1. Introduction

Cleaning the diaper area is an important step in the prevention of diaper dermatitis (Stamatas and Tierney 2014; Adam, 2008). Water and a washcloth were long considered the preferred approach for cleansing during diaper changes, but the polar nature of water limits its ability to remove lipophilic substances from the skin (Adam et al., 2009). Further, water is incapable of pH buffering (Adam, 2008). As a result, baby wipes with buffered lotion have become a common means of cleansing.

The skin compatibility of baby wipes products is well established. A recent review of the literature indicated that, in studies comparing the skin compatibility of baby wipes to water-and-washcloth cleaning, baby wipes produced no difference in the incidence of diaper dermatitis (Blume-Peytavi et al., 2014). Several studies indicate that use of lotioned baby wipes compared to water-and-washcloth cleaning lead to better skin barrier effects, less skin surface abrasion, improvement in diaper rash and repair of the damaged skin barrier function in compromised skin (Ehretsmann et al., 2001, Odio et al., 2001). Visscher et al. studied 131 infants in a Newborn Intensive Care Unit where two wipes formulated for sensitive skin were compared with water-and-washcloth cleaning. The wipe treatment resulted in significantly lower erythema and surface roughness (Visscher et al., 2009). In a study of skin tolerability in babies with atopic dermatitis, Adams and colleagues (Adam et al., 2009) reported that baby wipes used to clean skin during diaper changes were superior to soap or to water alone in maintaining skin pH.

As with other consumer products, manufacturers undertake extensive programs to ensure the safety of the ingredients and components of their products (Dey et al., 2014). The basic framework of risk assessment ensuring safety of an ingredient consists of: hazard identification, dose-response assessment, exposure assessment, and risk characterization (Rider et al., 2009; National Research Council, 1983). Ingredient hazard assessment and dose-response depend on the inherent biological effects of the ingredients or components of the products. Exposure assessment and risk characterization require an understanding of the type of product consumers’ use, the conditions under which the individual will be exposed, and a thorough understanding of the resulting
potential local and systemic dose. Accurate exposure assessment is critical for a robust exposure based risk assessment (EBRA).

Three key variables are important for an EBRA for baby wipes: frequency of wipe use, quantified lotion exposure for each wipe use, and body weight of the child. For products intended for babies, establishing the appropriate values for each variable is especially challenging. Children gain weight rapidly after birth, especially during the first few months of life making it a challenge to determine appropriate body weight. For baby wipes the usage patterns and frequency of use change rapidly as babies grow. The amount of lotion transferred can be affected by both the type of diaper change (wet only, soiled, type of soil, etc.) and the use of multiple wipes in that diaper change, in the sense that a fresh wipe applied to skin wetted by a previous wipe may transfer less than a fresh wipe applied to dry skin.

Baby wipes manufactured by Procter & Gamble consist of a non-woven substrate with 70% inert polymeric material (polypropylene and polyethylene fibers) and 30% cellulose. These are inert materials and have been used in diapers and feminine protection products for decades, and have a long history of safe use (Farage et al., 2004). A lotion is added to the substrate to act as a cleanser and emollient. The lotion is a watery emulsion that may contain mild surfactants, oils, pH balancing substances, skin conditioners, and moisturizers (Adam et al., 2009, Adam, et al., 2008). Robust safety assessments for ingredients in baby wipes with lotion rely on having a clear understanding of lotion exposure (Hossain et al., 2015).

The objective of this study was to estimate the amount of lotion transferred to skin from baby wipes for quantitative exposure assessments of the lotion. Daily exposure to wipes lotion is a function of the number of wipes used, and the amount of lotion transferred from those wipes. Lotion transfer can be a particularly complex process to measure, affected by both the type of diaper change (wet only, soiled, type of soil, etc) and the serial overlapping application of wipes to skin. The approach taken here is to measure the lotion transfer from individual wipe to dry diapered skin, apply our estimates of dry skin transfer values to all wipes used in a day with respect to diaper change, both with and without a reduction due to multiple overlapping wipes. Our exposure assessment is thus built from four component distributional models: the daily usage of wipes (frequency of use), the daily number of diaper changes, the amount of lotion transferred to skin from each baby wipe and the appropriate body weight for different age groups. These four distributional models were combined into a probabilistic exposure model using Monte Carlo simulation to estimate a distribution of the daily lotion transferred (mg/kg bw/day) from the use of baby wipes. The gender, age, weight and country of residence were evaluated for their influence on the distribution of lotion transfer. Lotion transfer was estimated for children over 0–36 months of age as the approximate diapering period of life (Rai et al., 2009). Results will be applied to EBRA as part of an overall safety assessment on lotion formulations or ingredients.

2. Materials and methods

2.1. Frequency of use (FOU) distribution for wipes

A multi-center diary study was conducted in 2013 to determine the number of wipes used per day. Participants were recruited in US (N = 98), UK (N = 232) and Germany (N = 201) by using a screening questionnaire (MarketVision Research, Inc., Cincinnati, OH). Families with young children in diapers who responded that they use at least 2 baby wipes per day for diaper changes were chosen for participation. Demographic information on the children is provided in Table 1. Study participants were given a supply of 64 count Pampers® baby wipes (Procter & Gamble Co., Cincinnati, Ohio, USA) to use during the one week study. Panelists were asked to record the number of wipes used after each diaper change. Two different product versions were used in the study: the North American (NA) version with wipes measuring 180 mm × 180 mm and containing 4.1 g lotion, and the Western European (WE) version with wipes measuring 170 mm × 179 mm and containing 2.8 g lotion. The NA version was evaluated in all three geographies, and the WE version was evaluated in Germany and the UK. When the wipes usage between the two product versions was compared, there were no apparent differences in the FOU (p = 0.913). Therefore, data from all geographies using both wipe variants (NA and WE) was combined to estimate FOU.

The first and last days of the subject diary count data were eliminated due to evidence that at least some of these days did not contain a complete record. Median daily totals were calculated for each household in all three studies. Regression models were fit to the median daily number of wipes as a function of age, while allowing for possible differences due to child’s gender and nationality. In cases where the relationship with age appeared to be nonlinear, a smooth monotonic regression was used. Monotonic regression techniques are a type of nonparametric regression smoother in which the prediction is constrained to be increasing (or decreasing) along the entire range of data (Ramsay, 1998), which we judged to be a reasonable assumption. The wipes count data were subjected to a square root transformation to stabilize the sample variance, and the spread of the distribution around the lines was assumed to be constant across the range of ages. The diaper change frequency per day was obtained from this multi-center diary study (data not shown).

2.2. Estimation of early life body weight distribution

Body weight and age can have critical impact on exposure assessment, particularly in the first four years of life, and having a good model for the effect of age and gender on distributions of body weights is important for understanding the distribution of exposure. Data from the CDC National Health and Nutritional Examination Survey (NHANES) (Centers for Disease Control and Prevention, 2015) for 6517 children between 0 and 48 months whose body weight was measured during the years 2001–2010 were used to determine age-specific body weight distributions for male and female children separately, using the approach described by Portier and colleagues (Portier et al., 2007). Similar sources of information on body weights were not available for Germany and the UK; therefore, US-based distributions from NHANES were used for all exposure calculations.

2.3. Lotion transfer

2.3.1. Lotion transfer from single baby wipe to baby diaper area skin

Lotion transfer from wipe to baby diapered skin was measured at the Procter & Gamble Skin Lab (German Innovation Center,
The test population was divided into 2 groups of 32 babies with a mean age of 3–12 kg. The study was carried out in a controlled environment room with a relative humidity of 45% (±5%) and temperature of 21 °C (±1 °C). The test population was divided into 2 groups of 32 babies with body weight ranges of 3–6 kg and 6–12 kg. Average body weights (Mean ± SD) of the groups were 4.96 (±0.66) kg and 8.37 (±2.05) kg respectively.

For the lotion transfer determination, primary caregivers were provided with baby wipes and asked to wipe the baby’s diapered area as they normally would while cleaning after a bowel movement and urine soiling but on a clean dry skin as a conservative measure. The wiping technique was observed to ensure all surface areas (i.e. buttocks, genitalia, perianal region, intertriginous zones or inguinal creases) were in contact with the wipe for maximum coverage. The body weight of the child was recorded.

Lotion transfer was determined gravimetrically (Sartorius BP221, Mettler, Toledo). The wipes were weighed before and after use. Two correction factors were applied to the gravimetric measure to determine the lotion transfer to the baby’s skin. First, a control wipe was left untouched during the wiping process, but weighed before and after to determine loss due to evaporation. Second, the primary caregivers were asked to wear disposable examination gloves during the wiping procedure. The gloves were weighed before and after to determine lotion transfer to the gloves. Three prototype product variations were used in the study. Products A and C were identical except for the amount of lotion on the product (3.6 g lotion/g substrate, and 5.1 g lotion/g substrate, respectively). Product G used a slight variation in the substrate, but used the identical lotion formulation and amount as Product C (5.1 g lotion/g substrate). Statistical analysis of the transfer results indicated there was no difference in transfer amount based on the specific wipe used; therefore, the data were combined for subsequent use in exposure calculations.

Smooth monotonic regression models were fit to the pooled lotion transfer data, similar to the models for FOU data except that in this case the model is monotonically increasing with weight. The lotion transfer data were subjected to a log transformation, which makes the data more evenly distributed around the regression line.

2.3.2. Forearm model of lotion transfer from sequential use of multiple baby wipes

The purpose of this study was to measure the impact of lotion transfer as a function of multiple wipes used on overlapping skin area. Participants were healthy, adult female volunteers (N = 30), 18–55 years of age. The study was conducted in a controlled environment at the Procter & Gamble Skin Lab (Cincinnati, OH). The study was conducted under ambient temperature (21 °C ± 1 °C) and relative humidity (45% ± 5%). The wipes used in this study were marketed Pampers Sensitive wipes with 4.6 g lotion/g substrate. Lotion transfer to marked areas of the volar surfaces of the forearms (approx. 3in. × 5in.) was determined using a gravimetric method by weighing the wipe before and after use to determine lotion loss or transfer to skin. For all subjects, the forearm was wiped successively by a single technician using first one wipe, followed by second, third and fourth wipe. Lotion transfer was compared between 1, 2, 3, and 4 successive wipe usage. Disposable examination gloves worn during the wiping procedure by the study technician were weighed before and after use to adjust for lotion transfer to the gloves. In addition, an adjustment to the weight differences was also made for evaporation. Evaporative loss was estimated prior to the wiping study by placing a wipe on a weigh boat on an analytical balance mass balance (Sartorius BP221, Mettler, Toledo) and recording the weight every 15 s for 5 min. Because each subject is measured multiple times, a simple linear statistical mixed model with terms for number of wipes used (as a regression variable) and subject (as a random effect to differentiate subject variability from individual measurement variability) was used to determine a relationship between number of wipes used and amount of lotion transferred.

Analytical assessment of two marker components in the lotion was conducted to further investigate the potential trend of lotion ingredient transfer deposition when using multiple wipes successively in an overlapping area. Two of the lotion components served as markers; the polar molecule citric acid, and the nonpolar molecule sodium benzoate. These materials were chosen since their differing molecular characteristics may result in differing interactions with other lotion components, the skin, and the wipes substrate. For this evaluation, test sites were wiped and allowed to dry. Deposited lotion was recovered by sequential tape stripping (22 mm D-Square discs, CuDerm Corporation) of areas within the test site. Specific sites used for tape strip collection were marked so the sites could be avoided when sampling after subsequent wipe applications. Material from tape strip samples was extracted with ultra-pure water (UPW) and compared to internal standards (13C6-CA and d3-BA). The internal standard (IS) stock solution was prepared by weighing approximately 10 mg of each stable isotope labeled compound (13C6-CA and d3-BA) into a glass scintillation vial and then dissolving it in UPW. The IS stock solutions were combined and further diluted to working IS solution at 10 µg/mL in UPW for 13C6-CA and 100 µg/mL in UPW for d3-BA. Citric acid and sodium benzoate, together with their stable isotope counterparts (13C6-CA and d3-BA) were analyzed using HPLC coupled with tandem Mass Spectrometry (MS). Recovery of the chemical markers was determined via liquid chromatography and mass spectrometry (LC/MS/MS). The same mixed model as for the gravimetric method was used to analyze the recovery of citric acid and sodium benzoate.

2.4. Monte Carlo modeling

Monte Carlo simulations have been used for a number of years as a means of deriving uncertainty estimates for medical and biological effects (Thompson et al., 1992; Finkel 1995). These simulations start with the generation of a random number from the distribution estimated for each input variable. In some cases, the distribution of one variable may depend on others previously generated. These random numbers are then fed into the particular formula that relates the inputs to the exposure variable of interest (here, lotion transfer) and the resulting value is intended to represent a single sample from the distribution of the variable of interest (Farrance and Frenkel 2014). When applied to EBRA this means that, for each variable used for an exposure calculation, values are drawn from the separate, representative distributions at random, and combined into a single exposure value. This is repeated many thousands of times to provide an estimated distribution of the potential exposures, which is more informative than a single determination using, for example, the mean for each variable.

The Monte Carlo analysis was similar to that described by McNamara and colleagues (McNamara et al., 2007). The analysis is performed separately for each country, and also for each gender in the UK due to gender differences in that geography. A closely-spaced set of ages is then specified to adequately characterize the effect of age on exposure. When genders are combined, an equal balance of male and female children is used. For a given age and...
gender, a body weight is generated from a distribution similar to those in Fig. 2. A random number of wipes was then generated for the age of child (again, a normal distribution on square root scale, so the random number is squared, and rounded to the nearest integer), and finally a lotion transfer value was simulated for each wipe from the log normal distribution corresponding to that body weight. If it was assumed that lotion transfer decreases with multiple sequential wipe usage in an overlapping area, the process took into account the number of diaper changes those wipes were spread across. After generating that distribution (a process nearly identical to the analysis of wipes FOU; not shown), the wipes were evenly distributed across the changes such that the total daily transfer is maximized. Finally, the daily lotion transfer was calculated (mg/kg bw/day). This series of steps was repeated many times for each combination of country, gender, and age group of interest to generate a distribution of simulated lotion transfers. In this study, 1,000,000 daily lotion transfer values were simulated for each combination of gender and country, for each week of life in the interval 0–36 months (The use of a large number of replicates produces smooth results by eliminating the sampling variability, as seen in figures below; a smaller number of replicates would also be adequate.) We used simple normal distributional models for all end points. In some cases these are on a transformed scale, such as log scale for body weights and square root scale for wipes FOU. The 50th, 90th, and 95th percentiles of the simulated distributions were calculated. For Germany and the US, these percentiles were calculated for male and female children collectively, whereas in the UK, the weekly percentiles were calculated separately for the genders due to gender differences and are the basis for average exposure levels for the 0–36 month’s interval. All models and Monte Carlo simulations were conducted using R environment software (R Core Team, 2015), and the smooth monotone regression fits were calculated with the R package fda (functional data analysis) (Ramsay et al., 2014).

3. Results and discussion

3.1. Frequency of use of baby wipes

A smooth monotonic regression analysis of the household median daily wipes usage as a function of age was performed on the square root scale for wipes (a standard statistical technique for count data). There was a high degree of household-to-household variability in the median number of wipes used per day, as shown by the individual data points (Fig. 1). The figure also shows the estimated 95th percentile of the distribution of data around the regression line, which was used to calibrate the Monte Carlo sampling.

Wipes usage was highest in the UK male children compared to the other geographies and significantly different from UK female children. For the youngest age group (0–10 months), the median number of wipes used was 11.2 wipes/day for males, and 9.3 wipes/day for females. Usage decreased in older children, with usage for the oldest age group (30–40 months) in the UK predicted to be a median of 7.0 for males and 5.0 for female children. In the Germany data, there is no evidence that gender affects the number of wipes used, so the model is the same for both genders. Similar to the UK, increasing age was found to reduce the number of wipes used. In the US neither the age nor gender of the child had a significant effect on usage, with median and 95th percentile usage consistently predicted to be 5.8 and 9.5 wipes/day, respectively. The relatively small size of the US study may play a role in the lack of both age and gender effects in the US study, rather than this observation being indicative of a true difference in the nature of the relationship.

Data and regression models for FOU data are presented in Fig. 1, and Table 2 provides selected age-specific values plus the overall averages for each geography. In Germany, the weekly usage of baby wipes decreased with child’s age. This is consistent with previously reported habits and practices data that indicate fewer diaper changes occur for larger diaper sizes. Rai and colleagues reported that caregivers using diaper sizes 1 and 2 (recommended for babies 4–6 kg and 5–8 kg, respectively) have a change frequency of 5–6 times per day (Rai et al., 2009). Size 4 and 5 diapers used for larger children (10–17 kg and 14–18 kg, respectively) have a change frequency of 3–4 times a day. We found a similar diaper usage frequency among different age groups in a diary study conducted in the US (Internal Data, Dey et al., 2015). The emergence of toilet training, usually at about ages 24–36 months also results in fewer diaper changes, and a reduced use of diaper wipes as some of the cleaning after toileting is done with toilet tissue. In the wipes usage study, the US data visually indicated a decreasing trend in the number of wipes used with increasing child’s age, but it was not statistically significant, possibly in part because of a smaller study population. It is also important to note, however, that the US wipes FOU is significantly lower than that of either the UK or GER, by an analysis of the goodness-of-fit for UK and GER models applied to the US data.

3.2. Body weight modeling

Results of body weight modeling for female children are shown in Fig. 2. In the upper panel, the points are NHANES-based estimates of mean and standard deviation, while the lines are the smooth model used to generate distributions. Representative distributions from those models are shown in the lower panel, in 10 month increments. In the application of this model, every unique age has its own distribution, each slightly different from ages close to it, even those separated by a single day. Both the mean and variance of the body weight distributions increase as the child ages. The results for male children, not shown, are very similar to those shown for female children. Matched on age, a female child weighs slightly less than a male child, but there is a large overlap in the corresponding gender-specific distribution of weights. The largest increase in body weight occurs in the first 10 months of life, with the mean body weight increasing by about 5 kg (Table 3). Between 10 and 20 months, body weight increases by about 2.5 kg. Body weight increase in each of the remaining 10 month intervals is < 2 kg.

3.3. Lotion transfer models

3.3.1. Single Wipe Model as basis of lotion exposure estimation

Results of lotion transfer from a single wipe to dry skin are shown in Fig. 3. The child’s body weight was found to be an important factor in lotion transfer amounts, with greater amounts transferred with larger children. The average amount of lotion transferred was 100–120 mg/wipe for babies at 4–6 kg, and increased to approximately 200 mg/wipe for children weighing 10 kg. Above 10 kg, the average amount transferred remained constant. Lotion transfer from a single wipe was 120 mg for babies weighing up to 6 kg, and 200 mg for babies weighing over 6 kg.

3.3.2. Exposure model based on Single Wipe Model

Single Wipe Model assumes that lotion transfer from all wipes is the same (equal to the lotion transfer from single wipe, without adjusting for potential lotion loss due to wiping with multiple wipes). This model translates to an very conservative, upper bound on total exposure in the sense that one would expect that in practice multiple wipes used in the same change will have some regions of overlapped wiping, and reduced transfer due to pre-
wetting. Using this model and the models for body weight and the wipes FOU, daily lotion exposure was modeled via Monte Carlo simulation. Results are shown in Fig. 4 and Table 4. The table provides exposure estimates for ages at 10 month intervals. Exposure is highest for younger children, with median value predictions between 170 and 320 mg/kg bw/day (for males age 0 months in the US and UK males children, respectively). Lowest predicted exposure levels were among older children, with the lowest median

Fig. 1. Daily frequency of use of baby wipes (Median daily number of wipes). Observed median daily number of wipes for each child are shown as points. The solid lines represent the estimated mean of the median daily number of wipes and dashed lines represent an upper 95% confidence limit on the 95th percentile of median daily wipe totals. The portion of the curves to the left of the vertical reference line at 36 months contribute to the calculation of average daily exposure over range of 0–36 months.
prediction of 80–100 mg/kg bw/day (for female children age 40 months in the UK and GER, respectively). Fig. 4 provides the exposures as a continuous function of age, where the upper boundary lines of each shaded region give the results of this section. Because no gender differences were found for US or GER on the exposure model components, they are combined into an average for the figure.

Body weight has two contrasting effects on lotion transfer. On the one hand, as the child grows, the surface area of the skin increases and, therefore, the contact area for baby wipes. This would tend to increase the amount of lotion that transfers to skin. This tendency is reflected in the increase in transfer amounts from a single wipe as children get older (Fig. 3). However, when determining the daily exposure, this increase in transfer due to greater surface area is more than offset by a reduction in the number of wipes used each day as children get older but larger (Table 2). As a result, the daily exposure expressed in mg/kg bw/day declines from infancy. (Table 4, Fig. 4).
In the previous section, daily lotion transfer estimates were generated using the assumption that the amount of lotion transferred from baby wipes was consistent, or wipes used subsequent to another transfer as much lotion as the first. A more accurate assessment on lotion exposure should consider the impact of sequential multiple wipe use on lotion transfer.

A forearm wipe study was conducted to determine the amount of lotion that transfers from multiple wipes used sequentially during the same cleaning operation. Three different measurement methods were employed, as described in section 2.3.2. In addition to simple gravimetric measurements, sodium benzoate and citric acid were chosen as markers because of their different molecular characteristics, which could lead to differing interactions with the lotion solute (water) and other components, the wipe substrate, and the skin. Fig. 5 shows results of the three measurement methods for the total cumulative transfer from wipes used consecutively on the same site. Each light grey line is the sequence of results of a single subject, while the dark straight line is the regression model, with confidence bands. Because each of the models in Fig. 5 is linear, it implies that the amount each new wipe transfers is a constant over the range 2–4 wipes, regardless of which wipe it is. Results in Fig. 5 also imply that the gravimetric method is estimating more lotion transferred per wipe, because that model has the steepest slope. For each measurement method, a statistical mixed model was used to determine a relationship between number of wipes used and amount of lotion transferred. Gravimetrically, the first wipe transferred a mean of 0.04 g of lotion, which each subsequent wipe (2 through 4) each transferred approximately 0.03 g of additional lotion.

Fig. 6 shows the estimated reduction in lotion transfer (in percentage) of multiple wipes along with confidence intervals. Using the gravimetric data, wipes 2–4 transferred about 75% of the amount of lotion compared to the first wipe used on the identical site. Transfer based on the two lotion ingredients citric acid and sodium benzoates showed a similar reduction trend, but the transfer rate from subsequent wipe is much less (<50% of initial wipe) than that estimated from the gravimetric method (75% of initial wipe). For the multiple wipe model, we chose to use a lotion deposition of 76.1% for wipes used after the first wipe, based on the more conservative gravimetric results.

3.3.3.1. Overall daily lotion transfer: Multiple Wipe Model (weighted population average). Monte Carlo estimation of lotion exposure for the multiple wipe model followed the same methods as section 3.3.2, except that a model for diaper changes in a day was required so that wipes are clustered within a diaper change, and that the first of these would receive 100% transfer, and all following wipes in that simulated change would assume 76.1% transfer. While in reality some diaper changes require the use of more wipes than others, in these analyses wipes were spread out equally among the diaper changes, which is conservative by maximizing the exposure. One of the goals of this project was to develop a single global exposure estimation method that accounts for the impact of multiple wipes used.
estimate for baby wipe lotion. To accomplish that we did a weighted population average of the 3 geographies which was deemed reasonable for EBRA, considering the potential differences in the data for UK male children being a very small proportion of the overall population. Table 5 presents the weighted population average for both lotion transfer scenarios for 0–36 months of age: the maximum exposure value assuming that all wipes transfer as much as the first on dry skin and the minimum exposure value assuming 100% overlap of all wipes used, after the first. These averages produce a range between which we expect truth is likely to lie. For the key percentiles 50th, 90th and 95th they are, at the low end, 130, 230, and 260 mg/kg bw/day, and at the high end 150, 270, and 310 mg/kg bw/day.

3.4. Study considerations

In this study we attempted to understand exposure to lotioned baby wipes for infants 0–36 months of age. It is difficult to directly measure lotion transfer in actual use, but our experimental methods have given a potential range between which the exposure could be, with the multiple models resulting in a more reasonable estimate, due to the total of our conservative assumptions. The primary uncertainties in our calculations concern the percentage of diaper-area skin that each wipe is used on, and how much wiping overlaps areas previously wiped at that change. This manuscript provides exposure estimates that range from 0% to 100% overlapping scenarios.

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Median child weight (kg)</th>
<th>Daily lotion transferred (mg/kg bw/day)</th>
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<tbody>
<tr>
<td></td>
<td>Daily lotion transferred</td>
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<tr>
<td></td>
<td>Median</td>
<td>90th %tile</td>
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<tr>
<td>Males</td>
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<tr>
<td>0</td>
<td>4.71</td>
<td>320</td>
</tr>
<tr>
<td>10</td>
<td>9.56</td>
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</tr>
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<td>20</td>
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<tr>
<td>40</td>
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<tr>
<td>Overall average</td>
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<td></td>
<td></td>
<td>0–48</td>
</tr>
<tr>
<td>Females</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>4.37</td>
<td>270</td>
</tr>
<tr>
<td>10</td>
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</tr>
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<td></td>
<td></td>
<td>0–48</td>
</tr>
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</table>
Estimates supplied in these calculations are likely to be conservative. Where any decisions are made that impact the conservatism of the results, the more conservative is chosen. Important decisions related to this were made for:

i. Amount transferred: gravimetric measures of transfer were made when a single wipe was used to wipe the entire diaper region, leading to an upper bound on transfer since in many cases, especially soiled diapers, the wipe will not be used on the entire diaper area. In many cases, soiling of the wipe would lead to its disposal before 100% of the diapered area skin is wiped.

ii. Adjustment for overlap in transfer per wipe was selected based upon gravimetric methods, which produced the highest transfer amounts for multiple-wipes changes.

iii. In section 3.3.3, the number of wipes used, in a given day, was spread out among the diaper changes so as to maximize transfer by considering wipe usage for diaper changes that did not use wipes.

iv. We have no data on which to estimate the diaper wipes usage of individuals over the duration of the diapering months of age. Our data are much closer to a snapshot in time, but this actually lends some degree of conservatism against this problem, because these data are more variable for estimating median daily usage than would be a more comprehensive analysis of wipes usage across the diapering months. Furthermore, our safety assessment process conservatively extrapolate chronic exposures to the full lifetime of an individual, even though exposure to diaper wipe lotion is typically restricted to a fraction of a lifetime as a diapered child (approximately 3 years), and later as a caregiver.

To account for variability in current products different wipe products were used for the FOU and lotion transfer phases of the overall study. Comparisons of the FOU data indicated that the number of wipes used daily did not differ for different wipes. Statistical analysis of the lotion transfer from the 3 different wipes

Table 5
Overall daily lotion transfer (mg/kg bw/day) for single and multiple wipe model (Weighted population average; 0–36 months).

<table>
<thead>
<tr>
<th>Wipes</th>
<th>50th percentile</th>
<th>90th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single wipe model: equal transfer for all wipes</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>UK</td>
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<td>190</td>
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</tr>
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<td>150</td>
<td>270</td>
<td>310</td>
</tr>
<tr>
<td>Multiple wipes model: 100% overlap (23.9% reduction in transfer after first wipe)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>Females</td>
<td>Males</td>
<td>Females</td>
</tr>
<tr>
<td>UK</td>
<td>190</td>
<td>160</td>
<td>330</td>
</tr>
<tr>
<td>Germany</td>
<td>150</td>
<td>160</td>
<td>250</td>
</tr>
<tr>
<td>US</td>
<td>120</td>
<td>120</td>
<td>200</td>
</tr>
<tr>
<td>Population average</td>
<td>130</td>
<td>230</td>
<td>260</td>
</tr>
</tbody>
</table>

* Population average: averages over genders within a geography, then population size weighted average of the geographies.
used did not show any difference in the transfer amount. However, with continuous product innovation, in case of substantial changes in substrate or lotion application, the amount of lotion transferred may change and may need to be addressed in the future.

4. Conclusions

In this study Monte Carlo Simulations estimated the daily lotion transferred (mg/kg bw/day) to infants from the use of baby wipes taking into account confounding factors of multiple sequential wipe usage representative of in use consumer habit and practice of diapered skin cleaning. The gender, age, weight, and country of residence were evaluated for their influence on lotion transfer. Age and body weight had the greatest influence on exposure; with the models predicting a declining number of wipes used/day and a reduction in lotion transfer as age and body weight increased, which more than offsets the increase in transfer per wipe as body weight increases. Gender influenced exposure only in the UK, with males having a higher daily exposure than female children. Studies on lotion transfer from using sequential wipes demonstrated that wipes used after the first would transfer approximately 76% of the amount of lotion compared to the first wipe as a conservative estimate. Overall, the weighted population average across the three geographies at 50th, 90th, & 95th percentiles, were between 130, 230, 260 mg/kg/day, respectively, and 150, 270, 310 mg/kg/day depending on whether a reduction due to overlap is implemented. Previously we used a deterministic approach where 400 mg lotion transfer from each wipe was applied to an average of 9 wipes/day. Probabilistic modeling provides a more scientifically defensible analysis and refines the previous average lotion transfer of 450 mg/kg/day [lotion 400 mg/wipe x average wipes 9]/8 kg bw] to a 95th percentile 260 mg/kg/day lotion transfer.

Overall, the probabilistic Monte Carlo model accounts for multiple factors of baby wipe exposure in the diapering area, to quantify ingredient transfer from baby wipes that can be used for exposure based safety assessment.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2016.05.006.

References