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Approaches to Safety Evaluation of Baby Wipes

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Abstract

Disposable baby wipes manufactured by Procter & Gamble, soft sheets bearing lotion that is balanced to maintain natural skin pH, are convenient for cleaning the diaper area and a quick cleanup on baby's face and hands. *Objective:* Develop a rigorous safety assessment process to ensure that baby wipes are safe and gentle to skin. This process is built-in from the start of product research and development. *Methods:* A systematic, iterative approach that includes (1) exposure-based safety assessment of all raw materials for systemic and local effects, which are consistent with established risk assessment paradigms; (2) when needed, testing of finished wipes in *in vitro* and/or clinical studies for skin and eye irritation, contact sensitization, or mechanical effects on skin in comparison to benchmark products that have a long history of wipe safety in marketplace; (3) prospective and randomized in-use studies in babies; and (4) in-market monitoring that is an integral part of the on-going product safety assessment. *Results:* Individual approaches and/or their combination show mildness of the test wipes. Further, in-market monitoring is testimony to baby skin compatibility of baby wipes. *Conclusion:* The approaches that have been developed demonstrate the skin compatibility and/or benefits of baby wipes relative to other modes of cleaning if needed. This article describes our safety assurance program, exposure-based safety assessment, and the range of robust testing strategies and approaches that can be employed to assure the safety of baby wipes.

Keywords

baby wipes, infant skin, premature infant skin, diapered skin, safety testing, skin irritation and sensitization, exposure assessment, skin pH, clinical study

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Introduction

Disposable baby wipes have been used in the care and hygiene of diapered baby skin for decades. Aside from portability and convenience, the most important product benefits are the ability to clean thoroughly while being gentle to baby skin. Caregivers find them convenient and effective for cleaning during diaper changes and quick cleanup on baby's hands and face.

Since we introduced a disposable wipe in 1996, design and formulation improvements have been incorporated to better meet the needs of babies, parents, and caregivers. Continuous innovations in the sheet, or substrate, have produced a soft and flexible wipe that effectively removes and absorbs soil. The substrate is wetted with a water-based cleaning and skin care formulation called "lotion" herein that not only aids in emulsifying and removing soil, but also helps maintain a natural skin surface pH.

As the products are refined and improved, we actively assess each change to assure (i) our baby care products continue to be safe and effective when used as intended and under reasonably foreseeable use conditions by caregivers, (ii) our operations are safe for employees and the environment, and (iii) all regulatory requirements are met or exceeded wherever our products are sold.[1,2] This article is focused on the comprehensive tiered and iterative approach that we employ to evaluate and ensure the safety of individual wipe constituents as well as the finished product. In addition, our worldwide in-market surveillance and monitoring allow us to

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collect and incorporate the feedback of caregivers into our manufacturing and safety evaluation processes. On an ongoing basis, caregiver complaints of product tolerance are compared with those seen historically providing confirmation of the safety of our baby wipes in the marketplace and our approach to safety assessment.

Baby Wipe Design

Our baby wipes consist of a substrate and lotion. The current substrate is a non-woven sheet made of regenerated cellulose and polypropylene/polyester fibers, which are blended to be soft and flexible with a cloth-like feel. The regenerated cellulose component provides absorptive and cleaning properties and the polypropylene/polyester adds softness and flexibility. A hydroentangled blend of fibers with different shapes serves to increase loft and softness, improve skin surface contact, and increase absorptive void space. The attributes above make the substrate more effective in physically removing soil and absorbing fluid while protecting the caregiver's hands. The components of the substrate may be modified or rebalanced to achieve the desired product attributes. The lotion is released from the sheet during use to loosen and facilitate soil removal. The lotion pH and its buffering capacity are effective in maintaining a natural skin surface pH (an important indicator of skin health) after bowel movement and urination.[3,4] The result is gentle yet effective skin cleaning.

Overview of the Safety Assurance Process

Our safety assurance program for baby wipes is outlined in Figure 1. This program is based on the exposure-based safety assessment paradigm (hazard identification, dose-response assessment, exposure assessment, and risk characterization) documented by National Academy of Sciences[5,6] and World Health Organization (WHO).[7] Each step is described in the following sections.

In the first step of this tiered approach, material compositions are disclosed by suppliers to enable evaluation by the toxicologist to ensure that the constituents in each wipe component can be considered safe when formulated into a baby wipe (See Section 4). Upon assurance of the safety of lotion and substrate, the finished wipe can be evaluated in a confirmatory battery of tests to demonstrate skin and eye compatibility (See Section 5). Evaluations of wipe exposure and tolerance for both healthy infants and neonatal intensive care unit (NICU) patients, including preterm infants are summarized (See Section 6). When appropriate, independent scientific review of our safety program is conducted by external scientific advisory groups to obtain additional perspective (See Section 7). Importantly, in-market surveillance and monitoring of consumer experience on an on-going basis provides further confirmation of wipe safety and the robustness of our safety approach (See Section 8).

Safety Assessment of Baby Wipe Chemical Constituents

Hazard Characterization

Wipe constituents (lotion ingredients and substrate components, including trace substances), are identified and characterized based on their safety profiles (Tier 1, Figure 1). Sources of safety data include, but are not limited to, *in silico* prediction, *in vitro* testing, non-clinical and clinical studies, as well as human case reports. The lotion ingredients all have adequate supporting toxicological data and ingredients with an extensive history of safe human use as cosmetic ingredients and/or food additives are preferred. Materials used in the substrate are primarily polymeric in nature that is, stable high-molecular-weight materials, which pose no systemic toxicological concern. Therefore, the safety assessment for the substrate tends to focus on the trace levels of non-polymeric substances for example, process aids, solvents, additives, and potential residual monomers.

Using literature data in the assessment for human safety of wipe constituents, the standard approach is followed such as identification of critical effect, characterization of the dose-response relationship, and application of appropriate uncertainty factors to account for areas of extrapolation within the dataset (e.g., differences between species, individual variation within the human population, duration of exposure, etc.). Additionally, internal dose metrics estimated by physiologically based toxicokinetic (PBTK) models may be utilized to replace conventional toxicokinetic uncertainty factors for extrapolating systemic toxicological data from experimental species to the target population of interest.[8-10]

With the ongoing drive to reduce animal use in toxicological testing, alternative approaches including Structure Activity Relationships (SAR) and Threshold of Toxicological Concern (TTC) can be considered for cases where gaps in the hazard data exist for one or multiple endpoints. SAR-based read-across has been developed for evaluating substances that have limited toxicological data.[11–14] The process includes identifying appropriate data-rich analogs based on evaluation of similarity of compound structure, reactivity, metabolic pathways, and physicochemical properties compared to those of interest. The possibility to read-across data from the analogs is assessed and determined case by

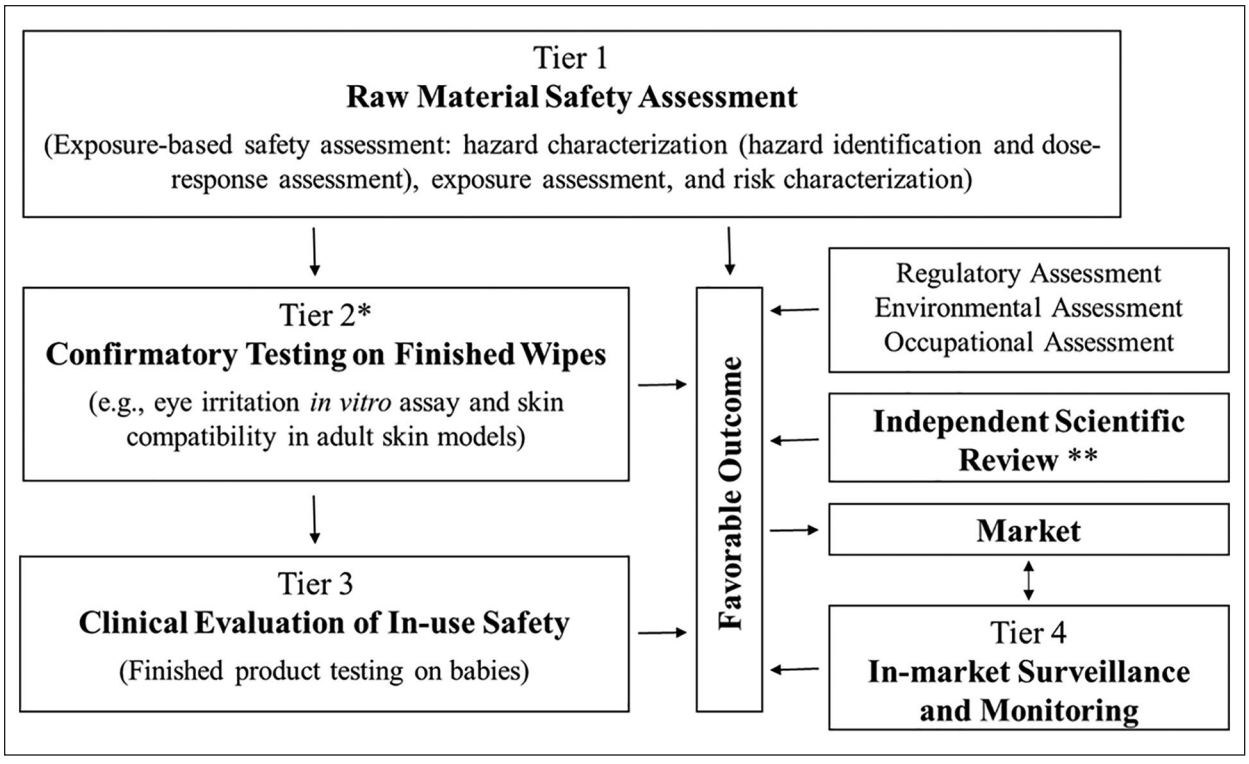

Figure 1. A systematic tiered safety assessment process for baby wipes.
*Expressed lotion of the finished wipe in eye irritation assay and expressed lotion or finished wipe in adult skin models when necessary based on each formulation revision.
**When appropriate.

case after consideration of all the available information and uncertainties. However, data of suitable analogs that are determined by our rigorous rating process are acceptable for appropriate read-across.[11] Consistent criteria for data adequacy are applied to wipe constituents and their structural analogs. For low-level substances that do not have structure-specific toxicological data, the TTC approach based on highly conservative assumptions may be employed.[15–18] There is a very low probability of adverse effects to human health when consumer exposures are below threshold values established with the TTC approach.[19] In addition to non-food consumer products, the TTC concept and approach have been adopted for food-contact materials, flavoring substances, and impurities in pharmaceuticals.[20–24]

In addition to systemic endpoints, potential site-of-contact effects such as irritation and allergic reactions following dermal exposure are assessed.[25] Intentionally formulated lotion ingredients are carefully screened for skin sensitization potential. In addition, low-level constituents (e.g., impurities) in the lotion and non-polymeric substances in substrate are thoroughly assessed for sensitization according to the exposure-based quantitative risk assessment (QRA) process. A No Expected Sensitization Induction Level (NESIL) is established using the Weight of Evidence (WoE) approach that considers all available data (e.g., human data, experimental data, and SAR) because individual data may vary in quality and robustness.[26] When there are insufficient data, a direct peptide reactivity assay can be performed to gather additional evidence.[27,28] This in vitro assay has been recommended as an alternative to animal testing by the European Union Reference Laboratory and European Centre for the Validation of Alternative Methods.[29] A QRA outcome of absence of a sensitization risk for individual wipe constituents is sufficient to rule out the risk of induction of contact sensitization for the finished wipe. When required or allowed based on local regulations, such as for product registration or claim support, the Human Repeat Insult Patch Test (HRIPT) may be conducted on the finished wipe. Consistent with our QRA conclusion, results of these studies confirm the compatibility of our baby wipes.

Wipe composition and safety profile of its constituents. Our baby wipe lotions contain water (>97% w/v), pH-buffering agents, emulsifiers, skin softening and conditioning agents, and a preservative. Scented wipes

contain a low level of perfume. Lotion ingredients are often commonly used in cosmetic and personal care products with a well-established, favorable safety profile. The regenerated cellulose (e.g., rayon), polypropylene and polyester fibers in the substrate are primarily used in clothes, fabrics, personal hygiene products, and other materials that are commonly in contact with the skin. They are biologically inert and not bioavailable due to their high molecular weight, which would pose no systemic toxicological concern. Therefore, the safety assessment tends to focus more on the low levels of non-polymeric substances in the substrate. These substances are usually reduced during the hydroentanglement process of non-woven manufacturing. Any residual constituents disclosed in the finished wipes are assessed using the same approach and iterative process described above to ensure their safety.

Quantitative Exposure Assessment and Safety Characterization

Baby wipes are primarily intended for cleaning feces and urine during diaper changes and the baby's exposure to wipe lotion from such use can be estimated to enable the safety assessment of the constituents in the wipe (lotion and substrate). First, the amount of lotion transferred to buttocks and genitalia from normal use of baby wipes has been measured in babies following the use of single and multiple wipes. Then, distributions of lotion transfer per diaper change, the number of diaper changes each day, frequency of daily wipe usage, and body weight for different age groups are combined into a probabilistic exposure model using Monte Carlo simulation and a distribution of lotion exposure (mg/kg body weight [bw]/day) has been estimated for babies of 0 to 36 months old (See lotion deposition during daily diaper changes, Table 1).[30]

To estimate the lotion exposure from cleaning baby's hands and face, we also utilized the results estimated for diaper changes by the probabilistic exposure model (Table 1). The assumption for extrapolating the data from cleaning buttocks and genitalia to baby's hands and face is that daily lotion deposition on each of these body surface areas is proportional to the size of the skin area wiped and number of wipes used to wipe that area each day. Surface area of each body part is expressed as "percentage of total body surface area" in diapered babies that is, buttocks and genitalia (7%), hands (5%), and face (10% including half area of baby's neck).[31] Distribution of the number of wipes used to clean baby's face and hands each day is based on a survey conducted in the US (n = 700), UK (n = 705), and Germany (n = 200) (data not shown), which are the same regions used to estimate the number of wipes used for daily diaper changes. Summation of the lotion transferred to baby's hands and face at various percentile levels is shown in Table 1.

Both potential systemic exposure to lotion (mg/kg bw/day) and skin exposure (mg of lotion/cm^2/day) for assessing the contact sensitization potential of individual wipe constituents were calculated. In detail, lotion transferred to each body surface such as baby's buttocks and genitalia, hands, and face via daily wipe usage (mg/cm^2/day) is estimated by the multiplication of systemic lotion exposure (mg/kg bw/day) and ratio of baby's body weight (kg) to this surface area (cm^2). Since the body weight and Total Body Surface Area (TBSA) change over time, distribution of the ratios "body weight to TBSA" is estimated for children 0 to 36 months of age based on the exposure factors.[32,33] Then the mean ratio of body weight (kg) to TBSA (cm^2) is applied to the calculation for local exposure with consideration of the 7%, 5%, and 10% of TBSA for baby's buttocks and genitalia, hands, and face, respectively. Given the greater lotion transfer per unit area resulting from the cleaning during daily diaper changes than that of cleaning baby's hands/face (Table 1), the local exposure via diaper changes is chosen to assess the skin sensitization endpoint for conservatism.

Among the distributions of lotion exposure (Table 1), values of the 90th percentile (450 mg/kg bw/day and 6.4 mg/cm^2/day for systemic and local exposure, respectively) are chosen in our safety assessment for individual wipe constituents because this percentile represents high-end exposure in consumers.[19,34,35] Additionally, lotion exposure, for instance, 450 mg/kg bw/day (Table 1) used to assess systemic endpoints is calculated by summing the lotion deposition (90th percentile) on baby's hands, face, buttocks, and genitalia. The deterministic basic aggregation could be further refined by probabilistic aggregation for the population.[36]

When necessary, our conservative assumptions applied to the first step of the iterative safety assessment process are considered for refinement. For example, the default assumption (100% dermal absorption) may be refined by dermal penetration data. For trace non-polymeric substances that are disclosed by substrate suppliers, we assume very conservatively that the small-molecule substances in the substrate are mobilized into the lotion and get absorbed into the skin. This conservative default assumption for a given constituent may be refined by analytical quantification of its presence in the expressed lotion and/or its dermal penetration data.[37]

Lastly, hazard characterization and quantitative exposure assessment are used to inform the subsequent

Table 1. Exposure Parameters and Estimate Used to Assess the Safety of Ingredients and Other Constituents in Baby Wipes.

Parameters	Values and units
Raw material constituent concentration	% (g constituent/100 g substrate or lotion)
Lotion load	g lotion/g substrate
Dermal absorption	100% (as default)
Exposure duration	Daily (leave-on assumption)
Lotion deposition during daily diaper changes	130, 230, and 260 mg/kg bw/day (50th, 90th, and 95th percentile, respectively)[30]
Estimated lotion deposition on hands and face	75, 220, and 280 mg/kg bw/day (50th, 90th, and 95th percentile, respectively) (unpublished data)
Total lotion exposure estimate	205, 450, and 540 mg/kg bw/day (50th, 90th, and 95th percentile, respectively) (unpublished data)
Estimated lotion deposition for local exposure	3.6, 6.4, and 7.3 mg/cm^2/day (50th, 90th, and 95th percentile, respectively) (unpublished data)

Exposure to lotion ingredients and impurities:

- Systemic exposure: Total lotion exposure (mg/kg bw/day) × constituent concentration in the lotion formulation (%) × dermal absorption (default assumption, 100%) × leave-on exposure duration (24 hours per day).
- Local exposure: Lotion deposition (mg/cm^2/day) × constituent concentration in the lotion formulation (%) × dermal absorption (default assumption, 100%) × leave-on exposure duration (24 hours per day).

Exposure to substrate constituents:

- Systemic exposure: Total lotion exposure (mg/kg bw/day) × (constituent concentration in the substrate [%]/lotion load) × dermal absorption (default assumption, 100%) × leave-on exposure duration (24 hours per day).
- Local exposure: Lotion deposition (mg/cm^2/day) × (constituent concentration in the substrate [%]/lotion load) × dermal absorption (default assumption, 100%) × leave-on exposure duration (24 hours per day).

risk characterization. There would be no appreciable risk of deleterious health effects in humans during a lifetime when consumer exposure is below the safe values established during the hazard characterization and accounting for uncertainties within the available dataset. For contact sensitization, an Acceptable Exposure Level (AEL) for a given wipe constituent is derived based on its WoE NESIL and sensitization assessment factor. When its local exposure is below the AEL, no risk is expected for the induction of contact sensitization.[26] Importantly, ratios of risk values to consumer exposures via wipe uses must be adequate for systemic effects of individual wipe constituents and the same criteria are applied to potential skin sensitizers to ensure the safety of finished wipes before any testing in volunteers and market introduction of the product.

Testing of Finished Wipes

After the safety evaluation of individual constituents in the wipe, the full wipe may be subjected to a battery of tests including *in vitro* eye irritation testing, human patch tests and on-skin wiping tests using adult skin models (Tier 2, Figure 1) as well as in-use studies in babies (Tier 3, Figure 1) to confirm skin and eye compatibility of the finished wipe. Table 2 outlines our typical safety program to demonstrate the eye and skin compatibility of new baby wipes. Not all the tests are required for every wipe revision. When necessary, new test methods are developed, for example to evaluate a new caregiver behavior.

Eye Irritation Testing

Accidental eye contact is foreseen via the wiped baby's hands and/or during cleaning of the baby's face by parents and caregivers. Eye irritation potential of baby wipes is evaluated with an *in vitro* assay that is, a 3D structure of stratified human keratinocytes, which was originally developed at Procter & Gamble (P&G)[41] and further studied using EpiOcular™.[42] In this *in vitro* assay, expressed lotion is applied to the tissue surface for several exposure times up to 24 hours. Cell viability is determined by MTT (3-[4,5-dimethylthiazol-2-yl]−2,5-diphenyltetrazolium bromide) assay and the measure is the time (t_{50}) to reduce cell viability by 50% as calculated from the time-response curve. Consistently, t_{50} values greater than 24 hours in our historical formulations and current expressed lotions from finished wipes have shown that cell viability is comparable with the negative control (sterile deionized water) over the entire 24-hour exposure period. As shown in Table 2, this in vitro test is considered, and conducted when appropriate, as part of our safety program. Results of finished wipes are expected to be consistent with the outcome of our individual ingredient assessment and their levels formulated in the finished wipe. The same conclusion was drawn from a human eye instillation test (n=31 subjects) on an early version of low pH lotion formulation

Table 2. Safety Program for Eye and Skin Compatibility of Finished Wipes.[a]

Safety endpoint	Type of test	expected outcome[c]
Eye irritation (Expressed lotion, *in vitro*)	EpiOcular™ Human stratified squamous epithelial cells	Non-irritating to eye: Comparable with sterile deionized water
Cumulative skin irritation[b] (expressed lotion or layers of wipes in adult volunteers)	21-Day cumulative irritation patch test (confirmatory, under occlusive patch conditions)	Non-irritating to skin (n = 30-40 subjects)
Contact sensitization[b] (expressed lotion or layers of wipes in adult volunteers)	Human repeat insult patch test (HRIPT) (confirmatory, under occlusive patch conditions)	Non-sensitizer (n = minimum 100 subjects)
FCAT on intact skin in adults[b] (effect of exaggerated wiping)	Forearm controlled application test (FCAT)	Effect of repeated wiping on intact skin: Milder than cotton washcloth and water (n = 40-50 subjects)
TS-FCAT on compromised skin by tape stripping in adult volunteers[b] (impact of repeated wiping on barrier repair and maturation)	Tape strip—Forearm Controlled Application Test (TS-FCAT)	Effect of repeated wiping on compromised skin: Superior to washcloth and water based on TEWL measurement and erythema grading (n = 40-50 subjects)[38]
In-use study in babies (erythema of perianal area, inguinal folds, genitalia and buttocks)	Eight-day randomized, double-blind study on test and benchmark baby wipes	Erythema grading of the 4 anatomical sites: Consistently gentle (n = minimum 50 subjects per test wipe product)

[a]Tests in this safety program are applicable when necessary depending on each product revision.
[b]Adult subjects with self-assessed sensitive skin based on our sensitive skin questionnaire and opinion of each study principle investigator when needed.
[c]Outline of our safety program and expected outcomes (data not shown on marketed products). See Table 3 for the published studies that were conducted before 2009.

that is similar to those tested in the *in vitro* method described above. In this acute eye irritation test, subjects were examined by an ophthalmologist for the parameters including, but not limited to hyperemia, edema, erosion, and lacrimation. Additionally, subjective assessments by subjects for sensorial endpoints such as stinging, burning, itching, and foreign body sensation reinforce compatibility with the eye (P&G unpublished data). Eye compatibility is further confirmed by lack of eye complaints in our in-market safety surveillance.

Skin Compatibility Testing in Adult Skin Models

Patch testing in adult volunteers. The use of skin compatibility patch testing data generated on intact adult skin is considered an appropriate surrogate for intact baby skin. Infant versus adult intact skin has been discussed in detail in our publications.[1,37] Briefly, all skin structures are present when baby is born at full-term and anatomically these structures do not change dramatically after birth. In addition to the skin structure, skin barrier properties have been shown to be comparable between full term babies and adults. SCCS[43] emphasized that when the skin is intact, the dermal absorption through full-term newborn skin is similar to that observed in adult skin. Taken together, the totality of clinical, pharmacological and toxicological literature supports that anatomy and barrier function of infant skin are comparable with adult skin such that data from non-invasive patch testing in adult volunteers (such as Cumulative Irritation Human Patch Tests and Human Repeat Insult Patch Tests) can be used to confirm skin compatibility of our wipes in babies.

Human cumulative skin irritation patch test. To confirm the lack of irritation potential, test material for example, the lotion expressed from the whole wipe is applied to a typically 2 cm × 2 cm patch on the upper arm or back of adult subjects for approximately 23 hours daily for 21 consecutive days.[44–46] Erythema of patch sites is evaluated each day according to a 9-point, 0 to 4 scale. This protocol exaggerates exposure to the test wipe by generally including occlusive patches instead of semi-occlusive conditions of diapered skin experienced in babies, no recovery time between the patch applications, and higher product exposure compared with the estimated consumer exposure. Lack of irritation potential is expected for the finished wipe under the test conditions (Table 2), which is consistent with the conclusion based on the assessment for irritation potential of individual constituents and their levels in the finished wipe.

Human repeat insult patch test. Skin sensitization testing is sometimes required by the board of health of some countries for product registration to demonstrate the absence of skin sensitization response. Additionally, this test is often used to support product claims and credentialing. Test substances, patch size, and the amount of

product applied are described above in the "human cumulative skin irritation patch test." In our protocol, at least 100 subjects are expected to complete the test. As described in the "human cumulative skin irritation patch test," exposure via patch is exaggerated compared to consumer exposure during product use. Occlusive patches are applied to the upper arm or back for a 24-hour period, 3 days a week for 3 consecutive weeks. After a subsequent 2-week rest period, the test substance is applied to the original site of application and to a naive alternate site for 24 hours and graded; sites with scores >0 are evaluated at 48-, 72- and 96-hour post-exposure.[47] For our wipes, there is no evidence of skin sensitization under the test conditions (Table 2), which is consistent with the QRA conclusion for individual constituents.

Adult forearm-controlled application test. Skin such as the arms, trunk and buttocks share relatively similar properties and thickness[48] and the forearm is often used to study skin responses to topically applied substances. Also, it was reported that both basal and post-hydration Trans-Epidermal Water Loss (TEWL) rates were comparable between forearm and buttock skin.[49] Adult forearm-controlled application test (FCAT; intact skin) and Tape-Strip FCAT (TS-FCAT; compromised skin) are our clinical skin models designed to evaluate potential chemical and mechanical effects of a wipe product on the skin after exaggerated, repeated wiping.[38,50] Intact or damaged adult skin (via tape stripping) is tested using a wiping protocol intended to represent a substantial exaggeration of product use. Typically, 3 fresh wipes per designated forearm site are tested by swiping 10 or 20 times per wipe (30 or 60 swipes per session) for each of the 4 daily wiping sessions for a total of 120 or 240 swipes per day for 5 consecutive days. The FCAT directly compares mechanical and chemical irritation potential of baby wipes versus cotton washcloth and water (the standard recognized for skin mildness) on intact skin (Table 2).

The TS-FCAT is designed to evaluate the impact of repeated wiping on the repair process of compromised stratum corneum and maturation of immature barrier. Barrier compromise is accomplished by serial tape-stripping on adult forearm until a TEWL value of 40 to 50 g/m^2/hour is achieved. The resulting skin condition is sensitive to both mechanical/frictional force and chemical irritants. This range of TEWL values was selected based on reports in children presenting relatively severe diaper rash[51,52] or in premature infants.[53,54] In this test, TEWL measurement and erythema grading (a 9-point, 0-4 scale) via expert, trained skin graders are defined as primary and secondary outcomes, respectively. Results of the test wipe as evaluated both instrumentally and visually are compared with those of cotton washcloth and water. The impact of repeated wiping with test baby wipes on barrier repair and maturation is expected to be consistently more closely matched to that of the control site than the cotton washcloth and water (Table 2), suggesting that the baby wipes produce less perturbation of the barrier repair and maturation compared to the cotton washcloth and water standard.

In-Use Study on Babies

The standard in-use study in our safety program entails the use of test wipes for the routine care of baby skin with an unrestricted number of wipes. Skin conditions can be evaluated as change from baseline for a single product, or a benchmark wipe product with a history of safe use can be included for comparison in a randomized, double-blind clinical study. A standard, non-test wipe is used during the 1-week "washout" period to standardize baseline skin condition. Erythema is evaluated at 4 anatomical sites (perianal area, inguinal folds, genitalia, and buttocks).[55] Baseline erythema grading is performed on Day 1 after the washout period and repeated on Day 8 following the 1-week test wipe use. The results of baby wipes are expected to confirm a favorable skin profile as described in Table 2. Our studies have shown that a minimum 8-day in-use study is deemed reasonable to determine erythema endpoint of diaper grading areas between treatments (e.g., baby wipe versus cotton washcloth and water) or a comparison of before and after the use of test baby wipes in babies of 3 years of age and under.[39]

Additionally, in-use studies of various durations were used to evaluate the impact of baby wipes on clinical endpoints such as skin integrity,[39] skin surface pH, and skin conditions of babies with Atopic Dermatitis (AD) (Table 3). Two 14-day prospective and randomized studies have shown that skin surface pH is significantly closer to the normal values in babies when the wipe was used versus cotton washcloth or soap and water.[3] Further, our unpublished two 14-day studies suggest that current baby wipes restore physiological skin pH of soiled skin more rapidly than the early version of P&G wipes with higher lotion pH values. In two 28-day studies in babies with clinically diagnosed AD,[56] a general clinical and dermatologic examination of the diaper area for pruritus, erythema, dryness, roughness, and desquamation were performed by a dermatologist. Severity of erythema and all other measures for AD conditions declined at the end of each study.[3,40] Results summarized in Table 3 show the skin benefits provided by baby wipes, suggesting that these baby wipes are not only gentle and mild to baby skin, but also help maintain natural skin

Table 3. Application of In-Use Study to Evaluation of Various Clinical Endpoints.

Study protocol	Outcomes evaluated	Results	References
Eight-day prospective in-use study of baby wipes compared with cotton washcloth and water	Diapered skin erythema, skin barrier integrity (TEWL), and skin surface microtopography (n = 90, 45 per group)	Significant reduction in severity of skin erythema and skin roughness with wipes. Neither treatment had a negative impact on skin barrier.	Odio *et al*[39]
Two-week prospective, examiner-blind study of baby wipes vs usual cleaning routine (typically water and cotton balls)	Diaper dermatitis (perianal area, inguinal folds, genitalia, and buttocks) (n = 102, approximately 50 per group)	A significant improvement in diaper rash in the intertriginous areas for the wipe group vs. the water and cleaning material group	Ehretsmann *et al*[40]
Two-week prospective study of impact on skin pH: baby wipes vs cotton washcloths and water	Change in skin pH of diaper area vs upper thigh (n = 30, 15 per group)	Skin pH was significantly closer to the pH of non-diapered control that is, +0.4 and +1.15 pH units (mean change) by wipes and washcloth and water, respectively	Adam *et al*[3]
Skin pH measurement following stool cleaning with 2 test wipe formulations, washcloth, and water, or 2 different soaps and water over a period of 2 week of usage	Skin pH measured 6 minutes after stool removal (n = 50, 10 per group)	Only wipes maintained skin surface pH below 6.0	Adam *et al*[3]
Four-week in-use study of wipes in infants with atopic dermatitis	Erythema (n = 56, 3-18 months old)	Incidence of erythema in the diaper area declined each week	Ehretsmann *et al*[40]
Four-week in-use study of wipes in infants with atopic dermatitis	Grade for erythema, roughness, dryness, pruritus, and desquamation (n = 32, 3-24 month old)	All the measures declined compared with baseline values. The dryness value was significantly lower.	Adam *et al*[3]
Randomized study of infants (5-14-day exposure) with measurements at diaper and chest control sites using 2 wipe formulations (pH 3.8-4.0 and 5.2) and a NICU standard washcloth	Erythema, skin rash, TEWL, and skin surface acidity (pH) 130 NICU patients (gestational age 23-41, 30-51 week at enrollment, adaption time 0.4-17 week)	Wipes are appropriate for use on medically stable NICU patients including preterm infants; wipes (pH 3.8-4.0) provide more normalized skin (pH, TEWL, and erythema) than the NICU washcloth standard	Visscher *et al*[4]

surface pH of diapered area and reduce the symptoms associated with AD.

Studies in Patients of a NICU

Baby wipes may also be used in NICU because of the convenient and effective cleaning provided by the wipes during diaper changes. Though NICU patients are vulnerable due to their prematurity and/or medical status, their epidermis matures rapidly in the extra-utero environment.[57] It has been reported that the structure and dimension of epidermis of most premature infants are similar to that of full-term infants by about 2 weeks of postnatal age based on limited literature.[57–59] However, maturation of all skin functions continues throughout the first year of life.[60,61]

To assess the safety of wipe constituents for NICU patients, we determined the lotion transferred to the skin of preterm and term infants (n = 121) after evaluating 703 diaper changes based on the NICU practice.[62] Additionally, the effect of baby wipes (with different pH values) and a NICU washcloth on diapered skin (erythema, TEWL, and skin surface pH) was investigated in medically stabilized NICU patients (n = 130, gestational age 23-41, 30-51 weeks at enrollment, adaption time 0.4-17 weeks).[4] Results indicated that baby wipes are appropriate for use on the patients enrolled in this study according to the practices in this NICU. Furthermore, the wipe with pH of 3.8 to 4.0 produced a significant decrease in skin surface pH of the infants when compared with a pH 5.2 wipe and the NICU washcloth (Table 3). These results suggest that the pH 3.8 to 4.0 wipe helps facilitate acid mantle development, which assists in colonization, infection control, dermatitis prevention, and eventually barrier maturation in NICU patients though a controlled multicenter study would further demonstrate wipe safety and benefits in this population.[4] Also, we recognize that not all baby's experiences are the same and NICU medical professionals are the ultimate decision makers on the appropriate individual care of their patients.

Scientific Review

Baby wipes have been continuously improved to meet the caregivers' needs for cleaning effectiveness without compromising the health of baby skin. The safety and comfort of babies is our top priority. The process for safety assurance includes, but not limited to sourcing only safe materials from the start and investing in clinical studies and safety testing as needed. We pay close attention to the related areas of leading medical and healthcare professionals and experts of skin sciences. When deemed necessary, principles and approaches we apply to the safety evaluation of novel technologies as well as the results of related clinical and safety studies are reviewed by ad hoc scientific advisory groups consisting of leading pediatricians, pediatric dermatologists and baby skin science experts. Feedback, input and comments from these external experts are taken into consideration before a novel technology is applied to our baby care products.

In-market Surveillance and Monitoring

In-market monitoring provides information on the experience and satisfaction of caregivers after they purchase and use the product. Caregivers provide feedback through a number of ways including but not limited to a toll-free telephone number on the package, by letter, by email, and via the manufacturer's sponsored social media and web sites. This feedback helps to confirm that our expectations for product safety and performance are met. Health-related caregiver complaints are continually monitored by internal experts for any unanticipated issues or unusual trends. The nature of health-related complaints is routinely analyzed to assure that the comments are consistent with those seen historically based on the long history of safe use of our baby wipes. The number and frequency of health-related complaints (generally skin-related effects) are consistently within the expected range for this type of product, and the reported effects are typically of a transient nature. Over time, the in-market monitoring data further confirm the rigor of our safety assurance process described herein.

Conclusions

This article describes a systematic and iterative, tiered approach for evaluating the safety of baby wipes, including (1) the exposure-based safety assessment for individual material constituents; (2) testing, when appropriate, of the finished wipes in a battery of tests for eye irritation, skin compatibility, the effect of repeated swiping on intact and compromised or "immature" barrier in adult volunteers; and (3) prospective and randomized in-use studies in babies and infants (term and preterm) with no restriction of wipe usage. These results have demonstrated consistently that baby wipes are suitable for routine cleaning of baby skin and at least as gentle as the cotton washcloth and water standard. Importantly, our baby wipes help to maintain natural skin surface pH in babies. In addition, clinical safety in-use study on babies demonstrated potential skin care benefits associated with daily use of baby

wipes including populations with sensitive skin (e.g., compatible with atopic dermatitis). The long history of safe use of baby wipes shown by the in-market surveillance and monitoring data further supports the safety of our baby wipes. This rigorous approach to safety assurance, tailored to the specific product type and conditions of use, provides confidence that our baby wipes are safe under intended and reasonably foreseeable product use conditions and help maintain natural skin surface pH, an indicator of skin maturation and health in babies.

Author Contributions

Ning Li, PhD: Contributed to the approach and estimate for baby exposure to wipe lotion via hand and face cleaning, and aggregate exposure to wipe lotion via the three uses (cleaning baby's bottom, hands, and face); contributed to study design, data analysis and interpretation of human patch tests and *in vitro* eye irritation test; drafted the manuscript; critically revised the manuscript; agrees to be accountable for all aspects of manuscript integrity and accuracy.
Swatee Dey, PhD: Contributed to the exposure to wipe lotion via diaper changes in term and preterm infants; agrees to be accountable for all aspects of systemic exposure estimated for diaper changes; critically reviewed the manuscript; gave her alignment to the final version.
Robert O'Connor, MS: Contributed to study design, data analysis and interpretation of all clinical studies except for human patch tests; agrees to be accountable for all aspects of these clinical studies; critically reviewed the manuscript; gave his alignment to the final version.
Joan Abbinante-Nissen, PhD: Helped provide direction for development of the content; critically reviewed the manuscript; gave her alignment and approval for the final version.
Jeff White, BS, MBA: Contributed to the update on habit & practice (H&P) data of wipe use via cleaning baby's bottom, face, and hands; critically reviewed the wipe compositions and functions; agrees to be accountable for all aspects of the updated H&P data, wipe compositions and functions.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors are employees of the P&G Company.

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