Short Communication

INSECT REPELLENT INTERACTIONS: SUNSCREENS ENHANCE DEET (N,N-DIETHYL-M-TOLUAMIDE) ABSORPTION

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ABSTRACT:
Toxicology studies are typically performed on single compounds, which we hypothesized would miss adverse synergies from chemical mixtures. This hypothesis was tested using an insect repellent and sunscreens because both groups include known permeation enhancers, with prior pediatric reports of toxicity from highly concentrated DEET (N,N-diethyl-m-toluamide). Using real-time mass spectroscopy in a hairless mouse skin model, we confirmed substantial penetration of a 20% DEET standard. Despite a lower (10%) DEET content, a commercially marketed sunscreen formulation had a 6-fold more rapid detection (5 versus 30 min) and 3.4-fold greater penetration at steady state. We also tested the efficacy of DEET microemulsion products and confirmed that one successfully slowed the onset of absorption, but not the steady-state permeation. Risks from mixtures of potential toxins are worthy of routine testing, which can be accomplished by simple assays, and are of utmost importance for pediatric applications.

Toxicology studies are fundamental to our approach for using an enormous variety of environmental, industrial, and medicinal compounds, which are of particular importance to the pediatric population. We were concerned that mixtures of chemicals might unintentionally enhance toxicity, and chose to study a topical insect repellent in this regard. The routine use of N,N-diethyl-m-toluamide (DEET) has been widely advocated by the medical community and media after recent illnesses from West Nile encephalitis and other infectious agents. Despite DEET’s efficacy and superb safety record, we believe it is imperative that this and other topical agents not be used in commercial mixtures that unintentionally enhance their transdermal absorption.

This raises a much wider and more important concern that serious adverse interactions between common potential intoxicants may be underappreciated because typical industry testing does not include that of mixtures. Some sunscreens and even DEET itself have been described as permeation enhancers (Windheuser et al., 1982; Benson, 2000; Hayden et al., 1997), and awareness of problematic formulations would be of value to the public, children in particular. Especially with case reports and media stories of alleged pediatric behavioral or neurotoxicity, there has been a longstanding concern that transdermal absorption of high-concentration products might pose a health risk (Robbins and Cherniack, 1986; Selim et al., 1995; Briassoullis et al., 2001).

We hypothesized that some topical formulations might influence their component’s permeation, but could not be detected by prior steady-state models utilizing single agents. We used a mouse skin model and liquid chromatography/mass spectrometry to quantify real-time absorption kinetics of DEET in various concentrations and in a commercial sunscreen product.

Materials and Methods

A flow-through cell was devised that would permit mounting of 1.27-cm² full-thickness hairless mouse skin and allow quantification of transdermal penetration into a small-volume well mixed receptor compartment containing 50% ethanol/water. Fresh fluid entered the device by vortex forces and was pumped out at 100 μl/min using the highly regulated micropump of a high-performance liquid chromatograph (model 1100; Hewlett Packard, Palo Alto, CA) into a Finnigan/MAT LCQ liquid chromatography/mass spectrometry apparatus (Thermo Finnigan, San Diego, CA) with an atmospheric pressure chemical ionization source. All data were acquired and subsequently analyzed, with each compound identified by the mass spectroscopy. This flow cell has been extensively validated (by comparison with fractionated collections from static Franz cells) for single compounds as well as mixtures, including each member of the 4-hydroxybenzoate ester series (methyl to octyl), various parabens, caffeine, and theophylline. The experimental animal procedures were in accordance with institutional and international standards for the care and use of laboratory animals (Animal Welfare Assurance Publication A5427-01, Office for Protection from Research Risks, Division of Animal Welfare, National Institutes of Health). Experiments were performed in duplicate, and the skin preparation integrity was documented by the reproducibility of the caffeine standard permeation. Test solutions were applied to the skin without occlusion. We determined the times to first detection and steady state, as well as final signal intensity, with the results expressed as relative abundance: a 20% DEET standard was compared with a 9.5% product with the sunscreens octocrylene, octyl-methoxycinnamate, and benzophenone-3 (Off! Skintastic Insect Repellent with Sunscreen, S. C. Johnson and Son Inc., Racine, WI). We also tested two proprietary products marketed as having less absorption due to a microemulsion formulation: 3M Ultrathon Insect Repellent (31.58% DEET; 3M, St. Paul, MN), and Sawyer Controlled Release DEET Formula (19.00%; Sawyer Products, Safety Harbor, FL).

Results

All of the DEET preparations had profound transdermal penetration (Table 1). The 20% standard had a time to detection of approximately 30 min with steady state at 85 min. One microemulsion product (Sawyer) had transdermal penetration no different from the pattern for the repellant at that same concentration (20%) in ethanol/water. However, the other microemulsion formulation (3M) demonstrated a

ABBREVIATIONS: DEET, N,N-diethyl-m-toluamide.
somewhat different profile: despite a higher concentration of DEET (30 versus 20%) and a similar time to first detection (40 min), the time to reaching steady state was delayed to 200 min. Even with slower absorption, there was still substantial absorption at steady state (3.1 times that of the 20% standard).

The sunscreen product demonstrated a markedly different penetration profile with enhanced DEET permeation (Table 1; Fig. 1). Despite a concentration approximately half the standard, the lag time to detection of absorption decreased from 30 min to just 5 min, time to steady state decreased from 85 to 60 min, and there was 3.4 times greater absorption at steady state. There was a dramatic biphasic penetration profile, as illustrated in Fig. 1. Notably, there was no measurable penetration by any of the three sunscreen compounds in the commercial mixture.

### Discussion

DEET is the most popular insect repellant and has had a remarkably low incidence of adverse side effects (Robbins and Cherniack, 1986). Extensive animal studies did not detect chronic toxicity, except at extremely high oral doses (Schoenig et al., 1999). Nevertheless, other animal and human studies have reported transdermal penetration ranging from 9 to 56%, with 17% absorption into the circulation (Robbins and Cherniack, 1986; Selim et al., 1995). Multiple human case reports have described primarily neurotoxic symptoms (albeit rare and typically with overdoses or misuse) including tremor, seizures, toxic encephalopathy, acute manic psychosis, altered behavior, and even death (Tenenbein, 1987; Briassoulis et al., 2001). Many authors were concerned that even routine topical application of high-concentration products might be problematic in children because of their high surface area to body mass ratios, and recommended that DEET toxicity be studied more rigorously (Robbins and Cherniack, 1986; Tenenbein, 1987).

We found that the absorption profile was not altered by the dilution of DEET down to 20%. Although there have been reports of sunscreens having 2 to 10% transdermal absorption or being permeation enhancers (Hayden et al., 1997; Benson, 2000), our disturbing finding that one preparation (with a pediatric logo) can dramatically enhance DEET penetration was unexpected. Despite the prior reports of sunscreens modifying permeation, we cannot exclude a role of some other agent present in these formulations. One hypothesis for the prominent two-phase kinetic profile is that the sunscreens induced an initial flux through pores, followed by the phase of diffusion through skin layers temporally corresponding to that of DEET alone. Unfortunately, we could not demonstrate any benefit from one of the commercial microemulsion preparations, and the other brand still had substantial absorption, albeit with the penetration taking approximately 3 times as long.

DEET has also been used as an intentional permeation enhancer for topical medications (Windheuser et al., 1982), and this raises the specter of it increasing the absorption of potentially more harmful intoxicants in the environment or commercial formulations. Mass spectrometry methodology can be used to study that possibility, in that it overcomes the historic analytic problem of resolving fluxes of individual components in mixtures.

In summary, we have demonstrated an example of our broad concern over unappreciated toxicity of mixtures of chemicals that are traditionally studied as just single agents. This raises a number of issues relating to analytic and industry testing methodologies for toxins, not limited to dermal preparations. In this particular case, there is the important issue of limiting use of some sunscreen formulations in children because of the health risk of inducing enhanced absorption of DEET. Safety concerns caused by combining topical toxins or vehicles are underappreciated, warrant the time-dependent study of these widely used mixtures, and identify potential but easily avoidable risk in products currently marketed to susceptible populations such as children.

**References**


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