Carroll-Loye Biological Research

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24 September 2007

Mr. John Carley
Program Analyst
U.S. Environmental Protection Agency
Office of Pesticide Programs

Dear John,

This letter is a response to your request for information regarding the amendment to Carroll-Loye protocol SCI-001. On June 30, 2007, I received a request from the sponsor to substitute a version of the liposomal repellent LipoDeet containing 34.34% deet for one of the test articles, Insect-Guard II. I was informed of two straightforward rationales for this request. First, a chief objective of the study was to compare performance of a suite of extended duration deet products to the military issue Ultrathon, a repellent utilizing deet at 34.34%. Yet the sponsor had, to that point, proposed test articles at or below 30% deet (i.e., 12% less deet minimally). The sponsor recognized that employing a LipoDeet version at 34.34% deet would enhance the quality of the comparison. At the same time, in the interval between the drafting of the protocol and the conduct of the test, the sponsor had decided to discontinue the marketing of Insect-Guard II. These developments, then, led to the request that the substitution be made.

To make that substitution, I ultimately drafted an amendment to that effect, which was approved by the sponsor and is included with the report. In deciding to accept the substitution, I evaluated the proposition on both scientific and ethical grounds. Likewise, in determining whether to seek IRB approval for the substitution, I considered whether the change had any reasonable likelihood of increasing any of the participation-associated risks of the test subjects.

In discussing best conduct for amending protocols with HSRB members, California EPA staff, and IRB administrators, I have come to understand that the PI takes considerable responsibility, and has considerable authority, in determining whether an amendment represents a sufficiently great change to the risk-benefit profile of a study to require additional ethical review. The study-associated risks identified *a priori* were of three types: exposure to the test materials themselves, exposure to biting arthropods, and possible exposure to vectors of arthropod-borne diseases. Changes to the risk profile through the amendment could obtain either from predictable alterations of likely events or experiences, or from the introduction of unknown or poorly known variables. I judged there to be no basis for concern regarding changes in the risk profiles for any of the three risk types from either of the two liability sources identified, for several reasons.

First, there was no change in the number of participants.

Second, the duties and actions required of the participants were unaltered.

Third, there was no risk to subjects caused by removing the Insect-Guard II treatment, given that it was replaced by another repellent that could reasonably be anticipated to function appropriately within the test design.

Fourth, the introduced formula was exceedingly similar to the 30% LipoDeet already approved for testing, differing only in having 4.34% more deet and 4.42% less water (technical deet is 98.11% concentration).

Fifth, in addition to being similar to the approved LipoDeet formulation, the substituted formulation has a deet concentration intermediate in the range of approved, registered insect repellents, which includes 100% deet products.

Sixth, while there is limited information regarding quantitative skin absorption data of Deet from controlled release formulations, studies performed by Reifenrath (references 1 and 2) for the US Army provide some insight. He compared skin penetration rates of three controlled release Deet formulations *in vitro* using excised pig skin in an absorption cell. The Deet products were labeled Biotek, 3M, and Army issue (no other identifiers were provided). It was reported that percutaneous penetration through 24 hours measured 6% (Biotek), 11% (3M), and 8% (Army issue). In an earlier study performed by Reifenrath, using essentially identical methods, he reported the absorption of technical Deet at 34%.

Two recent reports (references 3 and 4) describe reductions in Deet absorption rates as measured by *in vitro* methods similar to those of Reifenrath. In each case skin penetration of Deet was markedly reduced when formulated with various polymers, in one case by as much as 62%. In the second report, Deet absorption was reduced 9-fold when the repellent was combined with varying formulations of polyethylene glycol mixtures.

Clearly, the controlled release products minimize skin penetration of the active ingredient. LipoDeet is already known to extend the duration of deet efficacy, indicating that it has the controlled release properties its developer claims (reference 5). Indeed, Mouse studies using radio-labeled DEET (reference 6) resulted in a dramatic reduction of DEET Absorption through the skin when applied in a LipoDEET formula Fig. 1). The reported studies (1-4) indicate that about a one- to two-thirds reduction would be expected. Accordingly, while we do not know the comparative skin absorption rates of deet from applications of LipoDeet at 34.34% deet versus Insect Guard II (17.5% DEET with 5% N-octyl bicycloheptane dicarboximide and 2.5% Di-n-propyl isocinchomeronate) we could reasonably estimate that the rate for the 34.34% product would not be above, and would likely be well below, that of many other registered deet products that lack controlled-release formulation.

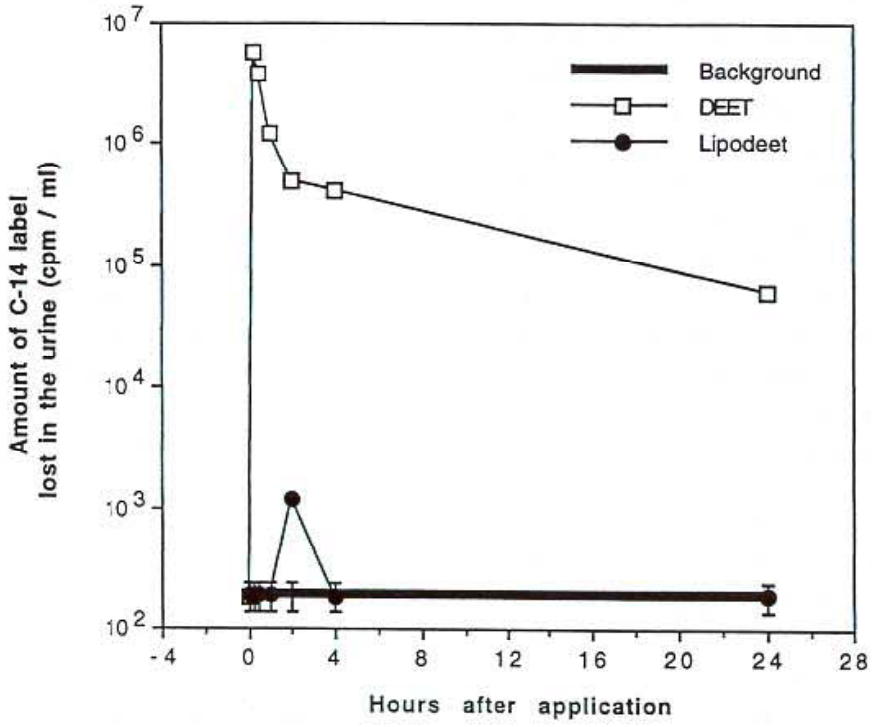

Figure 1. Levels of radioactivity in the urine after a single application of 14C-labeled DEET or LIPODEET to the abdominal skin. Values are the mean ± SD of 10 animals per group. From Salafsky et al. 1999.

While the risk profile of the study likely remained unchanged, a reasonably likely benefit accrued, through the improvement of the study design to better meet its principle objective of providing data on, as the sponsor emailed in his request, '*… a substitute product for our beloved soldiers that is substantially better… This gives a level playing ground as regards the amount of DEET available, leaving the differing formulations as the only variable. The more we discussed it, the more sure we were that this would be important to do… The formula is exactly the same as the LIPODEET 30 except for 4.34% less water and 4.34% more DEET, so the safety information for DEET 30 should apply to this formula as well….*'

In Margin of Exposure calculations described in reports SCI-001.1 and SCI-001.2, we found that the values from our dosimetry analyses were similar for the LipoDeet formulations at 30.00% and 34.34% (520 and 492, respectively).

In summary, as a PI making the planned change to the protocol, I determined that additional ethical oversight was unwarranted in the present case. However, I fully welcome EPA and HSRB feedback on that decision.

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In addition to this explanatory letter, you will also find the MSDS and Confidential Statement of Formula for LipoDEET 3434 together in an attachment to the cover email. In addition, I have attached the Salafsky et al. (1999) reference for your information.

Thank you very much.

Sincerely,

Scott P. Carroll, PhD

References

1. Reifenrath, WG, et. al. (Oct – Nov 1986) Report: Controlled release personal use arthropod repellent formulation, Phase II evaluations. Division of Cutaneous Hazards, Letterman Army Institute of Research, Presidio of San Francisco, CA 94129.

2. Reifenrath, WG (1985) Presentation Paper No. 18: Use of skin of non-primate strains for determination of percutaneous penetration. Division of Cutaneous Hazards, Letterman Army Institute of Research, Presidio of San Francisco, CA 94129.

3. Qiu, H., et. al. (1997) Reduced transdermal absorption of N,N-diethyl-m-toluamide from a new topical insect repellent formulation. Pharm Dev Technol. 2(1):33-42.

4. Ross, JS and Shah, JC (2000) Reduction in skin permeation of N,N-diethyl-m-toluamide (DEET) by altering the skin/vehicle partition coefficient. J. Control Release. 2000, Jul 3; 67(2-3):211-21.

5. Salafsky, B et al. (2000) Study on the efficacy of a new long-acting formulation of N,N-diethyl-m-toluamide (DEET) for the prevention of tick attachment. J. Trop. Med. Hyg., 62(2):169–172.

6. Salafsky, B et al. (1999) Development and Evaluation of LipoDEET, a new long-lasting formulation of N ,N-diethyl-m-toluamide (DEET) for the prevention of schistosomiasis. J. Trop. Med. Hyg., 61(5): 743-750.