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January 31, 2002

In reply, please refer to:
HEER OFFICE
Coqui3

Mr. Sydney Ross Singer
Medical Anthropologist
P.O. Box 1880
Pahoa, Hawaii 96778

Dear Mr. Singer:

Thank you for your letter of January 7, 2002. We appreciate your mention of your credentials in that letter. We did not mean to insult your intelligence in past letters when speaking in generalities. We now appreciate what level of detail you require. The Deputy Director for Environmental Health, Gary Gill, asked me to reply to you for him.

“Skin permeation can be measured in living humans or animals, or in vitro by using excised (human) skin in diffusion cells. Studies with excised skin seem feasible, since passage through the skin is a passive diffusion process and the primary barrier, the stratum comeum, is composed of nonliving tissue.” (Robert L. Bronaugh, Raymond F. Stewart, Elaine R Congdon, and Albert L. Giles, Jr., “Methods of in Vitro Percutaneous Absorption Studies. I. Comparison with in Vivo Results,” *Toxicology and Applied Pharmacology* 62: 474-480(1982).)

The first thing to note is the passive diffusion, not active transport, through the nonliving stratum comeum layer. Based on this statement by experts, sir, would you agree that the skin of a human being, a land mammal whose skin has adapted a stratum comeum to protect against water loss due to existence in relatively arid land environments, would be much more protective against water intrusion than the thin skin of a frog which had originally adapted to existence in an aquatic environment? An Olympic swimmer who trains in a pool for hours does not absorb pool water or chlorine beyond his skin into his bloodstream and emerge waterlogged or edematous. Also, if you recall dissecting frogs in Comparative Anatomy class, you may remember how thin a frog’s skin is, with no stratum comeum, and how easy it is to snip with tiny scissors, compared to the difficult scalpel work in cutting the thick skin of a cat. One would expect that a frog’s skin absorption of water or of an aqueous solution of caffeine would be much greater than that of a land mammal. The greater absorption of caffeine by a frog would account for the toxic accumulation and greater effect of caffeine on a frog than on a human.

Also, the in vivo experiments in the aforementioned study used [¹⁴C-labeled] caffeine and demonstrated the removal of caffeine from the bloodstream by the kidney and its excretion via the urine. As you know, the accumulated concentration of caffeine in a tiny frog with a small internal volume of water would be much greater per unit of body weight, compared to the concentration of a heavy dog or human with a large internal volume of water. The concentration of caffeine in a mammal would then be reduced by the kidney's removal and excretion actions.

The aforementioned study employed four compounds that had been previously studied by other researchers, including caffeine, to verify that certain in vitro methods using rat skin gave similar results to test methods using live animals, in vivo. For example, caffeine was found to have permeability constants of 2.1×10^4 cm/hr in vivo and 3.1×10 cm/hr in vitro for percutaneous absorption through shaved rat skin.

The permeability constant, k_{p3} , is defined as the steady-state rate of absorption (amount/cm²/hour) divided by the concentration of solute applied to the skin (amount/cm³), which is then expressed in centimeters per hour (cm/hr). The permeability constant accounts for applying different concentrations of caffeine to the skin. These authors verified that caffeine is absorbed through the skin at a very limited rate by passive diffusion, not active transport.

The principal author, Dr. Robert Bronaugh, wrote a book with another nationally recognized expert, Dr. Howard Maibach of the University of California medical school in San Francisco, titled Percutaneous Absorption (Marcel Dekker publishers, 1989). Chapter 32 of this book, pp. 555-565, is titled "Facilitated Percutaneous Absorption of Charged Drugs," and is written by Jonathan Hadgraft, Philip G. Green, and Paul K. Wotton. In this chapter, the permeability constant (also called permeability coefficient) of caffeine is compared to other substances. The test system used fall-thickness human skin in vitro that had been pretreated with ethanol and Ethomeen S-12 to increase skin absorption, and 0.01M pH 5 aqueous solutions of various substances. Pentachlorophenol, a pesticide notorious for being absorbed through the skin, had a permeability coefficient of 0.7 cm/hr. Two other substances which have been found to be skin absorbed, benzene and toluene, had coefficients of 0.02 cm/hr and 0.05 cm/hr. Metal ions, such as iron, chromium, lead, and mercury, had coefficients of approximately 0.001 cm/hr. Caffeine had a permeability coefficient of 0.002 cm/hr, which possibly implies that caffeine may be as unlikely to be absorbed through the skin as metals which are commonly found in Hawaiian soil.

These experimental results confirm the theoretical application of the log octanol-water partition coefficient (K_{ow}) which was mentioned in a previous letter. There are supporting studies, such as one by A-L. Bunge and R.L. Cleek, "A new method for estimating dermal absorption from chemical exposure: 2. Effect of molecular weight and octanol-water partitioning," *Pharmacology Research* 12(1): 88-95, Jan. 1995, or more than 50 studies coauthored by either Jonathan Hadgraft or Philip Green, who appear to be two more well-published authorities on percutaneous absorption.

You stated that caffeine and nicotine have "similar chemical properties." We agree that caffeine and nicotine are both water-soluble, but beyond that, they do not appear to be similar. We said that the solubility of caffeine in oils and lipids determines the percutaneous absorption, not the water solubility. Nicotine has a K_{ow} of 1.17, and besides being soluble in water, it is very soluble in oils, kerosene, ether, chloroform, and alcohol. This accounts for its easy absorption through the skin. After sitting on a bench wet with a 40% nicotine solution for 15 minutes, a florist showed signs of toxicity

(Faulkner JM, "Nicotine poisoning by absorption through the skin," Journal of the American Medical Association 100: 1664-65, 1933). A look at its chemical structure in any edition of The Merck Index shows pyrrolidine rings with one attached methyl group, which accounts for its nonpolar character and its solubility in nonpolar oils and lipids, as found in the skin. Caffeine, however, has a K_{ow} of -0.07, is very soluble in polar solvents such as water or alcohol, but is only slightly soluble in ether and other nonpolar solvents. The Merck Index shows its structure as purine rings with two attached oxygen atoms, which make it polar and thus insoluble in nonpolar oils and lipids. Also, "Aqueous solutions of caffeine salts dissociate quickly," (The Merck Index. Tenth Edition, 1983) which makes caffeine even less absorbable through the skin.

We still believe that caffeine is unlikely to be absorbed through the skin in quantities sufficient to pose a public health threat. If you are still unconvinced by our reasoning, backed up by the scientific evidence in our citations, we welcome your statements to the contrary, backed up by your citations.

Sincerely,

LESLIE K.L. AU, M.Sc.
Toxicologist, HEER Office