



Safety evaluation for ingredients used in baby care products: Consideration of diaper rash



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ABSTRACT

Diaper rash can adversely impact the barrier properties of skin, with potential implications for increased absorption of chemicals through the skin, and this should be accounted for in any exposure assessment used in the safety evaluation of consumer products used in the diaper (“nappy”) area. In the absence of a quantitative evaluation of the potential impact of diaper rash, a default assumption of 100% dermal penetration is often made for substances applied in the diaper area. We consider here the extent, duration and severity of diaper rash and make a recommendation for conservative assumptions to incorporate into exposure assessments. Using a time-weighted average, the potential impact of diaper rash is illustrated for substances that have varying degrees of absorption through healthy skin. Results confirm that for assessments that already assume dermal absorption of 50% or higher, there is no impact on the overall exposure assessment. For substances that have a very low degree of dermal penetration (1%) through healthy skin, the impact of rash is expected to be less-than four-fold. This can be refined with additional data as there are many examples of poorly absorbed compounds for which dermal penetration is still low even for compromised skin.

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1. Introduction

Cosmetics and personal care products are often used with direct application to the skin such that safety assessments must consider both the site-of-contact as well as systemic exposures for chemicals absorbed through the skin. In estimating consumer exposure to products used on the skin, many safety assessments start with a default assumption of 100% dermal penetration. As the skin generally provides a significant barrier to dermal penetration of many substances, this initial assumption usually provides an opportunity for refinement. An estimate of more realistic dermal penetration might come from *in vivo* data, *ex vivo* studies, or *in silico* modeling. Unless specifically designed otherwise, these methods all involve healthy skin, raising questions as to whether the results are applicable to compromised skin, which can have diminished barrier integrity, resulting in the potential for increased

dermal penetration. This question is especially relevant to infant skin in the nappy area since most infants experience diaper rash at some point, which, if sufficiently severe, can affect the barrier properties of skin. Thus, the implications of diaper rash on the exposure assessment are important to consider.

As a quantitative estimation of the potential impact of diaper rash has not been published, it is often recommended that a safety assessment of ingredients used in the nappy area be based on an assumption of 100% dermal penetration. This is clearly a conservative assumption as diaper rash is not experienced continually, and typically only a fraction of the skin is involved when rash is present. Furthermore, even when diaper rash is present, the severity is usually mild such that the skin retains a functional barrier. This paper provides a review of the literature as well as historical P&G data on diaper rash, including the frequency and severity of rash as well as the amount of skin involved and the time to resolution. The implications of diaper rash for altering the dermal penetration of chemicals is considered, recognizing that this will depend on physical-chemical characteristics such that dermal penetration is not impacted to the same extent for all

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chemicals. This is all considered in a holistic way to provide a summary of the implications of diaper rash for the exposure assessment of consumer products used in the nappy area of infants. It is noted that this is only one part of the overall safety assessment; consideration of infants and children as a potentially sensitive life stage in safety assessments has recently been addressed (e.g., Felter et al., 2015; Neal-Kluever et al., 2014).

2. Infant vs. adult healthy skin

The skin is the largest organ in the human body. It is comprised of the epidermis, dermis and hypodermis, which allow for the internal and external regulation of the body. The epidermis consists of several layers which function as physical, chemical and immunological barriers (Elias, 2005, 2012). The outermost barrier is the stratum corneum, which mainly serves as a physical barrier and is the primary regulator of percutaneous penetration. Although the skin continues to develop and mature during the first year of life, the barrier properties of skin in a full-term neonate are comparable to adult skin at or shortly after birth (Chiou and Blume-Peytavi, 2004; Fluhr et al., 2012; Telofski et al., 2012; Ludriksone et al., 2014; Visscher et al., 2015). This conclusion is based primarily on the results of trans-epidermal water loss (TEWL), which has been used as a surrogate measure of skin barrier properties (Maibach et al., 1984; Morgan et al., 2003). Investigators have shown that even with the first few weeks after birth, TEWL measurements of infant skin are in the same range as that of healthy adults (Hoeger, 2011; Kelleher et al., 2013). While there is not a simple correlation between TEWL and percutaneous absorption of chemicals, most studies evaluating TEWL and percutaneous absorption report a positive correlation and conclude that overall the weight of evidence supports a relationship between these measures (Morgan et al., 2003; Levin and Maibach, 2005).¹

It is recognized that the skin of full-term infants has barrier properties comparable to adults² and that minor differences are within the range of inter-individual differences that are accounted for by the default uncertainty factors used in quantitative safety evaluations (Felter et al., 2015). However, these statements are generally made with regard to healthy skin and little has been done to explore the potential implications of diaper rash, as this has the potential to impact skin integrity. In fact, questions about exposure to chemicals in the nappy area of infants have been raised. The EU Scientific Committee on Consumer Safety (SCCS) Notes of Guidance for the Testing of Cosmetic Ingredients for their Safety Evaluation (SCCS, 2016) concludes that an additional safety factor is not needed for assessments of infants and children involving exposure to intact skin. However, it was suggested that a specific safety assessment is appropriate for cosmetic products used in the “nappy area” (diapered area) because of factors that may increase risk relative to the rest of baby skin:

“In the nappy area special circumstances are present resulting from the close confining clothes and nappies, uncontrolled urination and defecation and resulting problems with potential damage of the skin in the nappy zone. Modern nappy

technology has shown to provide increasingly good skin compatibility, leading to a decline in the frequency and severity of nappy dermatitis. However, irritant nappy dermatitis cannot be completely avoided and might have an impact on dermal absorption of substances

For the development of baby cosmetics and the risk assessment of products intended to be used in the nappy area, the potential impact of irritation on dermal absorption of the chemical needs to be considered by the safety assessor in the final quantitative risk assessment of their products.”

Further guidance was not provided in terms of how a specific safety assessment should be done for the nappy area. Many manufacturers of products intended to be used for infants, including diapers and wet wipes, start with an assumption that 100% of any chemical in contact with skin in the nappy area will be absorbed. However, this is clearly an over-exaggeration in many cases. This manuscript provides an analysis of the potential impact of diaper rash and makes recommendations for how this can be considered in the overall safety assessment process.

3. The “Nappy Area”: consideration of skin under a diaper

Diapers play an important role in infant hygiene, and the greater absorbency of modern disposable diapers has led to an improvement in skin health with a decreased frequency and severity of diaper rash (Odio and Thamen, 2014). These diapers are also constructed with a breathable back sheet to help keep the skin drier. However, it is recognized that a diaper is not changed right away every time an infant urinates/defecates, so there can be increased hydration of the skin under a diaper compared to non-diapered skin. However, under good hygiene practices of frequent diaper changes, the overall impact of diapering is quite minor and skin under a diaper in general stays quite healthy. Saadatmand et al. (2017) developed a computer simulation of skin under a diaper and found that under normal diapering conditions (modeled as a 4-h wear period during the day and 8-h overnight), there can be short-term changes in the thickness (hydration level) of the skin but that these remain very close to baseline conditions (without a diaper) such that diapering per se is not expected to have a significant impact on barrier properties of otherwise healthy skin. This leaves then the question of the impact of diaper rash, which occurs in most infants at some time during the diapering years.

4. Diaper rash: implications for safety assessments

Diaper (or nappy) rash, also known as diaper dermatitis, is one of the common skin disorders affecting babies. In most cases, the rash is restricted to confined anatomic areas (e.g., genital, perianal) and does not involve all (or even most) of the skin under a diaper. The factors that lead to diaper rash are multi-factorial (physical, chemical, enzymatic, and microbial factors) and are generally not directly related to the diaper itself. If a soiled diaper is not changed right away, the presence of bile salts and other irritants in feces can break down the protective lipids and proteins in the stratum corneum. A mixture of urine and feces can increase the pH of the skin (Berg et al., 1986; Fluhr et al., 2012), which can activate fecal enzymes that can further contribute to skin irritation. Friction and mechanical abrasion, especially if the skin is already compromised, can also lead to irritation. In addition, if a diaper is not changed frequently, extended periods of wetness can lead to over-hydrated skin which can leave it more vulnerable (Klunk et al., 2014; Visscher et al., 2015). Most rashes in the diaper area are simple cases of irritant contact dermatitis (e.g., from frequent contact with urine

¹ This correlation is stronger when the analysis is focused on a single anatomical site. In studies conducted on the volar forearm of volunteers, Morgan et al. (2003) found a linear relationship ($r^2 = 0.996$) between the number of tape strips (method used to remove the stratum corneum) and the log of TEWL, and a similarly strong correlation between the absorption of penciclovir and TEWL ($r^2 = 0.9283$).

² It is noted that in neonatal skin, dermal papillae are not yet observed and only start to become apparent after one month (Miyachi et al., 2016). This lack of dermal papillae and its associated capillary loops in neonates could potentially even minimize the ability for chemicals to be absorbed through neonatal skin and gain entrance into the systemic circulation.

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