Chemical Uptake Into Human Stratum Corneum *In Vivo* from Volatile and Non-Volatile Solvents

Audra L. Stinchcomb,[1,2,7] Fabrice Pirot,[1,3] Gilles D. Touraille,[1] Annette L. Bunge,[4] and Richard H. Guy[1,3,5,6]

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Purpose. Simple, safe and quick *in vivo* methods for estimating chemical uptake into the stratum corneum (SC) from volatile and non-volatile solvents are invaluable to health risk assessors. This study compares the human *in vivo* SC uptake of a model compound (4-cyanophenol) from water and acetone using quantitative attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectroscopy.
Methods. Small areas on the ventral forearms of human volunteers were treated with 4-cyanophenol (CP) dissolved either in water or acetone. After the skin was cleansed of remaining surface CP, SC samples were taken by a standard tape-stripping method. CP concentration profiles across the SC were quantitated by direct measurement of the permeant on the individual tape-strips using ATR-FTIR.
Results. Increasing the duration of exposure to CP aqueous solutions resulted in increasing CP uptake into the SC; the kinetics of uptake correlated well with predictive diffusion equations. Increasing the 'dose' of CP in acetone also resulted in increasing uptake into the SC, but uptake eventually plateaued at a maximum level. The amount of CP taken up into the SC from acetone was 2 to 8-fold greater than that from water following similar short-time exposures.
Conclusions. These safe, simple experimental methods provide practical and predictive assessments of chemical uptake into human SC *in vivo*.

KEY WORDS: percutaneous absorption; stratum corneum; risk assessment; volatile solvents; ATR-FTIR; acetone.

INTRODUCTION

Dermal absorption of chemicals dissolved in evaporating vehicles, such as acetone and ethanol, is relevant to both drug delivery and to the assessment of environmental and occupational exposure via the skin. The concentration of chemical in the "vehicle" changes as the solvent evaporates thereby altering the diffusional driving force; in addition, after the solvent has evaporated, percutaneous absorption may be quite different from that when the solvent was present. Often, the exposure time is short, meaning that dermal absorption of chemicals from volatile vehicles is invariably an unsteady-state process. Consequently, it is not clear how to transfer information collected from steady-state experiments involving occluded (i.e., non-evaporating) aqueous solutions to situations in which exposure to chemicals occurs via evaporating solvents. While the permeation of solvent-deposited chemicals have been previously reported (1–7), the controlling mechanisms of dermal absorption under these conditions remain poorly understood.

The objectives of this work were to evaluate and quantify SC uptake during and after evaporation of a volatile vehicle. Specifically, uptake of a test chemical (4-cyanophenol, CP), from water and acetone, into human stratum corneum (SC) *in vivo* was studied using attenuated total reflectance Fourier-transform infrared (ATR-FTIR) spectroscopy. CP was chosen as the model compound because it is nontoxic and amenable to analysis by FTIR.

ATR-FTIR has been used to qualitatively and quantitatively measure SC uptake *in vivo* in humans (8–12). Typically, ATR-FTIR is used to determine the amount of chemical in sequentially tape-stripped layers of the SC after relatively brief periods of exposure (on the order of 15–120 minutes). Only small amounts of chemical are absorbed during such short exposures, and most of the chemical taken up into the SC can therefore be recovered by tape-stripping and then quantified. Traditional *in vivo* experimental techniques require relatively long periods of exposure to the penetrating chemical (24 hours has been common), and either blood sampling, or collection of urine and/or fecal samples over several days, has been necessary. By comparison, ATR-FTIR represents a faster, safer, and more versatile tool with which to study SC barrier function *in vivo*, in humans.

MATERIALS AND METHODS

Materials

4-Cyanophenol (CP) and ACS-grade acetone were purchased from Aldrich Chemical Co. (Milwaukee, WI) and Fisher Scientific (Pittsburgh, PA), respectively. The log{octanol/water} partition coefficient of CP is 1.6 (17), its molecular weight 119, with a melting point of 110–113°C (18). Aqueous solutions of CP were prepared with deionized water. The system used for the cutaneous application of CP aqueous solutions consisted of a saturated gauze pad (2.5 × 8 cm, Johnson and Johnson Medical, Arlington, TX), a polyester film (2.5 × 8 cm, Scotchpak, 3M, St. Paul, MN), and an occlusive transparent dressing (approx. 7 × 12 cm, OpSite, Smith & Nephew, Largo, FL). Acetone solutions were confined to a 2.5 × 8 cm area of skin with a 0.5 cm high rim of White Petrolatum, USP (E. Fougera & Company, Melville, NY). 3M Book Tape 845 was used for sequential SC removal by stripping.

Instrumentation

ATR-FTIR spectra were recorded using a Nicolet (Madison, WI) 520 FT-IR spectrometer equipped with a Balston BFS-400 FT-IR air purifier (Balston, Lexington, MA) and a liquid

[1] Departments of Biopharmaceutical Sciences and Pharmaceutical Chemistry, University of California-San Francisco, San Francisco, California 94143-0446.
[2] Present address: Albany College of Pharmacy, Albany, New York 12208-3492.
[3] Institut des Sciences Pharmaceutiques et Biologiques, Université Claude Bernard Lyon I, 69373 Lyon, France.
[4] Chemical Engineering and Petroleum Refining Department, Colorado School of Mines, Golden, Colorado 80401.
[5] Centre Interuniversitaire de Recherche et d'Enseignement, "Pharmapeptides", Campus Universitaire, Parc d'Affaires International, F-74166 Archamps, France.
[6] Faculté des Sciences, Section de Pharmacie, Laboratoire de Pharmacie Galénique, Université de Genève, CH-1211 Genève, Switzerland.
[7] To whom correspondence should be addressed. (e-mail: stinchca@panther.acp.edu)

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nitrogen-cooled mercury-cadmium-telluride detector. The sampling compartment (Contact Sampler, Spectra Tech, Stamford, CT) was a horizontal internal reflection accessory holding a zinc selenide crystal (7 × 1 cm, 45°) with a refractive index of 2.4 at 1000 cm^{-1}, a density of 5.27 g/cm^3, and a transmission range of 20,000–650 cm^{-1}. All spectra obtained represented an average of 100 scans over the frequency range of 20,000–650 cm^{-1}.

Quantitative Analysis

Strips of adhesive tape used to remove the SC post-treatment were analyzed for CP as previously described (9). Tape was placed adhesive side down directly onto the zinc-selenide crystal, and the integrated C≡N stretching vibration absorbance in the spectral region between 2250 and 2200 cm^{-1} was determined.

A calibration curve over the CP concentration range of interest was obtained from the C≡N absorbances on tapes containing known amounts of CP which had been evenly distributed as an aqueous solution (10–20 μL) over a specified area of the adhesive side. Because the IR signal was attenuated in the presence of SC, the tapes used in the calibration also contained typical amounts of stripped SC. The mass of SC on each tape strip was determined by weighing before and after SC stripping using a high-precision balance sensitive to 10 μg (Sartorius BP210D, Goettingen, Germany). The calibration curve had the form:

$$A_{peak} = 0.004 m_{4CP}\, e^{-0.014 m_{SC}} \quad (1)$$

where A_{peak} is the peak C ≡ N area, m_{4CP} is the area normalized mass of CP ($nmol/cm^2$), and m_{sc} is the mass of SC also normalized by the tape area ($\mu g/cm^2$). Eq. (1) was validated in a separate analysis using [^{14}C]-radiolabeled CP (9).

In Vivo SC Uptake

All studies were approved by the Committee on Human Research at the University of California, San Francisco. The healthy volunteers, aged 25–30, had no history of dermatologic disease. The ventral forearm surface was used for all experiments.

In the aqueous solution experiments, 1.4 ml of a saturated CP solution (315 mM, containing excess solid) was applied to a 20 cm^2 area of skin (22μmol CP/cm^2) for 1, 5, 15, or 30 minutes. At the end of the exposure period, the application system was removed, excess CP was gently wiped from the skin surface with a water-dampened cotton ball, and the skin was dried with a fresh cotton ball. Immediately after cleaning, the SC at the treated site was progressively removed with 20 adhesive tape-strips. These tapes were quickly weighed to determine the stripped mass of SC normalized by the tape area (m_{SC}), and were then analyzed for CP by ATR-FTIR. Assuming that the removed SC is uniformly distributed on each tape strip, the molar concentration of CP (i.e., mol/L) in each tape strip was calculated (with the appropriate unit conversions) from:

$$C = \rho_{SC} \frac{m_{4CP}}{m_{SC}} \quad (2)$$

where ρ_{SC}, the hydrated density of the SC, was assumed to be 1 g/cm^3 (13). The average concentration of CP in the SC ($\langle C \rangle$) was calculated by dividing the total amount of CP in all tape strips by the total mass of SC removed in all tape strips. That is,

$$\langle C \rangle = \rho_{SC} \sum_{\substack{\text{all tape}\\ \text{strips}}} m_{4CP} \Big/ \sum_{\substack{\text{all tape}\\ \text{strips}}} m_{SC} \quad (3)$$

with appropriate unit conversions.

In the acetone solution experiments, 400 μl of CP solution (4.2–335.6 mM, 84–6712 $nmol/cm^2$) was applied to a skin area of 20 cm^2. After the acetone evaporated, which required 30–40 seconds, the White Petrolatum border was quickly removed from the skin. The CP solid film was then gently wiped from the skin surface with a water-dampened cotton ball, and the skin was dried with a fresh cotton ball. In two experiments, the CP solid film remained on the skin for a total of 5 or 30 minutes before it was removed. Tape-stripping and quantitative analysis were performed as described for the aqueous solution experiments.

RESULTS

Figure 1 shows the concentration of CP in the SC from a single subject (#3) after exposures to a saturated aqueous solution for 1, 5, or 15 minutes. These data are plotted as a function of position within the SC(x) normalized by the total thickness of the SC(L). The ratios x/L were determined assuming that L equals the total mass of SC removed by tape stripping divided by the product of the SC area stripped and the SC density, and that the SC is uniformly distributed on each tape strip. Thus, the relative location (x/L) within the SC following removal of

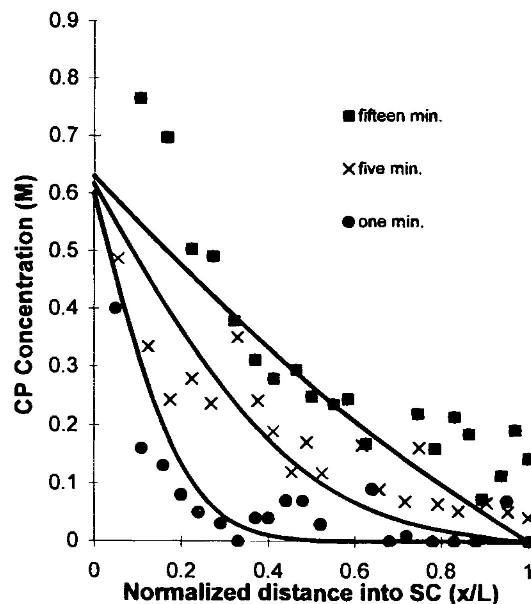

Fig. 1. The concentration profile of CP as a function of normalized position (x/L) in the SC for one subject (#3) after exposures of 1, 5, and 15 minutes to a saturated aqueous solution of the chemical. The data points were experimentally determined; the lines through the results represent the best fits of Eq. (1) corresponding to the values of D/L^2 and K in Table 1.

the nth tape strip is given by:

$$\frac{x}{L} = \sum_{i=1}^{n} m_{SC,i} \Big/ \sum_{i=1}^{N} m_{SC,i} \quad (4)$$

where $m_{SC,i}$ is the mass of SC removed per area for tape i, and N is the total number of tape strips removed.

Chemical transport across the SC can be described by Fick's 2nd law of diffusion through a simple, pseudo-homogeneous membrane (14). If (a) the concentration of chemical in the vehicle (C_{veh}) does not change during the exposure, (b) the chemical equilibrates rapidly between the outermost layer of the SC and the aqueous solution, and (c) chemical concentration in the innermost layer of the SC remains negligible, then the concentration profile $C(x)$ in the SC can be described by:

$$qlC = KC_{veh}\left[1 - \frac{x}{L} - \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{\sin(n\pi x/L)}{n}\exp(-Dn^2\pi^2 t/L^2)\right] \quad (5)$$

where D is the effective diffusivity based on the apparent SC thickness L, K is the equilibrium partition coefficient of the chemical between SC and the vehicle, and t is the time of chemical exposure. In developing Eq. (5), it was also assumed that all chemical transport occurs by passive diffusion, that the vehicle does not modify the SC, and that no other skin layers (e.g., the viable epidermis) contribute to the total barrier. For this situation, the steady-state permeability coefficient of the chemical across the SC from a given vehicle is defined: $P_{veh} = K{\bullet}D/L$. Note that it is not possible to determine P_{veh} from the chemical's concentration profile across the SC; rather it must be evaluated from the deduced values of D/L^2 and K, and an assumed value of L.

The curves in Fig. 1 were calculated from Eq. (5) with $D/L^2 = 0.9\ hr^{-1}$ and $K = 5.7$, values which were determined by nonlinear regression of the diffusion equation to the data from all three exposure times. The results for the 4 subjects studied are summarized in Table 1.

Table 1. Measured and Regressed Parameters Characterizing CP Transport Across Human SC *in Vivo* After Application of an Aqueous Solution[a]

Subject	Exposure time (min)	⟨C⟩ (M)	L^b (μm)	K	D/L^2 (hr^{-1})	$P_{veh}{}^c$ (cm/hr)
1	1	0.37	5.6			
	5	0.53	4.8	22.9	0.8	0.009
	15	1.22	4.7			
2	1	0.25	5.3			
	5	0.63	4.0	10.3	2.7	0.015
	30	0.66	6.5			
3	1	0.07	12			
	5	0.18	9.5	5.7	0.9	0.006
	15	0.34	11			
4	1	0.16	4.5			
	15	0.43	9.1	7.5	2.3	0.012
Mean	—	—	7.0	11.6	1.7	0.011
± SD	—	—	2.8	7.8	1.0	0.004

[a] C_{veh} = 110 mM; the area of exposure was 20 cm^2.
[b] Calculated from the total mass of SC removed, assuming SC density = 1 g/cm^3.
[c] Calculated from K • (D/L^2) • L, where L is each subject's average L.

An alternative approach is to analyze the time variation of the average concentration of CP in the SC (i.e., the total mass of CP in the SC normalized by the volume of the SC). Theoretically, the average concentration in the SC (⟨C⟩) is obtained from the integral of Eq. (5) with respect to x (i.e., over the interval $0 \le x \le L$, i.e.:

$$\langle C\rangle = KC_{veh}\left[\frac{1}{2} - \frac{4}{\pi}\sum_{n=0}^{\infty}\frac{\exp[-D(2n+1)^2\pi^2 t/L^2]}{(2n+1)^2}\right] \quad (6)$$

However, for short exposure times [i.e., $t < \sim 3{\bullet}t_{lag} = L^2/(2D)$], ⟨$C$⟩ can be found from a simpler equation representing Fickian diffusion into a semi-infinite medium (15,16):

$$\langle C\rangle = 2\,K\,C_{veh}\sqrt{\frac{Dt}{L^2\pi}} \quad (7)$$

Based on the average $D/L^2 = 1.7\ hr^{-1}$ measured for CP (see Table 1), exposure times less than about 18 minutes would be considered short. Figure 2 presents ⟨C⟩ for $t \le 15$ min, plotted as a function of $t^{1/2}$ for 4 subjects. The average of the slopes (linear regression analysis, $r^2 > 0.95$) through the individual data points is 25 ± 14 (mean ± standard deviation) $mM/s^{1/2}$, which is very similar to the value of 31 $mM/s^{1/2}$ calculable from the experimentally determined solubility at room temperature (C_{veh} = 110 mM) and the average parameters for K and D/L^2 in Table 1.

The data in Table 1 and Figures 1 and 2 are reasonably consistent with those reported previously (9) for transport of CP across human SC *in vivo*: average values of K and D/L^2 were 8 and 0.32 hr^{-1}, respectively, corresponding to a permeability coefficient of about 0.01 cm/hr when one uses the average experimentally estimated SC thickness (note that, if one assumes L = 15 μm, as was the case in the earlier work (9), then the estimated P_{veh} would be closer to 0.05 cm/hr which compares well with the published result (9)).

Figure 3 compares the average concentration of CP in the SC of three subjects following either a 1-minute exposure to a saturated aqueous solution or a 40-second exposure to an acetone solution (40 mg/ml; 20 μL/cm^2). The period of exposure

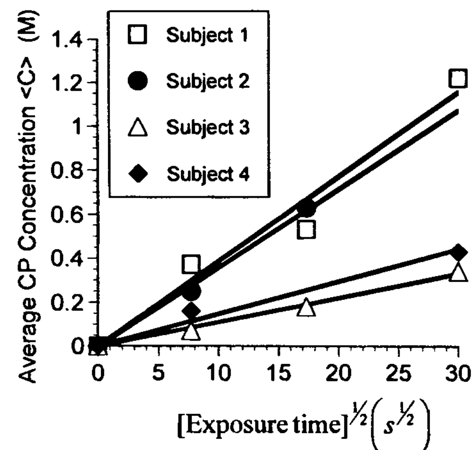

Fig. 2. Average concentrations of CP in the SC of 4 subjects after exposures of different duration to a saturated aqueous solution of the chemical; the results are plotted as a function of square root of the exposure time according to Eq. (7) (lines of linear regression have been drawn through the data).

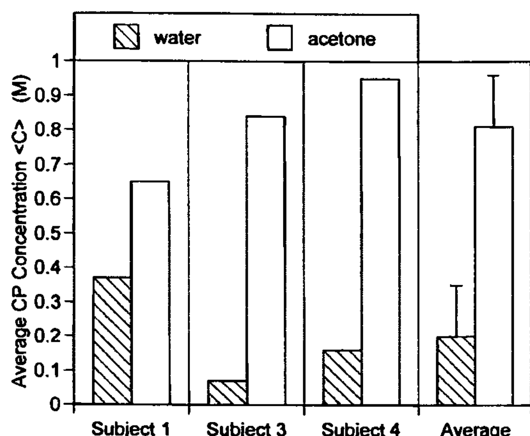

Fig. 3. Uptake of CP into the SC of three subjects following either a 1-minute exposure to a saturated (315 mM) aqueous solution, or a 40-second exposure to the chemical dissolved in acetone (corresponding to a surface "dose" of 6.7 μmol/cm²).

in the latter case corresponds to the time necessary for the applied volume of acetone to evaporate completely. It can be seen that the mass of CP in the SC following exposure to the acetone solution was significantly ($p < 0.05$), i.e., 2 to 8-fold, higher than that after application of the saturated aqueous solution.

Figure 4 shows the concentration of CP in the SC (averaged over all subjects) following a 40-second exposure to different amounts of the chemical presented in the same volume of acetone (20 μL/cm²). These data indicate that CP uptake increased to a maximum and plateaued at an applied dose of about 3 μmol CP/cm². Further increases in the amount of CP

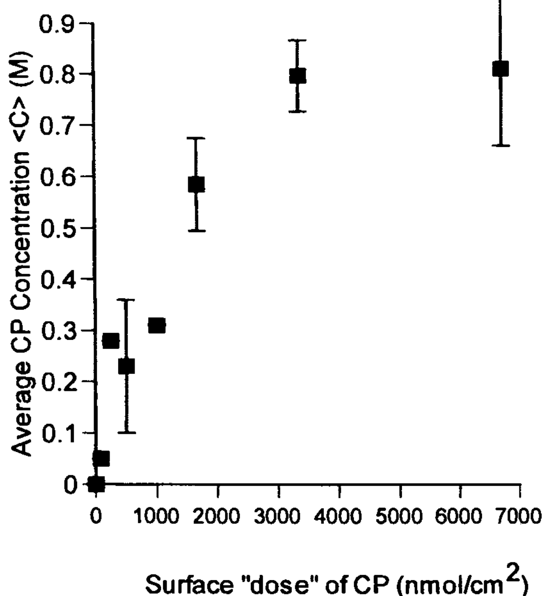

Fig. 4. Absorption of CP from acetone into human SC *in vivo* as a function of the amount of chemical initially dissolved in 20 μL/cm² of the evaporating solvent. In each case, the exposure period was 40 seconds, the time required for the acetone to evaporate completely. {Data shown are mean ± S.D.; n ≤ 3}.

applied did not significantly change the amount of chemical taken up into the SC.

Figure 5 compares CP uptake into the SC (averaged over all subjects) as a function of exposure time for saturated water and acetone (5–40 mg/mL, 20 μL/cm²) vehicles. It is clear, at least up to 15 minutes of exposure, that increasing the time of contact between a CP aqueous solution and the skin leads to an increased uptake of the chemical into the SC. On the other hand, when exposure occurs to the evaporating vehicle acetone, it appears that most, if not all, of the chemical which absorbs into the SC does so during the time that the solvent is present—after complete evaporation of the acetone, little additional uptake seems to take place. However, additional experiments with more subjects, examining periods longer than those considered here, are necessary before completely firm conclusions can be drawn.

DISCUSSION

The results obtained from the simple ATR-FTIR analysis of SC tape-strips show that CP uptake into SC from water fits a standard predictive model well and agrees generally with previously published data (9). The concentration profile provided by this type of experiment is easily translated to parameters of human SC diffusion. The complex extrapolation step, for example, from an *in vitro* measurement to the *in vivo* situation, or from animal to man, is bypassed in these experiments. Health risk assessors may therefore find this expeditious methodology useful in predicting potentially dangerous dermal absorption scenarios. While the ATR-FTIR approach used here is of course limited to chemicals which absorb in the infrared in a manner distinct from the SC itself, it should be noted that other analytical methodologies (e.g., HPLC) can be used to quantify the permeant removed with the SC on the tape-strips.

It might also be pointed out that the determination of a concentration profile may not always be necessary for a useful risk assessment; the strategy illustrated by which an average SC concentration is evaluated may be quite sufficient. However, to calculate the permeability coefficient from values of $\langle C \rangle$ requires measurements at both short ($t < 3 \cdot t_{lag}$) and longer

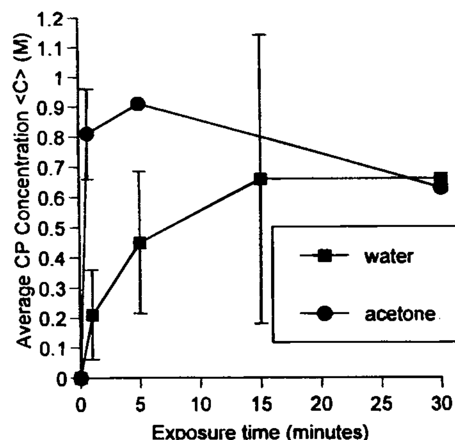

Fig. 5. Comparison between the amount (mean ± S.D.; n ≤ 3) of CP penetrated into the SC, as a function of exposure time, following treatment of the skin with either a saturated aqueous solution, or an acetone solution, of the chemical.

times ($t > 3 \cdot t_{lag}$). From the former, the product $K \cdot P_{veh}$ can be calculated. To determine P_{veh} uniquely therefore requires an independent evaluation of K. This is most easily accomplished from an experiment in which the exposure time is sufficient to ensure that steady-state is established: in this case, $\langle C \rangle = K \cdot C_{veh}/2$.

In addition, it must be admitted that, as the tape-stripping procedure at the end of the exposure period requires several minutes (i.e., for short exposures, about as long as the exposure itself), the concentration profile will change during the sampling time. Recent calculations and theory (19,20), based on situations such as this, are attempting to shed light on the significance of the error introduced by assuming (as we have here) that the concentration profile does not adjust while the tape-strips are removed.

As shown in this work, others have reported that the initial uptake of a chemical from acetone is more rapid than that from aqueous solution (e.g., for hydrocortisone (4) and flurbiprofen (5)). That is, although absorption from aqueous solution eventually surpasses that from the acetone-deposited film, the early unsteady state uptake is greatest from the evaporating vehicle solvent. Clearly, the time for which the chemical remains in solution on the skin surface is important. With an aqueous solution, close to the saturation solubility of the chemical, the driving force for uptake remains more or less constant throughout the exposure period. On the other hand, for a volatile vehicle which begins evaporating from the moment of application, the surface concentration of the chemical increases with time up to the point at which the solvent has disappeared; one is now left with a solid film of the chemical from which continued uptake into the SC may now be very slow and dissolution-limited. The results with CP are consistent with this scenario: from water, uptake increases progressively with time; from acetone, on the other hand, absorption is the same from a 40-second exposure (the time required for complete evaporation of the solvent) as that when the chemical is allowed to stay on the skin for a further 30 minutes. The same conclusion has been reached for other chemicals, including hydrocortisone, mannitol, progesterone, ibuprofen, and flurbiprofen (4,5). Risk assessment following dermal exposure to volatile vehicles should pay particular attention, therefore, to the duration of contact between the evaporating solvent and the skin. In addition, careful consideration should be given to the extent that the solvent itself can enter the SC and (potentially) change, i.e., increase, its permeability.

The other parameter of importance which has been examined here to some extent is the amount of the chemical dissolved in the volatile solvent. Increasing the 'dose' of CP in acetone resulted in increasing absorption of the chemical into the SC up to a maximum level, beyond which no additional material was taken up. Similarly, increasing the amount of acetone-deposited chemical on the skin surface has been reported to increase dermal penetration in the same way for (e.g.) ibuprofen and flurbiprofen (5); however, in these cases, a plateau in absorption was not observed. It may be suggested that the phenomenon of a limiting absorption indicates that the maximum capacity of the SC to accept the chemical has been reached; that is, the chemical has attained its solubility limit in the barrier layer.

In conclusion, the straightfoward experimental methods described here provide practical and predictive SC uptake estimates in humans *in vivo*. Further studies with different penetrants and solvents, and using alternative analytical methods to ATR-FTIR, will provide a more complete picture of the unsteady state dermal absorption process, and offer new information with which more reliable estimates of the risk associated with chemical exposure to the skin can be made.

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