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Original Article

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Comparison of Hydration Index, Percent Hydration, and Trans-Epidermal Water Loss Measurements for Dermal Exposure and Risk Assessment

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Abstract

Skin hydration and the barrier properties of the stratum corneum have been reported to be influential factors in the potential for retention of solid and semi-solid substances on the skin surface. The measurement of these characteristics of the skin, however, remains relatively uncommon in exposure assessments performed by industrial or occupational hygienists, even when the focus of the assessment is exposure to the skin. This study provides measurements of skin hydration using multiple instruments and multiple relevant skin site locations for comparative analysis. Three different measurement metrics, trans-epidermal water loss (TEWL), hydration index (HI), and percent hydration, were measured for 25 healthy volunteers at two different body locations for comparison: the center of the volar forearm, as previously recommended for interindividual comparison of hydration and barrier property measurements, and also the palmar tip of the index finger. The purpose of the comparative measurements was to allow for comparison between other published baseline volar forearm measurements and the palmar skin, which has not often been quantitatively assessed and reported in the literature, but is a relevant skin surface for sampling of the hands. This comparison will allow for consideration of the potential influence of palmar wipe sampling protocols on TEWL or skin hydration, and for the evaluation of the influence of skin hydration and TEWL on measured dermal transfer values. Collectively, the skin hydration levels and barrier properties at these two different measurement locations were found to be statistically significantly different, and as a result it is suggested that they be measured and recorded separately. Both measurement types and locations are likely to be important for the purposes of establishing skin hydration and health. Volar forearm measurements can also be important for understanding the underlying condition and barrier function of the skin, and palmar index finger measurements are necessary to understand the influence of both TEWL and skin hydration on quantitative dermal loading and transfer of solids and semi-volatile materials.

Keywords: dermal; exposure assessment; skin hydration; trans-epidermal water loss; skin hydration; hydration index; risk assessment

What's important about this paper?

This research represents the first known analysis to quantitatively evaluate the range of measurements for trans-epidermal water loss (TEWL) and skin hydration index (HI) on both the palmar surface of the hand and the volar forearm for baseline comparison. It is not well understood whether TEWL and HI measurements could be associated with the amount of quantitative dermal loading of substances on the human skin surface. The study presents important baseline data for comparison between the palmar index finger and volar forearm, provides recommendations for measurement collection, and explores the potential for these measurements to influence the amount of quantitative dermal loading at the site of sampling.

Introduction

Historically, skin exposure potential has been studied far less than inhalation exposure potential, and yet concerns about skin exposures are increasingly common, particularly with the reduction of the use of volatile substances in the workplace over time in order to minimize inhalation exposure potential (Jansen van Rensburg *et al.*, 2019). Both physical (mechanical) and chemical stressors in the workplace can weaken the skin barrier. Impaired skin barrier function or abnormally hydrated skin can influence transfer to the skin surface and permeation of a variety of solid and semi-volatile compounds (Filon *et al.*, 2006; Kezic and Nielsen, 2009; Jansen van Rensburg *et al.*, 2019).

The skin is typically coated by a thin liquid layer that has been estimated to be between 0.4 and 4 μm thick. It is composed of sweat and oily secretions from glands on the skin (Edwards and Lioy, 2001). Although this layer has the potential to influence the adherence of chemicals to the skin, sparse data are available to evaluate this relationship. According to Edwards and Lioy (2001), these adhesive properties of the skin are likely to be dependent on both the activities of an individual and metabolic processes. Following direct contact with the skin, substances may partition into or between this layer on the surface of the skin and the skin itself, and the properties of the substance will determine this relationship, i.e., whether the contaminant is present in a liquid or solid form, the octanol/water partition coefficient (log K_{ow}), chemical reactivity, polarity, skin pH, and particle size, and any effect of mixture components (Edwards and Lioy, 2001; Stefaniak *et al.*, 2014).

The hydration level of the skin has been studied and found to have inconsistent effects on the transfer of substances to and from the skin surface. A number of studies have found no significant association between skin hydration or moisture levels and dermal transfer for substances such as pesticides (chlorpyrifos, piperonylbutoxide, pyrethrins); dusts (calcium acetate, Epsom salts, zinc oxide); and strontium (Roff, 2000; Beamer *et al.*, 2009; Gorman Ng *et al.*, 2013). Other studies, however, have at times reported unexpected results associated with the level of skin hydration on transfer to the skin surface. For example, Brouwer *et al.* (1999) noted that an increase in adherence of Tinopal powder was expected with increasing skin hydration, but the opposite effect was observed. Christopher *et al.* (2007), Rodes *et al.* (2001), Brouwer *et al.* (1999), and Edwards *et al.* (2001) reported a decrease in the transfer of multiple substances to the hands with increased skin hydration or wetting for saffron, Tinopal, house dust, and the pesticides diazinon and chlorpyrifos. Conversely, Avissar *et al.* (2004), Cohen Hubal *et al.* (2005) and Hubal *et al.* (2008) reported an increase in surface loading on the skin with an increase in hydration or wetting for iron and riboflavin. The effects of skin hydration, therefore, warrant more study to determine the relationships to dermal transfer and loading.

Bioengineering measurements that can quantitatively assess the quality of the skin barrier have been recommended for use in occupational settings to characterize the health and barrier properties of the skin, as well as the influences of skin moisture on dermal adherence and permeation. These measurements include the skin surface pH, trans-epidermal water loss (TEWL) and hydration index (HI), as well as skin temperature (Berardesca, 1997; du Plessis *et al.*, 2013; Stefaniak *et al.*, 2013; Berardesca *et al.*, 2018; Jansen van Rensburg *et al.*, 2019). These measurements are noninvasive and can be performed in field environments, including a variety of occupational settings (Berardesca *et al.*, 2018).

Skin surface pH can influence the solubility (or dissolution) of chemicals or mixtures on the skin surface, which can, in turn, affect skin loading and absorption rates. However, the influence of dissolution in sweat could be a relatively minor contribution overall to total exposure depending on the substance, especially if the risk for hand to mouth transfer or ingestion is substantial. As pointed out by Stefaniak *et al.* (2014), the total amount of mass measured on the surface of the skin, a common metric for dermal exposure and risk assessment, may substantially overestimate the amount of a substance that ultimately dissolves in the surface skin liquids in certain instances.

Skin temperature can also affect the barrier properties of the skin, including the chemical state of a contaminant, and may increase evaporation of volatile or semi-volatile substances compared to evaporation at room temperature (Sahmel *et al.*, 2009). Skin temperature also has the potential to alter the barrier properties of personal protective equipment such as gloves if these are tested for effectiveness at room temperature vs. skin temperature (Klingner and Boeniger, 2002).

Trans epidermal water loss

Trans epidermal water loss (TEWL) is a measure of the amount of hydration or water vapor lost from the deeper layers of the skin and up through the skin surface under normal conditions, and has units of grams of water per square meter per hour that evaporate from the skin surface. It is considered to be an appropriate indicator of skin barrier health and homeostasis (Rogiers, 2001; Chew and Maibach, 2003; Du Plessis *et al.*, 2010; du Plessis *et al.*, 2013; Berardesca *et al.*, 2018; Jansen van Rensburg *et al.*, 2019). If the skin or stratum corneum becomes damaged, the result is a loss of skin barrier function, which can be measured by water vapor loss using the TEWL measurement (Sotoodian and Maibach, 2012; Berardesca *et al.*, 2018; Jansen van Rensburg *et al.*, 2019). In general, low TEWL values are suggestive of good barrier function and low water loss, while higher values point to reduced barrier function. It has been reported that TEWL is generally independent of age among individuals of working age, but TEWL has also been reported to decrease with age and may be lower in individuals over age 60 (du Plessis *et al.*, 2013; Berardesca *et al.*, 2018). A decrease in skin water content and corresponding increase in TEWL may be more apparent in skin areas with previous sun exposure and damage (Berardesca *et al.*, 2018). There is insufficient evidence to suggest that gender affects TEWL, and the potential for influences due to ethnicity are unclear or may be insignificant (du Plessis *et al.*, 2013; Young *et al.*, 2019). TEWL has been demonstrated to vary by different anatomical areas of the body, and measurements have been reported to be highest on the palm. TEWL measurements on the volar forearm can be higher and more variable when they are collected closer to the wrist and elbow (du Plessis *et al.*, 2013). It has also been reported that TEWL measurements can be sensitive to the temperature of the instrument probe (Rogiers, 2001; Imhof *et al.*, 2009; Steiner *et al.* 2011).

There are several different types of instruments available to measure TEWL, including open-chamber methods, semi-open methods, and closed-chamber methods (Steiner *et al.*, 2011; du Plessis *et al.*, 2013; Berardesca *et al.*, 2018). Advantages and disadvantages have been identified for the different methods. Closed-chamber methods can be better suited to unpredictable field conditions, but can interfere with the evaporation of water from the skin surface, and may not be useful for direct reading over time (du Plessis *et al.*, 2013; Berardesca *et al.*, 2018). Open-chamber TEWL instruments can have limitations for practical use in the field, since the sensor can be significantly influenced by environmental conditions such as air movement, temperature, and humidity (Steiner *et al.*, 2011; du Plessis *et al.*, 2013; Berardesca *et al.*, 2018). However, according to Berardesca *et al.* (2018), the open-chamber design appeared to be more sensitive and was able to detect smaller differences in water vapor than the closed-chamber design. The authors reported that while they found the closed-chamber design to be inferior to the open-chamber design with respect to measurement capability, it was nevertheless more appropriate for field studies due to the limited effects of environmental conditions, small size, and flexibility. As of 2018, validation of the different methods for measuring TEWL has remained difficult, and there has been no standard developed for the comparison of results between instruments (Berardesca *et al.*, 2018).

Stratum corneum hydration or skin HI

The stratum corneum hydration or skin HI has been described as a measure of the surface skin/stratum corneum hydration or moisture content. It is measured in arbitrary units (a.u.) of skin hydration, or a unitless scale of relative hydration. The stratum corneum is primarily hydrated by the loss of water vapor from the deeper layers of the skin (Sotoodian and Maibach, 2012; Jansen van Rensburg *et al.*, 2019). It is important for this hydration level to be maintained to ensure successful function of the stratum corneum, which includes retention of water inside the body, maintenance of body temperature, and protection from external biological stressors such as bacteria or viruses (USEPA, 1992). The hydration level of the stratum corneum is also important for skin flexibility, the pliable properties of the skin, and the proper function of enzymatic reactions within the skin related to the life cycle of the corneocytes (Packham, 2005; Sotoodian and Maibach, 2012; Jansen van Rensburg *et al.*, 2019).

It has been reported that stratum corneum hydration decreases with age; there is little evidence to suggest that gender influences skin hydration (du Plessis *et al.*, 2013). Although influences due to ethnicity have not been well characterized, Young *et al.* (2019) reported that stratum corneum hydration was significantly lower in African vs. Caucasian nursing students. Large differences in skin hydration have been reported for different anatomical sites on the body, and higher values have been reported for the forehead and the palm, while lower values have been associated with the stomach and legs (du Plessis *et al.*, 2013). It has also been noted that the skin on the extremities is drier than the skin on the trunk (Berardesca *et al.*, 2018).

With certain types of skin disease such as eczema or psoriasis, an inverse relationship between the TEWL and stratum corneum hydration has been observed, such that as the hydration decreases, the TEWL increases, showing reduced barrier function (Berardesca *et al.*, 2018). Skin hydration may also be influenced by substantial or recurring exposure to water or smoking, as well as body fat percentage (du Plessis *et al.*, 2013; Berardesca *et al.*, 2018).

Stratum corneum hydration can be measured using direct methods that employ different types of electrical measurement to assess the water or hydration content in the skin (Berardesca, 1997; Berardesca *et al.*, 2018). It has been reported that due to the complexities of the biology of the skin barrier, it is insufficient merely to refer to the electrical 'capacitance' of the skin without also describing the experimental conditions tested and the characteristics of the electrical measurements collected. In the skin, it is not possible to test the true electrical capacitance because of the existence of a frequency dependence, and therefore the frequency of measurement should also be reported (Berardesca, 1997; Martinsen and Grimnes, 2001; Berardesca *et al.*, 2018). In a basic sense, the impedance or conductance of the skin measures the ability of electric current to flow through the skin, and conductance of the skin will generally increase with increasing hydration of the skin, although the relationship with the skin and its components, or added substances such as moisturizers, is not straightforward (Berardesca, 1997; Berardesca *et al.*, 2018). It is also important to consider that certain substances when in contact with the skin surface, such as polar compounds, may affect the measured electrical signal in the skin and may skew the results of measurements. Some newer technological methods allow for 2D analysis of electrical capacitance to map the hydration on the skin surface or provide an evaluation of skin hydration using high-resolution magnetic resonance imaging (Mirrashed and Sharp, 2004; Berardesca *et al.*, 2018).

The depth of measurement of the skin can be an important factor in the selection of an instrument using electrical methods to measure skin hydration (Martinsen and Grimnes, 2001). It has been noted that in healthy skin, the hydration of the corneocytes is often approximately 40 a.u. or greater, which equates to approximately 10–20% skin hydration or moisture (Heinrich *et al.*, 2003; Jansen van Rensburg *et al.*, 2019). This level of hydration is significantly lower than the deeper layers of the epidermis, where the level of hydration is typically closer to 75–85% (Chew and Maibach, 2003; Krutmann and Merk, 2018; Jansen van Rensburg *et al.*, 2019). As previously mentioned, it has also been noted that the measurement depth using these methods is strongly affected by the electrical frequency used, and could be a factor in the variability of measurement methods observed depending on the method employed by the instrument used to measure skin hydration (Berardesca, 1997; Martinsen and Grimnes, 2001; Berardesca *et al.*, 2018). It has been suggested that smaller and more closely spaced electrodes in an instrument may help to decrease the influence of the viable skin compared to the stratum corneum, as well as the collection of low frequency measurements (Martinsen and Grimnes, 2001).

Measurement of TEWL and stratum corneum hydration in occupational or field settings

In 2013, international guidelines were published for the *in vivo* assessment of TEWL, skin hydration, and skin surface pH in non-clinical settings (du Plessis *et al.*, 2013; Stefaniak *et al.*, 2013). For TEWL and HI specifically, Du Plessis *et al.* provided a list of methodological recommendations for performing TEWL and HI measurements in the workplace or other non-clinical settings. In 1997, the European Group for Efficacy Measurements on Cosmetics and Other Topical Products

(EEMCO) also published guidance on the measurement of skin hydration, and updated these guidelines in 2018 (Berardesca, 1997; Berardesca *et al.*, 2018). Where practicable, these recommendations have been incorporated into the methods described in this study for both TEWL and HI measurements (du Plessis *et al.*, 2013; Berardesca *et al.*, 2018).

According to a recent review of TEWL and HI measurements in occupational settings, there are significant limitations to the available literature due to substantial differences in methodologies used, or limited descriptions of methodology (Jansen van Rensburg *et al.*, 2019). There are no apparent studies that have previously concurrently evaluated the actual site of dermal contact or sampling used in a dermal exposure assessment study along with the standard recommended baseline measurement locations and procedures (i.e., use of the volar forearm for TEWL measurements) (Jansen van Rensburg *et al.*, 2019). The aim of this study, therefore, was to collect a series of comparative measurements of both TEWL and skin hydration on multiple relevant skin sites on the same volunteers for the purpose of understanding the potential for differences or variability in these measurements. A secondary aim of this study was to compare the results of corneometer instrument measurements with a simple instrument that measured the percent moisture content of the stratum corneum to determine if this might be a cost-effective alternative to estimating skin hydration in the field when a more expensive instrument such as a corneometer is unavailable.

Methods

The University of Minnesota Institutional Review Board (IRB) approved the study design prior to start of the study. TEWL, HI and percent hydration were measured for 25 healthy volunteer participants (13 females and 12 males) at two different body locations for comparison. These included the volar forearm, as previously recommended for interindividual comparison of measurements, and also the tip of the palmar index finger. The purpose of these comparative measurements was to enable the data to be used for evaluating the influence of skin wipe sampling protocols, such as the sample medium itself, on TEWL or skin hydration. A secondary purpose was to aid in the understanding of potential influences of skin hydration and TEWL on measured dermal loading or transfer values.

Consistent with the recommendations of the international guidelines published by du Plessis *et al.* (2013), prior to all measurements, the instruments and study participants were allowed to acclimate to the temperature and humidity conditions of the study area for at least 30 minutes. Ambient temperatures ranged from 20.6 to 23.3°C during all measurements, and relative humidity ranged between 16% and 50%. All participants reported performing standard office functions as part of their routine workplace duties at the time of measurement, and none of the participants reported working in extreme environments or having routine contact with chemicals known or believed to influence skin health. Self-reported good skin health was a requirement of the study through the IRB informed consent process; no participants reported or were observed to have compromised skin health during the study. Additionally, prior to data collection, all participants washed their hands thoroughly with the same foaming cleanser. It is expected that the use of this product would minimize the effects of lotions or other products applied by the participants to their hands or forearms prior to the study.

TEWL was measured using an open-chamber TEWL instrument from DermaLab (Cortex Technology ApS, Denmark, www.cortex.dk) with a draft-shield to minimize any air movement directly over or around the probe. The probe was kept level during measurements, and volunteers rested their arm and hand on a horizontal level surface during the measurements to minimize any effects of movement during the approximately 1- to 2-minute measurement duration. The TEWL probe was handled with a gloved hand (nitrile) to reduce effects of skin temperature on the probe. The TEWL is measured in units of grams of water vapor per square meter per hour ($g/m^2/h$), although as previously noted, the measurements of TEWL from different manufacturers or instruments can be variable and a standard for measurement values has not been established (Berardesca *et al.*, 2018).

For reference, Imhof *et al.* (2009) reported average values for the volar forearm of 13.6 $g/m^2/h$ and 7.3 $g/m^2/h$ for two different TEWL instruments (Tewameter, Courage & Khazaka, Cologne, Germany; Vapometer™, Delphin Technologies Ltd, Kuopio, Finland), similar to other results in the literature (Pan *et al.*, 2015). For the hands, Steiner *et al.* (2011) reported a mean of 25.3 $g/m^2/h$ for an open-chamber instrument and means of 24 $g/m^2/h$ and 26.4 $g/m^2/h$ for two closed-chamber instruments (Steiner *et al.*, 2011). Average values for the dorsal side of the hand were lower than for the palmar side, and mean dorsal hand TEWL values for all instruments were <10 $g/m^2/h$. For the palmar side of the hand, mean values across all instruments were between 25 and 50 $g/m^2/h$ (Steiner *et al.*, 2011). Some TEWL instruments may report measurement values using an index rather than a quantitative value related to grams of water vapor (Du Plessis *et al.*, 2010; Berardesca *et al.*, 2018). Du Plessis *et al.* (2010) provided a summary of the interpretation of TEWL measurements using an instrument that reported TEWL as an index (EDS12, EnviroDerm Services, Evesham, UK) rather than as a quantitative measurement.

Stratum corneum hydration was measured using two different methods for comparison. The first instrument employed a direct method based on the capacitance of the skin surface, evaluated as a change in the dielectric constant, and measured and expressed in a.u. It was noted by the manufacturer that the depth of measurement is 10–20 µm, which is effectively the stratum corneum, so that deeper skin layers do not affect the measurement results. The instrument used in this study converted the a.u. results into a qualitative rating or skin HI which was reported on a unitless scale from 1 to 12 (Model EDS10, EnviroDerm, Evesham, UK) and was manufactured by Courage & Khazaka (www.enviroderm.co.uk). According to EnviroDerm, the relative scale of the HI index measurement method is approximately 10 a.u. to 1 unit on the HI index based on corneometer measurements (CM825, Courage & Khazaka, Cologne, Germany) (Personal Communication, EnviroDerm Services). Table 1 provides recommended guidance from EnviroDerm regarding the interpretation of skin hydration measurements using the EDS10 and the HI output. For comparison, volar forearm HI measurements have been reported to be in the range of approximately 50-80 a.u., which is largely in the range of normal skin hydration based on the EnviroDerm instrument used (Pan *et al.*, 2015).

The second stratum corneum hydration monitor was an inexpensive instrument that employed electrical conductance, referred to by the manufacturer as bioelectric impedance analysis, rather than the capacitance method of the first instrument. This instrument reported the measurement results as percent hydration (0–100%). In this second instrument, the electrode was arranged in a 'zig zag pattern' on the surface of the instrument to measure the electrical conductance/impedance (SK-IV, Pandawill).

Both the TEWL and HI instrument probes were routinely cleaned during the study using a decontamination wipe to minimize any potential for infection transfer or influence on quantitative transfer measurements that were collected concurrently with the skin hydration measurements (Hygenall LeadOff™ Disposable Cleaning Wipes). The instrument was allowed to dry completely between measurements following cleaning.

Temperature and humidity were measured during the study using a portable hand-held thermo-hygrometer that was accurate to approximately ±5% (Acurite, Wisconsin, USA).

Measurement collection locations

According to Du Plessis *et al.* (2013), the recommended anatomical position for measurement of both TEWL and skin hydration 'is the volar forearm away from the wrist'. TEWL and skin hydration measurement collection was performed as close as possible to the center of the volar forearm on the dominant arm, and also on the tip of the palmar index finger on the dominant hand. The same researcher collected all TEWL and skin hydration measurements to ensure as much consistency as possible in the measurement collection strategy, including for such factors as probe placement, probe pressure on skin, etc. When a stable TEWL measurement could not be achieved after 1-2 minutes (which occurred infrequently), two sequential measurements were collected and averaged together. Duplicate skin hydration measurements were also collected for each anatomical location, and when the two measurements were different, they were averaged together.

Data analysis

A multivariate regression analysis was performed to investigate the relationships between gender, temperature, humidity, TEWL on the volar forearm, TEWL on the palmar index finger, HI on the volar forearm, HI on

Table 1. Range and interpretation of hydration index (HI) measurements (EnviroDerm Services, Evesham, UK)

Hydration index	Skin condition
1	Very dry, very poor skin condition
2	Very dry, poor skin condition
3	Dry, not good skin condition
4	Slightly dry, borderline skin condition
5–8	Normal, skin in good condition
9–12	Abnormally hydrated (could be due to sweating or residual moisture on skin from contact with water or moisturizers)

the palmar index finger, percent hydration on the volar forearm, and percent hydration on the palmar index finger. Box and whisker plots were also created to compare the range, distribution, and mean of the values for the measurement methods. The box and whisker plots represent the 75th, 50th, and 25th percentile values of the dataset, and the 'x' denotes the mean. The upper and lower whiskers represent the minimum and maximum values for the dataset, unless outliers were identified. For the purposes of the boxplot analysis, data points were considered outliers if they were 1.5 times the interquartile range (IQR) larger than the third quartile, or 1.5 times the IQR smaller than the first quartile. The IQR is defined as the distance between the third quartile and the first quartile. Comparisons were performed for each measurement method between the forearm and index finger skin.

Additionally, Pearson correlations with significance and *t*-test comparisons were calculated for the relationships between the forearm and index finger for TEWL, HI, and percent hydration. The correlations were performed both with and without outliers included for comparison.

Results

The comparative skin hydration and barrier property measurements were collected for 25 participants, including 13 females and 12 males, with self-reported healthy skin condition. Measurements were collected for comparison using the three different methods described (TEWL, HI, and percent hydration) and were collected for comparison on both the volar forearm and the tip of the dominant index finger. Detailed results of all measurements, as well as a summary of descriptive statistics for the data by gender and overall, are presented in Table 2.

Overall, the TEWL and HI data were normally distributed and also lognormally distributed based on log probability plots. The mean volar forearm TEWL for all participants was 7.5 g/m^2/h (range 3.2–25.3; SD 5.4), and the mean volar forearm HI was 4.4 (unitless index, range 3–6; SD = 0.9). For TEWL, the mean baseline for the volar forearm for female participants was 6.8 g/m^2/h compared with 8.3 g/m^2/h for male participants; this difference was not statistically significant (t-test; P = 0.9). However, the results demonstrated that the mean baseline skin hydration (HI) level on the volar forearm for the female participants was significantly different (P = 0.006) from male participants (for volar forearm: HI = 4.8 for females; HI = 4.0 for males). The mean volar forearm percent hydration was 25.2% (range 14.4–63.9%; SD = 0.1 or 9.8%). For the mean of the HI forearm measurements, the results indicated that the measured skin was normal to slightly dry, suggesting borderline skin health (Table 1). No comparable benchmarks could be identified for the evaluation of TEWL or percent hydration measurements. Comparisons between TEWL, HI, and percent hydration measurements for the volar forearm and palmar index finger are shown in Fig. 1a–c. Outliers are noted as circles on these figures. Data correlations and analyses were initially performed both with and without the outliers included. However, since there were no significant differences between the two sets of results except in one instance, all data points were considered and included in the analysis presented in the results and figures. For the comparison between HI and percent hydration measurements for the volar forearm, a difference in statistical significance was noted when outliers were removed and both results are reported and discussed.

Since many skin wipe samples are collected on the hands, and particularly on the palmar surface of the hands, comparative measurements were also collected for each participant on the tip of the palmar index finger of the dominant hand. Results showed that the mean index finger TEWL was 58.4 g/m^2/h (range 21.1–88.9; SD = 21.7) and the mean index finger HI was 5.8 (range 2–9; SD = 1.9). The mean index finger percent hydration was 50.2% (range 11.8–77%; SD = 0.2 or 15.1%). The index finger TEWL measurements were significantly different between males and females (49.8 for females vs. 67.7 for males; t-test, P = 0.03). The index finger HI measurements were not found to be significantly different between genders (5.2 for females and 6.4 for males).

A statistical comparison of the TEWL measurements and HI measurements between the volar forearm and the fingertip found them each to be significantly different from the other (t-tests; P values < 0.004). Overall, the multivariate regression analysis showed no apparent relationships between temperature and humidity and TEWL, HI, and percent hydration, although the range of temperature and humidity evaluated was limited. For the forearm, there was no correlation found between the TEWL and HI measurements (Pearson correlation = 0.018; R^2 = 0.0003; P = 0.9). For the index finger, a positive correlation was observed between the TEWL and HI measurements (Pearson correlation = 0.44; R^2 = 0.19; P = 0.024), and was statistically significant (see Fig. 2a and b).

It was also of interest to evaluate whether the HI measurements were comparable to the percent hydration measurements in order to determine whether percent

Table 2. Results of comparative skin hydration and barrier function measurements, with summary statistics for ambient conditions and comparative skin hydration and barrier function measurements (by gender and overall)

	Temp (° C)	Humidity (%RH)	TEWL: volar forearm ($g/m^2/h$)	TEWL: palmar index finger ($g/m^2/h$)	Hydration index: volar forearm	Hydration index: palmar index finger	Hydration %: volar forearm	Hydration %: palmar index finger
Females								
	22.8	19.0	5.2	88.9	5.0	9.0	22.8	61.1
	22.8	18.0	25.3	31.2	5.0	5.0	29.5	28.8
	22.2	17.0	5.9	64.7	4.0	6.0	17.2	56.3
	22.8	18.0	4.1	81.3	5.0	6.0	28.6	58.2
	22.8	17.0	6.1	68.0	4.0	4.0	18.0	40.0
	21.7	16.0	3.3	43.1	4.0	5.0	16.4	55.9
	21.7	22.0	5.1	49.3	4.0	2.0	14.9	11.8
	22.8	40.0	4.3	48.6	6.0	5.0	29.9	21.8
	23.3	39.0	4.9	26.3	6.0	6.0	29.0	45.0
	21.7	47.0	8.4	21.1	5.0	6.0	28.9	45.9
	22.2	48.0	5.8	53.3	5.0	5.0	28.6	54.0
	21.1	26.0	6.2	22.0	6.0	5.0	29.4	48.3
	21.7	25.0	3.2	49.2	4.0	3.0	16.8	35.3
Mean	22.3	27.1	6.8	49.8[a]	4.8[b]	5.2	23.8	43.3
SD	0.7	12.0	5.7	21.7	0.8	1.7	6.2	15.2
Males								
	22.8	18.0	7.4	72.3	4.0	5.0	28.6	41.1
	22.8	16.0	7.3	87.3	5.0	8.0	25.9	59.2
	22.8	17.0	23.6	84.1	4.0	6.0	26.9	56.0
	22.8	17.0	7.7	61.2	4.0	5.0	63.9	63.5
	22.2	17.0	5.2	63.5	5.0	4.0	29.1	48.6
	22.8	18.0	7.3	84.2	3.0	9.0	20.1	60.8
	22.8	20.0	12.1	84.2	5.0	6.0	28.7	57.8
	21.1	27.0	5.9	71.0	4.0	9.0	20.0	77.0
	21.1	24.0	5.6	70.4	3.0	9.0	14.4	76.0
	21.1	23.0	6.2	46.4	4.0	6.0	17.8	55.1
	23.3	39.0	4.2	64.2	4.0	6.0	28.0	56.8
	22.2	49.0	6.9	23.9	3.0	4.0	17.1	41.5
Mean	22.3	23.8	8.3	67.7[a]	4.0[b]	6.4	26.7	57.8
SD	0.8	10.3	5.2	18.3	0.7	1.9	12.8	11.2

Table 2. Continued

	Temp (° C)	Humidity (%RH)	TEWL: volar forearm (g/m^2/h)	TEWL: palmar index finger (g/m^2/h)	Hydration index: volar forearm	Hydration index: palmar index finger	Hydration %: volar forearm	Hydration %: palmar index finger
Overall								
Mean	22.3	25.5	7.5[c]	58.4[c]	4.4[c]	5.8[c]	25.2	50.2
SD	0.7	11.1	5.4	21.7	0.9	1.9	9.8	15.1
Mim	21.1	16.0	3.2	21.1	3.0	2.0	14.4	11.8
Max	23.3	49.0	25.3	88.9	6.0	9.0	63.9	77.0

[a]The mean index finger TEWL was statistically significantly different between genders (*t*-test; $P = 0.03$).
[b]The mean volar forearm HI was statistically significantly different between genders (*t*-test; $P = 0.006$).
[c]The TEWL measurements and HI measurements between the volar forearm and fingertip were each statistically significantly different from the other (*t*-test; P values < 0.004).

hydration could be a reasonable surrogate for HI when a corneometer or similar instrument is not available (Fig. 3a and b). Although the measurements were significantly different between each other for both the forearm and the index finger locations (*t*-tests; P values < 0.005), there was a positive correlation between the two methods for the index finger that was statistically significant (Pearson correlation = 0.77; $R^2 = 0.60$; $P = 0.000004$) (Fig. 3a). For the forearm, these two measures were also positively correlated, but this relationship was not significant (Pearson correlation = 0.34; $R^2 = 0.12$; $P = 0.09$) (Fig. 3b). A potential outlier was retained in Fig. 3b (denoted with an open circle) based on its biological plausibility and uncertainties regarding the variability in measurement methods for TEWL. If the potential outlier in Fig. 3b is removed, the relationship becomes statistically significant and very similar to the relationship between HI and percent hydration for the index finger (Pearson correlation = 0.75; $R^2 = 0.56$; $P = 0.00001$).

Discussion

The results of this analysis provide a helpful comparison for exposure and risk assessment practitioners with respect to the collection and consideration of skin hydration measurements in dermal exposure assessments. This study offers a number of novel analyses, including relative measurements of skin hydration and barrier function between the volar forearm and the palmar skin. While the volar forearm has been recommended as the location for baseline TEWL and HI measurements, the hydration and barrier properties of the palmar skin of the hands are more likely to be relevant for assessing dermal loading of solids and semi-volatile solids as part of exposure assessments. Both measurements are important; the volar forearm is integral to establishing a baseline for relative skin hydration and skin barrier health, and the index finger or palmar skin is necessary to allow for the quantitative consideration of the influences of hydration on dermal loading and transfer. Significant differences have been noted in the literature in the skin structure on the palmar surface compared to forearm skin (USEPA, 1992). It was therefore not surprising that the palmar index finger measurements were clearly distinct from the volar forearm measurements, and a statistical comparison of the TEWL measurements and HI measurements between the volar forearm and the fingertip also found them each to be significantly different from the other (*t*-tests; P values < 0.004). Other studies have noted substantial differences in TEWL values for different anatomical sites. It has generally been noted that the palm exhibits the highest TEWL values, while the

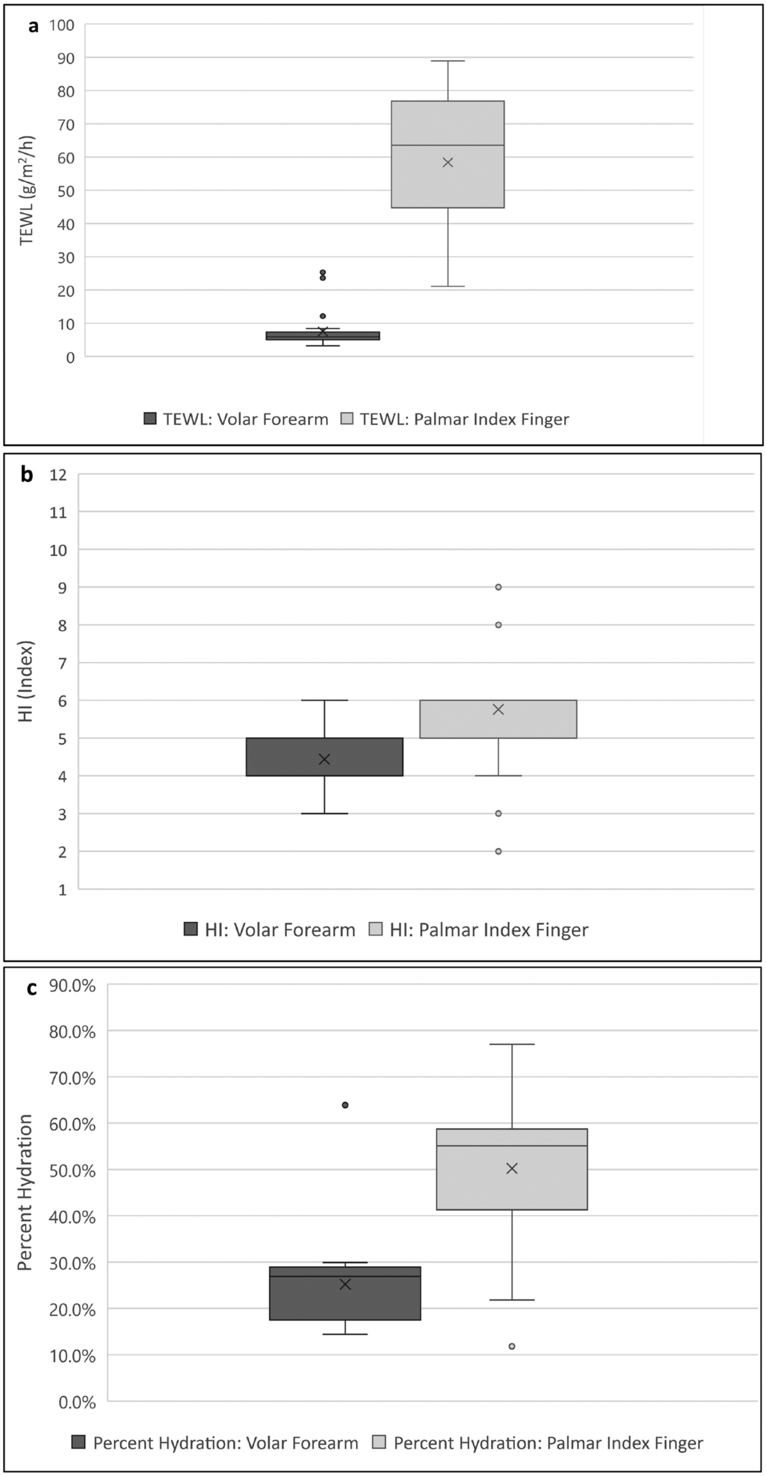

Figure 1. The box plots shown represent the 75th, 50th, and 25th percentile values of the dataset, and the '*x*' denotes the mean. The upper and lower whiskers represent the minimum and maximum values for the dataset, unless outliers were identified as described in Methods section; when outliers were identified, they are denoted as circles on the chart. (a) Comparison between TEWL measurements for the volar forearm and the palmar index finger. (b) Comparison between HI measurements for the volar forearm and the palmar index finger. (c) Comparison between percent hydration measurements for the volar forearm and the palmar index finger.

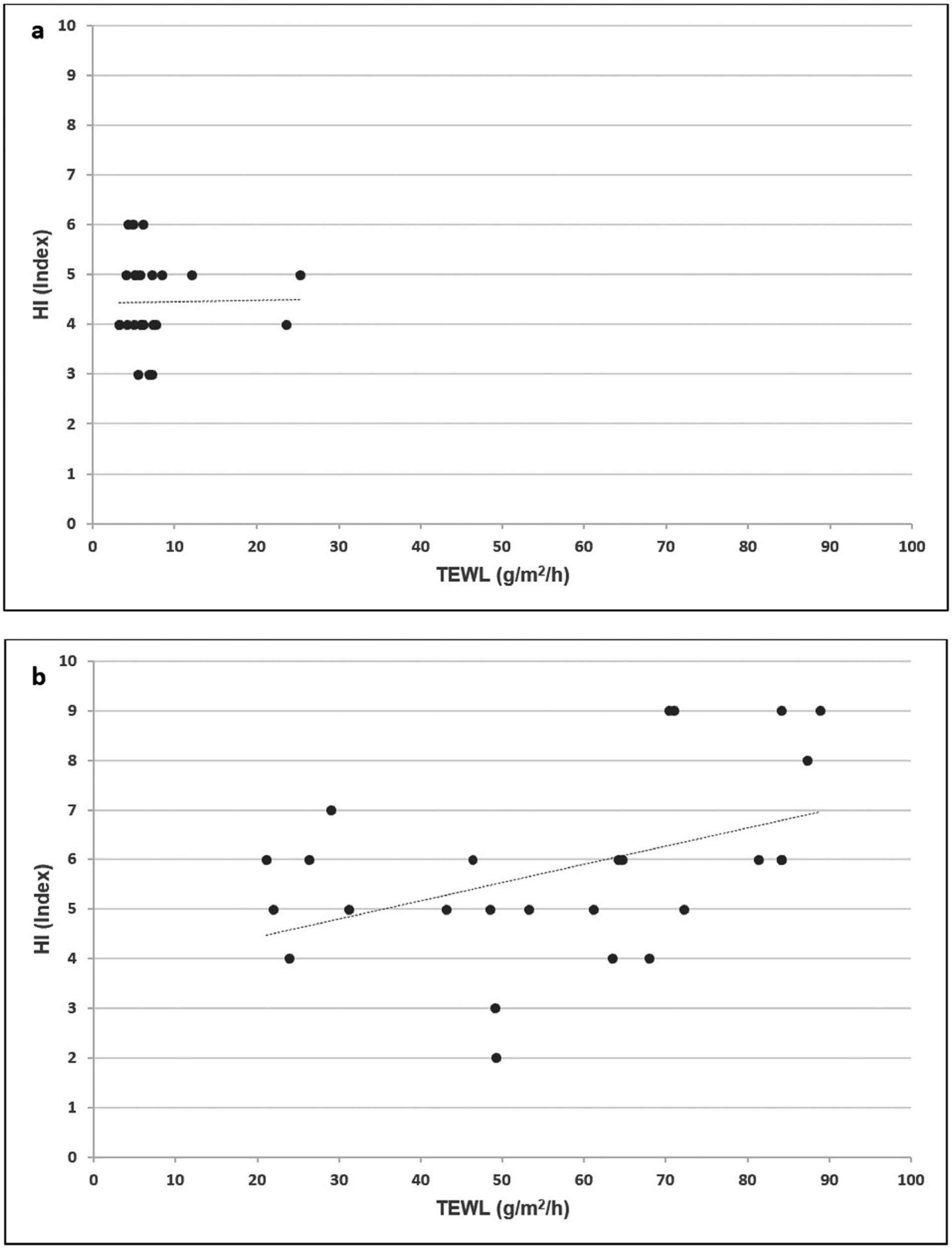

Figure 2. Relationship between TEWL and HI, including the relationship between forearm TEWL and HI; R^2 = 0.0003, which was not statistically significant (P = 0.9) (a) and the relationship between palmar index finger TEWL and HI; R^2 = 0.19, which was statistically significant (P = 0.024) (b).

forearms, upper arms, thighs and torso have the lowest values (Pinnagoda *et al.*, 1990; Rogiers, 2001). The results of our study are consistent with the TEWL values reported by Steiner *et al.* (2011) for palmar skin.

Regarding differences between males and females, the results of volar forearm TEWL measurements were not found to be statistically significantly different, but volar forearm HI measurements were found to be significantly different between genders (t-test; P = 0.006). For the index finger, the opposite was true, and the index finger TEWL measurements were significantly different between genders (*t*-test; P = 0.03), while the index finger

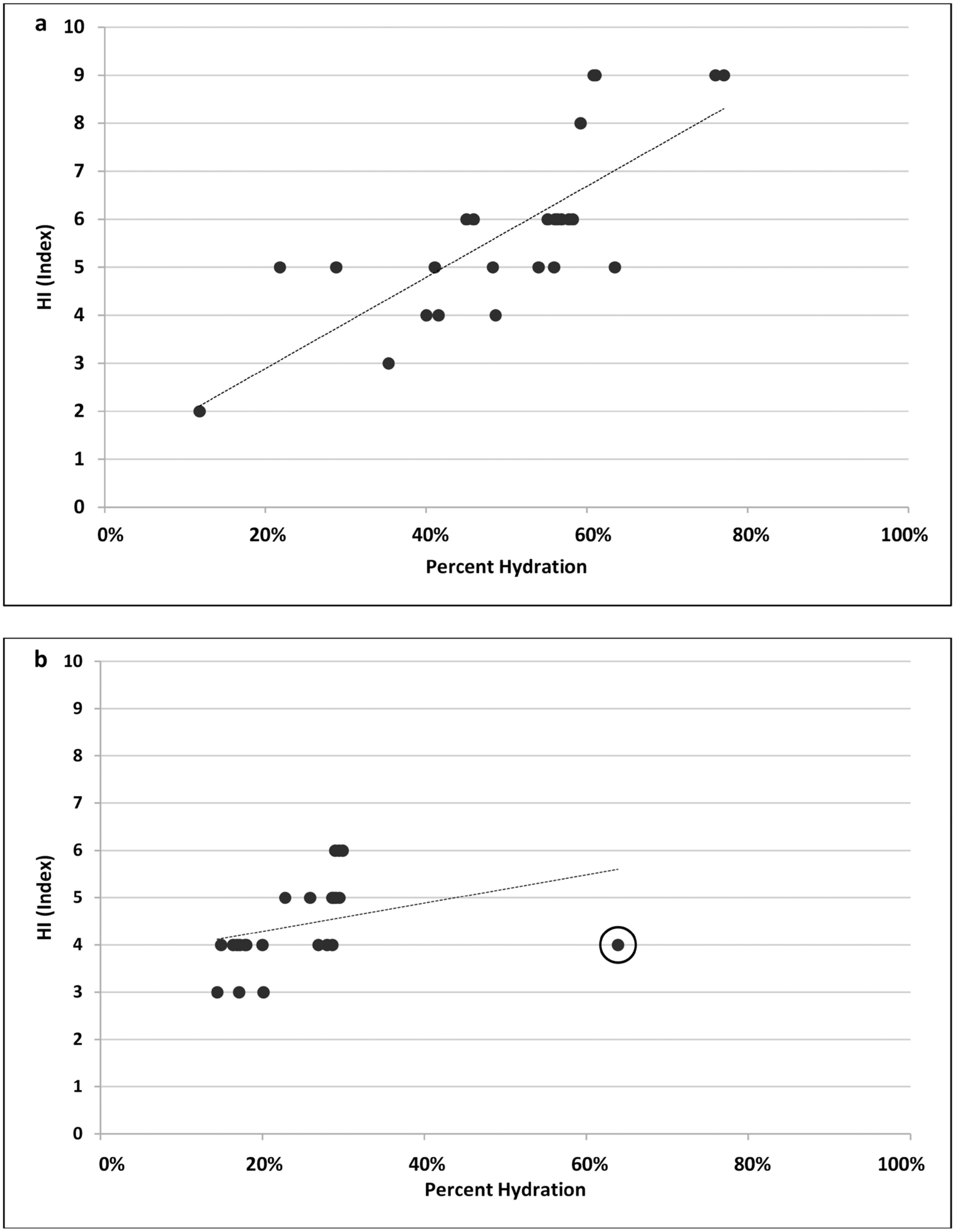

Figure 3. Correlation between HI and percent hydration for index finger measurements; $R^2 = 0.60$, which was statistically significant ($P = 0.000004$) (a) and correlation between HI and percent hydration for forearm measurements; $R^2 = 0.12$, which was not statistically significant ($P = 0.09$) (b). A potential outlier that was biologically plausible was retained in (b) (denoted with an open circle). If the potential outlier in (b) is removed, the change in the relationship would result in $R^2 = 0.56$, which is statistically significant ($P = 0.00001$) and similar to the R^2 value for (a).

HI measurements were not found to be significantly different between genders overall.

The comparative measurements provided here may assist practitioners in better understanding the inter- and intra-individual differences in these measurements when collected for dermal exposure and risk assessment purposes. For example, the development of guidance on the normal range of TEWL and HI measurements on the palmar index finger would be helpful to supplement the guidance currently available for baseline forearm measurements. However, given the reports of inconsistencies between instruments for TEWL and HI measurements generally, additional research is needed in this area. Furthermore, minimal data are available to understand the range of values for the palmar skin and the potential for influences on dermal transfer or absorption. This is a potentially important limitation that should be addressed in future studies.

The results of this study also suggested that percent hydration measurements, which can be collected with an inexpensive, readily available instrument, may be useful in addition to or in place of HI measurements collected with a corneometer. Comparative results of the percent hydration and HI measurements collected for the palmar index finger specifically demonstrated a positive correlation that was statistically significant (P = 0.000004) and suggested that percent hydration measurements may be useful for understanding skin hydration during dermal exposure assessment sampling studies when a corneometer is not available. Furthermore, a potential outlier was identified in evaluating the relationship between percent hydration and HI for the forearm. This outlier is biologically plausible based on the measurement ranges in the literature that were previously discussed above (mean values ranged from 7.3 to 50 g/m^2/h for the hands) (Imhof *et al.*, 2009; Steiner *et al.*, 2011; Pan *et al.*, 2015). Due to the biological plausibility and uncertainties regarding the variability in measurement methods, the outlier was retained for the purposes of the analysis and has been denoted with an open circle on Fig. 3b. Recent research has also suggested generally that it is most appropriate to present results both with and without outliers included due to differences in the methods used for identifying outliers and other factors (Pollet and van der Meij, 2017; Gress *et al.*, 2018; Gibbert *et al.*, 2021). If this outlier is removed, the change in the relationship between percent hydration and HI for the forearm becomes statistically significant and very similar to the relationship between HI and percent hydration for the index finger (P = 0.00001). Westermann *et al.* (2020) also reported positive correlations for skin hydration measurements between a corneometer (Corneometer® CM825) and a portable, inexpensive percent moisture measurement device manufactured by SkinUp®.

Relationship of HI to TEWL measurements

Several other studies have also analyzed the relationship between TEWL and skin hydration measurements. Caberlotto *et al.* (2019) collected relative measurements of skin hydration and TEWL on the forearms of healthy volunteers, and reported that the results suggested these two measures were inversely related to each other, which was inconsistent with the results of the current study. The results from Caberlotto *et al.* (2019) do, however, appear to be consistent with reported measurements for potentially damaged skin, as previously noted. Halkier-Sorensen *et al.* (1991) also reported on the relationships and differences in TEWL and skin hydration measurements taken at different anatomical sites. Also distinct from the results of the current study, a negative linear correlation was observed between TEWL and skin hydration for the fingers. Berardesca *et al.* (2018) reported that the correlation between electrical measurements of skin hydration can be positively correlated and linear, negatively correlated and linear, or scattered, depending on the study and conditions, and reported that additional comparison studies were important for better understanding this relationship. They also pointed to the lack of standardization of methods to collect these measurements and validate them between instruments as a limitation, despite many new technologies to collect data on these important parameters of skin health.

Measured workplace values for the relationships between worker skin hydration and TEWL measurements

Only a small number of studies could be identified that have reported field measurement results for worker skin hydration levels. Young *et al.* (2019) collected TEWL and stratum corneum hydration measurements for 50 female nursing students (19 African students and 31 Caucasian students). There were no statistically significant differences in TEWL measurements between the two groups. Consistent with this study, the authors found that the TEWL was substantially higher on the palms compared with other anatomical areas. In African students, a negative correlation was observed between TEWL and stratum corneum hydration, but for Caucasian students (or all students together), no correlation was observed between TEWL and stratum corneum hydration, which is consistent with the results of this study. Additionally, distinct from the relationships measured in this study, the authors noted that stratum corneum hydration measurements were highest for the volar forearm, followed by the dorsal hand, and then lowest for the palms. In this study, no statistically significant difference in HI forearm and palmar index finger measurements was observed. (Young *et al.*, 2019).

Du Plessis *et al.* (2010) measured both TEWL index and HI before, during and at the end of the worker shift at a base metal refinery and evaluated the skin of the index finger, palm, neck, and forehead. The authors reported that the TEWL index for the index finger had a pre-shift mean of 15.538 (unitless; SD = 4.51; range 5–20) and a post-shift mean of 17.769 (unitless; SD = 2.72; range 11–20); measurements for the palm were very similar. The authors reported that the increase in the mean TEWL index between the start of the shift and the end of the shift was highly statistically significant ($P = 0.003$ for index finger; $P < 0.001$ for forehead). For HI, although the HI measurements decreased during the shift, they returned to consistent levels post-shift that were measured at pre-shift. The authors hypothesized that the decrease in HI on the index finger and palms during the shift was due to direct contact with a nickel-electrolyte solution with a pH of 3.5 (Du Plessis *et al.*, 2010).

Implications for skin hydration and condition measurements on dermal risk assessment

To date, limited measurements exist to aid the risk assessor in considering the potential influence of skin hydration or condition on the results of dermal exposure and risk assessments. However, given the potential for statistically significant effects of skin hydration on dermal transfer, further investigation of this factor is warranted. For example, the limited data currently available in the published literature suggest that skin hydration may have either a positive or negative effect on dermal transfer and loading (Edwards and Lioy, 2001; Rodes *et al.*, 2001; Avissar *et al.*, 2004; Cohen Hubal *et al.*, 2005; Christopher *et al.*, 2007; Hubal *et al.*, 2008), and that these results can sometimes be unexpected (Brouwer *et al.*, 1999). Further, a number of these studies have reported statistically significant associations with skin hydration and loading on the skin. These data suggest that factors related to the physical-chemical properties of various substances such as water solubility, fat solubility, pH, and polarity may result in differences in either skin loading or absorption based on skin hydration properties. However, there are a number of issues that currently exist in considering these potential effects. These include the substantial variability in available skin hydration measurements and instrumentation, as well as the limited hydration measurements collected at the actual site of dermal sampling, where hydration is likely to be most influential on dermal exposure or transfer measurements. Given these limitations, additional quantitative data are needed to better evaluate these properties for characterizing skin hydration and condition. Without additional data, a potentially important data gap may remain that will preclude a better understanding of the influences on dermal loading for a wide variety of substances, and dermal exposure and risk assessment efforts may be inadequate without this information. Further data are required to better understand if and when such characterizations of skin hydration and condition should become a necessary part of the dermal risk assessment process.

Conclusions

The results of this study are likely to be useful to exposure and risk assessment practitioners with respect to the collection and use of skin hydration measurements in dermal exposure assessments. This study offers a number of novel comparisons, including relative measurements of skin hydration and barrier function between the volar forearm and the palmar skin. These comparative measurements are likely to be helpful in establishing baseline values for evaluating relative hydration at the site of sampling when skin surface wipe samples are collected from the palmar surface of the hands for the purpose of evaluating the potential influence of skin hydration level on quantitative dermal transfer.

Furthermore, a quantitative comparison between measurements was performed for an instrument designed for assessing the unitless skin HI and an inexpensive instrument that measures the percent hydration of the skin surface. The two methods were significantly positively correlated for the index finger and also for the volar forearm once outliers were removed. The index finger is more likely to be the site of interest for skin wipe sampling study purposes. These results suggest that similar instruments capable of measuring percent hydration at the skin sampling site could be a reasonable surrogate for characterizing hydration during skin sampling studies in place of the measurement of HI using a corneometer, if the more expensive instrument is unavailable.

Acknowledgement

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Conflict of interest

JS is a current employee of Insight Exposure and Risk Sciences, a consulting firm that provides scientific advice to entities including governments, corporations, law firms, and various scientific/professional organizations. JS has previously served as a testifying expert in the area of exposure and risk assessment, but not for the specific topics addressed in this study.

Data availability

All data underlying this article are available in the article, or will be clarified or made available on reasonable request to the corresponding author.

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