



Safety evaluation of superabsorbent baby diapers

Kirstin Kosemund^a, Harald Schlatter^a, Jennifer L. Ochsenhirt^b, Edburga L. Krause^a,
Daniel S. Marsman^{b,*}, Geetha N. Erasala^b

^a Procter & Gamble Service GmbH, Schwalbach am Taunus, Germany

^b The Procter & Gamble Company, Winton Hill Business Center, 6280 Center Hill Ave, Cincinnati, OH 45224-1708, USA

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ABSTRACT

Superabsorbent disposable baby diapers are sophisticated, well-engineered products that provide many benefits including convenience, comfort, exceptional leakage protection, improved hygiene and skin care benefits compared with cloth diapers. Safety assurance is an integral part of the diaper development process at Procter & Gamble, with the goal of ensuring safety for both caregivers and babies. A systematic, stepwise approach to safety assessment starts with a thorough evaluation of new design features and materials, using the principles of general risk assessment including, as appropriate, controlled trials to assess clinical endpoints or independent scientific review of safety data. The majority of the diaper materials are polymers that are safe and do not have inherent toxicity issues. Trace amounts of non-polymeric materials, such as colorants, are assessed based on their skin contact potential. New materials or design features are introduced in marketed products only if they have been shown to be safe under the conditions of recommended or foreseeable use. The product safety continues to be confirmed after launch by means of in-market monitoring. This article provides a broad overview of human safety exposure-based risk assessment used at Procter & Gamble for absorbent hygiene products.

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1. Introduction

Since the introduction of Pampers® (Procter and Gamble, Cincinnati, Ohio) in the US in 1961, the use of disposable diapers has increased in developed nations. Today, it is estimated that 90–95% of diapers used in these countries are disposable (Odio and Friedlander, 2000). European data indicate an average diaper change frequency of 4–5 diapers/day over a diapering period of 2.5 years (UK Environment Agency, 2005). The growth in the use of disposables has been accompanied by several improvements in the design of the diaper itself. The most important improvement was the introduction of superabsorbent polymers (polyacrylates) as a component of the diaper core in the 1980s. Depending on the ionic strength of the fluid, these materials can absorb many times their own weight in aqueous liquids—in the case of tap water, about 200 times (European Disposables and Nonwovens Association, 2007). Unlike traditional cellulose materials, polyacrylates have the ability to retain liquid in the diaper core, keeping it away from the baby's skin, even under pressure. Other improvements have included features that permit faster acquisition of liquid, an apertured topsheet for efficient “liquid feces management”, new materials that provide a cloth-like feel, breathable materials, improved fit, and flexible re-sealable fasteners. These

innovations have transformed disposable diapers from a convenience item into a product that improves the comfort and skin health of the infant (Adam, 2008).

Benefits of the improvements in superabsorbent baby diapers have been widely documented. Clinical evaluations have shown that these product improvements help to reduce skin over-hydration and friction (key elements in diaper dermatitis) (Odio et al., 2000a,b; Campbell, 1987; Davis et al., 1989) and have demonstrated statistically significant reductions in the occurrence of diaper dermatitis in users of disposable baby diapers with superabsorbent core compared with users of cloth diapers or cellulose-only disposable diapers (Campbell, 1987; Davis et al., 1989; Campbell et al., 1987; Seymour et al., 1987a,b; Lane et al., 1990; Wilson and Dallas, 1990). A retrospective examination of clinical trials performed before and after the widespread use of disposable diapers with super-absorbent cores has demonstrated the reduction in the incidence of severe diaper dermatitis with modern diapers (Odio and Friedlander, 2000) and this overall reduction has been confirmed by physicians' anecdotal reports (Spraker et al., 2000). Additional advantages of superabsorbent diapers include the improvement of hygienic conditions (reduction of fecal bacterial contamination) in day-care settings (Campbell et al., 1988; Kubiak et al., 1993; Van et al., 1991a,b).

The many obvious advantages of today's superabsorbent disposable baby diapers undoubtedly account for the high degree of consumer acceptance and satisfaction with the product. The

* Corresponding author. Fax: +1 866 357 7849.

E-mail address: marsman.ds@pg.com (D.S. Marsman).

convenience, fit, and comfort benefits compared with traditional cloth diapers are immediately evident, as are the benefits of drier baby skin. Many consumers (and indeed many physicians) are probably unaware of the rigorous and extensive safety programs that have been designed and implemented to ensure that superabsorbent diaper product innovations are safe and effective under practical use conditions. For example, the super-absorbent material alone has been evaluated in numerous comprehensive studies assessing safety aspects ranging from skin irritation, sensitization, to possible systemic toxic effects, to accidental swallowing (Spraker et al., 2000).

Procter & Gamble is committed to the safety of its products to ensure that only products with an excellent safety profile are placed on the market. The following detailed description presents the first in-depth discussion of Procter & Gamble's human safety risk assessment model applied to chemical safety of baby diapers. Other safety evaluation routes which are followed but not discussed here address:

- Environmental assessment including disposal of manufacturing waste with recycling and reuse where possible and compatibility with all local forms of solid waste handling (landfills, incineration) for consumer disposal of used product.
- Physical hazard assessment to ensure product efficacy and integrity. The focus for the physical hazard assessment in the context of baby diapers is primarily choking and suffocation but also to confirm the absence of hard edges or tight seams which might cause abrasions or red marks on the baby's skin.
- Workers safety assessment for material handling and product making.

The article is an example of human safety exposure-based risk assessment for diapers. Similar approaches are used for other absorbent hygiene products.

2. Anatomy of a disposable diaper

While disposable diapers are offered in a variety of styles with different consumer features, the basic “anatomy” of a disposable baby diaper remains essentially the same. The typical design elements and raw materials of today's typical superabsorbent disposable diaper are shown in Fig. 1.

The modern superabsorbent disposable diaper consists of three basic functional product zones, as described below.

2.1. Direct skin contact materials

The topsheet is the layer in direct contact with the baby's skin. It consists of a soft nonwoven synthetic sheet, composed of polypropylene/polyethylene, either alone or as a blend, which allows liquids to pass through while remaining relatively dry and soft. The main function of this layer is to transfer urine and other liquids quickly to the layers beneath. In addition, the topsheet may carry a lotion to protect the skin from overhydration and irritation.

2.2. Indirect skin contact materials

2a. The acquisition/distribution layer is usually composed of a modified cellulose patch and a polyester-based layer sandwiched between the topsheet and the core, which is not in direct contact with the skin. Its main function is to facilitate the movement of liquid away from the baby and to distribute it more evenly across the entire diaper core for efficient and maximal absorbency.

2b. The absorbent core is the inner-most layer of the diaper. It typically consists of a blend of polyacrylate granules blended with fluff cellulose pulp (bleached by an elemental chlorine-free process) and encapsulated by either a cellulose or polypropylene nonwoven layer. The cellulose portion of the core functions to quickly absorb and transfer urine to the polyacrylate superabsorber. The superabsorber is able to absorb urine and to lock it within its polymeric structure to keep it away from baby's skin, even under pressure as when a baby sits on a full diaper.

2.3. Backsheet and fastening system

3a. The backsheet is the water-resistant outer layer of the diaper, typically made of a polyethylene film laminated with a soft-textured, cloth-like polypropylene. Its function is to prevent liquid from leaking out of the diaper into the outer clothing.

3b. Additional elements include features primarily designed to ensure a good fit to the diaper. Such design elements may include stretch side panels, fastening systems and tapes to improve fit, and leg cuffs to prevent leakage.

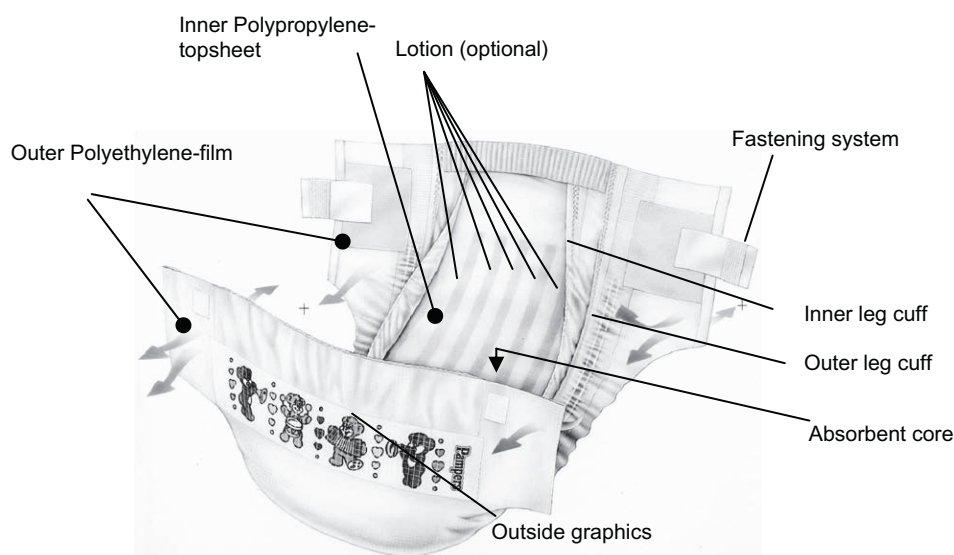


Fig. 1. Schematic representation of modern diaper design.

In some products, aesthetics such as colorants or scents may be added. The functional elements may vary depending on the style of diaper, the manufacturer, and consumer preference.

3. Risk assessment framework

Materials used in diapers are mainly of polymeric nature. These materials are safe and no inherent toxicity issues are associated. However as for any product, there will be low levels of non-polymeric components that may be introduced into the product for example from process aids used in the making process, or they could be aesthetic ingredients such as colorants or scents that are added at low levels. To provide a high level of safety assurance we focus on the assessment of such substances prior to consumer studies or widespread human exposure in the marketplace. Although the exact process may vary depending upon the components and design of the product, the following paragraphs provide an example of the typical safety qualification of a material intended to be used in a baby diaper product.

As a first step the complete compositions of each new material proposed for use in the diaper are obtained. Details may include component information from secondary and tertiary suppliers. Data are entered into a comprehensive, proprietary database for access by safety assessors. After all components of the new material are known, an in-depth safety evaluation is completed.

The process for this evaluation utilizes an approach known as an exposure-based risk assessment in which the inherent hazards of the raw materials and low level components are evaluated within the context of the potential for human exposure, given the intended use of the material in a diaper. A simplistic representation of the evaluation process followed prior to marketing can be found in Fig. 2.

The risk assessment (RA) process by nature is an iterative process, whereby conservative default assumptions are commonly used in the first tier (e.g., an exaggerated assumption is that a chemical is completely released from a diaper or fully absorbed from the body following dermal exposure), and the assessment may be refined if needed by replacing conservative default assumptions with new data. The RA paradigm was broadly estab-

lished in 1983, by the National Academy of Sciences (National Academy of Sciences, 1983). It describes the approach as a four-step process: hazard identification, dose-response assessment, exposure assessment and risk characterization. A robust RA is a key component of a comprehensive risk management decision which also incorporates aspects of public perception of risks, regulatory aspects, and other issues.

The RA paradigm has been applied widely by regulatory agencies and institutions to assess health endpoints related to exposure to chemicals present in food, air or drinking water. Slightly different approaches and terminology for risk assessment is used; however, the basic principles are the same (US EPA, 1993, 2002; International Programme on Chemical Safety, 1999; Organisation for Economic Co-operation and Development, 2007). Another area where RA is used is to assess for potential site-of-contact effects such as allergic reactions following dermal exposure (Felter et al., 2003, 2002; Gerberick et al., 2001a; RIFM QRA Expert group, 2006). The four RA elements established by the National Academy of Sciences (1983) are explored in more detail below as they apply to the safety qualification of materials for baby diapers.

4. Exposure assessment

The key to an accurate and robust assessment of exposure to a particular substance present in a baby diaper is a deep understanding of the habits and practices of caregivers and babies, as well as experience in the intended and actual consumer use of disposable baby diapers. This actual-use experience forms the foundation for characterizing exposure relating to product use such as frequency and duration. Understanding the way diapers are designed and manufactured helps guide the toxicologist to properly evaluate the potential exposure of the consumer to the materials present in a diaper.

In keeping with the iterative nature of RA, Procter & Gamble's exposure assessment starts with conservative default assumptions that are commonly used in the first tier. The assessment then may be refined as needed by replacing these conservative default assumptions with actual data. In assessing the safety of diapers, consideration is given to both the baby and the

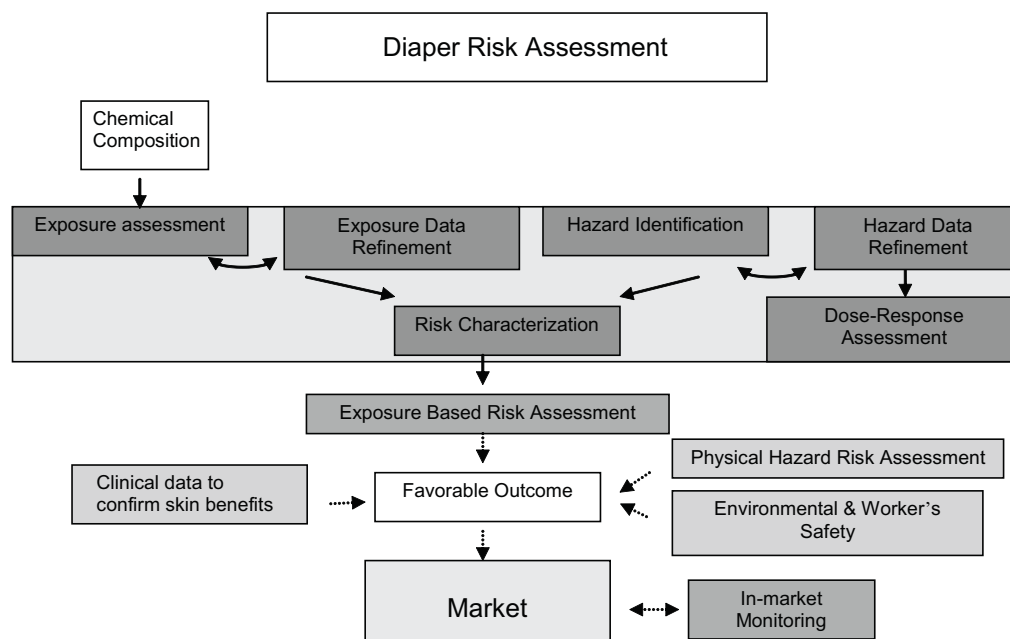


Fig. 2. Diagram of the risk assessment process.

caregiver. Because skin integrity is similar in babies and adults, and exposure/kg body weight and exposure/person are known to be greater for babies, if the safety margin is sufficient to support exposure to babies, then a lower exposure to the caregiver is considered acceptable.

In order to refine exposure assumptions, chemical and physical analyses may be performed under conditions that simulate the exposure in question. For example, release of a chemical present in a diaper material when it comes into contact with urine may be simulated to understand whether the baby wearing the diaper would be exposed to that chemical under a real in-use situation. This simulation can be useful if extraction conditions (such as relevant extraction media) are well defined. In addition, a variety of mathematical models have been developed to estimate exposure levels for specific exposure scenarios.

A key principle for diaper exposure assessments is the fact that disposable diapers are a solid product based primarily on solid and inert polymeric materials. Thus, the majority of chemicals are of limited concern since they are large polymers which are usually inert and not absorbed through the skin (Krause et al., 2006). The remaining substances for further evaluation are the non-polymeric ones. For relevant exposure to the skin, these ingredients must be released from the polymer and migrate to the surface of the diaper to be available for dermal exposure. An assessment of this release and migration from the polymer is important in order to obtain a realistic exposure estimate. When no data are available, a conservative default value of 100% migration of the free fraction is typically assumed.

A diaper is a three-dimensional product featuring different materials with different functions and exposures to these materials range from continual direct skin contact to very transient or negligible skin contact (Fig. 3). Potential exposure of the skin to non-polymeric substances is sorted into three categories, depending upon the type of material and the exposure that is possible, based upon design of the diaper (Herrlein, 1996).

4.1. Direct skin contact materials

This category consists of raw materials in direct and close contact with the skin. Materials in this category primarily include the topsheet, barrier leg cuffs, and ingredients such as lotion that can be transferred from the topsheet or cuffs to the skin. Studies using a lotion ingredient tracer (stearyl alcohol) in older, mobile babies showed that only a limited amount (i.e., less than 10%) of a prototype lotion was transferred from the topsheet to the skin (Odio et al., 2000b). Accordingly, for ingredients contained in or added to a direct skin contact raw material, a transfer factor may be used to calculate the level of ingredient available to come in contact with the skin.

Using a lotion transfer factor provides a useful estimate for most topsheet ingredients, since it is reasonable to assume that a lotion will have maximum opportunity to transfer to the skin. Lotion is deliberately applied to the outer surface of the topsheet and is intended to be delivered to the skin while other topsheet materials are typically incorporated into large polymers and must migrate to the top before they can be transferred. Most ingredients that are tightly integrated into the polymeric matrix do not migrate or transfer very readily, so using the lotion transfer estimate would lead to a highly conservative risk assessment. Per this conservative assessment, if the margin of safety is considered to be insufficient, further analytical testing may be carried out to determine the actual release from the matrix and transfer rate of the chemical in the raw material.

The lotion transfer factor may also be the default value used for some other diaper materials with partial or indirect contact with the skin, such as the puckered or corrugated leg cuff materials. Although elastics are not in contact with the skin, exposure can theoretically result due to sweat or humidity facilitating migration of raw materials to the skin. In this case, the lotion transfer factor is used even though actual values are expected to be much lower.

4.2. Materials with indirect skin contact

This category includes raw materials beneath the topsheet that are not in direct contact with the skin, but may contain ingredients that have the potential to migrate or resurface and come into contact with the skin. The relevant diaper structures in this category are the acquisition layer and absorbent core, which consist of superabsorber, polyester, modified cellulose fibers, pulp and adhesives. These materials typically require a carrier to reach the skin, for example the retrograde migration of urine. Typical values for retrograde fluid migration range between 0.25% and 2.5% depending on the test system, product design and fluid loading, and diaper change frequency (Krause et al., 2006; Herrlein, 1996; Herrlein et al., 1998).

4.3. Materials with negligible skin contact

This category includes the raw materials of the backsheet and the fastening system which have no or transient contact with the baby's skin. Data from historical experience, comparison with previous raw material composition, product integrity standards, and analytical leachability evaluation can frequently be used to support the assumption for no or negligible skin exposure to material ingredients.

Exposure assessment also takes into consideration a baby's body weight, age, and the daily number of diaper changes. Habits and practices data are used to determine health protective values

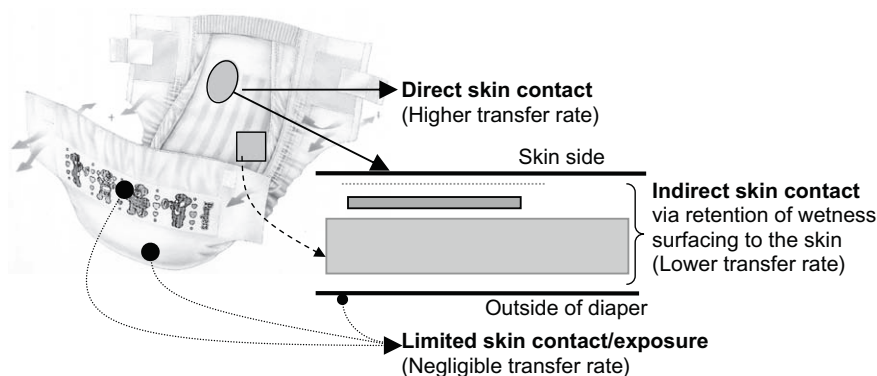


Fig. 3. Illustration of types of exposure encountered with material components of the diaper.

for risk assessment (UK Environment Agency, 2005; EU Scientific Committee on Toxicity, Ecotoxicity and the Environment, 1998). If differences in the makeup of diaper dimensions exist for a certain age range or diaper size, the assessment can be further refined by using the actual size/dimension values to define the absolute amount of chemical present in a material.

Greater precision in the exposure estimate may be obtained by analytical quantification of the release and migration of a specific chemical ingredient. For example, synthetic urine and other products that may be on the baby's skin (e.g., baby oil or mineral oil, saline/isopropanol disinfectant) can be evaluated in tests to measure the migration of chemicals from the substrate. Evaluation of exposure may also include consideration of the permeation of the chemical through the skin and into the body. This permeation is effected by many factors, including the body site of exposure (e.g., occlusion level), and condition of the skin (e.g., intact, hydrated, or compromised by irritation) (Scientific Committee on Consumer Products, 2006). Because of these uncertainties and for better comparison with data derived from toxicity studies (administered dose vs. absorbed dose), a conservative approach is used in which reduction factors for skin permeation are not applied unless data indicate that use of such factors is appropriate.

5. Hazard identification

Another step in the risk assessment process is known as hazard identification. It is the phase during which a toxicologist evaluates the inherent toxicity of a chemical to identify whether it can cause an adverse health effect given the relevant route of exposure. Formal descriptions of the purpose of hazard identification vary between the US and in Europe, but each is based on assessing the toxic effects of the chemical in question. In addition to gathering information on the raw material or ingredient(s) as such, it is important to gather information on known or expected contaminants of the ingredient and to conduct similar searches for hazard information on the contaminant(s). As outlined previously, the majority of materials used in diapers are large polymers which are chemically inert. They do not penetrate the skin and therefore, are of negligible concern. Special attention is given to trace level, non-polymeric substances like process aids, aesthetic ingredients such as colorants or scents or potential levels of monomers, solvents, and additives used in polymerization reactions or syntheses. Understanding the chemistry of the substance is often helpful in this regard. The exact source must be considered, as different purity grades may be available and different suppliers may provide material with different impurity profiles. The full complement of hazard identification information can be drawn from several sources, including data from toxicity testing, evaluation of chemical structure to identify structural alerts, and data from human experience.

6. Evaluation of potential risk

The initial analysis of a substance focuses on the evaluation of those physico-chemical parameters such as molecular weight and solubility which help the assessor to predict for its likelihood to migrate out of the diaper and be available for skin exposure or even to be bioavailable via skin permeation.

Should there be any evidence for skin exposure or bioavailability, the chemical is further screened for alerts of concern using a tiered approach:

In silico and *in vitro* methods are available to determine for example potential for DNA reactivity, sensitization or developmental toxicity. Hazard potential can be further evaluated by using available human and laboratory animal data. Only occasionally

human epidemiology data (e.g., from workplace exposure) may exist that provide more information about the toxicological profile of a chemical. Sometimes there are data on human sensitization on exposed populations. More often however risk assessors have to rely on non human data on extrapolation of data from laboratory animals. These data include *in vitro* and *in vivo* data from toxicity testing of the actual chemical. The major toxicological endpoints to consider relevant in the diaper context include but are not limited to systemic toxicity (acute, subchronic, or chronic toxicity, reproductive and developmental toxicity, genetic toxicology, carcinogenicity, neurotoxicity) and local effects, (skin irritation, allergic contact dermatitis).

The safety data sought in this review process come from a variety of sources, including reports of toxicology studies conducted in-house or by the supplier and the published scientific literature.

Animal toxicity testing has historically been the primary and most reliable way to confirm the safety of new ingredients and products. Today, animal testing has been greatly reduced by increased use of historical data, the increased sophistication of computer models. This is in line with Procter & Gamble's commitment to establishing and applying the "Three Rs" (Replacement, Reduction, Refinement) as an overriding principle for hazard identification in risk assessment. This includes the development and use of new methods substituting the use of animals for safety testing (Replacement), methods that result in using fewer animals to acquire necessary information (Reduction) and methods that alter procedures to eliminate and minimize discomfort (Refinement).

Additional hazard identification tools are available or can be developed. The qualitative structure-activity (SAR) relationships approach which incorporates molecular substructures or fragments related to the presence or absence of toxicity has enjoyed broad acceptance in the field of genetic toxicology and carcinogenicity, and has been used to identify and eliminate from consideration a large number of reactive chemical substructures that are potentially mutagenic and carcinogenic. Other more sophisticated developments include quantitative structure-activity relationship (QSAR) (OECD, 2007; Veith, 2006; Jaworska et al., 2003; Eriksson et al., 2003; Cronin et al., 2003a,b) and Physiologically Based Pharmacokinetic (PBPK) modeling (Jones et al., 2006). The latter is a mathematical modeling technique for the characterization of a chemical's pharmacokinetics in a complex biological system, which can be used in human health risk assessment and investigation of toxicity. Such approaches provide strong support for the toxicological "bridging" associative process within the development of the chemical risk assessment.

The hazard information contains critical contextual information specific to the mode of action, species differences in response, route of exposure, and characteristics of the dose-response relationship. For example, a chemical may pose a risk only if it is inhaled—for example, mineral oil is safe to apply to the skin, but can be highly dangerous if it is inhaled. Any modification of this scenario (e.g., lowered dose, shorter duration) would then alter the hazard and redefine the risk.

7. Dose-response

Dose-response evaluations assess the relationship between the dose of a chemical and the incidence or severity of an adverse health effect in the exposed population. Rigorously reviewed methods for all human safety endpoints are available to calculate acceptable exposure levels of chemicals e.g. for contaminants in food, air or drinking water. The same principles can be used for consumers which may be exposed to low levels of chemicals.

The threshold of toxicological concern (TTC) approach (Kroes et al., 2004, 2005) provides an acceptable method to determine a

conservative estimate of exposure levels below which there is very low probability of risk for consumers when chemicals are present at very low levels. This approach has been used for decades to support safe exposures to indirect food additives in the absence of complete chemical-specific human toxicological data. Over the years, the method has been refined and additional work has been done to extend the underlying database so that it can be used more broadly. Blackburn et al. (2005) and Kroes et al. (2007) have specifically addressed the use of TTC for cosmetics and other personal care products.

For exposures that exceed a TTC-based limit, quantitative methods of risk assessment have been established by a number of international/regulatory agencies (National Academy of Sciences, 1983; US EPA, 1993, 2002; International Programme on Chemical Safety, 1999; Organisation for Economic Co-operation and Development, 2007). These quantitative risk assessment methods are used to support human safety from a variety of exposures ranging from contaminants in the air and drinking water, to pesticides and other contaminants in food. Procter & Gamble applies these same conservative, health-protective methods to assure the safety of consumer products, including diapers. An in-depth review of these methods is beyond the scope of this document. Briefly, however, these methods most commonly involve extrapolating toxicity data from laboratory animal studies to establish an acceptable exposure limit for humans that takes into account (e.g., through the application of conservative uncertainty factors) differences between species and the potential for sensitive subpopulations. In addition, uncertainty factors may be applied to account for sub-chronic to chronic (exposure duration) extrapolation, or for the adequacy or completeness of the database (e.g. lack of a reproductive/developmental toxicity study). In addition, there may be other areas of data extrapolation for which uncertainty factors have not been established, but which should still be considered in a risk assessment. These areas include route-to-route extrapolation (e.g. using data from an oral toxicity study to conduct a risk assessment for a product applied to the skin), vehicle or matrix effects in extrapolations from test conditions to diaper-relevant conditions, and accounting for the biological or micro-environmental differences of the intimate diaper area. As described above for exposure assessment, dose-response assessment is also an iterative process. A first-tier assessment generally utilizes conservative (health-protective) default assumptions, recognizing that these can be refined with data as appropriate.

8. Risk characterization and final risk assessment

Risk characterization is the final step in RA, integrating exposure assessment, hazard identification and characterization and dose-response assessment, into advice suitable for use in decision-making or risk management. There are two terms commonly used in risk characterization: margin-of-exposure (MOE) and margin-of-safety (MOS).

8.1. margin-of-exposure (MOE)

A MOE is a comparison of the estimated human exposure to an experimental or extrapolated dose such as a NOAEL, LOAEL, or benchmark dose. It does not take into account any areas of data extrapolation or uncertainty.

8.2. margin-of-safety (MOS)

A MOS is a comparison of the estimated human exposure to a risk value for which the risk causing adverse effects is considered to be minimal such as an RfD (reference dose), ADI (acceptable dai-

ly intake), or other risk value that has already incorporated areas of data extrapolation and uncertainty. With these incorporated uncertainty factors, a MOS equal to or greater than 1 can be considered to be acceptable.

In the best case, risk assessment indicates that the ingredient or product is safe for its intended use and that an adequate margin of safety exists even if the diaper is misused in a foreseeable way. Once this determination is made, the product is ready to continue its journey towards the store shelves. In some cases, data gaps are identified that result in the design of an additional safety testing program. If the initial risk assessment leads to unfavorable results and the safety of the ingredient cannot be confirmed for the intended use, then a suitable alternative to the ingredient in question is sought. As noted previously, it is often not the material itself that raises any concern, but rather the presence of contaminants that must be controlled. This process can include working with new materials or suppliers to find ingredients that meet the product's technical needs while ensuring the safety of consumers. For the estimation of risk, conservative default assumptions are used often for elements of the process. Numerous conservative default assumptions have already been described in the Exposure section. For hazard characterization at very low exposure levels, the threshold of toxicological concern approach described earlier is used. In cases in which the initial safety margin estimate is lower than desired, more accurate data may be obtained to refine many of these conservative default assumptions. For example, actual skin permeation studies or dermal penetration modeling can be conducted to refine the estimation of systemic exposure.

9. New material testing and clinical studies

Since skin contact is the predominant type of exposure during baby diaper use, clinical skin irritation tests may be conducted to confirm that new materials or new diaper designs do not negatively affect skin health in the diaper area. The relevant clinical endpoints include parameters such as skin dryness, skin pH, and the absence of rash and mechanical irritation (Adam, 2008). In order to ensure an adequate level of safety for even the most sensitive user, these tests normally are conducted under conditions that exaggerate potential in-market exposure both in terms of test concentration and duration of exposure. To assess the skin irritation potential, an appropriate Human Patch Application Test may be conducted (Andersen et al., 1994; Rhein et al., 1990; Shellow and Rapaport, 1981; Bowman et al., 2003).

Allergic contact dermatitis is another important area of concern when evaluating the safety of raw materials coming in contact with the skin (Gerberick et al., 2001b). The approach for conducting skin sensitization risk assessments utilizes the same quantitative risk assessment approach as described in the above paragraphs. International industry associations such as the Research Institute for Fragrance Materials and the International Fragrance Association have formally adopted the RA approach as the core strategy for primary prevention of skin sensitization to these materials in consumer products. Based on deep understanding of the biology associated with induction of skin sensitization, the science of structure-activity relationship and RA for skin sensitization has matured to provide substantial guidance in the determination of the safe level of a sensitizing ingredient in a consumer product. The output of the assessment is the comparison of the anticipated consumer exposure level (CEL) to the acceptable exposure level (AEL). The AEL/CEL represents a Margin of Safety (MOS with its embedded conservatism and safety factors, and provides the necessary reassurance of safety for ingredients which may contain trace levels of materials with sensitization potential (e.g., perfume raw materials). Generally, an MOS greater than 1 is considered

adequate to allow the material to be used in a marketed product, while an MOS below 1 is not appropriate for product release to market without additional safety work. For those materials with an MOS less than 1, the toxicologist may consider reformulation, reevaluation of assumptions used in the exposure assessment or further research to generate more safety data.

It should be noted that there is insufficient scientific rationale to apply any additional infant uncertainty factor for higher susceptibility of infant skin (SCCNFP, 2002; Renwick et al., 2000). Structural and functional skin barrier properties have been shown to be equal between full term neonates, infants and adults. Several studies and observations support the conclusion that newborns and young infants are even less susceptible to skin sensitization owing to an immature or developing immune system, respectively. This position is supported by several pieces of information related to epidermal skin biology:

1. Epidermal thickness, density of epidermal cell layers and cellular structure are identical between adults and newborns (Fact Book, 1996; Fairley and Rasmussen, 1983; Holbrook, 1982). The reduced thickness of neonatal skin relative to adult skin, particularly the dermis which has smaller collagen fibre bundles and immature elastic fibers (Rook et al., 1992), is irrelevant when considering the potential for induction or elicitation of a sensitization response since sensitization processes are initiated in the epidermis and not the dermis.

2. Full-term newborn infants have a functional stratum corneum and a mature skin barrier function equal to adults (Fact Book, 1996; Kalia et al., 1998; Cunico et al., 1977; West et al., 1981). Importantly, structural and functional cellular constitution required to build up a mature stratum corneum is already present in the late pregnancy (Hammarlund and Sedin, 1979; Harpin and Rutter, 1983). Age-dependent studies have shown clear evidence that skin barrier remains virtually constant from infancy to late adulthood (Leveque et al., 1984; Ghadially et al., 1995).

3. *In vivo* as well as *in vitro* studies have shown that percutaneous absorption of chemicals is similar in infants and adults (Rasmussen, 1978; Wester and Maibach, 1982; McCormack et al., 1982).

4. The skin is less reactive to potent contact sensitizers in early infancy than it is later in life (Rietschel and Fowler, 1995). Allergic dermatitis to poison ivy-oleoresin as well as to certain topical medications is rare in early life (Epstein, 1971). The skin reactivity to 2,4-dinitrochlorobenzene has been shown to be very low in neonates and low in babies up to 3 months of age compared with adults. Importantly, the sensitization incidence in 9-month-old infants was shown to be equal to adults, however at a 30 times higher dose per unit area concentration than that required to achieve equal sensitization incidences in adults (Cassimos et al., 1980). This observation supports the conclusion that infants are not more susceptible to sensitization than adults, and might well be less susceptible given equivalent exposures. Babies may be less susceptible to sensitization because of the immaturity of their immune systems, which has been shown to have limited immune cell function, reduced cytokine release, limited antibody synthesis, and deficiency of cell-mediated immunity (Gotoff, 1996).

10. Accidental ingestion

On rare occasions, misuse of diapers can lead to the ingestion of diaper components. In these situations, the immediate concern is the potential choking or suffocation hazard associated with physical components of the product. Therefore, the structural integrity of the baby diapers is assessed by objective criteria to ensure the integrity and safety of the product for the consumer (Olsen, 1998; van Prooijen and de Winter, 1996; Krische, 1997; Rimell

et al., 1995). Consequently, Quality Assurance parameters are established as part of the product release criteria and the products are manufactured according to Good Manufacturing Practice to their integrity. Since accidental exposure through ingestion of diaper parts is considered a foreseeable scenario, the level of systemic exposure and risk is also routinely assessed. The safety assessments routinely conducted for raw materials generally are also sufficient for this unique situation and primarily include evaluation of existing data in the literature relating to systemic exposure to the ingredients. Technical assessments include evaluation of the potential risk of an acute ingestion. For example, in the case of the super absorbent polymers found in the core of the diaper, a risk assessment taking into account acute and subchronic toxicity data demonstrates that accidental ingestion of the small superabsorber granules would not lead to an increased health risk for the baby. While not recommended, accidental ingestion of this material will not result in any internal toxic responses to this inert polymer or any low-level contaminants that might be present (Greim, 1998). Even under rare product failure situations, such as when superabsorber may come in contact with the skin, sufficiently high margins of safety exist for such an accidental exposure.

11. Scientific review

In order to help ensure that the most up-to-date information and sound scientific judgment have been employed in the safety assurance program, safety assessors may decide to gather objective feedback and input from external experts in pertinent disciplines before introducing major changes to a product.

12. In-market monitoring

The final element of a complete safety strategy for diapers is the monitoring, recording and follow up of safety-related comments from caregivers in the market. This tool provides continuous consumer feedback, enabling the manufacturer to be aware of any concerns by users and to maintain a high standard of product quality and consumer satisfaction. This is accomplished by including the manufacturer's local contact details on every product (e.g., a toll-free telephone number or local address). Trained consumer relations personnel and safety personnel monitor these calls to ensure that any alleged safety concerns are investigated and addressed by appropriate follow up.

13. Conclusion

Each year, millions of consumers and caregivers rely on the superabsorbent disposable diaper as a convenient, effective and safe product. The major components of diapers are inert polymers that are inherently safe and all materials are carefully assessed before introducing into marketed products. Procter & Gamble has established a systematic approach for evaluating diaper safety as an integral part of the product development process. The approach follows the principles of general risk assessment including hazard identification, dose–response assessment, exposure assessment and risk characterization and, controlled trials to assess relevant clinical endpoints and/or independent scientific review, as appropriate. Additionally, post-marketing surveillance with consumer feedback provides added assurance that safe, quality products serve babies and caregivers around the world. The continued safe marketing of diaper products for over 45 years bears testimony to the company's rigorous and conservative safety assessment strategy that is described in this manuscript.

Conflict of interest statement

The authors are employees of Procter & Gamble.

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