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Medicines Evaluation Committee

A review of the regulation of head lice treatments in Australia

October 2003

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Prepared for the Medicines Evaluation Committee by Dr Susan James

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ABBREVIATIONS USED IN THE REVIEW

APVMA	Australian Pesticides and Veterinary Medicines Authority
ARGOM	Australian Guidelines for the Registration of Medicines
ARTG	Australian Register of Therapeutic Goods
ASMI	Australian Self Medication Industry
Car	carbaryl
DSEB	Drug Safety and Evaluation Branch
FDA	Food and Drug Administration
Hrs	hours
Lin	lindane
Mal	malathion
MEC	Medicines Evaluation Committee
Mins	minutes
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemical Notification and Assessment Scheme
NRA	National Regulatory Authority [Note: replaced by the APVMA in 2003]
OTC	over-the-counter
PB	piperonyl butoxide
Per	permethrin
PSA	Pharmaceutical Society of Australia
Pts	patients
Pyr	pyrethrin(s)
TGA	Therapeutic Goods Administration

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SUMMARY

Concerns about the safety and efficacy of currently available head lice treatments, and the suitability of the current system of regulation of these treatments, including the suitability of labelling guidelines, are the subjects of the Review.

There is a paucity of good-quality evidence supporting the effectiveness of many head lice treatments. In particular, there is very little published evidence on the efficacy of herbal head lice treatments. The Review recommends that the TGA seek evidence of efficacy from sponsors of these products for evaluation. Evidence suggests that currently available head lice preparations result in few side effects when used as directed, and additional restrictions or safety warnings are not warranted.

There is little information in the literature regarding the effect of formulation on product efficacy. What evidence there is suggests that efficacy is formulation dependant, and therefore applications for new product registrations should be supported by clinical data on the formulation intended for marketing. *In vitro* data is not considered suitable in most cases. The Review considers that there are significant difficulties in translating the results of *in vitro* studies to conditions in the field.

There is evidence to suggest that resistance to the majority of active ingredients in head lice preparations either has or will develop in Australia as it has overseas. Further research into this issue is required, however, clinical studies undertaken overseas may not be applicable in Australia, as resistance patterns are likely to vary in different locations.

Current labelling guidelines, developed in the early 1990s, are in some areas out of step with evidence currently available in the literature. The Review recommends changes to the labelling guidelines, to restrict misleading or confusing claims, to enhance treatment effectiveness, and to provide additional evidence-based advice to consumers.

Chemical treatment is only one aspect of treating head lice infestation, and there is a clear need for good quality, authoritative information on all aspects of head lice infestation to be made available to the public. The Review suggests that State Health Authorities are best placed to address this issue in the first instance.

RECOMMENDATIONS

Recommendation 1: It is recommended that claims for efficacy and safety of head lice products should generally be supported by relevant clinical trials, rather than *in vitro* data only. *In vitro* data may be acceptable, at the discretion of the evaluation body, where the formulation of a product is similar to an existing product that has been fully evaluated.

Recommendation 2: It is recommended that the existing MEC guideline requiring a contact time of 12 hours or more for malathion-containing lotions be deleted.

Recommendation 3: It is recommended that, unless product sponsors can provide clinical evidence to the contrary, retreatment with pediculocide products should occur 7-10 days after the first treatment.

Recommendation 4: Given the paucity of studies on the efficacy of listed herbal head lice products, it is recommended that TGA review the evidence held by sponsors to support the listing of these products.

Recommendation 5: It is recommended that, regarding registration versus listing of pediculocide products, the current situation be maintained, in which herbal products making general or medium level claims require listing, and products containing non-listable ingredients and/or making high level claims require registration.

Recommendation 6: It is recommended that for new registration applications, efficacy should be demonstrated for the formulation under consideration.

Recommendation 7: More definitive data on the existence and pattern of resistant head lice in Australia would be of use in determining a procedure for treating head lice in cases where initial treatment fails. It is recommended that the NHMRC be requested to encourage research into this issue.

Recommendation 8: It is recommended that label claims on registered products be limited to control/treatment of head lice and their eggs. Label claims should not state or imply that one treatment will kill all lice and eggs. Because the claims for efficacy on the labels of some "grandfathered" products are meaningless, inaccurate or misleading, the TGA should review the labels of these to ensure safe and effective use in the community.

Recommendation 9: It is recommended that the current sections of the Guideline recommending contact times and application methods for various pediculocide ingredients be replaced with a recommendation that directions for use of pediculocide products should be consistent with clinical trial data on the pediculocide product in question.

Recommendation 10: It is recommended that the labels of products containing malathion, pyrethrins, piperonyl butoxide or permethrin include a warning to the effect that the product is not to be used during pregnancy unless advised by a doctor.

Recommendation 11: It is recommended that the proposed guidelines in Attachment 4 be considered by the TGA for inclusion in the relevant guidelines documents for OTC and complementary medicines.

Recommendation 12: It is recommended that the State and Territory health departments adopt consistent evidence-based public health advice for provision to the public.

Recommendation 13: It is recommended that regulatory changes be put in place to transfer the responsibility for regulating head lice repellent or preventative products from the APVMA to the TGA.

1 INTRODUCTION

1.1 Justification for the review

Head lice infestation is a major public health problem throughout Australia, particularly in rural and remote communities. The cost of head lice infestation in Australia is unknown, but in the USA it has been estimated that the annual cost is US$367 million, including the cost of pediculocides, school absences by infested children, loss of work time by parents required to stay home to treat children, or who become infested themselves, and costs to the school system in trying to deal with the problem (Gratz 1997).

There are a large number of stakeholders with an interest in the regulation of head lice products. These include:

- The public
- Manufacturers of head lice products and their organisations
- Medical practitioners and other health professionals
- Education departments and school bodies
- Various government departments including the TGA and NRA / APVMA.

Recently concerns about the regulation of head lice products have been expressed with regard to the following issues in particular:

- Treatment failures have been reported with commonly used pediculocides, and there are questions about whether these treatment failures are due to resistance developing to these products;
- Inappropriate formulations or directions for use may encourage the development of resistance;
- Questions about the efficacy of products containing low levels of essential oils;
- Public concerns about the safety of existing products;
- Existing guidelines for the labelling of head lice products have been criticised, and there are concerns that these guidelines may be out of date.

For these reasons it was decided by the TGA to engage a consultant to undertake a review of head lice treatments, with the aim of establishing guidelines for packaging and labelling to ensure safe and effective use in the community, to make recommendations on regulatory control (registration or listing), and to advise on the regulatory interface between the TGA and APVMA.

1.2 Terms of reference

The terms of reference of the consultancy were as follows:

To establish evidence based-guidelines for the registration of head lice preparations including appropriate packaging and labelling to ensure safe and effective use in the community. In particular, the following issues should be addressed:

- Resistance of head lice to insecticides
- Directions for use by consumers including contact times and reapplication times
- The need for efficacy testing on a product by product basis
- Whether all head lice preparations should require registration as medicines (i.e. head lice treatment be made a "registrable disease")
- Whether the regulation of head lice repellents by the APVMA leads to inappropriate treatment in the community

Consultation with relevant stakeholders should be part of the process.

1.3 Methodology of the review

A comprehensive literature search for relevant references, focussing on clinical trials, was conducted. The literature search was conducted on Embase and Medline, up to July 2000. References were also identified from review articles on head lice, and from the reference lists of clinical trials retrieved in the search. The review was restricted to English language articles or articles with an English language abstract. Relevant references that were published between July 2000 and July 2003 were also included in the review. A search through the TGA database for clinical studies submitted for evaluation with registration applications was also undertaken. Permission was sought to include unpublished studies identified in this manner.

Separate searches on adverse events/toxicity of individual pediculocide ingredients, and overseas regulatory decisions relating to pediculocides were also undertaken.

A list of stakeholders was prepared, and a letter outlining the terms of reference of the review, and requesting comments and/or data relevant to the review was sent to all identified stakeholders. Any clinical data provided by stakeholders was included in the review.

2 HEAD LICE

2.1 Life cycle

The head louse, *Pediculus humanus capitis*, is a host-specific parasite that lives exclusively on human heads and feeds by sucking blood from the scalp (Ibarra 1996). Female head lice lay eggs on the hair shaft close to the scalp, held by a glue (Ibarra 1996, Burgess 1995b). The eggs are difficult to detect, as they blend well with the hair shaft (Ibarra 1996). The eggs hatch 7-10 days after laying (Ibarra 1996, Anon 1998), depending on the temperature (Burgess 1995b). Nymphs go through three stages of development (1^{st} instar, 2^{nd} instar, 3^{rd} instar) each of which lasts 3-5 days, after which a final moult gives rise to the adult form (Burgess 1995b). Females may mate within 1-2 days of moulting to the adult form, and lay eggs soon after (Burgess 1995b). The cycle of the head louse, from egg to egg, is around 20 days (Anon 1998). In captivity, head lice may live for 30 days in the adult form, but the life span is likely to be shortened by host activity in the field (Burgess 1995b). After the eggs have hatched, the empty eggshell turns white, and becomes easier to detect as the growing hair carries it away from the scalp (Ibarra 1996).

Head lice breathe through spiracles, but it has been reported that they have the ability to close down their respiratory airways for up to 30 minutes when immersed in water (Raimer 2000). This has important implications for head lice products designed to be applied to wet hair.

2.2 Transmission and role of fomites

Nymphal stages tend to remain on the head where they hatched (Ibarra 1996). Adults cannot jump, but may move from head to head quickly when head-to-head contact occurs (Ibarra 1996, Anon 1998). Whether this movement occurs as a passive expansion to fill a habitat space, or a more active movement to colonise new territory, is still debated (Burgess 1995b).

The role of inanimate objects (fomites) such as hats, hair brushes and bed linen in the transmission of head lice has long been debated. There is no conclusive evidence to suggest that head lice can be transmitted by fomites. Although living head lice have been observed on fomites (Maunder 1983), individual lice probably cannot live for more than a couple of days at most off the head, as they dehydrate rapidly if not able to feed frequently (Burgess 1995b). It has been proposed that any head lice observed on fomites are senile or injured, and are effectively non-viable (Maunder 1977, 1983), although there is much debate about this is the literature, with some authors contending that transmission via fomites is common (Burkhart and Burkhart 2000), while others argue that head to head contact is the major route of transmission (Spear and Buettner 2000). What is not debated is the need for additional studies to confirm the predominant method of transmission.

The probability of transmission of head lice may depend on the prevailing climatic conditions. In cold conditions, head lice are likely to stay close to the warmth of the scalp, reducing the likelihood of transmission. However, in tropical conditions, head lice may be more active and more likely to move away from the scalp, and hence onto new hosts if the opportunity arises (Burgess 1995b).

2.3 Pathology

Pruritus is the most common symptom of head lice infestation, but does not occur in all cases. It has been reported that as few as 14% (Courtade 1993) to 30% (Mumcuoglu 1991) of those infested with head lice itch. Excoriations and secondary infection, with possible adenopathy, can accompany the infestation (Burkhart 1998). Transmission of diseases such as relapsing fever and rickettsial diseases is associated with clothing lice, but **not** head lice (Burgess 1995b). There is no evidence to suggest that head lice are capable of transmitting viruses (such as HIV) from person to person (Burgess 1995b).

2.4 Incidence of infestation

The prevalence of head lice infestation varies widely from area to area, and is difficult to determine accurately. Accurate determination relies on detection of live lice and/or viable eggs on the head, which in turn depends upon the skill and diligence of the investigator. This is especially true in the case of light infestations, where only a few lice and/or eggs may be present. The majority of studies on the prevalence of head lice infestation are done in school age or pre-school children – very few studies are performed in adults. In 1997, the WHO published a review of head, body and pubic lice prevalence and treatment (Gratz 1997). This study reviewed the prevalence of head lice on each continent, and found wide variations. The prevalence of head lice infestation is generally less than 10% in school children from Western countries, but within individual schools or classes may be much higher. The prevalence is usually greater than 10%, and in some cases greater than 50%, in children from developing countries, especially those in the tropical regions.

There are few published studies on the prevalence of head lice infestation in Australia. These studies are summarised in the following table:

Ref	*Location*	*Year*	*Population sampled*	*Number sampled*	*Prevalence*
Jorm 1994	Sydney	1992	Children attending long day care centres	6092	4.9%
Speare & Buettner 1999	Brisbane	1997	School children	456	35.1%
Monheit & Norris 1986	Melbourne	1985	School children	479	5-12%
Goldsmid 1989	Tasmania	1978-1979	School children	70000	1.3-2.0%

One study on the incidence of communicable diseases in long day care centres in Sydney in 1992 reported 297 cases of head lice infestation amongst the 6092 children attending all 92 long day care centres in Western Sydney (an incidence of 4.9%) (Jorm 1994). A study in a primary school south of Brisbane in 1998 examined 456 of a total of 725 children in grades prep to five, and found a prevalence of 35.1% infection (live lice or viable eggs found). This study noted that the incidence of infection varied greatly between classes, from zero to 72.2% (Speare and Buettner 1999). A study of 479 primary school students conducted in two primary schools in Melbourne in 1985 found an incidence of between 5% and 12% (Monheit and Norris 1986). In Tasmania in 1978-79, it was reported that the incidence of head lice infestation in the 70,000 school children in that state was 1.3-2.0% (Goldsmit et al 1989).

No conclusions can be drawn as to whether the incidence of head lice infestation is increasing over time, as has been suggested, as standardised studies comparing the incidence of infestation in a given location over time have not been published.

3 CURRENT REGULATION OF HEAD LICE PREPARATIONS

3.1 Australian Regulation

Either the TGA or the APVMA regulates chemical head lice treatments in Australia. The majority of products are regulated by the TGA. Products claiming to treat head lice infestation are required to be **listed** or **registered** on the Australian Register of Therapeutic Goods, which is administered by the TGA.

In general, head lice products containing herbal ingredients such as melaleuca oil, lavender oil and eucalyptus oil are required to be **listed** on the ARTG. These products do not undergo evaluation for efficacy prior to listing, but product sponsors are required to possess evidence to support the claims made on the product label, and this evidence can be requested for assessment by the TGA. Listed products may only contain approved ingredients, which have been previously assessed for safety and quality. Generally, listed head lice products are unscheduled, meaning they can be sold freely in retail outlets and advertised to the public. Since 19 April 2000 (the date of introduction of the new Therapeutic Goods Advertising Code) listed products may only make "general" or "medium" level claims (defined in the *Guidelines for levels and kinds of evidence to support indications and claims*). The following claims (or claims of like intent) are currently accepted for listed products:

- Aids in the management/control of head lice infestation;
- Relieves the symptoms of head lice infestation;
- Aids in the removal of head lice and/or their eggs.

Listable products that were making high level claims (see below) prior to 19 April 2000 must either apply for registration or amend the claims to those acceptable for listing by 19 April 2004.

Head lice products making "high" level claims or those containing non-listable ingredients such as malathion, permethrin, and pyrethrins are required to be **registered**. High level claims included the following (or claims of like intent):

- Kills/eradicates/destroys head lice and/or their eggs/nits;
- Treats head lice infestation;
- Prevents head lice infestation.

Prior to registration, individual products are evaluated for safety, efficacy and quality by the OTC section of the TGA. These products are also unscheduled, so they too can be sold freely in retail outlets and advertised to the public. However, products with higher levels of malathion, permethrin and pyrethrins than those commonly found in head lice products are scheduled, meaning there are controls over their availability.

Currently products containing lindane or carbaryl are not available in Australia. Such products have been discouraged because of concerns over the toxicity of lindane and carbaryl, but if any new products were to come onto the Australian market, they would first require registration (and hence evaluation for safety, efficacy and quality) by either

the OTC or DSEB sections of the TGA. Carbaryl-containing products would require a prescription, and lindane products would be restricted to sale in pharmacies.

Products requiring registration must currently comply with the guidelines relating to pediculocide products in the *Australian regulatory guidelines for OTC medicines* (ARGOM) (see attachment 3).

A list of products registered or listed on the ARTG as at July 2000 is contained in attachment 6.

The APVMA regulates agricultural chemicals. Insect repellents, including products that claim to repel head lice, require registration with the APVMA through the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Products that claim to kill head lice and repel them require registration by both bodies. The registration process for repellent products similar to those already on the market involves only limited evaluation of safety and efficacy. Evaluation of products which differ substantially from existing products generally require laboratory studies to establish efficacy, although products containing "new" actives require field trials. Currently there are no head lice repellents registered with the APVMA, although a survey of head lice products available in Australia revealed several products claiming to repel head lice that should be registered with the APVMA.

3.2 Overseas regulation

In other countries, as in Australia, head lice treatments are generally available for over-the-counter (general retail) sale, although some products require a prescription. In the USA, products containing pyrethrins (usually combined with piperonyl butoxide), permethrin, malathion and lindane are available. Those containing malathion and lindane require a prescription, while products containing pyrethrins and permethrin are available OTC. The US FDA has regulatory requirements for labelling non-prescription (OTC) pediculocides. The US FDA has also banned the following ingredients from use as pediculocides, due to lack of evidence of efficacy and/or safety: benzocaine; benzyl alcohol; benzyl benzoate; chlorophenothane; coconut oil soap; copper oleate; docusate sodium; formic acid; isobornyl thiocyanate; picrotoxin; propylene glycol; sabadilla alkaloids; sublimed sulfur; and thiocyanate.

In the UK, pediculocides containing malathion, permethrin and d-phenothrin are all available over-the-counter. Carbaryl-containing pediculocides are available by prescription.

In New Zealand, head lice products containing bioallethrin, malathion, permethrin, pyrethrins and piperonyl butoxide are all available through over-the-counter (general retail) sale, although, as in Australia, products containing higher levels of malathion (more than 2%) or permethrin (more than 5%) are restricted to sale in pharmacies (malathion) or by prescription (permethrin).

3.3 Head lice as a "registrable disease"

Part of the brief for this review is to consider the issue of whether head lice infestation should be made a "registrable disease" by the TGA. In this context, registrable disease means that all products making claims about efficacy against head lice infestation would require registration (and hence evaluation of efficacy, safety and quality prior to marketing), as opposed to the current situation where some products require registration, but some require listing (no evaluation of efficacy prior to marketing), depending upon their active ingredients.

A "registrable disease" should not be confused with "notifiable disease", where health workers are required to notify health authorities of all cases of the disease. There is no suggestion that head lice infestation should be made a notifiable disease.

4 TREATMENT OF HEAD LICE INFESTATION

There are a large number of different head lice treatments on the market, which can be divided into two broad categories, chemical and physical. Physical methods include combing with "nit combs" (one method is known as "Bug Busting"), and use of electronic combs (such as Robicomb). Very little evaluation of the efficacy of these physical methods has been undertaken, but the popularity of these methods is growing, due both to a reluctance on the part of parents to expose children to chemicals, and to a perceived lack of efficacy of the existing chemical methods of treatment available.

Chemical methods of treatment include topical treatments (both herbal treatments and treatments containing pyrethrins, permethrin, carbaryl, lindane or malathion) and oral treatments such as ivermectin and cotrimoxazole. Only treatments containing herbal ingredients, permethrin, pyrethrins or malathion are available in Australia at the present time. Topical treatments are by far the most common initial method of treatment of head lice infestation.

4.1 Overview of clinical trials

A number of studies evaluating the efficacy and safety of these treatments have been published. A summary of these clinical trials is presented in attachment 2. However, many of the studies are difficult to evaluate due to methodological flaws. A recent Cochrane review (Dodd 2000, updated in Dodd 2003) identified 71 clinical trials of head lice preparations, but found only 4 trials of suitable quality to allow adequate evaluation. Another review (Vander Stichele et al 1995) identified 28 published studies of which 7 were found to meet the criteria for acceptance by this reviewer.

Methodological flaws in many published studies include:

- Inappropriate definition of infestation (definition should require live lice to be seen, not just eggs);
- Failure to exclude patients treated for infestation in previous 2-4 weeks (prior treatment may have a residual effect);
- Failure to standardise additional treatments (such as use of nit combs, additional shampooing, etc.);
- Failure to differentiate between reinfestation and treatment failure (this can be done by determining whether the lice are adults (implies reinfestation) or nymphs (implies treatment failure));
- Failure to choose an appropriate time to examine for efficacy (examination at 7 days after treatment does not allow for hatching of eggs not killed by the treatment);
- Inadequate randomisation or blinding

In addition, some studies had the treatment applied by study personnel (thus standardising the application method), while others had the treatment applied by the patient or the patient's parents or guardians. Treatments are unlikely to be standardised by this method,

but studies utilising this technique may give a better indication of the effectiveness of a given treatment "in the field".

Also, in some studies, other family members or contacts were treated or offered treatment (either as part of the study, or separately), while in other studies this did not occur. Treating other family members or contacts reduces the likelihood of reinfestation, thus affecting the perceived efficacy in the study patients. This is particularly relevant in studies in which lice were not categorised as adult, nymph, etc, during the evaluation stage (in studies in which lice were categorised, reinfestation by adult lice can often be differentiated from treatment failure, where nymphs may be present).

The majority of studies determined pediculocidal activity and/or ovicidal activity and/or overall treatment effectiveness as measures of efficacy. Pediculocidal activity is determined by the proportion of dead versus live lice, or proportion of patients with live lice, detected within 24 hours of treatment. The accuracy of the pediculocidal activity is dependent upon the investigator's ability to detect live lice when they are present. Detection is usually done by "detection combing" (combing with a fine tooth comb onto white paper), or by rinsing the hair and straining the rinse water through cheesecloth to "catch" any lice present. Detection of all live lice can be quite difficult, and requires experience by the investigator. For studies in which the presence of live lice (as opposed to only viable ova) is not an inclusion criteria, the significance of pediculocidal activity rates is dubious: if live lice were not present prior to treatment, they would not be expected to be present post-treatment.

Ovicidal activity is generally determined by incubating for 14 days samples of ova taken from the subject both before and immediately after treatment. The ovicidal rate is calculated as the difference between the proportion of pretreatment ova hatching and the proportion of post-treatment ova hatching. Some studies have found very low hatching rates even in pretreatment ova, suggesting problems with the incubation techniques used in these studies – the ovicidal rates from these studies may be less reliable than from studies where high pretreatment hatching rates were observed.

Overall treatment effectiveness is generally determined 14 days post-treatment by the number of subjects with no live lice or viable ova (that is, the number of patients "cured" of the infestation). This also depends on investigator experience, as, in addition to the difficulties of detecting live lice, it can be difficult to differentiate between live and dead or hatched ova. Determination of treatment effectiveness is undertaken at 7 days post-treatment in some studies, but does not allow for hatching of ova which may not have been killed by the treatment, and hence is not as good a measure of the true ability of a product to stop an infestation. In studies in which only the presence of viable ova is required for inclusion (not live lice), the reliability of the results for treatment effectiveness is dependant in part upon the investigators ability to differentiate between viable and non-viable ova.

4.2 *In vitro* studies

The efficacy of a number of pediculocides has been evaluated using *in vitro* methodology.

The standard methodology involves using laboratory-bred clothing lice and eggs. No laboratory stocks of head lice are currently available. Lice are exposed to pediculocide by immersion for an appropriate time (10 seconds to 10 minutes generally), after which they are rinsed in water or washed with shampoo, then blotted dry prior to incubation under standard conditions. Only adult or third instar lice are used, and should not be used within 4-5 hours of feeding (to avoid accidental death due to rupturing of the gut during processing). Eggs are laid on gauze, and treated similarly.

There has been considerable controversy over the clinical significance of such *in vitro* data. Some obvious issues with regard to *in vitro* studies include:

1. Laboratory stocks of lice are chemically naive and may be more susceptible to pediculocides than "field" lice. In addition, the laboratory-bred lice used in *in vitro* studies are clothing or body lice, not head lice; which may affect susceptibility;

2. Exposure of lice to pediculocides in *in vitro* studies, usually by immersion, is not representative of exposure in clinical use;

3. Some early *in vitro* studies found high ovicidal activity because the eggs were laid and incubated on material which retained insecticide even after rinsing or washing, giving an artificial residual effect;

4. There are concerns that the basic treatment of the lice and eggs (immersing, washing, rinsing, drying etc) may have a detrimental effect. Hence studies which do not include both a vehicle control and a "water" control, are of little value.

The recently conducted Cochrane Review (Dodd 2000) of head lice treatments commented, in regard to the usefulness of *in vitro* data, *"… the results obtained from these investigations do not give an accurate representation of the effectiveness of a product when used in the field …", "The susceptibility of laboratory lice to insecticides may be greater than that of field collected lice…"*, and *"… in in vitro studies insecticide is often applied directly onto the louse which is not representative of a real life situation"*.

In addition, Burgess, who has conducted a number of *in vitro* studies on the efficacy of various pediculocides over the last two decades, points out that field investigations are necessary to confirm the findings of *in vitro* studies (Burgess 1990).

Burgess also states *"While in vitro studies cannot replace tests on patients, they can be used effectively for comparison of products…"* (Burgess 1996). This statement is based

on the fact that *in vitro* studies remove much of the variability experienced in clinical trials, by standardising the environment of the louse, the exposure to insecticides, and by removing as an issue the difficulty of observing and identifying live lice on the head. For these reasons, *in vitro* studies may be valuable in identifying potential new pediculocide active ingredients, which can be compared to existing active ingredients to determine whether clinical trials are warranted. However, *in vitro* studies may have less value in the comparison of different formulations, as differences in formulation may lead to differences in ease of use (for instance, how well the product spreads through the hair), and to other differences in the hair and scalp environment that may effect the life cycle of the louse (for instance, a product that covers the scalp for 12 hours may reduce the ability of the lice to feed during this time, thus reducing their viability). Such factors will not play a part in the results of *in vitro* studies.

Comments from stakeholders were divided on the suitability of *in vitro* studies to support the efficacy of head lice preparations, with some feeling that *in vitro* studies were suitable, and others commenting that field studies were necessary. Stakeholders did note, however, that irrespective of the suitability of *in vitro* studies or otherwise, such studies could not currently be undertaken in Australia, as no laboratories currently offered suitable testing facilities.

For these reasons, it is considered that *in vitro* studies alone do not provide sufficient evidence of the efficacy of pediculocide products, and that *in vitro* data without supporting clinical trial data would generally be inadequate for product evaluation. However, where the formulation of a product is substantially similar to the formulation of a previously evaluated product, data showing *in vitro* equivalence to the original product may be acceptable.

Recommendation 1: It is recommended that claims for efficacy and safety of head lice products should generally be supported by relevant clinical trials, rather than *in vitro* data only. *In vitro* data may be acceptable, at the discretion of the evaluation body, where the formulation of a product is similar to an existing product that has been fully evaluated. In such cases the evaluation body could be contacted to discuss whether *in vitro* data would be acceptable.

4.3 Malathion

4.3.1 Products available in Australia

There are at least eight products containing malathion registered for use in Australia (see attachment 6). However, only three of these products were found to be available for purchase in a survey of retail outlets in Canberra and Melbourne[1]. These products are generally lotion formulations containing 0.5% malathion or shampoo/foam applications

[1] Approximately six retail premises (pharmacies and herbal/health food stores) in both Melbourne and Canberra were surveyed, and samples of all head lice products available (including products claiming to repel head lice) were purchased. All samples were examined for directions for use, and label claims.

containing 1% malathion. The directions for use of these products require application to wet hair for 10-20 minutes prior to rinsing out. It is notable that despite the current guidelines for head lice products (attachment 3) recommending at least a 12 hour contact time for malathion lotions, the one lotion found in the retail survey only recommended a minimum 12 hour contact time if a residual effect is required.

4.3.2 Efficacy studies:

Fifteen clinical trials included malathion-containing products (see attachment 2). Studies compared malathion to vehicle (3,25), to 1% lindane shampoo (4, 17), to 0.2% phenothrin lotion (5, 22) or shampoo (8), to Bug Busting (mechanical method of treatment) (10), to 1.8% bioresmethrin/7.2% piperonyl butoxide (12), to 0.5% carbaryl lotion (17,20), to a herbal preparation (29), to other malathion products (30) or to a range of other products (17,20,34). Two studies were not comparative or controlled (20,31).

There were methodological flaws in each of the studies that included treatment with malathion, as follows:

Table 1.

Ref	*Major flaws*
3	No exclusion for previous pediculocide treatment in last two weeks Identification of live lice not required for inclusion in study (eggs only) Only determined efficacy at 7 days
4	No exclusion for previous pediculocide treatment in last two weeks Identification of live lice not required for inclusion in study (eggs only) Only determined efficacy at 7 days and 4-6 weeks Not blinded
5	No exclusion for previous pediculocide treatment in last two weeks Identification of live lice not required for inclusion in study (eggs only) Not blinded
8	No exclusion for previous pediculocide treatment in last two weeks Only determined efficacy at 7 days and 4 weeks Not blinded
10	Not blinded
12	No exclusion for previous pediculocide treatment in last two weeks Not blinded
17	No exclusion for previous pediculocide treatment in last two weeks Infestation not defined Not blinded
19	No exclusion for previous pediculocide treatment in last two weeks Only determined efficacy at 1 and 10 days Not blinded

Ref	*Major flaws*
20	No exclusion for previous pediculocide treatment in last two weeks Infestation not defined Only determined efficacy at 7 days Not blinded
22	No exclusion for previous pediculocide treatment in last two weeks Only determined efficacy at 1 and 7 days
25	No exclusion for previous pediculocide treatment in last two weeks Only determined efficacy at 1 and 7 days
29	No exclusion for previous pediculocide treatment in last two weeks Claims to be double blind but methods section indicates this may not be so.
30	No exclusion for previous pediculocide treatment in last two weeks Identification of live lice not required for inclusion in study (eggs only) Time of post-treatment assessment not stated
31	No exclusion for previous pediculocide treatment in last two weeks Infestation not defined Only determined efficacy at 7 days Not blinded Contact time and method of application not stated
34	No exclusion for previous pediculocide treatment in last two weeks Efficacy only determined at 24 hours Not blinded Detection method/definition of louse-free not suitable

Despite these flaws, pediculocidal and ovicidal rates for malathion are calculated in these studies and are summarised below:

Table 2.

Ref	*Treatment*	*Live lice*[1]	*No of subjects*[2]	*Pediculo-cidal activity*[3] *24 hrs*	*Treatment success*		*Ovicidal activity*[4]
					7 days	*14 days*	
3	0.5% lotion, dry hair, 8 hrs		61	90.2%	85.2%		60.6%
4	0.5% lotion, dry hair, 2 hrs		29		93%		
5	0.5% lotion, dry hair, 2 hrs		23	74%	96%	100%	
8	0.5% lotion, dry hair, 2 hrs	✓	38		95%	82%	
10	0.5% lotion to wet hair, 8-10 hrs	✓	40			78%	
12	0.5% in ethanol to dry hair	✓	51		67%	65%	

Ref	*Treatment*	*Live lice*[1]	*No of subjects*[2]	*Pediculo-cidal activity*[3] *24 hrs*	*Treatment success*		*Ovicidal activity*[4]
					7 days	*14 days*	
17	0.5% lotion to dry hair, 24 hrs		108	100%		98.1%	
19	0.4% solution (+ 0.1% allethrin)to wet hair, 10 mins	✓	50	100%	98%		
20	0.5% lotion to dry hair, 24 hrs		15	100%	100%		86%
22	0.5% lotion to dry hair, 8-12 hrs	✓	95	92%	95%		
25	0.5% lotion to dry hair, 8-12 hrs	✓	68	100%	95%		86%
29	0.5% foam to wet hair, 20 mins	✓	74			47.3%	
30	0.5% lotion, 12 hrs 0.5% lotion, 12 hrs 0.5% shampoo		6 6 7				
31	0.5% solution		226		100%		100%
34	0.3% lotion to dry hair , 5 mins	✓	255	100%			

1. Live lice required for inclusion in study
2. Number of subjects in malathion group, not total number in study.
3. Pediculocidal rate is generally calculated as the percentage of subjects with no live lice after treatment. This makes pediculocidal rate of dubious value in studies in which only viable ova were required for inclusion in the study, as subjects may not have had live lice prior to treatment.
4. Ovicidal rates are calculated by comparing hatching rate of viable ova taken from the head prior to treatment, versus hatching rate of viable ova taken from the head immediately after treatment. Hatching rate determined after 14 day incubation period.

As can be seen from the table above, three studies utilised a contact time of 20 minutes or less, three studies utilised a contact time of 2 hrs, 7 studies utilised a contact time of 8 hrs or more, and in two studies the contact time was not stated. From the above studies, the following comments can be made about the efficacy of malathion products in relation to contact time:

1. Ovicidal activity: Ovicidal activity was only reported for studies with a contact times of 8 hours or greater (except for one study in which the contact time was not stated). Thus no relationship between contact time and ovicidal activity can be determined. There are no data to support ovicidal activity with a contact time of less than 8 hrs.

Apart from one study in which insufficient detail was provided in the report to allow adequate evaluation, malathion lotion was not 100% ovicidal in any study.

2. Pediculocidal activity: Determination of pediculocidal activity is only reasonable in studies in which the presence of live lice were required for inclusion in the study, and inspection for the presence of live lice was undertaken within 24 hrs of treatment. Only four studies meet these criteria (19,22,25,34). In all four of these studies pediculocidal activity was greater than 90%. Two of the studies used a contact time of 8-12 hrs. One study used a contact time of 5 minutes, but the method used to detect live lice (no of live lice found during a 5 minute combing) is not considered suitable (other studies use combing for 20 minutes or examination of rinse water strained through cheesecloth). A fourth study used a contact time of 10 minutes, but the malathion lotion also contained 0.1% allethrin as an active ingredient. The effect of the allethrin on the pediculocidal activity is not known. Hence there is no good evidence to support pediculocidal activity with a contact time of less than 8 hours.

3. Treatment efficacy: Using "success" at 14 days post-treatment as an indicator of treatment efficacy, there appears to be a trend towards increasing treatment efficacy with increasing contact time (for instance 47.3% efficacy with 20 minute contact time, versus 98% efficacy with 24 hour contact time). However, the authors of the study using a 20 minute contact time propose that the low efficacy in this study is due to resistance to malathion in the head lice population, rather than inappropriate contact time. Additionally, this study used a foam formulation, and applied the product to wet hair, hence formulation and application methods may have reduced the efficacy. If "success" at 7 days post-treatment is used as the indicator of efficacy, the majority of studies found a greater than 90% efficacy, and no relationship between efficacy and contact time was evident.

It is considered that there is sufficient evidence from the combination of studies, despite their individual flaws, to indicate that malathion at a concentration of approximately 0.5% has acceptable efficacy in the treatment of pediculosis when used with a contact time of 8 hours or more. The available information is insufficient to allow any conclusions to be drawn about efficacy after a contact time of less than eight hours. However, given the number of studies of malathion-containing products where a contact time of less than eight hours has been utilised, the existing MEC guideline which requires a contact time of twelve hours or more for all malathion-containing lotions is considered no longer appropriate.

Recommendation 2: It is recommended that the existing MEC guideline requiring a contact time of 12 hours or more for malathion-containing lotions be deleted.

Products, including lotions, proposing a contact time of less than 12 hours should be accepted for evaluation, but should provide clinical trial data to support the directions for use, including contact time.

4.3.3 Safety

WHO has classified malathion as slightly hazardous (JMPR 1997). It has a relatively low acute toxicity of itself, but impurities, including isomalathion, malaoxon and trialkyl phosphorothioates, can increase the toxicity of malathion, as well as being toxic themselves. Thus more purified preparations of malathion are less toxic than impure preparations. Impurities may develop in malathion products upon storage, and hence the stability of malathion products requires careful assessment to ensure continued safety of the product to the end of the shelf life.

The TGA has recently reviewed the toxicity of malathion (TGA 2000 – see Attachment 5). Malathion has not been implicated as an insecticide that causes delayed neurotoxicity, and has not been shown to be a carcinogenic risk in humans. Systemic exposure to malathion after dermal application is low (3-8% dermal absorption), and systemic exposure after application of head lice products containing malathion is below the oral acceptable daily intake of 0.2 mg/kg/day.

Of the 15 clinical trials examined in which malathion head lice products were used, 8 did not report adverse events. Of the remaining seven studies, 4 reported no adverse events after malathion application (3,8,17,30). Three studies reported dermal adverse events with an incidence ranging from 1.5% (25) to 13% (5). No other adverse events were reported after malathion application in any study.

Fifteen adverse events from malathion-containing head lice products were reported to ADRAC to July 2003. Nausea or vomiting occurred in 4 of these cases, a reaction at the application site occurred in 7 cases, loss of hair occurred in 2 cases, headache occurred in 2 cases, and in 2 cases adverse events of the nervous system (ataxia, somnolence, confusion, convulsions) occurred. One case of miscarriage was reported after use of a malathion head lice product, which was classed as possibly related to use of the product. Topical malathion is in pregnancy category B2 (ADEC 1999) (see section 7.2 for further discussion of pregnancy categorisation).

The available evidence suggests there are no new or significant safety concerns with malathion head lice products. Dermal adverse events are possible after the use of any topical products, especially in patients with pre-existing skin damage.

4.4 PERMETHRIN

4.4.1 Products available in Australia

There are at least six products registered and available in Australia containing permethrin as the active ingredient (see attachment 6). The majority of these products are lotion or solution formulations containing 1% w/w of permethrin. One product contains 0.2% permethrin in a herbal base. There are no permethrin-based shampoo products registered in Australia. Directions for use for these products generally require application to dry or

damp hair with a contact time of 10-20 minutes before rinsing off, although the product containing 0.2% permethrin recommends applying and leaving on.

4.4.2 Efficacy studies:

Ten clinical trials included permethrin-containing products. Studies compared permethrin to pyrethrin (18), pyrethrin/piperonyl butoxide (14,27,28,32), lindane (15,18,21,23,40), vehicle (21), trimethoprim/sulfamethoxazole (42) and a permethrin/tea tree oil product (39). One study compared two different contact times of the same permethrin product (2), and one compared permethrin with and without adjunctive combing (43).

There were methodological flaws in many of the studies that included treatment with permethrin, as follows:

Table 3.

Ref	*Major flaws*
2	No exclusion for previous pediculocide treatment in last two weeks Identification of live lice not required for inclusion in study (ova only) Not blinded
14	Not blinded
18	Identification of live lice not required for inclusion in study (ova only) Not blinded
27	No exclusion for previous pediculocide treatment in last two weeks Post-treatment examination at variable times
28	Infestation not defined
32	Contact time not stated
39	No exclusion for previous pediculocide treatment in last two weeks Identification of live lice not required for inclusion in study (viable eggs only)
40	Exclusion criteria not stated Infestation not defined Contact time not stated Degree of blinding not stated
41	Exclusion criteria not stated Not blinded Identification of live lice not required for inclusion in study (viable eggs only))
42	No exclusion for previous pediculocide treatment in last two weeks Identification of live lice not required for inclusion in study (ova only) Not blinded

Four studies had no major flaws (15,21,23,43). Despite these flaws, pediculocidal and ovicidal rates for permethrin are calculated in the above studies and are summarised below:

Table 4.

Ref	*Treatment*	*Live lice*[1]	*No* [2]	*Pediculocidal activity*[3] *2 hrs*	*Treatment success*		*Ovicidal activity*[4]
					7 days	*14 days*	
2	1% lotion, dry hair, 2 hrs 1% lotion, dry hair, 10 mins		10 10	100% 97.6%	100% 100%		74% 79%
14	1% crème rinse, wet hair, 10 mins	✓	27		96.3%	100%	
15	1% crème rinse, wet hair, 10 mins	✓	287		99.6%	99.2%	
18	1% crème rinse, wet hair, 10 mins		32		90.6%	87.5%	
21	1% crème rinse, wet hair, 10 mins	✓	29		100%	97%	60%
23	1% crème rinse, wet hair, 10 mins	✓	659		99%	98%	
27	1% crème rinse, wet hair, 10 mins	✓	10		100%		8%
28	1% crème rinse, wet hair, 10 mins		231		98%	97%	
32	1% crème rinse, wet hair,	✓	81		100%	100%	
39	1% crème rinse, wet hair, 20 mins		49		51.2%	61.9%[5]	
40	1% shampoo		15		94%	100%	
41	1% crème rinse, wet hair, 10 mins		20		100%		
42	1% crème rinse, wet hair, 10 mins		39			79.5%	
43	1% crème rinse, wet hair, 10 mins	✓	61		45.8%[6]	78.5%[6]	

1. Live lice required for inclusion in study
2. Number of subjects in permethrin group, not total number in study.
3. Pediculocidal rate is generally calculated as the percentage of subjects with no live lice after treatment. This makes pediculocidal rate of dubious value in studies in which only viable ova were required for inclusion in the study, as subjects may not have had live lice prior to treatment.
4. Ovicidal rates are calculated by comparing hatching rate of viable ova taken from the head prior to treatment, versus hatching rate of viable ova taken from the head immediately after treatment. Hatching rate determined after 14 day incubation period.
5. Evaluation at 28 days post treatment, not 14 days.

6. Number of patients lice free in group with no adjunctive combing. In group with adjunctive combing (n=34), treatment success rates were 33.3% and 72.7% on days 7 and 14 respectively.

As can be seen from the table above, the majority of studies used a 1% crème rinse formulation applied to wet hair for 10 minutes prior to washing off. The only exceptions to this were one study (2) in which both a 2 hr and 10 minute contact time applied to dry hair were used, one study (39) in which a 20 minute contact time was used, and two studies (32, 40) in which the contact time was not stated. From these studies, the following comments can be made:

1. Ovicidal activity: Ovicidal activity was only reported in 3 studies. Permethrin was not 100% ovicidal in any study.

2. Pediculocidal activity: Determination of pediculocidal activity is only possible in studies in which the presence of live lice were required for inclusion in the study, and inspection for the presence of live lice was undertaken within 24 hrs of treatment. No studies meet these criteria, and hence no comments on pediculocidal activity can be made.

3. Treatment efficacy: Using "success" at 14 days post-treatment as an indicator of treatment efficacy, the efficacy of a 1% crème rinse formulation of permethrin applied to wet hair for 10 minutes is 97% or greater in all but three studies. One of these studies found a much lower treatment efficacy (39) – this may have been due to the presence of head lice resistant to permethrin in the study population. If "success" at 7 days post-treatment is used as the indicator of efficacy, the majority of studies found a greater than 95% efficacy. Since the majority of studies used a 10 minute contact time, no relationship between efficacy and contact time was evident.

It is considered that there is sufficient evidence from the combination of studies, despite their individual flaws, to indicate that permethrin at a concentration of approximately 1% in a crème rinse formulation has acceptable efficacy in the treatment of pediculosis when used with a contact time of 10 minutes or more. The available information is insufficient to allow any conclusions to be drawn about efficacy after a contact time of less than ten minutes, or in different formulations.

The current guidelines indicate that retreatment with permethrin crème rinse products should be delayed until 14 days after the first treatment. Data available to this review provides no evidence that permethrin should be any different to any other head lice product in respect of retreatment period.

Recommendation 3: It is therefore recommended that, unless product sponsors can provide clinical evidence to the contrary, retreatment with pediculocide products should occur 7-10 days after the first treatment.

4.4.3 Safety

Permethrin has a low acute toxicity (WHO 1990). Considering the wide use of permethrin as a pediculocide, there have been relatively few adverse events reported from its use. In the 10 clinical trials summarised in this report, 4 studies did not report adverse events. 2 studies found no adverse events from permethrin treatment (18,27), and the remaining four studies (14,23,28,32) found an incidence of 1.2%-12.9% adverse events in the permethrin group – these adverse events were almost exclusively dermal, with pruritus and rash being the most common findings. No serious or life-threatening adverse events were reported after permethrin treatment in any study. It should be noted that most clinical trials excluded patients with allergies, thus reducing the likelihood of allergic reactions in the studies. The results from the clinical trials were mirrored in a post-marketing survey of a 1% permethrin crème rinse product (Andrews et al 1992). This survey examined 18950 patients treated with the permethrin product for head lice. The adverse event rate in the permethrin group was 2.2 per 1000 treatments. The majority of these adverse events were pruritus and rash. Only 5 significant adverse events were reported: 2 cases of breathing difficulties, 2 cases of shaking arms and 1 case of swollen face. Only in the cases of breathing difficulties were the events thought likely to be related to the permethrin treatment.

The Australian Drug Reactions Advisory Committee has received 16 reports of adverse reactions from permethrin products to July 2003. Of these, 7 had dermal reactions, 2 had breathing difficulties, 5 had nausea and/or vomiting, 2 had headache and 3 had change to or loss of hair. It is recognised that adverse reactions to OTC products may be under-reported to ADRAC, as it is usually only reactions that require the intervention of a medical practitioner that are reported. However, the overall pattern of ADRAC reports is consistent with that found in the clinical trials and post-marketing survey.

Despite public concerns about the safety of permethrin products, they have a low overall toxicity, and a low incidence of adverse events. Dermal adverse events are possible after the use of permethrin head lice products. However, it should be noted that in patients with severe infestations, where skin damage has already occurred, the application of any product to the damaged area could potentially cause adverse events.

4.5 PYRETHRINS/PIPERONYL BUTOXIDE

4.5.1 Products available in Australia

There are at least 8 products registered in Australia containing pyrethrins in combination with piperonyl butoxide, although a survey of retail outlets found only three products readily available. The products are generally lotion formulations containing 0.165-0.175% pyrethrins (total) in combination with 1.65-1.75% piperonyl butoxide, although at least one shampoo formulation is registered. The products generally require application to dry or wet hair for 10 minutes prior to rinsing or washing out.

4.5.2 Efficacy studies

Ten clinical studies on head lice products containing pyrethrins/piperonyl butoxide have been identified. Lotion, shampoo and mousse formulations containing 0.15% to 0.33% pyrethrins and 0% to 4% piperonyl butoxide were compared to lindane shampoo (13), lindane lotion (18), malathion solution (19), carbaryl lotion (19) and shampoo (19), bioallethrin (19), permethrin crème rinse (14,18,27,28,32), and to a variety of other pyrethrin formulations (18,37,38). One study was not comparative (33).

There were methodological flaws in many of the studies that included treatment with pyrethrins, as follows:

Table 5.

Ref	*Major flaws*
13	Identification of live lice not required for inclusion in study (ova only) Not blinded Concentration of actives and formulation not stated Variable use of nit combs "Successful" treatment not defined
14	Concentration of actives not stated
18	Identification of live lice not required for inclusion in study (ova only) Not blinded
19	Identification of live lice not required for inclusion in study (ova only) Not blinded
27	No exclusion for previous pediculocide treatment in last two weeks Post-treatment examination at variable times
28	Infestation not defined
32	Contact time not stated Pretreatment infestation not uniform between groups
33	Identification of live lice not required for inclusion in study (ova only) Not blinded No exclusion for previous pediculocide treatment in last two weeks
37	Identification of live lice not required for inclusion in study (ova only) Not blinded No exclusion for previous pediculocide treatment in last two weeks Contact time, formulation and concentration of actives not stated
38	Not blinded No exclusion for previous pediculocide treatment in last two weeks Contact time not stated

Despite these flaws, pediculocidal and ovicidal rates for pyrethrin products are calculated in these studies and are summarised below:

Table 6.

Ref	*Treatment*	*Live lice*[1]	*No* [2]	*Pediculocidal activity*[3] *2 hrs*	*Treatment success*		*Ovicidal activity*[4]
					7 days	*14 days*	
13	Lotion to dry hair for 10 mins		92		94.6%		
14	Liquid to dry hair for 10 mins, repeat after 7 days	✓	31		96.3%	100%	
18	0.3% Pyr to dry hair for 10 mins, repeat after 7 days (5 formulations)		32 33 33 31 32		78% 76% 58% 74% 78%	87.5% 94% 82% 84% 84%	
19	0.3%pyr/3%PB shampoo to wet hair for 10 mins		50	86%		52%[5]	
27	0.165%pyr/1.65%PB mousse to dry hair for 10 mins	✓	42		100%[6]		34.2%
28	0.3%pyr/3%PB to dry hair for 10 mins		204		85%	63%	
32	0.3%pyr/4%PB shampoo to wet hair, repeat after 7 days	✓	79		100%	100%	
33	0.15%pyr/1.65%PB to dry hair for 10 mins, repeat after 7 days		112		93.8%	99.1%	
37	Pyr/PB lotion Pyr/PB shampoo	✓[7]	20 20	85% 100%			19.5% 29.5%
38	0.3%pyr/3%PB lotion 0.3%pyr/3%PB shampoo	✓	20 20	100% 100%			25% 50%

1. Live lice required for inclusion in study
2. Number of subjects in pyrethrin group, not total number in study.
3. Pediculocidal rate is generally calculated as the percentage of subjects with no live lice after treatment. This makes pediculocidal rate of dubious value in studies in which only viable ova were required for inclusion in the study, as subjects may not have had live lice prior to treatment.
4. Ovicidal rates are calculated by comparing hatching rate of viable ova taken from the head prior to treatment, versus hatching rate of viable ova taken from the head immediately after treatment. Hatching rate determined after 14 day incubation period.

5. Evaluation of efficacy on day 10, not day 7
6. Evaluation of efficacy variable, up to 8 days post-treatment. 100% success claimed, but 2 patients had reinfestation.
7. Although live lice not required for inclusion, live lice were recovered from all patients.

As can be seen from the table above, the majority of studies used a contact time of 10 minutes to either dry or wet hair. In three studies the contact time was not stated (32,37,38). From these studies, the following comments can be made:

1. Ovicidal activity: Ovicidal activity was only reported in 3 studies. Pyrethrin formulations appear to have low ovicidal activity, although it should be noted that the pretreatment hatching rate in these studies was quite low (50-80%) compared to other studies.

2. Pediculocidal activity: Determination of pediculocidal activity is only possible in studies in which the presence of live lice were required for inclusion in the study, and inspection for the presence of live lice was undertaken within 24 hrs of treatment. Two studies met these criteria, both showing high pediculocidal rates. However, the contact times for the pyrethrin products were not stated in either study, and one study in particular (37) was considered to be inadequately documented.

3. Treatment efficacy: Using “success” at 7 days post-treatment as an indicator of treatment efficacy, pyrethrin products were effective in greater than 85% of cases in all but one study. This study compared a number of different pyrethrin formulations, and found lower efficacy than other studies for all formulations. There was no clear difference in efficacy between products applied to wet versus dry hair, or shampoo versus lotion formulations. Using “success” at 10-14 days post-treatment as a measure of efficacy, there is a clear difference between those studies in which the product was reapplied at 7 days and those in which a single application was used. In studies using a single application, the success rate was 52-63%, whereas studies using a repeat application at 7 days showed a success rate of 80-100%. This is consistent with the low ovicidal rate found for pyrethrin products in other studies. Since the majority of studies used a 10 minute contact time, no relationship between efficacy and contact time was evident.

It is considered that there is sufficient evidence from the combination of studies, despite their individual flaws, to indicate that pyrethrin/piperonyl butoxide products can have acceptable efficacy in the treatment of pediculosis when used with a contact time of 10 minutes and a repeat application after 7 days. However, one study suggests that formulation differences can affect efficacy. Since the majority of studies utilised a contact time of 10 minutes, the available information is insufficient to allow any conclusions to be drawn about the relationship between contact time and efficacy.

The existing MEC Guideline already recognises that retreatment with pyrethrin/piperonyl butoxide products is almost always necessary, and hence no specific amendments relating to this issue are required. For comment on formulation differences, see section 5.

4.5.3 Safety

Like permethrin, pyrethrins also have low toxicity. A review of pyrethrin toxicity in 1999 stated "the available data on humans did not show a causal relationship between exposure to modern pyrethrin-containing products and significant adverse health effects" (JMPR 1999).

Piperonyl butoxide has negligible acute toxicity (JMPR 1995), and is not considered to have carcinogenic, teratogenic or genotoxic effects of significance to humans.

Of ten clinical trials examined, 1 did not report adverse events. Of the remaining 9 studies, 7 found no adverse events after application of pyrethrin/piperonyl butoxide products (13,18,19,27,33,37,38). One study (32) reported a dermal adverse event in one patient (incidence of 1.2%), and the remaining study found an incidence of 16% dermal adverse events. The reason for the higher incidence of dermal adverse events in this study is not known. The concentration of pyrethrin/piperonyl butoxide in the product used is higher than in some other products (0.3%/3% versus 0.175%/1.75%), but some other studies also used this concentration and did not note such a high incidence.

Only one adverse reaction to a pyrethrin-containing head lice product has been reported to ADRAC to July 2003. This was a report of an application site reaction and change in hair texture.

Overall, pyrethrin/piperonyl butoxide head lice products are recognised as having a good safety profile, and adverse events from these products are rare.

4.6 BIOALLETHRIN

4.6.1 Products available in Australia

There is one product available in Australia containing 0.66% bioallethrin and 2.6% piperonyl butoxide. This product is a spray formulation that recommends application to dry hair for 30 minutes prior to shampooing out.

4.6.2 Efficacy studies

Three clinical trials including studies on head lice products containing bioallethrin have been identified. One study (12) compared a product containing 1.8% bioallethrin/7.2% piperonyl butoxide in isododecane with 0.5% malathion in ethanol. A second study (19) compared a spray product very similar to that marketed in Australia (containing 0.66% bioallethrin/2.6% piperonyl butoxide) with a variety of other head lice products

containing carbaryl, malathion or a pyrethrin/piperonyl butoxide combination. The third study (34) compared a lotion containing 0.66% bioallethrin/2.6% piperonyl butoxide with a variety of head lice products containing malathion, pirimiphos methyl or d-phenothrin. There were major flaws in the methodologies of all three studies, as follows:

Table 7.

Ref	*Major flaws*
12	No exclusion for previous pediculocide treatment in last two weeks Contact time not stated
19	No exclusion for previous pediculocide treatment in previous two weeks Live lice not required for inclusion in study Not blinded
34	No exclusion for previous pediculocide treatment in previous two weeks Evaluation of treatment at 24 hours only Inappropriate method of detection of lice (combing for 5 mins only) Not blinded

Despite these flaws, the ovicidal, pediculocidal and treatment success rates for the bioallethrin studies are summarised in the following table:

Table 8.

Ref	*Treatment*	*Live lice*[1]	*No*[2]	*Pediculocidal activity*[3] *24 hrs*	*Treatment success*		*Ovicidal activity*[4]
					7 days	*14 days*	
12	1.8% bio/7.2%PB solution to dry hair	✓	76		77%	77%	
19	0.66% bio/2.6%PB spray to dry hair for 10 mins		50	82%	52%[5]		
34	0.66% bio/2.6%PB lotion to dry hair for 5 mins	✓	17	45%			

1. Live lice required for inclusion in study
2. Number of subjects in bioallethrin group, not total number in study.
3. Pediculocidal rate is generally calculated as the percentage of subjects with no live lice after treatment. This makes pediculocidal rate of dubious value in studies in which only viable ova were required for inclusion in the study, as subjects may not have had live lice prior to treatment.
4. Ovicidal rates are calculated by comparing hatching rate of viable ova taken from the head prior to treatment, versus hatching rate of viable ova taken from the head immediately after treatment. Hatching rate determined after 14 day incubation period.
5. Results from 10 days post-treatment, not 7 days.

It is notable that one of the three published studies including bioallethrin (34) utilised a product very similar to that marketed in Australia, although the contact time used in this

study was 10 minutes, whereas the contact time recommended on the Australian product is 30 minutes. From the above studies, the following comments can be made:

1. Ovicidal rate: None of the studies examined the ovicidal effect of bioallethrin products, and hence no comment can be made on this issue.

2. Pediculocidal rate: Only one study met the criteria of both requiring the presence of live lice for inclusion in the study and examining for the presence of live/dead lice within 24 hours of treatment. In this study, a pediculocidal rate of 45% was found. Putting this in context, the same study showed a pediculocidal rate of 100% for a malathion lotion, and a pirimiphos lotion and shampoo. The malathion shampoo used in this study had a pediculocidal rate of 53.6%. It should be noted that this study had only a small number of subjects in each treatment group, reducing the reliability of the results somewhat.

3. Overall efficacy: Using "success" at 14 days as a measure of efficacy, one study found a success rate of 77%. However, the contact time used in this study was not stated. A second study examined "success" at 10 days post-treatment, and found a success rate of 52% after a contact time of 10 minutes, compared to a success rate of 98% for a malathion solution and carbaryl lotion in the same study.

There are insufficient studies containing bioallethrin-based products to be able to draw any conclusions about appropriate contact times and formulations for the treatment of head lice with bioallethrin. The studies available do suggest that bioallethrin/piperonyl butoxide products are less effective than malathion or carbaryl products when a contact time of 10 minutes or less is used, but no comments can be made on the efficacy of bioallethrin products if longer contact times are utilised.

4.6.3 Safety

Bioallethrin is a synthetic pyrethroid, in the same class as permethrin. Like permethrin it has low toxicity. No reports of adverse events from the use of bioallethrin head lice products have been reported to ADRAC to July 2000.

Of the three clinical trials examined which included product containing bioallethrin, two did not report adverse events. In the one study in which adverse events were reported (19), no adverse events were observed after bioallethrin treatment.

The toxicity of bioallethrin is similar to others in the permethrin group, and the lack of adverse events reported to ADRAC is consistent both with the low level of adverse events expected, and the lower number of products containing bioallethrin used in Australia.

4.7 HERBAL PRODUCTS

4.7.1 Products available in Australia

There are more than 20 products listed for use in Australia containing a variety of herbal ingredients. The majority of products contain a combination of melaleuca oil, lavender oil, eucalyptus oil or rosemary oil. Other ingredients include *Echinacea purpura*, *Adhatoda vasica*, geranium oil, thyme oil, citronella oil, lemon oil, lemongrass oil, *Stemona sessifolia*, clove leaf oil and anise oil. The directions for use of these products generally require a contact time of 10 minutes to 1 hour, although some product labels state that the product may be left on overnight if desired.

4.7.2 Efficacy studies on listed products

There are no published studies on the efficacy of listed herbal pediculocide products. However, two unpublished studies are available comparing the efficacy of herbal products with more conventional treatments. Both studies have been conducted in Queensland.

The first study (29) was a randomised trial comparing a product containing *Echinacea purpurea*, *Stemona sessifolia*, *Tanacetum cineriifolium*, Melaleuca oil and *Adhatoda vasica* (herbal product) with a 1% malathion foam. Both products were applied for 20 minutes, the herbal product to dry hair or hair combed free of conditioner (conditioner was applied to some heads to aid in detection of lice) and the malathion product to wet hair, and treatment was repeated after 7 days in both groups. The study was reported as double blind, but since the application method for the two treatments differed, it may not have been truly double blind. All subjects (primary school children – 74 in herbal group, 70 in malathion group) were required to have live lice evident prior to treatment. Exclusion criteria were not stated in the study report, and hence it is not known whether subjects with previous pediculocide treatment in the last 2 weeks were excluded. Post-treatment efficacy was observed at 20 minutes, 7 days and 14 days post-treatment, by means of combing the hair and wiping the combings onto white paper to examine any lice or eggs present. In this study, presence of live lice at 20 minutes or 7 days post study was regarded as evidence of resistance to treatment. Treatment success was assessed at 14 days as the absence of live lice (adult or 3rd instar). No active lice were found on days 1 and 7 after treatment with herbal product (recorded as 0% resistance). Active lice were found on 5 subjects in the malathion group at days 1 or 7 (recorded as 3.1% incidence of resistance). At 14 days 71.4% of patients were rated as cured in the herbal product group, and 47.3% in the malathion group. The study authors suggest that the low success rate with the 1% malathion foam may have been due to the presence of resistant lice, although it is not possible to rule out contact time being too short– despite the fact that the 20 minute contact time used in the study was the recommended contact time on the product label, a majority of published studies utilise an 8-12 hour contact time for malathion products (generally these are lotion formulations).

The second study, (39) performed by the same investigator, was a randomised clinical trial comparing a product containing 1% permethrin and 2% tea tree oil with a product containing 1% permethrin. Both products were applied by a hairdresser or assistant for 20 minutes, the permethrin/tea tree oil product to dry hair and the permethrin-only product to wet hair, and both treatments were repeated after 7 days. The study was reported as double blind, but since the application methods for the two treatments differed, it may not have been truly double blind. Subjects (primary school children in grades prep to five – 35 in permethrin + tea tree oil group and 49 in permethrin-only group) had either live lice or viable eggs prior to treatment. Exclusion criteria were not stated in the study report. Post-treatment efficacy was evaluated 7 days after first treatment (prior to second treatment), and 28 days after first treatment. Post-treatment assessment was by combing the hair and wiping the combings onto white paper to examine any lice or eggs present. For the final assessment (28 days after first treatment) 1% permethrin was applied to the hair to assist in detection of lice, but was not part of the treatment schedule. Treatment success (no live lice or viable eggs) was reported in 46.9% and 70.9% of the permethrin/ tea tree oil group at 7 and 28 days respectively, and in 51.2% and 61.9% of the permethrin-only group at 7 and 28 days respectively. There was no statistically significant difference between the groups. This suggests that the tea tree oil had no effect on the efficacy of the product, but no firm conclusions on the contribution of the tea tree oil can be made as the two formulations differed in other respects as well.

There is inadequate information available on the efficacy of herbal head lice preparations. The only two studies available are unpublished, and no firm conclusions can be reached from either of these studies because of methodological flaws. There are no studies available that point to a possible mechanism of action for the herbal products, and no studies examining the ovicidal activity of these products.

Concern has been expressed about the possibility that herbal products containing low levels of pyrethrins may encourage the development of resistance to pyrethrins (see section 6 for discussion of pyrethrin resistance). There is no evidence available to confirm whether this occurs or not, but it is a theoretical risk, especially with products that have a low level of efficacy. This issue is not restricted to pyrethrin-containing products, but should be considered in relation to any product containing sub-therapeutic levels of active ingredients.

Recommendation 4: Given the paucity of studies on the efficacy of listed herbal head lice products, it is recommended that the TGA review the evidence held by sponsors to support the listing of these products.

4.7.3 Efficacy studies on other herbal products

Several *in vitro* and *in vivo* studies have been conducted on the pediculocidal properties of herbal ingredients, not necessarily those used in products listed in Australia. The following examples, whilst no means comprehensive, give an indication of the sorts of studies that have been carried out overseas on herbal products. It is notable that most of

the studies are small and of a preliminary nature – no major clinical trials on herbal pediculocides have been identified.

One *in vitro* study (Downs et al 2000) examined the mortality of freshly collected head lice after exposure to tea tree (melaleuca) oil and to some of the individual components of the oil (gamma-terpinene, tetralin, terpinen –4-ol, α-terpeniol) as well as to copper oleate (a component of a commercial pediculocide shampoo). Exposure was for 2 hours via filter papers impregnated with either 10% or 1% concentrations of the various test chemicals. The results of the *in vitro* testing are tabulated below:

Mortality (%) after 2hr exposure

	Concentration of test chemical	
	10%	*1%*
Tea tree oil	86%	0%
Gamma-terpinene	57%	0%
Tetralin	100%	26%
Terpinen-4-ol	100%	26%
α-terpeniol	100%	22%
Copper oleate	0	0

All the chemicals tested, except for copper oleate, produced relatively high mortality after 2 hour exposure to 10% concentrations, but mortality was markedly reduced (to 0-26%) when the concentration was reduced to 1%.

An *in vitro* study was also carried out on the pediculocidal effect of *Lippia multiflora* essential oil (Oladimeji et al 2000). In this study, 0.02 mL of the oil (in various concentrations) was applied directly to the dorsal part of freshly collected head lice. Lice were observed, and the time to "knockdown effect" (cessation of movement) recorded. This study demonstrated a concentration-dependant knockdown time from Lippia oil (time to knockdown: 2.33 min at 100% concentration cf. 21.95 min at 10% concentration). Knockdown time was reduced if the test system was covered immediately after application of the oil (closed system), allowing build-up of oil vapour. However, the significance of this is unknown, since the study report does not indicate % mortality, and it is known that lice can be "knocked down" but subsequently recover. In addition, the use of a direct application of the oil to the lice is an unusual method of exposing the lice, and does not allow comparison with other *in vitro* studies.

Several clinical trials have also been conducted on herbal pediculocides. A trial in Israel (Mumcuoglu et al 2002) compared the efficacy of a herbal spray containing coconut, anise and ylang ylang oils applied to the hair 3 times for 15 minutes at 5 day intervals with a spray product containing 0.5% permethrin, 0.25% malathion and 2% piperonyl butoxide, applied twice for 10 minutes with a ten day interval. The natural remedy resulted in successful treatment in 60/70 (92.3%) children, while the conventional product was successful in 59/73 cases (92.2%).

A shampoo containing 0.5% extract of paw paw, 1% thymol and 0.5% tea tree oil was also tested in a clinical trial (McCage et al 2002). The shampoo was applied to the dry hair of 16 children with head lice, left for one hour and then rinsed out. Shampoo was reapplied 8 and 16 days after the first applications. After the third application, children were inspected for the presence of lice or live eggs. A 100% success rate was found in this small uncontrolled study.

A cream containing 20% extract of custard apple seed (*Annona squamosa* seed) was compared to cream base and a 25% benzyl benzoate emulsion in another clinical trial (Tiangda et al 2000). One of the three treatments was applied to the head of school girls (n=6-11 per treatment group) with at least 3 live lice and eggs, for 3 hours before being washed off. Lice were combed from the head immediately after treatment, and the proportion of live and dead lice were calculated. In the group treated with custard apple cream, 89-99% (depending on the age of the cream) of the lice were dead, while only 47% and 60% were dead in the cream base and benzyl benzoate groups. No adverse events were detected in the custard apple cream group, although skin irritation was reported in the benzyl benzoate group.

4.7.4 Safety

There is very little published information available on the safety of listed herbal head lice preparations. There are no ADRAC reports on these products to July 2003, and no reports of adverse events in the two studies conducted on these products (see section 4.7.2).

Herbal head lice products in general are listed (as opposed to registered) in Australia because they are considered to have a lower level of risk than other products. However, it is known that high concentrations of essential oils can be irritant to the skin, and can even burn skin. The concentrations of essential oils in head lice products are generally well below the levels at which significant dermal adverse events might be expected. However, a head lice product containing 10% melaleuca oil and 1% lavender oil was recently the subject of approximately 22 reports to the sponsor of dermal adverse events (stinging, burning sensation). It is estimated that the incidence of these reactions was of the order of 0-3% (based on the number of units of product sold). The mechanism of these adverse events is not known, but their existence indicates that herbal head lice products should not be automatically regarded as “safe”.

4.7.5 Listing versus registration of herbal pediculocides

One issue specifically to be addressed in this review is the issue of whether head lice infestation should be made a “registrable disease/condition” (as opposed to notifiable disease – see section 3.3). The implication of making head lice infestation a registrable condition is that **all** pediculocide products would require registration (evaluation of safety, efficacy and quality prior to sale), as opposed to the current situation where herbal pediculocides making general or medium level claims require listing (no evaluation prior

to sale, but data required to be held) and other products (such as those containing malathion and permethrin, and/or those making high level claims) require registration.

The theoretical basis for the registration/listing system of drug regulation in Australia is that products considered to have a higher level of risk require registration (and hence pre-market assessment of safety, efficacy and quality). It is recognised that some products have a low level of risk (many herbal products, for instance) – these products require listing, and do not undergo product by product evaluation. Rather, the ingredients from which these products are formulated are assessed by the TGA as being safe for use in listed medicines. Listed products may only be supplied if they contain approved ("listable") substances.

In determining the level of risk associated with medicines, a number of factors are taken into account, including the strength of the product, side effects, potential harm through prolonged use, toxicity, the seriousness of the medical condition for which the product is to be used, and whether medical advice is required for diagnosis and treatment of the condition. In general, conditions for which listable products are considered suitable are those that are self-limiting (i.e. will ultimately resolve with or without treatment) and non-transmissible. The following claims (or claims of like intent) are currently accepted for listed head lice products:

- Aids in the management/control of head lice infestation;
- Relieves the symptoms of head lice infestation;
- Aids in the removal of head lice and/or their eggs.

There is no suggestion that uncomplicated head lice infestation can cause serious illness, and equally there is no evidence to suggest that it requires diagnosis or treatment under medical advice. However, head lice infestation is not a self-limiting condition, and it does require effective treatment in order to reduce transmission to other people.
Another factor in determining whether treatments for a particular condition should be registrable is whether the condition is regarded as a public health problem. State and Territory Health Authorities were questioned on a number of issues related to head lice treatments, including whether head lice infestation was considered a public health problem. The responses of the Health Authorities are summarised in Attachment 7. When a broad definition of public health was used, 5/8 States and Territories considered the issue a public health problem, as well as a significant social problem when issues of cost of treatment, interruption to school and work attendance, and social stigma were considered. The majority of State and Territory Health Authorities recommended that head lice products should require pre-market evaluation of clinical data (that is, should be registrable). These factors, combined with the issues of transmission and the need for effective treatment, suggest that pre-market evaluation of all head lice treatments should be undertaken, and hence that head lice treatments should all be registrable. This would ensure that only products effective in the clinical situation are available to the public.

It is important to consider the potential consequences of this proposed regulatory approach. The majority of currently listed head lice treatments are herbal or other

"natural" products, many sponsored by small companies. It has long been recognised that one of the main obstacles to mainstream acceptance of many herbal products is the lack of good quality clinical data to support their safety and efficacy. A contributing factor to this lack of data is the inability of many sponsors to finance such studies. This may be due both to the small size of many sponsors, and to the fact that most herbal products are not patented, and therefore financing appropriate clinical studies is not justified by guaranteed financial returns.

The likely effect of making currently listable products registrable is that many such products will simply disappear from the marketplace, not necessarily because they are not efficacious, but because the sponsor has insufficient financial resources or clinical know-how to produce suitable evidence of efficacy. Those few clinical studies that have been undertaken on herbal pediculocides (see sections 4.7.2 and 4.7.3) suggest that some herbal formulations have the potential to be at least as effective as the more "conventional" treatments, especially in areas where resistance to conventional treatments has developed. The potential disappearance of many listable products would result in much less choice for consumers regarding treatment options. This would be a negative outcome since many parents are uncomfortable with using "chemical" pesticide treatments on their children. In this context, public acceptance of herbal products is high (one sponsor has estimated that they represent 40% of total head lice treatment sales) despite their relatively high price.

Although requiring all pediculocide products to be registered seems a logical step, based on the probable consequences stated above, this action is unlikely to achieve the outcome of giving consumers the widest possible choice of safe treatments.

Acting on Recommendation 4 (by reviewing the efficacy of listed products – see section 4.7.2) and Recommendation 8 (by reviewing and restricting the label claims of registered products – see section 7.1) should ensure that only safe and effective treatments are available in the marketplace without the need to require that all products be registered.

Recommendation 5: It is therefore recommended that, regarding registration versus listing of pediculocide products, the current situation be maintained, in which herbal products making general or medium level claims require listing, and products containing non-listable ingredients and/or making high level claims require registration.

4.8 NEW/INVESTIGATIONAL TREATMENTS

With concern that head lice are developing resistance to many, if not all, of the current pediculocide treatments (see section 7 for discussion of resistance), the development of new therapies to which resistance has not yet developed is of great importance. Some of the new treatments under examination as potential pediculocides are discussed below. In general, these treatments are at an experimental stage, and none have been studied

sufficiently to confirm their suitability as safe and effective pediculocide treatments in Australia.

4.8.1 Levamisole

Levamisole, an acetylcholine nicotine receptor agonist used as an anthelmintic, has been considered worthy of study as a potential pediculocide because head lice have similar cholinergic neuronal systems to the nematodes that levamisole is currently effective against. One clinical study (Namazi 2001) has been carried out on the effectiveness of oral levamisole in the treatment of pediculosis.

The study involved 28 patients (females, 7-12 years) with confirmed pediculus capitis (defined as living eggs and/or lice in the hair), who were treated with oral levamisole 3.5 mg/kg once daily for 10 days. Subjects were examined at the initiation and conclusion of the treatment period for the presence of live lice and lice eggs (status of eggs determined by examination under high magnification hand lens or low power microscope for presence of opercula). Complete responsiveness (no live eggs or live lice), partial responsiveness (some live eggs and live lice but less than at start of treatment) or unresponsiveness (equal or more live lice or live eggs than at start of treatment) was determined at the end of the treatment period. The results were as follows:

Complete responsiveness	67%
Partial responsiveness	19%
Unresponsive	15%

The study author suggests that partial responsiveness or unresponsiveness may be due to resistance having been developed to levamisole during prior treatment of the local population with levamisole for nematodes, or to re-infestation, since family members and close contacts were not treated. The author suggests that levamisole may be worthy of further study as a pediculocide.

4.8.2 Imidacloprid/Fipronil

An *in vitro* efficacy study has examined the effect of two animal flea treatments, imidacloprid (Advantage®) and fipronil (Frontline®)on both laboratory-reared body lice and on head lice collected from British school children (Downs et al 2000). The lice were exposed to the insecticides for 2 hours by placing them on filter papers impregnated with varying concentrations of insecticides. Both positive (lindane-impregnated papers) and negative (untreated papers) controls were included. After 2 hours, half the lice were removed to untreated papers to determine in recovery occurred. The other half were exposed for a further 22 hours. Morbidity was assessed after 2 hours exposure, and mortality was assessed after 2 and 24 hours exposure.

Fipronil demonstrated 100% mortality against body lice after 2 hours exposure to concentrations of 0.016% or greater. However, only 97% mortality was achieved against

head lice with 2 hours exposure to 0.25%. The authors suggest that the reduction in effectiveness against head lice may be due to cross resistance between fipronil and lindane, since the positive control demonstrated lindane resistance in the head lice population.

Imidacloprid was equally effective against head lice and body lice. Twenty four hour exposure to 0.2% resulted in 100% mortality. However, after 2 hour exposure to the same concentration 91-98% morbidity was achieved, but the majority of lice recovered when transferred to the untreated paper, demonstrating the necessity of longer exposure time for imidacloprid .The study authors suggest that imidacloprid may be worthy of further study since it has a long residual effect against fleas on animals, a rapid knockdown effect, and low mammalian toxicity.

4.8.3 Trimethoprim/sulfamethoxazole

The effect of oral trimethoprim/sulfamethoxazole on head lice was noted in 1978, and was the subject of an uncontrolled trial in 20 patients (Shashindran et al 1978), treated with varying doses of trimethoprim/sulfamethoxazole. All 10 patients in the study who received a minimum dose of 80 mg trimethoprim/400 mg sulfamethoxazole twice daily for at least 3 days (repeated after 10 days) were completely free of lice and nits at a follow up 25 days after first treatment. Lower doses were found to be ineffective.

Recently two clinical trials have reported on its use in combination with conventional topical treatment.

In one study (Hipolito et al 2001) oral trimethoprim/sulfamethoxazole (10 mg/kg/day based on trimethoprim, daily for 10 days – TMP/SMX group) was compared with 1% permethrin crème rinse (applied to wet hair for 10 minutes, rinsed off, and reapplied 1 week later if head lice were still present – PER group) in children with confirmed head lice infestation (presence of live lice or live eggs). A third group of patients was treated with both 1% permethrin crème rinse and oral trimethoprim/sulfamethoxazole (PER + TMP/SMX group). Treatment success was defined as the absence of adult or nymphal stage lice or eggs (presence of eggs alone did not constitute treatment failure). At the 2 week follow-up, treatment was successful in 79.5%, 83% and 95% of patients in the PER, TMP/SMX and PER + TMP/SMX groups respectively. At the 4 week follow-up, treatment was successful in 72%, 78% and 92.5% of patients in the PER, TMP/SMX and PER + TMP/SMX groups respectively. Three patients were removed from the study because of allergic reaction (rash) to TMP/SMX. Other adverse reactions in patients treated with TMP/SMX included nausea, vomiting and transient pruritus.

In a second study (Sim et al 2003) a comparison was made between the effectiveness of 1% lindane shampoo (applied to dry hair and rinsed after 10 minutes)alone or in combination with oral trimethoprim/sulfamethoxazole (8 mg/kg/day based on trimethoprim, in two divided doses for 12 days) in patients with confirmed head lice infestation (presence of live lice or viable eggs). At the two week follow-up, the success

rate (success not defined) was 76.8% in the lindane alone group, and 86.7% in the combined treatment group. Patients with treatment failure at the two week follow-up were retreated, and followed up two weeks later, at which time the success rate was 91.3% in the lindane alone group and 97.8% in the combined treatment group. There was no statistically significant difference between the two groups in success rate at either follow up time.

4.8.4 Ivermectin

Oral ivermectin has not been used to treat head lice in Australia. However, in the US, ivermectin in a single oral dose of 200 μg/kg repeated after 10 days is available as a prescription pediculocide (Burkhart et al 1997). The potential for ivermectin to be used as a pediculocide was noted in a double blind placebo controlled study of its effectiveness in the treatment of onchocerciasis. It was noted during this study that children treated with ivermectin has a lower incidence of head lice than children in the control group (Dunne et al 1991). Subsequent studies demonstrated that oral ivermectin was indeed effective against head lice (Glaziou et al 1994).

One uncontrolled study has examined the effectiveness of topical ivermectin (in liquid form at 0.8%) in the treatment of scabies and head lice (Youssef et al 1995). The study included 50 patients with scabies (treated over the whole body on two occasions 5 days apart) and 25 with head lice (treated once over the head and hair). Examination of both groups of patients for two weeks after the last treatment found a 100% cure rate in both groups. According to the study report, topical ivermectin killed both live lice and eggs in the head lice group.

5 FORMULATION-DEPENDENCE OF EFFICACY

Nine clinical trials compared one or more different formulations of the same active ingredients, as follows:

Ref	*Products compared*
9	0.2% phenothrin: alcoholic lotion vs. aqueous/alcoholic lotion
17	0.5% carbaryl: lotion vs. shampoo. 0.5% lindane lotion vs. 1% lindane shampoo
18	Five different 0.3% pyrethrin lotions
19	0.6% carbaryl shampoo vs. 0.5% carbaryl lotion
24	0.5% carbaryl lotion vs. 1% carbaryl shampoo
30	0.5% malathion: 2 lotions vs. shampoo. 1% lindane: lotion vs. shampoo
34	0.3% malathion lotion vs. 0.4% malathion shampoo. 0.3% pirimiphos-methyl lotion vs. 0.7% pirimiphos shampoo
37	Pyrethrin/piperonyl butoxide lotion vs. shampoo
38	0.3% pyrethrin/3.0% piperonyl butoxide lotion vs. shampoo

Of these clinical trials, one (30) had too few patients per group, and significant methodological and reporting inadequacies to allow meaningful evaluation of results.

Shampoo versus lotion: Two studies (17, 19) found that carbaryl shampoo formulations were less effective than the corresponding lotion formulations. However, the shampoos were applied to wet hair for 3-5 minutes, while the lotions were applied to dry hair for 8-24 hours. Hence differences in contact time and application method rather than any differences inherent in the formulations themselves, may have been responsible for the lower efficacy of the shampoos. In another study (34), malathion lotion was found to be more effective than the corresponding shampoo, although both were applied for 5 minutes (lotion to dry hair, shampoo to wet hair). In this study, although the application times were the same, application of the shampoo to wet hair may have reduced the efficacy of this formulation. Using the same application methods as for the malathion shampoo and lotion, the same study found that a 0.7% pirimiphos shampoo was equally as effective as a 0.3% pirimiphos lotion. Again, differences in formulation may be outweighed by other factors (in this case concentration difference).

Two other studies (37, 38) went against the trend of the other studies, in finding a higher ovicidal activity from a pyrethrin/piperonyl butoxide shampoo than the corresponding lotion formulation. Both studies found similar pediculocidal activity from the two formulations, although the shampoo formulation appeared to kill lice faster than the lotion. The authors of these studies suggest that the surfactant activity of the shampoo base may allow greater penetration of the active ingredients, especially into the ova. However, contact times and application methods were not stated in the study reports, and hence the significance of these results is in doubt.

An additional reference (24) contained too few subjects in the lotion subgroup to allow meaningful evaluation of results. It is, however, curious that in this study, in contrast to previously mentioned studies, the shampoo formulation was deemed to be 100% effective.

Lotion versus lotion: Several studies compared different lotion formulations. One (18) compared five different pyrethrin lotions. The interpretation of results in this study is complicated by the fact that nit combing with the nit comb supplied with each different product was undertaken as part of the treatment, and it was recognised that some combs were more effective than others. However, it does appear that there were differences in the efficacy of the treatments, with treatment failures at day 7 ranging from 22-42%, and at day 14 from 6-18%. In this study, all products were applied in a standard manner, so differences in application methods and contact times do not complicate the results.

Another study (9) found no statistically significant difference in efficacy between the two lotion formulations examined. Both formulations were considered to be 100% effective at evaluation 3 weeks post-treatment.

Despite the reservations expressed in section 4.2 about the value of *in vitro* pediculocide studies, it is of interest to note that in one *in vitro* study, comparing 6 different carbaryl lotions, the pediculocidal activity after a 2 hour exposure time varied from 59% to 100%, and the ovicidal activity varied from 9% to 93% (Burgess 1990). This large variability in such standard test conditions is surprising, as the variability under field conditions might be expected to be even more marked.

Another *in vitro* study (Mougabure Cueto et al 2002) compared the pediculocide activity of a range of aliphatic alcohols (1-octanol, 1-nonanol, 1-decanol, 1-undecanol and 1-dodecanol) against both permethrin resistant and non-resistant head lice. The pediculocide activity varied according to the length of the carbon chain, with 1-octanol the least effective, and 1-dodecanol the most effective. 1-dodecanol was equally effective against both permethrin resistant and non-resistant lice. The study authors suggest that the inclusion of pediculocidal aliphatic alcohols in pediculocide formulations may enhance their efficacy, and refer to an unpublished study (Mougabure Cueto et al 2000) in which the modification of pediculocide formulations was able to enhance insecticidal activity.

There is a paucity of good quality information on the effects of different formulations on the efficacy of head lice products. It does appear that in general lotions have superior efficacy to the corresponding shampoos, but whether this is due to differences in formulation or in application methods and contact times cannot be determined. One clinical study (18) suggests that differences in lotion formulation do affect product efficacy, although the use of different nit combs and lack of statistical analysis in this study complicate the issue. However, the results of this study are supported by the results of an *in vitro* study (Burgess 1990). Work by Mougabure and coworkers (2002, 2000) also supports the suggestion that formulation differences can effect efficacy.

There are little data to confirm or deny the suggestion (from ASMI) that the effects of formulation on the efficacy of pediculocides are related to the stability of the formulation, rather than its chemical characteristics.

Recommendation 6: It is recommended that for new registration applications, efficacy should be demonstrated for the formulation under consideration (see section 4.2 for discussion of suitability of *in vitro* versus *in vivo* evidence of efficacy). Comments from several stakeholders support the need for product-specific efficacy testing.

6 RESISTANCE TO PEDICULOCIDE TREATMENTS

There is no doubt that resistance to the major pediculocide ingredients used in Australia, malathion and permethrin, has developed in many parts of the world (Gratz 1997). Convincing evidence of this resistance has been found in the UK (Burgess et al 1995a), the US (Meinking et al 2002), Israel (Mumcuoglu et al 1995), the Czech republic (Rupes 1994) and France (Coz et al 1993). Studies suggest that permethrin resistance in particular has developed in some countries within 3 years of the introduction of permethrin treatment for head lice in these countries (Mumcuoglu et al 1995). Resistance to lindane and DDT is also well documented (Gratz 1997). The exact mechanism of this resistance is not known, but it is likely that resistance to permethrin (and cross-resistance to other pyrethroids) is due mostly to nerve insensitivity (known as "kdr" resistance), although mono-oxygenase resistance mechanisms may also be involved (Hemingway et al 1999). This may help to explain the rapid development of permethrin resistance, as resistance to DDT, used prior to the development of more modern head lice treatments, is also via the kdr mechanism, and hence permethrin resistance may be a form of cross resistance to DDT (Mumcuoglu et al 1995). Malathion resistance has been suggested to be due to specific esterase mechanisms, and is unlikely to involve the acetyl choline binding site, as cross-resistance between malathion and carbaryl (which also binds to the acetyl choline site) does not occur (Downs et al 1999). In at least one study, head lice resistant to both permethrin and malathion were discovered.

In order to demonstrate that resistance has occurred, studies should ideally compare the susceptibility of field-collected head lice to a pediculocide both before (or soon after) the introduction of the pediculocide, and at some time after general use of the pediculocide in the same population. Resistance can be said to have developed if the field-collected lice are less susceptible than lice collected before the introduction of the pediculocide into the population. If this comparison over time is not possible (often because studies of susceptibility were not undertaken before the introduction of the pediculocide), it is difficult to differentiate between genuine resistance and treatment failure due to lack of efficacy.

Resistance has not been conclusively documented in Australia (i.e., by comparison of sensitivity over time). However, there are suggestions that resistance to malathion has occurred in both Tasmania (Goldsmid 1990) and Queensland (Speare 2000[clinical reference 29]). A recently published case report (Bailey and Prociv 2000) of a persistent head lice infection within a single family also lends support to the belief that multiply resistant head lice have developed in Australia. In this case live adult lice were observed after multiple treatments containing (variously) malathion, permethrin, pyrethrins, bioallethrin, and crotamiton, although treatment failure due to inadequate application cannot be conclusively ruled out from the study report. Additionally, a number of stakeholders have provided anecdotal evidence of resistance to most of the pediculocides currently used in Australia. Based on experience in other parts of the world, it is probable that resistance to commonly used ingredients will occur here, if it has not already.

Recommendation 7: More definitive data on the existence and pattern of resistant head lice in Australia would be of use in determining a procedure for treating head lice in cases where initial treatment fails. It is recommended that the NHMRC be requested to encourage research into this issue.

Although the development of resistant head lice has not been well-studied, most researchers believe it develops through exposure to sub-lethal doses of pediculocides, in the same way that antibiotic resistance develops in bacteria, and other forms of pesticide resistance develop in other insects (Brainerd et al 1998). This suggests that any actions that increase exposure to sub-lethal doses of pediculocides, such as the use of ineffective products, the prophylactic use of low doses of pediculocides, and the use of products with a residual effect (the long half life presumably allows longer duration of exposure to ineffective doses), can enhance the development of resistance, and should be avoided.

Some authors suggest that rotating the pediculocides used (for instance, permethrin for one year, malathion for one year) can reduce the development of resistance. However, the effectiveness of this strategy has not been proven, and in any case is difficult to enforce in a situation where consumers are able to purchase products over the counter, although it may be practical in communities where the local council or health centre provides treatment (see Burgess 1995b). In individual cases, it is suggested that a mosaic approach is used: if treatment with one product fails, the patient should be switched to a product with a different ingredient type (for instance, if permethrin fails after two applications 10 days apart, switch to malathion, but not pyrethrins).

It should be noted that many supposed cases of resistance are actually treatment failures due to inappropriate contact times or application methods, or ineffective products. These are much more common reasons for treatment failure than resistant head lice are.

The potential for head lice to become resistant to herbal products is not known. No cases of resistance to herbal products have been documented, but very few studies on the efficacy or mode of action of herbal pediculocides have been undertaken (see section 4.7.2). It has been suggested that products based on essential oils are less likely to cause resistance, as the ingredients are volatile and will quickly evaporate from the hair, avoiding the problem of residual sub-lethal doses of product remaining on the hair. However, without any data, this suggestion cannot be confirmed. In addition, without knowing the mechanism of action of the herbal products, it is difficult to predict their potential for inducing resistance. One group of herbal products that may be of concern in this regard is products based on plants containing low levels of natural pyrethrins. It is theoretically possible that these low levels of pyrethrins could encourage the development of resistance to pyrethroid insecticides in general. This issue has not been studied, but should be given consideration when such products are submitted for registration or listing.

Since so little is known about the mechanisms of development of resistance, it is difficult to predict which products may have the potential to cause or enhance resistance. A

requirement for clinical data to confirm the efficacy of new products (as suggested in Recommendation 1 of this Review) is of even more value under these circumstances, to confirm that new treatments kill a large majority of head lice, and do not allow significant exposure of head lice to sub-therapeutic concentrations of active ingredients. However, clinical studies overseas may not provide an accurate picture of the efficacy of the proposed product under Australian conditions, where the pattern of resistance may be quite different (the same could be said of studies undertaken in one part of Australia in relation to their applicability in other parts).

The existence of different resistance patterns in different parts of the world is one of the reasons behind action taken by the Ministry of Health in Israel in 1995. The Ministry of Health ordered that all pediculocides produced in or imported into Israel must be tested in a clinical trial in Israel to determine whether they are effective against local head lice (Mumcuoglu et al 2002).

7 LABELLING OF PEDICULOCIDE PRODUCTS

7.1 Efficacy claims

A number of stakeholders have commented on the plethora of label claims on currently available pediculocide products, and the confusion this causes amongst consumers. A table of label claims is presented in attachment 8. In particular, claims that a product *"kills with one application"*, or *"kills head lice (and their eggs) on contact"* or *"prevents reinfestation"* are considered meaningless, inaccurate or misleading. It was suggested by several stakeholders that less confusion would result from standardisation of label claims.

Recommendation 8: It is recommended that label claims on registered products be limited to control/treatment of head lice and their eggs. Label claims should not state or imply that one treatment will kill all lice and eggs. Because the claims for efficacy on the labels of some "grandfathered" products are meaningless, inaccurate or misleading, the TGA should review the labels of these products to ensure safe and effective use in the community.

7.2 Other labelling issues

Comments have been made about the issue of warning statements and directions for use on pediculocide products. There has also been discussion about the need for additional information about head lice infestation (such as the need to treat fomites and the use of nit combs). In particular, the need for warning statements about the use of pediculocide products by pregnant women and on infants have been mentioned, as has the need to apply all pediculocide products to dry hair.

It is considered that a general requirement to apply pediculocides to dry hair is not necessary. The application method (ie. to dry or wet hair) as well as the contact time should be determined by the methods supported by the clinical trials. If clinical trial data are required for the majority of head lice products (as recommended earlier in this report), there is little need for general guidelines (such as those currently in the ARGOM) to recommend standard contact times or application methods.

Recommendation 9: It is therefore recommended that the current sections of the guidelines recommending contact times and application methods for various pediculocide ingredients be replaced with a recommendation that directions for use of pediculocide products should be consistent with clinical trial data on the pediculocide product in question.

With regard to warning statements, the current guidelines recommend warning statements about not using the product on children under six months of age, and not getting the product in eyes. The FDA labelling requirements for OTC products in the US (Code of

Federal Regulations, Title 21, Volume 5, Parts 300-499[1]) also require warning statements about use on persons allergic to ragweed and about discontinuing use if irritation or infection develops (these requirements apply only to US OTC products, containing pyrethrins or permethrin). Given the relatively small number of ADRAC reports arising from the use of head lice products, additional general warning statements (such as the statement about ragweed allergy required in the US) are not considered necessary.
A suggestion has been made that malathion-containing head lice preparations should carry a warning not to use during pregnancy. Malathion, bioallethrin, permethrin and pyrethrins for topical use have all been evaluated by ADEC and included in pregnancy category B2[2]. Lindane and piperonyl butoxide have been included in category B3[3].

Given that malathion has the same pregnancy category as bioallethrin, permethrins and pyrethrin, it is not considered necessary to single out malathion for a warning statement with regard to use in pregnancy. However, since none of the active ingredients in currently registered head lice treatments have a category A rating[4], it is proposed that the labels of all products containing these active ingredients carry a warning statement about use in pregnancy. This is consistent with a recent decision that all OTC products (except those containing active ingredients in category A) carry a statement warning against use in pregnancy or stating the pregnancy category of the product.

Recommendation 10: It is recommended that the labels of products containing malathion, pyrethrins, piperonyl butoxide or permethrin include a warning to the effect that the product is not to be used in pregnancy unless advised by a doctor.

7.3 MEC Guidelines

The existing MEC Guideline on head lice treatments (see attachment 3) was developed in the early 1990s, and has been criticised as possibly out of step with current data on head lice and head lice treatments. As a consequence of this review of current data, it is considered that certain aspects of the existing Guideline (specifically, relating to malathion contact times, permethrin retreatment times, prophylactic use) require amendment. Hence a new Guideline is proposed (see attachment 4), based on the recommendations made earlier in this report. It is considered that this Guideline should apply not only to registered products, but also to products regulated through the Office of

[1] http://www.gpoaccess.gov/cfr/retrieve.html
[2] Category B2: Drugs which have been taken by only a limited number of pregnant women and women of child bearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage
[3] Category B3: Drugs which have been taken by only a limited number of pregnant women and women of child bearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans
[4] Category A: Drugs which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the fetus having been observed

Complimentary Medicines under the listing system. This would provide guidance to sponsors of listed products as to the sort of data that should be held in relation to the efficacy of their products, as well as assist in achieving consistency in labelling across the entire range of head lice products.

Recommendation 11: It is recommended that the proposed Guideline be considered by the TGA for inclusion in the relevant guidelines documents for OTC and complementary medicines.

8 EDUCATIONAL ADVICE

Most commentators recognise that pediculocide use is only one aspect of successful head lice treatment. Other aspects, such as the ability to detect lice and eggs, treatment of fomites, and removal of eggs and lice after treatment, are also important. These factors will impact upon the efficacy of chemical pediculocides, and thus it is in the sponsors best interests to ensure that the public has access to accurate information on these issues. Information on these issues is currently available in a piecemeal fashion, from pediculocide labels or package inserts, information pamphlets from State and Territory Health Departments or local councils, or web sites such as the one prepared by Associate Professor Rick Speare[1]. The information from these different sources is often contradictory, and in contrast to evidence from published studies.

Examples of the contradictory nature of some of the advice follows:

- The majority of education leaflets indicate that no product is 100% effective after one application and retreatment in 7-10 days will be necessary. However, some product labels indicate that one application may be sufficient to kill all lice and nits (eg. Pyrenel Foam AUST R 19414; KP24 Medicated Lotion AUST R 18869).

- Advice on the treatment of fomites ranges from *"wash all brushes, combs, hair ribbons, scrunchies, pillowslips and recently worn clothes in hot water and dry with heat or leave them in the sun. Items that cannot be washed can be placed in a plastic bag for 8-10 days"* (ACT Department of Health and Community Care) to *"wash combs and hair brushes after use in water at 60°C for at least 10 seconds. Put head gear into sealed bags for 2 days or leave them under strong sunlight for a few hours"* (joint leaflet from Queensland Govt., Queensland Health, Education Queensland and the Pharmaceutical Society).

- Most leaflets recommend following manufacturers instructions regarding contact times, but one information source recommends leaving preparations on the hair for at least 20 minutes (Assoc. Prof. Rick Speare's web site).

There is a clear need for authoritative information on head lice to be made available to the public. There appears to be a need for the States and Territories to coordinate in developing consistent, evidence-based educational advice covering areas including the detection of head lice and eggs, removal of lice and eggs after treatment, effective alternatives to chemical treatment, suitable treatment of fomites, and strategies to employ if chemical treatment fails.

Recommendation 12: It is recommended that the State and Territory health departments adopt consistent evidence-based public health advice for provision to the public.

[1] www.jcu.edu.au/school/phtm/PHTM/hlice/hlinfo1

This coordinated information could be disseminated via current mechanisms including local councils, pharmacies, State and Territory Health Departments and/or product sponsors.

Addendum July 2004: Several States have individually developed comprehensive, evidence-based information packages (eg. 'Scratching for Answers', Victorian Department of Human Services, first released in 2001; 'Healthy Heads….Without Nits', South Australian Department of Health; 'Head Lice in Primary Schools Kit', ACT Health). Unfortunately, the effect of such evidence-based information will be diminished if information from other sources, such as web sites, product labels, and information sheets developed by pharmacy and or medical groups, is not consistent.

9 STAKEHOLDERS COMMENTS

Stakeholders comments were elicited as discussed under "Methodology of the review". A summary table of stakeholders comments is included in attachment 1. In general, there was little consensus between different groups of stakeholders on the issue of whether head lice should be made a registrable disease (that is, all head lice products should require registration rather than listing). There was also disagreement as to the value of *in vitro* studies to support the efficacy of products. However, the majority of stakeholders, including the NRA / APVMA, agreed that regulation of all head lice products, including repellent products, should come under the auspices of the TGA.

10 REGULATORY RESPONSIBILITY

As mentioned in section 3.1, the current situation with regard to the regulation of head lice preparations in Australia is that products claiming to treat head lice infestation (including claims to kill head lice), are regulated by the TGA, while products claiming to prevent head lice infestation or repel head lice are regulated by the APVMA. This anomalous situation arises because of the APVMA's responsibility for pest control products, which has traditionally included insect repellents. Head lice repellents have been included in this category. The majority of stakeholders who commented on this matter, including the APVMA itself, are of the opinion that responsibility for the regulation of head lice repellent products should be transferred to the TGA. This makes sense on the grounds that head lice repellent products are applied to human heads, usually in a similar manner to head lice treatment products, and so the safety of the repellent products should be evaluated in the same way as the treatment products. Also, there are implications for the development of resistance to treatment products from repellent products that contain low (sub-lethal) levels of pyrethrum derivatives or other active ingredients present in treatment products. This issue is best addressed by the TGA. Additionally, some products claim to both treat head lice and prevent further infestation. There seems little advantage in terms of control, and some disadvantage in terms of resources, in having these products evaluated by both the TGA and the APVMA.

Recommendation 13: It is therefore recommended that regulatory changes be put in place to transfer the responsibility for regulating head lice repellent or preventative products from the APVMA to the TGA.

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12 ATTACHMENTS

12.1 ATTACHMENT 1: SUMMARY OF STAKEHOLDERS COMMENTS

Attachment 1A: Initial stakeholder comments (elicited by letter prior to drafting review)

Contributor	Comments/Information provided
Regulatory Concepts for: Laboratories Pharmacare	• Resistance not an issue for malathion • Supports mandatory directions for use (based on *in vitro* testing for new actives/formulations) • *In vitro* testing required/sufficient for major formulation changes/new actives (but *in vitro* testing not available in ANZ) • Either listing or registration required (listed products to be supported by *in vitro* tests) • NRA (APVMA) registration inappropriate
Dr A Bailey* Dept of Microbiology and Parasitology Uni of QLD	• Treatment should be undertaken only if live lice seen, and in conjunction with physical methods • If live lice found after 2 weeks, use only physical methods • Resistance may be more common reason for treatment failure, not poor technique • Supports efficacy testing on product-by-product basis • No evidence to exclude cross-resistance, therefore mosaic treatment may not be effective • Physical removal should be at least adjunctive treatment, if not first line
Dermatech Laboratories	• Permethrin is drug of choice because of effectiveness and safety • Resistance to permethrin not proven to occur • Guidelines should be flexible and not specify directions for use • Expert comment provided – suggests 2 hr contact time for permethrin and revised instructions for use • Clinical data on permethrin provided

Contributor	Comments/Information provided
Christine Bell Listing Process and Policy Unit TGA	• Under old TGAC, lice treatments did not require registration • New TGAC may require registration (not listing) of lice products, but Listing Unit not yet acting to restrict claims (waiting for review) • Provides details of listable product recently removed from ARTG due to adverse events and lack of efficacy data • Indications for listed products include: - control and treatment of head lice and nits - kills headlice and their eggs on contact
Key Pharmaceuticals	• Resistance to malathion and permethrin developing • Standard tests not suitable for determining skin irritation • Evidence of efficacy for most products poor – suggests TGA review efficacy of all products, using *in vitro* data • Registration required for all products • NRA (APVMA) regulation inappropriate • Comparative clinical data on permethrin, malathion and tea tree oil provided
Regulatory Concepts for: Stafford Miller Ltd.	• Registration (and hence some efficacy data) required for all products • Product-by-product efficacy testing only for new actives (*in vitro* tests and at least one clinical trial) • Directions for use should be based on clinical data (product/ingredient specific) • Directions should include recommendations on physical removal, mandatory reapplication, and treatment of contacts and fomites
Dr J Carnie Vic Dept Human Services	• Supports need for review • Health Dept information sheet supplied
Peter Saunders PSA	• Pharmacy information sheets and some clinical data supplied
Christine Brenton WA Health Dept	• Product labelling should state: - no product 100% ovicidal - retreatment after 1 week required - hair conditioner may inactivate insecticide - nymphs should be combed out daily • plastic combs provided with treatment are often ineffective (metal combs better) • other directions for use require evidence • repellent claims should be substantiated by evidence

Contributor	Comments/Information provided
A Petrie Qld Health Dept	• NRA (APVMA) regulation inappropriate • Supplied Health Department information sheet
Eucanol Pty Ltd	• Does not support declaring head lice a "disease" • Critical of current labelling (both mandatory and product specific) • Supports labelling amendments and suggests standardised label wording (especially claims) to reduce consumer confusion.
Jenny Bergin PGA	• All products should require registration • Supports product specific efficacy testing • Anecdotal evidence of consumer concerns provided
George Stefanoff ACT Health Dept	• Health Department information sheet supplied
SA Health Dept	• Health Department information sheet supplied
John Woods CTFA	• Members currently have no products and no information to submit
Debbie Munro, Director, Emerald Forest Pharmaceuticals	• Submitted clinical data on several products • Resistance does occur, but can be managed • Field trials important to establish efficacy – *in vitro* studies not sufficient • Does not agree that all pediculocides should be registrable • Currently no products available that kill with one application – a second application is always necessary • Repellents (with proof of efficacy) needed in some communities, but should be regulated by TGA, not NRA (APVMA)
S Logan, K Spies, T Knight (concerned consumers)	• Expressed concerns over the safety and efficacy of currently available head lice treatments, especially malathion-based treatments. • Recommends additional testing of products on children, and additional warning statements on labels about side effects, precautions, and safety directions. • Recommends additional parent education and resources • Inclusions: testimonials about lack of efficacy and/or toxicity of head lice treatments; information (Internet/library – based) on safety of insecticides including malathion and permethrin

Contributor	Comments/Information provided
Dr A Northridge General Practitioner	• Reports anecdotal evidence of resistance to commonly used chemical pediculocides, and preventative treatment occurring • Suggests need for more education, especially about non-chemical methods of treatment (eg. Nit-combing)

Attachment 1B: Stakeholder comments on draft review

Stakeholder	Comment
Recommendation 1: *It is recommended that claims for efficacy and safety of head lice products should generally be supported by relevant clinical trials, rather than in vitro data only. In vitro data may be acceptable, at the discretion of the evaluation body, where the formulation of a product is similar to an existing product that has been fully evaluated.*	
Queensland Cosmetic Laboratories	Points out practical difficulties with conducting relevant clinical trials.
Association of Therapeutic Goods Consultants	Agree in general terms, but use of in vitro data needs to be carefully considered.
Pharmacare	Disagree since a) clinical trials impossible to conduct in Australia, and b) allowing competitors to submit in vitro data discourages innovators from developing new products.
Ketorac Pty Ltd.	Need to determine criteria for "relevant" clinical trials. In vitro data may only be suitable if formulation is identical, not similar.
Key Pharmaceuticals	Does not agree due to difficulties in undertaking clinical trials – in vitro studies are appropriate. If clinical trials requirement imposed, guidance from TGA on acceptable protocols required.
Australian Self Medication Industry	Agrees that clinical trials are preferred method for determining efficacy, but due to difficulties in undertaking clinical trials, rejects the view that in vitro testing has little use. Proposes framework for standards of evidence required for different product categories (ie. existing, new, etc)
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Recommendation avoids specifying what tests are acceptable for obtaining efficacy data, and what level of efficacy is required for registration approval.
Complementary Healthcare Council of Australia	Performing clinical trials in Australia is difficult and expensive since testing facilities not readily available in Australia

Stakeholder	Comment
Recommendation 2: *It is recommended that the existing MEC guideline requiring a contact time of 12 hours or more for malathion-containing lotions be deleted.*	
Pharmacare	Agree, but contact time on existing lotions should not have to change.
Australian Self Medication Industry	Disagree based on lack of evidence to support change.
Environmental Health Branch, NSW Health Department, NSW	Experience in NSW Nitbusters Program suggests 0.5% malathion is not effective.
Association of Therapeutic Goods Consultants	Reasonable recommendation
Queensland Cosmetic Laboratories	Suggests re-examination of malathion safety data
Recommendation 3: *It is recommended that, unless product sponsors can provide clinical evidence to the contrary, the current guideline should be amended to indicate that, when necessary, retreatment with permethrin crème rinse products, as with other pediculocide products, should occur 7-10 days after the first treatment.*	
Pharmacare	Agree
Australian Self Medication Industry	Agree
Ketorac Pty Ltd	Agreed
Environmental Health Branch, NSW Health Department, NSW	Experience in NSW Nitbusters Program suggests 1% permethrin is not effective.
Association of Therapeutic Goods Consultants	Agreed
Recommendation 4: *Given the paucity of studies on the efficacy of herbal head lice products, it is recommended that as part of a post-marketing strategy, the listing section of the TGA target head lice treatments for review. Particular importance should be placed on the efficacy of products containing low levels of active ingredients, because of the theoretical risk that they might encourage the development of resistance.*	
Pharmacare	Agree. Definition of “low levels” required.
Environmental Health Branch, NSW Health Department, NSW	Disagree, since registration is required.
Australian Self Medication Industry	Agree, but may not be necessary of Recommendation 5 accepted
Key Pharmaceuticals	Agree if Recommendation 5 not adopted, but sponsors would need guidance on data requirements.
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Agree in principle, but requires more definition.

Stakeholder	Comment
Ketorac Pty Ltd	Agreed, but should extend to all head lice products, not just herbals (especially residual activity).
Association of Therapeutic Goods Consultants	All products (not just herbals) should be subject to review.
Queensland Cosmetic Laboratories	Suggests that targeting of herbal products and those with low levels of actives is not necessarily appropriate.
Recommendation 5: *Given the level of concern over head lice infestation, and the need for effective treatment to minimise the spread of infestation and to reduce social and public health consequences, it is recommended that all head lice treatments be required to be registered, rather than listed. If it is decided that registration is required for head lice treatments, consideration should be given to the development of guidelines or some other form of assistance to sponsors in determining appropriate studies to support applications for registration.*	
Australian Self Medication Industry	Does not support this recommendation at this stage. Preferred proposal to implement Recommendation 4, using same criteria for both registrable and listable products.
Key Pharmaceuticals	Does not agree. Proposes regulation analogous to listable sunscreens (ie. testing according to prescribed methodology).
Environmental Health Branch, NSW Health Department, NSW	Agree
Ketorac Pty Ltd	Suggests public health policy of retreatment after 7-10 days in all cases – review regulatory position if this doesn't work.
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Agree if assistance given to sponsors.
Pharmacare	Agree, if in vitro trials are the standard measure of efficacy.
Association of Therapeutic Goods Consultants	Does not agree that head lice treatments require registration. Should apply "levels of evidence" guidelines for listable products before considering registration.
Queensland Cosmetic Laboratories	Does not agree. Review of evidence held by sponsors should be undertaken first. Implementation of this recommendation will remove many products from the market without necessarily leaving the more efficacious products.
Complementary Healthcare Council of Australia	Does not support this recommendation for "non-toxic complementary substances"

Stakeholder	Comment
Recommendation 6: *Without a clear indication from studies published to date that formulation does not effect efficacy, it is recommended that for evaluation purposes, efficacy should be demonstrated for the formulation under consideration.*	
Pharmacare	Agree, if efficacy based on in vitro studies
Australian Self Medication Industry	Agree
Key Pharmaceuticals	Agree
Ketorac Pty Ltd	Agreed
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Agree
Association of Therapeutic Goods Consultants	Requirements should be consistent with other classes of therapeutics
Queensland Cosmetic Laboratories	Agree
Recommendation 7: *More definitive data on the existence and pattern of resistant head lice in Australia would be of use in determining a procedure for treating head lice in cases where initial treatment fails. It is recommended that the NHMRC be requested to encourage research into this issue.*	
Pharmacare	Agree
Australian Self Medication Industry	Agree
Association of Therapeutic Goods Consultants	Agreed. Timetable for this should be provided.
Key Pharmaceuticals	Agree
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Recommendation useful for public health policy, but not consumers. Suggests alternative expanded wording.
Ketorac Pty Ltd	No objection
Environmental Health Branch, NSW Health Department, NSW	NSW interested in collaborating in research through Nitbusters Program
Queensland Cosmetic Laboratories	Agree
Recommendation 8: *It is recommended that products or product application methods that encourage exposure to lower than accepted doses of pediculocides should be discouraged. Registration applications for any such products in the future should address the issue of potential to cause resistance. The TGA should seek evidence to support the ongoing registration or listing of such products already available in Australia. This evidence should include argument or data on the potential to cause resistance.*	

Stakeholder	Comment
Pharmacare	Does not agree – recommendation premature prior to results of recommendation 7.
Australian Self Medication Industry	Does not agree. Policy regarding minimisation of resistance should be developed from results of Recommendation 7.
Key Pharmaceuticals	"lower than accepted doses" should be defined. Results of Recommendation 7 required.
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Agree with principle, but residual products should also be discouraged. Also implies "accepted doses" will not encourage resistance – not true
Association of Therapeutic Goods Consultants	"Lower than accepted dose" difficult to define since efficacy is formulation dependent.
Ketorac Pty Ltd	Agreed
Queensland Cosmetic Laboratories	Implementation should be based on data
Recommendation 9: *It is recommended that label claims be limited to control/treatment of head lice and their eggs. Label claims should not state or imply that one treatment will kill all lice and eggs. Since the labels on many grandfathered products are meaningless, inaccurate or misleading, the TGA should consider undertaking a review of these products under Section 66 (3A) as a matter of urgency to ensure safe and effective use in the community.*	
Australian Self Medication Industry	Does not agree to limit claims. Claims should be permitted based on evidence. Agrees with labelling review of **all** products (not just grandfathered ones).
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Agree
Pharmacare	Claims should be based on in vitro trial data. Strongly objects to removal of the claim "kills head lice and their eggs on contact".
Key Pharmaceuticals	Agree, but urges realistic time frame for compliance (2 years at manufacturer level).
Ketorac Pty Ltd	Agreed
Association of Therapeutic Goods Consultants	Label claims should reflect supporting evidence.
Queensland Cosmetic Laboratories	Agree
Complementary Healthcare Council of Australia	Supports review of labelling guidelines to restrict misleading/confusing claims.

Stakeholder	Comment
Recommendation 10: *It is recommended that the current sections of the Guideline recommending contact times and application methods for various pediculocide ingredients be replaced with a recommendation that directions for use of pediculocide products should be consistent with clinical trial data on the pediculocide product in question.*	
Australian Self Medication Industry	Agree, but directions should be consistent with clinical studies **or** in vitro data.
Pharmacare	Agree for new products, if based on in vitro data.
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Meaningless unless acceptable end point of clinical trials is defined.
Key Pharmaceuticals	Agree
Ketorac Pty Ltd	Agreed
Association of Therapeutic Goods Consultants	Agreed
Queensland Cosmetic Laboratories	Directions for use should also include other factors (ie. application methods etc.)
Recommendation 11: *Given that malathion has the same pregnancy category as permethrin, pyrethrins and bioallethrin, it is not considered necessary to single out malathion for a warning statement with regard to use in pregnancy. Comment should be sought from ADRAC on the need for a warning statement on all head lice products that pregnant women should seek professional advice before applying head lice products to themselves or other persons.*	
Drug Information Centre, Women's and Children's Hospital, Adelaide	Permethrin recommended over malathion as treatment in pregnancy.
Australian Self Medication Industry	Agree
Key Pharmaceuticals	ADRAC should establish which products require pregnancy warning – blanket warning statement should not be required.
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Agree
Pharmacare	Agree
Ketorac Pty Ltd	Malathion pregnancy category should be reviewed.
Association of Therapeutic Goods Consultants	Agree malathion should not be singled out; warning statements should reflect toxicities of all ingredients in formulation
Queensland Cosmetic Laboratories	Recommends re-examination of malathion toxicity.

Stakeholder	Comment
Recommendation 12: *It is recommended that the proposed Guideline be considered by the MEC and the Office of Complimentary Medicines for inclusion in the AGRM.*	
Australian Self Medication Industry	See detailed comments on Guideline
Key Pharmaceuticals	See detailed comments on Guideline
Choice Magazine	Agree
Pharmacare	See detailed comments on Guideline
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	See detailed comments on Guideline
Ketorac Pty Ltd	Agree – see specific comments
Pharmaceutical Society of Australia	Statement regarding use of product in pregnancy may be necessary
Association of Therapeutic Goods Consultants	Guideline should have appropriate industry consultation
Queensland Cosmetic Laboratories	See detailed comments on Guideline
Recommendation 13: *It is recommended that the Commonwealth be involved in developing evidence-based educational advice to be made available to the public.*	
Australian Self Medication Industry	Agree
Key Pharmaceuticals	Does not agree, since much information already available.
Pharmacare	Agree
Ketorac Pty Ltd	No objection
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Commonwealth involvement welcome if lack of evidence acknowledged
Environmental Health Branch, NSW Health Department, NSW	Suggests enHealth Council (subgroup of National Public Health Partnership) may be forum for this.
Pharmaceutical Society of Australia	Agree that consistent information must be available to all health professionals.
Association of Therapeutic Goods Consultants	Agreed. Strategies need to be put in place to ensure advice remains current.
Queensland Cosmetic Laboratories	Agree but should be expanded to include interested stakeholders and other programs.
Recommendation 14: *It is recommended that regulatory changes be put in place to transfer the responsibility for regulating head lice repellant or preventative products from the NRA to the TGA.*	
Australian Self Medication Industry	Agree

Stakeholder	Comment
Key Pharmaceuticals	Strongly agree
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Agree
Environmental Health Branch, NSW Health Department, NSW	Agree.
Ketorac Pty Ltd	No objection
Association of Therapeutic Goods Consultants	Agree.
Pharmacare	Agree
Queensland Cosmetic Laboratories	Agree

General Comments

Stakeholder	Comment
Choice Magazine	Supports all recommendations
Environmental Health Branch, Department of Human Services, SA	Supports all recommendations. Recommendations 13 and 7 especially important
A Bailey, Dept. of Microbiology, University of Queensland	Detailed comments on use of in vitro vs clinical trials, and ethical/practical considerations of regulations.
Prof. R Speare, School of Public Heath and Tropical Medicine, James Cook University	Detailed comments on evaluation of studies in the report.
Communicable Diseases Section, Department of Human Services, VIC	Supports all recommendations. Supplied Information kit currently circulated in Victoria
Poisons Control, Territory Health Services, NT	Supports all recommendations. Reliable information for consumers particularly important.
Emerald Forest	Expressed concern that regulatory requirements may hinder introduction of new products from small manufacturers.
Communicable Diseases Unit, Queensland Health, QLD.	Supports all recommendations (specific comments on proposed guidelines also made).
Chief Health Officer, ACT Department of Health, Housing and Community Care, ACT	Supports all recommendations, especially recommendation 13.
Queensland Cosmetic Laboratories	Some report recommendation impractical, and target herbal preparations with no real evidence of a problem.

Stakeholder	Comment
Peter Hull, The Apothecary	Not enough emphasis on treatment failures due to non-compliance – this is a major issue and needs addressing. Discusses confusion over how to determine resistance vs non-compliance vs reinfestation.

12.2 ATTACHMENT 2: SUMMARY OF CLINICAL TRIALS

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
1	FT	159 children (5-18 yrs) involved in double blind trials of oral ivermectin for onchoceriasis.	100-200 µg/kg ivermectin (74 pts) vs placebo or no treatment (85 pts)	Within 2 months of 4th dosage, manual examination (combing onto white sheet) for live lice.	Infestation found in 16% of ivermectin treated and 30% of control group (stat sig).	Not reported	Conducted in Sierra Leone. Incidental finding of study on onchoceriasis.
2		20 children (4-14 yrs) with >10 viable ova	1% Per lotion applied to dry hair for 2 hours (10 pts) or 10 mins (10 pts)	Evaluation of lice (live, dead) retrieved after treatment. 14 day incubation of pre and post-treatment ova samples. Manual examination for live lice after 7 days.	2 hr treatment: 100% kill of lice, 90% kill of ova, no live lice after 7 days, reduction in developing ova from 86% to 12%. 10 min treatment: 98% kill of lice, 88% kill of ova, no live lice after 7 days, reduction in developing ova from 89% to 10%.	Not reported	Conducted in Spain. Subject numbers small.. Authors suggest increasing contact time increases pediculocidal but not ovicidal activity..
3	DB, PC, Parallel group	119 children (5-15 yrs) with >20 viable ova	0.5% Mal lotion to dry hair for 8 hours (61 pts) vs vehicle to dry hair for 8 hours (58 pts)	14 day incubation of pre and post treatment ova samples. Examination for live lice 24 hours and 7 days after treatment.	Hatching reduced from 92.8% pre to 32.2% post treatment with Mal vs 90% pre and 58.8% post treatment with vehicle. At 24 hrs, live lice found in 9.8% Mal and 63.8% of controls. At 7 days live lice in 14.8% Mal and 82.8% of controls. All differences stat. sig.	No a.e. observed	Study conducted in Nicaragua. Cannot exclude reinfestation as cause of failures at 7 days.
4	Parallel group, C	62 children (3-11 yrs) with live lice and/or >20 viable ova	0.5% Mal lotion for 2 hrs (29 pts) vs 1% Lin shampoo for 5 mins (33 pts).	14 day incubation of pre and post treatment ova. Examination for live lice immediately after treatment and at 7 days and 4-6 weeks.	At least 1 nit hatched in 63% of pretreatment sample compared to 35% post treatment (either treatment). Immediately post treatment, no live lice found in either group. At 7 days, live lice in 7% of Mal and 12% of Lin group. At 4-6 weeks live lice found in 17% Mal and 9% Lin group. Differences not stat. Sig.	Not reported	Study conducted in Vancouver. Lower pretreatment hatching rate than other groups due to incubation difficulties. Re-infestation may have occurred by 4-6 weeks.
5	Parallel group, C	101 children (5-21 yrs) with live lice and/or viable ova.	Part 1: 0.2% d-phenothrin lotion for 12 hrs (29 pts) vs 0.5% Car lotion for 12 hrs (28 pts). Part 2: 0.2% d-phenothrin lotion for 2 hrs (21 pts) vs 0.5% Mal lotion for 2 hrs (23 pts)	Part 1: Examination for live lice or viable eggs at 1, 2, and 4 weeks post treatment. Part 2: Examination for live lice or viable eggs at 24 hrs, 2 and 4 weeks post treatment.	At 24 hrs, infestation found in 1/29 phenothrin 2hr group (lice only) and 6/23 Mal group (eggs only). At 1 week, no infestation in either phenothrin 12 hr or Car groups. At 2 weeks infestation in 1/29 phenothrin 2 hr group (lice only) and 1/23 Mal group (eggs only). At 4 weeks infestation in 3/27 Car (live and eggs)	Dermal a.e. observed in 2/50 phenothrin-treated, 3/23 Mal-treated and 5/28 Car treated.	Study conducted in England. Most cases of "treatment failure" likely to be reinfestation (especially when no eggs found).

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
6	R, C	50 children (4-11 yrs) with live lice and/or viable ova..	0.2% d-phenothrin shampoo for 5 mins (25 pts) vs 0.5% Car shampoo for 5 mins (25 pts). Treatments onto wet hair repeated 3 times at 3 day intervals	Examination for live lice and viable eggs at 14 days after initial treatment	At 14 days, 1/25 d-phenothrin had infestation (lice and eggs) and 2/25 Car had infestation (1 eggs only, 1 lice and eggs). Differences no stat.sig.	No a.e. observed	Study conducted in Ireland. Retreatment protocol unusual. Cannot exclude reinfestation as cause of treatment failure
7	FT	110 children with live lice.	1% Lin solution (contact time not stated). Retreatment after 7 days	Examination 1-2 days after second treatment	Treatment failure (adult lice present) in 35% of cases	Not reported	Study conducted in Netherlands. Authors suggest results suggest resistance to Lin. *In vitro* study also conducted – see table 2
8	R, C	77 children (4-10 yrs) with live lice and eggs (2 pts per group) or viable eggs only (all other pts)	0.2% phenothrin shampoo (39 pts) (contact time not stated) vs 0.5% Mal lotion for 2 hrs (38 pts)	Examination 1 and 4 weeks post-treatment	No live lice post treatment At 1 week 2/38 Mal and 0/39 phenothrin had eggs. At 4 weeks 5/39 phenothrin and 7/38 Mal had eggs.	No a.e. observed	Study conducted in Birmingham. Authors suggest results at 4 weeks suggest reinfestation, but may reflect failure to detect live lice at earlier examination.
9	DB, R, C	56 patients (5-10 yrs, plus two adult pts) with "confirmed head lice infestation" (31 pts had eggs only)	0.2% phenothrin lotion for 2 hrs (32 pts treated with aqueous/alcoholic lotion, 24 pts treated with alcoholic lotion)	Examination at 24 hrs and 3 wks post treatment	At 24 hrs, no live lice seen but 8/32 aq/alc and 6/24 alc had viable eggs. At 3 weeks, no live lice or eggs seen in either group. Differences not stat. Sig.	Dermal a.e. occurred in 9/32 aq/alc and 4/24 alc	Study conducted in England. Authors comment on difficulty of distinguishing viable from non-viable eggs at 24 hrs.
10	R, C	72 children (3-14 yrs) with live lice. Excluded if treated in last 2 weeks.	0.5% Mal lotion (aqueous or alcoholic) for 8-10 hrs to wet hair, repeat in 7 days (40 pts) vs "Bug busting" (detector comb and conditioner repeated every 3-4 days for 2 weeks) (32 pts)	Examination 7 days after treatment started, and 7 days after treatment finished.	7 days after treatment finished 38% bug buster and 78% Mal had no signs of infestation. A subgroup of patients who had not used pediculocides in the 4 wks prior to study showed no infestation in 58% bug buster and 78% Mal. Differences stat.sig.	Not reported	Study conducted in UK where previous evidence of intermediate resistance to Mal.

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
11	C	76 children (5-11 yrs) with live lice and/or eggs.	0.2% phenothrin shampoo (42 pts) vs 1.5% Car gel shampoo (34 pts). Treatments applied to wet hair for 5 mins, rinsed and repeated. Treatments applied 3 times in 7 days.	Examination 1-2 weeks and 6 weeks after first treatment.	At 1-2 weeks, no nymphs or live lice seen in either group. At 6 weeks 3/34 in Car group had reinfestation. No stat. analysis	No a.e. in Car group. 3/42 had a.e. (dry skin) in phenothrin group	Study conducted in Hampstead
12	C	126 children (age not stated) with live lice.	0.5% Mal in ethanol to dry hair (51 pts) vs 1.8% Bio/7.2% PB to dry hair (76 pts). Contact time not stated.	Examination for live lice 3, 7, and 14 days after treatment.	At 3 days, 4% of Mal and 4% of Bio group had live lice. At 7 days 33% Mal and 23% Bio had live lice. At 14 days 35% of Mal and 23% of Bio had live lice. No stat. Analysis.	Not stated	Study performed in Netherlands. *In vitro* study also conducted – see table 2
13	MC. C	158 children (3-13 yrs) with live lice (68.4%) and/or viable eggs (91.8%). Excluded if treated in last month.	Lin shampoo to dry hair for 4 minutes (66 pts) vs Pyr lotion to dry hair for 10 mins (92 pts)	Examination for lice and viable eggs, and symptoms at 7-10 days post-treatment.	Treatment "successful" in 94.6% Pyr and 87.9% Lin group (not stat sig).	No a.e. in Pyr group. 2 a.e. (burning scalp) in Lin group	Study conducted in NE USA. "Successful treatment" not adequately defined. Variable use of nit combs.
14	R, C	58 patients (4-39 yrs) with >1 live lice and >9 viable ova. Excluded if treated in last 4 weeks.	Pyr/PB liquid to dry hair for 10 minutes, then repeated after 7 days (31 pts) vs 1% Per crème rinse to wet hair for 10 mins (27 pts)	Examination before and after treatment on days 0 and 7, and again at 14 days.	At day 7 96.3% of Per and 45.2% Pyr group were lice free. At 14 days 100% Per and 93.5% Pyr were lice free. Differences not stat.sig.	Not reported	Study conducted in USA. ½ of Pyr treatment failures at day 14 probably reinfestation.
15	SB, R, C MC	559 patients (1-72 yrs) (508 evaluable for efficacy) with live lice. Excluded if treated in last week.	1% Per crème rinse to wet hair for 10 mins (287 pts) vs 1% Lin shampoo to dry hair for 4 mins (272 pts)	Safety examination at 1hr, 24 hrs, 7 and 14 days. Efficacy examination at 7 and 14 days post treatment	At 7 days 99.6% of Per and 91.9% of Lin pts were lice free. At 14 days 99.2% Per and 85.2% Lin pts were lice free (both differences stat sig).	12.9% Per and 11.8% Lin pts had dermal a.e.	Study conducted in USA Cannot exclude reinfestation as cause of treatment failure at 14 days, as family members not treated.

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
16	R, C	53 patients (3-40 yrs) with viable eggs. Excluded if treated in last 30 days.	Lin shampoo to dry hair for 4 mins (25 pts) vs Per shampoo to dry hair for 10 mins (28 pts). Retreatment in both groups after 7 days, then nit combing for 7 days.	Examination for live nymphs at 14 days after initial treatment. Ova (pre and post treatment samples) incubated for 14 days.	At 14 days no patient in either group had nymphs (1 pt had adult lice therefore reinfestation). Hatched ova occurred in 27% of pre- and 28% of post-treatment Lin samples, and in 50% of pre- and 43% of post-treatment Per samples.	Not reported	Study conducted in Vancouver. Ova hatching results not reliable, as hatching rate of untreated ova very low. Differences in ability to observe nymphs thought to be reason for diff b/w groups at 7 days.
17	?	549 children (primary school age) with "active infestation" (not defined)	0.5% Car lotion (81 pt) vs 0.5% Mal lotion (108 pt) vs 0.2% bioresmethrin lotion (49 pt) vs 0.2% chlorphenamidine lotion (93 pt) vs 0.5% Lin lotion (97 pt) vs o.5% Car shampoo (64 pt) vs 1% Lin shampoo (57 pt). Lotions applied to dry hair for 24 hrs; shampoos applied to wet hair for 3 mins.	Examination for live lice at 24 hrs and 14 and 28 days (to give a measure of residual effect).	% with live lice at 24 hr 14d 28d Car lotion 0 0 2.5 Car shampoo 1.6 3.1 10.9 Mal 0 1.9 2.8 bioresmethrin 0 8.2 12.2 chlorphenamidine 0 14.0 21.5 Lin lotion 0 8.8 19.6 Lin shampoo 2.1 14.4 31.6 Stats not performed.	No a.e. observed	Study conducted in England. Commercial formulations not used. Suggests shampoos less effective than lotions, but commercial lotions often not recommended for 24 hr contact time. *In vitro* study also conducted – see table 2

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
18	R, C	223 children (5-12 yrs) with live lice and/or >9 viable eggs. Excluded if treated in last 4 weeks.	1% Per (Nix crème rinse – to wet hair for 10 mins, no repeat) vs 0.33% Pyr (A-200) vs 0.33% Pyr (Pronto) vs 0.3% Pyr (R&C) vs 0.3% Pyr (Rid) vs 0.3% Pyr (Triple X) vs 1% Lin (Kwell – to dry hair for 4 mins, repeat 7-10 days)). All groups had 29-33 pts). All treatments to dry hair for 10 mins then repeat at 7-10 days, with nit combing for 20 mins after treatment unless stated)	Examination for lice and nits at 7 and 14 days post initial treatment	% with lice/nits on day 7 day 14 A-200 22 12.5 Kwell 20 7 Nix 9 12.5 Pronto 24 6 R&C 42 18 Rid 26 16 Triple X 22 16 Stats not performed on pediculocides, but in combination with nit comb, Nix most effective.	No a.e. observed.	Study conducted in Florida. Suggests activity may be formulation dependant, but may also have something to do with packaged nit combs (Nix comb rated as most effective, Kwell comb least effective)
19	R, C	250 children (2-15 yrs) with >2 live lice and/or >4 viable eggs.	Pyracide shampoo (0.3% Pyr/3% PB) to wet hair for 10 mins vs Kin-X spray (0.66% Bio/2.6% PB) to dry hair for 10 mins vs Monocide solution (0.4% Mal/0.1% allethrin) to wet hair for 10 mins vs Hafif shampoo (0.6% Car) to wet hair for 10 mins) vs Hafif lotion (0.5% Car) to dry hair for 12 hrs. 50 pts per group	Examination for lice and nits 1 and 10 days post treatment	% with lice/nits on day 1 day 10 Monocide 0 2 Hafif lotion 0 2 Hafif shampoo 8 32 Pyracide 14 48 Kin-X 18 48 Monocide and Hafif lotion stat sig better than other treatments	10% in Monocide and 6% in Hafif lotion had dermal a.e.	Study conducted in Israel. Mal solution and Car lotion most effective but also most adverse events. Lotion appears more effective than shampoo.

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
20	?	15 children (1-11 yrs) with "intense" head lice infestation (not defined)	0.5% Mal lotion to dry hair for 24 hrs.	Pre and post treatment ova samples taken and incubated for 14 days. Head lice also sampled post treatment immediately and at 2 hrs.	Hatching rate of ova was 100% pre treatment vs 14% post-treatment. Immediately after treatment 78.6% of lice were dead – this rose to 100% at 2 hrs post treatment. No reinfestation observed 7 days post treatment.	Not reported	Study conducted in Spain. Definition of "Intense" infestation not stated. 100% survival of pre-treatment ova unusual.
21	PC, DB*, R *Lin group not blinded	93 patients (2-23 yrs) with live lice and >19 viable eggs. Excluded if treated in last 3 months.	1% Per crème rinse to wet hair for 10 mins (29 pts) vs 1% Lin shampoo to dry hair for 10 mins (30 pts) vs crème rinse base to wet hair for 10 mins (34 pts)	Examination at 7 and 14 days post treatment. Pre and post treatment ova samples taken for incubation.	% lice free at 7 days 14 days Per 100 97 Lin 67 43 placebo 9 6 % ova hatched pre post Per 90 30 Lin 92 55 placebo 94 86 Per stat sig better than placebo. Stats not performed on Lin group.	Not reported	Study conducted in Panama. Suggests lower efficacy of Lin may be due to resistance as treatment in previously unexposed population nearby resulted in 90% lice free at 14 days.
22	R, SB	193 children (school age) with live lice and >5 viable eggs.	Mal lotion (95 pts) vs d-phenothrin lotion (98 pts) – both treatments to dry hair for 8-12 hrs. Fomites treated with commercial pediculocide powder.	Examination at 1 and 7 days post treatment	At day 1, 92% Mal and 40% d-phenothrin lice-free. At day 7, 95% Mal and 39% d-phenothrin lice free. Differences stat. Sig.	Not reported	Study conducted in France. Authors suggest this implies resistance to d-phenothrin. *In vitro* study also performed – see table 2.
23	R, SB, C	1040 patients (age not stated) with live lice. Excluded if treated in last week.	1% Per crème rinse to wet hair for 10 mins (659 pts) vs 1% Lin shampoo to dry hair for 4 mins (381 pts)	Examination at 1hr, 24hrs (sfaety), 7 and 14 days (efficacy)post treatment.	At day 7, 99% Per and 89% Lin were lice free (stat sig). At day 14 98% Per and 74% Lin were lice free (stat sig.)	1.2% Per and 2.6% of Lin group had a.e. (not stat sig). Pruritus and erythema most common	Study conducted in Mexico.

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
24		31 children (age not stated) with live lice and/or viable eggs	0.5% Car lotion to dry hair (contact time not stated) (5 pts) vs 1% Car shampoo to wet hair for 4-5 mins (26 pts).	Examination at 1-2 weeks and 6 weeks post treatment.	100% efficacy in both groups at both time points.	Not reported	Study conducted in Britain.
25	R, DB, PC	115 patients (2-36 yrs) with live lice and >20 viable eggs.	0.5% Mal lotion (68 pts) vs lotion vehicle (47 pts) to dry hair for 12 hrs.	Examination at 24 hrs and 7 days post treatment. Pre and post treatment ova samples incubated.	Live lice present in 0/68 Mal and 5/47 placebo at 24 hrs; 3/65 Mal and 26/47 placebo group at 7 days. Ovicidal activity 55% for Mal and 29% for control. At day 7 and 86% Mal and 47% control at day 14. All differences stat. Sig.	1 case of stinging in Mal group	Study conducted in USA
26	R, C, SB	50 patients (5-38 yrs) with live lice and/or viable eggs.	0.2% phenothrin shampoo to wet hair for 5 mins then repeat (27 pts) vs 0.5% Car lotion to dry hair for 2 hrs (23 pts).	Examination at 24 hrs and 3-4 weeks.	At 24 hrs, no patients had live lice in either group, but 5/27 in phenothrin and 6/23 in Car group had viable eggs. At 3-4 weeks 0 patients in phenothrin group and 3/23 in Car group had live lice. 1/27 patient in phenothrin and 2/23 in Car had viable eggs. No stat sig differences b/w groups	7/23 patients in Car group had dermal a.e.. No other a.e reported	Study conducted in Britain. Report indicates difficulty in distinguishing b/w viable and non-viable egs..
27	SB, R, C	52 patients >6 years of age with live lice and eggs.	0.165% Pyr/1.65% PB aerosol mousse to dry hair for 10 mins (42 pts) vs 1% Per crème rinse to wet hair for 10 mins (10 pts).	Examination at 30 mins, twice in first eight days, (also 4 pts at 14 days) post treatment. Pre and post treatment ova samples incubated.	No live lice found in either group at any time except 2 cases of reinfestation on day 6 in mousse group. % ova hatched in Pyr group was 52% pre and 17.8% post treatment. % hatched in Per group was 48.5% pre and 40.5% post treatment. Stat. sig. Diff in favour of Pyr.	No adverse reactions observed.	Study conducted in U.K. Ova hatching rate quite low. *In vitro* study also conducted – see table 2.
28	SB, MC	435 patients aged > 1 year with head lice infestation (not defined). Excluded if treated in last week.	1% Per crème rinse to wet hair for 10 mins (231 pts) vs 0.3% Pyr/3% PB to dry hair for 10 mins (204 pts)	Examination at 7 and 14 days.	At day 7 98% of Per and 85% of Pyr/PB had no live lice. At 14 days 97% Per and 63% of Pyr/PB had no live lice.	7% of Per and 16% of Pyr/PB had dermal a.e..	Study conducted in USA and Mexico.

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
29	R, DB, C	144 primary school children with live lice.	0.5% mal foam (74 pts) to wet hair for 20 mins vs herbal product (70 pts) to dry hair for 20 mins. Both products repeated at 7 days.	Examination 20 mins post-treatment (for resistance), and at 7 and 14 days after first treatment. Note: If lice active at 20 mins post-treatment, considered this evidence of resistance)	Cure defined as no live lice on day 14, **and** no live lice immediately post-treatment. 71.4% of herbal and 47.3% of mal were recorded as cured (stat sig difference). Resistant lice were found in 3.1% of mal treatments. No resistance to herbal product was noted.	Not reported	Study conducted in Townsville. Although study stated "double blind", methods section suggests this was not true.
30	R, DB, C	39 children with live lice or viable eggs.	0.5% mal lotion (Ovanit)(6 pts) vs 0.5% mal lotion (KP24) (6 pts) vs 0.5% mal shampoo (KP24) (7 pts) vs 1% lin shampoo (9 pts) vs 1% lin lotion (11 pts). Lotions applied for 12 hours. Contact time for shampoos not stated. Wet or dry hair not stated.	Examination post-treatment (time not stated). Pre and post-treatment ova samples incubated.	Treatment was successful (not defined) in 5/6 subjects for the two malathion lotions, 5/7 malathion shampoo, 7/11 lindane lotion and 3/9 lindane shampoo. Samples were too small for statistical analysis. Ovicidal results not properly reported, but "hatching occurred despite treatment with the lindane preparations – again confirming that lindane is not ovicidal".	No adverse reactions occurred	Study conducted in Tasmania. Results reported inadequately, and serious methodological flaws.
31		226 patients with lice infestation (not defined)	0.5% malathion solution (contact time and method of application not stated).	Post-treatment examination for live lice and eggs at 7 days.	No live lice seen post-treatment in any patient. No eggs hatched post-treatment.	Not reported	Study conducted in England. Results and methods reported inadequately, and serious methodological flaws
32	R, SB, C	160 patients (mean age 9 yrs) with live lice and >10 viable nits. Excluded if treated in last 4 weeks	0.33% Pyr/4%PB shampoo (RID) (79pts) vs1%Per crème rinse (NIX) (81 pts). Both products applied to wet hair (contact time not stated). RID applied on days 1 and 7. NIX applied on day 1 only.	Post treatment examination for live lice and/or eggs on days 7 and 14	No live lice or eggs seen in any patient at day 7. 1 patient reinfested in NIX group at day 14.	3 dermal adverse evetns (2 in NIX group and 1 in RID group	Study conducted in California. Confounded by the use of different nit combs in each treatment group. Also, initially more severe infestation in NIX group.
33	FT	112 patients with live lice and/or eggs	0.15% Pyr/1.65%PB (Pyriderm) applied to dry hair for 10 mins and repeated at 7 days.	Post treatment examination for live lice at 7 days (prior to second treatment) and 14 days.	Prior to treatment, 60 pts had live lice, and 52 had eggs only. At day 7, 6 pts had live lice (all newly hatched) and 1 had eggs only. At day 14 1 pt had live lice (newly hatched) and no pts had eggs only.	No a.e. observed	Study conducted in Denmark. Resistance to chlophenothane (lindane-type) had been previously observed.

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
34	FT	425 children (5-15 yrs) with live lice	0.3% mal lotion (255 pts) vs 0.3% pirimiphos-methyl lotion (69 pts) vs 0.3% d-phenothrin lotion (17 pts) vs 0.66% bio/2.64%PB lotion (17 pts) vs 0.4% mal shmapoo (28 pts) vs 0.7% pirimiphos methyl shampoo (39 pts). Lotions applied to dry hair for 5 mins. Shampoos applied to wet hair for 5 mins, then rinsed and dried with hair dryer.	Post-treatment examination at 24 hrs by combing for 5 mins. If no lice found in 5 mins, declared louse-free.	% de-loused 24 hrs after treatment: Mal lotion 100% Pirimiphos lotion 100% d-phenothrin lotion 52.9% Bio lotion 45.0% Mal shampoo 53.6% Pirimiphos shampoo 100%	Not reported	Study conducted in Czech Republic. *In vitro* study also conducted – see table 2
35		20 hospital in patients aged 17-46 years (infestation not defined)	Cotrimoxazole (varying doses) (12 pts) vs trimethoprim (160 mg twice daily for 3 days) (4 pts) vs sulphamethoxazole (800 mg twice daily for 3 days (4 pts)	Daily examination	Minimum effective dose of cotrimoxazole was 1 tablet twice daily. After 3 days all 10 pts who received this dose had no live lice present. After 10 days, treatment was repeated to 8 pts, to treat newly hatched lice. Follow-up for 15 more days showed all retreated patients to be lice-free. Trimethoprim or sulphamethoxazole alone had no effect on lice.	Not reported	Study conducted in India. Method of action appears to be to repel lice, as lice were seen to migrate away from the scalp and move onto bed clothes, where they subsequently died.
36		25 pts with live lice. (50 pts with scabies also treated)	0.8% w/v ivermectin solution	Examination 4 days post-treatment, then every second day for a further 2 weeks	4 days post-treatment, all lice were moribund, and all eggs appeared non-viable. 100% treatment success.	Not reported	Study conducted in Egypt.

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
37	C, SB	40 children (5-15 yrs) with >20 nits. No exclusion criteria stated.	Pyrethrin/Piperonyl butoxide lotion vs shampoo (20 pts /group) (no other details given	Examination of lice collected by rinsing 2 hrs and 24 hrs post-treatment. Also incubation for 14 days of pre and post-treatment ova samples.	At 2 hrs post-treatment 99.5% of lice collected from shampoo group and 83% from lotion group were dead. At 24 hrs post treatment 100% of lice collected from shampoo group and 85% from lotion group were dead. In the shampoo group 20.5% of pretreatment and 49.5% of post-treatment ova were dead (29.5% ovicidal activity). In the lotion group 21% of pretreatment and 40.5% of post-treatment ova were dead (19.5% ovicidal activity)	None observed	Study location not stated. Very poor study – insufficient information in study report. Although live lice not required for study inclusion, lice were recovered from all patients. Authors suggest that lowering of surface tension by shampoo ingredients may allow better penetration of active into ova.
38		40 children (4-9 yrs) with live lice and nits	0.3%Pyrethrin/3.0%Piperonyl butoxide lotion vs shampoo (20 pts/group) (contact time or application method not stated.	Examination of lice collected by rinsing immediately, 2 hrs and 24 hrs post-treatment. Also incubation for 14 days of pre and post-treatment ova samples.	At 0 hrs post-treatment 95% of lice collected from shampoo group and 60% from lotion group were dead. At 2 hrs post-treatment this rose to 97% of lice collected from shampoo group and 75% from lotion group were dead. At 24 hrs post treatment 100% of lice collected from both groups were dead. In the shampoo group 30% of pretreatment and 80% of post-treatment ova were dead (50% ovicidal activity). In the lotion group 34% of pretreatment and 59% of post-treatment ova were dead (25% ovicidal activity)	None observed	Study conducted in Mexico. Similar methodology to study above, but better inclusion criteria.
39	R, DB	84 school age children with live lice and/or viable eggs	1%permethrin/2% tea tree oil (35 pts) to dry hair for 20 mins versus 1% permethrin crème rinse (49 pts) to wet hair for 20 minutes. Both treatments repeated at 7 days	Examination of lice and eggs in combings 20 minutes, 7 days and 28 days post initial treatment.	At 7 days, 46.9% of per+tea tree oil and 51.2% of per pts had no live lice or viable eggs. At 28 days, 70.9% of per+tea tree oil and 61.9% of per had no live lice or viable eggs.	I case of stinging eyes after accidental splashing in eyes in per+tea tree oil group. No other a.e.	Study conducted in Qld. Authors suggest inclusion of 2% tea tree oil increased efficacy, but this could also have been due to application to dry hair versus wet hair.
40	R, C,	30 patients	1% permethrin shampoo vs 1% lindane shampoo	Examination at 7, 14 and 21 days after treatment	At 7 days, 94% of permethrin and 42% of lindane patients were lice free. At 14 and 21 days, 100% of both groups were lice free.	No a.e. reported	Abstract only – few details

Ref	Design	Subjects	Treatment	Evaluation	Efficacy	Safety	Comments
41	O	62 Kosovar refugees with visible crawling lice	40 patients given supervised treatment with 1% oermethrin, 22 patients self-treated with permethrin	Re-examination on day 1 and day 7 for live lice in supervised treatment group, and on day 1 for self-treated group.	100% efficacy in both groups at re-examination times	Not examined	Study carried out in New Jersey. Only visible crawling lice examined – eggs not included in study
42	R, MC, C	115 children (2-13 yrs) with live lice and/or eggs	1% permethrin crème rinse for 10 mins (Gp 1, n=39) vs trimethoprim/sulfamethoxazole (10 mg/kg) daily for 10 days (Gp 2, n=36) vs 1% permethrin + trimethoprim/sulfamethoxazole (Gp 3, n=40)	Manual examination 2 and 4 weeks after treatment.	Success rate (not defined) at wk 2 was 79.5%, 83% and 95% for Gps 1, 2 and 3 respectively. Success rate at wk 4 was 72%, 78% and 92.5% respectively	Mild scalp irritation (3/39 in Gp 1) and nausea/vomiting/rash in 5/36 in Gp 2)	Study conducted in California. No definition of "success".
43	R, C, SB	95 patients (>2 yrs of age) with live lice	1% permethrin crème rinse for 10 mins with (Gp 1, n=34) and without (Gp 2, n=61) adjunctive combing. Retreatment on day 8	Examination on days 2, 8, 9, and 15 by visual inspection and combing, and by rinsing hair and straining rinse water.	In Gp 1, 72.7%, 33.3%, 63.6% and 72.7% were lice free on days 2, 8, 9 and 15 respectively. In Gp 2, 83.1%, 45.8%, 77.6% and 78.3% were lice free on days 2, 8, 9, and 15 respectively.	3 a.e.s in Gp 2 (one rash, 2 vomiting and upper respiratory infection)	Study conducted in Florida. Good study – suggests combing does not increase success rate, and that resistance to permethrin is present in the lice population.

Abbreviations:
DB = double blind; R = randomised, PC = placebo controlled; SB = single blind, MC = multicentre, C = comparative, FT = field trial, Mal = Malathion, Car = Carbaryl, Lin = Lindane, Pyr = Pyrethrin, Per = Permethrin, PB = Piperonyl Butoxide, Bio = Bioallethrin Pts = patients, Stat.sig = statistically significant. A.e. = adverse events.
In general patients were excluded if they were sensitive to treatments, or had skin damage to the scalp (except head-lice-induced), or were pregnant/ breastfeeding. Not excluded for prior pediculocide treatment except as stated.

12.3 ATTACHMENT 3: CURRENT MEC GUIDELINES ON PEDICULOCIDES

Head lice treatment products

Because the efficacy of head lice products is formulation dependent, sponsors should provide data to support the efficacy of their specific formulation when used according to the directions for use on the product's label. The use of lindane and benzyl benzoate for treatment of head lice infestation is discouraged.

Instructions for use on labels or package inserts should include statements to the effect of the following:

1. *Other members of the patient's family should be checked, and if necessary treated, to avoid re-infestation.*
2. *Sufficient product should be used to thoroughly wet the scalp, including the back of the neck and behind the ears.*
3. *The product should be kept out of the eyes. The eyes of the patient should be covered with a shampoo shield when applying the product. If the product gets into the eyes, they should be flooded with water.*
4. *The product should not be used on children under the age of 6 months, except on medical advice.*
5. *The product must not be used regularly or for prophylaxis.*
6. *Lotions containing malathion or carbaryl should not be washed out for 12 hours. Products containing pyrethroids should be washed out after a 10-20 minute application.*
7. *To ensure that complete eradication has occurred, an inspection should be made for live lice and/or eggs at the scalp level, 7 to 14 days after treatment. If necessary, the treatment should be repeated.*
   (a) For permethrin creme rinse preparations the re-treatment should be delayed until 14 days after the first treatment.
   (b) For all other products, including other preparations of permethrin, re-treatment should be carried out between 7 and 10 days after the first treatment.

   For products containing pyrethrins/piperonyl butoxide combinations and shampoo products, a second application will almost certainly be necessary.

12.4 ATTACHMENT 4: PROPOSED GUIDELINES

Head lice treatment products

Evidence suggests that the efficacy of head lice treatment products is formulation dependent. Sponsors of new products should provide data to support the efficacy of their specific formulation when used according to the directions for use on the product's label.

The efficacy and safety of head lice products should generally be supported by relevant clinical trials, rather than in vitro data only. In vitro data may be acceptable, at the discretion of the evaluation body, where the formulation of a product is similar to an existing product that has been fully evaluated.

Efficacy data should ideally consist of clinical trials conducted in Australia, to address location-specific resistance issues. Claims for registered products must be limited to control / treatment of head lice and their eggs (except see below regarding prophylactic use. Since no pediculocides have been shown to be 100% insecticidal and ovicidal under all conditions of use, claims must not state or imply that one treatment can kill all lice and their eggs.

Sponsors must not claim prophylactic use (preventative or repellent action) as an indication unless they can provide satisfactory evidence that such use of the product will not promote the development of resistance. Safety and efficacy of prophylactic use must also be supported by clinical trial data.

The use of lindane and benzyl benzoate in products registered for the treatment of head lice infestation is discouraged.

Labels and / or package inserts should include the following statements (or words to that effect) immediately after the dosage instructions:

1. *Use enough to thoroughly cover the scalp, including the back of the neck and behind the ears.*
2. *If the product gets into the eyes, rinse out immediately with water.*
3. *Remove all the eggs (nits) you can find after treatment (this is easier with a fine tooth comb and hair conditioner on wet or dry hair)*
4. *Repeat the treatment after 7-10 days to kill lice that have hatched from any remaining eggs that were not killed by the first treatment.*
5. *If you find live lice or more eggs appear after the second treatment, seek advice from a health care professional.*
6. *Only use the product when you can see live lice or their eggs. Don't use regularly or to prevent head lice.*
7. *Check other people in the household and treat if necessary. Lice can quickly spread back to people who have already been treated.*
8. *Don't use on babies under 6 months, except on medical advice.*

Consistent with requirements for other OTC products, the labels of pediculocide products containing active ingredients with an ADEC pregnancy category other than Category A should include a warning to the effect that the product should not be used in pregnancy unless advised by a doctor. This includes products containing malathion, pyrethrins or permethrin (in category B2), and products containing piperonyl butoxide (category B3).

Because education is an important component of treatment, sponsors are encouraged to make available relevant public health information on the treatment of head lice infestation in a package insert, a web site referenced on the label or by other means (e.g. a telephone information service).

12.5 ATTACHMENT 5: TGA REVIEW OF TOXICITY OF MALATHION

Toxicology Report: Malathion (Maldison) – February 2000

This report addresses the issue of potential toxicity in humans using products containing malathion (0.5 or 1.0%) for the treatment of head lice. Malathion is an organophosphate compound of the phosphorodithioate class, used as an insecticide and acaricide with reported broad-spectrum activity. Preparations/formulations containing malathion are listed in schedules 2, 4, 5 and 6 of the SUSDP. Malathion is rapidly pediculocidal and niticidal; lice and their eggs (nits) are killed within 3 seconds by 0.003% and 0.06% malathion in acetone, respectively (2).

Assessment:

In general, pure malathion has been identified as having a low acute oral toxicity in animal species tested. It would appear that the main concern with the use of malathion is the formation of toxic degradants (impurities) in storage and not so much the metabolism of malathion *in vivo* in humans. In products containing malathion, reported impurities such as isomalathion and various trialkyl phosphorothioates are known to increase the toxicity of malathion, as well as possessing a significant acute toxic effect of their own. Different sources of malathion with different amounts of these impurities (related to storage conditions) may have different toxicity profiles.

The NDPSC recently considered an application for rescheduling a product containing 440 g/L malathion from schedule 6 to 5; included in the relevant documentation was a toxicology evaluation completed by the Chemical Products Assessment Section (1). The report noted that impurities (*isomalathion* and various *trialkyl phosphorothioates*), found in formulations with malathion technical as the active insecticide, are known to increase the toxicity of the active and hence malathion from different sources may have different toxicity profiles. These impurities may arise during the manufacturing process or be formed on prolonged storage. Formation of isomalathion in storage was greatly accelerated under extreme conditions, with an increase of 125 times (88.6 ppm to 11100 ppm) its content when kept at 54°C over a period of 14 days. This result demonstrates the potential for enhanced isomalathion formation, which would cause a potentiation of the toxicity of malathion.

It was noted that the acute oral LD_{50} for technical malathion in rats ranged from 390 to 5843 mg/kg, depending on the vehicle and the purity; the higher value (5843 mg/kg) was obtained with a technical grade of 99% purity; the low result was obtained with 90% purity. Degradation to form isomalathion was described as an internal rearrangement, which occurs under adverse storage conditions with unpredictable results. It was noted that the formation of degradation impurities such as isomalathion and trialkylphosporothioates in malathion products can result in a variation in toxicity of at least two orders of magnitude (depends of concentrations of degradants).

Potential systemic exposure (based on dose given and not AUC) to malathion and its impurities is low following dermal application. Products available for head lice treatment contain either 0.5 or 1.0% malathion in a liquid base for application to the scalp. If 10 mL of a 1.0% solution was used for treatment of lice a dose of 100 mg malathion would be applied to the scalp. Potential systemic burden would be limited by the dermal absorption of the malathion, which has been shown to range from 3-8% in humans. Potential systemic burden would be up to 8% of 100 mg, which results in 8 mg malathion. In a 50 kg human, the total potential systemic burden would be 8/50 = 0.16 mg/kg.

Estimation of the potential exposure to isomalathion can be made from this figure of 0.16 mg/kg malathion. If we assume isomalathion is present (after degradation) at 5% (highest value tested in ref. 14) of the malathion concentration then the contribution of isomalathion to this overall acute toxicity would be minimal. Isomalathion would be present at a very low amount (up to 5% of malathion content = 0.008 mg/kg) with little toxicological significance. Levels of isomalathion found in KP24 lice treatment products (retail batches) have not exceeded 0.008% (analysis submitted by company) after up to 12 months storage.

The potential enhancement of malathion toxicity by either isomalathion and/or trialkyl phosphorothioates can be estimated by using information from reference 14. Data were generated indicating isomalathion and trialkyl phosphorothioates (up to 5%) caused a maximum 10 fold enhancement of the toxicity of malathion in the rat. If you assume that a 10 fold enhancement of malathion toxicity occurred following application of the topical products in humans, this could equate to a potential systemic burden equivalent to the effect of 10 x 0.16 mg/kg = 1.6 mg/kg malathion. This value of 1.6 mg/kg is 5000 times lower than the LD_{50} value (approx. 10000 mg/kg) for pure malathion.

In general, a safety margin of 1000 fold is employed when using acute toxicity data generated in animal species to determine estimates of allowable exposure in humans. The estimated difference in exposure (1.6 mg/kg) and LD_{50} (>10000 mg/kg for pure malathion) in this case was greater than 5000 fold. Therefore, if the presence of impurities did enhance the toxicity of malathion the resultant exposure would be well below the arbitrary safety margin based on available acute toxicity data.

It should be noted that malathion has not been implicated as an organophosphate insecticide that causes delayed neurotoxicity. It has not been shown to be carcinogenic and an experiment in humans found no adverse effects following dermal application of 10% malathion powder (14). Studies in rats and rabbits have indicated that malathion is not teratogenic in these species at doses up to 800 and 50 mg/kg/day, respectively. A dose of 240 mg/kg/day delivered in the diet to rats for 10 weeks caused a reduction in litter size, while survival of the progeny at 7 and 21 days post-partum was reduced (1).

Recommendation:

This report addresses issues arising from the findings of extensive degradation of malathion in OTC products used for the treatment of head lice in humans. These products are most likely to be used on limited occasions, with chronic exposure to malathion not expected. Products containing concentrations of 0.5% and 1.0% malathion applied to the skin in approximate amounts of 10 to 20 mL do not appear to possess a risk to human health when impurities isomalathion and trialkyl phosphorothioates are present at low concentrations (see above).

Review of data

Background:

Malathion is an organophosphate compound of the phosphorodithioate class, used as an insecticide and acaricide with reported broad-spectrum activity. Chemically it is the O,O-dimethyl dithiophosphate of diethyl mercaptosuccinate. Malathion is considered to be one of the least toxic of all the organophosphate compounds; its toxic potency is at least a hundred times less than that of parathion (4). Impurities were identified as a source of toxicity seen with the use of malathion as an insecticide in agricultural (5). The lower toxicity of malathion compared with other organophosphates has been associated with its relative inefficiency as an anticholinesterase agent; an oxidative metabolite (malaoxon) of malathion has much greater anticholinesterase activity (5).

In general, organophosphorus compounds for use as insecticides are esters of phosphoric or phosphorothioic acids, suitable substituents at side chains being alkyl or alkoxy groups and, in a few instances, alkylamido, alkoxy or aryl groups. Organophosphorus ester insecticides inhibit acetylcholinesterase, which is the enzyme responsible for terminating the action of the neurotransmitter, acetylcholine. Biotransformation of anticholinesterase insecticides can proceed by complicated, multiphase pathways involving oxidative, reductive and hydrolytic (phase I) processes that contribute to both activation and detoxification, or conjugative and dealkylation (phase II) processes associated with detoxification. The pathways and the rates of biotransformation are species-specific and highly dependent upon the nature of the substituents attached to the nucleus of the ester (2).

Pharmacokinetics/chemistry:

Malathion has the empirical formula $C_{10}H_{19}O_6PS_2$ and a molecular weight of 330. The pure material forms a clear amber liquid with a boiling point of 156-157^{0}C at 0.7 mmHg. The density is 1.23 at 25^{0}C. The melting point of malathion is 2.85^{0}C. The solubility of malathion in water at room temperature is 145 ppm. Malathion is rapidly hydrolysed at pH above 7.0 or below 5.0, but is stable in aqueous solution buffered at pH 5.26 (14).

It was noted that commercial preparations of malathion are unlikely to be totally free of impurities, but it seems possible that their initial concentrations are higher in the products of some factories than in those of others (14). Certainly, all preparations, but especially water-wettable powders, are subject to chemical change during storage. The change is faster under tropical conditions (14).

Formation of metabolites and impurities: Malathion contains an asymmetric carbon centre on the succinyl ligand. Commercial malathion is a racemate (RS) mixture of the R and S forms arising from an asymmetric carbon in its diethyl thiosuccinate group. During insect metabolism, malathion is bio-activated to malaoxon via oxidative desulfuration. The R enantiomer of malaoxon is 8.6 fold more potent than the S enantiomer at inhibiting rat brain acetylcholinesterase, with the strength of the RS mix lying between that of the two (R & S) enantiomers (10). Interestingly, activation to malaoxon is carried out in both mammals and insects, but insects are relatively deficient in the carboxylesterases used by mammals for detoxification (10). Isomalathion results from the thermal or photochemical isomerization of malathion and has been identified in certain commercial formulations. Malathion has been described as virtually non-toxic, but the racemates of malaoxon and isomalathion are potent inhibitors of acetylcholinesterase and are toxic (9, 10). Isomalathion contains two asymmetric centres, one at the phosphorus and the other at the carbon in the diethyl thiosuccinate moiety, yielding four stereoisomers. Inhibitory potencies of these isomers differ by as much as 29 fold for inhibition of acetylcholinesterase activity in rat brain (10).

The most obvious difference between the metabolism of malathion and that of the majority of organic phosphorus compounds used as insecticides depends on the presence of two carboxy groups. The compound is subject to the various kinds of metabolism that other organic phosphorus insecticides undergo. In addition, the splitting of either carboxy ester linkage renders the compound non-toxic (14).

Absorption: Malathion is rapidly absorbed from the GIT of rats, mice, cows, hens and humans. The equivalent of 23% of an ingested oral dose of 58 mg was recovered in 16.3 hours from the urine of a human volunteer. Workers exposed to dusting powders containing approximately 1-10% malathion were found to have related metabolites at a concentration of 4-10% in their urine. A series of studies found (2) about 3-8% of a dermal dose of malathion was absorbed through the intact skin of humans.

Distribution: In rats (25 mg, route not stated), it would appear that malathion does not have a large volume of distribution, with elimination of labelled malathion within hours (10).

Metabolism: In the species mentioned above, malathion is oxidised to its active form, malaoxon, and is also hydroxylated to produce 6-8 less toxic metabolites. In humans, malathion is metabolised by hydrolytic cleavage of ethyl groups from the succinic acid moiety of the molecule by carboxylesterase enzymes; and hydrolysis of the succinate moiety from the dialkyl thiophosphate. The hydrolysis of the carboxyl ester linkage by

carboxylesterases detoxifies malathion, and the relative activity of this enzyme dictates species resistance. This detoxification reaction is much more rapid in mammals and birds compared to insects, which conveys a degree of selectivity in its toxicity against insects (7). Cytochrome P450s are responsible for converting phosphorothioates containing a P=S bond to phosphorates with a P=O bond, resulting in their activation; this process results in malathion being converted to the active anticholinesterase malaoxon.

Excretion: The main metabolites, malathion mono- and di-acids are eliminated mainly in the urine with small amounts being found in milk and eggs. In lactating cows, the urinary excretion (as the mono- and di-acids) accounted for some 69% of the administered dose, while faecal excretion accounted for 8% of the dose. Of the faecal elimination, 85% was as the unchanged parent compound and 12% as malaoxon. Workers exposed to malathion excreted 0.45 to 1.07 μg/mL potassium dimethyldithiophosphate in the urine. Following administration of 25 mg (route not stated) of labelled malathion to rats, radio-label appeared in the urine within 2 hours and 91.7% was eliminated within 24 hours. Overall, excretion was predominantly in the urine (83.44%), while lower concentrations were found in the faeces (5.51%) and exhaled (2.77%) carbon dioxide. Malathion was metabolised rapidly, with no unmetabolised malathion detectable at 8 hours or longer after dosing (10).

Toxicity

Epidemiological/clinical evidence:

During a malaria eradication program in Pakistan in 1976, out of 7500 spraymen, 2800 became poisoned and 5 died (13). The major determinant of this poisoning has been identified as isomalathion present as an impurity in the malathion (50% water dispersible powder). It seemed almost certain that the isomalathion was produced during storage of the formulated malathion. This presumption was based on a quantitative correlation between isomalathion content and toxicity of many field samples of malathion and a comparison with mixtures of pure compounds. Laboratory storage of malathion at 38^0C increases both its isomalathion content and toxicity; it is possible that storage in a hot climate in Pakistan was the cause of the increased isomalathion content (6). It has been shown isomalathion results from the thermal isomerization of malathion and has been identified in certain commerical formulations (9). An examination of impurities found in malathion also identified trimethyl phosphorothioates as behaving in similar manner to isomalathion in potentiating the toxicity of malathion (6).

Supporting evidence for an inhibitory effect of isomalathion on malathion carboxylesterase activity was provided in vitro using liver tissue obtained at autopsy. Human carboxylesterase activity was dose-dependently inhibited by isomalathion, which would result in diminished capacity of the human liver to detoxify malathion. Interestingly, O,S,S-trimethyl phosphorodithioate, O,O,S-trimethyl phosphorothioate and O,O,S-trimethyl phosphorodithioate did not inactivate the carboxylesterase enzyme in this system (8).

Malathion has not been identified as an organophosphate that causes delayed neurotoxicity, which has been investigated in studies measuring NTE (neurotoxic esterase). Malathion did not produce OPIDN (organophospate induced delayed neurotoxicity) in hens at doses up to 1000 mg/kg SC (1, 2, 10). Analysis of structure-activity relationships has provided information suggesting that malaoxon and isomalathion isomers would be expected to be poor inhibitors of NTE and unlikely to cause delayed neurotoxicity. This expected result occurred in hens, with isomalathion isomers not causing OPIDN (10).

A case report was presented detailing an attempted suicide using a commercial preparation of malathion (15% garden spray in isopropyl alcohol). A 65 year-old woman ingested about 100 mL of the preparation that had been stored for 5 years at room temperature. The initial cholinergic crisis had concluded before being followed by cardiac, pulmonary, neurological and renal manifestations. Chemical analysis of the preparation revealed the presence of isopropylmalathion and O,O,S-trimethylphosphorothioate. The author concluded that although malathion is regarded as one of the safest organophosphate insecticides, storage for long periods at room temperature (wide fluctuations over seasons) could result in the formation of toxic degradation products (12).

Malathion produces signs and symptoms of typical organophosphorous compounds, due to inhibition of acetylcholinesterase (2). Malathion is metabolised to malaoxon, an active cholinesterase inhibitor (1, 2). Malathion has been shown to be relatively inefficient as an anticholinesterase, with an excretion rate of 220 mg/day in humans not associated with an effect on cholinesterase activity (3). In general, evidence of acute toxicity only arises with suicide attempts or deliberate poisoning (2). The LD_{50} in mammals is approximately 1 g/kg taken orally (2). Assessment of toxicity in humans has identified that the acute oral lethal dose is estimated to be below 1 g/kg, with almost all reported fatalities from malathion occurring after oral ingestion, compared to other routes of inhalation or dermal absorption.

The KP products contain malathion at concentrations of 0.5 and 1.0% in solution. Assuming approximately 10 mL is used on the scalp to treat the lice an amount of up to 100 mg of malathion could come in contact with the skin. Assuming 1 g = 1 mL, therefore 1% of 10 mL is 100 mg. Data indicates that approximately 3 to 8% of malathion is absorbed following dermal application, which could result in up to 8 mg absorbed on application to the scalp. Data has shown there were no adverse effects associated when 220 mg/day malathion was excreted from humans, which represents administration of a dose greater than 220 mg when taking into account metabolism and distribution throughout the body. Therefore, the possible exposure to 8 mg of malathion does not appear to pose a health threat. Studies in rats have shown that the oral and dermal LD_{50} values for pure malathion are >5000 mg/kg (1). Malathion was not a skin irritant in rabbits or a sensitiser in guinea pigs (1).

Preclinical data

a) Malathion

The acute toxicity of preparations of malathion has been extensively studied in a variety of animal species. In a study by Gaines (1960), the acute oral and dermal toxicity of malathion, as measured by LD_{50} values, were 1000-1375 mg/kg and 4444 mg/kg, respectively. This study was the only investigation where both oral and dermal administration of the test material was tested under similar conditions. The results (4-fold difference) do not appear to support the expected difference in toxicity based on dermal absorption (3-8%) data for malathion. This could be due to differences in vehicles used, levels of impurities (early samples [1950s] only 65-70% pure), strains of animals (variation in susceptibility) and condition of rats used in the study (14).

In 2-year feeding studies, even a dietary concentration of 5000 ppm (250 mg/kg/day) did not increase mortality of rats, although food intake was reduced and weight gain was below control groups. The rats remained asymptomatic, despite the finding that plasma and brain cholinesterase activity was reduced to 5-40% of normal values. General condition and weight gain were unaffected by a dose of 1000 ppm (50 mg/kg/day) in this study, although plasma, red cell and brain cholinesterase activity was reduced. A dose of 100 mg/kg (5 mg/kg/day) had no detectable effect on any parameter measured during the study (14).

b) Impurities

Malathion technical can contain isomalathion and trialkyl phosphorothioates (and dithioates) as impurities, which have been shown to enhance the anticholinesterase activity (toxicity) of malathion. Isomalathion is a direct inhibitor (by blocking the action of carboxylesterase) of malathion metabolism, resulting in the prevention of malathion detoxification (6). Blocking the breakdown of malathion by carboxylesterase may result in greater metabolism via the oxidative route leading to the formation of malaoxon, which is a potent anticholinesterase (6).

As a result of the incident in Pakistan, follow-up examination of these impurities mixed in varying proportions with pure malathion and under variable storage conditions has provided a clearer assessment of their influence on the toxicity of malathion. Recrystallised malathion (purity 99.7%) had an oral LD_{50} of 10700 (9300-12300) mg/kg in rats (6 & 7). The LD_{50} for isomalathion was 113 (90-143) mg/kg in rats. The acute toxicity of trimethyl phosphorothioates varied in acute toxicity as follows:

O,O,S-trimethyl phosphorodithioate	O,S,S-trimethyl phosphorodithioate	O,O,S-trimethyl phosphorothioate
Study 1. LD_{50} 638 mg/kg	LD_{50} 26 mg/kg	LD_{50} 60 mg/kg
Study 2. LD_{50} 450 mg/kg	LD_{50} 96 mg/kg	LD_{50} 47 mg/kg
Study 3. LD_{50} 660 mg/kg	LD_{50} 110 mg/kg	LD_{50} 260 mg/kg

It should be noted that the range of LD_{50} values above suggested a fair degree of variability, which was not discussed. The variation in LD_{50} values for the same compound could be associated with a difference in strain of rat, vehicle for test agent, sex of rat, rate of administration of dose, size/age of rat used in study, source of product, etc. It is clear that O,S,S-trimethyl phosphorodithioate and O,O,S-trimethyl phosphorothioate could contribute to the acute toxicity of malathion if present in sufficient amounts, since they appear to be slightly more acutely toxic than isomalathion (6).

Calculations to determine possible additive or potentiation toxicity of mixtures of isomalathion and trimethyl phosphorothioate with pure malathion were carried out. It was found that all compounds except O,O,S-trimethyl phosphorothioate potentiated the toxicity of malathion. Calculated additive LD_{50} for mixtures of malathion with isomalathion (1%) and O,O,S-trimethyl phosphorothioate (4%) were 4826 mg/kg and approximately 5000 mg/kg, respectively. Measured LD_{50} values for isomalathion (1%) and O,O,S-trimethyl phosphorothioate (4%) in combination with malathion were both 500 mg/kg, respectively. The presence of isomalathion and O,O,S-trimethyl phosphorothioate (4%) appeared to cause an approximate ten fold increase in toxicity. However, a second set of figures (estimated additive LD_{50} value 1794 mg/kg vs measured LD_{50} value of 1250 mg/kg) for isomalathion (5%) at a higher concentration suggested that there was much less potentiation of the toxicity of malathion (6). No data on a direct potentiation assessment was presented for O,S,S-trimethyl phosphorodithioate in this study, but a separate study confirmed potentiation of malathion toxicity in rats and to a lesser extent in mice (7). Storage of technical malathion for 3 to 6 months at 40^0C resulted in materials that were noticeably more toxic to mice (7, 14).

In the rat, the greatest potentiation activity was observed with O,S,S-trimethyl phosphorodithioate and S-methyl malathion. When the concentration of various impurities varied from 0.05 to 5%, the factor of potentiation for the rat varied from 1.4 to 10 fold. Potentiating effects were significantly smaller in the mouse than in the rat (14).

A NDPSC report (1984) on malathion identified the toxicity enhancing effect of isomalathion, which has an oral LD_{50} value of 89 mg/kg (species not stated) while the LD_{50} values for pure malathion were approximately 1 g or greater in mammals.

Target organ toxicity for O,O,S-trimethyl phosphorothioate and O,S,S-trimethyl phosphorodithioate (40-60 mg/kg PO) was investigated in rats dosed orally with the test agents. Results from this study indicated that these substances induced kidney tubule damage characterised by swelling, distortion and distension of glomeruli, as well as narrowing of the first part of the proximal tubule (11)

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12.6 ATTACHMENT 6: LIST OF PEDICULOCIDE PRODUCTS ON ARTG AS AT JULY 2000

Head lice products have been grouped according to their status as registrable or listable goods.

Status	Product name	ARTG number	Active ingredient(s)
Registered	Orange Medic Head Lice Treatment solution	10924	Permethrin
	HLT Foam application	10962	Maldison
	Lice Rid lotion	12783	Malathion
	Cleensheen lotion	12784	Maldison
	Meditox Foam lotion	13960	Pyrethrins; piperonyl butoxide
	Amcal Head Lice Foam	16519	Piperonyl butoxide; pyrethrins
	Pyrifoam lotion	18200	Pyrethrin i; pyrethrin ii; piperonyl butoxide
	K.P. 24 Lice Egg Remover lotion	18866	Ammonium acetate; glacial acetic acid
	K.P. 24 Medicated Foam application	18867	Maldison
	K.P. 24 Medicated Lotion	18869	Maldison
	Nick Off Nits lotion	19321	Maldison
	Pyrenel Foam application	18939	Pyrethrin i; pyrethrin ii; piperonyl butoxide
	Pyrenel Lotion	19414	Pyrethrin i; pyrethrin ii; piperonyl butoxide
	Dewitt's Paralice Aerosol spray	20918	Bioallethrin; piperonyl butoxide
	Exitte Head Lice Shampoo	21154	Pyrethrin I; pyrethrin ii
	Lyban Foam application	27816	Piperonyl butoxide; pyrethrins
	HL 7 Shampoo application	28655	Maldison
	Gold Cross Exolice Medicated Foam	28756	Maldison
	Quellada Head Lice Treatment For Long Hair application	37003	Permethrin
	Nix Cream Rinse (reformulation) lotion	45800	Pennethrin
	Quellada Head Lice Treatment For Short Hair application	45849	Pennethrin
	Banlice Mousse aerosol	46708	Pyrethrins, piperonyl butoxide
	Ravine Anti-Lice Medicated Treatment Lotion (NB. product also included in a listed kit AUST L 70728 — see below)	49802	Permethrin

Status	Product name	ARTG number	Active ingredient(s)
	Pyrifoam Head Lice Treatment Lotion	51722	Permethrin
	Orange Medic Plus Head Lice Treatment lotion (reformulation)	69377	Permethrin
Listed	Emerald Forest Lice Blaster lotion	66390	*Echinacea purpurea*; *Stemona sessifolia*; *Tanacetum cineriifolium*; Melaleuca oil; *Adhatoda vasica*
	Quit Nits All Natural Head Lice Treatment lotion	66958	Eucalyptus oil; Lavender oil; Geranium oil
	Neutralice lotion	67693	Melaleuca oil; Lavender oil
	Lice Attack lotion	68513	*Echinacea purpurea*; *Stemona sessifolia*; Melaleuca oil; *Adhatoda vasica*
	Herbs For Headlice lotion	68515	*Echinacea purpurea*; *Stemona sessifolia*; Melaleuca oil; *Adhatoda vasica*
	Wild Child All Natural Head Lice Treatment lotion	68790	Eucalyptus oil; Lavender oil; Geranium oil
	Sunspirit Aromatherapy Lice Scents to Kill lotion	69276	*Melaleuca alternifolia*; *Lavendula* angustifolia; *Eucalyptus fruticetorum*; *Pelargonium graveolens*; *Rosmarinus officinalis*; *Sassafras albiduni*
	Lice Attack lotion	70188	Melaleuca oil; lavender oil
	Natural Head Lice Treatment spray	70386	Melaleuca oil; lavender oil
	Neutralice Mousse solution	70637	Melaleuca oil; lavender oil
	Ravine Lice Treatment Kit	70728	Kit containing AUST R 49802: permethrin
	Herbs of Gold Exit Lice lotion	70798	Melaleuca oil; anise oil; *Picrasma excelsa*
	Gentle Remedies Lice Ban spray	71842	Melaleuca oil; thyme oil; lavender oil; lemon oil; rosemary oil
	Gentle Remedies Lice Shield spray	71843	*Melia azedarach*; rosemary oil; citronella oil; lemongrass oil
	Electric Blue Head Lice Cream	72511	Clove leaf oil; melaleuca oil; rosemary oil
	Eucanol for Headlice spray	72592	Eucalyptus oil; *Eucalyptus citriodora*; lavender oil
	Tea Tree Lice Foam solution	72710	Melaleuca oil
	Head Lice Hair Gel	73337	Melaleuca oil
	Natural Headlice Buster application	73627	*Thymus vulgaris*; *Eucalyptus globulus*; *Rosmarinus officinalis*; *Melaleuca altemifolia*; *Lavandula angustifolia*
	Natural Headlice Repellent application	73628	*Thymus vulgaris*; *Eucalyptus globulus*; *Rosmarinus officinalis; Melaleuca altemifolia*; *Lavandula angustifolia*

Status	Product name	ARTG number	Active ingredient(s)
	The Oil Garden Head Lice Control Naturally application	73634	Melaleuca oil; *Sassafras albidum*; rosemary oil; *Cymbopogon schoenanthus*; lavender oil; bois de rose oil
	Herba Lice liquid	74046	*Melaleuca alternifolia*; *Lavendula angustifolia*
	Natures Botanicals Lice Check liquid	74112	*Melaleuca altemifolia*; *Lavendula angustifolia*

12.7 ATTACHMENT 7: RESPONSES FROM STATE AND TERRITORY HEALTH AUTHORITIES TO HEAD LICE ISSUES

QUESTIONS	STATES/TERRITORIES RESPONSE							
	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
a) Do you regard head lice infestation as a "public health" or a "social" problem?	Regarded as a social problem, however, chronic consequences of incorrect use of medication.	Regarded as public health problem due to interruption to lifestyle, stigma, annoyance & parent's concern.	Primarily public health problem. It is a standard communicable/infectious disease. Only a social problem due to the stigma.	Considered a social problem in view of stigma, cost of tx & school absences. Also considered a health problem if broader definition of health is considered.	Considered a social and public health issue. The Public and Environmental Health Act, 1987 (section 43A) includes penalties for infested persons not taking reasonable measures to prevent transmission.	Not a public health problem.	Community based problem rather than public health concern.	Considered a public health problem although not a significant one. Conflict between parents, teachers & school nurses re management of infestation in primary schools consumes considerable time & resources of public health authorities.
b) Do you have a view on the regulation of products for treatment of head lice infestation – should all products be required to undergo clinical trials before marketing?	Recommend products undergo clinical trials - would prevent inappropriate use & expense of some herbal products	Appropriate to undergo clinical trials given inadequacies of currently available products.	Due to high prevalence of resistance and toxic side effects, all head lice products should undergo clinical trials. Regulation of packaging & labelling also important as much incorrect information is provided on products.	Should be listable. Qld Health supports efficacy studies but this does not mean that clinical trials should be mandated. Labelling should be informative and claims supported by evidence.	All products should undergo some form of clinical testing. There is only anecdotal evidence as to the efficacy of the 'plethora' of herbal products coming on to the market.	Prefer greater regulation including clinical trails. Greater regulation could address preventative claims, repeated use of chemicals regardless of safety & promotion of 'natural' products as safe when no evidence available.	Should undergo clinical trials. Data should support the specific claims made.	The provision of evidentiary support as set out in the "Guidelines for the levels and kinds of evidence to support claims for therapeutic goods" would seem to be a more effective mechanism.
c) Do you have any data / information on the efficacy or otherwise of head lice treatments used in your State?	No.	NSW Health & QLD Uni about to collect data on head lice in schools through the Nitbuster program. Will look at use, efficacy & resistance.	Only have a survey conducted in 1995 and published in the Disease Control Bulletin. Survey questioned families about effectiveness of specific products.	A trial has been conducted by QLD Health but results not yet published. Trial included composite tx with conditioner and combing vs. Lice Blaster. Results indicated no signif diff between 2 txs.	No. Efforts made in past, without success, to obtain such data from some manufacturers.	No data collected. Parents perception that products no longer "work" and nurses observation that head lice are "getting bigger"	No. Anecdotal reports from practitioners about increasing malathion & pyrethrin resistance; reports of poor effectiveness largely due to potentially misleading label instructions which may be contributing to product failure and confusion.	No. Dept uses data obtained from a study conducted by James Cook Uni demonstrating the effectiveness of hair conditioner.

QUESTIONS	STATES/TERRITORIES RESPONSE							
	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
d) Are children with head lice excluded from school in your State?	Yes.	Dept doesn't advocate exclusion, however, some principals do exclude. No evidence to suggest exclusion is effective in reducing infestations.	Yes.	Decision to exclude made by school principal.	Yes.	Yes.	Must be excluded from school or children's service centre.	Yes.
e) What are the terms of the exclusion (e.g. until first treatment administered)?	Until effective treatment has begun. Contacts are not excluded.	Where children are excluded, allowed to return following commencement of treatment.	Until first treatment administered.	Determined by school principal.	Until one day after appropriate treatment has commenced. Contacts are not excluded.	Until treatment has commenced and head lice and eggs are removed.	Until treatment has commenced. Can return even if some eggs present.	Until treatment has commenced & hatchlings or adult lice have been removed.
f) Do you have any data on the number of cases where children have been excluded from school?	No data available, however, have numerous reports of extensive infestations within primary schools.	No. Anecdotal evidence suggests up to one third of schools have excluded children on basis of head lice.	No.	No.	No.	No data available.	No data available.	No data available.
Other information provided		NSW Health have introduced the "Nitbuster" program in response to growing concerns, to educate parents & schools about head lice removal techniques.				Head Lice Policy. Provides direction for the management of head lice infestation within schools.	*As causes community concern, Dept is undertaking a 12-month head lice cross-community, education & awareness program.	

12.8 ATTACHMENT 8: LABEL CLAIMS AS AT JULY 2000

Product	AUST No	Label claims	Preventative claim
Wild Child Quit Nits Head Lice Treatment	L 66958	"Effectively kills head lice and makes nits easy to remove"	
Amcal Head Lice Foam	R 16519	"Kills head lice and pubic lice"	
Pyrifoam Head Lice Treatment	R 51722	"For the control of head lice and their eggs"	
Exolice Medicated Foam	R 28756	"Kills head lice and pubic lice and treats eggs on contact"	
Paralice Aerosol Spray	R 20918	"An aid in the prevention and elimination of lice, head lice, body lice and their eggs (nits)"	✓
Lice Blaster	L 66390	"For the control and treatment of human head lice and nits in adults and children over the age of 6 months"	
Exit Lice	L 70798	"For the control and treatment of human head lice and nits in adults and children"	
Herbs for Head Lice	L 68515	"For the treatment of human head lice and nits"	
Tea Tree Lice Foam	L 72710	"Kills head lice chemical free"	
KP24 Soaking Solution	-	"Eradicates head and body lice, fleas, bedbugs and similar insects"	
Lice Buster	-	"All natural herbal lice oils"	
Lice Scent to Kill	L 69276	"Aromatherapy lotion for the treatment and control of head lice and nits in adults and children"	
Lice Attack	L 70188	"Kills head lice and their eggs on contact"	
Pyrenel Foam	R 19414	"Kills head lice, body lice and their eggs in one application"	
Lice Guard	-	"Head lice repellent. Prevents and controls head lice. Control is 100%. Stops eggs hatching and prevents reinfestation".	✓
Orange Medic Plus	R 69377	"For the treatment of human head lice and nits in adults and children over 6 months"	
Orange Medic	R 10924	"For control of all human head and body lice and nits"	

Product	AUST No	Label claims	Preventative claim
KP24 Lice egg remover	-	"Removes dead lice and their eggs. Helps end infestation"	
KP24 Lice Spray	-	"helps prevent head lice infestation. During a five week clinical trial all children treated daily with KP24 spray remained lice free"	✓
Wild Child Quit Nits Head Lice Preventative	-	"Discourages head lice infestation"	✓
Quellada Crème Rinse for long hair	R 37003	"Kills head lice on contact. For the treatment of head lice and their eggs"	
Quellada Head Lice Treatment for short hair	R 45849	"Kills head lice on contact. For the treatment of head lice and their eggs"	
HLT Head Lice Treatment Medicated Foam	R 10962	"Kills both lice and nits (eggs)"	
Neutra Lice	L 67693	"Kills head lice and their eggs on contact"	
Banlice Mousse	R 46708	"Treats head lice and eggs on contact with one application"	
KP24 Medicated Lotion	R 18869	"Kills head lice and eggs on contact. One application only. Prevents reinfestation"	✓
KP24 Medicated Foam	R 18867	"Kills head lice and eggs on contact. One application only. Prevents reinfestation"	✓