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Review

Review

Rapid Review of Dermal Penetration and Absorption of 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 models. Average calculated diffusion rates for the pool of animal and human skin data ranged from 10^{-7} to 10^{-4} mg cm^{-2} h^{-1}, and K_p values ranged from 10^{-7} to 10^{-5} cm h^{-1}. Study design and documentation were 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^{-1}. This estimation could represent over 100% of 5 μg dl^{-1}, 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

What's Important About This Paper?

The potential for dermal penetration and absorption of inorganic lead (Pb) compounds has been understudied relative to other exposures routes (inhalation, oral). The dermal route may have increased contributions to cumulative Pb exposure because exposure mitigation has focused on inhalation and oral routes. This paper is important because it identifies and evaluates published literature on dermal Pb exposures to support the estimation of key percutaneous absorption parameters (K_p, flux) for use in occupational risk assessment. Additionally, the paper summarizes Pb concentrations in organ tissues after dermal dosing of compounds to evaluate the evidence of Pb absorption through the skin.

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 are needed to allow for improved evaluation of Pb exposures in an occupational risk assessment context.

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

Introduction

Adverse health outcomes associated with Pb exposure are well established and include a 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^{-1} (NTP, 2012; Lanphear *et al.*, 2018). Annually, as many as 1.5 million workers are exposed to lead (Pb) in the workplace in the USA (ATSDR, 2020a). 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 Pb compounds include workplaces such as battery manufacturing, refineries, and construction settings in which other contributing factors, such as heat load and skin abrasions, may increase the potential for dermal absorption of Pb (Filon *et al.*, 2006; NIOSH, 2016). Identification and evaluation of the available data on dermal Pb exposures and Pb uptake from the dermal route are 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, 2020b). Inorganic Pb exists in three oxidation states of +0, +2, and +4, and exists in metallic, oxides, salts, and soap forms. Pb compounds are the most common in environmental exposures (ATSDR, 2020b). 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, 2020b). 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 is well described (Kehoe, 1987; Leggett, 1993; O'Flaherty, 1993; NTP, 2012; ATSDR, 2020b; Vork and Carlisle, 2020; Sweeney, 2021). 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

Table 1. Water solubility and uses of Pb compounds with available dermal penetration and absorption data.

Compound (CAS#)	Water solubility	US manufacturing (where available) and uses	Studies with dermal penetration/absorption data
Pb nitrate (10099-74-8)	59.7 g/100 ml @ 25°C	19,278 kg $year^{-1}$ manufactured in US (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, 2020b; Pubchem, 2021d)	Sun *et al.* (2002) and 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 USA as of 2017) • Coatings for other metals • Antifouling and paint additives • Insecticide • Gold cyanidation processing • Analytical reagent • Dyeing of textiles (ATSDR, 2020b; FDA, 2021; Pubchem, 2021a,b)	Pounds (1979), Moore *et al.* (1980), Bress and Bidanset (1991) and Pan *et al.* (2010)
Pb subacetate (1335-32-6)	6.25 g/100 ml @ 15°C	Uses: • Clarifying and decoloring agent (Pubchem, 2021g)	King *et al.* (1978)
Pb sulphate (7446-14-2)	32 mg l^{-1} at 15°C	2.03×10^8 kg $year^{-1}$ manufactured in US (estimated) Uses: • Battery manufacturing • Pigments in paint, photography • Manufacturing of electrical and vinyl compounds requiring high heat stability (Pubchem, 2021h)	Sun *et al.* (2002)
Pb oxide (1317-36-8)	Insoluble	9.57×10^7 kg $year^{-1}$ manufactured in US (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, 2020b; Pubchem, 2021f)	Bress and Bidanset (1991), Sun *et al.* (2002) and Filon *et al.* (2006)
Pb ortho-arsenate (7645-25-2)	Insoluble	Uses: • Historical use as pesticide; current usage unknown (Pubchem, 2021e)	Kunze and Laug (1948)
Pb metal (7439-92-1)	Insoluble	1.58×10^9 kg $year^{-1}$ manufactured in US (estimated) Uses: • Production of batteries, alloys, solder, sheeting, pipes, ammunition, and other products (ATSDR, 2020b; Pubchem, 2021c)	Sun *et al.* (2002) and Julander *et al.* (2020)

these routes are likely the largest contributors of historical aggregate exposures (ATSDR, 2020b).

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

$$\text{Flux } (\text{mg cm}^{-2}\,\text{h}^{-1}) = K_p\ (\text{cm h}^{-1}) \times \text{concentration } (\text{mg cm}^{-3})\ \text{(at steady state)}.$$

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

$$\text{Diffusion rate } (\text{mg cm}^{-2}\,\text{h}^{-1}) = K_p\ (\text{cm h}^{-1}) \times \text{concentration } (\text{mg cm}^{-3})\ \text{(at non-steady state)}.$$

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 is evaluated based on assumptions, rather than on 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,b, 2011; EFSA, 2012) and if tissue compartment-specific data were collected over multiple time points. Where possible, the fundamental percutaneous rate constant (K_p), flux (Jss; steady state), diffusion rate (non-steady state), and the dermal absorption rate 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) (Supplementary Table S1, available at *Annals of Work Exposures and Health* online). The chemical structures of the Pb species were evaluated to remove all organic Pb compounds from this review. Next, a search strategy was developed to identify scientific literature related to dermal exposures (Supplementary Table S2, available at *Annals of Work Exposures and Health* online). Using the National Library of Medicine PubMed®, three literature searches were conducted, including: (i) CASRN (Supplementary Table S1, available at *Annals of Work Exposures and Health* online) with dermal exposure-related terms (Supplementary Table S2, available at *Annals of Work Exposures and Health* online); (ii) inorganic Pb species (Supplementary Table S1, available at *Annals of Work Exposures and Health* online) names with the dermal exposure terms (Supplementary Table S2, available at *Annals of Work Exposures and Health* online); (iii) 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 (Supplementary Table S2, available at *Annals of Work Exposures and Health* online). 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,b, 2011; EFSA, 2012). Where available, relevant data for PBPK modeling efforts to better elucidate the impact of dermal Pb exposure on systemic Pb distribution were 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 assessments 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 Supplementary Materials (available at *Annals of Work Exposures and Health* online). 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 using the abstract of each study, including:

> Inclusion criteria: experimentally based dermal penetration studies of any inorganic Pb species in humans or animals (*in vivo* or *in vitro*).
> Exclusion criteria: (i) studies in languages other than English; (ii) organic Pb penetration/absorption data; (iii) studies that did not identify the species of Pb; (iv) cell culture studies (*in vitro*); (v) case studies and studies with no variability determinants (i.e. where only one participant was evaluated in one trial); (vi) studies where exposure dose was unknown; and (vii) studies where the route of exposure was not controlled.

Results

The literature identification and evaluation process included 1419 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 ortho-arsenate, and Pb sulfate. Over 1.88×10^9 kg of these Pb materials are manufactured in the USA per year (ATSDR, 2020b) and are used in a variety of industries such as manufacturing of plastics, batteries, dyes, coatings, and pigments, among other uses (Table 1).

A summary of percutaneous absorption parameters that were calculated or identified in the literature is provided in Table 2. No articles identified dermal absorption rate constant (Ka; h^{-1}). The predominant Pb compounds evaluated were Pb acetate (n = 11, 46%) (Table 3), Pb oxide and Pb metal (n = 7, 29%) (Table 4), and Pb nitrate (n = 3, 13%) (Table 5). Additional studies for other Pb 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 two 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 most suffer from one or more elements of inadequate experimental design (described in the summaries below) and failed 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 four 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^{-1} 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-dose study (~2% uptake of applied dose) and multidose 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} to 3×10^{-4} cm h^{-1} among humans and animal species data (Pounds, 1979; Moore *et al.*, 1980; EPA, 1992; Hostýnek, 2003); diffusion rates ranged from 1×10^{-6} to 3×10^{-4} mg cm^{-2} h^{-1} (Pounds,

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^{-1})	5×10^{-7} to 4×10^{-6}[a,b,c]		2×10^{-6} to 3×10^{-5}[d]	5.9×10^{-7} to 1.0×10^{-6}[e]		
Diffusion rate (mg cm^{-2} h^{-1})	1×10^{-6} to 8×10^{-6}[a]	1.6×10^{-4}[f]	3×10^{-5} to 3×10^{-4}[c,d,i]	1.3×10^{-5} to 4.0×10^{-5}[e]	9.6×10^{-5} to 1.6×10^{-4}[f,i,j,k]	
Pb oxide						
K_p (cm h^{-1})						
Diffusion rate (mg cm^{-2} h^{-1})		1.21×10^{-7}[g,h]			$<3.0 \times 10^{-5}$[f,i,k]	
Pb metal						
K_p (cm h^{-1})						
Diffusion rate (mg cm^{-2} h^{-1})						1.1×10^{-7} to 7.8×10^{-7}[h]
Pb nitrate						
K_p (cm h^{-1})				5.0×10^{-7} to 1.1×10^{-6}[e]		
Diffusion rate (mg cm^{-2} h^{-1})				1.9×10^{-5} to 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).
[k]Hostýnek *et al.* (1993) and Franken *et al.* (2015) identified the values reported in Bress and Bidanset (1991) as flux.

1979; Moore *et al.*, 1980; Bress and Bidanset, 1991; EPA, 1992; Hostýnek *et al.*, 1993; Hostýnek, 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 multidose study, respectively (Pounds, 1979). Two additional *in vitro* penetration studies in human abdominal skin (undefined), and in full-thickness mouse skin and guinea pig skin (undefined) detected Pb acetate in receptor fluid after either 10 or 24 h 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 delta-aminolevulinic acid dehydratase and tissue doses (kidney, liver, and muscle) of Pb 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 with controls (Kunze and Laug, 1948; Bress and Bidanset, 1991; Pan *et al.*, 2010).

These studies suggest 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, which reduces 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.

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: 5 mg 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 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} to 9×10^{-6} cm h^{-1} (Hostynek *et al.*, 1993) 14 days: 4×10^{-6} to 8×10^{-6} cm h^{-1} Diffusion rate: 7 days: 3×10^{-5} to 9×10^{-5} mg cm^{-1} h^{-1} (Hostynek *et al.*, 1993) 14 days: 4×10^{-5} to 8×10^{-5} mg cm^{-1} h^{-1} *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: 5 mg in 500 µl solution (Grecian formula or distilled water or 70% ethanol), applied 3 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 and 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 weeks: 2×10^{-5} to 3×10^{-5} cm h^{-1} 8 weeks: 2×10^{-6} cm h^{-1} Diffusion rate: 4 weeks: 2×10^{-4} to 3×10^{-4} mg cm^{-2} h^{-1} (Hostynek *et al.*, 1993) 8 weeks: 2×10^{-4} mg cm^{-2} h^{-1} *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: 1.3 cm^2 Dose of Pb applied: 10 mg Applied dose (load): 7.7 mg cm^{-2} Contact time (duration of application): 24 h	K_p: n/a Diffusion rate: 1.6×10^{-4} mg cm^{-2} h^{-1} (Hostynek *et al.*, 1993; Franken *et al.*, 2015)[c] *F* (% bioavailable): n/a

Table 3. Continued

Design	Results[a]
Infinite or finite dose: infinite Flow type (static or continuous): static Recovery phase (time from dose removal to end of experiment): 0 h 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 l^{-1} of colloidal lotion, radiolabeled with Pb^{203} acetate (0.74 mBq) (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 h Recovery phase (time from dose removal to end of experiment): 12 h 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-h collection; blood—1, 2, 4, 8, 12, and 24 h; whole body measurement—12 and 24 h 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^{-1}	K_p: 4×10^{-6} to 5×10^{-7} cm h^{-1} (EPA, 1992; Hostynek, 2003) Diffusion rate: 1×10^{-6} to 8×10^{-6} mg cm^{-2} h^{-1} *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: 1.3 cm^2 Dose of Pb applied: 10 mg Applied dose (load): 7.7 mg cm^{-2} Contact time (duration of application): 24 h Infinite or finite dose: infinite Flow type (static or continuous): static Recovery phase (time from dose removal to end of experiment): 0 h Total mass balance (applied-collected): unknown Mass balance reported?: no	K_p: n/a Diffusion rate: @3 7°C: 9.6×10^{-5} mg cm^{-2} h^{-1} @ 23°C: 1.6×10^{-4} mg cm^{-2} h^{-1} *F* (% bioavailable): n/a

Table 3. Continued

Design	Results[a]
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	
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 (39.03 mg ml^{-1}) Surface area of skin treated: 0.785 cm^2 diameter Applied dose (load): 24.86 mg cm^{-2} Contact time (duration of application): 10 h Infinite or finite dose: infinite Flow type (static or continuous): static Recovery phase (time from dose removal to end of experiment): 0 h Total mass balance (applied-collected): unknown Mass balance reported?: no Standard test guideline-compliant methods: no Sample media: pH7.4 buffer solution (unspecified) Frequency of collection: every 2 h Lower limit of detection or quantitation for each sample tested: not reported	K_p: intact skin (water): 5.9 × 10^{-7} cm h^{-1} SC-stripped skin (water): 1.0 × 10^{-6} cm h^{-1} Intact skin (syn sweat): 3.3 × 10^{-7} cm h^{-1} Diffusion rate: intact skin (water): 2.3 × 10^{-5} mg cm^{-2} h^{-1} SC-stripped skin (water): 4.0 × 10^{-5} mg cm^{-2} h^{-1} Intact skin (syn sweat): 1.3 × 10^{-5} mg cm^{-2} h^{-1} *F* (% bioavailable): n/a

[a]Citations added where percutaneous absorption values were identified in the literature.
[b]The dosing was reported as 10 mg 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.

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^{-1} in human skin based on Filon *et al.* (2006). Flux was also calculated by Hostýnek *et al.* (1993) to be <3 × 10^{-5} mg cm^{-2} h^{-1} 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-h exposure period. One *in vitro* study dosed Pb oxide on guinea pig skin using a *J*-diffusion tube design, and also did not detect Pb above the limit of detection (Bress and Bidanset, 1991).

One study found Pb concentration in urine was statistically significantly increased compared with 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 suggest 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

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 h Infinite or finite dose: infinite Flow type (static or continuous): static Recovery phase (time from dose removal to end of experiment): 0 h 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: $<3 \times 10^{-5}$ mg cm^{-2} h^{-1} (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^{-1} 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 Applied dose (load): 8.3 mg cm^{-2} Contact time (duration of application): 12 days	K_p: n/a Flux or diffusion rate: n/a *F* (% bioavailable): n/a

Table 4. Continued

Design	Results[a]
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: not reported. Applied dose (load): 5 mg cm^{-2} Surface area of skin treated: 3.14 cm^2 Contact time (duration of application): 24 h Infinite or finite dose: infinite Flow type (static or continuous): static Recovery phase (time from dose removal to end of experiment): 24 h 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^{-1}	K_p: n/a Diffusion rate: 1.2×10^{-7} mg cm^{-2} h^{-1} (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	

Table 4. Continued

Design	Results[a]
Species: pig (skin—still born piglets) *N* (technical and biological replicates each dose group): 4 Concentration of Pb applied: 29–132 mg kg^{-1} (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 h Infinite or finite dose: infinite Flow type (static or continuous): static Recovery phase (time from dose removal to end of experiment): 0 h 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	K_p: n/a Diffusion rate: 1.1×10^{-7} (24 h)– 7.8×10^{-7} (2 h) mg cm^{-2} h^{-1} (Julander *et al.*, 2020) *F* (% bioavailable): n/a

[a]Citations added where percutaneous absorption values were identified in the literature.
[b]The dosing was reported as 10 mg 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) (Clemons and Seeman, 2011).

estimates. The 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 (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} to 7.8×10^{-7} mg cm^{-2} h^{-1} 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, 2004a). Experiments were conducted for 2, 4, or 24 h. At the end of the experiments, concentration of Pb 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 with 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 PBPK 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 was conducted using guideline-compliant methods (Julander *et al.*, 2020). Neither of the studies 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 it 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} to 1.1×10^{-6} cm h^{-1} and diffusion rates ranged from 1.9×10^{-5} to 4.3×10^{-5} mg cm^{-2} h^{-1}. In this study, Pb penetration was evaluated through full-thickness and stratum corneum-stripped mouse skin using a

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 weeks 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): 53 mg 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^{-1}) Surface area of skin treated: 0.785 cm^2 Applied dose (load): 24.86 mg cm^{-2} Contact time (duration of application): 10 h Infinite or finite dose: infinite Flow type (static or continuous): static Recovery phase (time from do`se removal to end of experiment): 0 h 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 h Lower limit of detection or quantitation for each sample tested: not reported	K_p: intact skin (water): 5.0×10^{-7} cm h^{-1} SC-stripped skin (water): 1.1×10^{-6} cm h^{-1} Intact skin (syn sweat): 4.8×10^{-7} cm h^{-1} Diffusion rate: intact skin (water): 2.0×10^{-5} mg cm^{-2} h^{-1} SC-stripped skin (water): 4.3×10^{-5} mg cm^{-2} h^{-1} Intact skin (syn sweat); 1.9×10^{-5} mg cm^{-2} h^{-1} *F* (% bioavailable): n/a

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 h Recovery phase (time from dose removal to end of experiment): 0 h 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 min Recovery phase (time from dose removal to end of experiment): 0 min 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 and 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 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

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

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 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 suggest 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, and 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 volunteer (age 25) and sampled by tape stripping after 20 and 90 min (Table 6) (King *et al.*, 1978). At both time points, Pb penetrated through all four layers of stripped stratum corneum, with an increased concentration of Pb noted in the tape samples collected in the 90-min sample. However, statistical inference testing was not performed to compare concentrations in different skin layers between the two time points (20 and 90 min).

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 min; 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 rats *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 in 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 of Pb sulfate in rats (Table 6) (Sun *et al.*, 2002). Pb concentration in urine was statistically significantly increased compared with 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 these data were collected using a non-standardized method. The available study did not provide data useful for PBPK 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 with 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 is 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 identified suggest dermal absorption of water-soluble and -insoluble inorganic Pb compounds is not only possible, but highly likely. These studies suggest Pb in contact with skin can enter the blood and be distributed more widely in the body. However, the preponderance of studies evaluating route of exposure were not conducted under standard test guideline-compliant methods, and/or did not collect data that were conducive for calculating percutaneous absorption parameters.

Together, K_p and flux define the skin permeability of chemicals (Samhel *et al.*, 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 independent of time, flux should be determined under steady-state conditions. 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 are 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 (Hostýnek, 2003; Mitragotri *et al.*, 2011).

However, absorption of metals through skin does not always seem to follow 'Fickian' behavior. It has been proposed that protein–metal ion bond in substratum corneum layers of the skin leads to accumulation of metals (i.e. depot effect), which could then act as a reservoir for extended exposure (Hostýnek, 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) (McCarley and Bunge, 2001; Mitragotri *et al.*, 2011). A general mechanism by which metals penetrate into and absorb through skin has been proposed by Hostýnek (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 Pb 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. Pb 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. Hostýnek *et al.* (2001) determined that nickel nitrate is the only nickel salt that has been tested, slowly penetrates through the stratum corneum suggesting that the relatively higher lipophilicity of this salt may drive transcellular absorption. In a follow-up experiment, it was determined that molecular volume is also playing a substantial role (Hostýnek, 2003).

Despite the lack of data on specific absorption mechanisms, there are absorption parameters of inorganic Pb 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 (Hostýnek, 2003; Hostýnek 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 is provided in Table 2. Most calculated values were available for Pb acetate, 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; FDA, 2021). The data identified in this paper suggest K_p values for percutaneous absorption of Pb compounds across both human and animal skin to be in the range of 10^{-5} to 10^{-7} cm h^{-1}. The diffusion rates were calculated to be of even broader range from 10^{-4} to 10^{-7} mg cm^{-2} h^{-1}, likely reflecting non-steady-state 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 for inorganic copper through human skin are in the range of 10^{-4} to 10^{-6} cm h^{-1} (K_p) and 10^{-2} to 10^{-6} mg cm^{-2} h^{-1} (flux); chromium compounds range from 10^{-3} to 10^{-6} cm h^{-1} (K_p) and 10^{-3} to 10^{-7} mg cm^{-2} h^{-1} (flux); and inorganic nickel compounds in the order of 10^{-3} to 10^{-7} cm h^{-1} (K_p) and 10^{-5} mg cm^{-2} h^{-1} (flux) (Hostýnek *et al.*, 1993; Hostýnek, 2003; Hostýnek and Maibach, 2006; Franken *et al.*, 2015). Flux estimates have been calculated by Hostýnek *et al.* (1993) and Franken *et al.* (2015) for some organic Pb

compounds including tetrabutyl Pb (2×10^{-2} mg cm^{-2} h^{-1}, Pb nuolate (oleate and linoleate) (4.2×10^{-3} mg cm^{-2} h^{-1}), and Pb naphthenate (1×10^{-3} to 8×10^{-5} mg cm^{-2} h^{-1}) based on the experimental data from Bress and Bidanset (1991) and Rasetti *et al.* (1961). A K_p value for Pb napthenate, based on the data in Rasetti *et al.* (1961), was estimated to be 2×10^{-3} to 3×10^{-3} cm h^{-1} (EPA, 1992; Hostýnek *et al.*, 1993). 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 K_p 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) (Hostýnek *et al.*, 1993; Hostýnek, 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 2). 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 with 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 Pb levels. Filon *et al.* (2006) used human skin to estimate percutaneous absorption of Pb oxide and calculated a diffusion rate of 1.21×10^{-7} µg cm^{-2} h^{-1}, which would result in a steady-state increase in blood Pb levels of 2.5 µg dl^{-1} (confidence intervals—0.3, 5.1), if the exposure were to occur on unwashed hands and arms for 250 days $year^{-1}$. Julander *et al.* (2020) estimated that steady-state blood Pb levels would increase from 3.34 to 6.33 µg dl^{-1} from dermal absorption of Pb 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 Pb acetate occurring 3 times a week for 4 weeks would result in an estimated dose of 7.2 µg day^{-1}. The U.S. Food and Drug Administration has currently set an Interim Reference Level for dietary Pb exposure for women of childbearing age and other adults to be 12.5 µg day^{-1}, which is estimated to increase blood Pb levels by 0.5 µg dl^{-1} (FDA, 2020; Flannery *et al.*, 2020). In occupational environments where other routes of exposure to Pb may be relevant, these dermal exposure estimates could represent a significant relative source contribution to overall body burden of Pb 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^{-1}, which would represent >100% of blood Pb levels 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-h diffusion rates like Filon *et al.* (2006) and Julander *et al.* (2020) compared with multidosing 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 only skin contact were not identified, since environments where Pb exposure occurs through the dermal route would also likely have exposures through gastrointestinal and inhalation routes. 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; Pounds, 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 does 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 (Pounds, 1979; Moore *et al.*, 1980). The K_p (10^{-7} to 10^{-5} cm h^{-1}) and flux/diffusion rates (10^{-6} to 10^{-4} µg cm^{-2} h^{-1}) 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 time point 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 an 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 standard test guideline-compliant methods (EPA, 1992, 1998, 2007; OECD, 2004a,b, 2011; EFSA, 2012) and according to recommendations outlined by Franken *et al.* (2015) and Hostýnek (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 standard test guideline-compliant methods. Additionally, future research is 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 blood Pb levels. 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 is 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} to 10^{-4} mg cm^{-2} h^{-1} and K_p values ranging from 10^{-7} to 10^{-5} cm h^{-1}. These values are within the same order of magnitudes of other inorganic metals and organic Pb compounds where dermal absorption is of concern (Hostýnek *et al.*, 1993; Hostýnek, 2003; Hostýnek 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 Pb compound.

Several lines of evidence suggest that dermal exposure to inorganic Pb compounds is 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 variability over 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,b, 2011; EFSA, 2012) and also follow other recommendations on *in vitro* permeation studies provided in the scientific literature (Hostýnek, 2003; Franken *et al.*, 2015).

Supplementary Data

Supplementary data are available at *Annals of Work Exposures and Health* online.

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Conflict of interest

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the

National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

Data availability

The supplementary materials provide data used in this study.

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