Evaluation of transdermal exposure of phthalates in children's products

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Abstract
In this study, 16 children’s products with the highest detection potential of phthalates were selected, and a phthalate assay and transdermal delivery analysis (NIER, US EPA Wipe [stress condition], US EPA Wipe [physiological condition], and US EPA Hand Wipe) were conducted with these products. The content of 6 controlled phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) was measured and most products contained more phthalates than the regulated guidelines (a total content of 6 phthalates to be ≤0.1%). For transdermal delivery, all items were found to be lower in the NIER transdermal delivery test method compared to the US EPA Hand Wipe (stress condition and physiological condition) transdermal delivery test method. For the US EPA Hand Wipe (stress condition and physiological condition) transdermal delivery test method, a similar result was observed, except for DINP. The average daily dose (ADD) estimated by determining the exposure algorithm for each transdermal delivery test method was highest in mats with a large contacting surface area and a long exposure time in the respective test methods. Conclusively, there was a difference between the NIER transdermal delivery test method and the US EPA Wipe transdermal delivery test method.

Keywords: children's products, phthalates, transdermal delivery amount, ADD

Introduction
Phthalates are plasticizers that soften plastic, and they are mainly used for PVC production that are restricted not only by the European Union Registration, Evaluation, Authorisation, and Restriction of Chemicals (EU REACH), but also by the Consumer Product Safety Improvement Act of the United States and other countries as reproductive toxic and endocrine-disrupting substances [17]. For the protection of children’s health in Korea, the Ministry of Environment stipulates that a list of the types of environmental risk factors and hazards are notified, and an applicable risk assessment is performed [12]. The Ministry of Commerce, Industry and Energy is also regulating phthalate with a common safety standard for children’s products in order to ensure the safety of products used by children who are vulnerable to chemical hazards [10]. The acceptable limit of 6 types of phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) is <0.1% in total [10,12]. Although most previous studies performed a survey of exposure to risk factors through children’s products, they were mostly based on the contents. However, the exposure based on the delivery test rather than the content is actually reported for children’s behavioral exposure to simulate the behaviors, such as touching with their hands and sucking their fingers after touching the product. In this study, the exposure factor and exposure algorithm suitable for each test method were determined by performing the content assay and transdermal delivery analysis of phthalates used in children's products to compare and evaluate the transdermal exposure for each substance. The objectives of this study are to measure the content of 6 controlled phthalates, to measure the transdermal delivery by substances through domestic and foreign transdermal delivery test methods (NIER, US EPA Wipe [stress condition], US EPA Wipe [physiological condition], and US EPA Hand Wipe), and to assess the transdermal exposure by substances by determining the exposure factor and exposure algorithm that are appropriate for each test method.

Materials and Methods
Selection of subject products
In this study, children’s products made with PVC material that showed a relatively high transdermal exposure in previous studies, including the study establishing the test method to evaluate exposure through children’s products (I) and survey of exposure to risk factors of children’s products, were selected. Among the children’s products made with PVC material, 4 products belonging to 4 product types, including bath toys, swimming tube/ beach ball, eraser, and mats, respectively, (a total of 16 products) were purchased and evaluated. Products, preferably KS certified products, were purchased in major supermarkets or local markets.
Methodology

Content assay method

Six controlled phthalates, DBP (Di-n-butyl phthalate), BBP (Benzyl butyl phthalate), DEHP (Bis(2-ethylhexyl)phthalate), DNOP (Di-n-octyl phthalate), DINP (Diisononyl phthalate), and DIDP (Diisodecyl phthalate), were analyzed.

An AccuStandard product was used for the phthalate standard solution and a Sigma Aldrich product was used for internal standard fluoranthene-d10. An HPLC level J.T.Baker product was used for the extraction solution, and specialized JUNSEI products were used for the rest of the reagents. HP-5MS (30 m × 250 μm × 0.25 μm) column was used to perform an internal standard method using GC-MS (Agilent, 5975C) for the qualitative and quantitative assay. The retention period and quantitative ions of phthalate are summarized in Table 1.

A 1 g of the pulverized sample was weighed with an accuracy of 0.001 g, transferred to a thimble filter, added a 100 mL of hexane, and extracted for 6 hours in a Soxhlet instrument. The extract was chilled to room temperature and concentrated to a volume of 5 mL to 50 mL, transferred to a vial, and the diluted internal standard fluoranthene-d10 was added and analyzed with GC-MS. The R² of the resulting calibration curve was ≥0.99, and the detection limits of 6 phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) were all ≤0.5 mg/L. The recovery rates of phthalate certified reference material (CRM) of DBP, BBP, DEHP, and DNOP were 101.6%, 95.7%, 95.1%, and 94.2%, respectively and the relative standard deviation (RSD) result was ≤10%.

Table 1. Phthalate retention time and quantification ion.

| Category          | Retention time (min) | M1 (m/z) | M2 (m/z) |
|-------------------|----------------------|----------|----------|
| Fluoranthene-d10[1] | 13.7                 | 212      | 213      |
| DBP               | 12.6                 | 149      | 223      |
| BBP               | 16.1                 | 149      | 91       |
| DEHP              | 17.6                 | 149      | 167      |
| DNOP              | 18.9                 | 149      | 70       |
| DINP              | 18.0~23.0            | 293      | 149      |
| DIDP              | 19.0~24.0            | 307      | 149      |

1 Internal standard.

NIER transdermal delivery test method

The NIER transdermal delivery test method is an assessment method based on transdermal absorption potential. The test method using artificial sweat according to the NIER notification is explained as follows. Artificial sweat was prepared by adding 1±0.01 g of urea, 5±0.01 g of NaCl, 940±20 μL of lactate to 900 mL of distilled water, and calibrating the pH to 6.5±0.1 by using ammonia solution and adding distilled water until the total volume was 1 L. The sample was added to 20 mL of 37 °C artificial sweat in a 250 mL glass container and extracted under 37 °C in a conditioning oven for 16 hours. The sample was removed from the glass container after the extraction, and the artificial sweat extract was transferred to a separatory funnel. After adding 10 mL of hexane to the emptied glass container twice, the container was sealed and shaken in order to rinse the inner surface, and this was added to the separatory funnel. Diluted internal standard fluoranthene-d10 was added, vortexed for 2 minutes, and incubated until the hexane was separated. Hexane was dehydrated with sodium sulfate anhydrous, and nitrogen was evaporated to 1 mL and analyzed with GC-MS. The same quantitative analysis reagent and analysis condition with the content assay and the R² of the resulting calibration curve was ≥0.99, and the detection limits of 6 phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) were all ≤0.5 mg/L.

US EPA Wipe transdermal delivery

The US EPA Wipe transdermal delivery test method is an assessment method based on transdermal adhesion potential. The transdermal delivery rate of US EPA Wipe is estimated, and isopropanol (50% water) is used as a stress condition as follows.
The sample was prepared by rubbing the product 30 times for 20 seconds with a cotton gauze pad wetted with 2 mL of isopropanol (50% water) solution. The sample was transferred to a Soxhlet thimble filter and 200 mL of acetone and DCM (methylene chloride) 1:1 mixture was added, extracted using Soxhlet equipment for 6 hours, and chilled to room temperature. After concentrating using the rotary evaporator (rotation 4-5 and heating at approximately 57 °C), the content was transferred to a vial and dried under a vacuum state in a desiccator. After adding 1 mL of methanol and diluted internal standard fluoroanisole-d10, the content was analyzed by using GC-MS.

As a physiological condition, the same artificial sweat used in the NIER transdermal delivery test method was used for the same method with the stress condition test method. For both stress condition and physiological condition, the same quantitative analysis reagent and analysis condition with the content assay and the R² of the resulting calibration curve was ≥ 0.99, and the detection limits of 6 phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) were all ≤0.5 mg/L.

**US EPA Hand Wipe transdermal delivery**

The sample was prepared by touching the product for 30 seconds and rubbing the same hand 30 times for 20 seconds with a cotton gauze pad wetted with 2 mL of isopropanol (50% water) solution. The sample was transferred to a Soxhlet thimble filter and 200 mL of acetone and DCM (methylene chloride) 1:1 mixture was added, extracted using Soxhlet equipment for 6 hours, and chilled to room temperature. After concentrating using the rotary evaporator (rotation 4-5 and heating at approximately 57 °C), the content was transferred to a vial and dried under a vacuum state in a desiccator, and after adding 1 mL of methanol and diluted internal standard fluoroanisole-d10, the content was analyzed by using GC-MS. The same quantitative analysis reagent and analysis condition with the content assay and the R² of the resulting calibration curve was ≥0.99, and the detection limits of 6 phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) were all ≤0.5 mg/L.

No plastic or rubber product was used during the pretreatment, and the analysis for all test methods and the transdermal delivery analysis results were processed by using Kruskal-Wallis among the independent distribution non-parametric tests with the IBM SPSS V25.0 statistics program.

**Transdermal delivery exposure algorithm**

In regard to the formula for calculating the exposure and exposure factors, the Ministry of Environment Procedure for the Risk Assessment of Environment Risk Factors (Ministry of Environment No. 585, 2016), the NIER Handbook of Children Exposure Factors (NIER, 2016), the Risk Assessment Study on Children Environment Risk Factors (NIER, 2011-2013), or Survey of Environmental Risk Factor Exposure through Children’s Products (Ministry of Environment, 2013, 2015) were referenced. The exposure factor included children ages 3-6 years with a body weight of 21.2 kg and transdermal absorption rate of 0.78, and the exposure factor applied values are presented in Table 2 [1]. The exposure algorithm according to each transdermal delivery test method was selected, as well as the transdermal delivery of toxic substances (ng/cm²/sec), product wipe concentration (ng/cm²/run), hand wipe concentration (ng/cm²/run), exposure time (sec/day), and exposure frequency (times/day), to calculate human body exposure. As an example, the NEIR exposure algorithm formula was shown below.

\[
ADD = \frac{M \times S \times ET \times ABs}{BW} \times \frac{1 \mu g}{1000 \text{ ng}}
\]

ADD: Average daily dose (µg/kg/day); M: Transdermal delivery of toxic substances (ng/cm²/sec)
S: Body surface area (cm²)
ET: Exposure time (sec/day); ABs: Transdermal delivery (unitless) BW: Body weight (kg)

**Table 2. Exposure factor applied values by product type.**

| Exposure factor   | S: Body surface area (cm²) | EF: Exposure frequency (times/day) | ET: Exposure time (sec/day) |
|-------------------|-----------------------------|-----------------------------------|-----------------------------|
| Bath toys         | 233                         | 5.6                               | 1926                        |
| Swimming tube     | 2188                        | 0.9                               | 1236                        |
| Beach ball        | 2188                        | 0.9                               | 894                         |
| Eraser            | 233                         | 2.3                               | 2460                        |
| Mats              | 4214                        | 7.6                               | 15960                       |

Source: Survey of environment risk factors in children products (2015), handbook of children exposure factors (2016).

**Results**

**Quantitative assay**
The contents of DBP, BBP, and DEHP were 14.18 ∼ 38.64 mg/kg, 35.90 ∼ 131.80 mg/kg, and 40.12 ∼ 104.34 mg/kg, respectively, and highest in swimming tube/beach balls. The content of DNOP was 29.47 ∼ 112.89 mg/kg and highest in mats, and the content of DINP was 65.86 ∼ 5634.01 mg/kg and highest in bath toys. Lastly, the content of DIDP was 64.88 ∼ 367.00 mg/kg and highest in swimming tube/beach balls. As a result, 13 out of 16 products contained 6 controlled phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) to 2-5 fold of the regulated limit 0.1% (Figure 1).

![Figure 1. Phthalate assay result by product type.](image)

**Transdermal delivery assessment**

According to the NIER transdermal delivery test result, DBP and BBP showed a similar concentration level in all products. Statistically, there was a significant difference between bath toys and swimming tube/beach balls, bath toys and erasers, and bath toys and mats. Meanwhile, there was no significant difference in other products. The concentrations of DEHP and DIDP were similar in all product types and showed no statistically significant difference. DNOP showed different concentration levels among the products, but statistically showed a significant difference only between swimming tube/beach balls and mats. DINP showed different concentration levels among the products, but statistically showed a significant difference only between swimming tube/beach balls and mats Table 3. However, all results were within the environment risk factor limitation of DINP for children’s products, which was 0.3667 ng/cm²/sec.

**Table 3. NIER transdermal delivery results of 6 phthalates.**

|                  | Bath toys (n=12) | Swimming tube/beach ball (n=12) | Eraser (n=12) | Mats (n=12) |
|------------------|------------------|---------------------------------|---------------|-------------|
| DBP**            | 0.010±0.007      | 0.010±0.001                     | 0.010±0.002   | 0.010±0.001 |
|                  | (0.007~0.031)    | (0.008~0.013)                   | (0.008~0.013) | (0.009~0.012) |
| BBP**            | 0.003±0.000      | 0.003±0.001                     | 0.004±0.001   | 0.004±0.001 |
|                  | (0.003~0.004)    | (0.003~0.007)                   | (0.003~0.007) | (0.003~0.007) |
| DEHP             | 0.007±0.002      | 0.007±0.003                     | 0.005±0.000   | 0.005±0.001 |
|                  | (0.005~0.012)    | (0.005~0.017)                   | (0.005~0.006) | (0.005~0.006) |
| DNOP*            | 0.15±0.33        | 0.013±0.035                     | 0.017±0.026   | 0.069±0.11  |
|                  | (0.003~0.86)     | (0.003~0.13)                    | (0.003~0.085) | (0.003~0.28) |
| DINP**           | 0.26±0.43        | 0.024±0.025                     | 0.022±0.017   | 0.010±0.005 |
|                  | (0.006~1.42)     | (0.007~0.098)                   | (0.006~0.055) | (0.006~0.25) |
| DIDP             | 0.007±0.002      | 0.007±0.001                     | 0.007±0.001   | 0.007±0.001 |
|                  | (0.006~0.012)    | (0.006~0.010)                   | (0.006~0.010) | (0.006~0.009) |

* p<0.05, ** p<0.01
According to the US EPA Wipe (stress condition) transdermal delivery test result, DBP, BBP, DEHP, and DIDP showed a similar concentration level in all products and showed no statistically significant difference between products. DNOP showed different concentration levels among products, but statistically showed a significant difference only between bath toys and erasers, and erasers and mats. DINP showed different concentration levels among products, but statistically showed a significant difference only between bath toys and swimming tube/beach balls, bath toys and erasers, and erasers and mats Table 4.

Table 4. US EPA wipe (stress condition) transdermal delivery results of 6 phthalates.

|                | Bath toys (n=12) | Swimming tube/beach ball (n=12) | Eraser (n=12) | Mats (n=12) |
|----------------|------------------|---------------------------------|---------------|-------------|
| DBP            | 2.93±1.39        | 2.90±0.93                       | 3.82±1.52     | 3.74±1.77   |
|                | (1.56~6.99)      | (1.61~5.04)                     | (2.24~7.21)   | (1.64~6.80) |
| BBP            | 0.96±0.10        | 0.97±0.10                       | 1.37±0.71     | 1.12±0.20   |
|                | (0.90~1.26)      | (0.91~1.27)                     | (0.90~3.13)   | (0.90~1.45) |
| DEHP           | 3.03±0.54        | 2.95±0.52                       | 3.24±0.92     | 3.21±0.93   |
|                | (2.17~3.95)      | (2.20~4.02)                     | (1.44~4.80)   | (1.84~5.11) |
| DNOP*          | 2.95±5.08        | 7.38±17.5                       | 2.38±2.73     | 1.45±1.35   |
|                | (0.87~17.7)      | (0.82~61.8)                     | (0.88~10.8)   | (0.87~4.42) |
| DINP*          | 4.48±1.64        | 41.2±78.2                       | 56.6±110      | 5.70±4.69   |
|                | (2.17~7.65)      | (3.38~268)                      | (1.89~389)    | (1.95~19.6) |
| DIDP           | 2.01±0.24        | 2.07±0.46                       | 2.52±1.16     | 2.03±0.46   |
|                | (1.74~2.55)      | (1.74~3.44)                     | (1.69~5.82)   | (1.73~3.26) |

* p<0.05, ** p<0.01

According to the US EPA Wipe (physiological condition) transdermal delivery test result, DBP, DEHP, DNOP, and DIDP showed a similar concentration level in all products and showed not statistically significant difference between products. BBP showed similar concentration levels among products, but statistically showed a significant difference only between bath toys and erasers, and swimming tube/beach balls and erasers. DINP showed different concentration levels among products, but statistically showed a significant difference only between bath toys and mats, and erasers and mats Table 5.

Table 5. US EPA wipe (physiological condition) transdermal delivery results of 6 phthalates.

|                | Bath toys (n=12) | Swimming tube/beach ball (n=12) | Eraser (n=12) | Mats (n=12) |
|----------------|------------------|---------------------------------|---------------|-------------|
| DBP            | 3.11±1.05        | 2.74±0.84                       | 2.92±0.96     | 3.36±2.44   |
|                | (1.57~4.37)      | (1.66~4.78)                     | (1.60~5.05)   | (1.58~9.96) |
| BBP*           | 1.00±0.15        | 0.98±0.05                       | 1.33±0.52     | 1.12±0.20   |
|                | (0.94~1.47)      | (0.93~1.08)                     | (0.96~2.23)   | (0.91~1.45) |
| DEHP*          | 2.25±0.14        | 2.05±0.37                       | 2.38±0.36     | 2.12±0.42   |
|                | (2.03~2.51)      | (1.02~2.48)                     | (1.57~2.95)   | (1.61~2.87) |
| DNOP           | 3.46±4.11        | 4.20±4.77                       | 1.46±0.47     | 10.3±15.4   |
|                | (0.90~14.5)      | (0.87~13.7)                     | (0.93~2.30)   | (0.87~41.1) |
| DINP*          | 56.9±92.6        | 20.4±20.4                       | 29.2±25.4     | 11.1±17.0   |
|                | (5.33~261)       | (1.56~60.5)                     | (4.88~69.9)   | (1.95~62.7) |
| DIDP           | 2.78±1.74        | 2.00±0.43                       | 2.34±0.70     | 2.00±0.46   |
|                | (1.72~6.90)      | (1.61~2.95)                     | (1.72~3.55)   | (1.64~3.20) |

* p<0.05, ** p<0.01
According to the US EPA Hand Wipe transdermal delivery test result, DBP, DEHP, and DIDP showed a similar concentration level in all products and showed no statistically significant difference between products. BBP showed similar concentration levels among products, but statistically showed a significant difference only between bath toys and erasers, bath toys and mats, and swimming tube/beach balls and erasers. DNOP showed different concentration levels among products but did not show a statistically significant difference between products. DINP showed different concentration levels among products, but statistically showed a significant difference only between bath toys and swimming tube/beach balls, and swimming tube/beach balls and mats Table 6.

**Table 6.** US EPA hand wipe transdermal delivery results of 6 phthalates. (Unit: ng/cm$^2$/run)

|                  | Bath Toys (n=12) | Swimming tube/beach ball (n=12) | Eraser (n=12) | Mats (n=12) |
|------------------|------------------|--------------------------------|---------------|-------------|
| **DBP**          | 2.59±0.78        | 3.61±1.15                      | 2.98±0.98     | 3.45±1.08   |
|                  | (1.66–4.73)      | (1.69–5.30)                    | (1.67–4.68)   | (2.05–5.49) |
| **BBP****        | 0.94±0.03        | 0.94±0.02                      | 1.29±0.72     | 1.07±0.15   |
|                  | (0.91–1.00)      | (0.91–0.98)                    | (0.91–3.50)   | (0.92–1.35) |
| **DEHP**         | 3.37±0.49        | 3.87±0.52                      | 3.88±0.65     | 5.66±3.38   |
|                  | (2.39–4.02)      | (3.17–4.70)                    | (2.96–4.80)   | (2.52–14.3) |
| **DNOP**         | 3.38±4.97        | 6.76±9.75                      | 0.92±0.04     | 6.88±11.7   |
|                  | (0.87–16.6)      | (0.87–29.8)                    | (0.87–1.00)   | (0.88–40.1) |
| **DINP****       | 11.0±19.3        | 18.4±15.2                      | 7.82±3.54     | 7.00±5.65   |
|                  | (3.08–71.6)      | (4.32–54.8)                    | (4.26–15.0)   | (2.41–22.5) |
| **DIDP**         | 2.19±0.45        | 2.11±0.19                      | 2.23±0.54     | 2.13±0.42   |
|                  | (1.76–3.50)      | (1.90–2.50)                    | (1.73–3.53)   | (1.70–3.00) |

* p<0.05, ** p<0.01.

**Estimation of average daily dose (ADD)**

For the average delivery dose (ADD) result according to the NIER transdermal delivery test method, DBP, BBP, DEHP, and DIDP were detected in the order of bath toys, eraser, swimming tube/beach ball, and mats, while DNOP and DINP were detected in the order of eraser, swimming tube/beach ball, bath toys, and mats. For the ADD result according to the US EPA Wipe (stress condition) transdermal delivery test method, DBP, BBP, DEHP, DNOP, and DIDP were detected in the order of eraser, bath toys, swimming tube/beach ball, and mats, while DINP was detected in the order of bath toys, eraser, swimming tube/beach ball, and mats. For the ADD result according to the US EPA Wipe (physiological condition) transdermal delivery test method, DBP, BBP, DEHP, DNOP, and DIDP were detected in the order of eraser, bath toys, swimming tube/beach ball, and mats, while DINP was detected in the order of bath toys, swimming tube/beach ball, bath toys, and mats. For the ADD result according to the US EPA Hand Wipe transdermal delivery test method, all items were detected in the order of eraser, bath toys, swimming tube/beach ball, and mats Figure 2.
Figure 2. Average daily dose by phthalates.
Discussion

In this study, 16 children’s products made with PVC material that showed relatively high transdermal exposure in previous studies were selected to perform a phthalate assay and a transdermal delivery test. As a result, 13 out of 16 children’s products contained 6 controlled phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) to 2-5 fold of the regulated limit 0.1%. This is similar to the data of the Ministry of Trade, Industry and Energy, which stated that among the children’s products that have received safety certification, there are many foreign products that were not conforming to the safety standards, and the rate of assay result exceeding the criteria was high [10]. In addition, possibly as a result of selecting products with a high concentration and from a country of origin with high rejection rate against safety standards for a comparison of the delivery test methods, the general rejection rate was higher.

While in previous studies conducted by the Ministry of Environment and the National Institute of Environmental Research [8-10], where DBP, DEHP, and DINP were not detected in bath toys, beach ball/swimming tube, and mats, DBP, DEHP, and DINP were detected at 0.001~0.003%, 0.004~0.01%, and 0.006~0.36%, respectively, in this study. While DBP was not detected in erasers in the previous studies, it was detected at 0.001~0.002% in this study. DEHP was detected at 0.004~0.006%, which was lower than 37.2~43.6% in the previous studies. DINP was detected at 0.01~0.56%, which was lower than 5.6~54.4% in the previous studies.

However, there were limitations that the data of children’s products according to the US EPA transdermal test method are not sufficient.

Also, the content in the eraser may have been detected higher in the US EPA Wipe (stress condition) transdermal delivery test as the surface of the eraser would have been eroded from the alcohol when it was wiped. In the preparation of samples, as the mat samples were collected by 20 cm × 20 cm from 3 areas (upper, middle, and lower) due to its wide surface without considering its pattern and illustration, it may have caused a fluctuation in the minimum and maximum results. The exposure time and exposure frequency were applied in the calculation of transdermal delivery results; however, the exposure of transdermal delivery test method was estimated unrealistically as the equilibrium state between the contact surface and the skin after a certain amount of time is not considered in this parameter and may lead to an unrealistic estimation of exposure. Therefore, exposure frequency is considered more suitable for a more reasonable measure of exposure for each transdermal delivery test method result, and as the number of analysis samples is not enough to determine the overall relationship, further research would be necessary.

Conclusions

Based on the result of this study, 13 out of 16 children’s products contained 6 controlled phthalates (DBP, BBP, DEHP, DNOP, DINP, and DIDP) to 2-5 fold of the regulated limit 0.1%. For transdermal delivery, all items were found to be lower in the NIER transdermal delivery test method compared to the US EPA Hand Wipe transdermal delivery test method (stress condition and physiological condition). For each transdermal delivery test method, the average daily dose throughout lifetime was highest in mats, which had the highest contact surface and longest exposure time. Lastly, the exposure time and exposure frequency were applied respectively for the transdermal delivery of each transdermal delivery test method. The exposure time was not suitable for a reasonable measure of exposure (RME) as the equilibrium state between the contact surface and skin after a certain amount of time is not considered in this parameter and may lead to an unrealistic estimation of exposure. Therefore, exposure frequency is suitable for a more reasonable measure of exposure for respective transdermal delivery test methods in terms of transdermal delivery result.

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Conflict of interest
The authors declare no conflicts of interest.

CRediT author statement
JHH: Conceptualization, Methodology, Visualization, Investigation, Formal analysis, Resources, Writing - Original draft Preparation; YWL: Validation, Writing - Review & Editing; JYY: Formal analysis, Validation, Supervision, Writing - Review & Editing; DCS: Validation, Writing - Review & Editing

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