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TITLE

Dermal uptake directly from air under transient conditions: Advances in modeling and comparisons with experimental results for human subjects

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ABSTRACT

To better understand the dermal exposure pathway, we enhance an existing mechanistic model of transdermal uptake by including skin surface lipids (SSL) and consider the impact of clothing. Addition of SSL increases the overall resistance to uptake of SVOCs from air but also allows for rapid transfer of SVOCs to sinks like clothing or clean air. We test the model by simulating di-ethyl phthalate (DEP) and di-n-butyl phthalate (DnBP) exposures of six bare-skinned (Weschler et al., 2015) and one clothed participant (Morrison et al., 2015b). The model predicts total uptake values that are consistent with the measured values. For bare-skinned participants, the model predicts a normalized mass uptake of DEP of 3.1 $(\mu g/m^2)/(\mu g/m^3)$ whereas the experimental results range from 1.0 to 4.3 $(\mu g/m^2)/(\mu g/m^3)$; uptake of DnBP is somewhat overpredicted: 4.6 $(\mu g/m^2)/(\mu g/m^3)$ vs the experimental range of 0.5 to 3.2 $(\mu g/m^2)/(\mu g/m^3)$. For the clothed participant, the model predicts higher than observed uptake for both species. Uncertainty in model inputs, including convective mass-transfer coefficients, partition coefficients and diffusion coefficients, could account for overpredictions. Simulations that include transfer of skin oil to clothing improve model predictions. A dynamic model that includes SSL is more sensitive to changes that impact external mass transfer such as putting on and removing clothes and bathing.

KEYWORDS

dermal uptake, exposure model, phthalates, clothing, skin lipids,

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PRACTICAL IMPLICATIONS

Dermal uptake may contribute considerably to overall body burden of phthalates and other species from indoor air. This enhanced model provides a reasonable match with experimental results in human subjects and can be extrapolated to various transient situations to improve population exposure estimates to phthalates and other indoor organic pollutants.

INTRODUCTION

It has been recently recognized that dermal uptake from air could be an important, or even dominant, mechanism for occupant uptake of some airborne semi-volatile organic compounds (SVOCs). Weschler and Nazaroff (2012; 2014) developed a steady-state model of transdermal uptake of SVOCs and predicted that dermal uptake would be important for many indoor-relevant SVOCs including certain plasticizers, pesticides, fragrances and preservatives. Their mass-transfer model was based on the assumption that transdermal uptake was well represented by a resistances-in-series model for the distinct physical layers (air, skin lipids/stratum corneum, viable epidermis) separating a molecule in room air from the blood. Recognizing that steady-state uptake is not realistic when exposure conditions are changing or there is insufficient time to achieve steady-state, Gong et al. (2014) developed a dynamic model of transdermal uptake. This model accounted for transfer from air to skin and assumed Fickian diffusion through two skin layers (stratum corneum and viable epidermis). They showed that for time periods less than those required to reach steady-state, a substantial amount of SVOC may reside in the skin before diffusing to the dermal capillaries or back out of the skin to air.

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Based on these models, diethyl phthalate (DEP) and di-n-butyl phthalate (DnBP) – ubiquitous in indoor environments – were predicted to have significant transdermal uptake directly from air. Weschler et al. (2015) designed human subject experiments to test these predictions. Six bare-skinned participants were exposed to elevated air concentrations of DEP and DnBP in a laboratory chamber. Two sets of 6 hour experiments were designed to separate inhalation from dermal uptake. In one set of experiments, participants wore a breathing hood to reduce the inhalation component of phthalate uptake. In a second experiment, participants did not wear a hood. Before and after the experiments, participants collected urine to quantify the total excretion of phthalate metabolites that resulted from uptake during the experiments. This study demonstrated that, for a six hour exposure period, inhalation and dermal pathways were equally important for overall uptake. In a parallel study, Morrison et al. (2015b) showed that clothing can impede or enhance dermal uptake of these phthalates depending on how much of the phthalates had been absorbed from air into the clothing. They hypothesized that clothing can increase mass-transfer to and from skin simply because of the very small air gap between cloth and skin.

Although the chamber experiments showed that dermal uptake of DEP and DnBP from air was comparable to inhalation intake, the total measured dermal uptake was substantially less than that predicted by the steady-state model (Weschler and Nazaroff, 2012; Weschler et al., 2015). The investigators suggested that the exposure time (6 h) was insufficient to achieve steady-state uptake and that after leaving the chamber, the phthalates in the participant's skin could desorb to air and their freshly donned clothing, reducing the total phthalate mass delivered to the blood (Weschler et al., 2015). Indeed, the transient model

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developed by Gong and colleagues predicted that it would take more than 48 hours of continuous exposure to approach steady-state for DEP and DnBP. However, as we will show in the results of the present study, the Gong et al. model still over-predicts uptake in all subjects. We believe that this is due, in part, to the fact that the Gong et al. model does not include skin surface lipids as a separate layer; adding SSL as a distinct layer results in greater sensitivity to changes that impact external mass transfer.

Skin surface lipids (SSL) are a combination of sebum exuded from the sebaceous glands and smaller quantities of epidermal lipids. They consist of triglyceride fatty acids, wax esters, squalene, cholesterol esters and cholesterol (Nicolaides, 1974). Their abundance varies among sites on the human body's surface, scaling approximately with the surface density of sebaceous glands (Greene et al., 1970). The layer of skin surface lipids (average thickness of ~1 μm) is much thinner than either the stratum corneum (~25 μm) or viable epidermis (~100 μm) but it acts as an additional resistance to dermal uptake. Phthalates are highly lipophilic and we estimate that the SSL layer contains about half of the DnBP that accumulates in these three layers under steady-state conditions. Because this layer is thin and directly adjacent to air, it can accumulate SVOCs and be depleted more rapidly by transfer of SVOCs to and from air. Therefore, a dynamic model that includes skin lipids would be more sensitive to changes in external mass-transfer conditions (such as putting on clothing, removing clothing, or entering an environment with different air concentrations). Further, SSL can be removed by transfer to clothing or by washing and bathing.

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To more accurately predict dynamic transdermal uptake of SVOCs, we have modified the Gong et al. (2014) model to include a layer of SSL. We apply this model to the conditions described in the Weschler et al. (2015) and Morrison et al. (2015b) studies and compare the predictions with their experimental results.

METHODS

The transdermal model developed here is an extension of that described by Gong et al. (2014) and is shown schematically in Figure 1. There are four layers separating the SVOC in room air from the dermal capillaries: air boundary-layer adjacent to skin (ABL), skin surface lipids (SSL), stratum corneum (SC) and viable epidermis (VE). This model framework is termed ASSV as a descriptive short-hand. We will also consider the Gong et al. model, termed ASV, that does not include SSL. The mathematical framework of the ASSV model is based on that of Gong et al. (2014), but it deviates enough that we repeat many of the equations and some of the description in the Gong et al. paper to clarify the differences.

Mass transfer through the SC and VE is assumed to occur by Fickian diffusion and the governing equations are

$$\frac{\partial C_{sc}}{\partial t} = D_{sc}\frac{\partial^2 C_{sc}}{\partial x^2} \qquad \text{for } L_{ve} < x < L_{sc} + L_{ve} \qquad (1)$$

$$\frac{\partial C_{ve}}{\partial t} = D_{ve}\frac{\partial^2 C_{ve}}{\partial x^2} \qquad \text{for } 0 < x < L_{ve} \qquad (2)$$

where C_{sc} and C_{ve} are the SVOC concentrations in the SC and VE, respectively; D_{sc} and D_{ve} are the diffusion coefficients in the SC and VE, respectively; and L_{sc} and L_{ve} are the thicknesses of the SC and VE, respectively. For simulations of subjects described in Weschler et al.

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(2015) and Morrison et al. (2015b), we assume that the initial concentration in skin layers is zero:

$$C_{ve} = 0, C_{sc} = 0 \qquad \text{for } 0 < x < L_{sc} + L_{ve},\ t=0 \qquad (3)$$

$$C_{ssl} = 0 \qquad \text{at } t=0 \qquad (4)$$

where C_{ssl} is the SVOC concentration in the SSL. The concentration at the interface between the viable epidermis and the dermal capillaries is assumed to be zero:

$$C_{ve} = 0 \qquad \text{for } x = 0,\ t > 0 \qquad (5)$$

Equilibrium exists at the VE-SC interface and the SC-SSL interface:

$$\frac{C_{sc}}{K_{sc\_g}} = \frac{C_{ve}}{K_{ve\_g}} \qquad \text{for } x = L_{ve},\ t > 0 \qquad (6)$$

$$\frac{C_{sc}}{K_{sc\_g}} = \frac{C_{ssl}}{K_{ssl\_g}} \qquad \text{for } x = L_{sc} + L_{ve},\ t > 0 \qquad (7)$$

where K_{sc_g}, K_{ve_g} and K_{ssl_g} are the coefficients for SVOC partitioning between the SC and the air, between the VE and the air, and between the SSL and the air, respectively. We also invoke a flux matching condition at the SC-VE interface:

$$D_{sc}\frac{\partial C_{sc}}{\partial x} = D_{ve}\frac{\partial C_{ve}}{\partial x} \qquad \text{for } x = L_{ve},\ t > 0 \qquad (8)$$

Accumulation in the SSL layer is matched by the flux into and out of that layer due to gas-side mass transfer and diffusion into the SC:

$$\frac{\partial C_{ssl}}{\partial t} = \frac{h_m}{L_{ssl}}\left(C_g - \frac{C_{ssl}}{K_{ssl\_g}}\right) - \frac{D_{sc}}{L_{ssl}}\frac{\partial C_{sc}}{\partial x} \qquad \text{for } x = L_{sc} + L_{ve}\ t > 0 \qquad (9)$$

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where h_m is the mass transfer coefficient between air and the SSL and L_{ssl} is the thickness of the SSL. The total mass transferred to blood, m, is given by the time integral of the flux at the blood-VE boundary times the body surface area, A:

$$m = -A \int_0^t D_{ve} \frac{\partial C_{ve}}{\partial x} dt \qquad \text{for } x = 0 \qquad (10)$$

We do not include the influence of epidermal turnover and desquamation on transdermal uptake in this model because we found the effect to be negligible for DEP and DnBP. However, this mechanism could be important for more lipophilic or higher molecular weight molecules (Reddy et al., 2000). We address the possibility that desquamation could be important while wearing clothing in the *Discussion* section. The model was solved using a finite-difference approach in Microsoft Excel. The approach was validated by simulating the ASSV model without the SSL layer and demonstrating that the output matched the ASV model of Gong et al. (2014).

Simulation and input parameters

We test the model by simulating experimental exposures reported by Weschler et al. (2015) and comparing predicted DEP and DnBP uptake mass (m_{DEP}, m_{DnBP}) to uptake based on measured values of metabolites in urine. Limitations are addressed in the Discussion section. The total simulation time is 54 hours, corresponding to a chamber exposure period (6 h) and a post experimental exposure period (48 h) over which urine was collected. In addition to the absolute mass absorbed by each individual in the experiment, we also calculated a value normalized by air concentration and effective body surface area ($m_{n,DEP}$, $m_{n,DnBP}$). A simple sensitivity analysis was performed by varying only one input parameter

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at a time and comparing results against values obtained from the use of nominal parameters.

Experimental and modeling values for air concentration, body-specific characteristics of the participants, and other modeling parameters are provided in Tables 1 and 2; a brief description of these parameters now follows.

Experimental and participant specific parameters

Air concentrations. Weschler et al. (2015) measured air concentrations of DEP (235-290 $\mu g/m^3$) and DnBP (115-140 $\mu g/m^3$) during the 6 hour exposure in the chamber for each group of participants and each test condition. During the following 48 hours, air concentrations are assumed to be zero because the reported mass absorbed has been corrected for background urine levels. Furthermore, typical indoor air concentrations of DEP and DnBP (0.15-1.5 and 0.070-0.70 $\mu g/m^3$, respectively (Butte, 2009; Rudel et al., 2010)) are much lower than those measured in the chamber.

Exposed body surface area. The total body surface area (BSA) is determined using the equation recommended by DuBois and DuBois (1916) and the reported height and weight of subjects in the Weschler et al. (2015) study. The amount of BSA covered by the breathing hood, shorts and the soles of feet was estimated to be 20%. Values of concentration, height, weight and exposed BSA used in the simulations are shown in Table 1.

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Nominal values for other parameters.

Nominal values for other parameters used in the model are shown in Table 2. Parameters for the dermal penetration model are largely based on the analyses of Gong et al (2014), but some values have been updated to reflect recent literature or specific conditions that prevail in the Weschler et al. (2015) experiments. We also chose a high and low value to perform a sensitivity analysis.

Convective mass-transfer coefficient. For the 6-h chamber exposure period, the convective mass transfer coefficient, h_m, is determined using the methods described in Gong et al. (2014), with the exception that the gas diffusivities of the phthalates are determined at 30^{o}C using "EPA On-line Tools for Site Assessment Calculation" (US EPA, 2013) which is based on equations described in Tucker and Nelken, (1982). For example, for a 2-degree temperature difference between human skin (32 ^{o}C) and chamber air (30 ^{o}C), the nominal convective mass-transfer coefficient for DEP is estimated to be 3.4 m/h. A low and high value were determined by assuming the temperature difference between skin and air ranged from 0.5 to 4 degrees.

After the chamber exposure period, participants donned full-coverage clothing (winter time). The results of Morrison et al. (2015) indicate that clothing can increase external mass transfer from contaminated clothing to skin. We assume that the same is true in the reverse direction: that clothing acts as an effective sink for phthalates that are released from the SSL to air. Buechlein et al (2014) observed that mass transfer of methamphetamine from clothing to simulated skin surface lipids was well-described by

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Fickian diffusion across a stagnant gas film and the mass transfer coefficient was equal to the gas diffusivity divided by air-gap thickness between cloth and skin. For both DEP and DnBP, we chose h_m to be 100 m/h for close-fitting clothing which corresponds to an air gap thickness approximately equal to the thickness of several human hairs (100-200 μm). For the sensitivity analysis, we chose a low value of 10 m/h corresponding to an individual with very loose fitting clothing and a high value of 200 m/h corresponding to an individual with a very small air gap between skin and clothing. A further simulation, for the purposes of comparing the ASSV and ASV models was performed using the assumption that participants did not don clothing after leaving the chamber. For this condition, h_m was set to a value corresponding to a temperature difference between skin and air of 6°C.

Partition coefficients. We have assumed that the partition coefficients between skin surface lipids and air (K_{ssl_g}) for DEP and DnBP can be approximated as the respective octanol/air partition coefficients (K_{oa}) at 32 °C (Weschler and Nazaroff, 2014). The nominal values for K_{oa} were taken from the values reported in Table 4 of Cousins and MacKay (2000), adjusted to 32 °C. The values for K_{sc_g} and K_{ve_g} for DEP and DnBP were taken from Table 2 of Gong et al. (2014). To account for the uncertainty in partition coefficients and the possibility that K_{ssl_g} may deviate somewhat from K_{oa} (Valiveti et al., 2008), we assigned the low (0.3333 times nominal value) and high (3 times nominal value) values used in the sensitivity analysis for K_{ssl_g} and K_{sc_g} such that each spans approximately 1 order of magnitude.

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Diffusion coefficients in the VE and SC. The nominal values for DEP and DnBP were taken directly from Gong et al. (2014). Rather than independently vary the effective diffusivity for the sensitivity analysis, we allowed them to vary with the partition coefficient because the effective diffusivity is approximately inversely proportional to the partition coefficient.

Thickness of VE, SC and SSL. The average thickness of the VE (100 μm) is also taken directly from Gong et al. (2014). The average thickness of the SC (23 μm) is based on the values reported in Table V of Holbrook and Odland (1974), multiplied by a factor of 2.25 to account for the difference in thickness between dehydrated and partially hydrated SC. The measurements reported in Holbrook and Odland were obtained via electron microscopy of intact, full thickness, dehydrated stratum corneum obtained from 3 males and 3 females, 25 to 31 years of age. The adjustment factor of 2.25 was obtained by comparing *in vivo* thickness measurements of partially hydrated SC with thicknesses reported by Holbrook and Odland for dehydrated SC from the same regions of the body. The *in vivo* thicknesses were obtained using confocal Raman spectroscopy (Egawa et al., 2007) or both confocal Raman spectroscopy and confocal laser scanning microscopy (Böhling et al., 2014). As a check on this approach, we calculated an average thickness of the SC using the number of cell layers measured for the SC at different body locations (Holbrook and Odland, 1974) and an average SC cell thickness of 1.23 μm/cell layer (Böhling et al., 2014). Reassuringly, the average value calculated in this fashion was almost identical to that calculated using our primary method. The low (15 μm) and high (30 μm) values chosen for the sensitivity analysis are based on the range of SC thickness values reported in Böhling et al. (2014) and Holbrook and Odland (1974).

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The average thickness of the SSL (1.2 μm) was based on an average total lipid level on the surfaces of the arms, chest, sides, back and legs (110 μg/cm2 as estimated from measurements reported in Table I of Greene et al. (1970) after adjusting by a factor of 1.4 based on the more accurate analytical method described in Saint-Leger et al. (1979)) and an average density of 0.9 g/cm^3 for the lipids on the surface of skin. The low (0.6 μm) and high (1.8 μm) values chosen for the sensitivity analysis are based on the spread of measurements reported in Green et al. (1970).

Simulation of uptake from exposed clothing

In addition to the participants in Weschler et al. (2015), the model was used to simulate the transdermal uptake for the participant in Morrison et al. (2015b). During one set of experiments, the participant wore, for 6 hours, a full set of clothing that had been exposed for 9 days to phthalates in the same chamber described in Weschler et al. (2015). We assume that the clothing had equilibrated with the phthalates and that the near-cloth air concentration when worn by the participant was equal to the concentration in the chamber during the 9-day exposure (250 and 123 μg/m^3 for DEP and DnBP respectively). This assumption was made in lieu of measured clothing concentrations, which were not obtained in the Morrison et al (2015b) experiments. This assumption is discussed in the Limitations section. Further, during the first 6 hours, the mass-transfer coefficient is enhanced while wearing exposed clothing and equal to 100 m/h; after exposure the subject dons fresh clothing, h_m is also equal to 100 m/h and the air concentration is set to zero. The

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exposed surface area of the subject was 1.8 m^2 and all other model inputs were "nominal", as described above and shown in Table 2.

RESULTS

To demonstrate the influence of SSL on predictions of transdermal uptake, we compare simulations of the model that includes SSL (ASSV) with the model that does not have SSL (ASV) for DEP and DnBP in Figures 2a and b. For these simulations, the air concentration was set to 250 μg/m^3 (DEP) and 123 μg/m^3 (DnBP), the exposed surface area was chosen as the average for six subjects (1.6 m^2) and other inputs were set to nominal values with exceptions noted. Curves labeled "no clothes" refer to simulations assuming participants did not don clothing after leaving the chamber. Curves labeled "clothes" indicate simulations which include donning fresh clothing after subjects leave the chamber. For either model (ASV or ASSV), clothing substantially reduces the total mass systemically absorbed, m_{DEP} or m_{DnBP}, by acting as a near-skin sink after the chamber exposure. Skin surface lipids, included in the ASSV model, act as an additional resistance. They delay uptake and reduce overall uptake compared with the ASV model. The clothing effect is more pronounced in the ASSV model because the phthalates sorbed into the SSL can more readily be removed. For example, the ASSV model predicts that clothing reduces uptake of DnBP by 65% but the ASV model only predicts a reduction of 50%. An additional "skin-wipe" simulation is shown in Figure 2. This simulation is identical to the "clothes" simulation except that we set the phthalate mass in skin oil = 0 at t =6h, as though donning clothing removed surface phthalates instantaneously (but only once; the thickness of SSL is

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unchanged). After this "wipe" episode, the simulation proceeds normally and surface lipids can continue to accumulate and release phthalates. The impact of a skin-wipe is small for DEP, but more pronounced for DnBP. In general, the presence of skin lipids is more important for DnBP than for DEP because the former has a higher partition coefficient in SSL.

Shown in Figure 3a and 3b is the total mass in each layer for the same parameters used to generate the curve labeled "ASSV, clothes" in Figures 2a and 2b. DEP mass accumulates early in the SSL but soon most of the mass is in the SC. Very little accumulates in the VE. Upon leaving the chamber at t = 6 h, the SSL are rapidly depleted of DEP by transfer to clothing across the air gap. The remainder of the DEP is almost entirely in the SC and decays by transfer to both blood and clothing for about 24 hours until almost completely depleted. For DnBP, the accumulation in the SSL is more pronounced and longer lasting. After leaving the chamber, mass in the SSL decays more slowly than is the case for DEP. Thus, anything directly altering the SSL, such as transfer of skin lipids to clothing, will affect transdermal uptake of DnBP more than DEP. Without the overlying SSL layer, the ASV model (not shown in Figure 3) predicts peak DEP and DnBP concentrations in the SC to be 1.4 and 2.3 times greater than predicted by the ASSV model which includes SSL.

Simulations of phthalate uptake in individual participants are shown in Figure 4a and 4b (also in Table 1) alongside values reported by Weschler et al. (2015). On average, the ASSV model does a good job of predicting DEP uptake but does not capture individual differences apparent among experimental participants. Weschler et al (2015) observed an age-related effect among participants that could be due to differences in the thickness of the SC or SSL. Since nominal parameters were applied, we could not capture individual differences in

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uptake dependent on unique values associated with the VE, SC or SSL. There was little difference in predictions of DEP uptake when including a skin-wipe in the simulations. In the case of DnBP, the ASSV model without skin-wipe over-predicts the uptake for all participants. The simulations that include skin-wipe still tend to over-predict, but more closely match the measured results.

The results of the sensitivity analysis are shown in Figure 5a and 5b. Experimental and model results for total mass absorbed are shown normalized by BSA and the air concentration present during the 6-hour chamber exposure ($m_{n,DEP}$ or $m_{n,DnBP}$). The predicted $m_{n,DEP}$, using nominal parameter values, is close to the average for all participants. Varying each parameter individually results in a range that generally falls within the measured values. One exception is the result for the lower bound of the post-chamber convective mass transfer coefficient (h_m =10 m/h) that predicts a much higher uptake of DEP for "loose-fitting clothing" than was observed among participants. Increasing h_m from 100 to 200 m/h has little effect, nor does including skin-wipe (as noted earlier). Participant ages are shown with measured results. Older participants tended to experience higher uptake than younger participants. This is consistent with the observation that the SC thins with age, and that a lower value of L_{SC} results in a higher uptake. The ASSV model tends to over predict $m_{n,DnBP}$ but the sensitivity analysis results in values that approach the upper end of the measured results. Including a skin-wipe in the simulation improves the predictions. A combination of parameters (e.g., lower h_m, thicker SSL and SC or thick layers and high values of partition coefficients) would generate results that better match experiments, but there is insufficient justification for choosing any particular combination.

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For the participant that had worn "exposed" clothing during the 6-hour chamber experiment, described in Morrison et al. (2015b), the model predicts somewhat higher transdermal uptake than observed in the experiment. For DEP, the measured and modeled total uptake values, m_{DEP}, are 4.7 and 7.4 mg respectively. For DnBP, these values are 3.3 mg (measured) and 19 mg (modeled). However, when comparing the clothed to the bare-skin participants, the measured and modeled ratios are similar. For example, the model predicts that the participant that wore exposed clothing would absorb 5.2 times more DEP than bare-skinned participants. The measured DEP uptake for the clothed participant was 2.5-11, with an average of 5.0, times greater than bare-skinned participants. For DnBP, the model predicts a 19 fold greater increase in uptake for the clothed participant than bare-skinned participants. The measured ratios were 4.7-32, with an average of 12. We also simulated skin-wipe transfer of phthalates to cloth (as described earlier) when exchanging the exposed clothing for fresh clothing after the 6-hour exposure period. The modeled uptake of DEP reduces only slightly from 7.4 to 7.1 mg. The uptake of DnBP is influenced more by skin-wipe transfer and reduces from 19 to 14 mg. Reducing h_m during the 6-h exposure period, simulating looser-fitting clothing, reduces total mass accumulated and results in a better match to measurements.

DISCUSSION

As shown in Table 1 and Figure 4, the model predicts total uptake values that are reasonably consistent with those observed in Weschler et al. (2015). This is particularly satisfying since the values for all parameters were derived from independent sources, not

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calibrated on results from human subject experiments. The results also highlight the importance of including skin surface lipids, uptake by clothing and possible transfer of SSL to clothing.

The agreement between modeled and measured results is better for DEP than for DnBP. The reasons for this are not clear. It may be that the key partition coefficients used in the model (K_{ssl_g} and K_{sc_g}) are better estimated for the former than the latter. In general it is easier to measure these partition coefficients for smaller SVOCs such as DEP compared to larger SVOCs such as DnBP. Note that the diffusivity of DEP and DnBP in the stratum corneum are proportional to their respective K_{sc_g} values.

The effect of wearing clothing was simulated by increasing the effective mass transfer coefficient assuming that "close-fitting" clothing was worn immediately after the chamber exposure. This assumption is consistent with the fact that the experiments were conducted during February in Denmark; the participants dressed accordingly after leaving the warm chamber for the cooler halls and offices of the adjacent building.

The effective mass transfer coefficient would also increase as a consequence of continuous removal of SSL (as opposed to the single "wipe" simulated here) or the continuous loss of the outer layer of the stratum corneum cells by desquamation. The effective mass-transfer coefficient due to continuous SSL transfer, $h_{m,ssl}$, is

$$h_{m,ssl} = \frac{m'_{ssl} K_{ssl\_g}}{\rho_{ssl}} \qquad \text{for } x = L_{sc} + L_{ve},\ t > 0 \qquad (11)$$

where m'_{ssl} is the SSL production rate (µg/cm^2/h) and ρ_{ssl} is the density of SSL (approximately 0.9 g/cm^3). The effective mass-transfer coefficient due to continuous desquamation, $h_{m,des}$, is

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$$h_{m,des} = \frac{m'_{des} K_{squame\_g}}{\rho_{squame}} \qquad \text{for } x = L_{sc} + L_{ve},\ t > 0 \qquad (12)$$

where m'_{des} is the desquamation rate of the stratum corneum (µg/cm^2/h), K_{squame_g} is the squame-gas partition coefficient and ρ_{squame} is the density of a squame (approximately 0.9 g/cm^3). Sebum production rates have been reported by Agache and Humbert (2004), and we use a value of 10 µg/cm^2/h as typical. Using the nominal values for K_{ssl_g} from Table 2, $h_{m,ssl}$ is 2.4 and 24 m/h for DEP and DnBP, respectively. Desquamation rates range from 30 to 90 mg/h (Milstone, 2004; Gowadia and Settles, 2005) which corresponds to an average of about 3 µg/cm^2/h for an individual with a total body surface area of 2 m^2. We assume that K_{squame_g} for a "dry" squame is half-way between K_{ssl_g} and K_{sc_g}. This results in effective mass-transfer coefficient, $h_{m,des}$, of 0.5 and 4.1 for DEP and DnBP . Therefore, transfer of SSL would have a greater impact than desquamation on removal of either DEP or DnBP from skin. Compared with the value of h_m (100 m/h) estimated to account for transport through the cloth-skin air gap, continuous transfer of SSL to clothing or desquamation would have a negligible effect on DEP. The effect is also small for DnBP, but this is because increasing h_m from 100 (without SSL transfer to clothing) to 128 m/h (an additional 28 m/h due to both SSL transfer and desquamation) only reduces m_{DnBP} by about 9%. We would estimate a lower h_m for looser clothing, as might occur in the summer, and consequently a more important role for continuous transfer of SSL and desquamation.

Wearing clothing exposed to, and equilibrated with, chamber air is predicted to increase uptake relative to bare skin. However, the model predicts significantly higher uptake for both DEP and DnBP than observed in Morrison et al. (2015b). This could be because we

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assume a cloth-skin gap (during exposure) that is too narrow; looser clothing would result in lower flux from cloth to skin. The discrepancy between model and measurement could also be due to the fact that we apply a simplifying assumption during the 6-h exposure period: namely that the concentration adjacent to the inside surface of the cloth is equal to the concentration that the clothing had been exposed to. This may be an over-estimate of the average concentration if the clothing had not reached equilibrium with DEP and DnBP in the air during the 9-days they were hanging in the experimental chamber. Also, since phthalates are transferring from clothing to skin, the total mass of phthalates in clothing will diminish. To determine whether significant cloth depletion occurs, we compare the modeled estimate of mass transferred to skin in the 6-h period to the mass estimated to be present in cloth after equilibrating with chamber air. Based on the measured partition coefficients of DEP and DnBP with cotton fabrics (Morrison et al., 2015a), we estimate 0.23 g of DEP and 1.73 g of DnBP were adsorbed to clothing prior to wearing. The model predicts that 0.03 g of DEP and 0.07 g of DnBP are transferred to the subject during the 6 h chamber exposure. Therefore, only about 13% and 4% of the mass in the clothing are predicted to transfer to skin. Although a small fraction of the total, if the depletion occurs primarily at the inside surface of the cloth, the air concentration at the surface of the cloth could be significantly smaller than the equilibrium value.

The treatment of clothing in the present model is somewhat simplistic. A detailed model of the transient concentration profile in cloth is beyond the scope of this paper, but is readily added to this model as a new "layer" as long as the transport mechanism through cloth is well established. Clothing is emerging as an important moderator of dermal exposure. There is clearly a need to develop a model describing SVOC uptake, release and transport

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for clothing. Such a model must account for the morphology, partitioning, geometry, weave and history of storage, wear and washing. Further, transfer of lipids to clothing can significantly alter overall dermal uptake, but could also change the effective partitioning of SVOCs to the clothing itself. More discussion of the relative importance of SVOC partitioning and clothing history can be found in Morrison et al. (2015a, 2015b).

Limitations and cautions

As shown in Table 1 and Figure 4, the agreement between measured and modeled results is reasonable, especially for DEP. However, there are limitations with the approach described in this paper. These include the accuracy with which we know the parameters used in the model, especially h_m from 6 to 54 hours as well as K_{ssl_g} and K_{sc_g}. The major uncertainty regarding h_m (6 - 54 h) is the thickness of the air gap between the skin and the clothing that covers the skin. This varies from location to location on the participants' bodies; at some locations the clothing will be touching the skin, and at other locations the air gap may be substantial. There are also likely to be differences among the participants regarding how tightly their clothing was fitting, and hence the average value for this air gap.

Another area with uncertainty is the loss of phthalates from the SSL and SC after the bare-skinned subjects leave the chamber. We know from everyday experience that skin oils are transferred to the clothing we wear. It is apparent from Figures 2 and 4 that accounting for some transfer of phthalate containing skin oil to clothing (the "skin-wipe" scenario in our simulations) improves agreement between modeled and measured results, especially for DnBP. However, our current approach to account for this – a one-time removal of

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phthalates from SSL when the participants leave the chamber – is fairly crude. The model does not account for removing clothing at end of the first day, approximately 8 hours after exiting the chamber, and subsequent transfers of skin oils to nightclothes and bedding. The thickness of the air gap between the skin and bedclothes or bedding is expected to be smaller, on average, which would result in a larger average value for h_m during the time in bed. Additional transfer of skin oils, and concomitant loss of phthalates, is anticipated the next morning when the subjects dress for the ensuing day.

The "measured" DEP and DnBP uptake masses (m_{DEP} and m_{DnBP}) taken from Weschler et al. (2015), are actually derived from the concentrations of DEP and DnBP metabolites measured in urine. Urinary excretion factors were used to convert masses of metabolites measured in urine to masses of parent compounds absorbed by the skin. These metabolite conversion factors for both phthalates were based on the fraction of an *oral* dose of DnBP that was excreted as a given metabolite in urine (Koch et al., 2012). A conversion factor for DEP has not yet been reported and could differ from DnBP. Further, the conversion factors appropriate for dermal absorption may be somewhat different from those appropriate for oral intake (Bekö et al., 2013). The manner in which conversion factors vary with exposure pathway is an area that requires further study.

There was significant subject-to-subject variability in the results reported in Weschler et al. (2015), with dermal absorption from air spanning a factor of four for DEP and a factor of six for DnBP, after normalizing for air concentrations and subject's body surface area (Table 1). Some of this subject-to-subject variability appears to be due to differences in the age of the participants. Dermal absorption increases in a surprisingly consistent manner as the participants' age increases. The present model does not attempt to adjust its predicted

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results for age. This might be done by increasing the thickness of the SC, the thickness of the SSL, or both, for the younger subjects and doing the opposite for the older subjects. However, even for subjects of the same age, differences are expected in the amount of sebum excreted/thickness of the SSL (Greene et al., 1970) as well as the thickness of the SC (Holbrook and Odland, 1974).

The experiment which was simulated in the present study used male participants. This was based on ethical considerations; it was deemed imprudent to expose potentially child-bearing females to DEP and DnBP. Hence, the present model has only been evaluated for males. There are known differences between male and female skin (e.g., amount of SSL, thickness of SC) and these differences should be considered when applying the present model to females.

Finally, the present model does not account for hand washing or bathing. During the chamber experiments the participants were asked not to shower until at least 24 hours after leaving the chamber, but they were at liberty to wash their hands. Hand washing and showering are known to remove skin surface lipids, but the amount removed varies with the temperature of the water, the use of soap and the rubbing/scrubbing of skin surfaces.

Despite these limitations, we judge that the treatment of skin surface lipids as a separate layer, coupled with the inclusion of clothing as a sink for compounds previously absorbed by the SC, has significantly improved the accuracy of assessments made with the dynamic model presented in this paper, especially for SVOCs that are highly soluble in skin surface lipids (i.e., have large values for K_{oa}).

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FIGURE CAPTIONS

Figure 1: Schematic illustrating skin layers simulated with the ASSV model. “Bare skin” is for the participants in the chamber wearing only shorts (Weschler et al., 2015) while “Clothed” is for the participant wearing clothes previously exposed to chamber air (Morrison et al., 2015).

Figure 2: Cumulative mass of phthalates absorbed as predicted by the ASSV and ASV models including post-exposure simulations with clothing, no clothing and instantaneous removal of phthalates at 6 hours by a “skin-wipe” for a) DEP and b) DnBP.

Figure 3: ASSV simulations of a) DEP and b) DnBP mass accumulated in each layer (VE, SC, SSL). For these simulations, the air concentration was set to 250 $\mu g/m^3$ (DEP) and 123 $\mu g/m^3$ (DnBP), the exposed surface area was chosen as the average for six subjects (1.6 m^2) and other inputs were set to nominal values (Table 2). These results correspond to “ASSV, clothes” curves in Figure 2a and 2b.

Figure 4: Measured and predicted total uptake of a) DEP and b) DnBP for participants in Weschler et al. (2015).

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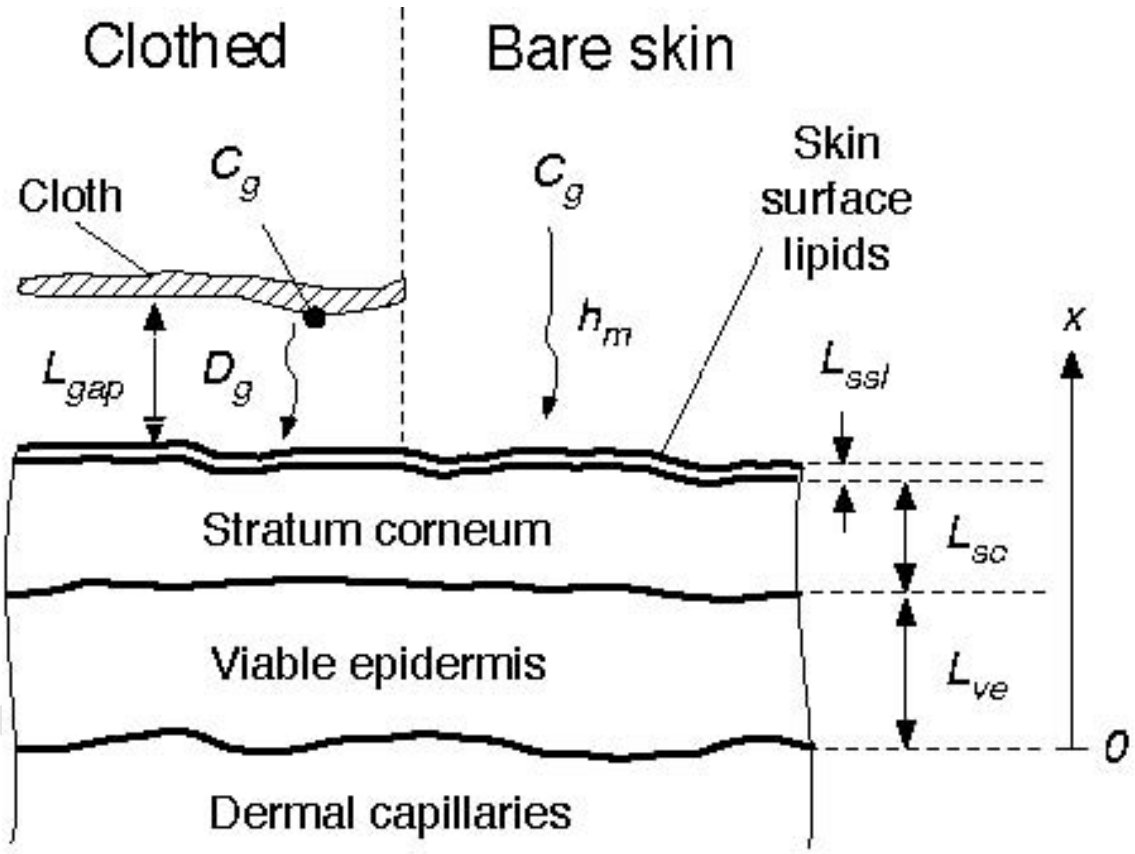
Figure 5: Sensitivity of normalized transdermal uptake mass to high and low values of parameters for a) DEP and b) DnBP. Also shown are results based on nominal parameters with and without skin wipe, and measured uptake from participants described in Weschler et al. (2015). Results shown are normalized by gas concentration present during 6-h chamber exposure. Normalized values cannot be generalized to daily exposure.



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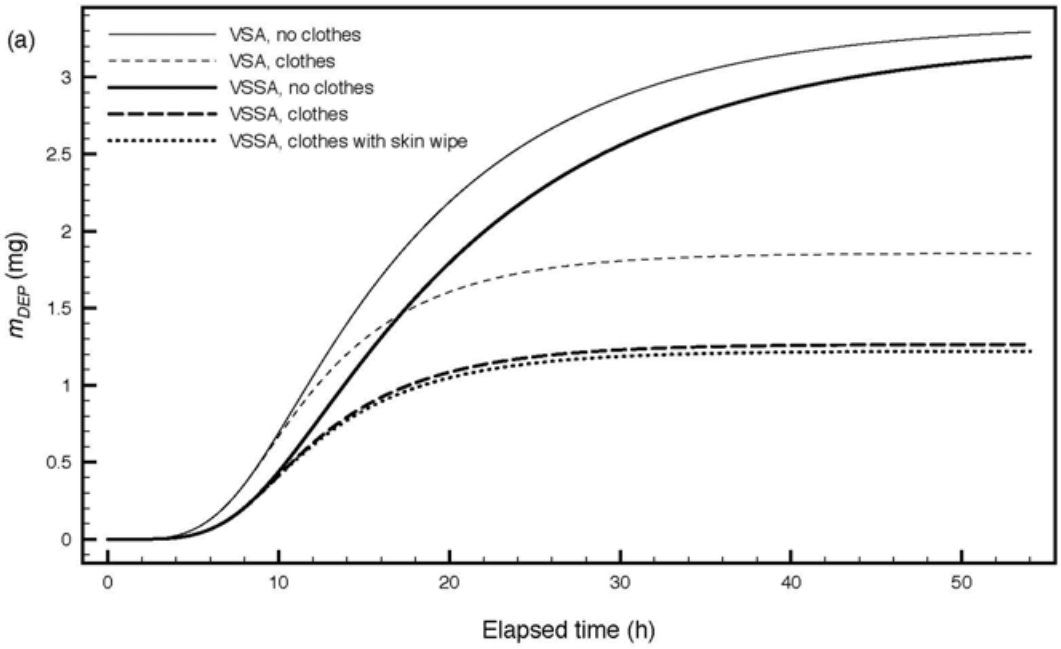

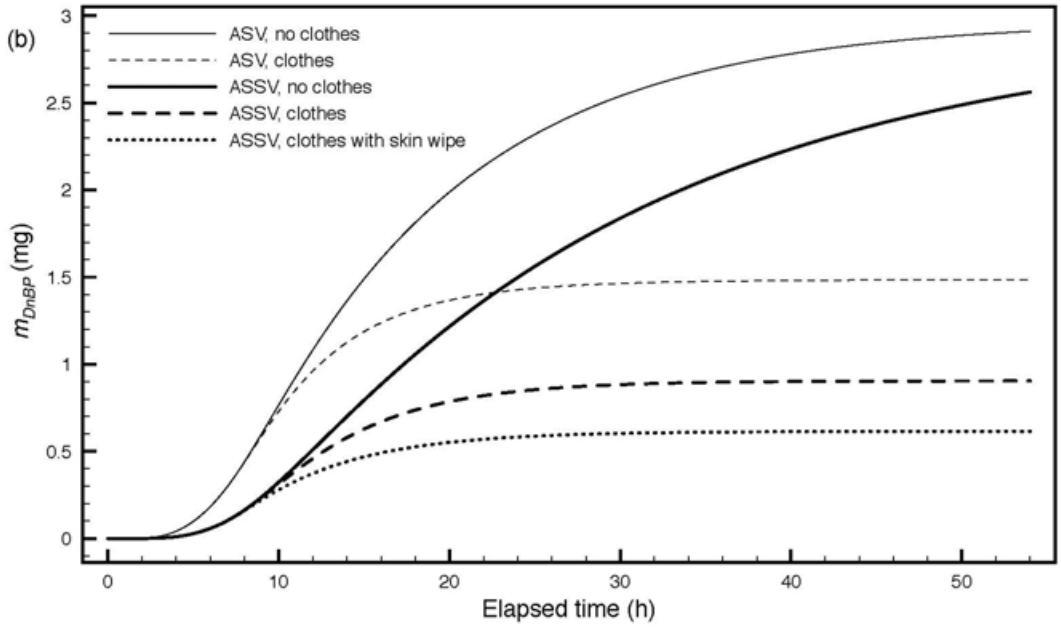

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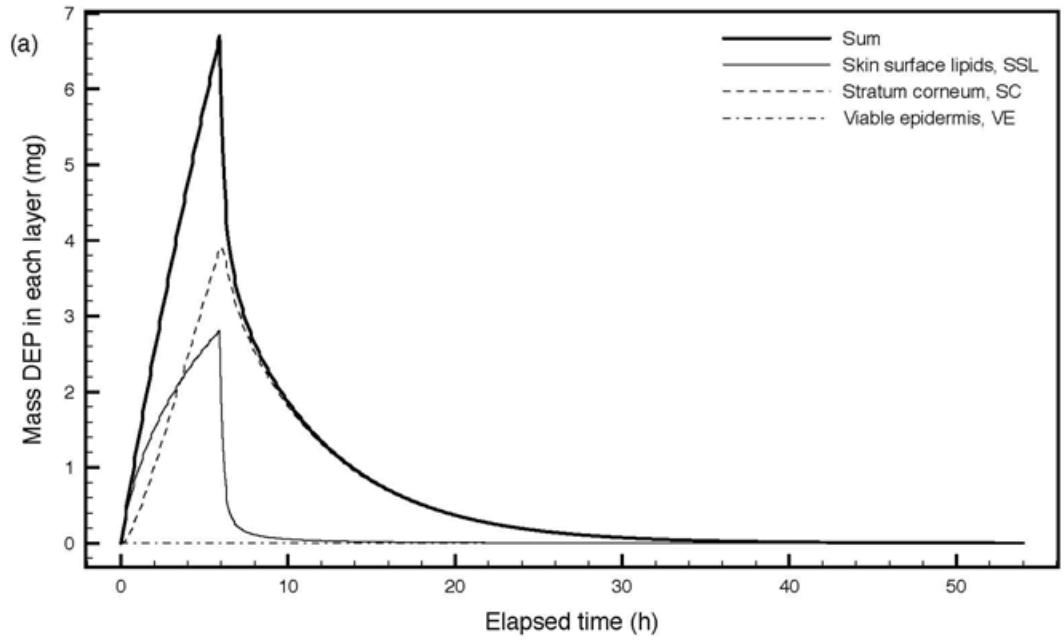

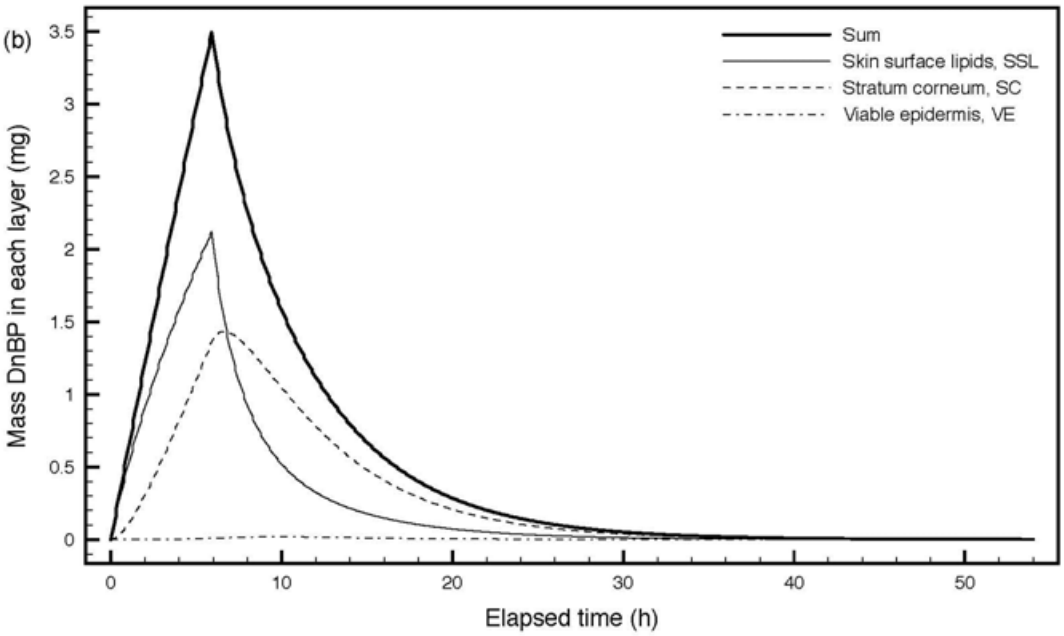

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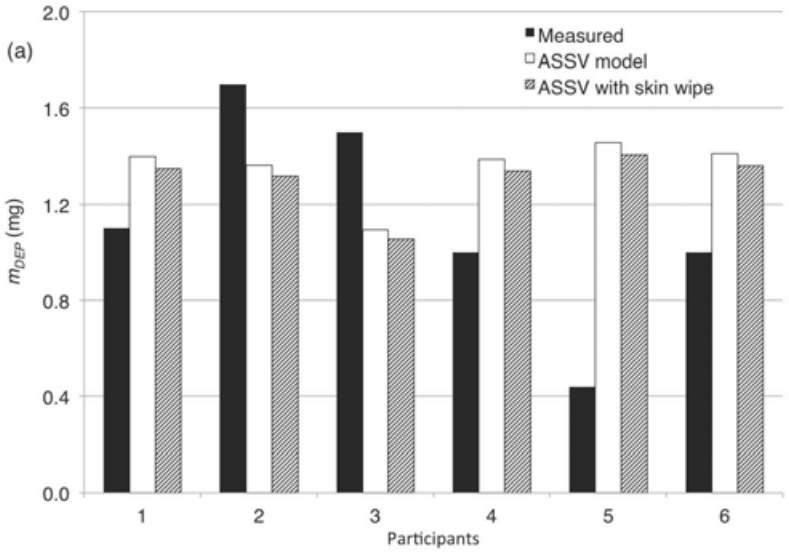

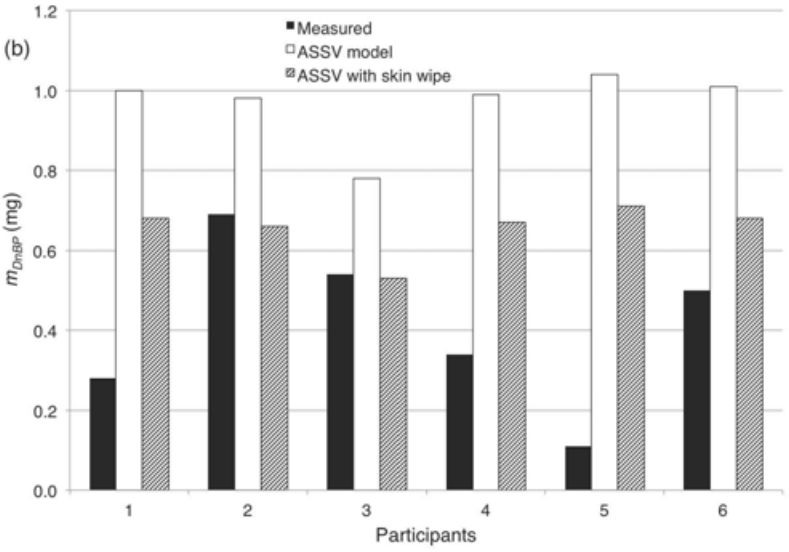

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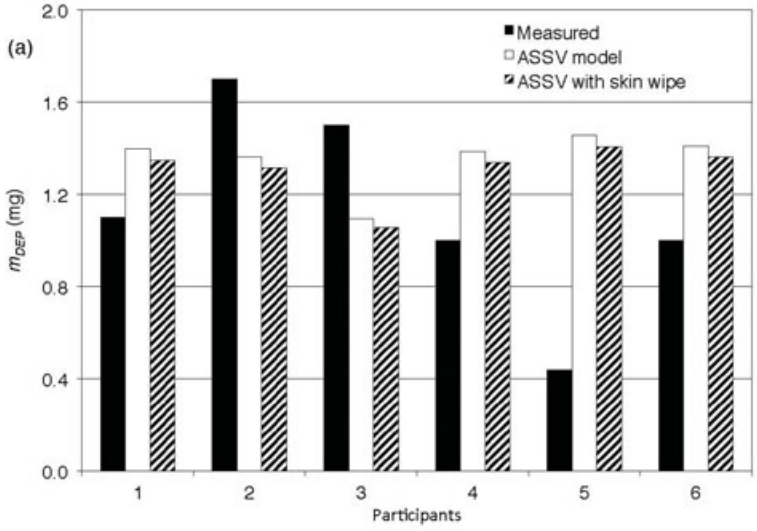

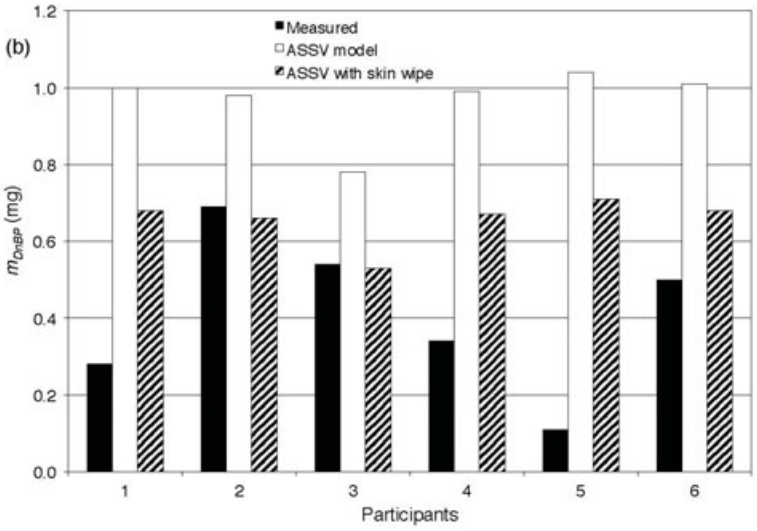

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