OCCUPATIONAL EXPOSURE TO ORGANOPHOSPHORUS PESTICIDES: EXPLORATORY CASE STUDIES OF FACTORS INFLUENCING GLOVE PERFORMANCE AND SKIN PENETRATION

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ABSTRACT

Problem statement

The widespread use of organophosphorus pesticides (OPs) in agriculture and urban pest control has seen significant morbidity and mortality. They are the most important cause of severe toxicity and death from acute poisoning worldwide, with more than 200,000 deaths each year in developing countries. OPs act to inhibit acetylcholinesterase in the nervous system, and may elicit acute and long term health effects. Some commercially available OPs are also classified as Chemicals of Security Concern by the Australian Government and are subject to special restrictions and surveillance.

Occupational exposure may occur in manufacture, storage, transport, usage, disposal and in emergency situations. For example, ambulance workers may be exposed when attending accidental or intentional OP poisonings. The profiles may vary from short term high exposures for emergency personnel, to long term low exposures for farming communities.

The World Health Organisation and a range of other agencies have determined that the continued use of these chemicals represents an important public and occupational health issue.

A major route of exposure is skin absorption, and the use of protective chemical gloves is recommended, especially for the concentrated product. Safety data sheets (SDS) are meant to provide the user with information on appropriate glove protection. However, the concentrates are typically formulated products with solvents and additives that may influence the glove permeation behaviour of the active ingredient. Testing by glove manufacturers is rarely with the formulated product, and pertains to room temperature experiments with new gloves. Cheap or disposable

gloves may not have been tested. In addition, the effects of elevated temperature, abrasion and ultraviolet (UV) exposure are poorly understood.

Although these environmental factors are likely to be present in Australian workplaces, there is scant evidence of their practical significance to inform risk assessment and interventions, including glove selection and use. Apart from gloves, skin uptake may be influenced by high ambient temperatures. The limited dermal toxicological research literature suggests that skin penetration rates may be dramatically increased, with concomitant increases in health risk. Compounding the problem is the situation where chemical is occluded between glove and skin.

Gap analysis

Based on a review of the occupational hygiene literature, knowledge gaps exist in three areas, relating to glove performance and skin penetration.

Firstly, suppliers and formulators of agricultural OPs recommend the use of long length polyvinyl chloride (PVC) gloves. Indeed, distributors stock cheap versions of such gloves, but as they are not considered disposable, repeated use is the norm. Scientific uncertainty exists as to the protection afforded under real world conditions of solar radiation, elevated temperature and abrasion.

Secondly, the chemical barrier performance of disposable gloves, as worn by ambulance workers in poisoning episodes, has not been investigated.

Thirdly, it is known that skin absorption of chemicals depends on physicochemical properties such as molecular size and water solubility. However, there appear to be no skin penetration studies which have compared a range of OPs of different properties. Moreover, the studies that have been

conducted have often used a finite dose model. An infinite dose model is more applicable for worst case occupational risk assessment.

Purpose statement

This research aims to provide a better understanding of dermal exposure to OPs (under simulated real world conditions) and to generate data useful for predictive dermal risk assessment models and optimising control measures. It is anticipated that the improved evidence base will assist in reducing morbidity and mortality from OPs.

A case study approach will be used, addressing both routine users and those in an emergency setting.

Broad Research Questions

The following questions were developed from a literature review and context scoping from fieldwork observations.

1. How do the recommended PVC gloves (unused, exposed to UV and abrasion) perform against OPs in various exposure conditions?
2. What are the effects of different variable conditions on the barrier performance of different types of disposable gloves worn by ambulance workers and is the current practice suitable?

3. How is skin penetration affected by physicochemical properties of OPs, concentration of OPs and elevated temperature?

Methodology

Four OPs widely used in Australia (omethoate, mevinphos, dichlorvos and diazinon) with differing physicochemical properties (e.g. octanol-water partition coefficient) were investigated. Tests were conducted at the full strength formulation (relevant for transport and mixing activities) and application strength (relevant for spraying), and at two temperatures.

In the glove permeation studies, American Society for Testing and Materials (ASTM) permeation cells were used at two temperatures (room temperature and 45°C).

Two case study scenarios were used, namely agricultural workers and ambulance workers.

For Case Study 1 two brands of elbow length PVC gloves recommended for handling OPs were tested in new unused condition, and following UV exposure or abrasion. In Case Study 2 disposable nitrile and neoprene gloves used by South Australia Ambulance Service (SAAS) workers were tested individually and in combination (as per current practice).

In the skin studies, human abdominal skin samples (heat separated epidermis) were exposed to the OPs (infinite dose) in static Franz cells according to OECD protocols for up to 8 hours, at room temperature and 37°C. Analysis for the OPs in both glove and skin experiments was undertaken using HPLC and UV detection.

Main Findings

Glove performance tests – Case Study 1

Differences were noted in breakthrough time and cumulative penetration at the end of the 8-hour experiments for the two PVC glove brands. In general, PVC gloves performed well against the four tested OPs. Full strength formulations had shorter breakthrough times and greater cumulative permeations. Breakthrough of diazinon did not occur unless at full strength at 45°C (120 - 180 mins). In contrast, breakthrough of dichlorvos was observed for all exposure conditions (between 60 to 240 mins) except for application strength at room temperature. Mevinphos, which was only tested at room temperature, demonstrated breakthrough only for one brand of gloves. In the case of omethoate, breakthrough was noted from 60 minutes onwards.

Permeation was uniformly higher at 45°C compared to room temperature. Gloves exposed to UV light (approximately equivalent to a week or more of extreme sunlight) or abrasion (5% thickness reduction) exhibited a small reduction in performance.

Glove performance tests – Case Study 2

In glove performance tests on gloves used by SAAS workers, disposable nitrile and neoprene gloves demonstrated good protection against the four tested OPs in 4-hour experiments. In general, the thicker neoprene gloves demonstrated longer breakthrough times than nitrile gloves.

At higher test concentration (full strength) of the four tested OPs, cumulative penetration at 8 hrs increased, and this was observed at both test temperatures. Elevated temperature to 45°C shortened

the breakthrough time (between 5 and 20 minutes) and resulted in greater cumulative penetration of the OPs.

Combining the disposable gloves (nitrile on neoprene) as practised by SAAS workers demonstrated better protection with longer breakthrough times and lower cumulative penetration of the tested OPs, compared to individual gloves.

In vitro skin studies

Dichlorvos was found to rapidly penetrate the skin. Elevated temperature and higher OP concentration resulted in faster penetration rate and increased cumulative penetration of the tested OPs.

Comparison of the skin penetration data with Acceptable Daily Intakes (ADIs) of the respective OPs showed that ADIs may be exceeded rapidly, with the order being dichlorvos, diazinon, omethoate and mevinphos.

Novelty of the research

This research uses an experimental design based on real life scenarios.

Unlike most glove permeation and skin penetration studies this research used formulated OP products that are commercially available in the market. All experiments were conducted using an infinite dose model to simulate the worst exposure scenario (prolonged skin contamination from spills and splashes), and thus to establish the maximum penetration rates for risk assessment.

Similarly, tests were conducted at elevated temperatures and with gloves exposed to ultraviolet (UV) and abrasion to mimic the common exposure conditions in real world scenarios.

Implications

The research has highlighted the importance of elevated temperature, and the dermal risks associated with dichlorvos. The increased barrier protection afforded by double gloving (combining relatively polar and non-polar materials), for OPs of different physico-chemical properties, was shown. This is reassuring for ambulance workers who may encounter a range of OPs. Surprisingly, the influence of UV exposure and abrasion on the performance of the thick PVC gloves was found to be relatively minor, under the conditions examined.

Data on the influence of physicochemical properties, concentration, and temperature are useful for refining dermal risk assessment models, and for worker education. On a broader public health level, the findings will allow a more rational use of gloves as chemical protective clothing to protect the population at risk from the danger of agricultural chemicals.

Conclusions and Recommendations

The data indicate that the use of concentrated OPs in warmer conditions will greatly increase skin uptake. Dichlorvos demonstrated rapid and extensive skin penetration, but the data for all the tested OPs suggest that toxicologically important uptake can occur in relatively short time periods without

skin protection. Glove permeation also increases with concentration, temperature, UV and abrasion. The practice of double gloving by ambulance workers is supported by the evidence.

Following these exploratory studies, it is recommended that more glove permeation tests be conducted under realistic exposure scenarios. The findings should be compiled in a database for advisory purposes and made publicly accessible. Warnings for potential ADI exceedance should be included on labels or SDSs of the OP products to alert the users of the risks when handling OPs. Where changes may be made in the OP formulation by manufacturers, the suitability of glove recommendations should be reviewed.

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LIST OF ABBREVIATIONS

AChE	Acetylcholinesterase
ADI	Acceptable Daily Intake
ANOVA	Analysis of Variance
APVMA	Australian Pesticides and Veterinary Medicines Authority
ASTM	American Society for Testing and Materials
AS/NZS	Australian Standards/New Zealand Standards
ATSDR	Agency for Toxic Substances and Disease Registry
BT	Breakthrough time
CAS	Chemical Abstracts Service Registry Number
EC	Emulsifiable concentrate
HPLC-UV	High Performance Liquid Chromatography – Ultraviolet Detection
IUPAC	International Union of Pure and Applied Chemistry
LD_{50}	50% lethal dose
Log K_{ow}	Log Octanol-Water Partition Coefficient
NIOSH	National Institute Occupational Safety and Health
NOEL	No Observable Effect Level
OPIDN	Organophosphate-induced delayed polyneuropathy
OP	Organophosphorus Pesticide
PPE	Personal Protective Equipment
PVC	Polyvinyl chloride
SAAS	South Australia Ambulance Service
SD	Standard deviation
SDS	Safety Data Sheet
WHO	World Health Organisation
WP	Wettable powder

GLOSSARY

Permeation A process that works by diffusion; the movement of molecules through a layer from a high concentration area to an area of less concentration. Permeation through gloves occurs by absorption, diffusion and desorption of the chemicals

For a chemical to permeate a glove material, the molecules of the chemical will absorb into the surface of the material, diffuse in the material and desorb to the opposite side of the material. Then, the chemical will come into contact with the skin and penetrates the skin. For the purpose of this research, the term 'permeation' is used for glove performance studies (Chapter 4 and 5).

Penetration Direct passage of molecules through porous materials, or imperfections such as pinholes, cracks, tears and seams at a non-molecular level. It is easier to understand by saying penetration is relative to pressure. Therefore, penetration will occur at a faster rate when a higher pressure is applied. An example of this is the pinhole water test, which is done by filling in a glove with water and squeezed to test for any signs of penetration. For the purpose of this research, the term 'penetration' is used for *in vitro* skin studies.

Flux

The rate of permeation or penetration (μg/cm^2/min) of which the amount of chemicals (μg) crossing a defined area (cm^2) in a set time (min). Flux is commonly used to define penetration and permeation characteristics.

Breakthrough time

For gloves, breakthrough time (BT) is the time where the flux reaches 1 μg/cm^2/min as set in the AS/NZS 2161 standard. Although BTs do not provide information on how much pesticide permeated through the gloves, it may be used to judge the quality of gloves, along with flux and cumulative permeation. Although some chemicals may have the same cumulative permeation after a set of exposure time, they may have different BTs. This information is useful in the selection of the correct type of gloves for hand protection.

However, breakthrough for the skin does not rely on the flux of the tested substances. As soon as the substances were proven to penetrate the skin regardless of the rate of penetration, it is considered a breakthrough.

PUBLICATIONS, PRESENTATIONS AND RECOGNITIONS

PEER-REVIEWED PUBLICATIONS (to date of submission)

Ismail, I., Pisaniello, D., Gaskin, S., & Edwards, J. W., (2015), Dermal Exposures to Organophosphorus Pesticides for ambulance workers - Permeation through disposable gloves: Findings for omethoate, *J Health & Safety Research & Practice* 7(1), 14-22

Ismail I, Pisaniello D, Gaskin S, Edwards JW. Dermal absorption of organophosphorus insecticides: effects of concentration and temperature on skin penetration of omethoate. 33rd Annual Conference of the Australian Institute of Occupational Hygienists, Perth, December 2015. Published in full in the *Proceedings of the 33rd Annual Conference of the Australian Institute of Occupational Hygienists*, Cross, M. (Ed). AIOH, Perth p71-79. ISBN 978-0-9775920-9-8.

Ismail I, Pisaniello D, Gaskin S, Edwards JW. Dermal exposures to organophosphorus pesticides for ambulance workers - Permeation through disposable gloves: Findings for Omethoate. 32nd Annual Conference of the Australian Institute of Occupational Hygienists, Melbourne, December 2014. Published in full in the *Proceedings of the 32nd Annual Conference of the Australian Institute of Occupational Hygienists*, R. Golec (Ed). AIOH, Melbourne p137-146. ISBN 978-0-9803010-1-4.

CONFERENCE AND PRESENTATIONS (to date of submission)

Dermal absorption of organophosphorus insecticides: effects of concentration and temperature on skin penetration of omethoate

- Abstract and Oral presentation
- 33rd Australian Institute of Occupational Hygienists AIOH Conference and Exhibition, Perth, Western Australia, 5th to 9th December 2015

Do concentration and temperature affect skin penetration of omethoate?

- Abstract and Poster presentation
- 2015 Florey International Postgraduate Research Conference, Adelaide, South Australia, 24th September 2015

The effects of temperature, ultraviolet (UV) and abrasion on the performance of gloves used by agricultural workers handling Organophosphate Pesticides (OPs)

- Abstract and Poster presentation
- 31st International Congress on Occupational Health, Seoul, South Korea, 31st May to 6th June 2015

Dermal exposures to Organophosphorus Pesticides for ambulance workers - permeation through disposable gloves: Findings for omethoate.

- Abstract and Poster presentation
- 32ndAustralian Institute of Occupational Hygienists AIOH Conference and Exhibition, Melbourne, Australia, 30th November to 3rd December 2014

Permeation of organophosphate pesticides through disposable gloves:

Are they protective enough for ambulance workers?

- Abstract and Poster presentation
- 2014 Florey International Postgraduate Research Conference, Adelaide, South Australia, 25th September 2014

AWARDS

- High Commendation (runner-up) for Academic Excellence in Postgraduate Research at the 2015 Study Adelaide International Student Awards, Adelaide, South Australia.
- Merdeka Award 2015 from Australia-Malaysia Business Council (South Australia) Inc. for outstanding academic achievement, ability to act as an ambassador for South Australia and contribution to the furthering of the South Australia-Malaysia relationship
- 1st place Student Poster Award for the best poster at the 31st International Congress on Occupational Health, Seoul, South Korea
- School of Population Health Prize for the best poster at the 2014 Florey International Postgraduate Research Conference, Adelaide, South Australia

THESIS OVERVIEW

The purpose of this overview is to assist the reader in rapidly appraising the content and key messages of individual chapters of the thesis. Structurally, this thesis has a traditional chapter format with a combination of introduction, literature review, research questions, methodology, empirical research findings, discussion, conclusions and recommendations.

It utilises a case study approach, informing laboratory experimentation, to enable a better understanding of dermal exposure to organophosphorus pesticides (OPs) in two settings; namely routine agricultural use and emergency ambulance response.

This thesis is comprised of eight chapters, with content and messages tabulated as follows:

Chapter	Chapter content	Key messages
1- Introduction and context	This chapter provides an overview of the working populations potentially exposed to organophosphorus pesticides (OPs). The public health and national security significance of organophosphorus pesticides in various settings are briefly described.	Large numbers of workers may be exposed to organophosphorus pesticides in manufacturing, storage, transport, use and disposal as well as in emergency situations. Significant mortality is evident in developing countries. Twelve of the 96 chemicals of security concern are organophosphorus pesticides used in Australian agriculture. The need for a review of these 12 chemicals and the issues associated with dermal exposure, e.g. work in hot weather, are highlighted.
2- Literature review	The objectives for the review are described and the search strategy is presented. The search yield is summarised to identify the knowledge gaps pertaining to dermal exposure and glove protection. A rationale for the selection of OPs and gloves for the proposed research is given. The aims and broad research	The dermal exposure assessment literature on the 12 OPs of security concern is sparse. A number of research opportunities were evident. It was decided that the broad research questions would relate to skin protection and uptake for a range of formulated OPs under a range of under-explored conditions, e.g.

	questions are derived from the literature review, particularly in relation to issues of formulated OPs, UV exposure and abrasion. Out-of-scope research aspects are defined.	elevated temperature and glove abrasion. It was decided that four OPs of varying physicochemical properties would be examined in an exploratory manner.
3- Materials and methods	Materials used and methods in the glove performance tests and *in vitro* skin studies are explained in detail. Statistical analyses used for experimental data are also described.	Standardised methods for skin penetration and glove permeation testing are used in this research i.e. an OECD protocol with static Franz cells and an Aust NZ Std 2161 protocol with ASTM cells. HPLC-UV was used for OP analysis. A UV exposure chamber and the glove abrasion technique are also described.
4- Case Study 1: Protective performance of Polyvinyl Chloride (PVC) gloves used by agricultural workers	This case study explores the performance of PVC gloves used by agricultural workers against formulated OPs under variable conditions of temperature, concentration, UV exposure and abrasion.	PVC gloves appear to perform well when challenged with the four formulated OPs (omethoate, mevinphos, dichlorvos and diazinon) particularly at application strength. Some differences between the two brands of PVC gloves tested were noted. Significantly reduced performance was observed for both brands with elevated temperature, and generally non-significant reductions were observed following UV exposure and glove abrasion.
5- Case Study 2: Protective performance of disposable gloves used by ambulance workers	In this case study, disposable gloves used by South Australia Ambulance Service (SAAS) workers were challenged with OPs. Gloves are tested individually and in combination (as currently in practice) under reasonable worst case conditions.	The current practice of double gloving method of disposable gloves provides good protection against formulated OPs, and superior to gloves worn individually. The use of combination of gloves (nitrile on neoprene gloves) also indicates protection against a wider range of OPs of different polarities. Again, significantly reduced performance is observed with elevated temperature.
6- Skin penetration studies of omethoate, mevinphos, dichlorvos and diazinon	Skin penetration of four formulated was assessed using an *in vitro* approach, at different concentrations under two temperature conditions. Extrapolated, worst case penetration data were compared with acceptable daily intakes.	Skin penetration outcomes vary across the four formulated OPs tested. Acceptable Daily Intakes (ADIs) can be rapidly exceeded (0.5 minutes) for skin contact with concentrated OPs, irrespective of temperature conditions.

7- General discussion	The novelty and significance of the research are highlighted and the findings discussed in the context of the international literature.The generalisability of the findings are discussed and strengths and limitations of the research are presented.	Real world conditions, e.g. potentially elevated temperature and use of formulated products at variable strengths, influence skin penetration and glove performance. The use of double gloving using complementary glove polymers is advantageous, particularly for unknown OP mixtures.
8- Conclusion and recommendations	Conclusions from the research findings are presented followed by recommendations for researchers and specific stakeholders.	The research has raised a number of questions about real world exposures and the evidence needed for practical control. It is recommended that further research be conducted, e.g. under intermediate conditions, with used gloves and with consideration of co-solvents. A database on glove performance under various conditions is recommended.

The specific content and orientation of each chapter is outlined as follows:

Chapter 1 General Introduction

It is argued that the extensive use of organophosphorus pesticides worldwide is a significant public health issue. Evidence is provided for large scale health impacts in developing countries. Given the availability, toxicity and possible misuse of OPs, the Australian government has classified some OPs as Chemicals of Security Concern. On the basis of ongoing impact and the national concern, the general topic of OPs was considered worthy of further research.

It is well known that skin absorption is a major route of exposure of OPs, and it is self-evident that a good understanding of both skin penetration and the effectiveness of skin protection is needed. However, this knowledge needs to be contextualised in real world conditions, where formulated products rather than pure active ingredients are used, and where work may be conducted in hot environments.

In order to provide a focus, the topic (and subsequent literature review) is limited to those OPs of security concern and the occupational hygiene issues associated with dermal exposure.

Chapter 2 Literature Review

This chapter rationalises the development of the research questions. It starts with the objectives of the review, followed by the search strategy and a tabulation of the yield for each of the 12 OPs of security concern. A cross-cutting narrative review of existing dermal exposure-related literature is undertaken, highlighting the limited number, and types, of published glove permeation and skin penetration studies. The gaps in knowledge are summarised, justifying the aims and broad research questions. A case study approach, based on two real world situations, is proposed for subsequent research. A set of complementary glove and skin experiments, using a selected sample of formulated OPs, would allow exploration of the impact of high temperatures and practical issues such as glove abrasion and sunlight exposure. Finally, the scope of the proposed research is delineated.

Chapter 3 Materials and Methods

The test chemicals, equipment, instruments and methods used are described in this chapter. The arrangements for glove permeation testing according to Australian/New Zealand Standard 2161.10.3:2005 are outlined, along with a description of the PVC, nitrile and neoprene gloves, and formulated OPs under investigation. Details of the human skin samples, and the procedures for skin penetration testing, according to an OECD protocol are presented. A UV exposure chamber is described, along with a technique for glove abrasion. HPLC equipment and conditions for chemical analysis are presented.

Finally, the statistical tests used in the research are outlined. Apart from the glove abrasion and UV-exposure techniques, these represent standardised methods.

Chapter 4 Case Study 1: Protective performance of PVC gloves used by agricultural workers against OPs

Unused gloves were subjected to realistic worst case conditions, up to 8-hour duration. The resultant glove permeation data indicate that PVC gloves provide good protection against the four tested formulated OPs. When challenged with concentrated OPs, 8-hour cumulative chemical permeation is increased beyond that observed for application strength OP, especially under elevated temperature conditions. There is some variation between two brands of ostensibly the same glove. Reduced protective performance is noted for PVC gloves subjected to UV radiation (approximately equivalent to one continuous week of extreme sunlight) and abrasion (5% reduction in overall glove thickness, and 10% of the PVC coating). Statistically significant differences were noted for effects of concentration and temperature. The effects of UV and abrasion on gloves were relatively minor. The findings are discussed in terms of complementary research previously conducted in Tasmania.

Chapter 5 Case Study 2: Protective performance of disposable gloves used by ambulance workers against OPs

This case study simulates worst case OP dermal exposures for ambulance workers handling accidental or intentional poisoning patients. The permeation resistance of disposable nitrile and neoprene gloves used by SA Ambulance Service workers is examined. Cumulative permeation increased significantly with concentration and temperature. However, the data show that the current practice of double gloving by South Australian ambulance workers offers good short term protection against the tested formulated OPs. Wearing a combination of gloves is better than

individual gloves, and this may be attributed to the thickness, and the relative polarities of OPs and the glove materials. Consideration should be given on frequent changing of gloves when exposed to concentrated OPs under elevated temperature conditions.

Chapter 6 *In vitro* skin studies of omethoate, mevinphos, dichlorvos and diazinon

This Chapter reports on *in vitro* human skin penetration studies conducted with four OPs under conditions of variable concentration (application vs full strength OP) and temperature (room temperature to 37°C). An infinite dose arrangement was used with exposures up to 8 hours. Statistically significant increases were noted with increased concentration and temperature, and some significant differences between the formulated pesticides were also observed. Comparisons of extrapolated cumulative penetration with Acceptable Daily Intakes indicate rapid exceedances when concentrated OPs are handled with unprotected hands.

Chapter 7 General Discussion

This chapter begins by emphasising the novelty and significance of the research.

Unlike most glove permeation and skin penetration studies this research used formulated OP products that are commercially available in the market. All experiments were conducted using an infinite dose model to simulate the worst exposure scenario (prolonged skin contamination from spills and splashes), and thus to establish the maximum penetration rates for risk assessment. By combining glove and skin studies, a more complete picture of dermal exposure is available. The performance of the gloves was not only tested in new (unused) condition, but also after exposure to UV radiation and abrasion to reflect the common condition of gloves being used by agricultural workers. The effect of elevated temperature was shown to be important for both gloves and skin and is discussed in a real world context. Four OPs with differing physicochemical properties were

selected for comparison of glove permeation and skin penetration. The skin data can potentially be used for predictive dermal risk assessment models, although no simple trends between OPs were discerned.

The generalisability of the research outcomes is discussed, and the chapter is completed with a discussion of the strength and limitations of the overall research.

Chapter 8 Conclusion and Recommendations

The data indicate that the use of concentrated OPs in warmer conditions will greatly increase skin uptake. Toxicologically important uptake can occur in relatively short time periods without skin protection. Glove permeation also increases with concentration, temperature, UV and abrasion, and this needs to be better understood by users. The practice of double gloving by ambulance workers is supported by the evidence. Recommendations are made for future researchers, the glove users, manufacturers and suppliers of OPs and gloves as well as regulatory and enforcement bodies.

Broad Research Questions

The following questions were developed from the literature review and from preliminary field observations.

- How do the recommended PVC gloves (unused, exposed to UV and abrasion) perform against OPs in various exposure conditions?
- What are the effects of different variable conditions on the barrier performance of different types of disposable gloves worn by ambulance workers and is the current practice suitable?

How is skin penetration affected by physicochemical properties of OPs, concentration of OPs and elevated temperature?

Specific Research Questions

RQ1 Are the recommended PVC gloves suitable for protection against formulated OPs?

RQ2 What are the effects of UV radiation on gloves with respect to formulated OP permeation?

RQ3 How does abrasion of the PVC glove materials affect permeation of formulated OPs?

RQ4 What are the effects of variable experimental conditions (diluted and undiluted concentration, room temperature and hot conditions) on the protection provided by the disposable gloves used by ambulance workers?

RQ5 How do individual gloves perform in terms of protection afforded, as compared to when gloves worn in combination?

RQ6 To what extent are the workers protected when implementing double gloving (combination of nitrile and neoprene gloves) as currently in practice?

RQ7 How do skin penetration outcomes differ between formulated OPs?

RQ8 How does the concentration of OP formulations and an elevated temperature affect skin penetration?

RQ9 How does the amount of OPs penetrated through the skin compare to the respective Acceptable Daily Intake (ADI)?

CHAPTER 1

GENERAL INTRODUCTION

This first chapter sets the scene for the use of organophosphorus pesticides as an issue of public health concern as well as security concern. The nature of the health hazard, the sources of exposure, routes of exposure and populations potentially exposed are briefly described.

A focal point for this chapter and subsequent chapters is those organophosphorus pesticides which are also classified as Chemicals of National Security Concern, and which are registered for commercial use in Australia.Given that the toxicity of these compounds is often expressed as a result of uptake through the skin, another focal point is dermal exposure, with special consideration of the selection and use of chemical protective gloves.

1.1 ORGANOPHOSPHORUS PESTICIDES (OPs) – HAZARDS AND EXPOSURES

Organophosphorus pesticides, hereafter referred to as OPs, represent different types of organophosphorus compounds. Organic compounds containing phosphorus have a diverse chemistry and are used in many applications (Quin 2000). These include use as agricultural and urban pesticides, animal husbandry, oil additives, flame retardants, therapeutic agents, plasticizers, and ligands for solvent extraction/purification of metals such as uranium and thorium (Alibrahim and Shlewit, 2007). Historically, some were also used as chemical warfare agents.

Generically, pesticides are toxic chemicals dispersed into the environment with the purpose to kill or harm living organisms considered as pests including animals, plants, microorganisms or fungi. They are widely used in private homes, gardens, farms, and

buildings worldwide. Owing to their effectiveness, pesticides are known as a major contributor to significant productivity increase in the agricultural sector in the 20th century (van Emden & Peakall 1996). However, pesticides may cause environmental pollution, and can also be misused in poisoning and suicides. Some of them have the potential to significantly alter ecosystems, and may have the same toxicological endpoints that target humans.

Pesticides are categorised into classes depending on their target (insecticides, fungicides, herbicides, etc). Insecticides are further classified into several prominent groups based on their chemical structures and modes of action: e.g. organophosphorus, organochlorines, carbamates and pyrethroids.

OPs as Insecticides

OPs are the most commonly used insecticides in the world (Bey, Sullivan & Walter 2001).Most OPs undergo relatively rapid hydrolysis in the environment, and unlike the organochlorines, are not considered persistent chemicals (Kazemi et al. 2012; Kumar et al. 2010; Workplace Health and Safety Queensland 2012).

OPs are commonly applied as an aerosol dissolved in hydrocarbon solvents, in low pressure or high pressure applications (Yeung et al.1998). Many OPs are also popular in the veterinary and livestock industry due to the broad spectrum of activity and high effectiveness against internal and external parasites. OPs are typically used for sheep dips, controlling ticks, mites, nematodes, blowflies and lice. The use of OPs in the industry has been established for a long time as they are effective not onlyin immature stage (i.e. larvae, pupae, nymph), but alsoin adult stage of the parasites (Heatherly & Hodges 1998).

Among popular OPs used against these veterinary parasites include diazinon, dichlorvos, chlorpyrifos, coumaphos, malathion and ethion. Typically, the OPs are available as formulated productsin the forms of emulsifiable concentrates (EC) and wettable powders (WP) for dipping and spraying. In some regions e.g. Latin America, OPs are commonly applied as backliners (pour-ons) on cattle (Webster 2001). There are also ready-to-use topical OP products to be used against fly maggots, and impregnated ear-tags for the control of flies on cattle. In addition, OPs are also widely used in collars and care products (e.g. shampoo, soap and spray) against fleas and ticks of household pets, although in substantially smaller amounts (Rotkin-Ellman et al. 2009; Taylor, Coop & Coop 2015). There are also OPsimpregnated in polivynilchloride pellets to be released into the gastrointestinal system of the hosts, such as dichlorvos(Webster 2001).

Opportunities for Exposure

Occupational exposure may exist in all stages of OP handling. OP users such as farmers and pesticide sprayers, manufacturers and the workers involved in disposal are directly exposed due to the primary contact with high concentration OPs. Workers in charge of transportation, storage and emergency situations involving OPs are examples of sub-populations indirectly or secondarily exposed to these chemicals. This manufacturing-to-disposal conceptual model of occupational OP exposure is depicted in Figure 1.1.

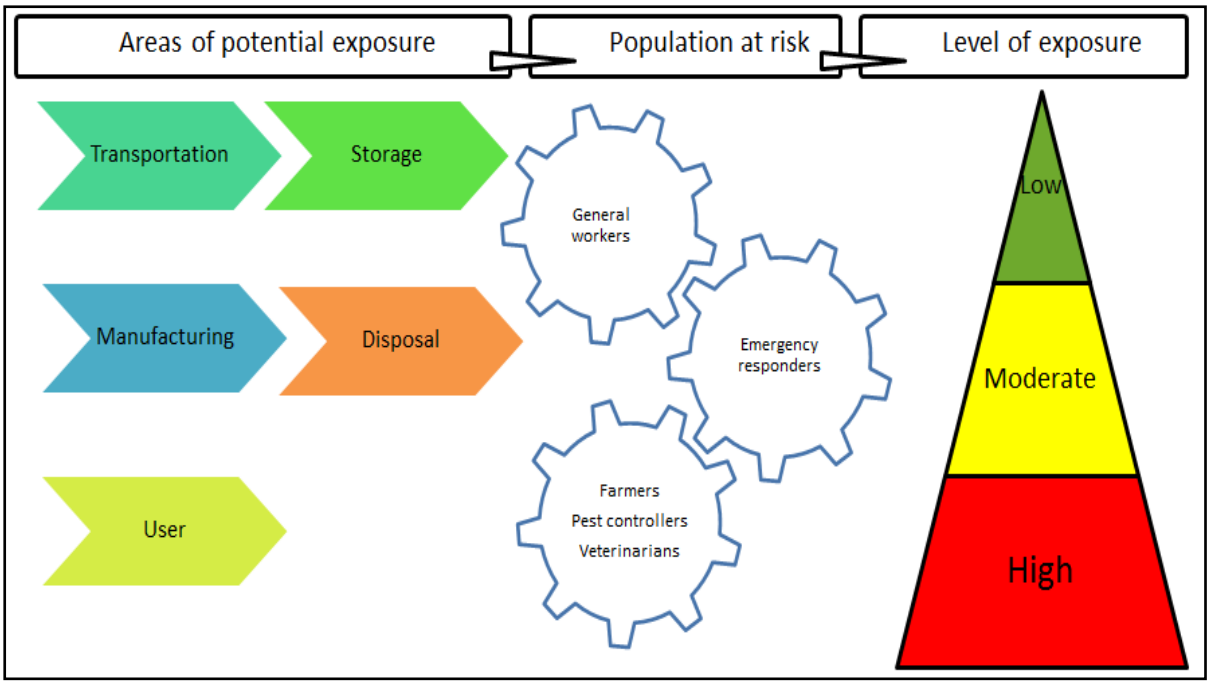


Figure 1.1 Conceptual model of occupational OP exposure

Exposure to OPs may occur to agricultural workers during spraying, re-entry of sprayed fields and harvesting sprayed crops or flowers (Blanco-Muñoz & Lacasaña 2011; Fenske & Day Jr. 2005; Hines et al. 2011; Iwata et al. 1977; Krieger, Driver & Ross 2006; Stewart et al. 2001; Strong et al. 2008). Other potential on-site exposures to OPs are when sowing pesticide-treated seeds, weeding sprayed fields and cleaning pesticide equipment and containers for disposal (Yoshida 1989).

Community exposure may potentially occur via spray drift but also through improper washing of fruits or vegetables treated with OPs(Savolainen & Kirsi 2009). Children may be exposed to high levels of pesticides, particularly if they live in agricultural areas by playing in nearby fields, by pesticides tracked into their homes by household members, or by breast milk from their farmworker mother (Eskenazi, Bradman & Castorina 1999).

Historically, inhalational exposure in the workplace has gained more attention than skin exposure and has been considered to be the most important pathway (CDC 2014; Schneider et al. 1999). For pesticides, however, skin absorption may be considered as a major route as the skin isthe human body's biggest organ and in view of the low to moderate vapour pressures of these chemicals (Ghafouriana et al. 2010; Rycroft, Menne & Frosch 2001; Thongsinthusak, Ross & Dong 1999).

Australian research on OPs has examined exposure in selected settings, notably fruitfly and termite control. This has included inhalation and dermal exposure assessment, biomonitoring, worker knowledge and effectiveness of skin protection (Yeung et al. 1998; Cattani et al. 2001; Dyer et al. 2001; Cattani 2004; Lee 2004; Johnstone 2006; Johnstone, Capra &Newman 2007; Edwards et al. 2007; Lee et al. 2009). Dermal exposure has been reported as a major route (Yeung et al. 1998).Research in Queensland has highlighted limited worker knowledge of the use of personal protective equipment (PPE). The majority of farmers did not wear gloves or overalls, and poor work practice was exacerbated by hot weather (Johnstone, 2006).

Although diluted OPs are used by farmers during spraying, overall uptake may be significant due to the repetitive and long period of exposure – i.e. multiple exposures may amplify the toxicity (Savolainen & Kirsi 2009). Exposure to concentrated OPs is possible when a splash occurs during loading and mixing. The risk is higher if exposure happens on skin areas which are not protected (e.g. ungloved hands). Previous studies have shown that hands can be an important contributor (50 to 90%) to the total body exposure (Abbott et al. 1987; Archibald, Solomon & Stephenson 1995; Karr et al. 1992). Apart from splashes, aerosol deposition and

transfer from contaminated surfaces are possible, and some data have been reported in fruitfly applications (Edwards et al. 2007).

OP Toxicity

Toxicologically, OPs act as acetylcholinesterase inhibitors, and affect the nervous system. Some may also directly stimulate nicotinic or muscarinic receptors (mimicking acetylcholine). Sarin, a chemical weapon, and diazinon, a common insecticide, are examples of these cholinomimetic substances.

Toxicity from the exposure to OPs is not limited to the acute phase, and their chronic effects have long been noted, usually in the peripheral nervous systems of adults. Generally, dose may affect the duration and severity of the symptoms. Individuals exposed to high levels of OPs may develop acute cholinergic syndrome, with symptoms like headache, salivation, lacrimation, tachycardia and convulsions (Breckenridge & Stevens 2008). In lower dose, neurotoxic effects have been reported, cumulative depression of cholinesterase activity may occur, that is the enzyme used for breaking down the neurotransmitter acetylcholine, into inactive metabolites, choline and acetate at the synaptic cleft of the neuromuscular junction (Tarter, Edwards & van Thiel 2013). As a result, overstimulation and/or potential paralysis of muscarinic and nicotinic receptors may occur, and in cases of severe intoxication, respiratory failure that potentially leads to death (Bullock & Manias 2013; Sachdeva & Nair 2005).

Symptoms include disorientation, delayed reaction times, impaired memory and concentration, speech difficulties, insomnia, nightmares, severe depression, irritability and flu-like conditions (Alikhan & Maibach 2011; Čolović et al. 2013). However, the severity of the symptoms does not necessarily correlate to the degree of cholinesterase inhibition

(Eskenazi, Bradman & Castorina 1999). Plasma cholinesterase is often more depressed than red blood cell cholinesterase, and it has been suggested that the greater use of pest control chemicals in Australia explains lower population plasma (pseudo) cholinesterase differences between Australia and the UK (Dyer et al.2001).

Various long-term neuropsychiatric effects and neurobehavioral abnormalities have been associated with acute and chronic exposure to OPs (Dassanayake et al., 2007; Salvi et al., 2003; Singh and Sharma, 2000; Steenland et al., 1994). Neurologic symptoms attributed to OP exposure were reported to be due to parasympathetic hyperactivity as a result of acetylcholinesterase inhibition (Rastogi, Tripathi & Ravishanker 2010). However, despite substantial evidence, there are several uncertainties on the real risks of developing neurobehavioral changes after long-term exposures to low doses of neurotoxic OPs (Binukumar & Gill 2011). On fetuses and young childrens, exposure to OPs (even in low level) has been linked with neurobehavioral functioning and development; e.g. abnormal neonatal reflexes, poorer mental development pervasive developmental disorder (PDD) and attention deficit/hyperactivity disorder (ADHD) (Bouchard et al. 2010; Engel et al. 2007; Eskenazi et al. 2007; Huen et al. 2009; Marks et al. 2010; Rauh et al. 2006; Young et al. 2005).

OP Dermal Risk Management – the Glove Option

One of the major approaches in dermal risk managementis through the use of chemical protective gloves. Theselection of gloves isnot always straightforwardfor the directly exposed population (e.g. is one type of glove suitablefor various types of OPs of different physicochemical properties, and in different formulations for various applications?). Management of risks of OPs is alsoproblematicfor the indirectly exposed population due to the nature of their main task that potentially deals with many types of hazards. It is even more

challengingin emergency situations, where incorrect selection of personal protective equipmentcan hasprofound consequences for the victims as well as first responders, e.g. ambulance workers who need to rapidly access the affected area and treat the victims.

Glove selection criteria include degradation and permeation resistance, durability, dexterity and comfort (Klingner and Boeniger, 2002; Nielsen 2004). It is very difficult to combine all the factors, and even if there are such gloves, the cost can be rather high. This means the gloves are unlikely to be a popular choice in developing countries, particularly amongst workers who need to change them frequently. Ideally, gloves worn by OP handlers should be changed often to ensure optimumprotection.

In real life scenarios, workers are exposed to commercial formulated OPs which contain the active ingredients and carrier solvents that act, for example, as solubilisers to improve stability and effectiveness of the former (Fenske & Day Jr. 2005). Solvents may increase the permeability of a formulation or independently damage the skin (Grandjean 1990). It is therefore important to investigate permeation and penetration closest to the realistic conditions to those which humans may be exposed to, as recommended in the OECD guidelines (OECD 2011). This will also assist in evaluating the (combined) toxicity of both active ingredients and the carrier solvents for risk profiling of the OPs. Better understanding of this problem can assist in minimising potential dermal exposures for workers(Sartorelli et al. 1997).

Glove performance tests often do not reflect the environment in which a glove may be used. The tests are usually conducted in laboratories in controlled conditions at room temperature, while the performance of the gloves could be greatly affected by environmental or task

factorse.g. elevatedtemperature, exposure to ultraviolet light (sunlight), flexing and abrasion (Perkins & Rainey 1997; Phalen &Que-Hee 2008, Phalen &Wong2011, 2012, Phalen, Le & Wong 2014).

Various models have been proposed and developed to bring forward dermal exposure prediction, assessment and management. Most dermal models realistically provide only simple prediction (Guy & Pelts 1993), and there appears to be no adequate glove performance prediction model for binary or higher order mixtures in formulated pesticide concentrates (Nelson et al. 1981).

1.2 ORGANOPHOSPHORUS PESTICIDES CLASSIFIED AS CHEMICALS OF SECURITY CONCERN

It is estimated that there are more than 400,000 trademarked products formulated from 40,000 chemicals approved for use in Australia (COAG 2008). Of that, approximately 700 products containing OPs are commercially available (Oglobline et al. 2001). These OPs are available (or accessible) from various sources including manufacturers, suppliers, distributors, industrial areas, farms and research laboratories.

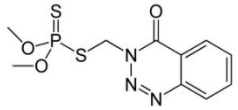
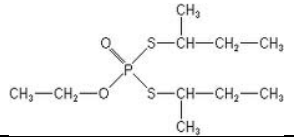
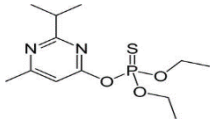
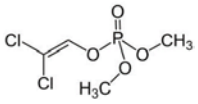
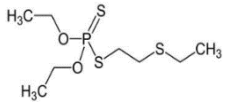
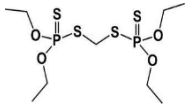
Besides the legitimate and intended uses of OPs e.g. for protecting crops, turf and ornamental plants against pests, treatment of stored grains, as well as pest control for industrial and domestic animals, the ready availability of toxic OPs may result in misuse – leading to accidental or intentional poisoning. In particular, the potential use of organophosphorus compounds as a weapon by terrorists was realised in the 1995 Tokyo subway attack involving

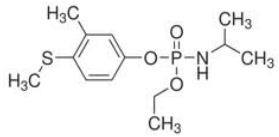
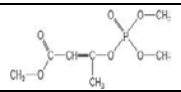
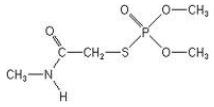
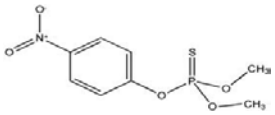
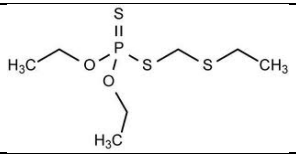
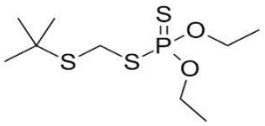
sarin. Due to heightened levels of domesticsecurity concern since 2001, the Council of Australian Governments (COAG) listed 12 OPs as Chemicals of Security Concern, owing to their potential to cause mass casualties (COAG 2008, 2013) – see Table 1.1.

Despite being prohibited for use by the European Union (EU), and classified by the World Health Organization (WHO) as moderately to extremely hazardous, the 12OPs of Security Concern are still being widely utilised in Australia with several registered products. These chemicals are currently under review by authorities such as the Australian Pesticides and Veterinary Medicines Authority (AVPMA) not only for their toxicity, but also for having occupational safety and health, public health, environmental and trade concerns (COAG 2013; APVMA 2011a, 2011b; Commonwealth of Australia 2013; Immig 2010; National Security Australia 2013).

For the purpose of this research, these 12 OPs of Security Concern will be further explored in Chapter 2. Selected features of the shortlisted OPs are summarised in Table 1.1.

Table 1.1 Shortlisting of organophosphorus pesticide (OP) chemicals from the Chemicals of Security Concern for this research

Chemicals of Security Concern	OPs	Chemical structure	EU status	WHO classification	Potential carcinogen	Potential endocrine disruptor	APVMA status	Log Kow	MW	Number of registered products in Australia	Examples of uses in Australia
Aldicarb Aluminium phosphide Ammonia (anhydrous) Ammonium nitrate Ammonium perchlorate Arsenic pentoxide Arsenic trioxide Arsine Azinphos methyl Bendiocarb Beryllium sulphate Bromine Cadusafos Calcium cyanide Carbofuran Carbon disulphide Carbon monoxide Chloropicrin Chlorfenvinphos Chlorine Cyanogen bromide Cyanogen chloride Diazinon Dichlorvos Diethyl phosphite* Dimethyl phosphite* Dimethyl mercury Dimethyl sulphate Disulfoton Endosulfan Ethion Ethyl mercury chloride Ethyldiethanolamine Fenamiphos Fluorine gas Fluoroacetic acid Fluoroethyl alcohol Fluoroethyl fluoroacetate	Azinphos methyl 86-50-0		Prohibited in EU	Highly hazardous			Under review since 1994. Spray drift priority list: Human health & environmental concerns	2.96	317.3	4	Fruit, macadamias
	Cadusafos 95465-99-9		Prohibited in EU	Highly hazardous	USEPA: evidence of non-carcinogenicity for humans			3.9	270.4	2	Bananas, citrus, ginger, sugar cane, tobacco tomatoes
	Diazinon 333-41-5		Prohibited in EU	Moderately hazardous	USEPA: unlikely to be carcinogenic to humans	EU 2, USEPA screen list)	Under review since 1996. Occupational, public health, environmental and trade concerns	3.3	304.3	54	Turf, pastures, field crops, vegetables, plantation and orchard crops, household pests, flea & tick control (pets), cattle, pigs, goats
	Dichlorvos 62-73-7		Prohibited in EU	Highly hazardous	USEPA: suggestive evidence of carcinogenicity, but not to assess human carcinogenic potential. IARC: possibly carcinogenic to humans		Under review since 1996. Occupational, public health, environmental and trade concerns	1.2-1.5	221.0	15	Stored cereal grains, industrial and domestic pest control
	Disulfoton 298-04-4		Prohibited in EU	Extremely hazardous	USEPA: evidence of non-carcinogenicity for humans		Nominated for review (priority 4): Potential to cause harm	3.95	274.4	1	Lucerne, cotton, potatoes, peas, beans, bubs, gladioli
	Ethion 563-12-2		Prohibited in EU	Moderately hazardous	USEPA: evidence of non-carcinogenicity for humans			5.07	384.5	56	Cotton, cattle, horses, cats, dogs

Hydrochloric acid Hydrogen chloride Hydrogen cyanide Hydrogen peroxide Hydrogen sulfide Magnesium phosphide Mercuric chloride Mercuric nitrate Mercuric oxide Mercurous nitrate Mercury cyanide Methamidophos Methidathion Methiocarb Methomyl Methyl fluoroacetate Methyldiethanolamine Mevinphos Nitric acid Nitric oxide Nitromethane Omethoate Osmium tetroxide Oxamyl Paraquat Parathion methyl Perchloric acid Phorate Phosgene Phosphine Phosphorus Phosphorus oxychloride Phosphorus pentachloride Phosphorus trichloride Potassium chlorate Potassium cyanide Potassium nitrate Potassium perchlorate Propoxur Sodium azide Sodium chlorate Sodium cyanide Sodium fluoroacetate Sodium perchlorate Sodium nitrate Strychnine Sulfur dichloride Sulfur monochloride Sulphuric acid Terbufos	Fenamiphos 22224-92-6			Highly hazardous	USEPA: evidence of non-carcinogenicity for humans		Under review since 2003. OHS, public health, environmental and residues in food concerns	3.3	303.4	14	Aloe vera, bananas, citrus, crucifers, cucurbits, carrots, beetroot, onions, celery, sweet potatoes, lettuce, endive, parsnips, grapevines, mushrooms, pineapples, potatoes, strawberries, sugarcane, tobacco, tomatoes, turf, ornamentals
	Mevinphos 7786-34-7		Prohibited in EU	Extremely hazardous	USEPA: unlikely to be carcinogenic to humans	EU 2	Review completed 2002 Restricted chemical product	0.13	224.1	2	Brassicas (cabbage, cauliflower, broccoli), Brussel sprouts
	Omethoate 1113-02-6		Prohibited in EU	Highly hazardous		EU 1	Under review since 2004. Toxicology, OHS, residues and trade concerns	-0.74	213.2	13	Pastures, cereals, oilseed, legumes, lucerne, cotton, apples, bananas, citrus, lupins, onions, pears, potatoes, ornamentals, fruit, vegetables (home garden)
	Parathion methyl 298-00-0		Prohibited in EU Listed under Rotterdam Convention (EC or above 19.5% AC and dusts 1.5% AC)	Extremely hazardous	IARC: not classifiable	EU 2, USEPA (screen list)	Under review since 1996. OHS, environmental concerns, high toxicity to bees. Spray drift priority list: Human health & environmental concerns	3.0	263.2	5	Cotton, cruciferous forage, citrus, pome and stone fruits, grapevines, tobacco
	Phorate 298-02-2		Prohibited in EU	Extremely hazardous	USEPA: evidence of non-carcinogenicity for humans		Nominated for review (Priority 2) Human health concerns	3.92	260.4	7	Cotton, ornamentals, carrots, onions, cabbage, broccoli, cauliflower, brussel sprouts, potatoes, tomatoes
	Terbufos 13071-79-9		Prohibited in EU	Extremely hazardous	USEPA: evidence of non-carcinogenicity for humans		Nominated for review (Priority 2) Environmental& Human health concerns	4.5	288.4	5	Bananas, maize, sorghum, swet corn, wheat, peanuts, sunflowers, barley

Thallium sulphate Thionyl chloride Thiophosphoryl chloride Triethanolamine Triethyl phosphite* Trimethyl phosphite* Zinc cyanide Zinc phosphide											

Source: Our Stolen Future, book by Dr Theo Colborn, Dianne Dumanoski and Dr John Peterson Myers, 1997
USEPA screen list: Final list of Initial Pesticide Active Ingredients and Pesticide Inert Ingredients to be screened under the Federal Food, Drug and Cosmetic Act

Shaded boxes indicate the four OPs shortlisted for studies in this thesis (Chapters 4,5 and 6)
*Not an organophosphorus pesticide

1.3 PUBLIC HEALTH SIGNIFICANCE OF OP POISONINGS

Human exposures to pesticides are widespread in both developed and developing countries (Jeyaratnam 1990; Stellman 1998; Thundiyil et al. 2008). The wide use of toxic OPs in agricultural, veterinary and pest control industries worldwide has public health implications.

The World Health Organization (WHO) estimated 3 million acute pesticide poisoning cases occur annually with 600 million workers at risk by exposure to pesticides on a regular basis (Cwikel 2006; Jeyaratnam 1990; WHO/UNEP 1990). Although 80% of the annual production of pesticides is used in developed countries, the majority of the pesticide-related poisonings and fatalities occur in developing and underdeveloped countries (Pimentel & Greiner 1996; WRI/UNEP/UNDP 1994). In developed countries, annual incidence rate of acute pesticide poisoning was reported to be approximately 18 per 100,000 full time agricultural workers (Calvert et al. 2004). In Australia, a total of 507 pesticide accidents cases were reported from 1999-2000 (Fragar et al. 2003). There were 388 hospital separations recorded for the same years with OPs and/or carbamates dominating 41% of the total cases; 130 identified as accidental and 69 intentional (Harrison& Henly 2003).

In developing countries, a largepopulation is involved in the agricultural sector accounting for 75% of the case fatalities (Jeyaratnam, Lun & Phoon 1986). The proportion of cases varies, however in Southeast Asia alone, approximately 200,000 deaths are reported every year (Cwikel 2006). Among the factors contributing to higher incidence rates in developing countries include larger exposed populations, lack of enforcement and training, unavailability or poor maintenance of personal protective equipment, as well as poor labelling and illiteracy (Pimentel & Greiner 1996; Thundiyil et al. 2008).

The use of the cheapest, and perhaps less-safe, pesticides is common in under-developed countries. Hence, the health of the farmers and family members are affected by the exposure to these pesticides (Kato, Ratcliffe & Hobson-Rohrer 2004). Several authors have asserted that OP poisoning seems to be more common in the Third World regions where highly toxic OPs (WHO Class I toxicity) are available (McConnell & Hruska 1993; Rosenthal 2003).

1.4 THE NEED FOR RESEARCH ON DERMAL EXPOSURE ASSESSMENT AND CONTROL

Unacceptable numbers of occupational cases of OP-induced poisoning continue to occur and this problem is compounded by security concerns.In addition, the diversity of OPs is problematic.Table 1.1 shows that OPs have varying chemical structures and molecular properties. It is therefore unlikely that OPs can be treated as a simplegroup for dermal risk assessment.

A preliminary scan of the occupational hygiene literature suggests that these substances have been primarily examined on an industry basis – e.g. in agriculture, pest control, manufacture etc., with no comprehensive appraisal. From an epidemiology standpoint, research studies have suffered from a lack of detailed exposure data, and crude methods have been adopted, particularly in cohort studies (Alavanja &Bonner 2012). Finally, a conceptual model of dermal exposure assessment is only relatively recent (Schneider et al. 1999).

Overall, there appears to be a need to better understand dermal exposure as well as the effectiveness of gloves, across the various OPs, the various exposed populations (i.e. users, emergency workers etc.) the various formulated products and the various real world situations, e.g.hot weather etc.

Such research will assist in reducing the occupational disease burden due to skin exposure, which is often under-recognised (Boeniger 2003; Semple 2004). In addition, it will assist in rationalising glove selection and use, and in training of workers and inspectors.

The next chapter represents a literature review ofthe 12 OPs identified as Chemicals of Security Concern. The review has an emphasis on what is known about dermal exposure, including empirical studies of skin penetration and skin protection.

CHAPTER 2

LITERATURE REVIEW

In the previous chapter, a range of issues associated with dermal exposure to OPs were discussed, including the importance of skin protection.

This chapter presents a literature review of the 12 OPs identified as Chemicals of Security Concern, with narrative synthesis. The review has an emphasis on what is known about dermal exposure, including empirical studies of skin penetration and skin protection.[1]

Uncertainties and knowledge gaps regarding dermal exposure are considered, and a set of broad questions justified for further research. In view of the large numbers of workers potentially exposed, and the circumstances of exposure, a case study approach utilising a purposive subset of the 12 OPs will be recommended for this research.

[1]Note that the terms *permeation* and *penetration* as applied to skin and glove studies need clarification. Both have been used in the toxicology and pharmacology literature in relation to transdermal chemical uptake into the body. Another term is *percutaneous absorption*. In contrast, chemical permeation of glove materials refers to molecular diffusion in the polymer (following absorption and desorption).

For the purpose of this thesis, penetration will be the term used for the transdermal process (leading to systemic circulation of the chemical), and permeation will be used in the context of gloves. This is because, penetration has a special meaning in the chemical protective clothing literature, that is the movement of chemical by mass flow though pinholes, seams and zippers.

2.1 OBJECTIVES OF THE LITERATURE REVIEW

The objectives were as follows:

- Systematically search, extract, categorise and interpret relevant literature, from various disciplines – i.e. epidemiology, occupational hygiene, toxicology, pertaining to the 12 OPs of security concern.
- Relate the literature to populations at risk from OPs, either from occupational use or incidental exposure, as described in Chapter 1.
- Identify literature gaps and research opportunities
- Inform and justify broad questions to be addressed in subsequent research

Owing to the likely diversity of information sources, including technical literature, narrative synthesis, without quality assessment was used.

2.2LITERATURE SEARCH STRATEGY

An initial computerised search was conducted utilising the following electronic bibliographic databases:

- Scopus; provided by Elsevier
- PubMed and Medline, produced by the United States National Library of Medicine (NLM)
- Web of Science, maintained by Thomson Reuters

The logic grid, including search terms and limiters, is given in Table 2.1.

Table 2.1 Logic grid used in the literature search strategy

Individual name of the 12 OPs • Azinphos methyl • Cadusafos • Diazinon • Dichlorvos • Disulfoton • Ethion • Fenamiphos • Mevinphos • Omethoate • Parathion methyl • Phorate • Terbufos	AND (skin OR dermal) AND (penetration OR permeation)	1975 - English language
Organophosphorus pesticides OR organophosphate pesticides	AND glove* AND (ultraviolet OR UV) OR (abrasion)	

Besides the individual name of the 12 OPs listed as Chemicals of Security Concern, keywords such as 'skin', 'dermal', 'penetration' and 'permeation' were also used to identify literature of interest on skin studies. For glove permeation studies, index terms such as 'organophosphorus pesticides', 'organophosphate pesticides', 'glove, 'ultraviolet', and 'abrasion' were also used. The initial search was limited to English language articles published in the past 40 years. Functions provided by the electronic literature databases and search engines such as 'related articles' or 'articles citing this article' were utilised to identify further related articles – i.e. forwards and backwards searching. Additionally, research reports, dissertations as well as reference lists from the retrieved reports and publications from selected authors were also examined to identify any additional papers. Generic search engines such as Google Scholar were also explored.

2.3 SEARCH OUTCOMES

Articles obtained from the search methods (Section 2.2) were shortlisted and imported into *Endnote* (Version X5) bibliographic software. Duplicate references were deleted. Titles and abstracts were reviewed to determine their relevance to the scope of the research. Then, the full texts were examined. Those items that were not related to dermal exposure, *per se*, were not shortlisted. An example of this was:

> Peterson, RP, Picard, GL & Devine 1985, 'Methods for the determination of total terbufos-[phosphorodithioic acid, S-(tert-butylthio)methyl O,O-diethyl ester] related residues in dermal exposure pads and air collection tubes and related alkyl phosphate metabolites in urine', J. Agric. Food Chem., vol. 33, pp. 1041-1044.

This paper only referred to the adequacy of the analytical chemistry, and did not provide exposure data for terbufos.

2.3.1 Compilation of the key literature

The shortlisted articles (and other literature) were perused and the key findings are summarised in Table 2.2, in alphabetical order of the OPs.

Table 2.2 Key findings from the shortlisted articles

OPs/ Chemicals of Security Concern	Type of study	Authors / Year/ Title	Findings
Azinphos methyl	Toxicological studies	WHO/Available from, as of 19th October 2015/Azinphos methyl- Evaluation for Acceptable Daily Intake, viewed at http://www.inchem.org/documents/jmpr/jmpmono/v91pr02.htm	Buehler patch test- dermal application of a concentration of 12.5% induced sensitization in approximately 50% of the test animals when challenged using a 6% concentration, but using a challenge concentration of 0.6% failed to elicit any relevant skin reactions. Acute Exposure- dermal application of a concentration of 25%, sensitisation was induced in approximately 50% of the guinea pigs tested. Acute exposure- skin irritation study, 24-hr exposure to azinphos-methyl at intact and abraded skin sites did not cause any signs of irritation
		Bingham, et al./ 2001/ Patty's Toxicology	Dermal absorption of azinphos methyl 68%, 78%, and 76% after 10 hrs reported in rats exposed to 0.93, 9.3, and 93 µg azinphos-methyl/cm^2 as wettable powder (equivalent to 0.056, 0.56, or 5.6 mg/kg) on their clipped dorsal skin. 42%, 22%, and 18% of the applied dose was recovered in urine, feces, carcass, and cage wash combined for the 0.056, 0.56, and 5.6 mg/kg doses, respectively. In humans, 16% of an applied dermal dose (4 µg/cm^2 on ventral forearm) was absorbed within 5 days. Excretions in urine were 5.5% of the applied dose (1^{st} 24 hrs), 5% (2^{nd} 24 hrs) and 3% (3^{rd} 24 hrs), suggesting considerable dermal absorption of azinphos-methyl
		Skinner et al./ 1982/Acute dermal toxicities of various organophosphate insecticides in mice	Acute Exposure- Dermal LD_{50} values were determined in mice by application of azinphos methyl to hind feet. LD_{50} values were higher than reported values for mice treated on shaved back skin. ChE ED_{50} values roughly paralleled the LD_{50} values. Acute Exposure- Dermal toxicity investigated with a mouse intermittent self-exposure model (blood ChE and foliar concentrations). Responses were much greater in unmuzzled than in muzzled animals due to oral contamination, however azinphos-methyl produced no significant responses in muzzled mice at maximal foliar concentrations

Azinphos methyl	Epidemiological and occupational hygiene studies	Formoli/ 2001/ Estimation of exposure of persons in California to pesticide products that contain azinphos-methyl	Volunteers were exposed to azinphos methyl at ventral forearms of volunteers (intravenous). Skin absorption was found to be 15.9% in 5 days, and under occlusion was increased to 56.1% absorption at 24 hrs. Urine samples collected from the second group of volunteers showed the rate of elimination in urine varied with time, in both groups. Excretion of urine and feces from the third group dosed with aqueous suspension of Guthion 25 WP showed the majority of the absorbed dose was excreted in urine. Total recovery of the applied dose for all three groups ranged from 102 to 105%, suggests that azinphos methyl did not accumulate in the body during the study period.
		McCauley et al./ 2001/ Work characteristics and pesticide exposures among migrant agricultural families	Levels of azinphos methyl in migrant farm worker homes were monitored to determine children's exposure; concentration in farm worker homes was 1.45 ppm; in grower homes was 1.64 ppm; median concentration in play areas of grower homes was 0.71 ppm, suggesting potential exposure to children. The levels are associated with the number of workers in the home and the distance from fields.
		Fenskeet al./1999/ Comparison of three methods for assessment of hand exposure to azinphos-methyl (Guthion) during apple thinning	Apple thinners were assessed for 2-hr exposure to azinphos methyl using glove, handwash, and wipes. Foliar residue samples collected on each day of hand exposure sampling were constant during the four-day study. Exposure rates were 6.48, 1.83, and 0.28 mg/hr for the glove, handwash, and wipe methods respectively. Different methods may overestimate or underestimate exposure, sampling methods should be carefully described and potential for measurement bias recognised.
		Aprea et al./ 1994/ Biological monitoring of exposure to organophosphorus insecticides by assay of urinary alkylphosphates: influence of protective measures during manual operations with treated plants	Workers in peach orchard exposed to azinphos methyl and chorpyrifos-methyl showed high levels of urinary excretion of alkylphosphates. The hand-wash liquid of the workers was also analysed to evaluate skin contamination. Skin absorption appeared to be the main route of absorption and inhalational absorption seemed significant with reference to urinary excretion.
		McCurdy et al./ 1994/ Assessment of azinphosmethyl exposure in California peach harvest workers	Azinphos methyl was detected on skin and clothing of workers at 95 to 14,498 µg/sample of clothing, with the greatest concentrations (2,953 to 14,498 µg/shirt) were reported on the shirts. Urinary metabolites indicated good correlation with RBC-AChE, and moderate correlation for dermal and clothing levels.

Azinphos methyl	Epidemiological and occupational hygiene studies	Franklin et al./ 1986/ The use of biological monitoring in the estimation of exposure during the application of pesticides	Dermal exposure to azinphosmethyl for orchard workers in British Columbia, Canada was reported as 1200-18,400 µg/kg with a mean of 5200 µg/kg. Compared to patch data, urinary metabolite data is more reliable and accurate for estimating exposure.
		Wester et al./1985/ *In vivo* percutaneous absorption and decontamination of pesticides in humans	*In vivo* percutaneous absorption of guthion in humans is 15.9%. Ventral forearm site of application for 24-hr exposure. Effect of occlusion (covering the applied dose) on *in vivo* percutaneous absorption of guthion is 56.1% dose absorbed. Effect of damaged skin *in vivo* percutaneous absorption of guthion in humans is 60.5%. Rate and extent of percutaneous absorption on many factors.
		Franklin et al./1981/ Correlation of urinary pesticide metabolite excretion with estimated dermal contact in the course of occupational exposure to Guthion	Skin patches beneath the clothing indicated traces of Guthion (azinphos methyl) on the skin. No significant depression of either red blood cell or serum ChE activity in any workers. There was a high correlation between 48-h alkyl phosphate excretion and amount of azinphos methyl sprayed
		Lamb/ 1980/ Early studies with azinphos methyl to determine re-entry times for citrus pickers	Depression of Plasma ChE was observed from blood analysis, after 10th days the plants were sprayed with azinphos methyl (prepared from a wettable powder 6 oz/100 gallons). Pickers of fruit sprayed with a lower concentration showed erythrocyte ChE depression but not of the plasma enzyme. Dermal exposure was more serious than inhalation exposure.
		Fluckeet al./1980/ Gusathion-M active ingredient (R 1582) subacute cutaneous study of toxicity to rabbits	Subchronic or Prechronic Exposure/ dermal toxicity study in rabbits, azinphos-methyl applied for 6 hrs per day, to the shaved dorsal and lateral skin, at dose levels of 0 (control), 2, or 20 mg/kg b.w, for 5 days per week for 3 weeks. Approximately 30% depression of erythrocyte activity observed, compared to controls treated with 20 mg/kg. ChE activity in plasma and brain, and erythrocyte activity at 2 mg/kg, remained undisturbed by treatment. No difference found between the groups with intact and abraded skin.
		Richards et al./ 1978/ A controlled field trial of physiological responses to organophosphate residues in farm workers	The daily mean % change in ACh and pseudoChE activity was <-10% of baseline values for group of workers in a Guthion treated plot and in an adjoining OP-free plot. Outcomes were different from previous studies for comparison, indicating difficulty in setting re-entry intervals based on time elapsed from pesticide application.
	Glove studies/ skin studies	Hafeez et al./ 2013b/ Occlusion effect on *in vivo* percutaneous penetration of chemicals in man and monkey: partition coefficient effects	Although longer occlusion (*in vivo*) can increase penetration of guthion (azinphos methyl), this does not apply to all compounds. Effects of occlusion is remarkable on very lipophilic compounds more than that of very hydrophilic compounds, thus partition coefficients cannot completely predict the effect of occlusion on percutaneous penetration.

Azinphos methyl	Glove studies/ skin studies	Gattu et al./ 2010/ Modest but increased penetration through damaged skin: An overview of the *in vivo* human model	A modest enhancement in penetration through damaged human skin *in vivo* was found, favouring hydrophilic molecules over lipophilic molecules. It also depends on method of measurement, different types and degrees of damaged skin.
		Keeble et al./ 1996/ Effect of laundering on ability of glove fabrics to decrease the penetration of organophosphate insecticides through *in vitro* epidermal systems	Both the skin and the knit glove fabrics provided protection against AchE inhibition caused by exposure to azinphos-methyl suspensions (3000 ppm), whether after 4 or 24 h of exposure. Neither glove laundering nor abrasion followed by laundering altered the capability of the *in vitro* epidermal systems to absorb azinphos-methyl suspension. Protection of cotton gloves against several OPs may be best before laundering.
Cadusafos	Toxicological studies	USEPA/ Acute Dietary Toxicity Endpoint and Review of Reproduction Study. Available from, as of 15 September 18, 2014: http://www.epa.gov/oppsrrd1/op/cadusafos.htm	Acute dermal LD_{50} Rabbits 24 mg/kg (male) and 41 mg/kg (female). Death occurred within 24 hrs post dose as a result of cholinergic over stimulation (respiratory failure), with signs of cholinergic toxicity between 2 and 24 hrs e.g. excess salivation, lacrimation, ataxia, chromodacryorrhea, tremors, decreased activity, labored breathing
		USEPA/ 2000/ Report on FQPA Tolerance Reassessment Progress and Interim Risk Management Decision Cadusafos; Available from, as of 11th September 2013: http://www.epa.gov/pesticides/reregistration/REDs/cadusafostred.pdf	Inhalation and dermal contact to cadusafos are potential through for occupational exposure where it is produced. In general population, exposure to cadusafos should be low or non-existent, as it is no longer registered for use in the USA
	No epidemiological and occupational hygiene studies found on cadusafos		
	No glove permeation studies or skin studies found on cadusafos		

Diazinon	Toxicological studies	APVMA/ July 1999 (revised September 2002/ Review of the mammalian toxicology and metabolism/ toxicokinetics of diazinon; Available from, as of 1st March 2013 http://www.apvma.gov.au/products/review/docs/diazinon_tox.pdf	Dermal LD_{50} Rat >2150 mg/kg Dermal LD_{50} Rat (male) 900 mg/kg Dermal LD_{50} Rat (female) 455 mg/kg Dermal LD_{50} Rabbit >2020 mg/kg b.w
		Skinner et al./ 1982/ Acute dermal toxicities of various organophosphate insecticides in mice	50% depression in plasma or RBC ChE from foliar pesticide levels. The greatest responses for emulsifiable concentrate (EC) was observed and encapsulated formulations were found with diazinon, followed by parathion and methyl parathion. Dermal LD_{50} values were determined in mice by application of solutions to hind feet. LD_{50} values were higher than reported values for mice treated on shaved back skin. Diazinon appeared much more inhibitory of blood than neuronal ChE.
	Epidemiological and occupational hygiene studies	Hayes, et al./ 1991/ Handbook of Pesticide Toxicology	Case report: A man survived subcutaneous injection of diazinon (14 mg/kg) with symptoms including sweating, abdominal pain, nausea, and coma when 80 mg of active ingredient (1% solution) was applied to the skin. Formulation is responsible for intoxication of 3 applicators and a herd of cattle. The material was found to be 30 times more toxic than a recently formulated emulsion concentrate of equivalent concentration.
		Wolfe / 1976/ Air Pollution From Pesticides and Agricultural Processes	During air blast spraying in fruit orchards, potential exposure were 23.4 mg/hr (dermal) and 0.06 mg/hr (respiratory). The risk of dermal exposure is higher than respiratory.
	Glove studies/ skin studies	Sugino et al./ 2014/ Safety prediction of topically exposed biocides using permeability coefficients and the desquamation rate at the stratum corneum	Permeability coefficient of diazinon was smaller than the desquamation rate; very low skin concentrations of compounds permeated the skin.
		te Brake et al./ 2012/ Effects of street clothing, sunscreen, and temperature on skin absorption of organophosphate pesticides – a review and case study of diazinon	While skin was found to be a good barrier to penetration, the use of sunscreen and denim fabric provided extra barrier for absorption and penetration. Human skin –from 418min (23°C) to 98 min (37°C). Pig skin –from 53 min (23°C) to 7 min (37°C).

Diazinon	Glove studies/ skin studies	Canning, et al./1998/ Laboratory simulation of splashes and spills of organophosphate insecticides on chemically protective gloves used in agriculture	Interaction of formulated chlorpyrifos and diazinon withglove surfaces was investigated, simulating splashes and spills (exposed to concentrated OPs for 1 min, diluted and concentrated OPs for 24, 36 and 48 hrs) PVC gloves: two classes of defects, cavities and convexities (all test conditions) Nitrile butadiene rubber gloves: significant cracking after 24 hrs. For routine agricultural use, more robust chemically protective gloves should be developed.
		Moody et al./ 1994/ *In vitro* dermal absorption of pesticides: IV. *In vivo* and *in vitro* comparison with the organophosphorus insecticide diazinon in rat, guinea pig, pig, human and tissue-cultured skin	Total percentage *in vitro* dermal absorptions 48 hr after exposure for the five skin types were: 47 +/- 3.4% (rat), 36 +/- 0.9% (tissue cultured Testskin), 33 +/- 2.8% (hairless guinea pig), 20 +/- 3.1% (human) and 15 +/- 13.1% (pig). *In vitro* data for dermal absorption of [^{14}C] diazinon for rats and hairless guinea pigs agreed with the data observed for rats and hairless guinea pigs *in vivo. In vitro* skin absorption tests can be used as an alternative to *in vivo* animal testing.
		Moody et al./ 1994/ Nitrile butyl rubber glove permeation of pesticide formulations containing 2,4-D-amine, DDT, DEET, and Diazinon	In 12% formulation: glove test strip appeared crenulated in all test cells at 24 hrs, visible surface cracks, one had 0.9% permeation in comparison with the other 3 replicates (mean of 0.1). Corrosive effect due to presence of xylene, enhanced permeability. Large reservoir of pesticide in the glove membrane at 24 hrs (not removed by a surface wash of soapy water) indicated continued permeation at a constant rate.
		Wester et al./ 1993/ Percutaneous absorption of diazinon in humans	<u>*In vivo*</u> Diazinon in acetone (2µg/cm^2) applied to forearm or abdomen, diazinon in lanolin (1.47µg/cm^2) applied to the abdomen, exposed for 24 hrs. Absorption: from 2.87 +/- 1.16% to 3.85 +/- 2.16% of the applied dose. No significant differences with regard to site or vehicle of application. <u>*In vitro*/ human abdominal skin</u> 14.1 +/- 9.2% of the applied dose accumulated in the receptor fluid over 24 hrs of exposure to 0.25 µg/cm^2 (acetone vehicle). The calculated mass absorbed was the same (0.035 µg/cm^2) for both *in vitro* and *in vivo* absorption through human skin.

Dichlorvos	Toxicological studies	ATSDR/Toxicological profile for dichlorvos, Available from, as of 1st March 2013; http://www.atsdr.cdc.gov/toxprofiles/tp65.pdf	Subchronic or Prechronic Exposure: Three cynomolgus monkeys were given daily dermal doses of dichlorvos in xylene on a shaved area between the shoulder blades. A monkey receiving 100 mg/kg/day died after 4 days. A monkey given 50 mg/kg/day died after 8 doses over 10 days and a monkey given 75 mg/kg/day died after 10 doses over 12 days. Clinical signs occurred within 10-20 minutes after dosing. Signs in their order of appearance were nervousness, gritting of teeth, incoordination, muscle fasciculations, excessive salivation, labored breathing, miosis, and flaccidity.
		Luty et al./ 1998/ Toxicity of dermally absorbed dichlorvos in rats	Female rats dermally exposed to dichlorvos (37.5 mg/kg - 1/2 LD_{50}; or 7.5 mg/kg - 1/10 LD_{50}) for 4 hrs daily for 4 weeks Dermally absorbed dichlorvos caused histopathological changes in lungs, lymphatic glands, thymus, liver, kidneys and heart muscle
		Mathias/ 1983/ Persistent contact dermatitis from the insecticide dichlorvos)	Case report: Dermatitis developed on the neck, anterior chest, dorsal hands, and forearms of a truck driver one day after dermal contact with pesticide containing 5% dichlorvos, 15% petroleum distillates, and 80% trichloroethane, in a spill. A faint papular dermatitis was present over the dorsal arms, hands, and V neck. Vertical erythematous, slightly scaling streaks were present over the lateral and posterior neck, a pattern suggesting that liquid droplets had produced the dermatitis. The dermatitis was treated with 1% hydrocortisone ointment. After 6 weeks, there were persistent vertical, mildly erythematous streaks over the posterior and lateral neck; the arms and anterior chest had cleared.
	Epidemiological and occupational hygiene studies	Perger et al./ 1991/ Measurements of the exposure to dichlorvos (DDVP) and biological monitoring of users	Without PPE, serum ChE activity showed significant depression and the total body dermal exposure (9.489 mg/hr) was higher than the respiratory exposure (0.613 mg/hr). Total body exposure (assessed by skin pads) decreased to 5.977 mg/h with the use of PPE during work, suggesting the efficacy of PPE for protection.
		Gold et al./ 1984/ Dermal and respiratory exposure to applicators and occupants of residences treated with dichlorvos (DDVP)	Low total dermal exposure of 2.354 mg/hr (0.028 mg/kg/hr in 85 kg body weight) with the use of PPE. Rubber gloves minimised exposure to dichlorvos (0.9% of total dermal exposure), but approximately 20% of dichlorvos in contact with the outer garments penetrated to the skin surface beneath, causing depression of serum ChE activity. In terms of acute toxicity, there was not a significant risk, to either the pesticide applicators or the residents of treated structures when DDVP was used for cockroach control.

Dichlorvos	Glove studies/ skin studies	Moore et al./2014/ Percutaneous absorption and distribution of organophosphates (chlorpyrifos and dichlorvos) following dermal exposure and decontamination scenarios using *in vitro* human skin model.	Human skin exposed for 24 h (infinite dose, 1 mg/cm^2 and 10 mg/cm^2; finite dose, 5 mg/cm^2) using 3 different vehicles isopropanol (IPA), isopropyl myristate (IPM) and propylene glycol (PG). Greatest absorption of dichlorvos in IPA (38.6% absorbed, lag time 0.6 hr). The 10-fold difference in applied concentration resulted in approximately 10- fold difference in absorption from IPA and a 10-fold difference in maximum flux. Upon skin contact with dichlorvos and chlorpyrifos (and chemicals with similar properties), quick skin surface decontamination would be required to reduce delayed systemic absorption.
		Moore et al./2014/ Use of a human skin *in vitro* model to investigate the influence of 'every-day' clothing and skin surface decontamination on the percutaneous penetration of organophosphates	Absorption of dichlorvos was significantly greater through unclothed skin compared with clothed skin for all vehicles tested (10% (501.7 ± 113.5 ng/cm^2) in IPA), followed by PG (8.9%) and IPM (6.4%). 'Every-day' clothing is useful to reduce exposure to chemicals and prompt washing of the skin surface after removing exposed clothing can further reduce exposure, depending on the properties of the chemical and vehicle applied.
		Mircioiu et al./ 2013/ Evaluation of *in vitro* absorption, decontamination and desorption of organophosphorous compounds from skin and synthetic membranes	Human skin/ dichlorvos (0.3 mL)/receptor volume 12.6 mL, flow rate 2 mL/min) Skin with intact stratum corneum had lag-time of several hrs, and no lag time for skin without stratum corneum. 10 hrs: less than 2% of applied dose (but greater than 50% of the applied dose for skin without stratum corneum). Adsorptive powders either applied either alone or as mixtures, can significantly reduce the toxicant amount transferred across all membrane models.
Disulfoton	Toxicological studies	ATSDR/ 1995/ Toxicological profile for disulfoton; Available from, as of 1st March 2013; http://www.atsdr.cdc.gov/toxprofiles/tp65.pdf	Subchronic or Prechronic Exposure: 1 of the 4 rats died when a granular formulation containing 10% disulfoton was applied at a dose of 1,280 mg/kg. The difference in dermal LD_{50} values is probably related to the different formulations of disulfoton. In a range-finding study, rabbits died after 1 or 2 applications of 10 mg/kg/day disulfoton was applied to the shorn, unabraded skin and left for 6 hrs. Rabbits similarly treated with 0.4 or 2.0 mg/kg/day for 5 days did not die. Female rabbits died after in a 3-wk experiment, similar treatment of rabbits 5 day/wk with treatment with 6.5 mg/kg/day after 1-6 treatments, but after 3-10 treatments for males.

Disulfoton	Toxicological studies	Warren/1984/ Dermal absorption of ^{14}C-disulfoton from the Disyston 8 formulation	Dermal absorption of 0.85, 8.5, or 85 µg/cm^2 (approximately 0.05, 0.5, and 5.1 mg/kg bw) of a labelled disulfoton formulation ranged from 39-44% of an applied dose applied to the clipped back (15 cm^2) of rats. After 168 hrs, a total of 31-37% of the administered dose was excreted in the urine and 2.7-3.3% in the faeces. At 1, 4, and 10 hrs, absorption percentages were 5.9, 13.7 and 26% (low dose); 4.6, 15.9, and 32.7% (mid dose) and 3.6, 12.5, and 25.6% (high dose).
		Mihail,/1978/ S 276 (Disyston active ingredient) acute toxicity studies	Dermal LD_{50} Wistar rats (male) 15.9 mg/kg Dermal LD_{50} Wistar rats (female) 3.6 mg/kg
		Weil, et al./ 1971/ Correlation of four hour vs. 24 hour contact skin penetration toxicity in the rat and rabbit and use of the former for prediction of relative hazard of pesticide formulations	Dermal LD_{50} Rats 0.285 mL/kg (187 mg/kg) (liquid formulation containing 65.7% disulfoton)
		Savage et al. /1971/ Pesticide poisonings in rural Colorado	A farmer who had worn disulfoton-contaminated gloves for several days developed signs of disulfoton toxicity (weakness, fatigue, and cyanosis and had to be hospitalized. Because a considerable amount (not otherwise specified) of disulfoton was detected in the serum and because blood ChE activity was severely depressed, it can be assumed that the patient had absorbed a considerable amount of disulfoton through the skin. The patient recovered following treatment for the toxicosis.
	Epidemiological and occupational hygiene studies	Wolfe et al./ 1978b/ Exposure of fertilizer mixing plant workers to disulfoton	Dermal exposure during dry mix operations (0.1 to 10.5 mg/hr with a mean value of 2.0 mg/hr of work activity) was much greater than during wet mix operations. None of the blood ChE levels were below normal values. However, it does not indicate that wet mix operations are safer as heavy accidental exposure may be greater than during dry mix operations.
	No glove permeation studies or skin studies found on disulfoton		

Ethion	Toxicological studies	Mosha et al./ 1990/ Fate of ethion in goats after intravenous, oral and dermal administration	Goats dermally exposed with one application of 100 mg/kg ethion over a 600–700 cm^2 area, showed unchanged ethion in the blood and it stayed in the epidermis and is absorbed for a prolonged period. Unchanged ethion (0.04–0.05% of the dose) appeared in the goat milk. The study suggests that while dermal application may have prolonged and limited absorption, the absorbed ethion is rapidly eliminated through metabolism.
		Fisher et al./ 1985/ Dermal absorption of pesticides calculated by deconvolution	Skin-to-blood transfer rate of ethion was estimated using published human data on skin-to-urine transfer by two numerical deconvolution techniques. Dermal absorption rate was largest within 8 hrs of dosing and the deconvolution techniques allow for the calculation of the temporal aspect of dermal absorption for linear systems.
		Feldman et al./ 1974/ Percutaneous penetration of some pesticides and herbicides in man	Radiolabeled ethion [^{14}C] was applied to the ventral forearm of 6 male volunteers at a concentration of 4 $\mu g/cm^2$ in acetone and left unwashed for 24 hrs. Radioactivity in the urine was determined by combustion and liquid scintillation counting, and compared to results from a parallel experiment where labeled ethion was administered intravenously. Over 24 hrs, 3.3% of the dose was absorbed as calculated from urinary excretion of radioactivity. Excretion in urine accounted for 3.3% (SD +1.1%) of the [^{14}C] ethion radioactivity applied to the skin of volunteers for 24 hrs over the 5 days following application. The study suggests that absorption may be delayed and prolonged, and urinary excretion may be subject to certain limitations.
	Epidemiological and occupational hygiene studies	Wojeck et al./ 1981/ Worker exposure to ethion in Florida citrus	The mean dermal exposure of mixers and loaders was 1799 mg ethion/hr, and 1972.5 mg/hr for applicators (primary exposure on hands). Average dermal exposure in airblast spraying was 44.2 mg/hr. Larger decrease in ChE activity for suppliers than applicators. The total percent/hr of the probable human dermal LD_{50} was very low in all cases and no acute symptoms were observed.
		Wolfe et al./ 1978a/ Exposure of formulating plant workers to ethion and malathion	Calculated dermal exposure to ethion was 126 mg/hr Potential exposure at the bagging station was greater than at the mixing station. High exposure may not be subjected to amounts of pesticides, but safety precautions in practice.

Ethion	Epidemiological and occupational hygiene studies	Nigg et al./ 1993/ Quantification of human exposure to ethion using saliva	Urine of pest control workers demonstrated total ethion metabolites ranged from 0.30 to 7.0 ppm/day. Exposure is presumed to be primarily dermal. The study shows that saliva is a good medium for estimating internal pesticide dose.
	No glove permeation studies or skin studies found on ethion		
Fenamiphos	Toxicological studies	Geertsen/ 1997/ Toxicological and environmental evaluations 1994-Fenamiphos, viewed at http://www.inchem.org/documents/jmpr/jmpmono/v097pr06.htm	Subchronic or Prechronic Exposure: Body weight of New Zealand rabbits decreased when exposed to dorsal area of 10 mg/kg b.w of an aqueous formulation of technical-grade fenamiphos (89.8% purity) for 6 hrs per day, 5 days per week for 3 weeks. Slight erythema observed at the abraded skin sites, but cleared by day 7. Plasma and erythrocyte ChE activity was significantly depressed (by up to 65 and 34%, respectively), as well as brain ACh activity, especially in females.
	Epidemiological and occupational hygiene studies	Knaak et al./ 1986/ Estimating the hazard to humans applying Nemacur 3EC with rat dermal-dose ChE response data	Human-skin patches and hand wash The highest level of dermal exposure was on the worker's hands (at least 8-fold higher than exposures to other parts of the body). Male rats dermally exposed to 1 mL of 0, 2.5, 5.0 and 10 mg of fenamiphos/mL of acetone, red cell ChE activity observed.
	Glove studies/ skin studies	Bingham et al./ 2001/ Patty's Toxicology	*In vitro* studies on fenamiphos by human and rat skin found that dermal absorption of a granular formulation was less (0.01-0.03 $\mu g/cm^2/hr$) and dermal absorption of a liquid formulation was more (13.0 ±1.87 $\mu g/cm^2/hr$ (human) and 49.0 ±2.69 $\mu g/cm^2/hr$ (rat) during 24 hrs.
Mevinphos	Toxicological studies	Skinner et al./ 1982/ Acute dermal toxicities of various organophosphate insecticides in mice	Hind feet of Swiss Webster mice were applied with mevinphos to determine dermal LD_{50} values. Values were simultaneously generated for the ED_{50} (mg/kg) for both ChE. Lethality was greatest with mevinphos. LD_{50} values were higher than reported values for mice treated on shaved back skin. ChE ED_{50} values (ChE 39 mg/kg & AChE 3 mg/kg) roughly agreed with LD_{50} value (12 mg/kg).
		Skinner et al./ 1982/ Application of a dermal self-exposure model to worker re-entry	Blood ChE monitored pre- and post-exposure by mouse intermittent self-exposure model. Mevinphos produced no significant ChE responses in muzzled mice at maximal foliar concentrations. Symptomatology, food consumption, and body weight provided less sensitive indicators of response than ChE. No consistent relation existed between the mouse intermittent self-exposure toxicities and mouse dermal LD_{50} values.

Mevinphos	Epidemiological and occupational hygiene studies	Coye et al./ 1986/ Clinical confirmation of organophosphate poisoning of agricultural workers	31 lettuce harvesters exposed to mevinphos sent to emergency room with moderate cholinergic symptoms, and eye and skin irritation, with 76% of them reporting three or more symptoms. None of them had baseline ChE values, and plasma ChE activity for all but two workers was above the lower limit of laboratory normal range. Plasma ChE was estimated to be inhibited by an average of 15.6% and RBC ChE 5.6%, increased until 14 days after exposure. Sequential post-exposure plasma ChE may be used to confirm suspected OP-induced illness when baseline values are not available.
		Jauhiainen et al./1992/ Biological monitoring of workers exposed to mevinphos in greenhouses	The total exposure through the skin was calculated from the patch samples and hand washing samples taken from the workers. The sprayer with greatly decreased ChE activities had the greatest total exposure to mevinphos (about 90 µg/hr) through his skin. Metabolite of mevinphos (DMP) was detected in the urine of the sprayer, maximum concentration about 18 hrs after the spraying. Half-life of urinary metabolite was about 5 hrs, delayed maximum of the urinary elimination of DMP likely due to the dermal penetration of mevinphos.
		Kangas et al./ 1993/ Exposure of sprayers and plant handlers to mevinphos in Finnish greenhouses	Handwash samples showed concentration of mevinphos on workers hands, between 0 and 298.0 µg/hr immediately after application and from 0 to 13.2 µg/hr for 17-22 hrs after application. High values observed for a worker that used thin disposable PVC gloves. Patch samples showed that workers were exposed to small amounts of mevinphos through their clothing even on the second day after spraying. Wearing proper clothing indicated 80% reduction of the amount reaching the skin. Dermal exposure is well-correlated to the amount of mevinphos on the foliage, suggesting skin as the main route of exposure. The calculated re-entry interval for mevinphos was approximately 4.5 hrs, which is too short in practice as the risk of dermal exposure is considerable for more than 10 hrs after application.
	No glove permeation studies or skin studies found on mevinphos		

Omethoate	Toxicological studies	APVMA 2011, 'Draft review of the mammalian toxicology and metabolism/toxicokinetics of omethoate', Available from, as of 10th October 2012; http://www.apvma.gov.au/products/review/docs/omethoate_tox_review_draft.pdf	Acute dermal studies: Rats LD_{50} from 145 mg/kg bw to ~1400 mg/kg bw (LD_{50} decreasing with increased exposure duration). LD_{50} 865 mg/kg bw (female rats) following 24 h exposure under semi-occlusive dressings. Female rats are slightly more sensitive than males.
	Epidemiological and occupational hygiene studies	Aprea et al./ 2005/ Exposure to omethoate during stapling of ornamental plants in intensive cultivation tunnels: influence of environmental conditions on absorption of the pesticide	Total skin contamination was between 329.94 and 12,934.46 nmol/day; with estimated absorbed doses in tunnel 5 higher than the ADI. Higher urinary alkylphosphates than in the general population after work shift (tunnel 8) demonstrated a good correlation with estimated potential doses, and the fraction of omethoate absorbed through the skin during work is about 16.5%. The study revealed that cutaneous doses were much higher than respiratory doses, and contamination of unexposed skin was possibly due to incorrect or inadequate use of protective clothing.
		Aprea et al./ 2001/ Evaluation of respiratory and cutaneous doses and urinary excretion of alkylphosphates by workers in greenhouses treated with omethoate, fenitrothion, and tolclofos-methyl.	Skin pads, hand wash, personal sampling, and urinary alkylphosphates (24-hr urine samples) used to evaluate exposure pathways of greenhouse workers (exposure for 5 consecutive days). Doses of omethoate absorbed by one worker were more than 45 times the ADI of 1.41 nmol/kg body weight (b.w.) Hands were always a source of contact with pesticides and actual skin doses were higher than respiratory doses, hence the need for proper gloves for hand protection.
		Aprea et al./ 1994/ Evaluation of omethoate and fenitrothion absorption in greenhouse workers using protective equipment in confined areas	Levels of omethoate in air samples, on pads and on the hands, during manual operations on ornamental plants, were very low. No significant difference for urine analysis pre- and post-exposure samples. No significant difference between levels of urinary dialkyl phosphates (as biological index of exposure) in the control group and exposed workers. ChE activity (acetyl and butyryl) showed no significant reduction at the end of the workshift compared with baseline values.
	Glove studies/ skin studies	Sartorelli et al./ 1998/ Prediction of percutaneous absorption from physicochemical data: a model based on data of *in vitro* experiments	*In vitro* dermal absorption of omethoate using full thickness monkey skin Applied dose 61.6 nmol/cm^2, lag time of 58.8 (±33.6) min, permeability coefficient of 4.81 ±9.79 x 10^{-3} cm/hr.

Parathion methyl	Toxicological studies	Dikshith et al./1991/ Repeated dermal toxicity of technical HCH and methyl parathion (50EC) to female rats (*Rattus norvigicus*)	Repeated dermal application of hexachlorocyclohexane (HCH; 100 mg/kg/day) or methyl parathion (2 mg/kg/day) individually or in combination for 7, 15 and 30 days produced pathomorphological changes in skin, liver, kidney and brain of female rats along with significant enzymatic alterations in the activity of transaminase, alkaline phosphatase lactic dehydrogenase and AChE. In combination, the pesticides produced severe toxicity on day 30 than at other periods.
	Epidemiological and occupational hygiene studies	Muttray et al./2006/ External and internal exposure of winegrowers spraying methyl parathion	Dermal exposure of the winegrowers ranged up to 12,044 µg, maximum plasma concentration was 12.1 µg/L. Metabolite was not detectable, ChE activity did not decrease. This study shows that even with a low exposure to parathion methyl (50-min spraying), plasma concentrations were measurable. Brilliant sulfoflavine tracer deposition is a good tool for estimating internal exposure (with gloves).
		Wolff et al./ 1992/ Dermal Levels of Methyl-Parathion, Organochlorine Pesticides, and Acetylcholinesterase among Formulators	Wipe samples on workers exposed to methyl parathion showed positive correlation with erythrocyte AChE, especially with workers who did not wash their hands prior to testing. However dermal contamination was not significantly related to the date of last exposure nor to laundering of clothes. Skin penetration differs at different sites of the body exposed to.
	Glove studies/ skin studies	Sartorelli et al./ 1997/ *In vitro* percutaneous penetration of methyl-parathion from a commercial formulation through the human skin	Full thickness cadaver human skin used to investigate penetration of methyl-parathion dissolved in acetone and in formulation. Commercial formulation demonstrated higher absorption rate and percentage of applied dose (5.20%) than the one dissolved in acetone (1.35%) after 24 hrs. Percutaneous penetration was also faster for the commercial product and had lower mean lag time (<4 hrs) than for MPA in acetone (<8 hrs). This study emphasises the need to conduct assessment of dermal uptake to pesticides should be based on commercial products rather than active ingredients), to take into account the role of carrier solvents.
Phorate	Toxicological studies	Hayes/ 1982/ Pesticides Studied in Man	Phorate is rapidly absorbed that some animals die within an hour or two following even dermal exposure. The oral LD_{50} of the most toxic metabolite, the sulfone of the oxygen analog is in the range of 0.5 to 0.8 mg/kg. Dermal LD_{50} male rat 6.2 mg/kg, female rat 2.5 mg/kg.

Phorate	Epidemiological and occupational hygiene studies	Geno et al./ 1996/ Handwipe sampling and analysis procedure for the measurement of dermal contact with pesticides	Phorate was detected on the hands of farmers' children at a level of 15 ng, following application of the pesticide in the fields. The handwipe sampling method demonstrated good removal efficiency for dry residues, and pesticide residues that are deeply embedded in the skin. It is easily implemented, readily accepted by children and may also be applicable for a wide range of pesticides.
		Stone et al./ 1989/ Pesticide residues in clothing, Case study of a Midwestern farmer's coverall contamination	Phorate (Thimet) was detected in a Midwestern farmer's cotton coveralls, worn from 1985-1987 during pesticide applications, with concentrations ranging from 0.1 to 0.4 ng/cm^2. New cotton coveralls should be worn by applicators in minimum pesticide exposure situations for each application season.
		Moore/ 2010/ *In vitro* modelling of dermal absorption of chemicals following environmental or accidental exposure	*In vitro* studies/ finite doses of phorate applied on pig skin as a neat solution, and diluted in isopropyl alcohol. Lag time for absorption of dilute phorate in IPA (1.4h ± 0.4) was much shorter than for neat phorate, suggesting the role of vehicle in dermal absorption. More phorate was absorbed from neat than from dilute in terms of the actual amount, but lower by percentage of applied dose. Although not designed for protective purposes, cotton shirt material significantly reduced dermal absorption of all chemicals tested.
	No glove permeation studies found on phorate		
Terbufos	Toxicological studies	Bingham, *et al.*/ 2001/ Patty's Toxicology	Acute Exposure:- All rabbits died within 24 hrs after dosing with 0.5 mL or less of terbufos (primary eye and primary dermal irritation studies) Subchronic or Prechronic Exposure:- Rats given dermal doses of 5, 10, or 25 mg/kg/day (equivalent to 1, 2.5, or 6.75 mg/kg/day active ingredient) for 6 hrs/day, 5 days/wk for 4 weeks showed decreased RBC and brain ChE activity. No effect for dermal dose of 2 mg/kg/day. Neurotoxicity: Rats died when supplied with bedding contaminated with about 30 ppm terbufos, after developing cholinergic signs (muscle fasciculations, severe depression, exophthalmus, and ptyalism). Exposures were most likely primarily dermal but could also have been via ingestion and inhalation.

Terbufos	Toxicological studies	Francis *et al.*/ 1985/ Toxicity of organophosphorus esters to laying hens after oral and dermal administration	Multiple treatment of 14 OPs to investigate the potential to cause organophosphorus ester induced delayed neurotoxicity (OPIDN) on white leghorn hens found that the dermal administration resulted in death after varying periods of increasing weakness and difficulty in walking.
	Epidemiological and occupational hygiene studies	Stone *et al.*/ 1997/ Granular terbufos exposure and cleanup of glove materials	Following a 3-minute exposure to granular terbufos, no contamination observed for barrier laminate, neoprene and nitrile glove materials. Unlaundered glove fingers indicated contamination of the gauze, a larger amount in the ethyl acetate rinse solution, and measurable contamination after the soak period. Laundering the gloves had no significant decreases in the contamination levels, suggesting the importance of advice to pesticide applicators about washing off gloves.
		Stone *et al.*/ 1992/ Contamination of cotton denim with terbufos	Trace amounts of terbufos could be found in 4 out of 5 clothing worn under the coveralls and one out of six jean specimens. Cotton denim was easily contaminated with dry terbufos granules. Contamination was a function of contamination amount, exposure time, time delay before extraction, and moisture content of the specimen. Contamination was present after 96 hrs of ventilation, following 24 hrs of exposure.
		Stone *et al.*/ 1989/ Pesticide residues in clothing, Case study of a Midwestern farmer's coverall contamination	In a case study of coveralls worn in a farming operation, residues of terbufos remained on coveralls worn by a farmer over four crop seasons although they have been laundered after each wearing. This suggests that single extraction may underestimate the amount of terbufos but cotton coveralls offer more advantages over disposable protective clothing, provided they are replaced every crop season to avoid build up.
		Devine *et al.*/ 1986/ Farm worker exposure to terbufos [phosphorodithioic acid, S-(tert-butylthio) methyl O,O-diethyl ester] during planting operations of corn	The average dermal and respiratory exposure to terbufos were estimated to be 72 and 11 μg/hr, respectively, for 11 farmers monitored over a typical work day for workers planting corn and applying terbufos. Negative results of urinary alkyl phosphate analyses (no detectable absorption). No adverse physiological effects from exposure, shown by insignificant difference of plasma and RBC ChE activity with pre-exposure. This indicates that the use of formulated terbufos (COUNTER 15-G) does not present a significant hazard, in terms of acute toxicity.

Terbufos	Epidemiological and occupational hygiene studies	Bingham, *et al.*/ 2001/ Patty's Toxicology	Farmers applying a formulated terbufos (exposure duration averaged 7.4 hr), dermal exposure (using gauze patches) was 72 µg/hr (average), and respiratory exposure (using personal monitoring pumps) was 11 µg/hr (averagea). No alkyl phosphates were detected in urine, and no significant depression of RBC ChE activity occurred. Assuming an 8-hr day, 100% absorption, and a 10 m^3/day inhalation rate, a respiratory dose of 11 µg/hr would be achieved by exposure to roughly 0.009 mg/m^3 terbufos. Human NOEL suggested ≥0.009 mg/m^3
	Glove studies/ skin studies	Guo *et al.*/ 2001/ Effects of exposure time, material type, and granular pesticide on glove contamination	Permeation of granular terbufos against nitrile, neoprene, and barrier laminate gloves was tested with exposure to 300 mg of terbufos for 1, 2, 4, 8, 16, and 24-hrs in petri dishes, with cotton gauze and alpha cellulose as collection media. Terbufos was not detected in the alpha cellulose even after 24 h. Longer exposure times of terbufos causing higher contamination levels in the three glove materials. Contamination of nitrile was significantly less than neoprene or barrier laminate. This study suggests that gloves made of any of these materials can provide protection for at least 24 hrs, however the comparative safety of granular products still varies with the pesticide, so label precautions regarding use cannot be ignored.

2.3.2 Narrative synthesis of the relevant literature

2.3.2.1 Overview

Relevant literature on the 12 OPs of security concern, as it pertains to dermal exposure, is relatively sparse. No single empirical study or review covering all twelve OPs was found.

Some of the OPs of interest were considered as part of generic or specific reviews, for example the generic reviews by Maibach and coworkers on the effects of skin damage and occlusion on skin permeation (Gattu et al. 2010; Hafeez et al. 2013).

Laboratory Skin Studies

Comparative studies were rare. In a paper by Sartorelli and coworkers (1998), six OPs, including one on the list namely omethoate, could be compared with regard to skin penetration in identical conditions. In this study, the purpose was to assess whether skin penetration parameters could be predicted from water solubilities and the octanol-water partition coefficients. The effect of temperature was not examined.

Laboratory Glove Studies

Comparative studies of glove permeation by the OPs of interest are practically non-existent. In a study by Moody and Nadaeau (1994) a 12% diazinon formulation appeared to damage the nitrile butyl rubber glove material (Sol-Vex Cat No. 37-175, 0.38 mm thickness) after 24 hrs contact. The surface appeared crenulated and this was attributed to xylene. The authors also suggested that a reservoir of pesticide could build up within the glove material, and eventually permeate to the skin. This glove contamination would not be easily removed with

soapy water. Further studies were recommended to elucidate the glove pesticide reservoir effect. Problems with glove manufacture quality control (e.g. microholes), and exacerbation of defects by pesticide contact, were also reported in a forensic study of new and used gloves in Tasmania (Canning 1997). Nitrile butadiene gloves (as above) were found to be more susceptible to cracking, than the thicker, more commonly used, PVC gloves. Although Canning did not do functional assessment (i.e. permeation testing of gloves), the use of scanning electron microscopy, coupled with elemental analysis, to examine glove surfaces provided evidence for

- the presence of pesticide residues in used gloves;
- the effect of long term exposure to sunlight on gloves;
- the effect of >24hr exposure to formulated diazinon (Jetdip 200 g/L) on PVC and nitrile butadiene gloves, leading to cracks in the nitrile gloves, and cavities and convexities in the PVC gloves;

In addition, Canning (1997) reported the mean age of used gloves to be two years, implying usage over two years of spraying and/or dipping seasons.

Field Studies of Exposed Populations

Many studies considered occupational usage, particularly in agriculture. Some had multiple exposure metrics (e.g. personal air sampling, skin, rinses, wipes and pads, biological monitoring) and these tended to highlight the significance of the dermal route. For example, Aprea et al. (2001) found skin doses of pesticides for greenhouse workers were generally higher than respiratory doses. In the case of omethoate, more than 90% of the uptake was through the skin, and hands were always a source of contact with pesticides.

However, there were few papers for workers with incidental exposure.

In a case report by Mathias (1983), the driver of a truck transporting a commercial formulation of the insecticide, dichlorvos, developed unusually persistent contact dermatitis following accidental skin contact, as well as systemic signs of organophosphate toxicity.

There appeared to be no dermal exposure studies of emergency workers (e.g. firefighters and ambulance workers) attending fires, poisonings or other incidents involving the OPs of security concern.

Separate summaries for the 12 OPs are given in individual subsections below.

2.3.2.2 Azinphos methyl

Azinphos methyl is a lipophilic compound (log K_{ow} =2.96) known as a broad spectrum OP that acts as non-systemic insecticide, acaricide and molluscicide for controlling codling moth and light brown apple moth for pome and stone fruits, vegetables, crops and nuts. Its molecular weight is 317.3 and its popular trade name is Guthion®. Classified as highly hazardous (1B) by WHO, azinphos-methyl was placed under review by the APVMA due to concerns about its toxicity and associated risks to public health, occupational health and safety, residues, trade and the environment (APVMA 2013a).

Dermal toxicity of azinphos-methyl has been tested on rats, rabbits and guinea pigs. Although known as toxic by all routes of exposure; dermal exposure to azinphos methyl was found to be more serious than inhalational exposure in some of the working conditions investigated (Aprea, Sciarra, Sartorelli, Desideri, et al. 1994; Lamb 1980). Most biological monitoring studies on azinphos methyl analysed urine i.e alkylphosphate and blood i.e. plasma ChE and erythrocyte in agricultural settings, showing depression of cholinesterase and high correlation

with the amount the workers are exposed to (Feldmann & Maibach 1974a; Franklin et al. 1981; Franklin, Muir & Moody 1986; Lamb 1980; Richards et al. 1978; Simcox et al. 1999). Human *in vivo* studies by Gattu and Maibach (2010) showed that penetration through damaged skin may be pronounced with hydrophilic molecules but not and less so with lipophilics. However, when occlusion is involved, *in vivo* studies by Hafeez and Maibach (2013) reported that enhanced penetration of highly lipophilic compounds, compared to hydrophilic compounds.

In vitro studies conducted on skin and glove fabrics against azinphos methyl revealed the skin to be a good barrier to penetration for 4 hrs, but improved protective capabilities with the presence of glove materials (Keeble, Correll & Ehrich 1993). In another study, Keeble and co-workers reported that capability of knit glove fabrics (100% cotton and 100% polypropylene) to resist the penetration of Guthion (22% suspension in petroleum distillate) through artificial skin was not affected by glove laundering or with abrasion and laundering (Keeble, Correll & Ehrich 1996). In this study, the penetration of the parent chemical was not directly determined. Instead penetration was assessed by the underlying medium's capacity to inhibit brain AChE. Most absorption occurred in the first 4 hrs.

2.3.2.3 Cadusafos

Cadusafos is an insecticide and nematicide, used for bananas, citrus, ginger, sugar cane, tobacco and tomatoes. It is a lipophilic compound (log K_{ow} = 3.9), and has a molecular weight of 270.4. Classified as highly hazardous (1B), cadusafos is only registered in Australia, South Africa and Tanzania. Potential occupational exposures to cadusafos are by inhalation and dermal contact (USEPA 2000).

Acute exposure studies on animals were reported on rabbits with dermal LD_{50} 12 mg/kg and guinea pigs for sensitisation test (Paranjape et al. 2014). No field studies, glove permeation studies or *in vitro* skin studies were identified from the literature search, therefore the actual level of dermal absorption of cadusafos is not known.

2.3.2.4 Diazinon

Diazinon (0,0-diethyl-0-[2-isopropyl-4-methyl-6-pyrimidinyl]phosphorothioate) is a highly lipophilic (log K_{ow} =3.81) compound widely used in the agricultural and veterinary sector. It is classified as moderately hazardous by WHO (APVMA 2006). Reported applications involved a wide variety of crops including orchard and field crops, turf, parasite control in sheep and cattle and goats as well as pets (APVMA 2006; Garfitt et al. 2002; Worting & Hance 1991). For use in agriculture and by exterminators, the preparations contain 85 to 90% of the active compound (ATSDR 2013). Diazinon has been under review since 1996 and is a potential endocrine disruptor (Immig 2010). Besides Australia, diazinon products are also registered for use in the USA, Canada, African countries, Portugal, Hungary, Finland, New Zealand, India and the Philippines (APVMA 2006). Although most of these countries aim at discontinuing the use of diazinon, with no registration or sale of the products from 31st December 2004 onwards, there is potential for exposure from the available commercial products previously purchased home and garden products (ATSDR 2008; te Brake et al. 2012).

Literature review on dermal absorption of diazinon shows both human and animal studies have been published. Studies available on volunteers demonstrated absorption of small

amount of dermally-applied diazinon, rapidly metabolised and eliminated in the urine (Garfitt et al. 2002; Wester et al. 1993).

An *in vitro* study using heat separated epidermis and pure diazinon showed human skin provides a better barrier than pig skin. Longer lag times (418 min at 23°C for human skin), lower flux and maximum penetration were reported compared to pig skin (53 min at 23°C) (te Brake et al. 2012). Similar lag times was observed with the study conducted by Moody and Nadeau (1994), but with higher amount of maximum penetration through human skin compared to pig skin, possibly due to the use of dermatomed skin. It was also concluded that the penetrating amount of diazinon reported by Moody and Nadeau (1994) and Wester et al. (1993) were higher, possibly due to the higher applied dose (0.25µg/cm^2 and 9.5-10.5 µg/cm^2 respectively) and longer exposure times compared to the study by te Brake et al. (2012). In their study, Moody and Nadeau (1994) revealed good intrastudy agreement between the *in vitro* and *in vivo* data with penetrability to diazinon dissolved in acetone (9.5-16.7 µg/cm^2) on dermatomed skin ranked in decreasing order of rat > Testskin≥ hairless guinea pig > human ≥ pig skin. Percutaneous absorption of diazinon was also investigated by Wester et al. (1993) using both *in vivo* and *in vitro* approaches. Percutaneous absorption of diazinon in *in vivo* studies in acetone and lanolin showed the same calculated mass absorbed for *in vitro* (0.035 µg/cm^2) with *in vitro* studies), suggesting the amount of potential systemic delivery percutaneous absorption, unlike most substances of higher lipophilicity. In rhesus monkeys, 78.4% of the applied dose was excreted in urine and faeces over the test duration of 7 days (Wester et al. 1993).

Interestingly, a study by Sugino et al. (2014) comparing skin permeability coefficients and desquamation rate (the counter flux of permeability coefficient for chemical compounds

induced by skin turnover) following exposure, determined that diazinon could not permeate the skin due to the its permeability coefficient being smaller than the desquamation rate. In this study full thickness hairless rat skin was used in Franz cell system, and no diazinon was detected in the receiving chamber in 24 hrs. It was argued that diazinon might only permeate into the stratum corneum and hardly distribute and diffuse into the viable epidermis and dermis due to its high lipophilicity. Fetal bovine serum was used in the receptor fluid, in contrast to the use of 50% ethanol in the te Brake study (2012).

As for studies on gloves, pesticide splashes and spills on the external surfaces of PVC or nitrile butadiene rubber gloves that may compromise the integrity of the membrane was simulated by (Canning, McQuillan & Jablonski 1998) using chlorpyrifos (Lorsban 500 EC®) and diazinon (Jetdip®). PVC gloves showed defects, cavities and convexities, whereas nitrile butadiene rubber gloves had significant cracking after 24 hrs, suggesting the need for developing more robust gloves for routine agricultural use.

2.3.2.5 Dichlorvos

Dichlorvos is a moderately lipophilic (log K_{ow} =1.2 - 1.5) insecticide and parasiticide, commonly used for stored cereal grains and industrial domestic pest control. Classified as highly hazardous by WHO, dichlorvos is rapidly absorbed by dermal exposure (ATSDR 1995). Dichlorvos toxicity has been widely studied and reviewed due to its genotoxic potential (Booth, Jones & Elliott 2007; Luty et al. 1998; Tungul et al. 1991). Dermal toxicity data from animal studies tested with dichlorvos are available for rats, birds and rabbit dermal toxicity data (Ali & Abdalla 1992; Dikshith, Datta & Chandra 1976; Luty et al. 1998; Maslinska, Dambska & Maslinski 1979; Mineau 2012). An *in vivo*study on rats indicated

histopathological changes and rapid skin penetration of dichlorvos (Luty et al. 1998). *In vivo* studies assessing dermal exposure to dichlorvos on human have been conducted on pesticide workers, with significant serum cholinesterase depression and reduced total dermal exposure with the use of PPE (Gold et al. 1984; Perger et al. 1991).

In a recent *in vitro* study testing exposure to low concentration of dichlorvos using different vehicles in finite (5 µg/cm^2) and infinite dose (1 and 10 mg/cm^2) conducted by Moore et al. (2014a), the greatest absorption (38.6%) was observed from the isopropanol (IPA) vehicle. Lag times were short; 0.6 h from dichlorvos in IPA and isopropyl myristate (IPM) vehicles, and 0.4 h from dichlorvos in propylene glycol (PG) vehicle. This suggests the need for immediate skin decontamination upon skin contact with dichlorvos (and chemicals with similar properties) to minimise health effects.

In vitro skin studies by (Mircioiu et al. 2013) demonstrated that intact stratum corneum assisted in delaying penetration, with lag-time of several hours, whereas no lag time for skin without stratum corneum. At 10 hrs, the presence of stratum corneum indicated less than 2% of applied dose (as opposed to more than 50% of the applied dose for skin without stratum corneum).

Surprisingly, there appear to be few protective clothing studies of dichlorvos, and this appears to be a significant gap in the literature, given its usage. A study on dichlorvos permeation through rubberised fabric indicated a breakthrough time exceeding 480 mins, therefore validating suitability of the material for protection against concentrated dichlorvos (Krzemińska & Szczecińska 2001).

Moore et al. (2014b) investigated the protective effect of 'every-day' clothing against dermal exposure to dichlorvos in an *in vitro* setting using human skin. Great absorption of dichlorvos (5 μg/cm^2) was observed through unclothed skin for all vehicles (IPA, isopropyl myristate (IPM) and PG). However, after exposure, the absorption significantly reduced when the clothed skin was decontaminated at 30 min, compared with decontamination at 24 h. The findings indicated that protection afforded by 'every-day' clothing against chemical exposure is effective, supplemented with removal of the contaminated clothing and immediate washing to reduce exposure.

2.3.2.6 Disulfoton

Disulfoton, is a lipophilic compound (log K_{ow} = 3.95) and is formulated as granule, powder and emulsifiable concentrate, which is used to control insects and viruses on lucerne, cotton, potatoes, peas and beans. It is classified by WHO as extremely hazardous (1A) and has acute toxicity. While the use of disulfoton has been banned in Pakistan, India and Thailand, its use is still allowed in Australia and South Africa (Paranjape et al. 2014).

Toxicological studies by dermal exposure have been reported on rats and rabbits (ATSDR 1995; Mihail 1978; Weil, Condra & Carpenter 1971). *In vivo* studies on rats dermally exposed to disulfoton formulation was assessed by excretion through urine and faeces (Warren 1984).

In humans, it was reported that a farmer in rural Colorado was hospitalised after developed signs of disulfoton toxicity (weakness, fatigue, and cyanosis) from wearing disulfoton-contaminated gloves for several days (Savage et al. 1971). It was believed that the farmer had

dermally absorbed a considerable amount of disulfoton, indicated by severe depression of blood cholinesterase activity and substantial amount of disulfoton in the serum (Savage et al. 1971). A study on fertilizer mixing plant workers to disulfoton found that dermal exposure during dry mix operations was much greater than during wet mix operations, and blood cholinesterase levels were above normal values (Wolfe et al. 1978b). There were no glove permeation studies or *in vitro* skin studies available from the literature search.

2.3.2.7 Ethion

Ethion is highly lipophilic (log K_{ow} = 5.07) and has a high molecular weight (384.5). Although ethion is classified as moderately hazardous by WHO, there are 56 registered ethion products available for use in Australia, sold under many trade names including Bladan®, Rodicide®, and Nialate®. Ethion is commonly used on cotton and as pest control on animals such as cattle, horses, cats and dogs.

Exposure is mainly by skin contact e.g. with soil contaminated by ethion, although inhalational exposure is also possible (ATSDR 2000a, 2000b). Wojeck et al. (1981) reported that hands represented 42% of the total body exposure for applicators and 76% for suppliers, whereas less than 1% for respiratory exposure. However, high exposure may not only be subjected to amounts of pesticides, but also safety precautions in practice, as suggested by Wolfe, Staiff and Armstrong (1978a).

Toxicological studies of ethion on animals have been conducted on Sherman rats, rabbits and guinea pigs (ATSDR 2000b; Gaines 1969). An *in vivo* study on goats dermally exposed to ethion showed prolonged and limited absorption in the blood; however, it was rapidly

eliminated through metabolism (Mosha, Gyrd-Hansen & Nielsen 1990). While other studies on human exposed to ethion mainly focused on cholinesterase activity in blood samples and metabolites in urine samples (Feldmann & Maibach 1974a; Wojeck et al. 1981), saliva was also suggested as an appropriate substrate to confirm pesticide exposure and to estimate internal pesticide dose (Nigg, Stamper & Mallory 1993). Neither glove permeation studies nor *in vitro* skin studies on ethion were identified in the literature.

2.3.2.8 Fenamiphos

Fenamiphos is a popular insecticide and nematicide that works by systemic and contact with the pests. With 14 registered products in Australia, it is used on a number of field crops, grapes, citrus, ornamentals, vegetables and turf. It is lipophilic (log K_{ow} =3.3) and has a molecular weight of 303.4 (APVMA 2008). Popularly known with the trade name Nemacur®, fenamiphos are available as emulsifiable concentrates, granular and emulsion formulation. Fenamiphos is classified as highly hazardous by WHO (APVMA 2008). Due to the high acute toxicity and potential to cause chronic effects on human health, fenamiphos was nominated for review in the APVMA's Existing Chemical Review Program (APVMA 2013c).

Despite being extensively used in the agricultural sector, studies conducted on fenamiphos are scarce. Toxicological dermal studies have been conducted on rats and rabbits (Bingham, Cohrssen & Powell 2001; Geertsen 1997; WHO/FAO 1997). A study comparing exposure of pesticide handlers and rats to fenamiphos supported the use of animal dermal dose response studies to predict human response (Knaak, Jacobs & Wang 1986). It was also found that the

highest level of dermal exposure was on the worker's hands compared to other parts of the body (Knaak, Jacobs & Wang 1986).

Skin studies on fenamiphos, particularly *in vitro*, have not been extensively studied. *In vitro* studies of fenamiphos found dermal absorption was less in a granular formulation but more with a liquid formulation for both humans and rats (Bingham, Cohrssen & Powell 2001). There were no glove permeation studies on fenamiphos available from the literature search.

2.3.2.9 Mevinphos

Mevinphos is a hydrophilic (log K_{ow} 0.13) racemic mixture containing between 630-642 g/kg of the E-isomer and 170-276 g/kg of the Z-isomer. It is primarily used for controlling pests like Diamond Back Moth primarily for brassicas (cabbage, cauliflower, broccoli and Brussel sprouts). It is also used to control aphids, mites, grasshoppers, cutworms, leafhoppers, caterpillars on vegetables (Cochran et al. 1996; NRA 1997). WHO classified mevinphos as extremely hazardous (NRA 1997).Due to its high cost and toxicity, mevinphos is only used in small volumes e.g. 65 mL per 100 L (1100 g active ingredient/hectare) that is sprayed as fine to medium droplets. Mevinphos is known for its short withholding period, where no residue violations have been recorded (NRA 1997). There are two mevinphos products registered in Australia; for the technical grade and the formulated product named Phosdrin®.

In lab animal studies, mice were tested for blood cholinesterase (Skinner & Kilgore 1982a, 1982b), while rabbits were tested for brain cholinesterase activity (APVMA April 2007 (revised November 2008)). As for exposure to human, an accident case of a group of harvesters with symptoms of mevinphos poisoning was reported by Coye et al. (1986). Other

studies conducted in greenhouses found high dermal exposure to mevinphos from handwash samples (Jauhiainen et al. 1992; Kangas et al. 1993) and greatly decreased cholinesterase activities in blood and urine samples (Jauhiainen et al. 1992). At present, there appear to have been no glove permeation studies and *in vitro* skin studies conducted on mevinphos.

2.3.2.10 Omethoate

Omethoate (O,O-dimethyl S-[2-(methylamino)-oxoethyl] phosphorothioate) is an OP used on fruit trees, vegetables, cereals, and ornamental plants. As of May 2011, omethoate is registered in Australia, but is not registered in the USA, the UK, or in any European countries. Classified as extremely hazardous by WHO, itis hydrophilic (log K_{ow} = -0.74) and has a molecular weight of 213.2.

Acute toxicity dermal studies have been conducted on rats and mice (Worting & Hance 1991). Monitoring of exposure to omethoate has looked at cholinesterase activities and urinary excretion of workers in greenhouses and cultivation tunnels, showing good correlation with the dose absorbed (Aprea et al. 2005; Aprea et al. 2001; Aprea, Sciarra, Sartorelli, Ceccarelli, et al. 1994).

At present, there is only one study assessing omethoate absorption through skin *in vitro* by Sartorelli et al. (1998), where omethoate was dissolved in acetone, applied to monkey skin at 61.6 nmol/cm^2, demonstrating a lag time of 0.98±0.56 hr and a permeability coefficient of 4.81±9.79 x 10^{-3} cm/hr. No literature was found pertaining to glove permeation studies on omethoate.

2.3.2.11 Parathion methyl

Parathion methyl is lipophilic insecticide (log K_{ow} =3.0) commonly used on citrus, cotton, pome and stone fruits, grapevines and tobacco. It is an acutely toxic insecticide classified as extremely hazardous by WHO, and is listed under the Rotterdam Convention (emulsifiable concentrates (EC) at or above 19.5% active ingredient and dusts at or above 1.5% active ingredient). Parathion-methyl was under review by APVMA since 1996 due to concerns about worker health and safety, during end use and upon re-entry; high worker exposure scenarios; high potential acute and chronic toxicity risk, high toxicity to bees, and adverse environmental effects. However, APVMA has cancelled the registration of all parathion-methyl products available for use in Australia.

There were limited studies on parathion methyl to date. Dikshith, Datta and Chandra (1976) reported severe toxicity on female rats with repeated dermal application of methyl parathion. Assessment of blood samples in biological monitoring of agricultural workers handling parathion methyl showed dermal exposure exceeding inhalational exposure considerably (Muttray et al. 2006; Wolff et al. 1992). Good correlation with the level of exposure has also been demonstrated by the use of wipe samples (Wolff et al. 1992) and visualisation technique (Muttray et al. 2006).

In vitro studies using full thickness skin from a human cadaver (Sartorelli et al. 1997) showed faster penetration and higher percentage of absorption based on applied dose of formulated parathion methyl than in acetone solution, suggesting the important role of vehicle (solvent) in percutaneous penetration of pesticides. Therefore, skin penetration testing should be

determined using the commercial formulation rather than the active ingredients. Glove permeation studies on parathion methyl do not appear to have been conducted.

2.3.2.12 Phorate

Phorate (O, O-diethyl S-ethylthiomethyl phosphorodithioate), is a highly toxic organophosphorus insecticide with seven registered products in Australia used for brassicas, cotton, ornamental plants and potatoes. Phorate has moderately high molecular weight (260.38) and it is a lipophilic chemical (log K_{ow} = 3.56 to 3.92) which makes it readily absorbed by the stratum corneum (Moore 2010; Vettorazzi 1979). Phorate is classified as extremely hazardous and may have extensive dermal absorption based on the acute toxicity (WHO 2004).

It is still used in agricultural sector in many countries. Due to this fact, (Singh & Dogra 2009) developed methods for fast detection of serum organophosphate levels from occupational exposure using phorate and several other organophosphates.

Toxicological studies on animals have been reported on rats, rabbits and guinea pigs, with rapid absorption (Gangolli 1999; Hayes Jr. 1982; NIOSH 2015). Studies on dermal exposure of humans have been conducted on pesticide applicators and children in a non-occupational setting.

The literature search found no glove permeation studies on phorate. *In vitro* studies using phorate on pig skin in finite dose demonstrated that more phorate was absorbed from neat than from dilute in terms of the actual amount, but lower by percentage of applied dose.

2.3.2.13 Terbufos

Terbufos is ahighly lipophilic (log K_{ow} =4.5)mixed function organophosphorus pesticide) classiefied as extremely hazardous by WHO. There are five registered terbufos products in Australia which are commonly used on bananas, corn, peanuts, sunflower and wheat. Terbufos can be absorbed rapidly through the skin, with potential to result in progressively increased susceptibility to poisoning upon repeated and prolonged skin contact (Guo et al. 2001).

Animal studies on dermal exposure to terbufos have been previously reported on rats and white leghorn hens (Francis, Metcalf & Hansen 1985; Taylor 1999). There are several biological monitoring studies published on terbufos, mainly on the assessment of urinary excretion, plasma and blood cholinesterase (Bingham, Cohrssen & Powell 2001; Devine et al. 1986) but no *in vitro* skin studies have been published. Analytical methods used to estimate dermal and respiratory exposure of farmers to terbufos, as well as analysis of metabolites in urine or dialkyl phosphate metabolites (DAPs) have been described by Peterson, Picard and Devine (1985). Clothing and glove contamination were also assessed (Stone et al. 1997; Stone et al. 1992; Stone & Stahr 1989).

In a study on the effects of exposure time, material type, and granular terbufos on glove contamination, Guo et al. (2001) reported longer exposure time resulted in higher contamination levels of nitrile, neoprene, and barrier laminate gloves, however, the interaction of pesticide and glove material type may vary depending on the type of pesticides.

Glove reuse may be unsuitable as contamination of pesticide, although laundered prior to reuse, may not be fully removed, as reported on terbufos with neoprene and nitrile gloves (Guo et al. 2002).

2.4 EXISTING GUIDANCE ON GLOVE SELECTION

In Australia, PVC and nitrile butadiene rubber gloves appear to bethe most widely used gloves for OPs (Canning 1997; Canning, McQuillan & Jablonski 1998).

2.4.1 Specific Guidance

Table 2.3 shows recommendations of the type of gloves for hand protection from different manufacturers and suppliers in Australia for handling various types of OPs, compiled from internet searches and cross-reference with trade names of the OPs.

Table 2.3 List of typical commercially available OPs and recommended hand protection (gloves)

OPs used	Trade name and concentration supplied	Manufacturer or Supplier	Recommended glove	Comments for glove reuse and hygiene
Azinphos methyl	Farmoz Gusathion® 200 SC Insecticide (200 g/L)	Adama Australia	Suitable, impervious gloves (PVC, rubber)	Wash gently and thoroughly with warm water and non -abrasive soap (skin contact)
Cadusafos	Rugby® 100 g nematicide/insecticide (100 g/kg)	FMC Australasia	Elbow length PVC gloves Chemical protective gloves made of nitrile, Viton® brand or PVC	Before removing, clean gloves with soap and water
Diazinon	Barmac diazinon insecticide (800 g/L)	Barmac	Elbow length PVC gloves	Wash hands thoroughly after handling
	Diazol technical (95%)	Makhteshim Chemical Works	Suitable protective clothing/ gloves	Avoid skin contact Wash hands thoroughly after handling
Dichlorvos	Divap 1140 (1140 g/L)	United Phosphorus	Suitable protective clothing (PVC, rubber) Elbow length PVC gloves	Gloves are recommended to be washed after daily use
	FarmaLinx Dichlorvos Insecticide(1140 g/L)	Farmalinx	Impermeable gloves Suitable protective clothing (PVC, rubber)	Wash gently and thoroughly with warm water and non -abrasive soap (skin contact)
Disulfoton	David Grays Disulfoton 50 Granular Insecticide (5%)	David Grays	PVC or rubber gloves	Full length PVC and full length rubber gloves for large quantities or when heavy contamination expected
Ethion	Coopers Tixafly Cattle Dip and Spray (125 g/L)	Intervet Australia	Impervious gloves (PVC)	Wash gently and thoroughly with warm water and non -abrasive soap (skin contact)
Fenamiphos	Fenamiphos 400 Nematicide and Insecticide (400 g/L)	Apparent Pty Ltd	Elbow length PVC gloves	Gloves are recommended to be washed after daily use
	Farmalinx Neptune 400 EC Nematicide and Insecticide (400 g/L)	Farmalinx	Impermeable gloves Suitable protective clothing (PVC, rubber)	Avoid skin contact Wash hands thoroughly after handling
	Smart Fenamiphos 400 EC Insecticide (400 g/L)	Crop Smart	Impermeable gloves Suitable protective clothing (PVC, rubber)	Avoid skin contact Wash hands thoroughly after handling
Fenamiphos	AC Redback (400 g/L)	AxiChem	Suitable gloves Elbow length PVC gloves	Wash hands thoroughly after handling

			Barrier cream	Wash hands vigorously with water and soap (skin contact)
	Titan Fenamiphos 400 Nematicide and Insecticide (40%)	Titan AG	Chemical resistant gloves (PVC, rubber)	Wash hands after handling Wash hands with water and soap (skin contact)
	4 Farmers Fenamiphos 400 Nemacide and Insecticide (40%)	4 Farmers	Chemical resistant gloves (PVC, rubber)	Protective clothing are recommended to be washed before being reused
	Genfarm Fenamiphos 400 Nematicide (400 g/L)	Genfarm	Elbow length PVC gloves	Gloves are recommended to be washed after daily use Wash hands with water and soap (skin contact)
Mevinphos	Phosdrin® Insecticide (1,110 g/L)	Runge Agrichem	Elbow length PVC gloves	Wash hands thoroughly after handling Wash hands with water and soap (skin contact)
Omethoate	Folimat 800 Insecticide Spray (800 g/L)	Bayer	Elbow length PVC gloves	Gloves are recommended to be washed after daily use
	Ometho-Mite 290 SL Insecticide (290 g/L)	FarmaLinx	Impervious gloves (PVC)	Wash hands with water and soap (skin contact)
	FMC Omethoate 290 Miticide (290 g/L)	FMC Crop Protection	Elbow length PVC gloves	Gloves are recommended to be washed after daily use
	Agri West AW Omethoate insecticide (290 g/L)	Agri West	PVC gloves	Wash hands thoroughly after handling Wash hands vigorously with water and soap (skin contact)
Parathion methyl	Crop Care Methyl Parathion 500 Insecticide (500 g/L)	Crop Care Australasia	Elbow length PVC gloves (preparation and use) Impervious gloves (manufacture, packaging, transport)	Gloves are recommended to be washed after daily use
Phorate	Umet 100 G Systemic Soil Granular Insecticide (11.2%)	UPL Australia	Elbow length PVC gloves	Gloves are recommended to be washed after daily use Wash hands thoroughly after handling
Phorate	Zeemet 200G Systemic Soil Granular Insecticide (22.4%)	UPL Australia	Elbow length PVC gloves	Gloves are recommended to be washed after daily use Wash hands thoroughly after handling

Terbufos	Hunter 150G Systemic Granular Soil Insecticide/Nematicide	UPL Australia	Suitable, impermeable gloves Rubber, PVC, butyl rubber gloves	-

Note: Some of the OPs are available from one or more manufacturers or suppliers in Australia

Recommended gloves were compiled from the following sources:

- Azinphos methyl:.http://www.herbiguide.com.au/MSDS/MAZME200_62221-0812.PDF
- Cadusafos: http://www.fmccrop.com.au/wp-content/uploads/PDFs/Rugby%20100G%20Insecticide%20MSDS.pdf
- Diazinon: http://www.herbiguide.com.au/MSDS/MDIAZ800_50007-1098.PDF and Appendix 2.4
- Dichlorvos: http://www.uplonline.com/uplaustralia/productdata/Divapn_1140.pdfand http://www.farmalinx.com.au/SiteMedia/w3svc1005/Uploads/Documents/DICHLORVOS-msds.pdf
- Disulfoton: http://davidgray.com.au/storage/file-msds-list/MSDS%20Disulfoton%2050.pdf and http://www.cdms.net/ldat/mp68K014.pdf
- Ethion: http://www.coopersanimalhealth.com.au/msds/sp/TIXAFLY_29101641.pdf
- Fenamiphos:.http://www.apparentag.com.au/MSDS/MSDSApparentFenamiphos400%20%282%29.pdf, http://www.farmalinx.com.au/SiteMedia/w3svc1005/Uploads/Documents/NEPTUNE%20400%20EC-msds.pdf, http://www.cropsmart.com.au/wp-content/uploads/2014/04/SDS-Smart-Fenamiphos-400-EC.pdf, http://www.axichem.com.au/documents/AC%20Redback/AC%20Redback%20MSDS.pdf, http://www.titanag.com.au/Products/MSDs/TITAN_Fenamiphos_400_SDS.pdf, https://www.4farmers.com.au/resources/product_downloads/3_fenamiphos-400_4%20FARMERS%20FENAMIPHOS%20400%20NEMACIDE%20&%20INSECTICIDE.pdf and http://www.genfarm.com.au/Labels/129.pdf?v=1451588148
- Mevinphos: Appendix 2.2
- Omethoate: http://www.bayercropscience.com.au/resources/uploads/msds/file7226.pdf and http://www.farmalinx.com.au/SiteMedia/w3svc1005/Uploads/Documents/OMETHO-MITE%20290%20SL-msds.pdf,http://www.fmccrop.com.au/wp-content/uploads/PDFs/Omethoate%20290%20Insecticide%20MSDS.pdf and http://agriwest.com.au/item/common/upload/2014/4/1/102624GB.pdf
- Parathion methyl: http://www.herbiguide.com.au/MSDS/MPARA500_48224.PDF
- Phorate: http://www.uplonline.com/products/UmetM.pdf and http://www.uplonline.com/products/ZeemetM.pdf
- Terbufos:.http://www.uplonline.com/uplaustralia/productdata/Hunter_150G.pdf

In Table 2.3PVC gloves appear to be the most commonly recommended gloves.

However, generic descriptions are often used in SDSs – e.g. ‘wear suitable gloves’ or ‘use impervious gloves’. This of course, is not helpful in glove selection decisions. From anectodal information, it is likely that the cheapest option available will be chosen, without confirmation from other sources.

Relatedly, glove suppliers may be unaware of the details of exposure (e.g. what other chemicals will be handled, in high or low concentration, at normal or hot temperature), although these are the important factors that could affect the barrier properties of the gloves.

2.4.2 General Guidance

All gloves have different composition, thickness and properties because they are made of different raw materials, layering and coating. A ten-fold difference in protection factors was reported for generically equivalent gloves from different manufacturers (Mickelsen & Hall 1987). Even a particular brand and model of gloves manufactured by the same manufacturer from different production batch lot can still have a significantvariation due to poor quality control (Klingner & Boeniger 2002). It is unlikely that distributors and users are aware of these issues.

Gloves tend to be re-used and the thickness of these gloves may lead them to being used repeatedly. This is evident in the results reported by Canning (1997). It is also unsurprising as most SDSs (Table 2.3) recommend that the gloves are washed after daily use.

Safe Work Australia states that with respect to the use of PPE as a control measure (Regulations 44 and 46 of the Work Health and Safety Act noted in their 'Code of Practice on Managing the Risks of Hazardous Chemicals in the Workplace'); there should be an understanding of selection, use and maintenance standards.

The standards, AS/NZS 2161.10.3:2005 Occupational protective gloves Part 10: Determination of resistance to permeation by chemicals (EN 374-3:2003) have been developed based on the European Standards. Labelling of gloves for chemical resistance does not certify the glove as impervious for a specific chemical or mixture. It is widely acknowledged that in real life conditions and repeated use, published protection factors may not be achieved (HSE 2001; Perkins & Rainey 1997).

When selecting protective gloves for hand protection, it is important to know the task(s) to be performed, chemicals to be handled, exposure duration and conditions present. Generally, barrier resistance, durability and comfort are considered in the process of selection. However, to have the comfort factor combined with the barrier resistance for a type of gloves involves higher costs, therefore it will be unlikely to be the preferred option, especially in developing countries (Holmgaard & Nielsen 2009).

While selection of gloves is usually made based on the ability of the gloves to withstand contact with the substance for the longest time, selection is not simply determined by referring to SDSs or manufacturer's published data (Packham 2006). This is because some pesticide manufacturers do not describe the recommended gloves (e.g. type, length, thickness) in sufficient detail on the SDSs or labels of the formulated product, which means

the information may be misunderstood hence putting the users at risk of exposure through the use of ineffective gloves.

It is of concern that most pesticides contain active ingredients dissolved in carrier solvents e.g. hydrocarbon mixtureswhich may permeate the glove materials quicker than the active ingredients. This can complicate the selection and may indicate that advice given is misleading if most glove permeation charts are published based on tests performed with individual chemicals (active ingredients) only, without including the carrier solvents. Issues arise when the solvents are not disclosed on SDSs or labels due to the classification as inert ingredients or commercial confidentiality, whereas the resistance of the glove materials to the pesticides solvents is the opposite of the resistance for the active ingredients. For example, although PVC gloves are recommended for handling omethoate, the formulated product usually contains glycol ether as a carrier solvent that may behave differently with the glove.

Solvents often readily permeate the gloves, hence affecting breakthrough of the other chemicals in the mixture (Lara & Ketelson 1992). Therefore, prediction of a particular compound based on glove permeation charts is difficult and may be inaccurate. Neither is predicting permeation of pure (analytical grade or technical grade) chemicals easy, because it is very unlikely in most occupational exposure settings. Furthermore, some chemicals may cause degradation of the glove material (e.g. swelling), therefore affecting protection provided (Klingner & Boeniger 2002).

Although experimental lab test results provide good indicators for the desired protection, results obtained under field conditions are more representative as they relate to the factors that influence pesticide permeation through protective clothing in the real world scenario

(Thongsinthusak et al. 1990). There have been many studies on permeation of pesticide formulations, in mixture with carrier solvents, through gloves demonstrating greatly reduced breakthrough time (Ehntholt, Bodek & Valentine 1989; Ehntholt, et al. 1990; Mickelsen, Roder & Berardinelli 1986; Que-Hee 1989; Schwope & Goydan 1992).

When considering formulated OPs that contain more than one chemical (an active ingredient and a co-solvent), users might seek advice from glove suppliers (Dickson 2012). However, only general recommendations may be available if searching for selection advice for several brands of gloves made of the same type of materials based on the SDSs of the active ingredients.

2.5 UNCERTAINTIES AND GAPS IN KNOWLEDGE IN RELATION TO DERMAL EXPOSURE TO OPS

Based on a review of the literature pertaining to the OPs of security concern, knowledge gaps exist in three areas, relating to glove performance and skin penetration.

Firstly, suppliers and formulators of agricultural OPs recommend the use of long length PVC gloves. Indeed, distributors stock cheap versions of such gloves, but as they are not considered disposable, repeated use is the norm. Manufacturing quality issues have been identified (Moody and Nadeau 1994; Canning 1997), but are likely to be poorly understood by users. Although some forensic work has been done by Canning (1997) uncertainty exists as to the protection afforded under real world conditions of solar radiation, elevated

temperature and abrasion. In addition, there appear to be no glove studies comparing a range of OPs, particularly formulated products.

Secondly, the chemical barrier performance of disposable gloves, as worn by ambulance workers in poisoning episodes, has not been investigated. An evidence-based glove permeation database needs to be established for first responders who might have incidental exposure.

Thirdly, it is known that skin absorption of chemicals depends on physicochemical properties such as molecular size and water solubility. However, apart from the paper by Sartorelli and co-workers (1998) there appear to be no skin penetration studies which have compared a range of OPs of different properties. No combined studies of skin and gloves have been undertaken. Moreover, the skin studies that have been conducted have generally used a finite dose model. An infinite dose model is more applicable for worst case occupational risk assessment.

2.6 PROPOSED FOCUS FOR THE CURRENT RESEARCH

The abovementioned knowledge gaps will be addressed, with a focus as outlined below.

A limited set of formulated OPs

Within the 12 OPs of security concern, there is significant variation in physicochemical properties (see Table 1.1).

In order to address the third knowledge gap within the constraints of a PhD project, it was decided to look at only four OPs but spanning a wide range of properties relevant to glove permeation and skin penetration. These OPs are listed below, and in Table 2.4. These would be formulated OP products where possible.

The OPs areomethoate (available as Folimat®, concentration 800 g/L), mevinphos (available as Phosdrin®, concentration 1,110 g/L), dichlorvos (available as DDVP Technical Grade, 98% purity) and diazinon (available as Barmac Diazinon Insecticide, concentration 800 g/L), with their labels shown in Figure 2.1.

Table 2.4 Physicochemical properties of four OPs of interest that may influence skin penetration and glove permeation

Compound	**MW**	**Log K_{ow} (exp)**	**Log K_{ow} (pred)#**	**Solubility mg/L[a]**	**Calc Mol volume***	**Calc molecular polar surface area[b]**
Omethoate	213.2	-0.74	-0.787	readily soluble	174.95	64.65
Mevinphos	224.1	0.13	0.76	600,000	189.565	71.1
Dichlorvos	221.0	1.9	0.603	8,000	155.546	44.8
Diazinon	304.3	3.81	3.86	40	273.146	53.5

#Episuite US EPA

[a]HSDB Hazardous Substances Data Bank, National Library of Medicine

*http://www.molinspiration.com/cgi-bin/properties

Molecular volume: Calculated volume is expressed in cubic Angstroms
Method for calculation of molecule volume developed at Molinspiration is based on group contributions. These have been obtained by fitting sum of fragment contributions to "real" 3D volume for a training set of about twelve thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semiempirical AM1 method.
"Rule of 5" Properties is set of simple molecular descriptors used by Lipinski in formulating his "Rule of 5" [2]. The rule states, that most "drug-like" molecules have logP <= 5, molecular weight <= 500, number of hydrogen bond acceptors <= 10, and number of hydrogen bond donors <= 5. Molecules violating more than one of these rules may have problems with bioavailability. The rule is called "Rule of 5", because the border values are 5, 500, 2*5, and 5.
Number of Rotatable Bonds – nrotb This simple topological parameter is a measure of molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs [3]. Rotatable bond is defined as any single non-ring bond, bounded to nonterminal heavy (i.e., non-hydrogen) atom. Amide C-N bonds are not considered because of their high rotational energy barrier.

[b] Angstrom squared (from Molinspiration.com)

Figure 2.1 Labels of the commercial formulated OPs (omethoate- Folimat®; mevinphos- Phosdrin®; diazinon- *Barmac* Diazinon Insecticide) tested in this research

Laboratory simulation of worst case exposure conditions

Another focus is a worst case exposure scenario, i.e. infinite dose conditions, at the highest realistic skin or environmental temperature[2] for the longest likely daily duration, and with respect to both concentrate (highest available) and application strength. In addition, there would be exploration of the effects of UV and abrasion of glove performance.

[2]45°C was chosen as the high temperature for glove performance tests resembling the maximum temperature reached in South Australia during summer, and 37°C was selected for the *in vitro* skin testing.

A case study approach

Two case study situations would be simulated, namely (1) agricultural workers using OPs, and (2) ambulance workers, as first responders to incidents involving OPs. The first is based on the large population exposed and the second situation is one which is lacking an evidence base.

The degree of dermal exposure for agricultural workers varies depending on the OP-related tasks; with major ones being:

- Mixing and loading - Farmers often purchase pesticides in large volumes, packed in heavy and bulky containers which may result in spills and/or splashes if not properly handled (Fenske & Day Jr. 2005). The tasks usually involve measuring the concentrated products and mixing it with diluent i.e. water, stirring manually or by automatic pumping, and loading the diluted liquid formulations into the spraying equipment.
- Spraying – applying the diluted pesticides using various types of spraying equipment; backpack sprayers, spray rig within the vehicle, or spray rig connected to the mixing tank towed by trucks or tractors or aircraft.

Dermal exposure for ambulance workers may involve OPs in concentrated or dilute form, when handling patients.

This research is designed to simulate a real workplace exposure during spills and splashes, where OP chemicals come in contact with the skin in significant volume to investigate the maximum penetration rates for exposure risk assessment (Howes et al. 1996; OECD 2004b).

In the agricultural case study, two brands of elbow-length PVC gloves, as recommended by the manufacturers of the OPs, were selected for performance testing with formulated OPs. Since there are numerous brands of PVC gloves in the market, selection was made based on the most likely selection event which is based on the criteria of what is readily available at the lowest cost. It is believed that farm owners might not spend a lot of money on the gloves, especially if the gloves were to be changed occasionally, hence the decision to use the cheapest gloves from two different brands. This would also enable a comparison between gloves under identical conditions.

The second case study the performance of disposable neoprene and nitrile gloves, used by the South Australia Ambulance Service (SAAS) ambulance workers, would be tested individually and in combination (i.e. double gloving).

2.7 AIMS AND BROAD RESEARCH QUESTIONS

The broad aim of this research is to improve understanding of dermal exposure to OPs of security concern in routine and non-routine situations. It is anticipated that this research will also generate useful information for predictive dermal risk assessment models and optimising control measures. An improved evidencebase will ultimately assist in reducing morbidity and mortality from OPs.

The broad research questions addressed in this thesis are:

1. How do the recommended PVC gloves (unused, exposed to UV radiation and abrasion) perform against formulated OPs in various exposure conditions?
2. What are the effects of different variable conditions on different types of disposable gloves worn by ambulance workers and is the current practice suitable?
3. How does skin absorption of OPs of security concern vary with concentration and temperature, across formulated OPs with a range of physicochemical properties?

Chapters 4-6 have further specific research questions.

2.8 WHAT IS NOT ADDRESSED IN THIS THESIS

A wide variety of approaches and techniques can be used to assess exposure and uptake of OPs (Fenske & Day Jr. 2005). These include on site air monitoring (static and personal breathing zone), skin wipes/wash, neurobehavioural symptom assessment or biological monitoring (Cattani et al. 2001; Johnstone 2006; Lee 2004). The research reported in this thesis is restricted to laboratory experimentation, rationalised by some limited field observations. In addition, while there have been a number of glove studies, this thesis only address certain factors that may affect performance of gloves under various challenge conditions. Issues such as glove flexing and the interactions of individual constituents of formulated products with glove materials are not considered (Phalen &Que-Hee 2008, Phalen &Wong2011, 2012, Phalen, Le & Wong 2014).

CHAPTER 3

MATERIALS AND METHODS

This chapter describes the materials and step-by-step procedures employed for laboratory experimental work, aimed at determining glove permeation and skin absorption of OPs under different conditions. The methods are mainly based upon the specified protocols and recommendations of Australian and OECD guidelines (Australian/New Zealand Standard 2005; Howes et al. 1996; OECD 2004a) and other published methods mentioned in the respective sections. For the exploratory studies of UV and abrasion effects, in-house procedures were developed.

Materials and methods for Case Study 1 are presented first in Section 3.1. This includes test chemicals, temperatures etc. To avoid repetition, some information for Case Study 2 (Section 3.2) and skin testing (Section 3.3) may refer back to Section 3.1.

3.1 GLOVE PERFORMANCE STUDIES FOR CASE STUDY 1 (PVC GLOVES USED BY AGRICULTURAL WORKERS)

In this Case Study 1, the performance of PVC gloves recommended for handling OPs as previously discussed in Section 2.4.2 was tested to determine their suitability and effectiveness as chemical protective clothing for OPs.

3.1.1 Types of PVC gloves tested for performance against OP permeation

3.1.1.1 Agricultural PVC gloves (unused)

Safety data sheets for OPs formulated for agricultural use generally specify supported PVC gloves. Accordingly, elbow length (45 cm) PVC gloves of two different brands; namely *Excalibur* and *ProChoice* (Figure 3.1) were sourced locally, as would normally be done by agricultural workers. *Excalibur* gloves (RN No. #48583, Style W6218R, FTY11371110) were sourced from Protector AlSafe, Regency Park, South Australia. *ProChoice* gloves (106M-3-SFC-14014) were purchased from SafetyQuip, Dry Creek, South Australia. Both brands of gloves were labelled as being made in China, single-dipped with full coating and interlock lining. They were supplied as single batches from bulk cartons so as to ensure, as far as possible, manufacturing consistency.

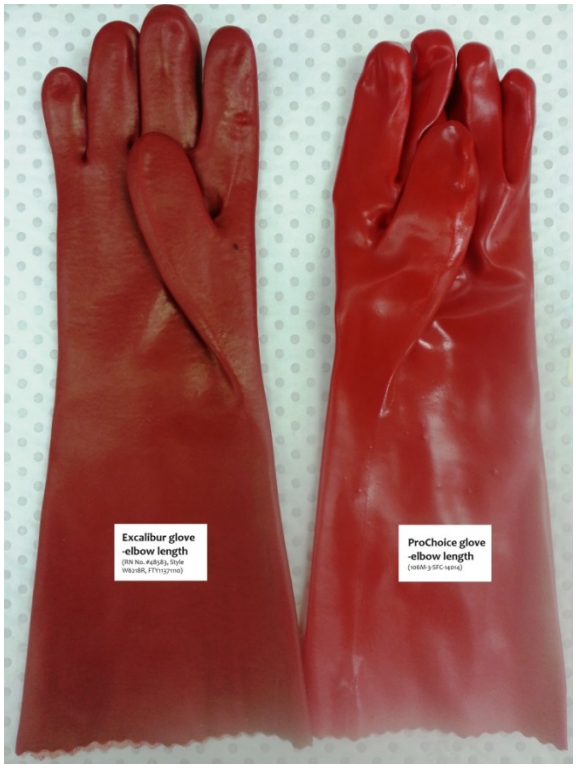


Figure 3.1 Elbow length PVC gloves tested; *Excalibur* (left) and *ProChoice* (right)

That said, it is understood that the quality of gloves may vary depending on manufacturer, and the thickness of the gloves may be dependent on the coating process. Palm, thumbs and forefingers are the areas with the highest likelihood for exposure to chemicals (Boeniger 1991; Lee, 2004) and abrasion (Vo 2002; Vo, Berardinelli & Boeniger 2001). For practical reasons, the palm section was chosen for the glove performance tests.

Glove swatches were cut out with scissors (approximately 4.5 cm in diameter; 15.9 cm^2 surface area) and the thickness was measured at several points with a digital thickness gauge (547-301, 0.01mm-10mm, Mitutoyo). The thickness of the *Excalibur* gloves varied between 1.05 and 1.26 mm, while *ProChoice* had thicknesses ranging from 1.07 to 1.28 mm.

3.1.1.2 PVC gloves exposed to ultraviolet (UV) radiation

As much of the farm work is conducted outdoors with potential for extended UV exposure, the permeation resistance of PVC gloves exposed to UV radiation was tested. This sub-study was conducted to address Research Question 2, as listed at the beginning of Chapter 4. To mimic exposure to UV radiation in real life, gloves were exposed to UV radiation in a UV box for 48 hours (Figure 3.2). This simple PVC box was fabricated by Flinders Medical Centre, with UV-A lamps (FL6BL 6W 350 nm) and UV-B lamps (FL8E 8W 302 nm) supplied by Ultra Violet Products (Aust) Pty Ltd.

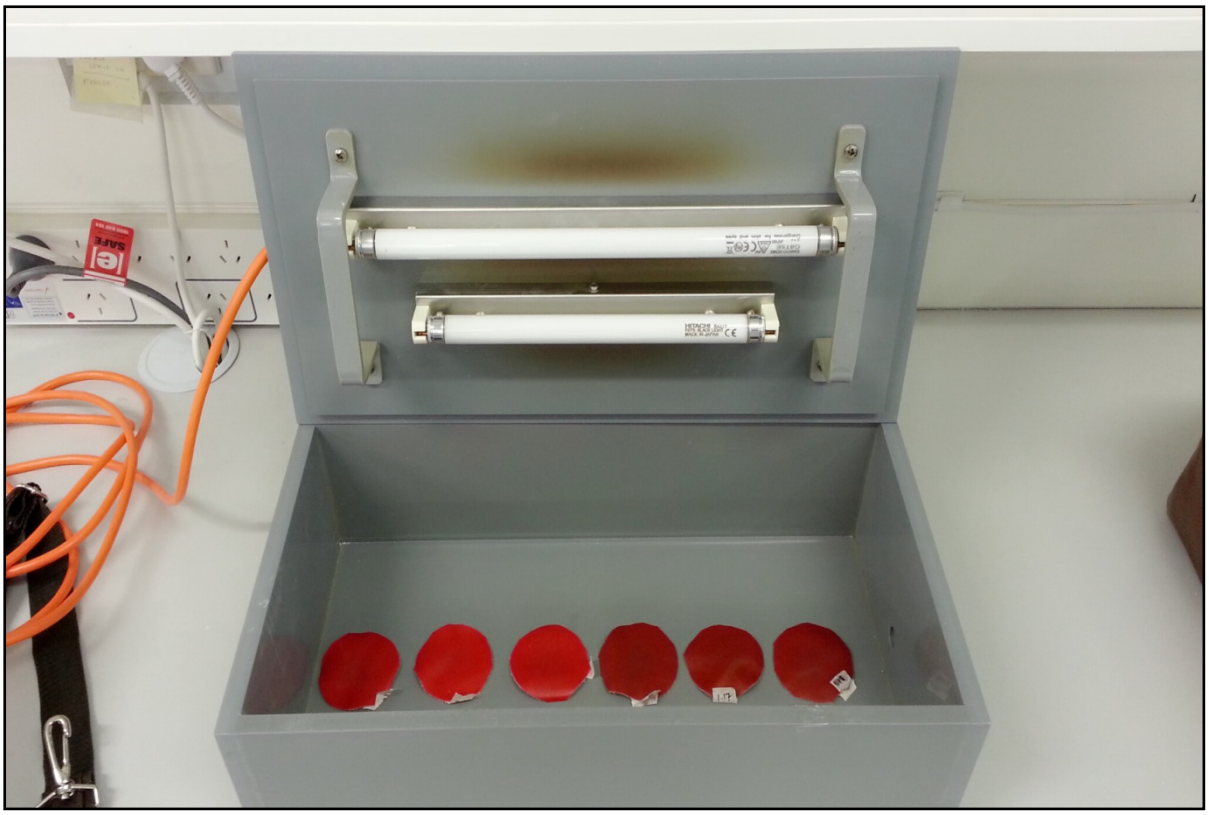


Figure 3.2 Swatches of PVC gloves exposed to UV radiation in the UV box

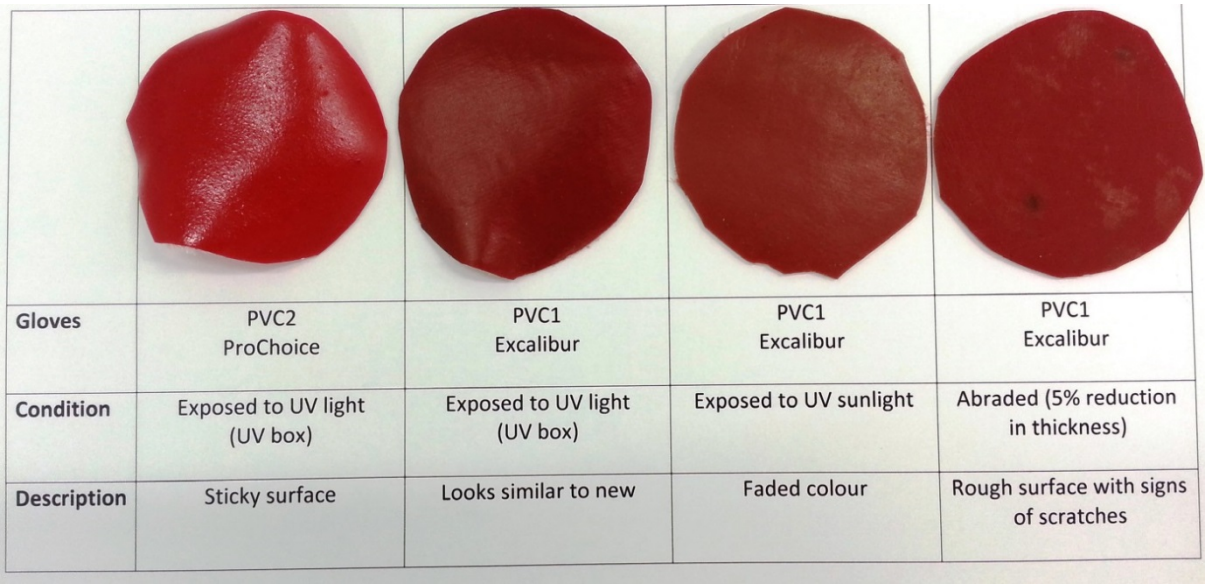
The UV radiation was measured with a IL 1700 Research Radiometer (International Light Inc.), (SED 038 UV-A probe and SED240 UV-B probe) and readings were 4 x 10^{-4} watts/cm^2 (4 watts/m^2) for UV-A and 2.6 x 10^{-4} watts/cm^2 (2.6 watts/m^2) for UV-B at the base of the box. This irradiance was approximately equal to seven days of exposure to the extreme midday sun (RReDC 2013; Skin Cancer Foundation 2013; WMO September 2013). Sunlight UV reaching the ground is mostly UV-A (depending on cloud cover and atmospheric conditions) and roughly 32 watts/m^2 at its maximum (Bolton and Colton, 2008). UV-B is likely to be the most damaging form of UV for glove materials, and at 2.6 watts/m^2 this UV B exposure level is at least as strong as the bright sun at the zenith in cloud free summer.

The exposed glove swatches were then used in the glove performance tests as described in Section 3.1.3.

3.1.1.3 PVC gloves with abrasion

Tests were also conducted on abraded agricultural PVC gloves, to mimic the real life situation where gloves are reused, and where wear may occur as a result of repeatedly handling objects etc. This sub-study was conducted to address Research Question 3 as explained at the beginning of Chapter 4. For this purpose, flat sections of gloves (palm) were cut out and the average thickness determined. The sections were then mounted on a foam-backed hand sander and carefully abraded by using a horizontal belt sander (Ryobi, RBDS4601G, 370W) until the thickness of the gloves was reduced by 5%, corresponding to a PVC top layer reduction of approximately 10% (0.06 mm). Then, the surfaces of the abraded gloves were vacuumed and wiped with a wet sponge to get rid of the small particles produced during the abrasion process. The abraded gloves were then used in the glove performance tests as described in Section 3.1.3.

Figure 3.3 shows the visual difference of the PVC gloves in different conditions (UV, abrasion). The first two images relate to the effect of the abovementioned UV exposure for the two PVC gloves (Section 3.1.1.2). The third image relates to one-month exposure to sunlight (natural outdoor conditions) and is presented simply for comparison. The image on the far right (4^{th} image) illustrates the abraded glove surface using the belt sander. It appeared non-glossy, had a rough surface and had signs of scratches.



Gloves	PVC2 ProChoice	PVC1 Excalibur	PVC1 Excalibur	PVC1 Excalibur
Condition	Exposed to UV light (UV box)	Exposed to UV light (UV box)	Exposed to UV sunlight	Abraded (5% reduction in thickness)
Description	Sticky surface	Looks similar to new	Faded colour	Rough surface with signs of scratches

Figure 3.3 Comparison between PVC gloves exposed to UV light and abrasion

3.1.2 Test compounds (organophosphorus pesticides) used in the study

The compounds chosen to investigate glove permeation and skin penetration in this study were OPs of security concern, as mentioned in Section 2.4.1. Four types of OPs of different physicochemical properties were tested on gloves and human skin; namely omethoate, mevinphos, dichlorvos and diazinon. In order to mimic real life exposure, these OPs were sourced as the commercial OP products which are formulated with carrier solvents sold in the market. Although the concentrates had additives as minor components in most cases, separate permeation studies of the additives were not conducted.

All OPs were tested as the full strength (undiluted concentrate) to mimic the exposure to workers during mixing or loading, as well as exposure to the public during chemical accidents, poisoning or terrorism cases. Application strength (diluted) was also tested to mimic low level exposure of farmers who may be exposed to them during spraying. All

dilutions were made based on the recommended dilution in the accompanying product booklets as summarised in Table 3.1, using ultrapure water i.e. deionised, filtered water (*Ibis* reverse osmosis unit).

Table 3.1 Summary of the OP concentrates tested

Test chemicals	Carrier solvent(s)	Full strength (g/L)	Application strength (g/L)
Omethoate	1-methoxy-2-propyl acetate	814	0.6
Mevinphos	Unnamed liquid concentrate	1,110	0.7
Dichlorvos	None	1,398	6.0
Diazinon	Hydrocarbon liquid	804	0.5

The first OP was formulated omethoate (IUPAC nomenclature (O,O-dimethyl-S-[2-(methylamino)-2-oxoethyl] phosphorothioate, CAS 1113-02-6) which was available as insecticide with the brand name Folimat® produced by Arysta Life Science (Victoria, Australia) and distributed by Ospray Pty Ltd (Queensland, Australia) (Figure 3.4). It contains 800 g/L omethoate as the active ingredient and 400 g/L 1-methoxy-2-propyl acetate as the carrier solvent (Appendix 2.1), however detail analysis on purity showed that there was 814 g/L omethoate in the formulation.

Figure 3.4 Formulated omethoate used in the study, available as Folimat®

With a log octanol-water partition coefficient (log K_{ow}) of -0.74; omethoate is soluble in water and is not likely to accumulate in fat. It has a calculated molecular volume of 175 cubic angstroms (Molinspiration.com) and its molecular weight is 213.2. In Australia, omethoate is classified in Schedule 7 of the Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) with a cut-off to Schedule 6 at 30% or less, or to Schedule 5 in pressurised spray packs containing 0.2% or less of omethoate. It is effective as direct and systemic insecticide and acaricide in both commercial and home garden situations. Therefore, it is used to control certain pests on apples, bananas, citrus, pears, onions, cottons, lupins, potatoes and ornamentals. Application strength of omethoate tested in this study was 0.6 g/L, based on the

75 mL per 100 L dilution with water as recommended in the accompanying product booklet (Table 3.1).

The second OP used in this research was mevinphos (IUPAC nomenclature: 2-methoxycarbonyl-1-methylvinyl dimethyl phosphate, CAS 7786-34-7) with the brand name Phosdrin®. It was manufactured by Runge Agrichems (New South Wales, Australia) and was purchased from E.E Muir & Sons Pty Ltd (Penola, South Australia) at 1,110 g/L (Figure 3.5). Phosdrin® contains 110% (w/v) mevinphos as mixed isomers, 0.1% stench agent and 0.025% red dye (Appendix 2.2). Mevinphos is water soluble (log K_{ow} 0.13) with a molecular volume of 190 cubic angstroms, and the molecular weight is 224.1.

Figure 3.5 The formulated mevinphos, manufactured as Phosdrin®

Mevinphos is used for the control of insects (particularly Diamond Back Moth) in brassica crops (broccoli, cabbage, cauliflower and Brussels sprouts), mainly in South Australia, Queensland, New South Wales and Tasmania. Despite the high cost and toxicity, mevinphos is used in Integrated Pest Management (IPM) programs and as part of the rotation of chemical groups in resistance management strategies due to its short withholding period. The application strength used in this study was 65 mL per 100 L, which corresponds to 0.7 g/L (Table 3.1).

The third OP tested in this research was dichlorvos (IUPAC nomenclature: 2,2-dichlorovinyl dimethyl phosphate (DDVP), CAS number 62-73-7), which was obtained as 1,398 g/L technical grade DDVP (Lot No. 212002AX0028) of 97% purity without co-solvent from Amvac Chemical Corporation (Appendix 2.3). Dichlorvos was unavailable in formulated form due to deregistration for use, however the dichlorvos used was the same technical grade used by the OP manufacturer for making formulated dichlorvos products. Dichlorvos is a volatile fumigant having a relatively high vapour pressure (1.6 Pa at 20°C) with a molecular weight of 221.0 and molecular volume of 156 cubic angstroms. It has a low log K_{ow} of 1.16, which means that it is moderately lipophilics (ATSDR 1997). The existing poisons schedule for dichlorvos in Australia is as follows; Schedule 5 for products containing 20% or less dichlorvos and impregnated in plastic resin strips or in sustained release resin pellets; Schedule 6 for products containing 50% or less of dichlorvos except when included in Schedule 5; Schedule 7 except when included in Schedule 5 or 6.

The regulatory status of dichlorvos in Australia shows some products are home garden products while others are intended for use by the professional agricultural, pest control or veterinary sectors (APVMA, 2011). Besides the full strength dichlorvos, it was also diluted to

6 g/L (application strength) as suggested in the product leaflet (various applications) for the glove tests and skin testing (Table 3.1).

The fourth OP tested in this research was *Barmac* Diazinon Insecticide, a contact organophosphorus insecticide with a broad range of insecticidal activity containing 800 g/L diazinon (IUPAC nomenclature: O,O-diethyl-O-(2-isopropyl-6-methylpyrimidin-4-yl)-phosphorothioate, CAS 333-41-5), and 80 g/L hydrocarbon liquid as the carrier solvent (Figure 3.6). However, detail purity analysis showed that there was 804 g/L of diazinon (active ingredient) in the formulation. *Barmac* Diazinon Insecticide was formulated by Accensi (Queensland, Australia) and was obtained from Barmac (Queensland, Australia) (Appendix 2.4).

Figure 3.6 Diazinon formulated by Barmac used in the study

In contrast to omethoate, diazinon is relatively insoluble in water and has a log K_{ow} value of 3.81. The molecular weight of diazinon is 304.3 and its molecular volume is 273 cubic angstroms. Diazinon has a long history of use in Australia and is presently in Schedule 6 (in Schedule 5 for dust preparations containing 2% or less of diazinon) of the SUSDP.

There are over 50 diazinon products in Australia used for pests in fruit and vegetable crops, as well as in various domestic, commercial and industrial areas. Dilution factor for spray application varies depending on the purpose and types of pests, but in this study, 0.5 g/L was selected as the application strength for tests because it is the intermediate value with many applications nationwide (Table 3.1).

All four OPs are skin sensitisers, may cause irritation and repeated exposure may have cumulative poisoning effects with toxic symptoms of cholinesterase inhibition in the nervous system with subsequent accumulation of toxic levels of acetylcholine (ACh) as a neurotransmitter (APVMA 2006, 2011a, 2011b, 2013b, July 1999 (revised September 2002)). Side effects may include hypersensitivity, decreased host resistance and autoimmunity (APVMA 2006, 2011a, 2011b; NRA 1997).

3.1.3 Glove performance tests using ASTM cells

The permeation test methods were in accordance with Australian/New Zealand Standard 2161.10.3:2005 (Occupational protective gloves Part 10.3: Protective gloves against chemicals and micro-organisms-Determination of resistance to permeation by chemicals. ASTM permeation test cells (Australian/New Zealand Standard 2161.10.3:2005) were used in

the glove performance test, which is a simple two-compartment cell with one part for the test chemical and the other part for the receptor fluid as shown in Figure 3.7.

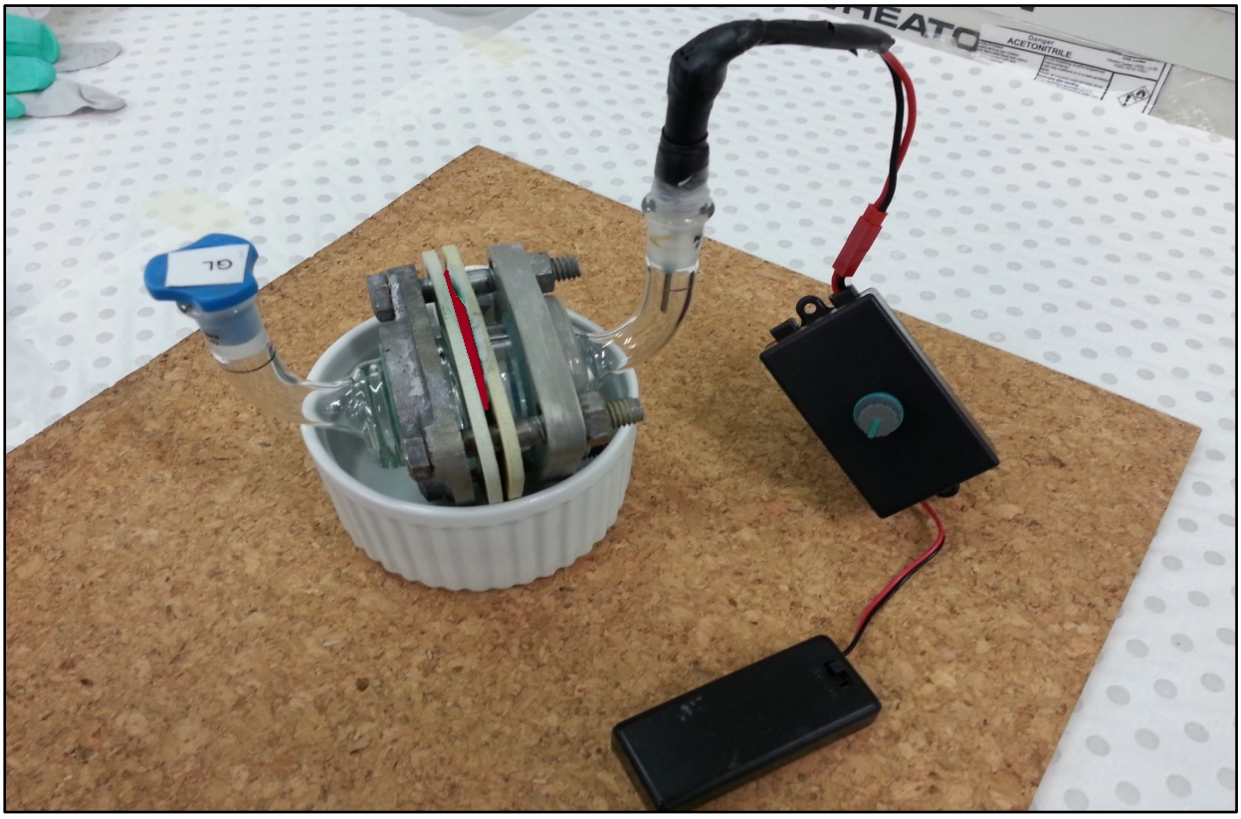


Figure 3.7 Assembly of the ASTM permeation test cell with glove swatch in between channelled stopper and modified stirrer

Glove swatches were cut out of the palm section and mounted between the glass donor chamber and the receptor chamber held by two aluminium flanges, with the outer surface of the glove swatch facing the test chemical and the inner surface in contact with the receptor fluid. The 1-inch ASTM cells (Pesce Lab Sales, PTC 500) had a diffusion-available surface area of 5.31 cm^2 and a receptor compartment volume of 16.4 mL. The two chambers were hand-tightened with three bolts and nuts and subsequently tightened using a torque wrench (*Torqueleader*, ADS4, Serial No. OEM100078) to 16 lb inch, as suggested by the manufacturer.

Receptor fluid (Section 3.1.3.2) was continuously stirred with a modified stainless steel/teflon stirrer (variable speed, typically 350 rpm) throughout the experiment duration to ensure an adequate degree of mixing. The donor chamber was loosely stoppered (with a channelled polypropylene stopper) to avoid any pressurization. Similarly, the receptor chamber, with stirrer, was not pressurized. At desired time intervals, 200 μL of the receptor fluid was drawn out from the receiving chamber for analysis, and replaced with the same volume of the receptor fluid.

For each variable condition, four replicates were carried out. Periodic positive control experiments were also undertaken. This was conducted by creating three pinholes in the middle of a glove swatch using a sharp needle.

3.1.3.1 Temperature setting and duration for glove tests

The glove performance tests were conducted at two different temperatures. The experiments were either set-up in the laboratory under room conditions (23(±2) °C) or in a heated incubator for 45°C to resemble the likely upper extreme, but plausible conditions. The maximum testing time was 8 hours to mimic 8-hour exposure for a work shift in a day.

Due to shortage in supply, mevinphos was only tested at room temperature (PVC gloves). Therefore, permeation through gloves was only compared with other OPs of the same variable conditions.

3.1.3.2 Receptor fluids for glove performance tests

Receptor fluids for dermal absorption studies were typically chosen based on suitability and chemical solubility. They are usually in aqueous form to limit partitioning of more lipophilic chemicals depending on the solubility (Moore 2010). In this study, ultrapure water was used as receptor fluid for omethoate, dichlorvos and mevinphos. For diazinon, 50% ethanol (v/v) in water was used to facilitate absorption of insoluble more lipophilic chemicals into the receptor fluid, as described in a previous study (te Brake et al. 2012).

3.1.4 Descriptors of permeation

The following variables were used as descriptors for the ability of OPs to permeate through the gloves into the receptor fluid: flux (μg/cm^2/min), breakthrough time (mins) and cumulative permeation (mg).

Flux (μg/cm^2/min) refers to the permeation rate of which the amount of OPs (μg) crossing a defined glove area (cm^2) in a set time (min). The formula for flux calculation by the equation based on AS/NZS standard 2161.10.3 (2005) is as follows:-

$$P_i = \frac{(C_i - C_{i-1}) \frac{[V_t - V_s]}{V_t} V_t}{(t_i - t_{i-1}) A}$$

in which

P = flux or permeation rate (μg/cm^2/minute)

i = an indexing number assigned to each discrete sample, starting with *i* =1 for the first sample

C*i* = the concentration of chemical in collecting medium at time T_i (μg /mL)

t_i = the time at which discrete sample *i* was removed (minutes)

V_t = total volume of the collection medium (L)

V_s = volume of discrete sample removed from the collection medium (L)

A = area of the material specimen in contact (cm^2)

In this present study, maximum fluxes were reported as an average, to demonstrate the maximal dermal, toxic or systemic effects (Magnusson et al. 2004).

For the glove performance tests, breakthrough time (BT, mins) is based on the AS/NZS 2161 standard which defines that breakthrough only occurs when the flux reaches 1 μg/cm^2/min. Cumulative permeation (mg) is the amount of OPs recovered in the receptor chamber after the test duration. Calculation of these descriptors was based upon measurement of OPs in the receptor chamber during the experimental period.

3.1.5 Quality assurance/ quality control

Prior to experiments, several checks were carried to ensure test quality. Visual inspection of each glove was performed to check for any abnormal condition resulting from manufacturing defects such as physical damage, tears and holes. Any such gloves were not used for experiments.

Appendix 3.2.1 illustrates some issues, e.g. running of coating on some of the PVC (*Excalibur*) gloves (i.e. non-uniform thickness) and tears.

One glove was also randomly selected from each pack in the batch box and was filled with tap water and squeezed tightly to observe if the water leaked through any pinholes, (Appendix 3.2.2). No pinhole leakage was observed.

In order to ensure no traces of OPs or other chemicals were present before the glove performance test started, a cell cleanliness test was conducted. This was done by assembling the ASTM permeation test cell with a piece of glove material in between (Figure 3.7) and both chambers were filled with ultrapure water. A volume of 100 μL of the receiving fluid was withdrawn for analysis with High Performance Liquid Chromatography- Ultraviolet

detector (HPLC-UV). The cell showed no evidence of OP contamination from previous experiments and the washing protocol was appropriate.

Since the same OP standard solutions were used for calibration for several weeks, stability of the OPs was tested over time. One µg/mL of the OP standard solutions were prepared and kept in tightly sealed Schott bottles, wrapped with aluminium foil and kept in the refrigerator (4°C) for weekly testing. The stability of the OPs was recorded and assessed based on the chromatograms and it was observed that the OPs were stable for over a month.

3.1.6 Analysis of OPs

All samples were analysed by High Performance Liquid Chromatography- Ultraviolet detector (HPLC-UV) with the operating conditions adapted from related studies (Cock & Ruebhart 2008; Sartorelli et al. 1998; Sigma-Aldrich GmbH 2012; te Brake et al. 2012; Wang, Xiang & Tan 2012)). Table 3.2 summarises the optimised mobile phases, flow rates, retention times and wavelength of the UV light for the OPs tested.

Table 3.2 Summary of HPLC setting for the tested OPs

	Omethoate	**Mevinphos**	**Dichlorvos**	**Diazinon**
Mobile phase	Aqueous methanol 30:70 v/v	Aqueous acetonitrile 40:60 v/v	Aqueous acetonitrile 40:60 v/v	Aqueous acetonitrile 70:30 v/v
Flowrate (mL/min)	0.5	0.8	1.4	1.0
Retention time (min)	5.4	4.2	5.1	6.2
Wavelength (nm)	220	210	220	250

For omethoate, 30% methanol was used as the mobile phase, while the other three OPs used acetonitrile in 40% (mevinphos and dichlorvos) and 70% (diazinon). Mobile phases were prepared in Schott bottles, mixed by shaking the bottle and sonicated (Unisonics Pty Ltd, Sydney, Australia) (Type FX8, Serial No. 278,) for 30 mins. Then they were connected to the system and bubbled with helium gas throughout the analysis. A GBC LC1120 HPLC Pump, Shimadzu Prominence SPD-20A UV/Vis Detector, PE Nelson 900 Series Interface, and an Alltech Alltima column (C18, 5 micron, length 150 mm, I.D 4.6 mm, Lot No. 030881) were used. A volume of 20 µL of sample was directly injected into the separation column, with a syringe filter (4mm, AF3-3107-52, Phenomenex). The software programs used for analysing the OPs were Perkin Elmer TotalChrom Navigator and ICI DP800 Chromatography DATA Station, Ver. 2.50.

3.1.7 Limits of detection/ limits of quantification of the OPs

The minimum limit of quantification of the four tested OPs was typically 0.01µg/mL for the UV detector, with the signal-to-noise ratio of 5:1. Data were calculated using peak area and compared with standards of known concentrations. In cases where high concentrations of OPs were expected, dilution was made prior to analysis.

3.1.8 Calibration graphs

Calibration graphs were prepared for determination of OPs on a daily basis. Analytical grade compounds (Fluka-36181 for omethoate, Fluka-45428 for diazinon, Fluka-45441 for dichlorvos from Sigma-Aldrich and N13037 for mevinphos from Supelco) were used to identify the retention time of the compound and create a standard line of known concentrations against which the commercial formulation was compared.

Stock of standard solutions (2,000 µg/mL for omethoate; 250 µg/mL for mevinphos and dichlorvos) were prepared by mixing the analytical grade compounds with ultrapure water. The exception was for diazinon (stock solution 250 µg/mL), in which the analytical grade was dissolved in pure methanol to ensure complete solubilisation before being further diluted with ultrapure water to make up calibration standard solutions. Taking into consideration the linearity for the OPs, the concentrations of working standards ranged from 0.01 to 1,000 µg/mL (omethoate) or 100 µg/mL (the other three tested OPs). Standards solutions were run on the HPLC prior to analysis of the unknown samples.

To generate a calibration graph, peak areas of were plotted as a function of the concentration. The equation from the graph was used to determine the concentrations in the experimental samples. After the analysis, the results were extrapolated to the standard curve of known OPs concentrations. Where samples were diluted to fit into the calibration graph range, the results were multiplied with the dilution factors to get the total concentration present in the whole sample.

3.2 GLOVE PERFORMANCE STUDIES FOR CASE STUDY 2 (DISPOSABLE GLOVES USED BY AMBULANCE WORKERS)

In Case Study 2, performance of two types of disposable gloves used by South Australia Ambulance Service (SAAS) workers was tested individually and in combination against the four selected OPs, to address Research Question 4,5 and 6, as listed at the beginning of Chapter 5.

3.2.1 Types of disposable gloves tested for performance against OP permeation

3.2.1.1 Disposable nitrile gloves

The first type of disposable gloves was Sterling® Nitrile which were powder-free exam gloves (KC300, Ref 13941, Lot SM204230CLXX, grey in colour) produced by Kimberly-Clark. Thickness of the nitrile gloves was consistently 0.07 mm at the palm section (Figure 3.8).

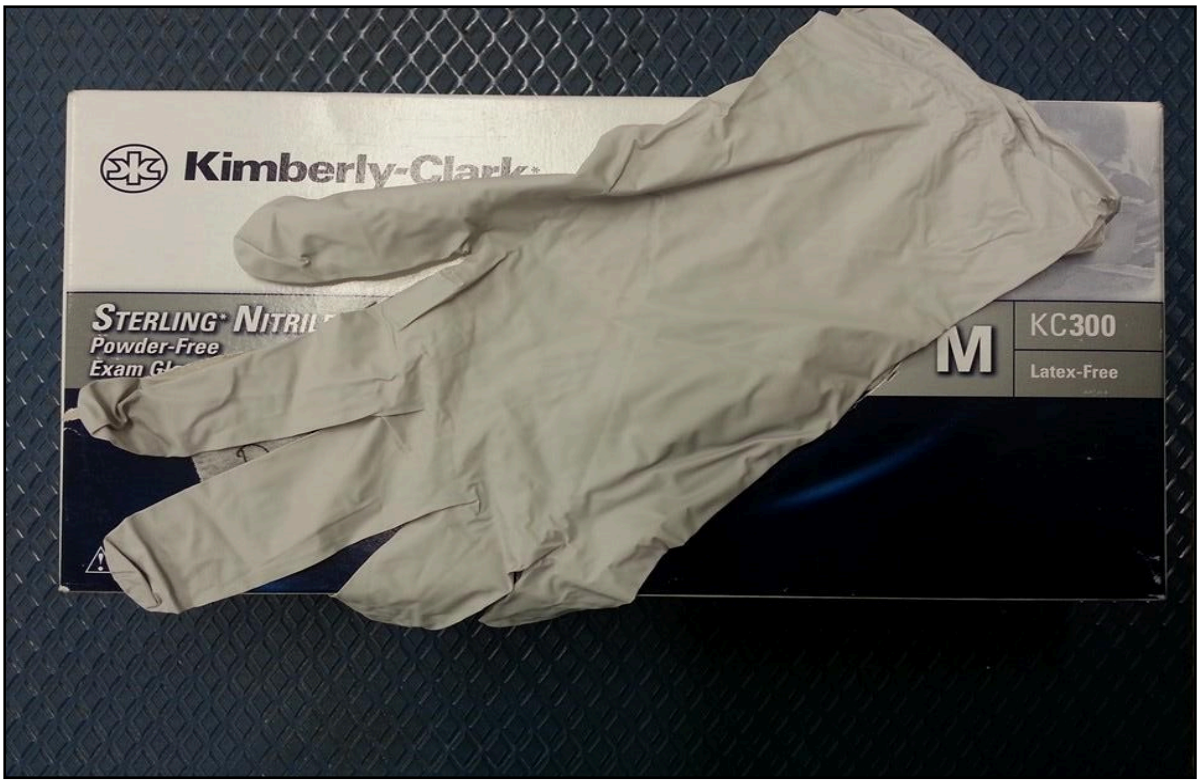


Figure 3.8 Disposable nitrile gloves (Sterling® Nitrile) used by the SAAS ambulance workers for attending chemical-related incidents.

3.2.1.2 Disposable neoprene gloves

The second type of disposable gloves was Micro-touch® Affinity® Neoprene (C/No 0362, Ref 3772, Lot 12082134EQ) manufactured by Ansell. The gloves were green in colour and labelled as non-sterile examination gloves. Thickness of the neoprene gloves was consistently 0.11 mm at the palm section (Figure 3.9).

Figure 3.9 Disposable neoprene gloves (Micro-touch® Affinity® Neoprene) used by the SAAS ambulance workers for attending chemical-related incidents.

3.2.1.3 Combination of disposable gloves (nitrile on neoprene)

As both nitrile and neoprene gloves (described in Sections 3.2.1.1 and 3.2.1.2) are used in combination for double gloving method by SAAS ambulance workers, tests on these disposable gloves were not only performed on individual gloves, but also in combination (nitrile on neoprene gloves). All gloves tested were cut from the palm section i.e. 4.5 cm in diameter (9.62 cm^2 surface area) for the 1'' ASTM test cell.

3.2.2 Test compounds (organophosphorus pesticides) used in the study

The test compounds for disposable gloves are the same as for Case Study 1. See Section 3.1.2.

3.2.3 Glove performance tests using ASTM cells

The glove performance test for the disposable gloves in Case Study 2 is similar to the test conducted for in Case Study 1 (See Section 3.1.3). The difference in the assembly was the glove swatches for the combination of gloves as described in Section 3.2.1.3 were sandwiched together, with the nitrile glove facing the test chemical in the challenge chamber and the neoprene glove facing the receptor fluid in the sampling chamber, as shown in Figure 3.10. This is to simulate the exposure in real life, in which SAAS workers wear nitrile gloves on top of neoprene gloves in the double gloving method (Section 5.11 and Figure 5.2).

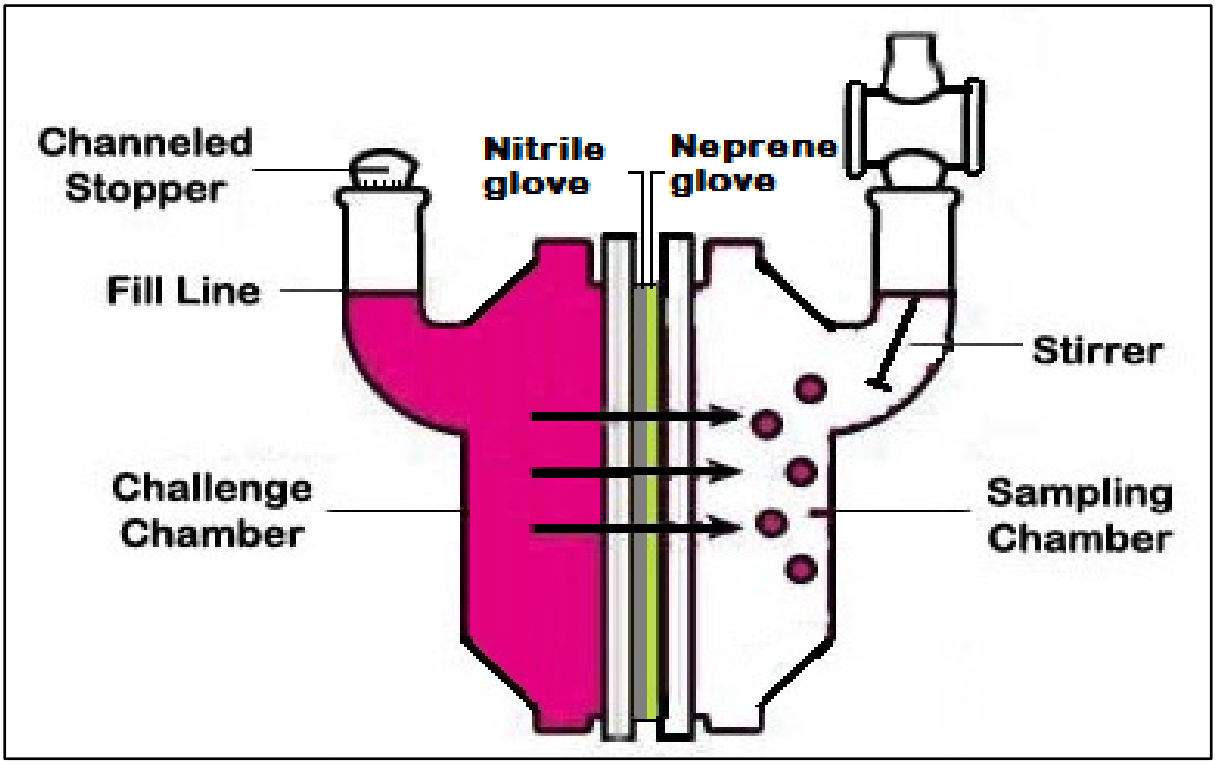


Figure 3.10 Cross section of the assembly of ASTM permeation test cells for testing the performance of combination of disposable gloves used by ambulance workers

3.2.3.1 Temperature setting and duration for glove tests

The disposable gloves were tested under two plausible temperature conditions as described in Section 3.1.3.1. However, the maximum duration for the tests on disposable ambulance gloves was 4 hours to represent the maximum duration of gloves worn when attending to emergency cases (David Casey, Rescue Paramedic, Hazmat Operations, SAAS 2014, personal communication).

3.2.3.2 Receptor fluids for glove performance tests

Receptor fluids for the glove performance tests on disposable gloves were the same as those for the agricultural PVC gloves. See Section 3.1.3.2.

3.2.4 Descriptors of permeation

Permeation of the test compounds through the disposable gloves were described as flux ($\mu g/cm^2/min$), breakthrough time (mins) and cumulative permeation (mg). See Section 3.1.4.

3.2.5 Quality assurance/ quality control

Several steps were performed for quality assurance/ quality control prior to glove permeation tests; including visual inspection and pinhole test on the disposable gloves. Cell cleanliness test and stability test of the standard solutions were also conducted. See Section 3.1.5.

3.2.6 Analysis of OPs

Testcompounds were analysed by High Performance Liquid Chromatography- Ultraviolet detector (HPLC-UV).See Section 3.1.6.

3.2.7 Limits of detection/ limits of quantification of the OPs

Similar to Case Study 1, minimum limit of quantification of the four tested OPs was 0.01µg/mL for the UV detector. See Section 3.1.7.

3.2.8 Calibration graph

Determination of OPs was made based on calibration graphs of peak areas plotted against the concentrations of analytical grade compounds. See Section 3.1.8.

3.3 SKIN TESTING OF OMETHOATE, MEVINPHOS, DICHLORVOS AND DIAZINON

This involved an *in vitro* system, with heat-separated human epidermis sandwiched in a static Franz cell. Procedures were in accordance with OECD protocols (see later).

In vitro skin testing with human skin was chosen as the approach for dermal exposure studies because it can simulate ‘real life’ exposure scenarios (Moore 2010). This method also allows for dermal absorption data relevant to human exposure (Bronaugh 2004), without issues of administering highly toxic chemicals to human volunteers *in vivo*. Data from the human *in*

vitro studies can be compared and aligned with animal *in vitro* studies, as well as *in vivo* studies for human and animals. For prediction and extrapolation of *in vivo* exposure scenarios, OECD test guidelines suggested that doses used *in vitro* should match '*in vivo*-relevant' exposure as closely as possible (OECD 2004a, 2004b). Nevertheless, absorption of some chemicals may not be accurately predicted due to lack of blood flow and/or inflammatory response systems that might affect penetration through the skin in *in vitro* studies (OECD 2004a; Williams 2006).

In order to address Research Question 7, 8 and 9 (Chapter 6) for better understanding of potential risks of skin absorption, the initial dermal exposure studies through human skin were conducted on a range of OPs with different physicochemical properties in different variable conditions (concentration, temperature) to investigate OP penetration.

3.3.1 Ethics approval for the use of human skin samples

Full thickness abdominal skin was obtained (with donor consent) from the Flinders Medical Centre immediately following reductive abdominal surgery. Approval for the use of human skin was gained from the Southern Adelaide Clinical Human Research Ethics Committee, Flinders Medical Centre and Repatriation Hospital (Ethics approval number 273/10, dated 2ndJuly 2010, Appendix 3.1).

3.3.2 Test compounds (organophosphorus pesticides) used in the study

Four test compounds were selected for this study, namely omethoate, mevinphos, dichlorvos and diazinon. See Section 3.1.2.

3.3.3 Acquisition of skin samples, harvesting and storage

Human skin is seen as the 'gold standard', as it provides the best results for comparison with human *in vivo* data (Howes et al. 1996). The use of human skin obtained from abdominoplasty or mammoplasty surgery has been practised in numerous *in vitro* studies (Bronaugh & Franz 1986; Harrison, Barry & Dugard 1984; Howes et al. 1996; Miller & Kasting 2010; Schreiber et al. 2005; Wester et al. 2000; Wilkinson & Williams 2002) for having reduced variability in penetration (Southwell, Barry & Woodford 1984).

Nonetheless, as it is almost impossible to obtain fresh human skin on daily basis, frozen human epidermal skin was used throughout this study. Frozen skin has been previously used in several studies, with no observable impacts of freezing on the barrier functions (Brain, Walters & Watkinson 1998; Dennerlein et al. 2013; Harrison, Barry & Dugard 1984; te Brake et al. 2012; van de Sandt et al. 2004)

Full thickness abdominal skin was obtained immediately following reductive abdominal surgery at Flinders Medical Centre. Human skin donors were three females, Caucasian, and aged from 35 and 58 with no obvious signs of skin damage or scarring/tattooing.

For the purpose of this study, heat-separated epidermal layer was used instead of dermatomed or full thickness skin. No significant differences in dermal absorption were reported between dermatomed and full thickness skin when testing highly water soluble compounds (Dick & Scott 1992; Moser et al. 2001; Wilkinson et al. 2006). However, dermatomed skin requires specialised skills and instruments, whereas full thickness skin is subject to inter- and intra-variability from human donors and animals that may compromise the comparison of skin

absorption parameters e.g. flux or percentage of absorption (van de Sandt et al. 2004; Wilkinson et al. 2006).

Prior to preparation, the full thickness skin slab was thoroughly washed with water. Then, subcutaneous tissue and fat was removed with a sharp dissection knife without damaging the skin, leaving the full thickness skin. The epidermal layer was removed from the full thickness skin by submerging it into water at 60°C for 60 seconds (Davies, Ward & Heylings 2004; OECD 2004a). After the heat treatment, the skin was gently stretched and pinned onto a corkboard with epidermal layer uppermost. The epidermal layer that represents a protective barrier from external environment was peeled carefully from the skin layer using a spatula as shown in Figure 3.11. Warm water (60°C) was periodically added to reduce drying out throughout the process.

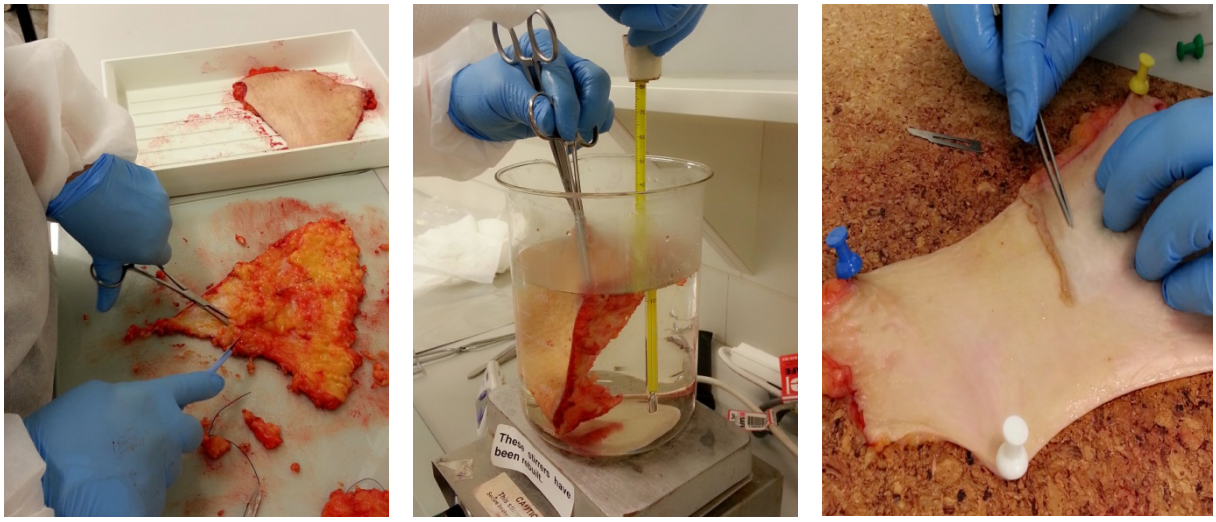


Figure 3.11 The process of harvesting the donated human skin

Recovered epidermal layers were placed into a dish containing a 0.9% physiological saline solution and left to roll out gently. Then they were laid onto an aluminium foil with stratum corneum layer uppermost, wrapped, labelled and stored in the freezer at -20°C (ECVAM

1999) for periods not exceeding four months. Harrison et al. (1984) and Bronaugh et al. (1986) found no effect on permeability of human skin stored at –20°C for a year. However, to ensure integrity of the skin, the barrier integrity test was always conducted prior to any skin tests (Figure 3.12)

3.3.4 Skin preparation and barrier integrity test

Skin samples were removed from the freezer and a sample area of approximately 2 cm^2 was cut from the epidermal sheet prior to each experiment. The skin was allowed to thaw naturally at room temperature and was hydrated with 0.9% physiological saline solution for approximately 30 mins prior to skin testing. Then, it was carefully assembled between the donor chamber and receptor chamber of the static Franz diffusion cells, with the stratum corneum side up (Refer to Section 3.3.5).

Prior to the beginning of skin study, skin barrier integrity test was conducted as specified in the OECD guidelines to ensure that the skin was still intact and not damaged (OECD 2004a). This is crucial to avoid overestimation of penetration of chemicals through the damaged skin.

In this study, barrier integrity was assessed by electrical impedance measurement of the skin because the method is quick, safer and cost effective (Davies, Ward & Heylings 2004; ECVAM 1999; Lawrence 1997). Other alternative methods are trans-epidermal water loss (TEWL) measurements (Elkeeb et al. 2010; Fluhr, Feingold & Elias 2006; Tsai et al. 2003) and penetration of tritiated water (^3H) (Heylings et al. 2001; Nangia et al. 1998; OECD 2004a).

A Tinsley LCR Databridge 6401 (Tinsley Prism Instruments) was set in modes of Resistance (R), Parallel Equivalent (PAR), and 100 Hz and measurement was done by placing an electrode into both donor and the second electrode into the receptor chambers containing 0.9% physiological saline solution, after being left to hydrate for 30 mins (Figure 3.12).

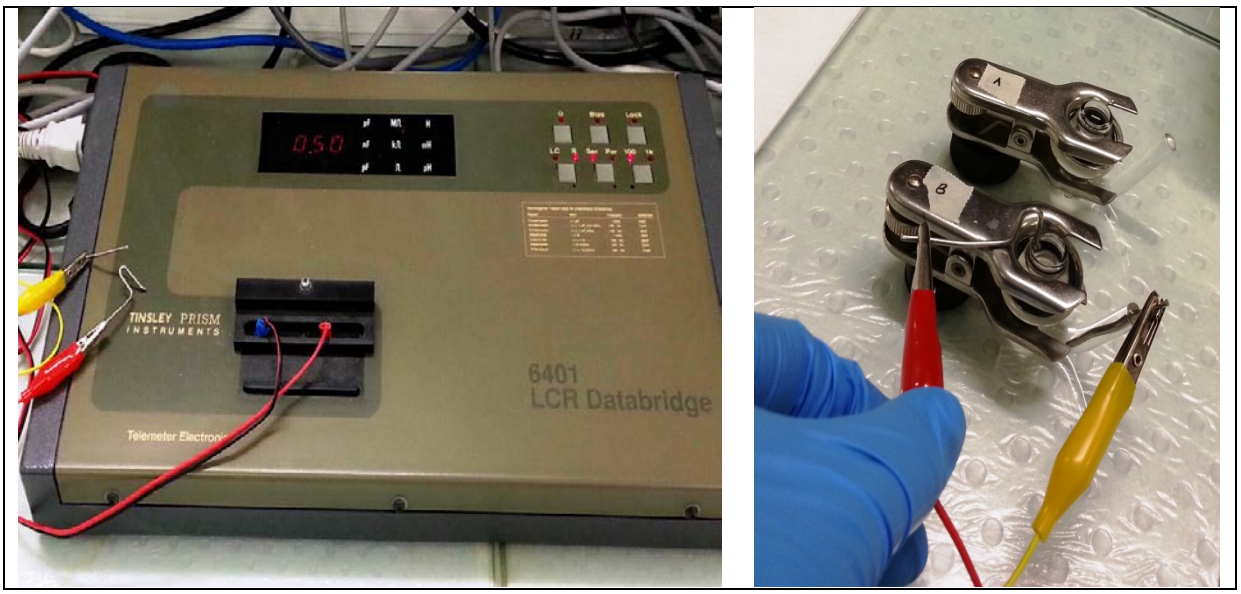


Figure 3.12 Skin barrier integrity was checked using Tinsley LCR Databridge 6401 by placing electrodes in the donor chamber and receptor chamber containing saline

Damaged skin samples and/or skin samples with an impedance lower than 10 kΩ were considered to have abnormally high permeability, thus replaced (Lawrence 1997).

3.3.5 *In vitro* skin testing using Static Franz diffusion cells

Diffusion cells mounted with skin is a common method for *in vitro* determination of skin absorption and penetration. There are two types of diffusion cells; the static diffusion cell and the flow through diffusion cell. Several studies have shown no differences in skin

permeability using static and flow-through cells (Bronaugh & Stewart 1985; Hughes et al. 1993).

For this study, a static Franz diffusion cell comprised of the (upper) donor chamber and the (lower) receptor chamber was used in accordance with a standard OECD protocol to determine skin penetration of pesticides (Franz 1975). The chambers were made of borosilicate glass to minimize interaction with the test chemicals (OECD 2004a). The diffusion-available surface area was 0.62 cm^2 and the receptor compartment volume was 2.0 mL. Figure 3.13 shows the assembly diagram of a static Franz diffusion cell used in the *in vitro* skin testing.

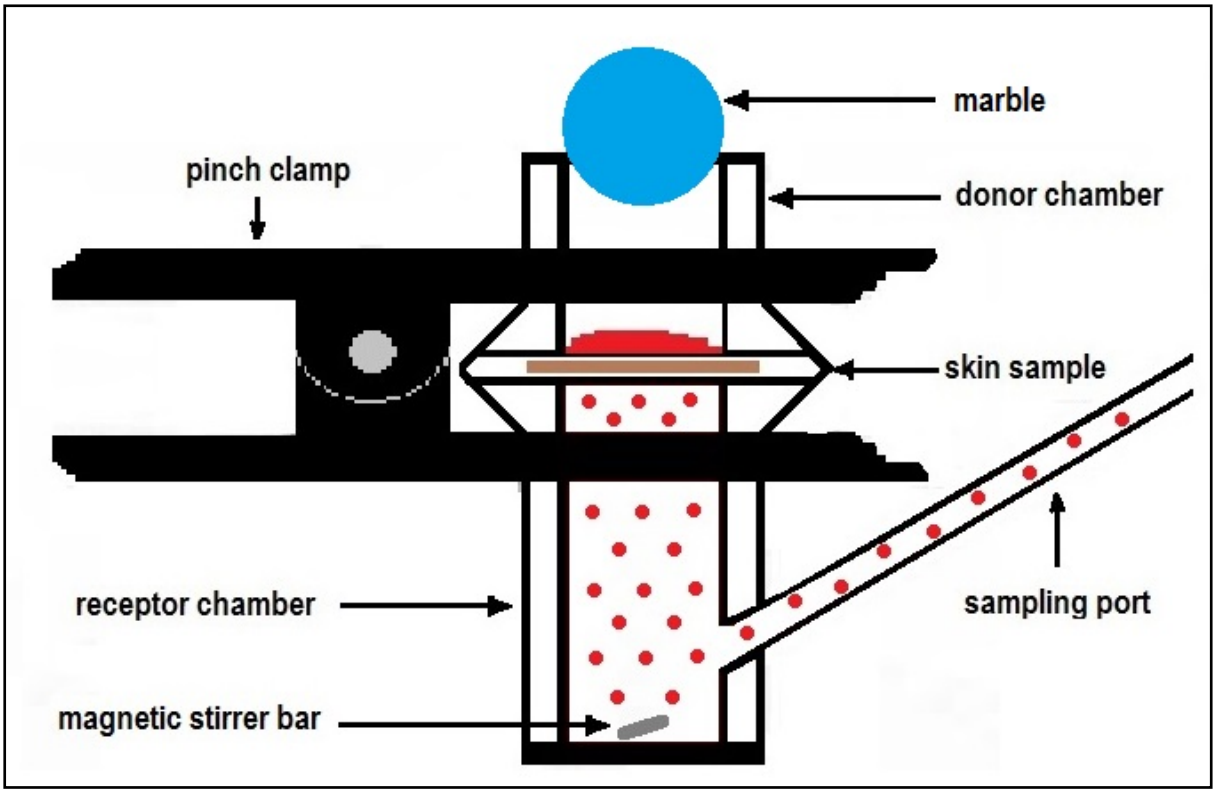


Figure 3.13 The static Franz diffusion cell was covered with a rough marble to avoid evaporation loss, without creating pressure differentials

The prepared epidermal sample (Section 3.1.9.1) was carefully mounted (with stratum corneum side up) between the donor chamber and the receptor chamber of the static Franz diffusion cells. A rubber ring was placed on top of the skin sample and the chambers were clamped together to ensure proper seal of the skin.

Two dosing regimens can be implemented for *in vitro* dermal diffusion studies; infinite dose or finite dose. In infinite dose, a large volume of a chemical at a high concentration is applied so that the dose concentration on the skin surface does not deplete significantly over time, whereas finite dose only involves application of a small volume of chemical to the skin surface. Infinite dose testing simulates the worst exposure scenarios based on maximum penetration rates, which can be applied in risk assessment of exposure and useful for modelling purposes (Howes et al. 1996; Moore 2010; OECD 2004a).

For the purpose of this initial study, sufficient test chemical (at least 100 µL) was put into the donor chamber to simulate infinite dose conditions.

During this study, the donor chamber was covered with a rough marble to minimise evaporation loss (Figure 3.13).

Receptor fluid was kept in contact with the skin under surface and continuously stirred with a Teflon-coated magnetic stirring bar at 350 rpm on a Variomag Multipoint Electronic Mat (Quantum Scientific). An amount of 200 µL of receptor fluid was withdrawn out through the side-arm (sampling port) using a syringe at desired time intervals to analyse if there was any penetration of OPs to the recipient chamber, and replaced with same amount of fresh receptor fluid throughout the experimental period.

A minimum of four replicates were conducted for each experiment to estimate the imprecision or random error of the analytical method. The data sets for each variable condition were used to detect smaller effects and increase the precision of the prediction model to be developed.

Positive controls of the experiments were also prepared concurrently with the ongoing experiments for validating the experimental procedure. For the *in vitro* skin testing, positive controls were conducted by piercingthe surface of the assembled skin to create a small pinhole, in order to produce the expected effects (penetration of test chemicals).

3.3.6 Temperature setting and duration for skin testing

In vitro skin testing was performed at two different temperatures of possible exposure conditions. Experiments were either set-up in the laboratory at room temperature conditions (23 ±2 °C) or in a heated incubator (Clayson, New Zealand) set at 37°C to represent exposure to an elevated temperature. Experiments were conducted for 8 hours to mimic exposure for a typical working day.

3.3.7 Termination of skin testing

On termination of each skin testing after the specified period, the static Franz diffusion cells were dismantled. The skin samples were visually examined under a microscope (Nikon Model C-LEDS (Japan)), for possible physical damage due to exposure to test chemicals. Post-exposure impedancewas also measured as described in Section 3.3.4.

3.3.8 Receptor fluids for the skin testing

Refer to Section 3.1.3.2. i.e. water was used as receptor fluid for omethoate, dichlorvos and mevinphos. For diazinon, it was 50% ethanol (v/v).

3.3.9 Descriptors of penetration

In skin studies, the term 'penetration' was used instead of permeation. Flux and cumulative penetration in the skin studies were described in a similar manner to the gloves as described in Section 3.1.4, but breakthrough was considered as soon as the OP chemicals were detected in the receptor fluid, without the flux reaching 1 μg/cm^2/min as in glove studies.

Calculation for extrapolation of penetration based on Acceptable Daily Intake (ADI) was done using the following formula:-

Exposure to hands only (surface area 800 cm^2)	$\frac{800\ cm^2}{0.62\ cm^2}$ x cumulative penetration (mg) of OP at *x* time
Exposure to hands and forearms (surface area 1,200 cm^2)	$\frac{1{,}200\ cm^2}{0.62\ cm^2}$ x cumulative penetration (mg) of OP at *x* time

3.3.10 Analysis of OPs

Analysis of samples was by High Performance Liquid Chromatography- Ultraviolet detector (HPLC-UV), as previously described inSection 3.1.6.

3.3.11 Limits of detection/ limits of quantification of the OPs

The limit of quantification was 0.01µg/mL for the four OPs, taking into account the signal-to-noise ratio of 5:1. See Section 3.1.7.

3.3.12 Calibration graph

Calibration graphs created from plots of peak areas against concentrations were used to determine the OPs. See Section 3.1.8.

3.4 DATA PROCESSING AND STATISTICS

Data obtained in this research were expressed as mean ± standard deviations. As a dilution factor is introduced every time 200 µL sample is removed from the receptor chamber and replaced by 200 µL fresh receptor fluid, all data on total permeation and penetration were corrected for these dilutions to avoid underestimating total permeation and penetration.

Calculation of breakthrough time, permeation rate, and cumulative permeation/penetration during the experimental period was based upon measurement of OPs in the receptor chamber.

Skin penetration outcomes were tested for normality using the Kolmogorov-Smirnov test with Dallal-Wilkinson-Liliefor corrected p values. In order to compare the sets of cumulative permeation/ penetration outcomes between OPs for data which are normally distributed, one-way ANOVA with Tukey's Multi Comparisons tests were used. However, where distribution of data is not normal, Kruskal-Wallis tests with Dunn's Multiple Comparisons tests were conducted for comparing cumulative permeation/penetration outcomes. For comparison of skin penetration outcomes within each concentration and temperature, two-way ANOVA with Bonferroni Multi Comparison tests were conducted.

CHAPTER 4

CASE STUDY 1

PROTECTIVE PERFORMANCE OF POLYVINYL CHLORIDE (PVC) GLOVES USED BY AGRICULTURAL WORKERS AGAINST ORGANOPHOSPHORUS PESTICIDES

This case study explores the protective performance of two types of elbow-length PVC gloves of different brands used by agricultural workers against four commercial formulated OPs of different physicochemical properties under two exposure conditions. This study aims to address the specific research questions listed below:

RQ1 Are the recommended PVC gloves suitable for protection against formulated OPs?

RQ2 What are the effects of UV radiation on gloves with respect to formulated OP permeation?

RQ3 How does abrasion of the PVC glove materials affect permeation of formulated OPs?

In this chapter, it will be revealed that the recommended PVC gloves are generally suitable for protection against formulated OP products, especially at application strength. However, there is a measurable difference between the brands and there is reduced protection at elevated temperature (45°C). It will also be shown that although exposure to UV radiation and abrasion of the glove materials affect the permeation of formulated OPs through both brands of PVC gloves, the difference shown in the cumulative permeation is not uniformly significant, compared to unexposed PVC gloves.

4.1. AGRICULTURAL WORKERS AS A STUDY POPULATION

OP exposures in agriculture

OPs are widely used throughout the world, including Australia, on a large variety of crops to control pests, notably insects. Indeed, agricultural workers are the biggest identifiable occupational group at risk (Davies 1990; UNEP 1986).These groups of workers have been an interesting study population in Europe, Canada, United States where exposure databases have been developed, and comprehensive reviews published (Curry & Ivengar 1995; van Hemmen 1992; Weichenthal, Moase & Chan 2010; Weichenthal, Moase & Chan 2012).

According to Fenske & Day Jr. (2005), agricultural workers who mix, load and spray formulated pesticides are the group at the highest risk for acute intoxications due to the nature of their work. The pesticides are usually dispersed as an aerosol of the active ingredient(s) dissolved in hydrocarbon solvents (Fragar, Sankaran & Thomas 2005). Pesticide sprayers, as well as those involved in mixing and loading of pesticides and those undertaking re-entry works may have significant exposures depending on the task, chemical properties and environmental conditions (Zandstra 1987; Hines et al. 2011). In small farms, some workers may undertake all tasks.

Thus, there is a range of exposure profiles, with potentially complex exposure pathways. A detailed understanding of exposure is essential for primary prevention, and attempts have been made to simplify these issues using the concept of similar exposure groups (SEGs) based on self-reports or field measurements/observations. Exposure data may be compiled to yield task exposure matrices, crop exposure matrices or other groupings. However, the seasonal nature of the use of OPs and the potential usage on animals as well as crops has

complicated epidemiological studies, especially those requiring retrospective exposure assessment (Blair et al. 1993; Brouwer et al. 2014). Further development of exposure assessment methods in agriculture is required(Blair et al. 2009).

Hand protection used by agricultural workers

Thick PVC gloves are generally used for handling OPs as they are relatively inexpensive and can be used for a wide range of chemicals such as acids, bases, oils, fats, peroxides, and amines (Ansell 2014; Showa Best Gloves 2015). However, no gloves are suitable for all chemicals and it has not been feasible to mathematically model the performance for various product formulation containing solvents (Coletta et al. 1978; Nelson et al. 1981; Samsone & Tewari 1978; Schwope et al. 1983).

It appears from the literature review that there is very limited glove permeation data available for formulated OPs, especially on permeation of concentrated pesticide formulations containing active ingredients and carrier solvents (Ehntholt et al. 1990). While tests with low concentration OPs are relevant for OP sprayers, glove permeation data for high concentration (full strength) OPs are also necessary for the workers involved in mixing and loading of OPs for splash or spillage incidents.

4.1.1 Opportunities for exposure from preliminary field observation on work practices and behaviours

Preliminary observations at four farms (greenhouses) in Virginia, South Australia were undertaken, and were used to check on local current work practices and behaviours, prior to the laboratory-based research. These visits were not meant to be representative of all farms in South Australia.

The general nature and type of information collected in the preliminary field observations are given in Appendix 4. Figure 4.1 illustrates opportunities for exposure during mixing and spraying.

Figure 4.1 Exposure to OPs may occur during loading, mixing (left) and spraying (right)

It was observed that all tasks (mixing, loading and application of pesticides) were performed by the same person, thereby warranting glove permeation studies at application and full strengths.

In the preliminary field observations, it was also evident that a variety of gloves were used, some of which were not of the correct types (glove materials) or length, according to the SDSs. It was also noted that the same gloves were used for handling concentrated pesticides and diluted pesticides. Some of the farmers did not wear gloves at all when handling pesticides.

Re-use of gloves was common with evidence of sunlight exposure and abrasion.

Agricultural tasks are often conducted in hot conditions with variable humidity. In South Australia, the maximum temperature might rise to 45°C in summer. These environmental conditions may have a profound effect on chemical volatility, perspiration rate, permeation rate, as well as the use of PPE (Franklin & Worgan 2005). However, published breakthrough times for glove materials are likely to be underestimated, because factors such as increased temperature and flexing are not included in the experimental measurements (HSE 2001; Perkins & Rainey 1997; Rawson et al. 2005), emphasising the rationale of testing performance of gloves at an elevated temperature.

Dermal exposures occur primarily due to skin contact with pesticides during mixing, loading and spraying (Blanco-Muñoz & Lacasaña 2011; Fenske & Day Jr. 2005), touching sprayed surfaces (Iwata et al. 1977; Krieger, Driver & Ross 2006; Strong et al. 2008) as well as re-entry of sprayed fields at limited intervals (Stewart et al. 2001; Strong et al. 2008). However,

worker's behaviours and use of PPE may also influence exposure to the workers to various extents (Ohayo-Mitoko et al. 1999). While none of the farmers in the preliminary field observation rubbed their eyes, scratched exposed skin or smoked cigarettes while handling the pesticides, transfer of contamination to the skin was observed upon skin contact with the steering of the tractor, hose rollers and harvesting vehicle and with bare hands (Figure 4.2 and Appendix 4.2.1). The majority of the farmers also practised incorrect techniques of glove removal, suggesting possible secondary contamination.

Figure 4.2 The hose roller and vehicle used for crop harvesting are potentially contaminated with pesticides from deposition and transfer from contaminated surface

Duration and frequency of task are also modifying factors that determine the level of exposure (Fenske & Day Jr. 2005). In the preliminary field observation, the farmers conducted pesticide-related tasks for 2 to 4 hours; however, it may be extended to 8 hours in a day. While some pesticides may be applied every week in a season, and some only needs once-a-year application, exposure and risk assessment should also consider the amount of pesticides handled, especially in mixing/loading tasks (Fenske & Day Jr. 2005).

According to the body map used in the preliminary field observation (Appendix 4.2.2), hands, sleeves of clothing e.g. waterproof overall, raincoats and long sleeved shirts worn by the farmers as the outer layer were common spots for pesticide contamination. This is similar to previous studies which found contamination of pesticides on hands, shoulders, chest, forearms and forehead (Fenske & Day Jr. 2005; Jurewicz et al. 2009). Although spraying was done by moving backwards at the farms, exposure to pesticides is possible because plants in greenhouses are usually in close rows and they can grow high, reaching all levels of the worker's body (Jurewicz et al. 2009).

4.1.2 Rationale and aims of study

Rationale

Chemical protective gloves sold to users should undergo chemical permeation testing, with challenges by numerous chemicals. Commonly, permeation test data and compatibility charts are published, and computer software created by glove manufacturers, as a guide to assist in selecting the appropriate type of gloves (Forsberg & Lawrence 1999; Forsberg & Mansdorf 2007; Goydan et al. 1988; Schwope et al. 1987). Nevertheless, permeation testing has usually been limited to tests performed at room temperature, whereas real world potential exposure

scenarios may involve variable temperature, glove damage from abrasion and/or UV exposure, flexing and poor maintenance. Besides the ambient temperature, transfer of heat from the body may also raise the temperature, and enhance permeation of OPs through gloves and subsequently the skin (Evans, McAlinden & Griffin 2001).

Experiments that address these issues are scarce, and more tests under real world conditions are needed to assist in understanding their effects on permeation (Bromwich 2005; Evans, McAlinden & Griffin 2001; Perkins & You 1992). The USEPA has affirmed that 'testing must subject the chemical protective clothing to the expected conditions of exposure' (EPA 2008). This is because solubility and diffusion coefficients of compounds through polymeric films vary non-linearly with temperature (Evans, McAlinden & Griffin 2001; Vahdat & Bush 1993).

Aims

This study aims to elucidate the protective performance of PVC gloves (unused, exposed to UV and abrasion) commonly used in agricultural farms against four OPs with different physicochemical properties in various exposure conditions.

Specific research questions have been given earlier and relate to OP permeation under conditions of variable concentration, temperature, abrasion and UV exposure. Four OP formulations and two brands of PVC gloves are explored in a multifactorial design.

For this research, two types of elbow length PVC gloves (*Excalibur* and *ProChoice*gloves) recommended for handling OPs (Section 3.1.1) were tested at full strength and at application strength. This is to mimic the exposure to agricultural workers when mixing and loading from

the containers into mixing drums, as well as to represent the exposure during spraying activities and re-entry (Section 3.1.2). Performance of the PVC gloves was tested against four formulated OPs having different physiochemical properties, as described in Section 3.1.2.

4.2 WORST CASE APPROACH

In the real world, not only new gloves are worn, but the use of gloves with potential degraded performance e.g. exposed to UV radiation or abrasion, is also being practised. Thus, in this study, gloves were tested out-of-box (unused), as well as after being exposed to UV light (equivalent to approximately seven days of exposure to midday sun radiation conditions) and abrasion (equivalent to 10% PVC top layer reduction).

The gloves were tested for up to 8 hrs to illustrate chronic splash exposure (infinite dose) for a full 8-hour working shift, assuming the same gloves are worn throughout the exposure duration. Besides the normal room temperature, the gloves were tested at an elevated temperature (45°C), the plausible condition for working outdoors on a hot sunny day (Section 3.1.3).

4.3 RESULTS

Results of the effects of concentration (full strength and application strength OPs) and exposure temperatures (room temperature; 23(±2)°C and 45°C) on the permeation of OPs through two types of PVC gloves under variable conditions are presented in Sections 4.3.1 to 4.3.2 respectively. Subsequently, outcomes of the effects of UV exposure and abrasion on

OP permeation through the PVC gloves are compared in Section 4.3.3 to 4.3.4. Statistical analysis outcomes of the variables are presented in Section 4.3.5.

4.3.1 OP permeation through unused (out of the box) PVC gloves

The data are initially presented according to glove brand.

4.3.1.1 *Excalibur* gloves

Table 4.1 summarises cumulative permeation outcomes of OPs at application strength and full strength through unused *Excalibur* glove types over the 8-hour test duration, under both temperature conditions. Breakthrough times are also presented.

Figures 4.3 and 4.4 complement the permeation data presented in Table 4.1

Table 4.1 Average 8-hour cumulative permeation (mg) of OPs, and breakthrough times (with asterisk) through unused *Excalibur* gloves at room temperature and 45°C

Exposure temperature	**Concentration of OPs**	**Average cumulative permeation (mg)**			
		Omethoate	Mevinphos	Dichlorvos	Diazinon
Room temperature (23±2°C)	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	8.0 (±1.8) *BT 180 mins	Not achieved	Not achieved	Not achieved
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	19.4 (±5.2) *BT 180 mins	4.5 (±0.2) *BT 300 mins	174 (±9) *BT 180 mins	Not achieved
45°C	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	15.1 (±0.9) *BT 180 mins	Not tested	12.3 (±0.4) *BT 180 mins	Not achieved
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	75.2 (±7.0) *BT 60 mins	Not tested	653 (±48) *BT 60 mins	54.6 (±4.0) *BT 120 mins

Notes:
Figures in brackets are standard deviations, replicates n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 8-hour test period
'Not tested' denotes test was not performed for the variable condition due to supply limitation

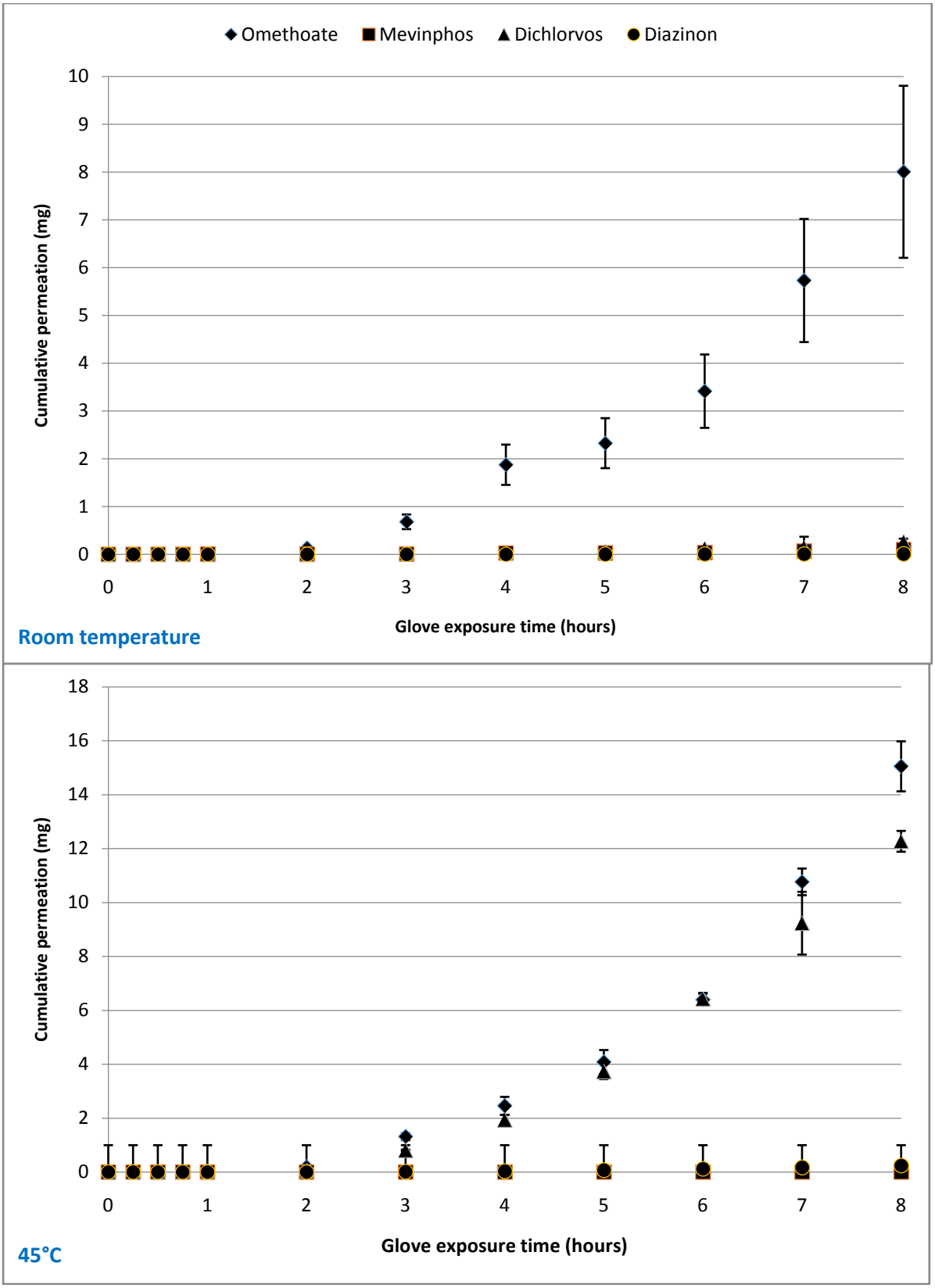


Figure 4.3 Comparison of cumulative permeation (mg) of OPs over the 8-hour test at application strength through *Excalibur* gloves at room temperature (top) and 45°C (bottom).

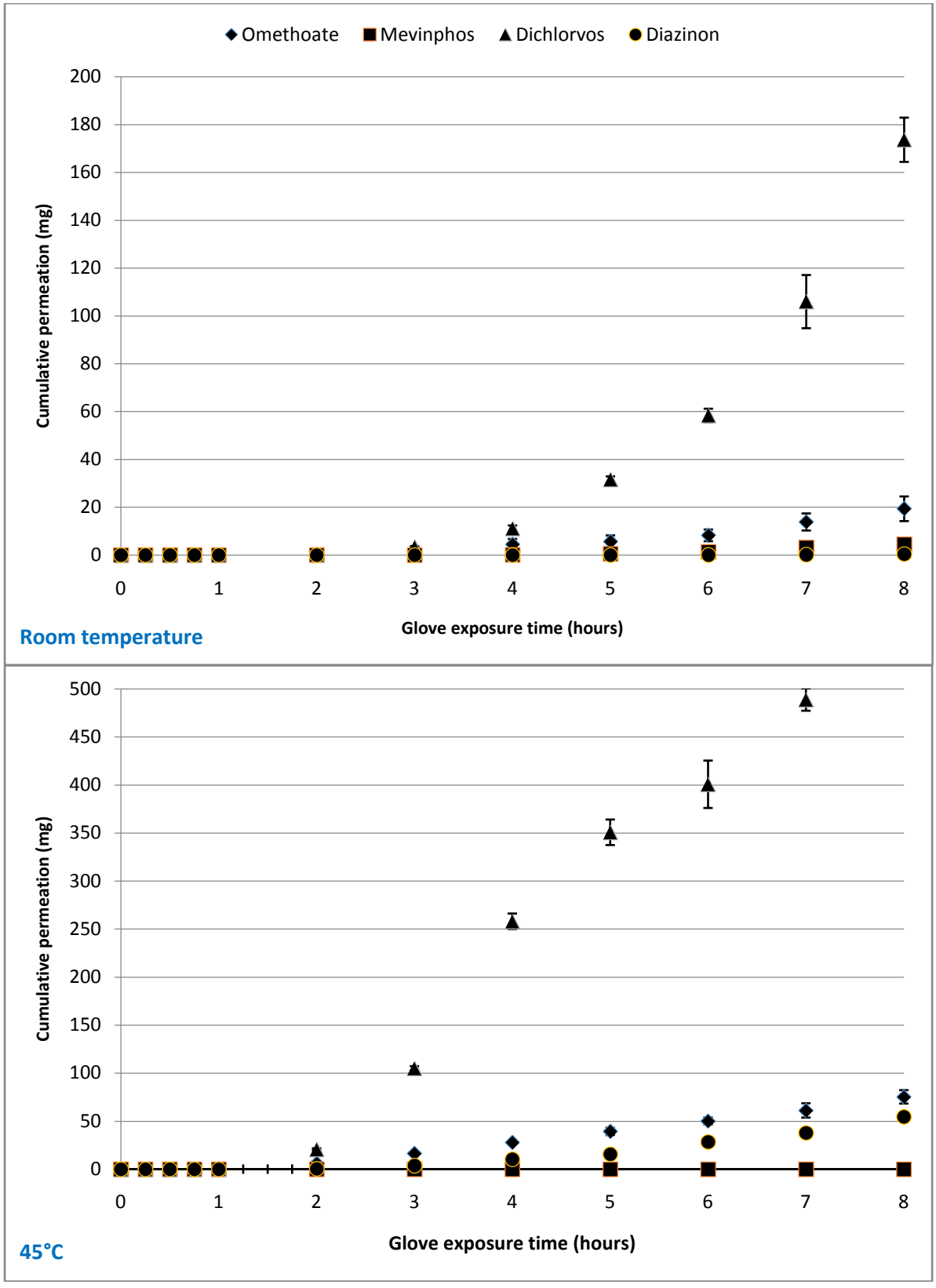


Figure 4.4 Comparison of cumulative permeation (mg) of OPs over the 8-hour test at full strength through *Excalibur* gloves at room temperature (top) and 45°C (bottom).

4.3.1.2 *ProChoice*gloves

Cumulative permeation outcomes of OPs at application strength and full strength for *ProChoice* gloves as well as breakthrough times are presented in Table 4.2, complemented by Figures 4.5 and 4.6.

Table 4.2 Average 8-hour cumulative permeation (mg) of OPs and breakthrough times (with asterisk) through unused *ProChoice* gloves at room temperature and 45°C

Exposure temperature	**Concentration of OPs**	**Average cumulative permeation (mg)**			
		Omethoate	Mevinphos	Dichlorvos	Diazinon
Room temperature (23±2°C)	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	1.4 (±0.2) *BT 420 mins	Not achieved	Not achieved	Not achieved
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	7.6 (±0.4) *BT 240 mins	Not achieved	142 (±12) *BT 180 mins	Not achieved
45°C	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	2.6 (±0.1) *BT 300 mins	Not tested	6.2 (±0.2) *BT 240 mins	Not achieved
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	35.1 (±1.4) *BT 60 mins	Not tested	555 (±3) *BT 60 mins	28.8 (±3.8) *BT 180 mins

Notes:
Figures in brackets are standard deviations, replicates n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 8-hour test period
'Not tested' denotes test was not performed for the variable condition due to supply limitation

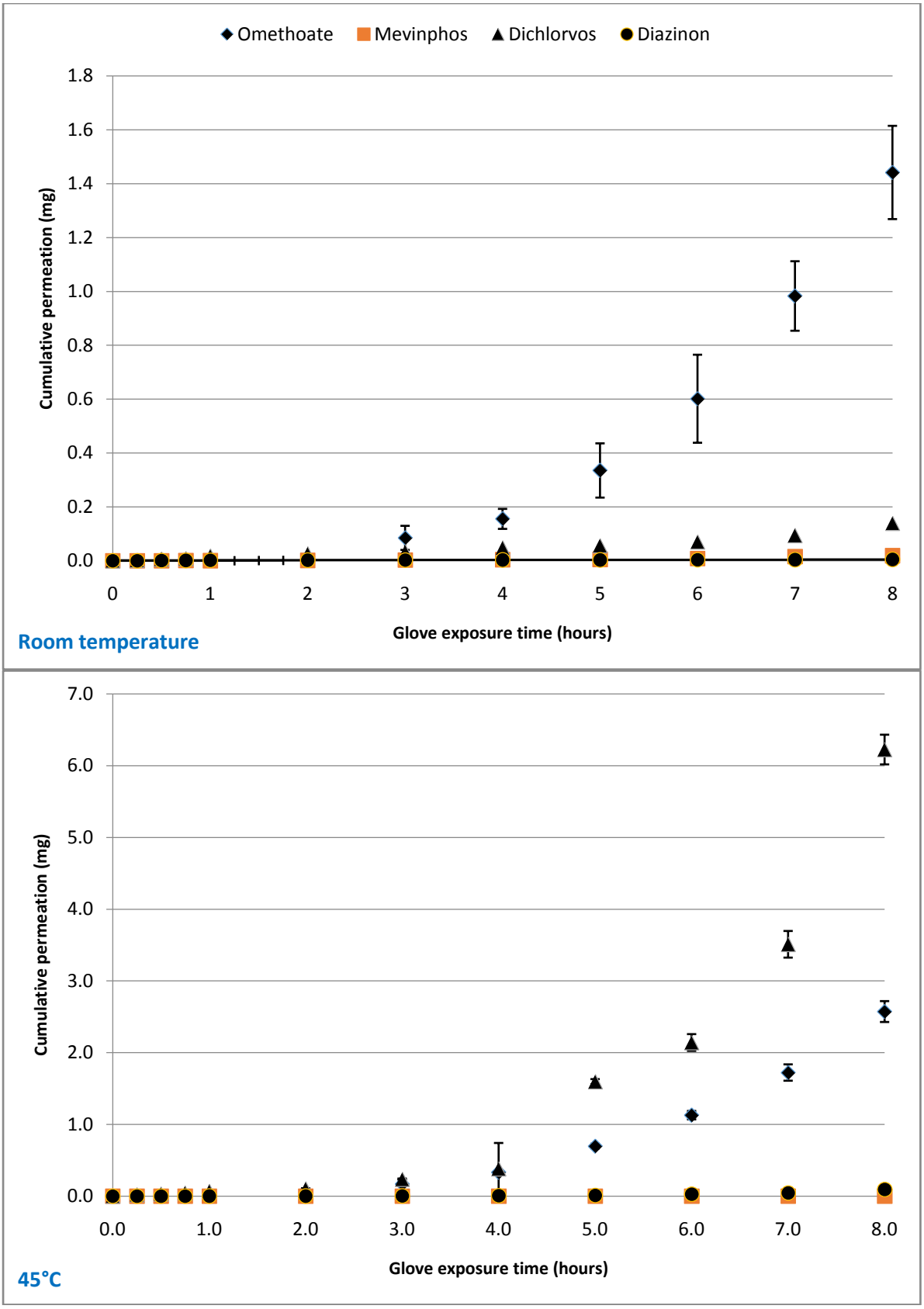


Figure 4.5 Comparison of cumulative permeation (mg) of OPs over the 8-hour test at application strength through *ProChoice* gloves at room temperature (top) and 45°C (bottom).

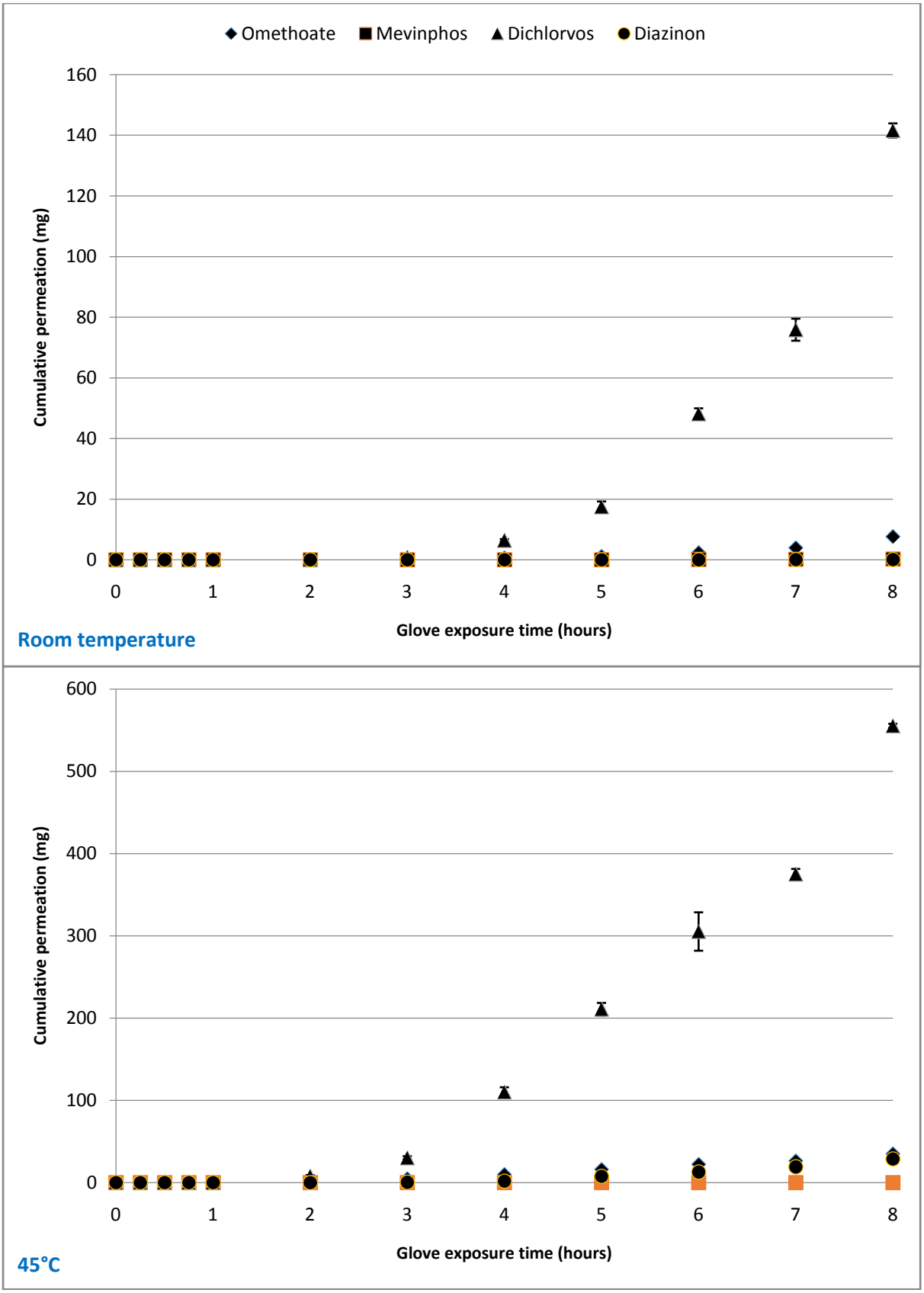


Figure 4.6 Comparison of cumulative permeation (mg) of OPs over the 8-hour test at full strength through *ProChoice* gloves at room temperature (top) and 45°C (bottom).

4.3.1.3 Comparative glove performance

Exposure under room temperature (23±2°C) condition

At application strength, breakthrough was not achieved for three out of four OPs for unused *Excalibur* gloves at room temperature over the 8-hour exposure (Table 4.1). The exception was omethoate. Similar breakthrough trend was observed for unused *ProChoice* gloves (Table 4.2).

For unused *Excalibur* gloves, breakthrough of omethoate was not shortened with the increased concentration (180 mins), although the average cumulative permeation nearly doubled. Increasing the concentration to full strength also resulted in breakthrough of mevinphos and dichlorvos (300 mins and 180 mins respectively), while breakthrough of diazinon at full strength remained unreached (Table 4.1).

As for unused *ProChoice* gloves, the average cumulative permeation of omethoate increased by 5-fold with increase in concentration (Table 4.2). Dichlorvos changed from no breakthrough over the 8-hour period, to breakthrough at 180 mins (average cumulative permeation 142 mg). Mevinphos and diazinon continued without achieving breakthrough, even after 8 hrs of exposure.

Exposure under elevated temperature (45°C) condition

Larger effects of increased concentration on breakthrough time and average cumulative permeation were observed at 45°C, compared to at room temperature. Breakthrough time of omethoate and dichlorvos were shortened to 60 mins when tested at full strength, with 5-fold and 13-fold increase in average cumulative permeation (omethoate) for *Excalibur* gloves (Table 4.1), and 53-fold and 90-fold greater cumulative permeation, and *ProChoice* gloves respectively (Table 4.2). Diazinon which did not record any breakthrough over the 8-hour exposure when at application strength, demonstrated breakthrough for full strength at 120 mins (*Excalibur* gloves) and 180 mins (*ProChoice* gloves) (Tables 4.1 and 4.2).

Exposure to application strength OPs

When temperature was elevated from room temperature to 45°C in the glove permeation tests using application strength OPs, only diazinon remained without breakthrough at the end of the 8-hour experiment on both unused *Excalibur* and *ProChoice*gloves (Tables 4.1 and 4.2).

Dichlorvos at application strength changed from no breakthrough within the test period to 12.3 mg (±0.4) (breakthrough time 180 mins) for unused *Excalibur* gloves (Table 4.1),and 6.2 mg (±0.2) (breakthrough time 240 mins) for unused *ProChoice*gloves with the increase of temperature (Table 4.2).

Approximately 2-fold increase in average cumulative permeation was observed for application strength omethoate through both unused gloves. However, breakthrough time for unused *Excalibur* gloves remained at 180 mins with the temperature increase (Table 4.1), while unused *ProChoice* gloves shortened from 420 mins to 300 mins (Table 4.2).

Exposure to full strength OPs

The effects of elevated temperature on average cumulative permeation at 8 hrs were more remarkable for full strength OPs (approximately 4-fold greater) than application strength OPs (approximately 2-fold greater). Breakthrough times were shortened to 60 mins for full strength omethoate and dichlorvos, for both unused PVC gloves (Tables 4.1 and 4.2). Diazinon indicated breakthrough at 120 mins (*Excalibur* gloves, Table 4.1) and 180 mins (*ProChoice* gloves) (Tables 4.2). Effects of elevated temperature on mevinphos are unknown because tests were only conducted at room temperature, due to limited supply.

General remarks

Section 4.3.5 (see later) showed that there were statistically significant differences in 8hr cumulative permeation between the two brands of PVC gloves.That said, the most striking cumulative permeation data relate to dichlorvos and omethoate.Dichlorvos permeation increases rapidly with increase in concentration and temperature for both gloves.

4.3.2 OP permeation through UV-exposed PVC gloves

The UV exposure conditions are given in Chapter 3 (Section 3.1.1.2).

Cumulative permeation of the OPs tested on both PVC gloves with UV exposure and the outcomes were compared with unused PVC gloves with the same variable conditions.

In these experiments only full strength pesticide was used.

Detailed outcomes are summarised in Table 4.3 (for unused *Excalibur* gloves versus UV-exposed *Excalibur* gloves) and Table 4.4 (for unused *ProChoice* gloves versus UV-exposed *ProChoice* gloves). These data are complemented by Figure 4.7.

Table 4.3 Comparison of 8-hour cumulative permeation (mg) of OPs and breakthrough times (with asterisk) through unused *Excalibur* and UV-exposed *Excalibur* gloves at room temperature and 45°C

Exposure temperature	**Average cumulative permeation (mg)**							
	Omethoate		Mevinphos		Dichlorvos		Diazinon	
	Unused *Excalibur* gloves	UV-exposed *Excalibur* gloves	Unused *Excalibur* gloves	UV-exposed *Excalibur* gloves	Unused *Excalibur* gloves	UV-exposed *Excalibur* gloves	Unused *Excalibur* gloves	UV-exposed *Excalibur* gloves
Room temperature (23±2°C)	19.4 (±5.2) *BT 180 mins	Not tested	4.5 (±0.2) *BT 300 mins	6.7 (±0.2) *BT 360 mins	174 (±9) *BT 180 mins	Not tested	Not achieved	Not tested
45°C	75.2 (±7.0) *BT 60 mins	83.9 (±9.0) *BT 60 mins	Not tested	Not tested	653 (±48) *BT 60 mins	1,046 (±36) *BT 60 mins	54.6 (±4.0) *BT 120 mins	62.2 (±4.3) *BT 120 mins

Notes:
Figures in brackets are standard deviations, replicates n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 8-hour test period
'Not tested' denotes test was not performed for the variable conditions

Table 4.4 Comparison of 8-hour cumulative permeation (mg) of OPs and breakthrough times (with asterisk) through unused *ProChoice* and UV-exposed *ProChoice* gloves at room temperature and 45°C

Exposure temperature	**Average cumulative permeation (mg)**							
	Omethoate		Mevinphos		Dichlorvos		Diazinon	
	Unused *ProChoice* gloves	UV-exposed *ProChoice* gloves	Unused *ProChoice* gloves	UV-exposed *ProChoice* gloves	Unused *ProChoice* gloves	UV-exposed *ProChoice* gloves	Unused *ProChoice* gloves	UV-exposed *ProChoice* gloves
Room temperature (23±2°C)	7.6 (±0.4) *BT 300 mins	Not tested	Not achieved	Not achieved	6.2 (±0.2) *BT 240 mins	Not tested	Not achieved	Not tested
45°C	35.1 (±1.4) *BT 60 mins	38.8 (±2.3) *BT 60 mins	Not tested	Not tested	555 (±3) *BT 60 mins	1,300 (±62) *BT 60 mins	28.8 (±3.8) *BT 180 mins	36.2 (±6.1) *BT 180 mins

Notes:
Figures in brackets are standard deviations, replicates n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 8-hour test period
'Not tested' denotes test was not performed for the variable conditions

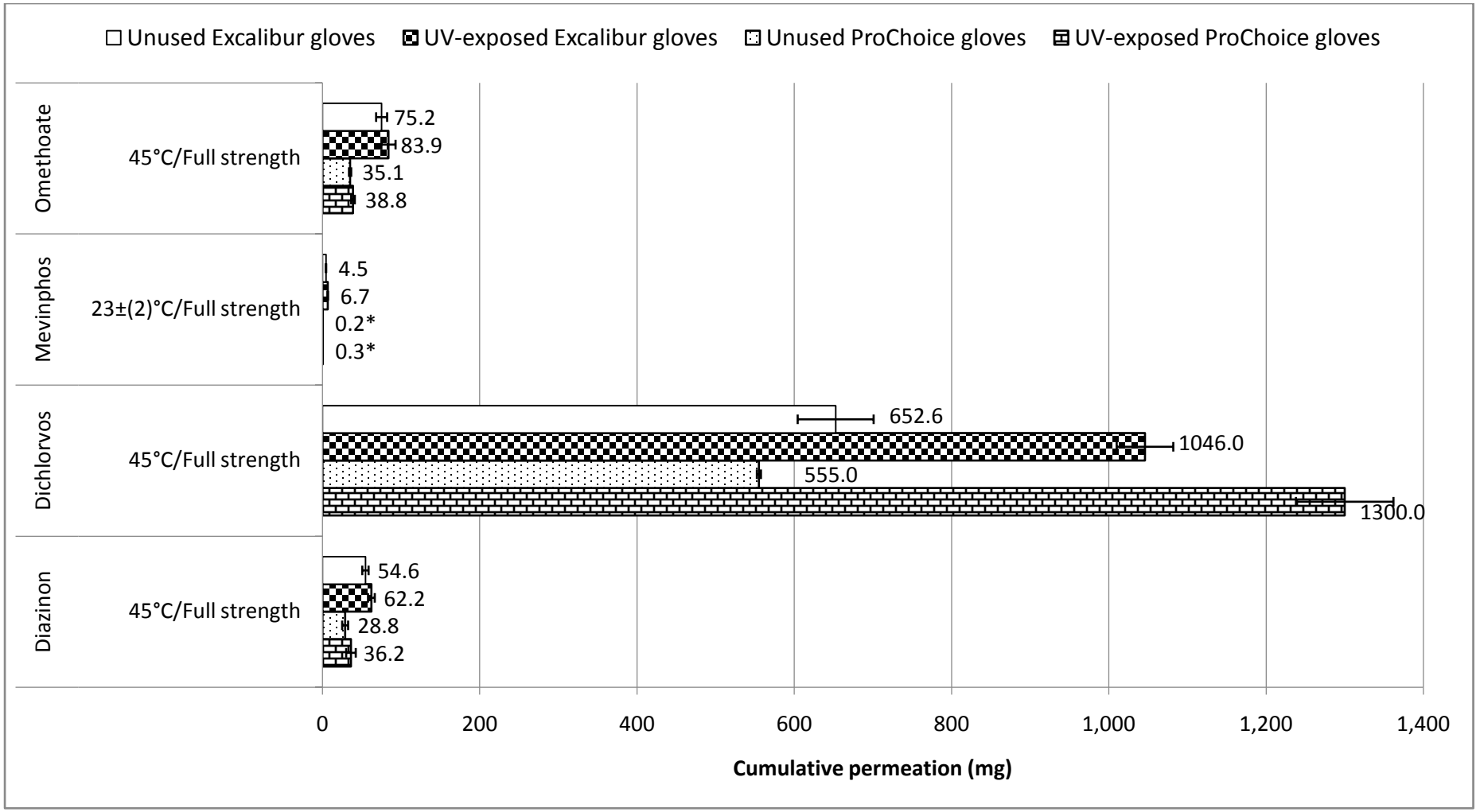


Figure 4.7 Comparison of 8-hour cumulative permeation of OPs (mg) through *Excalibur* and *ProChoice* gloves (unused gloves versus UV-exposed gloves) in various experimental conditions.

Values in asterisks denote the cumulative permeation at 8 hrs without achieving breakthrough (flux 1 µg/cm^2/min as per AS/NZS 2161 standard).

All tests on PVC gloves with UV exposure were tested with full strength OPs at 45°C to mimic the worst exposure conditions, except for mevinphos that was only tested at room temperature. Generally, cumulative permeation outcomes of the four formulated OPs through UV-exposed PVC gloves was slightly higher (less than 2-fold increase) than those tested on unused PVC gloves, except for dichlorvos.

Breakthrough times of the test OPs were neither delayed nor shortened for both glove conditions (unused and UV-exposed gloves), for both *Excalibur* (Table 4.3) and *ProChoice* gloves (Table 4.4). Although breakthrough time through UV-exposed gloves (*Excalibur* and *ProChoice*) for dichlorvos and omethoate are the same (60 mins), dichlorvos recorded the greatest cumulative permeation of all four OPs in the receptor fluid at the end of the 8-hour tests. This was noted for both *Excalibur* and *ProChoice* gloves exposed to UV; 1,046 mg (±36) and 1,300 mg (±62) respectively, which were approximately two-fold higher than the unused gloves.

Unlike dichlorvos, cumulative permeation outcomes of the other three OPs were only slightly higher than the mass permeated through the unused gloves. For omethoate, cumulative permeation outcomes at 8 hrs for the UV-exposed *Excalibur* and *ProChoice* gloves were 83.9 mg (±9.0) and 38.8 mg (±2.3) respectively. Comparatively, the mass of diazinon permeated through UV-exposed gloves at 8 hrs were 62.2 mg (±4.3) (*Excalibur* gloves, Table 4.3) and 36.2 mg (±6.1) (*ProChoice* gloves, Table 4.4).

For full strength mevinphos, which was only tested at room temperature, the 8-hr cumulative permeation for UV-exposed *Excalibur* gloves increased, but the breakthrough time was

longer (360 mins) than for the unused gloves (300 mins). Breakthrough of mevinphos was not achieved for *ProChoice* gloves.

Overall, it appears that *ProChoice* gloves afford better protection than *Excalibur* gloves out of the box and there is no appreciable relative deterioration under conditions of UV exposure (except for dichlorvos at 45°C). Visually there was no significant difference following UV exposure for *Excalibur* gloves. However, there appeared to be increased tackiness for *ProChoice* (see Figure 3.3).

4.3.3 OP permeation through abraded PVC gloves

Glove permeation tests were conducted on abraded PVC gloves to determine whether it affects the protective performance. As this was an exploratory study, only a 10% reduction in the PVC coating was investigated.

In order to simulate the worst exposure conditions, all tests on PVC gloves with abrasion were tested with full strength OPs at 45°C. The exception was for mevinphos which was tested at room temperature due to limited supply.

Values for 8-hr cumulative permeation of OPs are presented in Table 4.5 (for unused versus abraded *Excalibur* gloves) and Table 4.6 (for unused versus abraded *ProChoice* gloves), with breakthrough times in asterisks.

Outcomes for the tests on abraded *Excalibur* and *ProChoice* gloves are also summarised in Figure 4.8 for comparison with the unused gloves.

Table 4.5 Average 8-hour cumulative permeation (mg) of OPs with breakthrough times (with asterisk) through abraded *Excalibur* gloves at room temperature and 45°C

Exposure temperature	**Average cumulative permeation (mg)**							
	Omethoate		Mevinphos		Dichlorvos		Diazinon	
	Unused *Excalibur* gloves	Abraded *Excalibur* gloves	Unused *Excalibur* gloves	Abraded *Excalibur* gloves	Unused *Excalibur* gloves	Abraded *Excalibur* gloves	Unused *Excalibur* gloves	Abraded *Excalibur* gloves
Room temperature (23±2°C)	19.4 (±5.2) *BT 180 mins	Not tested	4.5 (±0.2) *BT 300 mins	5.5 (SD ±3.0) *BT 300 mins	174 (±9) *BT 180 mins	Not tested	Not achieved	Not tested
45°C	75.2 (±7.0) *BT 60 mins	97.3 (±20.5) *BT 60 mins	Not tested	Not tested	653 (±48) *BT 60 mins	1,430 (±32) *BT 45 mins	54.6 (±4.0) *BT 120 mins	74.0 (±4.8) *BT 120 mins

Notes:
Figures in brackets are standard deviations, replicates n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 8-hour test period
'Not tested' denotes test was not performed for the variable conditions

Table 4.6 Average 8-hour cumulative permeation (mg) of OPs with breakthrough times (with asterisk) through abraded *ProChoice* gloves at room temperature and 45°C

Exposure temperature	**Average cumulative permeation (mg)**							
	Omethoate		Mevinphos		Dichlorvos		Diazinon	
	Unused *ProChoice* gloves	Abraded *ProChoice*gloves	Unused *ProChoice* gloves	Abraded *ProChoice* gloves	Unused *ProChoice* gloves	Abraded *ProChoice* gloves	Unused *ProChoice* gloves	Abraded *ProChoice* gloves
Room temperature (23±2°C)	7.6 (±0.4) *BT 300 mins	Not tested	Not achieved	3.9 (±0.4) *BT 300 mins	6.2 (±0.2) *BT 240 mins	Not tested	Not achieved	Not tested
45°C	35.1 (±1.4) *BT 60 mins	37.6 (±1.7) *BT 60 mins	Not tested	Not tested	555 (±3) *BT 60 mins	1,306 (±12) *BT 45 mins	28.8 (±3.8) *BT 180 mins	50.0 (±4.6) *BT 180 mins

Notes:
Figures in brackets are standard deviations, replicates, n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 8-hour test period
'Not tested' denotes test was not performed for the variable condition

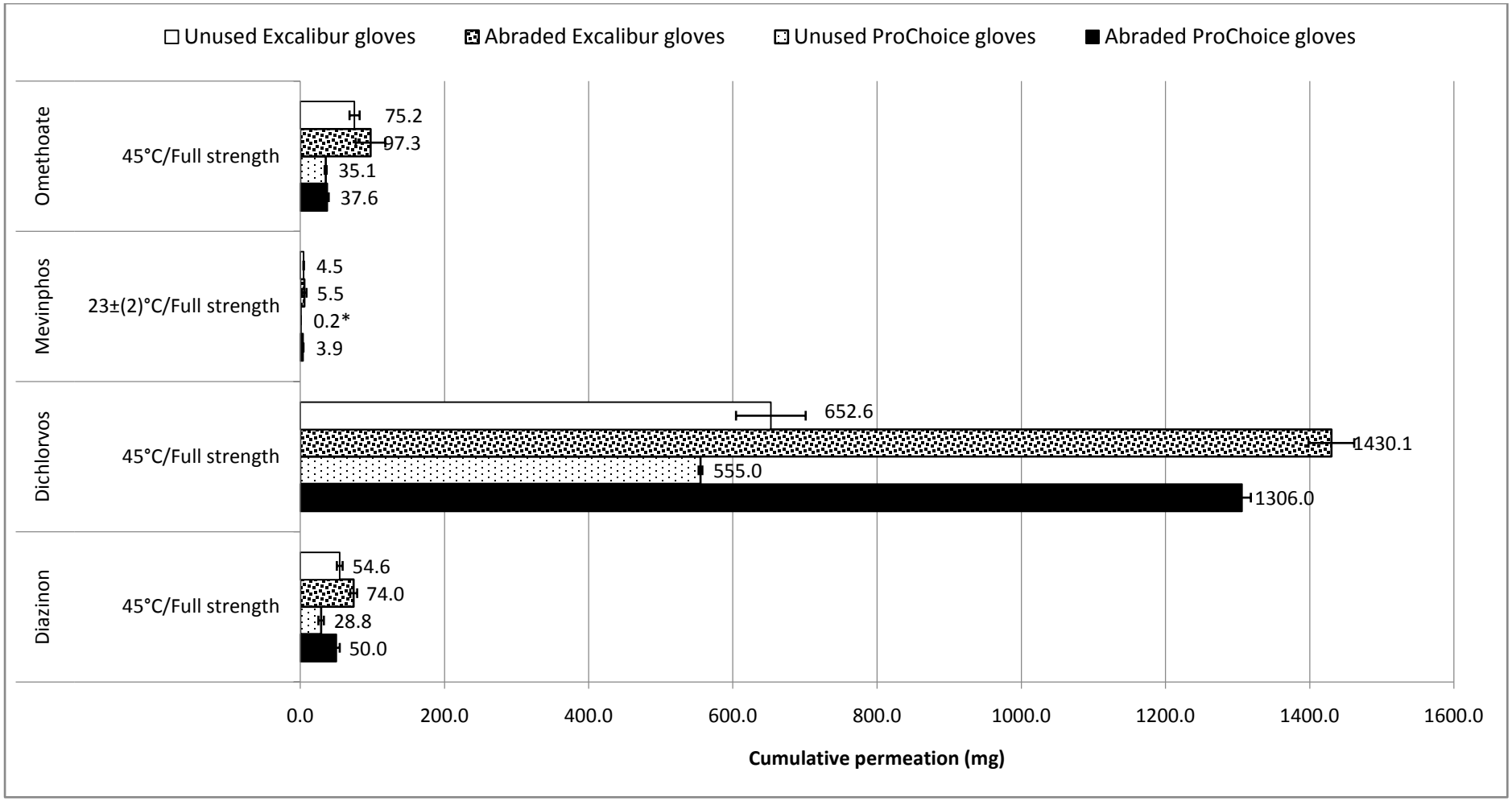


Figure 4.8 Comparison of cumulative permeation of OPs (mg) through *Excalibur* and *ProChoice* gloves (unused gloves versus abraded gloves) in various experimental conditions.
Value in asterisk denotes the cumulative permeation at 8 hrs without achieving breakthrough (flux 1 µg/cm^2/min as per AS/NZS 2161 standard).

Abraded PVC gloves (both *Excalibur* and *ProChoice*) showed consistently greater cumulative permeation of the four OPs compared to unabraded gloves.

For example, the mass of omethoate permeating through abraded *Excalibur* gloves was 97.3 mg (±20.5) (breakthrough time 60 mins), and 37.6 mg (±1.7) (breakthrough time 60 mins) for abraded *ProChoice* gloves over the 8-hour exposure.

Mevinphos, the OP which was only tested at room temperature, demonstrated increased cumulative permeation at 8 hrs i.e. 5.5 mg (±3.0) when tested on abraded *Excalibur* gloves, compared to only 4.5 mg (±0.2) for unused gloves. Effects of abrasion was also seen on the average cumulative permeation through *ProChoice* gloves, in which 3.9 mg (±0.4) of mevinphos was accumulated in the receptor fluid, instead of breakthrough not achieved for the 8-hour test period when tested on unused *ProChoice* gloves.

Abrasion of PVC gloves also resulted in more than 2-fold increase of the average cumulative permeation of dichlorvos, recording 1,430 mg (±32) for *Excalibur* gloves and 1,306 mg (±12) for *ProChoice* gloves. Breakthrough times for both abraded *Excalibur* and *ProChoice* gloves were shortened from 60 mins to 45 mins.

A cumulative permeation of diazinon was 74.0 mg (±4.8) (breakthrough time 120 mins) through abraded *Excalibur* gloves, compared to only 54.6 mg (±4.0) for unused *Excalibur* gloves. A total of 50.0 mg (±4.6) diazinon permeated (breakthrough time 180 mins) through *ProChoice* gloves, almost twice the mass permeated through unused *ProChoice* gloves.

Outcomes of statistical analysis for the abraded PVC gloves are presented in the following Section 4.3.5.

4.3.4 Statistical tests

Due to the limited chemical supply, time constraints and other factors, there were only four replicates conducted for each exposure conditions. It was not feasible to conduct tests of data normality.

The null hypotheses were that there was no effect of OP concentration, elevated temperature, UV exposure and abrasion; and there was no difference in cumulative permeation between the test OPs.

Effects of concentration of OPs on cumulative permeation outcomes

The glove permeation data tend to suggest an increase in cumulative permeation with increased OP concentration. Statistical analyses (Kruskal-Wallis test with Dunn's multi comparisons test) showed that cumulative permeation outcomes of the four formulated OPs at 8 hrs for full strength and application strength are significantly different ($p<0.0001$), under both temperature conditions i.e. at room temperature and elevated temperature. This is noted for both recommended PVC gloves i.e. *Excalibur* and *ProChoice* gloves.

Effects of elevated temperature on cumulative permeation outcomes

The glove permeation data tend to suggest an increase in cumulative permeation with increased exposure temperature to 45°C. Comparison of cumulative permeation outcomes at

8 hrs for *Excalibur* and *ProChoice* gloves indicates that there is a statistically significant difference ($p<0.0001$ for omethoate, dichlorvos and diazinon) between the two exposure temperatures. The significance is noted for OPs at application strength and full strength. Cumulative permeation for mevinphos cannot be compared at different temperatures, as it was only tested under room temperature conditions.

Overall, in answer to **Research Question 1**, it is evident that for infinite dose conditions, increased OP concentration and exposure temperature significantly increased permeation through PVC gloves.

Effects of UV exposure (equal to approximately 7 days of exposure to midday sun) on cumulative permeation outcomes

Glove permeation data tended to show an increase in cumulative permeation with UV-exposed gloves, compared to unused PVC gloves. Eight-hour cumulative permeation for UV-exposed *Excalibur* gloves were statistically significantly different from unused *Excalibur* gloves for OPs ($p\leq0.0001$), except for omethoate ($p=0.18$).

For UV-exposed *ProChoice* gloves, the difference is significant ($p<0.0001$) for mevinphos and dichlorvos only.

The effects of UV exposure on cumulative permeation outcomes through *ProChoice* gloves is not significant for omethoate ($p=0.239$) nordiazinon ($p=0.07$).

Therefore, in answer to **Research Question 2**, UV- exposure had variable and often relatively minor reductions in permeation resistance. The exception appeared to be for dichlorvos.

Effects of abrasion (5% thickness reduction or 10% top PVC layer reduction) on cumulative permeation outcomes

The effect of abrasion on 8-hr cumulative penetration was statistically significant for *Excalibur* gloves ($p<0.05$) for three of the four test OPs, except for omethoate ($p=0.088$). For abraded *ProChoice* gloves, cumulative permeation was statistically significantly different from the unabraded glove for all four OPs, but with marginal significance for omethate.

Hence, to answer **Research Question 3**, there are mostly significant differences between abraded gloves and unabradedPVC gloves on the permeation of formulated OPs. However, the effect is not consistent for omethoate.

As a whole, cumulative permeation outcomes between the two PVC gloves (*Excalibur* and *ProChoice* gloves) were not significantly different ($p>0.10$). However, when comparing average cumulative permeation data for the two types of gloves, some significant differences ($p<0.05$) were seen for some exposure conditions. In general, *ProChoice* gloves tended to provide better protection.

4.4 DISCUSSION

In this section, Research Questions 1 to 3 described at the beginning of this chapter are addressed by discussing the findings and points raised in light of Section 4.3 (Results). Section 4.4.1 discusses the effects of concentration and exposure temperature on the permeation of OPs through PVC gloves. The performance of gloves exposed to UV radiation and abrasion are discussed, and compared against unused gloves in Section 4.4.2 and 4.4.3 respectively, followed by discussion based on the findings from the preliminary field observations.

4.4.1 Effects of concentration and exposure temperature on permeation of OPs through unused PVC gloves

Cumulative permeation and breakthrough time are key measures of the effectiveness of a clothing material as a barrier against the test chemical. While breakthrough time may be used to judge the quality of gloves, cumulative permeation data are more relevant for exposure (ASTM-F739-12e1 2012).

Greater cumulative permeation (and shorter breakthrough) was uniformly observed at the end of the 8-hour tests when both types of unused PVC gloves were tested with concentrated (full strength) formulated OPs, compared to application strength.

There are no comparable glove permeation data available in the literature. However, the results are consistent with the work by Lee (2004). Here, PVC gloves were also tested under similar temperature conditions i.e. 22 (±1)°C and 37(±1)°C with technical grade malathion at

1% and 58%. The 58% technical grade malathion had shorter breakthrough times, under both temperature conditions i.e. 22 (±1)°C and 37(±1)°C. Breakthrough times were reduced at 37°C.

In the present study, three of the OPs at application strength did not demonstrate breakthrough over the 8-hour exposure at room temperature. Similarly, Lee found that 1% malathion (application strength solution) showed no breakthrough on PVC gloves for more than 1,440 mins (Lee 2004).

The greater cumulative permeation of dichlorvos at full strength through both types of PVC gloves could be attributed to the test concentration of dichlorvos (1,398 g/L), being the highest of the test OPs (mevinphos 1,110 g/L, omethoate 814 g/L and diazinon 804 g/L), and its smaller molecular volume and polar surface area (Table 2.4). Thus a combination of high concentration and a higher diffusion coefficient may be explanatory factors.

The effects of temperature on chemical protective clothing permeation resistance are described in the literature, but no reliable predictive models are available for glove-challenge chemical combinations (Perkins & You 1992; Zellers & Sulewski 1993). In addition, the glove material itself can independently degrade or alter with temperature – in practice, the lifespan of gloves can decrease significantly when used in hot conditions (Bromwich 2005).

In this study, elevated temperature resulted in breakthrough in as little as 60 mins for new gloves and full strength formulated OPs. This finding should be given attention, as wearing PPE while working may increase body heat and perspiration, hence affecting permeation and

penetration rate of chemicals through gloves and the skin, as suggested by Evans, McAlinden & Griffin (2001).

Generally, unused *ProChoice* gloves provide better protection than unused *Excalibur* gloves in all test conditions. According to Klingner & Boeniger (2002), considerable variation within a particular brand and model of gloves is still possible even if they are produced by the same manufacturer.

In conclusion, it appears that variable experimental conditions did have an influence on the protection afforded by PVC gloves commonly used by agricultural workers. Notwithstanding the issues raised by Canning (1997) regarding quality control, the permeation data suggest that PVC gloves are suitable for protection against OPs, but with reduced performance expected with high pesticide concentrates and elevated temperature **(Research Question 1).**

4.4.2 Effects of UV exposure on OP permeation through PVC gloves

Exposing gloves to UV radiation i.e. simulating wearing gloves while working outdoors, resulted in somewhat decreased barrier protection **(Research Question 2).**

This appears to be the first study that has shown, by permeation testing, a UV-induced reduction in resistance for PVC gloves used by agricultural workers.

PVC may be degraded at a wavelength of 310 nm, which is within the range of UV radiation from sunlight (UV-B) Seymour & Carraher (1981). This degradation may be manifested as loss of tensile strength, reduced resistance against impact and elongation prior to break.

In an empiricial study, heat and sunlight were found to cause degradation of PVC glove materials, i.e loss of strength, elastic properties and puncture resistance (Raheel & Dai 1997). In a study examining PVC gloves similar to the ones tested here, Canning (1997) found surface topographic and elemental changes after extended sunlight exposure, which were attributable to photo-oxidation. Interestingly, the number of cavities/depressions were not significantly different after short term (4 hrs) sunlight exposure, and were actually reduced following long term exposure (7 months). It was argued that the cavities were filled in as a result of the redistribution of the elements as embrittlement progresses. In the long term sunlight exposure study, some parts of the PVC glove surface became sticky after about 4 months – an outcome which is similar to the effect observed for *ProChoice* gloves (Figure 3.3). After 5 months, Canning observed visible dissociation, with a colour change from red to yellow/brown in blotchy raised areas.

The findings in this study are consistent with those of Moody & Nadeau (1992) where exposure of natural rubber gloves to UV-A radiation enhanced permeability to 2,4-D, although no effect was observed on the permeation of DDT.

In the present study, UV exposure represented about 449 kJ/m^2 of UV-B, whereas in Canning's 4-hr experiments (11 am – 3 pm) the exposure was at most 0.7 kJ/m^2(Canning 1997).If 0.7 kJ/m^2 is the typical daily sunlight UV-B exposure on a relatively clear day, the UV-B exposure in the present study would correspond to roughly 2 years – which, coincidentally, was the mean age of the used gloves reported by Canning (1997).

In actual farm conditions, gloves may be effectively exposed for a longer or shorter period of time. However, there may also be repeated heating/cooling and other weathering effects that are not simulated in the UV box (Figure 3.2).

Overall, Canning (1997) suggested that thicker PVC gloves are better than *Sol-Vex* nitrile butadiene gloves for farm use, because they can better withstand outdoor conditions.

4.4.3 Effects of abrasion on OP permeation through PVC gloves

Over time, farming activities can result in glove abrasion. In the abraded glove tests, reduced permeation resistance was observed **(Research Question 3)**.

Raheel & Dai (2002) reported that abrasion results in surface fuzziness that may affect pesticide retention and penetration. In the present study, it is likely that barrier thickness reduction is the prime reason for increased permeation. However, it is possible that the pores/cavities of the glove material were 'filled in' during the abrasion process (Section 3.1.1.3), modifying permeation behaviour.

The aim of the flat belt sanding process was to achieve a fairly uniform reduction in PVC thickness. This is unlikely to be the reality in farming situations. Differential wear is likely, especially for the dominant hand, and there is evidence for this in a study of fruit fly control workers (Lee at al 2009). Overall, glove thickness was found to decrease by 6.8% (palm) and 11.5% (arm) after 14 days.

A standard procedure for fabric abrasion is available. Aust/NZ Std 2161.3 -2005 refers to abrasion resistance, and specifies a Martindale wear and abrasion machine (section 6.1.3 of the Standard).The objective is to determine breakthrough – which in this case is when a hole is worn through the fabric specimen.However, the parameter of interest in this thesis is chemical resistance (permeation resistance). A particular standard machine to generate an abraded surface was not deemed necessary, as long as an even reduction of thickness was achieved, and the extent of reduction measured with a micrometer.In addition, the Martindale machine was considered too expensive for this exploratory study.

4.4.4 Glove use from preliminary field observations

The experimental design was informed by findings from the preliminary field observations – work periods, glove types etc.

It appeared that workers used one type of glove when handling a mixture of three to four chemicals. This finding is similar to that from a survey of pesticide applicators in the USA, in which most (73%) of the respondents indicated that they wear the same gloves for multiple products (Black et al. 2014). It is a concern if one type of glove is used for multiple pesticides merely due to convenience, and if the label requirement of the recommended type of glove is not met. The SDSs of these OPs may have different recommended glove material, depending on the physicochemical properties and compatibilities of the compounds.

However, in the present study involving a range of formulated OPs with different physicochemical properties, PVC gloves appear to be a reasonable choice for farmers. This is

also supported by Canning's work (1997) comparing various types of gloves, and also suggested in a study of diazinon-exposed sheep dip workers by Apthorpe et al. (1998).

4.5 CONCLUSIONS

With respect to the research questions given at the beginning of this chapter, the following conclusions may be drawn.

Generally, *ProChoice* gloves offer better protection than *Excalibur* gloves against permeation for all of the tested OPs.Cumulative permeation of the formulated OPs is different between OPs, which may be due to the physicochemical properties of the test OPs.

At room temperature, PVC gloves provided the desired protection (breakthrough not reached) for all three application strength OPs except omethoate. However, in hot conditions (45°C), breakthrough of application strength OPs may occur as soon as at 180 mins.
The efficacy of the gloves is significantly reduced when handling higher concentrations of pesticides (e.g. for mixing and loading pesticide concentrates) and at elevatedf temperature (45°C), where breakthrough time reduced from 180 mins to 60 mins and with greater cumulative permeation outcomes.

Reduced performance was observed with the UV-exposed and abraded gloves.

Of the four OPs tested, dichlorvos is problematic. It showed the greatest changes with concentration, temperature, and with UV-exposed and abraded gloves.

CHAPTER 5

CASE STUDY 2

PERFORMANCE OF DISPOSABLE GLOVES USED BY AMBULANCE WORKERS AGAINST ORGANOPHOSPHORUS PESTICIDES

This case study explores the performance of disposable gloves used by non-routine users i.e. South Australia Ambulance Service (SAAS) workers when attending accidental or intentional poisoning cases. It begins with an overview of the OP exposure potential arising from their current work practices. The rationale and aims of the study are then presented. Experimental data are presented for disposable nitrile and neoprene gloves, tested individually and in combination.

In this study, the following research questions are addressed in relation to glove permeability to OPs:

RQ4 What are the effects of variable experimental conditions (diluted and undiluted concentration, room temperature and hot condition) on the protection provided by the disposable gloves used by ambulance workers?

RQ5 How do individual gloves perform in terms of the protection afforded, as compared to whengloves worn in combination?

RQ6 To what extent are the workers protected when implementing double gloving method (combination of nitrile and neoprene gloves) as currently in practice?

In this chapter, it will be shown that the tested disposable gloves provided good protection against formulated OPs at application strength for up to 4 hours. Limited protection was observed for the concentrated formulated OPs at elevated temperature (45°C). It will be argued that the double gloving method using gloves of different surface polarities provides protection against a wide range of OPs.

5.1 AMBULANCE WORKERS AS A STUDY POPULATION

Occupational exposure to organophosphorus compounds is not only limited to those with direct use (e.g. agricultural workers), but also those with incidental or non-routine occupational exposure, e.g. ambulance workers handling accidents and self-inflicted poisoning cases. Exposure may occur from industrial incidents or from use of organophosphorus compounds as chemical warfare agents, such as the sarin attacks in Matsumoto (1994) and Tokyo subway (1995) (Morita et al. 1995; Okumura et al. 1996). Individuals may also attempt suicide by intentional ingestion of agricultural pesticides (Gunnell & Eddleston 2003; Konradsen 2007; Kumar et al. 2013).

Chemical accidents and poisonings may have significant public health impacts, as well as imposing substantial logistic demands on response agencies (Edwards et al. 2003). In South Australia, it is estimated that there are four to five intentional poisoning cases every month, with data unavailable regarding OP cases (David Casey, Rescue Paramedic, Hazmat Operations, SAAS 2014, personal communication). These poisoning cases are attended by ambulance workers who may be exposed to the toxic chemicals when rescuing the victims, as described in Section 5.1.1.

SA Ambulance Service (SAAS) is the principal provider of ambulance services in South Australia., and comprises more than 1,200 career and 1,500 volunteer staff providing emergency, non-emergency, rescue ambulance services and support services across the state.It is plausible to suggest that a large number of these ambulance workers will at some time experience occupational exposure when attending OP poisoning cases.

5.1.1 Opportunities for exposure and current work practices

As part of SAAS's health and safety management system, the risks associated with handling potential OP poisoning patients have been considered, and the organisation has developed a policy which includes the use of certain types of gloves.

Dermal exposure to OPs may potentially occur when an ambulance worker wearing short sleeved uniforms is providing first aid and/or emergency medical care to patients (Figure 5.1). Exposure may occur when touching the patient's skin or clothing contaminated with high concentration of OPs or the chemical is emitted from induced vomiting.However, it is evident that there are areas of unprotected skin, i.e. the arms, neck and head.

Figure 5.1 Simulation of exposure potential whenSAAS ambulance worker wearing double gloves attending to a pesticide poisoning case

In order to prevent skin contact of the hands with chemicals, a double gloving method using disposable neoprene gloves was recommended by SAAS approximately a decade ago. The recommendation was made based on a suggestion by the Australian Defence Force and US Paramedical/Fire Services (Pat Stevenson, Operations Manager, Special Operations, SAAS, 2013, personal communication). In turn, this was based on discussions with ambulance, health and fire service, and Chemical, Biological, Radiological and Nuclear (CBRN) managers in early 2002 to 2003.

However, it is understood that due to cost considerations, SAAS opted for a double gloving method using a combination of nitrile and neoprene gloves, and this is currently being practised (Figure 5.2). Details of gloves are provided in Chapter 3 (Section 3.2.1). A key requirement is dexterity, therefore thick gloves and laminates are not suitable options.

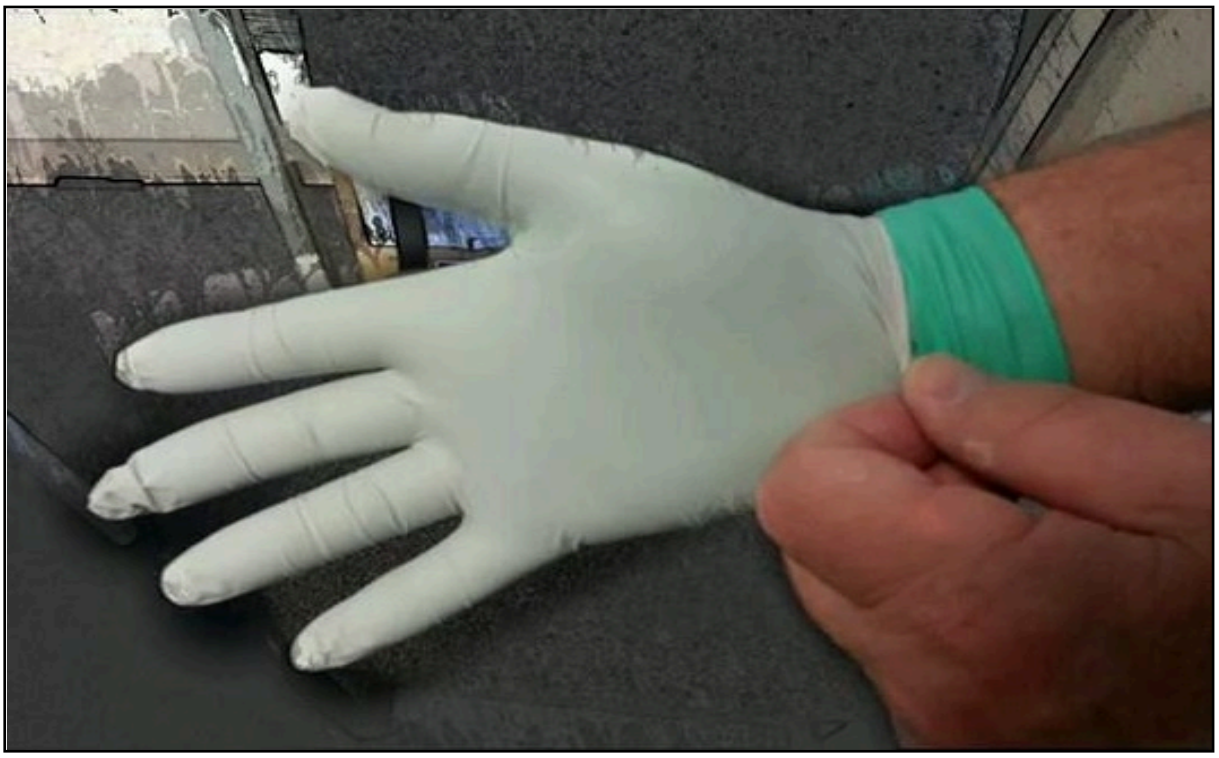


Figure 5.2 Double gloving method (nitrile on top of neoprene gloves) practised bySAAS ambulance workers

5.1.2 Rationale and aims of the study

Rationale

Perhaps because pesticides are usually associated with the agricultural and pest control sectors, and because the duties of an emergency worker cover a wide range of tasks, ambulance workers appear to be an under-studied group by occupational hygiene researchers investigating OP exposures.

There does not appear to be an empirical evidence base for the current glove policy by SAAS. Indeed, there appear to be no data on the chemical protective properties of thin disposable gloves towards OPs, and this is probably because relatively cheap disposable gloves (apart from laminated film gloves) are only recommended for incidental chemical protection.

Often the selection of gloves is made based on general glove selection guides. Guidance from Imperial College London (http://www3.imperial.ac.uk/pls/portallive/docs/1/52670.PDF) is as follows:

> *Disposable gloves are thin, generally 4 - 8 mils (0.1 – 0.2 mm) thick. This allows the user to retain good touch sensitivity and dexterity but they have poor chemical resistance. They are designed to protect against incidental rather than intentional contact with chemicals and should be changed after any splash. They are designed for single use only and should never be re-used.*

Aims

In the light of the above, the research presented in this Chapter aimed to assess the chemical protection afforded by the disposable gloves, as used by SAAS. This would inform future practice.

5.2 WORST CASE APPROACH

The experimental design here is based on a real world 'worst case' approach, with formulated OPs.

The highest concentration was deemed to be the full strength (concentrated) OP. The highest temperature was deemed to be 45°C, which is reasonable when working outdoors or in a hot environment indoors. The gloves were exposed to the test OPs for up to 4 hours - deemed to be the upper limit use time for any one pair of disposable gloves (Section 3.2.3.1).

Infinite dose conditions were selected to understand the maximum flux of the test OPs under the exposure conditions.

The OPs selected for the challenge represent a wide range of physiochemical properties, particularly lipophilicity (log octanol-water partition coefficient) (Section 3.2.2).

Thus the test conditions were:

- Application strength to full strength formulated OP.
- Room temperature to 45°C
- Four OPs – omethoate, mevinphos, dichlorvos, diazinon
- Infinite dose conditions, up to 4 hrs

Although contact with diluted OPs (application strength) could be a less likely scenario for ambulance workers attending poisoning/suicide cases, it was still considered worthwhile to test the gloves with application strength OPs.

Testing gloves individually was also considered worthwhile for extrapolation to other work situations, e.g. researchers handling OPs in the laboratory with single nitrile or neoprene gloves.

5.3 RESULTS

Outcomes of the effects of concentration on OP permeation through different types of gloves under different variable conditions are presented in Sections 5.3.1 to 5.3.3 respectively. Outcomes of the effects of two different exposure temperatures (room temperature; 23(±2)°C and 45°C) on permeation of OPs through different types of gloves are compared in Sections 5.3.4 to 5.3.6.

5.3.1 Effects of concentration on OP permeation through disposable nitrile gloves

Table 5.1 below summarises the average cumulative permeation of the OPs tested in application strength and full strength through nitrile gloves, including breakthrough times (presented with asterisk) at both room temperature and elevated temperature (45°C).

Table 5.1 Average 4-hour cumulative permeation (mg) of OPs and breakthrough times through disposable nitrile gloves at room temperature and 45°C

Exposure temperature	**Concentration of OPs**	**Average cumulative permeation (mg)**			
		Omethoate	Mevinphos	Dichlorvos	Diazinon
Room temperature (23±2°C)	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	Not achieved	Not achieved	Not achieved	Not achieved
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	18.4 (±2.6) *BT 15 mins	340 (±21) *BT 30 mins	433 (±16) *BT 5 mins	84 (±7) *BT 40 mins
45°C	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) 0.5 mg/mL (diazinon)	Not achieved	Not achieved	11.7 (±0.8) *BT 40 min	1.3 (±0.1) *BT 180 min
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	704 (±80) *BT 20 mins	1,671 (±54) *BT 5 mins	616 (±24) *BT 5 mins	341 (±26) *BT 15 mins

Notes:
Figures in brackets are standard deviations, replicates n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 4-hour test period

Exposure under room temperature (23±2°C) condition

When applied at application strengths onto nitrile gloves, breakthrough was not achieved for any OPs at room temperature. However, at full strengths, breakthrough was achieved for all OPs in all conditions when tested on nitrile gloves; 5 mins for dichlorvos, 15 mins omethoate, 30 mins mevinphos and 40 mins diazinon. Average cumulative permeation of full strength OPs at room temperature varied ranging from 18.4 mg (±2.6) for omethoate to 433 mg (±16) for dichlorvos.

Exposure under elevated temperature (45°C) condition

Application strength omethoate and mevinphos did not demonstrate breakthrough at elevated temperature (45°C). Application strength dichlorvos and diazinon were the only two OPs that achieved breakthroughs at high temperature (average cumulative permeation 11.7 mg (±0.8) and 1.3 mg (±0.1) respectively).

Average cumulative permeation of full strength OPs at elevated temperature was high for all OPs.

5.3.2 Effects of concentration on OP permeation through disposable neoprene gloves

Table 5.2 below summarises the average cumulative permeation of the OPs tested in application strength and full strength through neoprene gloves, including breakthrough times (presented with asterisk) at both room temperature and elevated temperature (45°C).

Table 5.2 Average 4-hour cumulative permeation (mg) of OPs with breakthrough times (with asterisk) through disposable neoprene gloves at room temperature and 45°C

Exposure temperature	**Concentration of OPs**	**Average cumulative permeation (mg)**			
		Omethoate	Mevinphos	Dichlorvos	Diazinon
Room temperature (23±2°C)	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	Not achieved	Not achieved	Not achieved	Not achieved
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	4.2 (±0.4) *BT 120 mins	68.4 (±8.3) *BT 40 mins	507 (±17) *BT 5 mins	104 (±22) *BT 30 mins
45°C	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	Not Achieved	Not Achieved	9.5 (±0.6) *BT 40 mins	2.8 (±0.2) *BT 50 mins
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	93.7 (±13.3) *BT 20 mins	367 (±24) *BT 15 mins	648 (±10) *BT 5 mins	486 (±43) *BT 10 mins

Notes:
Figures in brackets are standard deviations, replicates n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 4-hour test period

Exposure under room temperature (23±2°C) condition

At application strength, breakthrough was not achieved for all four OPs through neoprene gloves at room temperature for up to 4 hours of exposure. However, the outcomes uniformly changed when similar tests were conducted using full strength OPs. It was evident that dichlorvos had the greatest average cumulative permeation of 507 mg (±17) at 4 hours with a breakthrough time of only 5 mins, while omethoate accumulated the least; 4.2 mg (±0.4); with the longest breakthrough time (120 mins) of all four OPs.

Exposure under elevated temperature (45°C) condition

When application strength OPs were tested on neoprene gloves under elevated temperature (45°C) conditions, breakthrough was not reached for two out of the four OPs (omethoate and mevinphos) over the 4-hour tests. Nevertheless, at full strengths, breakthrough was achieved for these two test chemicals at 20 mins (average cumulative permeation 93.7 mg (±13.3)) for omethoate, and 15 mins (average cumulative permeation 367 mg (±24)) for mevinphos. Dichlorvos and diazinon showed shorter breakthrough and higher average cumulative permeation through neoprene gloves with the increase of temperature. The breakthrough time decreased from 40 mins to 5 mins, with average cumulative permeation increased by almost 70-fold for dichlorvos, and decreased from 50 mins to 10 mins, with 170-fold cumulative permeation greater than at application strength.

5.3.3 Effects of concentration on OP permeation through combination of nitrile and neoprene gloves

Comparison of average cumulative permeation of the OPs of different concentrations (application strength and full strength) tested on combination of nitrile and neoprene gloves are presented with breakthrough times (with asterisk) in Table 5.3.

Table 5.3 Average 4-hour cumulative permeation (mg) of OPs with breakthrough times (with asterisk) through combination of nitrile and neoprene gloves at room temperature and 45°C

Exposure temperature	**Concentration of OPs**	**Average cumulative permeation (mg)**			
		Omethoate	Mevinphos	Dichlorvos	Diazinon
Room temperature (23±2°C)	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	Not achieved	Not achieved	Not achieved	Not achieved
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	Not achieved	3.5 (±0.6) *BT 180 mins	257 (±9) *BT 30 mins	Not achieved
45°C	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	Not achieved	Not achieved	2.0 (±0.1) *BT 180 mins	Not achieved
	Full strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	31.4 (±3.5) *BT 50 mins	29.0 (±0.9) *BT 40 mins	519 (±28) *BT 20 mins	77.9 (±0.9) *BT 40 mins

Notes:
Figures in brackets are standard deviations, replicates, n=4
BT denotes breakthrough time observed when flux reaches 1 µg/cm^2/min, as per AS/NZS 2161 standard
'Not achieved' denotes breakthrough was not achieved over the 4-hour test period

Exposure under room temperature (23±2°C) condition

The combination of nitrile and neoprene gloves yielded relatively lower average cumulative permeation and longer breakthrough time, compared to individual gloves. At room temperature, there was no breakthrough of application strength OPs for combination of gloves. However, when at full strength, breakthrough occurred for two OPs. Mevinphos demonstrated breakthrough at 180 mins and dichlorvos at 30 mins, with average cumulative permeation of 3.5 mg (±0.6) and 257 mg (±9), respectively over the 4-hour exposure period.

Exposure under elevated temperature (45°C) condition

At elevated temperature, there was no breakthrough for application strength OPs when tested on combination of gloves, except for dichlorvos. Application strength dichlorvos reached a breakthrough at 180 mins. At full strength and at 45°C, all OPs permeated the glove combination.

5.3.4 Time series cumulative permeation data

Time series cumulative permeation data for the individual gloves and the combination are given in Figures 5.3-5.5. These relate to full strength OPs.

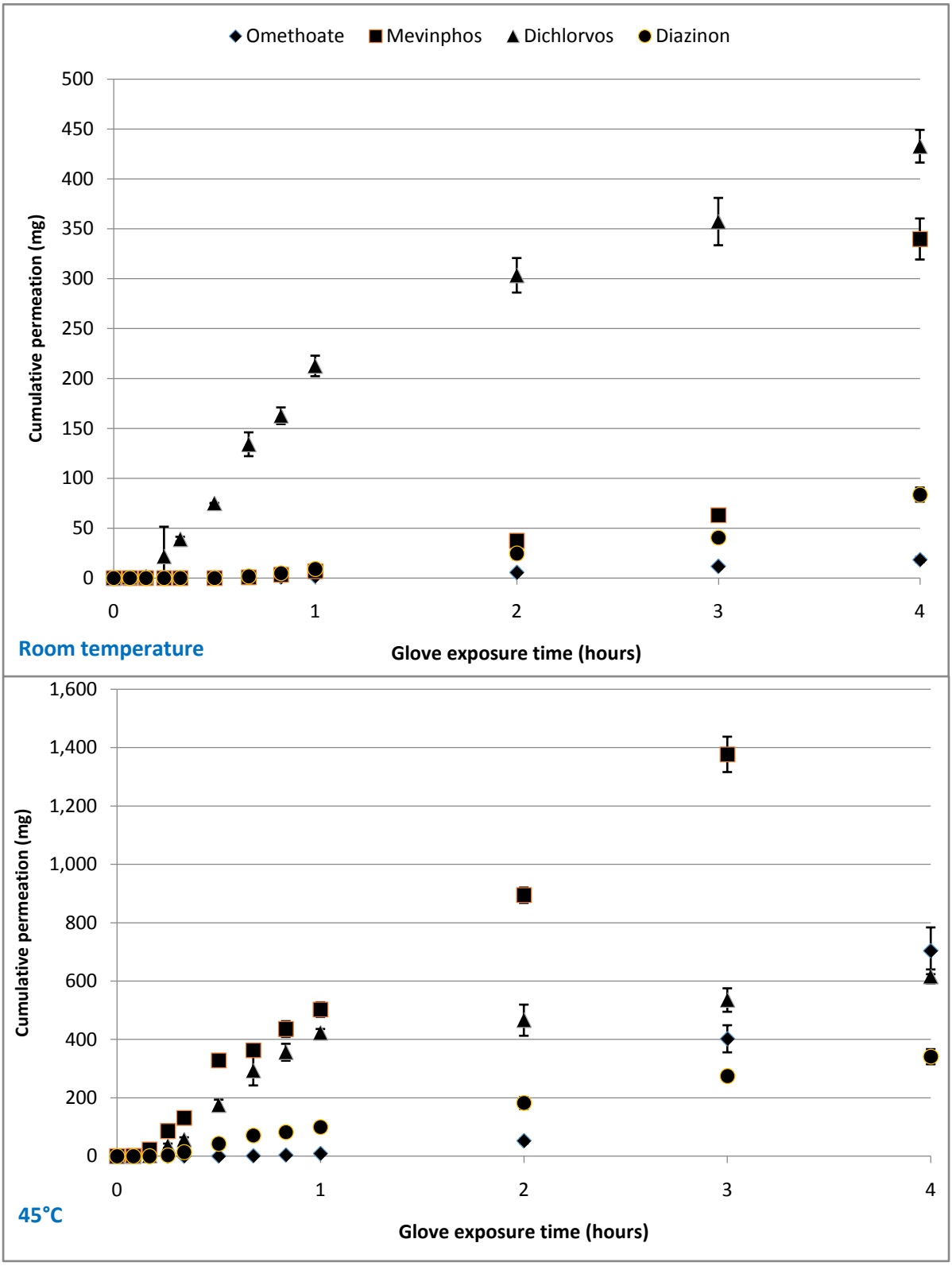


Figure 5.3 Comparison of average cumulative permeation (mg) of full strength OPs through disposable nitrile gloves at room temperature (top) and 45°C (bottom).

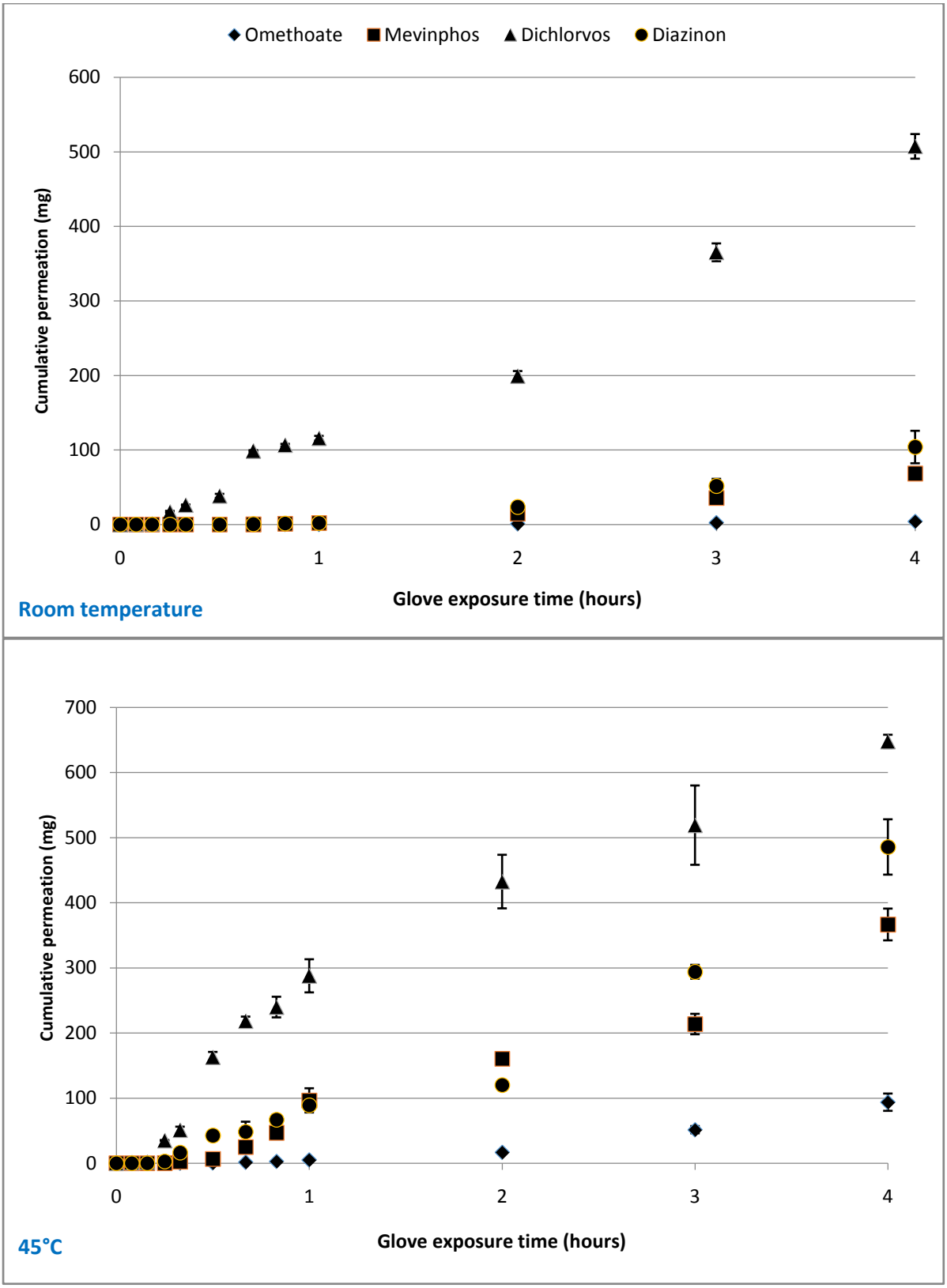


Figure 5.4 Comparison of average cumulative permeation (mg) of full strength OPs through disposable neoprene gloves at room temperature (top) and 45°C (bottom).

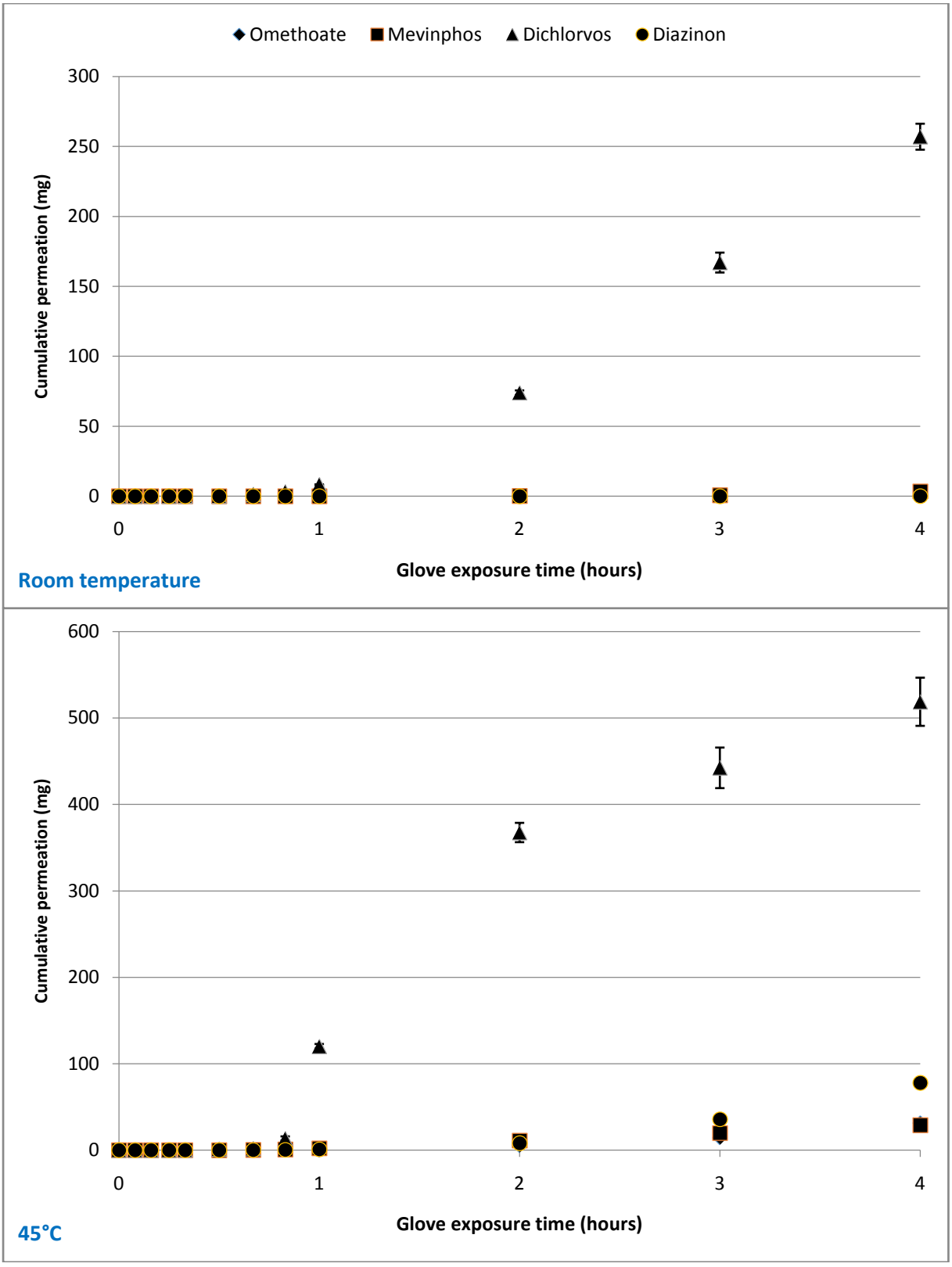


Figure 5.5 Comparison of average cumulative permeation (mg) of full strength OPs through combination of nitrile and neoprene gloves at room temperature (top) and 45°C (bottom).

5.3.5 Comparison of the protection provided by individual gloves and the gloves worn in combination

Figure 5.6 shows the comparison of average cumulative permeation of all four OPs (mg) of different concentrations (application strength and full strength) tested at room temperature and elevated temperature, by glove type.

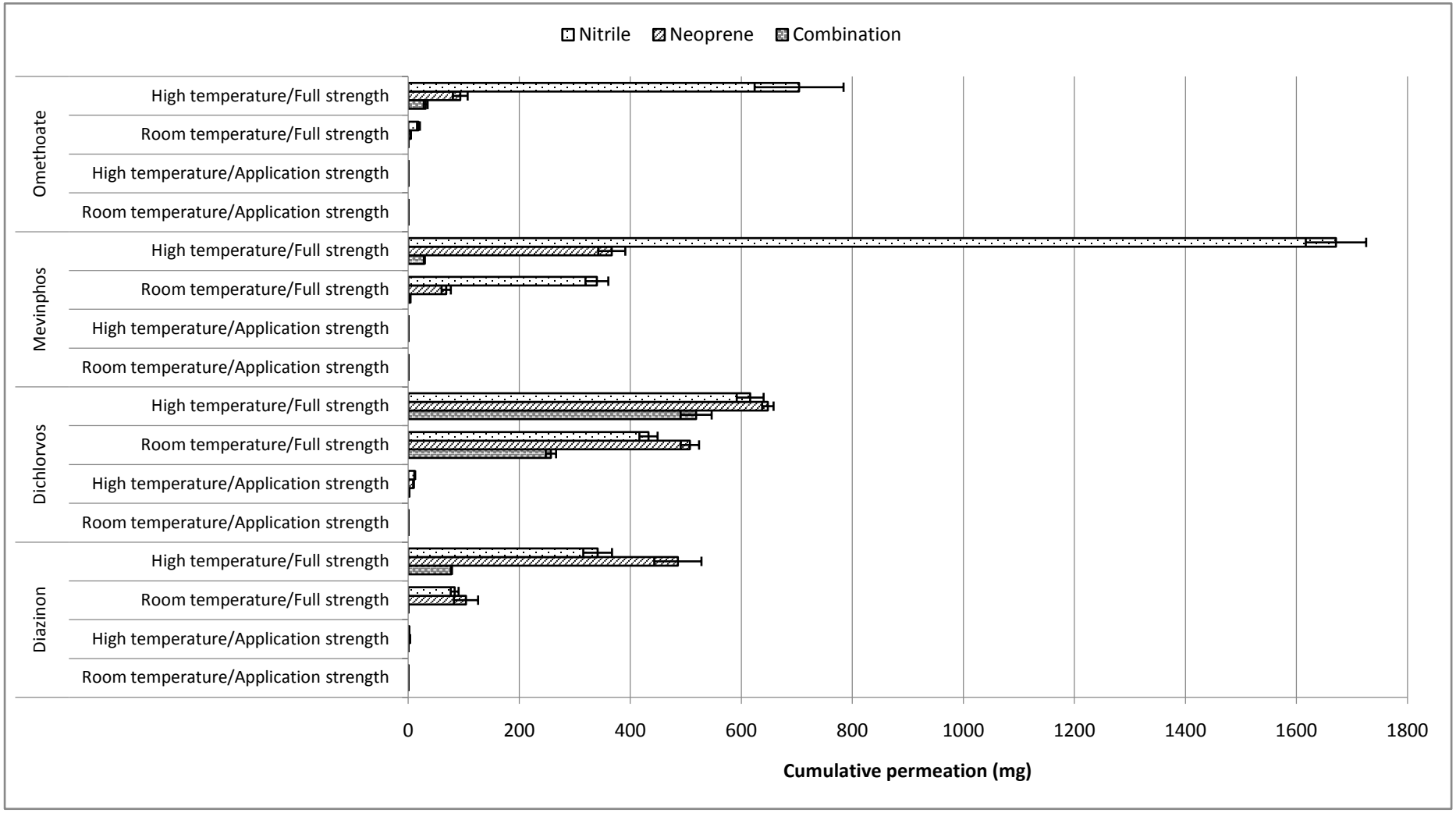


Figure 5.6 Comparison of average cumulative permeation of OPs (mg) in various experimental conditions by glove types

Across all test conditions (application strength and full strength, at room temperature and elevated temperature), average cumulative permeation of these two OPs were higher when tested on nitrile gloves, compared to on neoprene gloves.

Double gloving (with the combination of nitrile and neoprene gloves) resulted in lower average cumulative permeation in all test conditions. Longer breakthrough times were also observed for all OPs through the combination of gloves, than for individual nitrile or neoprene gloves.

Note that double neoprene and double nitrile, or neoprene on nitrile permutations were not tested.

5.3.6 Statistical tests

There were insufficient replicates for formal tests of data normality.

The null hypotheses were that there was no effect of OP concentration, elevated temperature, and double gloving method (nitrile on neoprene gloves); and there was no difference in cumulative permeation between the test OPs.

Effects of OP concentration on cumulative permeation outcomes

In general, the data show increased cumulative permeation with increased OP concentration. Comparisons between OP indicates that cumulative permeation outcomes at 4 hours for full strength and application strength are significantly different ($p<0.0001$). The significance is for individual gloves as well as gloves in combination, and also OPs. With regards to **Research Questions 4**, it shows that increased OP concentration significantly increased permeation through the disposable gloves used by ambulance workers.

Effects of elevated temperature on cumulative permeation outcomes

Another observed trend on the glove permeation data is increased cumulative permeation when the exposure temperature was elevated (45°C). Comparison of cumulative permeation outcomes at 4 hours shows that, except for omethoate, there is a statistically significant difference ($p<0.0002$) between the two temperatures, regardless of the test concentration or OP. This also addressed **Research Question 4**, in which elevated temperature significantly increased permeation through the disposable gloves, both individually and in combination.

Effects of double gloving (combination of nitrile and neoprene) on cumulative permeation outcomes

Glove permeation data suggest that double gloving results in lower cumulative permeation than for individual gloves (either nitrile or neoprene).

The Kruskal-Wallis test with Dunn's multi comparisons test showed mixed results.

Omethoate: could not be compared when tested at application strength at room temperature

Omethoate: $p< 0.05$ for the nitrile/combined gloves, when tested at application strength at 45°C

Omethoate: $p< 0.05$ for the nitrile/combined gloves, when tested at full strength

Mevinphos: $p< 0.05$ for the neoprene/combined gloves, when tested at application strength

Mevinphos: $p< 0.05$ for the nitrile/combined gloves, when tested at full strength

Dichlorvos: $p< 0.05$ for the nitrile/combined gloves, when tested at application strength

Dichlorvos: $p< 0.05$ for the neoprene/combined gloves, when tested at full strength

Diazinon: $p< 0.05$ for the neoprene/combined gloves

Therefore, to answer **Research Question 5**, it is evident that the combination of gloves (nitrile on neoprene) did show better protection for the four test OPs), compared to individual gloves. This was observed for both application strength and full strength OPs.

Interestingly, neoprene gloves provided better protection than nitrile gloves for omethate and mevinphos at full strength. However, the reverse was observed for dichlorvos and diazinon.

With regards to **Research Question 6**, it is recommended that the current practice by SAAS workers of wearing combined nitrile and neoprene gloves continue, as the combination providesprotection against a wider range of OPs of different polarities.

5.4 DISCUSSION

During emergencies ambulance workers do not have much time to plan ahead for specific incidents. The main concern is to treat the patients as soon as possible without introducing any additional risk, and with respect to gloves, to provide the required dexterity as well as adequate protection for their skin. There is great reliance on organisational policy and its specific PPE recommendations. Ideally, these recommendations should be evidence-based. However, as will be discussed later, there are inconsistent recommendations between ambulance agencies in Australia. The research presented here should help to inform policy and glove recommendations.

The effects of concentration and temperature on permeation of formulated OPs through disposable gloves are discussed in Section 5.4.1. The following section (5.4.2) discusses the performance of individual gloves as distinct from the gloves worn in combination, as well as the efficacy of the current double gloving method practised by SAAS ambulance workers.

As there appear to be no directly comparable permeation studies of disposable gloves, the discussion in relation to the effect of exposure variables is largely done in isolation.

5.4.1 Effects of concentration and exposure temperature on permeation of OPs through disposable gloves

The present study suggests that disposable nitrile and neoprene gloves may provide adequate protection at low OP concentrations, but do not offer adequate protection at high concentrations. In other words, glove recommendations for incidental exposure may be inappropriate if concentrated OPs are involved**(Research Question 4).**

Exposure temperature also affects the permeation of the tested OPs through individual gloves and the combination of gloves to varying degrees. Previous studies have shown that small variation in temperature can significantly affect permeation results with significant differences in breakthrough time and permeation rates (Lee et al. 2009).

In a real world context, if a SAAS ambulance worker wore only nitrile gloves when attending to a poisoning case involving full strength mevinphos at room temperature (23(±2)°C), breakthrough may be achieved as soon as after 30 mins of exposure. However, if the attendance takes place on a hot summer day in South Australia where the temperature reaches 45°C, breakthrough of mevinphos in the nitrile gloves could occur in 5 minutes. If the gloves are not changed for four hours under the elevated temperature, there could be significant uptake through the skin.

When handling the full strength formulated OPs, the combination of nitrile and neoprene gloves may be appropriate, but probably only under moderate temperature conditions. The exception appears to be full strength dichlorvos (breakthrough time 30 min).

When the exposure temperature increased to 45°C, it is advisable to change the gloves sooner, because breakthrough time through the combination of gloves varied, ranging from 20 mins to 50 mins. The influence of temperature is especially significant on full strength OPs. For example, at room temperature, permeation of OPs varied from breakthrough not achieved (omethoate and diazinon) to 257 mg (dichlorvos). At elevated temperature (45°C), 4-hour cumulative permeation for full strength OPs ranged between 29 mg for mevinphos and 519 mg for dichlorvos. The cumulative permeation in rank order from the highest to the lowest is dichlorvos > diazinon > omethoate > mevinphos.

5.4.2 Protection afforded by individual gloves vs combination of gloves against OPs

The data suggest that wearing single gloves (either nitrile or neoprene gloves) will provide less protection than wearing a combination of nitrile and neoprene gloves **(Research Question 5).** This feature applies across all test conditions over the 4-hour exposure.

Comparing individual gloves, significant differences in breakthrough times were also reported by Mickelsen & Hall (1987). Differences between nitrile and neoprene glove materials were observed across a range of challenge chemicals and brands, despite having the same generic name and nominal thickness. The differences were attributed to glove chemical composition or the fabrication process of the gloves.

The difference of protection provided by the combination of gloves compared to individual gloves does matter when handling different concentration of OPs. For example, with full strength omethoate and diazinon, the combination of gloves provided reasonably good protection with no breakthrough even after 4 hours, whereas in the same exposure conditions with individual gloves, breakthroughs were observed for the two OPs between 15 and 120 mins. That said, the interpretation of full strength data should be tempered by the fact that carrier solvents may also influence permeation through gloves, and this was not systematically investigated here.

In most conditions of this study, nitrile gloves demonstrated shorter breakthrough time and greater average cumulative permeation than neoprene gloves. This is especially applicable to water-soluble OPs such as omethoate and mevinphos. Interestingly, findings from nitrile gloves were the opposite when tested on diazinon, an insoluble OP, where breakthrough

times were longer and average cumulative permeation was lower for diazinon than omethoate and mevinphos.

Practising double gloving method as currently practised by SAAS ambulance workers sensibly creates extra protection, with relatively lower average cumulative permeation and longer breakthrough time than those using individual gloves **(Research Question 6).** Nonetheless, for exposure to full strength OPs in upper extreme exposure condition (45°C), it is advisable to remove the gloves as soon as practicable to avoid breakthrough.

While double gloving results in increased thickness (increasing breakthrough time), it is worth noting that thickness is not the only factor that determines the performance of gloves. Glove polymer composition and glove coating may also affect permeation of OPs. Indeed, laminate film gloves provide protection from a wide range of chemicals by virtue of polarity differences.

In the present study, nitrile gloves provided better protection for non-polar chemicals (i.e diazinon), while neoprene gloves performed better for protection against polar chemicals (i.e omethoate).

Nitrile gloves have the C≡N functional group which is of high polarity. Therefore, the use of 'polar' gloves could be recommended when handling non-polar materials to slow down permeation. Although nitrile gloves provided better protection for non-polar OPs like diazinon, it may not be appropriate to practise double gloving with only nitrile gloves. Ambulance workers attending OP poisonings may encounter OPs of low and/or high polarity.

Further research could test combinations of the same gloves (both neoprene gloves or both nitrile gloves). However, based on the data for the individual and combination gloves, the use of two different types of gloves in combination, as currently in practice, is appropriate, as it covers a range of chemicals of different polarity.

Interestingly, ambulance workers of the Queensland Ambulance Service (QAS) use the same brand nitrile gloves for attending to all emergencies including OP cases, but only single gloving is practised (Michelle Molyneux, Assistant Manager, Medical Inventory & Uniforms, Fleet & Equipment Operations, QAS, 2015, personal communication). In contrast, the Ambulance Service of NSW ambulance workers practise single gloving using laminate Barrier® gloves (Ansell, Style 02-100) for OP incidents, which were introduced approximately 10 years ago in response to a reported incident and/or staff exposure to OPs that WorkCover NSW were notified about (Kate Hipsley, Manager, Infection Control, Clinical Services, Ambulance NSW, 2014, personal communication). Ambulance Tasmania (AT) implements double gloving method with Purple Nitrile-Xtra gloves (Kimberley Clark, KC 500) as the inner layer and polyvinyl alcohol gloves (Ansell, 15-554) as the outer layer (Ky Wittich, Project Manager, Community Resilience (Emergency Management), Aeromedical and Special Operations,AT, 2015, personal communication).

5.5 CONCLUSIONS

Considering the research questions listed at the beginning of this chapter, several conclusions may be drawn. In hot conditions, gloves provide very limited protection for the concentrated OPs. Double gloving (of nitrile and neoprene gloves) as currently practised by SAAS is

recommended, with a change after 50 mins (for omethoate), 40 mins (mevinphos and diazinon) and 20 mins (dichlorvos) to avoid breakthrough.

At room temperature, double gloving appears to provide reasonably good protection (breakthrough not reached) for handling full strength formulated omethoate and diazinon.However, gloves should be changed as often as possible when handling full strength formulated OPs. As disposable gloves are meant for single use, they should not be worn for extended periods of time.

CHAPTER 6

SKIN STUDIES OF OMETHOATE, MEVINPHOS, DICHLORVOS AND DIAZINON

This chapter describes skin penetration experiments relevant to the target populations described in Chapter 4 (agricultural workers involved in mixing, loading and spraying of OPs) and Chapter 5 (ambulance workers attending to OP poisoning cases). It is also relevant to other OP workers involved in manufacturing, transport, storage, and disposal of OPs.

In this *in vitro* skin study, abdominal human skin was challenged with the four formulated OPs tested in the previous chapters, namely omethoate, mevinphos, dichlorvos and diazinon, in order to understand skin penetration of these OPs, should gloves are not worn when handling them. Experiments were conducted using the full strength and application strength of the formulated OPs at room temperature and an elevated temperature (37°C), to address the following research questions:

RQ7 How do skin penetration outcomes differ between formulated OPs?

RQ8 How does the concentration of OP formulations and an elevated temperature affect skin penetration?

RQ9 How does the amount of OPs penetrated through the skin compare to the respective Acceptable Daily Intake (ADI)?

In this chapter, it will be demonstrated that skin penetration outcomes differ between formulated OPs, and this may be related to the physicochemical properties of the OPs. It will be shown that the penetration of formulated OPs was more rapid at high concentration and under high temperature conditions. It will also be shown that the skin penetration for short periods may exceed the Acceptable Daily Intakes (ADIs).

6.1 INTRODUCTION

With the exception of certain fumigants, dermal exposure to pesticides has been a longstanding occupational health concern (Durham, Wolfe & Quinby 1965; Simpson 1965; Wolfe, Armstrong & Durham 1966). In recent times, the prominence given to dermal exposure *vis a vis* inhalation exposure has increased, following success in efforts aimed at the control of the latter (Fiserova-Bergerova 1993; Semple 2004). A number of models of potential dermal exposure have been developed, and most recently in response to European REACH (Registration, Evaluation and Authorization of CHemicals) requirements. Here, exposure scenarios form an essential basis for chemical risk assessment reports to show that chemicals can be used safely. In their review, Tielemans et al. (2007) outlined, and highlighted the limitations of, current models. So called, 'Tier 2' models, producing robust and realistic exposure assessments, are currently not available, and the authors argue that more development work is required.

With regard to skin penetration models, Anissimov et al. (2013) described theoretical models and software packages that have been developed for estimating steady state flux and skin disposition of chemicals. However, several empirical studies have demonstrated that many chemicals without known reasons do not fit the present mathematical models (Holmgaard &Nielsen, 2009). The homogeneous membrane model is inadequate even for water penetration and desorption (Anissimov et al. 2013). In addition, Riviere and Brooks (2011) have highlighted further issues relating to complex dosing situations and real world exposures.

The skin is a complex structure and the rate of penetration of a chemical through the skin will depend, *inter alia*, on its partitioning between aqueous and non-aqueous components, i.e. its hydrophilicity ('water-liking') or lipophilicity ('fat-liking') character, as well as the molecular size (Holmgaard & Nielsen 2009; McDougal & Boeniger 2002; Nielsen et al. 2004, Magnusson et al. 2004).

The skin itself is dynamic and is influenced by ambient humidity and temperature. High skin temperature and increased blood flow to the skin in hot weather may contribute to increased dermal absorption via increased fluidity of stratum corneum lipids and accelerated diffusion rates (Clarys et al. 1998; Lee 2004; te Brake et al. 2012). Akomeah et al. (2004) found more than a ten-fold increase in penetration flux for methylparaben from 23-45°C. An approximate two-fold increase in flux was found for each 7-8°C rise.

The implications of increased skin absorption of toxic chemicals at elevated temperatures do not appear to have been the subject of systematic investigations but the issue is relevant for workers in hot environments.

Humans generally do not work naked, and thus another consideration is exposed skin locations, and in particular, task-related opportunities for contaminant loading on exposed skin. Fenske and Day (2005) pointed out that overalls generally do not include important areas such as the neck, face, head and hands, and therefore do not provide complete skin coverage. The hands are particularly important for skin absorption. Relatedly, when gloves are worn for hand protection, the skin is rendered insensitive to detect subtle glove breakthrough of chemicals, especially because it is not associated with immediate sensation which acts as a warning sign for exposure (Klingner & Boeniger 2002). Typically, workers

may experience problems after years of dermal exposure to toxic chemicals. Once the pesticides permeate through the gloves, the next stage will be skin absorption of the OPs which may result in local effects on the skin or systemic effects if absorbed (Dooms-Goossens, Garmyn & Degreef 1991; Rawson et al. 2005).

6.1.1 Dermal exposure to OPs at work

Dermal contact with OPs may occur for routine users i.e. agricultural workers during mixing, loading as described in Chapter 4, as well as to non-routine users i.e. ambulance workers attending accidental and intentional poisoning cases, as explained in Chapter 5. In addition, workers involved in manufacturing, formulation, transport, storage, harvesting, cleaning of OP containers for disposal are also at risk of exposure.

Skin exposure pathways

Exposure may occur as a result of splash or spill of formulated OPs that contain a high percentage of active ingredients, aerosol deposition from wind drift when spraying and contaminant transfer from re-entry into sprayed fields (Tielemans, Louwerse & de Cock 1999; Wolfe, Armstrong & Durham 1966). Residues on spraying equipment, PPE or treated surfaces after pesticide application may also contribute to dermal exposure of OPs to the workers. The problem of liquid splash of diluted pesticide on equipment may be underestimated once the water has evaporated – leaving a concentrated film of pesticide on the contaminated surface.

Touching the exterior of contaminated gloves during glove removal is almost unavoidable, and there have been studies showing that both inside and outside of the gloves may be

equally contaminated (Creely & Cherrie 2001; Garrod, Phillips & Pemberton 2001; Machera et al. 2003). Hands contaminated inside the gloves may have an intimate contact with the OPs, as much as using gloves contaminated on the inside that may create an occlusive condition. Occlusion has been proven to increase skin penetration of all substances especially hydrophilic substances, and therefore should be avoided (Hafeez & Maibach 2013a, 2013b; Idson 1971; Wester & Maibach 1983; Wurster & Kramer 1961).

In principle, non-use or incorrect use of gloves may exacerbate dermal exposure e.g. gloves are worn longer than recommended (reused), or cross contaminated (Edwards et al. 2007; Garrod, Phillips & Pemberton 2001).Finally, whether in concentrated formulations or in diluted from, OPs have the potential to be absorbed through skin (Kamanyire & Karalliedde 2004; Riviere 2006a).

6.1.2 Rationale and aims of study

Previous *in vitro* studies on the rate and extent of dermal absorption of OPs have focused on the effects of vehicles or surfactants (Clarys et al. 1998; Cooper, Merritt & Smith 1985; Moore et al. 2014a; Stoughton 1982), clothing (Moore et al. 2014b; te Brake et al. 2012), and personal products (te Brake et al. 2012). Variations of the skin were also studied; interspecies variation (Bartek, Labudde & Maibach 1972; Grissom, Brownie & Guthrje 1985; Reinfrath et al. 1984; te Brake et al. 2012), age of the donor (Shah et al. 1987; Wester et al. 1977) and anatomical site (Maibach et al. 1971; Shehata-Karam, Monteiro-Riviere & Guthrje 1988; Skinner & Kilgore 1982c).

The rationale for the study reported in this chapter is four-fold: (1) the need to understand the skin penetration of formulated OPs, and in particular for OPs of security concern; (2) the need to understand worst case scenarios where absorption is flux-limited rather than supply-limited; (3) the need to understand the influence of elevated temperature conditions; and (4) the need to understand the influence of concentration, within (2), i.e. whether or not the flux is proportional to dilution.

To date, there is little information on skin penetration of commercial formulated pesticides, as most studies are conducted using the active ingredients or the pure compounds (Riviere & Brooks 2011). The gap in knowledge is more critical for Chemicals of Security Concern, due to the health effects arising deliberate dermal exposure.

Although it has been reported by Cherrie and Robertson (1995) that the flux through the skin is determined by the concentration instead of the mass, many previous studies focused on the

skin loading i.e. quantity of material deposited on the workers' skin (mg/cm^2) (Semple 2004). Because dermal exposure is complicated, concentration is not the sole driving force and this has been demonstrated by faster absorption of aqueous solutions of 2-butoxyethanol compared to concentrated solutions (Patel, ten Berge & Cronin 2002).

Overall, the literature of the effects of concentration and temperature on skin penetration warrant further exploration (Chang, Brownie & Riviere 1994; Chang & Riviere 1991; Clarys et al. 1998; Moore et al. 2014a; Patel, ten Berge & Cronin 2002; Thongsinthusak, Ross & Dong 1999).

The aim of this chapter is to explore these variables in order to provide a better understanding of OP penetration through the skin. Outcomes from this study will be useful in developing risk assessment strategies to reduce effects of exposure, especially as this topic is fast becoming a challenging aspect of occupational hygiene.

6.2 A WORST CASE APPROACH

In the absence of robust models of dermal exposure, the precautionary principle dictates a conservative or 'worst case' approach. The design of experiments in this Chapter reflects this philosophy (Tielemans et al.2007).

Infinite dose conditions allow for a maximum rate of penetration of the test substance (per unit area of skin) to be obtained (EHC235 2006). This may be relevant for OPs occluded between glove and skin.

Skin was exposed for up to 8 hrs, and comparisons are made of cumulative penetration at 8 hrs. This duration is designed to represent a full shift, with no, or inappropriate skin protection.

The upper limit of temperature was deemed to be 37°C, as higher temperature may cause physical damage to skin. The highest concentration was deemed to be the concentrated OPs. Thus, the ranges of conditions were: room temperature to 37°C; application strength to full strength formulated OP, 0- 8 hour duration, infinite dose (Sections 3.3.5 and 3.3.7).

Materials and methods used in this study were detailed out in Section 3.3 of Chapter 3. Implicit in the choice of OPs was a variation in physiochemical properties, notably lipophilicity expressed as octanol-water partition coefficient (Section 3.3.2).

6.3 RESULTS

This section presents the outcomes of the *in vitro* skin testing using the four tested OPs in variable conditions. An assessment of skin integrity following 8-hour chemical challenge is presented in Section 6.3.1. This is followed by the outcomes of concentration of OPs (full strength and application strength) and exposure temperatures (room temperature; 23(±2)°C and 37°C) on skin penetration of OPs in Sections 6.3.2 and 6.3.3 respectively. Statistical comparisons are presented in Section 6.3.5. Comparisons of cumulative penetrations with acceptable daily intakes are presented and discussed in Section 6.3.6.

6.3.1 Skin integrity checks pre- and post-chemical challenge

Pre- and post-chemical challenge electrical impedance measurements were conducted in the Franz cells. It was found that the readings at the end of the 8-hour experiments were lower than the pre-exposure measurements, indicating somewhat reduced skin barrier performance. Reductions of electrical impedance were between 4.6 and 7.2 kΩ for omethoate, between 5.0 and 9.9 kΩ (mevinphos), between 2.0 and 8.3 kΩ (dichlorvos) and between 1.0 and 15.9 kΩ (diazinon). However, the post-challenge impedance measurements were still above the cut-off limit i.e 10 kΩ, as explained in Section 3.3.4. This, coupled with no physical evidence of damage, suggests that the skin was not significantly degraded during the 8-hour period.

6.3.2 Skin penetration of omethoate, mevinphos, dichlorvos and diazinon

The overall outcomes of *in vitro* skin penetration experiments are summarised in Table 6.1, i.e. breakthrough times, flux and cumulative penetration of formulated OPs for application strength and full strength at room temperature and 37°C

At the end of the 8-hour challenge, it was observed that the average maximum flux as well as cumulative penetration increased with increased concentration and temperature. Conversely, breakthrough time decreased with increased concentration and temperature. This is what is expected and applied for all four OPs.

Comparing individual OPs at specific conditions did not demonstrate consistent trends, except for breakthrough times. Dichlorvos recorded the shortest breakthrough times of 0.5 min (the shortest practical time interval) regardless of the variable conditions, whilst omethoate and mevinphos had the longest breakthrough times. Breakthrough times tended to decrease with increased lipophilicity. Surprisingly, the highest cumulative penetration was observed for omethoate and mevinphos at full strength at elevated temperature.

Table 6.1 Summary of the outcomes of the *in vitro* skin studies on four OPs of full strength and application strength at two exposure temperatures for 8-hour challenge

Exposure temperature	**Concentration of OPs applied to skin**					
			Omethoate ($\log K_{ow} = -0.74$)	**Mevinphos** ($\log K_{ow} = 0.13$)	**Dichlorvos** ($\log K_{ow} = 1.16$)	**Diazinon** ($\log K_{ow} = 3.81$)
Room temperature (23±2°C)	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	Breakthrough time (mins)	15	10	0.5	1
		Average maximum flux (µg/cm^2/min)	0.2 (± 0.1)	0.003 (±0.0002)	0.6 (±0.1)	0.2
		Average cumulative penetration (mg)	0.025 (± 0.004)	0.00025 (±0.00002)	0.084 (±0.01)	0.033 (±0.004)
	Full Strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) • 804 mg/mL (diazinon)	Breakthrough time (mins)	6	2	0.5	0.5
		Average maximum flux (µg/cm^2/min)	4.9 (±1.7)	7.0 (±5.1)	9.8 (±2.4)	1.7*
		Average cumulative penetration (mg)	0.84 (±0.12)	0.21 (±0.005)	1.54 (±0.077)	0.23*
37°C	Application strength • 0.6 mg/mL (omethoate) • 0.7 mg/mL (mevinphos) • 6 mg/mL (dichlorvos) • 0.5 mg/mL (diazinon)	Breakthrough time (mins)	8	8	0.5	0.5
		Average maximum flux (µg/cm^2/min)	0.5 (±0.3)	0.013 (±0.006)	0.9 (±0.1)	0.9 (±1.1)
		Average cumulative penetration (mg)	0.043 (±0.003)	0.0014 (±0.00003)	0.114 (±0.001)	0.053 (±0.003)
	Full Strength • 814 mg/mL (omethoate) • 1,110 mg/mL (mevinphos) • 1,398 mg/mL (dichlorvos) 804 mg/mL (diazinon)	Breakthrough time (mins)	4	0.5	0.5	0.5
		Average maximum flux (µg/cm^2/min)	537 (±170)	280 (±110)	28.7*	3,895*
		Average cumulative penetration (mg)	45.8 (±5.8)	24.3 (±1.2)	4.2*	4.2*

Notes:
Figures in brackets are standard deviations, replicates, n≤ 7
Sampling times at 0.5, 1, 2, 4, 6, 8, 10, 15 and 30 mins, and hourly from one to 8 hrs
Cumulative penetrations presented are for the amount calculated at the end of the 8-hour test period
Breakthrough time denotes time when OP penetration was detectable in the receptor fluid, based on 0.01 µg/mL limit of detection for all four OPs.
*Values shown are for a single experiment (without replicate).

6.3.3 Effects of concentration of OPs on skin penetration

Application strength OPs

Figure 6.1 plots the cumulative penetrations of application strength formulated OPs through the skin over the 8-hour exposure duration, and complement the data in Table 6.1. The graph on top is for OPs exposed at room temperature and the bottom graph shows the OP penetration at elevated temperatures (37°C). Dichlorvos shows the greatest penetration with time. Across the four OPs, the 8-hour cumulative penetrations appear to increase by 36% (dichlorvos) to 560% (mevinphos) as temperature is elevated.

Full strength OPs

Figure 6.2 plots the cumulative penetrations of full strength formulated OPs through the skin over the 8-hour exposure duration, and complement the data in Table 6.1. The graph on top is for OPs exposed at room temperature and the bottom graph shows the OP penetration at elevated temperatures (37°C). Across the four OPs, the 8-hour cumulative penetrations appear to increase by 270% (dichlorvos) to 11,570% (mevinphos) as temperature is elevated. In other words, the effect of temperature on the cumulative penetration of full strength pesticide is more marked than the effect of temperature on application strength pesticide. This effect is strongest for mevinphos, and least for dichlorvos for both application and full strength.

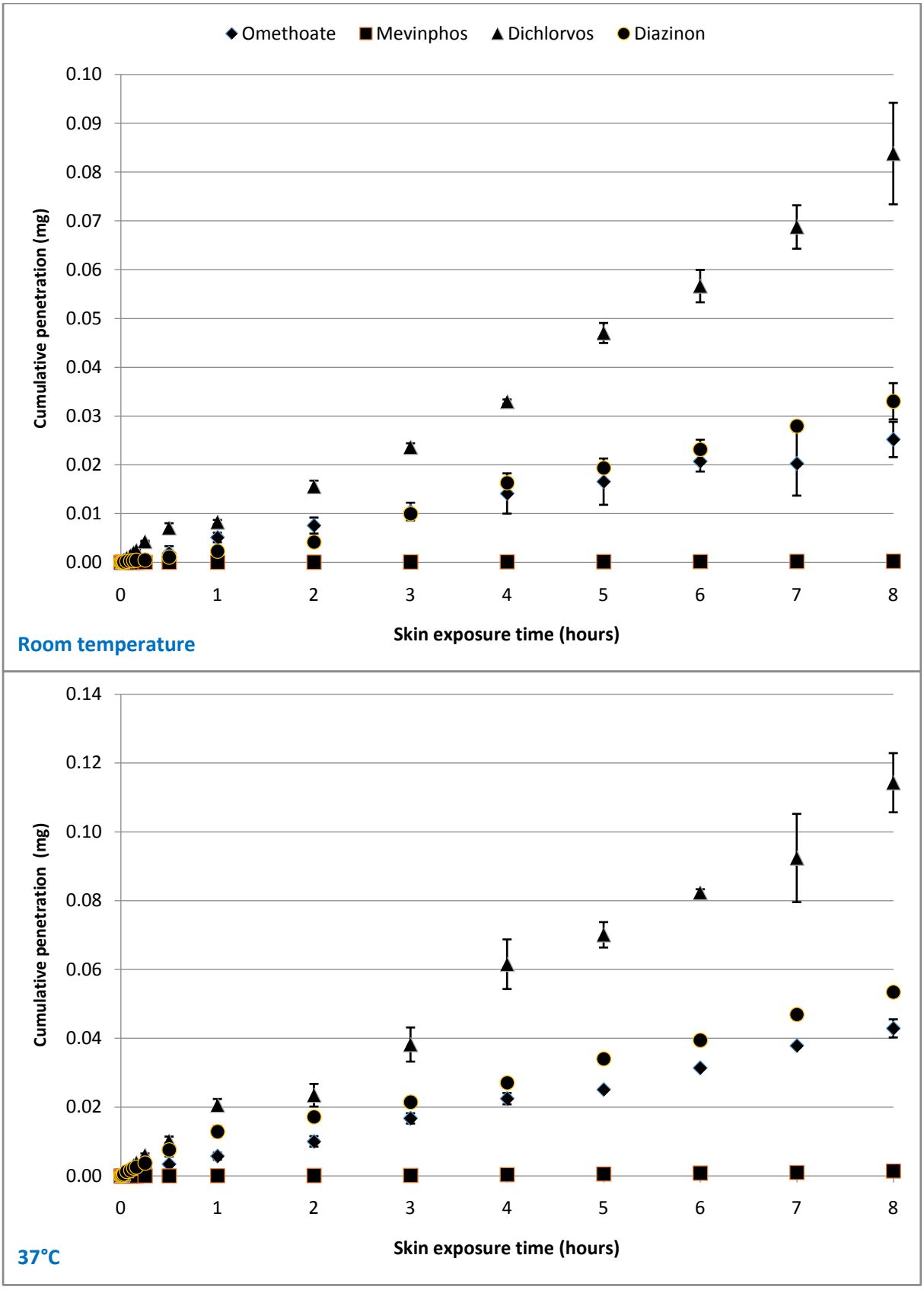


Figure 6.1 Cumulative penetration of application strength OPs (mg) through human skin at room temperature (top) and 37°C (bottom).

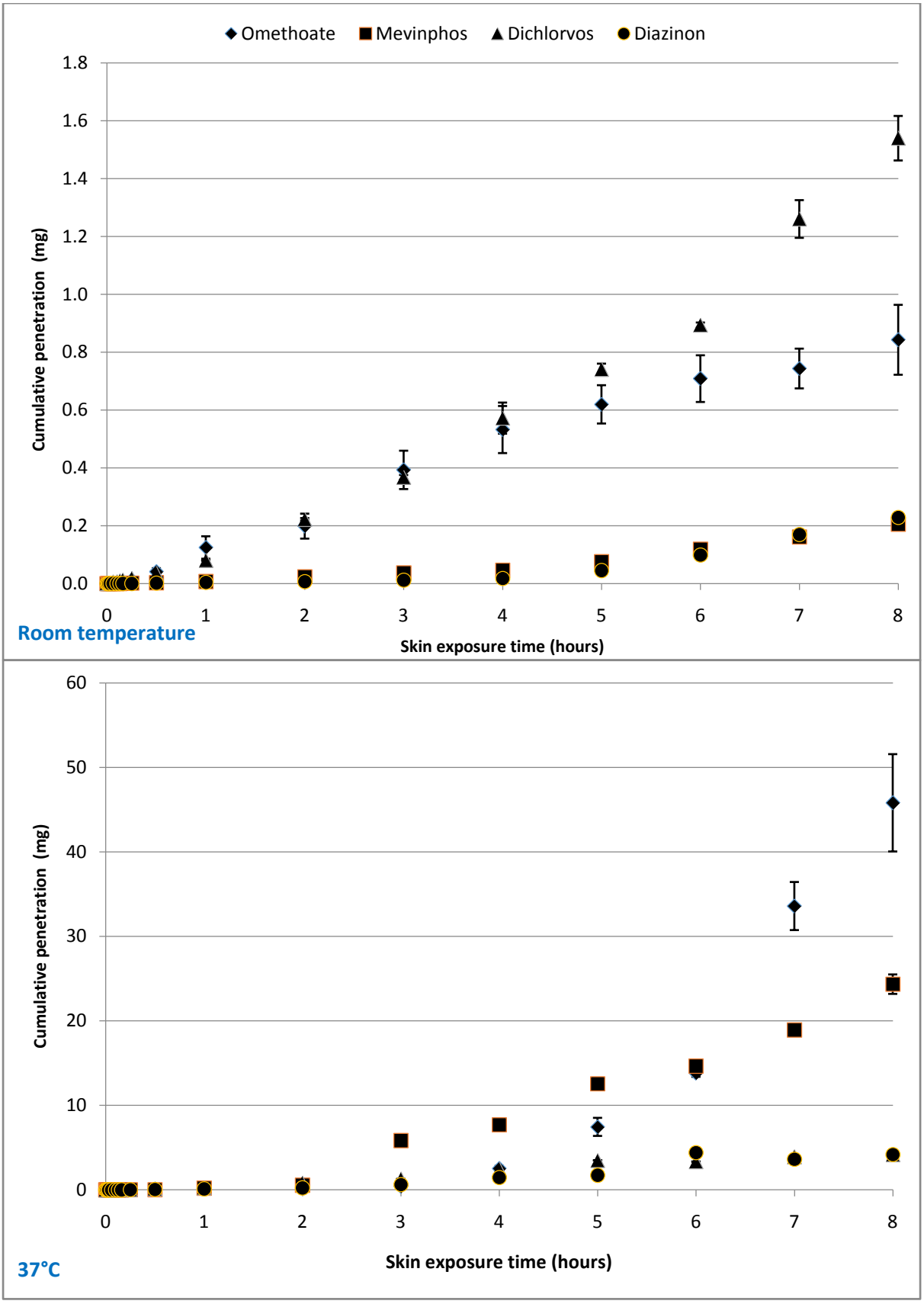


Figure 6.2 Cumulative penetration of full strength OPs (mg) through human skin at room temperature (top) and 37°C (bottom).

Breakthrough times for the four formulated OPs in warmer conditions were shortened to approximately half of the times recorded at room temperature.

A graphical representation of the cumulative penetration of OPs through the skin at room temperature (top) and 37°C (bottom) is given in Figure 6.3, in parallel with the results in Table 6.1.

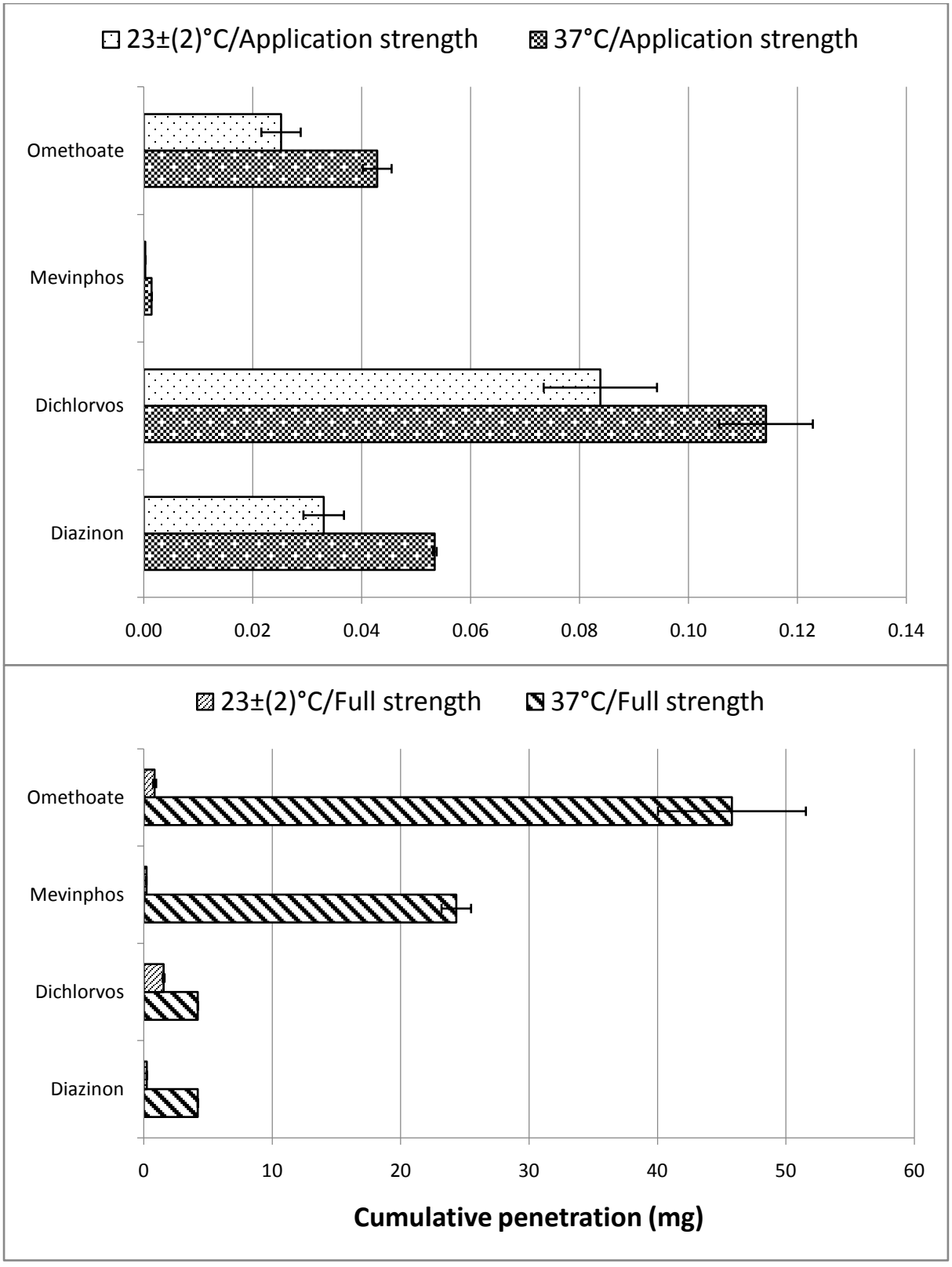


Figure 6.3 Comparison of cumulative penetration of OPs (mg) at application strength and full strength through human skin at room temperature (top) and 37°C (bottom).

6.3.4 Effects of exposure temperature on skin penetration

Despite temperature being an important factor in skin penetration, the largest changes were observed when going from application strength to full strength.

For omethoate (1,356-fold dilution), these were 33 (room temp) and 1065 (37°C); for mevinphos (1,585-fold dilution), 840 and 17,357; for dichlorvos (233-fold dilution) 18 and 37; for diazinon (1,340-fold dilution), 7 and 79. By comparison, the biggest effect for temperature was 115.7-fold in the case of mevinphos.

From a practical perspective, the primary emphasis should remain on preventing exposure to the concentrate.

6.3.5 Statistical tests

Owing to limitations with experimental apparatus, chemicals, availability of human skin and other factors, there was a variable number of replicates. It was not feasible to undertake tests of normality.

The null hypotheses were that there was no effect of concentrations or temperature; and that there was no difference in cumulative penetration between pesticides.

Within OPs – The effect of concentration and temperature

Two-way ANOVA and Bonferroni's multi comparisons test was undertaken. These showed statistically significant concentration and temperature effects for all four OPs ($p<0.0001$).

Between OPs

A one-way ANOVA with Tukey's multi comparisons test and Kruskal-Wallis test with Dunn's multi comparisons test were undertaken.

Comparing OPs at application strength at room temperature, it was found that all OP pairs were significantly different ($p<0.0001$) except for omethoate and diazinon. This was also shown for 37°C. There were insufficient data to use this test for full strength pesticides, although inspection of the relevant cumulative penetration data in Table 6.1 suggests significant differences, albeit with different pairs, depending on temperature.

Using the Kruskal-Wallis test, the following pairs were significantly different ($p<0.0001$) at room temperature, and application strength: omethoate/dichlorvos; mevinphos/dichlorvos and mevinphos/diazinon. At 37°C, only the mevinphos/dichlorvos pair was significant ($p = 0.0002$). There were insufficient data to use this test for full strength pesticides.

Overall, and in answer to **Research Question 7**, it is evident that there are significant differences between the formulated OPs in this infinite dose challenge arrangement. It is clear from Figures 6.1 - 6.3, that there are appreciable differences in cumulative penetration outcomes of different formulated OPs, particularly when compared against dichlorvos.

The cumulative penetration outcomes summarised in Table 6.1 and statistical analysis are also evidences showing the effects of OP concentration and temperature on skin penetration. In answer to **Research Question 8**, increased OP concentration and temperature significantly increased skin penetration.

6.3.6 Comparison of skin penetration outcomes with Acceptable Daily Intakes (ADIs)

Occupational exposure limits have not been set for dermal exposure. In addition, the OPs studied here do not have parent compound biological limit values.

The significance of the skin penetration data can be understood by comparison with Acceptable Daily Intakes (ADIs). This is done using a worst case scenario where workers' hands (or hands and forearms) are immersed in the pesticide for variable time periods.

Based on WHO (1986), the surface area of hands is 800 cm^2 and forearms 1,200 cm^2, which totals up to 2,000 cm^2 for the surface area of skin potentially exposed if the recommended elbow-length gloves are not worn by OP handlers.

The ADIs for the tested OPs in the present study are 0.0004 mg/kg b.w (omethoate), 0.002 mg/kg b.w (mevinphos) and 0.001 mg/kg b.w (dichlorvos and diazinon) (Department of Health Australia 2015).

Utilising time series data in Figures 6.1 and 6.2, Table 6.2 shows that the respective ADIs were exceeded in minutes to hours for a 70 kg person. There did not appear to be a safe time period for dichlorvos, at application or full strength.

Immersion of hands in any of the full strength OPs at 37°C exceeded the ADIs in less than 4 minutes.

In general, the ‘allowable times’ for application strength OPs were longer than for full strength OPs. In addition, at 37°C, allowable times were shorter. The estimated times for exposure were shorter for hands and forearms compared to hands only due to the larger surface area available for penetration.

Finally, in answer to **Research Question 9**, it is evident that the ADIs can be exceeded with relatively short exposures to unprotected hands. This is especially true for dichlorvos, in which ADI exceedance may occur as soon as in the first 0.5 min of exposure.

Table 6.2 Estimated time to exceed ADI for a 70-kg human with corresponding calculated cumulative penetration for hands only and hands and forearms for the four tested OPs in various exposure conditions (application strength, and full strength, at 23°C and 37°C) and the level of ADI exceedance.

OPs		**Omethoate**				**Mevinphos**				**Dichlorvos**				**Diazinon**			
		ADI 0.0004 mg/kg b.w, for 70 kg = 0.028 mg				ADI 0.002 mg/kg b.w, for 70 kg = 0.14 mg				ADI 0.001 mg/kg b.w, for 70 kg = 0.07 mg				ADI 0.001 mg/kg b.w, for 70 kg = 0.07 mg			
Test conditions		**23(±2)°C, A.S**	**37°C, A.S**	**23(±2)°C, F.S**	**37°C, F.S**	**23(±2)°C, A.S**	**37°C, A.S**	**23(±2)°C, F.S**	**37°C, F.S**	**23(±2)°C, A.S**	**37°C, A.S**	**23(±2)°C, F.S**	**37°C, F.S**	**23(±2)°C, A.S**	**37°C, A.S**	**23(±2)°C, F.S**	**37°C, F.S**
HANDS ONLY*	Estimated time to exceed ADI	10-15 min	6-8 min	4-6 min	2-4 min	3-4 hrs	1-2 hrs	4-6 mins	0 - 0.5 min	0 - 0.5 min	0 - 0.5 min	0 - 0.5 min	0 - 0.5 min	1-2 mins	0.5 -1 min	0-0.5 min	0-0.5 min
	Calculated cumulative penetration (mg)	0.195	0.529	1.409	1.348	0.163	0.177	0.186	0.357	0.270	0.358	1.069	0.970	0.119	0.132	0.082	0.391
	Exceedance factor	7.0	19	50	50	1.5	1.1	1.3	2.5	3.9	5.1	15	14	1.7	1.9	1.2	5.6
HANDS AND FOREARMS**	Estimated time to exceed ADI	10-15 min	6-8 min	4-6 min	2-4 min	1-2 hrs	20 – 30 mins	2-4 mins	0 - 0.5 min	0 - 0.5 min	0 - 0.5 min	0 - 0.5 min	0 - 0.5 min	0.5 -1 min	0 - 0.5 min	0 - 0.5 min	0 - 0.5 min
	Calculated cumulative penetration (mg)	0.488	1.324	3.524	3.492	0.147	0.153	0.172	0.892	0.675	0.895	2.672	2.424	0.147	0.419	0.204	0.978
	Exceedance factor	17	47	126	125	1.1	1.1	1.2	6.4	10	13	38	35	2.1	6.0	2.9	14.0

Note:
A.S denotes OPs in application strength, F.S denotes OPs in full strength
Time noted is the first time it exceeds the ADI. The first sample was taken at 0.5 min, followed by 1, 2, 4, 6, 8, 10, 15, 30 mins and hourly thereafter for up to 8 hours.
Calculated cumulative penetration is the corresponding cumulative penetration at the time noted for hands only and hands and forearms
*Surface area for hands only is 800 cm^2
** Surface area for hands and forearms is 2,000 cm^2

6.4 DISCUSSION

In this section, the major findings of the skin experiments are firstly considered in the light of existing literature. Secondly the strengths and weaknesses of the experimentation are outlined.

6.4.1 Major findings

Comparability between OPs

At the end of the 8-hour experiments, cumulative penetration of formulated OPs, average maximum flux and breakthrough time varied with different OPs **(Research Question 7)**. Dichlorvos showed a tendency to penetrate the skin quicker and to a greater extent, compared to the other three OPs. This may be due to its application strength of 6 g/L whereas application concentrations for the other three formulated OPs were between 0.5 to 0.7 g/L. It also had (marginally) the highest full strength (1,398 g/L), the second lowest molecular weight, the lowest molecular volume of 156 cubic angstroms and the lowest molecular polar surface area (Table 2.4).

The log octanol-water partition coefficient (log K_{ow}) has been reported as ranging from 1.2-1.5 (ATSDR 1997) making it moderately lipophilic. Substances with both hydrophilic and lipophilic characters and of small molecular size have the tendency to penetrate the skin rapidly and this is in agreement with Fick's law (Grandjean 1990, Friberg & Larsson 1975; Paranjape et al. 2014) and diffusion in intercellular lipids (Anissimov et al. 2013), as in Figure 6.4. The skin penetration outcomes for dichlorvos are in good agreement with

previous studies that showed optimal skin penetration of substances having a log K_{ow} around 2 (Cross et al. 2003; Morgan, Renwick, & Friedmann 2003).

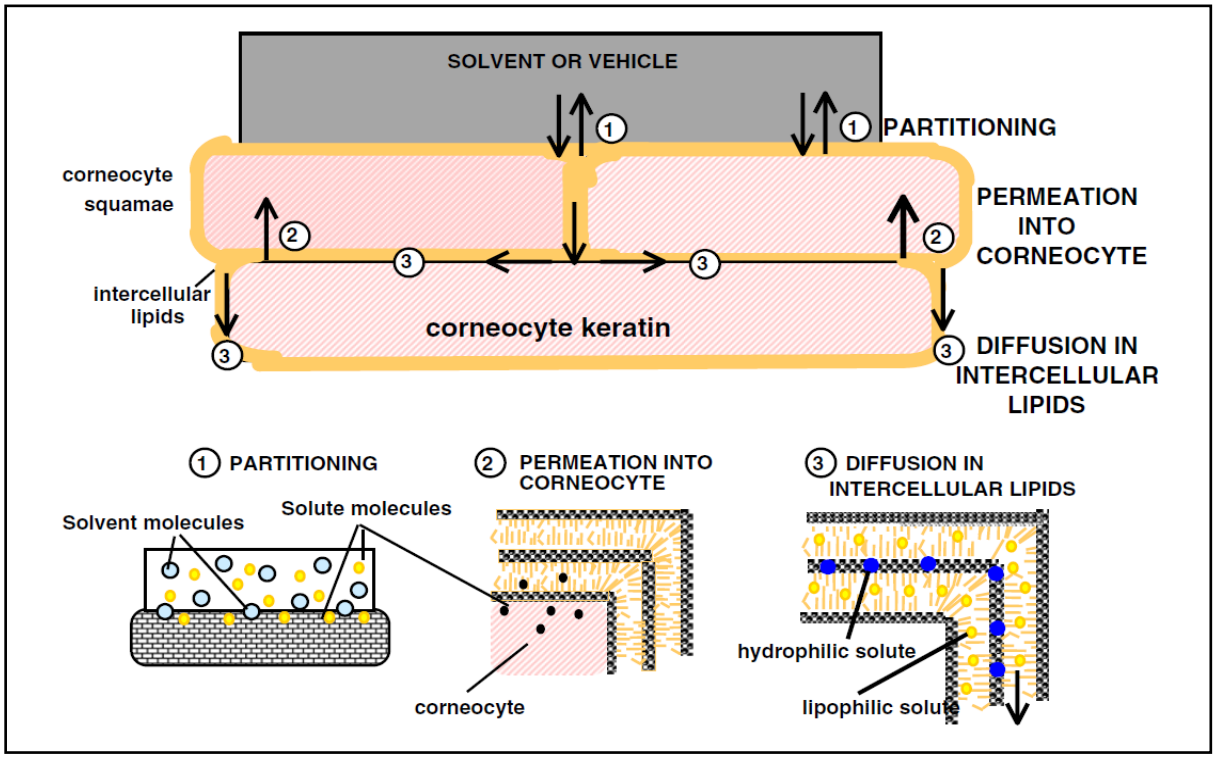


Figure 6.4 Intercellular and transcellular routes of chemical penetration through the 'brick and mortar' structure of the upper skin
Source: Anissimov et al. (2013)

This finding is potentially significant in that dichlorvos is present in approximately 15 registered products in Australia (Immig 2010). Dichlorvos has been classified by the International Agency for Research on Cancer as a group 2B human carcinogen – possibly carcinogenic, based on animal studies that showed increased rates of leukemia and forestomach and pancreatic tumours in rats, and increased esophageal and forestomach tumours in mice following exposure (WHO 2009). However, an analysis of the Agricultural Health Study cohort data in the U.S did not find elevated cancer rates in pesticide applicators

exposed to dichlorvos (Koutros et al. 2008).Nevertheless, with such short time for breakthrough and ADI exceedance, the correct type of gloves should be worn when handling dichlorvos to avoid skin contact and subsequent skin penetration.

Formulated diazinon demonstrated average cumulative penetration relatively comparable to that of dichlorvos. Lipophilic compounds like diazinon (log K_{ow} 3.81) may diffuse readily through the skin membranes as suggested by Goodfellow & Tahti (2001). The high log K_{ow} and high molecular volume (273.1) indicates the possibility of diazinon to favour uptake into the stratum corneum (Gibson 2009), hence affecting the penetration of diazinon in all test conditions, compared to the other three OPs.

The effect of additives in formulated OPs

Notwithstanding the physicochemical properties of the individual OPs, the formulated OPs (omethoate, mevinphos and diazinon) contained other substances e.g. hydrocarbon liquids that may accelerate penetration of OPs through the skin. Nielsen and Andersen (2001) demonstrated increased penetration of pesticides of various solubilities and enhanced delivery of active ingredients in the presence of nonylphenolethoxylate. Carrier solvents, in general, have been reported to accelerate OP penetration through the skin (Riviere 2006a; Riviere 2006b; Riviere & Brooks 2005; Sartorelli et al. 1997; USEPA 2007). These carrier solvents are packed in various ratios for different OP products.

In the present study, the reason for greater penetration of OPs containing a high concentration (full strength) of OPs could be partly due to the solvent effect of carrier solvents that disrupts the protective layer and increases partitioning into the stratum corneum, as suggested by Anderson & Meade (2014) and Baynes et al. (1998). Therefore, the higher the concentration

of the tested OPs, the higher the concentration of carrier solvent is, and greater cumulative penetration, as previously demonstrated for several pesticide formulations (Buist et al. 2007; Liu & Kim 2003).

The effects of OP concentration on skin penetration

This study demonstrated that the change of OP concentration from application strength to full strength accelerated penetration of omethoate, mevinphos, dichlorvos and diazinon through the skin **(Research Question 8).**

Cherrie, Semple and Brouwer (2004) showed that in general, uptake of undiluted chemicals will be faster than in dilute form, due to the large concentration difference between the skin layer and the blood supply. It has also been reported that the concentration of a substance on the skin has greater effects on skin uptake than mass of the substance (Cherrie & Robertson 1995).

The finding of increased penetration with increased concentration is also consistent with a study by Moody, Nadeau & Chu (1995), where lower skin absorption was reported for decreased doses N, N-diethyl-m-toluamide (DEET).

Moore et al. (2014a) reported a 10-fold increase in skin absorption and maximum flux when the applied concentration of infinite dose dichlorvos was increased from 1 mg/mL to 10 mg/mL. The trend of greater absorption for higher concentration is also supported by a work by Thongsinthusak, Ross & Dong (1999). Thongsinthusak and colleagues found that dichlorvos and three other pesticides (captan, hydrogen cyanamide and metam-sodium) in an *in vivo* study followed the pattern of higher percentage of absorption (9.8, 12.7 and 12.9 %) through the skin with increased dose (0.3, 3 and 30 μg/cm^2). Interestingly, the same study

demonstrated that the other 15 pesticides showed an inversely proportional relationship (Thongsinthusak, Ross & Dong 1999). This reverse trend (greater dermal absorption for low concentrations) was also reported on various pesticides, herbicides, benzoic acid and hydrocortisone (Chang & Riviere 1991; Feldmann & Maibach 1974a; Feldmann & Maibach 1974b; Wester & Maibach 1976).

This indicates that there is not a proportional relationship between applied concentration and skin penetration. In other words, low concentration of OPs does not necessarily mean low skin penetration, and vice versa (Edwards et al. 2007). Therefore, when evaluating product safety, users should not conclude that it is safer to use the formulations of lower concentrations and disregard safety precautions.

The effects of exposure temperature on skin penetration

This present study revealed that elevated temperature enhanced skin penetration of omethoate, mevinphos, dichlorvos and diazinon **(Research Question 8).**

Similar trend of increased skin penetration with elevated temperature was reported in a study on parathion despite several experimental differences (Chang, Brownie & Riviere 1994; Chang & Riviere 1991). Dermatomed porcine skin samples (thickness 0.5 mm) were used by Chang, Brownie & Riviere (1994) and Chang & Riviere (1991) with the temperature increased from 37°C to 42°C.

Greater skin absorption and penetration has also been reported for [S-{2-di-isopropylaminoethyl) o-ethyl methylphosphonothioate], an anticholinesterase liquid of low volatility known as VX in an *in vivo* study, due to increased temperature (Craig, Cummings

& Sim 1977). Although the *in vivo* study covered a wide temperature range i.e. from -18°C to 46°C and did not show whether the increase was due to weakened epidermal barrier function, it demonstrated the relationship between elevated temperature and skin uptake.

It has been argued that increased temperature may change the stratum corneumlipid fluidity or corneal hydration and thereby affecting the function of the epidermal layer (Chang, Brownie & Riviere 1994; Chang & Riviere 1991; Akomeahet al. 2004).

High temperature is also associated with the extent of skin hydration, hence affecting skin uptake (Bowman & Maibach 2000; Chang & Riviere 1991; Schafer et al. 2002; Vanakoski et al. 1996; Wiechers 1989). This present study was conducted by mimicking full hydration of the skin, therefore in the context where the target populations e.g. agricultural workers, ambulance workers and OP-related workers, may be exposed to these formulated OPs in warmer conditions i.e. 37°C with heavy sweating, penetration of OPs through the skin may be accelerated.

It may be sensible to infer that when assessing skin penetration of OPs, the factors tested (OP concentration and temperature) are notindependent variables and must be considered synergistic and interactive (Chang, Brownie & Riviere 1994). There also exist a complex relationship between lipophilicity of test compound, skin thickness and skin penetration, as noted by Wilkinson et al. (2006), Therefore, risk assessment calculations on skin uptake should take all the factors into consideration.It should also be noted that extrapolating the outcomes of the present study to other OP compounds should only be made with caution, as there exist many variabilities that affect skin penetration.

Comparison of Omethoate results with published data

The skin penetration studies were designed to be flux-driven rather than supply-driven, and involved excess quantities of challenge liquid in contact with skin. The chemical concentration at the challenge interface was not depleted, and the scenario is equivalent to immersing hands in pesticide.

The majority of skin penetration studies use finite doses and pure chemicals dissolved in vehicle, and so penetration data are not directly comparable. The use of finite doses facilitates mass balance calculations, but the purpose of this study was to assess worst case uptake kinetics and uptake through the skin, with formulate products.

For omethoate, Sartorelli et al. (1998) reported a longer breakthrough time of 58.8 (±33.6) minutes at a skin temperature of 32°C, and using saline/gentamycin sulphate and bovine serum albumin as receptor fluid. Apart from temperature and receptor fluid composition, the longer breakthrough time may be attributed to the differences in the detection methodology and the source/nature of skin, in which full thickness monkey skin was used by Sartorelli and colleagues, whereas epidermal layer of human skin was used in the present study. Although the behaviours of monkey skin is close to human skin with regards to skin absorption (Wester & Maibach 1985; Wester et al. 1977; Wester & Noonan 1980), there were arguments on the reliability of interpreting skin absorption data on animals for human risk assessment due to the differences in species (Korinth et al. 2007; Marks & Plewig 1991). Some interspecies differences could be partially due to differences in the site of application, concentration, effects of shaving of the skin and experimental conditions (Grandjean 1990). In addition, the interspecies differences have not been uniform with the few substances studied (Wester

&Maibach 1985a; Wester & Noonan 1980). Variable ability of chemicals to penetrate human skin has also been reported compared with other animal models (Bronaugh, Stewart & Congdon 1982; Dugard & Walker 1983). Thus, until the models used are further validated, experimental animal data should be carefully interpreted and the use of human skin is considered as the best option for comparison to human exposure.

In addition, Sartorelli et al. (1998) did not report the origin of omethoate used their study, whereas formulated omethoate which contains a glycol ether i.e. PGMEA as the carrier solvent was used in the present study which may have high skin penetration capacity (Nielsen et al. 2000; Venier et al. 2004).

Comparison of Mevinphos results with published data

No comparable data are available in the literature.

Comparison of Dichlorvos results with published data

Skin penetration of dichlorvos in the present study may be compared with the work by Moore (2010). He reported breakthrough time at approximately 36 mins (0.6 (±0.1) hr) for a 10 mg/mL dose of dichlorvos in isopropyl alcohol, accumulating approximately 6 mg/cm^2, and 24 mins (0.4 (±0.2) hr) for the lower dose (1 mg/mL). In contrast, the present study using infinite dose dichlorvos (6 mg/mL) showed penetration as early as at 0.5 min.

Moore (2010) used dermatomed breast skin whereas the present study used abdominal epidermal skin. These differences suggest variation in thickness, follicles, sebum composition and the distance of capillaries to the surface of the skin (Rougier et al. 1999). Moore (2010)

also pointed out that the use of different skin thicknesses may produce differing absorption, depending on the test compound.

Comparison of Diazinon results with published data

As for skin studies using diazinon, the outcomes of the present study may be compared with the work by te Brake et al. (2012). While the average maximum flux for the application strength diazinon at room temperature in this study was 0.2 µg/cm^2/min, te Brake et al. (2012) reported a much lower flux of 0.004 ±0.002 µg/cm^2/min and a lag time of up to 418 minutes for human skin at room temperature. In the te Brake study, the applied quantity was 10 micrograms. In the present study the mass available for application strength was at least 50 micrograms.

Increased temperature decreased the breakthrough time in both studies. In the study by te Brake (2012), it was also shown that pig skin demonstrated an increased penetration and flux with increased temperature. However, human skin did not show significant effects.

In this case the nature of the skin is unlikely to explain the differences. Although the skin samples in the present study were obtained from three different donors (35 to 58 years old), they were all Caucasians and the samples were from the abdomen. Epidermal skin was used instead of full thickness skin to minimise the variation and it has been shown to retain the major barrier function for skin penetration (Benford et al. 1999; Craig et al. 1977). The same type of skin, receptor fluid was used for both the te Brake and the present study.

6.4.2 Strengths and weaknesses

The use of formulated OPs is both a strength and weakness. On one hand, the formulated products are used in practice. On the other hand, results for full strength products may not be generalisable. That said, the effects of additives are much reduced at application strength and so the data for application strength should be generalisable in a worst case framework.

The comparisons across pesticides of deliberately different physicochemical properties allows for some generalisability. In this regard, significant differences were noted which suggests that it is not feasible to generalise the data. However, in the case of dichlorvos, there is some theoretical rationalisation of the observed behaviour.

The experiments at 37°C illustrate important variations, and are relevant for hot conditions, as might be experienced in many parts of Australia.

This was an exploratory study, and with only two concentrations and temperatures being examined. In addition, there was no independent evaluation of the additives/solvents in the full strength formulated product. Further research is warranted at intermediate concentrations and temperatures. The effects of additives should also be systematically examined.

It is tempting to suggest that the experimental model here approximates the situation where chemicals are occluded between glove and skin. Further research could be undertaken, whereby a glove swatch could be layered on top of the pesticide.

6.5 CONCLUSIONS

Based on the research questions listed at the beginning of this chapter, two conclusions may be drawn. Firstly, it appears that penetration of the four formulated OPs through human skin varies depending on the OP, especially in the full strength formulation, where behaviour is likely to be confounded by additives. Secondly, the data show that unprotected handling of concentrated OP formulations in hot conditions will result in OPs penetrating the skin faster and in greater amount. However, regardless of the OPs, the ADI comparisons indicate that toxicologically significant skin penetration can occur rapidly (CDC, 2014).

CHAPTER 7

GENERAL DISCUSSION

The main aim of this research was to achieve better understanding of the dermal exposure of OPs under various conditions and the information generated will be used for strategising better control measures to minimise dermal risk from OPs. In order to achieve this, ASTM permeation test cells were used to test gloves commonly used by agricultural workers for handling OPs and disposable gloves worn by ambulance workers. The influence of different exposure scenarios, including high and low concentrations of OPs, normal room temperature and higher temperature, UV exposure and abrasion on glove performance were studied. For an understanding of skin penetration, human skin was challenged in static Franz diffusion cells to investigate the effects of physicochemical properties and concentration of OPs as well as elevated temperature on dermal penetration.

The information obtained from the studies should be useful for improving the currently available predictive dermal risk assessment models as well as for informing *in vivo* dermal studies of OPs, as described by Williams (2006).

7.1 NOVELTY OF THE RESEARCH

This research adds significantly to the currently limited literature, and responds to calls for a more systematic approach to dermal exposure investigations (Nielsen and Sorensen 2012). It explores various modifying factors relating to permeation through gloves and penetration through the skin (Boeniger 2003; Boeniger & Klingner 2002; Cherrie, Semple & Brouwer 2004; Klingner & Boeniger 2002; Packham 2006; Semple 2004). It appears to be the only research which has combined skin and glove investigations, with a comparison of OPs.

Nielsen and Sorensen (2012) combined skin and glove investigations but used benzoic acid as a model penetrant. They were able to demonstrate that glove permeation was the rate limiting step, rather than skin penetration.

The work presented in this thesis is novel for several reasons.

Real world scenarios are used

The laboratory experimentation simulates the worst case of what is being practised in the real world, particularly in Australian settings. In particular, and unlike most glove permeation and skin penetration studies where testing is done on pure OP chemicals, the studies in this research used formulated OP products that are commercially available in the market. All tests were performed in infinite dose to simulate the worst case exposure scenario in situations like spills and splashes, as well as to provide information useful for modelling of exposure and estimating maximum penetration rates of OPs for health risk assessment (Howes et al. 1996; OECD 2004a).

Comparisons across OPs with different physicochemical properties are made

Four OPs namely omethoate, mevinphos, dichlorvos and diazinon were selected for the glove permeation and *in vitro* skin studies and they represent a range of physicochemical properties e.g. octanol-water partition coefficient (log K_{ow}), solubility, molecular polar surface area, molecular weight and molecular volume.

Chemicals of Security Concern are addressed

These OPs are categorised as Chemicals of Security Concerns by the Council of Australian Government and are listed for priority review under Australia's Chemicals Review Program.

This is the first study looking at Chemicals of Security Concern in Australia, and will be of interest to security agencies nationally and internationally.

Comparisons of disposable and non-disposable gloves under various conditions are made

Preliminary field observations (Chapter 4) conducted at four farms in Virginia, South Australia found that agricultural workers use one type of glove for all pesticide-related tasks; for mixing and loading high concentration (full strength) of pesticides, as well as for spraying low concentration (application strength) of pesticides. These include PVC gloves, which were reported as commonly used by farmers (Canning 1997). Thus, two types of elbow length PVC gloves from different brands and manufacturers were tested under a variety of conditions.

In addition, disposable nitrile and neoprene gloves used by South Australia Ambulance Service workers for attending to OP poisoning and accident cases were tested under similar conditions as the PVC gloves. They were tested individually as well as in combination (nitrile on top of neoprene) to investigate the difference in permeation. This appears to be the first study looking at both disposable and non-disposable gloves, for OPs.

7.2 MAJOR FINDINGS OF THE STUDIES

7.2.1 Real world protection provided by gloves

PVC gloves used by agricultural workers

PVC gloves are recommended in safety data sheets for handling OPs but glove brands and permeation data are typically not specified (see Table 2.3)[3]. It seems unlikely that manufacturers of the (cheap) PVC gloves would have commissioned permeation (or other performance) testing for formulated OPs, either with application strength or full strength. Rather, the recommendation for PVC gloves seems to be based on generic data and various assumptions (such as thickness and durability). Interestingly, the Ansell Glove Permeation Guide (2014) suggests that PVC gloves are suitable for aqueous solutions (including dilute acids and alkalis) but not hydrocarbons. Thus, the recommendation of PVC for OP concentrates appears to have no ready explanation.

Disposable nitrile and neoprene gloves used by ambulance workers

Similarly, for the two types of disposable gloves it is unclear whether there has been any formal permeation testing done by the manufacturers. It seems unlikely because the gloves are meant for single short term use.

Thus, downstream, it is evident that OP users and distributors are relying on generic information provided in the SDS, rather than the results of any specific permeation tests.

In other words, *caveat emptor*.

[3] The SDS for dichlorvos in Appendix 2.3 recommends chemical resistant gloves (preferably nitrile)

Sobering aspects of globe usability and user understanding have been described by Canning (1997), and unfortunately, this also seems to be the case from the preliminary field observations (Section 4.1.1).

7.2.1.1 The influence of concentration of OPs and exposure temperature on glove permeation

Influence of concentration

Outcomes from the present research demonstrate a strong relationship between permeation metrics (breakthrough times, flux rates and cumulative permeation) and OP concentration through all the gloves**.** The data support the findings in previous research with various substances at different concentrations (Ehntholt et al. 1990; Lee & Lin 2009). Nielsen and Sorensen (2012) examined benzoic acid and found the degree of protection offered by the thin nitrile and latex gloves was reduced at the high concentration. They argued that "this illustrates that a glove suitable for low dose exposure, during normal occupational use, may not be ideal for higher doses, e.g. during mixing and loading where undiluted chemicals are used. One explanation could be that the gloves act as temporary reservoir, but with a limited capacity"(page 90).

Influence of temperature

The effects of elevated temperature on gloves are consistent with other studies of various types of glove materials (Alexy & Buchan 1987; Evans, McAlinden & Griffin 2001; Perkins & You 1992; Zellers & Sulewski 1993; Vahdat &Bush 1993).

In addition, the effect of elevated temperatures was greatest for full strength OPs. This is evident in the ratios of cumulative penetration for application strength versus full strength, as temperture goes from 23 to 45°C. (Tables 4.1-2 and 5.1-3, especially for omethoate). This may be due to solvents and additives that are in much relative higher proportions in full strength compared with application.

Glove-chemical interactions

Different glove materials (and gloves) were found to offer different degrees of protection. These outcomes are in alignment with the concept of polarity and glove permeation as reported by Que-Hee (1996) in the liquid–liquid partition model, in which similar polarities of challenge chemical and the glove material will demonstrate rapid permeation.

The permeation resistance of the tested disposable gloves (Chapter 5) increased in combination (nitrile on top of neoprene gloves), compared to individual gloves. The thicker layer of gloves created when in combination (0.18) compared to individual thickness (0.07 mm nitrile gloves and 0.11 mm neoprene gloves) could be one of the factors that explains the longer breakthrough times of the OPs, as reported by Vo (2004). Although thicker gloves commonly reduce the effects of elevated temperature e.g. from hands or hot chemicals (Bromwich 2005), the present research demonstrated that performance of gloves did not solely depend on thickness of the gloves (Perkins & Pool 1997).

Therefore, it is insufficient to select gloves solely based on the type of materials or thickness

Implementing double gloving (combination of nitrile and neoprene gloves) as currently practised by South Australian ambulance workers seems to provide better protection than the

original suggestion of doubling neoprene gloves**.** This is explained by the wide range of chemical polarity covered by combination of two gloves of different materials, whereas the original suggestion of doubling neoprene gloves is not only slightly more costly but also seems to be limited to protection against polar chemicals only.

From a practical perspective, however, it is likely that ambulance worker exposure would be less than four hours, and both gloves removed and exchanged with new ones upon contact with the OPs. Workers would also be more likely to change gloves in hot weather due to discomfort from perspiration.

7.2.1.2 The influence of UV exposure and abrasion on glove permeation

Glove permeation studies in Chapter 4 showed somewhat shorter breakthrough times and greater average cumulative permeation of OPs with UV-exposed gloves and abraded gloves**.**

Raheel & Dai (2002) reported similar outcomes of material degradation, and higher permeation of two pesticide chemicals, that could occur due to repeated wear and laundering. Significant effects of compromised barrier integrity were also reported in controlled non-severe abraded conditions (Walsh et al. 2004). In real situations there is likely to be a combination of degradation factors e.g. gloves may be subjected to physical or chemical damage from reuse (abraded from previous use), dried under the sunlight (UV exposure), repeated flexing and stretching and poor storage conditions (Colligan & Horstman 1990; Nelson & Henry 2000; Nielsen & Sorensen 2012; Packham 2006; Perkins & Rainey 1997; Truscott & Stoessel 2001). These 'wear and tear' conditions can result in reduced thickness and degradation of materials, hence affecting the protective ability of the gloves (Evans,

McAlinden & Griffin 2001). As a result, reuse of UV-exposed and/or abraded gloves to save cost may lead to chronic dermal exposure.

7.2.2 Skin uptake at infinite dosing

7.2.2.1 Variability of skin penetration for different types of OPs

Preliminary observations (Section 4.3.1) conducted to contextualise the PVC glove permeation studies revealed that, despite recommendations, some farmers did not wear gloves when mixing, loading and spraying OPs. Among the common excuses reported are the gloves do not fit well, are uncomfortable, cause loss of dexterity, grip and tactile sensation when performing the tasks (Chang & Shih 2007; Drabek & Buffington 2010; Fry et al. 2010).

Without suitable hand protection, OPs in contact with the skin may be readily absorbed and carried by the blood and lymph systems to various organs, especially the nervous system (Luttrell, Jederberg & Still 2008). A splash or immersion of the hand in the liquid chemical may completely overwhelm the protective layer of the skin (Cherrie, Semple & Brouwer 2004) and rapidly exceed the ADI (Table 6.2).

However, it was found that at the end of the 8-hour experiments, cumulative penetration of OPs, average maximum flux and breakthrough times varied with different OPs.

Dichlorvos demonstrated the shortest breakthrough time (0.5 min) in all exposure conditions and, worryingly, is also classified as a possible carcinogen (B2) to humans with 54 registered products in Australia (Immig 2010; U.S. Environmental Protection Agency 1999; WHO 2009).

Another health concern is that concentrated forms of omethoate and mevinphos displayed very high cumulative penetrations at 37°C (Table 6.1). These two are the most hydrophilic (least lipophilic) of the four OPs. It has been argued that hydrophilic compounds will tend to penetrate the skin more readily at higher temperature than lipophilic compounds (Akomeah et al. 2004). This is thought to be because of a higher activation energy (greater steepness of the Arrhenius plot).

The data for omethoate and mevinphos support this argument. That said, the thermodynamics is complicated by parallel lipoidal and intracellular pathways (Figure 6.4).Relatedly, the size, shape and polarity of the molecule would be expected to influence kinetics.

Of the four OPs, dichlorvos had a tendency to penetrate the skin quicker and to a larger extent. As previously mentioned, dichlorvos has the second lowest molecular weight, the lowest molecular volume of 156 cubic angstroms and the lowest molecular polar surface area of 44 angstrom squared (Table 2.4). As such it presents itself as a compact molecule, with reduced steric hindrance.

The shorter breakthrough times of diazinon compared to omethoate in all variable conditions may be attributed to relative affinity for lipid phase (Mackay & Boethling 2000).

7.2.2.2 The influence of concentration of OPs and exposure temperature on skin penetration

As percutaneous absorption is a typically passive process, concentration of the OPs should play an important role in rate of absorption across the stratum corneum – that is, the diffusion from an area of high to low concentration over time will be greater when more molecules of a substance are available on the skin (Moore 2010). This may explain the outcomes from the present *in vitro* skin studies where breakthrough times were shorter, average maximum flux were higher and cumulative penetration were greater with increased concentration (full strength)**.** Concentrations of the full strength OPs in this study varied, but not greatly (804 – 1,398 mg/mL), and so this alone does not explain the variations observed across the OPs.
In addition, the magnitude of skin penetration was not proportional to the increase in concentration of OPs applied going from application strength to full strength (Moore et al. 2014a).

All four OPs in this study demonstrated significantly higher average maximum flux and greater cumulative penetration with shorter breakthrough times when the temperature was increased from 23 to 37°C. The exception was for dichlorvos which showed breakthrough at 0.5 min in all exposure conditions**.** It should be noted that 0.5 min was the shortest practical sampling time, and breakthrough might have occurred earlier.

The generic temperature dependence outcomes are in agreement with many previous studies that attributed the enhanced penetration of chemicals to increased thermodynamic activity in the lipid domain or alterations in the barrier function of the skin (Chang, Brownie & Riviere 1994; Clarys et al. 1998; Gay et al. 1994).

7.2.2.3 Other factors that might affect glove permeation and skin penetration of the tested OPs

While concentration of OPs and exposure temperature have been investigated in the present studies, glove permeation and skin penetration may be complex due to other factors e.g. carrier solvents, applied dose, OP mixtures and exposure pattern.

Carrier solvent(s) in the OPs

Glove permeation and skin penetration may be influenced by the presence of carrier solvents in the OP formulations. In gloves, it might cause molecular damage and affect the barrier properties of the protective layer (Bromwich 2005). In skin, if the solvent is more soluble, it is unlikely to penetrate the skin, whereas if the substance is less soluble in the carrier solvents than in the skin, penetration may be faster (Jacobi et al. 2006). Permeation and penetration of formulated OPs in the present study may have been enhanced by the presence of carrier solvents, as reported in previous works (Bach & Lippold 1998; Duracher et al. 2009; Williams & Barry 2004). This could occur by perturbing of the lipid domain that result in increased partitioning into the stratum corneum as suggested by previous researchers (Baynes et al. 2002); Baynes and Riviere (1998). However, this factor was not explored in this research and may not apply to those that have no carrier solvents.

Applied dose

In finite dose conditions, skin absorption may not achieve a steady state because the application dose is usually significantly depleted over time (Franz 1978). It may be more relevant to occupational exposure in typical exposure conditions, as workers would typically wipe off or wash off skin splashes. However, infinite dose was used in the present studies to

investigate the maximum penetration (Howes et al. 1996; OECD 2004a). Studies using infinite dose best reflect the worst exposure scenario i.e. spills and splashes, and are useful for exposure risk assessment as well as for exposure modelling.

OP mixtures

When handling mixture of chemicals the preferred gloves should be those that provide the best protection for the chemicals with the shortest breakthrough time. It is preferable to test each chemical in the same mixture ratios and exposure conditions. Rapidly permeating substances may accelerate permeation of the other substances in a mixture, thus enhancing permeation through the gloves (Schwope et al. 1983). Generalising permeation test results based on representative of chemical families may not provide accurate estimation, because many physicochemical properties of the chemicals may affect permeation (Truscott & Stoessel 2001).

Exposure pattern

Exposure of workers to OPs tends to be intermittent in nature (Krieger & Ross 1993). Typically, workers are exposed to OPs for several days in a week for a common type of OP, and once in several months for specialty use OPs. It is worth noting that the outcomes in the present studies represent the worst case of uninterrupted exposure. In reality, the pattern of exposure is usually intermittent thus the flux rates and permeation may be more concentration-dependant (Bromwich 2005). Studies should be in line with real life situations to avoid uncertainties in hazard risk assessment.

In addition, skin penetration may also be influenced by the biological factors of the skin itself (e.g. anatomical location, age and gender differences, skin thickness, skin condition, skin

metabolism, skin hairiness and pores). There have been efforts incorporating effects of individual factors; however, bringing all the factors into the real world makes it more complicated for prediction. In the present *in vitro* studies, although the abdominal skin samples were obtained from three female donors, variability may still occur from the age difference (35, 37 and 58 years old).

7.2.2.4 Comparison of skin penetration of OPs with Acceptable Daily Intakes (ADIs)

The outcomes of the *in vitro* skin tests were compared against ADIs of the respective OPs based on exposure for a 70-kg human. It indicates the allowable time that is considered 'safe' for infinite dose exposure before the mass penetrating through the skin surpasses the daily limit. In general, ADIs were exceeded to various degrees. As expected, it was found that the 'allowable times' before exceeding the calculated ADIs for exposure to OPs in application strength were longer than in full strength. Similarly, the estimated times for ADI exceedance were shorter at an elevated temperature (37°C), as the penetration of OPs was quicker irrespective of the concentrations. This could be explained by the shorter breakthrough times and greater cumulative penetration of OPs in warmer conditions, boosted by the synergistic acts and thermodynamic activity (Chang, Brownie & Riviere 1994; Chang & Riviere 1991).

Exceedance factors were greatest for omethoate which has the lowest ADI (0.0004 mg/kg bw), varying from 7 times to 50 times higher for exposure to hands only. This was followed by dichlorvos and diazinon (0.001 mg/kg bw) and mevinphos which has the highest ADI (0.002 mg/kg bw). In other words, the lower the ADI value was set, the easier it was to be exceeded.

It must be emphasised that the estimated penetration and exceedance factors in the present study are calculated based on infinite dose, e.g. extreme exposure conditions that involve continual skin contact with the OPs in infinite amount on the whole hands and/or hands and forearms over time. In a more realistic working scenario, although the concentrations and exposure temperature may be similar, such extreme exposure conditions may be limited to only a small area of the skin (e.g. 20 cm^2) and is usually wiped or washed within minutes after exposure. There is also a potential of OP splashes onto the skin, trapped on the inside of the gloves and occluded throughout the working hours before being washed. This information, therefore must be considered when evaluating hazard of the OPs. In interpreting the outcomes of this study, it should be noted that skin exposure time may be shorter and not continuous for 8 hours, and repeated every day or for weeks. However, it can be expected that the OP penetration increased with time, especially when in high concentrations and at an elevated temperature, hence may slowly reach the ADIs.

It is extremely difficult to combine the variables and simulate real life working conditions in the laboratory in order to produce a complete model that can accurately predict dermal uptake for a wide range of OP chemicals. This is underlined by the nature and complexities from the interactions in glove permeation and skin penetration of the chemicals to be studied, as well as limited resources.

Since the skin penetration outcomes suggested significant dermal risk on workers without hand protection when handling formulated OPs, the combination of controls should be re-examined and re-evaluated based on the hierarchy of control measures.

7.2.2.5 The application of skin penetration outcomes for predictive dermal risk assessment models

Significant time and resources are required to conduct *in vitro* and *in vivo* skin studies. Therefore, dermal absorption and penetration models are used for prediction of a wide range of chemicals. Predictive dermal risk assessment models are commonly developed based on physicochemical properties of chemicals and the nature of skin contamination (Anissimov et al. 2013). Where penetration data are scarce, limited generalisation is made based on penetration outcomes of groups of chemicals (Scheuplein & Bronaugh 1983; Wester & Maibach 1985). It is of significance, however, to note that one test condition may not reflect all dermal exposure situations in real workplace settings (Grandjean 1990). Interaction of mixture of chemicals (as found in formulated OPs) as well as the complexities of skin behaviours make it more difficult to develop a model that can accurately predict skin uptake. Several existing models have been reviewed, including multi-compartment models (Bouwman et al. 2008; Anissimov et al. 2013) and were identified as having limited prediction capability. The homogeneous membrane model is inadequate even for water penetration and desorption (Anissimov et al. 2013). In addition, Riviere &Brooks (2011) have highlighted further issues relating to complex dosing situations and real world exposures. Therefore, it is necessary to validate the predictions by conducting experiments in settings closest to the real exposure, as demonstrated in this present research.

Outcomes from the present *in vitro* studies showed that OP penetration through human skin varied depending on the types and physicochemical properties of the OPs. OPs of small molecular volume, low molecular polar surface areas and having both hydrophilic and lipophilic characters tend to penetrate the skin rapidly (Friberg & Larsson 1975; Grandjean

1990; Paranjape et al. 2014). High concentration of the OPs and elevated exposure temperature also suggested that penetration of the four tested OPs through the skin was enhanced to a considerable extent and may contribute to systemic toxicity (Dooms-Goossens, Garmyn & Degreef 1991; Rawson et al. 2005).

From the experimental evidence and discussion, it appears that assessing and evaluating skin penetration potential is complex and may be limited by the lack of information reported in scientific literature. A reliable predictive model of dermal absorption can help to reduce the number of *in vitro* or *in vivo* studies to be conducted for defining the risk of dermal exposure to a wide range of chemicals. In the meantime, and in the absence of robust Tier 2 models, all OPs should be treated as having the potential for skin penetration.

7.3 GENERALISABILITY OF RESULTS

It is difficult to be certain that the data obtained from research on specific OP products in certain test conditions are applicable for other conditions.

It is acknowledged that OP manufacturers may produce formulations with different concentrations (and with different additives), from the products tested in this research. The permeation and penetration data for these concentrates may thus be different. However, permeation and penetration outcomes for application strength formulated OPs are probably still valid across the OPs, provided the same concentrations are referred to. This is because the 'chemical atmosphere' is mostly water at application strength.

OPs with similar molecular weights and in the range of log K_{ow} covered in this research may behave in a similar manner, at least as far as trends are concerned. (Sartorelli et al. 1998)

This research was framed around two case studies for dermal exposure, namely agricultural workers and ambulance workers. Similar exposures may also be faced by other routine and non-routine users, as illustrated in Figure 1.1. For example, mixing and spraying processes are also relevant for urban pest control workers (Cattani et al. 2001).

7.4 STRENGTH AND LIMITATIONS OF THE OVERALL RESEARCH

Strengths

The main strength of this research lies in the combination of glove permeation studies and *in vitro* skin studies, informed by real world worst case conditions, and case studies. In Chapter 4, permeation resistance of two types of elbow-length PVC gloves recommended for handling OPs were tested. Performance of the gloves was not only tested in new (unused) condition, but also after exposure to UV radiation and abrasion to reflect the common condition of gloves being used by agricultural workers. In Chapter 5, permeation of disposable nitrile and neoprene gloves used by South Australian ambulance workers were tested individually as well as in combination, as currently in practice. This study provided evidence for the decision to double glove (nitrile on neoprene gloves).

The *in vitro* skin studies (Chapter 6) used human skin, considered as the 'gold standard' that best mimics live skin.

This research utilised commercial formulated OPs which are available for purchase in the market instead of pure chemicals (active ingredient only). Four OPs with differing physicochemical properties were selected for comparison of glove permeation and skin penetration. The research design was based on a practical model, the OPs were tested at two concentrations, relevant to mixing and loading (full strength) as well as during spraying (application strength). Exposure conditions were room temperature and elevated temperatures (45°C for glove studies, 37°C for *in vitro* skin studies) to simulate realistic exposure conditions in Australia.

Limitations

- This was an exploratory laboratory-based study, with limited scope. Only certain variables were examined and some non-standard methods were used (for UV and abrasion).

- Despite the fact that carrier solvents may enhance glove permeation and skin penetration as previously discussed, the effects of this factor were not explored in this research.

- Only two concentrations of OPs and two temperatures were tested in this research.
- Outcomes obtained from tests at intermediate exposure temperatures and OP concentrations would have helped to generate Arrhenius plots, and clarify any non-linearity from intermolecular interactions. This is especially relevant for the skin studies, where the penetration behaviour is complicated due to the various structural components of the skin.

- In practice, glove re-use may affect glove integrity/performance and lead to internal contamination and occlusion. The latter issues were not examined.

- Finally, disposable nitrile and neoprene gloves used by ambulance workers were only tested out-of-box.

CHAPTER 8

GENERAL CONCLUSIONS AND RECOMMENDATIONS

8.1 GENERAL CONCLUSIONS FROM THE RESEARCH

This research has shown that PVC gloves as well as disposable nitrile and neoprene gloves can provide reasonable protection against the four tested OPs but only in limited conditions. Increased OP concentration and exposure temperature to 45°C can have significant impacts on permeation through gloves, evident from the shorter breakthrough times, higher average maximum flux and greater average cumulative permeation.

Gloves worn for handling low concentration OPs (e.g. spraying) at moderate temperatures may not be suitable for handling high concentration OPs (e.g. mixing and loading) in hot conditions.

The studies indicate that reduced protection is afforded by gloves exposed to UV light and abrasion; therefore, reuse of gloves should only be practised with care, even if the signs of degradation are not visible by visual inspection.

Disposable gloves worn by SAAS workers demonstrated better protection ability when combined (nitrile on neoprene), compared to individual gloves.

In vitro skin experiments indicate that dichlorvos has quick penetration through the skin and penetrates to a greater extent, compared to the other three OPs. On the other hand, omethoate and mevinphos are problematic at full strength and at high temperature.

It is apparent from this and other studies that users and distributors of OPs have limited understanding of issues of glove permeation and skin penetration.

8.2 GENERAL RECOMMENDATIONS

Based on the strength and limitations of the research addressed earlier (Chapter 7), several recommendations can be made. These apply to future researchers, glove users, manufacturers and suppliers of OP chemicals and gloves, as well as regulatory and enforcement bodies.

8.2.1 Recommendations for future researchers

Undertake further research on formulated OPs containing carrier solvents

The effect of carrier solvents and other additives appears to be important, especially at high tempertaures. However, little is known and there is a need for systematic study. Further investigations may provide a solid justification to encourage manufacturers to reduce the amount or substitute the carrier solvents with less hazardous solvents in their OP formulations. It will also assist in optimising glove selection.

Assess glove performance at intermediate exposure temperatures

Besides room temperature and 37°C (for *in vitro* skin studies) and 45°C (for glove permeation studies) in the present studies, exploring intermediate temperatures e.g. 30-35°C will establish a better understanding of these variables. Further work at these intermediate temperatures will provide more information on irregular behaviours of the OPs under various plausible exposure conditions that may affect the degree and extent of penetration and permeation.

Conduct further empirical studies of occlusion

The occlusive environment may enhance skin penetration, but there are very sparse data. It would enhance understanding on additional risks associated with occlusion and inform predictive dermal risk assessment models.

Assess the performance of non-disposable gloves within their usual life span

Permeation performance across the lifespan of gloves is poorly understood.The combined effects of storage conditions, abrasion, UV exposure and flexing will inform educational interventions and help to avoid underestimation of OP permeation.

8.2.2 Recommendations for glove users

While outcomes in this research showed gloves may need to be changed regularly to ensure appropriate protection, it may be impractical and not cost-effective.

Suitability of PVC gloves

Excalibur and *ProChoice* elbow length PVC gloves are recommended for use as they provide reasonable protection against formulated OP products at full strength and application strength. However, they should be inspected for visible cracks or holes prior to use, and replaced regularly (and when visibly contaminated) to minimise reservoir effects and the impact of internal contamination.

Double gloving by ambulance workers

It is recommended that the current practice of combining nitrile and neoprene gloves by SAAS continue. However, given the outcomes of accelerated permeation of OPs at elevated

temperature and the AS/NZS 2161 standard, considerations should be given on more frequent changing of gloves, especially when working in warmer conditions. It may also be worthwhile to have a consistent and national policy for ambulance workers exposed to OPs to ensure protection of this group.

Washing of skin splash

It is recommended that in situations of undiluted (full strength) OP splashed onto unprotected skin, it should be immediately washed or absorbed. This is justified by the ADI exceedance within 0.5 minute (dichlorvos and diazinon) and 6 minutes (omethoate and mevinphos) for exposure to hands at room temperature.

8.2.3 Recommendations for manufacturers and suppliers of OPs and gloves

Appropriate and accurate recommendations of gloves

Manufacturers and suppliers of OPs and gloves should provide appropriate and clear recommendations in SDSs for glove users by relating to the physicochemical properties of a substance and conditions in which they are to be handled.

Where gloves are to be used for handling chemicals at low concentrations (diluted for spraying), the recommendations may not be the same for handling full strength (undiluted OPs for mixing and loading). Similarly, recommendations should also consider temperature conditions to avoid underestimation of skin uptake.

Glove manufacturers should ensure that test data reflects the actual performance of their products under real exposure conditions, by conducting more glove permeation tests under

these plausible exposure conditions. The outcomes should be updated in the database as a source for advisory purposes and made available to the public for access.

Where changes may be made in the OP formulation by manufacturers, the suitability of glove recommendations should be reviewed.

8.2.4 Recommendations for regulatory and educational bodies

Sharing of resources and expertise

It is suggested that by sharing the outcomes of the present research with the agricultural and pest control communities, the research can be translated into practice for improvement. This is achievable by making the information available via newsletters or websites. The information may also be incorporated in the training syllabus for the certification of pesticide handlers.

Enforce strict regulations

Manufacturers and distributors of OPs should be required to include the details of appropriate type of gloves to be worn, especially when working with concentrates in hot conditions. Warnings for potential ADI exceedance should be included on labels or SDSs of the OP products to alert the users of the risks when handling OPs.

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APPENDICES

Appendix 1:List of Chemicals of Security Concern
Source:
http://www.nationalsecurity.gov.au/ChemicalSecurity/Documents/Code%20of%20practice.PDF

Appendix 2 Safety Data Sheets (SDSs) of the formulated products used in this research

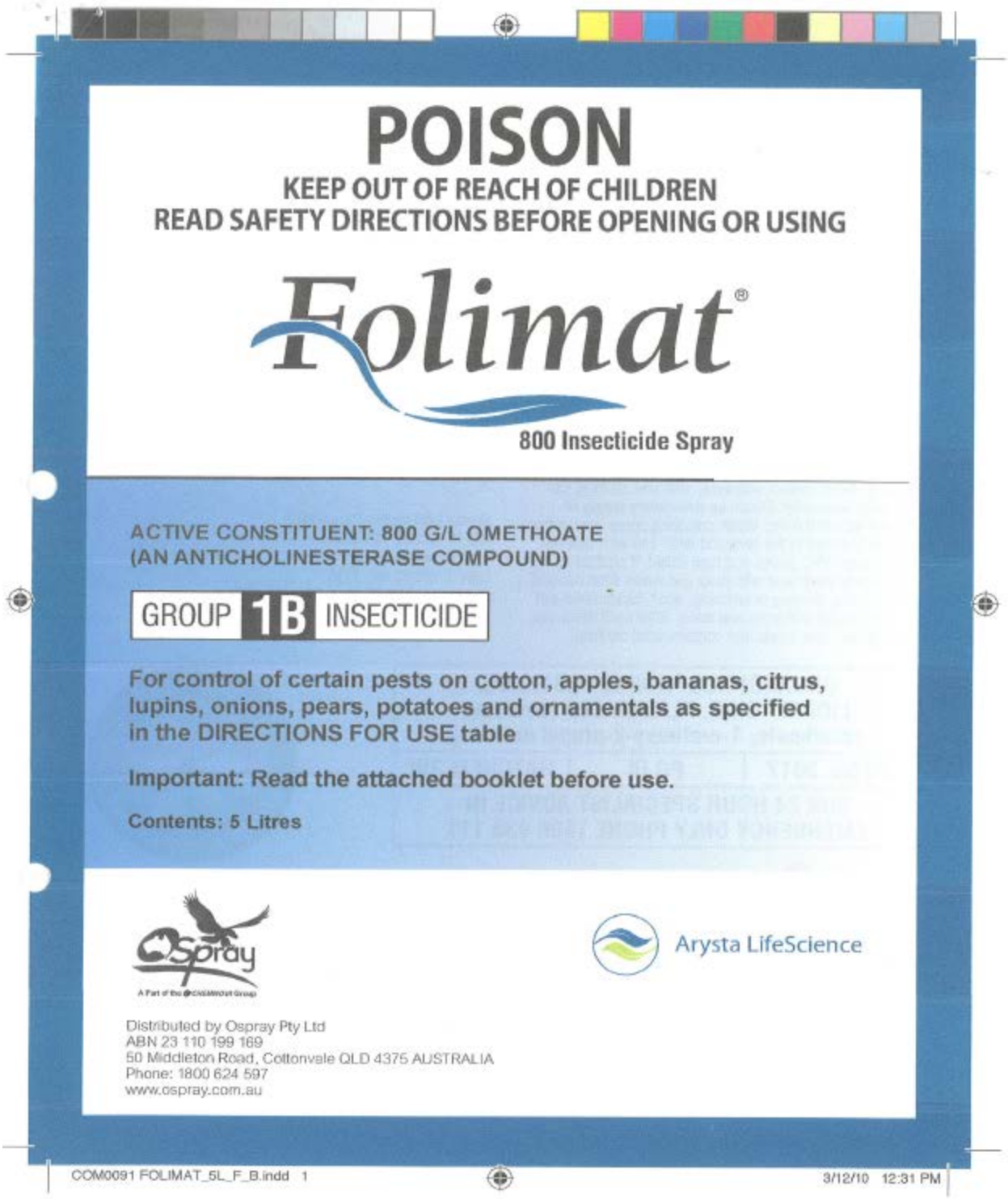
Appendix 2.1 Folimat® (omethoate)

Appendix 2.2 Phosdrin® (mevinphos)

Appendix 2.3 DDVP Technical Grade (dichlorvos)

Appendix 2.4 Barmac Diazinon insecticide (diazinon)

Appendix 2.1 Folimat® (omethoate)



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STORAGE AND DISPOSAL

Store in the closed, original container in a cool, dry and well ventilated area. Do not store for prolonged periods in direct sunlight. Store in a locked room or place away from children, animals, food, feedstuffs, seed and fertilisers.
Triple or preferably pressure rinse container before disposal. Add rinsings to spray tank.
Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

SAFETY DIRECTIONS

Very dangerous, particularly the concentrate. Product and spray are poisonous if absorbed by skin contact, inhaled or swallowed. Repeated exposure may cause allergic disorders. Repeated minor exposure may have a cumulative poisoning effect. Sensitive workers should use protective clothing. Avoid contact with eyes, skin and clothing. Do not inhale spray mist. Obtain an emergency supply of atropine tablets 0.6 mg. When preparing spray wear cotton overalls buttoned to the neck and wrist and washable hat, elbow-length PVC gloves and face shield. If product on skin, immediately wash area with soap and water. After use and before eating, drinking or smoking, wash hands arms and face thoroughly with soap and water. After each day's use wash gloves, face shield and contaminated clothing.

FIRST AID

If swallowed, splashed on skin or in eyes, or inhaled, contact a Poisons Information Centre (Phone Australia 131126) or a doctor at once. Remove any contaminated clothing and wash skin thoroughly. If swallowed, activated charcoal may be advised. Give atropine if instructed.

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet, which can be obtained from www.arysta-na.com.

EXCLUSION OF LIABILITY

This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Arysta LifeScience Corporation accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.
® Folimat is a registered trademark of Arysta LifeScience

Arysta LifeScience

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ORGANOPHOSPHORUS PESTICIDE, LIQUID,TOXIC, FLAMMABLE (contains omethoate, 1-methoxy-2-propyl acetate)		
UN No. 3017	PG III	HAZCHEM 3W
FOR 24 HOUR SPECIALIST ADVICE IN EMERGENCY ONLY PHONE 1800 033 111		

drumMUSTER eligible container

Batch No.
D.O.M.

9 335944 004212

APVMA Approval No.: 33055/5L/0706

File name	33055_xxxxx_5L_Back_V1.pdf
Dimensions	Size 175mm H x 135mm W
Scale	Prints at 100% A4
Date	03/12/2010

Section 1 - Identification of Chemical Product and Company

Arysta Lifescience Corporation
77-79 Canterbury Rd
Canterbury Vic 3126

Tel: 03 9830 7011
Fax: 03 9830 7611

Chemical nature:	Omethoate is an organophosphorus derivative.
Trade Name:	**Folimat 800 Insecticide Spray**
Product Use:	Agricultural insecticide for use as described on the product label.
Creation Date:	**October, 2010**
This version issued:	**October, 2010** and is valid for 5 years from this date.

Section 2 - Hazards Identification

Statement of Hazardous Nature

This product is classified as: Xi, Irritating. T, Toxic. N, Dangerous to the environment. F+, Highly Flammable. Hazardous according to the criteria of SWA.

Dangerous according to the Australian Dangerous Goods (ADG) Code.

Risk Phrases: R10, R21, R25, R33, R36, R43, R50, R57. Flammable. Harmful in contact with skin. Toxic if swallowed. Danger of cumulative effects. Irritating to eyes. May cause sensitisation by skin contact. Very toxic to aquatic organisms. Toxic to bees.

Safety Phrases: S20, S23, S28, S29, S33, S45, S61, S1/2, S24/25, S36/37. When using, do not eat or drink. Do not breathe vapours or spray mists. After contact with skin, wash immediately with plenty of soap and water. Do not empty into drains. Take precautionary measures against static discharges. In case of accident or if you feel unwell, contact a doctor or Poisons Information Centre immediately (show this MSDS where possible). Avoid release to the environment. Refer to special instructions/Safety Data Sheets. Keep locked up and out of reach of children. Avoid contact with skin and eyes. Wear suitable protective clothing and gloves.

SUSMP Classification: S7

ADG Classification: Class 6.1: Toxic Substances. Sub Risk: Class 3, Flammable liquids.

UN Number: 3017, ORGANOPHOSPHORUS PESTICIDE, LIQUID, TOXIC, FLAMMABLE, flash point not less than 23 °C

Emergency Overview

Physical Description & Colour: Clear, light brown liquid.

Odour: Aromatic odour.

Major Health Hazards: toxic if swallowed, danger of cumulative effects, harmful in contact with skin, eye irritant, possible skin sensitiser. Signs and symptoms associated with mild exposures to organophosphate and carbamate pesticides include: headache, fatigue, dizziness, loss of appetite with nausea, stomach cramps and diarrhoea; blurred vision associated with excessive tearing; contracted pupils of the eye; excessive sweating and salivation; slowed heartbeat, often fewer than 50 per minute; rippling of surface muscles just under the skin. These symptoms may be mistaken for those of flu, heat stroke or heat exhaustion, or upset stomach. Moderately severe organophosphate and carbamate insecticide poisoning cases exhibit all the signs and symptoms found in mild poisonings, but in addition, the victim: is unable to walk; often complains of chest discomfort and tightness; exhibits marked constriction of the pupils (pinpoint pupils); exhibits muscle twitching; has involuntary urination and bowel movement. Severe poisonings are indicated by incontinence, unconsciousness and seizures.

Potential Health Effects

Inhalation:

Short Term Exposure: Symptoms are described fully above.

Long Term Exposure: No data for health effects associated with long term inhalation.

Skin Contact:

Short Term Exposure: Symptoms are described fully above.

Long Term Exposure: No data for health effects associated with long term skin exposure.

Eye Contact:

DANGEROUS POISON

KEEP OUT OF REACH OF CHILDREN
READ SAFETY DIRECTIONS BEFORE OPENING OR USING

Folimat

800 Insecticide Spray

ACTIVE CONSTITUENT: 800 g/L OMETHOATE
(AN ANTICHOLINESTERASE COMPOUND)

GROUP 1B INSECTICIDE

For control of certain pests on cotton, apples, bananas, citrus, lupins, onions, pears, potatoes and ornamentals as specified in the DIRECTIONS FOR USE table

IMPORTANT: READ THIS LEAFLET BEFORE USE

Arysta LifeScience

DIRECTIONS FOR USE
Tree and Vine Crops

RATE					CRITICAL COMMENTS
In the following table, all rates given are for **dilute spraying**. For **concentrate spraying**, refer to the **Application** section.					For all uses in this table: Apply by dilute or concentrate spraying equipment. Apply the same total amount of product to the target crop whether applying this product by dilute or concentrate spraying methods. For concentrate spraying, DO NOT use at rates greater than 5 times the dilute spraying rate.
Crop	**Pest**	**State**	**Rate**	**WHP**	
Apples Pears	Twospotted mite (not in MIA or Goulburn valley)	NSW, Vic, SA, Tas, WA only	75 mL/100 L	7 days	Spray thoroughly at beginning of mite build up. Repeat at beginning of renewed mite activity. Do not apply during flowering. This product is not compatible with integrated mite control programs.
	European red mite	NSW, Vic, SA, WA only			
		Tas only	65 mL/100 L		
	Woolly aphid	WA only	75 mL/100 L		Spray when pests are first seen.
Citrus	California red scale	NSW, Vic, SA Only	50 mL plus 1 L spraying oil/100 L	7 days	Apply thoroughly as a full cover spray, timed according to previous schedule, eg between January and early March. Do not apply to Meyer Lemon or Seville orange.
		WA only	75 mL plus 1 L spraying oil/100 L		
	Aphids		75 mL/100 L		Spray when pests are seen.
Glen Retreat mandarins	California red scale	Qld only	65 mL/100 L	7 days	Apply thoroughly as a full cover spray. Apply two sprays – one in early December to coincide with peak hatching and one in late January.

Non-Tree/Vine Crops

Crop	Pest	State	Rate	WHP	CRIRICAL COMMENTS
Cotton	Thrips Mirids	Qld, NSW, WA, NT only	140-280 mL/ha	21 days	Apply by ground rig or air. Aircraft may use double track spacing with a reliable cross wind for thrips only. Use higher rate for longer residual control of thrips, or where mird populations exceed 1/m of row.
	Aphids		250 mL/ha		
	Jassids		280 mL/ha		
Bananas	Corky scab caused by flower thrips	Qld, NSW only	Bell injection 50 mL/5 L	6 weeks	At bunch emergence, apply 40 to 60 mL of mix while the emerging bell is still upright by injecting into the bell about 1/4 of its length from the upright tip. Inject to a depth of 30-50 mm so as not to damage the bunch stem. Use the higher rate for larger bunches.
		NSW only	Individual plant treatment 125 mL/100 L	4 days	Apply 500 mL of spray mix to the throat of the plant at the bunch leaf stage during the period of flower thrips' activity.
Lupins	Blue green aphid, cowpea aphid, green peach aphid, (suppression only)	WA only	250 mL/ha	14 days	Can be applied ULV in water using 20% anti-evaporative oil (eg Ulvaprore).
Onions	Thrips	All States	700 mL/ha or 65 mL/100 L		Apply thoroughly as a full cover spray. Add wetting agent.
	Lucerne flea	Vic, SA, Tas only	35 mL/ha		
Potatoes	Aphids	WA only	75 mL/100 L	7 days	Spray when pests are first seen and repeat when necessary.
Carnations Chrysanthemums Pelargoniums Roses Callistemons Eucalyptus spp. Grevillea spp. Paperbarks Wattles	Aphids, lace bugs, mealybugs, mites, thrips, whiteflies	All States	75 mL/100 L	–	Spray thoroughly as a full cover spray. Repeat at beginning of renewed pest activity. See note on ornamentals.

NOT TO BE USED FOR ANY PURPOSE, OR IN ANY MANNER, CONTRARY TO THIS LABEL UNLESS AUTHORISED UNDER APPROPRIATE LEGISLATION
THIS PRODUCT IS TOO HAZARDOUS FOR USE IN THE HOME GARDEN

WITHHOLDING PERIODS (WHP)

Lupins, Onions: DO NOT HARVEST FOR 14 DAYS AFTER APPLICATION
Cotton: DO NOT HARVEST FOR 21 DAYS AFTER APPLICATION
Bananas (bell injection): DO NOT HARVEST FOR 6 WEEKS AFTER APPLICATION
Bananas (throat spray): DO NOT HARVEST FOR 4 DAYS AFTER APPLICATION
Other edible crops: DO NOT HARVEST FOR 7 DAYS AFTER APPLICATION

GENERAL INSTRUCTIONS

GROUP 1B INSECTICIDE

Insecticide Resistance Warning

For insecticide resistance management, Folimat is a Group 1B insecticide. Some naturally occurring Folimat and other Group 1B insecticides may exist through normal genetic population. The resistant individuals can eventually dominate the insect and other Group 1B insecticides are used repeatedly. The effectiveness of Folimat on resistant individuals could be significantly reduced. Since occurrence of resistant individuals is difficult to detect prior to use, Arysta LifeScience Corporation accepts no liability for any losses that may result from the failure of Folimat to control resistant insects. Folimat may be subject to specific resistance management strategies. For further information contact your local supplier, Arysta LifeScience representative or local agricultural department agronomist.

Export of Treated Produce

Growers should note that MRLs or import tolerances do not exist in all markets for edible produce treated with Folimat. If you are growing edible produce for export, please check with Arysta LifeScience Corporation for the latest information on MRLs and import tolerances before using Folimat.

Mixing

Add the required quantity of Folimat 800 to water in the spray vat while stirring or with agitators in motion.

Application

Dilute Spraying

- Use a sprayer designed to apply high volumes of water up to the point of run-off and matched to the crop being sprayed.
- Set up and operate the sprayer to achieve even coverage throughout the crop canopy. Apply sufficient water to cover the crop to the point of run-off. Avoid excessive run-off.
- The required water volume may be determined by applying different test volumes, using different settings on the sprayer, from industry guidelines or expert advice.
- Add the amount of product specified in the Directions for Use table for each 100 L of water. Spray to the point of run-off.
- The required dilute spray volume will change and the sprayer set up and operation may also need to be changed, as the crop grows.

Concentrate Spraying

- Use a sprayer designed and set up for concentrate spraying (that is a sprayer which applies water volumes less than those required to reach the point of run-off) and matched to the crop being sprayed.
- Set up and operate the sprayer to achieve even coverage throughout the crop canopy using your chosen water volume.
- Determine an appropriate dilute spray volume (see ***Dilute Spraying*** above) for the crop canopy. This is needed to calculate the concentrate mixing rate.
- The mixing rate for concentrate spraying can then be calculated in the following way:

EXAMPLE ONLY

1. Dilute spray volume as determined above: For example 1500 L/ha
2. Your chosen concentrate spray volume: For example 500 L/ha
3. The concentration factor in this example is: 3 X (ie 1500 L ÷ 500 L = 3)
4. For the dilute label rate of 75 mL/100 L, the concentrate rate becomes 3 x 75, that is 225 mL/100 L of concentrate spray.

- The chosen spray volume, amount of product per 100 L of water, and the sprayer set up and operation may need to be changed as the crop grows.
- DO NOT use a concentrate rate higher than that specified in the **CRITICAL COMMENTS.**
- For further information on concentrate spraying, users are advised to consult relevant industry guidelines, undertake appropriate competency training and follow industry Best Practices.

On Ornamentals

Folimat 800 Insecticide Spray has been used on a wide range of ornamental plant species without damage. However, some species and varieties are particularly sensitive to chemical sprays and as this is often related to local conditions it is advisable to treat only a small number of plants first, in order to ascertain their reaction before treating the whole crop.

Compatibility

Folimat 800 is compatible with Antracol®, Nitrofol®, white oil, misting oil, water miscible oil. Do not mix concentrates together but add each to the spray tank separately. As formulations of other manufacturers' products are beyond the control of Arysta LifeScience Corporation, all mixtures should be tested prior to mixing commercial quantities. As changes in climatic conditions can alter the sensitivity of plants to mixtures of sprays, Arysta Lifescience cannot be responsible for the behaviour of such mixtures.

PRECAUTION

Re-entry

Do not allow entry into treated areas for 1 day after treatment. When prior entry is necessary, wear cotton overalls buttoned to the neck and wrist and a washable hat, chemical resistant gloves and impervious footwear. Clothing must be laundered after each day's use.

PROTECTION OF LIVESTOCK

Dangerous to bees. Do NOT spray any plants in flower while bees are foraging.

PROTECTION OF WILDLIFE, FISH, CRUSTACEANS AND ENVIRONMENT

DO NOT contaminate streams, rivers or waterways with the chemical or used containers.

STORAGE AND DISPOSAL

Store in the closed, original container in a cool, dry and well ventilated area. Do not store for prolonged periods in direct sunlight. Store in a locked room or place away from children, animals, food, feedstuffs, seed and fertilisers. Triple or preferably pressure rinse container before disposal. Add rinsings to spray tank.

Do not dispose of undiluted chemicals on site. If recycling, replace cap and return clean containers to recycler or designated collection point. If not recycling, break, crush or puncture and bury empty containers in a local authority landfill. If no landfill is available, bury the containers below 500 mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should not be burnt.

SAFETY DIRECTIONS

Very dangerous, particularly the concentrate. Product and spray are poisonous if absorbed by skin contact, inhaled or swallowed. Repeated exposure may cause allergic disorders. Repeated minor exposure may have a cumulative poisoning effect. Sensitive workers should use protective clothing. Avoid contact with eyes, skin and clothing. Do not inhale spray mist. When preparing spray wear cotton overalls buttoned to the neck and wrist and washable hat, elbow-length PVC gloves and face shield. If product on skin, immediately wash area with soap and water. After use and before eating, drinking or smoking, wash hands arms and face thoroughly with soap and water. After each day's use wash gloves, face shield and contaminated clothing.

FIRST AID

If swallowed, splashed on skin or in eyes, or inhaled, contact a Poisons Information Centre (Phone Australia 131126) or a doctor at once. Remove any contaminated clothing and wash skin thoroughly. If swallowed, activated charcoal may be advised. Give atropine if instructed.

MATERIAL SAFETY DATA SHEET

Additional information is listed in the Material Safety Data Sheet, which can be obtained from www.arysta-na.com.

EXCLUSION OF LIABILITY

This product must be used strictly as directed, and in accordance with all instructions appearing on the label and in other reference material. So far as it is lawfully able to do so, Arysta Lifescience Corporation accepts no liability or responsibility for loss or damage arising from failure to follow such directions and instructions.

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Short Term Exposure: This product is an eye irritant. Symptoms may include stinging and reddening of eyes and watering which may become copious. Other symptoms may also become evident. If exposure is brief, symptoms should disappear once exposure has ceased. However, lengthy exposure or delayed treatment may cause permanent damage.
Long Term Exposure: No data for health effects associated with long term eye exposure.

Ingestion:

Short Term Exposure: Symptoms are described fully above.
Long Term Exposure: No data for health effects associated with long term ingestion.

Carcinogen Status:

SWA: No significant ingredient is classified as carcinogenic by SWA.
NTP: No significant ingredient is classified as carcinogenic by NTP.
IARC: No significant ingredient is classified as carcinogenic by IARC.

Section 3 - Composition/Information on Ingredients

Ingredients	CAS No	Conc,%	TWA (mg/m^3)	STEL (mg/m^3)
Omethoate	1113-02-6	800g/L	not set	not set
1-methoxy-2-acetoxypropane	108-65-6	400g/L	274	548

This is a commercial product whose exact ratio of components may vary slightly. Minor quantities of other non hazardous ingredients are also possible.

The SWA TWA exposure value is the average airborne concentration of a particular substance when calculated over a normal 8 hour working day for a 5 day working week. The STEL (Short Term Exposure Limit) is an exposure value that may be equalled (but should not be exceeded) for no longer than 15 minutes and should not be repeated more than 4 times per day. There should be at least 60 minutes between successive exposures at the STEL. The term "peak "is used when the TWA limit, because of the rapid action of the substance, should never be exceeded, even briefly.

Section 4 - First Aid Measures

General Information:

You should call The Poisons Information Centre if you feel that you may have been poisoned, burned or irritated by this product. The number is 13 1126 from anywhere in Australia (0800 764 766 in New Zealand) and is available at all times. Have this MSDS with you when you call.

If swallowed, splashed on skin or inhaled, contact a Poisons Information Centre or a doctor at once. Remove any contaminated clothing and wash skin thoroughly. Hospital treatment may be necessary.

Inhalation: No first aid measures normally required. However, if inhalation has occurred, and irritation has developed, remove to fresh air and observe until recovered. If irritation becomes painful or persists more than about 30 minutes, seek medical advice.
Skin Contact: Quickly and gently blot away excess liquid. Wash gently and thoroughly with warm water (use non-abrasive soap if necessary) for 10-20 minutes or until product is removed. Under running water, remove contaminated clothing, shoes and leather goods (e.g. watchbands and belts) and completely decontaminate them before reuse or discard.
Eye Contact: Immediately flush the contaminated eye(s) with lukewarm, gently flowing water for 20 minutes or until the product is removed, while holding the eyelid(s) open. Take care not to rinse contaminated water into the unaffected eye or onto the face. Obtain medical attention immediately. Take special care if exposed person is wearing contact lenses.
Ingestion: If swallowed, do NOT induce vomiting; rinse mouth thoroughly with water and contact a Poisons Information Centre, or call a doctor at once. Give activated charcoal if instructed.

Section 5 - Fire Fighting Measures

Fire and Explosion Hazards: This product is classified as flammable. There is a moderate risk of an explosion from this product if commercial quantities are involved in a fire. Firefighters should take care and appropriate precautions. Violent steam generation or eruption may occur upon application of direct water stream on hot liquids. Vapours from this product are heavier than air and may accumulate in sumps, pits and other low-lying spaces, forming potentially explosive mixtures. They may also flash back considerable distances.
Fire decomposition products from this product may be toxic if inhaled. Take appropriate protective measures.
Extinguishing Media: Suitable extinguishing media are carbon dioxide, dry chemical, foam, water fog. Alcohol resistant foam is the preferred firefighting medium but, if it is not available, normal foam can be used. Try to contain spills, minimise spillage entering drains or water courses.

Fire Fighting: If a significant quantity of this product is involved in a fire, call the fire brigade. There is a danger of a violent reaction or explosion if significant quantities of this product are involved in a fire. Recommended personal protective equipment is liquid-tight chemical protective clothing and breathing apparatus.

Flash point:	45°C
Upper Flammability Limit:	10%
Lower Flammability Limit:	1.5%
Autoignition temperature:	332°C
Flammability Class:	Flammable

Section 6 - Accidental Release Measures

Accidental release: In the event of a major spill, prevent spillage from entering drains or water courses. Evacuate the spill area and deny entry to unnecessary and unprotected personnel. Immediately call the Fire Brigade. Wear full protective chemically resistant clothing including eye/face protection, gauntlets and self contained breathing apparatus. See below under Personal Protection regarding Australian Standards relating to personal protective equipment. No special recommendations for clothing materials. Eye/face protective equipment should comprise as a minimum, protective goggles. If there is a significant chance that vapours or mists are likely to build up in the cleanup area, we recommend that you use a respirator. It should be fitted with a type G cartridge, suitable for agricultural chemicals. Otherwise, not normally necessary.
Stop leak if safe to do so, and contain spill. Absorb onto sand, vermiculite or other suitable absorbent material. If spill is too large or if absorbent material is not available, try to create a dike to stop material spreading or going into drains or waterways. Because of the toxicity of this product, special personal care should be taken in any cleanup operation. Sweep up and shovel or collect recoverable product into labelled containers for recycling or salvage, and dispose of promptly. Recycle containers wherever possible after careful cleaning. Refer to product label for specific instructions. After spills, wash area preventing runoff from entering drains. If a significant quantity of material enters drains, advise emergency services. Full details regarding disposal of used containers, spillage and unused material may be found on the label. If there is any conflict between this MSDS and the label, instructions on the label prevail. Ensure legality of disposal by consulting regulations prior to disposal. Thoroughly launder protective clothing before storage or re-use. Advise laundry of nature of contamination when sending contaminated clothing to laundry.

Section 7 - Handling and Storage

Handling: Keep exposure to this product to a minimum, and minimise the quantities kept in work areas. Check Section 8 of this MSDS for details of personal protective measures, and make sure that those measures are followed. The measures detailed below under "Storage" should be followed during handling in order to minimise risks to persons using the product in the workplace. Also, avoid contact or contamination of product with incompatible materials listed in Section 10.
Storage: This product is a Scheduled Poison. Observe all relevant regulations regarding sale, transport and storage of this schedule of poison. Store in a cool, well ventilated area. Check containers periodically for leaks. Containers should be kept closed in order to minimise contamination. Make sure that the product does not come into contact with substances listed under "Incompatibilities" in Section 10. If you keep more than 2500kg or L of Dangerous Goods of Packaging Group II, you may be required to license the premises or notify your Dangerous Goods authority. If you have any doubts, we suggest you contact your Dangerous Goods authority in order to clarify your obligations. Check packaging - there may be further storage instructions on the label.

Section 8 - Exposure Controls and Personal Protection

The following Australian Standards will provide general advice regarding safety clothing and equipment:

Respiratory equipment: **AS/NZS 1715**, Protective Gloves: **AS 2161**, Occupational Protective Clothing: AS/NZS 4501 set 2008, Industrial Eye Protection: **AS1336** and **AS/NZS 1337**, Occupational Protective Footwear: **AS/NZS2210**.

SWA Exposure Limits	**TWA (mg/m^3)**	**STEL (mg/m^3)**
1-methoxy-2-acetoxypropane	274	548

The ADI for Omethoate is set at 0.0004mg/kg/day. The corresponding NOEL is set at 0.04mg/kg/day. ADI means Acceptable Daily Intake; NOEL means No-observable-effect-level. Data from Australian ADI List, March 2010.

No special equipment is usually needed when occasionally handling small quantities. The following instructions are for bulk handling or where regular exposure in an occupational setting occurs without proper containment systems.
Ventilation: This product should only be used in a well ventilated area. If natural ventilation is inadequate, use of a fan is suggested.

Eye Protection: Protective glasses or goggles should be worn when this product is being used. Failure to protect your eyes may cause them harm. Emergency eye wash facilities are also recommended in an area close to where this product is being used.
Skin Protection: If you believe you may have a sensitisation to this product or any of its declared ingredients, you should prevent skin contact by wearing impervious gloves, clothes and, preferably, apron. Make sure that all skin areas are covered. See below for suitable material types.
Protective Material Types: We suggest that protective clothing be made from the following materials: PVC.
Respirator: Usually, no respirator is necessary when using this product. However, if you have any doubts consult the Australian Standard mentioned above. Otherwise, not normally necessary.
Eyebaths or eyewash stations and safety deluge showers should be provided near to where this product is being used.

Section 9 - Physical and Chemical Properties:

Physical Description & colour:	Clear, light brown liquid.
Odour:	Aromatic odour.
Boiling Point:	146°C at 100kPa (solvent)
Freezing/Melting Point:	No specific data. Liquid at normal temperatures.
Volatiles:	No specific data. Expected to be low at 100°C.
Vapour Pressure:	3.3×10^{-5} hPa at 20° C (omethoate); 0.49 kPa at 20° C (solvent)
Vapour Density:	4.6
Specific Gravity:	1.2 approx at 20°C
Water Solubility:	Soluble.
pH:	2.8-3.8 (1% in water)
Volatility:	No data.
Odour Threshold:	No data.
Evaporation Rate:	No data.
Coeff Oil/water Distribution:	Omethoate -0.74 (log P octanol/water)
Autoignition temp:	332°C

Section 10 - Stability and Reactivity

Reactivity: This product is unlikely to react or decompose under normal storage conditions. However, if you have any doubts, contact the supplier for advice on shelf life properties.
Conditions to Avoid: This product should be kept in a cool place, preferably below 30°C. Keep away from heat, flames and sparks. Keep away from sources of sparks or ignition. Any electrical equipment in the area of this product should be flame proofed. Protect this product from light. Store in the closed original container in a dry, cool, well-ventilated area out of direct sunlight.
Incompatibilities: acids, bases, oxidising agents.
Fire Decomposition: Combustion forms carbon dioxide, and if incomplete, carbon monoxide and smoke. Water is also formed. May form nitrogen and its compounds, and under some circumstances, oxides of nitrogen. Occasionally hydrogen cyanide gas in reducing atmospheres. May form oxides of sulfur (sulfur dioxide is a respiratory hazard) and other sulfur compounds. Most will have a foul odour. May form oxides of phosphorus and other phosphorus compounds. Carbon monoxide poisoning produces headache, weakness, nausea, dizziness, confusion, dimness of vision, disturbance of judgment, and unconsciousness followed by coma and death.
Polymerisation: This product will not undergo polymerisation reactions.

Section 11 - Toxicological Information

Local Effects:
Target Organs: There is no data to hand indicating any particular target organs.

Classification of Hazardous Ingredients

Ingredient	Risk Phrases
Omethoate	Conc>=25%: T; R25; R21
1-methoxy-2-acetoxypropane	Conc>=20%: Xi; R36

Omethoate is an anticholinesterase compound. Symptoms typical of cholinesterase inhibition (for all routes of entry):
Mild cases

Headache, blurred vision, weakness, sweating, mild chest pain, nausea and vomiting.
Severe cases
Cyanosis (blueness of the skin, as from lack of oxygen), muscular twitching, spasms, miosis (pinpoint pupils) and respiratory paralysis. These symptoms commence from one to three hours after excessive exposure.

Inhalation	Poisonous by inhalation.
Skin contact	Poisonous if absorbed by skin contact. Will irritate the skin.
Eye contact	Irritating to the eyes.
Ingestion	Very dangerous. Poisonous if swallowed.

ANIMAL TOXICITY DATA
Acute:

Oral toxicity	LD_{50} rat: approx. 40 mg/kg *(derived from data for Folimat SL 500)*
Dermal toxicity	LD_{50} rat: approx. 500 mg/kg *(derived from data for Folimat SL 500)*
Inhalation toxicity	LC_{50} (4 h) rat: 0.3 mg/L aerosol *(omethoate)*
Skin irritation	Non irritant (rabbit) *(derived from data for Folimat SL 500)*
Irritation to mucous membranes	Slightly irritating (rabbit) *(derived from data for Folimat SL 500)*
Sensitisation	Omethoate is a skin sensitiser.

Chronic:
Repeated exposure to omethoate may cause allergic disorders. Repeated minor exposure may have a cumulative poisoning effect. The main health effects from repeated exposure would be toxic symptoms of cholinesterase inhibition as described above. Animal studies with omethoate have shown no evidence of oncogenic effect, no evidence of carcinogenic effects and no teratogenic potential.
The long term effects in animals noted for the solvent, 1-methoxy-2-propyl acetate, were headaches, dizziness and possible nausea. The solvent was not mutagenic in the Ames test, and did not cause teratological or other developmental effects.

Section 12 - Ecological Information

This product is very toxic to aquatic organisms. This product is toxic to bees. This product is biodegradable. It will not accumulate in the soil or water or cause long term problems.

Very toxic to aquatic invertebrates. Dangerous to bees.
DO NOT contaminate streams, rivers or waterways with Folimat 800 or the used containers.
Ecotoxicity
Omethoate:
Fish toxicity:
LC_{50}: 30 mg/L (96 h); golden orfe (*Leuciscus idus melanotus*)
LC_{50}: 9.1 mg/L (96 h); rainbow trout (*Oncorhynchus mykiss*)
Aquatic invertebrate toxicity:
EC_{50}: 0.022 mg/L (48 h); *Daphnia magna*
Algae toxicity:
IC_{50}: 167.5 mg/L (72 h); green algae (*Scenedesmus subspicatus*)
Bird toxicity:
LD_{50}: 79.7 mg/kg; male Japanese quail
LD_{50}: 83.4 mg/kg; female Japanese quail
Environmental fate, persistence and degradability, mobility
Omethoate has a relatively high mobility in soil but is very rapidly metabolised.
DT_{50}: only a few days. The main metabolite is CO_2. Aged leaching studies revealed that metabolites have only a low leaching potential.

Section 13 - Disposal Considerations

Disposal: This product may be recycled if unused, or if it has not been contaminated so as to make it unsuitable for its intended use. If it has been contaminated, it may be possible to separate the contamination in some way. Only if neither of these options is suitable, we suggest that you contact a specialist disposal company to arrange disposal. Disposal by untrained personnel may cause a dangerous incident.

Section 14 - Transport Information

ADG Code: 3017, ORGANOPHOSPHORUS PESTICIDE, LIQUID, TOXIC, FLAMMABLE
Hazchem Code: •3W
Special Provisions: 61, 274
Limited quantities: ADG 7 specifies a Limited Quantity value of 100 ml for this class of product.
Dangerous Goods Class: Class 6.1: Toxic Substances.
Sub Risk: Class 3, Flammable liquids.
Packaging Group: II
Packaging Method: P001, IBC02

Class 6 Toxic Substances shall not be loaded in the same vehicle or packed in the same freight container with Classes 1 (Explosives), 3 (Flammable Liquids where the Flammable Liquid is nitromethane), 5.1 (Oxidising Agents where the Toxic Substances are Fire Risk Substances), 5.2 (Organic Peroxides where the Toxic Substances are Fire Risk Substances), 8 (Corrosive Substances where the Toxic Substances are cyanides and the Corrosives are acids), Foodstuffs and foodstuff empties. They may however be loaded in the same vehicle or packed in the same freight container with Classes, 2.1 (Flammable Gases), 2.2 (Non-Flammable, Non-Toxic Gases), 2.3 (Toxic Gases), 3 (Flammable liquids, except where the flammable liquid is nitromethane), 4.1 (Flammable Solids), 4.2 (Spontaneously Combustible Substances), 4.3 (Dangerous When Wet Substances), 5.1 (Oxidising Agents except where the Toxic Substances are Fire Risk Substances), 5.2 (Organic Peroxides except where the Toxic Substances are Fire Risk Substances), 7 (Radioactive Substances), 8 (Corrosive Substances except where the Toxic Substances are cyanides and the Corrosives are acids), 9 (Miscellaneous Dangerous Goods)

Section 15 - Regulatory Information

AICS: All of the significant ingredients in this formulation are compliant with NICNAS regulations.

Section 16 - Other Information

This MSDS contains only safety-related information. For other data see product literature.

Acronyms:

ADG Code	Australian Code for the Transport of Dangerous Goods by Road and Rail (7th edition)
AICS	Australian Inventory of Chemical Substances
SWA	Safe Work Australia, formerly ASCC and NOHSC
CAS number	Chemical Abstracts Service Registry Number
Hazchem Code	Emergency action code of numbers and letters that provide information to emergency services especially firefighters
IARC	International Agency for Research on Cancer
NOS	Not otherwise specified
NTP	National Toxicology Program (USA)
R-Phrase	Risk Phrase
SUSMP	Standard for the Uniform Scheduling of Medicines & Poisons
UN Number	United Nations Number

Please read all labels carefully before using product.

This MSDS is prepared in accord with the SWA document "National Code of Practice for the Preparation of Material Safety Data Sheets" 2nd Edition [NOHSC:2011(2003)]

http://www.kilford.com.au/ Phone (02)9251 4532

Appendix 2.2 Phosdrin® (mevinphos)

RUNGE AG PHOSDRIN INSECTICIDE

MATERIAL SAFETY DATA SHEET

Date of issue 12th Sep 2008

STATEMENT OF HAZARDOUS NATURE Hazardous according to criteria of Worksafe Australia.
HAZARD SYMBOL T+ Very Toxic.

COMPANY DETAILS

Company:	Runge Agrichems Pty Ltd
Address:	79 Windemere Road, Robin Hill NSW 2795
Telephone:	02 6334 2124
Emergency Tel:	As above.

IDENTIFICATION

Product Name:	PHOSDRIN® INSECTICIDE
UN Number:	3018
Dangerous Goods Class:	6.1
Subsidiary Risk Class:	Not applicable
Poisons Schedule Number:	Schedule 7
Hazchem Code:	2WE
Use:	Organophosphate insecticide
Dangerous Goods:	Initial Emergency Response Guide 36

Physical Description/Properties:

Appearance:	Clear, red liquid with obnoxious odour
Specific Gravity:	1.235
Melting Point:	not available
Boiling Point:	325 degrees C.
Flashpoint:	79.4 degrees C.
Evaporation Rate:	
Percent Volatiles:	not available
Vapour Pressure:	2.9×10^{-3} mm Hg @25 degrees C.
Vapour Density:	heavier than air
Auto Ignition Temp:	Not applicable
Solubility (Water):	miscible in water

Ingredients:

Chemical Name:	CAS Number:	Proportion (w/v):
Mevinphos (mixed isomers)	7786-34-7	110.0%
Stench agent	-	0.1%
Red dye		0.025%

HEALTH HAZARD INFORMATION

RESTRAINTS:

An individual must NOT handle and/or apply mevinphos in excess of thirty days in any 12-month period.
An individual must NOT handle and/or apply more than 12 kg of PHOSDRIN on any day.
(Explanatory note: Handling on one day and spraying on another day constitutes two days of handling and/or applying. That is, each separate activity counts).
Do NOT apply under meteorological conditions or from equipment which could be expected to cause spray drift onto adjacent areas, particularly wetlands, waterbodies or watercourses.
Do NOT use PHOSDRIN Insecticide for the control of pests that are suspected to be resistant to organophosphate insecticides.
Do NOT apply with fogging machines or mist-blowers.
Do NOT apply with a back mounted knapsack. Do NOT apply by aircraft.

FIRST AID

If poisoning occurs, contact a doctor or Poisons Information Centre. Telephone 131126 Australia-wide.

If swallowed, give one atropine tablet every 5 minutes until dryness of the mouth occurs - if poisoned by skin absorption or through lungs, remove any contaminated clothing, wash skin thoroughly and give atropine tablets as above. Get to a doctor or hospital quickly.

The provisions of the Health (Use of Pesticides) Regulations 1984 made under the Health Act 1958 of Victoria apply to the use of this pesticide.

SYMPTOMS OF POISONING

The early symptoms may be excessive tiredness, nausea, headache, giddiness, blurred vision, contraction of pupils of the eyes, vomiting. On the first appearance of any of these symptoms, immediately cease work and call a doctor.

IMPORTANT

Repeated mild effects may be very dangerous. If affected at all avoid further contact until medical clearance has been given. Obtain an emergency supply of atropine tablets 0.6 mg and keep them handy on the job.

ADVICE TO DOCTOR

PHOSDRIN contains mevinphos, an organophosphate insecticide which causes acute cholinesterase depression. Atropine is the emergency antidote.

In all cases of severe intoxication and as early as possible inject preferably IV, atropine sulphate 2-4mg for adults (0.04-0.08 mg/kg body weight for children) and repeat at 2mg for adults (0.04mg/kg for children) every 3-10 minutes until adequately atropinised as shown by dilated pupils, flushing of the skin, dry mouth. If the IM route has to be used, take care not to overdose. Also administer, if available, an oxime eg. 2-PAM or $P2_S$ or Toxigonin, as directed by manufacturer.

MORPHINE OR OTHER OPIATES ARE CONTRAINDICATED

Maintain airway and vital functions. Artificial respiration may be required. Observe patient in hospital for at least 24 hours. Diagnosis should be confirmed by estimating the cholinesterase activity in the blood.

TOXICITY

Acute toxicity LD50	(mg /kg)
Rat Oral	3-12
Rat Dermal	4-90

PRECAUTIONS FOR USE

Exposure Limits: Threshold Limit Value (TLV) – 0.01ppm, 0.1mg/m^3 (skin) TWA ACGIH – mevinphos.

Engineering Controls: Do not inhale spray mist. Wear protective clothing as detailed below.

Personal Protection: See following:-

SAFETY DIRECTIONS

Very dangerous, particularly the concentrate. Product and spray are poisonous if absorbed by skin contact, inhaled or swallowed. Repeated minor exposure may have a cumulative poisoning effect. Avoid contact with eyes, skin and clothing. Do NOT inhale spray mist. Obtain an emergency supply of atropine tablets 0.6 mg. When opening the container and preparing spray, wear protective waterproof clothing, cotton overalls buttoned to the neck and

wrist and washable hat, elbow-length PVC gloves, chemical resistant footwear, and a full-face piece respirator with combined dust and gas cartridge. Mevinphos must only be applied using air-conditioned closed cabs, fitted with pesticide filters designed to remove particulate matter and vapours. When applying the spray, waterproof clothing, gloves and respirator may be removed, however clean waterproof clothing, gloves and respirator must be carried in the cab when applying the spray. If there is a need to exit the cab (for example, to check spray nozzles or remove an obstacle) when applying the spray, it is preferable to drive outside the sprayed field and then protective waterproof clothing, gloves and respirator must be worn before attending to equipment or re-entering field. If it is necessary to exit the cab in the field, the clean waterproof clothing, gloves, footwear and respirator must be worn.

If clothing becomes contaminated with product or wet with spray remove clothing immediately. If product or spray on skin, immediately wash area with soap and water. After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water. After each day's use, wash gloves, contaminated clothing and respirator, and if rubber wash with detergent and warm water.

FLAMMABILITY
Combustible.

SAFE HANDLING INFORMATION

STORAGE AND TRANSPORT

Store in the closed, original container in a cool, well-ventilated locked room or place away from children, animals, food, feedstuffs, seed and fertilisers. Do NOT store for prolonged periods in direct sunlight.

Ensure containers are correctly labelled and securely sealed.

Classified as a dangerous substance for transport purposes.

Eye-wash and washing facilities must be readily available. For decontaminating clothes and equipment have soda ash (sodium carbonate) on hand and for decontaminating and disposing spills, have lime, soda ash, absorbent material and open head drums on hand.

SPILLS AND DISPOSAL:

Clear area of all unprotected personnel. Wear full protective equipment including breathing apparatus. Stop leak if safe to do so by manoeuvring the container. Decant leaking container into a clean empty container, remote from the storage area and label.

Do not flush to drains or sewers. Do not contaminate streams, rivers or water courses.

Absorb spill in lime or wet area with 5% soda ash (sodium carbonate) solution and absorb on sand, earth or non-combustible absorbent material. Place material in open top drum, clean up with small amount of detergent and water, absorb and place in drum. Scatter lime over the area and leave for 1 hour. Decompose contaminated absorbent and surplus material with 5% soda ash solution. Leave in a safe place for one month. Seal drum and bury in an area approved by the local waste disposal authority. Soak protective equipment in 5% soda ash solution for at least 24 hours. Rinse and dry. Wash overalls.

Triple rinse containers before disposal. Add rinsings to spray tank. Do NOT dispose of undiluted chemicals on

site. Break glass containers and dispose of at a local authority landfill. If no landfill is available, bury the containers below 500mm in a disposal pit specifically marked and set up for this purpose clear of waterways, desirable vegetation and tree roots. Empty containers and product should NOT be burnt.

FIRE/EXPLOSION HAZARD:

Decomposition may give rise to toxic and noxious fumes. Alcohol resistant foam, carbon dioxide or dry chemical extinguishers required. Ensure respiratory equipment is available.

Evacuate immediate area. Advise Fire Brigade of nature of hazard. Wear full protective equipment, including breathing apparatus. Remove containers from site of fire, if possible, as overheating may cause some of the containers to break. Cool surrounding containers with a fine water spray.

Avoid contact of water with material as toxic run-off will form. In this event, consideration should be given to allowing the fire to burn out. Contain run-off.

OTHER INFORMATION

PROTECTION OF WILDLIFE, FISH, CRUSTACEA AND ENVIRONMENT
Dangerous to fish. Do not contaminate fish ponds, dams, rivers or streams with PHOSDRIN or the used container.

PROTECTION OF LIVESTOCK
PHOSDRIN is toxic to bees and should not be applied during active foraging of bees.

PROTECTION OF OTHERS
Do not spray directly on to humans, exposed food or foodstuffs. Keep away from food.
Workers should not enter areas or handle treated crops until one day after spraying unless wearing protective clothing.

PRECAUTIONS

RE-ENTRY TO TREATED AREA: THE FOLLOWING CONDITIONS MUST BE OBSERVED WHEN RE-ENTRY IS REQUIRED WITHIN A PERIOD OF TWO DAYS AFTER APPLICATION:

WEAR COTTON OVERALLS BUTTONED TO THE NECK AND WRISTS (OR EQUIVALENT CLOTHING) AND ELBOW-LENGTH PVC GLOVES.

AFTER EACH DAY'S USE, WASH GLOVES AND CLOTHING.

DISCLAIMER

The information provided in these MSDS's is based upon sources believed to be accurate. However the Company assumes no responsibility for the accuracy, completeness or suitability of this information. The product user is responsible to determine the suitability of this information for their particular purposes.

CONTACT POINT:

Police and Fire Brigade, dial 000.

Or: Runge Agrichems Pty Ltd
79 Windemere Road, Robin Hill, NSW 2795
Phone: (02) 6334 2124

Or:

Manufacturer: AMVAC Chemical Corporation, USA
Phone (24hr) : (International) +1 323-264-3910
Transportation (CHEMTREC, 24hrs) : (International) +1 800 424 9300

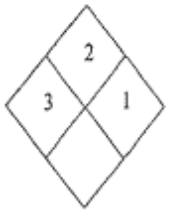
Date of Issue: 12th September 2008

SUPERCEDES: Cyanamid 11 June 1998
& Rotam 13 August 2003
See also: AMVAC MSDS # 144_13 (18th March 2003)

® PHOSDRIN is a trademark of AMVAC CHEMICAL CORP, USA

Appendix 2.3 DDVP Technical Grade (dichlorvos)

MATERIAL SAFETY DATA SHEET



1. CHEMICAL PRODUCT AND COMPANY IDENTIFICATION

PRODUCT NAME(S): DDVP TECHNICAL GRADE; DDVP (DICHLORVOS) TECHNICAL GRADE ACTIVE INGREDIENT; DICHLORVOS (DDVP) TECHNICAL; AMVOS™ LIQUITECH™; AMVOS™ RESTECH™
GENERAL USE: Insecticide - For formulating Use Only
PRODUCT DESCRIPTION: A colorless to slightly yellow liquid with a mild chemical odor.
CAS NUMBER: 62-73-7
MOLECULAR FORMULA: $C_4H_7Cl_2O_4P$
MOLECULAR WEIGHT: 221.0
EPA REGISTRATION NUMBER: 5481-96; 5481-461; 5481-462
HEALTH CANADA Reg. No.: 19723
MSDS NUMBER: 115_24
CURRENT MSDS Revision Date: 21 June, 2011

MANUFACTURER:
AMVAC CHEMICAL CORPORATION
4100 E. Washington Blvd.
Los Angeles, CA, USA 90023-4406
PHONE: 323-264-3910
FAX: 323-268-1028

EMERGENCY TELEPHONE NUMBERS:
MANUFACTURER: 323-264-3910
TRANSPORTATION (24 HOURS)
CHEMTREC: 800-424-9300
OTHER (24 HOURS)
AMVAC: 323-264-3910

2. COMPOSITION/INFORMATION ON INGREDIENTS

COMPONENT	WT %	CAS No.
Dimethyl 2,2-dichlorovinyl phosphate (DDVP)	98.0%(typical)	62-73-7
Related Compounds	2.0%(typical)	

OSHA HAZARDOUS COMPONENTS (29 CFR1910.1200)

COMPONENT	HAZARD	OSHA PEL*	ACGIH TLV*
DDVP	POISON	1.0 mg/m^3	0.1 mg/m^3

3. HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW:

DANGER! POISON! Poisonous if swallowed, inhaled or absorbed through skin and eyes. Rapidly absorbed through skin. Repeated inhalation or skin contact may, without symptoms, progressively increase susceptibility to Dichlorvos (DDVP) poisoning.

Toxic to fish, birds, and other wildlife. Do not contaminate bodies of water.

POTENTIAL HEALTH EFFECTS

ROUTE(S) OF ENTRY: Ingestion, inhalation, and absorption through the eye or skin are all possible routes of entry for this product. Exposure by any of the routes may cause acute cholinesterase depression. Severe cholinesterase depression may be fatal.

SIGNS OF ACUTE OVEREXPOSURE: Acute cholinesterase depression may be evidenced by headache, nausea, vomiting, diarrhea, abdominal cramps, excessive sweating, salivation and tearing, constricted pupils, blurred vision, tightness in chest, weakness, muscle twitching and confusion; in extreme cases, unconsciousness, convulsions, severe respiratory depression and death may occur.

SIGNS OF CHRONIC OVEREXPOSURE: Repeated exposures to small doses of DDVP and other organophosphates may lower the cholinesterase to levels where the above symptoms of acute overexposure are observed.

CARCINOGENICITY: EPA under its 1999 proposed Guidelines for Carcinogen Risk Assessment has classified DDVP as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential." IARC lists DDVP (Dichlorvos) as being possibly carcinogenic to humans (Group 2B). **CARE SHOULD BE EXERCISED IN HANDLING DDVP AND ITS FORMULATIONS.**

MEDICAL CONDITIONS AGGRAVATED BY EXPOSURE: Preexisting conditions which lower cholinesterase levels increase vulnerability to cholinesterase depression. These include: (for plasma) genetic cholinesterase deficiency; advanced liver disease; chronic alcoholism; malnutrition; dermatomyositis; existing toxicity from exposure to carbon disulfide; benzalkonium salts, organic mercury compounds, ciguatoxins or solanines; and (for RBC) hemolytic anemias.

4. FIRST AID MEASURES

DDVP IS A CHOLINESTERASE INHIBITOR. A PHYSICIAN SHOULD BE CONTACTED IN ALL CASES OF EXPOSURE TO DDVP AND ITS FORMULATIONS.

EYES: Immediately flush the eyes with copious amounts of clear, cool running water for a minimum of 15 minutes. Hold the eyelids apart during the flushing to ensure rinsing of the entire surface of the eyes and lids with water. Contact a physician immediately. If there will be a delay in getting medical attention, rinse the eyes for at least another 15 minutes.

INHALATION: Remove victim to fresh air. If breathing has ceased, clear the victim's airway and start mouth-to-mouth artificial respiration. If breathing is difficult, give oxygen. Contact a physician immediately.

INGESTION: Induce vomiting immediately by giving two glasses of water and sticking finger down throat. Never give anything by mouth to an unconscious person. Contact a physician immediately.

SKIN: Immediately flush all affected areas with large amounts of clear water for at least 15 minutes. Remove contaminated clothing. Do not attempt to neutralize with chemical agents. Wash clothing before reuse. Contact a physician immediately.

NOTE TO PHYSICIANS: This is an Organophosphate (OP) Insecticide. Do not wait for laboratory confirmation to treat patients with strong clinical evidence of poisoning. In the USA and other countries, contact your local or national poison control center for more information.
Do Not handle the patient without the following protective equipment in place: chemical resistant gloves and apron (preferably nitrile). Remove contaminated clothing and do not reuse without thorough cleaning with detergent and hot water. Dispose of heavily contaminated clothing, including shoes, as a hazardous waste.
Establish airway and oxygenation. IV Atropine sulfate is the antidote of choice. Moderately severe poisoning: use 0.4-2.0 mg in adults or 0.05 mg/kg in children. Repeat every 15 minutes until atropinization is achieved. Severe poisoning may require larger doses. Cholinergic toxicity may recur as atropinization wears off; monitor patient closely. Draw blood for RBC and plasma cholinesterase. In addition, Pralidoxime (2-PAM) is indicated during the first 36 hours in severe poisonings. Slow IV administration (no less than 2 minutes) of 1 g in adults or 20-50 mg/kg in children may be repeated in 1 to 2 hours if muscle weakness, twitching, and/or respiratory depression persist. Avoid morphine, aminophylline, phenothiazines, reserpine, furosemide and ethacrynic acid.
Bathe and shampoo contaminated skin and hair. If ingested, empty stomach; activated charcoal is useful to further limit absorption. If victim is alert, Syrup of Ipecac (2 tablespoons in adults, 1 tablespoon in small children) followed by water (2 glasses for adults, 1 glass for children) is indicated. If symptoms such as loss of gag reflex, convulsions, or unconsciousness occur before emesis, gastric lavage should be considered following intubation with a cuffed endotracheal tube.

5. FIRE FIGHTING MEASURES

FLAMMABLE PROPERTIES

Flash Point: 175°F/79°C (TCC)
Autoignition Temperature: Not available
Flammable Limits:
Lower flammable limit: Not available
Upper flammable limit: Not available
Flammability: This is a combustible liquid that will support fire if it is preheated (NFPA rating = 2)

EXPLOSIVITY

Mechanical Impact: Not explosive
Static Discharge: Will not occur

HAZARDOUS COMBUSTION PRODUCTS: This product will emit toxic fumes when burned, including hydrogen chloride and carbon monoxide. Vapors of the unburned product may also be hazardous. Contact with the fumes and vapors should be avoided by staying upwind and by wearing chemical resistant clothing and positive pressure self-contained breathing apparatus.

EXTINGUISHING MEDIA: Foam, dry chemical, carbon dioxide, water spray (fog).

FIRE FIGHTING INSTRUCTIONS: Evacuate nonessential personnel from the area. Keep upwind. Wear self-contained breathing apparatus and full bunker gear, including gloves and eye protection. Clean all clothing before reuse.

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6. ACCIDENTAL RELEASE MEASURES

GENERAL: Evacuate personnel and thoroughly ventilate the area. Use adequate ventilation and appropriate personal protective equipment (PPE, Section 8). Keep bystanders upwind and away from the spill.

SMALL SPILL: Cover with absorbent (clay, sawdust, straw, kitty litter, etc.) to absorb the liquid. Sweep into an open drum. Decontaminate the area and equipment with dilute alkali or ammonia (less than 5% solution) and detergent. Flush the area with water. Absorb and sweep into the same open drum. Close the drum and dispose of as a hazardous waste.

LARGE SPILL: Dike the spill to prevent contamination of local water sources. Siphon the majority of the liquid into drums for use or disposal, depending on the circumstances. Clean the area as described for a small spill.

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7. HANDLING AND STORAGE

HANDLING: Prevent skin contact. Do not breathe fumes or vapors. Wear appropriate personal protective equipment (Section 8). Wash thoroughly and change clothes after handling. Keep product away from food drink, cosmetics, and tobacco products. See product label for more detailed handling procedures.

STORAGE: Do not contaminate water, food or feed by storage or disposal. Store product in a cool, dry, locked place out of reach of children. Store in original container.

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8. EXPOSURE CONTROLS/PERSONAL PROTECTION

ENGINEERING CONTROLS: A well-ventilated area is recommended for handling DDVP. Use of mechanical or local exhaust systems is recommended.

RESPIRATORY PROTECTION: When respiratory protection is required, or concentrations may exceed the PEL, use a NIOSH/MSHA approved air-purifying respirator equipped with organic vapor cartridges or canisters. It is recommended that the canisters be changed whenever breakthrough occurs or eight (8) hours of use has occurred, whichever comes first. For emergency and other conditions where the exposure limit may be greatly exceeded, use an approved positive-pressure, self-contained breathing apparatus or positive-pressure airline with auxiliary self-contained air supply.

SKIN PROTECTION: Prevent skin contact. Chemical resistant gloves(preferably nitrile), coveralls or long-sleeved shirt and pants, and chemical resistant shoes or boots, are necessary to prevent skin contamination. A chemical resistant apron or chemical resistant clothing will provide additional protection when there is a risk of spillage or splashing. Remove contaminated clothing as soon as possible. Wash dirty or contaminated clothing separately from other clothes. Wear clean clothes daily. Wash well with soap and water after handling this product. See the label for more specific instructions.

EYE PROTECTION: Safety glasses should be worn whenever working with chemicals. In addition, goggles or a faceshield are required if there is a chance of splashing.

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9. PHYSICAL AND CHEMICAL PROPERTIES

PHYSICAL STATE:	Liquid
APPEARANCE:	A colorless to a slightly yellow color.
ODOR:	Mild chemical odor.
ODOR THRESHOLD:	Not available
BOILING POINT:	189°F/87°C @ 1-3 mm Hg
FREEZING/MELTING POINT:	< -76°F/-60°C
SPECIFIC GRAVITY:	1.424 g/mL @ 20°C/4°C(68°F/39°F)
DENSITY:	11.88 lb/gal
VAPOR PRESSURE (mm/Hg):	0.01 mm Hg @ 25°C
VAPOR DENSITY:	Heavier than air
PERCENT VOLATILE BY VOLUME:	Not available

9. PHYSICAL AND CHEMICAL PROPERTIES, cont'd

SOLUBILITY (Water):	1.5% @ 25°C
SOLUBILITY (Other):	This product is soluble in aromatic hydrocarbons, chlorinated hydrocarbons, ketones, and esters.
PARTITION COEFFICIENT (O/W):	38.4 @ 25°C
pH:	Approx. 4 (as 1% solution)
EVAPORATION RATE:	Not available

10. STABILITY AND REACTIVITY

CHEMICAL STABILITY (Conditions to avoid): This product is stable under normal use and storage conditions.

REACTIVITY: DDVP will slowly react with water to form acids.

INCOMPATIBILITY: Avoid strong oxidizers, strong acids, strong bases, heat, and sources of ignition.

HAZARDOUS DECOMPOSITION PRODUCTS: Heating product to decomposition will cause emission of acrid smoke and fumes of hydrogen chloride, phosphorous oxides, and carbon oxides.

HAZARDOUS POLYMERIZATION: This product will not polymerize.

11. TOXICOLOGICAL INFORMATION

INGESTION:	Oral LD_{50} (rat):	80/56 mg/kg (male/female)
INHALATION:	Inhalation LC_{50} (rat):	> 198 mg/m^3(4 hr, head only, vapor)
DERMAL:	Skin LD_{50} (rat):	107/75 mg/kg (male/female)
IRRITATION:	Eye irritation:	Irritant
	Skin irritation:	Irritant
SENSITIZATION:	Skin sensitization: (guinea pig)	Possible Sensitizer

TERATOGENICITY: No evidence of teratogenicity in laboratory animals.

MUTAGENICITY: No clear evidence of *in vivo* mutagenicity activity in mammalian assay systems.

CARCINOGENICITY: Two laboratory studies have shown a low incidence of forestomach tumors in the mouse and mononuclear cell leukemia in the F344 rat. EPA under its 1999 proposed Guidelines for Carcinogen Risk Assessment has classified DDVP as having "suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential". IARC lists DDVP (Dichlorvos) as being possibly carcinogenic to humans (Group 2B). **CARE SHOULD BE EXERCISED IN HANDLING DDVP AND ITS FORMULATIONS.**

REPRODUCTIVE TOXICITY: Reproductive effects have only been seen at a dose level which produced a generalized toxicity in the rat.

TOXICOLOGICALLY SYNERGISTIC PRODUCTS: No data are available.

12. ECOLOGICAL INFORMATION

GENERAL: This product is toxic to fish, birds, and other wildlife. Keep out of any body of water. Do not contaminate water when disposing of equipment washwaters or wastes.

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL: Pesticide wastes are acutely hazardous. Improper disposal of excess pesticide, spray mixture or rinsate is a violation of Federal law. If these wastes cannot be disposed by use according to label instructions, contact your nearest State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA regional office for guidance. Open dumping is prohibited.

CONTAINER DISPOSAL: Triple rinse (or equivalent). Then offer for recycling or reconditioning, or puncture and dispose of container in a sanitary landfill or by incineration, or, if allowed by State and local authorities, by burning. If burned, stay out of smoke. Contact your nearest State Pesticide or Environmental Control Agency, or the Hazardous Waste representative at the nearest EPA regional office for guidance. Open dumping is prohibited.

14. TRANSPORTATION INFORMATION

DOT CLASS:	6.1
UN NUMBER:	3018
IMDG CLASS (sea):	6.1
MARINE POLLUTANT:	Yes
PACKING GROUP:	III
Hazard Label(s):	TOXIC
ADR CLASS (road):	6.1
PROPER SHIPPING NAME(S):	Organophosphorus pesticide(s), liquid, toxic, (Dichlorvos)
REPORTABLE QUANTITY:	Yes

PACKAGING

GENERAL DESCRIPTION:	55 gallon polyethylene drums

15. REGULATORY INFORMATION

U.S. FEDERAL REGULATIONS: This product is registered under EPA/FIFRA Regulations. It is a violation of Federal Law to use this product in any manner inconsistent with its labeling. Read and follow all label directions. This product is excluded from listing requirements under EPA/TSCA.

15. REGULATORY INFORMATION, cont'd

CANADIAN REGULATIONS: This product is registered under the Pest Control Product Act of Canada. It is a violation of Canadian Law to use this product in any manner inconsistent with its labeling. Read and follow all label directions.
This product has been classified according to the hazard criteria of the CPR and the MSDS contains all the information required by the CPR.

EUROPEAN UNION REGULATIONS: This product is registered in the European Union.

SARA TITLE III DATA

Section 311 & 312 Hazard Categories:

Immediate Health Hazard:	Yes
Delayed Health Hazard:	Yes
Fire Hazard:	No
Reactive Hazard:	No
Sudden Pressure Release Hazard:	No

Section 302 Extremely Hazardous Substances: DDVP (Dichlorvos, 62-73-7)
Section 313 Toxic Chemicals: DDVP (Dichlorvos, 62-73-7)

CERCLA/EHS Reportable Quantities (RQ): DDVP (Dichlorvos) - 10 lbs

STATE REGULATIONS:
CALIFORNIA (Proposition 65): This product contains a chemical known to the State of California to cause cancer - DDVP.

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16. OTHER INFORMATION

MSDS STATUS:
Date This Revision: 21 June, 2011
Date Previous Revision: 22 April, 2008
Person Responsible for Preparation: Gary A. Braden

REASONS FOR REVISION: Annual Review. Formatting changes were made throughout the MSDS to reflect current practice. Information was updated in sections 11 and 14 to reflect current knowledge.

DISCLAIMER: This information is provided for the limited guidance to the user. While AMVAC believes that the information is, as of the date hereof, reliable, it is the user's responsibility to determine the suitability of the information for its purposes. The user is advised not to construe the information as absolutely complete since additional information may be necessary or desirable when particular, exceptional, or variable conditions or circumstances exist (like combinations with other materials), or because of applicable regulations. No express or implied warranty of merchantability or fitness for a particular purpose or otherwise is made hereunder with respect to the information or the product to which the information relates.

16. OTHER INFORMATION, cont'd

ABBREVIATIONS:

ACGIH	-	American Conference of Governmental Industrial Hygienists
CERCLA	-	Comprehensive Environmental Response, Compensation, and Liability Act
EPA	-	Environmental Protection Agency
FIFRA	-	Federal Insecticide, Fungicide, and Rodenticide Act
IARC	-	International Agency for Research on Cancer
NTP	-	National Toxicology Program
OSHA	-	Occupational Safety and Health Administration
SARA	-	Superfund Amendments and Reauthorization Act
TSCA	-	Toxic Substances Control Act
DOT	-	Department of Transportation (USA)
IMDG	-	International Maritime Dangerous Goods
IATA	-	International Air Transport Association

This is the last page of this MSDS. There should be 9 pages.

Appendix 2.4 Barmac DiazinonInsecticide(diazinon)

DATE OF ISSUE: 24TH DECEMBER 2007

BARMAC INDUSTRIES PTY LTD
BOX FLAT ESTATE SWANBANK RD. SWANBANK Q 4306

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: BARMAC DIAZINON INSECTICIDE

PHONE: (07) 3280 3000
EMERGENCY AFTER HOURS NUMBER: (07) 3280 3000

Classified as hazardous by Worksafe Australia Criteria

IDENTIFICATION

OTHER NAMES: Neocid
USE: An Insecticide
UN NUMBER: 3018
HAZCHEM CODE: 2X
DANGEROUS GOODS CLASS: 6.1
POISONS SCHEDULE: S6

PHYSICAL DESCRIPTION/PROPERTIES

APPEARANCE: Brown, slightly viscous liquid, Strong odour.
FLASHPOINT (^{0}C): >61 ^{o}c
BOILING POINT (^{0}C): Approx 130^{o}c
VAPOUR PRESSURE (___): N/A
FLAMMABILITY LIMITS (%): N/A
SPECIFIC GRAVITY: Approx. 1.08
SOLUBILITY IN WATER (g/L): Insoluble. Will emulsify.

INGREDIENTS

CHEMICAL ENTITY	CAS NO	PROPORTION
Diazinon	333-41-5	80% w/v
Hydrocarbon Solvent & Inert Ingredients		20% w/v

DATE OF ISSUE: 24TH DECEMBER 2007

BARMAC INDUSTRIES PTY LTD
BOX FLAT ESTATE SWANBANK RD. SWANBANK Q 4306

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: BARMAC DIAZINON INSECTICIDE

PHONE: (07) 3280 3000
EMERGENCY AFTER HOURS NUMBER: (07) 3280 3000

Classified as hazardous by Worksafe Australia Criteria

HEALTH HAZARD INFORMATION

HEALTH EFFECTS
ACUTE:

SWALLOWED: Product is considered to be moderately toxic. The product is a cholinesterase inhibitor.

EYES: Eye contact should be avoided. Will irritate eyes. A potential for poisoning due to absorption through the eyes exists, particularly if product is not washed out immediately.

SKIN: Skin contact should be avoided. Absorption through the skin is the most likely industrial route of exposure, particularly when handling the undiluted material. Skin irritation varies from very mild to none depending on the skin sensitivity of the individual.

INHALED: Inhalation should be avoided. Product is slightly toxic by this route of exposure.

CHRONIC: All cholinesterase inhibitors will have a cumulative poisoning effect. Repeated minor exposure of this group of products may prove to be harmful. Levels of cholinesterase may not return to normal for upto 3 weeks after the last exposure.

FIRST AID

SWALLOWED: If swallowed contact a doctor or Poisons Information Centre. Give one atropine tablet every 5 minutes until dryness of the mouth occurs. If unconscious give nothing by mouth and do not induce vomiting.

EYES: If in eyes, hold eyelids open, flood with water for at least 15 minutes and see a doctor. If poisoning symptoms develop give atropine tablets as above.

SKIN: If skin contact occurs remove contaminated clothing and wash skin thoroughly. If poisoning symptoms develop give atropine tablets as above.

DATE OF ISSUE: 24TH DECEMBER 2007

BARMAC INDUSTRIES PTY LTD
BOX FLAT ESTATE SWANBANK RD. SWANBANK Q 4306

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: BARMAC DIAZINON INSECTICIDE

PHONE: (07) 3280 3000
EMERGENCY AFTER HOURS NUMBER: (07) 3280 3000

Classified as hazardous by Worksafe Australia Criteria

INHALED: Move victim to fresh air. Seek medical advice. If poisoning symptoms develop give atropine tablets as above.

FIRST AID FACILITIES: Obtain an emergency supply of atropine tablets 0.6 mg

ADVICE TO DOCTOR: Treat as a cholinesterase inhibitor. Atropine is antidotal.

PRECAUTIONS FOR USE

EXPOSURE STANDARDS: The exposure limit for product is 0.1 mg/m^3 (8 hrs TWA)

ENGINEERING CONTROLS: Use in well-ventilated area only.

PERSONAL PROTECTION: Use good industrial hygiene. Wear face shield or goggles, elbow length PVC gloves, cotton overalls buttoned to the neck and wrist, washable hat and half face respirator with dust and vapour cartridge. After use and before eating, drinking or smoking wash hands, arms and face thoroughly with soap and water.

FLAMMABILITY: Product is combustible.

SAFE HANDLING INFORMATION

STORAGE AND TRANSPORT: Material is classified as a dangerous good for transport purposes. Product should be stored in a cool, dry place and out of direct sunlight. Keep out of reach of children. Store away from food or foodstuffs. Do not store near other pesticides or seed. Keep container tightly closed when not being used.

DATE OF ISSUE: 24TH DECEMBER 2007

BARMAC INDUSTRIES PTY LTD
BOX FLAT ESTATE SWANBANK RD. SWANBANK Q 4306

MATERIAL SAFETY DATA SHEET

PRODUCT NAME: BARMAC DIAZINON INSECTICIDE

PHONE: (07) 3280 3000
EMERGENCY AFTER HOURS NUMBER: (07) 3280 3000

Classified as hazardous by Worksafe Australia Criteria

SPILLS AND DISPOSAL: Contain spills, adsorb and sweep up. Store in sealed drums for disposal. Materials should be disposed in a land fill area approved by local authorities.

FIRE/EXPLOSION HAZARD: If involved in a fire, protective clothing and breathing apparatus should be worn.

OTHER INFORMATION

LD 50 oral is 850 mg/Kg. (Based on similar products).

LD 50 dermal is >2150 mg/Kg (Based on similar products)

Product is highly toxic to birds and bees and moderately toxic to fish.

Appendix 3 Document for skin testing and quality check of the PVC gloves

Appendix 3.1 Ethics approval for the use of human skin samples

Appendix 3.2 Quality assurance/quality control of the PVC gloves studied

Appendix 3.2.1 Running of coating of the gloves and tearing on unused gloves

Appendix 3.2.2 Pinhole water test conducted on randomly selected gloves

Appendix 3.1 Ethics approval for the use of human skin samples

This research project used the ethics approval for anon-going project in the Occupational and Environmental Hygiene Laboratory for chemicals involved in chemical, biological and radiological (CBR) incidents

Risk-based decision making for chemical, biological and radiological (CBR) incidents

Office Use Only	
RM Code:	Revision Number: 1
Receipted Date:	Printed Date: 27/02/2013

Project Start Date 01/08/2010
Project End Date 31/12/2015

1. Human Ethics Research Approval

Approval Obtained From	The Southern Adelaide Clinical Human Research Ethics Committee (Flinders Medical Centre and Repatriation Hospital)
Approval Number	273/10
Approval Date	02/07/2010

PhD CANDIDATE : ISMANIZA ISMAIL (1618465)

2. Chief Investigator Details

Name	Dr S E Gaskin
Work Phone	83134957
Email	sharyn.gaskin@adelaide.edu.au
Department	Public Health
University Classification	General
University Type	Staff Member
Employing Institution if title holder	n/a

3. Co-investigator Details

Name	Associate Professor D L Pisaniello
Work Phone	(08) 8313 3571
Email	dino.pisaniello@adelaide.edu.au
Department	Public Health
University Classification	Academic
University Type	Staff Member
Employing Institution if title holder	n/a
Name	Dr J Edwards
Work Phone	(not specified)
Email	(not specified)
Institution/Organisation	Flinders University
University Classification	
University Type	External
Employing Institution if title holder	n/a

4. Project Aim & Description

Aim — Accidental or intentional toxic chemical releases can have significant public health impacts and resource implications. The research will develop a predictive skin absorption model to support decisions by first responders about skin decontamination of exposed persons, and will have a focus on

Description	Sections of skin will be obtained (with written consent) from patients undergoing surgical reduction treatment at the Flinders Private Hosptial and Flinders Medical Centre.

5. Project Scope

Scope Classification	Human Research Scope/Other
Project Location	Occupational Hygiene laboratory, University of Adelaide, Environment and Health, Flinders University.
Sponsor/Source of Funding	DSTO of the Department of Defence under scheme Australian Government MOU concerning Combating Terrorism Research and Development with the US Government.

6. Indemnification

Indemnification by Sponsor	No
Indemnification by Hospital	No
Indemnification by University	No

7. Participant Numbers and Potential Risk

Year	Number
2013	20
2014	20
2015	20
Total	60

Potential Risks To Participants	Participants will be selected from those undergoing surgical reduction procedures. Donors will be provided with a project information sheet and will be asked to complete a donor consent form. Consenting participants wil be advised that there will be NO RISK to them personally, and we will use only the skin that is removed as part of their required surgical procedure. The skin is normally discarded but will be used in our in vitro procedures. Consenting subjects may withdraw their consent at any time up to 2 hours following collection, thereafter samples will be anonymised.

8. IP and Ownership

Is there an Intellectual Property Agreement in place?	Yes
Is there an Ownership and Use Agreement in place?	Yes

9. Declaration

Human Research Approval Notification: "Risk-based decision making for chemical, biological and radiological (CBR) incidents"

Signoff (Chief Investigator Signature)

Print Name Dr S E Gaskin

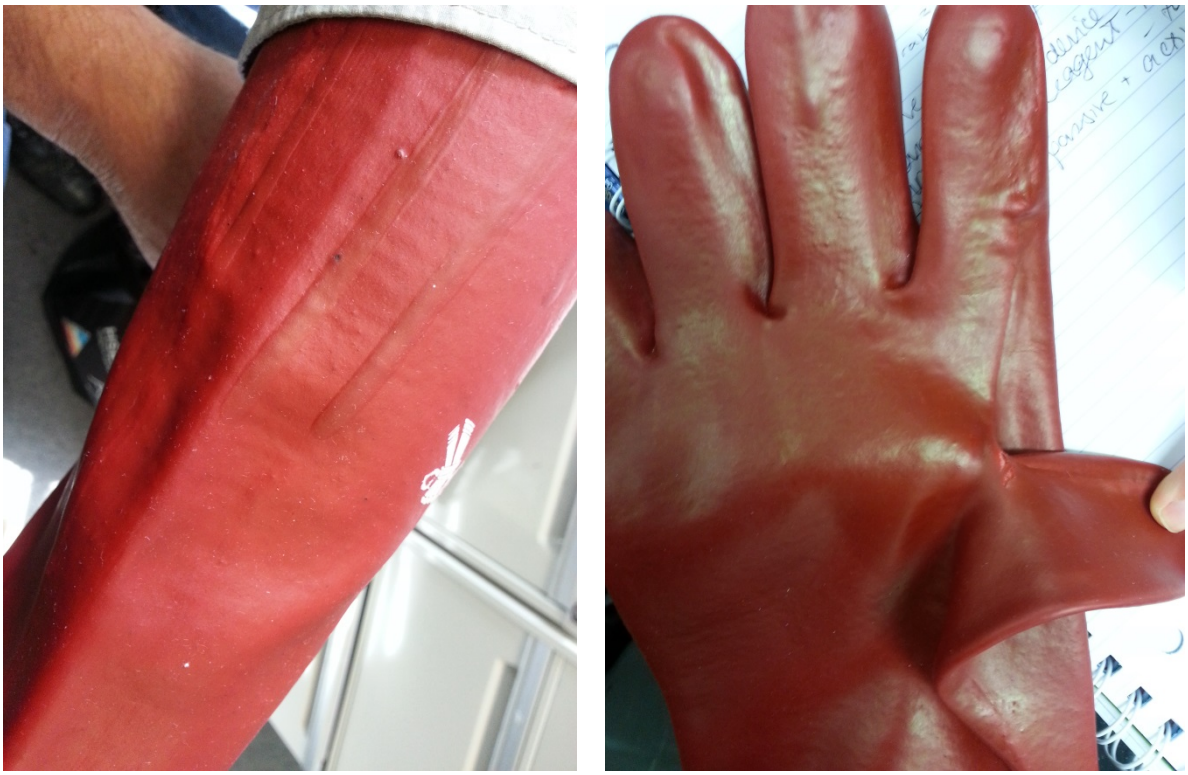
Date 27-02-2018

Please submit this form to:

The Secretary, Human Research Ethics Committee,
Office of Research Ethics, Compliance and Integrity, Research Branch,
Level 7, 115 Grenfell St,
Adelaide, SA 5005.

Appendix 3.2 Quality assurance/quality control of the PVC gloves studied

Appendix 3.2.1 Running of coating of the gloves and tearing on unused gloves



Photos showing PVC gloves (Excalibur) with running of coating (left) and tearing near the thumb (right) despite being new and unused.

Appendix 3.2.2 Pinhole water test conducted on randomly selected gloves

Photo showing randomly selected PVC glove (from each pack in the batch box) tested for pinhole leakage, by filling it up with tap water and squeezing it tightly.

Appendix 4 Documents for preliminary field observation in Virginia, South Australia

Appendix 4 compiles the documents related to the preliminary field observation conducted in Virginia, South Australia. Appendix 4.1 consists of the documents relevant to ethics approval, while Appendix 4.2 is comprised of examples of the completed checklist and body map used on site for recording background information from the observation.

Appendix 4.1Ethics approval for preliminary field observation

Appendix 4.1.1 Participant information sheet

Appendix 4.1.2 Consent form

Appendix 4.2 Examples of information recorded in preliminary field observation

Appendix 4.2.1 Checklist for preliminary field observation

Appendix 4.2.2 Body map for observed exposure

Appendix 4.1Ethics approval for preliminary field observation

No ethics approval was necessary in the preliminary field observation of the agricultural workers in Virginia, South Australia. However, workers were provided with a Participant Information Sheet (Appendix 4.1.1) to assist the participants in making an informed decision to involve in the observation. The sheet provides brief information to ensure that participants can consider their participation without pressure and have the information that they need in order to give informed consent.

Appendix 4.1.1 Participant information sheet

THE UNIVERSITY of ADELAIDE

Department of Public Health
Faculty of Health Science
The University of Adelaide

PARTICIPANT INFORMATION SHEET

Study of work practices and behaviours contributing to dermal exposure to pesticides in South Australian farms

Investigators: Professor Dino Pisaniello, Ms. Ismaniza Ismail

The University of Adelaide is carrying out a study of organophosphorus pesticides widely used in agricultural industry. The main purpose of the study is to identify the potential source of dermal exposure contributed by work practices and behaviours in farms.

This study will focus on dermal exposure to pesticides to agricultural workers, particularly in handling of pesticides (mixing, loading and spraying of pesticides).

You are invited to participate in a research project examining dermal exposure to pesticides among farmworkers in South Australian farms. Your participation in this study is entirely voluntary and you are free to decline to participate or to withdraw from participation at any time. You may refuse to answer any questions that you feel too personal or intrusive. You have been chosen for the study because you are a farmworker aged 18-60 years of age. This form is part of a process called 'informed consent' to allow you to understand this study before deciding whether to take part.

Summary of procedures

- This study consists of only one visit to your workplace.
- Observation will be made at a reasonable distance to minimise interference during the task.
- The workers will be observed on several aspects to help identify work practices and controls leading to potential exposure, which include type and purpose of pesticides, how the pesticides are mixed, duration of pesticide handling, personal protective equipment (PPE) worn, etc.
- A checklist of the observed aspects will be used by the researcher to record the observation to ensure consistency and reproducibility of data collected
- We will ask you several demographic questions (e.g. name, age, duration of work experience), which will take around 5-10 minutes.
- No bodily samples (e.g. blood, urine) will be taken from the site or from the workers.

The findings of this research should provide a better understanding of potential exposure to pesticides. The information obtained from the observation is useful to complement the experimental data of glove permeation obtained in the laboratory and should also assist in optimising control measures for pesticide-exposed workers.

Your participation in this study should cause no significant risks or discomfort to participants. If you suffer injury as a result of participation in this research or study, compensation might be paid without litigation. However, such compensation is not automatic and you may have to take legal action to determine whether you should be paid.

Under Australian privacy law all information we have collected about you must be kept confidential, unless you agree to it being released. If you wish to find out the results of the observation, these results will be made available to you.

If you consent to take part in this study, no information that could identify you will be given to anyone else, except if required by law. The project outcomes will be published in conference papers, journals or other venues but you will not be identified by name in any report or publication. Records and data about your participation in this study may be used for study purposes or for further analyses in the future. All such records and your right to them will be protected in accordance with Australian law.

You will not receive any payment for participation in this study.

You may ask any questions you have now. Or if you have questions later, you may contact the researchers via 08 83134959 or ismaniza.ismail@adelaide.edu.au. If you wish to talk privately about your rights as a participant, you may contact:

Prof Dino Pisaniello,
Head of Dept. of Public Health, University of Adelaide
Ph: 08 8313 3571

This study has been reviewed by the Southern Adelaide Clinical Human Research Ethics Committee Approval Number 319.13). If you wish to discuss the study with someone not directly involved, in particular in relation to policies, your rights as a participant, or should you wish to make a confidential complaint, you may contact the Executive Officer on 8204 6453 or email research.ethics@health.sa.gov.au.

Appendix 4.1.2 Consent form

A consent form was given to each participant to be signed in support of the Participant information sheet (Appendix 4.1.1).

CONSENT FORM

THE UNIVERSITY of ADELAIDE

See also Information Sheet attached.

1. I _____ (please print) hereby consent to take part in the research project entitled:
   Work practices and behaviours contributing to dermal exposure to pesticides in South Australian farms
2. I acknowledge that I have read the Information Sheet.
3. I have had the project, so far as it affects me, fully explained to my satisfaction by the researcher. My consent is given voluntarily.
4. I have been given the opportunity to have a member of my family or a friend present while the project was explained to me.
5. I have been informed that, while information gained during the study may be published, I will not be identified and my personal results will not be disclosed.
6. I understand that the involvement of my employees in this research project may not be of any direct benefit to me and that I may withdraw my consent at any stage without affecting my rights or the responsibilities of the researchers in any respect.
7. I declare that I am over the age of 18 years.
8. I acknowledge that I have been informed that should my business be adversely affected as result of taking part in this study, I may need to start legal action to determine whether my business should be compensated.
9. I am aware that I should retain a copy of this Consent Form, when completed, and the relevant.

Signed _____ Date: _____

Name of witness: _____ Date: _____
Signed _____

I, _____ have described to _____ the nature of the procedures to be carried out. In my opinion, he/she understood the explanation.

Signed _____ Date: _____

Appendix 4.2 Examples of information recorded inpreliminary field observation

During the preliminary field observation in Virginia, South Australia, a checklist (example in Appendix 4.2.1) was used to record observations. The checklist included details of the pesticides used, tasks, the use of PPE, details of the gloves, work practices and behaviours, skin exposure and facilities available that could help to reduce dermal exposure to pesticides handled.

Although pesticides sprayed in the farms during the observation were not OPs, information on the pesticides were recorded to note potential similarities in pesticide handling. The purpose, brand, active ingredient and storage of the pesticides provided information on the risk of exposure to the pesticide handlers i.e. participants involved in the field observation. Emphasis was put on understanding opportunities for dermal exposure during mixing, loading and spraying of pesticides; in which different concentrations (full strength and application strength) were involved at the farms.

When the mixing, loading and spraying tasks were conducted, information on the tool used for mixing and type of sprayer was noted, as it indicated how much potential contact with the pesticides is involved. Duration of shift length, actual exposure duration to pesticides and frequency of exposure provided information on the likelihood of exposure and severity of the risk faced by the participants. Work temperature and weather condition were also recorded, noting potential temperature rise with intense sunlight during summer.

Observation was also made on the personal protective equipment (PPE) worn by the participants i.e. protective clothing, head protection, eye protection, respiratory protection, hand protection and foot protection. Conditions of the PPE worn were observed as they may signify a possibility of degraded protection, while cross contamination may occur if the PPE were not cleaned after previous use and/or brought back home.

Themain section in the observation checklist was the glove section, which verified that gloves were actually used in various conditions that may unknowingly affect the integrity or performance. Whilst gloves were worn by most participants, observation was focused on the types (material), length and conditions of the gloves. It was noted that reuse of gloves was

practised (signs of abrasion) and gloves were dried under the sunlight, indicating exposure to UV. The age of gloves being reused may denote the deteriorated glove performance which is associated with the reservoir capacity. In a way, it assists in understanding the effects of these modifying factors on glove permeation in real world conditions, and not only based on tests by the glove manufacturers which are mainly conducted at room temperature.

Work practices and behaviour of the participants may suggest sources of contamination transfer. This was noted from incorrect techniques of removing gloves, transfer of contamination to and from the body (e.g. smoking, scratching, rubbing eyes) and/or other contaminated surfaces(e.g. surfaceof vehicle steering and hose rollers). Poor hygiene practices i.e. not washing hands during breaks or after completing the pesticide handling tasks may also contribute to prolonged contact with pesticides, and possibly lead to ingestion from hand-to-mouth transfer.

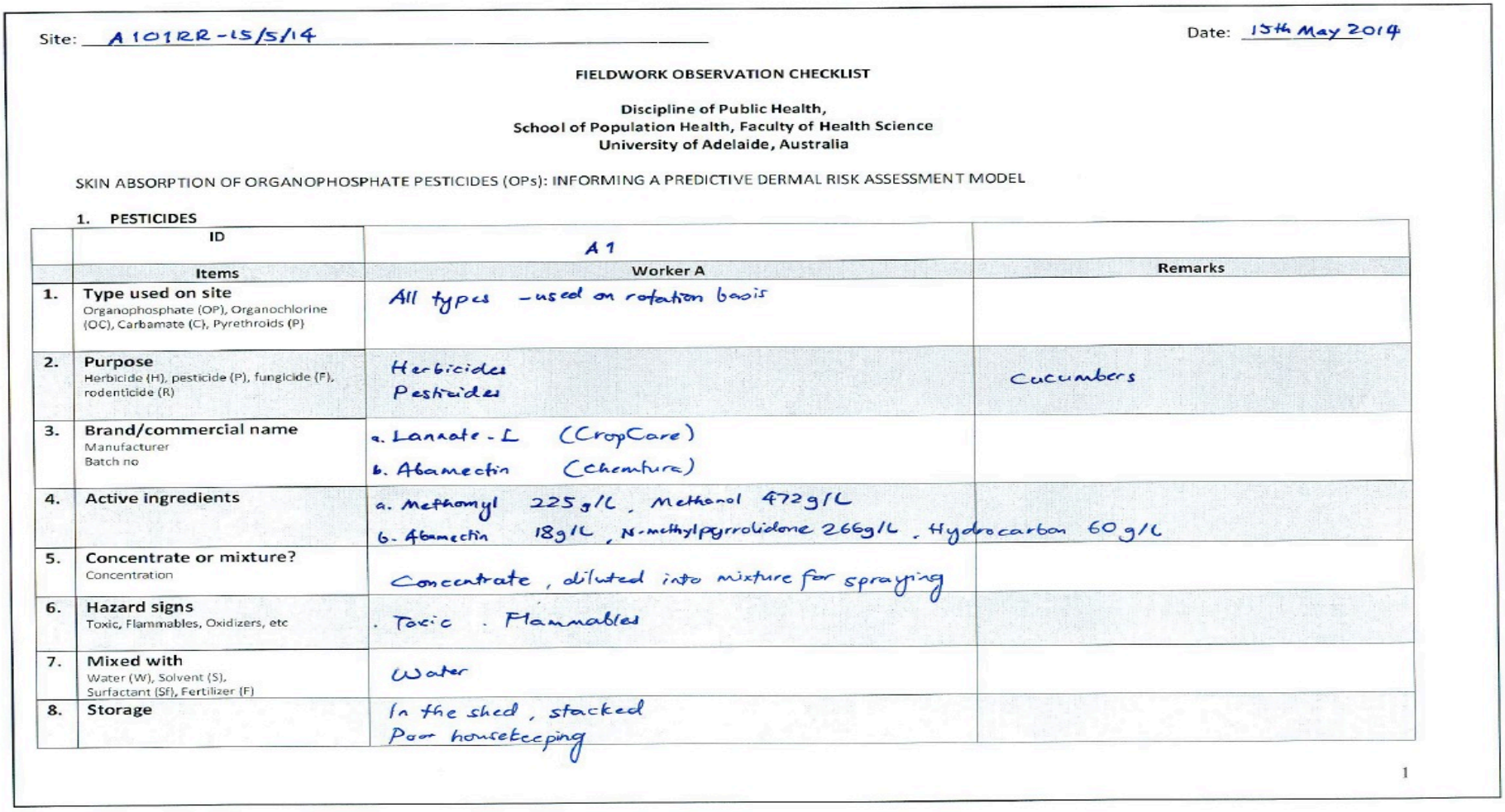
A body map (example in Appendix 4.2.2) was used to visualise the observed pesticide exposure on the participants. In this observation, hands, forearms, legs and feet were the common parts contaminating the PPE and skin. The findings provided evidence that skin exposure to pesticides is still possible, even with the use of PPE. In addition, signs of skin diseases were also observed on the hands of the participants, as it may indicate potential for greater skin absorption.

Another aspect observed at the farms was the available facilities that may contribute to higher exposure to pesticides, such as tap water for washing hands in case of spills and splashes as well as drinking water in bottles that may be touched with contaminated hands during breaks. Handwash basins were generally not provided with soap or towels, similar to the bathrooms, toilets and the eating areas. This indicated the possibility of improper handwashing and remaining pesticide residue on the skin for an extended duration.

The information collected from this field observation verified the real life exposure to pesticides, thus was manipulated to design the glove permeation studies (Chapter 4) and skin penetration studies (Chapter 6) in this thesis.

Appendix 4.2.1 Checklist for preliminary field observation

Example of completed checklist for one out of five workers observed at four greenhouses in Virginia, South Australia



Site: A101RR-15/5/14 Date: 15th May 2014

FIELDWORK OBSERVATION CHECKLIST

Discipline of Public Health,
School of Population Health, Faculty of Health Science
University of Adelaide, Australia

SKIN ABSORPTION OF ORGANOPHOSPHATE PESTICIDES (OPs): INFORMING A PREDICTIVE DERMAL RISK ASSESSMENT MODEL

1. PESTICIDES

	ID	A1	
	Items	**Worker A**	**Remarks**
1.	**Type used on site** Organophosphate (OP), Organochlorine (OC), Carbamate (C), Pyrethroids (P)	All types - used on rotation basis	
2.	**Purpose** Herbicide (H), pesticide (P), fungicide (F), rodenticide (R)	Herbicides Pesticides	Cucumbers
3.	**Brand/commercial name** Manufacturer Batch no	a. Lannate-L (CropCare) b. Abamectin (Chemtura)	
4.	**Active ingredients**	a. Methomyl 225g/L, Methanol 472g/L b. Abamectin 18g/L, N-methylpyrrolidone 266g/L, Hydrocarbon 60g/L	
5.	**Concentrate or mixture?** Concentration	Concentrate, diluted into mixture for spraying	
6.	**Hazard signs** Toxic, Flammables, Oxidizers, etc	. Toxic . Flammables	
7.	**Mixed with** Water (W), Solvent (S), Surfactant (Sf), Fertilizer (F)	Water	
8.	**Storage**	In the shed, stacked Poor housekeeping	

1

Site: A1012 - 15/5/14

Date: 15th May 2014

2. TASKS

	ID Items	Worker A	Remarks
1.	Mixing Using hands, sticks/ paddle, auto stirrer Ventilated/non-ventilated area	Stick Open area / on the vehicle	Started 11.15 am
2.	Spraying Hand spray, backpack sprayer, airblast, mist fogger	Hand spray	Spray nozzle no.3 (medium size droplets)
3.	Shift length (hrs) Number of shifts per week	8 hrs 0.5 (spray fortnightly)	
4.	Time of actual exposure (hrs/day)	4 hrs	
5.	Working Direction: up-wind or down-wind Speed:	No wind (under roof, in greenhouses)	16 greenhouses (0.1 ha, 1440 m², 12 rows) Walk to the end, move backwards
6.	Frequency of task How many times per week	0.5 to 1 / week	1135 - 1140 am - 8 greenhouses 1145 - 1215 pm - 8 greenhouses
7.	Temperature range (°C) when the task is conducted	26.5 to 26.8	
8.	Sunlight Sunny or cloudy	Sunny	

Site: A101RR - 15/5/14

Date: 15th May 2014

3. PERSONAL PROTECTIVE EQUIPMENT (PPE)

	ID Items	Worker A	Remarks
1.	Body protection Short/long sleeve shirt, long pants/shorts, Coveralls Conditions	Long sleeve shirt (outer), T-shirt (inner) OK	Outer long-sleeve shirt only used for spraying task
2.	Head protection Cap, wide brim hat Conditions	Cap OK	
3.	Eye protection Safety glasses, goggles, face shield Conditions	Goggles OK	
4.	Respiratory protection Face mask, respirator, air supplying respirator Conditions Type of filter/cartridge When was last changed Storage	Full mask with cartridge Looks good AP 3 quarterface (nose/mouth) Everyday	
5.	Hand protection Gloves, type, length, layers Conditions	Neoprene gloves Super Guard (blue) ProChoice OK	
6.	Foot protection Slippers, sneakers, chemical resistant, waterproof boots Conditions Changed after tasks?	Waterproof boots OK Yes	
7.	PPE brought back home	Mask, boots, goggles	

Site: A101RR - 15/5/14 Date: 15th May 2014

4. GLOVES

	ID		
	Items	**Worker A**	**Remarks**
1.	Right or left-handed	Right	
2.	Type of gloves	ProChoice Super Guard (blue) Neoprene EN 388, 4121	
3.	Length	Wrist length with elastic grips (fabric)	
4.	Storage	-	
5.	Abrasion	Yes	
6.	Dried under sunlight	-	
7.	Age of gloves/ reused? How many times?	Claimed to be used only once but gloves didn't look new	

Site: A1012R-15/5/14 Date: 15th May 2014

5. WORK PRACTICES/ BEHAVIOUR

ID	Items	Worker A	Remarks
1.	Respirator fit check	No	
2.	Beard (unshaven)	No	
3.	Rubbing eyes	No	
4.	Scratching face	No	
5.	Smoking	No	
6.	Contact during or after tasks (between gloves and...) and frequency 1- Mobile phones 2- Door handles 3- Steering wheels 4- Others (please specify)	3 - Yes 4 - Hose coiler	
7.	Techniques in removing gloves Correct/incorrect technique 1- Glove first, then clothing 2- Clothing first, then gloves	Incorrect 1	
8.	Wash hands For breaks After task is completed	N/R Hands & face ✓	

Site: A101RR - 13/5/14

Date: 15th May 2014

6. SKIN EXPOSURE

	ID Items	Worker A	Remarks
1.	Signs of skin contamination Which part? 1- Finger 2- Palm 3- Back of hand 4- Arm 5- Face 6- Other How much 1- None 2- Not obvious 3- Visually obvious	2 2 2 1 2	
2.	Clothing contamination Which part? How much 1- None 2- Not obvious 3- Visually obvious	Shirt 2 Boots 3	
3.	Skin abrasion/ dermatitis or other conditions potentially affecting absorption	Yes Back of hand and between fingers	

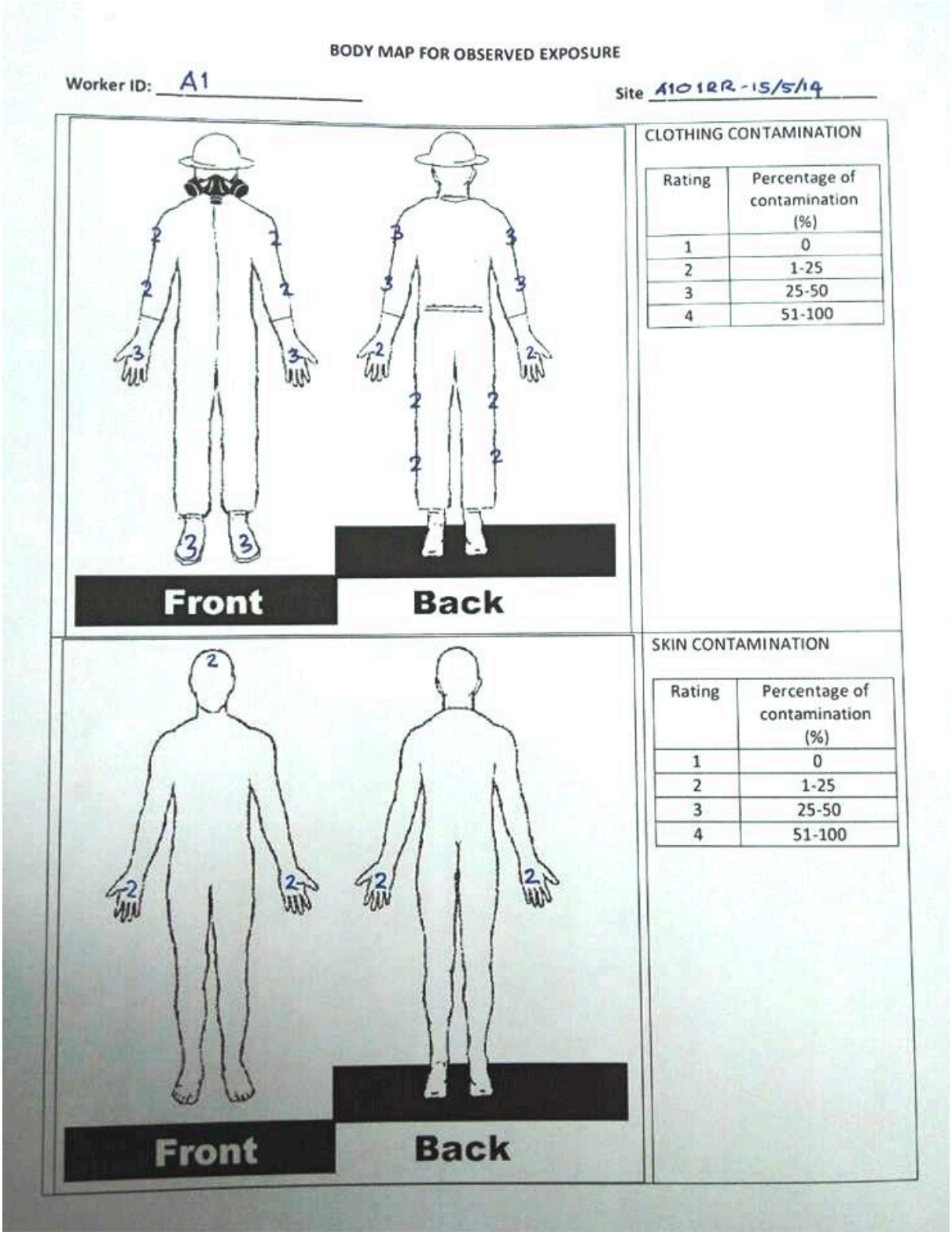
Site: A101RR -15/5/14 Date: 15th May 2014

7. FACILITIES

ID	Items	Worker A	Remarks
1.	Tap water for washing hands	Far from the farm	
2.	Drinking water	From drinking bottle	
3.	Soap -bar -liquid	–	
4.	Towel -washable towel -paper towel	No	
5.	Eating area	Yes	
6.	Bathroom	Yes	
7.	Toilet	Yes	

Appendix 4.2.2 Body map for observed exposure

The body map completed for one out of five workers observed at four greenhouses in Virginia, South Australia.



Statement of Authorship

Title of Paper	Dermal Exposures to Organophosphorus Pesticides for ambulance workers - Permeation through disposable gloves: Findings for omethoate
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Ismail, I., Pisaniello, D., Gaskin, S., & Edwards, J. W., (2015), Dermal Exposures to Organophosphorus Pesticides for ambulance workers - Permeation through disposable gloves: Findings for omethoate, Journal of Health & Safety Research & Practice 7(1), 14-22

Principal Author

Name of Principal Author (Candidate)	ISMANIZA ISMAIL		
Contribution to the Paper	Performed analysis on all samples, interpreted data, wrote manuscript and acted as corresponding author.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	05.02.2016

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	DINO PISANIELLO		
Contribution to the Paper	Supervised development of work, helped in data interpretation and manuscript evaluation.		
Signature		Date	05.02.2016

Name of Co-Author	SHARYN GASKIN		
Contribution to the Paper	Supervised development of work, helped in data interpretation and manuscript evaluation.		
Signature		Date	05.02.2016

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Contribution to the Paper	Performed analysis on all samples, interpreted data, wrote manuscript and acted as corresponding author.		
Overall percentage (%)	85%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

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