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Toxicology Directorate

In Vitro Dermal Absorption of Carfentanil, July - September 2018

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14. ABSTRACT
Permeation of carfentanil formulated in three vehicles, water, ethanol, and hand sanitizer was measured under infinite-dose conditions in an in vitro static diffusion cell system using the EpiDerm™ (EPI-606-X) RHE model. The permeation rate was fastest for carfentanil in water (3.60 x 10-3 cm/hr), followed by hand sanitizer (0.88 x 10-3 cm/h), and slowest for carfentanil in ethanol (0.17 x 10-3 cm/hr). In ethanol and hand sanitizer, a lag-time between exposure and permeation of approximately 1 hour was observed, while the lag-time in water was 30 minutes. These data indicate that small skin exposures may not result in rapid, significant toxicity as previously reported.

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Good Laboratory Practice Compliance Statement

All analytical chemistry and work with carfentanil were performed at a collaborating organization, US Army Medical Research Institute of Chemical Defense (MRICD) and were not conducted in compliance with Title 40, Code of Federal Regulations (CFR), Part 792, Good Laboratory Practice (GLP) Standards. This work was, however, conducted in accordance with the collaborating organization's standing operating procedures (SOPs) and the approved protocol. The protocol, data analysis, and final report were prepared in compliance with GLP standards.

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1 Summary

1.1 Purpose

There is growing concern regarding potential occupational exposures to the ultra-potent synthetic opioid carfentanil. This study was conducted to assess the potential for dermal absorption of carfentanil using an *in vitro* static diffusion cell system with reconstructed human epidermis (RhE). The aims of this study were 1. To determine the permeability coefficient, flux, and lag-time for carfentanil following infinite dose administration in a live human epidermal model and 2. To compare penetration of carfentanil administered in three vehicles: water, ethanol, and hand sanitizer.

1.2 Conclusions

Permeation of carfentanil formulated in three vehicles: water, ethanol, and hand sanitizer was measured under infinite-dose conditions in an *in vitro* static diffusion cell system using the EpiDerm™ (EPI-606-X) RhE model. The permeation rate was fastest for carfentanil in water (3.60×10^{-3} cm/hr), followed by hand sanitizer (0.88×10^{-3} cm/h), and slowest for carfentanil in ethanol (0.17×10^{-3} cm/hr). In both ethanol and hand sanitizer, a lag-time between exposure and permeation of approximately 1 hour was observed, while the lag-time in water was 30 minutes. Flux at steady-state was greater at 50.6 µg/ml than at 5.3 µg/ml for both water and ethanol; however, the percent of dose absorbed did not differ between doses for either vehicle. The slight difference in percutaneous permeation of carfentanil observed between the two brands of hand sanitizer evaluated may have been due to differences in the relative proportion of alcohol and skin penetration enhancers in the products. These data indicate that the use of alcohol-based hand sanitizers following exposure to carfentanil may not pose the threat previously suspected. Additionally, small skin exposures may not result in rapid, significant toxicity as previously reported.

2 References

See Appendix A for a listing of references.

3 Authority

This study was sponsored by the U.S. Army Medical Command, Office of the Surgeon General and identified as WBS element S.0055513.

4 Background

Carfentanil citrate (methyl 4-(1-oxopropyl) phenylamino-1-(2-phenylethyl)-4-piperidine carboxylate-2-hydroxy-1,2,3-propanetricarboxylate) is an analogue of the synthetic μ-opioid agonist fentanyl. It's only approved use was as a large-animal tranquilizing agent (Wildnil®) in the veterinary field, however, commercial production of Wildnil ceased in 2003. Like other opioids, carfentanil acts on the central nervous system, inducing respiratory depression, suppression of the cough reflex, and pupil constriction, as well as side effects such as drowsiness and sedation.

Carfentanil is one of the most potent opioids known. In rats and mice, the LD_{50} of carfentanil is 3.39 and 18.75 mg/kg, respectively, after intravenous (IV) administration [1, 2]. After intraperitoneal injection, lethality is observed at 326.4 μg/kg in rats and 83.1 μg/kg in ferrets [3, 4]. Signs of carfentanil intoxication including catalepsy, loss of righting reflex, and apnea/respiratory depression are observed at 18.2 and 8.92 μg/kg in rats and ferrets, respectively [3, 4]. The lowest reported lethal inhalation concentration in rats is 300 mg/m^3 [5], while exposure to concentrations as low as 0.4 mg/m^3 for 1 minute induces loss of consciousness in mice [6]. Because carfentanil has no approved human uses, the potency in humans has not been determined. It is estimate to be 100 times more potent than fentanyl and 10,000 times more potent than morphine, with an estimated lethal dose in humans of 20 μg (0.286 μg/kg) [7]. Data are available from one study in which healthy, non-drug using volunteers were given an IV bolus of 0.019 μg/kg carfentanil; dizziness, nausea, vomiting, and itching were observed [8].

Additional human exposure data are available from a case report of a veterinarian that was splashed in the face, eyes, and mouth while pulling a misfired dart (1.5 mg of carfentanil and 50 mg xylazine hydrochloride) from a tree [9]. Despite decontamination with water, within 2 minutes he became nauseated, sedate, and hypotensive, but was returned to baseline after receiving 100 mg of intramuscular naltrexone [10]. Nearly 800 people taken hostage in a Moscow theater in October 2002 were exposed to aerosolized carfentanil [11, 12]. Although nearly all were incapacitated, only 15% died despite the weaponization of carfentanil for maximal absorption and delayed availability of naloxone [12].

Carfentanil has recently entered the illicit drug market resulting in multiple overdoses and deaths across the U.S. Carfentanil and other non-pharmaceutical fentanyls (NPFs) are frequently shipped from China to the US, Canada, and Mexico where they are used as adulterants in heroin, cocaine, and methamphetamine [13]. Overdoses occur because many users are not aware that they are being exposed to carfentanil. Although the true incidence rate of carfentanil overdose is not clear because routine toxicology

tests do not identify carfentanil [14], 9,580 opioid overdose deaths were caused by fentanyl and fentanyl analogs in 2015 [13].

There is growing concern about the safety of law enforcement and emergency medical providers in the event of inadvertent exposures to ultra-potent opioids. Media reports describe reports of officers suffering symptoms after exposure to powdered substances suspected to be fentanyl, as well as officers requiring several doses of naloxone after skin and mucous membrane exposure [15]. Drug Enforcement Agency (DEA) guidance for first responders indicates that, due to their lipophilicity, fentanyl analogs are absorbed rapidly and efficiently by all exposure routes including injection, oral ingestion, mucous membranes, inhalation, and transdermal transmission. Further, DEA guidance indicates that due to the high potency of fentanyl analogs, exposure to even small quantities could rapidly cause severe health effects including death [13]. Controversy exists regarding the true risk posed to first responders as pharmacokinetic and clinical data as well as routine handling of fentanyl-related substances by drug users suggest the risk may be lower than suggested [16]. Regardless, use of appropriate personal protective equipment (PPE) and, if contamination occurs, prompt decontamination are recommended [13, 17, 18]. Use of alcohol-based hand sanitizers is strongly discouraged as it is believed this will enhance the dermal absorption of fentanyl-related substances [13, 18].

Although the dermal absorption of fentanyl was assessed during the development of the transdermal delivery patch (Duragesic®) [19], the dermal absorption of carfentanil has not been studied. Further, the effects of hand sanitizer on the dermal absorption of carfentanil have not been determined.

5 Materials and Methods

5.1 Materials

5.1.1 Test Substances

Carfentanil citrate (CASRN: 61380-27-6; Lot: HF-15-056) was obtained from Edgewood Chemical and Biological Center. Caffeine (CASRN: 58-08-2; Lot: BCB59512V) was purchased from Sigma (St. Louis, MO).

5.1.2 Test System, Controls, and Reagents

The reconstructed human epidermal model EpiDerm™ was acquired from MatTek (EPI-606X, MatTek, Ashland). The EpiDerm™ tissues are shipped as kits, containing 6 tissues on shipping agarose together with culture media – Dulbeco's Modified Eagle's Medium (DMEM) based, Dulbeco's Phosphate Buffered Saline (DPBS), and 6-well plates. Additional DPBS without calcium, magnesium or phenol red was purchased from

Gibco, Inc. (a subsidiary of ThermoFisher, Waltham, MA) and Krebs-Ringer bicarbonate solution was purchased from Fisher Scientific (Hanover Park, IL). Sufentanil citrate, was purchased from Cerilliant Corporation (Round Rock, TX) in flame sealed ampoules formulated at 100 µg/mL in methanol (CASRN: 60561-17-3, Lot FE013012-01) for use as an quantitative analytical internal standard. All test systems, reagents, and chemicals were stored according to the manufacturer's instructions.

5.2 Quality Assurance

5.2.1 Quality Control of Test System

The EpiDerm™ System is manufactured according to defined quality assurance procedures. All biological components of the epidermis and the culture medium are tested by the manufacturer for viral, bacterial, fungal, and mycoplasma contamination. MatTek determines the effective time for 50% viability (ET-50 value) following exposure to Triton X-100 (1%) for each EpiDerm™ lot. The ET-50 must fall within the range of the EpiDerm historical database of 4.77 – 8.72 hours. If tissue lots fail quality control (QC) or sterility testing, the manufacturer notifies the customer. All tissue lots used in this proficiency demonstration passed QC and sterility testing.

5.3 Study Personnel

Appendix B lists the names of individuals contributing to the study performance.

5.4 Methods

5.4.1 Preparation of Test Substances

5.4.1.1 Carfentanil

Carfentanil citrate was dissolved in three vehicles: water (18 MΩ), ethanol, or hand sanitizer at 5.3 (water and ethanol) and 50.6 µg/ml. Two carfentanil stock solutions were prepared (Lot 140818M, 0.092 mg/ml in methanol and Lot 230718E, 1.15 mg/ml in ethanol) from neat carfentanil. Donor solutions in ethanol and water were prepared at 5.32 µg/ml by diluting 55 µl carfentanil stock (0.092 mg/ml) in vehicle (9.505 ml). Hand sanitizer (Leader Brand Lot 0326977) donor solution was prepared at 50.6 µg/ml by diluting 440 µl carfentanil stock (1.15 mg/ml) in hand sanitizer (9.56 ml).

5.4.1.2 Carfentanil with Caffeine as Internal Standard

Carfentanil citrate was also tested in three vehicles: water (18 MΩ), ethanol, or hand sanitizer using caffeine as an internal standard to monitor epidermal integrity. Donor solutions in ethanol and water were prepared at 50.6 µg/ml by diluting 440 µl carfentanil stock (1.15 mg/ml) in vehicle (9.56 ml) and adding 522 and 505 mg neat caffeine, respectively. Hand sanitizer donor solution was prepared at 50.6 µg/ml by adding 9.7

mg neat caffeine to 19.2 ml hand sanitizer (Purell lot 232198) and stirring vigorously to dissolve prior to adding 880 µl carfentanil stock (1.15 mg/ml).

5.4.2 EPI-606-X Dermal Absorption Test

5.4.2.1 Experimental Design

All reference substances were tested using an infinite-dose and were sampled 7 times over a 6 hour period with the exception of the carfentanil in ethanol at 5.03 µl/ml and Leader Brand hand sanitizer which were run for 24 hours with additional samples collected at 23 and 24 hours. The carfentanil vehicle combinations were tested in 6 replicates of RhE in a single run with the exception of carfentanil/caffeine in water and ethanol. Carfentanil/caffeine in water and ethanol were tested in 3 replicates each in 2 runs on successive days.

5.4.2.2 Day of Receipt

Upon receipt of assay kits, all components were stored according to the manufacturer's instructions. The EpiDerm tissues were maintained in the original packaging and stored at 4°C.

5.4.2.3 Day of Testing

Prior to use each day, the receptor chambers of all Franz cells (water jacketed, 12 ml, 15 mm orifice) were filled approximately ¾ full with Krebs-Ringer bicarbonate solution and the dermal absorption system (Logan Instruments FDC-6/VTC-300, Somerset, NJ) was allowed to equilibrate to 37±0.1°C. The EpiDerm samples were removed from the tissue culture inserts by inverting the insert on lab bench paper wetted with DPBS and cutting the tissue and underlying membrane from the insert using a sharp scalpel. The resultant disc was then placed stratum corneum side up (membrane side down) on the top of the receptor chamber of the Franz cell. The donor chamber was tightly clamped on top of the EpiDerm disc and the receptor chamber was filled to volume taking care to remove all air bubbles. Tissues were then allowed to equilibrate for 30 minutes prior to dosing. Tissues were visually inspected for integrity. Tissues were rejected if there was moisture/receptor media present on the tissue surface or defects were apparent. The donor solution was then pipetted (1.0 ml) onto the stratum corneum in the donor chamber. All donor solutions were brought to room temperature prior to use. Both the donor chamber and the sampling arm were covered with Parafilm. The receiver solution was continuously stirred (500-600 rpm) using a Teflon-coated magnetic stir bar.

The receiver solution was sampled at 0.5, 1, 2, 3, 4, 5, and 6 hours (and 23 and 24 hours on 2 occasions) by withdrawing a fixed volume (500 µl) from each receptor chamber via the sampling arm using an 18 gauge blunt end stainless steel pipetting needle and syringe. The sampled receiver solution was replaced with fresh Krebs-Ringer solution. The donor solution was sampled prior to dosing and at the conclusion of the exposure period to verify concentration and ensure the concentration remained

constant throughout the exposure. Samples were either analyzed on the day of testing or stored at -20°C prior to analysis.

5.4.3 Receiver Fluid Analysis

Receiver fluid samples were prepared for analysis by spiking 99 µL of sample with 1 µL of an analytical internal standard, sufentanil (10 µg/mL). Donor solution samples were diluted by adding 5 µL of each sample to 490 µL water with 0.1% formic acid and spiking with 5 µL of sufentanil (10 µg/mL). Samples were analyzed on a Shimazu Nexera UPLC interfaced with a SCIEX 4000 QTrap hybrid quadrupole-ion trap mass spectrometer. Samples (5 µL) were injected on a 2.1mm x 100 mm x 1.7 µm F5 column (Phenomenex Kinetex, PN: 00D-4722-AN, SN: H18-042762 and/or SN: H18-207601) using a 4 minute gradient from 2-90% acetonitrile with 0.1% formic acid (mobile phase A was water with 0.1% formic acid) at 0.4 mL/min at 30°C column temperature. The method was validated by determining both intra- and inter-day (three days) limits of detection (LOD), limits of quantification (LOQ), precision, and accuracy; the method LOD and LOQ were 46 and 230 pg/mL, respectively. To properly quantify carfentanil across such a large concentration range, two calibration curves were used, 0.23-46 ng/mL and 46-920 ng/mL. Caffeine was quantified against a calibration curve ranging from 11.88-19,800 ng/mL. Correlation coefficients of all calibration curves were ≥0.995. Three carfentanil positive quality control standards (0.98, 37.05, and 312.52 ng/ml) and blanks were analyzed in quintuplicate to assess intra-day performance. Accuracy and precision acceptance criteria for calibration curve standards and positive QC's were 100 ± 20% and percent coefficient of variation (%CV) ≤ 15%, respectively. Calibration curves, quality control standards, and blanks were formulated the same day as analysis.

5.5 Data Calculations, Analyses, and Interpretation

Experimental data generated during the course of this study were recorded by hand and tabulated, summarized, and/or analyzed using SCIEX MultiQuant, Microsoft Excel and GraphPad Prism.

5.5.1 Total Flux, Permeability Coefficient, and Lag Time

Receiver fluid concentrations were multiplied by the receptor chamber volume to determine the amount of test substance in the receptor chamber at each sampling point. The result was added to the amount of test substance removed in the previous sampling as determined by multiplying the volume of receiver fluid removed by the receiver fluid concentration. The receiver fluid data were plotted as the cumulative amount of test substance in the receptor chamber as a function of time. The permeability coefficient was calculated from the following equation.

$J_T = A\ P\ \Delta C$

Where:

J_T is the total flux at steady state (µg/hour)
A is the area of the membrane, 1.8 cm^2
P is the effective permeability coefficient (cm/hr)
ΔC is the concentration differential between the donor and receptor chambers, taken as the initial donor solution concentration (µg/cm^3)

Flux at steady state, J_T, was estimated based the following equation.

$J_T = V\ dC/dt$

Where:
V is the volume of the receptor chamber, 12 ml
*d*C/*d*t is the rate of change in concentration in the receptor fluid at steady state
Flux at steady state, J_T, was estimated as the slope of the linear regression analysis of the linear portion of the cumulative penetration versus time plot. Lag time (t_L) was determined by extrapolating the steady-state curves to the x-axis (i.e., determining the x-intercept).

Data are presented as the mean, standard deviation, and %CV of replicate runs for each test substance.

6 Results

Flux, permeability coefficient (K_p), lag-time, and percent penetration at 6 hours for carfentanil through RhE are presented in Table 1. These parameters were determined for carfentanil dissolved in water and ethanol at two doses and in two types of hand sanitizer at a single dose. Caffeine was used as an internal standard to verify epidermal integrity. The internal standard demonstrated consistent permeability rates among tissues within vehicle, indicating that all tissues used maintained integrity throughout the first six hours of the experiments. Data from exposures extended beyond six hours (ethanol at 5.03 µg/ml and Leader Brand hand sanitizer) were dropped as caffeine permeation indicated a decline in barrier integrity.

There were no differences in the permeability coefficients, lag-times, or percent permeation of carfentanil among doses (Table 1). The permeability constant (K_p) and percent permeation at 6 hours differed across the three vehicles ($p<0.001$ and $p<0.001$, respectively). Both were highest for carfentanil in water, lowest in ethanol, and were intermediate in hand sanitizer (Figure 1). Lag-time was longest for carfentanil in ethanol ($p<0.001$) and did not differ between carfentanil in water and hand sanitizer. Flux of carfentanil differed both across doses ($p<0.001$) and vehicles ($p<0.001$). A significant interaction effect was noted; however, this was due to the absence of the 5.3 µg/ml dose in the hand sanitizer. As would be expected, flux was higher in the 50.6 µg/ml group in

both the water and ethanol vehicles. For both concentrations of carfentanil, flux was higher in the water vehicle than ethanol or hand sanitizer (Table 1).
For the internal standard, caffeine, flux, permeability constant, lag-time, and percent permeation at 6 hours all differed across the vehicles ($p<0.001$ for all endpoints) (Table 2). Flux, K_p, and percent permeation were highest for caffeine in hand sanitizer, intermediate in water, and lowest in ethanol. Lag-time was shortest for caffeine in water and did not differ between ethanol and hand sanitizer.

Data for each run, from individual replicate tissues can be found in Appendix D.

Table 1. EpiDerm (EPI-606-X) dermal permeation assay results. Mean flux, permeability coefficient (Kp), lag-time, and permeation (%) at 6 hours for carfentanil.

		Flux (ng/cm^2/hr)		K_p (10^{-3} cm/hr)		Lag time (hours)		Permeation (%)	
Vehicle - Test Substance	**n**	**mean ± SD**	**CV (%)**	**mean ± SD**	**CV (%)**	**mean ± SD**	**CV (%)**	**mean ± SD**	**CV (%)**
Water									
Carfentanil 5.3 µg/ml	6	15.67 ± 3.37[a]	10.32	3.41 ± 0.9	26.39	0.50 ± 0.08	16.00	3.23 ± 0.71	21.98
Carfentanil 50.6 µg/ml	5	162.13 ± 35.77[x]	11.69	3.83 ± 0.9	23.50	0.48 ± 0.09	18.75	3.97 ± 1.12	28.21
Carfentanil - mean	11	82.24 ± 79.80	97.03	3.60 ± 0.9[a]	25.00	0.50 ± 0.08[a]	16.00	3.57 ± 0.95[a]	26.61
Ethanol									
Carfentanil 5.3 µg/ml	5	0.37 ± 0.34[b]	10.81	0.089 ± 0.05	56.18	1.13 ± 0.83	35.96	0.09 ± 0.06	66.67
Carfentanil 50.6 µg/ml	6	7.00 ± 5.40[y]	26.48	0.24 ± 0.18	75.00	1.62 ± 0.31	40.54	0.21 ± 0.18	85.71
Carfentanil - mean	11	3.99 ± 5.16	129.32	0.17 ± 0.15[b]	88.24	1.40 ± 0.62[b]	44.29	0.15 ± 0.15[b]	100.00
Hand Sanitizer									
Carfentanil - Leader Brand	6	41.47 ± 8.05	40.72	1.28 ± 0.24	18.75	1.00 ± 0.14	14.00	1.36 ± 0.28	20.59
Carfentanil - Purell Brand	6	19.61 ± 2.15	29.93	0.48 ± 0.03	10.77	0.59 ± 0.14	23.73	0.37 ± 0.02	5.41
Carfentanil - mean	12	30.54 ± 12.73[y]	41.68	0.88 ± 0.45[c]	51.14	0.80 ± 0.25[a]	31.25	0.86 ± 0.55[c]	63.95

SD: standard deviation; CV: coefficient of variation; Kp: permeation coefficient; n: number of replicates

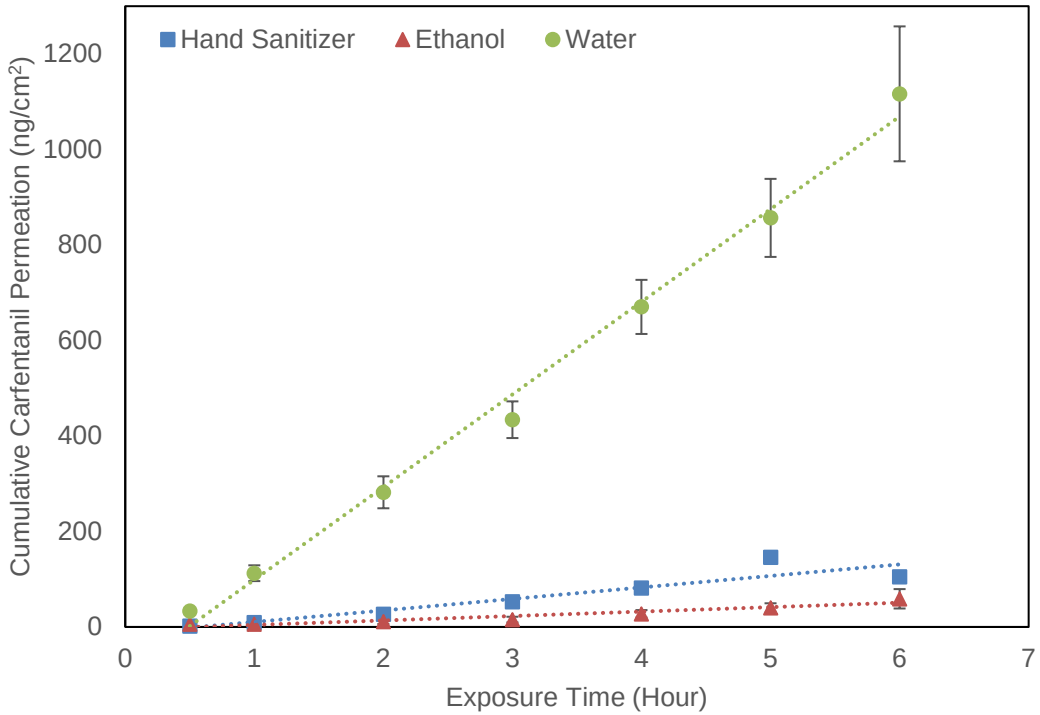

Figure 1. Permeation profile (mean, SEM) for carfentanil (50.6 µg/ml) through reconstructed human epidermis (RhE) at 37±0.1°C administered in three vehicles: water, ethanol, and hand sanitizer.

Table 2. EpiDerm (EPI-606-X) dermal permeation assay results. Mean flux, permeability coefficient (Kp), lag-time, and permeation (%) at 6 hours for caffeine.

		Flux (ng/cm^2/hr)		K_p (10^{-3} cm/hr)		Lag time (hours)		Permeation (%)	
Vehicle - Test Substance	**n**	**mean ± SD**	**CV (%)**	**mean ± SD**	**CV (%)**	**mean ± SD**	**CV (%)**	**mean ± SD**	**CV (%)**
Water									
Caffeine	5	2490.84 ± 57.45[a]	2.31	4.93 ± 1.0[a]	20.28	0.12 ± 0.14[a]	116.67	5.33 ± 1.08[a]	20.26
Ethanol									
Caffeine	6	1183.53 ± 225.25[b]	19.03	3.03 ± 1.0[b]	33.00	0.66 ± 0.15[b]	22.73	3.12 ± 1.14[b]	36.54
Hand Sanitizer									
Caffeine-Purell Brand	6	5847.04 ± 1711.14[c]	29.27	13.92 ± 1.4[c]	10.06	0.48 ± 0.15[b]	31.25	10.93 ± 1.13[c]	10.34

SD: standard deviation; CV: coefficient of variation; Kp: permeation coefficient; n: number of replicates

7 Discussion

The dermal penetration of the pharmaceutical opioids fentanyl and sufentanil has been studied to develop transdermal delivery methods for pain management. Because carfentanil has no approved human-use applications, dermal penetration in humans has not been studied. The growing opioid crisis and potential occupational exposure of public safety professionals highlights the need for these data.

Fentanyl and sufentanil have been reported to readily permeate human skin due to the relatively high lipophilicity of these compounds ($\log K_{ow}$ 2.9 and 3.5, respectively), with permeability of fentanyl being 1.4-fold less than that of sufentanil [20]. The lipophilicity ($\log K_{ow}$ 3.4) and molecular weight (394.5) of carfentanil is similar to sufentanil (387.5), suggesting that the permeability rates may be similar.

The permeation rate for carfentanil in water observed in this study (K_p 3.6 x 10^{-3} cm/hr) was comparable to *in vitro* permeability of fentanyl citrate in water (K_p 1.1 x 10^{-3} cm/hr) through full-thickness human abdominal and breast skin [21]. Although dermal absorption is reported to vary across body sites, likely due to a variety of mechanisms acting synergistically and antagonistically (*i.e.*, density of appendages, corneocytes surface area, intercellular lipid content, and blood flow) [22], permeability of fentanyl and sufentanil was similar across body sites [23]. For most compounds, permeation through RhE is approximately 5 times faster than through heat separated epidermis, potentially due to differences in micromorphology of the RhE including thicker stratum corneum, thinner lamellar layer between corneocytes, and different and varying lipophilicity of the stratum corneum [24, 25]. This suggests that permeation of carfentanil through heat separated human abdominal epidermis would be comparable to that reported for fentanyl and sufentanil (K_p 11.3 x 10^{-3} cm/hr and K_p 15.2 x 10^{-3} cm/hr, respectively) [20].

Permeability of fentanyl and sufentanil salts does not differ between heat separated epidermis and split- and full-thickness human skin [20, 21], but is >30-fold higher through tape-stripped skin, indicating that the stratum corneum is the barrier to penetration for these lipophilic compounds [20]. In contrast, Roy and Flynn (1989) demonstrated a biphasic relationship between lipophilicity and permeability such that a change from stratum corneum to aqueous tissue control of transport occurs when K_{ow} exceeds 40. As was demonstrated for fentanyl and sufentanil salts [23], the permeability of carfentanil salt is likely controlled by transport through aqueous tissue as its K_{ow} exceeds 40. For these compounds, higher lag-times may be expected with the aqueous tissue acting as a reservoir. The short lag-time observed for carfentanil citrate in water (0.5 hr) in the current study was similar to that reported for fentanyl (0.3 hr) and sufentanil (0.2-1.5 hr) salts in heat separated epidermis and split-thickness skin [20]. It is of note that although lag-time is positively correlated with molecular weight, fentanyl, sufentanil, and carfentanil salts have demonstrated permeation lag-times that are about ¼ to ½ what would be expected based on their molecular weights [26]. In studies using full-thickness

skin, although lag-times were not reported, data suggest lag-times on the order of 5 to 10 hours for fentanyl and sufentanil salts [21], indicating that the additional aqueous tissue (i.e., dermis) serves as a reservoir and slows penetration. This reservoir will potentially result in continued systemic absorption after dermal exposure has ended (i.e., after decontamination) and raises concerns about sustained exposure of public safety professionals. Elimination half-lives of 13-22 hours have been reported for fentanyl HCl following use of transdermal delivery systems due to slow release of fentanyl from the skin reservoir [27]. It should be noted, however, that these patients likely had much longer exposures and larger reservoirs than would be expected in occupational exposures.

Although ethanol is used to enhance the dermal penetration of drugs in transdermal delivery systems [28], the permeation rate of carfentanil citrate in ethanol was over an order of magnitude lower than in water (95% lower). At low concentrations, ethanol serves as a penetration enhancer by increasing solubility and causing structural modifications in the stratum corneum including lipid extraction, increased lipid fluidity, changes in hydration, and denaturation of keratin proteins, and formation of pores [29-31]. However, at higher concentrations, the short lamellar structures of the stratum corneum form an aligned structure [29] and the lipid bilayer is stabilized [32]. Thus, the penetration of carfentanil in pure ethanol was likely hindered by structural changes in the stratum corneum. However, the penetration rate of caffeine in ethanol was only reduced by approximately 40% relative to water. In studies with split-thickness human skin, however, caffeine demonstrated an approximately 75% reduction in permeation in ethanol relative to water [33]. These differences may be attributable to the minimal amount of ethanol present in the water vehicle as the carfentanil stock solution was prepared in ethanol as well as differences in composition of the stratum corneum between the RhE and human skin and resultant differences in effects of ethanol. Additionally, differences in the physical properties of carfentanil and caffeine may have contributed to the effects of solvent on permeation rates.

Because compounds are absorbed by passive diffusion through the skin according to the pH partition theory, absorption rates for ionized molecules are approximately 1-2 orders of magnitude lower than the corresponding un-ionized forms [34, 35]. Addition of ethanol to donor solutions has been shown to lower the permeability coefficient of lipophilic compounds (i.e., caffeine) and increase permeability coefficients for hydrophilic compounds [36]. Addition of ethanol to donor solutions has been reported to increase pK_a values, which would shift the ratio of ionized to un-ionized forms at physiological pH [36]. For carfentanil (pK_a=8.05), this increase would cause the ionized to un-ionized ratio to increase and reduce permeability. The effect of ionization state on permeability of both fentanyl and sufentanil demonstrated that permeability increased as dosing solution pH approached the pK_a with a resulting shift from protonated to free-base forms [20]. In contrast, for caffeine (pK_a=14.0) an increase in pK_a is not likely to have appreciably affected the ionization state.

In hand sanitizer, carfentanil permeation rates were intermediate between water and ethanol vehicles and differed about 2-fold between the two brands. Although both hand sanitizer brands contained 70% ethanol, the other ingredients differed. The primary differences include the addition of approximately 10% isopropanol in the Purell brand. Water is the primary inactive ingredient in both brands and comprises approximately 30% of the Purell brand. Percent composition could not be verified for the Leader brand, however, because the formulation contains no isopropanol, water likely comprises a greater proportion of the Leader brand. In both brands the concentration of alcohol is near the inflection point where increasing alcohol concentrations begin to decrease rather than increase permeation rates [37-39]. Thus, the higher alcohol concentration in the Purell brand may have reduced the permeation rate of carfentanil compared to the Leader brand. Additionally, the Leader brand contains two skin penetration enhancing agents (glyceryl caprylate/caprate and benzophenone-4) that may have increased the permeation rate through osmotic force or other action. The Purell brand also contained a buffering agent (aminomethyl propanol) that may have reduced the permeation rate by maintaining a neutral pH thus resulting in a higher proportion of ionized relative to un-ionized carfentanil. These data indicate that the use of alcohol-based hand sanitizers following exposure to carfentanil may not pose the threat previously suspected.

Although this study was designed to determine permeation rates and lag-times rather than risk posed by exposure to specific doses, information about occupational risk can be gleaned from this study. This study was conducted with carfentanil citrate in solution at infinite doses and permeation rates were determined at steady state which will result in overestimation of the potential for incidental or occupational exposure to carfentanil. Because carfentanil has not been studied in humans, information on its potency is lacking. However, carfentanil has been described as being 100 times more potent than fentanyl [7, 9, 16, 40] with a lethal dose of 20 µg [7]. A dose of 1 µg carfentanil may similarly be considered to be analgesic/euphoric. Using the highest flux observed in this study, 162.1 ng/cm^2/hr for carfentanil in water and assuming absorption through both palmar surfaces (0.5% palmar surface area, 17,000 cm^2 total body surface area [41]), it would take approximately 44 minutes for 20 µg of carfentanil to be absorbed. Although the analgesic dose of 1 µg could be absorbed in approximately 2 minutes, again, these calculations are based on steady-state conditions using carfentanil dissolved in water. The rates of absorption at steady-state are higher than in the beginning of exposure and would overestimate absorption in short-term incidental/occupation exposures. This also does not take into account the 30 minute lag-time between application of carfentanil on the skin and occurrence in the receptor fluid, which would allow for removal or decontamination before significant absorption or toxicity has occurred. Additionally, the tablet and powder forms of carfentanil typically encountered would have lower absorption rates due to their lower surface area and need for dissolution prior to absorption. Therefore, based on this dermal absorption data and the limited understanding of carfentanil toxicity in humans, it is unlikely that small skin exposures would result in significant toxicity.

8 Conclusions

Permeation of carfentanil formulated in three vehicles: water, ethanol, and hand sanitizer was measured under infinite-dose conditions in an *in vitro* static diffusion cell system using the EpiDerm™ (EPI-606-X) RhE model. The permeation rate was fastest for carfentanil in water (3.60 x 10^{-3} cm/hr), followed by hand sanitizer (0.88 x 10^{-3} cm/h), and slowest for carfentanil in ethanol (0.17 x 10^{-3} cm/hr). In both ethanol and hand sanitizer, a lag-time between exposure and permeation of approximately 1 hour was observed, while the lag-time in water was 30 minutes. Flux at steady-state was greater at 50.6 µg/ml than at 5.3 µg/ml for both water and ethanol; however, the percent of dose absorbed did not differ between doses for either vehicle. The slight difference in percutaneous permeation of carfentanil observed between the two brands of hand sanitizer evaluated may have been due to differences in the relative proportion of alcohol and skin penetration enhancers in the products. These data indicate that the use of alcohol-based hand sanitizers following exposure to carfentanil may not pose the threat previously suspected. Additionally, small skin exposures may not result in rapid, significant toxicity as previously believed.

9 Point of Contact

Questions pertaining to this report should be referred to Emily May Lent at DSN 584-3980, commercial 410-436-3980, or by e-mail: usarmy.apg.medcom-aphc.mbx.tox-info@mail.mil.

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Appendix A

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Appendix B

Quality Assurance Statement

Appendix B

QUALITY ASSURANCE STATEMENT

For: Toxicology Study No. S.0055513-18, Protocol No. No. 99-IV18-05-01b, *In Vitro* Dermal Absorption of Carfentanil, July - September 2018, the following Good Laboratory Practice Standard Inspections were conducted:

Study Specific Critical Phase Inspected/Audited	Date Inspected /Audited	Date Reported to Management/SD
Type Protocol Good Laboratory Practice Standard Review	03/18/2018	03/18/2018
Study Raw Data Good Laboratory Practice Standard Review	01/13/2019	01/14/2019
Final Study Good Laboratory Practice Standard Report Review	01/13/2019	01/14/2019

Note 1: *All findings were made known to the Study Director and the Program Manager at the time of the audit/inspection. If there were no findings during the inspection, the inspection was reported to Management and the Study Director on the date shown in the table.*

Note 2: *This report has been audited by the Quality Assurance Unit (QSARC), and is considered to be an accurate account of the data generated and of the procedures conducted.*

Note 3: *In addition to the study specific critical phase inspections listed here, general facility and process based inspection not specifically related to this study are done monthly or annually in accordance with QA Standard Operating Procedure.*

Michael P. Kefauver
Good Laboratory Practice Standards
Quality Assurance Specialist, QSARC

28 FEB 2019
Date

Appendix C

Archives and Study Personnel

C-1 Archives

All raw data, documentation, records, protocol, and a copy of the final report generated as a result of this study will be archived in room 1026, building E-2100, APHC, for a minimum of five (5) years following submission of the final report to the Sponsor. If the report is used to support a regulatory action, it shall, along with all supporting data, be retained indefinitely.

Some ancillary records pertaining to this study, such as instrument maintenance logs will not be archived until those logbooks have been completed. Once complete they will be archived in room 1026, building E-2100, APHC.

C-2 Personnel

Management: Dr. Mark S. Johnson, Director, Toxicology; MAJ Jarod Hanson, Executive Officer, Toxicology; Mr. Arthur J. O'Neill, Chief, Toxicity Evaluation Division (TEV); Dr. Michael J. Quinn, Chief, Health Effects Research Division (HEF).

Study Director: Dr. Emily May Lent, Toxicologist, TEV.

Analytical Chemistry: Kathleen J. Maistros, Chemist, MRICD; Jonathan M. Oyler, Chemist, MRICD.

Quality Assurance: Michael P. Kefauver, Quality Assurance Specialist, Quality Systems and Regulatory Compliance Office.

Archivist: Lee C.B. Crouse, Biologist, TEV.

Appendix D

Dermal Absorption Data

CF Epidermal Dosing Results Summary

Analyst: Kathleen Maistros
Instrument: Shimadzu Nexera UPLC/Sciex 4000 Qtrap
Column: Phenomenex Kinetex 2.1 x 100 mm x 1.7 µm F5
Method: Reversed Phase/Positive Mode

Solvent	H_2O							
Dose	**5.32 µg/mL**							
Sample Collection Time	**Sample Name**	**Measured Conc. (ng/mL)**	**Amnt in cell (ng)**	**sampled amnt removed**	**Amnt incl sample removal (ng)**	**Permeation (ng/cm2)**	**Flux (ng/cm2/hr)**	**% Absorption**
0.5	SkinPerm_Carf in H2O_0.5h_1	0.14	1.67	0.06	1.67	0.93	1.85	0.03
	SkinPerm_Carf in H2O_0.5h_2	0.45	5.39	0.18	5.39	2.99	5.99	0.10
	SkinPerm_Carf in H2O_0.5h_3	0.13	1.58	0.05	1.58	0.88	1.76	0.03
	SkinPerm_Carf in H2O_0.5h_4	0.63	7.54	0.25	7.54	4.19	8.37	0.14
	SkinPerm_Carf in H2O_0.5h_5	0.41	4.96	0.17	4.96	2.75	5.51	0.09
	SkinPerm_Carf in H2O_0.5h_6	0.38	4.52	0.15	4.52	2.51	5.03	0.09
Mean		**0.36**	**4.28**	**0.14**	**4.28**	**2.38**	**4.75**	**0.08**
STDEV		**0.19**	**2.30**	**0.08**	**2.30**	**1.28**	**2.55**	**0.04**
%CV		**53.77**	**53.77**	**53.77**	**53.77**	**53.77**	**53.77**	**53.77**
1	SkinPerm_Carf in H2O_1h_1	0.84	10.12	0.42	10.17	5.65	5.65	0.19
	SkinPerm_Carf in H2O_1h_2	1.51	18.17	0.76	18.35	10.19	10.19	0.34
	SkinPerm_Carf in H2O_1h_3	0.70	8.35	0.35	8.40	4.67	4.67	0.16
	SkinPerm_Carf in H2O_1h_4	1.85	22.18	0.92	22.43	12.46	12.46	0.42
	SkinPerm_Carf in H2O_1h_5	1.06	12.71	0.53	12.87	7.15	7.15	0.24
	SkinPerm_Carf in H2O_1h_6	1.24	14.89	0.62	15.04	8.36	8.36	0.28
Mean		**1.20**	**14.40**	**0.60**	**14.54**	**8.08**	**8.08**	**0.27**
STDEV		**0.43**	**5.15**	**0.21**	**5.22**	**2.90**	**2.90**	**0.10**
%CV		**35.77**	**35.77**	**35.77**	**35.92**	**35.92**	**35.92**	**35.92**

2	SkinPerm_Carf in H2O_2h_1	12.92*						
	SkinPerm_Carf in H2O_2h_2	4.24	50.88	2.12	51.64	28.69	14.34	0.97
	SkinPerm_Carf in H2O_2h_3	2.77	33.24	1.39	33.59	18.66	9.33	0.63
	SkinPerm_Carf in H2O_2h_4	5.57	66.82	2.78	67.74	37.63	18.82	1.27
	SkinPerm_Carf in H2O_2h_5	3.84	46.07	1.92	46.60	25.89	12.94	0.88
	SkinPerm_Carf in H2O_2h_6	3.90	46.84	1.95	47.46	26.36	13.18	0.89
Mean		**4.06**	**48.77**	**2.03**	**49.40**	**27.45**	**13.72**	**0.93**
STDEV		**1.01**	**12.07**	**0.50**	**12.28**	**6.82**	**3.41**	**0.23**
%CV		**24.74**	**24.74**	**24.74**	**24.85**	**24.85**	**24.85**	**24.85**
3	SkinPerm_Carf in H2O_3h_1	5.63	67.58	2.82	67.58	37.55	12.52	1.27
	SkinPerm_Carf in H2O_3h_2	6.80	81.60	3.40	83.72	46.51	15.50	1.57
	SkinPerm_Carf in H2O_3h_3	4.49	53.89	2.25	55.28	30.71	10.24	1.04
	SkinPerm_Carf in H2O_3h_4	8.71	104.47	4.35	107.26	59.59	19.86	2.02
	SkinPerm_Carf in H2O_3h_5	5.96	71.53	2.98	73.45	40.81	13.60	1.38
	SkinPerm_Carf in H2O_3h_6	6.73	80.78	3.37	82.74	45.96	15.32	1.56
Mean		**6.39**	**76.64**	**3.19**	**78.34**	**43.52**	**14.51**	**1.47**
STDEV		**1.42**	**16.98**	**0.71**	**17.64**	**9.80**	**3.27**	**0.33**
%CV		**22.16**	**22.16**	**22.16**	**22.52**	**22.52**	**22.52**	**22.52**
4	SkinPerm_Carf in H2O_4h_1	7.40	88.79	3.70	91.60	50.89	12.72	1.72
	SkinPerm_Carf in H2O_4h_2	9.03	108.38	4.52	111.78	62.10	15.53	2.10
	SkinPerm_Carf in H2O_4h_3	7.54	90.44	3.77	92.69	51.49	12.87	1.74
	SkinPerm_Carf in H2O_4h_4	12.28	147.37	6.14	151.73	84.29	21.07	2.85
	SkinPerm_Carf in H2O_4h_5	9.49	113.84	4.74	116.82	64.90	16.23	2.20
	SkinPerm_Carf in H2O_4h_6	12.14	145.73	6.07	149.09	82.83	20.71	2.80
Mean		**9.65**	**115.76**	**4.82**	**118.95**	**66.09**	**16.52**	**2.24**
STDEV		**2.15**	**25.78**	**1.07**	**26.37**	**14.65**	**3.66**	**0.50**
%CV		**22.27**	**22.27**	**22.27**	**22.17**	**22.17**	**22.17**	**22.17**
5	SkinPerm_Carf in H2O_5h_1	9.52	114.19	4.76	117.89	65.50	13.10	2.22
	SkinPerm_Carf in H2O_5h_2	13.38	160.56	6.69	165.08	91.71	18.34	3.10
	SkinPerm_Carf in H2O_5h_3	8.45	101.39	4.22	105.16	58.42	11.68	1.98
	SkinPerm_Carf in H2O_5h_4	16.18	194.10	8.09	200.24	111.24	22.25	3.76
	SkinPerm_Carf in H2O_5h_5	14.37	172.44	7.19	177.18	98.44	19.69	3.33

	SkinPerm_Carf in H2O_5h_6	15.85	190.25	7.93	196.32	109.07	21.81	3.69
Mean		**12.96**	**155.49**	**6.48**	**160.31**	**89.06**	**17.81**	**3.01**
STDEV		**3.26**	**39.10**	**1.63**	**40.10**	**22.28**	**4.46**	**0.75**
%CV		**25.15**	**25.15**	**25.15**	**25.01**	**25.01**	**25.01**	**25.01**
6	SkinPerm_Carf in H2O_6h_1	11.10	133.24	5.55	137.99	76.66	12.78	2.59
	SkinPerm_Carf in H2O_6h_2	15.23	182.77	7.62	189.46	105.26	17.54	3.56
	SkinPerm_Carf in H2O_6h_3	10.31	123.76	5.16	127.98	71.10	11.85	2.41
	SkinPerm_Carf in H2O_6h_4	18.71	224.52	9.36	232.61	129.23	21.54	4.37
	SkinPerm_Carf in H2O_6h_5	14.26	171.10	7.13	178.28	99.05	16.51	3.35
	SkinPerm_Carf in H2O_6h_6	13.13	157.51	6.56	165.44	91.91	15.32	3.11
Mean		**13.79**	**165.48**	**6.90**	**171.96**	**95.53**	**15.92**	**3.23**
STDEV		**3.04**	**36.50**	**1.52**	**37.83**	**21.02**	**3.50**	**0.71**
%CV		**22.06**	**22.06**	**22.06**	**22.00**	**22.00**	**22.00**	**22.00**

*outlier removed from analysis

CF Epidermal Dosing
Results Summary
Analyst: Kathleen Maistros
Instrument: Shimadzu Nexera UPLC/Sciex 4000 Qtrap
Column: Phenomenex Kinetex 2.1 x 100 mm x 1.7 µm F5
Method: Reversed Phase/Positive Mode

Solvent	***EtOH***							
Dose	**5.32 µg/mL**							
Sample Collection Time	**Sample Name**	**Measured Conc. (ng/mL)**	**Amnt in cell (ng)**	**sampled amnt removed**	**Amnt incl sample removal (ng)**	**Permeation (ng/cm2)**	**Flux (ng/cm2/hr)**	**% Absorption**
0.5	SkinPerm_Carf in EtOH_0.5h_1	BDL						
	SkinPerm_Carf in EtOH_0.5h_2	BDL						
	SkinPerm_Carf in EtOH_0.5h_3	BDL						
	SkinPerm_Carf in EtOH_0.5h_4	BDL						
	SkinPerm_Carf in EtOH_0.5h_5	BDL						
	SkinPerm_Carf in EtOH_0.5h_6	BDL						
Mean		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
STDEV		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
%CV		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
1	SkinPerm_Carf in EtOH_1h_1	BDL						
	SkinPerm_Carf in EtOH_1h_2	BDL						

	SkinPerm_Carf in EtOH_1h_3	0.34*						
	SkinPerm_Carf in EtOH_1h_4	BDL						
	SkinPerm_Carf in EtOH_1h_5	BDL						
	SkinPerm_Carf in EtOH_1h_6	BDL						
Mean		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
STDEV		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
%CV		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
2	SkinPerm_Carf in EtOH_2h_1	0.06	0.70	0.03	0.70	0.39	0.19	0.01
	SkinPerm_Carf in EtOH_2h_2	0.06	0.70	0.03	0.70	0.39	0.19	0.01
	SkinPerm_Carf in EtOH_2h_3	1.896*						
	SkinPerm_Carf in EtOH_2h_4	0.08	0.95	0.04	0.95	0.53	0.26	0.02
	SkinPerm_Carf in EtOH_2h_5**	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	SkinPerm_Carf in EtOH_2h_6	0.31	3.76	0.16	3.76	2.09	1.04	0.07
Mean		**0.10**	**1.22**	**0.05**	**1.22**	**0.68**	**0.34**	**0.02**
STDEV		**0.12**	**1.46**	**0.06**	**1.46**	**0.81**	**0.41**	**0.03**
%CV		**119.87**	**119.87**	**119.87**	**119.87**	**119.87**	**119.87**	**119.87**
3	SkinPerm_Carf in EtOH_3h_1	0.12	1.42	0.06	1.45	0.80	0.27	0.03
	SkinPerm_Carf in EtOH_3h_2	0.08	0.91	0.04	0.94	0.52	0.17	0.02
	SkinPerm_Carf in EtOH_3h_3	2.048*						
	SkinPerm_Carf in EtOH_3h_4	0.09	1.03	0.04	1.07	0.60	0.20	0.02
	SkinPerm_Carf in EtOH_3h_5**	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	SkinPerm_Carf in EtOH_3h_6	0.42	5.00	0.21	5.16	2.87	0.96	0.10
Mean		**0.14**	**1.67**	**0.07**	**1.72**	**0.96**	**0.32**	**0.03**

STDEV		**0.16**	**1.93**	**0.08**	**1.99**	**1.11**	**0.37**	**0.04**
%CV		**115.57**	**115.57**	**115.57**	**115.67**	**115.67**	**115.67**	**115.67**
4	SkinPerm_ Carf in EtOH_4h_1	0.15	1.85	0.08	1.91	1.06	0.26	0.04
	SkinPerm_ Carf in EtOH_4h_2	0.17	2.00	0.08	2.04	1.13	0.28	0.04
	SkinPerm_ Carf in EtOH_4h_3	4.5*						
	SkinPerm_ Carf in EtOH_4h_4	0.19	2.22	0.09	2.26	1.26	0.31	0.04
	SkinPerm_ Carf in EtOH_4h_5	0.08	0.94	0.04	0.94	0.52	0.13	0.02
	SkinPerm_ Carf in EtOH_4h_6	0.52	6.25	0.26	6.46	3.59	0.90	0.12
Mean		**0.22**	**2.65**	**0.11**	**2.72**	**1.51**	**0.38**	**0.05**
STDEV		**0.17**	**2.07**	**0.09**	**2.15**	**1.19**	**0.30**	**0.04**
%CV		**78.10**	**78.10**	**78.10**	**79.02**	**79.02**	**79.02**	**79.02**
5	SkinPerm_ Carf in EtOH_5h_1	0.19	2.27	0.09	2.35	1.30	0.26	0.04
	SkinPerm_ Carf in EtOH_5h_2	0.19	2.26	0.09	2.34	1.30	0.26	0.04
	SkinPerm_ Carf in EtOH_5h_3	4.472*						
	SkinPerm_ Carf in EtOH_5h_4	0.27	3.20	0.13	3.30	1.83	0.37	0.06
	SkinPerm_ Carf in EtOH_5h_5	0.09	1.02	0.04	1.06	0.59	0.12	0.02
	SkinPerm_ Carf in EtOH_5h_6	0.68	8.12	0.34	8.38	4.66	0.93	0.16
Mean		**0.28**	**3.37**	**0.14**	**3.48**	**1.94**	**0.39**	**0.07**
STDEV		**0.23**	**2.77**	**0.12**	**2.85**	**1.58**	**0.32**	**0.05**
%CV		**81.97**	**81.97**	**81.97**	**81.84**	**81.84**	**81.84**	**81.84**
6	SkinPerm_ Carf in EtOH_6h_1	0.29	3.53	0.15	3.62	2.01	0.34	0.07
	SkinPerm_ Carf in EtOH_6h_2	0.29	3.48	0.15	3.57	1.99	0.33	0.07
	SkinPerm_ Carf in EtOH_6h_3	4.471*						
	SkinPerm_ Carf in EtOH_6h_4	0.27	3.20	0.13	3.34	1.85	0.31	0.06

	SkinPerm_ Carf in EtOH_6h_5	0.15	1.75	0.07	1.79	1.00	0.17	0.03
	SkinPerm_ Carf in EtOH_6h_6	0.85	10.25	0.43	10.59	5.88	0.98	0.20
Mean		**0.37**	**4.44**	**0.19**	**4.58**	**2.55**	**0.42**	**0.09**
STDEV		**0.28**	**3.33**	**0.14**	**3.44**	**1.91**	**0.32**	**0.06**
%CV		**74.86**	**74.86**	**74.86**	**75.04**	**75.04**	**75.04**	**75.04**
23	SkinPerm_ Carf in EtOH from 7/17_23h_1	0.29	3.53	0.15	3.68	2.04	0.09	0.07
	SkinPerm_ Carf in EtOH from 7/17_23h_2	0.29	3.48	0.15	3.63	2.01	0.09	0.07
	SkinPerm_ Carf in EtOH from 7/17_23h_3	4.471*						
	SkinPerm_ Carf in EtOH from 7/17_23h_4	0.27	3.20	0.13	3.34	1.85	0.08	0.06
	SkinPerm_ Carf in EtOH from 7/17_23h_5	0.15	1.75	0.07	1.83	1.01	0.04	0.03
	SkinPerm_ Carf in EtOH from 7/17_23h_6	0.85	10.25	0.43	10.68	5.93	0.26	0.20
Mean		**0.37**	**4.44**	**0.19**	**4.63**	**2.57**	**0.11**	**0.09**
STDEV		**0.28**	**3.33**	**0.14**	**3.46**	**1.92**	**0.08**	**0.07**
%CV		**74.86**	**74.86**	**74.86**	**74.86**	**74.86**	**74.86**	**74.86**
24	SkinPerm_ Carf in EtOH from 7/17_24h_1	0.29	3.53	0.15	3.68	2.04	0.09	0.07
	SkinPerm_ Carf in EtOH from 7/17_24h_2	0.29	3.53	0.15	3.67	2.04	0.09	0.07
	SkinPerm_ Carf in EtOH from 7/17_24h_3	0.294*						
	SkinPerm_ Carf in EtOH from 7/17_24h_4	0.29	3.53	0.15	3.66	2.03	0.09	0.07
	SkinPerm_ Carf in EtOH from 7/17_24h_5	0.29	3.53	0.15	3.60	2.00	0.09	0.07

	SkinPerm_ Carf in EtOH from 7/17_24h_6	0.29	3.53	0.15	3.96	2.20	0.10	0.07
Mean		**0.29**	**3.53**	**0.15**	**3.71**	**2.06**	**0.09**	**0.07**
STDEV		**0.00**	**0.00**	**0.00**	**0.14**	**0.08**	**0.00**	**0.00**
%CV		**0.00**	**0.00**	**0.00**	**3.73**	**3.73**	**3.73**	**3.73**

BDL: below detection limit; *outlier removed from analysis

CF Epidermal Dosing
Results Summary
Analyst: Kathleen Maistros
Instrument: Shimadzu Nexera UPLC/Sciex 4000 Qtrap
Column: Phenomenex Kinetex 2.1 x 100 mm x 1.7 µm F5
Method: Reversed Phase/Positive Mode

Solvent	***Leader Brand Hand Sanitizer***							
Dose	**50.60 µg/mL**							
Sample Collection Time	**Sample Name**	**Measured Conc. (ng/mL)**	**Amnt in cell (ng)**	**sampled amnt removed**	**Amnt incl sample removal (ng)**	**Permeation (ng/cm2)**	**Flux (ng/cm2/hr)**	**% Absorption**
0.5	SkinPerm_Carf in Hand Sanitiz from 7/24_0.5h_1	0.41	4.86	0.20	4.86	2.70	5.40	0.01
	SkinPerm_Carf in Hand Sanitiz from 7/24_0.5h_2	0.51	6.16	0.26	6.16	3.42	6.84	0.01
	SkinPerm_Carf in Hand Sanitiz from 7/24_0.5h_3	0.68	8.21	0.34	8.21	4.56	9.12	0.02
	SkinPerm_Carf in Hand Sanitiz from 7/24_0.5h_4	0.39	4.63	0.19	4.63	2.57	5.15	0.01
	SkinPerm_Carf in Hand Sanitiz from 7/24_0.5h_5	0.43	5.15	0.21	5.15	2.86	5.72	0.01
	SkinPerm_Carf in Hand Sanitiz from 7/24_0.5h_6	0.59	7.03	0.29	7.03	3.91	7.81	0.01
Mean		**0.50**	**6.01**	**0.25**	**6.01**	**3.34**	**6.67**	**0.01**
STDEV		**0.12**	**1.40**	**0.06**	**1.40**	**0.78**	**1.56**	**0.00**
%CV		**23.38**	**23.38**	**23.38**	**23.38**	**23.38**	**23.38**	**23.38**
1	SkinPerm_Carf in Hand Sanitiz from 7/24_1h_1	1.62	19.48	0.81	19.68	10.93	10.93	0.04
	SkinPerm_Carf in Hand Sanitiz	1.91	22.97	0.96	23.22	12.90	12.90	0.05

	from 7/24_1h_2 SkinPerm_Carf in Hand Sanitiz from 7/24_1h_3 SkinPerm_Carf in Hand Sanitiz from 7/24_1h_4 SkinPerm_Carf in Hand Sanitiz from 7/24_1h_5 SkinPerm_Carf in Hand Sanitiz from 7/24_1h_6	3.06	36.76	1.53	37.10	20.61	20.61	0.07
		1.72	20.63	0.86	20.82	11.57	11.57	0.04
		1.27	15.23	0.63	15.44	8.58	8.58	0.03
		1.64	19.73	0.82	20.02	11.12	11.12	0.04
Mean		**1.87**	**22.46**	**0.94**	**22.71**	**12.62**	**12.62**	**0.04**
STDEV		**0.62**	**7.44**	**0.31**	**7.48**	**4.16**	**4.16**	**0.01**
%CV		**33.11**	**33.11**	**33.11**	**32.95**	**32.95**	**32.95**	**32.95**
2	SkinPerm_Carf in Hand Sanitiz from 7/24_2h_1 SkinPerm_Carf in Hand Sanitiz from 7/24_2h_2 SkinPerm_Carf in Hand Sanitiz from 7/24_2h_3 SkinPerm_Carf in Hand Sanitiz from 7/24_2h_4 SkinPerm_Carf in Hand Sanitiz from 7/24_2h_5 SkinPerm_Carf in Hand Sanitiz from 7/24_2h_6	5.80	69.61	2.90	70.42	39.12	19.56	0.14
		5.99	71.93	3.00	72.89	40.49	20.25	0.14
		10.37*						
		5.63	67.61	2.82	68.47	38.04	19.02	0.14
		6.73	80.78	3.37	81.42	45.23	22.62	0.16
		6.65	79.76	3.32	80.59	44.77	22.39	0.16
Mean		**6.16**	**73.94**	**3.08**	**74.76**	**41.53**	**20.77**	**0.15**
STDEV		**0.50**	**5.99**	**0.25**	**5.92**	**3.29**	**1.64**	**0.01**
%CV		**8.10**	**8.10**	**8.10**	**7.92**	**7.92**	**7.92**	**7.92**
3	SkinPerm_Carf in Hand Sanitiz from 7/24_3h_1 SkinPerm_Carf in Hand Sanitiz from 7/24_3h_2	13.00	155.95	6.50	158.85	88.25	29.42	0.31
		11.02	132.28	5.51	135.27	75.15	25.05	0.27

	SkinPerm_Carf in Hand Sanitiz from 7/24_3h_3	18.14	217.67	9.07	217.67	120.93	40.31	0.43
	SkinPerm_Carf in Hand Sanitiz from 7/24_3h_4	11.45	137.39	5.72	140.21	77.89	25.96	0.28
	SkinPerm_Carf in Hand Sanitiz from 7/24_3h_5	11.75	141.04	5.88	144.40	80.22	26.74	0.29
	SkinPerm_Carf in Hand Sanitiz from 7/24_3h_6	15.62	187.38	7.81	190.70	105.95	35.32	0.38
Mean		**13.50**	**161.95**	**6.75**	**164.52**	**91.40**	**30.47**	**0.33**
STDEV		**2.82**	**33.79**	**1.41**	**32.84**	**18.25**	**6.08**	**0.06**
%CV		**20.86**	**20.86**	**20.86**	**19.96**	**19.96**	**19.96**	**19.96**
4	SkinPerm_Carf in Hand Sanitiz from 7/24_4h_1	22.81	273.67	11.40	280.17	155.65	38.91	0.55
	SkinPerm_Carf in Hand Sanitiz from 7/24_4h_2	18.28	219.34	9.14	224.85	124.92	31.23	0.44
	SkinPerm_Carf in Hand Sanitiz from 7/24_4h_3	28.56	342.66	14.28	351.73	195.41	48.85	0.70
	SkinPerm_Carf in Hand Sanitiz from 7/24_4h_4	22.89	274.69	11.45	280.42	155.79	38.95	0.55
	SkinPerm_Carf in Hand Sanitiz from 7/24_4h_5	19.40	232.82	9.70	238.70	132.61	33.15	0.47
	SkinPerm_Carf in Hand Sanitiz from 7/24_4h_6	24.99	299.88	12.50	307.69	170.94	42.73	0.61
Mean		**22.82**	**273.84**	**11.41**	**280.59**	**155.88**	**38.97**	**0.55**
STDEV		**3.74**	**44.87**	**1.87**	**46.17**	**25.65**	**6.41**	**0.09**
%CV		**16.39**	**16.39**	**16.39**	**16.45**	**16.45**	**16.45**	**16.45**
5	SkinPerm_Carf in Hand Sanitiz from 7/24_5h_1	41.60	499.19	20.80	510.59	283.66	56.73	1.01
	SkinPerm_Carf in Hand Sanitiz from 7/24_5h_2	25.73	308.74	12.86	317.88	176.60	35.32	0.63
	SkinPerm_Carf in Hand Sanitiz	40.44	485.29	20.22	499.57	277.54	55.51	0.99

	from 7/24_5h_3 SkinPerm_Carf in Hand Sanitiz							
	from 7/24_5h_4 SkinPerm_Carf in Hand Sanitiz	29.48	353.75	14.74	365.19	202.89	40.58	0.72
	from 7/24_5h_5 SkinPerm_Carf in Hand Sanitiz	34.50	414.01	17.25	423.71	235.40	47.08	0.84
	from 7/24_5h_6	38.95	467.41	19.48	479.91	266.62	53.32	0.95
Mean		**35.12**	**421.40**	**17.56**	**432.81**	**240.45**	**48.09**	**0.86**
STDEV		**6.41**	**76.91**	**3.20**	**78.22**	**43.45**	**8.69**	**0.15**
%CV		**18.25**	**18.25**	**18.25**	**18.07**	**18.07**	**18.07**	**18.07**
6	SkinPerm_Carf in Hand Sanitiz from 7/24_6h_1 SkinPerm_Carf in Hand Sanitiz	59.04	708.46	29.52	729.26	405.14	67.52	1.44
	from 7/24_6h_2 SkinPerm_Carf in Hand Sanitiz	37.55	450.56	18.77	463.43	257.46	42.91	0.92
	from 7/24_6h_3 SkinPerm_Carf in Hand Sanitiz	62.42	748.98	31.21	769.20	427.33	71.22	1.52
	from 7/24_6h_4 SkinPerm_Carf in Hand Sanitiz	45.48	545.75	22.74	560.49	311.38	51.90	1.11
	from 7/24_6h_5 SkinPerm_Carf in Hand Sanitiz	64.78	777.34	32.39	794.59	441.44	73.57	1.57
	from 7/24_6h_6	65.18	782.10	32.59	801.58	445.32	74.22	1.58
Mean		**55.74**	**668.86**	**27.87**	**686.42**	**381.35**	**63.56**	**1.36**
STDEV		**11.51**	**138.12**	**5.76**	**140.88**	**78.27**	**13.04**	**0.28**
%CV		**20.65**	**20.65**	**20.65**	**20.52**	**20.52**	**20.52**	**20.52**
23	SkinPerm_Carf in Hand Sanitiz from 7/25_23h_1 SkinPerm_Carf in Hand Sanitiz	218.49	2621.88	109.25	2651.40	1473.00	64.04	5.24
	from 7/25_23h_2 SkinPerm_Carf in Hand Sanitiz	552.32	6627.85	276.16	6646.63	3692.57	160.55	13.14
	from 7/25_23h_3	302.19	3626.33	151.10	3657.54	2031.96	88.35	7.23

	SkinPerm_Carf in Hand Sanitiz from 7/25_23h_4	393.44	4721.30	196.72	4744.04	2635.58	114.59	9.38
	SkinPerm_Carf in Hand Sanitiz from 7/25_23h_5	591.83	7101.95	295.91	7134.34	3963.52	172.33	14.10
	SkinPerm_Carf in Hand Sanitiz from 7/25_23h_6	362.34	4348.09	181.17	4380.68	2433.71	105.81	8.66
Mean		**403.44**	**4841.23**	**201.72**	**4869.10**	**2705.06**	**117.61**	**9.62**
STDEV		**144.15**	**1729.85**	**72.08**	**1728.07**	**960.04**	**41.74**	**3.42**
%CV		**35.73**	**35.73**	**35.73**	**35.49**	**35.49**	**35.49**	**35.49**
24	SkinPerm_Carf in Hand Sanitiz from 7/25_24h_1	212.43	2549.15	106.21	2658.39	1476.89	64.21	5.25
	SkinPerm_Carf in Hand Sanitiz from 7/25_24h_2	545.64	6547.70	272.82	6823.86	3791.04	164.83	13.49
	SkinPerm_Carf in Hand Sanitiz from 7/25_24h_3	303.36	3640.33	151.68	3791.43	2106.35	91.58	7.49
	SkinPerm_Carf in Hand Sanitiz from 7/25_24h_4	521.59	6259.10	260.80	6455.83	3586.57	155.94	12.76
	SkinPerm_Carf in Hand Sanitiz from 7/25_24h_5	585.59	7027.02	292.79	7322.93	4068.30	176.88	14.47
	SkinPerm_Carf in Hand Sanitiz from 7/25_24h_6	355.30	4263.60	177.65	4444.77	2469.32	107.36	8.78
Mean		**420.65**	**5047.82**	**210.33**	**5249.54**	**2916.41**	**126.80**	**10.37**
STDEV		**151.26**	**1815.13**	**75.63**	**1882.57**	**1045.87**	**45.47**	**3.72**
%CV		**35.96**	**35.96**	**35.96**	**35.86**	**35.86**	**35.86**	**35.86**

*outlier removed from analysis

CF Epidermal Dosing
Results Summary
Analyst: Kathleen Maistros
Instrument: Shimadzu Nexera UPLC/Sciex 4000 Qtrap
Column: Phenomenex Kinetex 2.1 x 100 mm x 1.7 µm F5
Method: Reversed Phase/Positive Mode

Date: 20-12 August 2018

Solvent	***H_2O***
Dose	**50.6 µg/mL**

Sample Collection Time	Sample Name	Measured Conc. (ng/mL)	Amnt in cell (ng)	sampled amnt removed	Amnt incl sample removal (ng)	Permeation (ng/cm2)	Flux (ng/cm2/hr)	% Absorption
0.5	SkinPerm_Carf in H2O_0.5h_1	3.65	43.74	1.46	43.74	24.30	48.60	0.09
	SkinPerm_Carf in H2O_0.5h_2	3.78	45.32	1.51	45.32	25.18	50.36	0.09
	SkinPerm_Carf in H2O_0.5h_3	2.97	35.69	1.19	35.69	19.83	39.65	0.07
	SkinPerm_Carf in H2O_0.5h_4	NA	NA	NA	NA	NA	NA	NA
	SkinPerm_Carf in H2O_0.5h_5	7.63	91.58	3.05	91.58	50.88	101.76	0.18
	SkinPerm_Carf in H2O_0.5h_6	6.88	82.52	2.75	82.52	45.85	91.69	0.16
Mean		**4.98**	**59.77**	**1.99**	**59.77**	**33.21**	**66.41**	**0.12**
STDEV		**2.11**	**25.37**	**0.85**	**25.37**	**14.10**	**28.19**	**0.05**
%CV		**42.45**	**42.45**	**42.45**	**42.45**	**42.45**	**42.45**	**42.45**
1	SkinPerm_Carf in H2O_1h_1	12.24	146.93	6.12	148.39	82.44	82.44	0.29
	SkinPerm_Carf in H2O_1h_2	10.89	130.72	5.45	132.23	73.46	73.46	0.26
	SkinPerm_Carf in H2O_1h_3	16.62	199.49	8.31	200.68	111.49	111.49	0.40
	SkinPerm_Carf in H2O_1h_4	NA	NA	NA	NA	NA	NA	NA
	SkinPerm_Carf in H2O_1h_5	19.40	232.84	9.70	235.89	131.05	131.05	0.47
	SkinPerm_Carf in H2O_1h_6	24.43	293.12	12.21	295.87	164.37	164.37	0.58
Mean		**16.72**	**200.62**	**8.36**	**202.61**	**112.56**	**112.56**	**0.40**
STDEV		**5.49**	**65.89**	**2.75**	**66.53**	**36.96**	**36.96**	**0.13**
%CV		**32.84**	**32.84**	**32.84**	**32.84**	**32.84**	**32.84**	**32.84**
2	SkinPerm_Carf in H2O_2h_1	32.90	394.78	16.45	400.90	222.72	111.36	0.79
	SkinPerm_Carf in H2O_2h_2	29.69	356.29	14.85	361.74	200.97	100.48	0.71

	SkinPerm_Carf in H2O_2h_3	41.31	495.71	20.65	504.02	280.01	140.01	1.00
	SkinPerm_Carf in H2O_2h_4	NA	NA	NA	NA	NA	NA	NA
	SkinPerm_Carf in H2O_2h_5	57.14	685.73	28.57	695.43	386.35	193.17	1.37
	SkinPerm_Carf in H2O_2h_6	46.98	563.77	23.49	575.99	319.99	160.00	1.14
Mean		**41.60**	**499.26**	**20.80**	**507.61**	**282.01**	**141.00**	**1.00**
STDEV		**11.05**	**132.57**	**5.52**	**134.75**	**74.86**	**37.43**	**0.27**
%CV		**26.55**	**26.55**	**26.55**	**26.55**	**26.55**	**26.55**	**26.55**
3	SkinPerm_Carf in H2O_3h_1	50.11	601.27	25.05	617.72	343.18	114.39	1.22
	SkinPerm_Carf in H2O_3h_2	52.29	627.49	26.15	642.34	356.85	118.95	1.27
	SkinPerm_Carf in H2O_3h_3	62.38	748.56	31.19	769.21	427.34	142.45	1.52
	SkinPerm_Carf in H2O_3h_4	NA	NA	NA	NA	NA	NA	NA
	SkinPerm_Carf in H2O_3h_5	76.24	914.88	38.12	943.45	524.14	174.71	1.86
	SkinPerm_Carf in H2O_3h_6	75.82	909.78	37.91	933.27	518.48	172.83	1.84
Mean		**63.37**	**760.40**	**31.68**	**781.20**	**434.00**	**144.67**	**1.54**
STDEV		**12.45**	**149.42**	**6.23**	**154.60**	**85.89**	**28.63**	**0.31**
%CV		**19.65**	**19.65**	**19.65**	**19.79**	**19.79**	**19.79**	**19.79**
4	SkinPerm_Carf in H2O_4h_1	89.81	1077.76	44.91	1102.81	612.67	153.17	2.18
	SkinPerm_Carf in H2O_4h_2	70.27	843.24	35.14	869.39	482.99	120.75	1.72
	SkinPerm_Carf in H2O_4h_3	103.42	1241.04	51.71	1272.23	706.79	176.70	2.51
	SkinPerm_Carf in H2O_4h_4	NA	NA	NA	NA	NA	NA	NA
	SkinPerm_Carf in H2O_4h_5	107.36	1288.34	53.68	1326.46	736.92	184.23	2.62
	SkinPerm_Carf in H2O_4h_6	118.61	1423.26	59.30	1461.17	811.76	202.94	2.89
Mean		**97.89**	**1174.73**	**48.95**	**1206.41**	**670.23**	**167.56**	**2.38**
STDEV		**18.56**	**222.69**	**9.28**	**228.02**	**126.68**	**31.67**	**0.45**
%CV		**18.96**	**18.96**	**18.96**	**18.90**	**18.90**	**18.90**	**18.90**
5	SkinPerm_Carf in H2O_5h_1	99.99	1199.84	49.99	1244.75	691.53	138.31	2.46
	SkinPerm_Carf in H2O_5h_2	93.28	1119.34	46.64	1154.47	641.37	128.27	2.28
	SkinPerm_Carf in H2O_5h_3	133.32	1599.80	66.66	1651.51	917.51	183.50	3.26
	SkinPerm_Carf in H2O_5h_4	NA	NA	NA	NA	NA	NA	NA
	SkinPerm_Carf in H2O_5h_5	140.33	1683.94	70.16	1737.62	965.34	193.07	3.43
	SkinPerm_Carf in H2O_5h_6	155.19	1862.27	77.59	1921.57	1067.54	213.51	3.80
Mean		**124.42**	**1493.04**	**62.21**	**1541.98**	**856.66**	**171.33**	**3.05**
STDEV		**26.67**	**320.07**	**13.34**	**328.96**	**182.76**	**36.55**	**0.65**

%CV		**21.44**	**21.44**	**21.44**	**21.33**	**21.33**	**21.33**	**21.33**
6	SkinPerm_Carf in H2O_6h_1	125.52	1506.22	62.76	1556.21	864.56	144.09	3.08
	SkinPerm_Carf in H2O_6h_2	115.22	1382.62	57.61	1429.26	794.03	132.34	2.82
	SkinPerm_Carf in H2O_6h_3	157.20	1886.41	78.60	1953.07	1085.04	180.84	3.86
	SkinPerm_Carf in H2O_6h_4	NA	NA	NA	NA	NA	NA	NA
	SkinPerm_Carf in H2O_6h_5	183.95	2207.44	91.98	2277.60	1265.33	210.89	4.50
	SkinPerm_Carf in H2O_6h_6	229.51	2754.07	114.75	2831.67	1573.15	262.19	5.60
Mean		**162.28**	**1947.35**	**81.14**	**2009.56**	**1116.42**	**186.07**	**3.97**
STDEV		**46.32**	**555.81**	**23.16**	**568.59**	**315.88**	**52.65**	**1.12**
%CV		**28.54**	**28.54**	**28.54**	**28.29**	**28.29**	**28.29**	**28.29**

NA: tissue torn

CF Epidermal Dosing
Results Summary

Analyst: Kathleen Maistros
Instrument: Shimadzu Nexera UPLC/Sciex 4000 Qtrap
Column: Phenomenex Kinetex 2.1 x 100 mm x 1.7 µm F5
Method: Reversed Phase/Positive Mode

Date: 8/20-21/2018

Solvent	***EtOH***							
Dose	**50.6 µg/mL**							
Sample Collection Time	**Sample Name**	**Measured Conc. (ng/mL)**	**Amnt in cell (ng)**	**sampled amnt removed**	**Amnt incl sample removal (ng)**	**Permeation (ng/cm2)**	**Flux (ng/cm2/hr)**	**% Absorption**
0.5	SkinPerm_Carf in EtOH_0.5h_1	BDL						
	SkinPerm_Carf in EtOH_0.5h_2	BDL						
	SkinPerm_Carf in EtOH_0.5h_3	BDL						
	SkinPerm_Carf in EtOH_0.5h_4	0.89	10.67	0.44	10.67	5.93	11.85	0.02
	SkinPerm_Carf in EtOH_0.5h_5	BDL						
	SkinPerm_Carf in EtOH_0.5h_6	BDL						
Mean		**0.89**	**10.67**	**0.44**	**10.67**	**5.93**	**11.85**	**0.02**
STDEV		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
%CV		**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**	**#DIV/0!**
1	SkinPerm_Carf in EtOH_1h_1	0.38	4.50	0.19	4.50	2.50	2.50	0.01
	SkinPerm_Carf in EtOH_1h_2	0.39	4.69	0.20	4.69	2.61	2.61	0.01
	SkinPerm_Carf in EtOH_1h_3	BDL						
	SkinPerm_Carf in EtOH_1h_4	1.83	21.91	0.91	22.36	12.42	12.42	0.04
	SkinPerm_Carf in EtOH_1h_5	1.24	14.88	0.62	14.88	8.27	8.27	0.03
	SkinPerm_Carf in EtOH_1h_6	0.41	4.91	0.20	4.91	2.73	2.73	0.01
Mean		**0.85**	**10.18**	**0.42**	**10.27**	**5.70**	**5.70**	**0.02**
STDEV		**0.66**	**7.90**	**0.33**	**8.07**	**4.48**	**4.48**	**0.02**
%CV		**77.66**	**77.66**	**77.66**	**78.60**	**78.60**	**78.60**	**78.60**
2	SkinPerm_Carf in EtOH_2h_1	2.27	27.26	1.14	27.45	15.25	7.63	0.05
	SkinPerm_Carf in EtOH_2h_2	0.56	6.67	0.28	6.87	3.82	1.91	0.01

	SkinPerm_Carf in EtOH_2h_3	ND						
	SkinPerm_Carf in EtOH_2h_4	4.32	51.80	2.16	52.72	29.29	14.64	0.10
	SkinPerm_Carf in EtOH_2h_5	0.63	7.50	0.31	8.12	4.51	2.26	0.02
	SkinPerm_Carf in EtOH_2h_6	0.55	6.62	0.28	6.83	3.79	1.90	0.01
Mean		**1.66**	**19.97**	**0.83**	**20.40**	**11.33**	**5.67**	**0.04**
STDEV		**1.65**	**19.86**	**0.83**	**20.08**	**11.15**	**5.58**	**0.04**
%CV		**99.42**	**99.42**	**99.42**	**98.43**	**98.43**	**98.43**	**98.43**
3	SkinPerm_Carf in EtOH_3h_1	5.66	67.94	2.83	69.08	38.38	12.79	0.14
	SkinPerm_Carf in EtOH_3h_2	0.61	7.31	0.30	7.59	4.21	1.40	0.01
	SkinPerm_Carf in EtOH_3h_3	0.76	9.06	0.38	9.06	5.03	1.68	0.02
	SkinPerm_Carf in EtOH_3h_4	4.18	50.15	2.09	52.31	29.06	9.69	0.10
	SkinPerm_Carf in EtOH_3h_5	1.28	15.31	0.64	15.62	8.68	2.89	0.03
	SkinPerm_Carf in EtOH_3h_6	1.06	12.71	0.53	12.98	7.21	2.40	0.03
Mean		**2.26**	**27.08**	**1.13**	**27.77**	**15.43**	**5.14**	**0.05**
STDEV		**2.13**	**25.54**	**1.06**	**26.20**	**14.56**	**4.85**	**0.05**
%CV		**94.33**	**94.33**	**94.33**	**94.33**	**94.33**	**94.33**	**94.33**
4	SkinPerm_Carf in EtOH_4h_1	6.84	82.02	3.42	84.85	47.14	11.78	0.17
	SkinPerm_Carf in EtOH_4h_2	3.07	36.78	1.53	37.08	20.60	5.15	0.07
	SkinPerm_Carf in EtOH_4h_3	1.35	16.24	0.68	16.61	9.23	2.31	0.03
	SkinPerm_Carf in EtOH_4h_4	8.16	97.97	4.08	100.06	55.59	13.90	0.20
	SkinPerm_Carf in EtOH_4h_5	1.70	20.44	0.85	21.07	11.71	2.93	0.04
	SkinPerm_Carf in EtOH_4h_6	3.08	37.00	1.54	37.53	20.85	5.21	0.07
Mean		**4.03**	**48.41**	**2.02**	**49.53**	**27.52**	**6.88**	**0.10**
STDEV		**2.81**	**33.67**	**1.40**	**34.62**	**19.23**	**4.81**	**0.07**
%CV		**69.56**	**69.56**	**69.56**	**69.89**	**69.89**	**69.89**	**69.89**
5	SkinPerm_Carf in EtOH_5h_1	9.28	111.30	4.64	114.72	63.73	12.75	0.23
	SkinPerm_Carf in EtOH_5h_2	3.22	38.69	1.61	40.22	22.34	4.47	0.08
	SkinPerm_Carf in EtOH_5h_3	3.24	38.89	1.62	39.57	21.98	4.40	0.08
	SkinPerm_Carf in EtOH_5h_4	11.12	133.40	5.56	137.49	76.38	15.28	0.27
	SkinPerm_Carf in EtOH_5h_5	3.55	42.61	1.78	43.46	24.15	4.83	0.09
	SkinPerm_Carf in EtOH_5h_6	4.39	52.73	2.20	54.27	30.15	6.03	0.11
Mean		**5.80**	**69.60**	**2.90**	**71.62**	**39.79**	**7.96**	**0.14**
STDEV		**3.48**	**41.76**	**1.74**	**43.13**	**23.96**	**4.79**	**0.09**

%CV		**60.00**	**60.00**	**60.00**	**60.23**	**60.23**	**60.23**	**60.23**
6	SkinPerm_Carf in EtOH_6h_1	13.44	161.30	6.72	165.94	92.19	15.36	0.33
	SkinPerm_Carf in EtOH_6h_2	3.33	39.90	1.66	41.51	23.06	3.84	0.08
	SkinPerm_Carf in EtOH_6h_3	2.66	31.94	1.33	33.56	18.65	3.11	0.07
	SkinPerm_Carf in EtOH_6h_4	21.29	255.53	10.65	261.09	145.05	24.17	0.52
	SkinPerm_Carf in EtOH_6h_5	5.17	62.02	2.58	63.79	35.44	5.91	0.13
	SkinPerm_Carf in EtOH_6h_6	5.73	68.78	2.87	70.98	39.43	6.57	0.14
Mean		**8.60**	**103.25**	**4.30**	**106.15**	**58.97**	**9.83**	**0.21**
STDEV		**7.32**	**87.80**	**3.66**	**89.51**	**49.73**	**8.29**	**0.18**
%CV		**85.04**	**85.04**	**85.04**	**84.32**	**84.32**	**84.32**	**84.32**

BDL: below detection limit

CF Epidermal Dosing Results Summary

Analyst: Kathleen Maistros
Instrument: Shimadzu Nexera UPLC/Sciex 4000 Qtrap
Column: Phenomenex Kinetex 2.1 x 100 mm x 1.7 µm F5

Method: Reversed Phase/Positive Mode

Date: 27 August 2018

Solvent ***Purell Brand Hand Sanitizer***

Dose **50.60 µg/mL**

Sample Collection Time	Sample Name	Measured Conc. (ng/mL)	Amnt in cell (ng)	sampled amnt removed	Amnt incl sample removal (ng)	Permeation (ng/cm2)	Flux (ng/cm2/hr)	% Absorption
0.5	SkinPerm_Carf in Hand Sanitiz from 8/27_0.5h_1	0.23	2.79	0.12	2.79	1.55	3.11	0.01
	SkinPerm_Carf in Hand Sanitiz from 8/27_0.5h_2	0.35	4.21	0.18	4.21	2.34	4.68	0.01
	SkinPerm_Carf in Hand Sanitiz from 8/27_0.5h_3	0.17	2.01	0.08	2.01	1.12	2.23	0.00
	SkinPerm_Carf in Hand Sanitiz from 8/27_0.5h_4	BDL						
	SkinPerm_Carf in Hand Sanitiz from 8/27_0.5h_5	0.39	4.71	0.20	4.71	2.62	5.23	0.01
	SkinPerm_Carf in Hand Sanitiz from 8/27_0.5h_6	0.14	1.62	0.07	1.62	0.90	1.80	0.00
Mean		**0.26**	**3.07**	**0.13**	**3.07**	**1.71**	**3.41**	**0.01**
STDEV		**0.11**	**1.35**	**0.06**	**1.35**	**0.75**	**1.50**	**0.00**
%CV		**43.95**	**43.95**	**43.95**	**43.95**	**43.95**	**43.95**	**43.95**
1	SkinPerm_Carf in Hand Sanitiz from 8/27_1h_1	1.38	16.58	0.69	16.70	9.28	9.28	0.03
	SkinPerm_Carf in Hand Sanitiz from 8/27_1h_2	1.56	18.71	0.78	18.88	10.49	10.49	0.04
	SkinPerm_Carf in Hand Sanitiz from 8/27_1h_3	1.00	11.95	0.50	12.03	6.68	6.68	0.02
	SkinPerm_Carf in Hand Sanitiz from 8/27_1h_4	1.16	13.94	0.58	13.94	7.75	7.75	0.03

	SkinPerm_Carf in Hand Sanitiz from 8/27_1h_5	1.46	17.48	0.73	17.68	9.82	9.82	0.03
	SkinPerm_Carf in Hand Sanitiz from 8/27_1h_6	1.65	19.79	0.82	19.86	11.03	11.03	0.04
Mean		**1.37**	**16.41**	**0.68**	**16.52**	**9.18**	**9.18**	**0.03**
STDEV		**0.25**	**2.96**	**0.12**	**3.00**	**1.66**	**1.66**	**0.01**
%CV		**18.05**	**18.05**	**18.05**	**18.14**	**18.14**	**18.14**	**18.14**
2	SkinPerm_Carf in Hand Sanitiz from 8/27_2h_1	3.83	45.92	1.91	46.62	25.90	12.95	0.09
	SkinPerm_Carf in Hand Sanitiz from 8/27_2h_2	4.17	50.00	2.08	50.78	28.21	14.11	0.10
	SkinPerm_Carf in Hand Sanitiz from 8/27_2h_3	3.51	42.07	1.75	42.57	23.65	11.82	0.08
	SkinPerm_Carf in Hand Sanitiz from 8/27_2h_4	3.50	42.02	1.75	42.61	23.67	11.83	0.08
	SkinPerm_Carf in Hand Sanitiz from 8/27_2h_5	5.35	64.14	2.67	64.87	36.04	18.02	0.13
	SkinPerm_Carf in Hand Sanitiz from 8/27_2h_6	3.46	41.51	1.73	42.33	23.52	11.76	0.08
Mean		**3.97**	**47.61**	**1.98**	**48.30**	**26.83**	**13.42**	**0.10**
STDEV		**0.73**	**8.73**	**0.36**	**8.77**	**4.87**	**2.44**	**0.02**
%CV		**18.33**	**18.33**	**18.33**	**18.16**	**18.16**	**18.16**	**18.16**
3	SkinPerm_Carf in Hand Sanitiz from 8/27_3h_1	9.26	111.07	4.63	112.99	62.77	20.92	0.22
	SkinPerm_Carf in Hand Sanitiz from 8/27_3h_2	7.98	95.74	3.99	97.82	54.34	18.11	0.19
	SkinPerm_Carf in Hand Sanitiz from 8/27_3h_3	5.35	64.15	2.67	65.91	36.61	12.20	0.13
	SkinPerm_Carf in Hand Sanitiz from 8/27_3h_4	6.92	83.05	3.46	84.80	47.11	15.70	0.17
	SkinPerm_Carf in Hand Sanitiz from 8/27_3h_5	9.96	119.57	4.98	122.24	67.91	22.64	0.24
	SkinPerm_Carf in Hand Sanitiz from 8/27_3h_6	7.22	86.59	3.61	88.32	49.07	16.36	0.17
Mean		**7.78**	**93.36**	**3.89**	**95.35**	**52.97**	**17.66**	**0.19**
STDEV		**1.67**	**20.06**	**0.84**	**20.34**	**11.30**	**3.77**	**0.04**
%CV		**21.48**	**21.48**	**21.48**	**21.33**	**21.33**	**21.33**	**21.33**
4	SkinPerm_Carf in Hand Sanitiz from 8/27_4h_1	12.41	148.92	6.21	153.55	85.30	21.33	0.30

	SkinPerm_Carf in Hand Sanitiz from 8/27_4h_2	14.86	178.32	7.43	182.31	101.28	25.32	0.36
	SkinPerm_Carf in Hand Sanitiz from 8/27_4h_3	12.26	147.12	6.13	149.79	83.22	20.80	0.30
	SkinPerm_Carf in Hand Sanitiz from 8/27_4h_4	10.25	123.00	5.13	126.46	70.26	17.56	0.25
	SkinPerm_Carf in Hand Sanitiz from 8/27_4h_5	12.70	152.40	6.35	157.38	87.43	21.86	0.31
	SkinPerm_Carf in Hand Sanitiz from 8/27_4h_6	8.91	106.90	4.45	110.50	61.39	15.35	0.22
Mean		**11.90**	**142.78**	**5.95**	**146.67**	**81.48**	**20.37**	**0.29**
STDEV		**2.07**	**24.86**	**1.04**	**25.13**	**13.96**	**3.49**	**0.05**
%CV		**17.41**	**17.41**	**17.41**	**17.14**	**17.14**	**17.14**	**17.14**
5	SkinPerm_Carf in Hand Sanitiz from 8/27_5h_1	22.29	267.48	11.15	273.69	152.05	30.41	0.54
	SkinPerm_Carf in Hand Sanitiz from 8/27_5h_2	21.24	254.88	10.62	262.31	145.73	29.15	0.52
	SkinPerm_Carf in Hand Sanitiz from 8/27_5h_3	22.73	272.76	11.37	278.89	154.94	30.99	0.55
	SkinPerm_Carf in Hand Sanitiz from 8/27_5h_4	20.38	244.56	10.19	249.69	138.71	27.74	0.49
	SkinPerm_Carf in Hand Sanitiz from 8/27_5h_5	23.24	278.88	11.62	285.23	158.46	31.69	0.56
	SkinPerm_Carf in Hand Sanitiz from 8/27_5h_6	18.22	218.64	9.11	223.09	123.94	24.79	0.44
Mean		**21.35**	**256.20**	**10.68**	**262.15**	**145.64**	**29.13**	**0.52**
STDEV		**1.85**	**22.20**	**0.92**	**22.92**	**12.73**	**2.55**	**0.05**
%CV		**8.66**	**8.66**	**8.66**	**8.74**	**8.74**	**8.74**	**8.74**
6	SkinPerm_Carf in Hand Sanitiz from 8/27_6h_1	14.11	169.32	7.06	180.47	100.26	16.71	0.36
	SkinPerm_Carf in Hand Sanitiz from 8/27_6h_2	15.61	187.32	7.81	197.94	109.97	18.33	0.39
	SkinPerm_Carf in Hand Sanitiz from 8/27_6h_3	13.90	166.80	6.95	178.17	98.98	16.50	0.35
	SkinPerm_Carf in Hand Sanitiz from 8/27_6h_4	14.80	177.60	7.40	187.79	104.33	17.39	0.37
	SkinPerm_Carf in Hand Sanitiz from 8/27_6h_5	16.49	197.88	8.25	209.50	116.39	19.40	0.41

	SkinPerm_Carf in Hand Sanitiz from 8/27_6h_6	14.17	170.04	7.09	179.15	99.53	16.59	0.35
Mean		**14.85**	**178.16**	**7.42**	**188.84**	**104.91**	**17.48**	**0.37**
STDEV		**1.02**	**12.22**	**0.51**	**12.56**	**6.98**	**1.16**	**0.02**
%CV		**6.86**	**6.86**	**6.86**	**6.65**	**6.65**	**6.65**	**6.65**

BDL: below detection limit