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Rapid Review of Dermal Penetration and Absorption for Inorganic Lead Compounds for Occupational Risk Assessment

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Abstract

Lead (Pb) exposure continues to be a significant public health issue in both occupational and non-occupational settings. The vast majority of exposure and toxicological studies have focused on effects related to inhalation and gastrointestinal exposure routes. Exposure to inorganic Pb compounds through dermal absorption has been less well studied, perhaps due to the assumption that the dermal pathway is a minor contributor to aggregate exposures to Pb compounds. The aim of this rapid review was to identify and evaluate published literature on dermal exposures to support the estimation of key percutaneous absorption parameters (K_p, flux, diffusion rate) for use in occupational risk assessment. Eleven articles were identified containing information from both *in vitro* and *in vivo* systems relevant to percutaneous absorption kinetics. These articles provided 24 individual study summaries and information for seven inorganic Pb compounds. The vast majority of study summaries evaluated (n=22, 92%) reported detectable amounts of dermal absorption of inorganic Pb. Data were identified for four Pb compounds (Pb acetate, Pb nitrate, Pb oxide, and Pb metal) that may be sufficient to use in evaluating physiologically-based pharmacokinetic (PBPK) models. Average calculated diffusion rates for the pool of animal and human skin data ranged from 10^{-7}–10^{-4} mg/cm^2/h, and K_p values ranged from 10^{-7}–10^{-5}cm/h. Study design and documentation was highly variable, and only one of the studies identified was conducted using standard test guideline-compliant methodologies. Two studies provided quality estimates on the impacts of dermal absorption from water insoluble Pb compounds on blood Pb levels. These two studies reported that exposures via dermal routes could elevate blood Pb by over 6 μg/dl. This estimation could represent over 100% of 5 μg/dl, the blood Pb associated with adverse health effects in adults. The utility of these estimates to occupational dermal exposures is limited because the confidence in the estimates is not high. The literature, while of limited quality, overall strongly suggests inorganic Pb has the potential for dermal uptake in meaningful amounts associated with negative health outcomes based on upper bound diffusion rate estimates. Future standard test guideline-compliant studies are needed to provide high confidence estimates of dermal uptake. Such data is needed to allow for improved evaluation of Pb exposures in an occupational risk assessment context.

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Keywords

Lead; Pb; dermal exposure; review; occupational; percutaneous absorption; dermal penetration; metals; inorganic lead; lead acetate; lead nitrate; lead metal; lead oxide; lead sulfate; lead ortho-arsenate; lead subacetate

Introduction:

Adverse health outcomes associated with Pb exposure are well established and include variety of effects at low levels of exposure including cardiovascular, kidney, neurological effects, and reproductive and developmental effects in pregnant women with blood lead levels below 5 μg/dL (NTP 2012, Lanphear et al. 2018). Annually, as many as 1.5 million workers are exposed to lead (Pb) in the workplace in the U.S. (ATSDR, 2021). Skin contact is a significant exposure route in the workplace and understanding this exposure pathway's overall contribution to body burden is necessary for a full aggregate occupational risk assessment. The need for dermal exposure and uptake information is likely to increase; regulatory focus on inhalation and oral exposure to Pb has increased exposure mitigation by these exposure routes. Over time, the dermal pathway may represent a greater proportional contribution of aggregate or combined route occupational dose (OSHA, 1978; Julander et al., 2020). Additionally, industrial uses of lead compounds include workplaces such as battery manufacturing, refineries, and construction where other contributing factors, such as heat load and skin abrasions, may increase the potential for dermal absorption of lead (NIOSH 2016, Filon et al. 2006) Identification and evaluation of the available data on dermal Pb exposures and Pb uptake from the dermal route is a key step to understanding the role of dermal exposures on body burden for improving occupational risk assessments.

Pb compounds exist in both organic and inorganic forms with most current occupational exposures coming from inorganic Pb compounds (ATSDR 2020). Inorganic Pb exist in three oxidation states of +0, +2, and +4, and exist in metallic, oxides, salts, and soap forms. Pb compounds are the most common in environmental exposures (ATSDR, 2020). However, inorganic Pb^{+4} compounds are also relevant for risk assessment, particularly for Pb in drinking water attributed to the release of Pb directly from pipe materials and Pb-containing solder (Wang et al., 2010). Additionally, most organic Pb compounds, including tetraethyl Pb, have the +4-oxidation state (ATSDR, 2020). Occupational uses and water solubilities of Pb compounds identified in this review are provided in Table 1.

The toxicokinetic behavior associated with oral and inhalation inorganic Pb exposures are well described (Sweeney, 2021; ATSDR, 2020; Vork and Carlise, 2020; NTP, 2012; O'Flaherty, 1993; Leggett, 1993; Kehoe, 1987) However, very few studies have evaluated dermal penetration (passive diffusion of a compound through the skin barrier) and dermal absorption (diffusion into skin layers that may become available for systemic distribution) of inorganic Pb compounds. The kinetics associated with dermally absorbed inorganic Pb compounds are largely unknown. Although physiologically-based pharmacokinetic (PBPK) models have been published for the estimation of blood Pb levels through inhalation and oral exposure routes, the contribution of dermal exposure to body burden has not been included in these models (Leggett, 1993; O'Flaherty, 1993; Vork and Carlisle, 2020; Sweeney,

2021). The focus of the scientific community on inhalation and oral exposures to Pb is understandable as these routes are likely the largest contributors of historical aggregate exposures (ATSDR, 2020).

To our knowledge, there are only a few studies have attempted to evaluate the kinetics of inorganic Pb absorption through the skin, including the fundamental percutaneous zero-order rate constants (K_p cm/h), flux (Jss; mg/cm^2/h), diffusion rate, and the first-order rate constant (Ka; h^{-1}). K_p represents the rate at which a chemical penetrates through the skin (cm/h) (EPA, 1992). Flux refers to the amount of chemical absorbed across a defined surface area of the skin per unit time (mg/cm^2/h), at steady state conditions, (EPA, 1992) and is the permeability coefficient multiplied by the test compound concentration in the vehicle applied to the skin:

Flux (mg/cm^2/h) = K_p *(cm/h) × concentration (mg/cm^3) (at steady state).*

Diffusion rate is calculated using the same formula above, however the calculate value does not assume steady state absorption:

Diffusion rate (mg/cm^2/h) = K_p *(cm/h) × concentration (mg/cm^3) (at non-steady state)*

These rate constants are essential for determining human risks associated with dermal Pb exposures, since they enable estimation of systemic Pb doses (i.e., internal) resulting from skin deposition. In the absence of this knowledge, systemic Pb doses attributable to dermal exposure are highly uncertain. As a result, the risk from dermal Pb exposures are evaluated based on assumptions rather than scientific data.

The primary objective of this paper was to identify and evaluate published articles on dermal absorption kinetics of inorganic Pb, and to evaluate their utility for pharmacokinetic modeling such as, whether the studies were conducted according to standardized test guideline-compliant methods (EPA, 1992, 1998, 2007; OECD, 2004a, 2004b, 2011; EFSA 2012) and if tissue compartment specific data were collected over multiple time points. Where possible, the fundamental percutaneous rate constant (K_p; cm/h), flux (Jss; mg/cm^2/h) (steady state), diffusion rate (mg/cm^2/h) (non-steady state) and the dermal absorption rate constant (Ka h^{-1}) were catalogued or calculated using the available study data. A secondary objective of this effort was to summarize Pb concentrations in organ tissues after dermal dosing of lead compounds to evaluate the evidence of Pb absorption through the skin.

Methods:

A rapid review methodology was used to identify and evaluate literature related to the dermal exposure of inorganic Pb. First, a search was conducted in ChemIDPlus (2021) to identify inorganic Pb species and Chemical Abstract Service Registry Numbers (CAS RN) (Supplemental Table S1). The chemical structure of the Pb species were evaluated to remove from this review all organic Pb compounds. Next, a search strategy was developed to identify scientific literature related to dermal exposures (Supplemental Table S2). Using Pubmed, three literature searches were conducting, including: 1) CAS

identification numbers (CAS#) (Supplemental Table S1) with dermal exposure-related terms (Supplemental Table S2); 2) Inorganic lead species (Supplemental Table S1) names with the dermal exposure terms (Supplemental Table S2); 3) Lead [MESH] OR Lead poisoning [MeSH] OR "lead poisoning" OR "blood lead level" OR "lead intoxication" OR "lead toxicity" OR "Plumbism" OR "Saturnism" OR "lead exposure" OR "lead hazard" with the dermal exposure terms (Supplemental Table S2). The search strategy was conducted in the National Library of Medicine Pubmed in May 2017 with no date restrictions on the literature search. A follow-up literature search was conducted in May 2021 to identify additional articles published since the first literature search.

Two analyses were conducted to filter the results obtained from the PubMed searches. In the first analysis, references and abstracts were downloaded into Abstrackr (Wallace et al., 2012) and repeats were deleted. All abstracts were manually screened by the same researcher, applying the inclusion and exclusion criteria listed below. In a second level of literature analysis, references that met the inclusion criteria were downloaded for a full review of manuscript text. Articles were then categorized into human and animal experimental studies. Several methodological and result parameters were collected from identified articles to identify relevant data to determine whether rates of dermal penetration of inorganic Pb species across human skin could be determined. Study methodologies were evaluated to compare to standard test guideline-compliant methods (EPA, 1992, 1998, 2007; OECD, 2004a, 2004b, 2011; EFSA 2012). Where available, relevant data for PBPK modeling efforts to better elucidate the impact of dermal Pb exposure on systemic Pb distribution was collected or calculated, including documentation of K_p and flux values or tissue compartment specific data collected over multiple time points. If the study did not determine a permeation rate at steady state conditions, a diffusion rate was calculated instead of flux. The assessment of the full text and data extraction were completed by the same researcher. All three researchers collaborated to evaluate data against the guidelines and synthesize the findings. Calculations for K_p, flux, and diffusion rates, based on data identified in the articles, can be found in the supplemental materials. Where available, K_p, flux, and diffusion rates found in the literature are also provided and referenced accordingly.

Inclusion and Exclusion Criteria Inclusion and exclusion criteria were applied for an initial screening review of using the abstract of each study, including.

Inclusion criteria: experimentally based dermal penetration studies of any inorganic lead species in humans or animals (*in vivo* or *in vitro*).

Exclusion criteria: 1) studies in languages other than English; 2) organic lead penetration/absorption data; 3) studies that did not identify the species of lead; 4) cell culture studies (*in vitro*); 5) case studies and studies with no variability determinants (i.e., where only one participant was evaluated in one trial); 6) studies where exposure dose was unknown, and studies where the route of exposure was not controlled.

RESULTS:

The literature identification and evaluation process included 1,419 abstracts screened, with 98 publications reviewed. Eleven articles were selected for inclusion in this review

containing data for seven inorganic Pb compounds. Since most of the articles provided results for different experimental conditions (e.g., multiple animal species tested) or multiple Pb compounds tested within the same publication, the results below are reported as study summaries (n=24).

Pb compounds identified in this paper include, Pb acetate, Pb nitrate, Pb oxide, Pb metal, Pb subacetate, Pb orthoarsenate, and Pb sulfate. Over $4.4.5\times10^{8}$ kg of these Pb materials are manufactured in the U.S. per year (ATSDR 2020) and are used in a variety of industries such as manufacturing of plastics and batteries, dyes, coatings and pigments, among other uses (Table 1).

A summary table of percutaneous absorption parameters that were calculated or identified in the literature are provided in Table 2. No articles identified dermal absorption rate constant ($Ka\ h^{-1}$). The predominant Pb compounds evaluated in the study summaries were Pb acetate (n=11, 46%) (Table 3), Pb oxide and Pb (11) metal (n=7, 29%) (Table 4), and Pb nitrate (n=3, 13%) (Table 5). Additional studies for other lead compounds (n=3, 13%) are provided in Table 6. Most studies were conducted in animals (or animal skin) (n=20, 83%) versus humans (or human skin) (n=4, 17%). Additionally, most studies were conducted *in vivo* (n=16, 67%).

The vast majority of study summaries (n=22, 92%) reported detectable levels of dermal absorption of inorganic Pb. Only 2 study summaries (8%) failed to show Pb absorption above the limit of detection. Both of these studies evaluated dermal absorption of Pb oxide and were conducted in *in vitro* systems using human and guinea pig skin (Bress and Bidanset, 1991). An in-depth review of all 24 study summaries showed that most suffer from one or more elements of inadequate experimental design, described in the summaries below, that fail to adequately quantify Pb absorption. Among these 24 study summaries, dermal absorption was reported for all seven inorganic Pb species, including both water soluble and water insoluble forms.

Only one study was conducted using a standard test guideline-compliant method (Julander et al., 2020).. This study dosed 4 different types of metal cutting fluids on *in vitro* stillborn pig skin using static Franz diffusion cells (Julander et al., 2020). The metal cutting fluids obtained from computer numeric controlled machines in a brass foundry operation contained up to 20% Pb metal. Pb was detected in washed skin and Franz cell receptor fluid. Based on data collected in this study using both worker exposure and the *in vitro* animal testing data, the authors estimated that skin absorption could contribute 3.3 – 6.3 μg/dl blood in this exposure scenario (Julander et al., 2020). In another study, percutaneous uptake of radiolabeled Pb acetate was demonstrated in rats in both a single dosing study (~2% uptake of applied dose) and multi-dosing study (~4% uptake of applied dose) (Pounds, 1979).

A summary of dermal penetration and absorption data for several Pb compounds is provided below.

Pb acetate

Eleven study summaries were identified for the potential of dermal penetration and absorption of Pb acetate, including both *in vitro* skin penetration and *in vivo* assays in multiple animal species and humans (Table 3). Percutaneous penetration parameters were calculated or identified in the literature for humans and three animal species (rats, mice, guinea pigs) (Table 2). K_P values ranged from 5×10^{-7}— 3×10^{-4} cm/h among humans and animal species data (Pounds, 1979; Moore et al., 1980; EPA, 1992; Hostynek, 2003; diffusion rates ranged from 1×10^{-6}—3×10^{-4} mg/cm^2/h (Pounds, 1979; Moore et al., 1980; Bress and Bidanset, 1991; Hostynek et al., 1993; EPA, 1992; Hostynek, 2003; Pan et al., 2010; Franken et al. 2015). This included one human *in vivo* study that demonstrated increased urine and whole body Pb levels after dermal dosing (Moore et al., 1980). An *in vivo* study in rats using radiolabeled Pb, estimated a percutaneous absorption rate of 2% and 4% in a single and multi-dosing study, respectively (Pounds, 1979). Two additional *in-vitro* penetration studies in human abdominal skin (undefined), full thickness mouse skin and guinea pig skin (undefined) detected Pb acetate in receptor fluid after either 10 or 24 hours of exposure (Bress and Bidanset, 1991; Pan et al., 2010).

Other results include *in vivo* studies conducted in two animal species, where authors reported significant ($p \leq 0.05$) increases in ALA-D and tissue doses (kidney, liver, muscle) of Pb and after dermal dosing of Pb acetate (Rastogi and Clausen, 1976; Pan et al., 2010; Fang et al., 2014). Three additional studies also suggested accumulation of Pb in tissues after dermal dosing, though these results were not statistically tested compared to controls (Kunze and Laug, 1948; Bress and Bidanset, 1991; Pan et al., 2010).

These studies suggests that Pb acetate has the potential to penetrate through the skin and result in measurable absorbed systemic doses. This conclusion is based on data for multiple animal species and dose accumulation data in serum and tissues. However, none of the studies identified were conducted using guideline-compliant methods leading to reduced confidence in quantitative percutaneous absorption related kinetic parameter estimates. The *in vivo* studies were not adequate for PBPK modeling efforts because they did not provide a fractional analysis of the dose applied, appropriate statistical analyses, or multiple time-point collections of tissue dose.

Pb monoxide and Pb metal

Pb monoxide

Four studies of Pb oxide dermal penetration and absorption were identified, including two *in vitro* penetration assays using human skin, and two *in vivo* studies conducted in guinea pigs or rats (Table 4). Two percutaneous absorption parameters were identified. Diffusion rate was calculated by Julander et al. (2020) to be 1.21×10^{-7} mg/cm^2/h in human skin based on Filon et al. (2006). Flux was also calculated by Hostynek et al. (1993) to be $<3\times10^{-5}$ mg/cm^2/h in guinea pig skin based on Bress and Bidanset (1991). Two human *in vitro* skin penetration studies were identified for Pb oxide. The first study used a static Franz cell under infinite dosing conditions using full-thickness skin (Filon et al., 2006). A second study using a J-diffusion tube method did not detect Pb oxide in the receptor solution after a 24

hr exposure period. One *in vitro* study dosed Pb oxide on guinea pig skin using a j-diffusion tube design also did not detect Pb above the limit of detection (Bress and Bidanset, 1991).

Other results include Pb concentration in urine was statistically significantly increased compared to controls following dermal dosing with Pb oxide in rats over a 12 day study (Sun et al., 2002). Another study, conducted in guinea pigs, evaluated Pb levels in several tissue compartments after a 7-day study (Bress and Bidanset, 1991). Though Pb was identified in blood, brain, liver, and kidney, the authors indicated that the Pb levels were similar to those found in control animals, but they did not provide a statistical comparison of Pb-exposed versus control animals (Bress and Bidanset, 1991).

These studies suggests that Pb oxide has the potential to penetrate through the skin and result in measurable absorbed systemic doses. However, none of the studies identified were conducted using guideline-compliant methods leading to low confidence in quantitative percutaneous absorption related kinetic parameter estimates. The two *in vivo* study were not adequate for PBPK modeling efforts because they did not provide a fractional analysis of the dose applied, appropriate statistical analyses, or multiple time-point collections of tissue dose (Bress and Bidanset, 1991; Sun et al., 2002).

Pb metal

Two studies evaluated dermal exposures of Pb metal (Table 4). Percutaneous absorption parameters were available including a range of diffusion rates from 1.1×10^{-7}—7.8×10^{-7} $mg/cm^2/h$ for stillborn pig skin (Julander et al., 2020) (Table 2). This range of values represents studies conducted using four metal cutting fluids in a static Franz diffusion cell under infinite dosing conditions according to OECD method 428 (OECD, 2004). Experiments were conducted for 2, 4, or 24 hrs. At the end of the experiments, concentration of lead in the skin was 2.11–10.9% of the amount dosed and 0.0001–0.004% in receptor fluid. Another study evaluated dermal absorption in rats (Sun et al., 2002). Pb concentration in urine was statistically significantly increased compared to controls by dermal dosing of Pb metal in rats over a 12-day study (Sun et al., 2002). The available study did not provide data that may be useful for pharmacokinetic modeling because it did not provide a fractional analysis of the dose of Pb applied or tissue dose in other compartments other than urine (Sun et al., 2002). Percutaneous absorption parameters could not be calculated based on this study (Sun et al., 2002).

These studies suggest that Pb metal has the potential to penetrate through the skin of multiple animal species and accumulate in organ tissues, however, only one of the studies identified were conducted using guideline-compliant methods (Julander et al., 2020). Neither of the studies identified accounted for the total mass balance of the Pb in the experimental systems. Mass balance is crucial for assessing the overall recovery of the administered dose. The *in vivo* study was not adequate for PBPK modeling efforts because they did not provide a fractional analysis of the dose applied, appropriate statistical analyses, or multiple time-point collections of tissue dose (Sun et al., 2002).

Pb Nitrate

Three studies were identified for the potential of dermal penetration and absorption of Pb nitrate, including both *in vitro* skin penetration and *in vivo* assays in multiple animal species (Table 5). Percutaneous absorption parameters were calculated based on the data in Pan et al. (2010) (Table 2). K_p values ranged from 5×10^{-7}—1.1×10^{-6} cm/h and diffusion rates ranged from 1.9×10^{-5}—4.3×10^{-5} mg/cm^2/h. In this study, Pb penetration was evaluated through full thickness and stratum corneum-stripped mouse skin using a static Franz cell methodology under infinite dosing conditions. Pb was detected in receptor fluid solutions in both full thickness and stratum corneum stripped skin (Pan et al., 2010)

Other results include in animal studies evaluating dermal absorption of Pb nitrate in mice and rats over multiple day exposures. Both studies detected an increase of Pb in different organ systems including skin, liver and kidney in the mouse study (Pan et al., 2010) and in urine for the rat study (Sun et al., 2002), however mass balance of the Pb in the experimental system was not documented.

These studies suggests that Pb nitrate has the potential to penetrate through the skin and result in measurable absorbed systemic doses. However, none of the studies identified were conducted using guideline-compliant methods leading to low confidence in quantitative percutaneous absorption related kinetic parameter estimates. Two *in vivo* studies were not adequate for PBPK modeling efforts because they did not provide a fractional analysis of the dose applied, appropriate statistical analyses, or multiple time-point collections of tissue dose.

Other Pb Compounds (Pb subacetate, Pb ortho arsenate, Pb sulfate)

Three additional studies were identified for other lead compounds and are summarized below

Pb subacetate

One human experimental study was identified in which Pb subacetate was painted onto the forearm of one female (age 25) volunteer and sampled by tape stripping after 20 minutes or 90 minutes (Table 6) (King et al., 1978). At both time points, Pb penetrated through all 4 layers of stripped stratum corneum with an increased concentration of Pb noted in the tape samples collected in the 90-minute sample. However, statistical inference testing was not performed to compare concentrations in different skin layers between the two time points (20 minutes and 90 minutes).

Data are inadequate to provide a conclusion regarding percutaneous absorption. The data set does not have a sufficient number of studies and the available data were collected using a non-standardized method. The one available study suggests that Pb subacetate may have potential to penetrate into the stratum corneum layers of human skin during a time period of 90 minutes, however this study was not conducted using a standard protocol and is not useful for PBPK modeling. Percutaneous absorption parameters could not be calculated based on this study (King et al., 1978).

Pb Ortho Arsenate

One study evaluated the dermal penetration of Pb ortho arsenate in animals *in vivo* (Table 6) (Kunze and Laug, 1948). Although this study was a controlled study in animals, no statistical analysis was completed to determine whether Pb detected in kidneys after exposures was significantly higher than control animals. The data are inadequate to provide a conclusion regarding percutaneous absorption. The data set does not have a sufficient number of studies and the available data were collected using a non-standardized method. This study did not provide data that may be useful for PBPK modeling (Kunze and Laug, 1948). Percutaneous absorption parameters could not be calculated based on this study (Kunze and Laug, 1948).

Pb Sulfate

One study was identified that evaluated the dermal penetration in rats (Table 6) (Sun et al., 2002). Pb concentration in urine was statistically significantly increased compared to controls by dermal dosing over a 12-day period (Sun et al., 2002). The data are inadequate to provide a conclusion regarding percutaneous absorption. The data set does not have a sufficient number of studies and theses data were collected using a non-standardized method. The available study did not provide data useful for pharmacokinetic modeling because it did not provide a fractional analysis of the dose of Pb applied or tissue dose in other compartments other than urine (Sun et al., 2002).

Discussion

A rapid review methodology was used to evaluate dermal penetration and absorption of inorganic Pb compounds. Though rapid reviews are rigorous and transparent, they may provide fewer quality checks compared to systematic reviews due to limited resources (Hempel et al., 2016). Additionally, rapid reviews provide a less rigorous documentation of the *a priori* search strategy and formulaic documentation of the application of exclusion and evaluation criteria. Lastly, in this rapid review, only one reviewer evaluated all studies identified in the literature search. Because the number of studies on dermal Pb absorption are limited, we do not think these limitations significantly impacted the results of this review. We considered a more formal systematic approach including both quality assessment and evidence integration steps, however most studies were not guideline compliant designed and thus there was no clear value for separating studies based on formal scoring quality and confidence metrics. Rather, an overall evidence integration from the pool of studies, most of which had limited design, was employed.

The studies that were identifiedsuggest that dermal absorption of water soluble and insoluble inorganic Pb compounds is not only possible, but highly likely. These studies show Pb in contact skin with can enter the blood and be distributed more widely in the body. However, the vast majority of studies evaluating route of exposure were not conducted under standard test guideline-compliant methods, and/or did not collect data that was conducive for calculating percutaneous absorption parameters.

Together, K_p and flux define the skin permeability of chemicals (AIHA, 2009; Keil, 2009). K_p is ideally determined under steady state conditions, however, this is technically challenging to determine for metals because permeation rates are slow (Hostýnek et al., 1993). To be independet of time, Flux should be determined under steady state condition. If steady state is not achieved, rates of permeation are more simply described as a "diffusion rate" (Julander et al. 2020). -Although flux provides more certainty about the rate of permeation, diffusion rates still provide a rough approximation that could be useful for dermal risk assessment purposes, if better data is not available. Exposure factors including concentration, area of exposure, and time of exposure can be related to absorbed dose using Fick's first law, which, when applied to the skin, implicitly assumes that the stratum corneum acts as a homogenous barrier that is independent of time or position (Hostynek, 2003; Mitragotri et al., 2011).

However, absorption of metals through skin do not always seem to follow Fickian behavior. It has been proposed that protein-metal ion bond in sub-stratum corneum layers of the skin leads to accumulation of metals (i.e. depot effect), which could then act as a reservoir for extended exposure (Hostynek, 2003; Franken et al., 2015). Data collected by both Julander et al. (2020) and Filon et al. (2006) suggest that a reservoir effect may be occurring with inorganic Pb compounds in exposures. This phenomenon has been observed with other metals as well, including chromate ions and mercuric chloride, where increasing dermal doses resulted in lowered permeability coefficients (Friberg et al., 1961; Wahlberg and Skog, 1965; Gammelgaard et al., 1992).

Three mechanisms of dermal chemical absorption have been proposed: transcellular (through cells), intercellular (around cells), and transappendageal (via skin appendages such as hair follicles, sebaceous glands, and sweat glands) (Mitragotri et al., 2011, McCarley and Bunge, 2001). A general mechanism by which metals penetrate into and absorb through skin has been proposed by Hostynek (2003) and is dependent on several exogenous factors (e.g., dose applied, vehicle, molecular volume, counter ion, etc.) and endogenous factors (e.g., age of skin, anatomical site, homeostatic control, skin layers/shunts). The mechanism(s) that drive(s) inorganic lead absorption is likely related to several of these factors. However, it has been hypothesized that the predominant pathway for diffusion of strong electrolytes (e.g., lead salts) is through skin appendages such as hair follicles and sweat ducts (Tregear, 1966). The same mechanism, in reverse, is associated with the loss of essential elements in sweat (Cohn and Emmett, 1978). However, other mechanisms may also be important for absorption as well. Hostýnek et al. (2001) determined that nickel nitrate is the only nickel salt that has been tested, and it slowly penetrated through the stratum corneum, suggesting that that the relatively higher lipophilicity of this salt may drive transcelluar absorption. In a follow-up experiment, it was determined that molecular volume is also playing a substantial role (Hostynek, 2003).

Despite the lack of data on specific absorption mechanisms, there are absorption parameters of inorganic lead that can inform occupational risk assessment. The K_p and flux in Pb compounds have been previously reviewed, but these evaluations considered fewer studies and have looked at both inorganic and organic forms of Pb (Hostynek, 2003; Hostynek and Maibach, 2006; Franken et al., 2015). A summary of calculated and literature referenced K_p,

flux, and diffusion rate values from relevant studies collected in this review are provided in Table 2. Most calculated values were available for Pbacetate, with only a few available for Pb nitrate, Pb oxide, and Pb metal. This is not an unexpected finding given Pb acetate's former usage in hair dye, which was once a public health concern given the total number of people potentially exposed (Marzulli et al. 1978). The data identified in this paper suggests K_p values for percutaneous absorption of Pb compounds across both human and animal skin to be in the range of 10^{-5} — 10^{-7} cm/h. The diffusion rates were calculated to be of even broader range from 10^{-4} — 10^{-7} mg/cm^2/h, likely reflecting non-steady sate time and model dependencies. K_p estimates for other inorganic metals, have also been reviewed and are spread over the same order of magnitudes. K_p and flux values, respectively for inorganic copper through human skin are in the range of 10^{-4} — 10^{-6} cm/h and 10^{-2} — 10^{-6} mg/cm^2/h, chromium compounds 10^{-3} — 10^{-6} cm/h and 10^{-3} — 10^{-7} mg/cm^2/h, and inorganic nickel compounds in the order of 10^{-3} — 10^{-7} cm/h and 10^{-5} mg/cm^2/h (Hostynek, 2003;Hosynek et al. 1993, Hostynek and Maibach, 2006; Franken et al., 2015). Flux estimates have been calculated for some organic lead species including tetrabutyl Pb (2×10^{-2} mg/cm^2/h, Pb nuolate (oleate and linoleate) (4.2×10^{-3} mg/cm^2/h), and Pb naphthenate (1×10^{-3}— 8×10^{-5}mg/cm^2/h) based on the data from Bress and Bidanset (1991) and Rasetti et al. (1961) (Hostynek et al. 1993; Franken et al. 2015). A K_p value for Pb napthenate, based on the data in? Rasetti et al (1961), was estimated to be 2×10^{-3} — 3×10^{-3} cm/h (Hostynek et al., 1993; EPA, 1992). Overall, the K_p, flux, and diffusion rate values identified and calculated for inorganic Pb compounds are within the same order of magnitudes of other inorganic metals and organic Pb compounds.

The wide range of estimated Kp and flux values increases uncertainty in application to risk assessments. The wide range of K_p values for these different metal compounds likely reflects differences in the exogenous and endogenous factors of both the metal species tested and test systems (e.g., different animal species, total experimental times, and solvents) (Hostynek 1993, 2003). Although it is difficult to rigorously assess absorption kinetics for Pb compounds based on the limited data available, different test species likely contribute to the wide range of absorption metrics reported. Jung and Maibach (2015) evaluated dermal absorption and found that rat, rabbit, and guinea pig skin tend to overestimate rates of absorption of chemicals across human skin, whereas monkey, pig, and hairless guinea pig skin are more predictive of human skin absorption rates. This is attributable to the phylogenetic similarities (monkeys), similar hair coats, epidermis and dermis structure, follicular structures, stratum corneum protein fractions and other epidermal/dermal structural similarities (pigs), and similar epidermis structure, stratum corneum thickness and blood vessel density (hairless guinea pigs) (Jung and Maibach 2015). Only one Pb compound, Pb acetate, had data available to compare across different animal species and humans in this review (Table 8). In this case, human absorption, for both *in vivo* and *in vitro* skin penetration studies suggested *greater* absorption potential relative to rat, mouse and guinea pig. This finding is unexpected since these animal species have lower skin thicknesses and a higher density of hair follicles compared to humans. However, confidence in the magnitude of these differences is relatively low, since these studies were not conducted using standard test guideline-compliant methods.

Some investigators have used a subset of these studies to estimate the impact of dermal absorption of Pb on blood lead levels dose for skin exposure scenarios. Filon et al. (2006) used human skin to estimate that percutaneous absorption of lead oxide and calculated a diffusion rate of 1.21×10^{-7} μg/cm^2/h, which would result in a steady-state increase in blood Pb levels of 2.5 (CI-0.3, 5.1) μg/dL, if the exposure were to occur on unwashed hands and arms for 250 days/year. Julander et al. (2020) estimated that steady-state blood Pb levels would increase from 3.34 — 6.33 μg/dL blood from dermal absorption of lead through metal cutting fluids based on inhalation, hand-to-mouth, and skin absorption parameters observed in a brass foundry environment using pig skin data. Pounds (1979) estimated that the total absorbed dose for dermal exposures to lead acetate occurring 3 times a week for 4 weeks would result in an estimated dose of 7.2 μg/day. The U.S. Food and Drug Administration has currently set an Interim Reference Level for dietary lead exposure for women of childbearing age and other adults to be 12.5 μg/day, which is estimated to increase blood lead levels by 0.5 μg/dL (Flannery et al. 2020; FDA 2020). In occupational environments where other routes of exposure to lead may be relevant, these dermal exposure estimates could represent a significant relative source contribution to overall body burden of lead exposure. Though the methodological issues with these studies may not fully translate to the occupational environment, nor were two of them conducted according to standard test guideline-compliant methods, the estimated impact on blood Pb levels could be increased by greater than 6 μg/dl, which would represent > 100% of blood Pb level that are associated with adverse health effects in adults, determined by the National Toxicology Program (2012). Further analysis of these data using PBPK modeling, including the impact of 24 hr diffusion rates like Filon et al. (2006) and Julander et al. (2020) compared to multi-dosing studies (Pounds 1979) may better elucidate whether skin may be serving as a reservoir for exposure, which is an important consideration in the occupational setting.

An alternative way to validate dermal absorption of inorganic Pb compounds would be to evaluate high confidence epidemiology data. However, studies where Pb exposure is limited to skin contact only were not identified, since environments where Pb exposure occurs through the dermal route would also likely have exposures through gastrointestinal and inhalation routes as well. However, several *in vivo* animal pharmacokinetics studies support percutaneous absorption as an important source of systemic Pb exposure. (Kunze and Laug, 1948; Rastogi and Clausen, 1976; King et al., 1978; Pound, 1979; Moore et al., 1980; Bress and Bidanset, 1991; Sun et al., 2002; Pan et al., 2010; Fang et al., 2014). In seven of these studies, the analysis of Pb dermal exposures do not permit the fundamental kinetic rate constants to be determined due to study design limitations. Two studies provided enough information to calculate kinetic values, however, these studies were not concordant with standard test guideline-compliant methods since they preceded adoption of these methods, and thus there is uncertainty with the calculated values (Pound, 1979; Moore et al., 1980;). The Kp (10^{-7}—10^{-5}) and flux/diffusion rates (10^{-6}—10^{-4}) calculated in these studies were in the same orders of magnitude of the other in vitro studies identified in this review (Bress and Bidanset, 1991; Filon et al., 2006; Pan et al., 2010; Julander et al., 2020).

Limitations point to directions for emphasis in future research. These include the absence of statistical analyses of differences between treatment groups, absence of adequate details on controls for oral exposures, and availability of only single timepoint measurements

of tissue-dose estimations rather than time course estimates. Furthermore, across all in vitro skin penetration studies, mass balance of the applied dose was either not tracked or not provided. Mass balance is a important check of the experimental system to ensure the internal validity of the test system. This includes recovery of the test material from receptor and donor solutions, skin, and skin washes as an integrity check of the experimental system including conformation of the analytical method, wash collection methods, and skin dissolution and analysis. Emphasis on future research should include conducting studies according to standardized standard test guideline-compliant methods (EPA, 1992, 1998, 2007; OECD, 2004a, 2004b, 2011; EFSA 2012) and according to recommendations outlined by Franken et al. (2015) and Hostynek (2003). Only one study was conducted using a standard test guideline-compliant method (Julander et al., 2020);it is unclear why the other studies identified did not follow guideline-compliant methods. Additionally, future research in needed to better understand the mechanisms of absorption, important exogenous factors that drive absorption, and the potential impact of a reservoir effect to better estimate the impact on BLLs. The results of this review suggest that further efforts to reduce Pb contamination on the skin and Pb removal from skin are needed. Use of soaps and wipes designed for heavy metal removal from skin are important as hand washing with soap and water does not effectively remove Pb contamination from skin (Filon et al. 2006; Esswein et al. 2011; Guth et al 2020).

Conclusion:

Data were identified for four inorganic Pb compounds (Pb acetate, Pb nitrate, Pb oxide, and Pb metal) that may inform PBPK models for the purpose of better understanding the systemic dose resulting from dermal exposures. These data included the calculation of average diffusion rate values across animal and human skin ranging from 10^{-7}— 10^{-4} mg/cm^2/h and K_p values ranging from 10^{-7}—10^{-5} cm/h. These values are within the same order of magnitudes of other inorganic metals and organic Pb compounds where dermal absorption is of concern (Hostynek et al., 1993; Hostynek, 2003; Hostynek and Maibach, 2006; Franken et al. 2015). Given the uncertainty in the data based on study design, we chose to present these values as ranges instead of selecting a single diffusion rate or K_p value for each lead compound.

Several lines of evidence suggest that dermal exposure to inorganic Pb compounds are an important exposure pathway for absorption of Pb into the body, but the majority of these studies are difficult to interpret or use to estimate the body burden of Pb exposure using PBPK modeling. However, the estimates identified in this review may permit screening assessments that support the need for data collection using standard test guideline-compliant methods that can then be used for quantitative risk assessments. The data yielded estimates of high variable and orders of magnitude and need refinement for generating an assessment with reasonable degree of confidence. Nevertheless, the calculated values and limited in vivo data all strongly support that a significant contribution of dose from the dermal route cannot be excluded.

Future studies should be conducted to better elucidate the impact of dermal exposures of inorganic Pb compounds on systemic dose. These studies should be conducted according to

standard test guideline-compliant methods (EPA, 1992, 1998, 2007; OECD, 2004a, 2004b, 2011; EFSA 2012) and also follow other recommendations on *in vitro* permeation studies provided in the scientific literature (Franken et al., 2015; Hostynek, 2003).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Water solubility and uses of Pb compounds with available dermal penetration and absorption data

Compound (CAS#)	Water solubility	U.S. Manufacturing (where available) and Uses	Studies with dermal penetration/ absorption data
Pb nitrate (10099-74-8)	59.7 g/100ml @ 25° C	19,278 kg/year manufactured in U.S. (estimated) Uses: • dyeing, photography, and printing industries as a mordant • oxidizer and sensitizer in photographic, tanning, lithography, tanning, and process engravings industries • ore processing for titanium, electrolytic refining of Pb • recovery of precious metals from soils • manufacturing of plastics (rayon delustering, heat stabilization of nylon, and polyester catalyst) • production of matches, pyrotechnics, and explosives • electroluminescent and for electrodepositing Pb dioxide on nickel anodes. (ATSDR, 2020; Pubmed, 2021d)	Sun et al., 2002; Pan et al., 2010
Pb acetate (301-04-2) Pb acetate trihydrate (commercial form) (6080-56-4)	44.3 g/100 ml @20°C	Uses: • hair dye (no longer used in U.S. as of 2017) • coatings for other metals • antifouling and paint additives, • insecticide • gold cyanidation processing. • analytical reagent • Dyeing of textiles (ATSDR, 2020; Pubmed, 2021a, b; FDA 2021)	Pounds, 1979; Moore et al., 1980; Bress and Bidanset, 1991; Pan et al., 2010
Pb subacetate (1335-32-6)	6.25 g/100 ml @ 15° C	Uses: • clarifying and decoloring agent (Pubmed, 2021g)	King et al., 1978
Pb sulfate (7446-14-2)	32mg/L at 15°C	2.03×10^{8} kg/year manufactured in U.S. (estimated) Uses: • battery manufacturing, • pigments in paint, photography • manufacturing of electrical and vinyl compounds requiring high heat stability (Pubmed, 2021h)	Sun et al., 2002
Pb oxide (1317-36-8)	Insoluble	9.57×10^{7} kg/year manufactured in U.S. (estimated) Uses: • manufacturing of lead-acid batteries • vulcanizing agent and accelerator in the rubber industry • paints, enamels, varnishes and pottery glazing • assay of precious metal ores, • manufacture of red lead and other lead compounds, • cement additive (with glycerol) • acid resisting and match compositions (ATSDR, 2020; Pubmed, 2021f)	Bress and Bidanset, 1991; Sun et al., 2002; Filon et al., 2006
Pb ortho arsenate (7645-25-2)	Insoluble	Uses: • historical use as pesticide; current usage unknown (Pubmed, 2021e)	Kunze and Laug, 1948
Pb metal (7439-92-1)	Insoluble	1.58×10^{9} kg/year manufactured in U.S. (estimated) Uses:	Sun et al., 2002; Julander et al., 2020

Compound (CAS#)	Water solubility	U.S. Manufacturing (where available) and Uses	Studies with dermal penetration/ absorption data
		• production of batteries, alloys, solder, sheeting, pipes, ammunition and other products (ATSDR, 2020; Pubmed, 2021c)	

Table 2.

Summary of K_p and Flux/Diffusion rates for inorganic lead compounds

	Human		Rat	Mouse	Guinea Pig	Pig
	In vivo	**In vitro**	**In vivo**	**In vitro**	**In vitro**	**In vitro**
				Pb acetate		
K_p (cm/h)	5×10^{-7}—4×10^{-6} [a–c]		2×10^{-6}—3×10^{-5} [d]	5.9×10^{-7} —1.0×10^{-6} [e]		
Diffusion rate (mg/cm^2/h)	1×10^{-6} —8×10^{-6} [a]	1.6×10^{-4} [f]	3×10^{-5}—3×10^{-4} [c, d, i]	1.3×10^{-5}—4.0×10^{-5} [e]	9.6×10^{-5} —1.6×10^{-4} [f, i, j, l]	
				Pb oxide		
K_p (cm/h)						
Diffusion rate (mg/cm^2/h)		1.21×10^{-7} [g, h]			<3.0×10^{-5} [f, i, l]	
				Pb metal		
K_p (cm/h)						
Diffusion rate (mg/cm^2/h)						1.1×10^{-7}—7.8×10^{-7} [h]
				Pb nitrate		
K_p (cm/h)				5.0×10^{-7}—1.1×10^{-6} [e]		
Diffusion rate (mg/cm^2/h)				1.9×10^{-5}—4.3×10^{-5} [e]		

[a] (Moore et al., 1980)

[b] (EPA, 1992)

[c] (Hostynek, 2003)

[d] (Pounds, 1979)

[e] (Pan et al., 2010)

[f] (Bress and Bidanset, 1991)

[g] (Filon et al., 2006)

[h] (Julander et al., 2020)

[i] (Hostynek et al. 1993)

[j] (Franken et al., 2015)

[l] Hostynek et al., (1993) and Franken et al. (2015) identified the values reported in Bress and Bidanset (1991) as Flux.

Table 3.

Dermal penetration and absorption studies identified for Pb acetate

Design	Results[a]
Reference: (Pounds, 1979) **Model (in vitro/in vivo):** in vivo **Study design**: experimental **Species:** Male Sprague-Dawley rats (300–400 g weight) **N (technical and biological replicates each dose group):** 4/group **Concentration of Pb applied:** 5mg in 500 µl solution (Grecian formula or distilled water or 70% ethanol) **Surface area of skin treated:** 10 cm^2 **Applied dose: (load):** 0.5 mg/cm^2 **Contact time (duration of application):** 1 week or 2 weeks **Recovery phase (time from dose removal to end of experiment):** 0 days **Total mass balance (applied-collected):** unknown **Mass balance reported?:** No **Standard test guideline-compliant methods:** No **Sample Media:** Urine, feces, total body burden **Frequency of collection:** Cumulative; end of study **Lower limit of detection or quantitation for each sample tested:** Not reported	**K_p**: 7 days: 3×10^{-6}—9×10^{-6} cm/h (Hostynek et al. 1993) 14 days: 4×10^{-6}cm/h—8×10^{-6} cm/h **Diffusion rate:** 7 days: 3×10^{-5}—9×10^{-5} mg/cm/h (Hostynek et al. 1993) 14 days: 4×10^{-5}—8×10^{-5} mg/cm/h **F (% bioavailable):** 2
Reference: (Pounds, 1979) **Model (in vitro/in vivo):** in vivo **Study design**: experimental **Species:** Male Sprague-Dawley rats (400–500 g weight) **N (technical and biological replicates each dose group):** 4/group **Concentration of Pb applied:** 5mg in 500 µl solution (Grecian formula or distilled water or 70% ethanol), applied three times per week for 4 weeks. **Surface area of skin treated:** 10 cm^2 **Applied dose: (load):** 0.5 mg/cm^2 **Contact time (duration of application):** 4 weeks, 8 weeks **Recovery phase (time from dose removal to end of experiment):** 4 week study: 0 days 8 week study: 28 days **Total mass balance (applied-collected):** unknown **Mass balance reported?:** No **Standard test guideline-compliant methods:** No **Sample Media:** Urine, feces, total body burden **Frequency of collection:** Cumulative; end of study **Lower limit of detection or quantitation for each sample tested:** Not reported	**K_p**: 4 week: 2×10^{-5}—3×10^{-5} cm/h 8 week: 2×10^{-6} cm/h **Diffusion rate:** 4 weeks: 2×10^{-4}—3×10^{-4} $mg/cm^2/h$ (Hostynek et al. 1993) 8 weeks: 2×10^{-4} $mg/cm^2/h$ **F (% bioavailable):** 2
Reference: (Bress and Bidanset, 1991) **Model (in vitro/in vivo):** in vitro **Study design:** experimental, J diffusion tube **Species:** human (skin) **N (technical and biological replicates each dose group):** 20 **Concentration of Pb applied:** unknown[b] **Surface area of skin treated:** 1.3c m^2 **Dose of Pb applied:** 10 mg **Applied dose: (load):** 7.7 mg/cm^2 **Contact time (duration of application):** 24 hours **Infinite or finite dose:** infinite	**K_p**: n/a **Diffusion rate:** $1.6\times10^{-4}$$mg/cm^2/h$ (Franken et al., 2015, Hostynek et al. 1993)[c] **F (% bioavailable):** n/a

Design	Results[a]
Flow type (static or continuous): static **Recovery phase (time from dose removal to end of experiment):** 0 hours **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods:** no **Sample Media:** saline receptor solution **Frequency of collection:** Cumulative; end of study **Lower limit of detection or quantitation for each sample tested:** Not reported	
Reference: (Moore et al., 1980) **Model (in vitro/in vivo):** In vivo **Study design:** Experimental **Species:** human (males) **N (technical and biological replicates each dose group):** 8 **Concentration of Pb applied:** 6 mM/liter of colloidal lotion, radiolabeled with Pb^{203} acetate (0.74mBq) (1.95 mg/cm^3) 0.1 ml applied **Surface area of skin treated:** 8 cm^2 **Applied dose: (load):** 2.44×10^{-2} mg/cm^2 **Contact time (duration of application):** 12 hrs **Recovery phase (time from dose removal to end of experiment):** 12 hrs **Total mass balance (applied-collected):** unknown **Mass balance reported?:** No **Standard test guideline-compliant methods:** No **Sample Media: urine, blood, calf whole body measurement via gamma counter** **Frequency of collection:** urine- 24 hr collection; blood- 1, 2, 4, 8, 12, 24 hrs; whole body measurement- 12, 24 hr **Lower limit of detection or quantitation for each sample tested:** Sensitivity for whole body measurement and urine- 37 Bq (based on dose of 0.74 mBq); blood Pb measurements- 01 µmol/l	**K_p**: 4×10^{-6} cm/h— 5×10^{-7} cm/h (EPA, 1992; Hostynek, 2003) **Diffusion rate:** 1×10^{-6}mg/cm^2/h— 8×10^{-6} mg/cm^2/h **F (% bioavailable):** n/a
Reference: (Bress and Bidanset, 1991) **Model (in vitro/in vivo):** in vitro **Study design:** experimental, J diffusion tube **Species:** guinea pig (skin) **N (technical and biological replicates each dose group):** 20 (10/group at 37°C, 10/group at 23°C) **Concentration of Pb applied:** unknown[b] **Surface area of skin treated:** 1.3c m^2 **Dose of Pb applied:** 10 mg **Applied dose: (load):** 7.7 mg/cm^2 **Contact time (duration of application):** 24 hours **Infinite or finite dose:** infinite **Flow type (static or continuous):** static **Recovery phase (time from dose removal to end of experiment):** 0 hours **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods:** no **Sample Media:** saline receptor solution **Frequency of collection:** Cumulative; end of study **Lower limit of detection or quantitation for each sample tested:** 1 µg	**K_p**: n/a **Diffusion rate:** @37°C: 9.6×10^{-5} mg/cm^2/h @ 23°C: 1.6×10^{-4} mg/cm^2/h **F (% bioavailable):** n/a
Reference: (Pan et al., 2010) **Model (in vitro/in vivo):** In vitro **Study design:** experimental, static Franz cell **Species:** Nude mice (ICR-Foxn1nu strain) (dorsal skin) **N (technical and biological replicates each dose group):** 12 (4 per group) (Groups-intact skin in double distilled water (n=4), stratum corneum-	**K_p**: Intact skin (water): 5.9×10^{-7} cm/h SC stripped skin (water): 1.0×10^{-6} cm/h Intact skin (syn sweat): 3.3×10^{-7} $cm^{/h}$ **Diffusion rate:** Intact skin (water): 2.3×10^{-5} mg/cm^2/h

Design	Results[a]
stripped skin in double distilled water (n=4), or intact skin in synthetic sweat (n=4)) **Concentration of Pb applied:** 120 mM Pb in 0.5 ml in double distilled water or synthetic sweat (39.03 mg/ml) **Surface area of skin treated:** 0.785 cm^2 diameter **Applied dose: (load):** 24.86 mg/cm^2 **Contact time (duration of application):** 10 hours **Infinite or finite dose:** infinite **Flow type (static or continuous):** static **Recovery phase (time from dose removal to end of experiment):** 0 hours **Total mass balance (applied-collected):** unknown **Mass balance reported?:** No **Standard test guideline-compliant methods:** No **Sample Media:** pH 7.4 buffer solution (unspecified) **Frequency of collection:** every 2 hours **Lower limit of detection or quantitation for each sample tested:** Not reported	SC stripped skin (water): 4.0×10^{-5} $mg/cm^2/h$ Intact skin (syn sweat): 1.3×10^{-5} $mg/cm^2/h$ **F (% bioavailable):** n/a

[a] Citations added where percutaneous absorption values were identified in the literature

[b] The dosing was reported as 10mg of total Pb. No information was provided on how the Pb was dosed on the skin

[c] Franken et al. (2015) and Hostynek et al. (1993) reported this value as Flux

Table 4.

Dermal penetration and absorption studies identified for Pb oxide and Pb metal [a]

Design	Results[a]
Reference: (Bress and Bidanset, 1991) **Compound:** Pb oxide **Model (in vitro/in vivo):** in vitro **Study design:** experimental, J diffusion tube **Species:** guinea pig (skin) **N (technical and biological replicates each dose group):** 20 (10/group at 37°C, 10/group at 23°C) **Concentration of Pb applied:** unknown[b] **Surface area of skin treated:** 1.3 m^2 **Applied dose: (load):** 7.7 mg/cm^2 **Contact time (duration of application):** 24 hours **Infinite or finite dose:** infinite **Flow type (static or continuous):** static **Recovery phase (time from dose removal to end of experiment):** 0 hours **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods:** no **Sample Media:** saline receptor solution **Frequency of collection:** Cumulative; end of study **Lower limit of detection or quantitation for each sample tested:** 1 μg	**K_p**: n/a **Diffusion rate:** $<3\times10^{-5} mg/cm^2/h$ (Hostynek et al., 1993; Franken et al., 2015)[c] **F (% bioavailable):** n/a
Reference: (Bress and Bidanset, 1991) **Compound:** Pb oxide **Model:** In vivo **Study design:** Experimental **Species:** Guinea Pig **N: 8** **Concentration of Pb applied:** Not reported **Surface area of skin treated:** 2 cm^2 **Applied dose:** reported as 300 mg/kg BW (calculated as 343 mg)[d] **Contact time (duration of application):** daily for 7 days **Recovery phase (time from dose removal to end of experiment):** 0 days **Mass balance reported?:** No **Total mass balance (applied-collected):** unknown **Standard test guideline-compliant methods:** No **Sample Media:** Blood, brain, liver, kidney **Frequency of collection:** Cumulative; end of study **Lower limit of detection or quantitation for each sample tested:** Not reported	**K_p**: n/a **Flux or Diffusion Rate:** n/a **F (% bioavailable):** n/a
Reference: (Sun et al., 2002) **Compound:** Pb oxide **Model (in vitro/in vivo):** in vivo **Study design:** experimental **Species:** Albino Wistar rats **N (technical and biological replicates each dose group):** 4 **Concentration of Pb applied:** unk[b] **Surface area of skin treated:** 12 cm^2	**K_p**: n/a **Flux or Diffusion Rate:** n/a **F (% bioavailable):** n/a

Design	Results[a]
Applied dose: (load): 8.3 mg/cm^2 **Contact time (duration of application):** 12 days **Recovery phase (time from dose removal to end of experiment):** 0 days **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods:** no **Sample Media: urine** **Frequency of collection:** every 2 days **Lower limit of detection or quantitation for each sample tested:** not reported	
Reference: (Sun et al., 2002) **Compound:** Pb metal **Model (in vitro/in vivo):** in vivo **Study design:** experimental **Species:** Albino Wistar rats **N (technical and biological replicates each dose group):** 4 **Concentration of Pb applied:** unk[b] **Surface area of skin treated:** 12 cm^2 **Applied dose: (load):** 8.3 mg/cm^2 **Contact time (duration of application):** 12 days **Recovery phase (time from dose removal to end of experiment):** 0 days **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods:** no **Sample Media: urine** **Frequency of collection:** every 2 days **Lower limit of detection or quantitation for each sample tested:** not reported	**K_p**: n/a **Flux or Diffusion Rate:** n/a **F (% bioavailable):** n/a
Reference: (Filon et al., 2006) **Compound:** Pb oxide **Model (in vitro/in vivo):** in vitro **Study design:** experimental, static Franz cell **Species:** human skin (Full-thickness abdominal skin) **N (technical and biological replicates each dose group):** 8 **Concentration of Pb applied:** unk.* **Applied dose: (load):** 5mg/cm^2 **Surface area of skin treated:** 3.14 cm^2 **Contact time (duration of application):** 24 hours **Infinite or finite dose:** infinite **Flow type (static or continuous):** static **Recovery phase (time from dose removal to end of experiment):** 24 hours **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods:** no **Sample Media:** receptor solution (disodium phosphate-based solution) **Frequency of collection:** cumulative, end of study **Lower limit of detection or quantitation for each sample tested:** 0.2 μg/L	**K_p: n/a** **Diffusion Rate:** 1.2×10^{-7} mg/cm^2/h (Julander et al., 2020) **F (% bioavailable):** n/a
Reference: (Julander et al., 2020) **Compound:** Pb metal **Model (in vitro/in vivo):** in vitro **Study design:** experimental, static Franz cell **Species:** pig (skin-still born piglets)	**K_p: n/a** **Diffusion Rate:** 1.1×10^{-7} (24 hr)–7.8×10^{-7} (2 hr) mg / cm^2/h (Julander et al. 2020) **F (% bioavailable):** n/a

Design	Results[a]
N (technical and biological replicates each dose group): 4 **Concentration of Pb applied:** 29–132 mg/kg (in metal cutting fluids) **Surface area of skin treated:** 0.64 cm^2 **Applied dose: (load):** 48.4–290 ug/cm^2 **Contact time (duration of application):** 2, 4, or 24 hours **Infinite or finite dose:** infinite **Flow type (static or continuous):** static **Recovery phase (time from dose removal to end of experiment):** 0 hours **Total mass balance (applied-collected):** unknown **Mass balance reported?:** partial **Standard test guideline-compliant methods:** OECD 428 **Sample Media:** Phosphate Buffer Solution **Frequency of collection:** Cumulative; end of study **Lower limit of detection or quantitation for each sample tested:** <0.06 ppb	

a. Citations added where percutaneous absorption values were identified in the literature

b. The dosing was reported as 10mg of total Pb. No information was provided on how the Pb was dosed on the skin.

c. Franken et al. (2015) and Hostynek et al. (1993) reported this value as Flux.

d. Guinea pig body weight was not reported. Dosage estimates were calculated off the average of standard body weights of male and female guinea pigs (average-875 g) [Laboratory Guinea Pig 2000].

Table 5.

Dermal penetration and absorption studies identified for Pb nitrate

Design	Results
Reference: (Sun et al., 2002) **Model (in vitro/in vivo):** in vivo **Study design:** experimental **Species:** Albino Wistar rats **N (technical and biological replicates each dose group):** 4 **Dose of Pb applied:** 100 mg **Surface area of skin treated:** 12 cm^2 **Applied dose: (load):** 8.3 mg/cm^2 **Contact time (duration of application):** 12 days **Recovery phase (time from dose removal to end of experiment):** 0 days **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods:** no **Sample Media: urine** **Frequency of collection:** every 2 days **Lower limit of detection or quantitation for each sample tested:** not reported	**K_p**: n/a **Flux/Diffusion Rate:** n/a **F (% bioavailable):** n/a
Reference: (Pan et al., 2010) **Model (in vitro/in vivo):** In vivo **Study design:** Experimental **Species:** Female nude mice (ICR-Foxn1nu strain) (8 wk old) **N:** 6 **Concentration of Pb applied:** 120 mM solution in 0.6 ml vehicle **Surface area of skin treated:** 2.25 cm^2 **Applied dose: (load):** 53mg/cm^2 (over 5 days) **Contact time (duration of application):** 5 days **Recovery phase (time from dose removal to end of experiment):** 0 days **Mass balance reported?:** No **Total mass balance (applied-collected):** unknown **Standard test guideline-compliant methods:** No **Sample Media:** Skin, liver, kidneys **Frequency of collection:** Cumulative; end of study **Lower limit of detection or quantitation for each sample tested:** Not reported	**K_p**: n/a **Flux/Diffusion Rate:** n/a **F (% bioavailable):** n/a **Lag phase:** n/a
Reference: (Pan et al., 2010) **Model (in vitro/in vivo):** In vitro **Study design:** experimental, static Franz cell **Species:** Nude mice (ICR-Foxn1nu strain) (dorsal skin) **N (technical and biological replicates each dose group):** 12 (4 per group) (Groups-intact skin in double distilled water (n=4), stratum corneum-stripped skin in double distilled water (n=4), or intact skin in synthetic sweat (n=4)) **Concentration of Pb applied:** 120 mM Pb in 0.5 ml in double distilled water or synthetic sweat (39.74 mg/ml) **Surface area of skin treated:** 0.785 cm^2 **Applied dose: (load):** 24.86 mg/cm^2 **Contact time (duration of application):** 10 hours **Infinite or finite dose:** infinite **Flow type (static or continuous):** static **Recovery phase (time from dose removal to end of experiment):** 0 hours **Total mass balance (applied-collected):** unknown **Mass balance reported?:** No	**K_p**: Intact skin (water): 5.0×10^{-7} cm/h SC stripped skin (water): 1.1×10^{-6} cm/h Intact skin (syn sweat): 4.8×10^{-7} $cm^{/h}$ **Diffusion Rate:** Intact skin (water): 2.0×10^{-5} $mg/cm^2/h$ SC stripped skin (water): 4.3×10^{-5} $mg/cm^2/h$ Intact skin (syn sweat); 1.9×10^{-5} $mg/cm^2/h$ **F (% bioavailable):** n/a

Design	Results
Standard test guideline-compliant methods: No **Sample Media:** pH 7.4 buffer solution (unspecified) **Frequency of collection:** every 2 hours **Lower limit of detection or quantitation for each sample tested:** Not reported	

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Table 6.

Dermal penetration and absorption studies identified for other lead compounds (Pb subacetate, Pb ortho arsenate, Pb sulfate)

Design	Results
Reference: (Kunze and Laug, 1948) **Compound:** Pb ortho-arsenate **Model (in vitro/in vivo):** in vivo **Study design:** experimental **Species:** rat **N (technical and biological replicates each dose group):** 6 **Concentration of Pb applied:** 102 mg of aqueous Pb acetate solution **Surface area of skin treated:** 29 cm^2 **Applied dose: (load):** 3.5 mg/cm^2 **Contact time (duration of application):** 24 hr **Recovery phase (time from dose removal to end of experiment):** 0 hr **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods:** no **Sample Media:** kidney **Frequency of collection:** cumulative, end of study **Lower limit of detection or quantitation for each sample tested:** not reported	**K_p**: n/a **Flux/Diffusion Rate:** n/a **F (% bioavailable):** n/a
Reference: (King et al., 1978) **Compound:** Pb subacetate **Model (in vitro/in vivo):** in vivo **Study design:** experimental **Species:** human **N (technical and biological replicates each dose group):** 5 **Concentration of Pb applied:** 19–21.5% (W/W Pb acetate solution) **Surface area of skin treated:** 6 cm^2 **Applied dose: (load):** unknown **Contact time (duration of application):** 90 minutes **Recovery phase (time from dose removal to end of experiment):** 0 minutes **Total mass balance (applied-collected):** unknown **Mass balance reported?:** no **Standard test guideline-compliant methods: no** **Sample Media:** skin **Frequency of collection:** 2 time periods (20 min, 90 min) **Lower limit of detection or quantitation for each sample tested:** not reported	**K_p**: n/a **Flux/Diffusion Rate**: n/a **F (% bioavailable)** : n/a
Reference: (Sun et al., 2002) **Compound:** Pb sulfate **Model (in vitro/in vivo):** in vivo **Study design:** experimental **Species:** Albino Wistar rats **N (technical and biological replicates each dose group):** 4 **Concentration of Pb applied:** unk.[a] **Applied dose: (load):** 8.3 mg/cm^2 **Surface area of skin treated:** 12 cm^2 **Contact time (duration of application):** 12 days **Recovery phase (time from dose removal to end of experiment):** 0 days **Total mass balance (applied-collected):** unknown	**K_p**: n/a **Flux/Diffusion Rate:** n/a **F (% bioavailable):** n/a

Design	Results
Mass balance reported?: no **Standard test guideline-compliant methods:** no **Sample Media: urine** **Frequency of collection:** every 2 days **Lower limit of detection or quantitation for each sample tested:** not reported	

[a]*The dosing was reported as 100 mg of total Pb. No information was provided on how the Pb was dosed on the skin.