Evaluation of the Utility of Deterministic Models for Dermal Exposure Assessment of Solids and Investigation of the Potential Influence of Repeated Contacts and Skin Hydration on Quantitative Dermal Loading and Transfer

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Jennifer Sahmel Elliott

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Advisor: Dr. Peter Raynor, Division of Environmental Health Sciences,

School of Public Health

Co-Advisor: Dr. Gurumuthy Ramachandran,

Department of Environmental Health and Engineering,

Bloomberg School of Public Health,

Johns Hopkins University

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Abstract

Exposure assessment is an important tool for occupational, environmental and consumer health professionals to evaluate the level of risk associated with various scenarios. While exposure assessment methods have been well defined for inhalation exposures for many decades, dermal exposure assessment methods are often lacking in quality and accuracy. A number of deterministic models have been developed to evaluate the potential for dermal exposure and uptake or ingestion in the absence of substance-specific or scenario-specific dermal loading measurement data. These models typically use default assumptions regarding the quantity of loading on the skin surface, frequently requiring the use of data with unknown relevance. Further, these models routinely incorporate an assumption of additive transfer with each successive or routine contact with the substance of interest. Overall, however, relatively few data are available to characterize the factors or determinants most likely to influence the accurate estimation or calculation of dermal exposure potential for specific substances. The purpose of the research in this dissertation was therefore to quantitatively consider the influence of current loading-related assumptions used in deterministic dermal exposure models available to exposure assessment practitioners and to explore these influences further. This research included several specific aims. First, a study of the accuracy of exposure assessment practitioners when using available deterministic, scenario-specific dermal exposure assessment models was performed. Second, the outcomes of this analysis were used along with a comprehensive literature review to identify determinants with the greatest potential to influence dermal loading and transfer. Two specific determinants, repeated dermal contacts and skin hydration, were noted to have a statistically-significant influence on quantitative dermal loading in the literature and were

reported to have potentially complex relationships with dermal loading and transfer. These two determinants were therefore identified for additional quantitative analysis with respect to their potential to influence dermal loading and transfer. To assess the influence of repeated contacts on dermal loading, a study design based on a dermal conceptual model was developed for human skin *in vivo* to characterize the different pathways and compartments and their contributions to dermal loading following repeated contacts with a dermal test substance (elemental metallic lead). To assess the influence of skin condition and hydration, first, different measurement methods were quantitatively compared for multiple skin sites and were evaluated for their utility in skin surface sampling studies. The quantitative influence of normal skin hydration on dermal loading was then also investigated for the same test substance. Overall, the results suggested that, contrary to the general acceptance and use of additive loading principles for many dermal exposure assessment models, the application of this assumption for repeated contact scenarios in dermal exposure modeling resulted in overestimates or substantial overestimates of dermal exposure by exposure assessment practitioners. When tested using experimental measurements for scenarios including source-to-skin, skin-to-skin, and skin-to-gloves, repeated transfer tests appeared to approach a steady state loading on the skin between five and ten contacts with the test substance, consistent with other data in the literature. The results also suggested that substantial variability exists in skin hydration characteristics between different skin sites, and that skin hydration may influence quantitative dermal loading and transfer. Although additional data are needed for other substances, the measurement data collected point to a need to reconsider the way that influences on dermal loading and transfer, and particularly the additive loading assumption, are used in current deterministic dermal exposure assessment models.

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Chapter 1

A Review of Measured Dermal Loading and Transfer Values and Quantitative Influences on Dermal Transfer of Solids for Human Skin *In Vivo*

1.1 Dermal Exposure Assessments

Dermal exposure has been described as a complex process regarding the contact of a substance with the skin over time (McDougal et al. 2002; USEPA 1996; WHO 2014). Dermal exposures are increasingly of greater relative concern in many scenarios, particularly as inhalation hazards to chemicals and other substances of concern are progressively identified and mitigated (Schneider et al. 2000). In 2018, 25,000 recordable skin diseases were reported by the U.S. Bureau of Labor Statistics (BLS) at a rate of 2.2 injuries per 10,000 employees, compared to 19,600 respiratory illnesses with a rate of 1.7 illnesses per 10,000 employees (BLS 2018; OSHA 2020). This trend of a greater number of recordable skin diseases compared to respiratory illnesses has continued for more than a decade (NIOSH 2016).

The stratum corneum, or the outermost layer of the skin, is the primary protective barrier of the skin and body to the general environment. The stratum corneum is composed of flattened dead cells made up primarily of keratin protein cells held together by lipids and sebum, and stacked in layers approximately 15-25 cells thick (Madison 2003). This is equivalent to approximately 10-16 μm in thickness, but varies on different locations on the body. The stratum corneum structure is often described using a "bricks and mortar" model, in which the dead keratin protein cells are the "bricks" and the fatty or sebaceous material holding these cells together is the "mortar". The primary functions of this layer are to help retain the body’s water balance; to keep bacteria, viruses, and water-soluble compounds and solid materials out of the body; and to assist in the

regulation of body temperature. In addition to these key functions, an intact stratum corneum can also be effective at slowing chemical permeability through the skin for certain substances. Certain water-soluble chemicals can more readily absorb into the skin through the protein cells, while certain fat-soluble chemicals can absorb more easily through the lipid substrate (Madison 2003). A number of environmental factors, including frequent hand washing or excessive sun exposure, as well as certain skin conditions, can significantly alter the barrier properties of the stratum corneum and allow increased absorption or penetration of certain substances. Damage or insult to the stratum corneum from either external factors or a substance itself can also result in an increase in the absorbed or systemic dose of a substance that may rise to levels of concern (Ghadially et al. 1996).

Exposure assessment methods using modeling approaches are a critical tool for environmental and public health professionals in the absence of measured data for evaluating relevant exposure scenarios. Over time, models have been developed by academics, organizations, and agencies around the world to help improve the characterization of dermal exposure pathways. However, the U.S. EPA (2007) has pointed to the difficulty in harmonization of these methods, due in part to the use of "input variables that are not interchangeable" and a lack of methods standardization. The relative dearth of dermal exposure assessment methodologies with demonstrated accuracy and precision validated through comprehensive measurements such as skin surface sampling and biological monitoring has confounded the development of exposure guidance for the dermal route, and has also resulted in a lack of environmental monitoring data collection for dermal exposures, which has the potential to adversely impact public health (Anderson et al. 2014).

Although there are many different approaches to performing exposure assessments and different definitions of exposure and dose (i.e., exposure or external dose, absorbed or internal dose, target tissue dose, and biologically effective dose), the focus of this research centered on external exposure or dose (Sahmel et al. 2010). For the purposes of this analysis, therefore, dermal exposure assessment was specifically defined as the amount of a substance that can reach the external surface of the body or superficially lodge in the external skin layer, such that it remains available for measurement externally. According to the World Health Organization's International Programme on Chemical Safety (IPCS) 2014 criteria document on dermal exposure, dermal loading is defined as the mass or amount of an agent in contact with a specific area of the skin. The dermal loading rate has also been defined by the WHO as the mass loaded on the skin per unit time, and is typically related to the sample duration. However, the authors noted that there is no clear evidence that a longer duration will result in greater exposure, despite general acceptance of this assumption. The WHO further indicated that although a term for frequency or duration of dermal exposure is often included in deterministic dermal models, the basis for this assumption and the use of this parameter are not typically presented in a transparent manner in available models. The term dermal transfer, in comparison, is defined as the migration rate or relative amount of transfer of a substance to the skin. It has been noted that dermal transfer coefficients can be used to indirectly estimate loading on the skin surface when direct measurements are not available. Accurate dermal transfer values are therefore critical to dermal modeling efforts (WHO 2014). To date, however, the relationship between dermal loading and transfer is not well characterized for specific substances.

The availability of a quantitative approach for estimating dermal exposures that addresses all exposure pathways (i.e., object-to-skin, skin-to-skin, skin-to-clothing, etc.) and compartments (i.e., working surfaces, glove surfaces, skin surfaces, etc.), that has also been validated against quantitative dermal exposure measurements is therefore a critical need for human exposure assessment. Currently, no dermal exposure assessment prediction model exists that is both comprehensive with respect to dermal transfer via the available exposure pathways and compartments but also quantitative in nature. Many of the identified compartments and pathways with the potential for dermal transfer and loading have been only minimally quantitatively studied, if at all, and in general dermal transfer efficiency has not been well characterized (WHO 2014). As a result, few data are available to inform the relative importance of each pathway and compartment in accurately estimating quantitative dermal exposure potential.

In 2003, it was suggested that, up to that time, modelling of dermal exposure had "largely been based on commonsense rather than knowledge of the underlying processes or the results of experimental studies" (Marquart et al. 2003, p. 603). While the science has advanced since that time, there are still a substantial number of unknowns and potential gaps in dermal exposure assessment modeling efforts. Dermal transfer mechanisms are typically a significant aspect of dermal exposure models, and may influence the estimates of loading and overall dermal exposure potential more than other parameters (Xue et al. 2006). In a recent review of models using chemical transfer pathways for consumer products, the authors stated that, "Methods to predict the transfer-related parameters [from object surfaces to skin surfaces] are in urgent need" (Huang et al. 2017, p. 1192). Specifically, improved characterization of the quantitative transfer to and from the skin and the most common and relevant sources in the

environment are extremely important to improving dermal exposure assessment accuracy. A primary purpose of the research described in this dissertation was therefore to evaluate the influence of both dermal loading and dermal transfer of non-volatile chemical substances on the outcomes of available deterministic models for dermal exposure assessment. A secondary purpose was to characterize the effects of important determinants such as repeated contacts and skin hydration levels on quantitative dermal loading and transfer for the dermal exposure pathways of interest using a robust conceptual model. Ultimately, an enhanced model or series of models for different types of substances encompassing the measured transfer associated with all relevant pathways and compartments using an appropriate human *in vivo* cohort should ideally be developed. Such an updated modeling approach and associated datasets would substantially improve the ability of practitioners to quantitatively assess dermal exposures for specific substances for both regulatory compliance and exposure acceptability purposes, both crucial functions of exposure and risk assessment.

1.1.1 Approaches to Dermal Exposure and Risk Assessment, 1990-2020

Many of the common public health and regulatory agency approaches to dermal exposure and risk assessment to date have been qualitative or semi-quantitative in nature. For example, agencies and other groups in countries around the world have designated skin notations for specific substances that contain varying levels of information and detail (NIOSH 2009; ACGIH 2018; Boeniger et al. 2003; OSHA 2014; Nielsen et al. 2004). Generally, these notations qualitatively identify the potential for dermal uptake, irritation, or significant toxicity following skin exposure. While the skin

notations generally can be informative, they do not allow for a quantitative evaluation of dermal exposure and risk.

Approaches to quantitative dermal exposure limits have also been proposed by a number of different researchers and organizations over time. Some of these include: quantitative dermal exposure limits based on the total daily exposure at existing inhalation exposure limits, quantitative limits based on assessment of the dermal absorption rate or percentage, quantitative limits based on associations with contaminated surface loading, or quantitative limits based on levels of contamination on the skin (Bos et al. 1998; Brouwer et al. 1998; Fenske et al. 1994; EPA 1992; Fenske 1993; McDougal et al. 2002; Sahmel et al. 2009; ACGIH 2018). Alternatively, the use of biological exposure values, such as the biological exposure indices (BEIs) from the ACGIH, can be used as quantitative exposure limits to determine exposures by all routes (Fenske 1993; Fenske et al. 1994; ACGIH 2018).

There are a number of established dermal exposure and risk assessment prediction models, ranging from qualitative to semi-quantitative or quantitative. It has been noted that the development of dermal exposure models has been restricted by the availability of quantitative data and the variability in sampling methods that have limited the aggregation of the available data for exposure assessment modeling development (Kasiotis et al. 2020). See **Appendix A: A Brief Summary of Semi Quantitative and Quantitative Methods for Assessing Dermal Exposures** for an overview of the dermal exposure assessment approaches, models and methodologies that have been developed chronologically over time. A number of these methods have used or recommended quantitative or semi-quantitative dermal loading values or dermal transfer efficiency values (as noted in **Appendix A**).

It has been noted generally that approaches to dermal exposure modeling in the U.S. compared to Europe have been more deterministic in nature, consisting of calculations using equations that employ first order scientific principles. By comparison, approaches to dermal exposure modeling in Europe have often taken more of a "knowledge-based" approach, in which exposure factors are categorized and groups of possible combinations of exposure determinants are presented based on previous measurements. Marquart et al. (2001) reported that the advantages of knowledge-based models include that they are more user-friendly at all levels of technical expertise, that they require data only on activity patterns and sources, and that they can be broadly applied to many different kinds of exposure scenarios. They noted that deterministic models, on the other hand, can be more useful for detailed calculations to quantitatively determine dermal exposure and uptake; they can also be coded into computer programs for ease of use and may be better for understanding the challenges and complexity of calculating dermal doses. The researchers also noted the limitations of both types of approaches, pointing to the limitations in accuracy and precision of knowledge-based models, the need for validation, and questions regarding the relationship between skin contamination and the relevant biological dose. Regarding deterministic models, the authors reported that the results of deterministic models can be difficult to interpret and apply in risk assessments; that they require specific measurement inputs, such as dermal loading data or dermal uptake data; and that the accuracy and precision of the measurement methods used may limit the utility of these models (Marquart et al. 2001).

1.1.2 Determinants of Dermal Exposure Assessment

There is a list of common determinants that are routinely employed in dermal exposure assessment. Semple (2004) noted that the factors needed to determine the mass of dermal uptake of chemicals included exposure intensity, surface area exposed, duration of skin contact, and frequency of repeated exposure. Marquart et al. (2003) broadly divided the determinants of dermal exposure into three categories: direct contact factors, surface contact factors, and deposition factors. Within each of these categories, the authors further identified important categories of parameters, including substance and product characteristics, tasks done by the worker or user, process techniques and equipment, exposure control measures, worker or user characteristics, and area and situation. Different types of models have been used to consider these determinants. The more general scenario-based or knowledge-based models can be efficient when assessing dermal exposures in many different operations with activities that can be classified into basic types of tasks, such as pouring, mixing, or spreading. However, when drilling down to the individual worker and task level, a more deterministic modeling approach based on task-specific quantitative information and physical-chemical properties of relevant substances often becomes necessary. Ultimately, the determinants of dermal exposure assessment can be used qualitatively or assessed quantitatively to refine estimates of dermal exposure potential. See **Appendix B: Dermal Exposure Modeling Determinants** for additional information and background on these primary exposure determinants that have been previously considered in dermal exposure modeling.

Broadly, there are two types of deterministic, physical properties-based approaches that have been used to perform dermal exposure assessments. The first of

these employs a mathematical approach to estimating dermal exposure using assumptions or measurements regarding the quantitative loading of substances on the skin surface and the subsequent absorption of these substances through the skin (see **Appendix B: Eq. B-1**). This screening-level method typically employs a basic approach to dermal absorption assuming either 100% absorption of the applied dose, or some fractional absorbed dose expressed as a percentage of the applied dose. However, this approach can have substantial limitations based on the number of screening-level assumptions that must be made and the accuracy of the dermal absorption assumption for the scenario of interest. The second broad approach builds on the first approach, and substitutes empirical data regarding the flux, or rate of absorption or penetration, of specific substances through the skin barrier rather than using more simplistic assumptions regarding the fraction absorbed. These flux data, along with quantitative estimates or semi-quantitative assumptions about loading on the skin surface, can be used to estimate or calculate dermal exposure (See **Eq. 1**). However, both types of approaches may use similar assumptions or data regarding the quantitative loading of a substance on the skin surface, and therefore may be subject to similar limitations.

For human health risk assessment purposes, the dermal loading parameter has often been given quantitative measurement units of mass per surface area of skin (surface density) in mg/cm^2 or $\mu g/cm^2$, which then allows for the calculation of dermal uptake or flux through the skin in $\mu g/cm^2$-hour, depending on the surface contact time or the amount absorbed into the skin before removal. The flux or steady-state flux (J_{ss}) is the rate at which the mass of a substance is absorbed across a defined skin area over time, and is a frequent metric for the quantitative uptake of substances through the skin (McDougal et al. 2002; Sahmel et al. 2009; Frasch et al. 2014; Frasch et al. 2018b;

Frasch et al. 2018a). For an event with a known time duration and skin surface area of contact (assuming steady state flux, or an infinite reservoir of the chemical of interest), this can be characterized as:

$$D_{event} = J_{ss} \times A \times t_{event} \quad \textbf{(Eq. 1)}$$

where D_{event} is the mass of uptake of the chemical of interest (mg/event), J_{ss} is the steady state flux for the chemical, assuming an infinite reservoir of the chemical of interest (mg/cm^2-hr), A is the surface area of skin exposed in cm^2, and t_{event} is the duration of the exposure event in hours (McDougal et al. 2002; Sahmel et al. 2009; Paustenbach 1990; Paustenbach et al. 2008). This equation is useful for solids or for substances with a known or measured steady-state flux value. Alternatively, the concentration of the substance of interest and the dermal permeability coefficient (K_p) in units of length or depth of skin penetration per time (cm/h), also described as the concentration-normalized penetration rate, can be substituted for J_{ss} where appropriate, particularly for liquids or aqueous solutions.

The quantitative loading on the skin or dermal transfer efficiency can be estimated using default data published or relied upon by regulatory agencies such as the U.S. EPA, the California OEHHA, REACh in the E.U., and other individual studies for certain types of agents or scenarios (Refer to **Appendix B** for a summary of default dermal loading and transfer values). These default values cover a wide range and include estimates of between 1 to 3 mg/cm^2 based on experimental data for liquids and between 0.005 and 14 mg/cm^2 for solids, depending on the scenario (USEPA 2011; COEHHA 2011; Finley et al. 1994; Cinalli et al. 1992; Camann et al. 2000b; Clothier

2000b; Clothier 2000a; Edwards et al. 2001; Gorman Ng et al. 2012a; IOM ND; Kissel et al. 1998; Rodes et al. 2001; van Wendel de Joode et al. 2005b; van Wendel de Joode et al. 2005c). A substantial number of these values were experimentally determined rather than collected in real-world scenarios or circumstances.

When the refined, flux-based approach to dermal exposure assessment (**Eq. 1**) is more appropriate for a given scenario, experimental measurements or estimates of the amount retained on the skin can be used instead of relying on default assumptions. The physical properties (i.e., liquid, solid, aerosol, gas) of the agent being evaluated are very important for understanding the potential for uptake and therefore for determining an appropriate metric for the quantity on the skin surface. For example, Belsey et al. (2011) found that certain substances in an aqueous form will readily permeate the skin, but the same substances applied on the skin as a dry residue can have a significantly lower absorption potential. If a substance has some solubility in surface sweat, however, a dry residue can become an aqueous solution. Some analyses have therefore noted that, based on the nature of the diffusion process of contaminants through the skin surface, the concentration, rather than the mass, on the skin surface can be more relevant to quantifying dermal uptake (Cherrie et al. 1995; Vermeulen et al. 2002).

Despite this distinction between mass vs. concentration loading, the mass loading on the skin surface is more easily and directly measured, allowing for an estimate of the reservoir on the skin surface, whereas the concentration must be evaluated based on the solubility of the substance in human sweat (or sometimes using water as a surrogate and therefore the concentration in an aqueous solution). The amount of a liquid that can be retained on the skin surface before it drips off or evaporates is also far more difficult to estimate than the mass loading of solids or semi-

volatile compounds. This loading range has been estimated, although often using higher viscosity liquids that may be an inappropriate surrogate for low viscosity liquids (Vermeulen et al. 2002; Stefaniak et al. 2014; Cinalli et al. 1992). It may also be true that in practice, the distinction between the mass loading and the concentration loading do not substantially influence the outcome of the assessment, such as when there is a single contaminant at a constant concentration, or if the amount of loading is very small (Vermeulen et al. 2002). Ultimately, the mass loading on the skin may be an appropriate upper bound of the potential concentration on the skin surface for any substance that is not 100% soluble in water or surface sweat, since mass loading alone may overestimate uptake potential (Stefaniak et al. 2014; Stefaniak et al. 2006). In an evaluation of the relative suitability of mass per time vs. volume per time to describe dermal exposure, it was found that mass per time has been recommended by researchers for certain dermal exposure models based on analyses of variance, although both metrics can be used (McNally et al. 2019; Kromhout et al. 2004). It has also been reported that, in actual practice, there is a correlation between the amount of a substance that is removed from the skin and the amount absorbed (Brouwer et al. 1998; Brouwer et al. 2000).

Other methods and models have also been proposed to estimate dermal exposure directly from surface contamination and can be useful in scenarios where the dermal loading of a chemical or substance is unknown. Such models can be used with the assumption that 100% of the substance loaded on the skin is absorbed, as an upper bound estimate. However, the dermal transfer coefficient must be very well characterized for this approach to provide reliable results (Cohen Hubal et al. 2000). It is apparent from these models that an accurate characterization of loading on the skin surface itself is critical to accurately estimating dermal exposure for risk assessment

purposes. It is rare that a steady state flux condition, or an infinite amount of loading on the skin surface, is present (i.e., immersion in a bath of the substance of interest, or availability of a continuous, complete layer of a substance on the surface of the skin). Far more commonly, skin contacts with substances of interest occur as incidental, repeated, or splash events. As a result, a more detailed examination and characterization of the quantitative dermal loading parameter is warranted to improve the quality and accuracy of dermal exposure assessment efforts.

1.2 Characterization and Measurement of Dermal Loading and Transfer

The extent to which estimates of dermal transfer mechanisms affect the results of an exposure assessment using available dermal models is often unknown. However, the available data in the published literature indicate that an accurate determination of dermal absorption is fundamentally dependent on an accurate understanding of the dermal loading. Buist et al. (2009) reported that inaccurate loading estimates or measurements may influence absorption estimates by up to a factor of 100. They further noted that, “in order to prevent unsafe or overly conservative outcomes of risk assessments, the dermal loading dependency of relative dermal absorption should be taken into account” (Buist et al. 2009, p. 227). The relationship between dermal loading and dermal absorption is also often a complex one. As noted by Beamer et al. (2009), part of the difficulty in adequately quantifying transfer to the skin is that it may be related to a number of other relevant parameters, including surface characteristics; the nature of contact (including frequency, duration, and pressure); time since application or contact; and temperature and humidity. This study also reported that there was significant

variability, as well as methodological inconsistency, noted in the reporting of dermal transfer efficiency values in the literature over time.

Potentially adding to the complexity of the relationship between dermal loading and absorption, some studies have reported an inverse relationship between dermal loading and absorption. However, this phenomenon is often associated with the use of "infinite" loading in *in vitro* scenarios where the absorptive capacity of the skin reaches a maximum rate of absorption that ultimately limits the amount of a substance that can be absorbed, regardless of the amount loaded on the skin (Buist et al. 2009; Wester et al. 1976; Bunge 2005; Hostynek 2003). This inverse relationship has been observed more often for scenarios with wider ranges of reported dermal loading values, and less often for scenarios in which the range of dermal loading values only covered one or two orders of magnitude (Buist et al. 2009). These data further point to a need for increased accuracy in dermal loading estimates or measurements using realistic, real-world scenarios. Another potential complexity is the three-dimensional nature of skin loading; substances may be present both on and in the skin barrier, and assessment of dermal loading must take this factor into account (Schneider et al. 2000). Despite these potential variabilities, complexities, and limitations, as previously noted, the amount of a substance that is removed from the skin correlates with the amount absorbed (Brouwer et al. 1998; Brouwer et al. 2000).

1.2.1 Frameworks for the Characterization of Dermal Loading and Transfer

To develop a robust estimate or framework for dermal loading, a comprehensive approach must be used to characterize all relevant exposure sources and pathways. One robust example is the Schneider et al. (1999) conceptual model for dermal

exposure assessment, which includes the following dermal exposure compartments: Source, Surface contaminant layer, Air, Outer clothing/Gloves contaminant layer, Inner clothing contaminant layer, and Skin contaminant layer. The model has also been updated to include the Oral compartment by Gorman Ng et al. (2012). Some of the key pathways described in this model include: (1) air-to-skin, (2) source-to-skin, (3) skin-to-skin, (4) surface-to-skin, (5) clothing-to-skin, (6) gloves-to-skin, and (7) saliva-to-skin (See **Figure 1-1**). Few published data are currently available to address most of the individual pathways described in this conceptual model, and nearly all available data address only surface-to-skin or object-to-skin transfer. Per Gorman Ng et al. (2012b), these data comprised approximately 84% of available measurements as of 2012; of these transfer efficiency measurements, the variability in published values has also been significant (0-157%).

Other approaches to evaluating dermal transfer have identified micro-activity and macro-activity approaches (Zartarian et al. 2000; Cohen Hubal et al. 2005). A micro-activity approach is one in which each exposure is estimated or modeled as a series of individual or discrete events with specific descriptions and durations that are assumed to be additive with each contact. The macro-activity approach, in contrast, was conceptualized to provide dermal transfer efficiency coefficients that had been empirically derived in an effort to consolidate all of the mass transfer occurring over a series of contact events into a single estimate (Zartarian et al. 2000). The micro-activity approach was used in the U.S. EPA's Residential Stochastic Human Exposure and Dose Simulation Model for Pesticides (SHEDS) algorithm. For a particular exposure scenario, this probabilistic model allows for the simulation of a progression of contact events with a source or object, characterized by the surface characteristics (such as

textured, smooth, water, food, etc.). Each object or source contact is then linked with an exposure pathway (such as skin-to-surface contact, skin-to-water contact, or hand-to-mouth contact). Using a simulation that creates a snapshot at each 5 seconds of the scenario or day, transfer values are calculated using surface residues with randomly-sampled exposure factors (Zartarian et al. 2000).

1.2.2 Measurement of Dermal Loading and Transfer

Once a framework for characterization of dermal exposures has been established, an appropriate methodology must also be developed to directly measure the transfer of substances within the framework. A number of publications have described the methodologies available for measuring or monitoring dermal exposures to the human body. Broadly, these categories include indirect methods, such as surface or environmental wipe sampling or biological monitoring, and direct methods, which aim to directly characterize exposures to or on the skin surface (Boeniger et al. 2015; McArthur 1992). While sometimes very useful, indirect methods are beyond the scope of the current evaluation. The categories of direct methods include three general types of techniques: surrogate or interception techniques from the skin surface, techniques for removal from the skin surface, and *in situ* techniques such as fluorescent tracers (See **Appendix C: Measurement of Skin Surface Loading and Transfer**) (Boeniger et al. 2015; Fenske 1993; Cherrie et al. 1995; Kasiotis et al. 2020). It is important to note that in many scenarios, direct methods of skin surface sampling may not fully characterize dermal exposure. This could be due to rapid absorption into the skin surface, evaporation from the skin surface, or incomplete recovery of the substance of interest from the skin surface. It is also possible that the skin surface area measured using a

specific sampling method may be insufficient to fully characterize exposure (i.e., handwashes or skin patches on the hands will not consider the potential for splashing exposure to the forearms or the face) and these factors must be considered before designing a sampling study (Kromhout et al. 2001; Vermeulen et al. 2002). And finally, many dermal sampling methods or approaches may offer only a snapshot in time and will not accurately characterize loading over time, such as the unique characteristics of loading following repeated contacts (Brouwer et al. 1999; Hubal et al. 2008).

In some situations, multiple methods used together may be necessary to accurately measure dermal loading both on and in the stratum corneum within a defined exposure duration period, and sampling intervals must be carefully determined based on known chemical properties and the duration of exposure (Schneider et al. 2000). Further, the complementary use of indirect methods such as biological monitoring may be necessary to confirm dermal loading measurements (Boeniger et al. 2015). Depending on the method used, skin wiping may also result in higher exposure measurements than skin rinsing, although the inverse relationship has also been noted, depending on the substance evaluated (Gorman Ng et al. 2013; Kasiotis et al. 2020; Fenske et al. 1999; Ng et al. 2014a). However, overall, it is more useful to have imperfect data which nonetheless offer an initial characterization of the overall potential for dermal transfer and loading, rather than no data at all. Sampling methods with less than 100% accuracy and efficiency may still offer highly useful information for risk assessment purposes when used appropriately and with some caution regarding the results.

1.3 METHODS: Literature Review of Dermal Loading and Transfer Values

Given the uncertainty and tremendous variability in default values for dermal loading of solids in the published literature as cited by certain regulatory agencies and used in certain dermal exposure and risk assessment screening models (approximate range: 0.00054-14 mg/cm^2), and the reported finding that models using these values can overestimate or substantially overestimate dermal exposure potential (Creely et al. 2005; Marquart et al. 2001), a literature review was undertaken to better understand the range of quantitative, measured values available to characterize dermal loading under a variety of conditions and for a range of different types of solid and semi-volatile substances. Some default loading values are now 10 to 20 years old, and it was of interest to understand the current range of reported quantitative loading values in the literature compared to these values. Measured transfer values, where available, are also important to defining an appropriate dermal exposure assessment framework and to ensure that the appropriate pathways and compartments are considered. Further, observed trends in certain influences on quantitative dermal loading (such as the effects of dermal contact pressure and contact duration, the effect of repeated contacts, and the effects of dermal hydration or wetting) are likely to have a substantial influence on the development and refinement of this framework.

The literature review sought to include all quantitative analyses of dermal loading or transfer to human skin that have been performed since 1990 to measure skin loading of non-volatile and semi-volatile compounds in various forms and measured transfer efficiencies for these substances where relevant. For reference, a volatile compound has been defined as a compound for which more than 95% by weight will volatilize within six months under ambient conditions, while a semi-volatile compound has been defined as

a compound for which 5-95% will evaporate under the same conditions (Võ et al. 2014). Regulatory bodies have sometimes used 0.1 mm Hg as a cut point for vapor pressure between volatile and semi-volatile or non-volatile compounds, although it has been acknowledged that vapor pressure is very difficult to measure at these levels (Võ et al. 2014). This review was limited to *in vivo* human studies with reported skin loading or transfer measurement values to or from the living skin surface itself (i.e., studies using interception methods such as dosimeters or patch samplers were excluded). Hand to mouth exposures have also been reviewed elsewhere and are not included here (Gorman Ng et al. 2016; Gorman Ng et al. 2012b; Ng et al. 2014b; Christopher et al. 2007a; Sahmel et al. 2015b).

An initial literature search using the PubMed and Web of Science databases to determine the total number of available studies addressing dermal loading and transfer was ultimately determined to be very incomplete, primarily due to the wide variations in terminology used in published studies to describe dermal exposure, loading, and transfer. Relevant studies were therefore also identified by a combination of literature searches using a variety of search terms (“dermal transfer” and “chemical”, “skin transfer” and “chemical”, “dermal loading” and “chemical”). These additional searches resulted in about 1,000 additional references, of which approximately 10% were determined to be possibly relevant. The search was subsequently updated and augmented by a review of the cited references in the studies that were identified as relevant. Additionally, targeted searches were performed of the U.S. NIOSH website, and in particular of the Health Hazard Evaluation (HHE) database, as well as the websites of identified institutions including the Institute for Occupational Medicine (IOM) in Scotland, the Environmental Protection Agency (EPA) and the Occupational Safety

and Health Administration (OSHA) in the U.S., and the U.K.'s Health and Safety Executive (HSE). As noted above, a key goal of the literature review was to capture all studies addressing either quantitative dermal loading or transfer, even though there can be important differences in these types of data. In practice, however, a majority of the data reported in the literature are for dermal loading as a snapshot in time based on available sample collection methods, and these values account for some often unknown combination of loading and transfer factors that need to be further considered in order to better characterize the data and to improve default values for modeling purposes.

In total, approximately 130 potentially relevant references were identified. First, each study was screened to confirm that it contained measured loading and/or transfer to or from human skin *in vivo*. Studies that used other methods of loading measurement, such as interception on surrogate surfaces, were excluded. The purpose of this exclusion was to allow for the characterization of the range of loading values that has been reported specifically for human skin. The remaining relevant studies were then categorized according to the type of quantitative data reported. These categories included (1) measurement data for source-to-skin loading and transfer, typically for a specific substance; (2) measurement data for other pathways of loading and transfer to and from the skin (i.e., skin-to-skin, skin-to-clothing, skin-to-gloves, and skin-to-surfaces); and (3) measurement data on determinants that could quantitatively influence dermal loading or transfer. A total of ten determinants with evidence of quantitative influence were identified, including: physical nature of the solid material, texture of the contact surface, body location by skin surface, contact duration, contact pressure, nature or motion of contact, repeated contacts, skin hydration, surface hydration or moisture, and surface loading. For studies where quantitative loading or a loading rate was not

reported in μg/cm^2 or μg/cm^2/hour, loading estimates were calculated in these units where possible for direct comparison among the studies, and are noted in a separate column in each results table. When needed for the calculations, skin surface areas were taken from the U.S. EPA's Exposure Factors Handbook and included a mean of 1,070 cm^2 for both adult hands and a mean of 500 cm^2 for both child hands, as well as 400 cm^2 for the face and 1,700 cm^2 for the neck (USEPA 2011).

1.4 RESULTS: Literature Review of Dermal Loading and Transfer Values

1.4.1 Quantitative Source-to-Skin Dermal Transfer for Chemical-Specific Substances

Quantitative measurements for transfer from source-to-human skin *in vivo* of solids and semi-volatile substances were identified in a total of 52 studies (See **Tables 1-1 to 1-8**). These studies measured transfer to and from the skin for pesticides, fragrance residues, Tinopal powder, soils, metals, polybrominated diphenyl ethers (PBDEs), polycyclic aromatic hydrocarbons (PAHs), antineoplastic drugs, and alkanolamines. Most studies measured transfer primarily to the hands, although transfer to the face and neck was also reported in some instances. Consistent with air sampling data, surface and skin sampling results were generally found to be lognormally distributed (Beamer et al. 2009; Adgate et al. 1995; Klein et al. 1997). Analyses of variability for dermal exposure measurements have shown total, within-worker, and between-worker geometric standard deviations of 2.55, 1.98, and 1.47, respectively, which are exceedingly similar to published standard deviations for inhalation exposure measurements (Kromhout et al. 2001). However, there have been some reported

departures from lognormality for quantitative dermal loading distributions (Rajan-Sithamparanadarajah et al. 2004).

For nearly all studies and all substances evaluated, it was observed that the mean or GM dermal loading on human skin *in vivo*, regardless of the scenario or source, appeared to be approximately 1,000 μg/cm^2 (1 mg/cm^2) or less (See **Tables 1-1 to 1-8**). Dusts may be an exception to this general observation for dermal transfer and loading measurements, although this appeared to be true primarily for immersion scenarios, which were also characterized as maximum loading tests. Immersion of the hands into zinc metal dust resulted in a mean of 4,840 μg/cm^2 in one study (Hughson et al. 2005), although for other scenarios involving powders or dusts, skin loading levels did not approach 1,000 μg/cm^2. For dermal contact specifically with mud or very wet soils, such as children playing in the mud, mean dermal loading also exceeded or substantially exceeded 1,000 μg/cm^2 (1 mg/cm^2), and reported results were in the range of 0.47-140 mg/cm^2 (470-140,000 μg/cm^2) for this specific scenario (Kissel et al. 1996b). Other soil loading scenarios reported GM adherence values of between 0.5 and 1,500 or 2,100 μg/cm^2 (Finley et al. 1994; Holmes et al. 1999; Shoaf et al. 2005; Choate et al. 2006)

For many scenarios and substances, dermal loading on human skin *in vivo* was one to four orders of magnitude below 1,000 μg/cm^2. The results of this analysis suggest that some existing default values for estimating dermal loading of substances on human skin *in vivo* may be too high or orders of magnitude too high, although it is also unlikely that the existing default values will underestimate dermal loading. However, it is possible that some of the reported measurements in the literature underestimated the total dermal loading for certain scenarios. These results could be due to the sampling method and incomplete removal, or could be the result of substances that had already been

absorbed into the skin prior to sampling. The level of toxicity of the substances studied could also have influenced contact with and subsequent loading on the skin surface. Further, a number of studies did not report the sampling method efficiency or perform a validation to understand the total removal efficiency. Given the consistency in the measured loading range over a large number of measurements and studies, however, the mean value of 1,000 μg/cm^2 or 1 mg/cm^2 may be appropriate to consider as a potential benchmark for loading on human skin, with additional substance or scenario-specific analyses where warranted. This value is also consistent with the research that has been previously conducted in support of development of the dermal Advanced Reach Tool (dART) model, in which a value of 1 mg/cm^2 was noted for solids as part of an analysis of maximum retention capacity on the skin surface (Goede et al. 2018).

1.4.2 Contribution of Transfer Pathways Other Than Source-to-Skin

There are far fewer studies and measurements in the literature describing the potential pathways for dermal exposure as described by Schneider et al. (1999) and subsequently updated (Schneider et al. 1999; Gorman Ng et al. 2012b). A total of 20 studies were identified in the published literature that either directly or indirectly addressed air-to-skin transfer of semi-volatile organic compounds (SVOCs), air-to-skin and settled surface dust-to-skin transfer, clothing-to-skin transfer, gloves-to-skin transfer, and skin-to-skin transfer. Of these, there were five studies identified containing direct measurement data of the transfer between these pathways and compartments, and the relevant results from these studies are presented in **Table 1-9**.

1.4.2.1 Air-to-Skin Transfer of Semi-Volatile Organic Compounds (SVOCs)

There is sufficient evidence in the literature to support the significance of the air-to-skin transfer pathway for certain volatile compounds, and in some instances, this exposure can constitute a substantial proportion of the total body exposure (Garrido et al. 2019). Some examples of these compounds include phenol, nicotine, and nitrobenzene, all with vapor pressures between approximately 0.2 and 1 mm Hg at room temperature (Piotrowski 1971; Piotrowski 1967; Beko et al. 2018; Beko et al. 2017; Jones et al. 2003). Other researchers have also reported that transfer of semi-volatile compounds (with vapor pressures that are 4 to 14 orders of magnitude below volatile compounds) to the skin could be greater than initially assumed or estimated (Wei et al. 2019). Weschler and Nazaroff (2012) reported that semi-volatile compounds measured in handwipes may reflect exposure from both contaminated surfaces and direct deposition from the air. Garrido et al. (2019) also measured the passive dermal exposure potential of a number of phthalates with forehead wipe samples using isopropanol-soaked gauze pads (approximately 15 cm^2 skin surface). The results showed substantial variation in loading for the detected phthalates, ranging from 11 $\mu g/m^2$ to 11,095 $\mu g/m^2$ (0.0011-1.1 $\mu g/cm^2$). The authors reported that some phthalates penetrated deeper into the skin over shorter time periods and were found at higher concentrations at greater depths.

1.4.2.2 Air-to-Skin and Settled Surface-to-Skin Transfer of Dusts

Hughson and Cherrie (2005) noted that dermal loading measurements increased with increasing airborne dust concentration data, which is not surprising given that higher airborne dust levels are more likely to settle out onto surfaces. Perhaps

unsurprisingly, in an evaluation of solids that examined the effect of dustiness on transfer, Gorman Ng. et al. (2013) found that deposition is unlikely to be a potential pathway of exposure for non-dust solids or “coarse dusts, granules, flakes, or pellets”. However, for dusty materials, the deposition pathway cannot be ruled out. For the dustiest material tested, dermal loading ranged from <0.07 μg/cm^2 to 3.35 μg/cm^2. Edwards et al. (1998) reported that the dust fall rates indoors averaged 0.37 μg/cm^2/day in the summer and 0.22 μg/cm^2/day in the winter. Winter deposition was primarily associated with combustion sources and summer deposition was associated with ventilation from the outdoors. Regarding the potential for SVOC exposure from settled dust, it has been reported that the direct contact or transfer pathway appears to be more important than the air to surface pathway for certain semi-volatile substances (Salthammer et al. 2018; Sukiene et al. 2016).

1.4.2.3 Clothing-to-Skin Transfer of Semi-Volatile Organics

Weschler et al. (2012) noted that based on the available evidence, only a small amount of protection appeared to be provided with clothing from contact and absorption of semi-volatile compounds. The authors further reported that the transfer of skin oils to clothing appears likely to enhance the partitioning of semi-volatile chemicals into the clothing from the air. Morrison et al. (2016) similarly found that phthalate exposure increased approximately 3- to 6-fold when the subject was wearing previously contaminated clothing. On the other hand, other studies have demonstrated a protective effect associated with clean, previously unexposed clothing (Morrison et al. 2017a; Beko et al. 2018; Morrison et al. 2017b; Morrison et al. 2016).

1.4.2.4 Influence of Clothing or Gloves on Skin Transfer

Driver et al. (2007) investigated the effects of different types of pesticide use activities on the penetration potential of single-layer clothing using data from the U.S. EPA's pesticide handlers' exposure database (PHED). Comparisons of 2,129 paired samples from inside and outside clothing were analyzed for quantitative differences; for just under 60% of the pairs, the inside sample was below the limit of detection, and approximately 70% of the outside samples were found to be at or below 1 μg/cm^2. Percent clothing penetration by pesticide application ranged from a mean of 4.14% for airless sprayers to 24.97% for rights-of-way sprayers; mean penetrations for liquid pesticides ranged from 11.71% to 19.98%, and for solid pesticides ranged from 7.43% to 10.69%. The authors noted that the U.S. EPA's default assumption of 50% clothing penetration represents an upper bound value relative to the measured data (Driver et al. 2007).

Lees et al. (2018) evaluated the transfer efficiency of explosive residues from cotton or polycarbonate (clothing or luggage) material to either the skin or latex or nitrile gloves, and then subsequently to a second surface. One study participant pressed a gloved index finger onto the first surface, and then pressed the gloved fingertip onto a second surface to measure the potential for transfer from the first surface to the fingertip and then to the second surface. According to the authors, a fingertip pressing time of 3 seconds was used with an applied mass (described as force) of 1 kg on the surface; three samples were collected for each of nine explosive residues. Transfer was quantified using a pixel-counting imaging method, and was reported as a percentage. Results demonstrated that cotton retained a greater mass of the explosive residues than the polycarbonate, and the adhesion of residues to the fingertip was greatest for skin,

followed by latex, followed by nitrile. It was hypothesized that the hygroscopic nature of the explosive residues comprised of inorganic salts enabled their preferential transfer to the skin (Lees et al. 2018). Christopher et al. (2007b) reported that the use of gloves appeared to increase transfer to the skin for saffron, although the result was not statistically significant.

1.4.2.5 Skin-to-Skin Transfer

Zainudin et al. (2004) reported that while the dermal transfer efficiency of Tinopal powder from a source to the skin had a mean of 38%, the subsequent transfer of the powder from the skin of the hands to the mouth or lips had a mean of 8.2%. Christopher et al. (2007b) reported a skin-to-skin transfer efficiency for saffron of 38% contact between the hands and the face. This was also similar to a reported hand-to-lip transfer efficiency of micro-biologicals of between 34 and 41% (Rusin et al. 2002), although a thorough comparison between chemical and microbiological dermal transfer efficiencies is beyond the scope of this review.

1.4.2.6 Skin-Back-to-Surface Transfer for Solids

For scenarios evaluating the subsequent transfer of dermal residues back off of the skin with subsequent additional contacts with other surfaces, Lees et al. (2018) reported that nearly all explosive residues tested remained adhered to the skin after initial transfer regardless of the pattern of transfer between the initial and final contact surface. The authors noted that <7% transferred to the final contact surface, whether cotton or polycarbonate.

1.4.3 Quantitative Characteristics of the Data on In Vivo Human Dermal Transfer of Solids and Semi-Volatile Compounds

1.4.3.1 General Characteristics of Dermal Transfer

Dermal transfer characteristics have sometimes been reported to vary substantially between different types of solid substances. It has been noted that the physical-chemical properties of different solids are very important (Cohen Hubal et al. 2005). As part of the literature review, the available studies were analyzed to identify trends in the effects or characteristics of direct transfer to human skin in vivo. Information on the following effects was evaluated and is discussed below: influence of the physical nature of a solid material; influence of skin contamination by body location; influence of contact duration; influence of contact pressure; effect of repeated contacts; effect of skin hydration (or wetting); effect of surface hydration or surface moisture content; and influence of clothing, gloves, and secondary surfaces on dermal transfer. Although the effect of surface loading available for transfer was also considered, it was at times difficult to differentiate this broader determinant from other related influences (such as skin hydration, repeated contacts, contact motion, etc.); further, this parameter was not always reported.

1.4.3.2 Influence of the Physical Nature of a Solid Material

The physical properties of a solid with the potential to contact the skin demonstrated the potential for significant influences on dermal transfer. Gorman Ng. et al. (2013) reported an effect of dustiness on dermal exposure by surface contact, independent of particle size, particularly for smooth surfaces. The results suggested that

“dusty substances may transfer from smooth surfaces to the skin more favorably than non-dusty substances”, but that this effect was smaller for textured surfaces such as fabric or wood.

Multiple studies have suggested that the particles most likely to adhere to the skin are less than 100 μm in diameter, and closer to an upper bound of 60 μm (Edwards et al. 1999; Rodes et al. 2001). Similarly, Kissel et al. (1996a) and Spalt et al. (2009) reported that for dry soils, particles available for dermal transfer were likely to be 65 μm or less, but for wet soils, could be up to 150 μm or more at high moisture contents (>10%). Rodes et al. (2001) found that for fluorescein-tagged particles of less than 80 μm in diameter, the mean surface loading ranged from approximately 30 $\mu g/cm^2$ to 45 $\mu g/cm^2$. Avissar et al. (2004) reported that the transfer of iron in the elemental metallic form to skin appeared to be largely attributable to chemical transfer through dissolution rather than by physical or mechanical removal or dislodgement.

1.4.3.3 Influence of Texture of the Contact Surface

Christopher et al. (2007a) found that the texture of the surface in contact with the skin influenced the rate of transfer. The authors reported that smooth, non-porous surfaces such as glass appeared to result in the greatest transfer to the skin. This was followed by smooth, porous surfaces, and finally by textured surfaces such as carpet, which had the lowest transfer efficiency. However, these results were not statistically significant. Additionally, in an initial study in 2005, it was reported that the characteristics of the contact surface did not appear to result in statistically significant differences in skin loading (Cohen Hubal et al. 2005). However, in a second study in 2008, the authors did find a statistically significant difference in the effects of contact surface transfer, but only

for the first contact (Hubal et al. 2008). Rodes et al. (2001) found that textured surfaces such as carpet reduced or limited transfer to the skin. Their results suggested that for a clean hand and a single press onto a surface loaded with house dust, the transfer efficiency was approximately 70%, whereas transfers from carpeting were only about 7% of the transfer associated with a solid surface. Zainudin and Semple (2004) also reported that smooth surfaces resulted in a higher percentage of skin contact and transfer compared to rougher surfaces, and Gorman Ng et al. (2013) found that dermal transfer efficiencies were greatest for metal surfaces and lowest for textured surfaces, specifically fabrics. Studies of the dermal transfer of pesticides have also reported higher transfer to the skin of residues from smooth surfaces than from textured surfaces such as turf or carpet (Zartarian et al. 2000; Camann et al. 2000a; Clothier 2000b; Clothier 2000a).

1.4.3.4 Influence of Body Location of Skin Surface

Rajan et al. (2004) found that for solids versus liquids transfer through handling objects, transfer to the hands was significantly lower for solids than liquids. However, for spray dispersion, solid and liquid transfer to the hands was far more consistent. Hughson and Cherrie (2005) reported that higher levels of zinc deposited on the palmar surface of the hands than the dorsal surface during normal industrial operations involving zinc powders and zinc oxide. They estimated that the ratio of loading on the palmar surface vs. the dorsal surface was approximately a factor of 3.

Kasiotis et al. (2020) also found that for exposure scenarios such as pouring, handling, immersed objects, and handling contaminated objects, the majority of the exposure was to the hands; however, this was not the case for spraying or dumping

scenarios. Differences in exposure were also observed at times between the dominant and non-dominant hands, and the hand with higher exposure depended on the scenario being evaluated. During the handling of contaminated objects, there was no difference noted in exposure between the two hands. Rodes et al. (2001) reported that after single, dry whole-hand presses on hard surfaces, a substantial fraction of the skin of the palmar surface of the hand did not contact the surface (>60%), particularly at the center of the palm. Brouwer et al. (1999) reported a similar effect.

1.4.3.5 Influence of Contact Duration

Brouwer et al. (1999) found no significant difference in loading for durations of contact for Tinopal powder ranging from 3 to 30 seconds. However, when skin loading, skin moisture, and contact frequency were also considered in additional ANOVA analyses, the duration of contact was a significant determinant of skin loading. McArthur and Lees (1995) reported an increased transfer of mass for oil to a surface sampling medium after between 5 and 20 minutes. However, it was possible that this increased transfer was a result of the nature of the test substance and the sampling medium, and may have unknown relevance regarding the transfer to human skin. Roff et al. (2000) reported that transfer efficiency of strontium increased linearly with contact times from 5 to 30 seconds. Cohen Hubal et al. (2005) found no significant difference between two different contact durations (2s and 20s) in a study of transfer of Tinopal powder from carpets and laminate to the hands. Similarly, Hemond et al. (2004) reported that short periods of contact with pressure-treated wood that were seconds in length produced nearly the same skin loading of arsenic as longer contact periods of up to a minute.

Christopher et al. (2007a) also reported no association between the duration of hand contact and the dermal transfer of saffron.

1.4.3.6 Influence of Contact Pressure

Rodrigues et al. (2001), in a guidance document prepared by the European Group for Efficacy Measurements on Cosmetics and Other Topical Products (EEMCO), reported that the skin is capable of enormous changes in shape or size through the application of both internal and external pressure. In 2003, Silver et al. reviewed the effects of internal and external mechanical forces on the skin. With respect to the epidermis, the authors reported that external tension exerted on this layer (such as in the form of contact pressure) could stretch the corneocytes in the epidermis and potentially change their shape. They also indicated that longer-term or routine external mechanical loading could cause thickening of the epidermis. It is unclear, however, whether such effects could alter the potential for dermal transfer or adherence of substances to the external skin surface (Silver et al. 2003).

McArthur and Lees (1995) reported an increase in dermal transfer with increasing pressure of contact. However, Roff et al. (2000) reported that contact pressures of up to 400 g/cm^2 did not appear to have a significant effect on transfer efficiency of strontium. Cohen Hubal et al. (2005) similarly found that transfer differences with contact pressure variations (i.e., light vs. heavy) were not significant when using the fluorescent tracer riboflavin.

1.4.3.7 Influence of Nature or Motion of Contact

The nature of contact (i.e., a press compared to a swipe or a smudge) appeared to have a significant effect on transfer for a number of different studies, although not for all. For whole hand presses on a stainless-steel panel to evaluate adherence of fluorescein-tagged dust, magnification of the hand skin surface demonstrated that the substantial majority of particles were transferred only to the epidermal ridges, with little in the valleys in between the ridges. However, moving the skin laterally (or smudging the presses) forced particles into the valleys as well, enhancing the transfer significantly. Although the dermal contact area was essentially the same for these smudging events, it was estimated that the actual surface area contacting the panel may have increased by approximately 30%, although the source of this estimate was unclear (Rodes et al. 2001). Lu and Fenske (1999) reported similar transfer results for hand press and hand drag techniques. Christopher et al. (2007a) reported only marginal differences between a hand press and a hand smudge when evaluating surface loading of saffron (1.5 mg for smudge type contact, 1.1 mg for press type contact), and the difference was not statistically significant. Sleeuwenhoek and van Tongeren (2006) reported the results of a single experiment that suggested rubbing may remove more lead from a surface then simply placing the had on the surface, but they also noted that the surface in contact with the skin was an unpolished rail that had not been touched in quite some time, and was covered with dirt and debris. Cohen Hubal et al. (2008) also reported a statistically significant increase in transfer when using a smudge contact motion versus a press.

1.4.3.8 Influence of Repeated Contacts

Several studies have reported a statistically significant association between dermal transfer and number of contacts or repeated contacts. Brouwer et al. (1999) found that loading of the skin indicated a transfer increase that was close to linear for the first six contacts, followed by a decline in additional loading with further consecutive contacts, as well as a small decrease in further adherence with additional frequency. Zainudin and Semple (2004) also reported a linear increase in loading of Tinopal up to six repeated contacts. Christopher et al. (2007a) similarly reported increased skin transfer of saffron with each repeated contact, but only evaluated repeated contacts up to four total contacts. Sleeuwenhoek and van Tongeren (2006) reported geometric mean results for 1, 5, and 10 repeated contacts for multiple materials containing lead, including lead sheeting, rolled sheeting, and lead ingots. The authors noted that they found statistically significant increasing linear trends in the surface loading with increased number of contacts, despite the fact that total loading declined slightly between 5 and 10 repeated contacts for the lead ingots. In a fluorescent tracer study using riboflavin, Cohen Hubal et al. (2005) reported that for a single contact, transfer efficiencies ranged from 1% to 14%. The percent of residue transferred to the hands declined with each sequential press in a series of five contacts, taking into account total surface area of repeated contact by adding up the surface area of all of the presses. When the results for repeated contacts were evaluated for different surfaces (carpet vs. laminate), no significant differences were observed. In a follow-up study, Cohen Hubal et al. (2008) found that quantitative dermal loading of riboflavin resulted in statistically significant increases with individual successive contacts of 2 seconds up to seven contacts. In comparison, dermal loading in an earlier study they had performed appeared to reach a

maximum level of loading by the fourth or fifth contact. In the follow-up study, the authors also calculated the percent dermal transfer, again taking into account the total surface area of contact following repeated contacts. For the first single contact, transfer efficiency ranged from 0.8% to 45.5%, and after seven contacts, transfer efficiency ranged from 0.6% to 19.4% (Hubal et al. 2008).

Other studies have demonstrated a lack of statistical association with dermal transfer and repeated contacts. Hughson and Cherrie (2005) examined the average dermal loading with repeated contacts to zinc oxide, and reported that there was no significant increase in skin surface loading with an increasing number of contacts up to eight. Similarly, Freeman et al. (2005) reported that hand loading in children with chlorpyrifos was significantly correlated with applied concentrations. Hand loadings after 1 hour of child activity were not statistically significantly different, which indicated that the maximum hand loading was reached after less than 1 hour. The authors also reported no difference in dermal loading between 3 hours and 4 hours.

Studies with larger numbers of repeated contacts point to the trend that may emerge over time with many additional repeated contacts. Rodes et al. (2001) found that upon repeated contacts with fluorescein-tagged house dust, the transfer factor gradually increased as the skin surface became loaded. They noted that although the transfer factor following a single press was approximately 65%, a further 40 presses resulted in only an additional 30% increase in skin loading. The authors also reported observing regular losses of particles back to the original contact surface, and estimated that a minimum of 100 presses would be necessary to produce an equilibrium scenario. They predicted that the final dermal transfer factor for this equilibrium would be approximately 15-20% (Rodes et al. 2001). Similarly, Rhodes et al. (1997) reported that the loading of

dust on the hands did not increase linearly with an increase in the number of contacts with a surface. Rather, a pattern was observed where the dust built up on the hands and then was deposited back on to the original surface.

1.4.3.9 Influence of Skin Hydration (or Wetting)

There was considerable variation in the literature regarding the degree to which skin was considered hydrated or "wetted" during a study. Some researchers evaluated the natural or typical range of skin hydration without additional wetting of the skin surface, while others actively wetted the skin during the study. Often, the mechanisms or techniques for wetting were not described and could not be readily compared between studies. Sometimes these artificial moisture conditions were created in an effort to simulate specific conditions, such as the skin of young children with frequent hand to mouth activity. There appeared to be a substantial difference in effects related to dermal transfer when considering the range of normal or typical skin hydration levels compared with intentional wetting of the skin surface.

For normal or typical skin hydration measurements, Beamer et al. (2009) reported a lack of significant association for dermal loading and skin hydration based on the data collected. The authors stated that based on the pooled analysis they performed of dermal transfer efficiencies identified in the literature, the results suggested that "skin moisture may not affect transfer efficiency" (Beamer et al. 2009, p. 280). Similarly, Gorman Ng et al. (2013) reported that variations in typical skin moisture or hydration were not significantly associated with an increase in transfer efficiency. Roff et al. (2000) also reported that skin hydration did not appear to affect dermal transfer efficiency of strontium.

A number of other studies reported an inverse relationship between skin hydration and dermal transfer. Brouwer et al. (1999) reported results suggesting that an increase in normal skin hydration or moisture limited the transfer of Tinopal to the hands, when in fact an enhanced transfer was expected because of the relatively high solubility of Tinopal in water. Similar to Brouwer et al. (1999), Christopher et al. (2007a) measured a decrease in the transfer of saffron to the hand with increased skin hydration. This association was statistically significant for the fingers, but not the palm. Rodes et al. (2001) wetted the skin using a hand press onto a foam pad with surrogate saliva at a pressure of 3.6-4.5 kg to evaluate dermal transfer, and reported that increasing skin moisture or dampness resulted in a decrease in dermal transfer of house dust. Edwards and Lioy (2001) reported that for certain pesticides, skin hydration was negatively correlated with collection efficiency at higher Log K_{ow} values (above 3), which the authors suggested was related to limits on the solubility of the test substances in sweat on the skin surface. Similarly, they noted that when a compound solubilized more readily into the aqueous component of the skin surface layer due to a lower Log K_{ow}, there was a more positive effect on skin collection efficiency due to hydration (Edwards et al. 2001). Although Du Plessis et al. (2010) reported on the results of skin hydration measurements before, during, and after metals wipe sampling, it appeared that the authors did not attempt to correlate skin hydration level with quantitative loading.

Several studies performed for the U.S. EPA specifically evaluated the differences in relative transfer to the skin for dry versus wetted palms (Camann et al. 2000a; Clothier 2000b; Clothier 2000a). Camann and Clothier (2000) evaluated the relative dermal transfer efficiency of a pesticide mixture (chlorpyrifos, pyrethrins, and piperonyl butoxide) from different types of surfaces to the palm of the hand using a single hand press for a

hand that was either dry or was wetted with water, human saliva, or the surfactant DSS. The researchers reported that transfer efficiency was highest for palms wetted by water, followed by saliva, followed by DSS, and finally the dry (normal) palm had the lowest transfer efficiency. The transfer of these pesticides to wetted palms was 2 to 5 times greater than to dry palms, but transfers were relatively consistent when wetted with water vs. saliva. The two studies by Clothier in 2000 looked at the effect on transfer to the skin for dry and wetted palms from new vinyl sheet flooring and turf grass. Results of the vinyl sheet flooring study indicated that greater transfer was observed for a wetted palm vs. a dry palm and was between 3-fold and 4-fold higher for chlorpyrifos, piperonyl butoxide, and pyrethrin. For the dry palms, the transfer of pyrethrin was higher relative to chlorpyrifos or piperonyl butoxide (3.64% vs. 1.53% and 1.41%, respectively). It was also observed that the amount of transferable residue available declined substantially within a short time (58-63.5%). For turf grass, the transfer efficiency of chlorpyrifos, chlorothalonil, and cyfluthrin increased with palms wetted with either water or saliva relative to a dry palm by 1.4-fold for cyfluthrin, 2.2-fold for chlorothalonil, and 3-fold for chlorpyrifos. Mean reductions in available surface residues for transfer were substantial after 24 hours (59-69%) (Clothier 2000b; Clothier 2000a).

Rodes et al, (2001) investigated the effect of skin moisture level during a study of dust adherence to the skin. During the study, the skin of volunteers was classified as dry, damp, or wet. For one volunteer the skin moisture characteristics appeared to be an important determinant in the relative transfer of particles to the skin, but for another volunteer, there did not appear to be a consistent relationship. It was suggested by the authors that wetting the dermal surface provides static charge neutralization which enhances transfer.

Edwards and Lioy (2001) noted that a very weak positive correlation was observed between Corneometer levels and atrazine collection, but reported that this finding may have been coincidental. Similarly, a small positive correlation was observed between surface moisture levels of the hand and malathion collection efficiency by the skin and may also have been coincidental. For both chlorpyrifos and diazinon, there was a negative correlation between skin correlation and collection efficiency (Edwards et al. 2001). The results also showed that skin hydration was negatively correlated with collection efficiency at higher Log K_{ow} values (above 3), which the authors suggested was related to limits on the solubility of the test substances in sweat on the skin surface. Similarly, they noted that when a compound solubilized more readily into the aqueous component of the skin surface layer due to a lower Log K_{ow}, there was a more positive effect on skin collection efficiency due to hydration (Edwards et al. 2001).

Hemond et al. (2004) reviewed the available literature on the dermal transfer of arsenic from treated wooden decks and playground structures. The authors reported a mean overall transfer of arsenic to moist hands from the available studies of 91 µg/100 cm^2 (SD 106 µg/100 cm^2), although the removal of two apparent outliers from the dataset reduced the mean to 70 µg/100 cm^2 (SD 63 µg/100 cm^2). The authors did not report a mean loading value for the dataset which evaluated transfer to dry hands, but noted that the central tendency of the data appeared to be closer to approximately 21 µg/100 cm^2, or approximately 3.3-fold lower than the data for moist hands. The methodology for creating moist vs. dry hand conditions in the various studies considered was not described (Hemond et al. 2004).

When using a colorimetric staining method to quantify the transfer of iron to the skin from handling firearms, Avissar et al. (2004) reported that relatively higher skin

hydration measurements using a Corneometer correlated very well with increased stain intensity on the skin. Similarly, it was reported that surface loading level and skin condition (dry vs. actively wetted) significantly affected skin loading for riboflavin and pesticides (Cohen Hubal et al. 2005; Hubal et al. 2008).

Beidermann et al. (2010) reported that following contact with receipt paper containing Bisphenol A for approximately 5 seconds, between 0.2 and 6 µg was transferred to the skin of the index and middle fingers while the skin was considered dry. Approximately 10 times the mass was transferred when the skin was wet or greasy.

In a study that evaluated artificial sweat rather than skin hydration, Midander et al. (2016) reported that similar levels of metals (range: 0.0571 – 1.97 µg/cm^2) were released from a number of different types of metal materials with the use of two different artificial sweat solutions. The first was a comprehensive sweat model intended for research use, and the second was the artificial sweat EN1811 that is intended for compliance testing for nickel under REACh (Midander et al. 2016).

1.4.3.10 Influence of Surface Hydration or Surface Moisture Content

According to Williams et al. (2002), moisture appeared to enhance transfer from carpets treated with chlorpyrifos. The researchers reported that small changes in percent moisture of the carpet produced significant changes in transferable chemical residue. They stated that the reason for the association was not clear, but could have resulted from resuspension of chlorpyrifos in water or possibly from the water suspending and removing adsorbed particles.

1.4.3.11 Influence of Surface Loading

The effects of surface loading can be difficult to separate from all the other determinants addressed above, which are also likely to substantially affect skin transfer in many situations. In general, however, researchers have noted a non-linear association between increases in surface loading compared to increases in dermal transfer efficiency, with dermal transfer increasing more slowly than surface loading. It was noted that dermal transfer of Tinopal powder was less than 2% of the surface contamination, and a 10-fold increase in loading on the skin was observed following a 30-fold increase in surface loading (Brouwer et al. 1999). Cohen Hubal et al. (2008) reported that dermal transfer from the source surface was between 0.8 and 45.5% for a single contact and 0.6 to 19.4% for repeated contacts. It has also been reported generally that quantitative surface loading was found to be very weakly correlated with dermal loading (Gorman Ng et al. 2013). Christopher et al. (2007a) reported that the “surface load” was a statistically significant determinant in the transfer to the hands. However, it was unclear what additional values or characteristics beyond just surface load (such as particle size, or surface and contact material hydration level) might have affected the rate of transfer and influenced this result. Surface loading is also analogous to the dislodgeable foliar residue, which has been reported to be the most significant dermal exposure determinant during field re-entry following pesticide application (de Cock et al. 1998a).

1.5 DISCUSSION

1.5.1 The Relative Influence of Key Effects on the Dermal Loading and Transfer of Non-Volatile Substances

Brouwer et al. (1999) noted that default adherence factors used in dermal exposure and risk assessment approaches were approximately 500 to 5,000 times higher than the measured transfer. The authors noted that this overestimate of dermal transfer, often combined with an assumption that surface contact occurs over the surface area of the entire hand or the entire hand plus other skin surfaces, can result in significantly higher quantitative estimates of dermal exposure than what can ultimately be measured in actual dermal transfer scenarios. Additionally, it has been noted by Stefaniak et al. (2014), for example, that the total mass of a chemical present on the surface of the skin may still represent an overestimate of exposure in terms of bioaccessibility from skin absorption, because the mass of a chemical detected using laboratory reagents during sample analysis may not be representative of the dissolution rate of a substance in the surface sweat and sebum. However, dermal uptake alone does not take into account other pathways of dermal exposure such as hand to mouth exposure, which may also be relevant.

With respect to the relative effects of different influences on dermal transfer, few authors have quantitatively compared multiple determinants and their relative effects on dermal transfer. Brouwer et al. (1999) noted that repeated contacts had the greatest influence on dermal loading, explaining 35% of the skin loading, and transfer increased with each repeated contact up to six. Although the effect of surface loading was statistically significant, according to the ANOVA results it explained far less of the skin

loading compared to the effect of repeated contacts (less than 1%). While skin hydration measurements appeared to have a slightly larger effect on skin loading than surface loading, the influence did quite not reach the level of significance. Additionally, while duration of contact also had a statistically significant effect on skin loading, it was far less influential than the repeated contacts (Brouwer et al. 1999). Zainudin and Semple (2004) reported similar results with respect to both repeated contacts, which demonstrated a substantial influence on dermal transfer, and contact duration, which was reported to have little influence on transfer to the skin. Cohen Hubal et al. (2008) evaluated the effects of surface loading, skin moisture, surface texture, contact type (press vs. smudge), and contact frequency on the transfer of riboflavin to the skin. They reported that the specific substance evaluated for dermal transfer appeared to have a significant effect on the relative influence of the different determinants on dermal transfer. Although contact pressure and duration were initially considered for evaluation, they were not found to result in substantial differences in transfer in previous tests, and therefore were kept constant during the study. They also reported that, similar to other studies, the effect on increase of skin loading with repeated contacts was close to linear through seven contacts. Surface loading (at either 0.2 or 2 μg/cm^2) and contact motion (press or smudge) were found to be statistically significant. Increased surface loading resulted in increased transfer, and smudge contacts showed increased transfer over press contacts. Additionally, surface type (carpet vs. laminate) was significant for the first contact only, and the skin moisture content was significant only after repeated contacts (Hubal et al. 2008). Christopher et al. (2007b) reported quite similar results to both Cohen Hubal et al. (2008) and Brouwer et al. (1999), finding that the significant determinants associated with dermal transfer for saffron were surface loading and

number of hand contacts, as well as skin hydration or moisture, which was negatively associated with loading.

1.5.2 Summary, Data Gaps, and Future Data Needs: Human Skin In Vivo Dermal Loading and Transfer Data

Characterizing dermal loading and transfer is integrally connected with broader strategies for performing dermal exposure assessments. Among the important factors to consider are the number of substances for which dermal loading samples can or should be collected, how frequently dermal samples should be collected, and how many dermal samples are needed statistically or will be possible to collect. The importance or relevance of each transfer pathway and compartment must also be evaluated for the scenario(s) of interest if the data are to be useful for modeling efforts. For example, can certain compartments or transfer pathways be eliminated either before or after a study? Also, what is the relationship of dermal loading to transfer for a specific substance or class of substances?

In addition to critical questions regarding the influence of dermal loading and transfer assumptions and the default values used in dermal exposure assessment modeling, there are several trends that can be observed from the available *in vivo* human loading data for solids and semi-volatile solids. For influences on dermal loading and transfer that have been reported to be statistically significant, including repeated contacts, skin hydration, surface loading or contamination, and the nature of dermal contact, there are potentially important data gaps to be addressed in order to improve current models.

Based on the available data in the literature, accounting for repeated contacts becomes more complicated when designing a dermal exposure modeling strategy. It was found that repeated contacts had a significant effect on transfer in multiple studies, but only up to a certain number of contacts, which was typically between approximately 5 and 10. After this approximate number of contacts, some studies reported that transfer leveled off or decreased. Recent reports and evaluations of repeated contacts have noted support for an assumption of “near-linear” increases in dermal exposure level with repeated contacts, with the caveat that equilibrium will be reached after some unknown number of multiple contacts, often at a number over six (Goede et al. 2018 , p. 17). Such an assumption is limited when evaluating routine contact with a substance of interest over a longer period of time or over a full work shift. Semi-quantitative or qualitative assumptions regarding the estimation of loading and transfer following repeated contacts are still routinely applied in dermal exposure models, including in the new dART model (Goede et al. 2018). Given the significant effect of repeated contacts on both dermal loading and transfer in several studies, further data collection will be important to better characterize the influence of this factor.

Skin hydration is another factor for which a statistically-significant influence on dermal loading and transfer has been reported. The comparative evaluation of skin hydration or moisture between studies is challenging to consider, however, based on the available measurement data. There are varied protocols employed to compare dry vs. hydrated skin, such as natural skin hydration vs. active wetting and measurement methods or units. Additionally, there appeared to be a potentially mixed effect of skin hydration on dermal transfer, with a number of studies reporting no effect on transfer within the range of normal skin hydration, but at least two studies reporting a statistically

significant association between normal skin loading and hydration. Interestingly, increased skin hydration was sometimes associated with a decrease and sometimes associated with an increase in dermal transfer. It has been noted that the relative solubility of the substance of interest in the aqueous film on the skin surface may be responsible for these differences. Active wetting of the skin was more frequently associated with an increase in dermal transfer, and similarly, contact with surfaces that were wet appeared to increase the amount of transfer for some substances. Additional data on the influence of skin hydration are therefore important to better understand its potential influences on dermal transfer.

Contact duration and pressure appeared to be consistently less significant than other determinants in influencing the amount of dermal transfer, and appear to be a lower priority for additional data collection. Surface texture, however, appeared to have a significant influence in many studies, with smooth, nonporous surfaces resulting in higher transfer compared to textured surfaces such as carpet, fabric, or artificial turf. Additional data would also be beneficial in this area. The nature of the contact, such as a press compared to a smudge or wipe, also appeared to significantly influence transfer. Although surface loading was often positively associated with dermal transfer, it was difficult to understand the effect of surface loading alone compared to the influence of the other determinants present. Further, increases in surface loading were not linearly associated with increases in dermal transfer in many instances. This determinant is another important area for further study.

Overall, a better understanding of the potential for transfer to and from the skin for common materials that are routinely in contact with the skin such as clothing or protective glove material is another important data gap where further study is needed.

The ability for environmental health professionals to arrive at the correct judgment regarding dermal exposure assessment and risk given the dermal model used is not currently a transparent process, and the effect of dermal loading and transfer values on these assessments must be better understood quantitatively.

1.6 Specific Aims Investigated in This Dissertation

The purpose of the research in this dissertation was to quantitatively consider influences on the current dermal loading and transfer assumptions used in deterministic dermal exposure models available to exposure assessment practitioners. This analysis included an investigation of the role of dermal loading on the outcomes of deterministic modeling efforts by practicing professionals. Based on results of this analysis and a detailed literature review, repeated contacts and skin hydration were observed to have statistically-significant influences on loading and transfer, and appeared to exert potentially complex effects on dermal loading and transfer. These two determinants were therefore selected for the collection of additional measurement data to better understand their potential effects on dermal loading and transfer. The following specific aims were identified for this dissertation:

1. Evaluate the ability of public health professionals to arrive at accurate judgments about dermal exposure assessments using available deterministic dermal exposure models. Examine the influence of the dermal loading parameter on modeling efforts using qualitative information, semi-quantitative inputs and default assumptions, and scenario-specific quantitative dermal loading data.

2. Examine the influence of repeated contacts on dermal exposure assessments by measuring the mass transfer, transfer efficiency, and total mass loading for repeated contacts between the relevant compartments and pathways in a conceptual approach based on the Schneider et al. (1999) and Gorman Ng et al. (2012) model for a test substance in the solid form using a series of controlled experiments in a cohort of 18 people. Employ comparative sampling methods to assess repeatability of results.
3. Examine skin hydration and its potential influences on dermal exposure assessment. Collect comparative measurements using the methods available for characterizing skin hydration and condition, and particularly at the site of skin sampling, where the skin hydration level is most relevant for dermal transfer.
4. Measure the level of normal skin hydration and TEWL across of cohort of at least 10 participants and compare these measurements with the quantitative transfer for a solid test substance in human skin *in vivo*.

Chapter 1 provides a review of the available background information in the literature relevant to quantitative dermal loading and transfer. This information includes a review of the literature on the measured transfer of substances to and from human skin *in vivo* for solid and semi-volatile substances, and provides an analysis of determinants that have been studied to determine their quantitative influence on dermal exposure assessment for solids. Chapter 2 investigates the accuracy of exposure assessment practitioners in performing dermal exposure assessments using currently-available deterministic models and methods for specific substances. This chapter specifically considers the utility of qualitative information, default values, and quantitative

measurement data on practitioner accuracy for dermal exposure assessments. Chapter 3 presents measurements of the relative influence of repeated contacts on the quantitative transfer of elemental metallic lead to and from human skin for multiple pathways on total transfer or loading and transfer efficiency. Chapter 4 quantitatively evaluates the results of three comparative measurement methods for skin hydration/condition and examines the potential for relevance of these methods to dermal loading and transfer assessments. Chapter 5 investigates the influence of skin hydration specifically on the loading of elemental metallic lead on the skin surface. And finally, Chapter 6 provides a summary of the analyses performed in this dissertation, and considers the implications of the data collected for future efforts to refine deterministic dermal exposure assessment approaches.

Table 1-1: Quantitative Source-to-Skin Dermal Transfer for Pesticides

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Pesticides						
Pyrethrin and chlorpyrifos mixture; other pesticides	2 children in families with agricultural workers	Self-Wipe of both hands; Sof-Wick sponge wetted with isopropyl alcohol	Up to 400 ng/wipe for a specific pesticide	0.0008 $\mu g/cm^2$	88-101% recovery efficiency from sample media	(Geno et al. 1996)
Captan	Agricultural workers during field re-entry – thinning, pruning, tying up, harvesting	Hand rinse with 50% ethanol	37.5, 20.1, 16.2, and 19.0 mg/m^2/hour	1.62-3.75 $\mu g/cm^2$/hr		(de Cock et al. 1998b)
Chlorpyrifos	Carpet/furniture contact following indoor residential pesticide application	Hand shaken in enclosed bag with 250 ml 10% isopropanol/distilled water solution	2.4-5.2 ng/cm^2 for carpet contact; 12.4 ng/cm^2 for furniture contact	0.0024 – 0.012 $\mu g/cm^2$	0.04-0.69% transfer efficiency compared to surface deposition	(Lu et al. 1999)
Azinphos methyl	Children in families with agricultural workers (take-home exposure)	Gauze pads wetted with 100% isopropanol; separate samples for front/back of fingers and palms/backs of each hand (4 samples)	0-1.2 µg/2 hands (13% detection)	0 - 0.0024 $\mu g/cm^2$		(Lu et al. 2000)
Phosmet			0-0.3 (3% detection)			
Dimethyl OPs			0-1.2 µg/2 hands (16% detection)			

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Atrazine	Background pesticide exposures to 102 children in houses, mostly not recently treated	Hand rinse with 150 ml isopropanol; sample bag manipulated around hand	0.24-1.4 µg/ml	0.00004 – 1.9 µg/cm^2		(Lioy et al. 2000)
Diazinon			0.02-0.17 µg/ml			
Malathion			1.6-944 µg/ml			
Chlorpyrifos			0.0-2.9 µg/ml			
Chlorpyrifos	28 farmers mixing and applying pesticide	Triplicate alpha cellulose wipes wetted with 10% isopropanol	Mean 791 (µg/observation period for both hands (range 15.1 µg – 7,266 µg)	0.014 – 6.8 µg/cm^2	Highest correlations between exposure and volume of application, hand washing, manipulation of equipment, and spray nozzle position	(Lopez et al. 2009)
Imidacloprid	10 greenhouse/ cultivation workers during field re-entry- handling plants	Hand washes with 95% ethanol, poured over hands while rubbing them together, followed by soaking for 30 sec	Mean recovery over 3-5 days of 70.26 µg/sample for both hands	0.066 µg/cm^2	Workers wore cotton and/or latex gloves	(Aprea et al. 2009)
Captan, malathion, permethrin, cypermethrin, diazinon, and benzimidazole	10 tree planters	Cotton wipes moistened with 70% ethanol; wipes collected on the back of the hand, inside of forearm, perimeter of hand	ND	0.00037 – 0.1 µg/cm^2	>95% of workers wore gloves, but only 33% were chemical resistant; 5.6% of participants washed their hands during the day	(Gorman Ng et al. 2011)
Chlorothalonil			0.37-106.3 ng/cm^2 (60-90% detectable)			

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Iprodinone			0.7-15.9 ng/cm^2 (10-70% detectable)			
Captan	74 pesticide applicators	Hand rinses using 150 ml isopropanol	Mean 230 µg/hand (95% CI: 130-380 µg)	0.21 $µg/cm^2$	Use of chemical resistant gloves significantly reduced exposure	(Hines et al. 2011)

Table 1-2: Quantitative Source-to-Skin Dermal Transfer for Fragrance Residues and Tinopal

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Fragrance Residues						
Cinnamic aldehyde	10 subjects grasping five different scented candles for 20 sec each	Hands were wiped in between each candle using dressing sponges wetted with 5 ml isopropanol	Mean 0.254 µg/cm^2 for both hands		Removal efficiencies were reported to be >100%	(Api et al. 2007)
Eugenol			Mean 0.279 µg/cm^2 for both hands			
d-Limonene			ND			
Tinopal						
Tinopal Powder	Subjects performing hand presses on glass plates loaded with 6 µg/cm^2 and 177 µg/cm^2	Quantitative video imaging using fluorescent tracer	0.11 and 0.27 µg/cm^2 following a single press; 0.38 and 0.8 µg/cm^2 after six presses		Transfer efficiency was 2% and 0.14% following a single press	(Brouwer et al. 1999)
Tinopal Powder	Subjects touching smooth surface or tools loaded with 550 mg in workplace simulations	Quantitative video imaging using fluorescent tracer	Mean 86 µg/cm^2 after single press; 344 µg/cm^2 after six presses		Mean transfer efficiency 2.1% after single contact and 39% after six contacts	(Zainudin et al. 2004)

Table 1-3: Quantitative Source-to-Skin Dermal Transfer for Soils

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Soils						
Soil	Soil adherence to skin		Mean range: 0.2-1.5 mg/cm^2; or per Finley et al., a 95th percentile of 1.7 mg/cm^2	200 – 1,500 $\mu g/cm^2$ (95% upper bound of 1,700 $\mu g/cm^2$)	Based on review of soil adherence studies	(USEPA 1992; Finley et al. 1994)
Wet soils (12-18% moisture content)	Soil adherence to skin following hand press and gentle agitation for 30 seconds	Soil mass of source measured pre- and post-hand press/agitation	For wet soils >150 µm in diameter, means 2.96-5.98 mg/cm^2	2,960 – 5,980 $\mu g/cm^2$	Mean soil adherence for all moisture contents 0.42-1.3 mg/cm^2 for soils ≤150 µm in diameter	(Kissel et al. 1996a)
Dry soils (<2% moisture content)			For dry soils >150 µm in diameter, means 0.14-0.34 mg/cm^2	140 – 340 $\mu g/cm^2$		
Soil	Soil adherence to skin following a variety of activities (greenhouse work, farming, soccer, rugby, groundskeeping, irrigation installation, reed gathering, and children playing in mud)	Recovered soil mass following pre- and post-washing with water of hands, forearms, lower legs, faces, and feet	Range for all activities and body locations 0.0008 – 0.69 mg/cm^2; except up to 14 mg/cm^2 on the feet of adults for activities involving mud exposure (reed gathering) and 1.7 - 140 mg/cm^2 in children playing in mud	0.8 – 690 $\mu g/cm^2$ (for mud exposures, up to 1,400 $\mu g/cm^2$ for adults and up to 140,000 $\mu g/cm^2$ for children)	Average loading on hands was typically higher than average loading on other body locations; pre-activity loading was approximately 0.1 mg/cm^2 or less (100 $\mu g/cm^2$ or less)	(Kissel et al. 1996b)

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Soil	Soil adherence to skin following various occupational and recreational activities (rugby, daycare, construction workers, indoor child play, landscapers, heavy equipment operators, utility workers, and gardeners)	Soil mass collected using skin wash with water pre- and post-activity	Range 0.0005-2.1 mg/cm^2; geometric mean 0.076 mg/cm^2 hands, 0.035 mg/cm^2 forearms, 0.023 mg/cm^2 lower legs, 0.039 mg/cm^2 face, 0.013 mg/cm^2 feet	Range 0.5 - 2,100 $\mu g/cm^2$; geometric means 130 – 760 $\mu g/cm^2$	All activities other than children playing in mud produced geometric mean loadings below 1.0 mg/cm^2	(Holmes et al. 1999)
Sediment (predominantly sand)	Children exposed to sediment from playing on a tide flat	Soil mass collected using skin wash with water pre- and post-activity	Geometric mean 0.042 mg/cm^2 face, 0.17 mg/cm^2 forearms, 0.49 mg/cm^2 hands, 0.70 mg/cm^2 lower legs, 21 mg/cm^2 feet	Geometric means 42 – 700 $\mu g/cm^2$; for feet, 2,100 $\mu g/cm^2$	Loading was not dependent on duration of activity	(Shoaf et al. 2005)
Soils of various moisture contents and sizes	Soil adherence to skin for 108 volunteers following hand contact	Tape stripping	Mean soil adherence 0.7 mg/cm^2; most particles which adhered to the skin were <64 µm in diameter	700 $\mu g/cm^2$	Soil moisture content only influenced adherence for soils with highest moisture content (9.36% vs. 1.85% and 3.81%); Adhered mass increased by a factor of two at the highest hydration level.	(Choate et al. 2006)

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Soil	Soil adherence to skin at different moisture levels following hand press and gentle shakes	Hand wash in bottle of ultrapure water	17.4-82.0 mg/hand	0.033 – 0.15 $\mu g/cm^2$	Amounts of adhered soil were increased with decreased dry blotting time; Finer soil particles tended to adhere more efficiently to hands; Hand surface area for children based on data reported by U.S. EPA for 4-year olds	(Yamamoto et al. 2006)
	Soil adherence to skin among children following outdoor play		mean 26.2 mg/hand; mean 0.125 mg/cm^2 (assuming 210 cm^2 hand surface area)	125 $\mu g/cm^2$		

Table 1-4: Quantitative Source-to-Skin Dermal Transfer for Metals

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Metals						
Lead	25 employees at a lead-acid battery manufacturing facility	Hand wash of both hands with tap water	Geometric means, 29.0-53.7 µg/500 ml water on Monday; 1,133-1,144 µg/500 ml on Thursday	0.027 – 1.1 µg/cm^2	A 30-fold increase was noted between Monday and Thursday	(Far et al. 1993)
Lead	96 employees at a lead battery assembly plant	Tape stripping	Geometric means: 66.4 µg/cm^2 on gloves; 4.94 µg/cm^2 on clothing sleeves; 0.8 µg/cm^2 on cheeks; 3.33 µg/cm^2 on the bare hands before washing (0.79 µg/cm^2 after washing); 0.0015 µg/cm^2 on lips		Supervisors had the highest loading on the lips of 0.0052 µg/cm^2	(Hwang et al. 2000)
Lead	Automotive repair technicians performing vehicle resurfacing	Wipe sampling with PaceWipes; additional details of method not described	2.64-211 µg/hand	0.005 – 16.0 µg/cm^2		(Enander et al. 2004)
Barium			60.9-459.6 µg/hand			
Zinc			60.1-8,580 µg/hand			
Iron			324-6,750 µg/hand			
Aluminum			<12.5-766 µg/hand			
Arsenic	Literature review of treated wood on decks and play structures	Comparative hand washing using an HCl acid solution, distilled water, and 5% acetic acid solution	76.4 µg/100 cm^2 (range 30-196 µg/100 cm^2) for “moist” skin; 20.7 µg/100 cm^2 (range 3.6-86.6 µg/100 cm^2) for “dry” skin	0.036 – 1.96 µg/cm^2		(Hemond et al. 2004)

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Chromium	15- 16 workers performing electroplating work	Handwashing with deionized water containing 1.0 ml/l of liquid soap and rubbing hands together (EN method 1499)	0.12 mg/hour	0.11 µg/cm^2/hr	Hand surface area was not reported; TWA calculation was not described	(Makinen et al. 2004b, 2004a)
Stainless and Acid-Proof Steel			2.74 mg/hour	2.6 µg/cm^2/hr		
Iron	Individuals handling firearms	Quantitative colorimetric indicator method using staining intensity that was evaluated spectrophotometrically	55-190 ng/cm^2 for weak, average, and good colored stains on hands	0.05 – 0.19 µg/cm^2		(Avissar et al. 2004)
Zinc Oxide	Industrial facilities with galvanizing and molten metal work	Wet wipes of the hands, forearms, forehead, neck, and chest	0.73 mg/cm^2 (range 0.39-0.94 mg/cm^2) for immersion in controlled setting	390 – 940 µg/cm^2	GM exposures for all hand/arm sampling: 0.009-0.215 mg/cm^2 for field studies; sampling method consistent with Schneider et al., (1999)	(Hughson et al. 2005)
Zinc Metal Dust			4.84 mg/cm^2 (range 3.75-6.41 mg/cm^2) for immersion in controlled setting	3,750 – 6,410 µg/cm^2		

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Lead Sheets	Subjects handling and contacting lead-containing surfaces	Wipe sampling of palms after 1, 5, and 10 repeated contacts	Geometric means: 0.04, 0.37, and 0.61 $\mu g/cm^2$ for 1, 5, and 10 contacts		Statistically significant increase in surface loading with increased number of contacts	(Sleeuwenhoek et al. 2006)
Rolled Lead Sheets			Geometric means: 0.33, 0.57, 0.69 $\mu g/cm^2$ for 1, 5, and 10 contacts			
Lead Ingots			Geometric means: 0.32, 0.84, and 0.76 $\mu g/cm^2$ for 1, 5, and 10 contacts			
Arsenic	130 children playing on playsets made of pressure treated wood	Hand washes of children's hands	321 ng/sample, which was determined to be 0.0016 $\mu g/cm^2$		The U.S. EPA used a loading value of 0.0334 $\mu g/cm^2$ in the SHEDS-Wood model	(Barraj et al. 2007)
Beryllium	Workers at a copper beryllium alloy facility	Self-collected duplicate 1-min wipe samples of the face and neck using GhostWipes (wetted with deionized water)	Geometric mean for neck: 0.04 µg/sample (range: ND-0.58 µg); Geometric mean for face: 0.04 µg/sample (range: ND-1.44 µg). LOD=0.005 µg	ND – 0.0036 $\mu g/cm^2$	Approximately 15% of samples were ND	(Day et al. 2007)
Nickel	Skin of cashiers handling coins and	Wipe sampling of thumb, index finger, middle finger, and palm	0.005-2.07 $\mu g/cm^2/h$ for cashiers; 0.053-0.63 $\mu g/cm^2/h$ for locksmiths			(Liden et al. 2008)

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Cobalt	locksmiths handling keys/locks/knobs	using wipes wetted with 1% nitric acid	0-0.011 $\mu g/cm^2/h$ for cashiers; 0.0002-0.003 $\mu g/cm^2/h$ for locksmiths			
Chromium			0.0002-0.018 $\mu g/cm^2/h$ for cashiers; 0.004-0.15 $\mu g/cm^2/h$ for locksmiths			
Cobalt	Workers in tungsten carbide plants; activities included powder handling, metal separation and forming/machining	Self-collected 1-min wipe samples of the hands and neck using Wash 'n Dri Wipes (wetted with 10-15% ethanol in water)	GM 88-388 µg on the hands; 5-55 µg on the neck	0.003 – 0.36 $\mu g/cm^2$	Workers wearing gloves had higher levels of metals on hands, more glove changes associated with higher levels	(Day et al. 2009)
Chromium			GM <4 µg on the hands; low levels on the neck	ND		
Nickel			GM 7-24 µg on the hands; 0.7-6 µg on the neck	0.0004 – 0.22 $\mu g/cm^2$		
Nickel (metallic nickel and liquid nickel sulfate solution)	26 workers at a metal refinery	Wipe samples using GhostWipes (wetted with distilled/deionized water)	Index finger 0.236-177.772 $\mu g/cm^2$; palm 0.045-229.86 $\mu g/cm^2$; neck 0.034-16.969 $\mu g/cm^2$; forehead 0.056-8.599 $\mu g/cm^2$			(Du Plessis et al. 2010)

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Nickel (metallic nickel and nickel in solution)	Workers involved in electro-winning/electrolysis processes and packing of nickel powders	Wipe samples of hands and forearms using commercially-available wipes wetted with ingredients including water and propylene glycol	GM 0.34 µg/cm^2 for soluble nickel and 0.56 µg/cm^2 for total nickel			(Hughson et al. 2010)
Nickel Powders			2.59 µg/cm^2 for soluble nickel and 8.73 µg/cm^2 for total nickel			
Nickel	Manufacturing facility for gas turbines and space propulsion components	Wipe sampling of the forehead, back of hand, and palm using wipes wetted with 1% nitric acid	<0.000001-5.3 µg/cm^2/h			(Julander et al. 2010)
Cobalt			<0.000001-0.26 µg/cm^2/h			
Chromium			0.00004-0.085 µg/cm^2/h			
Lead	Tree planters using fertilizers	Wipe sampling of the back of the hand, inside of the forearm, and perimeter of the hand and fingers using GhostWipes wetted with deionized water	Mean 4.5 ng/cm^2	0.0025 – 0.0068 µg/cm^2	>95% of workers wore gloves, but only 33% of gloves were chemical-resistant	(Gorman Ng et al. 2011)
Nickel			Mean 2.7 ng/cm^2			
Chromium			Mean 6.8 ng/cm^2			
Cadmium			4.7-5.6 ng/cm^2			
Arsenic			2.5 ng/cm^2			

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Cobalt	Handling of cemented tungsten carbide discs	Wipe sampling of the tips of the thumb, index finger, and middle finger using wipes wetted with 1% nitric acid after 30 min of handling	1.1 $\mu g/cm^2$ (range 0.5-1.7 $\mu g/cm^2$) for discs with 6% cobalt; 0.7 $\mu g/cm^2$ (range 0.3-1.6 $\mu g/cm^2$) for discs with 15% cobalt		Higher level of transfer from discs with lower % of cobalt likely due to smaller tungsten carbide grains and greater toughness	(Midander et al. 2014)
Zinc Oxide	Transfer of micro and nano zinc oxide aerosols from steel and pine wood to hands	NR	NR		Transfer efficiencies ranged from 0.9-27% for microparticles and 14-106% for nanoparticles	(Brouwer et al. 2016)
Lead, Beryllium, Cadmium, Indium, Lithium	Workers at an electronics recycling facility	Wipe sampling of the hands for 30 sec using GhostWipes wetted with deionized water	Results in µg/sample; Beryllium: mean 0.012 (ND-0.02); cadmium: mean 0.15 (ND-0.27); indium: ND; lead 0.99 (0.23-3.2); lithium 0.35 (ND-0.66)	ND – 0.0009 $\mu g/cm^2$	All processing employees had detectable metals on the hands after washing hands at end of shift	(Grimes et al. 2019)

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Lead, Beryllium, Cadmium, Chromium, Cobalt, Copper	Workers at an electronics recycling facility	Wipe sampling of the hands for 30 sec using GhostWipes wetted with deionized water	0.9-40 µg/sample	0.0008 – 0.37 $\mu g/cm^2$	All employees had detectable levels of cadmium, chromium, and lead on the hands	(Grimes et al. 2018)
Lead	Workers at a small arms repair shop	Wipe sampling of the front and back of both hands using Palintest wipes wetted with benzalkonium chloride	4.3-92 µg for both hands; 1.1-2.4 µg for both hands after washing with soap and water	0.004 – 0.086 $\mu g/cm^2$		(Beaucham et al. 2018)
Cobalt Powder	Workers at a tungsten carbide production facility	Wipe sampling of 2 cm^2 surface of index finger using wipes wetted with 1% nitric acid	Mean 0.86 $\mu g/cm^2$ (range 0.065-135) in first study; 1.51 $\mu g/cm^2$ (range 0.25-28 $\mu g/cm^2$) in second study			(Kettelarij et al. 2018a; Kettelarij et al. 2018b)
Cobalt	Workers at a hard metal production plant	Wipe sampling of the hands using wipes wetted with 1% nitric acid after two hours of exposure	Mean 29 $\mu g/cm^2$/hour for the pressing department; 3 $\mu g/cm^2$/hour for the powder department (0.046 – 100 $\mu g/cm^2$/hour overall)			(Klasson et al. 2017)

Table 1-5: Quantitative Source-to-Skin Dermal Transfer for PBDEs

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Polybrominated Diphenyl Ethers (PBDEs)						
Total PBDE Mass	Transfer of PBDE to the hands among U.S. residents	Hand wipes of the front and back of both hands with gauze soaked in isopropanol	2.6-1,982 ng/hands (normalized median loading 135 pg/cm^2)	0.00014 $\mu g/cm^2$	Average recovery efficiency for different congeners ranged from 50-84%	(Stapleton et al. 2008)
PentaBDE	Transfer of PBDE to the hands among office workers	Hand wipes of the front and back of both hands with gauze soaked in isopropanol	14-2,864 ng/hands (geometric mean loading 70 ng/hands)	0.000013 – 2.68 $\mu g/cm^2$	Participants who washed their hands <4 times per day had 3x the mass of PentaBDE on their hands	(Watkins et al. 2011)
Total PBDE Mass	Hands of individuals setting up fabric tents	Hand wipes of the front and back of both hands with gauze soaked in isopropanol	<0.05-18,300 ng/hands	<0.00000005 – 0.017 $\mu g/cm^2$		(Keller et al. 2014)
PentaBDE			0.96-117 ng/hands			
TCDPP			<34-8,530 ng/hands			

Table 1-6: Quantitative Source-to-Skin Dermal Transfer for PAHs

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Polycyclic Aromatic Hydrocarbons						
PAHs	Transfer of PAHs to the skin of firefighters following fire response	Wipe samples of the hands and necks with Texwipe cloth wipes wetted with corn oil	Hand median loading: 16.3 $\mu g/m^2$ (range 5.2-125 $\mu g/m^2$); 135 $\mu g/m^2$ and 226 $\mu g/m^2$ for attack and search operations; neck median loading: ND	0.00052 – 0.023 $\mu g/cm^2$	A substantial percentage of samples were below the limit of detection; the PAHs present at 20% or greater on hands were dibenzo[a,h]anthracene, fluoranthene, phenanthrene, and pyrene	(Fent et al. 2017)
PAHs	Workers performing stone mastic asphalt paving and remixing	Hands rubbed together with sunflower oil and wiped with Kleenex tissue	4.6-10 ng/cm^2	0.005 – 0.01 $\mu g/cm^2$	The primary PAH compounds found on skin were dimethylphenanthrene, phenanthrene, 1-methyl-phenanthrene, naphthalene, pyrene, and fluoranthrene	(Vaananen et al. 2005)

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Pyrene	Workers exposed to 250 µL of used gasoline engine oil; field samples of automotive repair technicians	Hands rubbed with corn oil and both palms wiped with cellulosic (Whatman) filter paper or polyester (Alpha) wipes for 30 sec	6.87-14.69 µg per 2 hands (filter paper); 5.5-14.24 µg per 2 hands (polyester wipes); for field samples, upper bound of 1.06 µg per 2 hands	0.001 – 0.014 $\mu g/cm^2$		(Boeniger et al. 2008)

Table 1-7: Quantitative Source-to-Skin Dermal Transfer for Antineoplastic Drugs

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Antineoplastic Drugs						
Cyclophosphamide	Hospital workers at four Dutch hospitals	Hand washes with a 10% isopropanol solution and wipe sampling of foreheads using cotton wetted with 10% isopropanol	Handwash: pharmacy technicians, 0.002 $ng/cm^2/min$; oncology nurses, <0.0008-0.02 $ng/cm^2/min$; cleaning personnel, <0.001 $ng/cm^2/min$. Forehead wipe samples: pharmacy technicians, 0.01 $ng/cm^2/min$; oncology nurses, <0.036-0.05 $ng/cm^2/min$; cleaning personnel, <0.047 $ng/cm^2/min$	<0.0000008 – 0.00005 $\mu g/cm^2/min$	Participants wore gloves during the tasks of interest	(Fransman et al. 2004)
Cyclophosphamide, ifosfamide, methotrexate, 5-fluorouracil, etoposide, cytarabine, gemcitabine, chlorambucil	Laundry facility receiving laundry from 12 hospitals	Hand washes with a 10% isopropanol solution	All hand wash samples were ND	ND	Samples taken of disposable gloves worn by workers were ND	(Fransman et al. 2007)

Table 1-8: Quantitative Source-to-Skin Dermal Transfer for Alkanolamines

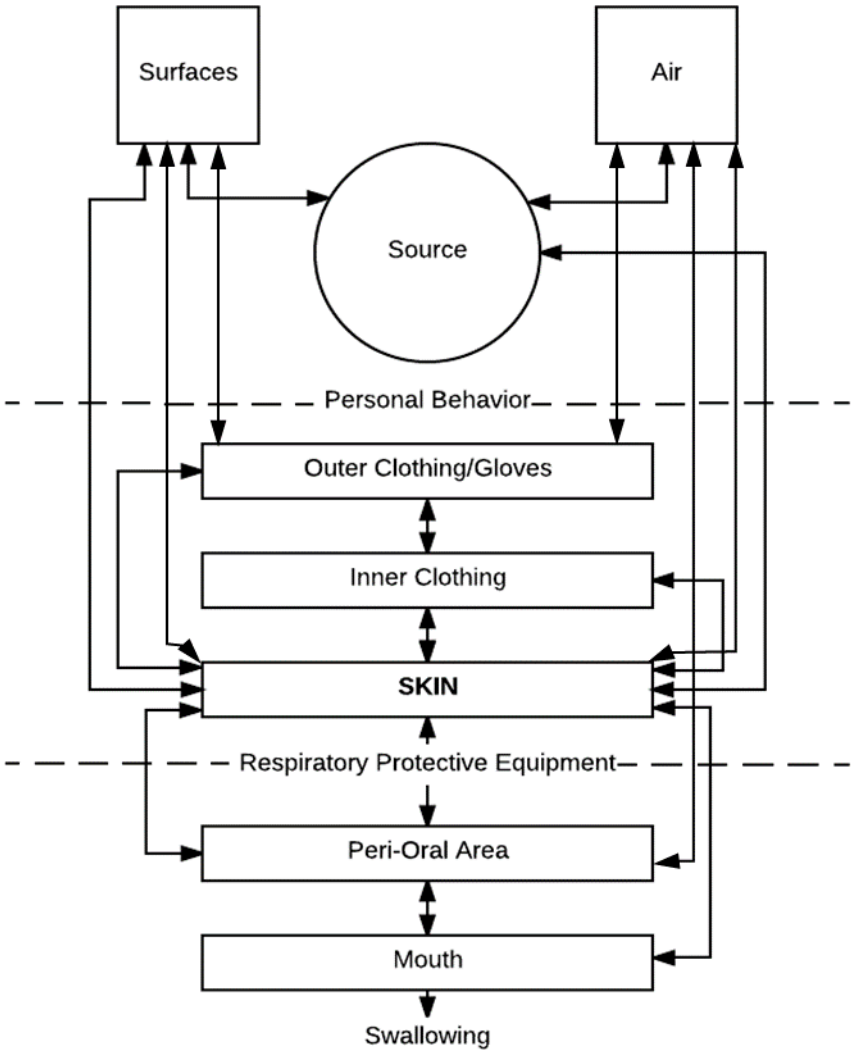
Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Calculated Dermal Loading or Loading Rate per Square Surface Area of Skin (cm^2)	Notes	Reference
Alkanolamines						
Alkanolamines	Machine shop workers using metal-working fluids	Hand rinses with 20% isopropanol for 1 min	Median recovery: 7.4 mg/hand for monoethanolamine; 12 mg/hand for diethanolamine; 2.2 mg/hand for triethanolamine; 1.1 mg/hand for a second set of monoethanolamine samples	1.03 – 6.9 µg/cm^2	The authors reported that the primary exposure to triethanolamine was through the dermal route	(Henriks-Eckerman et al. 2007)

Table 1-9: Quantitative Transfer Pathways Other Than Source-to-Skin

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Notes	Reference
Air-to-Skin Transfer of SVOCs					
Phthalates	Human environmental exposure	Three forehead wipes (approx. 15 cm^2); gauze soaked in isopropanol	11 $\mu g/m^2$ to 11, 095 $\mu g/m^2$ (0.0011 $\mu g/cm^2$ to 1.11 $\mu g/cm^2$)	Some phthalates penetrated deeper into the skin over shorter periods of time and were found at higher concentrations over greater depths	(Garrido et al. 2019)
Air-to-Skin and Settled Surface-to-Skin Transfer of Dusts					
Calcium acetate	Participants placed their hands inside a test chamber for 30 min while dusts of the test substances were generated inside	Gauze wipes moistened with deionized water; palms, fingers, back of hand wiped three times	<0.07 – 3.35 $\mu g/cm^2$ (mean dust concentration 43.98 mg/m^3)		(Gorman Ng et al. 2013)
Zinc oxide			<0.5 $\mu g/cm^2$ (mean dust concentration 0.57 mg/m^3)		
Epsom salts			<0.32 $\mu g/cm^2$ (mean dust concentration 0.92 mg/m^3)		
Influence of Clothing or Gloves on Skin Transfer					
Cotton-to-skin transfer of explosive residues	Volunteers in simulated scenarios exposed to powdered residues	Transfer to/from index finger quantified using a pixel-counting imaging method	20-90% transfer		(Lees et al. 2018)
Skin-to-cotton transfer of explosive residues			<7% transfer		
Glove-to skin transfer of saffron	Volunteers in simulated scenarios to evaluate transfer from the hands to the peri-oral region	Hand wash and face wash using water	0.44 mg transfer (range 0.22 – 0.97)	The use of gloves appeared to increase transfer to the skin for saffron, but results not significant	(Christopher et al. 2007b)

Dermal Contaminant(s)	Scenario Evaluated	Sampling Method Used	Range of Reported Dermal Transfer Values	Notes	Reference
Skin-to-Skin Transfer					
Tinopal powder	Volunteers in simulated scenarios	Fluorescence imaging intensity	8.2% mean transfer from the hands to the mouth or lips		(Zainudin et al. 2004)
Saffron	Volunteers in simulated scenarios to evaluate transfer from the hands to the peri-oral region	Hand wash and face wash using water	0.34 mg transfer (range: 0.08-0.51 mg); 37% transfer efficiency		(Christopher et al. 2007b)

Figure 1-1: An Adaptation of the Schneider et al. (1999)/Gorman Ng. et al. (2012) Conceptual Model for Dermal Exposure Assessment (Simplified to remove pathway parameter descriptors)



Chapter 2

Accuracy of Professional Judgments for Dermal Exposure Assessment Using Substance-Specific Deterministic Models

Abstract:

Assessment of the accuracy of exposure judgments, particularly for scenarios where only qualitative information is available, have been evaluated and shown to have a relatively low level of accuracy in the absence of additional information or a specific approach to the assessment process. This is particularly true for dermal exposures, where less information is generally available compared to inhalation exposures. Relatively few quantitative validation efforts have been performed for scenarios where dermal exposures are of interest. In this study, a series of dermal exposure judgments were collected from 37 volunteer U.S. occupational health practitioners in a workshop format to assess the accuracy of their judgments for three specific scenarios. The participants received progressively additional information and training regarding dermal exposure assessments and scenario-specific information during the workshop, and the relative accuracy of their judgments over time was compared. The results of the study indicated that despite substantial education and training in exposure assessment generally, the practitioners had very little experience in performing dermal exposure assessments and a low level of comfort in performing these assessments. Further, contrary to studies in the literature evaluating the initial accuracy of practitioners in performing inhalation exposure assessments in which they tend to underestimate exposure potential, it was observed that the participants consistently overestimated the potential for dermal exposure without quantitative data specific to the scenario of interest. Finally, it was found that participants were able to identify the reference or “true”

category of dermal exposure acceptability when provided with relevant, scenario-specific dermal and/or surface loading data for use in the assessment process. These results support the need for additional training and education of practitioners on performing dermal exposure assessments, and a closer analysis of default loading values used in dermal exposure assessments to evaluate their accuracy relative to real-world or measured dermal loading values. Improvements in the current models used by practitioners to assist in the performance of dermal exposure assessments are also needed.

2.1 INTRODUCTION

Assessing the accuracy and consistency of exposure assessment approaches for human health risk assessment is a critically important exercise. Recent efforts have highlighted some of the important determinants of exposure assessment judgment accuracy, and have evaluated or identified methods of improving this accuracy (Vadali et al. 2012b; Banerjee et al. 2014; Arnold et al. 2016; Logan et al. 2011; Logan et al. 2009). As noted by Arnold et al. (2016), a majority of exposure assessments are performed without the benefit of a substantial quantitative exposure dataset specific to the scenario of interest. Rather, semi-quantitative or qualitative approaches are often employed to reach conclusions about the acceptability of exposures. These authors also noted that qualitative judgment accuracy is often low, and there is a propensity for exposure assessment practitioners to underestimate actual exposure potential when using qualitative or semi-quantitative approaches without additional information or training. It was further noted that tools or frameworks, such as checklists, to identify the most important factors or rules when performing a qualitative exposure assessment have shown an ability to reduce biases and improve exposure judgment accuracy (by a factor of 2). Additionally, newer practitioners were able to reach the same level of accuracy as experienced practitioners when using an exposure assessment tool with the appropriate critical inputs (Arnold et al. 2016). The quality of exposure judgments can have a number of consequences. Many epidemiology studies rely heavily on judgments of exposure made using a variety of techniques ranging from qualitative to quantitative in nature, although many are purely qualitative in their approach. Inaccurate exposure judgments can have a significant influence on the results of these studies (Sahmel et al. 2010; Sakhvidi et al. 2015). As a result, understanding the weaknesses in the approaches

employed and identifying methods to improve the outcomes of these assessments are both extremely important.

For dermal exposure assessments specifically, a number of tools or approaches have been proposed to help practitioners make objective decisions about dermal exposure and risk, including the assessment of dermal uptake potential based on physicochemical properties (Magnusson et al. 2004; van Hemmen et al. 2003; Sahmel et al. 2009; Goede et al. 2019; McNally et al. 2019; Tibaldi et al. 2014; Warren et al. 2003). Examples of semi-quantitative and quantitative dermal exposure assessment models in current use include the RISKOFDERM model (Marquart et al. 2006; Warren et al. 2006); the DeRmal Exposure Assessment Methodology or DREAM (Van-Wendel-de-Joode et al. 2003; van Wendel de Joode et al. 2005b; van Wendel de Joode et al. 2005c); the AIHA conceptual dermal exposure assessment model (Boeniger et al. 2015; Sahmel et al. 2015a); the IH SkinPerm model (Tibaldi et al. 2014), and the ECETOC Targeted Risk Assessment (TRA) Model (ECETOC 2004, 2009a, 2009b). Additionally, the Advanced REACh Tool (ART) has a dermal component that will be known as Dermal ART or dART and which is currently in the validation stages (Tielemans et al. 2011; Gorman Ng et al. 2012a; Goede et al. 2019; McNally et al. 2019). Blanco et al. (2008) developed a qualitative dermal exposure assessment checklist method called the Determinants of Dermal Exposure Ranking Method (DERM) for performing expert ratings of pesticide exposure potential in developing countries. The researchers reported that the checklist allowed subsistence farmers to correctly identify the determinants of dermal exposure based on the key transport mechanisms found in the Schneider et al. (1999) dermal conceptual model. They also noted that the specificity of the checklist and rating tool to the particular pesticide application scenarios being evaluated likely

improved the performance of the tool (compared to the measured reliability of other more broad or general dermal models such as RISKOFDERM and DREAM) (Blanco et al. 2008).

It has been acknowledged that gaps in accuracy and consistency remain for both qualitative and quantitative approaches to dermal exposure assessment (Marquart et al. 2001; Marquart et al. 2003; Marquart et al. 2017; van Wendel de Joode et al. 2005b; Warren et al. 2003). The authors of a recent external evaluation of the models used in support of the REACH legislation reported that the small number of dermal exposure estimates compared to inhalation exposure estimates ultimately prevented the researchers from including the dermal exposures in the validation process (Tischer et al. 2017). It has further been noted that the results of comparative analyses of dermal exposures using different tools, such as Tier 1 screening models under REACH, cannot always be directly compared since the outputs of the tools are often reported in different units (Lamb et al. 2017). Research has indicated that the ECETOC TRA model is likely to overestimate or substantially overestimate dermal exposures, particularly at exposures that are considered low, and may underestimate dermal exposures at high levels of exposure (Marquart et al. 2017). Further, comparative results for dermal exposures using the RISKOFDERM toolkit were higher relative to other dermal models (Lamb et al. 2017). The need for a robust validation of the new dermal component of the Advanced Reach Tool (dermal ART or dART) prior to completion has also been noted (Goede et al. 2019). Calibration analyses of this new dART model have noted that "inputs to the model are based upon user judgement, [and] in practical use, the reliability of predictions will be dependent upon both the competence of users and the quality of contextual information available on an exposure scenario" (McNally et al. 2019, p. 650).

Given the other recent publications noting concerns addressing the level of accuracy of user judgments, additional analysis of the quality of these dermal exposure judgments may be warranted (Arnold et al. 2016).

2.1.1 Application of an Exposure Assessment Strategy to Dermal Exposure Assessments

The exposure assessment process or strategy is a systematic, cyclical process of identifying, evaluating, and controlling, and then validating or confirming those controls, for agents of concern or other hazards present in the environment or workplace (Jahn et al. 2015). However, for dermal exposure assessment, this cycle is currently incomplete for many agents, since the methods used to identify, evaluate, and control agents of concern for dermal exposures have not often been appropriately validated. Substantially more research gaps exist for dermal exposure assessment approaches compared to inhalation assessment approaches. On the other hand, since many scenarios pose a concern for both inhalation and dermal exposures, it would be inappropriate to overlook dermal exposure potential. Further, federal regulatory standards in many countries, such as the from Occupational Safety and Health Administration (OSHA) in the U.S., have promulgated requirements related to the assessment and control of dermal exposures (OSHA 1971). While important gaps in methodologies and approaches for dermal exposure assessments exist, the goals for dermal exposure assessment are consistent with inhalation exposure assessment, including (Jahn et al. 2015):

- The identification of methodologies for performing a systematic basic characterization of dermal exposure potential;
- The definition of similar exposure groups (SEGs) and exposure profiles that consider dermal exposure factors;
- The determination of appropriate criteria for judging whether dermal exposures in a given scenario are acceptable, unacceptable, or uncertain; and
- Methods for collecting appropriate and informative data to evaluate uncertain dermal exposures.

This process can be performed either qualitatively or quantitatively, and methods exist to consider both.

2.1.2 Dermal Exposure Judgment Categories

In order to make decisions about the acceptability of dermal exposures, criteria must be established to make these determinations. Both qualitative and quantitative criteria have been established in some instances to rate whether the determinants of dermal exposure assessment are unexpected or unlikely, small/improbable, midsize or possible, or large/probable (Sahmel et al. 2015a). Some common factors considered in dermal exposure assessments include the surface area of contact in cm^2; the quantity of a mixture or contaminant deposited on the skin in mg/cm^2 per time or per event, or sometimes in concentration of mg/cm^3; the contact frequency in number of events per day or the percentage of the work day for which the event occurs; and the amount of the applied dose absorbed through the skin in mg/cm^2-hour, or the fraction absorbed using a unitless factor if quantitative absorption data or estimates are not available (Sahmel et

al. 2009). These factors can be used to calculate or estimate a semi-quantitative or quantitative dose in mg/day.

Default values are available for some of these inputs from such sources as the U.S. EPA's Exposure Factors Handbook and other publications and resources (See **Appendix B** for a summary of default dermal loading and transfer values) (USEPA 2011; Cherrie et al. 2006; USEPA 2012; Brouwer et al. 1999; Vermeulen et al. 2002; Kromhout et al. 2001; Hubal et al. 2008; Sahmel et al. 2009; Williams et al. 2011; Fransman et al. 2011; Frasch et al. 2014; McDougal et al. 2002; Stefaniak et al. 2014; Stefaniak et al. 2006). Similar types of dermal exposure determinants have been used and described in other dermal exposure assessment models (Goede et al. 2019; Van-Wendel-de-Joode et al. 2003; Warren et al. 2003; Tibaldi et al. 2014). Some of the limitations and concerns inherent in these determinants have been previously discussed, and should be taken into account when performing dermal exposure modeling (Sahmel et al. 2009; Sahmel et al. 2015a; Frasch et al. 2014; Brouwer et al. 1999).

Since dermal exposure limits and guidelines (other than qualitative Skin Notations) are often unavailable, an alternative method must be used to establish exposure acceptability criteria (NIOSH 2009). In certain instances, an airborne occupational exposure limit (OEL) may be an appropriate basis for developing an acceptability criterion for dermal exposures. Such an approach is appropriate in scenarios where the contaminant or compound of concern has the potential to cause systemic effects, such as carcinogens or compounds with a known target organ (Sahmel et al. 2009). Note that such an approach would not be appropriate for scenarios in which the compound or agent of concern is associated with a localized response such as irritation, corrosion, or contact allergens. It is also important to review and understand

the basis for the OEL assignment, and to ensure that the analysis was based on systemic toxicity by more than just the inhalation route; if not carefully reviewed, factors such as percent absorbed through inhalation may make an inhalation OEL unsuitable for adaptation to the dermal route (Sahmel et al. 2009). However, if determined to be appropriate, the following relationship can be used:

Systemic Equivalent OEL (mg/day) = OEL (mg/m^3) x inhaled air volume (m^3/day or work shift) **(Eq. 2-1)**

The appropriate inhalation rate can be estimated using the data in the U.S. EPA's Exposure Factors Handbook, and can range from approximately 4 to 32 m^3 of air per eight-hour workday, depending on the exertion level of the activities being performed, or an average of 15-17 m^3 per 24-hour day (EPA 2011).

Exposure acceptability judgments (whether for dermal or inhalation exposure assessment) can be ranked according to four categories (Jahn et al. 2015). When performing quantitative analyses of exposure, these category judgments are determined using an upper tail statistic decision based on the available quantitative exposure data or model output for a specific SEG using the 90^{th}, 95^{th}, or 99^{th} percentile of the decision metric, which in this case is the occupational exposure limit (OEL) or dermal/systemic OEL equivalent. The 95^{th} percentile is the most common decision statistic.

These categories include an identified acceptability rating of 1 or 2 (typically considered an acceptable exposure relative to the OEL when variability is not large), 3 (uncertain acceptability or moderate to high exposure relative to the OEL), and 4 (unacceptable exposure relative to the OEL) (See **Table 2-1**). While this approach is

commonly used by exposure assessment practitioners to evaluate the acceptability of inhalation exposures in a variety of scenarios, it is less commonly used to evaluate the acceptability of dermal exposures.

There are concerns that when evaluating dermal exposure potential specifically, exposure practitioners may more frequently perform these assessments or make decisions about exposure acceptability without the benefit of any substantial background knowledge or training about dermal exposure assessment, and also without the benefit of any exposure assessment tools or frameworks. The purpose of this analysis was to evaluate the judgments made by exposure assessment practitioners when evaluating the acceptability of dermal exposures to understand what information was most influential to their decision-making process, and what information or tools were required for them to reach an accurate determination about dermal exposure potential.

2.2 METHODS

A workshop was held with 52 participants from the American Industrial Hygiene Conference and Exposition to evaluate the consistency and accuracy of environmental health practitioners in making judgments about the acceptability of inhalation, dermal, and noise exposure assessments. Of these, 37 volunteers participated in the dermal exposure assessment workshop exercise. Institutional Review Board (IRB) approval was obtained prior to the study from the University of Minnesota (#1212M25182). Before the start of the workshop, participants were asked to provide their level of formal education (i.e., associate degree or no degree, undergraduate degree, Master's degree, or advanced degree such as PhD or ScD), as well as their level of certification [i.e., certified industrial hygienist (CIH) or certified safety professional (CSP)]. Respondents were also

asked to respond to five questions (Shown in **Figure 2-1**) regarding their experience and training related to dermal exposure assessments specifically, including: (1) prior formal education in dermal exposure assessment, (2) prior professional training in dermal exposure assessment, (3) experience in performing qualitative dermal exposure assessments, (4) experience in performing quantitative dermal exposure assessments, and (5) their level of comfort or certainty in making dermal exposure judgments. The questions were designed to elicit specific differences in training by education level or certification in dermal exposure assessment capabilities and experience.

The participants were randomly assigned to evaluate one of three previously-identified dermal-specific occupational exposure scenarios, including (1) shell core molding in an iron foundry using a phenol-containing resin (evaluation of dermal phenol exposure potential); (2) form molding of component parts out of advance composites for the aerospace industry (evaluation of dermal methylene dianiline or MDA exposure potential); and (3) maintenance pitching (placement of partition components into pipes) at a petrochemical plant (evaluation of dermal benzene exposure potential).

To track the judgment process, the volunteers formally logged judgments at periodic points during the workshop using polling software (www.PollEverywhere.com). The practitioners were first asked to make an initial exposure acceptability judgment, followed by judgments that were associated with successive training sessions using interactive tools designed to assist in the performance of increasingly refined exposure assessments for each of the relevant scenarios. Overall, the participants were asked to make a total of five exposure acceptability determinations or judgments for the same scenario, and each exposure judgment was made with progressively more information, training, data and assistive tools to aid in the judgment and acceptability process. At

each point where a dermal judgment acceptability determination was required, the participants were asked to assign their judgment to one of the four categories of exposure acceptability (1 to 4) (See **Table 2-1**).

For the initial judgment, participants were provided with basic scenario information and physicochemical properties information about the substances of interest, and were asked to make their best acceptability determination regarding the dermal exposure potential (See **Appendix D: Supplemental Information on Scenarios Evaluated by Participants**). For the second judgment, the participants were provided with training on qualitative dermal exposure assessment determinants and given a tool for making qualitative dermal exposure assessments, and then asked to determine the acceptability of the exposure by refining their previous judgment. For the third judgment, the participants were provided with quantitative dermal exposure assessment training that built on the concepts in the qualitative training, along with an exposure model and interactive tool to allow quick trials of various quantitative model inputs. For the fourth judgment, the participants were provided with a set of scenario-specific quantitative dermal and surface sampling data for use in the quantitative dermal modeling tool. And finally, for the fifth judgment, participants were provided with an interactive tool that allowed the user to select parameters for dermal exposure loading and uptake through the skin (IH SkinPerm) (Tibaldi et al. 2017).

The model-predicted output for each participant for each scenario was recorded for comparison and was also publicly shared with the group of participants in real time following the logging of each judgment. General exposure assessment experience, as well as responses to the questions regarding experience specifically related to dermal

exposure assessment, and formal education and certification levels of the volunteer participants were also recorded and compared with the judgments provided.

2.3 RESULTS

Of the 37 participants, 75.7% (n=28) reported having obtained a master's degree, 19% (n=7) reported having obtained an undergraduate degree, and 5.4% (n=2) reported having either no degree, an associate degree, or an advanced degree. A total of 67.6% (n=25) reported being certified as a CIH and 21.6% (n=8) reported being certified as a CSP (See **Figure 2-2**).

For the five dermal-specific exposure assessment screening questions, 81% of participants reported having received no formal education in performing dermal exposure assessments, while 14% reported receiving some formal qualitative education on dermal exposure assessments and 4.8% reported receiving some formal quantitative education. Regarding prior professional training in dermal exposure assessment, 76% reported receiving no prior professional training and 4.8% had attended a course specific to dermal exposure assessment, while the remainder had received some training as part of another course or training effort. With respect to prior experience in performing qualitative dermal exposure assessments, 37.5% reported that they had never previously performed a qualitative dermal assessment, while 56.3% reported using professional judgment to perform a dermal exposure assessment, and 6.3% had previously used a qualitative dermal assessment tool or system. When asked about past experience performing quantitative dermal exposure assessments, 81.3% of participants reported never having done a quantitative dermal exposure assessment; 9.4% had performed some type of dermal sampling, and another 9.4% reported performing other

types of quantitative dermal exposure assessments. A majority (56.3%) reported that they were “not at all comfortable or certain” in performing dermal exposure assessments, while 28.1% were “slightly” comfortable regarding dermal assessments and 12.5% were “somewhat” comfortable or certain in performing dermal exposure assessments. No participants reported that they were “very” comfortable with the dermal exposure assessment process (See **Figure 2-3**).

The judgment results indicated that for both the initial and qualitative dermal judgments (Judgments #1 and #2), participants consistently judged the dermal exposure for their assigned scenario to be at a moderate to high risk level (category 3 or 4) (See **Figures 2-4 and 2-5**). For two of the three scenarios, practitioners overestimated the reference category. These two scenarios each had a reference category of 1, and so the practitioners overestimated the reference category for these scenarios by two to three categories. The third scenario had a reference category of 4, and so for this scenario, the reference category was either accurately estimated or underestimated, but it was unclear if this was due to an accurate estimate of exposure or was the result of the same qualitative judgment approach used generally by the practitioners for all scenarios. It was therefore observed that, inconsistent with inhalation exposure assessments, practitioners provided a category judgment that overestimated the “true” or reference dermal exposure category for 2 of the 3 scenarios evaluated (See **Table 2-2**). Contrary to this result, Arnold et al. (2016) reported that 50.8% of practitioners underestimated the reference exposure category in baseline inhalation exposure assessments.

When the participants were provided with a semi-quantitative approach and input tool to assess dermal exposure for their assigned scenario, along with the available default parameters for dermal loading and dermal absorption (Judgment #3), the

acceptability judgments for Scenarios #1 and #3 rose to a category 4, or unacceptable exposure, and were split between a category 3 and 4 for Scenario #2. Essentially, using the available default parameters, all scenarios were judged to be “unacceptable” for dermal exposure, or approaching “unacceptable” (See **Figure 2-6**).

Following the semi-quantitative modeling judgment using default inputs, the participants were provided real-world sampling data for skin and surface loading for their respective scenarios (Judgment #4). With the addition of these data to the assessment process, a majority of participant judgments for Scenarios #1 and #3 dropped by three categories, from a Category 4 to a Category 1. For Scenario #2, the split rating between a Category 3 and 4 increased to a category 4 (See **Figure 2-7**).

The addition of a dermal loading and absorption tool (IH SkinPerm) for use in the final judgment (Judgment #5) did not change the majority of the participant judgments, which remained at a Category 1 for scenarios 1 and 3, and a Category 4 for scenario 2. Further, the addition of the training and quantitative tool associated with Judgment #5 (IH SkinPerm) did not decrease the accuracy in the dermal judgment output and was not observed to negatively affect the accuracy of the participant judgments (See **Figure 2-8**). However, it should be noted that the default loading values in the IH SkinPerm model were consistent with other default values provided to the participants for use in the quantitative modeling calculations (1 mg/cm^2/hour, and a maximum of 7 mg/cm^2). It is therefore expected that the use of IH SkinPerm alone to assess dermal exposure potential, without the addition of scenario-specific (or real-world) sampling data, may have shown some degree of overestimation, consistent with the semi-quantitative dermal exposure assessment modeling results using available default parameters.

The model-predicted output (with respect to the reference category, as determined by quantitative measurement data prior to the workshop, see **Table 2-2**) improved most significantly when dermal and surface loading measurement data were made available to the participants for use in the assessments, and changed by up to 3 categories for two of the three scenarios. Overall, the results indicated that with scenario and agent-specific quantitative dermal loading data, a majority of participants were able to identify the correct exposure category for all three different dermal exposure scenarios, despite minimal prior education or training on either qualitative or quantitative dermal exposure assessments for a majority of participants.

2.4 DISCUSSION

This study examined the ability of exposure assessment practitioners to make accurate judgments about the model-predicted exposure category for dermal exposure and uptake. Several important findings were noted in this study. First, it was observed that occupational health practitioners have very little experience with dermal exposure assessments, despite often having many years of professional experience, as well as certifications and advanced degrees. Second, distinct from the experience of judgment accuracy investigations for inhalation exposure assessments, the participants tended to overestimate the potential for dermal exposure when they had limited information to perform the assessment. Third, the availability of appropriate scenario-specific data, and specifically skin surface loading data, enabled a majority of participants to reach the correct judgment regarding the accurate dermal exposure category, despite being incorrect by as many as three categories in their initial judgments.

Regarding the first of these findings, initial training and experience in dermal exposure assessments were minimal for a majority of the participants, despite substantial education in exposure assessment generally. Similar results have been noted in previous studies; in an evaluation of Tier 1 REACH assessment tools, Lamb et al. (2017) reported that more participants in the evaluation process noted “major uncertainty” in choosing the dermal activity or task compared to the inhalation activity/task. With respect to the level of practitioner experience and its effects on judgment accuracy, Vadali et al. (2012a) noted that practitioners with experience or expertise often use that knowledge to identify patterns in problems or questions to arrive at a judgment regarding appropriateness or accuracy. The results of this analysis demonstrated that such expertise or training in dermal exposure assessments, both perceived and real, is lacking among exposure assessment practitioners in the U.S. The same may be true elsewhere for similar practitioners. It has previously been reported that total years of experience in performing exposure assessments, as well as the possession of relevant professional certifications, were significantly associated with judgment accuracy (Vadali et al. 2012a; Sakhvidi et al. 2015). Based on the participant responses in this study, a near complete lack of experience with dermal exposure assessments was reported despite substantial education or the attainment of relevant professional certifications, as reported by a majority of the participants. As a result, the progressive addition of information and tools to the participants in this study for performing dermal exposure assessments likely contributed significantly to each participants’ knowledge and information. Consistent with this finding, De Cock et al. (1996) noted that when asked to evaluate a scenario related to pesticide exposures, a group of exposure assessment practitioners adjusted their estimates of the relative

contributions to exposure from different routes as they received additional information. Initially, the practitioners determined that the majority of exposure would be associated with the inhalation route, but later adjusted their judgment to indicate that dermal exposure was likely to be more significant. This adjustment may have been due to biases related to past education on exposure assessment that focused on inhalation exposure potential.

In the second significant finding of this study, the participants systematically overestimated dermal exposure potential when presented with limited or non-specific information to perform the assessment for each dermal exposure scenario. This effect is different than that observed for inhalation exposure assessments, where practitioners have tended to underestimate exposures, particularly for initial judgments (Arnold et al. 2016). Interestingly, the lack of background or expertise in dermal exposure assessments may have reduced potential biases related to prior assessments or experience that can result in inconsistent or inaccurate judgments by experienced participants for inhalation exposure scenarios, A similar effect was observed by Arnold et al. (2016) for novice exposure assessment practitioners compared to experienced practitioners.

Third, an understanding of the critical inputs needed, and the process with which those critical inputs must be used, were observed in this study to be the most important factors in accurately judging dermal exposure scenarios rather than level of training or experience. Unlike previous studies of exposure judgment accuracy, the initial judgments in this study were routinely assigned by participants at a moderate to high exposure category regardless of the reference exposure category for the scenario. The progressive addition of tools and information for the dermal exposure assessment

scenarios evaluated in this workshop essentially encouraged the participants to follow an appropriate algorithm for assessing dermal exposures rather than disproportionately applying “professional judgment”, with its inherent biases, based on previous assessments or experience. When scenario-specific data were provided to the participants, a majority of the participants were able to identify the correct reference category for all three scenarios evaluated. These results indicate that existing default data to evaluate dermal exposure potential do not necessarily allow for an accurate analysis of dermal exposure potential, and appeared to overestimate or substantially overestimate total dermal exposure. The determination and use of default or baseline parameters for dermal exposure assessment was therefore observed to be a substantial barrier to accuracy in this study. Marquart et al. (2006) also noted that there can be questions around defining default parameters, such as for dermal loading or transfer. In the RISKOFDERM tool, the researchers defined parameters consistent with “typical exposure”, and “reasonable worst case”; they noted that “reasonable worst case” is likely used more often than “typical exposure”. It was also acknowledged that a large amount of “expert judgment” is involved in determining these values, and indicated that substantial variability in estimated dermal exposure levels can be expected.

For this particular analysis, information on a number of quantitative default parameters was initially provided to the participants, including skin surface area of contact, dermal concentration or loading, and potential for dermal uptake. Accurate semi-quantitative or quantitative information on dermal loading or transfer was observed to be the critical input required by a substantial number of practitioners to reach an accurate judgment regarding dermal exposures in several specific scenarios. These results are consistent with Xue et al. (2006), who found that the two most important

parameters in determining children's exposure were the surface residue-to-skin transfer efficiency and surface residue levels. This finding is also consistent with de Cock et al. (1996), who reported that dislodgeable foliar residue was found to be the most significant determinant of pesticide exposure. It has also been reported that, in actual practice, the amount of a substance that is removed from the skin correlates with the amount absorbed (Brouwer et al. 1998; Brouwer et al. 2000). In an evaluation of dermal exposure assessment for occupational epidemiology research, Vermeulen et al. (2002) similarly reported that the intensity of a contaminant on the skin surface was either very or extremely important for the estimation of dermal exposure, but rated the level of knowledge regarding this parameter as either poor or limited.

In evaluating the variability of task-based estimates of dermal exposure for different industries, Kromhout et al. (2004) found that differences in dermal exposure can range over 3 to 5 orders of magnitude for groups or scenarios with similar exposure patterns. They found that these differences were directly influenced by the local conditions surrounding the actual handling of a material, as well as the material's physical/chemical properties, and concluded that "actual dermal exposure measurements" and an improved understanding of the determinants of dermal exposure were required for appropriate dermal exposure assessments. Similarly, Blanco et al. (2005) reported that work practices and the type of equipment used accounted for a substantial amount of the dermal exposure variability. In evaluations of the dART tool, researchers noted that the vast majority of dermal loading or transfer measurements were collected using cotton gloves, an interception method which has been previously noted to overestimate or significantly overestimate dermal loading (Ng et al. 2014a; McNally et al. 2019). While such overestimates may have a small influence on the

relative amount of dermal exposure for various tasks (depending on the absorptive properties of the cotton glove samplers over time, as well as the duration of sampling), their use makes the determination of true quantitative loading on the skin surface difficult (McNally et al. 2019).

Given the apparent influence of accurate dermal transfer or loading data on arriving at an appropriate dermal exposure judgment for a particular scenario, improved default data and training with respect to the ranges of dermal loading and transfer should be developed to assist practitioners in improving the quality of judgments for dermal exposure scenarios. Another critical need is skin surface sampling data for a larger range of substances. As noted by Beamer et al. (2009), part of the difficulty in adequately quantifying transfer efficiency is that it may be related to a number of different parameters, including surface characteristics; the nature of contact (including frequency, duration, and pressure); time since application or contact; and temperature and humidity. The skin loading over an accurate estimate of skin surface area is also critical (Vermeulen et al. 2002). While the range of scenarios evaluated in this study was limited and the number of participants was relatively small, increasing the risk for selection bias, the consistency of the results points to the specific types of data inputs that are likely to improve the ability of exposure assessment practitioners to select the appropriate category for dermal exposure acceptability. A careful evaluation of the existing dermal exposure assessment tools is needed with a focus on improving the quality of the existing default parameters, particularly with respect to dermal loading or transfer.

2.5 CONCLUSIONS

The results of this study demonstrated that despite substantial education and training in industrial hygiene generally, the practitioners evaluated in this study had very little experience in performing dermal exposure assessments. Further, contrary to studies in the literature evaluating the initial accuracy of practitioners in performing inhalation exposure assessments in which the practitioners tend to underestimate exposure potential, it was observed that the participants in this study consistently overestimated the potential for dermal exposure without quantitative data specific to the scenario of interest. Finally, it was found that participants in this study were able to identify the reference or “true” category of dermal exposure acceptability when provided with relevant, scenario-specific dermal and/or surface loading data for use in the assessment process. As previously noted by Arnold et al. (2016) and others, the accuracy of exposure assessments is fundamental to supporting the exposure and risk assessment process and being able to characterize the accuracy of these assessments. The results of this analysis support the need for a closer examination of default skin loading and other values used in dermal exposure assessments to evaluate their accuracy relative to real-world or measured dermal loading values.

Table 2-1: Quantitative Dermal Judgment Categories, for which X is the 95th Percentile of the Quantitative Data or Model Output for a Specific Exposure Group (SEG)

Category	OEL vs. Dermal Estimate (X)
1	X^A < 10% of OEL (as defined below)
2	10% of OEL < X < 50% of OEL
3	50% of OEL < X < OEL
4	OEL < X

[A]X denotes the decision statistic (i.e., the 95th or 90th percentile value)

Table 2-2: Summary of Results: Model-Predicted Category Analysis for Dermal Exposures Following Training

Dermal Scenario Number	Judgment #1: Initial Output	Judgment #2: Qualitative Dermal Determinant Output	Judgment #3: Semi-Quantitative Dermal Model Output	Judgment #4: Quantitative/ Sampling Data Output	Judgment #5: Quantitative Dermal Uptake Output	Reference Category
Scenario 1 (phenol)	3	3	4	1	1	1
Scenario 2 (MDA)	3	Split 3/4	4	4	4	4
Scenario 3 (benzene)	3	3	4	1	1	1

Figure 2-1: Dermal Exposure Assessment Prior Experience Questions



Figure 2-2: Level of Professional Education and Certification Reported

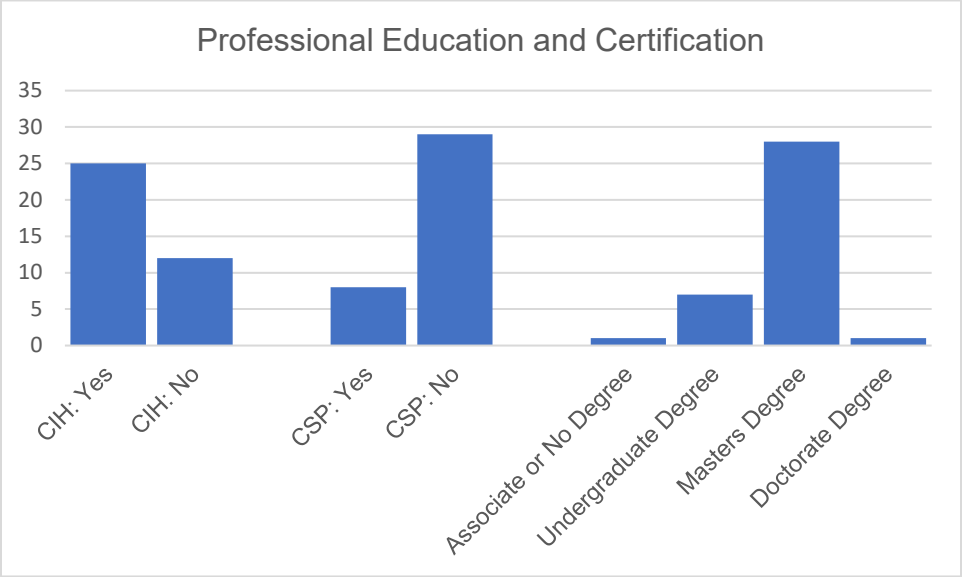


Figure 2-3: Prior Reported Experience by Participants with Dermal Exposure Assessments

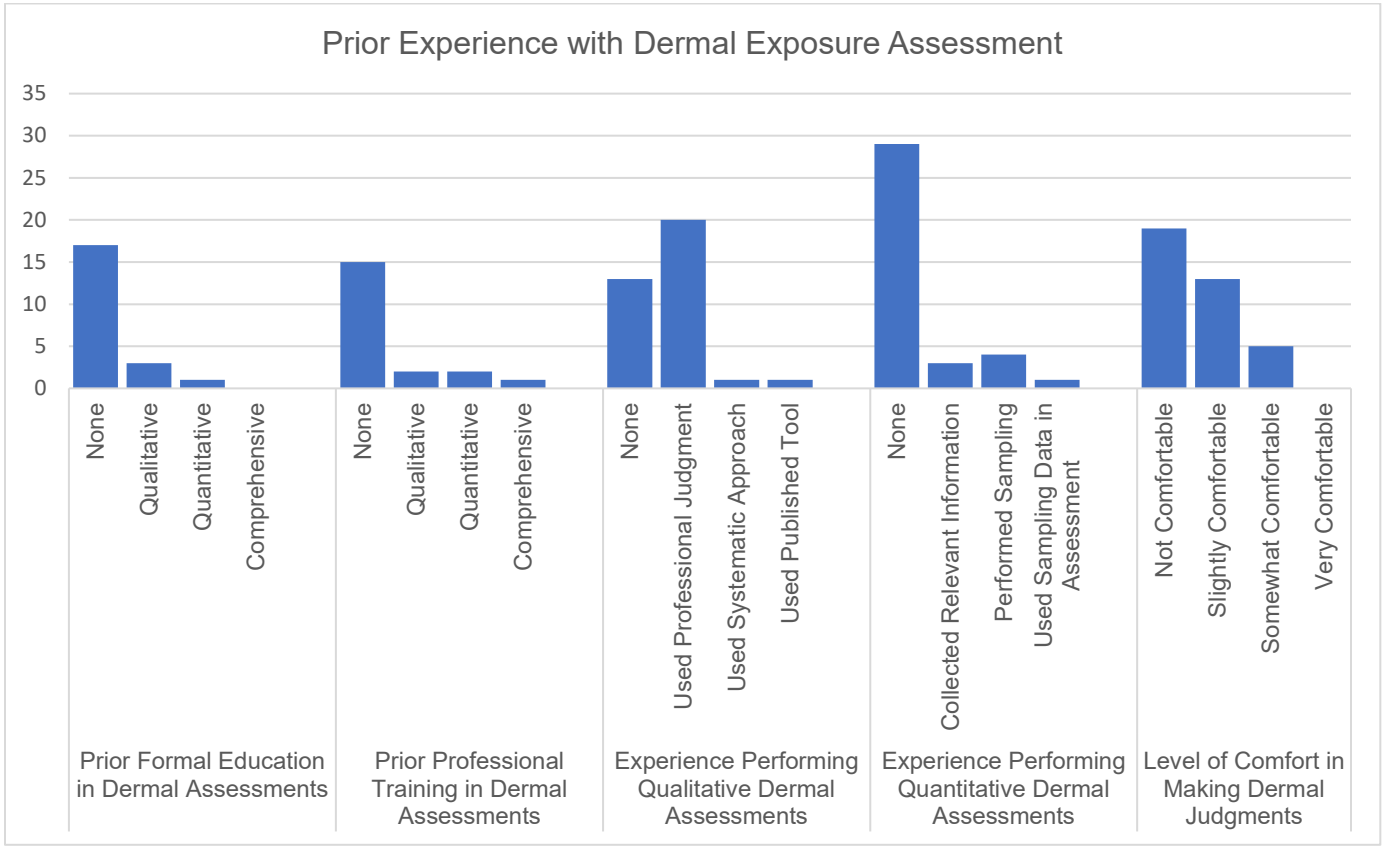


Figure 2-4: Participant Category Determinations for Judgment #1 (Initial Judgment)

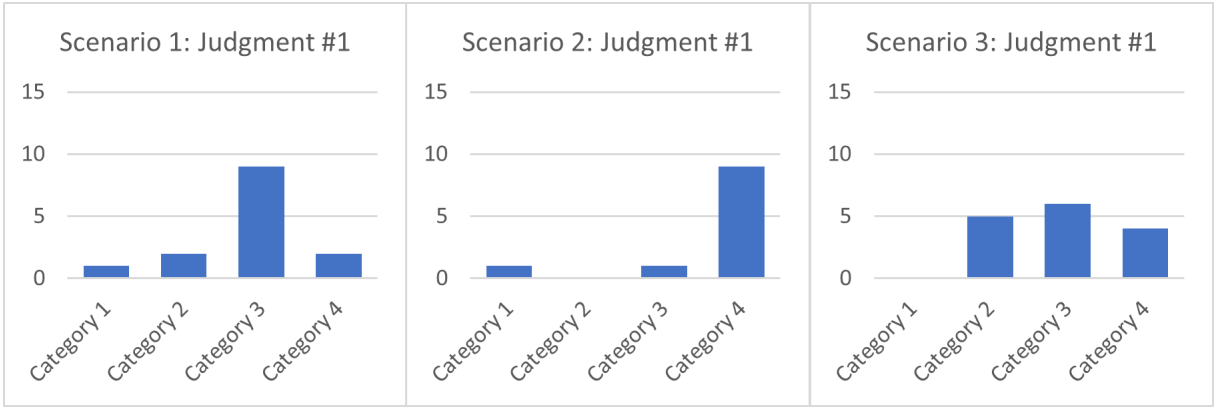


Figure 2-5: Participant Category Determinations for Judgment #2 (Qualitative Judgment)

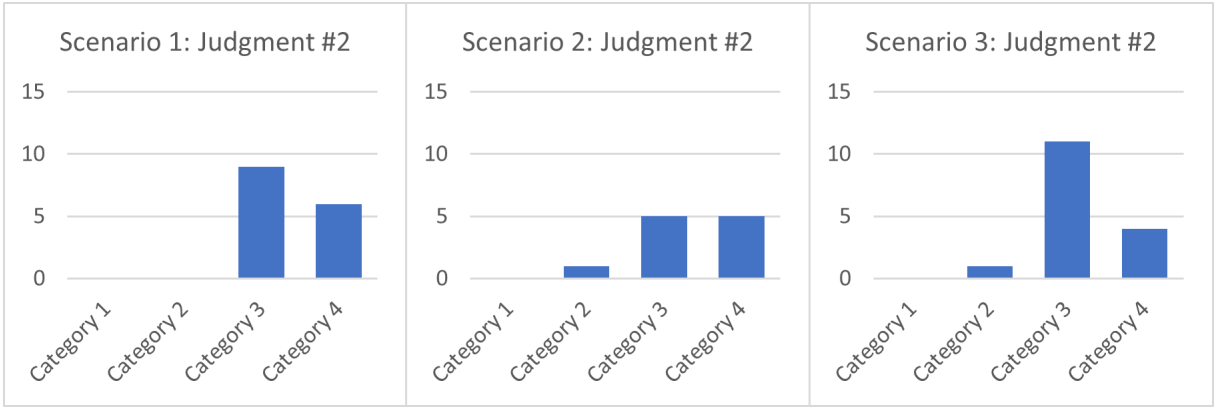


Figure 2-6: Participant Category Determinations for Judgment #3 (Semi-Quantitative Judgment)

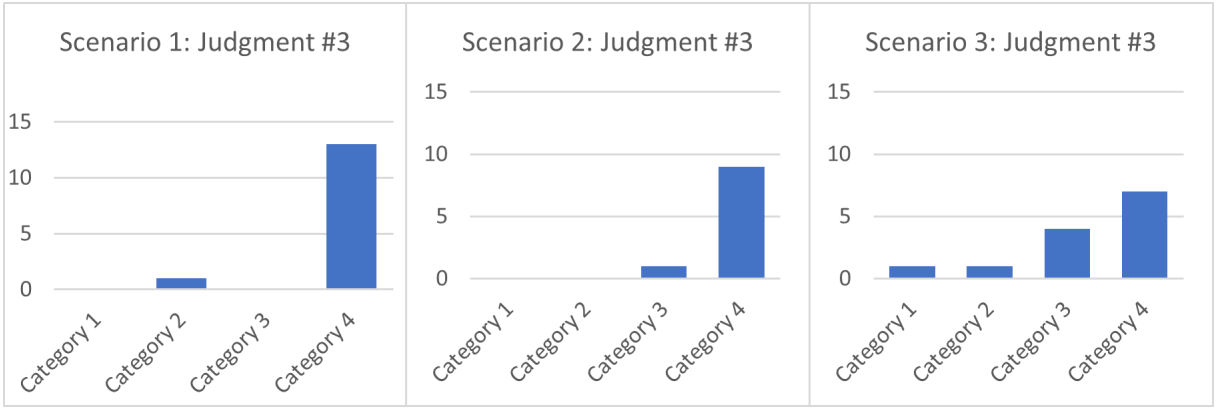


Figure 2-7: Participant Category Determinations for Judgment #4 (Quantitative/Sampling Data Judgment)

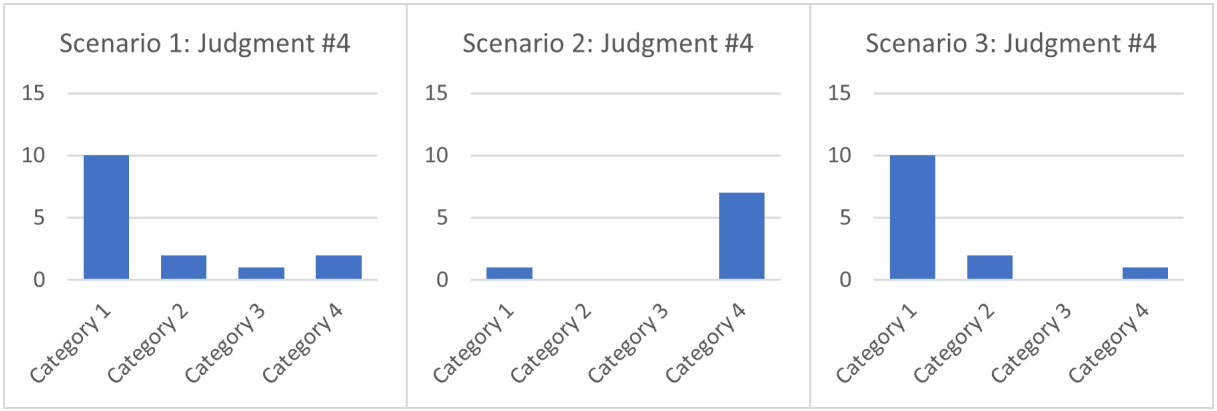
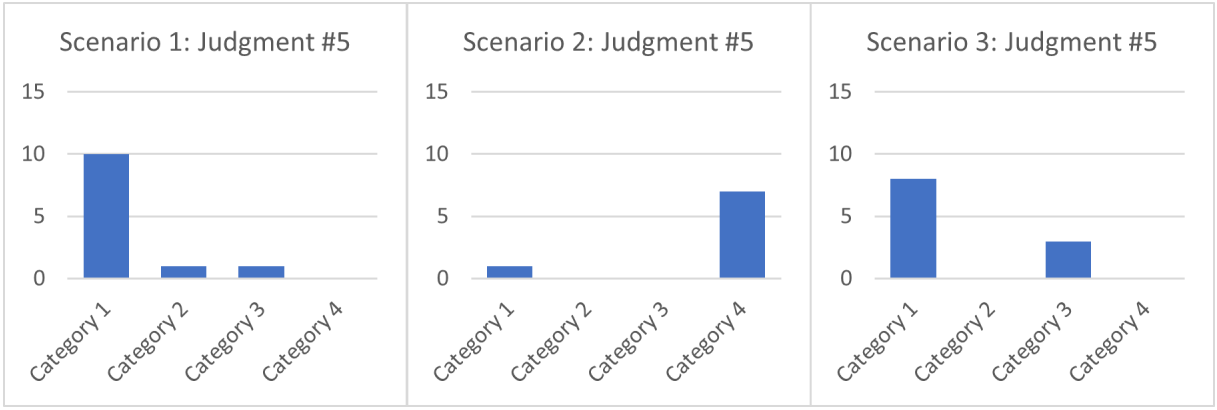


Figure 2-8: Participant Category Determinations for Judgment #5 (Quantitative/Uptake Estimate Judgment)



Chapter 3

Influence of Repeated Contacts on the Transfer of Elemental Metallic Lead Between Compartments in an Integrated Conceptual Model for Dermal Exposure Assessment

Abstract:

Transfer of contaminants to and from the skin surface has been hypothesized to occur through a number of different pathways and compartments, including: object(s) to skin, skin-to-skin, skin-to-clothing, skin-to-gloves, air-to-skin, skin-to-lips, and skin-to-saliva. However, many identified transfer pathways have been only minimally studied to determine the potential for measurable transfer. The purpose of this study was to quantitatively evaluate transfer between different compartments using elemental metallic lead in the solid form using a series of systematic measurements in human subjects (n=18). The results demonstrated that some transfer pathways and compartments are substantially more important than others. Transfer of lead could not be measured from the skin to cotton clothing or to laminate countertop surfaces, while transfer could consistently be measured between the skin and the surface of nitrile gloves, suggesting that these could become a reservoir for exposure. With repeated contacts, transfer increased non-linearly between one and five contacts, but appeared to approach a steady state distribution among the compartments within ten contacts. Consistent with other studies, relative to 100% transfer for a single contact, the quantitative transfer efficiency decreased with repeated contacts to 29% after five contacts and 11-12% after ten contacts; for skin-to-skin transfer measurements, transfer efficiency after either five or ten contacts was approximately 50%.

3.1 INTRODUCTION

As occupational inhalation hazards to chemicals and other substances of concern have been progressively identified and mitigated, dermal exposures are increasingly of greater relative concern for human health risk assessment. The large number of non-volatile substances in commerce and in consumer products has highlighted the need for improved approaches to systematic dermal exposure assessment for non-volatiles. However, many common dermal exposure assessment approaches have historically been lacking in a comprehensive or systematic approach or framework, and recently, exposure science researchers have pointed to an urgent need for additional information related to object-to-skin transfer-related parameters (Huang et al. 2017). Even when such a framework is available, quantitative data on the transfer of substances to and from the human skin surface are often lacking or unavailable, and semi-quantitative or qualitative data must be used. The goal of this analysis was to evaluate the utility of a conceptual model for assessing quantitative dermal exposures to solids, such as metals, using measurement-based refinements to improve the approaches used for similar assessments.

There are currently a number of available predictive dermal exposure assessment models ranging from qualitative to semi-quantitative or quantitative. In 1999, a robust conceptual model for dermal exposure assessment was published, and was subsequently updated in 2012 (Schneider et al. 1999; Schneider et al. 2000; Gorman Ng et al. 2012b). Since that time, the development of exposure models has been restricted by the limited availability of quantitative data and variability in sampling methods that have complicated the aggregation of the available data for exposure assessment model development (Kasiotis et al. 2020). Examples of dermal exposure assessment models in

current use include the RISKOFDERM model (Marquart et al. 2006; Warren et al. 2006); the DeRmal Exposure Assessment Methodology or DREAM (Van-Wendel-de-Joode et al. 2003; van Wendel de Joode et al. 2005b; van Wendel de Joode et al. 2005c); the AIHA conceptual dermal exposure assessment model (Boeniger et al. 2015; Sahmel et al. 2015a); and the ECETOC Targeted Risk Assessment (TRA) Model (ECETOC 2004, 2009a, 2009b). The U.S. EPA has a number of models with dermal components, including ChemSTEER, and more recently, the Consumer Exposure Model (CEM), which includes a total of seven dermal models (USEPA 2019). Additionally, the Advanced REACh Tool (ART) has a dermal component known as Dermal ART or dART and which is currently in the validation stages (Tielemans et al. 2011; Gorman Ng et al. 2012a; Goede et al. 2019; McNally et al. 2019).

Dermal transfer has been defined as the amount of material that moves from one surface to another following contact with the skin (IOM ND; Fenske 1993). The dermal exposure assessment models listed above often use some variation of five common types of dermal exposure determinants: (1) dermal contact area, (2) dermal contact frequency, (3) dermal retention time, (4) dermal loading and/or concentration, and (5) dermal penetration or absorption potential. The Schneider et al. (1999) dermal conceptual framework includes the following exposure compartments: source, surface contaminant layer, air, outer clothing/gloves contaminant layer, inner clothing contaminant layer, and skin contaminant layer. The model has also been updated to include the oral compartment (Schneider et al. 1999; Gorman Ng et al. 2012b). Such a conceptual model is a fundamental part of a systematic exposure assessment, since it describes how the different potential pathways for dermal exposure should be accounted for to produce an appropriate estimate of exposure through multiple pathways. Ignoring

a pathway may lead to an underestimate of exposure, but conversely, having a model that is too detailed for the scenario of interest is not efficient.

A modified version of the conceptual model that is relevant to the current research effort is shown in **Figure 2-1**, highlighting the pathways between which transfer may be relevant for solids: (1) contaminant source to/from skin, (2) skin to/from other skin, (3) surfaces to/from skin, (4) clothing to/from skin, (5) gloves to/from skin, and (6) saliva to/from skin. While potentially less important when scenario-specific dermal loading data are available, this model is valuable for adequately characterizing the relative importance of specific transfer compartments and pathways for dermal exposure modeling or estimation purposes. Few published data exist that address multiple individual pathways described in this conceptual model, and nearly all available data address only surface or object to skin exposures. According to Gorman Ng et al. 2012, these comprise approximately 84% of measurements. However, transfer mechanisms are a significant part of the conceptual model and may substantially influence the dermal loading values and the resulting dermal exposure estimates. Additionally, significant variability has been reported in the published values for dermal transfer efficiencies (0-157%) (Gorman Ng et al. 2012b). It has also been noted that differences in the effect of exposure determinants by various pathways or for different substances may have significant implications for the development of dermal exposure models (Gorman Ng et al. 2013). Additional dermal measurement data are needed to refine dermal exposure assessments consistent with this conceptual model and to improve the quality of existing dermal models and assessment frameworks for different types of contaminants.

Since elemental metallic lead in bulk form has a negligible vapor pressure, the pathways from the air to surfaces or skin, as well as the pathways from the source

directly to the peri-oral layer or oral cavity, have been removed from the conceptual model used in this analysis. However, these pathways may be relevant for other types of solids or semi-volatile compounds with a measurable vapor pressure, or which are heated to a gas or present as a dust or aerosol.

The amount of a substance retained on the skin, or the dermal loading/concentration, has been experimentally estimated in addition to being evaluated using default assumptions. For solids, this parameter is often defined as mass per surface area of skin (surface density) in $\mu g/cm^2$, which then allows for the estimation of time-weighted average loading and subsequently the calculation of dermal uptake or flux through the skin in $\mu g/cm^2$-hour, which is a frequent metric for quantitative uptake of substances through the skin (Frasch et al. 2014; Sahmel et al. 2009). Default loading values for skin adherence due to direct contact have been proposed or reported, including: 1-3 mg/cm^2 (USEPA 2013; Brouwer et al. 1999; EPA 2011); 0.2-1.7 mg/cm^2 for soils (EPA 1992; Finley et al. 1994); 0.0063 – 0.66 mg/cm^2 for loading of solids onto the hands in the U.S. EPA's Exposure Factors Handbook (EPA 2011); and 14 mg/cm^2 for loading and filling large containers or mixers, or 0.005 mg/cm^2 for careful mixing of small quantities (Marquart et al. 2006). However, ideally, dermal sampling data specific to a particular agent and scenario should be used to generate an estimate of dermal exposure potential.

Lead was proposed as a study agent for this analysis, because it poses important public health concerns to a variety of populations, including workers, consumers, and children, and transfer to the skin is likely to be a significant potential pathway for exposure. Ingestion via hand to mouth contact following loading on the skin is likely to be the primary route of exposure for lead rather than the inhalation or dermal

absorption routes (Manton 1985; Canales et al. 2007; Mahaffey 1977; COEHHA 2011). Studies of lead uptake into the body have suggested that dermal absorption of lead through the viable epidermis is limited compared to uptake by ingestion or inhalation (Florence et al. 1988; Florence et al. 1996; Stauber et al. 1994; Hostynek 2003; Hostynek et al. 1993). The ability of inorganic lead to form bonds with proteins in the skin may limit skin penetration. However, organic or lipid-soluble lead compounds are readily absorbed, and penetration or absorption of lead compounds also appears more likely under conditions in which metal dusts can ionize (Filon et al. 2006; Sun et al. 2002; Hostynek et al. 1993; Florence et al. 1988). It has been observed that small solid particles do not readily penetrate the intact stratum corneum and are more likely to become stuck in the outer skin layer. However, particles can more easily penetrate damaged skin, such as skin that had been washed with certain soaps or cleansers containing surfactants (Fogh et al. 1988; Filon et al. 2006; Tinkle et al. 2003). The ability of lead to enter the blood following dermal absorption appears to be limited, although lead can be measured in the sweat and saliva following exposure in certain forms. Its general ability to become biologically available following dermal absorption is unknown (Franken et al. 2015; Florence et al. 1988; Florence et al. 1996; Lilley et al. 1988; Stauber et al. 1994; Sun et al. 2002). Conversely, studies have demonstrated that lead ingested through hand to mouth contact can be substantial, and can readily reach the bloodstream (Mahaffey 1977; Manton 1985).

This study quantitatively assessed the potential for transfer of elemental metallic lead between relevant identified compartments of the updated Schneider/Gorman Ng conceptual model (**Figure 2-1**). Previous studies have confirmed that lead transfer can readily occur from handling solid lead ingots or during normal handling of consumer

product fishing tackle with as little as a single contact (Sleeuwenhoek et al. 2006; Sahmel et al. 2015b). A review of the literature has demonstrated that the factors most consistently associated with a statistically significant influence on dermal transfer are repeated contacts with the source, the level of skin hydration, and quantitative surface loading; these factors were therefore a focus of this study. Other factors, such as dermal contact pressure and contact duration, were found to be less influential and were therefore kept constant for the purposes of this analysis (Brouwer et al. 1999; Hubal et al. 2008; Zainudin et al. 2004; Christopher et al. 2007b). This study also focused on evaluating the potential for differences in results between different skin surface sampling methods, the variability of measured transfer values to and from the compartments within the conceptual model, and the effect of repeated contacts or transfer events for all compartments evaluated (**Figure 2-1**). While not specifically discussed here, the effects of skin hydration on loading (Sahmel et al. 2021) were also addressed in this study.

3.2 METHODS

3.2.1 Study Design, Materials Selection, and Volunteer Recruitment

It has been reported that the hands are the most contaminated part of the body following typical working contact (Rajan-Sithamparanadarajah et al. 2004). This study was designed to evaluate the quantitative assessment of lead transfer following contacts between the skin of the hands *in vivo* and other potential compartments. Of the transfer pathways identified in the updated dermal conceptual model, the following relevant pathways were identified for the current study: (1) object to skin, (2) skin-to-skin, (3) skin to cotton clothing, (4) skin to gloves, and (5) skin to countertop surface (Gorman Ng et

al. 2012b; Schneider et al. 1999). A sixth pathway, skin to saliva, was previously evaluated (Sahmel et al. 2015b), and the skin to air contact scenario was not addressed, since lead has a negligible vapor pressure, making air to skin or skin to air transfer unlikely (National Institute for Occupational Safety and Health (NIOSH) 2010). For each pathway, quantitative transfer was measured and transfer efficiency was calculated for multiple contacts between the skin and the pathway of interest.

A protocol using readily available solid lead consumer-product fishing tackle was developed. Institutional Review Board (IRB) protocol review and approval was obtained from the University of Minnesota prior to the study (Protocol #1506M73781). Lead contamination on the skin was carefully controlled throughout study, and after the study, the skin was thoroughly decontaminated using a patented, commercially-available formulation that has previously been demonstrated to be effective in removing lead from the skin surface (Sahmel et al. 2015b; Esswein et al. 2011).

Human volunteers were sought for this study in order to obtain data that were most similar and relevant to the interaction between metallic solids and the living human skin surface and its properties. Volunteers were accepted into the study if they were at least 21 years old and were able to understand and willing to sign a written consent form. Volunteers were excluded from the study if they were unwilling to follow the described protocol; had a self-described history of lead poisoning; had a concurrent contagious illness (for the safety of all volunteers and researchers); had compromised skin integrity on their hands (such as dermatitis or excema); or were pregnant, nursing, or trying to become pregnant.

Statistical power calculations demonstrated that a minimum of four volunteers was likely to be needed for sufficient statistical power for a GSD of 2 (SD of 0.5) or less,

based on previous data from a similar study, with a 95% decision statistic and an error rate of 2% or less (Sahmel et al. 2015b). To achieve an error of 1% or less, a sample size of 16 is required. A total of 18 human volunteers were recruited from the practicing environmental health professional community for sample collection in 2016 and 2017.

3.2.2 Contact Scenarios Evaluated

To test each pathway, participant volunteers performed repeated contact activities using a consistent protocol (e.g., identical number of contacts, type of material contacted, measured pressure of contact, measured time of contact) so that inter- and intra-individual variability could be characterized (See **Table 3-1; Figure 3-2**). Due to time constraints, not every participant completed all of the 15 pathways studied.

The contact surface for each participant included the palmar distal digits (fingertips) of the index finger, middle finger, and thumb of the dominant hand. All scenarios (except for the skin-to-skin scenario) were tested using a hand pressure on the object or test surface of approximately 1 psi and a duration of 2 seconds per contact, based on previous evaluations (Hubal et al. 2008). For each scenario, participants were asked to press on the metal product, or secondary surface such as a glove or clothing swatch, resting on a scale by applying approximately 0.454 kg of pressure downward onto the material or object with the palmar surface area of the finger (See **Figure 2-3a and 2-3b**).

The effect of repeated contacts was evaluated by comparing a single contact, five repeated contacts, and ten repeated contacts between the skin and the test surface were evaluated, consistent with data in the literature suggesting that maximum loading may be reached after approximately 5 to 7 consecutive contacts (Brouwer et al. 1999;

Hubal et al. 2008; Hughson et al. 2005; Rodes et al. 2001; Rhodes et al. 1997; Sleeuwenhoek et al. 2006). There was a wait time of at least one minute between each scenario to ensure that the skin was completely dry before the next scenario following a decontamination wipe procedure. Lead Off© soap and surface wipes were used to maximize the removal of lead from the skin of the participants in between sample sets and after sample collection (www.hygenall.com). For the skin to surface, clothing, and glove tests, an identical clean material was used for each of the volunteer participants to minimize variability due to factors other than dermal transfer efficiency (See **Table 3-1; Figure 3-2**) (Ross et al. 1990; Ramwell et al. 2010).

3.2.3 Sampling and Analytical Techniques

The commercially available solid smooth metallic lead ingots used in this study had a nominal mass of ~28.4 g each and were confirmed to be 100% lead prior to study commencement (ALS, Salt Lake City, UT, USA). Three previously published sampling methods were used to measure lead on the skin surface for comparison: two wipe sampling methods and one tape stripping method. For the two wipe sampling methods, a protocol using three serial wipe samples per transfer test was used to evaluate the removal efficiency of lead from the skin for each wipe. For the tape stripping method, three successive tape lifts each were aggregated into two samples, for a total of six tape lifts. Method #1, a wipe sampling method, was quantitatively compared to an analysis of Methods #2 and #3 combined, for a successive wipe sampling and tape stripping sampling technique. The sampling methods were selected on the basis of commercial availability, ease of use, and low cost, in order to identify methods that could be readily adopted for use by occupational health practitioners in field studies. The study

investigator collecting the samples wore nitrile gloves that were changed in between the collection of each sample to minimize the potential for any cross contamination between samples or scenarios.

Method #1: SKC Full Disclosure® lead wipe quantitative analysis kits were used to quantify metals removal from the skin (using NIOSH Analytical Method 7300, modified for wipes according to NIOSH Analytical Method 9102) and based on ASTM E1792-03; a total of 15 volunteers participated in this sampling protocol (Millson et al. 2003; Esswein et al. 2005; Ashley et al. 2011; Esswein et al. 2011; Sahmel et al. 2015b).

Method #2: A published and approved skin sampling method using 1% HNO_3 moistened Whatman filter wipes for the removal of metals and particulates from human skin was used for comparison to the SKC/NIOSH sampling protocol (Liden et al. 2006; Liden et al. 2008; Julander et al. 2010; Erfani et al. 2017). Whatman filter paper #41, a slightly thicker and sturdier filter paper, was used for this study to help maintain the wipe structure and integrity during sampling. A total of 11 volunteers participated in the second sampling protocol, comprising the second and third sampling methods in combination.

Method #3: A published tape lift sampling method developed as part of the U.S. FDA's research on human skin to investigate the dermato-pharmacokinetics (DPK) of topical dermatological products in the stratum corneum (SC) of human subjects *in vivo* was used immediately following the second wipe sampling method (Method #2) to dislodge and collect any residual lead that remained adhered to the skin surface after wipe sampling (Bunge et al. 2008; N'Dri-Stempfer et al. 2009).

Lead Off© soap and surface wipes were used to maximize the removal of lead from the skin of the participants during and after sample collection (www.hygenall.com).

Additionally, all study materials, including the adhesive tape, study surface paper covering, foil, sample vials, sample wipes, nitrile gloves, clothing swatches, and countertop laminate were tested prior to the study and confirmed to have lead content below the limit of detection (1.3 µg/sample) (ALS, Salt Lake City, UT, USA).

3.2.4 Skin Surface Area Evaluated

At the start of data collection, each volunteer was asked to wash their hands thoroughly with the lead-decontamination soap and water and to avoid contact with any other surfaces. The thumb and first two fingers of the volunteer's dominant hand were then taped at the crease of the last distal digit to visually control the skin surface area for both study objects and wipe sampling. An image of the hands was collected using a photocopier set to 100% image size to ensure consistent comparative images for measurement purposes. After the tape was applied for the purposes of measuring the two-dimensional surface area of the skin used in the study. Images were analyzed by calculating the pixels per square inch of the identified skin surface area (www.adobe.com; www.bluebeam.com). After imaging, two serial background wipes were collected for the two-dimensional surface of the three fingertips (See **Figure 3-4**).

3.2.5 Analytical Methods and Data Analysis

Wipe samples were analyzed using NIOSH Method 7300 modified for wipes, for elements by inductively coupled plasma with a nitric/perchloric ashing method, by ALS Laboratories, Salt Lake City, UT, which is accredited by the American Industrial Hygiene Association Accreditation Program (AIHA-LAP #101574). Bulk samples of the study materials (i.e., wipes, vials, gloves) were also analyzed for lead using a modified NIOSH

Method 7300. Descriptive statistics, t tests, and F tests (Microsoft Excel ®) were used to analyze the data in order to characterize the total mean quantitative transfer between the measured compartments, as well as the relative transfer between the different compartments and comparisons between sampling methods. Comparisons were also made between measured skin surface areas for males and females. For sampling values below the limit of detection (LOD), a value of half the limit of detection was used for statistical analysis purposes.

3.3 RESULTS

All bulk sampling results demonstrated that no detectable lead was present in the study materials (sample media, surface paper, medical tape, wipes, gloves). Similarly, all background skin wipe samples (taken in duplicate for each participant) were below the limit of detection for lead. The wipe sample results were found to be lognormally distributed, consistent with previous dermal sampling results (Beamer et al. 2009; Adgate et al. 1995; Klein et al. 1997; Kromhout et al. 2001). Geometric standard deviations for all datasets were between 1.65 and 2.5, which is consistent with other exposure assessment data.

3.3.1 Skin Surface Area Results

The skin surface area of all participants was calculated for the three fingertips of the study hand and was analyzed for total mean surface area, as well as differences between males and females. The surface area measurements (n=18) were normally distributed (mean= 15 cm^2; SD=3.02; range 9.05-19.42 cm^2). Some participants participated in the study in both 2016 and 2017. If so, the two surface area

measurements for these participants were averaged together. The average skin surface area of female volunteers (n=9) was 13.1 cm^2 (range 9.05-16.2; SD=2.09) and the average skin surface area of male volunteers (n=9) was 16.8 cm^2 (range 12.67-19.42; SD=2.68).

3.3.2 Source to Skin Transfer Results

Results for all transfer of lead for one, five and ten presses on the lead ingots are shown in **Tables 3-2, 3-3, and 3-4.** Relative transfer efficiencies for source to skin transfer and skin-to-skin transfer are shown in **Table 3-5**. For all source-to-skin samples collected for skin contact with a solid lead ingot (Methods #1 and #2 together), 100% of the results for the first wipe sample were above the limit of detection (n=42; LOD=1.3 µg/sample). For Method #1, 9.5% of samples for the second wipe were above the limit of detection, and for the third wipe, no samples were above the limit of detection. For Method #2, 38% of samples for the second wipe were above the limit of detection, and for the third wipe, 16% of samples were above the limit of detection.

Following the three successive wipe samples using Method #2, two serial tape strips were collected from the volunteers using Method #3 to confirm the removal efficiency of the second wipe sampling method. All sampling results using the tape strip method (Method #3) were below the limit of detection (<2.5 µg/sample), and therefore no further analysis was conducted for these samples.

A comparison of the results of the sampling methods demonstrated that, although the dermal loading results were not statistically significantly different using Methods #1 and #2/#3 (p=0.23 for the single contact scenario, p=0.23 for the five contact scenario, p=0.27 for the ten contact scenario), a greater total mass of lead was

recovered for some samples using Method #2. The use of a follow-up tape stripping method (Method #3) with no detectable results (LOD < 2.5 µg/sample) following Method #2 suggested a high level of removal efficiency for wipe sampling. Interestingly, the geometric mean for the three sample sets (one press, five presses, and ten presses) was higher using sampling Method #1 (at 0.7 µg/cm^2, 1.01 µg/cm^2, and 0.75 µg/cm^2, respectively) versus Method #2 (0.48 µg/cm^2, 0.69 µg/cm^2, and 0.58 µg/cm^2, respectively). Both sampling methods showed an increase in loading between one and five consecutive presses, followed by a leveling off or decrease in loading with ten consecutive presses (**Table 2-2**).

3.3.3 Skin-to-skin Transfer Results

For skin-to-skin transfer, sampling Method #1 only detected transfer for the skin-to-skin pathway for one scenario (five presses on the source-to-skin contact hand, followed by five presses onto the fingers of the transfer hand), with no detectable transfer for the other scenarios, suggesting that incomplete removal from the skin may have occurred compared to Methods #2 and #3. For Method #2, skin-to-skin transfer was detected for all three scenarios evaluated and was highest for the scenario evaluating five presses for the source-to-skin contact hand followed by ten presses onto the fingers of the transfer hand.

Although transfer was only observed using sampling Method #1 for one skin-to-skin scenario, the overall lead recovery from the skin for this scenario was higher than the overall recovery for the other scenarios using Method #2 (0.42 µg/cm^2 for contact hand + 0.23 µg/cm^2 for transfer hand = 0.65 µg/cm^2) vs. a total of 0.19 µg/cm^2 (0.15

μg/cm^2 + 0.04 μg/cm^2), 0.16 μg/cm^2 (0.11 μg/cm^2 + 0.05 μg/cm^2), and 0.34 μg/cm^2 (0.23 μg/cm^2 + 0.11 μg/cm^2), respectively, using Method #2 (**Table 2-3**).

3.3.4 Skin to Glove, Skin to Clothing, and Skin to Countertop Surface Transfer Results

No transfer could be measured from the skin to either the countertop surface material or cotton work clothing (<10 μg/sample), suggesting that lead remained preferentially adhered to the skin compared to these surfaces. For nitrile gloves, however, there was measurable transfer from the skin to the glove surface for each participant sampled, suggesting that nitrile glove material can readily remove lead from the skin surface and become a reservoir for potential transfer back to the skin or to other compartments. Further, the mean transfer from skin to gloves was higher than for the source-to-skin or skin-to-skin pathways (GM 1.89 μg/cm^2 for skin to gloves vs. a maximum of 1.01 μg/cm^2 for source to skin transfer and a maximum of 0.23 μg/cm^2 for skin-to-skin transfer) (**Table 2-4**).

3.3.5 Transfer Efficiencies: Relative Transfer by Repeated Contact

The dermal transfer efficiency of lead was also calculated for comparison to the absolute mass loading values. These values were calculated for the repeated loading scenarios looking at relative loading per press onto the lead source (**Table 2-5**). For the two sampling methods evaluated, the relative transfer per press was nearly identical. For sampling Method #1, following a baseline mean transfer for a single press of 0.7 μg/cm^2 (assuming a baseline of 100% transfer), at five presses, the transfer rate decreased to 29% (mean transfer of 1.01 μg/cm^2 ÷ 5 presses = 0.2 ÷ 0.7 = 0.29), and at ten presses, it

further decreased to 11% (mean transfer of 0.75 μg/cm^2 ÷ 10 presses = 0.075 ÷ 0.7 = 0.11). Similarly, for sampling Method #2/#3, following a baseline mean transfer for a single press of 0.48 μg/cm^2, at five presses, the transfer rate decreased to an identical value of 29% (mean transfer of 0.69 μg/cm^2 ÷ 5 presses = 0.14 ÷ 0.48 = 0.29), and at ten presses, further decreased to 12% (mean transfer of 0.58 μg/cm^2 ÷ 10 presses = 0.058 ÷ 0.48 = 0.12).

For skin-to-skin relative transfer, for Method #1, the transfer efficiency for five presses from the three study fingers of one hand to the same fingers of the other hand was 54% (0.23 μg/cm^2 ÷ 0.42 μg/cm^2). For Methods #2 and #3, the transfer efficiency for one press from the fingers of one hand to another was 27% (0.04 μg/cm^2 ÷ 0.15 μg/cm^2), for five presses was 45% (0.05 μg/cm^2 ÷ 0.11 μg/cm^2), and for ten presses was 48% (0.11 μg/cm^2 ÷ 0.23 μg/cm^2) (**Table 2-5**).

3.4 DISCUSSION

In this study, the relationships between several important parameters of dermal loading and transfer were evaluated for elemental metallic lead, including the potential for source-to-skin transfer for single and repeated contacts, the potential for skin-to-skin transfer with single and repeated contacts, and the potential for transfer from the skin to clothing, laminate countertop surfaces, and nitrile gloves. There were no statistically significant differences observed between the two different sampling methods, one that relied on wipe sampling alone and one that employed a combination of wipe sampling and tape stripping. Loading onto the skin was generally seen to increase non-linearly on a mass basis between one to five presses on the skin surface, and subsequently leveled off or declined slightly between five to ten presses. The transfer efficiency decreased

after five presses to 29% relative to the mass transfer for one press, and further decreased to 11-12% after ten presses. These results were consistent with previous research for other substances, in which it was generally reported that object-to-skin serial loading would decrease or transfer back to the original source between approximately five and ten repeated contacts (Hubal et al. 2008; Brouwer et al. 1999; Christopher et al. 2007b).

This study was also the first known analysis to systematically evaluate skin-to-skin transfer of lead. The results demonstrated that measurable skin-to-skin transfer occurred with both single and repeated contacts with previously contaminated skin. The relative transfer efficiency of skin-to-skin contact was 27% for a single contact and remained at approximately 50% for five to ten contacts for all sampling methods evaluated, consistent with other studies that have reported measurements of between approximately 30% and 38% for radium and saffron (Schirmer 2010; Christopher et al. 2007b).

Regarding the transfer of lead from the skin to other compartments including cotton clothing and laminate countertop surfaces, the results demonstrated that lead stayed preferentially adhered to the skin and transfer back to these surfaces following repeated contacts was not measurable, consistent with other research (Lees et al. 2018). Gorman Ng et al. (2013), reported that, generally, transfer efficiencies were highest for metal surfaces and lowest for fabrics. Conversely, consistent transfer was observed for contact from the skin-to-nitrile gloves, and at higher transfer rates than for either source-to-skin or skin-to-skin transfer, suggesting that for lead, the transfer pathway of skin-to-gloves in the dermal exposure model could become a reservoir for further lead transfer to other surfaces or compartments. For example, gloved hands

could result in hand-to-mouth exposures of concern if the gloves, after having been loaded with transferred lead, even if they never contacted the lead source directly, subsequently contact the mouth or the saliva.

The sampling methods selected for this study included a comparison between two different sampling protocols. The first sampling protocol (Method #1) used a handwipe method specific to lead that was developed by scientists at the National Institute for Occupational Safety and Health (NIOSH) in the U.S. and which is currently commercially available in the Full Disclosure© wipe test kit. The method was developed using pre-wetted Palintest™ Wipes (containing benzalkonium chloride) (Ashley et al. 2011; Esswein et al. 2011; Boeniger 2006). For the quantitative recovery using this wipe sampling method, previous testing demonstrated an efficiency of between 74% and 79% for the Palintest™ Wipes at two different spiked loading levels in removing lead from the skin in four consecutive wipes of the palmar surface of both hands for 30 seconds. The authors of the study also noted that ruggedness and surface roughness properties of the wipe material could influence collection efficiency (Boeniger 2006).

The second sampling protocol included both skin wipes and tape stripping (Method #2). The wipe sampling method for this protocol was developed by researchers in Sweden at the Karolinska Institutet. This method used a method with Whatman filter paper wipes moistened with 0.5 ml of 1% nitric acid (Liden et al. 2008; Liden et al. 2006; Erfani et al. 2017). Measured metal removal efficiencies from the skin using this method were reported to result in an average of 93% for nickel, cobalt, and chromium combined using three consecutive wipes (87%, 96%, and 95% removal efficiency for each individual metal, respectively) or an average of 69% collectively for a single wipe (Erfani et al. 2017). The researchers who developed this method indicated that it was designed

to measure the total dose of metals deposited on the skin rather than dermal absorption (Julander et al. 2010).

All tape strip samples collected during this protocol were below the limit of detection. The tape stripping method used in this study during the second sampling protocol was a secondary method following the weak acid sampling method (Method #2). Tape stripping has previously been reported to be an effective tool for the evaluation of metals on and in the stratum corneum (Cullander et al. 2000; Cullander et al. 2001; Hostynek et al. 2001b). It has been reported that a total of 7 repeated tape strips with a pressure of 225 g/cm^2 for approximately 10 seconds were sufficient to characterize stratum corneum nickel content following exposure to pure nickel discs (Ahlstrom et al. 2019; Ahlstrom et al. 2018). In this study, two composite samples including three tape strips each were collected for each participant (N'Dri-Stempfer et al. 2009). The use of tape stripping in this study to evaluate the recovery efficiency of the second wipe sampling method appeared to support the relatively high removal efficiency of the wipe sampling procedure for lead either on the skin surface or superficially absorbed into the skin surface.

3.4.1 Other Studies Using Wipe Sampling Methods to Measure Lead on the Skin Surface

Similar to this study, Que Hee et al. (1985) evaluated the effectiveness of hand rinses using weak nitric acid (HNO_3) solutions (0.1M or approximately 4% HNO_3). The authors noted that the acid rinses alone were not particularly effective at removing lead from the skin; by comparison, handwipes had absolute recovery efficiencies for 3-5 serial wipes of 16% to >100%. The combination of wiping and HNO_3 rinsing resulted in a

recovery of 84%. The authors noted that “the use of dilute nitric acid was not eagerly welcomed by the investigators for human studies”, and was slightly more concentrated than what was used in this study (4% vs. 1% in the current study). Sleeuwenhoek and van Tongeren (2006) measured the transfer of lead from solid ingots for one, five, and ten repeated contacts; geometric mean results were 0.32, 0.84, and 0.76 μg/cm^2, respectively, which was quite consistent with the current study. Also consistent with this study, Esswein et al. (2011) evaluated the removal efficiency of lead from the skin using several different combinations of wipe material and wetting agents, and demonstrated the effective removal of lead from the skin using a weak acid solute. The most effective combination was found to be a solution of 0.25% citric acid and 18.5% isostearamidopropyl morpholine lactate (IMSL) on a creped wipe. Researchers at NIOSH in the U.S. have performed multiple Health Hazard Evaluations (HHEs) at various facilities for dermal exposures to lead (Weber 2001; Harney et al. 2018; Grant et al. 2017; Methner 2017; Page et al. 2015; Beaucham et al. 2014; King et al. 2014; Beaucham et al. 2018; Grimes et al. 2019; Grimes et al. 2018). Hand wipe samples for lead and other metals were collected using NIOSH Method 9102; certain studies collected hand wipes with pre-packaged Ghost™ Wipe towlettes, while another used the NIOSH Full Disclosure ® lead sampling kit containing Palintest wipes moistened with benzalkonium chloride. Overall results ranged from 0.23 to 92 μg/sample, which was equivalent to between 0.0002 and 0.09 μg/cm^2 (Beaucham et al. 2018; Grimes et al. 2019; Grimes et al. 2018). These results were somewhat difficult to compare to the results of the current study, given the much larger skin surface area that was included in the wipe samples collected (either one or both sides of both hands). Further, it was reported in 2010 that Ghost™ Wipes contain measurable amounts of lead in each wipe,

and it is unknown whether the wipes used in these studies influenced the content of lead reported (Keenan et al. 2010; Grimes et al. 2019).

3.4.2 Skin Sampling Surface Area

The average fingertip surface areas measured in this study, 13.1 cm^2 for females and 16.8 cm^2 for males, were consistent with these previously reported ranges. The surface area of the first two fingertips and the tip of the thumb has been previously estimated in other studies, and this surface area has been determined to be approximately 11-17 cm^2 for females and 14-19 cm^2 for males (OEHHA 2008; COEHHA 2011; Sahmel et al. 2015b; Cherrie et al. 2006). Julander et al. (2010) estimated the skin surface area of the fingertips of the thumb, index, and middle finger to be approximately 8 cm^2.

3.4.3 Effect of Repeated Contacts

Several studies have reported a statistically significant association between dermal transfer and number of contacts or repeated contacts with a source. Brouwer et al. (1999) found that loading of the skin indicated a transfer increase that was close to linear for the first six contacts, followed by a decline in additional loading with further consecutive contacts, as well as a small decrease in further adherence with additional frequency. Zainudin and Semple (2004) also reported a linear increase in loading of Tinopal powder up to six repeated contacts. Christopher et al. (2007a) similarly reported increased skin transfer of saffron with each repeated contact, but only evaluated repeated contacts up to four total contacts. Sleeuwenhoek et al. (2006) reported statistically significant increasing linear trends in the surface loading with an increased

number of contacts, despite the fact that total loading declined slightly between 5 and 10 repeated contacts for the lead ingots. Consistent with the current study, in a fluorescent tracer study using riboflavin, Cohen Hubal et al. (2005) reported that for a single contact, transfer efficiencies ranged from 1% to 14%, and the percent of residue transferred to the hands declined with each sequential press in a series of five contacts (taking into account total surface area of repeated contact by adding up the surface area of all of the presses). When the results for repeated contacts were evaluated for different surfaces (carpet vs. laminate), no significant differences were observed. In a follow-up study, Cohen Hubal et al. (2008) found that quantitative dermal loading of riboflavin resulted in statistically significant increases with individual successive contacts up to seven, whereas the authors reported that, in comparison, dermal loading in an earlier study appeared to reach a maximum level of loading by the fourth or fifth contact. In the follow-up study, the authors also calculated the percent dermal transfer, again taking into account the total surface area of contact following repeated contacts. For the first single contact, transfer efficiency ranged from 0.8% to 45.5%, and after seven contacts, transfer efficiency ranged from 0.6% to 19.4% (Hubal et al. 2008).

However, other studies have demonstrated a lack of statistical association with dermal transfer and repeated contacts. Hughson and Cherrie (2005) examined the average dermal loading with repeated contacts to zinc oxide, and reported that there was no significant increase in skin surface loading with an increasing number of contacts up to eight.

Studies with larger numbers of repeated contacts perhaps point to a trend that may emerge over time with many additional repeated contacts. Rodes et al. (2001) found that upon repeated contacts with fluorescein-tagged house dust, the transfer

factor gradually decreased as the skin surface became loaded. They noted that although the transfer factor following a single press was approximately 65%, a further 40 presses resulted in only an additional 30% increase in skin loading. They also reported observing regular losses of particles back to the original contact surface and estimated that a minimum of 100 presses would be necessary to produce an equilibrium scenario. They predicted that the final dermal transfer factor for this equilibrium would be approximately 15-20%, which is consistent with the trends observed in this study. Similarly, Freeman et al. (2005) reported that hand loading in children with chlorpyrifos was significantly correlated with applied concentrations, but that hand loadings after one hour of child activity were not statistically significantly different, suggesting that the maximum hand loading was reached after less than one hour. The authors also reported no difference in dermal loading between 3 hours and 4 hours. Rhodes et al. (1997) reported that the loading of dust on the hands did not increase linearly with an increase in the number of contacts with a surface, but rather a pattern was observed where the dust built up on the hands and then was deposited back on to the original surface.

The results of the current study appear to support the weight of evidence in the literature, suggesting that additive or repeated contacts with the skin result in increased loading up to approximately four to eight contacts, after which the total quantitative loading appears to level off or approach a steady-state loading with further contacts. The relative transfer efficiencies with repeated contacts were also consistent in this study with the majority of other studies that showed a trend of decreasing transfer efficiency with increasing repeated contacts.

3.5 CONCLUSIONS

This study is one of the first to evaluate the quantitative transfer potential between multiple compartments using the Schneider et al. (1999) and Gorman Ng. et al. (2012) conceptual models for a single substance. The results indicated that some transfer pathways and compartments are more important than others. Based on the analysis, no transfer could be measured from the skin to clothing or laminate countertop surfaces, while substantial transfer could be consistently measured between the skin and the surface of nitrile gloves, suggesting that such gloves could become a reservoir for additional transfer and exposure. It was also demonstrated that either single or repeated skin-to-skin contacts consistently resulted in measurable transfer, creating a secondary skin exposure source.

Although the results of the two wipe sampling methods used in this study were not statistically significantly different, a two-phase sampling method including both wiping and tape stripping (i.e., Method #2/#3) may be more a reliable method than wipe sampling alone for certain scenarios, and could be a cost-effective approach for ensuring complete contaminant removal in a variety of dermal exposure and use scenarios. The results of this study confirmed other important findings with respect to repeated contacts with the skin surface, including that with repeated contacts, transfer increased non-linearly between one contact and five contacts, but appeared to level off and reach a balance after ten contacts. Consistent with other studies in the literature, the transfer efficiency decreased with repeated contacts to approximately 29% after five contacts and 11-12% after ten contacts; for skin-to-skin transfer measurements, transfer efficiency after either five or ten contacts was approximately 50%.

Table 3-1: **The 15 Dermal Transfer Scenarios Evaluated**

1	Lead object – single press with each of the three fingers on source
2	Lead object – five consecutive presses with each of the three fingers on source
3	Lead object – ten consecutive presses with each of the three fingers on source
4	Skin-to-skin – single press with each of the three fingers to the opposite finger on the other hand after five consecutive presses on source
5	Skin-to-skin – five consecutive presses with each of the three fingers to the opposite finger on the other hand after five consecutive presses on source
6	Skin-to-skin – ten consecutive presses with each of the three fingers to the opposite finger on the other hand after five consecutive presses on source
7	Clothing swatch – single press with three fingers simultaneously after five consecutive presses on source
8	Clothing swatch – five consecutive presses with three fingers simultaneously after five consecutive presses on source
9	Clothing swatch – ten consecutive presses with three fingers simultaneously after five consecutive presses on source
10	Nitrile glove swatch – single press with three fingers simultaneously after five consecutive presses on source
11	Nitrile glove swatch – five consecutive presses with three fingers simultaneously after five consecutive presses on source
12	Nitrile glove swatch – ten consecutive presses with three fingers simultaneously after five consecutive presses on source
13	Laminate countertop material – single press with three fingers simultaneously after five consecutive presses on source
14	Laminate countertop material – five consecutive presses with each of three fingers after five consecutive presses on source
15	Laminate countertop material – ten consecutive presses with each of three fingers after five consecutive presses on source

Table 3-2: Results for Dermal Transfer and Loading, Source-to-Skin

Method #1[A]	Source to Skin: Mass Transfer One Press	Source to Skin: Mass Transfer Five Presses	Source to Skin: Mass Transfer Ten Presses
	n=14[B]		
	µg/cm^2		
GM	0.70	1.01	0.75
GSD	1.91	2.00	1.86
Methods #2[A] and #3	**Source to Skin: Mass Transfer One Press**	**Source to Skin: Mass Transfer Five Presses**	**Source to Skin: Mass Transfer Ten Presses**
	n=11[B]		
	µg/cm^2		
GM	0.48	0.69	0.58
GSD	2.53	2.40	1.65

[A]Results are reported as the mean of the aggregate of the three wipe samples collected for each participant; 100% of the results for the first wipe sample for each triplicate wipe sample set was above the limit of detection.
[B]N shows the number of participants who completed the triplicate samples for this pathway.

Table 3-3: Results for Dermal Transfer and Loading, Skin-to-Skin

Method #1[A]	Skin-to-skin: Mass Transfer From (Five Presses)	Skin-to-skin: Mass Transfer To (One Press)		Skin-to-skin: Mass Transfer From (Five Presses)	Skin-to-skin: Mass Transfer To (Five Presses)		Skin-to-skin: Mass Transfer From (Five Presses)	Skin-to-skin: Mass Transfer To (Ten Presses)
	n=7[B]			n=7			n=7	
	µg/cm^2			µg/cm^2			µg/cm^2	
GM	ND	ND		0.42	0.23		ND	ND
GSD	ND	ND		1.95	1.79		ND	ND
Methods #2[A] and #3	**Skin-to-skin: Mass Transfer From (Five Presses)**	**Skin-to-skin: Mass Transfer To (One Press)**		**Skin-to-skin: Mass Transfer From (Five Presses)**	**Skin-to-skin: Mass Transfer To (Five Presses)**		**Skin-to-skin: Mass Transfer From (Five Presses)**	**Skin-to-skin: Mass Transfer To (Ten Presses)**
	n=3			n=4			n=4	
	µg/cm^2			µg/cm^2			µg/cm^2	
GM	0.15	0.04		0.11	0.05		0.23	0.11
GSD	2.02	1.08		2.69	1.52		1.55	1.94

ND = non-detect

[A]Results are reported as the mean of the aggregate of the three wipe samples collected for each participant.

[B]N shows the number of participants who completed the triplicate samples for this pathway.

Table 3-4: Results for Dermal Transfer and Loading, Skin-to-Gloves, Skin-to-Clothing, and Skin-to-Countertop Surface

Method #1[A]	Skin to Glove: Mass Transfer (One Press)	Skin to Glove: Mass Transfer (Five Presses)	Skin to Glove: Mass Transfer (Ten Presses)
	n=3[B]		
	µg/cm^2		
GM	3.24 (glove surface)	1.2 (glove surface)	1.73 (glove surface)
GSD	1.66		
Method #1	**Skin to Clothing: Mass Transfer (One Press)**	**Skin to Clothing: Mass Transfer (Five Presses)**	**Skin to Clothing: Mass Transfer (Ten Presses)**
	n=4		
	µg/cm^2		
GM	ND (clothing surface)	ND (clothing surface)	ND (clothing surface)
GSD	N/A		
Method #1	**Skin to Countertop: Mass Transfer (One Press)**	**Skin to Countertop: Mass Transfer (Five Presses)**	**Skin to Countertop: Mass Transfer (Ten Presses)**
	n=3		
	µg/cm^2		
GM	ND (counter surface)	ND (counter surface)	ND (counter surface)
GSD	N/A		

ND = non-detect. N/A = not applicable

[A]Results are reported as the mean of the aggregate of the three wipe samples collected for each participant.

[B]N shows the number of participants who completed the triplicate samples for this pathway.

Table 3-5: Relative Transfer Efficiencies by Number of Repeated Contacts

Method #1	**Source to Skin: (One Press)**	**Source to Skin: (Five Presses)**	**Source to Skin: (Ten Presses)**
% Transfer	Baseline (assumed 100%)	29%	11%
Methods #2 and #3	**Source to Skin: (One Press)**	**Source to Skin: (Five Presses)**	**Source to Skin: (Ten Presses)**
% Transfer	Baseline (assumed 100%)	29%	12%
Method #1	**Skin-to-skin: (One Press)**	**Skin-to-skin: (Five Presses)**	**Skin-to-skin: (Ten Presses)**
% Transfer	ND	54%	ND
Methods #2and #3	**Skin-to-skin: (One Press)**	**Skin-to-skin: (Five Presses)**	**Skin-to-skin: (Ten Presses)**
% Transfer	27%	45%	48%

Figure 3-1: An Adaptation of the Schneider et al. (1999)/Gorman Ng et al. (2012) Conceptual Model, Modified for Lead and Other Metals in the Solid Form with Negligible Vapor Pressure

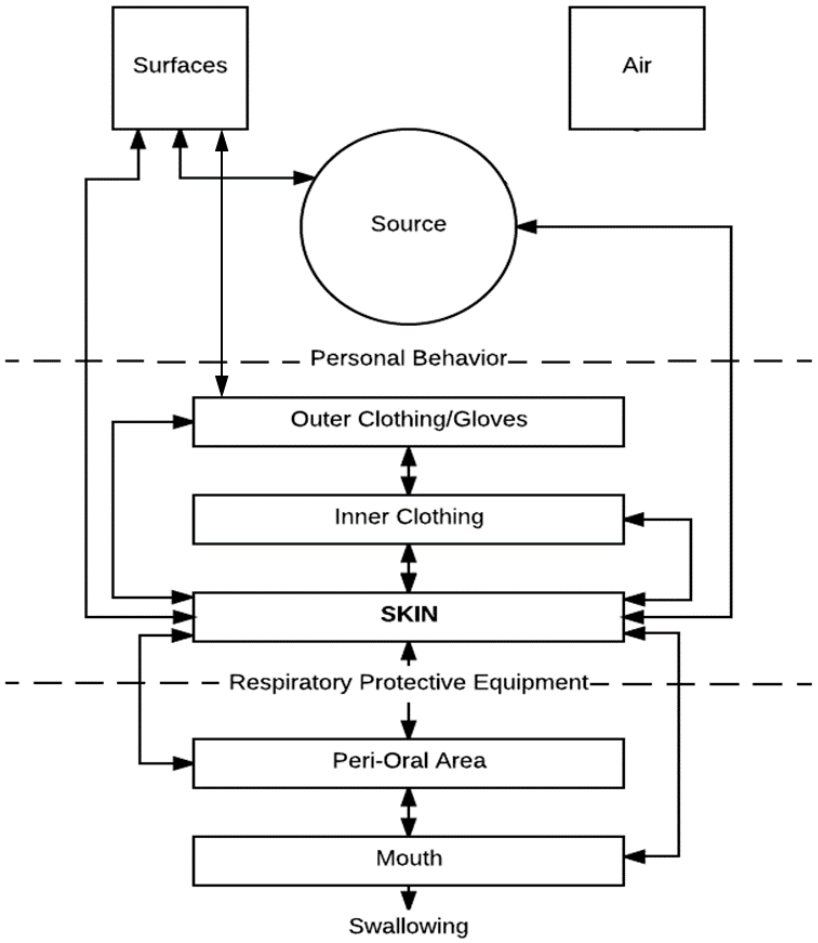


Figure 3-2: The Dermal Sampling Scheme

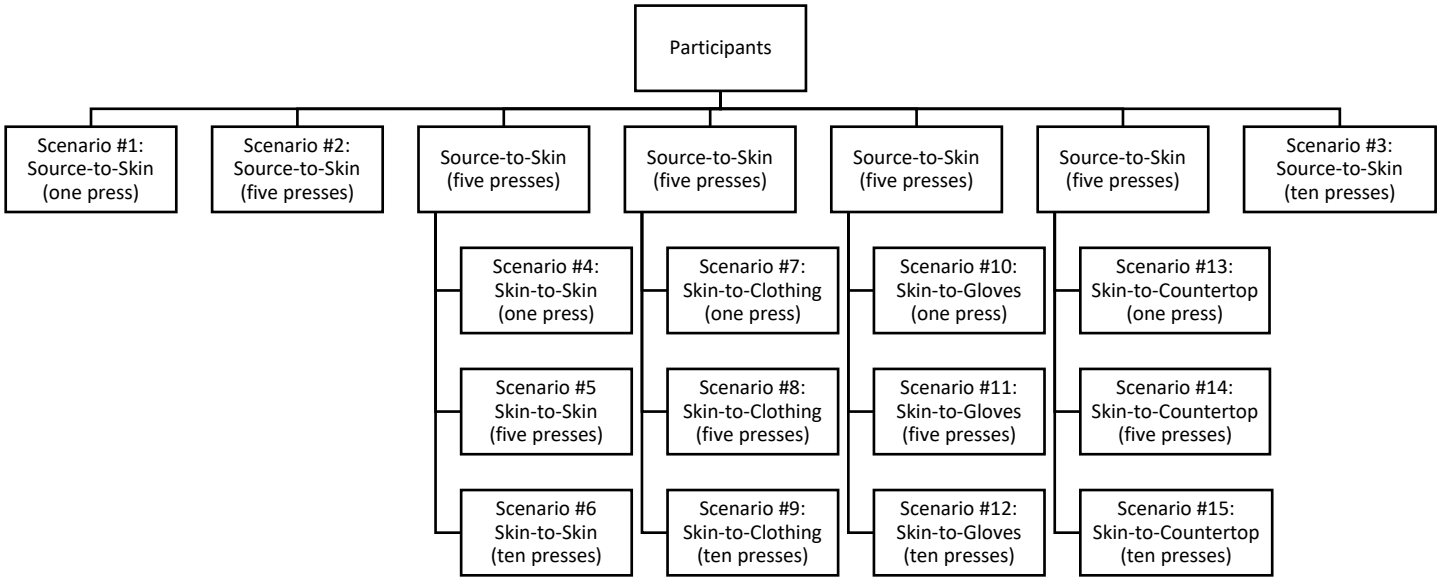
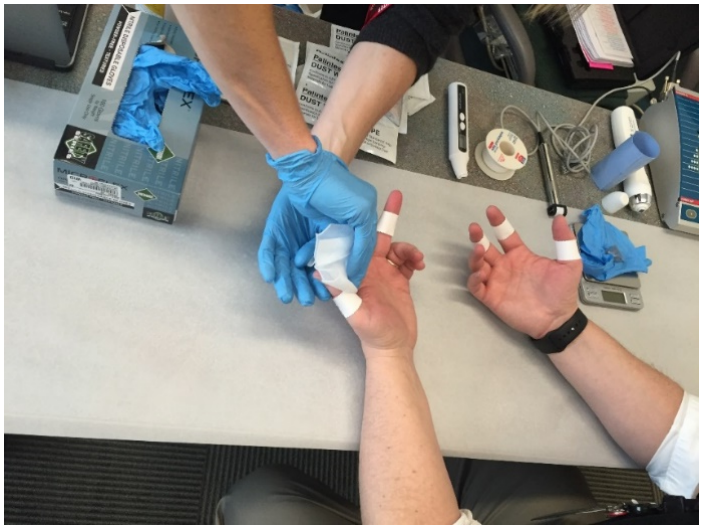


Figure 3-3a and 3-3b: Wipe Sampling and Presses. Figure 3a shows the skin wiping procedure, and Figure 3b demonstrates the skin press method that was used in the transfer analysis scenarios.



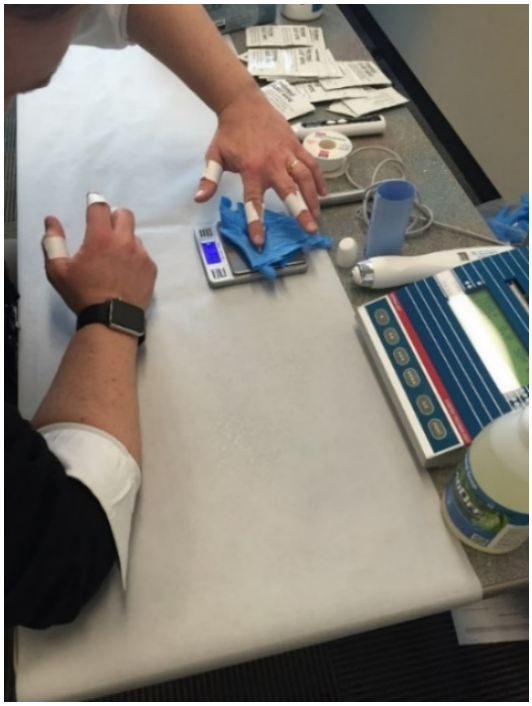
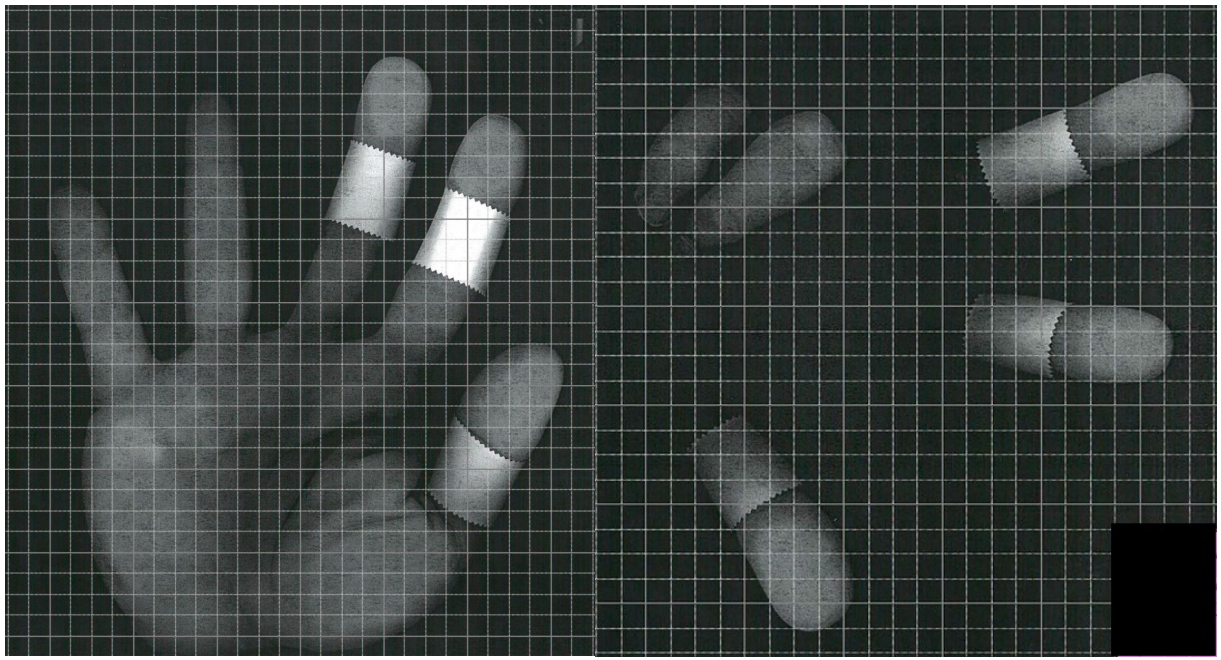


Figure 3-4: Examples of Identified Skin Surface Area for Sampling (two different study participants)



Chapter 4

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

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 field practitioners, 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 measurements 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.

4.1 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 (Jansen van Rensburg et al. 2019; Filon et al. 2006; Kezic et al. 2009).

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 et al. 2001). Although this layer has the potential to influence the adherence of chemicals to the skin, few 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 et al. 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 (Beamer et al. 2009; Gorman Ng et al. 2013; Roff 2000). Other studies, however, have reported at times unexpected results associated with the level of skin hydration on transfer to the skin surface (Brouwer et al. 1999). Christopher et al. (2007b), Rodes et al. (2001), Brouwer et al. (1999), and Edwards et al. (2001) all reported a decrease in the transfer of substances to the hands with increased skin hydration or wetting. Conversely, Avissar et al. (2004) and Cohen Hubal et al. (2005) and (2008) reported an increase in surface loading on the skin with an increase in hydration or wetting. 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 (Jansen van Rensburg et al. 2019; du Plessis et al. 2013; Stefaniak et al. 2013; Berardesca 1997; Berardesca et al. 2018). These measurements are non-invasive 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 et al. 2002).

4.1.1 Trans Epidermal Water Loss (TEWL)

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 (Du Plessis et al. 2010; du Plessis et al. 2013; Jansen van Rensburg et al. 2019; Chew et al. 2003; Rogiers 2001; Berardesca et al. 2018). 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(Jansen van Rensburg et al. 2019; Sotoodian et al. 2012; Berardesca et al. 2018). 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 (Berardesca et al. 2018; du Plessis et al. 2013). 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. It has also been reported that the TEWL on the volar forearm can be higher and more variable when the measurements are collected closer to the wrist and elbow (du Plessis et al. 2013).

There are several different types of instruments available to measure TEWL, including open-chamber methods, semi-open methods, and closed chamber methods (Berardesca et al. 2018; du Plessis et al. 2013). 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 (Berardesca et al. 2018; du Plessis et al. 2013). 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. 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).

4.1.2 Stratum Corneum Hydration or Skin Hydration Index (HI)

The stratum corneum hydration or skin hydration index (HI) has been described as a measure of the surface skin/stratum corneum hydration or moisture content. It is measured in arbitrary units (au) 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 et al. 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 (EPA 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, which are each of the individual cells of the stratum corneum (Jansen van Rensburg et al. 2019; Sotoodian et al. 2012; Packham 2005).

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 (Young et al. 2019). 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). See **Figure 4-1** for a summary comparison between certain characteristics of TEWL and HI.

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; Berardesca et al. 2018; Martinsen et al. 2001). 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 two-dimensional 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 (MRI) (Mirrashed et al. 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 et al. 2001). It has been noted that in healthy skin, the hydration of the corneocytes is often approximately 40 au 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% (Jansen van Rensburg et al. 2019; Chew et al. 2003; Merk 2018). 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 (Martinsen et al. 2001; Berardesca 1997; 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 et al. 2001).

4.1.3 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 (Stefaniak et al. 2013; du Plessis 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 purpose 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 purpose 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.

4.2 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 at two different body locations for comparison. These included the volar forearm, as previously recommended for inter-individual 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 69˚ F to 74˚ F 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.

TEWL was measured using an open chamber TEWL instrument from DermaLab (See **Figures 4-2a and 4-2b**) (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. **Table 4-1** provides a summary of the interpretation of TEWL measurements as suggested by Du Plessis et al. (2010). Although the TEWL is measured in units of grams of water vapor per square meter per hour, it has been noted that 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; Du Plessis et al. 2010).

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 au. The instrument used in this study converted the arbitrary units result into a qualitative rating or skin hydration index (HI) which was reported on a unitless scale from 1 to 12. The instrument used in the study was obtained from EnviroDerm Services, UK, (Model EDS10) and was manufactured by Courage + Khazaka electronic GmbH (www.enviroderm.co.uk). **Table 4-2** provides recommended guidance from EnviroDerm regarding the interpretation of skin hydration measurements using the

EDS10 and the HI output. The second stratum corneum hydration monitor was an inexpensive instrument that employed electrical conductance, referred to by the manufacturer as Bioelectric Impedance Analysis (BIA), rather than the capacitance method of the first instrument. In this second instrument, the electrical conductance/impedance was measured using a “zig zag pattern” of the electrode to increase the surface area of contact (SK-IV, Pandawill) (See **Figures 4-3 to 4-5**).

Both the TEWL and HI instrument probes were also routinely cleaned 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).

4.2.1 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.

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 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 each measurement method. Comparisons were performed for each measurement method between the forearm and index finger skin.

4.3 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 are presented in **Table 4-3**.

The mean volar forearm TEWL for all participants was 7.5 (range 3.2-25.3; SD-5.4), and the mean volar forearm HI was 4.4 (range 3-6; SD=0.9). For TEWL, the mean baseline for the volar forearm for female participants was 6.8 compared with 8.3 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=4.9 for females; HI=4.0 for males). The mean volar forearm percent hydration was 25.2% (range 14.4%-63.9%; SD=0.1). Overall, the data were approximately lognormally distributed. Based on previously published guidance on

the interpretation of TEWL measurements, the average baseline TEWL was in the "good" range (range 5-9), suggesting healthy skin. For the mean of the HI forearm measurements, the results indicated that the measured skin was normal to slightly dry, suggesting borderline skin health. No comparable benchmarks could be identified for the evaluation of percent hydration measurements. Comparisons between TEWL, HI, and percent hydration measurements for the volar forearm and palmar index finger are shown in **Figures 4-6a, 4-6b, and 4-6c.**

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 (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). The index finger TEWL measurements were significantly different between males and females (49.8 for females vs. 67.7 for males), although not tremendously so (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. There was also little to no apparent correlation between TEWL and HI measurements, either for the baseline forearm location or the palmar index finger

location. 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 weak 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 **Figures 4-7a and 4-7b**).

It was also of interest to evaluate whether the HI measurements were comparable to the percent hydration measurements in order to determine whether percent hydration could be a reasonable surrogate for HI when a corneometer or similar instrument is not available (See **Figure 4-8**). Although the measurements were significantly different between each other for both the forearm and the index finger locations (t tests; p values<0.005), the moderate correlation between the two methods for the index finger was statistically significant (Pearson correlation=0.77; R^2=0.56; p=0.000004). However, these two measures were only weakly correlated for the forearm, and that relationship was not significant (Pearson correlation=0.34; R^2=0.12; p=0.09).

4.4 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; 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). 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, although not tremendously so (t-test; p=0.03), while the index finger 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.

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 moderate 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. 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®. However, it was noted in this study that percent hydration measurements were only weakly correlated with HI measurements for the volar forearm and may not provide adequate results for this skin site.

4.4.1 Relationship of Hydration Index to TEWL Measurements

Several other studies have also analyzed the relationship between TEWL and skin hydration measurements. Inconsistent with the results of this study, 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. These results do, however, appear to be consistent with reported measurements for potentially damaged skin. Halkier-Sorensen et al. (1991) also reported on the relationships and differences in TEWL and skin hydration

measurements taken at different anatomical sites. Also different from the results noted here, 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.

4.4.2 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 to 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 and hydration index 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 for the index finger had a pre-shift mean of 15.538 (SD=4.51; Range 5-20) and a post-shift mean of 17.769 (SD=2.72; Range 11-20); measurements for the palm were very similar. The authors reported that the increase in the mean TEWL 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). The results of this study demonstrated index finger TEWL results that appeared to be lower and more consistent than the measurements collected during the current study. Given that the measurements reported all had a maximum value of 20, this could also be due to differences in scale on the measurement devices used.

4.5 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.

Further, a quantitative comparison between measurements was performed for an instrument designed for assessing the unitless skin hydration index (HI) and an inexpensive instrument that measures the percent hydration of the skin surface. The two methods were moderately correlated for the index finger, which is more likely to be the skin site of interest for skin wipe sampling study purposes (Pearson correlation=0.77; R^2=0.56; p=0.000004). 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.

Table 4-1: Recommended Range and Interpretation of Trans-Epidermal Water Loss (TEWL) Index Measurements (Du Plessis et al. 2010))

TEWL Index	Skin Barrier Function	Skin Condition
0-4	Excellent	Very Healthy
5-9	Good	Healthy
10-12	Normal	Normal
13-16	Low	Strained
17-20	Very Low	Critical

Table 4-2: 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)

Table 4-3: Results of Comparative Skin Hydration and Barrier Function Measurements

ID	Gender	Temp	Humidity	TEWL: Volar Forearm	Skin Moisture: Forearm %	Hydration Index: Forearm	TEWL: Palmar Index Finger	Skin Moisture: Palmar Index Finger %	Hydration Index: Palmar Index Finger
1	F	73	19%	5.2	22.8%	5	88.9	61.1%	9
2	M	73	18%	7.4	28.6%	4	72.3	41.1%	5
3	F	73	18%	25.3	29.5%	5	31.2	28.8%	5
4	F	72	17%	5.9	17.2%	4	64.7	56.3%	6
5	F	73	18%	4.1	28.6%	5	81.3	58.2%	6
6	F	73	17%	6.1	18.0%	4	68	40.0%	4
7	M	73	16%	7.3	25.9%	5	87.3	59.2%	8
8	M	73	17%	23.6	26.9%	4	84.1	56.0%	6
9	M	73	17%	7.7	63.9%	4	61.2	63.5%	5
10	F	71	16%	3.3	16.4%	4	43.1	55.9%	5
11	M	72	17%	5.2	29.1%	5	63.5	48.6%	4
12	M	73	18%	7.3	20.1%	3	84.2	60.8%	9
13	M	73	20%	12.1	28.7%	5	84.2	57.8%	6
14	M	70	27%	5.9	20.0%	4	71	77.0%	9
15	M	70	24%	5.6	14.4%	3	70.4	76.0%	9
16	M	70	23%	6.2	17.8%	4	46.4	55.1%	6
17	F	71	22%	5.1	14.9%	4	49.3	11.8%	2
18	F	73	40%	4.3	29.9%	6	48.6	21.8%	5
19	M	74	39%	4.2	28.0%	4	64.2	56.8%	6
20	F	74	39%	4.9	29.0%	6	26.3	45.0%	6
21	F	71	47%	8.4	28.9%	5	21.1	45.9%	6
22	M	72	49%	6.9	17.1%	3	23.9	41.5%	4
23	F	72	48%	5.8	28.6%	5	53.3	54.0%	5
24	F	70	26%	6.2	29.4%	6	22	48.3%	5
25	F	71	25%	3.2	16.8%	4	49.2	35.3%	3

Figure 4-1: Summary Comparison of HI and TEWL Properties as Noted in the Literature

Hydration Index (HI)	**TEWL**
• Skin hydration decreases slowly but steadily with age • Insufficient evidence for gender effects on skin hydration • Influence of race/ethnicity on both TEWL and skin hydration is unknown • There are no apparent differences between skin hydration of symmetrical sites of the body.	• Baseline TEWL is independent of age among persons in their working years • TEWL values may be slightly lower in persons over 60 years old • Insufficient evidence for gender effects on TEWL • Influence of race/ethnicity on both TEWL and skin hydration is unknown. • TEWL values vary among anatomical regions of the body

Figure 4-2a: DermaLab TEWL Sensor Wand

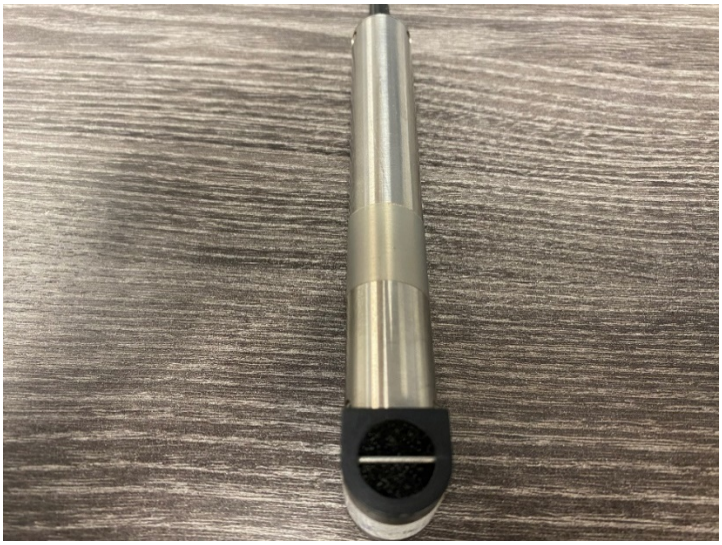


Figure 4-2b: DermaLab TEWL Open Chamber Sensor

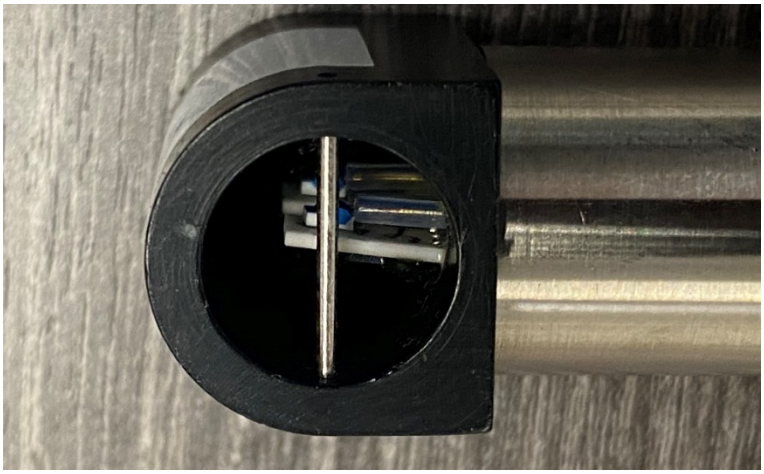


Figure 4-3: Side-by-Side Comparison of Skin Hydration Meters



Figure 4-4: Electrical Conductance/Impedance Sensor

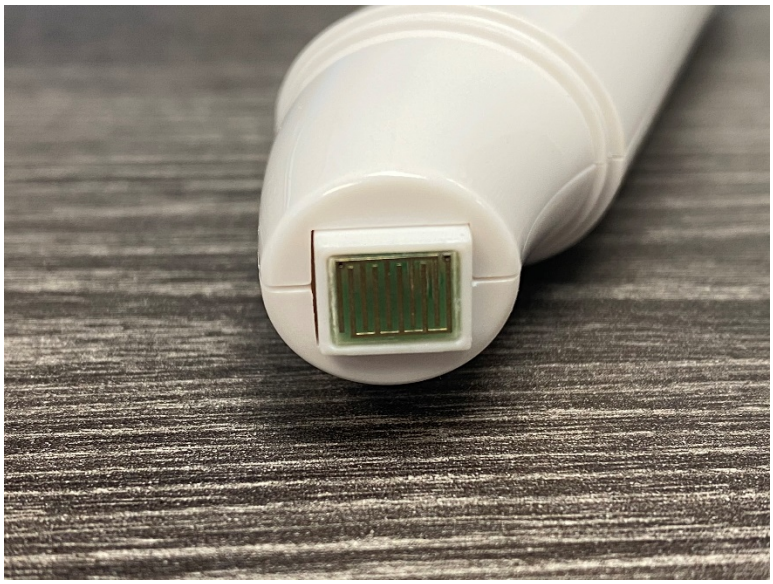


Figure 4-5: Electrical Capacitance Sensor



Figure 4-6a: Comparison Between TEWL Measurements for the Volar Forearm and the Palmar Index Finger

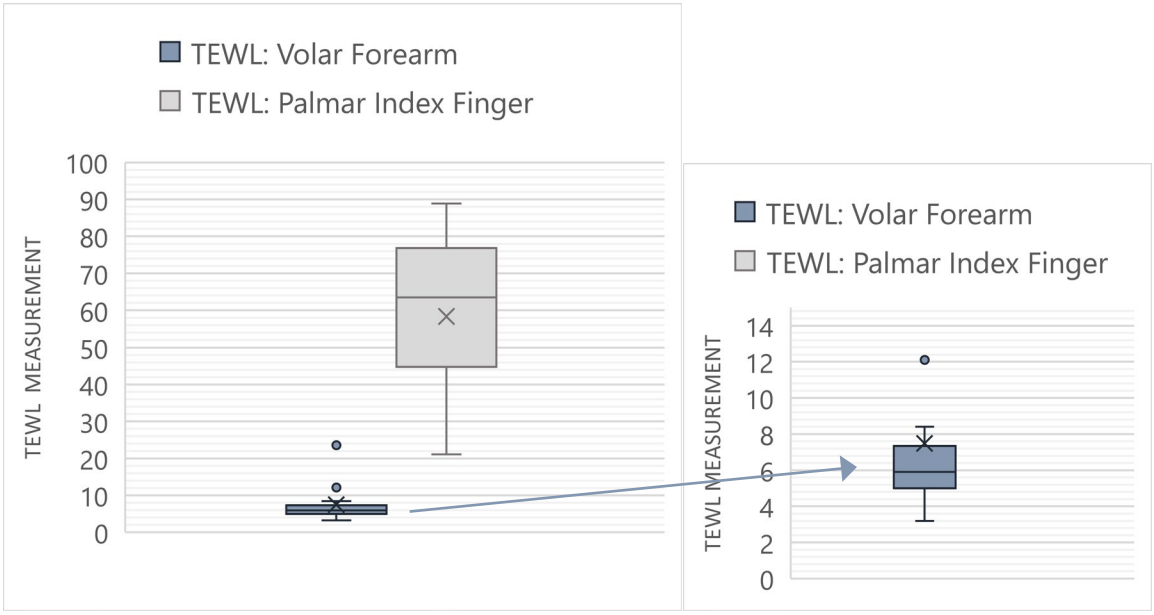


Figure 4-6b: Comparison Between HI Measurements for the Volar Forearm and the Palmar Index Finger

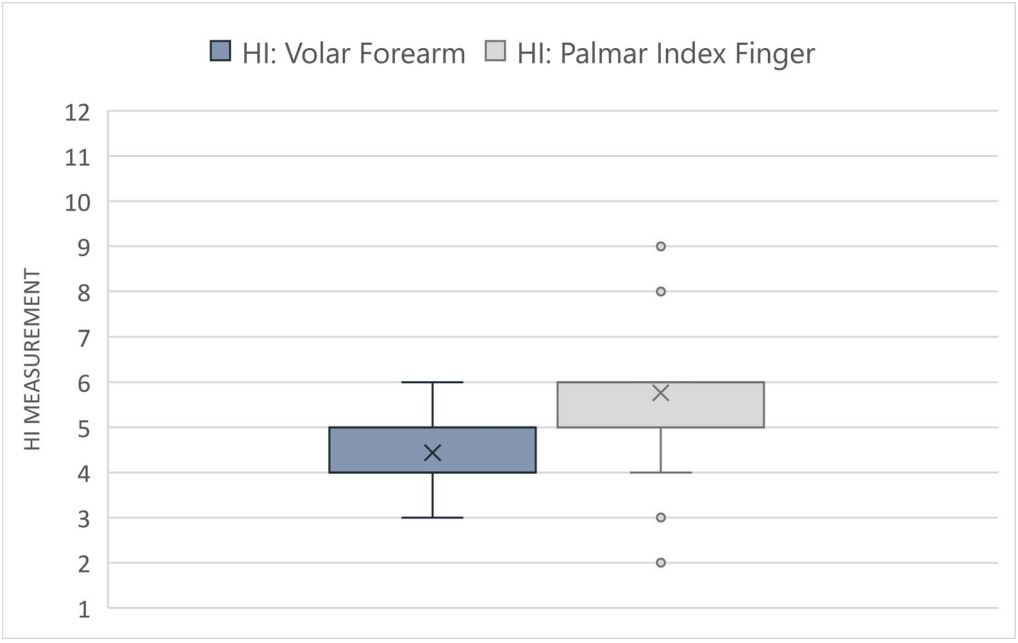


Figure 4-6c: Comparison Between Percent Hydration Measurements for the Volar Forearm and the Palmar Index Finger

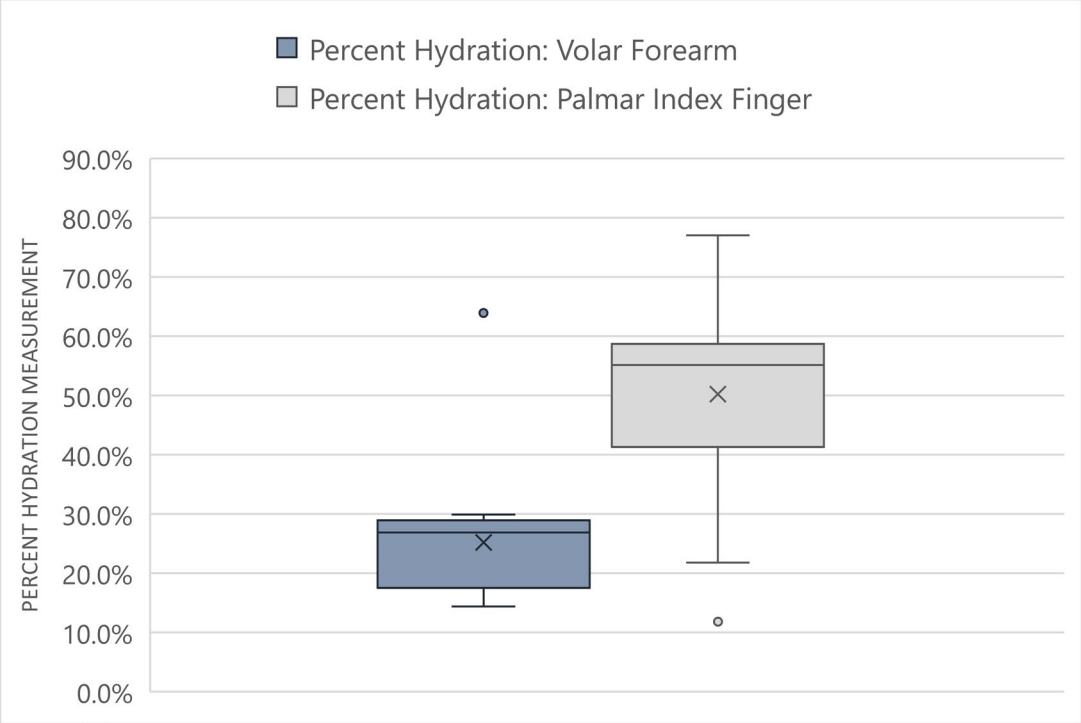
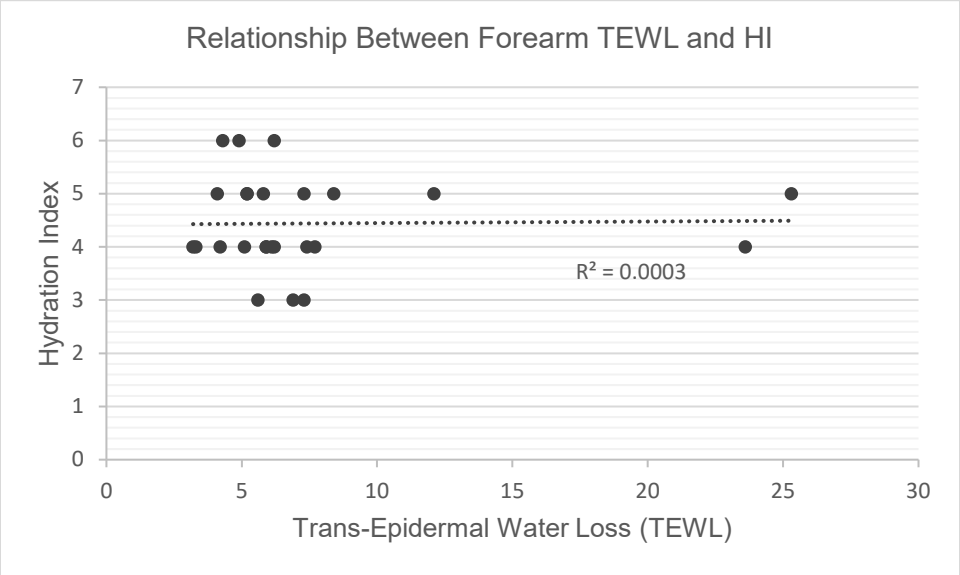


Figure 4-7a and 4-7b: Relationships Between TEWL and HI Measurements Between the Forearm and Index Finger Measurement Locations



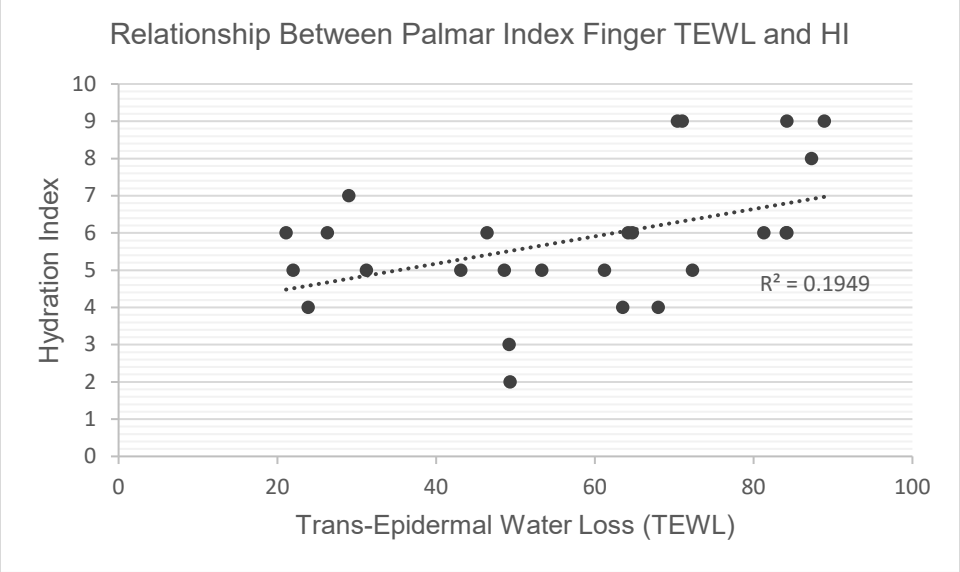
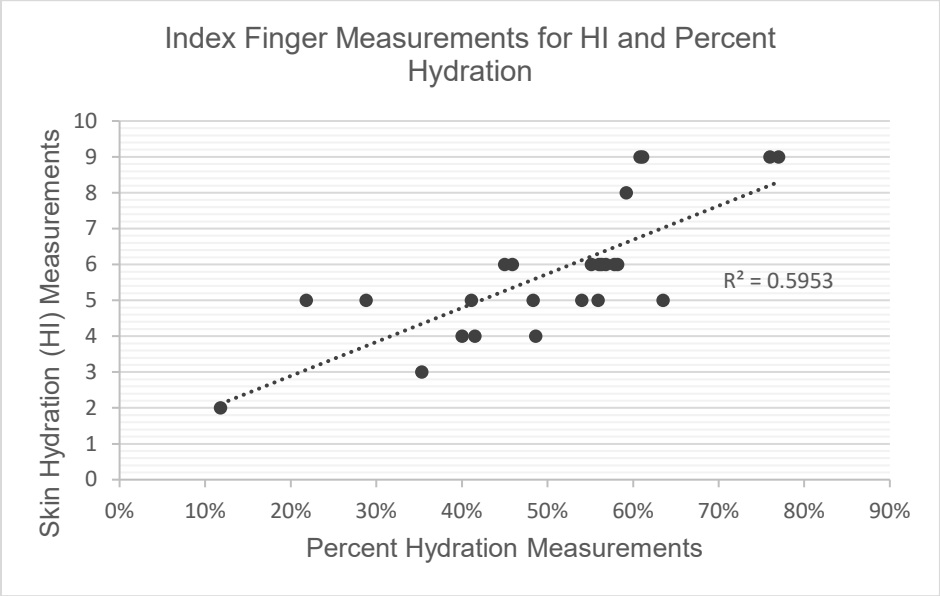


Figure 4-8: Correlation Between Index Finger Measurements for HI and Percent Hydration



Chapter 5

Investigation of the Potential Influence of Skin Hydration on the Dermal Transfer and Loading of Elemental Metallic Lead

Abstract:

Factors influencing the transfer of chemicals or other contaminants to and from the surface of the skin are often poorly understood. Previous research has indicated that environmental conditions, skin hydration, and repeated contacts may all influence the quantity of dermal transfer. The purpose of this analysis was to evaluate the influence of skin hydration and condition on the quantitative transfer of elemental metallic lead in the solid form in a series of systematic measurements using human subjects for five and ten repeated contacts with a solid lead source. Skin hydration was assessed using a corneometer and skin condition was measured using an open-chamber TEWL instrument. Two previously published sampling protocols were used in sequence to measure the transfer of lead to the skin, including triplicate skin surface wipes using a 1% weak nitric acid solute subsequently followed by a tape stripping method. The results indicated that for the palmar surface of the index finger where sampling was conducted, the relative hydration level of the skin was higher for males (n=6) vs. females (n=4), but this difference was not statistically significant (mean HI=4.0 for females; mean HI=5.5 for males). When the relationship between skin hydration levels and dermal loading was analyzed separately for males and females, the skin hydration level in the female cohort was negatively correlated with the loading of elemental metallic lead on the skin surface for both five skin contacts (Pearson correlation = -0.97; R^2=0.93; p=0.034) and ten skin contacts with the lead source (Pearson correlation = -0.86; R^2=0.73; p=0.145), and was statistically significant for the five contact scenario. However, when the results were

evaluated for males or for the participants overall, the skin hydration level was not significantly associated with dermal loading for either the five contact scenario (overall Pearson correlation=0.27; R^2=0.07; p=0.45) or the ten contact scenario (overall Pearson correlation=0.26; R^2=0.07; p=0.47). Further, when the results were stratified by higher vs. lower hydration levels (HI=1-5 vs. HI=5-10 for both males and females together), for the higher hydration levels (HI=5-10; mean HI=7) there was a moderately positive association between skin hydration and loading, but this was not statistically significant for either the five contact scenario (Pearson correlation=0.75; R^2=0.56; p=0.15) or the ten contact scenario (Pearson correlation=0.6; R^2=0.36; p=0.28). No clear relationship was observed between the lower hydration levels (HI=1-5) and dermal loading. The TEWL results also did not appear to have any clear relationship to the dermal loading of lead. The results of this study are consistent with the limited results of other analyses, which have suggested that there may be important nuances with respect to the effects of skin hydration on the quantitative dermal transfer to the skin and the measured hydration levels of the stratum corneum. Additional analyses are necessary to better characterize the effects of these differences on dermal loading and transfer.

5.1 INTRODUCTION

Dermal transfer has been defined as the amount of material that moves from one surface to another following contact with the skin (IOM, 2015). Recently, exposure science researchers have pointed to an urgent need for information related to object-to-skin transfer-related parameters (Huang et al. 2017). In 1999, Schneider et al. published a conceptual model for dermal exposure assessment with the goal of identifying all potential pathways and compartments that could affect dermal transfer or loading on the skin; the model was subsequently updated by Gorman Ng et al. in 2012 to include ingestion pathways. These pathways can include source to skin, skin to skin, skin to clothing, skin to surface, skin to glove transfer, skin to the per-oral area, and skin to saliva (Schneider et al. 1999; Schneider et al. 2000; Gorman Ng et al. 2012b). This conceptual model can be helpful, particularly in the absence measured dermal loading data, to assist in identifying the important pathways and compartments of interest for a particular dermal exposure scenario. This characterization can be useful for modeling and estimation scenarios to ensure that all exposures are considered.

The amount of a substance retained on the skin, or the dermal loading or concentration, has been measured using a variety of methods in addition to being evaluated using default assumptions. For solids, this parameter is often defined as mass per surface area of skin (surface density) in $\mu g/cm^2$, which then allows for the estimation of time-weighted average loading and subsequently the calculation of dermal uptake or flux through the skin in $\mu g/cm^2$-hour, which is a frequent metric for quantitative uptake of substances through the skin (Frasch et al. 2014; Sahmel et al. 2009). The U.S. EPA has previously provided default loading values for adherence due to direct contact of

between approximately 0.13 and 3 mg/cm^2 (USEPA 2013; Brouwer et al. 1999; EPA 2011).

The transfer of metals to and from the skin surface has been evaluated in a number of studies, although many of these studies focused on the transfer of metals from a known source to the skin surface. These studies have evaluated the potential for the dermal transfer of arsenic (Hemond et al. 2004; Barraj et al. 2007; Gorman Ng et al. 2011), iron (Enander et al. 2004; Avissar et al. 2004), aluminum and barium (Enander et al. 2004), zinc (Enander et al. 2004; Hughson et al. 2005), beryllium (Day et al. 2007), nickel (Gorman Ng et al. 2011; Hughson et al. 2010; Liden et al. 2008), cobalt (Klasson et al. 2017; Kettelarij et al. 2018b; Kettelarij et al. 2018a), chromium (Day et al. 2009; Gorman Ng et al. 2011; Julander et al. 2010; Liden et al. 2008), and cadmium (Gorman Ng et al. 2011).

The focus of the current study was the transfer of elemental metallic lead to and from the skin surface. Based on published literature that has previously evaluated lead transfer to the skin for all activities and industries evaluated, including workers at lead-acid battery facilities, handling of solid lead sheets or ingots, workers at a small arms repair shop, workers at an electronics recycling facility, and handling fishing tackle, dermal transfer and adherence was in the range of 0.00092 to 8.3 µg/cm^2 (Far et al. 1993; Hwang et al. 2000; Sleeuwenhoek et al. 2006; Gorman Ng et al. 2011; Grimes et al. 2019; Grimes et al. 2018; Beaucham et al. 2018; Sahmel et al. 2015b). The transfer efficiency of lead from the hands to saliva has also been reported to be in the range of 12-34% (Sahmel et al. 2015b).

Hostynek (2003) performed an analysis of the factors that can influence the dermal transfer and absorption of metals. These include the dose; the vehicle or solvent

in which the metal of interest is present (if applicable); the solubility of the metal of interest in that vehicle; and the molecular volume, valence, and effects of pH on metal solubility. Other factors may also include age of the skin; the anatomical site affected; the influence of homeostatic controls in the skin (which may mitigate toxic levels of certain metals with metal-binding proteins); the relative absorption from the different layers of the skin, including the stratum corneum, epidermis, and dermis; and the oxidation or reduction of metals in the skin layer through metabolic activity (Hostynek 2003). It has also been observed that certain metals will form deposits in their metallic state on or in the skin surface, and once the stratum corneum desquamates or renews itself over the course of two to three weeks, the bioavailability of a metal could be lower than what is suggested by measured absorption into skin tissue. Additionally, sweating can be a factor in the loss of water-soluble metal salts from the skin (Hostynek 2003).

5.1.1 Skin Condition and its Potential Effects on Transfer to and from the Skin

Different types of methods have been recommended to characterize the properties of the skin surface, including the measurement of the trans-epidermal water loss (TEWL), skin hydration index (HI), and skin pH (du Plessis et al. 2013; Stefaniak et al. 2013). 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 measurements of TEWL. TEWL can therefore be a helpful and effective measure of skin barrier function (Jansen van Rensburg et al. 2019; Sotoodian et al. 2012; Berardesca et al. 2018). In general, low TEWL values are suggestive of good barrier function and low water loss, while higher values point to reduced barrier function. By comparison, the hydration level of the stratum corneum, or skin hydration index (HI), is a measure of the actual hydration

or water content of the outer skin layer (Packham 2005; Sotoodian et al. 2012; Jansen van Rensburg et al. 2019). There have been measured differences reported in the hydration level of human skin by body location and by age (du Plessis et al. 2013; Berardesca et al. 2018). It has been reported that there is insufficient evidence to suggest differences in skin hydration according to gender (du Plessis et al. 2013). Additionally, although not well characterized, some differences due to ethnicity have also been reported (du Plessis et al. 2013; Young et al. 2019). The skin pH can also be an indicator of barrier function and can influence the amount of dermal absorption. At sufficiently low pH levels, some metals may undergo ionization, leading to increased absorption into the skin. For example, it has been reported that in tests using artificial sweat, the dissolution of nickel and beryllium increase as the pH of the sweat decreases (Stefaniak et al. 2013; Collins 1957; Wainman et al. 1994). However, the opposite can also be true; it has also been reported that the dissolution of mild steel, hexavalent chromium, and gold tend to increase as the pH of artificial sweat increases (Stefaniak et al. 2013; Hemingway et al. 1987; Haudrechy et al. 1994; Haudrechy et al. 1997; Stefaniak et al. 2011).

The factors most consistently associated with a statistically significant influence on dermal transfer appear to be repeated contacts with the source, the level of skin hydration, and quantitative surface loading. Other factors, such as dermal contact pressure and contact duration, have been found to be less influential (Brouwer et al. 1999; Hubal et al. 2008; Zainudin et al. 2004; Christopher et al. 2007b). The influence of skin hydration on dermal transfer and loading has not been well characterized in the literature and has pointed to potentially inconsistent or unexpected results. While some studies have reported no observed effect on dermal transfer associated with skin

hydration (Beamer et al. 2009; Gorman Ng et al. 2013; Roff 2000), others have reported a decrease in transfer with increased skin hydration (Brouwer et al. 1999; Christopher et al. 2007b; Rodes et al. 2001). Still others report an increase in dermal transfer with increased skin hydration (Avissar et al. 2004; Cohen Hubal et al. 2005; Hubal et al. 2008). Ideally, dermal sampling data specific to a particular agent and scenario should be used to evaluate dermal exposure potential, including the effect of skin hydration. This study therefore focused on evaluating the effect of skin hydration specifically on dermal loading and transfer of elemental metallic lead.

5.2 METHODS

Lead was identified for evaluation in this study since it raises important public health concerns in a variety of populations, including workers, consumers, and children, and transfer of lead to the skin is likely to be a significant potential pathway for exposure (Canales et al. 2007). According to the weight of evidence in the published literature, ingestion, including hand to mouth contact, appears likely to be the primary route of exposure for lead (Manton 1985; Mahaffey 1977; COEHHA 2011).

A protocol using readily available solid lead consumer-product fishing tackle was developed, and Institutional Review Board (IRB) protocol review and approval was obtained from the University of Minnesota prior to the study (Protocol #1506M73781). Human volunteers were sought for this study so that data could be obtained that were most similar and relevant to the interaction of metallic solids with the living human skin surface and its properties. Statistical power calculations demonstrated that a minimum of four volunteers was likely to be needed for sufficient statistical power for a GSD of 2 (SD of 0.5) or less, as previously observed for similar data, with a 95% decision statistic and

an error rate of 2% or less (Sahmel et al. 2015b).A total of 10 human volunteers (6 males and 4 females) were recruited from the practicing environmental health professional community for data collection in this study.

To test the quantitative transfer of lead from a solid elemental metallic source to the skin surface, participant volunteers performed repeated contacts of five and ten presses on a consumer fishing tackle product (Bass Pro Shops, Springfield, MO, USA) using the tips of the index and middle fingers and the thumb (mean skin surface area=13.1 cm^2 for females and 16.8 cm^2 for males). A consistent protocol was employed (e.g., identical number of contacts, type of material contacted, measured pressure of contact, measured time of contact) so that inter- and intra-individual variability could be characterized. The protocol used two sequential sample methods. The first sampling method (*Method #1*) was a published skin sampling method using Whatman filter wipes moistened with 1% HNO_3 that has previously been shown to be effective for the removal of metals and particulates from human skin (Liden et al. 2006; Liden et al. 2008; Julander et al. 2010; Erfani et al. 2017). Three sequential wipe samples were collected from each participant following five and ten contacts or presses with the lead source. The second method (*Method #2*), was combined in sequence with Method #1 to evaluate the potential for residual lead on or in the skin surface following the wipe sampling, and was a tape lift sampling method (Bunge et al. 2008; N'Dri-Stempfer et al. 2009). For the tape stripping method, three tape lifts each were aggregated into two samples, for a total of six tape lifts. Using this design, there were three sequential wipe samples collected for each of the 10 participants, for a total of 30 wipe samples. These were each analyzed separately to help characterize removal efficiency. Immediately following the three wipe samples, the six tape lifts were collected. The first three tape

lifts and the second three tape lifts were each aggregated into a single sample for a total of 20 tape lift samples over the 10 participants, since the purpose of the tape lifts was to confirm previous removal by the wipe sampling method. Additional details of the sampling protocol are discussed elsewhere in the published literature (Sahmel 2021a).

5.2.1 Skin Monitoring

The hydration or moisture content of each participant's skin was measured both prior to and following the sample collection using a corneometer. This is a non-invasive instrument which reported results using a hydration index (HI) on a unitless scale from 1 to 12, with 1 being extremely dry skin and 12 being excessively hydrated skin (EDS10 Skin Hydration Monitor manufactured by Courage + Khazaka electronic GmbH, EnviroDerm Services, UK, www.enviroderm.co.uk). The corneometer measures the hydration of the stratum corneum using electrical capacitance. To collect the measurements, the instrument was placed against the skin surface for a few seconds to determine the reading. Measurements were also collected at the site of wipe on the volar forearm for baseline comparison. Additional details of the instrument used and its capabilities and limitations are discussed elsewhere (Sahmel et al. 2021b).

For comparison, TEWL was also measured using an open chamber instrument from DermaLab (See **Figures 4-2a and 4-2b**) (Cortex Technology ApS, Denmark, www.cortex.dk). Measurements were collected using 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.

5.2.2 Analytical Methods and Data Analysis

Descriptive statistics, *t* tests, and *F* tests were used to analyze the data results in order to characterize the total mean quantitative transfer of lead to the skin for each participant. Comparisons were made between skin hydration levels for males and females, skin hydration levels by anatomical location, and pre and post-test skin hydration levels. Pearson's Correlation coefficient was used to evaluate the relationships between skin hydration levels before and after sampling, TEWL levels before and after sampling, and measured dermal loading.

5.3 RESULTS

A total of ten volunteers participated in the data collection, including 4 females and 6 males. The wipe sample results for all participants were found to be lognormally distributed, consistent with previous dermal sampling results (Beamer et al. 2009; Adgate et al. 1995; Klein et al. 1997; Kromhout et al. 2001). Geometric standard deviations for each dataset (five presses and ten presses) were 2.4 and 1.8, respectively, which is consistent with other exposure assessment data.

Results for transfer of lead for five and ten presses/contacts for the ten participants with the lead ingots are shown in **Table 5-1.** For all source to skin scenarios evaluated, 100% of the results for the first sample wipe were above the limit of detection. For the second wipe, 38% of samples for the second wipe were above the limit of detection (<1.3 µg/sample), and for the third wipe, 16% of samples were above the limit of detection (<1.3 µg/sample). The results for all three wipe samples for each participant

were summed together to determine total measured wipe sample loading; for sampling values below the limit of detection (LOD), a value of half the limit of detection was used for analysis and statistical purposes.

All sampling results using the secondary tape strip method (Method #2), which was selected to assess the removal efficiency of Method #1, were below the limit of detection (<2.5 µg/sample). No further analysis was conducted for these tape strip samples, as the results suggested a substantial removal efficiency from the skin for Method #1 after three consecutive wipes. The geometric means for the two sample sets (five presses and ten presses) were 11.25 µg (range 5.1-45 µg) and 9.43 µg (range 8.4-20.7 µg), respectively (See **Table 5-1**).

5.3.1 Skin Hydration Measurements and Comparison with Dermal Transfer and Loading

For measurements of skin hydration at the sampling site on the index finger of each participant, the average pre-sampling HI value was 4.9 (range 2-10; n=10) and average post-sampling HI value was 4.8 (range 3-9; n=10). The data were approximately lognormal. These results were not statistically different (t test) between the pre-sampling and post-sampling periods, suggesting that the overall hydration level of the skin did not change significantly during the sampling period despite the fluids introduced to the skin during the wipe sampling process. Overall, a negligible to weak positive correlation was observed for all participants between skin hydration level and skin loading. This difference was not statistically significant, suggesting no clear relationship between skin hydration and loading for either the five press scenario (Pearson correlation= 0.27;

R^2=0.07; p=0.45) or the ten press scenario (Pearson correlation= 0.26; R^2=0.07; p=0.47) (**Figure 5-1**).

Baseline HI measurements collected on the volar forearm indicated that baseline HI for the female participants was higher than for the male participants, but was not statistically significant (mean HI=4.3,range 3 to 5, SD=0.96 for females; mean HI=3.8, range 3 to 5, SD=0.98 for males; t test; p=0.006). However, for the palmar surface of the index finger, the relative hydration level of the skin was higher for males vs. females; this difference was also not statistically significant (t test; mean HI=4.0, range 2 to 5, SD=1.4 for females; mean HI=5.5, range 2 to 10, SD=3.4 for males) (**Table 5-2**).

Differences in the relationship between skin hydration and total lead loading, however, were observed for male skin versus female skin. For female participants' skin, the loading of lead onto the skin was negatively associated with loading for both the five contact (Pearson correlation= -0.97; R^2=0.93; p=0.034) and ten contact (Pearson correlation= -0.86; R^2=0.73; p=0.145) scenarios, suggesting that as the hydration level of the female skin increased, the loading of lead onto the skin surface declined. This difference was statistically significant for the five contact scenario but not the ten contact scenario. At the average hydration level of the male skin, a negligible to weak positive correlation was observed for both the five contact (Pearson correlation=0.67; R^2=0.45; p=0.15) and ten contact (Pearson correlation=0.37; R^2=0.14; p=0.4) scenarios, suggesting no consistent relationship between skin hydration and loading of lead on the skin of the male participants (**Figure 5-2**).

To further explore the differences in the relationships between skin hydration and skin loading, the results for the five contact scenario and the ten contact scenario were also divided into two groups by low skin hydration (HI=1-5; range=2-4; mean=2.8) and

high skin hydration (HI=5-10; mean=7) and compared to the measured skin loading level. When the results were stratified in this way, there was a negligible correlation between the low skin hydration level group and dermal loading for both the five contact (Pearson=0.023; R^2=0.0005; p=0.97) and the ten contact scenarios (Pearson = -0.30; R^2=0.09; p=0.62). When comparisons of the high skin hydration level group (HI=5-10; mean=7) and dermal loading were made, there was a weak to moderate positive correlation observed for both the five contact (Pearson = 0.75; R^2=0.56; p=0.15) and the ten contact scenario (Pearson = 0.60; R^2=0.36; p=0.28) although these relationships were not statistically significant (**Figure 5-3**).

TEWL baseline volar forearm measurements ranged from 3.7 to 7.9 (TEWL mean=6.0; n=10) and measurements for the palmar index finger ranged from 34.4 to 79.5 (TEWL mean=58.43; n=10). For the palmar index finger TEWL, there was a weak negative correlation for both the five contact (Pearson correlation=-0.45; R^2=0.2; p=0.19) and ten contact (Pearson correlation=-0.3; R^2=0.09; p=0.4) scenarios, but this was not statistically significant (**Figure 5-4**), also suggesting no clear relationship between skin lead loading and TEWL at the sampling site.

5.4 DISCUSSION

The results observed in this study with respect to the influence of skin hydration on quantitative dermal transfer of elemental metallic lead demonstrated several important nuances. Overall, a negligible to weak positive correlation was observed for all participants between skin hydration level and skin loading. This relationship was not statistically significant, suggesting no clear relationship between skin hydration and loading for both the five contact scenario (Pearson correlation= 0.27; R^2=0.07; p=0.45)

and the ten contact scenario (Pearson correlation= 0.26; R^2=0.07; p=0.47) There was also no clear relationship between palmar index finger TEWL and loading for either the five contact (Pearson correlation=-0.45; R^2=0.2; p=0.19) or ten contact (Pearson correlation=-0.3; R^2=0.09; p=0.4) scenario. However, for the female participants, skin hydration was negatively associated with loading, whereas for males alone, a weak positive correlation was observed between skin hydration and dermal transfer of elemental metallic lead. Further, when the skin hydration measurements were separated by high low skin hydration level (HI=1-5; range 2-4; average=2.8) and high skin hydration level (HI=5-10; average=7), there was a negligible to low negative correlation between the low skin hydration level group and dermal loading, but when comparisons of the high skin hydration level group and dermal loading were made, there was a low to moderate positive correlation observed for both the five contact and ten contact scenarios.

Although the relationship between female HI and the five-contact loading scenario was statistically significant, all other relationships between skin hydration and loading were not statistically significant. The reasons for the possible differences between the female vs. male groups and the combined male-female group were not immediately clear. These findings could be the result of the small sample size, which is an important limitation of this study. It is also possible that the negligible correlations observed overall were caused by combining the male and female results together. There are some differences that have been reported in the skin between females and males that may have influenced these results. Multiple studies have reported that the skin pH of females and males is statistically significantly different, although the findings are mixed regarding whether female skin has a higher or lower skin surface pH than male

skin (Ehlers et al. 2001; Dao et al. 2007; Kim et al. 2006; Jacobi et al. 2005a; Choi 2018). Given the reported differences in the literature between the solubility of metals in surface sweat based at least in part on acidity, this difference also has the potential to influence the levels of dermal loading of elemental metallic lead specifically (Stefaniak et al. 2006; Stefaniak et al. 2013; Stefaniak et al. 2011). Other gender-specific differences in the skin could also potentially influence loading results, such as protein absorption, sebum levels, or hormone levels (Jacobi et al. 2005a; Kim et al. 2006; Dao et al. 2007).

5.4.1 Other Studies Evaluating the Effects of Skin Hydration on Transfer

These results were generally consistent with other published research; the overall lack of a significant association between skin hydration and dermal loading based on the total set of data collected in this study is supported by the results of other studies for normal or typical skin hydration measurements (vs. skin that was actively wetted prior to contact or sampling). A number of other studies have evaluated the relationship between skin hydration levels and dermal loading, although many of these sample sets are similarly small (**Table 5-3**) (Beamer et al. 2009; Gorman Ng et al. 2013; Roff 2000; Edwards et al. 2001; Brouwer et al. 1999; Christopher et al. 2007b; Avissar et al. 2004; Cohen Hubal et al. 2005; Hubal et al. 2008; Rodes et al. 2001). However, no other identified studies reported evaluating the relationship between gender and skin loading. One other identified study (Avissar et al., 2004) also reported findings related to the relative intensity of hydration and skin loading.

The lack of a significant association between skin hydration and loading was reported by several studies. Based on a pooled analysis of dermal transfer efficiencies identified in the literature, the authors of one review study found the results suggested

that “skin moisture may not affect transfer efficiency” (Beamer et al. 2009, p. 280). Other studies have also reported that typical skin moisture or hydration levels were not significantly associated with dermal loading or transfer efficiency (Gorman Ng et al. 2013; Roff 2000).

Edwards and Lioy (2001) reported a weak positive correlation between Corneometer levels and atrazine and malathion collection, but indicated that these results may have been coincidental. However, for both chlorpyrifos and diazinon, they reported a negative correlation between skin moisture levels and collection efficiency. Further, they found that skin hydration was negatively correlated with collection efficiency at higher Log K_{ow} values (above 3), which may have been related to limits on the solubility of the test substances in sweat on the skin surface, and similarly at lower Log K_{ow} values, there was a more positive effect on skin collection efficiency due to hydration (Edwards et al. 2001).

Brouwer et al. (1999) reported results suggesting that an increase in normal skin hydration or moisture limited the transfer of Tinopal to the hands and was therefore negatively correlated, when in fact an enhanced transfer was expected because of the relatively high solubility of Tinopal in water; this result was not significant but approached statistical significance. Similar to Brouwer et al., Christopher et al. (2007a) measured a decrease in the transfer of saffron to the hand with increased skin hydration. This association was statistically significant for the fingers but not the palm. Rodes et al. (2001) artificially wetted the skin using a hand press onto a foam pad with surrogate saliva at a pressure of 3.6-4.5 kg to evaluate dermal transfer, and reported that increasing skin moisture or dampness resulted in a decrease in dermal transfer of house dust.

Conversely, other studies have reported the opposite relationship between skin hydration levels and dermal transfer, although two of these studies involved active wetting of the skin surface. Avissar et al. (2004) measured skin hydration using a Corneometer and reported that the range of values for 22 volunteers could be grouped into three clusters: “very dry” (n=5), “dry” (n=4) and “sufficiently moistured” (n=13). The authors reported that hydration levels correlated very well with the intensity of colorimetric staining of iron on the skin. Camann et al. (2000a) reported a substantially higher transfer of pesticides to the hands when the skin was wetted with water or saliva compared to dry skin that had not been actively wetted. It was similarly reported that surface loading level and skin condition (moist vs. dry) significantly positively affected skin loading for riboflavin and pesticides, demonstrating increased skin transfer or loading with increased skin moisture. For this study, the moist skin conditions were artificially created by holding the hands in front of a cool mist humidifier for 20 seconds prior to skin contact and sampling (Cohen Hubal et al. 2005; Hubal et al. 2008).

The results of this study, which suggested a weak positive relationship between increasing intensity of skin hydration and skin loading of lead, are consistent with the findings of Avissar et al. (2004), in which it was similarly noted that the level of skin hydration was generally associated with a positive increase in the skin loading level for metals (iron). However, this relationship was not statistically significant in the current study.

5.5 CONCLUSIONS

This study is one of few in the published literature to evaluate the influence of skin hydration on the quantitative transfer potential to the skin surface *in vivo*. It is also

the first study identified to evaluate the relationships between skin hydration and dermal loading associated with gender and the second identified study to evaluate the potential for effects associated with the relative intensity of hydration on dermal loading. The results of this study appeared to be generally consistent with the results of several other analyses indicating that there are important nuances with respect to the effects of skin hydration on quantitative dermal loading on the skin. When the results for skin hydration level were evaluated for the participants overall (mean HI=4.9), the skin hydration level did not appear to be associated with dermal loading for either five skin contacts or ten skin contacts (Pearson correlation = 0.26, 0.27; R^2=0.07; p=0.45, 0.47). When the relationship between skin hydration levels and dermal loading was analyzed separately for males and females, it was found that on the palmar surface of the index finger, the relative hydration level of the skin was higher for males vs. females, although this difference was not statistically significant. Further, the skin hydration level in the female cohort was negatively correlated with loading of elemental metallic lead on the skin surface for both five skin and ten skin contacts, whereas for males, there was a low to moderate positive correlation between skin hydration level and dermal loading for both scenarios. Additionally, at higher skin hydration levels generally, there was a moderate positive correlation between skin hydration and loading, while for lower skin hydration levels there was a negligible correlation between skin hydration and loading. These results provide data that can be used to further evaluate the influences of potentially important factors such as skin hydration on dermal loading and dermal exposure assessment. Based on these results, additional investigations of these nuances and the relative influence of skin hydration on loading are warranted.

Table 5-1: Results for Dermal Transfer and Loading, Source-to-Skin

Method #1	Source to Skin: Five Presses		Source to Skin: Ten Presses	
	µg (total)	µg/cm^2	µg (total)	µg/cm^2
GM	11.25	0.69	9.43	0.58
GSD	2.40		1.8	

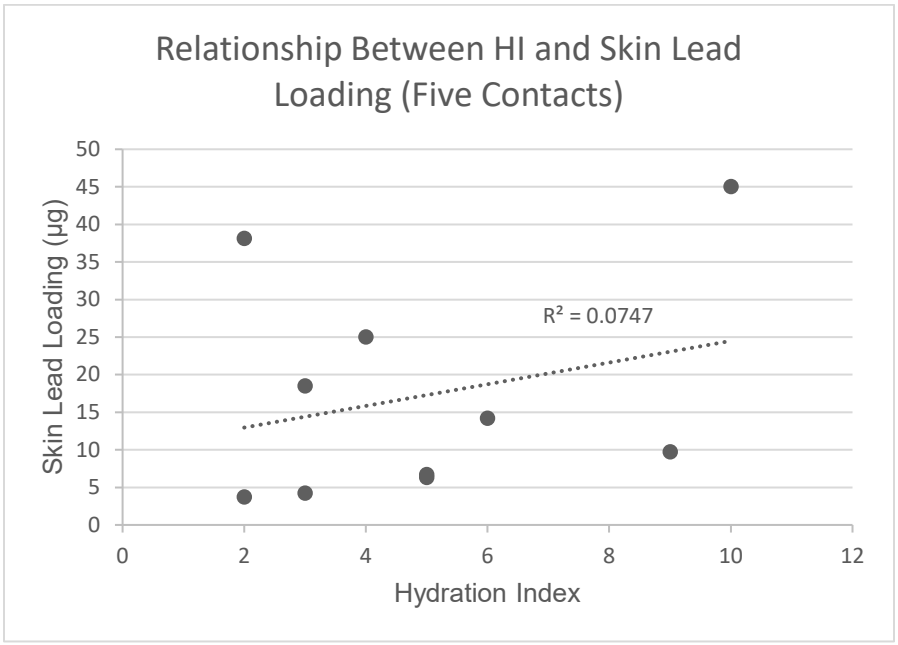
Table 5-2: Hydration Index (HI) Measurements by Skin Site Location and Gender

Participants	Baseline HI (Volar Forearm)	Baseline Sample Site HI (Palmar Surface of Index Finger)
Females (n=4)	mean 4.9 (range 3-5; SD=0.96)	mean 4.0 (range 2-5; SD=1.4)
Males (n=6)	mean 4.0 (range 3-5; SD=0.98)	mean 5.5 (range 2-10; SD=3.4)

Table 5-3: Summary of Studies Evaluating the Relationship Between Skin Hydration and Dermal Loading

Study	Number of Participants	Relationship Observed Between Skin Hydration and Dermal Loading
Brouwer et al. (1999)	3 participants in one trial, 18 in a second trial	Negative
Camann et al. (2000)	3 participants	Positive (skin artificially wetted)
Roff (2000)	8 participants: (4 male, 4 female)	Not significant
Rodes et al. (2001)	3 participants: (1 female, 2 male)	Negative (skin artificially wetted)
Edwards et al. (2001)	9 and 10 participants	Mixed
Avissar et al. (2004)	22 participants (12 males, 10 females)	Positive
Cohen Hubal et al. (2005)	3 participants	Positive (skin artificially wetted)
Hubal et al. (2008)	3 participants in one trial, 24 in a second trial	Positive (skin artificially wetted)
Christopher et al. (2007a)	15 participants	Negative
Gorman Ng et al. (2013)	4 participants: (2 male, 2 female)	Not significant

Figure 5-1: Overall Relationship Between Hydration Index (HI) Measurements and Skin Loading of Lead



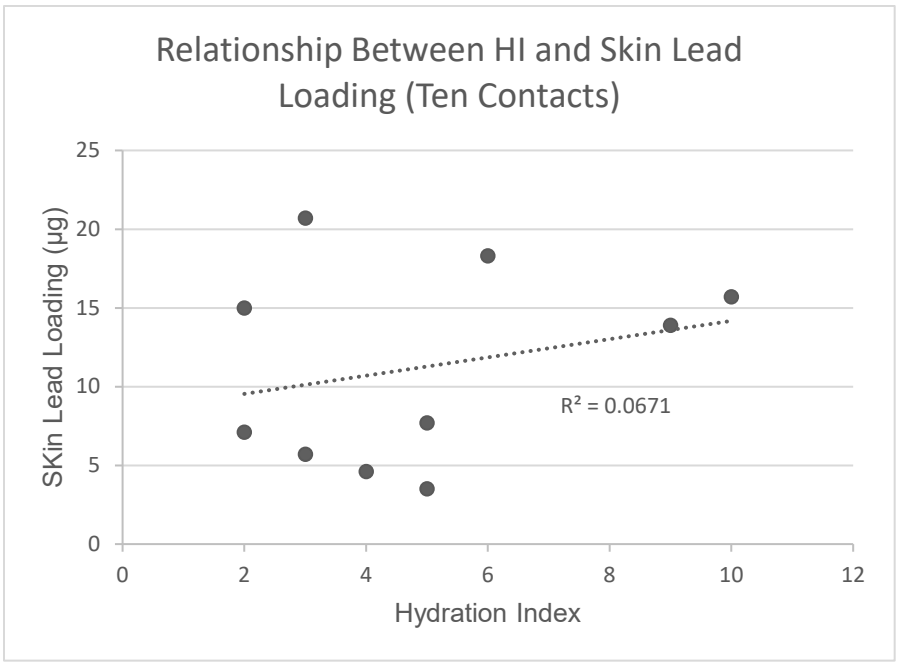


Figure 5-2: Relationship Between Female and Male Hydration Index (HI) Measurements and Skin Loading of Lead

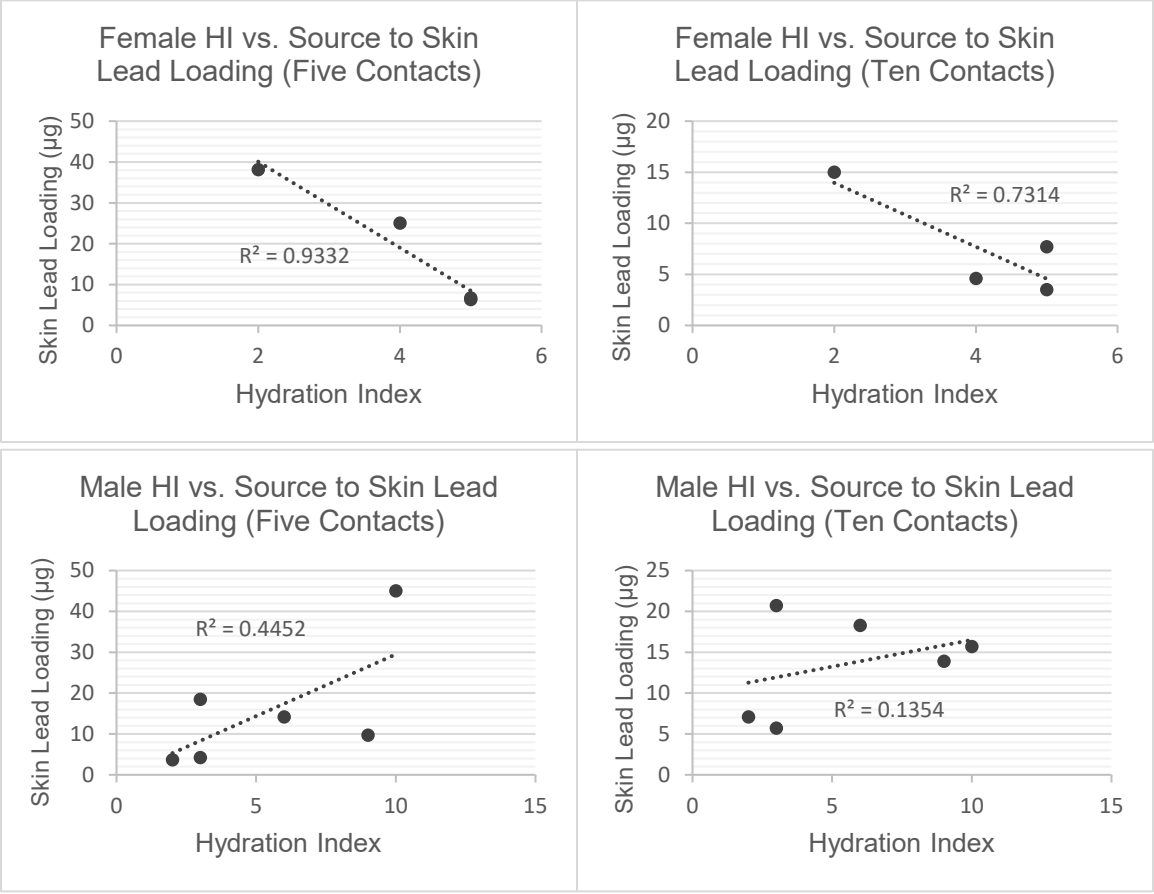


Figure 5-3: Relationship Between Low Hydration Index (HI = 1-5) and High Hydration Index Values (HI = 5-10) and Skin Loading of Lead

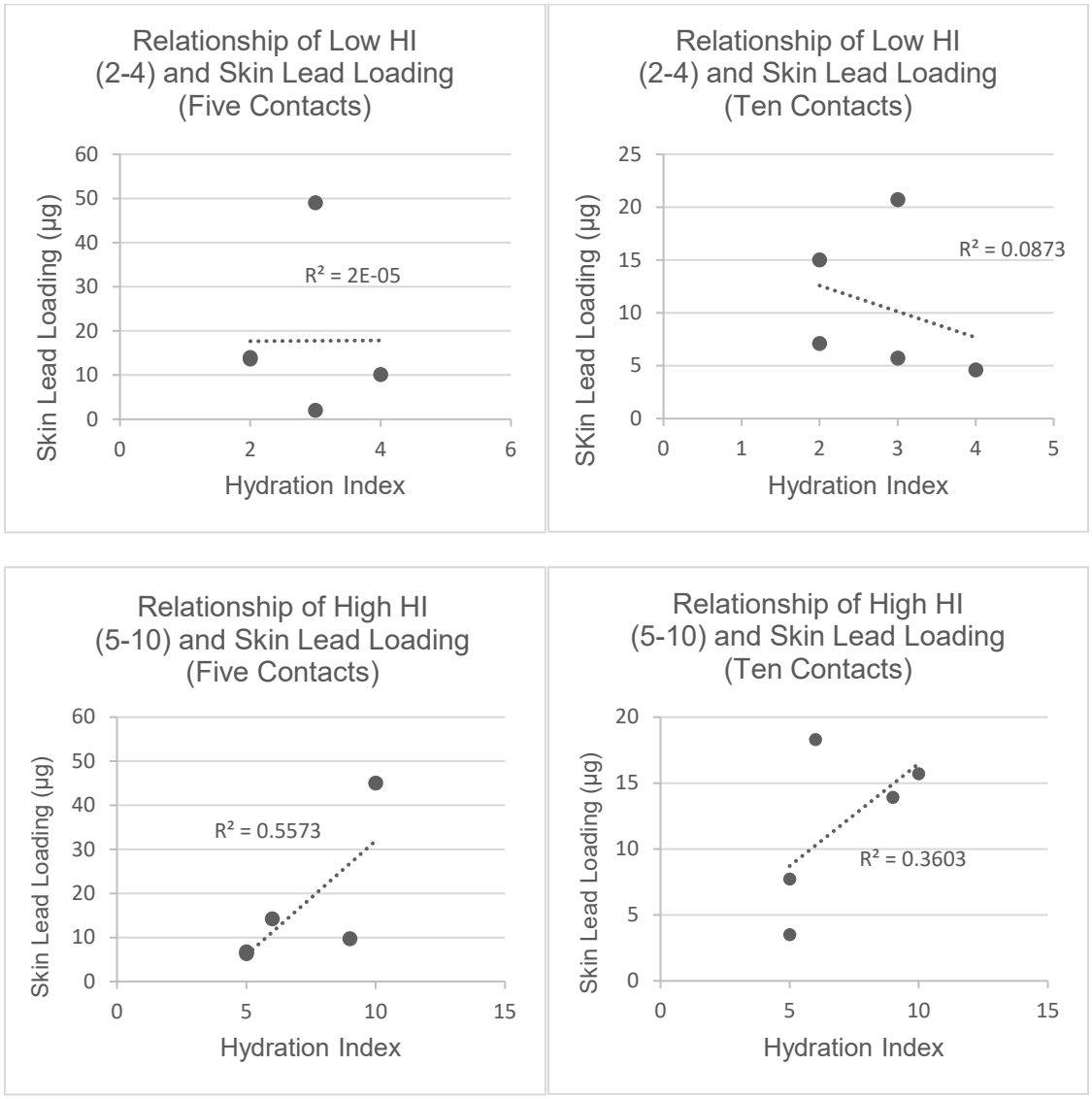
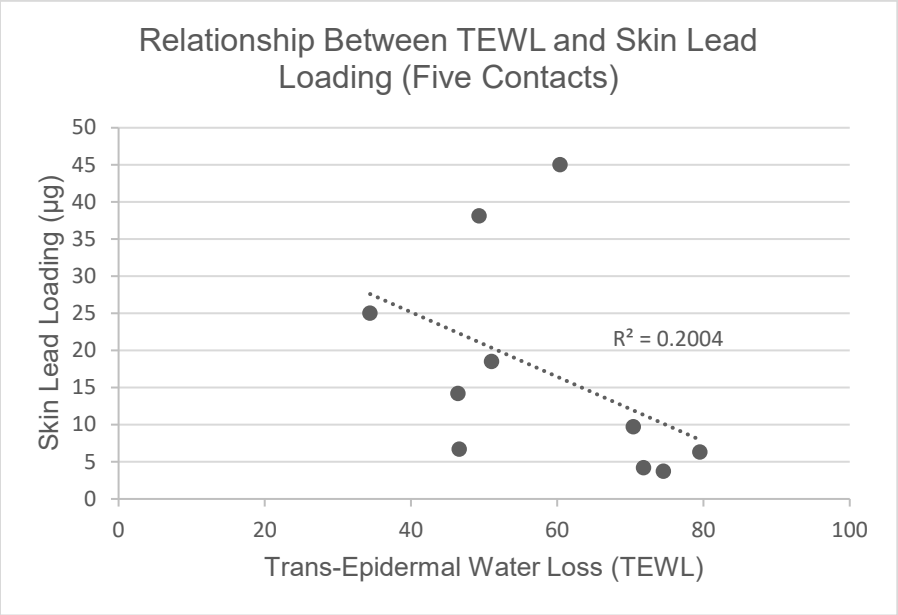
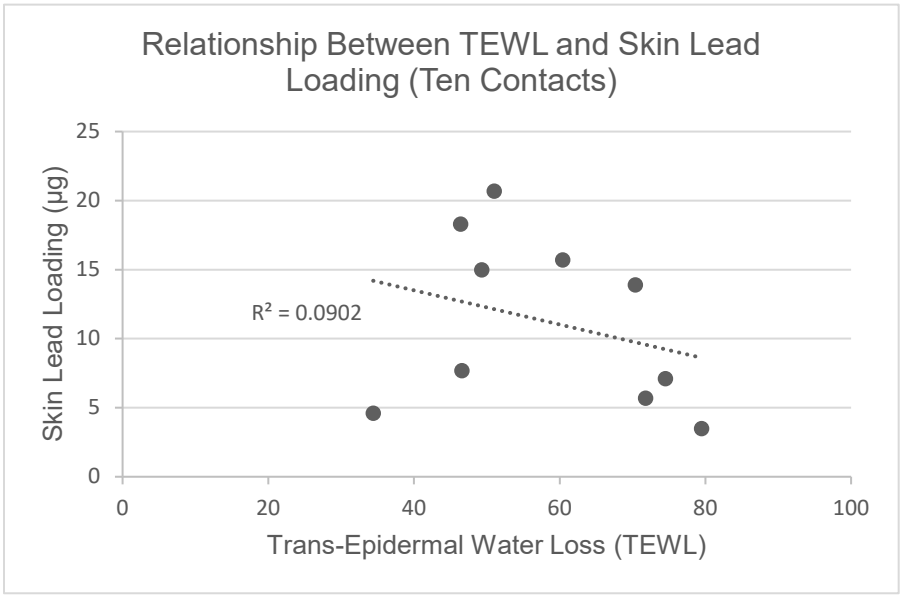


Figure 5-4: Relationship Between TEWL Measurements and Skin Loading of Lead





Chapter 6

Conclusions and Future Directions

6.1 OVERALL CONCLUSIONS

The purpose of the research in this dissertation was to quantitatively consider influences on the current loading and transfer-related assumptions used in deterministic dermal exposure models available to exposure assessment practitioners. This analysis included several specific aims. A primary goal was to evaluate the accuracy of exposure assessment practitioners in applying the available deterministic, scenario-specific dermal exposure assessment assumptions and models. Based on the results of this initial analysis, it was apparent that dermal loading and transfer default assumptions substantially influenced the accuracy of practitioners' judgments regarding dermal exposures and resulted in systematic overestimates of dermal exposure potential. A secondary goal of the analysis, therefore, was to quantitatively investigate the influence of specific determinants that were reported in the literature to have a statistically-significant influence on quantitative dermal loading. Of these determinants, both repeated contacts and skin hydration were noted to have potentially complex influences on dermal loading and transfer, and were therefore selected for additional analysis in this dissertation. To assess the influence of repeated contacts on dermal loading, a study design based on a dermal conceptual model was developed for human skin *in vivo*. This design allowed for the assessment of dermal loading and transfer via different pathways and compartments and evaluated the contributions to dermal transfer of elemental metallic lead as a test substance. As part of the third goal, which was to quantitatively evaluate the influence of skin hydration, multiple methods of measuring and assessing skin condition and hydration were evaluated and compared among

different skin sites. Following this analysis, fourth and finally, the potential for the quantitative influence of normal skin hydration on dermal loading was assessed for the same test substance.

With respect to key influences on dermal transfer, a review of the literature indicated that repeated contacts have been shown to exert the greatest influence on dermal loading compared to other determinants. The use of an additive loading assumption for modeling of dermal exposures was also identified as a key influence on the inaccuracy of current deterministic dermal models, and repeated contacts were therefore a substantial factor in this assumption. While the effect of surface loading was also found to be statistically significant, it explained less of the skin loading compared to the effect of repeated contacts. Additionally, skin hydration was found to have a significant effect on loading, both positively and negatively. Skin hydration appeared to have a slightly larger effect on skin loading than surface loading. Contact pressure and duration were generally found to have little effect on skin surface loading, although differences in the motion of contact were found to be statistically significant. For example, a “smudge” contact resulted in greater transfer than a press contact (Brouwer et al. 1999; Zainudin et al. 2004; Hubal et al. 2008; Christopher et al. 2007b). Based on these analyses, the determinants of repeated contacts and skin hydration were selected for further data collection in this dissertation.

According to the Schneider et al. (1999)/Gorman Ng et al. (2012) conceptual model, the available mechanisms for dermal transfer and loading include a number of identified pathways and compartments, such as object to skin, skin to skin (including skin to lips), skin to clothing, skin to gloves, air to skin, and skin to saliva. Few data are available to inform the relative importance of each pathway in accurately estimating

dermal transfer and total exposure potential, despite the possibility for significant impact to workers or consumers from dermal exposures. Based on a detailed literature review, solids and semi-volatile substances were evaluated for source-to-skin transfer in a total of 52 studies. For all of these studies, with the exception of immersion studies using zinc metal dust (Hughson et al. 2005), the mean or GM dermal loading on human skin, regardless of the scenario, appeared to be on the order of 1,000 μg/cm^2 or less, or up to a mean of 4,840 μg/cm2 for immersion scenarios involving zinc metal dust. Dusts may be an exception to this general observation for dermal transfer and loading measurements, although neither Tinopal powder nor nickel powder skin loading levels approached 1,000 μg/cm^2. For many measurements, dermal loading was one to four orders of magnitude below 1,000 μg/cm^2. It is possible that these measurements underestimated the total dermal transfer in some scenarios, depending on the sampling method, either due to incomplete removal or substances that had already been absorbed or partially absorbed into the skin prior to sampling. A number of studies did not report the sampling method efficiency or perform a validation to understand the total amount of removal achieved through sampling. It is also possible that the relative toxicity of the substances or other substance-specific characteristics influenced the amount of quantitative loading, although the range of human *in vivo* loading data observed in the literature included substances without specific toxicity, including soils and Tinopal powder, and all data remained within or below a GM or mean of 1,000 μg/cm^2 in nearly all scenarios. Recently, it has been similarly noted in the literature that 1,000 μg/cm^2 or 1 mg/cm^2 is a high level of skin loading for non-immersion scenarios (Goede et al. 2018). Although maximum retention values based on immersion scenarios have been suggested for liquids on the hands, similar maximum retention values for solids do not

appear to have been noted in a systematic way in the literature to date (McNally et al. 2019; Goede et al. 2018). This loading value for solids may therefore be useful as a potential comparative benchmark for loading on the skin, with additional substance or scenario-specific analyses where warranted. It also suggests that certain existing default values for dermal loading of chemicals may be too high or orders of magnitude too high. This finding is consistent with other reports in the literature that default loading or transfer factors used in dermal exposure and risk assessment approaches have been approximately 500 to 5,000 times higher than the measured transfer to human skin (Brouwer et al. 1999). However, existing default values for dermal loading may be appropriate for or consistent with some upper bound exposure scenarios and immersion scenarios.

The primary conclusions of this analysis include:

- The results of this study indicated that despite substantial education and training in industrial hygiene generally, the practitioners evaluated had very little, if any experience in performing dermal exposure assessments. It was also observed, contrary to studies in the literature that have evaluated the accuracy of practitioners in performing inhalation exposure assessments for which they tend to underestimate exposure potential, that the participants in this study consistently overestimated the potential for dermal exposure without quantitative data specific to the scenario. And finally, it was observed that participants in this study were able to identify the reference or “true” category of dermal exposure acceptability when provided with relevant, scenario-specific dermal and/or

surface loading data for use in the assessment process. The results of this analysis support the need for a closer examination of default loading values used in dermal exposure assessments to evaluate their accuracy relative to real-world or measured dermal loading values. Specifically, these results pointed to overestimates using the assumptions and default values available for these assessments.

- Based in part on these results, the repeated contacts determinant was identified for further analysis in this dissertation to further evaluate its influence on dermal loading and transfer. The results of this study confirmed other important findings with respect to repeated contacts with the skin surface, including that with initial repeated contacts up to approximately five to ten, the results of transfer increase non-linearly, but begin to approach a steady state with higher numbers of repeated contacts. Consistent with other studies in the literature, the transfer efficiency decreased with repeated contacts to 29% after five contacts and 11-12% after ten contacts. Given the consistency of these values with other studies for other substances in the literature, these data should be considered for the refinement of the assumptions used in current deterministic models for dermal exposure assessment.
- The results of a systematic analysis of samples from human subjects to quantitatively characterize dermal transfer efficiency between the different dermal conceptual model compartments demonstrated that some transfer pathways and compartments are significantly more important than others. Based on the analysis, transfer could not be measured from the skin to cotton clothing or to laminate countertop surfaces, while substantial transfer could be repeatedly

measured between the skin and the surface of nitrile gloves, suggesting that similar personal protective equipment could become a significant reservoir for additional transfer and exposure. It was also demonstrated that either single or repeated skin to skin contact consistently resulted in measurable transfer of lead, creating a secondary skin exposure reservoir or compartment.

- This study performed a series of novel comparisons regarding the measurement of skin hydration, including relative measurements of skin hydration and barrier function between the volar forearm and the palmar skin. For the participants evaluated, the mean volar forearm TEWL was 7.5 (range 3.2-25.3; SD-5.4), and the mean volar forearm HI was 4.4 (range 3-6; SD=0.9). For TEWL, the mean baseline for the volar forearm was not statistically significantly different between males and females ($p=0.9$). However, 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 comparison, the mean volar forearm percent hydration was 25.2% (range 14.4%-63.9%; SD=0.1). Since many skin wipe samples are collected on the hands, and particularly on the palmar surface of the hands, comparative skin hydration measurements were also collected for each participant on the tip of the index finger of the dominant hand for comparison. A statistical analysis of the TEWL measurements and HI measurements between the volar forearm and the palmar fingertip surface also found them to be significantly different from each other ($p<0.004$ for both TEWL and HI measurements between the volar forearm and the index finger). As a result, no direct comparisons were made between the index finger measurements and the established benchmark values in the literature for the

volar forearm. The relative measurements reported in this study are likely to be helpful in establishing comparison 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. Additionally, a quantitative comparison between measurements using an instrument designed for assessing the unitless skin hydration index (HI) and an inexpensive instrument that measures the percent hydration of the skin surface was performed to determine the relationship between these results. While measurements using the two different instruments were only weakly correlated for the skin of the volar forearm, the two methods were moderately correlated for the index finger and the association was statistically significant (Pearson correlation=0.77; R^2=0.56; p=0.000004). These results are useful, since this skin site is more likely to be the site of interest for skin wipe sample study purposes. These results suggested that an inexpensive instrument which can measure 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 this more expensive instrument is unavailable.

- Several potentially nuanced results were identified in the evaluation of the influence of skin hydration on dermal loading. For the palmar surface of the index finger (the location of skin surface sampling), the hydration level of the skin was higher for males than females, but this difference was not statistically significant. Overall, the results for all participants of this study showed a negligible to slight positive influence from the results of normal hydration of the skin and the

quantitative transfer of lead to the skin surface. When the results were evaluated for males and females separately, the results suggested that for female skin, skin hydration was negatively associated with dermal loading, whereas male skin was moderately positively associated with dermal loading. The relationship for female HI levels and skin loading was statistically significant for five contacts, but not ten contacts. For different levels of skin hydration, at higher skin hydration levels generally (for both males and females, HI=5-10), there was a moderately positive association between skin hydration and loading, whereas no relationship was observed for lower skin hydration levels generally (for both males and females, HI=2-4). However, these differences were not statistically significant. Based on these results, additional investigations of these differences and the relative influence of skin hydration on loading are warranted.

6.2 FUTURE DIRECTIONS

Based on the results of this dissertation, future research could focus on collecting additional data to determine the potential for other types of solids to transfer to and from the skin and personal protective equipment, such as gloves or respirators. These types of materials appear to readily allow for the transfer of lead from the skin surface and could become a reservoir for additional exposure in the workplace or other environments. First, additional research should include further analyses to evaluate the potential for loading and transfer according to the physical properties of substances, including particle size, chemical composition, and solubility in human sweat. Second, further sampling of the potential for solids to transfer from skin to skin is warranted, as this analysis would improve the understanding of transfer potential to and from the skin

on different areas of the body, or to another individual. Third, future analysis could focus on further exploring the role of skin hydration on dermal transfer, and whether dermal loading is affected systematically by gender or relative level of skin hydration, as well as the role of solubility on dermal loading for high and low skin hydration levels.

Another important recommendation for future work and research is the use of additional substance-specific sampling data by classes of materials to help refine the current deterministic models used for dermal exposure assessment. In particular, the results of this research and other consistent data in the literature point to a need to refine the additive loading assumption currently used in many deterministic models for dermal exposure. The current data point to the need for a revised factor to consider this parameter, possibly using an exponential factor rather than an additive assumption.

Several of the sample sizes in this study, and particularly for differences in the influences of skin hydration, were small, and additional research using larger groups of volunteers is warranted. These additional data are needed especially to better elucidate the reasons for positive versus negative correlations between skin hydration and dermal loading, and to better understand the potential for differences in the effects on dermal loading by gender.

Additionally, the data collected in this study focused on only one type of motion of contact, which was defined as one or more press events between the skin and various other compartments such as the source, other skin surfaces, other working surfaces, gloves, or clothing. A comparative analysis by compartment to understand the potential for differences with different motions, such as swipes, smudges, or other grips, could be important to better understand the quantitative transfer in the dermal conceptual model. While at least one study identified a statistically significant difference in loading between

different contact motions, an upper bound for human skin loading was also identified in a comprehensive literature review regardless of the motion of contact among the studies and was consistent with the conclusions of other researchers.

The focus of this study was to explore the characteristics of dermal loading on human skin *in vivo*. To date, very few studies have evaluated the total quantitative transfer and the relative transfer between the identified potential pathways of exposure, and therefore little is understood about the relative importance of these different compartments for different scenarios and substances. Additional studies are needed for a wide range of different types of substances with varying physical-chemical properties to better characterize the importance of these pathways and compartments.

Finally, the use of default loading data to estimate dermal loading on human skin for dermal exposure assessment purposes should be carefully examined regarding their relative accuracy against the results of assessments for scenarios with specific, measured dermal loading data. This analysis is also likely to require a modification of the current models used for dermal exposure assessment purposes, as these models currently do not account for determinants such as: repeated contacts in a manner consistent with the available data, the potential effects of skin hydration, or the potential for effects related to the motion or nature of contact. The results of this study and other relevant published data point the potentially significant influence of these determinants in assessing dermal loading and ultimately dermal exposure and risk.

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Appendix A: A Brief Summary of Semi Quantitative and Quantitative Methods for Assessing Dermal Exposures

Source	Model Description	Model Type	Application	Consideration of Quantitative Dermal Loading or Transfer Data?
US EPA, 1992	Provides an introduction to the science of dermal exposure assessment, key mechanisms and models of dermal exposure and uptake, and measurement techniques for dermal uptake (including in vivo and in vitro methods).	Deterministic; physical properties-based	Dermal exposure and risk assessment for chemicals in water or soil	Yes
Brouwer et al., 1994	Estimation method for long-term dermal and inhalation exposure to pesticides using information on mixing and loading methods, application methods, acreage of application, number of applications, number of containers handled, and exposure protection methods.	Knowledge-based approach to determining duration, frequency, and intensity	Estimation of exposure to pesticide applicators	No; semi-quantitative indices considered
Cleek and Bunge; Bunge and Cleek, 1992 and 1995	Methods for evaluating dermal uptake that consider exposure time and chemical properties of the compound of interest; the effects of chemical concentration, molecular weight, and octanol-water partitioning on dermal uptake.	Deterministic; physical properties-based	Modeling of dermal uptake using chemical properties	No
Leung and Paustenbach, 1994	Review of available methods for estimating dermal exposure and uptake of chemicals for risk assessment purposes in soil, in water, as neat liquids, and as vapors.	Deterministic; physical principals and properties-based	Dermal exposure and risk assessment for chemicals	Yes

Source	Model Description	Model Type	Application	Consideration of Quantitative Dermal Loading or Transfer Data?
Wilschut, Ten Berge, Robinson, and McKone, 1995	Review and validation of five different approaches to estimating skin permeation through modeling, including the revised Robinson model.	Physical principals and properties-based	Modeling of dermal uptake using chemical properties	No
EASE (Estimation and Assessment of Substance Exposure), 1996	Screening tool for regulatory risk assessments for new chemicals.	Screening model; knowledge-based	Chemical risk assessment screening method for inhalation and dermal exposures	Yes
Schneider et al. 1999	Conceptual model of all potential mechanisms of skin contact and a detailed, standardized approach to assessing and quantifying dermal exposure.	Conceptual model	Quantifying the total contaminant concentration on the surface of the skin for a specific exposure scenario	No
CONSEXPO (Consumer Exposure Model) (van Veen, 2001 and Bremmer, 2006)	To evaluate consumer exposures to chemicals typically found in different types of consumer products.	Combination of knowledge-based and physical properties-based	Dermal exposure and risk assessors	Yes

Source	Model Description	Model Type	Application	Consideration of Quantitative Dermal Loading or Transfer Data?
McDougal and Boeniger, 2002	Detailed review of the available methods for dermal risk assessment and mathematically evaluated the mechanisms of dermal uptake.	Physical principal and properties-based	Quantitative dermal risk assessment	Yes
Van Wendel de Joode et al. 2003	Semi-quantitative dermal exposure estimation model, a structured approach to dermal exposure assessment based on the conceptual dermal exposure model developed by Schneider et al.(1999).	Semi-quantitative knowledge-based; scenario-based source receptor *type model*	Semi-quantitative dermal exposure assessment for liquids and solids	No; semi-quantitative indices considered
Oppl et al. 2003 (Toolkit for Dermal Exposure Risk Assessment and Management or RISKOFDERM)	Interactive dermal risk assessment approach for evaluating both systemic and local toxicity following dermal exposure, using a decision tree method to assist the user in evaluating dermal risks for individual scenarios.	Knowledge-based; scenario-based source receptor *type model*	Small to medium-sized business owners and other individuals without expertise in exposure and risk assessment (approved for risk assessments associated with REACH)	Yes

Source	Model Description	Model Type	Application	Consideration of Quantitative Dermal Loading or Transfer Data?
The European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC) Targeted Risk Assessment (TRA) ECETOC TRA, 2004	Based on the EASE model, and modifies the data based on user inputs. Both RISKOFDERM and TRA are considered Tier I models, which are meant to provide screening-level, conservative exposure estimates. A validation of this model has been performed for use in dermal exposure modeling.	Screening level model; scenario-based source receptor *type model*	Dermal exposure and risk assessors	Yes
U.S. EPA, 2004	Summarizes available methods for quantitative dermal risk assessment for chemicals in water and soil and provided data for use in estimating risk when experimental or site-specific data are not available.	Physical principal and properties-based	Environmental site risk assessments	Yes
Registration, Evaluation, Authorization, and Restriction of Chemical (REACH) and DNELs, 2006	Under REACh, a key objective of the human health hazard assessment is to determine Derived No-Effect Levels (DNELs). Dermal exposure assessments are typically qualitative due to the paucity of validated measured methods, and so many registrants turn to models to produce their (semi) quantitative dermal exposure estimates, including RISKOFDERM and ECETOC TRA.	Screening-level model; physical principal and properties-based	Dermal exposure and risk assessors	No; semi-quantitative indices considered

Source	Model Description	Model Type	Application	Consideration of Quantitative Dermal Loading or Transfer Data?
Stoffenmanager, 2008	Interactive, web-based risk banding approach developed in the Netherlands by Arbo Unie and TNO that combines hazard banding (similar to COSHH Essentials) with exposure banding, including for dermal exposure assessment through RISKOFDERM, and has been approved for first tier REACH assessments.	Semi-quantitative knowledge-based; scenario-based source receptor *type model*	Interactive chemical risk assessment tool designed for use by small and medium-sized businesses	Yes
NIOSH, 2009	Summarizes methods for qualitatively assessing dermal hazards, including systemic, local, and sensitization hazards; provides a qualitative summary of the dermal contact hazards for specific chemicals; provides a framework for generally classifying dermal hazards.	Screening-level model; qualitative	Qualitative classification of the dermal hazards	No
AIHA, 2009	Provides models for the estimation of dermal exposure and uptake, including approaches that allow for the consideration of evaporation from the skin surface, and potential for loading and uptake.	Physical principal and properties-based	Occupational health and public health professionals	Yes
COSHH Essentials, 2003; 2010	Interactive risk assessment tool (from the U.K. Health and Safety Executive or HSE) for analyzing hazards from chemicals and chemical mixtures; tool is not specific to dermal exposures, but all routes of entry and exposure sources are considered.	Semi-quantitative knowledge-based model	Designed for use by small to medium-sized business owners and other individuals without expertise in exposure and risk assessment	No

Source	Model Description	Model Type	Application	Consideration of Quantitative Dermal Loading or Transfer Data?
U.S. EPA, 2010 (The Chemical Screening Tool for Exposures and Environmental Releases or ChemSTEER)	ChemSTEER is an interactive tool that to evaluate occupational inhalation and dermal exposure to a chemical during industrial and commercial manufacturing, processing, and use of a chemical.	Scenario-based source receptor *type model; p*hysical principal and properties-based	Dermal exposure and risk assessors	Yes
U.S. EPA, 2011 (Exposure Factors Handbook)	Summarizes basic methods and key defaults for conducting dermal exposure assessments and provides available quantitative data for assessing skin surface area and other key exposure assessment parameters.	Physical principal and properties-based	Dermal exposure and risk assessors	Yes
IH SkinPerm (Tibaldi, ten Berge, Drolet 2014)	Interactive estimation tool available from the AIHA for calculating dermal uptake for certain chemicals (additional chemicals with known properties can be added) using the revised Robinson model.	Physical principal and properties-based	Dermal exposure and Risk assessors	Yes
U.S. EPA, 2017 Stochastic Human Exposure and Dose Simulation (SHEDS)-Multimedia and Integrated Exposure Uptake and Biokinetic (IEUBK) Model	The SHEDS model is an exposure-dose modeling approach that can be used to determine the relationship of drinking water lead concentrations to blood lead, taking into consideration potential exposures from water, soil, dust, food, and air.	Probabilistic model; physical principal and properties-based	Dermal exposure and risk assessors	Yes

Source	Model Description	Model Type	Application	Consideration of Quantitative Dermal Loading or Transfer Data?
Dermal Advanced Reach Tool (ART), 2019	Tier 2 exposure modelling tool that is currently in development for evaluating dermal exposure to the hands (mg min^{-1}) for non-volatile liquid and solids-in-liquid products. The model uses information about the scenario to calculate a unitless score for prediction of exposure for the scenario of interest. The three key mass transport values used in the model include deposition, direct contact (or emission), and contact transfer for various liquid scenarios.	Semi-quantitative knowledge-based; scenario-based source receptor *type model*	Dermal exposure and risk assessors	Yes
U.S. EPA, Consumer Exposure Model (CEM), 2019	The Consumer Exposure Model (CEM) retains six existing models from the E-FAST model and adds fifteen additional models. It incorporates seven dermal models.	Combination of knowledge-based and physical properties-based	Dermal exposure and risk assessors	Yes

(USEPA 1992; Bunge et al. 1995a; Bunge et al. 1995b; Cleek et al. 1993; Leung et al. 1994; Brouwer et al. 1994; USEPA 2011; Schneider et al. 1999; McDougal et al. 2002; Van-Wendel-de-Joode et al. 2003; Goede et al. 2003; Oppl et al. 2003; van Hemmen et al. 2003; Hughson et al. 2004; USEPA 2004; NIOSH 2009; Garrod et al. 2003; Marquart et al. 2008; USEPA 2013; Goede et al. 2019; Gorman Ng et al. 2012a; McNally et al. 2019; Tielemans et al. 2011; Marquart et al. 2017; Zartarian et al. 2017; Warren et al. 2006; Williams et al. 2011; Sahmel et al. 2009; Keil et al. 2009; Wilschut et al. 1995; Marquart et al. 2003; Creely et al. 2005; Bremmer et al. 2006; Warhurst 2006; Koontz et al. 2006; Tibaldi et al. 2014; USEPA 2019)

Appendix B: Dermal Exposure Modeling Determinants

Using semi-quantitative or quantitative dermal exposure determinants, a task-based dermal exposure assessment model can be expressed as (Keil et al. 2009):

$$D = S \times Q \times WF \times FQ \times ABS \quad \textbf{(Eq. B-1)}$$

where: D = dermal uptake (μg/day), S = surface area of contact (cm^2), Q = amount of substance loaded or retained on the skin (μg/cm^2), WF = concentration or weight fraction of the material of interest in the substance (percent by weight), FQ = number of repeated contact events per day or total duration of task, and ABS = absorption (complete absorption or a fractional default absorption value is sometimes used, or empirically derived data may be used) (Sahmel et al. 2015a; Sahmel et al. 2009; McDougal et al. 2002). The U.S. EPA has proposed a similar model (USEPA 2013). For each of these determinants, there are often default parameter data sources available for use in the absence of environmental or scenario-specific data.

Surface Area (S)

Surface area (S) available for contact can be estimated using sources such as the U.S. EPA's Exposure Factors Handbook, such as 1,070 cm^2 for the surface area of both hands (USEPA 2011). Another useful estimate for dermal exposure assessment is the surface area of the first two fingertips and the tip of the thumb, and this surface area has been determined to be between approximately 11-17 cm^2 for females and 14-19 cm^2 for males (OEHHA 2008; COEHHA 2011; Sahmel et al. 2015b; Cherrie et al. 2006). The skin surface area of contact through hand to mouth exposure has been estimated to be approximately 10-20 cm^2 (Cherrie et al. 2006; USEPA 2012). A potential complexity of estimating skin surface area is the issue of loading density; for example, assuming uniform loading across the entire skin surface area of both hands may be an inaccurate assessment of the relevant skin surface area. It is more likely that specific areas of the skin surface (i.e., fingertips or the side and base of the palms) are the skin surface areas with the greatest density of loading (Brouwer et al. 1999; Vermeulen et al. 2002). It has also been reported that the variability from one day to the next in skin surface area of exposure can be relevant for a specific body location, is less likely to be relevant to the total exposure over all relevant surface areas (Kromhout et al. 2001; Vermeulen et al. 2002).

Loading on the Skin (Q)

The loading on the skin, Q, or transfer efficiency can be estimated using default data published or relied upon by the U.S. EPA, the California OEHHA, and other researchers for certain types of agents or scenarios (USEPA 2011; COEHHA 2011; Finley et al. 1994; Cinalli et al. 1992; Camann et al. 2000b; Clothier 2000b; Clothier 2000a; Edwards et al. 2001; Gorman Ng et al. 2012a; IOM ND; Kissel et al. 1998; Rodes et al. 2001; van Wendel de Joode et al. 2005b; van Wendel de Joode et al. 2005c). The U.S. EPA has previously provided default loading (Q) values for adherence due to direct contact of between 1 and 3 mg/cm^2, based on experimental data (USEPA 2013; Brouwer et al. 1999; EPA 2011). In 1992, the EPA also reported a mean range of dermal loading values for soils between approximately 0.2 and 1.5 mg/cm^2, or according to Finley et al. (1994), up to a 95th percentile value of 1.7 mg/cm^2 (EPA 1992; Finley et al. 1994). Values reported in the U.S. EPA's Exposure Factors Handbook (2011) for dermal surface loading of solids are in the range of approximately 0.0063 – 0.66 mg/cm^2 for adults (EPA 2011). The U.S. EPA also reported in 1996 that occupational dermal exposures following intermittent contact were in the range of 0.54 to 9.02 µg/cm^2 (0.00054 – 0.009 mg/cm^2) for liquid film contamination (USEPA 1996). Default loading data for dermal exposure to the hands was also investigated during the development of the RISKOFDERM model (Marquart et al. 2006). The authors reported default values for dermal loading of solids (assuming the surface of the hands was 830 cm^2) of 14 mg/cm^2 for loading and filling large containers or mixers, and 0.005 mg/cm^2 for careful mixing of small quantities (Marquart et al. 2006).

Weight Fraction (WF)

The weight fraction (WF) can also be relatively simple to estimate, and a helpful approximation for the purposes of simplicity could be to assume that the mass of a substance of interest for dermal uptake is proportional to the concentration of the substance in a known mixture; if exposure to a neat chemical is of interest, the WF would equal 1 (Sahmel et al. 2009). Caution must be applied, however, to using this approach in scenarios where a substance is present in a non-ideal mixture, as the properties of the mixture components and their relative chemical activity can affect the potential for and rate of dermal absorption (Sahmel et al. 2009; Williams et al. 2011; Fransman et al. 2011).

Frequency of Contact (FQ)

The frequency of contact (FQ) can be estimated using an assumption that dermal loading on the skin is additive for each subsequent contact with an agent of concern (known as the additive loading model) and then the number or frequency of contacts can be readily estimated through observation; however, data are also available in the

published literature which indicate that FQ may reach a limit with respect to amount loaded before transfer stops or even reverses (Brouwer et al. 1999; Hubal et al. 2008). The EASE model provided recommendations for default FQ values of incidental contact (one event per day), intermittent contact (2-10 events per day), and extensive contact (more than 10 events per day) (Brouwer et al. 1999). Such an approach assuming additive loading should be used with caution based on the literature pointing to numerous scenarios that do not exhibit additive loading; perhaps not surprisingly, it has also been noted that the EASE model has been found to substantially overestimate actual dermal loading, perhaps due in part to the use of default frequency values (Creely et al. 2005).

Absorption (ABS)

Absorption (ABS) can be estimated or measured; sometimes an assumption of 100% dermal absorption or some fractional percent absorbed is assumed, or, preferably as noted above, as an empirical dermal flux or uptake value from the literature for a specific agent, typically expressed in units of μg/cm^2-hour (Frasch et al. 2014; McDougal et al. 2002). The fractional absorption or percent absorbed approach has been advocated and used by a number of public health and regulatory agencies such as the U. S. EPA, the U.S. Army, the Department of Homeland Security, and NIOSH, as well as the European Community, because of its relative simplicity and its potential to provide a reasonable estimate of uptake in finite dose scenarios. But there can be significant limitations to the use of percent absorbed as a default or surrogate for measured or estimated flux values, and such estimates can result in significant error in risk assessment estimates (dermal penetration rates) (Spalt et al. 2009; Frasch et al. 2014). A number of studies have also reported an inverse relationship between dermal loading and fractional absorption (Buist et al. 2009; Kissel 2011). This is likely because in practice, and particularly for immersion scenarios or scenarios where loading on the skin is high, the relative percent or fraction of a substance that is absorbed will decrease as the amount of dermal loading increases, and then will change over time as the amount loaded on the skin is reduced (or is re-loaded at a higher amount) and therefore is not constant (Frasch et al. 2014).

Appendix C: Measurement of Dermal Transfer or Loading

There are three key types of skin sampling methods that are commonly used.

1. Surrogate Skin Sampling Techniques for Skin Surface Loading

The first of these is surrogate skin sampling techniques, in which a sampling medium is placed against the skin and used to intercept the agent of interest. These surrogate or interception methods rely on certain assumptions, including that the loading on the sampler or patch will accurately represent loading across all potentially affected skin surfaces, and that the collection efficiency of the sampling medium used will accurately represent the collection efficiency of human skin in vivo (Fenske 1993; Boeniger et al. 2015; Soutar et al. 2000; van Wendel de Joode et al. 2005a; Makinen et al. 2004a; Boeniger et al. 2002). Such methods will need to be tested to understand both the relative collection efficiency and retention efficiency compared to human skin (Boeniger et al. 2015). Therefore, while such surrogate methods may provide a useful index of exposure, they may not accurately represent the loading or collection of the agent on human skin (Schneider et al. 2000). For example, cotton gloves as a surrogate sampler have been demonstrated to considerably overestimate the adherence of many agents to human skin (Linnainmaa et al. 1997; Day et al. 2007; Brouwer et al. 1999; Roff et al. 2002; Edwards et al. 1999; Ramwell et al. 2006; Krieger et al. 2000; Lansink 1996; Tsakirakis et al. 2018; Weschler et al. 2015).

2. Direct Removal Techniques from the Skin Surface

The second method of direct skin sampling includes removal methods such as hand wiping, skin washing and tape stripping. Care must be taken when using such techniques to characterize removal efficiency, since uptake into the skin by agents of interest can often occur before direct sampling methods are employed for removal, and may result in an incomplete exposure picture (Boeniger et al. 2015; Fenske 1993; Brouwer et al. 2000). Brouwer et al. (2000) identified two distinct techniques for hand sampling, including hand washing and hand wiping (or surface skin sampling). Regarding skin washing removal methods, the authors defined two primary approaches: (1) handwashing, defined as “scrubbing the skin by mechanical agitation” in which the agent of interest is removed from the skin by a combination of mechanical force and dissolution; and (2) hand rinsing, defined as liquid skin contact, in which the agent of interest is removed using dissolution methods only (Brouwer et al. 2000). Examples of dissolution agents include water, soap and water, commercially available surfactants, or organic solvents such as ethanol or isopropanol (Brouwer et al. 2000; Marquart et al. 2002; Fenske et al. 1998; Davis et al. 1983). Regarding hand wiping or skin sampling, various researchers have indicated that different methods have been employed, including wipe materials such as filter paper, cotton, creped cotton, and other wiping

materials with specific roughness, porosity, or friction characteristics to assist in the removal of agents from the skin. These wiping materials can be used dry or wetted with a number of different agents to enhance removal, such as surfactants, water, or organic solvents (Brouwer et al. 2000; Boeniger et al. 2015).

Tape stripping can be an effective method of direct removal, as it combines the removal of agents both on the surface and in the stratum corneum (Cullander et al. 2000; Dickel et al. 2010; Dreher et al. 1998; Ahlstrom et al. 2019; Jacobi et al. 2005b; Lademann et al. 2006; Lademann et al. 2009; Loffler et al. 2004; N'Dri-Stempfer et al. 2009; Weigmann et al. 2005). Multiple authors have noted that the typical standard procedure for tape stripping involves the use of adhesive films of varying types that are applied and then removed successively from the skin in the same defined area (Lademann et al. 2009; Dickel et al. 2010). Lademann et al. (2009) reported that different methods have been employed for the determination of the amount of stratum corneum removed with each tape strip, and that the first tape strips often contain nearly a complete cell layer of the outer stratum corneum (Lademann et al. 2009). Other researchers have noted that the entire stratum corneum can be removed in no more than 20-25 tape strips, although at least one study has reported that it may take as many as 50 tape strips (Belsey et al. 2011; Hostynek et al. 2001a; Hostynek et al. 2001b; Jacobi et al. 2005b; Dreher et al. 1998).

In summary, hand washing, hand wiping, and tape stripping are the primary methods of direct skin measurement that have been employed in the literature to date, and more specific information regarding the use of these methods will be discussed below.

3. In Situ or Direct Reading Techniques for Skin Loading

The third method of direct skin sampling includes in situ methods, such as fourier transform infrared spectrometry (FTIR) with horizontal attenuated transfer reflectance (HATR) platform, as well as portable X-ray fluorescence spectrometry, fluorescent tracers, and colorimetric indicators (Boeniger et al. 2015). These methods can be used both qualitatively and quantitatively (Cherrie et al. 2000; Hautemaniere et al. 2009). The qualitative use of fluorescent tracers can be an effective training technique for workers to help limit dermal transfer and skin contamination, and if quantitative results are desired, video imaging can also be used to determine the changes in intensity of fluorescence with exposure to the skin and to estimate quantitative dermal exposure (Fenske 1993; Cherrie et al. 2000; Aragon et al. 2006; Brouwer et al. 1999; Cohen Hubal et al. 2005; Fenske et al. 2002; Ivancic et al. 2004; de Joode et al. 2007).

Appendix D: Supplemental Information on Scenarios Evaluated by Participants

Dermal Scenario Number: 1

Dermal Scenario Description:
Employees at a foundry work with a cured phenol-containing molding compound. The molding compound contains two parts that are mixed together to react and create the final resin.

Task:
Workers reach into the oven, pull out the cured mold, and then file the mold to remove any residual molding compound. Finally, they stack the mold and then repeat the process. It takes approximately 30 seconds to remove, file, and stack each mold. The worker continually repeats the process over the work shift.

Environmental conditions:
A fine yellow-orange powder is created from filing of the molds. The worker wears mid-forearm heat resistant gloves.

Agent Characterization:
According to the SDS:
1-5% phenol (CAS #108-95-2)
10-30% diisocyanate (CAS 101-68-8)
10-30% mixture succinate, glutarate, adipate

Physical Property	Value/Description
Chemical formula	C6H6O
Molecular weight	94.11 grams/mole
Physical appearance & state	Hazy liquid
Solubility (water)	8.28x10+4 mg/l @ 25 deg C
Log Kow	1.46
Vapor pressure	0.35 mm Hg @ 25 deg C

Dermal Scenario Number: 2

Dermal Scenario Description:
Employees at an aerospace manufacturing facility make component parts for aircraft jet engines out of advanced composites using form molding and manual lay-up procedures

Task:
Workers construct aircraft parts and components using a fiberglass cloth impregnated with a liquid polyimide-MDA resin. The liquid resin is blended as needed with 12.5% MDA content. The work involves manual lay-up using molds to press the layers of cloth into the desired shape. Large parts can take hours to create.

Environmental conditions: The PPE distributed to workers was reportedly primarily to protect the product rather than personnel.

Agent Characterization:
4,4-Methylenedianline (CAS 101-77-9)

Physical Property	**Value/Description**
Chemical formula	C13H14N2
Molecular weight	198.27
Physical appearance & state	Pale yellow crystalline solid
Solubility (water)	Poorly soluble in water (1 g/L at 25°C)
Solubility (organics)	Very soluble
Log Kow	1.59-2.24
Vapor pressure	2.15 x 10-7 mm Hg at 25°C; 1 mm Hg at 197°C

Dermal Scenario Number: 3

Dermal Scenario Description:
Routine maintenance of pipes during shut-downs and start-ups at a petrochemical plant. Pipes containing pyrolysis gasoline are drained and rinsed prior to maintenance but not steam cleaned.

Task:
Placement of partition components into pipes involves draining of the pipes, breaking into the pipeline by opening the pipe, and adding partition components. Opening of pipes occurs approximately 4-6 times per 8-hour shift.

Environmental conditions: Work performed in an outdoor environment; gloves and respirators were not worn.

Agent Characterization:
Benzene CAS# 71-43-2

Physical Property	**Value/Description**
Chemical formula	C6H6
Molecular weight	78.1
Physical appearance & state	Colorless to light yellow liquid
Solubility (water)	Poorly soluble in water (0.07 g/L at 25°C)
Solubility (organics)	Very soluble
Log Kow	2.13 at 25°C
Vapor pressure	75 mm Hg at 25°C

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