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Review

Safety Evaluation of Absorbent Hygiene Pads: A Review on Assessment Framework and Test Methods

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Abstract: Disposable absorbent hygiene products have evolved for superior performance, enhancing the convenience of daily lives. However, the use of disposable hygiene pads has brought safety concerns on chemical exposure, and significant efforts have been made to assess the potential risks associated with use of hygiene pads. This article intends to overview the safety assessment framework of diapers and feminine pads, which includes hazard identification, hazard characterization, exposure assessment, risk characterization, and post-market risk management. Risk assessment of various constituents are reviewed for quantification methods and conservative estimation of exposure parameters. By reviewing the up-to-date considerations in risk assessment, we aim to provide insightful discussion on safety evaluation of current versions of disposable absorbent products. More clinical testing and post-market surveillance are needed for continuous monitoring of potential health impacts of advanced products and constituents.

Keywords: absorbent hygiene pad; diaper; feminine pad; risk assessment; safety; hazard; exposure; test method

1. Introduction

Disposable absorbent hygiene products such as diapers and feminine pads have evolved with availability of the advanced materials, and their superior functions over cloth diapers have improved the quality of daily lives. Although feminine pads and baby/adult diapers are used for different purposes, the main constituents of the absorbent hygiene products share similar functions and materials. The absorption capacity of disposable absorbent products had significantly improved with the implementation of superabsorbent polymer (SAP) in the core absorbent layer [1–4]. The safety of SAP material has been evaluated rather thoroughly including its potential risks involving ingestion and dermal contact [2–4]. In addition, potential hazards associated with process aids and solvents were investigated for human health risks. For example, phthalates [5] that are used as plasticizers of polymers and chlorine compounds [1,6,7] that are used as bleaching agents are identified as potential hazards, and as the absorbent pads are worn in a prolonged skin contact, the safety assurance of products has been regarded significant.

Regulatory classifications of absorbent products including baby diapers, adult diapers and feminine hygiene pads are varied for countries, and are regulated by different disciplines [8–14]. For example, in US, menstrual pads are regulated under the guidelines (not mandatory) of the Food and Drug Administration (FDA) [10,11]; in EU, they are regulated as broadly applicable consumer products [14–16]; and, in Korea, baby and adult diapers are regulated by the Korean Mistry of Food and Drug Safety (MFDS) under "Sanitary Products," and menstrual pads are regulated under "Quasi-Drugs" [9]. While the specific criteria may vary among the regulatory bodies, human health risk of products needs to be assured with due diligence from any regulatory frameworks. The exposure-based quantitative risk assessment (QRA) approach is commonly adopted, which includes hazard identification, hazard characterization, exposure assessment, and risk characterization [4,5,14,17–27]. Many studies have followed such a procedural framework in assessing the human exposure risks involved with absorbent products. Within such a framework, various designs have been tested for the toxicological aspects of raw materials, the controlled clinical trials, and post-market surveillance [28,29].

Among absorbent pads, much risk assessment has been done dominantly for baby diapers [2–5,18,24,30–40], while similar potential risks for feminine hygiene pads and other absorbent products exists. This paper aims to review the risk assessment methodologies that have been applied to disposable absorbent products including baby/adult diapers and feminine hygiene pads. The constituents of absorbent pads and the potential risks associated with dermal exposure are reviewed with specific focus on assessment framework, quantification methods and exposure profiles. By reviewing the up-to-date considerations in risk assessment framework, it is intended to bring up insightful discussion on safety evaluation of current versions of disposable absorbent products.

2. Disposable Absorbent Hygiene Pads

2.1. Types of Disposable Absorbent Hygiene Pads

Disposable absorbent hygiene pads consist of several different product categories including baby diapers, feminine hygiene pads, and adult urinary incontinence diapers. Table 1 shows the user and usage profiles for different absorbent products. Among the product types, baby diapers have been studied rather thoroughly in the perspective of safety and risk assessment [1–5,18,21,24,30,33–41]. Baby diapers are generally used for 0–36 month-old babies to absorb urine and feces [3]. In assessing the risks associated with baby diapers, biometric profiles and usage characteristics have been surveyed, including body weight [3,42–45], surface area [46], frequency of use [3,24], length of wear, and exposure routes [2,3,47].

Feminine pads are used for menstrual hygiene by women approximately 14–49 years old. Unlike baby diapers, the pads are worn periodically for about a week per month [14]. The risk assessment frame for feminine hygiene pads has a lot in common with that of baby diapers, but with different users and application characteristics [14,17,29,41,48–52].

Adult incontinence diapers are used for protection from urine leakage, and few studies are available for this product category [53]. However, as the disposable absorbent pads share the common aspects of product constituents and usage habit, a similar assessment framework can be used, if relevant users and usage profiles are employed.

Table 1. Types of disposable absorbent hygiene pads.

Pad type		Baby Diaper	Feminine Hygiene Pad	Adult Incontinence Diaper
User profile	Age	0–36 months [1]	14–49 years [3]	NA
	Body weight	TWA body weight 10.2 kg [1]	50–60 kg [3]	60 kg [6]
Typical application	Frequency	4.7 diapers/day [2]	5–7.5 pads/day [4] 7 days/month [5]	2–5 pads/day [6]
	Length of use	36 months	35 years	NA

[1] TWA body weight is reference value from US EPA 2011 [44]. Values for mean body weight, 10th percentile and 95th percentile body weights for different age groups are reported in References [2,3]. [2] A 4.7 pads/day is a mean value for all size diapers from the US diary data from Dey et al.'s study [3]. [3] The 50 kg weight referenced from Woeller and Hochwalt's study [14] is noted, while it has a wide range. [4] Five pads/day is referred from Woeller and Hochwalt's study [14], while 7.5 pads/day is referred from Korean MFDS [54]. [5] Data based on Korean MFDS [54]. [6] Data based on Proctor & Gamble consumer research referenced in Rai et al.'s study [53]. USA institutional and home care uses 3–5 pads or briefs/day; Japan uses 3.5–4 pads/day or 1.5–1.75 pull-on diapers/day.

2.2. Layer Construction of Absorbent Hygiene Pads

Figure 1 shows a typical layer construction of a disposable absorbent hygiene pad, which consists of a fluid permeable top sheet, an optional acquisition layer, a superabsorbent core, and a fluid impermeable back sheet with and without adhesives [2,4,14,55]. The layer structure of baby diapers, feminine hygiene pads, and adult diapers are very similar, whereas the design of fastening systems (such as fastening cuffs/wings and adhesives) are different between baby diapers and feminine pads.

For the feminine pads, the main layer design has changed little since its earliest commercial product by Johnson & Johnson in 1896 [29], while the constituent materials have evolved for a higher level of protection and comfort. One of the main improvements was made in the 1970s when the fastening adhesive was added to the back sheet of the pads, replacing pins and belts of the fastening system. Further improvement was made with the incorporation of superabsorbent gel particles in the absorbent core, which allowed a higher capacity and quick absorption of fluids [1–4,29,30,40].

For all type of absorbent pads, the topsheet commonly consists of a thin layer of perforated polypropylene and/or polyethylene nonwoven and this layer is in direct contact with skin [56]. The main function of this layer is to transfer fluids and feces quickly to the layer beneath, thus a high wicking ability is desirable. Mostly, emollient or lotion is applied onto the topsheet material to grant protection from irritation and skin softness [2,14,49,50,52].

Between the topsheet and the absorbent core, an optional acquisition layer (also called the distribution layer) may exist for the modern design of pads [4]. This layer is composed of a cellulose patch and a polyester nonwoven, and its function is to facilitate the spread of fluid evenly across the entire area. In addition, this layer helps prevent fluid reflux by retaining the fluid, and helps fluid transfer to the next absorbent layer.

The absorbent core beneath the acquisition layer functions for fluid storage. This layer is composed of a blend of superabsorbent polymer granules and fluff cellulose, which are encapsulated by cellulose or polypropylene nonwoven. The superabsorbent polymer (SAP) is typically made from sodium polyacrylate granules [4,14,33,34], and it transforms into a gel-like substance once it is wet, absorbing up to 30 times its weight liquid. The superabsorbent material alone has been thoroughly evaluated in many studies for skin irritation, sensitization, systemic toxic effects, and concluded to be safe for human use [4,30,40]. The cellulose fluff in the absorbent core helps to absorb liquid quickly and transfer to SAP [4]. Then, fluid is locked and stored within this core layer even under applied pressure. For the core constituents to be transferred to skin, the constituents need to be first solubilized in the fluid vehicle and then released from the layer upon the applied pressure [2,3,47]. As SAP is not water soluble, it is hardly released from the pad by wetting or reflux.

The backsheet is typically made of a water-proof polyethylene or polypropylene film laminated with polypropylene nonwoven [2,14,55]. This layer prevents fluid from leaking. For feminine pads, the backsheet has adhesives to fix on cloth. Baby diapers employ different fastening system, thus do not have such adhesives on the backsheet. Constituents of the backsheet and adhesives are reported to have negligible skin exposure through reflux [14].

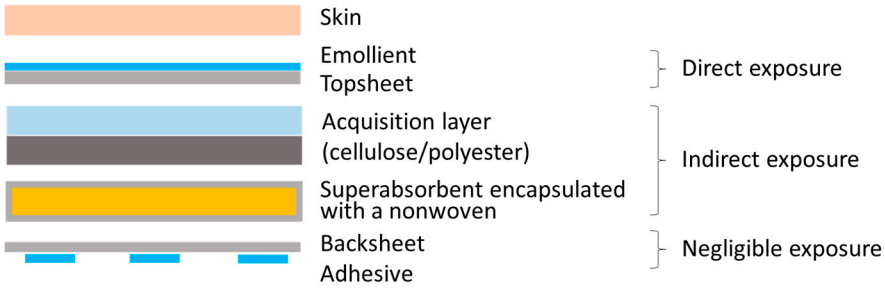

Figure 1. Layer construction of disposable sanitary pads and diapers.

2.3. Regulatory Classifications

Regulatory classifications of absorbent hygiene pads vary globally; it is subject to either mandatory legal enforcement or voluntary manufacturers' control depending on the country. In EU, sanitary pads are subject to consumer product regulations, which are less stringent [14–16]. In US, menstrual pads and adult incontinence diapers are regulated by FDA under Class I Medical Device [10,11]. This FDA regulation is not legally enforceable and regarded as guidance or recommendations for manufacturing control. For example, FDA recommends that chemicals and their quantities of all constituent materials be provided. From 510(k) premarket submissions guideline, a health risk of adverse tissue reaction is suggested to be identified for menstrual pads, and manufacturer's voluntary testing for biocompatibility is recommended in accordance with ISO-10993 (Biological Evaluation of Medical Devices Part-1: Evaluation and Testing). Tampons, as comparison to pads, are noted for more identified risks, which include adverse tissue reaction, vaginal injury, vaginal infection, and toxic shock syndrome [10,11]. In addition, 510(k) suggests identifying the bleaching process of pads, if any, such as "Elemental Chlorine-Free (ECF)." For new formulations that are dissimilar from the previously marketed, it is suggested to conduct voluntary risk analysis and provide clinical data [8,10,11].

In China, safety of baby diapers and sanitary pads are regulated under GB 15979-2002: Hygienic Standard for Disposable Sanitary Products (HS Code of 9619001000 Pull-up baby diapers, diapers/nappies; and HS Code of 9619002000 Sanitary napkins, panty liners, and tampons), which is a mandatory regulation [12]. Sanitary absorbent pads are also regulated under GB/T 8939-2008 [13], which is not a mandatory control. In accordance with those regulations, microbial indicators need to be reported for bacterial and fungal colonies, pathogenic purulent bacteria, and coliforms as well as other test results such as pH value, water absorbency, and infiltration capacity [12,13]. For the imported products into China, toxicological indicators need to be reported, such as skin irritation (for diaper), vaginal mucosa irritation (for menstrual pad), and dermal allergic reaction (for both menstrual pad and diapers).

In Korea, Korean Mistry of Food and Drug Safety (MFDS) regulates baby and adult diapers under "Sanitary Products" and menstrual pads under "Quasi-Drugs" [9]. The regulation has restrictions on substances such as fluorescent whitening agent, formaldehyde, chlorinated phenols (pentachlorophenol and tetrachlorophenol), azoic dyes, phthalates, and metal contaminants (antimony, barium, cadmium, chrome, lead, mercury, arsenic, selenium, etc.). However, a test protocol simulating exposure assessment has not been confirmed as of September 2018, and it could possibly create argument on risk management decisions for feminine pads [54,57]. Thus, an urgent need is brought upon revisiting and developing exposure-based risk assessment methodology for

absorbent hygiene pads. Safety regulations for hygiene pads in US, China, and Korea are summarized in Table 2.

Table 2. Safety regulations for diapers and sanitary pads.

	Product	Regulation	Restriction
US [10,11]	Baby diaper	Not available	Manufacturers are recommended to identify new formulations and bleaching process.
	Menstrual pad and adult diaper	FDA Class I Medical Device (guidance)	
China [12,13]	Baby diapers	GB 15979-2002 (mandatory)	Manufacturers should provide microbial and toxicological indicators.
	Sanitary pads	GB 15979-2002 (mandatory) GB/T 8939-2008 (guidance)	
Korea [9]	Baby and adult diapers	MFDS Sanitary Products (mandatory)	There are restrictions on chemicals and heavy metals for baby [1] and adult diapers. [2]
	Menstrual pad	MFDS Quasi-Drugs (mandatory)	

[1] For baby diapers, restricted chemicals and heavy metals include: fluorescent whitening agent, formaldehyde, chlorinated phenols (pentachlorophenol and tetrachlorophenol), azoic dyes, phthalates, antimony, barium, cadmium, chrome, lead, mercury, arsenic, and selenium [9]. [2] For adult diapers, restricted chemicals include: fluorescent whitening agent, formaldehyde, pentachlorophenol, tetrachlorophenol, and azoic dyes [9].

3. Safety Assessment Framework of Absorbent Hygiene Pads

In general, product safety assessment follows the process established by scientific committees [58,59], regulatory agencies [60,61], and other authoritative bodies [62]. Farage [28,29] suggested a step-wise process in assessing potential toxicological effects of raw materials, including hazard identification, hazard characterization, exposure assessment, and risk characterization. Additionally, clinical evaluation of product use and post-market surveillance can be conducted for thorough risk management of products. An overview of assessment approach is shown in Figure 2. Each step of assessment is summarized in the following section, with an emphasis on the exposure studies associated with diapers and feminine pads.

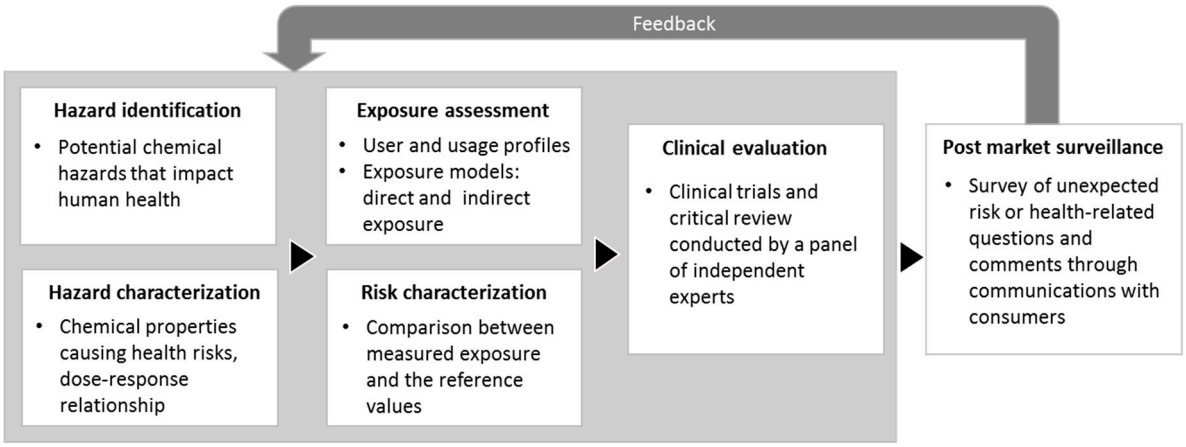

Figure 2. Safety assessment approach.

3.1. Hazard Identification and Characterization

Hazard identification is generally the first step of risk assessment and it is the process to identify the specific chemical hazard and to determine whether exposure to this chemical has the potential to harm human health, such as acute, cumulative and mechanical skin irritation, contact sensitization, and the potential for acute or subchronic effects [63].

Generally, the list of chemicals used in the industrial process as well as the associated safety data can be easily identified by the supplier's chemical safety data sheet. The identification may also include whether mixture of chemicals form other hazardous chemicals or behave differently. If the

identity of the chemical is unknown, the possible types of chemicals should be inferred from the descriptions of sources, production processes, or chemicals of other commercial industrial operations (available from emission scenario documents) published by Organization for Economic Cooperation and Development (OECD) [64]. Those documents are useful in quantifying the emission of chemicals into water, air, soil or solid waste, and such information supports the hazard identification process.

The potential hazard of a chemical can be determined from the available scientific database from toxicological or epidemiological studies provided by various international and national agencies [65,66]. For example, the International Agency for Research on Cancer (IARC) [65] coordinates epidemiological and laboratory research for the causes of human cancer, providing five categories based on the strength of evidence for carcinogenicity in humans. World Health Organization (WHO) works to establish the scientific basis for the sound management of chemicals for the safety of human health and the environment through the International Programme on Chemical Safety (IPCS) [67]. The Agency for Toxic Substances and Disease Registry (ATSDR) [68] also prepares toxicological profiles for hazardous substances found at National Priorities List sites. The Integrated Risk Information System (IRIS) [69] maintained by the U.S. Environmental Protection Agency (EPA) also provides an electronic database containing information on human health effects that may result from exposure to various chemicals in the environment. The European Commission (EC) in the framework of the Regulatory Fitness Programme (REFIT) [70] conducts studies that establish the links between the chemical substances and their impacts on human health and environment, to influence the legislation to reduce such impacts. The European Chemicals of Agency (ECHA) also provides a list of restricted substances under the framework of Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) [66].

For feminine pads, potential hazardous chemicals and descriptions of chemical sources have been published in several case studies [71–73]. From those studies, volatile organic compounds including styrene, chloromethane, chloroethane, chloroform, and acetone were detected from the commercial products [71–73], where those chemicals are identified as carcinogens, and reproductive and developmental toxins according to the National Toxicology Program ATSDR [68,74] and the State of California Environmental Protection Agency [75]. In another study [76], methyldibromo glutaronitrile (MDBGN) was identified from the adhesive used in the pad, which is known to cause dermatitis [76–80]. Cinnamaldehyde and cinnamic alcohol, which are reported to be causative agents of allergic skin reaction and rash by European Chemical agency (ECHA), were found from the scented pad [81].

Dioxins were detected from the fluff pulp of the absorbent core in pad products [82–84], where dioxins and dioxin-like compounds (DLCs) are highly toxic and environmental persistent organic pollutants. DLCs such as polychlorinated biphenyls can be produced from the bleaching process of wood pulps, and this compound is identified as Group 1 carcinogen by IARC. Acrylic acid, a residual monomer of SAP in the diaper core, is linked to skin irritations and toxic shock syndrome [85].

Hazard characterization is the qualitative or quantitative description of the inherent properties of chemicals that cause health risks, in terms of chemical toxicity, dose–response relationship, exposure route and time [23,24]. Based on the hazard characterization, health based references or point of departure (POD) are determined. The reference values include: no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), oral reference dose (RfD), inhalation reference concentration (RfC), benchmark dose limit (BMDL), acceptable daily intake (ADI), and tolerable daily intake (TDI).

To extrapolate such PODs to a large population, uncertainty factors are often employed. Uncertainty factors, also called safety factors, account for uncertainties such as in extrapolation from animals to humans; extrapolation from a small group individuals to a large population; possible synergistic effects of multiple exposures; bioavailability and absorption variability; and exposure models and estimation. Adequate selection of the uncertainty factor is a pre-requisite for determining an appropriate human exposure limit, and scientific studies are conducted for refining the uncertainty factor values. Typically, the uncertainty factor of 100 fold is used to extrapolate from an

animal based POD to a human exposure, whereas the uncertainty factor of 10 fold is used for inter-individual variability.

As the disposable absorbent hygiene pads including baby/adult diapers and feminine pads share the main constituent materials, analyses for hazard identification and characterization on those products can be shared to some extent. With the information on hazard identification and hazard characterization, policies and regulations may be established for the risk management associated with exposure to diapers and feminine pads. For example, phthalates, common plasticizers for polymeric materials, can be found from absorbent pads, and those chemicals are identified as potential carcinogens [86]. An example of phthalates, di(2-ethylhexyl)phthalate (DEHP), is regulated by EPA to limit its amount in drinking water to 6 ppb and in workplace air (8 h) to 10 mg/m^3. Likewise, certain phthalates for childcare articles are restricted in a concentration <0.1% by the European REACH [87] and the Japan regulation [88]. However, the carcinogenic potential from the dermal route has yet to be determined for many industrial chemicals.

3.2. Exposure Assessment and Risk Characterization

In Ishii's study [5,21], seven different phthalates were quantified from the topsheet of diapers using artificial sweat and urine as eluents. The eluted liquid was extracted using dichloromethane and analyzed by gas chromatography–mass spectrometry (GC-MS). The quantified contents were processed to produce daily exposure per body weight, taking an estimate of transdermal absorption rate of phthalates [5]. After the exposure assessment, risk characterization was conducted by calculating the margin of exposure (MOE), the ratio of a daily exposure to a No Observed Adverse Effect Level (NOAEL); as MOEs were greater than 1000, it was concluded that the tested diapers were safe from phthalate exposure [5]. The test was performed only on the topsheet, thus the phthalate contents could be underestimated as phthalates beneath the topsheet were not counted in the study.

Organic derivatives of tin such as dibuyltin (DBT), monobutyltin (MBT), tributyltin (TBT) and dioctyltin (DOT) are identified as potential hazard that can be present in diapers and pads as tin is used as a catalyst in manufacturing processes [89]. With the known harmful effect such as neurotoxicity, reproductive and developmental toxicity, immunotoxicity and endocrine disruption [89], organotin compounds were quantified from baby diapers by the energy dispersive X-ray fluorescence with ^{241}Am radioactive source [39]. Assuming the daily use of five diapers, daily organotin exposure was estimated to be 0.021 μg tin/kg weight·day. However, the dermal absorption rate of organotin compounds was not accounted in this study. Based on such information, risk characterization was conducted reporting that this content was 20–100% of the tolerable daily intake (TDI), and the risk of tin exposure is present [39].

Dioxins are another subject of attention regarding the potential risk of diaper wearing, as they can be generated from wood pulp bleaching with elemental chlorine, if total chlorine free (TCF) or elemental chlorine free (ECF) bleaching process is not used [1,6,7,21,82,90]. Ishii [21] performed the risk assessment of sanitary pads for the levels of dioxins, by comparing the daily exposure of dioxins from the tolerable daily intake (TDI). In this study [21], the amounts of polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and dioxin-like polychlorinated biphenyls (DL-PCBs) in fluff pulp samples of sanitary pads were determined by toluene extraction followed by GC-MS analysis. The quantified contents were converted to the toxic equivalency quantity (TEQ) using the World Health Organization's toxic equivalency factors (TEF) [26]. The TEQ concentration was then used to calculate the daily exposure [21] by considering the frequency of use, body weight, and reference absorption rate of dioxins (3%) [71,91]. From the result, the daily exposure was lower than 1/9500 times TDI, thus the risk of exposure was concluded to be negligible. This study did not consider the reflux of dioxins by fluids; instead, the total amount of dioxins extracted by toluene was quantified. As the fluff cellulose exists in the absorbent core, the actual exposure of dioxins in the fluff cellulose may occur only through fluid reflux, if ever; thus, actual daily exposure in real situation would be negligible, or be much lower than the values obtained from this study [21]. The bleaching of pulp can also leave chlorinated compounds in pulp products. Later, Wada et al. [7] updated the test protocol in assessing the exposure risk of total amount chlorine in pulp products,

using an artificial sweat as an eluent, extracting at 40 °C for 60 min. The eluted liquid was analyzed for chloroform, chloroketones, chlorophenols, chloroacetic acids and organically bound chlorine [7]. From this study, little residual chlorine was quantified in products, posing little health risk.

Recently, the emission of 74 types VOCs (including pesticides) from feminine products was investigated by Korean MFDS [54]. Test protocol was designed to measure the maximum amount of residual VOCs in products; in this method, pads were frozen at −196 °C to avoid evaporation of VOCs before detection, grounded at room temperature, and then the VOCs were analyzed at 120 °C by GC-MS. The systemic exposure was calculated based on the following usage assumptions: 7.5 pads/day, seven menstruation days/month, lifelong use. Risk characterization was performed by the margin of safety (MOS), calculated by the NOAEL values obtainable from US EPA-IRIS, ATSDR, or WHO IPCS. The MOS values for all tested pads were found to be greater than 5. It is probable that the VOCs measured by this method are an overestimation of the actual exposure, as the total amount of VOCs in the whole pad was counted (assuming 100% dermal absorption rate). A protocol that simulates the actual wearing environment may provide more accurate representation of exposure.

3.2.1. Exposure Model

While the main route of exposure for hygiene pads would be dermal exposure, the systemic exposure can be also considered with a conservative assumption that a dermal absorption through the sensitive body area can lead to a systemic effect. In this case, the systemic effect occurs through the dermal exposure, thus systemic exposure is estimated using the same parameters (except the body weight) as dermal exposure. The following equations [14] show the systemic and dermal exposure rates for the absorbent hygiene products:

$$\text{Systemic exposure } (\mu g/kg/d) = \frac{M \times C \times F \times D \times T_{direct} \text{ or } T_{indirect} \times A}{B} \quad (1)$$

$$\text{Dermal exposure } (\mu g/cm^2/d) = \frac{M \times C \times F \times D \times T_{direct} \text{ or } T_{indirect} \times A}{S} \quad (2)$$

where M is the raw material mass in product (g), C is the constituent concentration in the raw material (%), F is the frequency of the use (numbers/day), D is the exposure duration (% of day), T_{direct} (%) is the constituent transfer rate from materials to skin (in direct skin contact), $T_{indirect}$ (%) is the constituent transfer rate from materials to skin (indirect skin contact), A is the dermal absorption rate (%), B is the body weight (kg), and S is the exposed skin surface area (cm^2). Systemic exposure is calculated based on the body weight, and dermal exposure is expressed by dose per unit area of skin exposed.

Important parameters for exposure-based assessment include: the routes (oral, inhalation, and dermal exposure) and pathways of exposure (i.e., direct and indirect skin contact), exposure concentration, duration and frequency of exposure, and transfer media (air, water, soil). While the main exposure route of hygiene pads is dermal absorption, the pathways of exposure can be varied. The pathway of exposure refers to the physical course of chemical transfer as the chemical moves from a source to a point of contact. Common pathways of chemical transfer for pad products are direct skin contact and indirect skin contact by fluid reflux. Exposure assessments for different pathways are further discussed in the later section.

The user biometric parameters such as body weight and skin contact are critical parameters for the robust exposure-based risk assessment. Especially in diaper/pad product use, the body weight also accounts for the pressure applied onto the materials. Because infant body weight changes every day, the body weight should be specified during the given time period; thus, the US EPA Exposure Factors Handbook [44] and the Centers for Disease Control (CDC) [45] recommend using time-weighted average (TWA) body weights for the diapering period of 0–36 months. For assessment of skin sensitization, the surface area of the skin contact, instead of body weight, may be a relevant parameter for exposure-based assessment [92].

Frequency of use and length of wear are other key parameters in assessing the exposure. This information can be obtained through survey statistics for the affected individuals, demographic data,

behavioral observation, and activity diaries/models [62] . In applying human exposure models, WHO provides general guidance and suggestion of uncertainty factors [92,93].

3.2.2. Exposure by the Direct Skin Contact

Among the constituents of diapers and pads, polymeric materials are of little concern because large molecular weight polymers can be hardly transferred to skin. Of particular concern is small molecular weight materials such as aesthetic ingredients (scent and dyes), solvents and process additives (bleaching agent). In a simulation study by Farage [49,50,52], emollient transfer to skin was estimated to be lower than 20%, which was a conservative estimate. In Odio et al.'s study [36,37], a lotion was spread on the topsheet of a diaper, and then the transferred amount of lotion to the collection tape (Tegaderm™, 3M, St. Paul, USA) was measured during the children's diaper-wearing [37,38]. From this experiment, the lotion transfer to skin was estimated to be 3.0–4.3% of the initial amount of lotion per diaper [3,37,38,47]; this is half the amount that Rai et al. [24] used (7%) as the skin transfer rate by the direct contact.

3.2.3. Indirect Exposure by Reflux

Material transfer by the indirect skin contact involves rewetting of skin by fluid reflux under body weight, where rewetting was defined as the fraction of fluid that was resurfaced back from the absorbed state. Components of absorbent pads that are not in direct skin contact can be solubilized in aqueous carrier such as urine or menstruation, and can be resurfaced to the topsheet under body weight [3]. Rai et al. [24] explained that modern disposable diapers that contain SAP in the core have reflux value of merely about 0.25% as the resurfacing of liquid is minimized by SAP.

In Dey et al.'s study [2,3], rewetting test was performed employing a controlled gravimetric approach where collagen is used as a model skin. In this method, the rewetting by the prolonged exposure was simulated by applying a saline solution as a model urine under 0.41 psi, which was noted as the simulated pressure from an infant of 18–24 months. Sixty milliliters of 0.9% saline solution were loaded onto a diaper at an interval of 82 min, and the liquid transferred to the collagen sheet was measured after a predetermined time of wear [3]. Assuming that the applied pressure from a baby will not be on 100% of diaper area, rewetting fraction was adjusted to count 50% diaper area; the fraction of constituents transferred to skin by the reflux was estimated to be 0.32–0.66% (mean value of 0.46%). This value is higher than 0.25% that was suggested by Rai [24]. This conservative value of 0.46% was suggested by Dey et al. as a default rewet as the worst scenario [3].

The developed reflux protocol was applied to a target chemical, acrylic acid, which can exist as a residual monomer in the SAP [2,3,47]. The predetermined amount of acrylic acid was added to the SAP material, and then the resurfaced acrylic acid was collected on the collagen sheet. Quantification of acrylic acid from the extract of collagen sheet resulted in rewet value of 0.15–0.21%, which is lower than the suggested default value of 0.46% [3,47]. The authors discussed that using a default rewet value is a practical alternative to conducting a series of routine rewet testing for every constituent [3,47]. The concept of "default value" or "lotion transfer factor" was also mentioned by Kosemund et al. [4] as a practical approach to estimate the transfer rate of the chemicals by the indirect skin contact. When the added quantities of constituents are known, transferrable amounts of all constituents can be calculated using a conservative, default rewet value. Figure 3 overviews hazard characterization methods applied for different parts of products: (i) VOCs from the whole product construction were characterized; (ii) chemicals from the topsheet were analyzed based on the direct contact assumption; and (iii) refluxed chemicals were analyzed with simulated rewet testing.

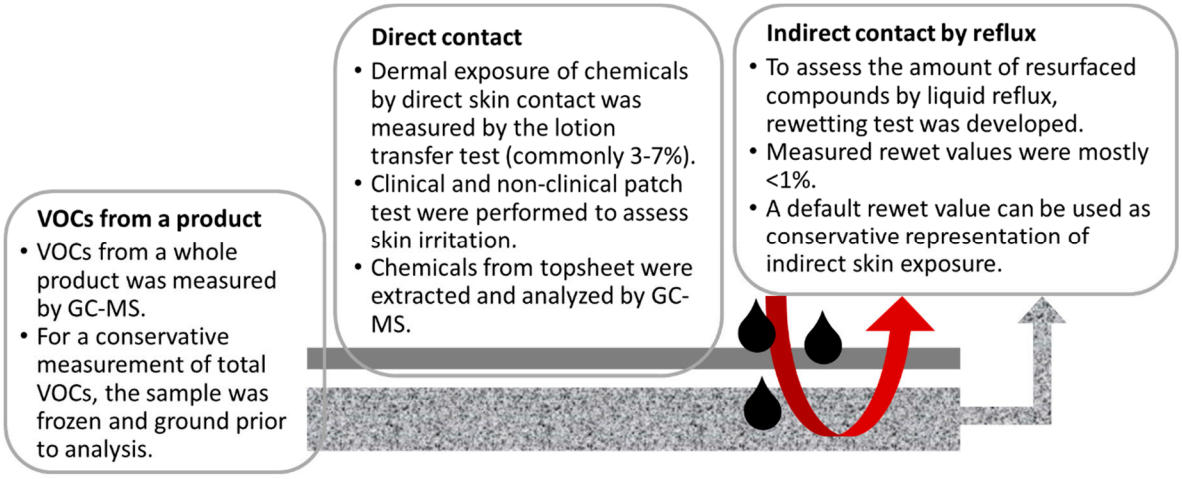

Figure 3. Exposure assessment for different pathways.

3.2.4. Risk Characterization

Risk characterization is a comparison between measured (or estimated) exposure and the reference values, such as NOAEL, LOAEL, RfD and RfC [94–96]. In this step, information obtained from previous steps of hazard identification, hazard characterization and exposure assessment is integrated, and the margin of exposure (MOE) or margin of safety (MOS) is calculated as a final evaluation for safety assurance.

MOE is the ratio of a point of departure (POD) dose such as NOAEL, LOAEL, and BMDL to an estimated human exposure, without consideration of uncertainty factor. NOAEL and LOAEL are obtained from animal toxicity studies and are noted in a unit of mg/kg body weight/day or ppm. BMDL, which incorporates the quantitative dose–response aspects, is also used for risk assessment associated with hazardous compounds.

MOS considers uncertainty factor, and is determined by the ratio of a derived reference dose with no or minimal adverse effects—which includes RfD, RfC, ADI, etc.—to an estimated human exposure level [22,26,97]. With uncertainty factor implemented, MOS ≥ 1 is considered to be acceptable; that is, if the product is used in its intended way or in foreseeable misuse, the product is safe with adequate margin of safety [4,24]. When MOS is lower than the desired, it is recommended to refine the conservative default assumptions. It is noteworthy that the reference values such as RfD, RfC, ADI, etc., are not the definite values, but rather evolve as new information or new scientific approach becomes available. While this fact does not invalidate the current reference doses, the reference values and MOS need to be regarded as the currently agreed ones.

3.3. Clinical Evaluation of Product Safety In-Use

Woeller et al. [14] conducted clinical studies on sanitary pads by the patch test to assess the overall mean erythema score (OMES) as a measure of cumulative irritation. During a 21-day study, the OMES of a finished sanitary product (with emollient) was significantly less irritating than that of product without emollient and that of absorbent core only [14]. On the other side, when an absorbent core is used in a finished product, hygiene benefits including reduced dermatitis [34–36,98–100] and reduced bacterial contamination [26,101–103] were demonstrated. The Behind-the-Knee (BTK) clinical test [29,104] was performed by applying a test pad to the popliteal fossa of one leg under an elastic bandage for 6 h per day for four consecutive days. From the BTK test, skin irritation and dryness were scored after 30–60 min after removal of products, and the score of erythema and dryness for the test product was compared with those of reference product that had safe use history [48,49,52].

Clinical studies before market introduction are desirable to assure product safety, especially for such cases as change of materials in use, introduction of the new process, and modification of product design. Such clinical studies are commonly conducted under practical or exaggerated conditions of

use. The clinical study generally follows the guidelines from the International Committee on harmonization/Good Clinical Practice (ICH/GCH) and gets approvals by the Institutional Review Board or ethical committee of the pertinent institution [29]. From the development of protocols to the investigation, independent academic physicians and medical experts in obstetrics and gynecology, dermatology, and microbiology are involved. Consumers habits and practices, as well as different geographic effect, are considered in the protocol design and investigation [105–106]. In US, although it is not legally enforceable, manufacturers are recommended to provide premarket notification submissions under FDA 510(k) for menstrual tampons and pads [8]. Then, a critical review on safety assurance is conducted by a panel of independent experts with the most up-to-date information and best scientific judgement.

3.4. Post-Market Surveillance

Risk management in the stage of consumer usage in market can be conducted through post-market surveillance by monitoring consumer's experience and satisfaction. Electronic media such as bulletin boards, social media, and manufacturer's website can facilitate the communication between consumers and manufactures. Any unexpected risk or health-related questions/comments would be alerted through such communications [71,107]. Especially for chemicals that have cumulative long-term effects, decades of after-market record would be very useful as critical references in various types and levels of comments.

While there are studies that revealed the symptom of skin irritation and allergic rash caused by the use of hygiene pads [108,109], in practice, it is not obvious for users and medical care providers to identify the problematic ingredients unless the whole product formulations are disclosed. In fact, it is not a mandatory requirement in many countries to disclose the formulations of hygiene pads. Recently in Korea, users of hygiene pads have claimed through social communities for the negative health signals after using specific brand pads, which include reduced menstrual bleeding, skin rashes and painful cramps. In 2017, the Korea MFDS collected all feminine pads sold in Korea, either manufactured or imported for the past three years, and investigated the levels of volatile organic compounds in products [54,55,57]. Such post-market surveillance and continuous monitoring would provide important cases that would explain unknown risks.

4. Conclusions

This article describes a systematic approach for risk assessment of disposable absorbent hygiene products such as feminine pads and diapers. The approach consists of: (i) hazard identification and hazard characterization; (ii) exposure assessment and risk characterization; (iii) evaluation of safety-in-use by means of prospective clinical trials; and (iv) post-market surveillance. More specifically, the following contents related to the absorbent pad products are reviewed [62]: identification of the concerned chemicals and their potential harms to human; characteristics of chemicals that can adversely affect health; chemical reference values that can be used with minimal harmful effects; relevancy of assumptions made in exposure assessment; pathways of chemical exposure in use; quantity, duration, and frequency of exposure; and comparison of the estimated exposure with the reference values. In exposure assessment of disposable hygiene pads, a protocol that simulates the actual wearing environment would provide more accurate representation of realistic impacts. For exposure models, it is important to use appropriate and conservative exposure parameters. Then, the risk characterization is conducted by comparing the estimated exposure with the appropriate reference values.

Consumers expect the safe use of disposable hygiene products in the extended period and frequent use, yet the expectation is challenged at times. A study by the non-profit organization for women safety and academic research have reported [57,72,81,110,111] that feminine pads include several chemicals of concern which are not identified by manufacturers. However, very limited data are available to confirm this claim or to demonstrate the effect of cumulative chemical exposure to health. More research and testing are clearly needed to better characterize and understand the potential health impact by the exposure [75,110,112]. In addition, it is critical to establish the rigorous

and effective post-market surveillance to monitor the product defects and health effects. Extensive review of collected consumers' feedback by the independent experts may provide unknown risks involved with long-term and cumulative exposure.

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