00	0.07	0.07	0.33	0.87	1.84	10.13	21.83
F3PBA	7.1	0.01	0.01	0.01	0.01	0.01	0.01	0.02	0.02
DBCA	7.1	1.27	1.20	1.20	1.20	1.20	1.20	2.41	2.41
DCCA	76.8	2.28	0.07	0.07	0.39	0.75	1.83	11.90	28.13

LOD: limit of detection. P5-p95: percentile.

9.3.3 Correlation between metabolites

The pyrethroid and OP metabolites showed substantial levels of correlation with metabolites from the same class, see Table 9-4. For example, TCPy was linearly correlated with DMP (ρ: 0.66, p <0.001), DMTP (ρ: 0.66, p<0.001), and PNP (ρ: 0.38, p = 0.004). PBA and DCCA were also highly correlated (ρ: 0.90, p<0.001). OP and pyrethroid metabolites were also correlated, however, the association was weaker than between metabolites of the same class.

Table 9-4 Pearson's correlation coefficients for insecticide metabolites

	lnTCPy	**lnDMP**	**lnDMTP**	**lnPNP**	**lnPBA**	**lnDCCA**
lnTCPy	1	-	-	-	-	-
p-value	<0.001					
lnDMP	0.66	1	-	-	-	-
p-value	<0.001					
lnDMTP	0.66	1	1	-	-	-
p-value	<0.001	<0.001				
lnPNP	0.38	0.40	0.40	1	-	-
p-value	0.004	0.003	0.003			
lnPBA	0.51	0.40	0.40	0.52	1	-
p-value	<0.001	0.003	0.003	<0.001		
lnDCCA	0.39	0.34	0.34	0.43	0.90	1
p-value	0.003	0.013	0.013	0.001	<0.001	

9.3.4 Linear regression analysis: questionnaire data and biomonitoring concentrations

When constructing regression models, DMTP was excluded due to the strong correlation between DMP and DMTP. Age (in months) was significantly associated with concentrations of DMP (β:0.10 95% CI: 0.03 to 0.17) and DMTP (β: 0.10 95% CI: 0.03 to 0.17). Age had a quadratic association with TCPy concentrations, with peak concentration occurring at approximately 20 months of age, see Table 9-5 and Figure 9-3.

Table 9-5 Regression analysis of the association of $\log_e$ adjusted insecticide metabolite concentrations and age.

	DMP	**DMTP**	**TCPy**	**PNP**	**PBA**	**DCCA**
Age in months	0.10 [0.03-0.17]	0.10 [0.03-0.17]	0.19 [0.12-0.26]	-0.001 [-0.04-0.04]	-0.000 [-0.06-0.06]	-0.005 [-0.08-0.07]
Age squared	-	-	-0.02 [-0.03--0.01]	-	-	-
Creatinine 10^{-6} ng/mL	1.85 [1.68-3.52]	1.85 [1.69 - 3.52]	2.30 [5.74-4.02]	1.54 [5.69 - 2.51]	3.53 [1.95 - 5.11]	3.36 [1.58 - 5.14]
Constant	-1.43 [-2.39--0.48]	-1.43 [-2.39--0.48]	-1.803 [-2.75--0.86]	-0.19 [-0.71-0.33]	-2.76 [-3.61--1.91]	-2.71 [-3.67--1.76]
R-squared	0.35	0.35	0.59	0.22	0.36	0.28
p-value	0.002	0.02	<0.001	0.001	<0.001	0.001

Linear regression analysis was performed to assess the association between questionnaire data and metabolite concentrations in urine, adjusted for age and creatinine, see Table 9-6 on the following page. Children who were walking regularly had lower concentrations of DCCA in their urine (β: -1.98 95% CI: -3.41 to -0.56). Mouthing behaviours were examined via two variables. In the first, measuring what objects children mouthed, children who mouthed 'just a few objects' had lower concentrations of TCPy in their urine that children who reportedly 'mouthed a wide variety of objects' (B: -1.33 95% CI:-2.41 to -0.25). In contrast, for the second mouthing variable, which asked specifically about frequency of mouthing hands and thumbs, children who exhibited less frequent hand-to-mouth behaviour had higher concentrations of TCPy in their urine. Concentrations of PBA were higher when less-frequent hand-washing was reported (β: 1.63 95% CI: 0.49 to 2.77 for hand washing <1/day versus >3/day).

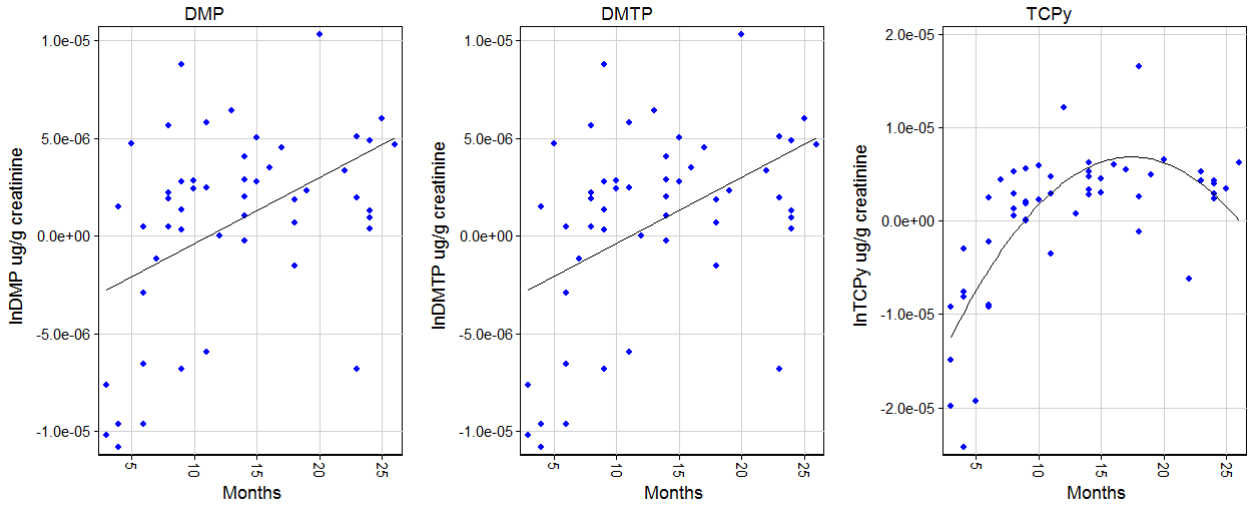


Figure 9-3 Association of log_e adjusted insecticide metabolite concentrations and age

Table 9-6 Questionnaire variables and their association with log_e transformed insecticide metabolite concentrations using linear regression; adjusted for age and creatinine. P-values are given for the variable of interest (i.e. not the whole model)

	N	lnTCPy	lnDMP	lnPNP	lnDCCA	lnPBA
Walking regularly		Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)	Mean difference (95% CI)
No: reference	29	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
Yes	26	-0.41 [-1.92-1.09]	-0.54 [-2.05-0.98]	0.46 [-0.39-1.30]	**-1.98 [-3.41--0.56]**	-1.32 [-2.64-0.01]
P-value		0.99	0.48	0.28	**0.01**	0.05
R2		0.61	0.35	0.23	**0.38**	0.40
Mouthing behaviour						
Mouths a wide variety of objects	37	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
Mouths just a few objects	11	**-0.92 [-1.93-0.10]**	-0.72 [-1.76-0.33]	0.02 [-0.57-0.61]	-0.501 [-1.55-0.54]	-0.55 [-1.47-0.37]
Doesn't really mouth objects	8	**0.82 [-0.47-2.10]**	-0.71 [-1.98-0.56]	0.21 [-0.56-0.98]	0.896 [-0.47-2.26]	0.84 [-0.37-2.04]
P-value		**0.03**	0.27	0.86	0.22	0.15
R2		**0.64**	0.38	0.23	0.33	0.41
Thumb/finger sucking						
Constant or very frequent: reference	7	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
Regular	21	**0.77 [-0.43-1.96]**	0.37 [-0.95-1.69]	-0.53 [-1.28-0.21]	0.15 [-1.24-1.54]	0.54 [-0.69-1.76]
Occasional or rarely	14	**1.63 [0.35-2.91]**	1.40 [0.02-2.78]	-0.62 [-1.39-0.16]	0.06 [-1.39-1.51]	0.50 [-0.77-1.78]
No interest at all	14	**2.24 [0.85-3.63]**	0.82 [-0.69-2.33]	-0.43 [-1.29-0.43]	0.38 [-1.23-1.99]	0.83 [-0.59-2.25]
P-value		**0.01**	0.06	0.26	0.97	0.66
R2		**0.69**	0.42	0.27	0.29	0.38
Hand-washing with soap and water						
> 3 /day: reference	10	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
1-2 / day	23	0.43 [-0.83-1.69]	-0.23 [-1.47-1.02]	0.20 [-0.54-0.94]	1.36 [0.10-2.63]	**1.41 [0.34-2.47]**
<1 / day	19	0.40 [-0.94-1.74]	0.06 [-1.29-1.41]	0.04 [-0.75-0.83]	1.39 [0.03-2.74]	**1.63 [0.49-2.77]**
P-value		0.67	0.82	0.78	0.09	**0.02**
R2		0.64	0.38	0.25	0.41	**0.53**
Organic food consumption frequency						
Sometimes: reference	32	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
Rarely or never	15	-0.46 [-1.45-0.54]	-0.48 [-1.46-0.51]	-0.17 [-0.72-0.38]	0.24 [-0.81-1.28]	-0.04 [-0.97-0.88]
P-value		0.21	0.33	0.53	0.65	0.93
r2		0.40	0.28	0.27	0.23	0.31
Consumption of bread						

	N	lnTCPy	lnDMP	lnPNP	lnDCCA	lnPBA
Less than weekly: reference	8	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
About once/week	8	0.66 [-0.95-2.27]	**1.56 [0.17-2.94]**	0.34 [-0.47-1.14]	-0.57 [-2.18-1.04]	-0.55 [-1.94-0.83]
About three/week	14	0.93 [-0.59-2.45]	**1.95 [0.67-3.23]**	-0.59 [-1.33-0.15]	-0.87 [-2.35-0.62]	-1.21 [-2.48-0.06]
About 7/week or more	17	0.79 [-0.93-2.50]	**2.34 [0.91-3.78]**	-0.26 [-1.11-0.58]	-1.32 [-3.02-0.38]	-1.35 [-2.81-0.10]
P-value		0.20	**0.03**	0.40	0.48	0.42
R2		0.41	**0.44**	0.38	0.28	0.39
Frequency that fruits and vegetables are washed prior to cooking or eating						
Sometimes or never: reference	22	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
Always or almost always	25	0.51 [-0.41-1.42]	**-1.09 [-1.95--0.22]**	-0.05 [-0.56-0.47]	0.43 [-0.54-1.40]	0.60 [-0.24-1.44]
P-value		0.19	**0.02**	0.86	0.38	0.16
R2		0.40	**0.36**	0.26	0.24	0.35
Consumption of vegetables (lettuce, carrots, tomato, potatoes, corn, pumpkin, broccoli, sweet potato)						
Bottom quartile: reference ~4 serves of vegetables/week	16	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
2nd quartile ~13 serves of vegetables/week	15	1.02 [-0.51-2.54]	**0.71 [-0.41-1.84]**	-0.39 [-1.03-0.25]	-0.04 [-1.18-1.11]	**0.08 [-0.91-1.08]**
3rd quartile ~16 serves of vegetables/week	13	0.71 [-0.77-2.18]	**0.97 [-0.17-2.11]**	-0.46 [-1.12-0.20]	0.19 [-1.00-1.37]	**0.18 [-0.85-1.21]**
4th quartile ~21 serves of vegetables/week	12	1.27 [-0.17-2.70]	**1.54 [0.30-2.78]**	0.15 [-0.56-0.86]	1.39 [0.12-2.66]	**1.47 [0.36-2.57]**
P-value		0.28	**0.04**	0.85	0.066	**0.04**
R2		0.62	**0.43**	0.29	0.37	**0.47**
Consumption of fruit (bananas, berries, apples, pears, stone fruit)						
Bottom quartile: reference ~1 serve of fruit/week		0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
2nd quartile ~8 serves of fruit/week		0.96 [-0.53-2.46]	**0.53 [-0.48-1.55]**	-0.01 [-0.66-0.65]	0.59 [-0.58-1.76]	0.73 [-0.31-1.76]
3rd quartile ~11 serves of fruit/week		0.54 [-1.10-2.18]	**2.11 [1.00-3.22]**	-0.19 [-0.91-0.53]	0.63 [-0.65-1.91]	0.36 [-0.78-1.49]
4th quartile ~18 serves of fruit/week		1.15 [-0.38-2.68]	**1.00 [-0.11-2.11]**	0.06 [-0.66-0.79]	1.06 [-0.24-2.35]	0.98 [-0.16-2.13]
P-value		0.46	**<0.001**	0.81	0.23	0.44

	N	lnTCPy	lnDMP	lnPNP	lnDCCA	lnPBA
R2		0.62	**0.52**	0.23	0.32	0.41
Frequency of use of pest-control sprays during the summer months						
Less than once a week: reference	43	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
Once a week or more	13	**1.05 [0.16-1.94]**	0.20 [-0.76-1.16]	0.50 [-0.02-1.01]	0.77 [-0.18-1.72]	**0.91 [0.09-1.74]**
P-value		**0.03**	0.68	0.06	0.12	**0.03**
R2		**0.63**	0.35	0.28	0.32	**0.42**
Pet dog						
No dog: reference	41	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
One or more dogs	15	-0.13 [-1.03-0.78]	0.32 [-0.60-1.24]	-0.01 [-0.52-0.50]	**1.16 [0.29-2.04]**	**0.96 [0.16-1.73]**
P-value		0.60	0.49	0.98	**0.01**	**0.02**
R2		0.59	0.35	0.22	**0.38**	**0.43**

Dietary factors that were assessed due to their potential to modify dietary intake of insecticides included individual food items, as well as consumption of organic food, store-bought food and washing of fruits and vegetables prior to cooking or eating. Following a very limited number of participants reporting consuming exclusively organic food diets, this response was not examined individually, and participants were subsequently divided into groups who ate organic food sometimes or more frequently, versus rarely or never. There were no significant associations between organic food consumption and insecticide metabolite concentrations. Higher frequency of washing fruits and vegetables was associated with lower DMP concentrations (β: -1.0 95% CI: -1.95 to -0.22). Dietary variables were examined by quartile of consumption. More frequent consumption of bread was associated with higher concentrations of DMP in children's urine (B: 2.34 95% CI:0.91-3.78 for at least 7 serves/week or more versus <1 serve /week). Greater consumption of vegetables (sum of the total intake of lettuce, carrots, tomato, potatoes, corn, pumpkin, broccoli, sweet potato) was associated with higher concentrations of DMP (β: 1.54 95% CI: 0.30 to 2.78) and PBA (β: 1.47 95% CI: 0.36 to 2.57) in children's urine. Higher consumption of fruit (sum of the total intake of bananas, berries, apples, pears, stone fruit) was associated with higher concentrations of DMP in children's urine (β: 1.00 95% CI: -0.11 to 2.11).

Pest-control practices in the home were also examined. Increased frequency (once a week or more versus less than once a week) of use of pest-control spray products was significantly associated with both the chlorpyrifos metabolite TCPy concentration (β: 1.05 95% CI: 0.16-1.94) and the generic pyrethroid metabolite PBA concentration (β: 0.91 95% CI: 0.09-1.74). Other pest-related questions, including pest-product use patterns, use of a professional pest-controller, attitude towards pests in the home, pest phobias, and whether respondents perceived that pests were a problem in the home were not significantly associated with any of the metabolite concentrations. Presence of a dog in the home was associated with increased concentration of DCCA and PBA in urine (DCCA β: 1.16 95% CI: 0.29-2.04, PBA β: 0.96 95% CI: 0.16-1.73). We assessed several variables associated with housing characteristics and quality. Increasing age of the home was positively associated with concentrations of TCPy in urine, but the association was not significant. There was no association between flooring types in the home, cleaning practices and biomonitoring results. No indicators of the quality of the home, including peeling paint, water damage, etc. were associated with insecticide metabolite concentrations.

Additional multivariable modelling was conducted only for PBA, a generic pyrethroid metabolite, to account for determinants of exposure: season and organic food consumption. We assessed whether PBA was associated with metabolite concentrations in urine after adjusting for these

potentially confounding variables. The base model included the variables previously identified to be significantly associated with PBA concentrations, including a dog in the home, frequency of pest-product spraying, vegetable consumption and hand-washing with soap and water, see Table 9-7. The base model explained 71% of the total variability in PBA concentrations. Only season was observed to have a significant association with PBA concentrations in the multivariable model, with significantly higher concentrations of PBA being recorded when sampling occurred during spring or summer compared to winter or autumn (β: 0.88 95% CI: 0.32-1.44). Once season was added to the model, the total variability explained was 77%.

Table 9-7 Multivariable modelling $\log_e$ PBA. Initial base model (all variables in the base model were significant at $p < 0.05$): creatinine, vegetable consumption, pet dog, pest-spray frequency, hand-washing with soap and water.

Variable	Base Model	Season	Organic Food
Creatinine ($\times 10^{-6}$) ng/mL	5.02 [3.80-6.25]	4.89 [3.78-5.99]	4.43 [3.19-5.66]
Pet dog			
No dog: reference	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
One or more dogs	0.73 [0.07-1.38]	0.75 [0.16-1.34]	0.80 [0.14-1.45]
Frequency of use of pest-control sprays during the summer months			
Less than once a week: reference	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
Once a week or more	0.88 [0.22-1.54]	0.95 [0.35-1.54]	1.08 [0.39-1.76]
Hand-washing with soap and water			
> 3 /day: reference	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
1-2 / day	1.29 [0.41-2.17]	1.25 [0.46-2.04]	1.12 [0.31-1.94]
<1 / day	1.69 [0.76-2.61]	1.28 [0.41-2.15]	1.06 [0.12-1.99]
Consumption of vegetables (lettuce, carrots, tomato, potatoes, corn, pumpkin, broccoli, sweet potato)			
Bottom quartile: reference ~4 serves of vegetables/week	0.00 (ref.)	0.00 (ref.)	0.00 (ref.)
2nd quartile ~13 serves of vegetables/week	-0.04 [-0.87-0.78]	-0.09 [-0.83-0.65]	-0.89 [-1.91-0.13]
3rd quartile ~16 serves of vegetables/week	0.00 [-0.87-0.87]	-0.03 [-0.81-0.75]	-0.83 [-1.86-0.20]
4th quartile ~21 serves of vegetables/week	1.11 [0.20-2.01]	0.90 [0.08-1.72]	0.00 [-1.13-1.13]
Season			
Winter and Autumn: reference	-	0.00 (ref.)	0.00 (ref.)
Spring and Summer	-	0.88 [0.32-1.44]	1.00 [0.39-1.60]
Organic food consumption frequency			
Sometimes: reference	-	-	0.00 (ref.)
Rarely or never	-	-	-0.07 [-0.77-0.62]
Constant	-5.29 [-6.49--4.10]	-5.51 [-6.60--4.43]	-4.40 [-5.87--2.93]
R-sqr	0.71	0.77	0.77
p-value (model)	<0.0001	<0.0001	<0.0001
p-value added variable		0.003	0.83

9.4 Discussion

In this study we report associations between environmental, behavioural and dietary factors associated with insecticide metabolite concentrations in urine from young Australian children. Organophosphate concentrations, but not pyrethroid metabolite concentrations, were associated with age (186). DMP and DMTP were linearly positively associated with age in months, but TCPy appeared to peak at around 20 months of age. These findings suggest that, with the exception of chlorpyrifos, peak childhood insecticide exposure to organophosphates may not have been captured by the age range included in the study (<2 years at recruitment). However, since our research group has previously reported that concentrations of insecticide metabolites are higher in samples collected from children aged 0-4 years of age compared to adults and older children, the age group included in this study is still likely to have relatively high exposures compared to older adults and older children (117).

9.4.1 Non-specific organophosphate metabolites

Exposure determinants varied between the insecticide metabolites. For the non-specific OP metabolite DMP consumption of bread, fruits, and vegetables was associated with urinary concentrations. Elsewhere, consumption of fruits or vegetables has been associated with OP and pyrethroid metabolite concentrations in urine from adults and children in several countries, including the US (185, 188, 193, 387), Germany (116), Chile (189), France (388) and Spain (389). The positive association between concentrations of DMP with age may by explained by increasing dietary solid food intake that occurs following weaning. In addition, increased frequency of washing of fruits and vegetables prior to cooking or eating was associated with lower DMP concentrations. Experimental studies have demonstrated that washing fruits and vegetables in tap water is associated with a significant reduction of 30-40% of insecticide residue concentrations (390, 391). These findings demonstrate that to estimate insecticide exposure from questionnaires it is necessary to consider not just the types and amounts of foods that are consumed but also cooking practices.

9.4.2 PNP

No questionnaire variables were associated with PNP concentrations in this study. Parathion use was completely phased out in 2011, prior to this study (392). Ongoing parathion exposure therefore supports previous research demonstrating persistence of parathion in the indoor environment (393).

9.4.3 TCPy

In this study, chlorpyrifos was the only OP insecticide with a specific metabolite (TCPy) that was measured above the limit of detection at a high frequency (89.3%). Chlorpyrifos residues are known to occur on fruits and vegetables in Australia (280). However, while increased consumption of fruits and vegetables was associated with higher TCPy concentrations, the association was non-significant. This may be attributable to measurement error in the questionnaire, such as condensing all fruit and vegetable items into just two variables, despite the fact that chlorpyrifos concentrations may vary considerably between individual food items. Additionally, there may have been other unaccounted for sources of variation in TCPy concentrations. TCPy concentrations were also associated with reported pest-spray use in the home and mouthing behaviours, suggesting a contribution from non-dietary sources of exposure to the observed variation in TCPy concentrations. Paradoxically, TCPy concentrations were higher when children were reportedly interested in mouthing fewer objects and their mouthing behaviour was less frequent; It is possible that these associations are confounded by age. Chlorpyrifos is not available in any domestic spray-products, so the association between reported pest-spray use in the home and TCPy concentrations is unexpected. This finding may be due to chance or confounding. For example, households frequently using spray products may also use other chlorpyrifos containing products, such as some garden products, more frequently. Alternatively, some determinants of chlorpyrifos may have been omitted from the exposure-assessment questionnaire. For example, elsewhere, chlorpyrifos concentrations in household dust have been found to correlate with reported termite and garden treatments at the home (394). Furthermore, insecticides can persist in the indoor environment for years (395). In this study, termite treatment was not specifically assessed, pest-control product use over only the past 12 months was assessed, and the sample size was too small to assess the association between reported garden insecticide use and biomonitoring data, which may explain why few questionnaire variables were found to be associated with TCPy concentrations.

9.4.4 PBA

Both dietary and several non-dietary variables were associated with pyrethroid metabolite, particularly PBA, concentrations. In multivariable modelling, a relatively high amount of the total variability (77%) of PBA concentrations was explained by these variables. Of the dietary variables, only vegetable intake was associated with PBA concentrations. The relatively greater influence of non-dietary exposure factors may explain why, unlike the OPs, age was not associated with metabolite concentrations. Non-dietary variables associated with PBA concentrations included frequency of domestic pest-spray product use in the summer months, season, a dog in the home, and

frequency of hand-washing. Elsewhere, pest-product use at home has also been associated with increased concentrations of both organophosphate (389) but particularly pyrethroid (116, 187, 388) metabolites in children's urine, depending on the country, local regulations and therefore the insecticides commonly found in consumer pest-control products.

Despite the relatively small size of the study, we were able to assess the association of pest-spray product use and biomonitoring concentrations because of the relatively high frequency of use of these products. At least 40% of respondents had used a pest-control spray product in the past twelve months and 23% of participants used a pest-spray product at least weekly during the summer months. This frequency of use is similar to the relatively high frequency of pest-control product use reported in Florida USA (133) and higher than levels reported in the UK and other areas of the US (246, 396). The similar high frequency of use may be attributable to the hot, humid climates in both Queensland and Florida associated with a higher pest burden. Insecticide exposure has previously been shown to vary seasonally, which has been attributed to seasonal variation in the availability of fresh fruits and vegetables as well as differences in frequency of application of domestic pest-control products (197, 249, 280). Insecticides that are applied in the domestic environment distribute to air and dust and are able to persist in the indoor environment (248, 394). Ongoing exposure of young children to insecticides that have been used in the domestic environment occurs predominantly via dermal absorption and non-dietary ingestion of household dust (7, 197, 388). Other factors that may modify insecticide concentrations in dust or contact with dust may therefore also affect children's insecticide exposure. For example, the association between higher PBA concentrations and the presence of a dog in the home may be explained by the fact that flea treatments and track-in of insecticides from outside the home by the dog lead to higher indoor dust insecticide concentrations (116, 233, 395, 397). The association between increased hand-washing frequency and decreased PBA biomonitoring concentrations observed in this study is likely due to increased hand-washing decreasing the duration and intensity of contact with insecticides in household dust.

9.4.5 Strengths and limitations of the study

The main strength of this study was the rigorous design and online format of the questionnaire. The questionnaire was designed following extensive literature reviews and primary research to identify insecticides that families are likely to be using in their homes, and the questionnaire was pre-tested prior to use, as previously described (386). To minimise error associated with question interpretation, we used several visual cues to clarify pest-control related questions. We also included questions with visual cues about treatment of specific insects, to trigger participant recall

of when pest-control products had last been applied. However, one of the main challenges with the design of the questionnaire was that data on insecticide use in Australia and human exposure pathways were relatively limited. As previously described, some important determinants of exposure may have been excluded from the questionnaire.

One of the main limitations of the study was that the questionnaire asked about behaviours over a period of weeks to months, whilst urine biomonitoring of insecticide metabolites only captures exposure in the order of hours to days (398, 399). Given that collecting urine samples from young children is practically difficult, parents were asked to collect just two urine samples from their child, although the ideal number for adequate exposure measurement is unknown (400). There was also an additional level of heterogeneity due to the study age group, since it included children pre and post-weaning. Limiting the study to children post-weaning may have reduced some of the variation. Another limitation of urine biomonitoring in young children is the difficulty of standardising concentrations to account for difference in urinary dilution. Heffernan described a urine flow method, which also has the advantage of enabling rapid calculation of estimated total daily intake, as well as excretion (118). However, the urine flow model lacks sufficient parameter information for children in the age group in this study, and therefore could not be applied. Urinary excretion rates can also be calculated by multiplying the concentration of a contaminant in urine by the total volume of one urinary void and then dividing it by the time since the last void (401). However, this is not practical in young children who are not toilet trained. Although creatinine is the most widely used method of standardising contaminant concentrations in urine, particularly in adult biomonitoring studies, the production of creatinine is more variable in young children (239). We therefore presented summary results unadjusted and adjusted for creatinine and in the multivariable models creatinine was included as a covariate. Another limitation of the study was the small sample size, which meant that some variables, such as organic food consumption, which is known to be an important determinants of dietary insecticide exposure (388, 402-405), could not be examined due to poor response distributions. Furthermore, some weak associations between exposure factors measured through the questionnaire and biomonitoring results may not have been detected and, conversely, some reported associations are likely to be spurious.

9.4.6 Future research directions

This study demonstrated that domestic pest-control practices and insecticide residues on food are likely to be the major contributors to young Australian children's insecticide exposure. However, more data in Australia is needed to better understand these sources of insecticide exposure. Specifically, more data is needed on insecticide usage patterns and insecticide residues on food.

This data is not only informative to exposure risk assessment and the design of the exposure-assessment questionnaire, but this data may also be combined with exposure-assessment questionnaires to improve their predictive capacity. For example, matrices of the insecticides commonly found in pest-control products can be used to better estimate exposure to specific insecticides from pest-control products (406), while combining food frequency questionnaire data with food surveillance data can improve dietary exposure estimates (387, 403). In this study, the value of the questionnaire-based approach for identifying important determinants of exposure was demonstrated. Validation studies to determine the accuracy of the questionnaire-based approach are warranted, given the utility that this approach would have for children's insecticide exposure assessment.

9.5 Conclusion

In the manuscript presented in this chapter we reported for the first time behavioural and dietary factors associated with biomarkers of insecticide exposure in infants and toddlers in Australia. Unlike PBDEs, the findings from the analysis of questionnaire-biomonitoring data for insecticides were concordant with previously predicted associations. Several factors were associated with insecticide metabolite concentrations, including diet, age, mobility, hand-washing frequency, frequency of pest-product use in the home environment and season. This agreement suggests that the findings in this study reflect actual exposure patterns, and are less likely to be due to chance. This study demonstrated that the questionnaire-based approach may be feasible when exposure pathways are known and relatively straightforward (not too numerous or complicated) and sources of exposure can be confidently identified via a questionnaire. In summary, given the findings presented in this chapter, a larger validation study of the insecticide exposure-assessment questionnaire is warranted, given that a validated insecticide-exposure-assessment questionnaire would have great utility in epidemiological studies in this area.

CHAPTER 10 DISCUSSION AND CONCLUSION

10.1 Introduction

Despite widespread domestic exposure of Australian children to the EDCs in this study, epidemiological studies to assess exposure-outcome associations for these chemicals are limited in their number and scope in Australia – the intensive resources required to characterise exposure using the current gold standard biomonitoring may be one of the main reasons for this. As previously described, the main limitations of biomonitoring and, therefore, the motivation for this study, include the difficulty of collecting biological samples from young children, the fact that multiple biological samples are required to characterise long-term exposure to chemicals that have variable exposure patterns and rapid metabolism, the expense of analysing samples and that resource intensive sampling and analytical methods are required to minimise contamination when the toxicants occur throughout the environment. These factors limit the applicability of biomonitoring to large-scale epidemiological studies.

In the first section of this chapter, each of the key principal findings with regards to the assessment of the feasibility of the questionnaire-based approach to exposure assessment are discussed, including the implications and recommendations of these findings with regards to the use of the questionnaire-based approach for exposure assessment. These findings are provided in the context of the literature reviews and primary research that were conducted prior to the design of the questionnaire, as well as the results of the questionnaire-biomonitoring study. The strengths and limitations of the study and how these impacted on the feasibility assessment of the questionnaire-based approach to exposure assessment are then discussed. The main conclusions of the thesis are then presented, including suggestions for areas of future research.

10.2 Finding One: a scarcity of data on exposure pathways affects the content validity of the exposure-assessment questionnaire

10.2.1 Introduction

The questionnaire-based approach to exposure assessment is not suitable when data on exposure pathways are scarce. Unfortunately, this may affect the applicability of exposure-assessment questionnaires to emerging contaminants – chemicals that have only recently been implicated in human exposure or human health risk and for which the human exposure-pathways are not well characterised. In this study, the design of the questionnaire was hindered by the lack of data regarding exposure pathways to the EDCs in Australia. In particular, as described previously, the

largest gaps included data on sources of PBDEs and plastics in Australia, patterns of insecticide use in homes and concentrations of all of the EDCs in food.

10.2.2 Justification

For example, consider the scarcity of data on insecticide residue contamination levels on foods. Although diet is expected to be a major contributor to young Australian children's insecticide exposure, in Australia, publically available food surveillance data are limited. Elsewhere, food surveillance data from large monitoring programs are publically available and this data has be used to improve the exposure estimates derived from the questionnaire-based approach, see section 10.8.2 (407). A scarcity of exposure pathway data affects the exposure-assessment questionnaire in two main ways:

1) Possible omission of major determinants of exposure, such as the omission of important dietary sources of insecticides that may have occurred in this study
2) Inappropriate reduction of individual questionnaire variables into summary variables, such as the reduction of fruits and vegetables into two summary variables: quartile of intake of fruit and quartile of intake of vegetables, as occurred in this study.

Measurement error attributable to these issues may have contributed to the lack of significant association that was reported between dietary variables and the chlorpyrifos metabolite TCPy in this study, see section 9.4.3 TCPy on page 157, and the fact that only vegetable intake was associated with pyrethroid metabolite concentrations, see section 9.4.4 PBA on page 157, as previous studies have demonstrated that dietary intake of a wide variety of food items contributes to pyrethroid and chlorpyrifos exposure (131, 388).

10.2.3 Implication of using the questionnaire-based approach in epidemiological studies

Omission of important determinants of exposure during the design of the questionnaire, as well as the production of summary variables with poor content validity, will affect the accuracy of the instrument and therefore the accuracy of exposure-outcome estimates. For example, because not all individual fruits and/or vegetables are associated with the same degree of insecticide exposure, combining all these items would be expected to attenuate exposure-outcome associations towards the null.

10.2.4 Recommendations

To address the objective of the thesis to "determine what items (exposure determinants) are required within the exposure-assessment questionnaire", I propose that these items should be determined

from comprehensive exposure pathway data for the hazard. What constitutes comprehensive exposure pathway data should include:

- Data characterising the distribution and concentration of the hazard in its primary sources
- Data characterising the distribution and concentrations of the hazard in its secondary sources (dust, air etc.) and factors in the domestic environment that affect these variables (ventilation, behaviour of residents etc.)
- Factors that affect contact and uptake

Where possible, the exposure pathways should be defined *quantitatively* prior to the design of the exposure-assessment questionnaire. For a thorough understanding of the exposure pathway, exposure pathways should be modelled using SBEM, or meta-analysis could be conducted on previously published exposure-assessment studies (408, 409). The advantage of this approach is that the exposure scenarios that are most relevant to exposure can be accurately identified. This enables a much more rigorous selection of items to be included in the exposure-assessment questionnaire and may also indicate if the number and complexity of exposure pathways are too numerous or complicated to be assessed via a questionnaire (see next section).

10.3 Finding Two: multiple and convoluted exposure pathways make it difficult to assess exposure through the questionnaire-based approach

10.3.1 Introduction

There are three main issues with using the questionnaire-based approach to exposure assessment when there a multitude of exposure pathways: possible decreased accuracy, practical challenges with the questionnaire design and acceptability, and finally issues with validation of the questionnaire.

10.3.2 Justification

The main objective for Part 1 of this thesis was to "identify what information is required to characterise exposure and evaluate whether this information can be obtained via an exposure-assessment questionnaire". In thesis I determined that when there are a multitude of possible exposure pathways it may be impossible to capture all possible determinants of exposure within an exposure-assessment questionnaire, or weak associations may not be detected, therefore reducing the accuracy of this approach.

For example, for the octa and penta-BDE congeners the exposure routes that need to considered when assessing children's PBDE body burden include: trans-placental transfer, dietary intake,

including breastmilk and lipid-dense foods, and non-dietary ingestion of dust (202). Assessing each of these items alone is associated with substantial challenges when using the questionnaire-based approach. Specifically:

- PBDE concentrations in dietary sources vary greatly, even amongst items that are commonly grouped together in food frequency questionnaires, such as fish (410). Including each of these items separately increases the length of the questionnaire.
- Since PBDEs are lipophilic, additional factors such as the specific fat content of the cut of meat being consumed or cooking practices may also affect dietary PBDE intake, but these are difficult to assess in FFQs (410).
- Due the long half-life of PBDEs, the shorter period typically measured by FFQs and variations in dietary habits over time, current dietary habits as assessed through the FFQ may not reflect present PBDE body burdens and the association between dietary or other habits and PBDE body-burdens may only become apparent after many years of regular intake (356).
- There are several behavioural factors that modify dust intake, including hand-to-mouth behaviour, and these factors are not easily measured via a questionnaire (127, 411).
- Because of the importance of trans-placental transfer and breastmilk to total PBDE body burdens, maternal pathways of exposure to these PBDEs also have to be considered when attempting to assess children's PBDE exposure via the questionnaire-based approach, which adds extra complexity and length to the questionnaire (412, 413).

Other than the design issues of the questionnaire, when there are a multitude of exposure pathways the instrument needs to be validated using a very large sample size prior to use. As the gold-standard is biomonitoring, this in itself may make the questionnaire-based approach non-feasible.

10.3.3 Implication of using the questionnaire-based approach in epidemiological studies

To use the questionnaire-based approach to assess exposure when there are numerous and convoluted exposure pathways, the exposure-assessment questionnaire may need to be quite long and detailed. For dietary assessment, alternative approaches, such as 24-hour food recalls or diaries, could be used in place of FFQs to obtain the very high resolution data that are required. However, previous exposure monitoring studies, in adults, have reported that participants perceive collecting duplicate diets and completing food diaries as hard or very hard 56% and 40% of the time, respectively (155). In contrast, only 2% of parents completing a simple food frequency survey for their children reported it as being difficult (414). How to meaningfully use the very

detailed data collected from a 24-hour food recall or diary to produce an exposure estimate using the questionnaire-based approach may also be challenging.

10.3.4 Recommendations

In the case where there a multitude of exposure pathways, the main advantage of the questionnaire-based approach becomes less prominent, because of the length of the questionnaire that is required. Furthermore, whether the questionnaire-based approach could meet the researchers' minimum requirements for accuracy are uncertain. One of the main advantages of using biomonitoring, as described in section 2.5.4 on page 32 is that aggregate exposure is measured, which is particularly advantageous when the sources and routes of exposure have not been described and there are a multitude of possible exposure pathways.

10.4 Finding Three: the content validity of the questionnaire is impaired when respondents are unable to identify sources

10.4.1 Introduction

When respondents are unable to confidently identify sources of the toxicant of interest, the accuracy of the exposure estimate from the questionnaire will be affected, because the content validity of the questionnaire is impaired.

10.4.2 Justification

For example, whilst electronics and electrical appliances were identified as the major source of PBDEs in Australian homes, it was not possible to identify via questionnaires which particular items in the home contain PBDEs, since concentrations vary greatly between goods of the same type and goods are not labelled with their PBDE content (415). It is not surprising that in this study, see section 8.4.3 on page 135, no electronics or electrical appliances were associated with PBDE biomonitoring concentrations, since similar findings have been reported previously (see Table 3-1 and van den Berg, Houba (360)). In contrast, the face validity of the domestic pest-control questions within the questionnaire appeared to be high. Building on previous research that had been done in the area, the pest-control product use questions were carefully worded and included visual cues so that participants could accurately identify pest-control products. Unlike PBDEs, major sources of insecticides could be confidently identified – particularly domestic pest-control products, such as sprays. In contrast to the PBDEs, sources of insecticides in the home were found to be significantly associated with pyrethroid biomonitoring concentrations.

10.4.3 Implication of using the questionnaire-based approach in epidemiological studies

In summary, when exposure sources are difficult to identify via a questionnaire, then the content validity of the questionnaire is affected and the questionnaire-based approach to exposure-assessment alone may not be suitable in these circumstances. However, the effect on the content validity may depend on the variability of the toxicant within that source. For example, although phthalate content of personal-care products is also not labelled, the phthalate content of personal-care products is relatively less variable than the PBDE content of electronics and electrical appliances (416). This may be one of the reasons why other studies report consistent associations between personal-care product use and phthalate biomonitoring concentrations.

10.4.4 Recommendations

The questionnaire-based approach may not be a suitable tool for assessing exposure to chemicals for which sources are highly variable and not readily identifiable via a questionnaire. Additional or alternative exposure-assessment methods may be required to confirm sources or measure exposure.

10.5 Summary of findings about the EDC groups studies for this thesis

10.5.1 Flame retardants

Biomonitoring should remain the exposure-assessment method of choice for the PBDEs. This is due to a variety of findings established during both parts of this thesis. A PBDE exposure-assessment questionnaire with adequate content validity was difficult to design, because relatively little was known about relevant PBDE exposure pathways and because PBDE sources are not easily identifiable via a questionnaire. The accuracy of the questionnaire-based approach was undermined because exposure pathways to PBDEs are numerous and convoluted and it was not possible to measure all exposure pathways without making the questionnaire excessively long. In Part Two of this thesis, few associations between questionnaire-data and PBDE biomonitoring data were reported; the content validity of the questionnaire appeared to be low.

10.5.2 Insecticides

The questionnaire-based approach to exposure-assessment may be feasible for assessing insecticide exposure. In terms of the first main objective of this study "Identify what information is required to characterise exposure and evaluate whether this information can be obtained via an exposure-assessment questionnaire", I determined that relatively more was known about children's exposure pathways to insecticides, than PBDEs, although data specific to Australia was still deficient in some areas. This information was easier to assess via the exposure-assessment questionnaire compared to

PBDEs, because there were relatively fewer exposure pathways and domestic sources of insecticides were more readily identifiable via the questionnaire. With regards to the second main objective of the thesis, "Design and assess the practicalities of administering exposure-assessment questionnaires; assess the content validity of the exposure-assessment questionnaire", I determined that the exposure-assessment questionnaire was practical, as it was time and cost efficient and completion rates were high. The content validity of the insecticide questionnaire appeared to be high as the associations between questionnaire data and biomonitoring data were similar to those predicted in this thesis and reported previously elsewhere.

10.5.3 Plastics/plasticisers

Because the plastics were not included in the final component of the study, fewer conclusions about the feasibility of the questionnaire-based approach for this group of chemicals have been presented, although some findings about the feasibility of the questionnaire-based approach for these chemicals were still obtained from both parts of this thesis. The questionnaire-based approach to exposure-assessment may be suitable for assessing exposure to the phthalates DEP and BBzP. The number of exposure pathways for the chemicals within the group 'plastics' varied greatly (212). For BBzP and DEP, relatively fewer and less convoluted exposure pathways are generally relevant than for the other plastics (408, 417). BBzP and DEP occur predominantly in vinyl and personal-care products, respectively. Questionnaires may be particularly suited to assessing BBzP exposure; Biomonitoring studies suggest that patterns of exposure are consistent and the contribution from exposure sources other than vinyl products in the home, such as diet, is minimal (213, 417). The main limitation of the questionnaire for this chemical is that in the questionnaire pre-testing study some participants misunderstood questions regarding PVC (vinyl) flooring since some flooring types, such as linoleum, look like vinyl but contain no BBzP.

Questionnaire-biomonitoring studies in children and adults have also consistently reported that personal-care product use is associated with DEP biomonitoring results, see Table 3-2. The strong association has been attributed to regular exposure to the source and close proximity between the source and the exposure route (for example direct application of the personal-care product to skin). However, no specific validation studies have been conducted for the questionnaire-based approach to assessing exposure to BBzP or DEP. These are needed before firm conclusions can be made about the suitability of the questionnaire-based approach to exposure-assessment for these chemicals.

10.6 Strengths and weaknesses of the study

The main strengths of the study can be classified into design strengths, including the extensive literature reviews, primary research, pre-testing and administration method of the questionnaire, and the strengths of the questionnaire-biomonitoring study, including the selection of an age group vulnerable to EDC exposure and the collection of two urine samples for insecticide biomonitoring.

Table 10-1 Strengths of the study, adapted from "Sources of Error" White et al. (2008)

	Strengths	
Category	Item	Effect
Design of the questionnaire	Extensive literature reviews	Aided in selection of items to include in the questionnaire; reduced measurement error by ensuring all items that affect the exposure pathway were measured via the questionnaire
	Additional primary research	Identified additional items to include in the questionnaire
	Pre-testing	Reduced error in the questionnaire by reducing misinterpretation of question stems and by ensuring that all participants had a response category that was appropriate
Protocol (questionnaire-biomonitoring study)	Collection of two urine samples	Reduced measurement error for the insecticide biomonitoring
Study protocol	-	-
Study participants	Wide age range – included group likely to have high exposure	Reduced analytical challenges by reducing number of participants with samples below the limit of quantification

The main weaknesses of the study included the small sample size and lack of reliability testing. The small sample size affected the biomonitoring-questionnaire analysis, leading to possible error in the interpretation of the feasibility of the questionnaire-based approach. In particular, the small sample size was likely to lead to both spurious biomonitoring-questionnaire associations, as well as power issues, such that weak questionnaire-biomonitoring associations may have been undetectable. The omission of reliability testing, i.e. test-retest agreement, makes it difficult to determine the variability of questionnaire responses and their contribution to measurement error in the questionnaire. This data is important in assessing the feasibility of exposure-assessment questionnaires – it may not be possible to reliably measure some exposure determinants via a questionnaire.

The study size was affected by the very factors for which a questionnaire-based method of exposure assessment may be advantageous over biomonitoring. Sample collection, processing and analysis was time consuming, taking two to three weeks per batch of eight samples. Sample analysis was

also costly, at approximately $200 per sample, limiting the total number of samples that could be included. Sample collection was burdensome (for guardians, participants and the author) and often not possible for practical reasons. The level of commitment required from participants may also have affected recruitment onto the study, which was poor, despite a broad recruiting campaign. During sample collection, general feedback was obtained verbally from families participating in the study about the ease or difficulty of sample collection. Difficulties were reported with urine collection bags, particularly for girls. Bags were reported to leak, fall off, or the child would pull them off or refuse to use them. Initially families were asked to complete two study visits, however, many participants declined to participate in further sampling because of issues with the urine bags. These difficulties further emphasised how useful an exposure-assessment questionnaire could be for epidemiological studies: compared to collection, processing and analysis of biomonitoring samples, collection of questionnaire data from the online questionnaire was time efficient, inexpensive and associated with lower levels of participant and researcher burden.

Table 10-2 Limitations of the study, adapted from "Sources of Error" White et al. (2008)

	Limitations	
Category	Item	Suggested improvement
Design of the questionnaire	Lack of exposure pathway data	Additional primary research
	Omission of reliability testing	Complete test-retest study
	Poor wording of questions or lack of appropriate responses	More extensive pre-testing, including behavioural coding, recording interviews for later review, analysing time taken to complete individual questions.
	Omission of socioeconomic variables	Careful cross-checking of questionnaire variables against items important for exposure
	Unreliable question responses	Intra and inter-method reliability testing
	Use of a proxy-respondent	Ask multiple family members or care-givers to complete the questionnaire
	Socially desirable reporting	Careful wording of questions related to socially desirable behaviours
	Change of behaviour during the study period	Collection of biological samples prior to questionnaire administration
Protocol (questionnaire-biomonitoring study)	Lack of guidelines in protocol about maximum storage duration in participants home freezers	Use of a courier system to minimise time samples stored in home freezers, guidelines on maximum acceptable time samples can be stored in home freezers
	Lack of specificity in inclusion criteria	More careful specification of inclusion/exclusion criteria
	Incorrect sample labelling	Use of automated barcode system
	Small sample size	Ensure sufficient resources are available to recruit and/or provide incentives for study completion
Study protocol	None identified	-
Study participants	Wide age range	Restrict studies in this age group to children pre or post-weaning unless the sample size is large

Questionnaire data processing	Combining variables that may not measure the same construct (for example, combining all fruits as a variable designed to measure insecticide intake when not all fruit items contain insecticides)	Obtain more comprehensive exposure pathway data to better guide the methods for item reduction
Samples	Insufficient sample volumes	Collect multiple samples and pool them
	Lack of standardisation methods	Ensure that biomonitoring concentrations can be standardised between study participants
	Sampling protocol (limited number of biological samples) may not be sufficient to accurately characterise long-term exposure	More studies are needed to clarify the number required
	Error due to methods of addressing sample concentrations <LOD	Employ statistical techniques that introduce the least amount of bias

10.7 Conclusion

In this thesis I aimed to assess the feasibility of the questionnaire-based approach to exposure assessment. In Part One of this thesis, I met the objectives to "Identify what information is required to characterise exposure and evaluate whether this information can be obtained via an exposure-assessment questionnaire" by completing three literature reviews and a primary research study. In Part Two, I designed an exposure-assessment questionnaire for three groups of EDCs. I assessed the practicalities of administering an exposure-assessment questionnaire by applying it for two of the three groups of EDCs to a human biomonitoring study. I then assessed the content validity of the questionnaire by comparing questionnaire data to biomonitoring data. Through both of these parts, I identified that the questionnaire-based approach to exposure-assessment is most suited to assessing exposure to hazards for which:

- There are relatively few exposure pathways
- Exposure pathways have been well characterised
- Sources of exposure are easily identifiable via a questionnaire

The small sample size in this study was attributable to the difficulties of recruiting families to a human biomonitoring study and the large resource demands associated with collecting and analysing biological samples. This in itself was informative to the feasibility of the questionnaire-based approach to exposure assessment. Compared to biomonitoring, design, administration, processing and analysis of the questionnaire data was efficient. Despite the limitations of the sample size, the study was informative as to the theoretical approach and practical methods of designing exposure-assessment questionnaires and illustrated that there are certain situations in which the use of a questionnaire-based approach may be particularly advantageous. In the case of the groups of EDCs studies for this thesis, the questionnaire-based approach was deemed most

suitable to assessing exposure to insecticides and potentially some phthalates, but not flame retardants. Based on the findings from the analysis of the feasability of the questionnaire-based approach to exposure assessment, priority should be given to revising the current questionnaire and validating it for use in children's environmental epidemiological studies assessing health outcomes associated with insecticide exposure.

10.8 Unanswered questions and future research

10.8.1 What is the accuracy of the questionnaire-based approach to exposure-assessment?

Ultimately, the use of the questionnaire-based approach for exposure assessment in epidemiology should depend on whether the exposure estimates are accurate. Although no EDC-exposure-assessment questionnaire has been validated for use in epidemiological studies, this approach to exposure assessment has already been applied for exposure characterisation in epidemiological studies. For example, exposure-outcome studies using this approach to estimate exposure to the chemicals in vinyl flooring, including BBzP, have demonstrated significant associations between childhood exposure and asthma prevalence (418-420). Similarly, pesticide-exposure-assessment questionnaires have been used to assess the role of early-life pesticide exposure and the aetiology of childhood cancer (75). Since no formal validation studies have been identified, it is difficult to determine what level of accuracy may be associated with this approach. Priority should be given to conducting a validation study to determine the accuracy of this approach, particularly for the chemicals for which the questionnaire-based approach is already most widely used. Additionally, a limitation of the questionnaire based approach is that, while it is able to assess behavioural and environmental factors that modify the exposure pathway, it is not readily able to assess physiological factors that may also affect exposure. For example, as described in Section 2.1, genetic variations in the expression and/or activity of some enzymes involved in chemical metabolism mean that for any given internal exposure the active dose may vary between individuals. The impact of this may vary between chemicals, depending on the underlying variability in their metabolism in the population. Methods to account for these physiological differences also need to be considered.

10.8.2 What would the most accurate questionnaire-based exposure-assessment tool look like?

In section 2.5.3 on page 30, I described how the integration of environmental data with qualitative data via modelling has been used to improve the accuracy and efficiency of exposure assessment.

Because of the numerous media in which the EDCs in this thesis occur, I argued that such an approach would not be feasible, due to the high cost and burden of conducting extensive environmental monitoring. However, several studies, including some that were published towards the completion of the research for this thesis, have assessed whether exposure assessment to the EDCs in this thesis can be improved by using this approach.

For example, PBDE exposure estimates derived from the questionnaire-based approach have been improved somewhat be combining the questionnaire with environmental data, including X-Ray fluorescence, dust analysis or, for children in particular, hand-wipe measurements, since the questionnaire alone cannot reliably estimate sources in the home (127, 162, 221, 222). Although slight improvements have been gained, the improvements were generally marginal, with the total variability in PBDE biomonitoring concentrations explained in these models being less than 40%.

In contrast, combining environmental data with the questionnaire-based approach appears to be more promising for the insecticides. For example, in 2016, Chiu et al. published the results of a study where they combined the data from a FFQ with nationwide surveillance data to better characterise dietary insecticide intake (387). The authors created pesticide residue burden (PRB) scores for specific fruits and vegetables derived from the nationwide surveillance data. Participants total intake of fruits and vegetables were then described in terms of quartile of total intake of high versus low PRB items. The authors tested the technique by comparing the exposure instrument to biomonitoring data. Although data were not reported on the total variability of biomonitoring concentrations explained by the instrument, the authors reported significant associations between estimated organophosphate and pyrethroid dietary insecticide intake and biomonitoring concentrations. The feasibility of applying this improved dietary insecticide exposure-assessment questionnaire to epidemiological research was then demonstrated by its application to a study of men and women undergoing treatment at a reproductive technology clinic. Significant associations were reported between higher (top quartile versus bottom quartile) intake of high-insecticide residue fruits and vegetables and lower (18% 95% CI: 5%-30%) incidence of pregnancy (421).

Similar to the examples provided in section 2.5.3 , the questionnaire-based approach combined with either publically available environmental monitoring data or even modelled environmental data, appears to be the most promising approach in terms of integrating the questionnaire-based approach with other exposure-assessment techniques to improve the accuracy of the exposure estimates obtained. This approach may actually be appropriate for some of the EDCs studied in this thesis. However, more comprehensive environmental data would be required to make this approach

feasible. Further research should prioritise obtaining this data and assessing the validity of the questionnaire-based approach to domestic chemical exposure integrated with environmental data.

10.8.3 Are there other viable alternative exposure-assessment methods?

Finally, for chemicals for which the questionnaire-based approach to exposure assessment is not suitable, it is worth asking if there are alternative methods of exposure-assessment that could be used in place of invasive biomonitoring or the questionnaire-based approach. For example, despite the reliability of serum biomonitoring for PBDE exposure-assessment, the invasiveness of this approach has led researchers to investigate many alternative exposure-assessment approaches. Examples include using parent serum PBDE concentrations as a proxy for the child's exposure, environmental and hand-wipe monitoring (see above), faeces biomonitoring (as in this thesis), the use of silicon wrist bands and teeth (162, 361, 422-425). Given the persistence of PBDEs in the indoor environment, ongoing research into this field for the purposes of developing non-invasive alternatives to exposure assessment is warranted. In particular, since there is a relative paucity of data on early-life exposures and health outcomes in adulthood, methods to retrospectively characterise exposure would be most beneficial (75).

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APPENDIX

Appendix A Ethics approvals

CHILDREN'S HEALTH QUEENSLAND
HOSPITAL AND HEALTH SERVICE
HUMAN RESEARCH ETHICS COMMITTEE

Professor John Pearn (Chair) 3365 5323
Mrs Amanda Smith (Co-ordinator) 3636 9167

Queensland Government

Level 3, RCH Foundation Building
Royal Children's Hospital
Herston QLD 4029 Australia
Telephone (07) 3636 9167

10th March 2015

Ms. Karin English
QCMRI,
Level 4 Foundation Building
Royal Children's Hospital
Herston QLD 4029

Dear Ms. English,

HREC Reference number: HREC/15/QRCH/40
Project title: Validating questionnaires designed to assess exposure of three to eighteen month old infants to insecticides and flame retardants in the home environment

Many thanks for the submission of the above Low Risk Project. This has now been reviewed.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

I am pleased to advise the proposal meets the requirements of the National Statement on Ethical Conduct in Human Research and the Committee is happy to give approval.

This project has Ethics approval for the following sites:

- Royal Children's Hospital, Brisbane/Lady Cilento Children's Hospital

Note: If additional sites are engaged prior to the commencement of, or during the research project, the Coordinating Principal Investigator is required to notify the HREC. Notification of withdrawn sites should also be provided to the HREC in a timely fashion.

The documents reviewed and approved include:

Document	*Version*	*Date*
Information sheet with consent form and withdrawal form.	Version 1	20 February 2015
Instructions for breast milk collection	Version 1	20 February 2015
Instructions for stool collection	Version 1	20 February 2015
Instructions for Urine collection	Version 1	20 February 2015
Protocol	1.0	27 February 2015
Questionnaire (paper copy of an online questionnaire)	Version 1	20 February 2015
Letter of invitation to participant: Study flier	Version 1	03 March 2015
Application		

J:\Ethics\Ethics\2015 Projects\HREC-15-QRCH-40\approval 100315.rtf

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Validation of Questionnaires Designed to Assess Exposure of 3 - 18 Month Old Infants to Insecticides and Flame Retardants in the Home Environment
Chief Investigator:	Ms Karin English
Supervisor:	Prof Peter Sly
Co-Investigator(s):	Peter Sly, Yiqin Chen, Chang He, Yan Li
School(s):	QCMRI / Children's Health and the Environment Program
Approval Number:	2015000397
Granting Agency/Degree:	APA Scholarship; PhD
Duration:	31st March 2017

Comments/Conditions:

Expedited review on the basis of approval from the Children's Health Queensland HREC dated 10/03/2015.

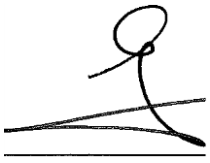
Please submit "results materials" for review as part of an Ethics Amendment Application when finalized.

Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee: Medical Research Ethics Committee

This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Signature  Date 24/3/15

THE UNIVERSITY OF QUEENSLAND

Institutional Human Research Ethics Approval

Project Title:	Products Project: Assessment of Environmental Pollutants in Humans and Their Indoor Environments
Chief Investigator:	Prof Jochen Mueller
Supervisor:	None
Co-lnvestigator(s):	Christie Gallen, Karin English, Leisa-Maree Toms, Andrew Banks, Phong Thai
School(s):	School of Medicine, Children's Health and the Environment Program and QCMRI; National Centre for Environmental Toxicology
Approval Number:	2015000153
Granting Agency/Degree:	Department of Environment; QCMRI and ENTOX
Duration:	31st March 2018

Comments/Conditions:
Please submit "results materials" for review as part of an Ethics Amendment Application when finalized.
Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Committee:
Medical Research Ethics Committee
This project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research* and complies with the regulations governing experimentation on humans.

Name of Ethics Committee representative:
Professor Bill Vicenzino
Chairperson
Medical Research Ethics Committee

Signature _____

Date 20/3/2015

CHILDREN'S HEALTH SERVICES QUEENSLAND
HUMAN RESEARCH ETHICS COMMITTEE

Professor John Pearn (Chair) 3365 5323
Mrs Amanda Smith (Co-ordinator) 3636 9167

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Level 3, RCH Foundation Building
Royal Children's Hospital
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9th December 2013

Professor Peter Sly
Queensland Children's Medical Research Institute
Level 4, Foundation Building
Royal Children's Hospital
Herston, QLD 4029

Dear Professor Sly,

HREC Reference number: HREC/13/QRCH/207
Project title: Pre-testing questionnaires designed to assess exposure risk of six and twelve month old infants to toxicants in the home environment

Many thanks for the application of the above study. This has now been reviewed.

This HREC is constituted and operates in accordance with the National Health and Medical Research Council's (NHMRC) *National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007)* and the *CPMP/ICH Note for Guidance on Good Clinical Practice.*

I am pleased to advise the proposal meets the requirements of the National Statement on Ethical Conduct in Human Research and the Committee is happy to give approval.

This project has Ethics approval for the following sites:

- Royal Children's Hospital, Brisbane

[Note: If additional sites are engaged prior to the commencement of, or during the research project, the Coordinating Principal Investigator is required to notify QLD Children's Health Services (RCH) Human Research Ethics Committee (HREC). Notification of withdrawn sites should also be provided to the QLD Children's Health Services (RCH) Human Research Ethics Committee (HREC) in a timely fashion.

The documents reviewed and approved include:

Document	*Version*	*Date*
Cover Letter		26 November 2013
Application	AU/10/54D518	
Parent/Guardian Information Sheet and Consent Form – Group 1	1	25 November 2013
Parent/Guardian Information Sheet and Consent Form – Group 2	1	25 November 2013
Research Protocol	1	26 November 2013
Participant Information Booklet	1	10 October 2013
2-Day Infant Feeding Diary at 6 & 12 months	1	25 November 2013
Time Activity Diary at 6 & 12 months	1	25 November 2013

Appendix B Studies assessing c-decaBDE content of consumer goods through destructive testing

Appendix Table 1 Studies Assessing c-decaBDE content through destructive testing

Reference	Country of product origin	Source	Product details (if applicable)	Study location	Study year	Year of manufacture	Total number of samples	Proportion Positive	Concentration Range	Average Concentration
Chen, Ma (220).	China	New Items	Hard plastic	China	2009	Not Specified (NS)	30	93.3	0 - 0.42%	0.02%
			Soft plastic				15	26.7	0 - 0.003%	0.0003%
			Foam				18	100	0 - 0.006%	0.0003%
			Stuffed				6	100	0 - 0.0001%	0.00003%
van Bergen and Stone (294).	NS	New items	Baby activity gym, tablets, stuffed toys	Washington State, US	2012-2013	NS	11	0	NA	NA
Bentley (289).	NS	NS		Australia	2012	NS	11	27	<0.001	<0.0001
Keet, Giera (46).	NS	NS		New Zealand	2010	NS	4	50	<0.001	<0.001
Chen, Ma (426).	NS	NS		China	2009	NS	5	60%	0 - 0.003%	0 - 0.0007%
van Bergen and Stone (294).	NS	NS		Washington State, US	2012-2013	NS	4	0	NA	NA
Bentley (289).	Malaysia	New items	General computer housing	Australia	2012	Various	1	100		0.13%
Abbasi, Buser (345).	NS	NA	General computer housing	USA and Canada	NA	NS	NA	NA	Not specified	0.01%
Aldrian, Ledersteger (427).	NS	E-waste facility	General computer housing	Austria	2014	NS	6	100	0.07-0.63%	0.28%

Reference	Country of product origin	Source	Product details (if applicable)	Study location	Study year	Year of manufacture	Total number of samples	Proportion Positive	Concentration Range	Average Concentration
Chen, Ma (426).	NS	Homes	General computer housing	China	2009	NS	<32	25	0 - 0.0006%	0.0002%
Keet, Giera (46).	NS	New items	Computer components/circuit board	New Zealand	2010	NS	1	100	NA	0.00001%
Kumari, Sharma (428).	NS	NS	Computer components/circuit board	India	2013	NS	1	100	NA	1.15%
Morf, Tremp (301).	NS	E-waste facility	General computer housing	Switzerland	2003	NA	NA	NA	NA (composite samples)	0.48%
	NS	E-waste facility	Computer components/circuit board		2003	NA	NA	NA	NA (composite samples)	0.003%
Kajiwara, Noma (429).	NS	New items	Computer components/circuit board	NS	2008	2011	6* different components of one laptop	100	0.000- 0.004	0.0007
van Bergen and Stone (294).	NS	New items		Washington State, US	2012-2013	2009+	1	0	NA	0%
Kajiwara, Noma (429).	NS	New items		Japan	2011	~2008	2	100	0.0000-0.0014	0.0007
Abbasi, Buser (345).	NS	NA		USA and Canada	NA	NS	NA	NA	0.7-4%	4%
Aldrian, Ledersteger (427).	NS	E-waste facility		Austria	2014	NS	6	100	0.06-0.75%	0.41%
Chen, Ma (426).	NS	Homes		China	2009	NS	<32	83.3	0-4.56%	0.79%

Reference	Country of product origin	Source	Product details (if applicable)	Study location	Study year	Year of manufacture	Total number of samples	Proportion Positive	Concentration Range	Average Concentration
Morf, Tremp (301).	NS	E-waste facility		Switzerland	2004	NA	NA	NA	NA (composite samples)	0.48%
Park, Kang (430).	NS	E-waste facility		Korea	2014	1987-1989	2	100	0.05-0.221	0.13%
	NS	E-waste facility		Korea	2014	1990-1993	1	100		0.02%
	NS	E-waste facility		Korea	2014	1995-1998	1	100		0.03%
	NS	E-waste facility		Korea	2014	2000-2005	1	100		0.03%
Sindiku, Babayemi (431).	Asia (58), Europe (100)	E-waste facility and other waste sources		Nigeria	2011	1981-2004	160	38.125	0.086 – 23.7%	0.86%
Kajiwara, Noma (429).	NS	New items		Japan	2011	~2008	2	100	0.0000-0.0013	0.0007
Bentley (289).	Various	New items	Packing foam, automotive foam and textiles, baby car seats, furniture foam, children's clothing	Australia	2012	Various	19	73	26.0273973	0.01%
Chen, Ma (426).	NS	Homes	Furniture, mattresses, pillows	China	2009	NS	0	5	NA	0.0000%
DiGangi and Strakova (432).	US, Canada, Asia, Europe	Canada, Hungary, Nepal, Kyrgyzstan,	Recycled carpet padding	NA	2011	NS	23	26	88.4615385	0.0028%

Reference	Country of product origin	Source	Product details (if applicable)	Study location	Study year	Year of manufacture	Total number of samples	Proportion Positive	Concentration Range	Average Concentration
		Thailand, and USA								
van Bergen and Stone (294).	NS	New items	Children's clothes and toys, furniture foam, carpet padding, mattresses, pillow, baby care items (change-pads etc.), baby car seats	Washington State, US	2012-2013	NS	2	80	2.5	<0.001%
Shin and Baek (433).	NS	New items	Curtains	Korea	2012	2012	3	100	0.0001-0.0002	0.0002
Kajiwara, Sueoka (306).	Japan	New Items	Curtain material	Japan	2008	2007	6	17		2[a]%
Keller, Raju (307).	Bangladesh, China, Indonesia, Korea, Taiwan	Used items	Tents	US	2014	NA	11	4	0 – 1.78%	0.4%

Appendix C Supplementary materials PBDE biomonitoring-questionnaire data analysis

Linear regression analysis results for BDE-47, BDE-153 and BDE-209 are displayed in the table below. P-values are shown for entire categorical variables, adjacent to the variable heading.

Appendix Table 2 Linear regression analysis BDE-47: Questionnaire and biomonitoring data

Parameter	**p-value**	**N**	e^{β} **(CI)**
Age in months	<0.01	46	0.93 (0.89-0.98)
Mobility	0.02		
Not walking or crawling		10	Reference
Crawling only		9	1.55 (0.60-4.00)
Crawling and walking		14	0.45 (0.19-1.05)
Walking only		12	0.81 (0.34-1.97)
Solid food consumption	0.06		
<1 month		7	Reference
>1 month		35	0.44 (0.19-1.02)
Flooring in parent's bedroom	0.06		
Flooring other than carpet		19	Reference
Carpet, age unknown		6	2.60 (0.10-6.75)
Carpet <2 years old		4	0.37 (0.12-1.14)
Carpet 2-10 years old		12	0.74 (0.35-1.56)
Carpet 10-30 years old		5	1.43 (0.51-3.99)
Infant formula consumption	0.08		
< Once / day		28	Reference
> Once / day		17	1.80 (0.94-3.44)
Cows milk consumption	0.07		
Less than weekly		25	Reference
Several times a week but not every day		9	0.76 (0.35-1.65)
Once a day or more frequently		11	0.33 (0.16-0.69)
Frequency of dusting	0.04		
Weekly or more frequently		22	Reference
About fortnightly or less		23	1.90 (1.02-3.54)
Number of TVs in the home	0.05		
1 or less		27	Reference
2 TVs		12	0.89 (0.43-1.87)
3 or more		5	2.78 (0.99-7.87)

Appendix Table 3 Linear regression analysis BDE-153: Questionnaire and biomonitoring data

Parameter	**p-value**	**N**	e^{β} **(CI)**
Age in months	<0.01	46	0.88 (0.81-0.94)
Mobility	0.03		
Not walking or crawling		10	Reference
Crawling only		9	0.34 (0.07-1.62)
Crawling and walking		14	0.15 (0.04-0.63)
Walking only		12	0.20 (0.05-0.87)
Interested in mouthing any objects	<0.01		
No		7	Reference
Yes		39	7.83 (2.03-30.12)
Interested in thumb or finger sucking	0.01		
No		13	Reference
Yes		33	4.08 (1.35-12.33)
Pests in the home	0.07		
No		19	
Yes		27	2.66 (0.94-7.54)
Pets – cat	0.033		
No		35	Reference
Yes		11	0.27 (0.08-0.90)
Consumption of dairy – quartile of consumption	0.057		
1st		10	Reference
2nd		10	0.90 (0.19-4.36)
3rd		12	0.42 (0.09-1.91)
4th/highest quartile		14	0.28 (0.06-1.20)
Breast feeding currently	0.003		
Yes		19	Reference
No		25	0.20 (0.07-0.56)

Appendix Table 4 Linear regression analysis BDE-209: questionnaire and biomonitoring data

Parameter	**p-value**	**N**	e^{β} **(CI)**
Age in months[1]	0.82	46	1.01 (0.91-1.13)
Mother removes shoes before entering home	0.09		
Always		20	Reference
Sometimes		19	1.58 (0.37-6.67)
Rarely		5	11.37 (1.19-107.73)
Frequency of walks outdoors	0.10		
Every day		10	Reference
Several times a week but not every day		24	2.81 (0.53 - 15.03)
Once or twice a week or less		12	10.6 (1.57-71.46)
Home	0.04		
Owned		28	Reference
Rented		16	1.47 (0.07-2.87)
Sunshade use in car when weather hot	0.03		
Yes		24	Reference
No		20	4.61 (1.21-17.62)

Age was not significantly associated with BDE-209 concentrations in faeces. It is included in this table for comparison to BDE-47 and BDE-153.