Exposure and Health (2024) 16:369–376
https://doi.org/10.1007/s12403-023-00558-9

ORIGINAL PAPER

Permeability of Dimethyl Phthalate Through Human Skin Models – Health Risk Assessment

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Received: 30 September 2022 / Revised: 21 October 2022 / Accepted: 17 April 2023 / Published online: 5 May 2023

Abstract

Dimethyl phthalate (DMP) is used widely in cosmetics and personal care products as a solvent, skin penetrant, moisturizer and softener as well as an anti-cracking agent. Dermal absorption is one of the major exposure routes for lower molecular weight phthalates such as DMP and assessing their dermal permeability is important for evaluating the impact and toxicity of such compounds in humans. The aim of this study was to evaluate DMP permeability through different human skin models (Strat-M® synthetic membrane, in vitro reconstructed human epidermis and human dermatomed skin) using solutions containing various types of surfactants, as a simulation of the types of mixtures occurring in cosmetics and personal care products, in order to ascertain the impact that surfactants can have on skin permeability. The results have shown that human skin is the least permeable of the used skin models, and that surfactants (in particular cationic and non-ionic) lead to a significant increase of DMP permeability through all skin models. The performed risk assessment however shows that, for all tested models, the margin of safety was not exceeded.

Keywords Dimethyl phthalate · Skin models · Permeation · Transdermal diffusion · Exposure · Health risk assessment

Introduction

Dimethyl phthalate (DMP) belongs to a group of compounds named phthalate esters, which are produced by esterification of phthalic acid with methanol. It is classified as a low molecular-weight (LMW) phthalate, containing a single carbon ester side-chain (HSDB 2009; Otero et al. 2015). DMP is primarily used in the production of cosmetics and personal care products (PCP), mainly as a solvent and perfume fixative or as a sealant in hair spray (FDA 2010; Li et al. 2021; Nicolopoulou-Stamati et al. 2015; Wang et al. 2019). According to available literature, the reported DMP concentration in cosmetics (deodorants, perfumes, hair sprays and conditioners, lotions, face powders and foundations) ranges from 0.00004% up to 34% (in combination with its analogue DEP) (SCCP 2007; NICNAS 2008; CPSC 2010; NICNAS 2014). Giovanoulis and co-authors (2020) have concluded that use of cosmetics and PCPs may have a significant impact on human transdermal exposure to phthalates, especially for LMW phthalates such as DMP. Due to the toxicological properties of DMP (low acute toxicity, low skin and eye irritation, low skin sensitizing potential), the occurrence, among consumers, of adverse acute effects resulting from use of cosmetics containing this phthalate is relatively low. However, long-term exposure through leave-on cosmetics containing DMP is related to potential health risks (NICNAS 2014).

To perform a health risk assessment (HRA) of phthalates exposure via the dermal route, researchers use data on the percutaneous penetration of these compounds (Olkowska and Gržinić 2022). Data on the dermal permeation behavior of DMP is limited. Elsisi et al. (1989), during their investigation of DMP absorption via male rat skin (5–8 mg/cm^2), observed that the cumulative percentage dose excreted in urine and faeces over one week was 20–40% (excretion rate 6–7.5%). Compared with diethyl phthalate (DEP), DMP is considered to be slowly absorbed via the skin membrane. Dermal absorption of DMP through rat skin is about 10–20 times higher than through human skin (410 vs 39.5 µg/cm^2/hr) (NICNAS 2014). Data on DMP absorption through two skin models was reviewed by Koniecki et al. (2011): in vitro

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rat skin model (25.57 ± 8.5%) and human skin (4%). According to the Australian Department of Health HRA protocol, based on difference in absorption through rat skin and the higher permeability rate of DMP vs. DEP through human skin, the dermal availability of DMP was suggested to be 10% (NICNAS 2014).

The investigation of dermal absorption of chemicals present in cosmetics under realistic use conditions is vital for reducing uncertainties in risk estimates. Skin penetration may depend on the physicochemical properties of the chemical, its dose, surface of exposed skin, time of exposure, skin condition and presence of specific chemical compounds (Jiang et al. 2020). Surface active agents or alcohols, which are ingredients of cosmetics and PCPs, can disturb the natural protective skin barrier and result in increased permeability to other compounds.

The aim of this study was to examine DMP permeability through different human skin models exposed to DMP solutions, with and without surfactants, as a simulation of the types of mixtures occurring in cosmetics. The study also compares DMP permeation through three skin models (Strat-M® membrane (SMM), in vitro epidermal model (Reconstructed Human Epidermis, RHE) and human ex vivo human skin (XenoSkin H, HS)). The DMP permeability results obtained with the different skin membranes were used to evaluate HRAs exposure via the dermal route for cosmetics containing DMP.

Materials and Methods

Chemicals and Materials

Dimethyl phthalate (CAS 131-11-3; molecular weight 194.18 g/mol; density 1.194 g/mL at 20 °C, boiling point 283.7 °C at 760 mm Hg; vapor pressure $< 1 \times 10^{-2}$ mm Hg at 20 °C, partition coefficient n-octanol/water logK_{ow} 1.47–1.6; water solubility 4.0–4.3 g/L at 20 °C (NCBI 2022) (≥ 99.0% pure) was obtained from Alfa Aesar (Kandel, Germany). Deuterated DMP (d_4-DMP; 98.0% pure) was obtained from Sigma Aldrich Pty Ltd (Darmstadt, Germany). All GC-MS grade solvents used (dichloromethane, ethanol, methanol, acetone) and phosphate-buffered saline (PBS, pH = 7.4) were purchased from Sigma Aldrich Pty Ltd (Darmstadt, Germany). The following surfactants were used due to their frequent usage in cosmetics formulations: sodium dodecyl sulfate (ASAA; ≥ 99.0%) and hexadecyltrimethylammonium chloride (CSAA; ≥ 98.0%) from Sigma Aldrich Pty Ltd (Darmstadt, Germany), caprylyl/capryl oligoglucoside (O110) (NSAA; technical grade) from Logis-Tech (Mirków, Poland).

Experimental work has been conducted under conditions which limit contamination of glassware and other laboratory equipment with phthalates (treatment with ethanol, acetone and/or high temperature). Plastic containers were eliminated from protocols unless they had phthalate-free certificates.

In transdermal diffusion testing, three types of human skin models were used: Strat-M® membrane (SMM), in vitro epidermal model (RHE) and ex vivo human skin (HS). The synthetic Strat-M® membrane (25 mm, non-animal based model) was obtained from Merck KGaA, (Darmstadt, Germany). This membrane has already been used as a permeation barrier for predicting phthalate penetration through skin (e.g. diethyl phthalate, dibutyl phthalate, diisononyl phthalate) (Pan et al. 2014). RHE membranes (Fraunhofer ISC-TLC in vitro epidermal 25 mm models in 6-well format) with the supporting cell culture medium were ordered from the Translational Center Regenerative Therapies TLC-RT, Fraunhofer Institute for Silicate Research ISC (Würzburg, Germany). Frozen abdominal dermatomed human skin XenoSkin H (art. no. H-D20D-24, 24 mm) was obtained from Xenometrix AG (Allschwil, Switzerland) under strict ethical restrictions and with informed consent. No sensitive personal information regarding the patients was retained.

Franz Diffusion Cell Experiments

DMP permeation experiments, with and without the addition of surface active agents, were performed according to OECD guidelines (OECD 2004). A 6-cell manual diffusion cell system with 2mag-Magnetic-Drive (2mag-AG, München, Germany) and circulating waterbath HE4 (JULABO GmbH, Seelbach, Germany) was obtained from Hanson Research (Chatsworth, CA, USA). All studies were performed using 7 mL vertical diffusion cells (donor medium) with open cell top (1.8 cm^2 diffusion area, 1 mL of donor medium) and cap. The temperature and stirring parameters were set to 32 ºC and 350 rpm, respectively. Except for the Strat-M® membrane, skin models were hydrated before diffusion cell experiments (Sugino et al. 2017). PBS solution with addition of 10% of ethanol was used as donor and acceptor media for all tested mixtures, which had a positive effect on DMP solubility and the solvent is compatible with aqueous buffer (Katakam and Katari 2021). The applied DMP dose per cm^2 of skin model was 1078 µg/cm^2. The amounts of surface active agents added were based on average values used in cosmetics formulations. The composition of the tested mixtures can be seen in Table 1. Fresh mixtures were prepared for every round of diffusion experiments and measurements were carried out in three replicates with each mixture, for every type of membrane. After preparation, the diffusion cells (filled with acceptor medium, with mounted skin model, covered with the cell top) were checked to ensure that there were no air bubbles between the skin model and the receptor medium. Aliquots (500 µL) were collected from

Table 1 Composition of tested dimethyl phthalate mixtures with surfactants

Sample name	Amount of applied chemicals				PBS with 10% ethanol
	DMP[1]	ASAA[2]	CSAA[3]	NSAA[4]	
DMP	10 mM	–	–	–	filled to 10 mL
DMP + ASAA		10%	–	–	
DMP + CSAA		–	2%	–	
DMP + NSAA		–	–	10%	

[1]DMP—dimethyl phthalate

[2]ASAA—anionic surface active agent

[3]CSAA—cationic surface active agent

[4]NSAA—non-ionic surface active agent

the receptor sections at specified time intervals (0 h, 1 h, 2 h, 3 h, 4 h, 6 h, 8 h) by injecting warmed PBS solution using a 1.0 mL chromatographic syringe. Next, samples were extracted using liquid–liquid extraction (LLE) and analyzed by gas chromatography coupled with mass spectrometry (GC–MS).

Chromatographic Analysis

The determination of DMP migration through the skin models was performed based on analytical methodologies proposed by Guo et al. (2010). Stock standard solutions of DMP and d_4-DMP (internal standard) at 1000 µg/mL were prepared separately. A calibration curve for both analytes, ranging from 0.025 µg/mL to 50 µg/mL, was prepared by dilution of the mentioned stock solution. Validation samples at concentrations of 1, 10 and 25 µg/mL were also prepared as above. Each sample was analyzed in triplicate with methanol injections between every three samples.

The amount of DMP in acceptor and donor samples, after LLE (double extraction with 1 mL of dichloromethane after addition of 10 µL d_4-DMP at 5 µg/mL), was investigated with a GC-2010 PLUS gas chromatograph coupled with an AOC-20ia auto injector and MS-TQ8040 mass spectrometer from Shimadzu Corp. (Kyoto, Japan). Before analysis, the extracts were evaporated and the residue was dissolved in 500 µL of methanol. The injection temperature was set to 280 °C in splitless mode. The GC oven temperature was programmed as follows: at 50 °C initially and held for 1 min, then ramped to 310 °C and held for 2.5 min. The separation was carried out on a fused silica capillary column GC Zebron ZB-5MS (30 m, 0.25 mm, 0.25 mm) with helium as carrier gas (99.999995% pure, flow rate of 1.0 mL/min). The ion source temperature was maintained at 220 °C and the transfer line was heated to 310 °C. The MS was operated in electron impact mode with electron energy of 70 eV. The target compounds were determined in full scan (SCAN) and selected ion monitoring (SIM) mode. LabSolution Analysis software (Shimadzu Corp., Kyoto, Japan) was used for GC-MS control and data acquisition. The identification was performed by using similarity search in the National Institute of Standards and Technology MS database (NIST 11).

Quality Assurance and Data Analysis

The analytical method has been evaluated using the following validation parameters: detection limit (DL), quantification limit (QL), linearity, recovery, and precision (ICH 2022). DL and QL were calculated based on the standard deviation of the linear response and the slope of the calibration curve as well as on a signal to-noise ratio of 3:1 and 10:1, respectively. The linearity was evaluated based on the coefficient of determination (R^2) of a 6-point calibration curve. Recovery of the target compound was performed at three different levels to evaluate the accuracy of the proposed protocol. Precision (as percent relative standard deviation, %RSD) was investigated by carrying out six independent sample analyses for three consecutive days.

The skin permeability of DMP was calculated from the quantity of target analyte, which permeated through the skin membrane, divided by the membrane surface and the time duration. The permeability coefficient (k_p) was determined from the steady-state flux (J_{ss}) and DMP levels in the donor phase. Phthalate flux was calculated from the slope of the penetration amount vs. time profile. Additionally, the ratio of total amount of DMP (Eq. 1) in the receptor fluid was compared to the amount of DMP in the donor phase to determine the total absorption rate (Hopf et al. 2014; Neri et al. 2022):

$$\text{Total absorption (\%)} = \text{amount of DMP acceptor/total amount DMP in donor} \times 100 \quad (1)$$

Total absorption of the test compounds can be used as one of the exposure parameters in human HRA. The obtained results were used in non-cancer risk assessment of DMP connected with its potential occurrence in cosmetics or personal care products (MFDS 2017; SCCS 2016; Kim et al.

2020). The systemic exposure dose (SED) was calculated using Eq. (2).

$$\text{SED (mg/kg/day)} = \text{B} \times 1000\ \text{mg/g} \times \text{C}/100 \times \text{A}/100/\text{BW} \quad (2)$$

where: SED—systematic exposure dosage for cosmetic ingredients (estimated amount of exposure, per body weight, per day) [mg/kg body weight/day]; B—amount of cosmetic products used in one day [g/day]; C—concentration of target ingredient in evaluated cosmetic products [%]; A—skin absorption rate expressed in real use conditions [%]; BW—average body weight (60 kg) [kg].

The results of the non-cancer HRA were taken as the margin of safety (MoS) (Eq. 3), with values above 100 indicating a safe value (MFDS 2017; SCCS 2016; Kim et al. 2020). If MoS is < 100 for an investigated compound, the ingredient is considered to be a potential cause of adverse health effects and there are safety concerns in terms of its use.

$$\text{MoS} = \text{NOAEL}/\text{SED} \quad (3)$$

where: MoS – margin of safety [-]; NOAEL—no observed adverse effect level [mg/kg body weight/day]; SED—systematic exposure dosage for cosmetic ingredients [mg/kg body weight/day].

All calculations were done using Microsoft® Excel® 2016 MSO.

Results and Discussion

Determination of Dimethyl Phthalate—Quality Control

Table 2 summarizes the parameters of the analytical protocol used to estimate DMP concentrations in the acceptor and donor medium, including validation parameters. The calibration curves obtained for DMP showed a good linear range of calibration ($R^2 = 0.996$).

The verification of the extraction method was performed by estimating the recoveries obtained from the blank samples and samples containing DMP standards. The analytes showed good recovery (more than 90%) and the %RSDs were lower than 10%, confirming good accuracy. With regards to precision, the results were within acceptable ranges according to guidelines (%RSD less than 15%).

Dimethyl Phthalate Permeation with Different Skin Models

The skin permeation profiles of DMP through synthetic membrane, in vitro epidermal model and ex vivo human skin, are shown in Fig. 1a–c, respectively. Based on data presented in Fig. 1, the highest skin permeability was observed for the in vitro epidermal model (solution with cationic surfactant). The lowest DMP concentration (presented as cumulative μg/cm^2) in the receptor phase was observed for human skin. Differences in permeability between the synthetic membrane and human skin are similar to previously reported values (Scott et al. 1987, 1989; Olkowska and Gržinić 2022). The lowest impact on DMP permeation was observed for solutions containing the anionic surfactant. Human skin and RHE permeability were most impacted when a cationic surfactant was used. The non-ionic surfactant increased permeability of DMP through all types of membranes. This surfactant has been reported as causing serious eye damage (ECHA 2022).

The permeation parameters are shown in Table 3, along with the percentage absorption used in HRA. The lowest penetration (1.2–3.0 μg/cm^2/h) was observed for human skin with all mixtures. Similar flux values (2.5–4 μg/cm^2/h) were described in CPSC (2010). Flux of DMP across the Strat-M and RHE membrane was similar, and comparable to values obtained for rat epidermis (40–50 μg/cm^2/h) (CPSC 2010). Such skin models can be a good alternative to *in-vivo* animal testing. Total absorption for human skin was lower that reported in guidelines (5–10%). Differences can be attributed to variables such as vehicle effects and/or study design (NICNAS 2014).

Table 2 Parameters of dimethyl phthalate determination using LLE-GC–MS protocol

Reference ions	Calibration curve	R^{2a}	DL[b] [μg/ml]	QL[c] [μg/ml]	Recovery (%)	RSD[d] (%)
DMP: 163 (133, 194) d_4-DMP: 167 (81, 198)	$y = 29665x - 23694$	0.9964	0.011	0.035	102.5 (1 μg/mL) 99.4 (10 μg/mL) 97.5 (25 μg/mL)	9.1 3.6 5.8

[a]R^2—coefficient of determination

[b]DL – detection limit

[c]QL – quantification limit

[d]RSD—the relative standard deviation

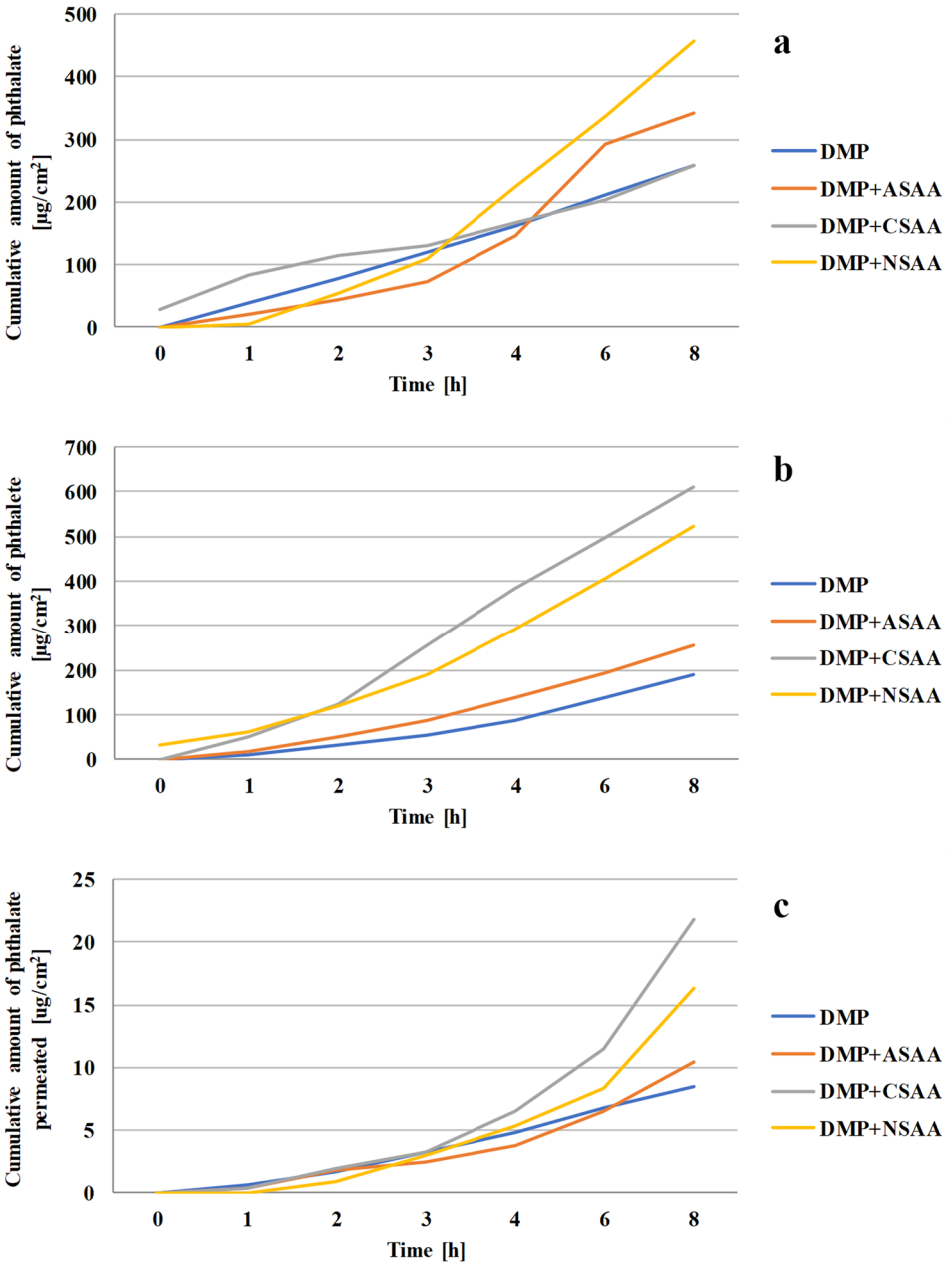

Fig. 1 Dimethyl phthalate (DMP) concentration (presented as cumulative amount ug/cm^2) in receptor phase over time (h) during permeation experiments with: a—Strat-M® membrane (SMM), b—in vitro epidermal model (Reconstructed Human Epidermis, RHE) and c – ex vivo human skin (HS). Where: ASAA—anionic surface active agent, CSAA – cationic surface active agent, NSAA – non-ionic surface active agent

Health Risk Assessment

Health risk assessment was performed using absorption data obtained for the three different skin models, assuming exposure via perfume (containing 2.5% DMP) and general cosmetics (containing 0.3% DMP), respectively (NICNAS 2014) (Table 4). Generally, the DMP margin of safety was not exceeded with any of the skin membranes. Similar data were presented in NICNAS (2014), where using a worst case scenario MoS was equal to 13,500. However, presence of the cationic surfactant, even at lower concentration than other surfactants, has generally led to an increase in permeability of the skin models.

Table 3 Results of skin model permeation experiments with dimethyl phthalate

Tested mixture of chemicals	Type of skin model	J_{ss}[8] [μg/cm^2/h]	k_p[9] [×10^{-3} cm/h]	Total absorption [%]
DMP[1]	SMM[5]	35.8	18.6	24
DMP + ASAA[2]		23.8	12.2	31
DMP + CSAA[3]		24.5	12.6	24
DMP + NSAA[4]		67.7	34.9	42
DMP	RHE[5]	24.8	12.8	18
DMP + ASAA		33.2	17.1	23
DMP + CSAA		81.4	41.9	56
DMP + NSAA		65	33.5	48
DMP	HS[7]	1.4	0.73	0.8
DMP + ASAA		1.2	0.61	1
DMP + CSAA		3.0	1.54	2
DMP + NSAA		2.2	1.14	1.5

[1]DMP—dimethyl phthalate
[2]ASAA—anionic surface active agent
[3]CSAA—cationic surface active agent
[4]NSAA—non-ionic surface active agent
[5]SMM—Strat-M® membrane
[6]RHE—Reconstructed Human Epidermis
[7]HS – human XenoSkin H
[8]J_{ss}—steady-state flux
[9]k_p—skin permeation coefficient

Table 4 Margin of safety (MoS ≥ 100 = safe) estimated for investigated mixtures of compounds and skin model (where: NOAEL = 600 mg/kg body weight/day (NICNAS 2014))

Type of membrane	exposure via perfume			
	DMP[1]	DMP+ASAA[2]	DMP-CSAA[3]	DMP-NSAA[4]
SMM[5]	8000	6194	8000	4571
RHE[6]	10667	8348	3429	4000
HS[7]	240000	192000	96000	128000
Type of membrane	exposure via all applied cosmetics			
	DMP[1]	DMP+ASAA[2]	DMP-CSAA[3]	DMP-NSAA[4]
SMM[5]	2811	2176	2811	1606
RHE[6]	3747	2933	1205	1405
HS[7]	84317	67454	33727	44969

[1]DMP—dimethyl phthalate
[2]ASAA—anionic surface active agent
[3]CSAA—cationic surface active agent
[4]NSAA—non-ionic surface active agent
[5]SMM—Strat-M® membrane
[6]RHE—Reconstructed Human Epidermis
[7]HS—human XenoSkin H

Conclusion

In this study, we have examined the permeability of DMP with different human skin models. While human skin remains the golden standard, reconstructed human epidermis and synthetic membranes provide results which can, with appropriate corrections, be useful in cosmetics health risk assessment. We have likewise tested different types of surfactants, which have been shown (in particular cationic and non-ionic ones) to increase DMP permeability through all skin models by a factor of at least two. Since such compounds are often used in cosmetics and personal care products, the assessment of their influence on skin absorption is crucial in cosmetic risk assessment. Nevertheless, the margin of safety, with all skin models, was not exceeded. Overall, risk assessment points to a relatively low risk related to surfactant use in combination with DMP, however additional research is needed for the determination of the impact of mixtures with other phthalates and of long term risk. Moreover, cumulative HRE assessments should also consider additional exposure routes to DMP such as transdermal absorption from indoor air, which can account for up to 35% of total exposure in indoor environments (Bu et al. 2016). Therefore, from a HRA perspective, efforts should focus on estimating overall DMP exposure via the dermal route resulting from different sources (cosmetics, detergents, clothes, indoor air, households items etc.).

Acknowledgements The author would like to thank Goran Gržinić (Department of Environmental Toxicology, Medical University of Gdansk) for the language critical review of our manuscript. The author would like to thank For laboratory assistance Additionally, the author would like to thank Paulina Antochowska and Maja Dzwoniarska, students who provided laboratory assistance.

Author Contributions EO: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Visualization, Writing—original draft, Writing—review & editing.

Funding This work was financially supported by the National Science Center (Poland), grant no. 2016/23/D/NZ7/03929.

Data Availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent to participate All the participants were duly informed about the study protocol and objectives and provided an informed consent.

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