Author's response to reviews

Title: Effectiveness of Isopropyl Myristate/Cyclomethicone Solution of Removing Cuticular Hydrocarbons from Human Head Lice (Pediculus humanus capitis)

Authors:

   Eric C Barnett (ebarnett@piedmontpharma.com)
   Kathleen G Palma (kpalma@piedmontpharma.com)
   Bert Clayton (bclayton@piedmontpharma.com)
   Timothy Ballard (tballard@en-cas.com)

Version: 2 Date: 25 July 2012

Author's response to reviews: see over
Responses to the Reviewer

Jacob Levitt:

I believe we met many years ago about this product when you were with Taro. I want to thank you for your thoughtful and constructive review.

Respectfully,

Kathleen G. Palma, Ph.D.

Abstract: All comments made concerning the abstract were relevant and constructive. Changes have been made.

Background: I concur that this was written in an unbalanced manner. This section has been revised and is more relevant and balanced in its presentation. There is one statement that needs correction: IPM does not dissolve the exoskeleton, only nitric and sulfuric acids can do that. IPM dissolves the wax on the epicuticle of the exoskeleton. IPM has no affect on the nits. The nits are made of at least 4 different proteins. IPM is a solvent for lipids such as lanolin and other fats found in cosmetics. Proteins would need some sort of denaturing activity such as change in pH or temperature. The issue has always been that anything that is going to affect the nit is probably going to be deleterious to the skin or hair. I added a statement about the lack of activity of IPM on embryonic eggs. IPM/Cyclomethicone only affects the nymphal louse once the operculum has started to open (4-5 days). If the formulation can get to the nymph the nymph will not emerge and die in the egg.

Methods: Cyclomethicone and IPM have been tested independently in vitro early on in development. It was determined that not all cyclomethicones have the same louse activity. D4 has 8 carbons and has no activity at all on the head louse. D5 has 10 carbons and has some activity but not the same activity as IPM. IPM at 100% shrivels everything up within hours. Lice become immobilized and start falling from the head after the 10 minute application. However 100% IPM does not feel very good so cyclomethicone was added as an excipient and improve the feel of the material. Dimethicone alone is a product and has been tested. 100% dimethicone is 100% effective in vitro. Again the feel of the material is less than perfect. The head lice for this study were collected from patients.
**Results:** This study was done as a descriptive, qualitative study. To quantify the amount of wax removed from the louse is beyond the scope of this work however insects much larger than head lice have had the lipid layers on the epicuticle measured to be only about 18 nm thick. To quantify this would be very interesting and challenging.

**Discussion/Conclusion:** The work showing dehydration of the lice came earlier in previous work that I believe has been published as a poster presentation. The early work with this formulation and mode of action was done at the International Congress of Entomology in Brisbane, Australia in 2004. Cyclomethicone does have activity but at concentrations higher than 50%. The mode of action of cyclomethicone is different from IPM. When 100% IPM was applied, the lice were shriveled within hours like prunes. When 100% cyclomethicone was applied, the lice were plump and blood red. The gut of the lice had ruptured. 100% IPM gives 100% efficacy; 100% Cyclomethicone gives approximately 79-80% efficacy. The results published for Hedrin (4% dimethicone and 96% cyclomethicone) showed 79% efficacy. I knew that the cyclomethicone was the active and not the excipient.
Responses to the Reviewers

Thank you for your constructive review of this paper.

Respectfully,

Kathleen G. Palma, Ph.D.

Ian Burgess:

Abstract: All comments made concerning the abstract were relevant and constructive. Changes have been made.

Background-Insect Exoskeleton: I concur with some of the statements made however I did not feel that detail concerning the physiology and morphology of the insect i.e. head louse would be of interest to the readership. As an entomologist I find that very interesting as the wax coating of the insect can fluctuate with the varying Order, Genus or Species of the insect. Even the environment in which the insect finds itself can have an impact on the wax composition as well as thickness (R.F. Chapman, The Insects: Structure and Function, 3rd Edition). As a graduate student this was the insect physiology bible. I believe there is a 6th Edition now. I agree with your comments about the cuticular hydrocarbons studies. There have been several studies using crickets and roaches that would be applicable to a point. Again this is not directed toward entomologists however a publication on Insect Physiology would be appropriate.

Background-Challenge, Therapies and Genetic Resistance: The Challenge section has been revised based on questions from the other reviewer. I have trimmed down Therapies to general statements concerning the historical perspective of various pesticide therapies. The Genetic section has some relevancy given that the mode of action of this product does not induce knockdown resistance (kdr gene and kdr-like mutations). As I do agree that there is physiological resistance, that resistance has a genetic basis. The enzymatic activity of breaking down pesticides i.e. DDTase found in the housefly has a genetic component.
Alternatives: That section has been removed. I concur that is redundant and not relevant.

Chemistry and Regulatory: I have revised this section removing all the regulatory references because that is not relevant to this readership. I do feel that the chemistry of this product is relevant to the fact that it can dissolve the wax layer of the epicuticle.

Results: I concur with the statement and have made the appropriate revision.

Conclusion: The final sentence of the conclusion has been revised.

Head lice - Global Issue: I don’t completely agree with your thoughts concerning the contentious nature of suggesting lice transmission can occur by sharing hats, hairbrushes, headbands or clothing. The statement that the most common way of transmission is head to head is made and the other possible methods are listed. You are very familiar with the literature on head lice and I challenge you to find papers that don’t suggest hats, hairbrushes, etc as fomites for head lice. I think suggesting that the stuffed animals and bed linens be thrown out and all the carpet steam cleaned might be contentious. I think most of the transmission data when it comes to fomites are anecdotal except for the hair work done showing how lice like hair oriented a certain way and certain distance apart.

Methods: I have tried to adjust this section as requested. I do not feel comfortable editing much because this is not my area of expertise.

Discussion-Fast Acting: I concur with your observation that this is not advertising copy and this paper originally read very much like it. I have revised hopefully to remove the advertisement. I do think that suffocation is a slow process that can take up to 8 hours which can be documented in the literature. I realize that Hedrin has since got a shorter treatment time. I knew all along that it worked faster than 8 hours with the 96% cyclomethicone in it. It is hard to imagine 4% dimethicone being a suffocant.
Overcoming Resistance: This section has been completely omitted. I concur that the point about the open circulatory system of the insect was not very well explained. The point that was trying to be made is that insects do not have the ability to compensate for excessive water loss because their organs like the Malpighian tubules are being bathed by hemolymph and not supported by veins, arteries or a lymphatic system that can minimize water loss by temporarily shutting down organs. Fluid is moved in and out of the insect organs via osmotic pressure. An example I actually witnessed during a study was >50% cyclomethicone causing the gut of a head louse to rupture. The cyclomethicone entered the insect via the spiracles and compromised cuticular wax. The hemolymph becomes hypertonic to the gut and the gut ruptures. Granted this is qualitative and descriptive but compelling.

Conclusion: I concur and the conclusion has been revised.