Regulatory Toxicology and Pharmacology 81 (2016) 183–193

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Exposure Factor considerations for safety evaluation of modern disposable diapers

Swatee Dey [a,*], Mike Purdon [a], Taryn Kirsch [b], HansMartin Helbich [b], Kenny Kerr [a], Lijuan Li [a], Shaoying Zhou [a]

[a] The Procter & Gamble Company, Cincinnati, OH, USA
[b] Procter & Gamble Service GmDH, Schwalbach, Germany

ARTICLE INFO

Article history:
Received 28 June 2016
Received in revised form
25 August 2016
Accepted 26 August 2016
Available online 28 August 2016

Keywords:
Baby
Exposure based safety assessment
Disposable baby diapers
Exposure
Diaper safety
Children

ABSTRACT

Modern disposable diapers are complex products and ubiquitous globally. A robust safety assessment for disposable diapers include two important exposure parameters, i) frequency of diaper use & ii) constituent transfer from diaper to skin from direct and indirect skin contact materials. This article uses published information and original studies to quantify the exposure parameters for diapers. Using growth tables for the first three years of diapered life, an average body weight of 10–11 kg can be calculated, with a 10th percentile for females (8.5–8.8 kg). Data from surveys and diary studies were conducted to determine the frequency of use of diapers. The overall mean in the US is 4.7 diapers per day with a 75th, 90th, and 95th percentile of 5.0, 6.0, and 7.0 respectively. Using diaper topsheet-lotion transfer as a model, direct transfer to skin from the topsheet was 3.0–4.3% of the starting amount of lotion. Indirect transfer of diaper core materials as a measure of re-wetting of the skin via urine resurfacing back to the topsheet under pressure was estimated at a range of 0.32–0.66% averaging 0.46%. As described, a thorough data-based understanding of exposure is critical for a robust exposure based safety assessment of disposable diapers.

1. Introduction

Disposable baby diapers have improved the lives of consumers in many parts of the world. It is estimated that the total number of disposable diapers used during the first 3 years is 4600–4800. The use of superabsorbent gelling materials has resulted in diapers with the capacity to absorb many times their weight in fluid, and to keep the fluid away from the skin resulting in reduced skin hydration and pH changes, and reductions in the frequency and severity of diaper dermatitis (Odio and Friedlander, 2000). In a recent review by Heimall et al. (Heimall et al., 2012), multiple expert opinion articles were cited recommending the use of super absorbent diapers as a key step in preventing and treating diaper rash.

The major components of the modern disposable diaper are inert polymers with a history of safe use in a number of absorbent consumer products (Dey et al, 2014, 2016). The basic structure and composition of diapers have been previously reviewed (Kosemund et al., 2009). It consists of four functional layers (Fig. 1). The topsheet is the layer in direct contact with the baby's skin, and is composed of soft, porous polypropylene developed to transfer urine and other liquids quickly to the layers beneath. The topsheet may also contain a lotion (emollient) to help protect the skin from over hydration and irritation (Baldwin et al., 2001). The acquisition layer is composed of modified cellulose and polyester, and facilitates the movement of liquid away from the skin to distribute it evenly to the diaper core. The diaper core or absorbent layer consists of superabsorbent polymer gel that may be blended with cellulose and contained within a cellulose or a porous polymer nonwoven layer. Urine is locked and stored within its polymeric structure even under pressure. The backsheet is the water-proof outer layer of the diaper, typically made of soft textured, cloth-like polypropylene laminated with a polyethylene film. Its function is to prevent liquid from leaking out of the diaper. Diapers also contain additional features primarily designed to ensure a good fit,

Abbreviations: EBSA, Exposure Based Safety Assessment; QRA, Quantitative Risk Assessment; BW, body weight; PERMID, Prolonged Exposure Rewet Method in Diapers; TWA, time-weighted average; FOU, frequency of use; LOW, length of wear; SABAP, Speed of Acquisition with Balloon Applied Pressure.

* Corresponding author. 6280, Center Hill Ave, Cincinnati, OH 45224, USA.
E-mail address: dey.s.3@pg.com (S. Dey).

http://dx.doi.org/10.1016/j.yrtph.2016.08.017

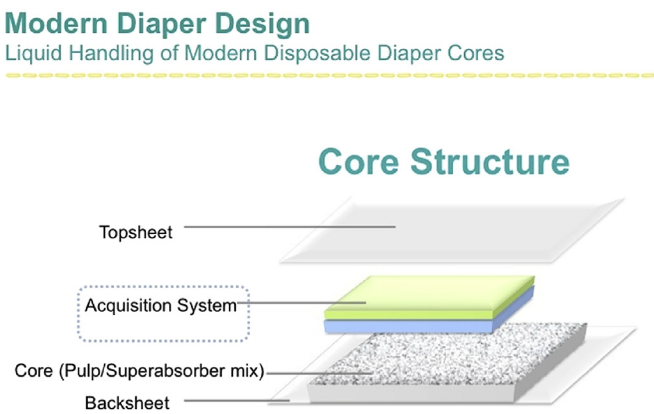

Fig. 1. Basic functional layers of a modern disposable diaper.

such as, fastening systems and tapes, and leg cuffs to prevent leakage.

The approach for safety assessment of baby diapers and other absorbent consumer products have been described previously (Kosemund et al., 2009 Rai et al., 2009; Dey et al., 2014), and it follows the same risk assessment process established by the US National Academy of Sciences (National Academy of Science (1983)). It consists of a 4-step process that includes hazard identification, dose-response assessment, exposure assessment, and risk characterization. Hazard assessment and dose-response depend on the potential biological effects of the constituents in the raw materials. Exposure assessment and risk characterization require an understanding of the consumers (children), the conditions under which diapers are used, and a thorough understanding of potential local and systemic exposures. The overall risk assessment approach and consideration for children's product have been recently reviewed where physiological and developmental differences that may result in differential sensitivity associated with early-life exposures have been discussed (Felter et al., 2015).

In addition to the polymeric materials, diapers may also have a small amount of small molecular weight non-polymeric constituents or impurities at very low levels for which a thorough assessment is conducted prior to marketing the product to ensure a high level of consumer safety assurance. This includes evaluation of all relevant toxicological endpoints. Appropriate uncertainty factors are incorporated into the safe threshold levels of individual constituents to account for interspecies and intra-species differences. In addition to a thorough assessment of the systemic endpoints of the diaper constituents, skin irritation and skin sensitization are evaluated for additional safety assurance to ensure absence of local skin effects. This is confirmed via adult skin patch test. Further, clinical in-use studies are conducted to confirm favorable skin compatibility when necessary. Once marketed, consumer health comments are monitored for continued product safety assurance under 'in-use' conditions.

For a robust exposure based safety assessment (EBSA), understanding exposure via accurate consumer habits and practices data and the exposure dynamics of a 3-dimensional product like a disposable diaper is needed. This paper focuses on key parameters used to develop an appropriate diaper exposure assessment. These include diaper user biometric information, including appropriate body weight and surface area for a growing user population (babies) collected from published literature, as well as product related parameters such as frequency of use, length of wear, and constituent transfer to skin (Table 1).

2. Diaper user biometric parameters

2.1. Body weight (BW)

Diapers are used by babies approximately for 36 months or less (AAP, 2003). During this period, children gain weight rapidly, especially during the first few months of life, as demonstrated by monthly body weight data on international growth standards published by US EPA Exposure Factors Handbook (US EPA, 2011) and the Centers for Disease Control (CDC) (Centers for Disease Control and Prevention, 2010, 2015) (Fig. 2). The US EPA has published recommendations for body weight for exposure assessment of children 0–1, 1–3, 3–6, 6–12 months, and 1–2 and 2–3 years old (US EPA, 2011). It is not practical to assess diaper exposure for multiple age brackets and for a specific point in time, because BWs in the diaper wearing children are transient and rapidly increasing. According to EPA guidance when exposure is likely to occur it is appropriate to sum across time-weighted values for all age periods. This approach is expected to increase the accuracy of risk assessments because it will take into account life stage differences in exposure (US EPA, 2005). A time weighted average (TWA) is used for exposure that is not constant at any one given time, for eg, infant BW changes every day; changing exposure over time. So, consistent with EPA guidance we have chosen to use a TWA BW based on US EPA recommended average BWs for the diapering period of 0–36 months (Table 2). A TWA BW for children 3 months to 2 years was used to determine ingestion of an environmental contaminant by non-dietary hand-to-mouth behaviors and the weighted average BW for 3 months to 2 years was 10.2 kg (US EPA, 2014). This is consistent with the approach taken in this manuscript for estimating TWA BW for the first 3 years to estimate diaper exposure. Human milk and lipid intake distribution was defined using TWA intake for children 0–6 months and 0–12 months for assessing cumulative exposure and risk (Arcus-Arth et al., 2005; US EPA, 2011). Daily inhalation rates for adults and children (10 years, 1 year old and new born babies) were estimated over a specified period of time based on a TWA of inhalation rates associated with physical activities (ICRP, 1981; US EPA, 2011). TWA was also used for health evaluation of exposure to CO_2 (NIOSH, 1976). For diaper exposure the TWA BW provides a conservative assumption over the diapering period of 3 years.

Based on US EPA data, the TWA for mean BW for a typical diapering age of 0–36 months for both genders combined is 11.0 kg. The 10th and 95th percentile TWA BW for both genders combined is 9.1 kg and 13.6 kg respectively. The TWA BW from EPA is in reasonable agreement with the TWA BW based on growth data published by the CDC (0–24 months and 24–36 months) (Centers for Disease Control and Prevention, 2010, 2015). Using CDC data the mean, 10th and 95th percentile TWA BW for both genders for children 0–36 months is 10.2 kg, 8.8 kg and 12.4 kg, respectively. The 10th percentile BW for females from this data set is 8.5 kg. For EBSA we use 8 kg BW for the entire diapering period. This is conservative since the TWA BW over 36 months is lower than 8 kg. Although the BW is < 8 kg in the first 6 months of an infant's life, the growth rate is rapid and is 3.5 times faster than between 7 and 36 months (calculation not shown); so the BW during majority of the diapering period is > 8 kg.

2.2. Surface area

Appropriate assumption of skin surface area is needed to estimate dermal exposure (mg/cm^2/day) to assess skin sensitization based on child specific dose per unit area. In a review of the available human and experimental animal data, Kimber et al. clearly provide evidence that under the majority of exposure

Table 1
Exposure considerations for safety assessment of raw material constituents in baby diapers.

Exposure Parameters	Abbreviation	Definition, as applicable to diapers
General considerations		
Body weight	TWA BW	Time-weighted average body weight for children 0–36 months of age
Skin surface area (exposed surface)	SA	For diapers, it is assumed that the surface area is the area of the diaper part in contact with the skin.
Specific for the product category		
Habits and practices (H&P)		
Frequency of use	FOU	Number of diapers used per day.
Constituent transfer to skin		
Direct skin contact	ITdirect	% Constituent transfer to skin from materials in direct skin contact.
Indirect skin contact (i.e., rewetting)	ITindirect	% Constituent present in diaper core materials that dissolve in fluids and reflux back to the skin (re-wetting)
Specific for the constituent raw material in the diaper		
Amount of constituent in product	Amt	Determined by product composition, given as μg or mg.
Dermal absorption	DA	Compound-specific (defaulted at 100% in the absence of data)

Examples of EBSA calculations: Systemic dose (mg/kg/day): [Amt (mg) × FOU (#/day) × (ITdirect% or ITindirect %) × DA%]/TWA BW (kg) = Exposure (mg/kg/day).
Dose per unit area of skin (mg/cm²/day): [Amt (mg) x FOU(#/day) (ITdirect% or ITindirect %) x DA%]/SA (cm²) = Exposure (mg/cm²/day).

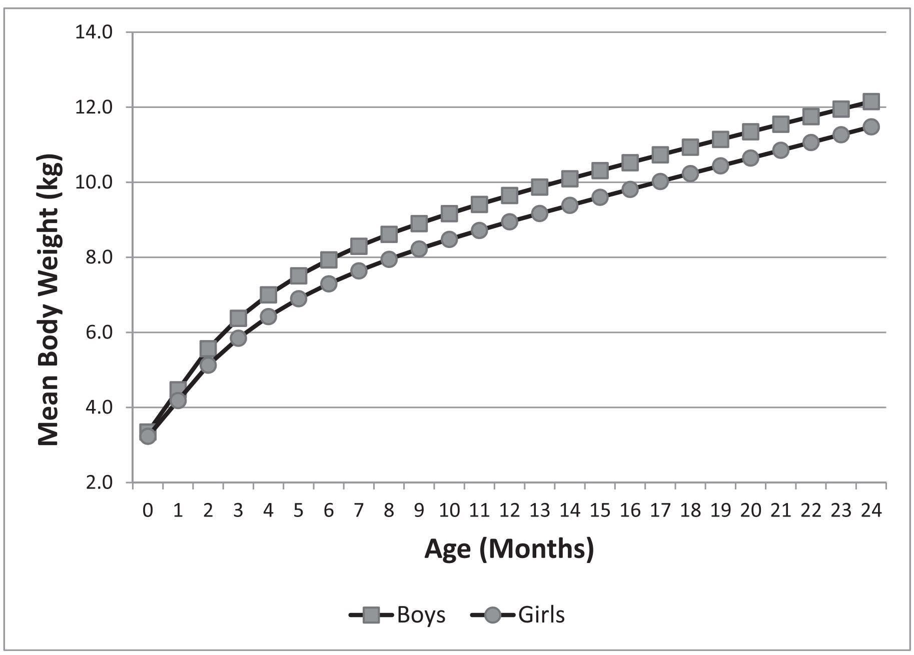

Fig. 2. Mean body weight during the first 2 years of life Figure adapted from monthly body weight data on international growth standards published by the Centers for Disease Control (CDC) (Centers for Disease Control and Prevention, 2015).

Table 2
Time-weighted average (TWA) of body weight for children 0–36 months (US EPA, 2011).

Age group	# Of Months in weight range	Mean body weight (kg)			10th percentile body weight (kg)			95th percentile body weight (kg)		
		Both genders	Males	Females	Both genders	Males	Females	Both genders	Males	Females
EPA recommended body weights (US EPA, 1992)										
Birth to <1 month	1	4.8	4.9	4.6	3.9	3.6	4	6.2	6.8	5.9
1 to <3 months	2	5.9	6	5.7	4.7	5	4.6	7.3	7.3	7.3
3 to <6 months	3	7.4	7.6	7.2	6.1	6.4	5.9	9.1	9.1	9
6 to <12 months	6	9.2	9.4	9	7.5	7.9	7.3	11.3	11.5	11.2
1 to <2 years	12	11.4	11.6	11.1	9.3	9.7	9.1	14	14.3	13.7
2 to <3 years	12	13.8	14.1	13.5	11.5	12	11	17.1	17	17.1
TWA body weight		11.0	11.2	10.7	9.1	9.5	8.8	13.6	13.7	13.5
Comparison to CDC data (from Fig. 2, calculations not shown) (Centers for Disease Control and Prevention, 2010, 2015)										
TWA body weight		10.2	10.5	9.9	8.8	9.1	8.5	12.4	12.6	12.2

Example of TWA calculation for mean and 10th percentile (both genders) for 0–36 months.
TWA (Mean) = [(1 × 4.8) + (2 × 5.6) + (3 × 7.4) + (6 × 9.2) + (12 × 11.4) + (12 × 13.8)]/36 = 11.0.
TWA (10th) = [(1 × 3.9) + (2 × 4.7) + (3 × 6.1) + (6 × 7.5) + (12 × 9.3) + (12 × 11.5)]/36 = 9.1.

conditions it is the surface area of contact, expressed as the dose per unit area of a chemical (e.g. mg/cm2) that has the greatest impact on the acquisition of skin sensitization, which is considered to be a local effect. So, accounting for the surface area of contact provides a reasonable estimate of the exposure to the constituent of interest (Kimber et al., 2008). Proportion of skin surface area in children (total body and specific body parts i.e., head, trunk, arms, legs, genitalia and buttock etc.) are available for estimation of dose per unit area (US EPA Exposure Factor handbook, 2011; Boniol et al., 2008; Sharkey et al., 2001). The area of skin exposed to specific consumer products can be extrapolated from these data. For diapers, the components (topsheet, back ear, etc) being assessed is measured for appropriate surface area to estimate exposure in mg/cm^2/day. No specific surface area for the different diaper components have been reported here, since it varies based on the size and design of the diaper.

3. Exposure parameters related to product use

3.1. Diaper frequency of use

Frequency of use (FOU) is a key parameter in evaluating exposure to diapers. We considered both survey and diary data. First, a representative global survey on disposable diaper use was conducted in 10 countries during 2007–2008 (P&G Global H & P Survey Data). Surveys were conducted via door-to-door interviews among mothers of babies 0–36 months of age in India, China, Philippines, Russia and Saudi Arabia. In France, Germany, UK, Japan and the US the survey was administered by mail to mothers of babies 0–48 months. Mothers recorded the average number of disposable diapers worn by their child in a typical day. The mean daily disposable diaper usage ranged from 0.3 to 5.9. The lowest reported FOU was in India, with 75% of responders indicating no use of disposable diapers. In China, 50% of responders reported 1 or fewer disposable diapers per day. The country with the highest FOU was the US with a mean of 5.9 and a reported 50th percentile of 6 (Table 3). One limitation for this survey was the absence of diaper size information.

Second, diary data collected in 2010–2012 for sizes 2–5 were analyzed (P & G Diaper H & P Diary Studies, 2010, 2011, 2012, 2012). Studies were conducted in the US (Cincinnati, OH), and participants were asked to use the test products for a period of 5 days. Participants kept a diary on a variety of performance characteristics including the number of diaper changes every day. Panelists were mothers of healthy children 0–48 months. Results indicate an inverse relationship between FOU and diaper size. The mean number of diaper changes was 5.6 ± 2.1 for babies using Size 2 diapers, and 4.1 ± 1.5 for babies using Size 5 diapers (Table 4). For comparison, a previous report (Rai et al., 2009) is also included in Table 4 that indicates an average change frequency of 4.5 diapers per day. A 2008 environmental assessment in the UK cited an average daily use for disposable diapers of 4.16 per day, based on 2001–2002 sales figures (Aumônier et al., 2008). Overall, these data are comparable between the current study and previous studies.

A comparison of data from the US reveals that the mean FOU differed between the survey and the diary study. The survey results (Table 3) indicated a mean diaper change of 5.9 and a 75th, 90th and 95th percentile of 7, 10 and 10 diapers respectively for the US. However, the diary data (Table 4) indicated an overall mean (all sizes) of 4.7, with a 75th, 90th, and 95th percentile of 5.0, 6.0, and 7.0 respectively. It is likely that this difference is related to the manner in which the data were collected. Survey data are limited by the accuracy of the responder's recall and often under or overestimates usage; whereas diary data represent a real-time record of product usage where parents record each use. In this case the survey data also lacked diaper size information.

3.1.1. Length of wear

Length of wear (LOW) of various diaper sizes were evaluated to estimate duration for which each size was worn. Based on diaper size and body weight per CDC growth chart, it is clear that for majority of the diapering period children use size 3 and 4 diapers (Tables 4 and 5). Hence, considering length of wear and rapid growth of children during the first 5 months after birth, using FOU parameters for sizes 3–4 seems reasonable. In addition, a higher FOU for size 2 and below may not necessarily mean a higher exposure since the time in each wet diaper will be less.

3.2. Constituent transfer from diaper to skin

Diapers are made primarily of inert large molecular weight polymeric materials which are not bioavailable. The safety assessment is mainly focused on small molecular weight non-polymeric constituents that can be potentially transferred to skin via two pathways: direct skin contact and/or indirect skin contact. In both cases transfer of constituents from diaper to skin is variable based on proximity to skin, and the physical and chemical properties of the constituent.

3.2.1. Direct skin contact

In a modern diaper, the only components of the diaper that are in direct contact with the skin are the diaper topsheet and those parts of the diaper intended for fit and to prevent leakage, i.e. the side panels/backears, barrier leg cuffs or the waistband. In some diapers the topsheet is coated with a lotion (emollient) to help provide skin benefits. Transfer of lotion was assessed in an experimental setup to determine a conservative default for potential transfer of constituents from diaper parts in direct contact.

Table 3
Diaper frequency of use by country (survey data).

Country	No. of participants	Diaper use per day				
		Mean	50th percentile	75th percentile	90th percentile	95th percentile
India [a]	285	0.3	0	0	1	2
China [a]	2267	1.5	1	2	4	4
Philippines [a]	461	2.3	2	3	4	5
Russia [a]	722	3.2	4	5	6	7
Saudi Arabia [a]	545	4	4	5	6	7
France [b]	587	4.7	5	6	7	7
Germany [b]	567	4.7	5	6	6	7
UK [b]	901	5	5	6	8	8
Japan [b]	326	5.5	5	7	8	10
US [b]	972	5.9	6	7	10	10

Parents recorded the average number of disposable diapers used each day.
[a] Interviewer administered, door-to-door.
[b] Self-administered by mail.

Table 4
Diaper frequency of use by size in the US (diary data).

Diaper size (BW range)	No. of participants	Diaper use per day				*Data reported in* Rai et al., *2009*
		Mean ± SD	75th percentile	90th percentile	95th percentile	Average change frequency
Size 1 (4–6 kg)	Not done	–	–	–	–	6
Size 2 (5–8 kg)	200	5.6 ± 2.1	7	8	9	5–6
Size 3 (7–13 kg)	150	4.7 ± 1.5	5	6	7	4–5
Size 4 (10–17 kg)	150	4.4 ± 1.5	5	6	7	4
Size 5 (14–18 kg)	150	4.1 ± 1.5	5	6	6	3
Overall (all sizes)	650	4.7 ± 1.8	5	6	7	

Parents kept a diary of disposable diaper usage for the performance consumer testing on diapers of various sizes.

Table 5
Estimated Length of Wear (LOW) for each diaper size for children up to 36 months of age.

Diaper size	Body weight range[a] (Manufacturer's recommendation - without overlap)	Using mean BW[b]		
		Age range (months)	LOW (months)	% Of total LOW [c]
Boys				
Size 1	4–5.5	0–2	2	6%
Size 2	5.5–7.5	2–5	3	8%
Size 3	7.5–11.5	5–21	16	44%
Size 4	11.5–15.5	21–36	15	42%
Size 5	15.5–17.5			
Girls				
Size 1	4–5.5	0–2	2	6%
Size 2	5.5–7.5	2–7	5	14%
Size 3	7.5–11.5	7–24	17	47%
Size 4	11.5–15.5	24–36	12	33%
Size 5	15.5–17.5			

[a] BW range for diaper sizes assumes size increases in the middle of the weight range overlap.
[b] Mean body weight (BW) based on CDC growth charts (Center for Disease Control and Prevention, 2010).
[c] The % of total LOW is based on 3 years (36 months) exposure to diapers.

Measurements for direct skin transfer of diaper components have been previously described (Odio et al., 2000). The test product was a diaper (Size 4) with 101 mg lotion spread on a topsheet of 83.7 cm^2 (1.207 mg/cm^2 lotion). Children who were routine users of disposable diapers were recruited for participation. A total of 60 children were randomly assigned to one of two groups of 30 children each. Sections of collection tape (Tegaderm™, 3M, St. Paul, MN) were affixed to the lower buttocks of all infants (2 tapes/child; one on each side of the gluteal cleft). In the first treatment group, one tape section was removed after wearing a single lotion-treated diaper for 3 h (3-h tape). The child was diapered with a fresh test product for an additional 3 h and the second tape was removed (6-h tape). In the second treatment group, the parents of each infant were given a full-day supply of lotion-treated diapers and were instructed to use the supplied product exclusively over the next 24 h for all normal diapering practices. One of the two tapes on each of these children was removed and saved by the parent at bedtime (18-h tape). The second tape was left undisturbed from initial application until removal at the next day's visit to the laboratory (24-h tape) (Odio et al., 2000).

Results of lotion transfer to skin are shown in Table 6. Results from group 1 indicate that transfer from a single diaper (3-h wear) was 48.6 ± 5.88 $\mu g/cm^2$ (Mean ± SE), or 4.0% of the starting amount of lotion on the diaper topsheet. In the 6 h wear collections, two diapers transferred 72.7 ± 7.82 $\mu g/cm^2$, or a total of 3.0% of the starting amount of lotion on two diapers. Results from group 2 indicate that transfer from a single overnight diaper was 52.2 ± 6.04 $\mu g/cm^2$ or 4.3% of the starting amount of lotion on the diaper topsheet. Two lotion transfer data points were derived from ad libitum use of multiple diapers over the course of 18 and 24 h. Total lotion transfer was 103.7 ± 6.88 and 169.7 ± 17.02, respectively. Without knowledge of the number of diapers used it is not possible to calculate a percent transfer. However, data reported in Table 4 indicate that an average of 4.4 Size 4 diapers is used each

Table 6
Direct transfer of lotion from diaper topsheet to skin.

Wear time	N	Amount of lotion transferred ($\mu g/cm^2$)	Number of diapers used	% Lotion Transfer per Diaper
		Mean ± SEM		
Group 1				
3 h	24	48.6 ± 5.88	1	4.0%
6 h	22	72.7 ± 7.82	2	3.0%
Group 2				
Overnight	20	52.2 ± 6.04	1	4.3%
18 h	15	103.7 ± 6.88	multiples	ND
24 h	12	169.7 ± 17.02	multiples	ND

Direct transfer measurements were conducted using a diaper with 0.101 gm lotion spread on a topsheet of 83.7 cm^2, or 1.207 mg/cm^2. The percentage of lotion transferred to collection tapes was calculated for those samples with a known number of diaper applications (i.e., 3-h, 6-h and overnight wear times).

day. If we assume 4.4 diapers are used in a 24-h period the transfer amount represents 3.2% of the starting amount of lotion on 4.4 diapers (calculation not shown in table). Estimation of lotion transfer using a higher percentile FOU of diapers will further reduce the percent lotion transfer. Rai et al. (2009). recommended the use of 7% in exposure calculations for the direct transfer of materials from diaper topsheets. This represents about a 2-fold exaggeration over the data reported by Odio et al. (2000).

3.2.2. Indirect skin contact

Diaper core constituents beneath the topsheet are not in direct contact with the skin. However, in the presence of urine, small fraction of the constituents within the core of the diaper may have the potential to migrate to the topsheet surface by the phenomenon of re-wetting. Re-wetting is defined as the fraction of total liquid load that resurfaces back to the topsheet after absorption due to changes in surface pressure on the absorbent material.

3.2.2.1. Rewet study. Rewet from diaper core has been described previously (Rai et al., 2009). Here, an updated rewet method in diapers has been established to mimic a more realistic diaper wear scenario (Prolonged Exposure Rewet Method in Diapers - PERMID) for EBSA purposes. This method uses a gravimetric approach where collagen is used as a skin mimic and takes into account a) the pressure an infant may apply to a diaper, b) a representative urine load during diaper wear, c) the gap between urine voids, d) exposed surface area and e) diaper wear time.

3.2.2.2. PERMID. The Speed of Acquisition with Balloon Applied Pressure (SABAP) equipment was used to measure rewet via the PERMID method. It is a pneumatic box with a latex membrane, pressure regulator, manometer, pneumatic pistons and acquisition hole with electrodes [FKV S.r.1.Via Fatebenefratelli, 3 Sorisole, Bergamo, Italy; Described in a European patent (Herrlein, 1997)]. Pressure applied by the pneumatic cushion in turn applies pressure on the diaper (**Fig. 3**).

The diaper was laid flat on the SABAP equipment and wetted intermittently with 3 loads of normal saline (0.9%) under a pressure of 0.41 psi over a 4-hr period (Fig. 3a). Saline was loaded at 60 ml per load at an interval of 82 min (at 0 min, 82 min and at 164 min with 5 min of acquisition time after each load). After the application of the first load of saline a set of 4 stacked rectangular collagen sheets (43 cm × 10.3 cm; Coffi Collagen, Globe Packaging Co. Inc) were placed on the diaper to cover the core. Then the SABAP lid was closed and pressure was applied at 0.41psi (Fig. 3b). This was repeated twice with the same collagen set re-applied to the same diaper after each saline load. The liquid transferred was determined gravimetrically by weighing the collagen sheets before (dry sheets) and after completion of the experiment (wetted due to rewet) (**Fig. 3c**). A percent rewet based on the total volume (180 ml) of saline added to the diapers was calculated**.**

3.2.2.3. Rewet parameters. Infant pressure was measured using a sensor mat (Force Sensing Array, Vista Medical, Winnepeg, Manitoba, CA) linked to a computer program (FSA software, Vista Medical) that measures pressure applied to the mat. Children (n = 174) ranging in age from 2 weeks to 52 months (diaper size newborn to size 6) completed the study. Pressure exerted by the child was measured in four positions: sitting upright, lying on back, lying on stomach, and plopping down on their bottom (Fig. 4) (Internal data, Baldwin, 2008). Since sleeping is a major part of the day for a diapered child the average pressure applied while lying on the back and front for children 18–24 months (0.41 psi) was considered for experimentation.

A wetting scenario was chosen to simulate realistic diaper wear conditions for an average 18–24 month old child. The most comprehensive information on urine volume and voiding patterns was reported by Goellner et al. (Goellner et al., 1981). A summary of

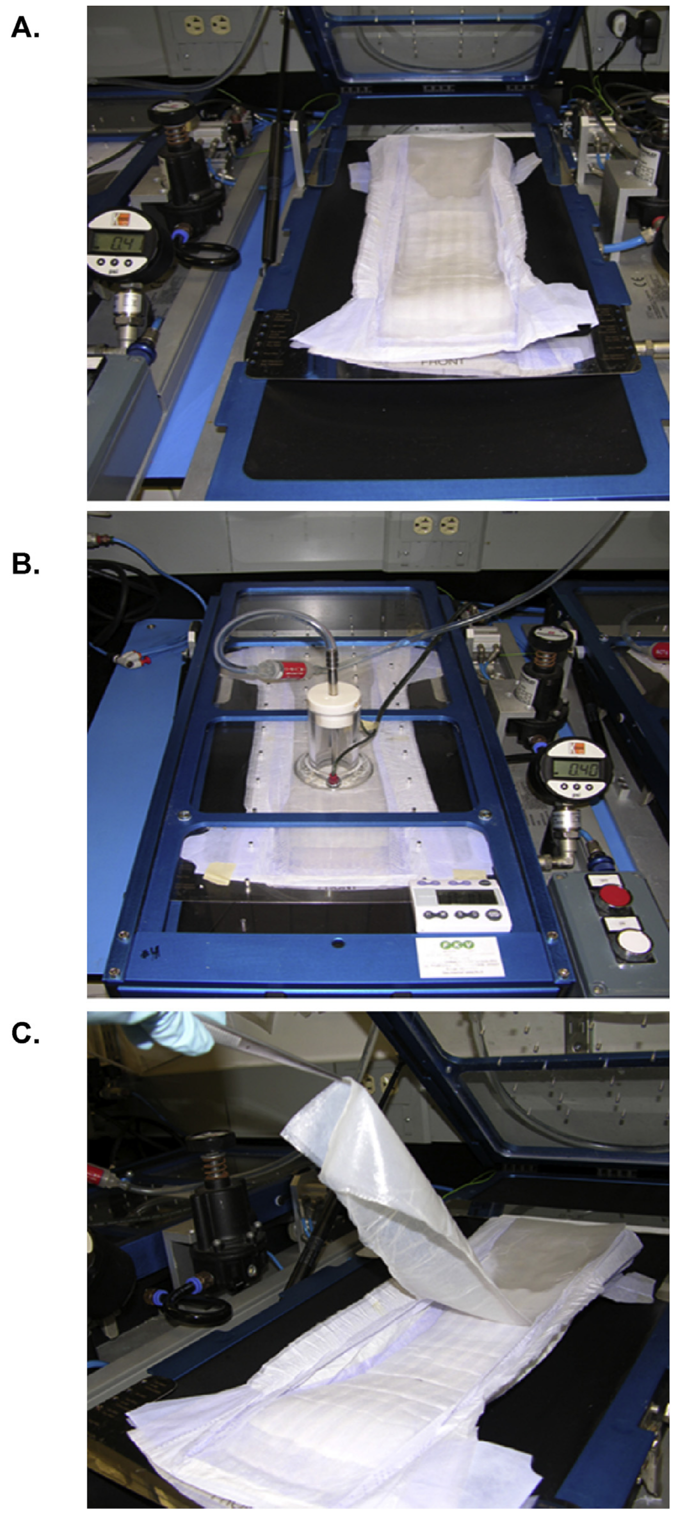

Fig. 3. Rewet test using the SABAP equipment a) Test diaper on the SABAP equipment. b) An aliquot of fluid being applied through the acquisition hole, following which the pre-weighted dry collagen sheets are laid on top to the diaper before closing the equipment lid and applying a pressure of 0.41 psi for the appropriate amount of time till the next load. c) Collagen sheet being removed after completion of fluid loads for gravimetric measurements.

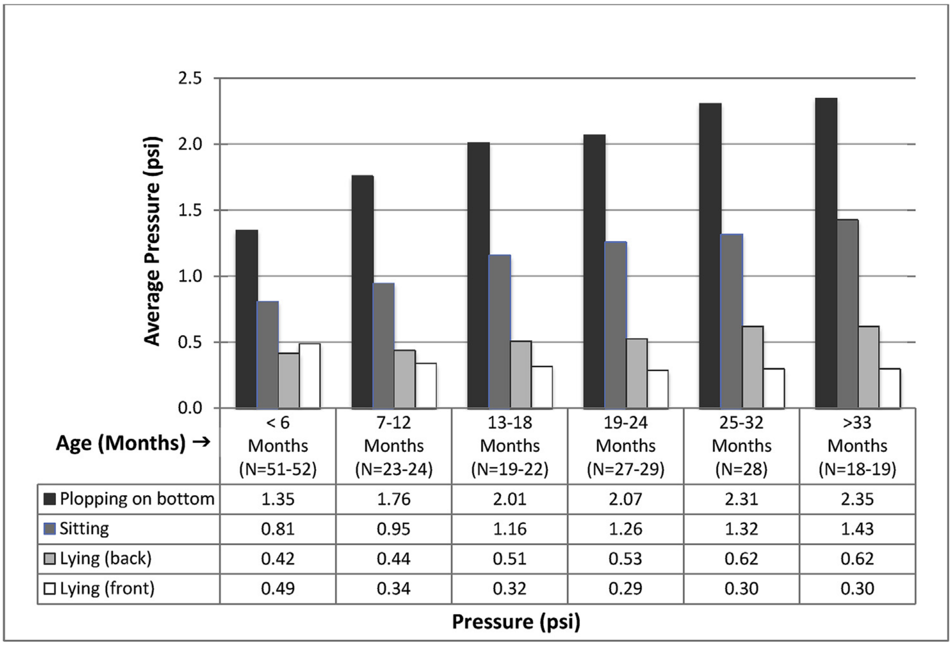

Fig. 4. Pressure applied by infants during various activities by Age A pressure mat was calibrated to 10 psi. Participants included 174 children ranging in age from 2 weeks to 52 months. The pressure exerted by each child was measured in four positions: sitting upright, lying on back, lying on stomach, and plopping down on their bottom (with the assistance of the child's caregiver). For the sitting and lying down positions, the pressure was measured for 10 s starting once the child settled into position. For plopping, the pressure was recorded immediately for 1 s. Due to physical limitations, plopping measurements were not attempted on very young children.

Table 7
Urination patterns among infants.

Age (months)	Weight (kg)	No. of participants	Voids per day (#) mean + SD	Volume per void (ml) mean + SD	Volume per day (ml) mean + SD	Voids during sleep[a] (#)	Time between voids when awake[b] (min)
0–1	3.58	10	20.1 ± 4.6	19.3 ± 4.1	378 ± 77	7.8	49
1–2	5	9	20.4 ± 2.4	27.1 ± 5.5	556 ± 140	7.1	50
2–4	5.82	14	19.5 ± 5.6	25.8 ± 6.8	496 ± 145	4.5	52
4–6	6.97	18	18.7 ± 6.6	28.4 ± 7.1	505 ± 150	3.0	56
6–12	8.26	39	20.1 ± 4.4	30.9 ± 8.3	610 ± 172	3.0	52
12–18	10.7	24	15.9 ± 3.7	57.3 ± 21.6	873 ± 287	2.5	68
18–24	12.01	21	13.5 ± 5.1	63.1 ± 19.9	782 ± 213	2.4	82
24–32	13.9	15	10.8 ± 3.1	79.3 ± 14.9	863 ± 300	2.1	102

Adapted from Goellner et al. (1981).
[a] Calculated based on the total number of voids per day and portion of time spent sleeping.
[b] Calculated based on the total number of voids while awake and portion of time spent awake.

relevant variables is presented in Table 7. A void volume of 60 ml with voiding every 82 min was used for experimental purposes. An older infant pressure and urine volume parameters were used as a conservative approach that would cover younger infants as well.

Control diapers were analyzed where dry collagen sheets were placed on the dry diapers with a 4 mm mesh nylon screen between the collagen stack and the diaper surface (~2 mm gap) to determine non-contact absorption of water vapor. This was done to normalize any weight gain of the collagen sheets due to absorption of moisture from the atmosphere.

3.2.2.4. Rewet results. Eleven different diapers were tested in triplicate. The rewet was measured for the entire diaper core surface area. However, during actual diaper in use conditions only a small portion of the diaper is under-pressure (either back or front of the diaper or when baby is sitting). Hence the applied pressure from the baby will not be on 100% of the diaper surface area at all times, so the percent transfer was adjusted by 50% and deemed reasonable for exposure assessments. So, the rewet ranged from 0.32 to 0.66% averaging at 0.46% (Table 8). Rewet results for the current study are fairly consistent with an earlier report by Rai et al., (2009). where a default of 0.25% rewet was used based on data and recommendation by the European Disposables and Nonwovens Association (EDANA, 2005). Current values are slightly higher probably because the previous method did not take into account prolonged exposure time and a larger surface area coverage which was acknowledged as a shortcoming.

The currently described rewet method provides a reasonably conservative default estimate for exposure to constituents not in direct contact with the skin because a) the gravimetric measure of the collagen sheets before and after use assumes the saline weight gain as the transfer of the diaper constituent without considerations for solubility potential of the chemical and b) the rewet parameters are based on older diaper wearing infants (18–24 months) with larger urine volume and higher pressure exerted during in use which would result in a higher rewet.

Table 8
Percent re-wet from diapers during simulated 4 h wear.

Diaper types (size 4)	Weight of collagen sheet (g)[a]		Re-wetting moisture on collagen sheet (g)[a]		Normalized collagen weight	% Rewet – Full diaper (total volume 180 ml)	% Rewet – 50% of diaper contact area
	Initial (dry collagen)	Post (wet collagen)	Wt difference in wet & dry collagen	Wt difference of pre and post blank collagen			
1	5.27	8.29	3.03	1.88	1.15	0.64	0.32
2	5.284	8.64	3.36	1.96	1.40	0.77	0.39
3	5.32	8.62	3.30	1.99	1.31	0.72	0.36
4	5.27	9.81	4.53	2.25	2.28	1.27	0.64
5	5.26	9.93	4.67	2.30	2.37	1.32	0.66
6	5.22	8.32	3.10	1.83	1.27	0.70	0.35
7	5.28	9.56	4.28	2.16	2.11	1.18	0.59
8	5.76	10.91	5.16	3.41	1.75	0.97	0.49
9	5.637	11.01	5.37	3.40	1.97	1.09	0.55
10	4.41	8.11	3.61	2.40	1.21	0.67	0.33
11	4.42	7.96	3.54	2.20	1.34	0.74	0.37
Mean ± SD	5.19 ± 0.13	9.20 ± 0.33	3.99 ± 0.25	2.34 ± 0.17	1.65 ± 0.14	0.92 ± 0.07	**0.46 ± 0.04**

Re-wetting was evaluated as described in Section 3.2.2. Normal saline was loaded onto the test diaper in 3 aliquots of 60 ml each (180 ml total). Aliquots were added at 82 min intervals. The amount of liquid that transferred to the collagen sheets was determined gravimetrically. Collagen sheets on control diapers (blank) were used to normalize any weight gain of the collagen sheets due to absorption of moisture from the atmosphere.

[a] All samples were tested in triplicates.

4. Targeted chemical analysis using PERMID (acrylic acid)

For targeted chemical analysis PERMID can be used followed by analysis of the collagen sheet for the specific chemical. Acrylic acid - a residual monomer in the super absorbent gel (SAP) present in the diaper core was analyzed (Table 9). Five diapers were tested in triplicate for the amount of extractable acrylic acid from the collagen sheets. The collagen sheets were extracted with 100 ml of analytical reagent grade water (ARW) by vortexing for 10 min. The analyte, acrylic acid (AA) and internal standard, acrylic acid-$^{13}C_3$ were subjected to reversed-phase high performance liquid chromatographic (HPLC) analysis on a Water's YMC-ODS-AQ column. Detection and quantitation was by tandem mass spectrometry (MS/MS) operating under multiple reaction monitoring (MRM) conditions. Results indicated acrylic acid was below level of quantitation (10 μg/diaper). Transfer of AA based on the quantitation limit and the amount of residual AA in the SAP, ranged from 0.15 to 0.21%, averaging at 0.19% (Dey et al., 2015a). This example confirms that the mean default rewet of 0.46% is a conservative estimate, considering AA is readily soluble in water.

It is important to point out that in most cases it may be impractical to generate chemical-specific rewet data for every starting material as disclosed by the supplier. An alternative approach could also be to understand the potential exposure to finished product constituents by extraction of the collagen sheet to detect transferred chemicals via total rewet using PERMID and quantifying the detected constituents for safety assessment. This may be resource intensive to do routinely; although a good alternative when needed. Hence, estimating a default rewet value via the gravimetric method is considered a reasonable alternative, when no chemical specific rewet value can be established. The estimate of acrylic acid is a good example to compare with the default rewet value since here chemical specific rewet value can be accurately measured, as acrylic acid is present only in the SAP material of the core. The total extractable acrylic acid was estimated by analyzing pure SAP via GC/MS. The collagen extracted values were compared with the total extractable amount to estimate transfer.

5. Dermal absorption

Understanding the systemic bioavailability of the constituents in the diaper components is important to predict exposure. Two important parameters to understand exposure are: i) the amount of the constituent in the product and ii) dermal absorption of these constituents (Table 1). The dermal absorption is dependent on compound-specific physical/chemical properties, such as the molecular weight, polarity, and chemical structure as well as the exposure condition (skin health, occlusive vs. semi occlusive) (Hoang, 1992). It is well understood that intact skin in healthy full-term infants' exhibit similar skin barrier properties based on TEWL values (Fluhr et al., 2012). However, skin in the diaper area may be compromised by diaper rash, mechanical irritation, or occlusion and hydration that may affect dermal absorption. Differences between the diapered area and the non-diapered area have reduced over time with the advent of modern diaper technologies that keeps moisture away from the baby skin in the diaper area (Adam, 2008; Akin et al., 2001; Wong et al., 1992). In a study conducted by Stamatas et al., 2011, Infants with diaper dermatitis were measured in the areas of lesional diapered skin, non-lesional diapered skin, and control (non-diapered skin on the outer thigh). Comparison of barrier function of diapered skin area vs. non-diapered skin showed that diapered skin area without rash (about 85–90% of diapered area) is normal and has similar barrier function (TEWL 47 ± 29 g/m^2/hr) as non-diapered skin area (outer thigh; TEWL 48 ± 30 g/m^2/hr), as indicated by similar TEWL. However, skin of children with diaper dermatitis showed higher TEWL (104 ± 67 g/m^2/hr) compared to non-diaper rash skin and non-diapered skin indicating that diaper rash skin can be vulnerable due to loss of stratum corneum resulting in increased TEWL (Stamatas et al., 2011). The authors indicated that all cases of dermatitis were either mild to moderate, and no severe cases were observed probably due to the use of modern disposable diapers (Stamatas et al., 2011).

Compromised skin conditions as in contact dermatitis and diaper dermatitis could potentially increase dermal penetration of constituents. The degree of impact depends on the constituent and the degree of damage to the skin. For example, skin compromised via diaper rash, mechanical, chemical, and UVB damage has shown variable penetration properties which were modest in magnitude, with only slightly higher dermal penetration rate compared to normal skin (Gattu and Maibach, 2011). Several other studies even indicate that compromised skin does not necessarily result in increased dermal penetration of constituents (McCormack et al., 1982; Dey et al., 2015b). A comparison penetration of alcohols after 6 h in adult, full-term and premature infant autopsy abdominal skin samples indicate a range of dermal penetration of 0.004–1.4%

Table 9
Experimental % rewet and QRA for acrylic acid in diaper SAP.

Acrylic acid (mg/kg)	SAP (15 g/Size 4)	Acrylic acid/Diaper (μg/diaper)	LOQ < 10 μg/Diaper	% Acrylic Acid/Diaper[a]
325	15	4875	BQL	0.21
380	15	5700	BQL	0.18
340	15	5100	BQL	0.20
323	15	4845	BQL	0.21
433	15	6495	BQL	0.15
AVERAGE				0.19

[a] Maximal rewet percent is based on QL (10 μg/diaper) as actual value (this is conservative and real value could be lower).

Table 10
Exposure Parameters for risk assessment of raw material constituents in baby diapers.

Exposure Parameters	Abbreviation	Definition, as applicable to diapers		
General considerations				
Body weight	TWA BW	8 Kg Time-weighted average body weight for children 0–36 months of age		
Skin surface area (exposed surface)	SA	For diapers, surface area is specific to the diaper part in contact with the skin (Variable by size and design)		
Specific for the product category				
Habits and practices (H&P)				
Frequency of use	FOU	Mean 4.4	90th %tile 6	95th %tile 7
Constituent transfer to skin				
Direct skin contact	ITdirect	4% Constituent transfer to skin from materials in direct skin contact.		
Indirect skin contact (i.e., rewetting)	ITindirect	1% or chemical specific data		
Specific for the constituent raw material in the diaper				
Amount of constituent in product	Amt	Determined by product composition, given as μg or mg.		
Dermal absorption	DA	Compound-specific or conservative estimate based on phys/chem properties in the absence of data		

Table 11
Exposure Based Safety Assessment for Acrylic Acid (AA) in Diapers.
Systemic Exposure (mg/kg/day) = [Amount of constituent x Frequency of use (FOU) × Transfer Factor (direct or indirect –TF) × Dermal absorption (DA)]/Body weight.

Total amount fo SAP in pad	15 g
Amount of free acrylic acid (extractable monomer)	500 ppm (manufacturer's upper limit)
Diaper – Frequency of Use/day	6
Rewet Factor (%)	0.19%
Dermal absorption	100%
Weight of baby	8 kg
Total available acrylic acid/day	500 μg/g monomer x 15 g × 6 × 0.19% × 100% × 1 mg/1000 μg = 0.086 mg/day
Total available acrylic acid/kg BW/day	0.086/8 = 0.011 mg/kg/day
RfD of acrylic acid (US EPA, 1994)	0.5 mg/kg/day
Margin of Safety (MOS) = RfD/consumer exposure	0.5/0.011 = 45

in adults, 0.002–1.6% in full-term infants and 0.04–35.5% in premature infants (McCormack et al., 1982). An *in vitro* skin penetration model using human *ex-vivo* skin to estimate penetration for intact and compromised skin barrier conditions indicated that overall penetration of [^{14}C]-PEG-7phosphate applied as a baby wipe lotion constituent ranged from 0.76 to 1.27% for intact skin and 3.19–4.42% for highly-compromised skin (premature skin mimic) under repeat and single dose applications respectively. Skin barrier deficiency was characterized by tape stripping and transepidermal-water-loss (Dey et al., 2015b). Therefore, although dermal penetration is increased in compromised skin conditions it is not increased to 100%.

6. Overall diaper exposure model

All of the above exposure parameters described is used in the safety assessment of diapers (Tables 10 and 11). The exposure parameters took into account specific exposed consumer (children), appropriate exposure routes and the duration and frequency of use of the product. For a complete safety evaluation of the constituent, it is important to understand the concentration range of the constituent in the product, and appropriate exposure based on intended use of the product (dermal exposure, inhalation, or oral ingestion) vs. reasonably foreseeable use.

Safety assessment for Acrylic acid: The superabsorbent polymer (SAP) is one of the main absorbent components of the diaper core (indirect skin contact). It is made up of inert polymeric material with high molecular weight. SAP is a polymerized form of acrylic acid. The EBSA for SAP is mainly for the residual acrylic acid monomer. In a urine wetted diaper most of the acrylic acid is present as a salt form (sodium acrylate) which does not penetrate skin as easily as acrylic acid (Rai et al., 2009). The hazard profile of acrylic acid was evaluated by the European Risk Assessment Program (EEC 793/93) (Institute for Health and Consumer Protection, 2002) and the US Environmental Protection Agency (US EPA, 1994). The US EPA reference dose (RfD) for acrylic acid has been determined as 0.5 mg/kg/day.The RfD of 0.5 mg/kg/day was based on the US EPA two-generation reproductive and developmental toxicity study in rats with acrylic acid administered via drinking water. In this study, the critical effect was decreased pup weight in the F1 and F2 generations at the mid dose of 240 mg/kg/day, resulting in a NOAEL of 53 mg/kg/day. Application of standard 10X uncertainty factors for interspecies and intraspecies extrapolation results in a chronic reference dose of 0.5 mg/kg/day. Use of this reference dose derived from oral data to support dermal risk assessment is considered conservative since toxicokinetic studies in rats and mice have demonstrated that approximately 80–90% of AA is absorbed orally while dermal absorption after cutaneous administration is about 20–25% (ECB, 2002). The margin of safety (MOS) is determined by dividing the AEL by the consumer exposure level (CEL). The CEL needs to be below the AEL in order to be safe for consumer use. Current, updated exposure parameters have been used for assessment of acrylic acid which includes a BW of 8 kg, 90th percentile FOU (6 diapers), experimental rewet transfer factor (0.19%), and 100% dermal penetration (Table 11). Based on the comprehensive risk assessment of acrylic acid using diaper EBSA and a MOS of 45; it can be concluded that there are no systemic human safety concerns for the residual acrylic acid that may be present in the SAP of disposable diapers.

7. Discussion and conclusions

When developing EBSA for products intended for children, special care is required to ensure that appropriate and conservative exposure parameters are used. An EBSA for disposable diapers is based on child specific exposure considerations, and takes into account the type of product, and specific habits and practices of product use, as well as age appropriate body weights and exposed skin surface areas. In addition, the EBSA must incorporate the potential amount of constituents transferred to the skin with direct contact and via re-wetting as urine resurfaces with changes in applied pressure.

EBSAs often use consumption by 'high-end' consumers to develop a conservative exposure assessment. The US Environmental Protection Agency (US EPA, 1992) and the European Scientific Committee on Consumer Safety (SCCS, 2012) use 90th percentile as the 'high-end exposure'. The World Health Organization defines the upper, high-end boundaries for exposure assessments at or above the 90th percentile (World Health Organization, 2008).

In the safety assessment of chemicals in diapers we use a body weight of 8 kg which is less than the TWA body weight for 0–3 yrs at 10th percentile (9.1 kg). Based on more accurate diary data (vs. surveys) across diaper sizes 3–5, a 90th percentile FOU of 6 is recommended. The FOU of diaper sizes 3–5 is considered for EBSA based on the LOW estimation which shows that during majority of the diapering period children wear diaper sizes 3–5 (80–86% of 3 years). This seems reasonable since infants grow rapidly during the first 5 months after birth. Also increased FOU of diapers may not necessarily increase the exposure since the duration of wear is less/diaper. Although a default dermal penetration of 100% is used in the absence of data, there is evidence that dermal penetration even for a compromised skin barrier is not 100%.

In conclusion, this manuscript provides a detailed perspective on the various conditions of exposure associated with diapers that have varied levels of skin contact due to its 3-D structure and composition. It provides updated information on consumer habits and practices and product exposure scenarios to enable a more robust EBSA to ensure continued consumer safety.

Conflict of interest

All authors are employees of the Procter and Gamble Company. No funding was received from any external source for any aspect of this submitted work.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2016.08.017

References

AAP.org, 2003. Toilet training your child: the Basics. Contemp. Pediatr. 21 (3). https://www2.aap.org/sections/scan/practicingsafety/Toolkit_Resources/Module7/barton_schmitt_protocol_guide_for_parents_1.pdf.

Adam, R., 2008. Skin care of the diaper area. Pediatr. Dermatol 25 (4), 1–7.

Akin, F., et al., 2001. Effects of breathable disposable diapers: reduced prevalence of Candida and common diaper dermatitis. Pediatr. Dermatol 18 (4), 282–290.

Arcus-Arth, A., Krowech, G., Zeise, 2005. Human milk and lipid intake distributions for assessing cumulative exposure and risk. J. Expos Anal. Environ. Epidemiol. 15, 357–365.

Aumônier, S., et al., 2008. An Updated Lifecycle Assessment Study for Disposable and Reusable Nappies, Science Report – SC010018/SR2. Environment Agency. Bristol. Available at: http://www.nappyinformationservice.co.uk/docs/SCHO0808BOIR-E-E.pdf.

Baldwin, S., et al., 2001. Skin benefits from continuous topical administration of a zinc oxide/petrolatum formulation by a novel disposable diaper. J. Eur. Acad. Dermatol Venereol. 15 (Suppl. 1), 5–11.

Boniol, M., et al., 2008. Proportion of skin surface area of children and young adults from 2 to 18 years old. J. Invest. Dermatol 128, 461–464.

Centers for Disease Control and Prevention, 2010. WHO Growth Standards. Available at: http://www.cdc.gov/growthcharts/who_charts.htm#The%20WHO%20Growth%20Charts.

Centers for Disease Control and Prevention, 2015. The National Health and Nutrition Examination Survey(NHANES) (accessed April 6, 2015). http://www.cdc.gov/nchs/data/series/sr_11/sr11_246.pdfnhanes.htm.

Dey, S., et al., 2014. Safety of disposable diaper materials: extensive evaluations validate use. Clin. Pediatr. 53 (95), 17S–19S.

Dey, S., et al., 2015a. Exposure factor considerations for risk assessment of modern disposable diapers. In: Society of Toxicology Meeting (SOT), Abstract # 505, San Diego, CA.

Dey, S., et al., 2015b. An *in vitro* skin penetration model for compromised skin: estimating penetration of polyethylene glycols ^{14}C-PEG-7 phosphate. Skin Pharmacol. Physiol. 28, 12–21.

Dey, S., et al., 2016. Modern diaper performance: construction, materials, and safety review. Int. J Dermatol. 55 (S1), 18–20.

European Chemicals Bureau, 2002. European Union Risk Assessment Report, Acrylic Acid Risk Assessment. Office for official publicaitons of the European Communities, ISBN 92-894-1272-0.

European Disposables and Nonwovens Association, 2005. Worldwide Strategic Partners: Standard Test Methods for the Nonwoven Industry http://www.edana.org/story.cfm?section=|edana_nonwovens&story=testmethods.xml.

Felter, S.P., et al., 2015. Assessment of health risks resulting from early-life exposures: are current chemical toxicity testing protocols and risk assessment methods adequate? Crit. Rev. Toxicol. 45 (3), 219–244.

Fluhr, J.W., et al., 2012. Infant epidermal skin physiology: adaptation after birth. Br. J. Dermatol 166, 483–490.

Gattu, S., Maibach, H.I., 2011. Modest but increased penetration through damaged skin: an overview of the in vivo human model. Skin. Pharmacol. Physiol. 24, 2–9.

Goellner, M.H., et al., 1981. Urination during the first three years of life. Nephron 28, 174–178.

Heimall, L.M., et al., 2012. Beginning at the bottom: evidence-based care of diaper dermatitis. MCN Am. J. Matern. Child. Nurs. 37, 10–16.

Herrlein, M.K., 1997. Method for assessing disposable absorbent structures. Patent # EP 0797967 A1, Assignee: The Procter & Gamble Company.

Hoang, K.T., 1992. Dermal Exposure Assessment: Principles and Applications. U.S. Environmental Protection Agency. Office of Health and Environmental Assessment, EPA/600/8–91/011B, Washington, DC. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=12188.

ICRP (International Comminssion on Radiological Protection), 1981. Report of the Task Group on Reference Man. IARC publicaiton 23. Pergammon Press, New York, NY.

Internal Data Baldwin, S., 2008. Infant Pressure Measurements. Studies BR11-06-05, BR 12-06-02, BR 1-07-8.

Kimber, I., Dearman, R.J., Basketter, D.A., et al., 2008. Dose metrics in the acquisition of skin sensitization: thresholds and importance of dose per unit area. Reg. Tox Pharm. 52 (1), 39–45.

Kosemund, K., et al., 2009. Safety evaluation of superabsorbent baby diapers. Regul. Toxicol. Pharmacol. 53, 81–89.

McCormack, J.J., et al., 1982. An in vitro comparison of the permeability of adult versus neonatal skin (Chapter 11). In: Maibach, Howard L., Boistis, Edward K. (Eds.), Neonatal Skin: Structure and Function. Publisher Marcel Dekker, pp. 149–164.

National Academy of Science, 1983. Risk Assessment in the Federal Government. National Research Council. National Academy Press, Washington, DC.

National Institute for Occupational Safety and Health (NIOSH), 1976. Criteria for a

Recommended Standard, Occupational Exposure to Carbon Dioxide. August.
Odio, M., Friedlander, S.F., 2000. Diaper dermatitis and advances in diaper technology. Curr. Opin. Pediatr. 12, 342–346.
Odio, M.R., et al., 2000. Continuous topical administration of a petrolatum formulation by a novel disposable diaper. 1. Effect on skin surface microtopography. Dermatology 200 (3), 232–237.
Rai, P., et al., 2009. Safety evaluation of disposable baby diapers using principles of quantitative risk assessment. J. Toxicol. Environ. Health A 72, 1262–1271.
Scientific Committee on Consumer Safety, 2012. The SCCS'S Notes of Guidance for the Testing of Cosmetic Substances and Their Safety Evaluation, 8th revision. Available at: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf.
Sharkey, I., et al., 2001. Body surface area estimation in children using weight alone: application in paediatric oncology. Br. J. Cancer 85 (1), 23–28.
Stamatas, G.N., et al., 2011. Documentation of impaired epidermal barrier in mild and moderate diaper dermatitis in vivo using noninvasive methods. Pediatr. Dermatol 28, 99–107.
US EPA, 1992. Guidelines for Exposure Assessment. U.S. Environmental Protection Agency, National Center for Environmental Assessment. Available at: http://www.epa.gov/raf/publications/pdfs/GUIDELINES_EXPOSURE_ASSESSMENT.PDF.
US EPA, 1994. Acrylic Acid Ingredient Risk Information Systems (IRIS)http//cfpub.epa.gov/ncea/iris/index.cfmfuseaction=iris.ShowQuickView&substance_nmbr=002.
US EPA, 2005. Guidance on Selectign Ager Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants. EPA/630/P-03/003F.
U.S. EPA, 2014. Child Specific Exposure Scenarios Examples. U.S. Environmental Protection Agency, Washington, DC. EPA/600/R-14/217F.
U.S. EPA, 2011. Exposure Factors Handbook. Edition (Final). U.S. Environmental Protection Agency, Washington, DC. EPA/600/R-09/052F.
Wong, D.L., et al., 1992. Diapering choices: a critical review of the issues. Pediatr. Nurs. 18 (1), 41–54.
World Health Organization, 2008. Harmonization Project Document No. 6. Available at: http://www.inchem.org/documents/harmproj/harmproj/harmproj6.pdf.