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PS 567 *IN VITRO* DERMAL ABSORPTION OF A METALWORKING FLUID ADDITIVE: DICYCLOHEXYLAMINE (DCHA).

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Dicyclohexylamine (DCHA) is commonly used in the metalworking industry to prevent corrosion of fabricated materials. There is no published information describing the dermal absorption of DCHA in metalworking fluid (MWF) formulations. Machine workers are most likely to be exposed to DCHA by the dermal route. The objective of this research was to quantify the dermal absorption of DCHA *in vitro* using porcine skin because of its similarity to human skin both anatomically and biochemically. DCHA was applied to pig skin in water and in 3 generic MWF formulations commonly used in industry: Soluble (SO), synthetic (SYN), and semi-synthetic (SS) oil. Dermatomed pig skin (n=4) was loaded onto a flow-through diffusion cell system with individual dose areas of 0.64 cm^2 and perfused with media containing 4.5% bovine serum albumin for 8h to mimic occupational exposure conditions. Pig skin was dosed with 5-10% DCHA in 7 vehicles: Water, water + 5% SO, SYN, or SS oil; or neat SO, SYN, or SS oil. Dermal absorption of DCHA was similar between SO, SYN, and SS oil mixed with water, as well as between neat SO, SYN, and SS oil. Dermal absorption of DCHA from water + SS (0.08%) > water + SO (0.02%) > water + SYN (0.005%). Dermal absorption of DCHA from neat SS (0.11%) > neat SYN (0.09%) > neat SO (0.03%). The highest overall dermal absorption was at 1.4% from the water vehicle. These results suggest that water facilitates the dermal absorption of DCHA across skin whereas DCHA in MWFs may partition more with the vehicle due to its partitioning behavior. In conclusion, the varied dermal absorption of DCHA across MWF formulations must be taken into account within the machining industry and MWF manufacturing as repeated occupational exposure to this metalworking fluid additive may prove to be detrimental to human health. (Supported by NIOSH grant R01-01-03669)

PS 568 A SCREENING METHOD TO ESTIMATE DERMAL ABSORPTION *IN VITRO*.

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Dermal absorption can be used in the evaluation of the effectiveness of pharmaceutical or cosmetic formulations, but often it as a critical parameter in risk assessment of pesticides or chemicals. Therefore, knowledge of dermal absorption is helpful in formulation development.
Skin absorption is routinely measured in vivo or in vitro following OECD TG 427 or 428. However, these tests are complex, time consuming and expensive. Therefore, a study was developed to allow simple and rapid screening. The method uses dermatomized skin in modified Franz type diffusion cells. 10 µl of test substance preparation are applied to the skin preparation. After 6h, the skin is washed and the amount of penetrated substance is quantified. The receptor fluid and the washing solutions are optimized for subsequent analyses by LC-MS. We performed dermal absorption screenings in parallel to our routine guideline studies demonstrated a good correlation of the results of both study types: The total recovery found in the screening studies is somewhat lower than in the corresponding guideline studies but is always in the acceptable range above 80%. The efficacy of the skin washing procedure is less efficacious than under routine conditions, most probably due to the change to an LC-MS-compatible washing solution. Overall, the dermal absorption screening is an easy, fast and cost-effective screening method for the estimation of dermal absorpttion of a wide variety of test substances and formulations.

PS 569 VEHICLE EFFECTS ON THE ABSORPTION OF FINITE AND INFINITE SATURATED DOSES OF CAFFEINE, MANNITOL, AND TESTOSTERONE IN PORCINE SKIN.

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The flow through diffusion cell system is an in vitro technique often used for the toxicological assessment of chemical absorption across skin. This approach routinely employs porcine skin as a surrogate membrane for human skin. Review of the literature highlights variations in experimental variables such as dosing solutions (infinite/finite or saturated/unsaturated and delivery vehicle), and receptor fluid. With such vast variations, data comparison can be difficult. This study aimed to standardize dosing solutions for three model 14C-labeled compounds (caffeine CF, mannitol MN, and testosterone TS) to evaluate the effect of delivery vehicle on absorption through porcine skin. A finite (20 µL) and infinite (1000 µL) saturated dose was applied in one of three vehicles: propylene glycol (PG), water (Wa) and ethanol (EtOH). Flux of each compound ($n \geq 3$) into the receptor phase was monitored over 24 hours. Levels of radioactivity were also determined in the stratum corneum (by tape stripping) and the remaining skin. Apparent permeability coefficients and absorbed dose (µg) were then calculated and compared. Each compound showed unique absorption (abs.) profiles, such that from the infinite Wa doses, absorption was greater from MN (solubility 81442 µg/mL; abs. 50.4 µg) > CF (solubility 29092 µg/mL; abs. 24.9 µg) > TS (solubility 15.8 µg/mL; abs. 0.65 µg). The same profile was observed in the amount remaining in skin after 24 hours: MN (264 µg) > CF (193 µg) > TS (0.49 µg). The absorption and skin deposition profile from the infinite PG and EtOH doses followed the pattern: TS > CF > MN. This same absorption and skin deposition profile was maintained for the finite EtOH doses for all three compounds, but altered for the finite PG and Wa doses. This data highlights the variable effects a vehicle may exert on dermal absorption, suggesting that the contribution from the vehicle should be incorporated in dermal absorption models. (Supported by Novartis Animal Health, Inc.)

PS 570 DERMAL VEHICLE EVALUATION OF 2-ETHYLHEXYL P-METHOXYCINNAMATE.

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2-Ethylhexyl p-methoxycinnamate (EHMC) is a widely used UVB filter ingredient in topically applied sunscreen formulations sold in the United States. With heightened societal awareness of the dangers of UV radiation, sunscreens are increasingly being applied for protection throughout a person's lifespan, leading to chronic exposure to sunscreen ingredients. Because of the reported EHMC estrogenic and reproductive effects, it has been selected for study by the National Toxicology Program.
In this work various solvents and formulation mixtures were evaluated as dermal vehicles for use in rodent dermal toxicology studies. These included combinations of coconut oil, light paraffin oil, beeswax, emulsifying wax, Polysorbate 80 and water, along with solubility, storability, and syringeability of the EHMC vehicles. In addition, viscosity measurements of commercial sunscreen lotions were compared to the EHMC dermal vehicles in order to achieve the desired consistency and texture. The resulting evaluations established the dermal vehicle formulation with the most appropriate characteristics was an oil-in-water emulsion of light paraffin oil:Polysorbate 80:water (60:12:28; v/v/v), abbreviated LPP80.
Further evaluation of LPP80 for optimal preparation temperature and EHMC solubility was conducted. Formulations at 10 and 400 mg/g EHMC resulted in emulsions with the consistency of a thin white lotion that mixed well and were syringeable through a syringe with no needle attached. Storage tests of these emulsions showed no visual changes over 14 days under ambient or refrigerated conditions except that the viscosity increased over the storage period, with the greatest increase observed in the refrigerated formulations, suggesting a gelation phenomenon. The performance of this formulation indicates that it is an acceptable vehicle for use in future toxicological dermal studies with EHMC.

PS 571 XENOBIOTIC METABOLISM CAPACITIES OF HUMAN SKIN IN COMPARISON TO 3D-EPIDERMIS MODELS AND KERATINOCYTE-BASED CELL CULTURE AS *IN VITRO* ALTERNATIVES FOR CHEMICAL TESTING: PHASE I AND II.

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The metabolic competence of skin has so far not been fully characterized, although human skin fulfills important tasks in uptake, distribution and metabolism of chemicals, such as voluntarily applied substances and anthropogenic pollutants. Since the 7th Amendment to the EU Cosmetics Directive will prohibit the use of

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