SKIN CYTOCHROME P_{450} STATUS AND PERCUTANEOUS PENETRATION: ENHANCED DERMAL ABSORPTION AND ALTERED LOCAL DISPOSITION OF 3,3',4,4'-TETRACHLOROBIPHENYL AND PENTACHLOROPHENOL

GL Qiao[1*] and JE Riviere[2]
[1]HELD, NIOSH, CDC, Morgantown, WV, USA and [2]Center for Cutaneous Toxicology and Residue Pharmacology, North Carolina State University, Raleigh, NC, USA

Chemical mixture and sequential chemical dermal exposure reflects the real-world scenario in the workplace, environment, or residential setting. Cutaneous metabolism has a great effect on the local and systemic health hazard of a topically applied chemical by modifying its disposition fate and biological activity. To quantify the effects of skin cytochrome (Cyt) P_{450} induction on local distribution and dermal absorption, ^{14}C labeled 3,3',4,4'-tetrachlorobiphenyl (TCB, in acetone) or pentachlorophenol (PCP, in ethanol) was topically applied to in vivo (n=3), ex vivo (isolated perfused skin, n=4), and in vitro (flow-through diffusion cells, n=7) porcine models, at 40 $\mu g/cm^2$ with or without Cyt P_{450} inducer benzo[a]pyrene (B[a]P) pretreatment. Skin Cyt P_{450} induction enhanced the dermal absorption of TCB and PCP in all the three models. A 2~4 fold increase in 8 h ^{14}C percutaneous absorption was observed in the ex vivo model (TCB 0.11 to 0.46%; PCP 1.1 to 3.2%) and in vitro (TCB 0.21 to 0.48%; PCP 0.20 to 0.66%) due to cutaneous P_{450} induction. Under P_{450} induction (control), 5% (2%) and 6% (3%) of the TCB and PCP doses were excreted in urine, respectively. The corresponding values in feces were 4% (3%) and 8% (6%). If the in vivo observation period was prolonged to several weeks, the total absorption was 23-30% for TCB and 50-70% for PCP regardless of skin Cyt P_{450} induction, indicating the observation duration has to be considered when designing a study to detect the effect of skin P_{450} on dermal absorption, perhaps as short as 3-5 days. Skin Cyt P_{450} induction also changed label penetration depth and distribution pattern in local cutaneous tissues, suggesting that the enhanced cutaneous TCB and PCP metabolism can change the toxicity profile (cutaneous vs systemic). On average, 82% and 83% of the topical TCB and PCP doses were recovered. In conclusion, the effects of cutaneous metabolism manipulation by pre-exposed or co-administered enzyme inducer(s) such as B[a]P need to be taken into account in dermal risk assessment and transdermal drug delivery.

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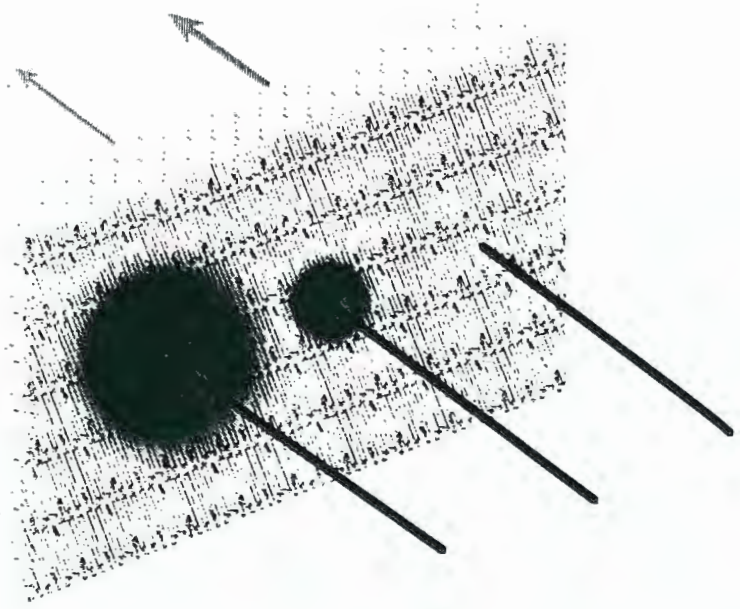

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