



Aggregate consumer exposure to isothiazolinones via household care and personal care products: Probabilistic modelling and benzisothiazolinone risk assessment[☆]



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ARTICLE INFO

Handling Editor: Heather Stapleton

Keywords:

Aggregated exposure
Tiered approach
Consumer product
Personal care products
Exposure factors
Cleaning agents
Sensitizer
Sensitization

ABSTRACT

Consumers regularly use household care and personal care products (HC&PCPs). Isothiazolinones are included in HC&PCPs as preservatives and are being held responsible for an epidemic rise in allergic contact dermatitis (ACD). The objective of this study was to assess the origin and extent of dermal exposure in order to evaluate the risk of ACD from isothiazolinones in HC&PCP.

Individual-based aggregate dermal exposure to four isothiazolinones was estimated using the newly proposed Probabilistic Aggregated Consumer Exposure Model–Kinetic, Dermal (PACEM-KD) by combining the reported individual use patterns for HC&PCP in Switzerland (N = 669 (558 adults), ages 0–91) with isothiazolinone concentrations measured in products used by the individual person. PACEM-KD extends the original PACEM by considering exposure duration, product dilution and skin permeability. PACEM-KD-based higher-tier exposure on palms (99th percentile) was 15.4 ng/cm², 1.3 ng/cm², 0.9 ng/cm², and 0.08 ng/cm² for the isothiazolinones 1,2-Benzisothiazol-3-(2H)-one (BIT), 2-Octyl-3(2H)-isothiazolinone (OIT), 2-Methylisothiazolin-3(2H)-one (MI), and 5-Chloro-2-methyl-4-isothiazolin-3-one (CMI), respectively. Major sources of exposure to BIT included all-purpose cleaners, dishwashing detergent, and kitchen cleaner, while exposure to OIT mainly stems from a fungicide. For MI, the main contributors were dishwashing detergent and all-purpose wet wipes, and for CMI all-purpose cleaner. A Quantitative Risk Assessment (QRA) for BIT using Sensitization Assessment Factors (SAFs) indicates that around 1% of the Swiss population is at risk to be sensitized by BIT in cosmetics and household chemicals. For isothiazolinones in general the presented higher-tier modelling approach suggests that household cleaners are currently more important sources of exposure than cosmetics.

1. Introduction

Consumer products with high water content, such as household cleaning and personal care products (HC&PCPs), are easily

contaminated by microorganisms, and this represents a health risk to the consumer. Biocidal substances are used to control microorganism growth, and isothiazolinones are among the biocides that are most frequently used as preservatives in consumer products, owing to their

Abbreviations: A.I.S.E., International Association for Soaps Detergents and Maintenance Products; ACD, allergic contact dermatitis; AEL, Acceptable Exposure Level; BIT, 1,2-Benzisothiazol-3-(2H)-one; CDFs, cumulative distribution functions; CEL, consumer Exposure Level; CMI, 5-Chloro-2-methyl-4-isothiazolin-3-one; EC, European Commission; ECETOC, European Centre for Ecotoxicology and Toxicology of Chemicals; EEAHC, European Executive Agency for Health and Consumers; EPHECT, Emissions, Exposure Patterns and Health Effects of Consumer Products in the EU (study name); GSA, global sensitivity analysis; HC&PCPs, household care and personal care products; HCPs, household care products; HRIPT, Human Repeat Insult Patch Test; IDEA, International Dialogue for the Evaluation of Allergens; K_{ow}, octanol-water partitioning coefficient [–]; k_p, permeability coefficient [–]; LLNA, local lymph node assay; MCSs, Monte Carlo Simulations; MI, 2-Methylisothiazolin-3(2H)-one; MW, molecular weight; NESIL, No Expected Sensitization Induction Level; OIT, 2-Octyl-3(2H)-isothiazolinone; PACEM, Probabilistic Aggregated Consumer Exposure Model; PACEM-KD, Probabilistic Aggregated Consumer Exposure Model–Kinetic, Dermal; PCPs, personal care products; QRA, Quantitative Risk Assessment; SAFs, Sensitization Assessment Factors; SCCP, Scientific Committee on Consumer Products; SCCS, Scientific Committee on Consumer Safety; SFSO, Swiss Federal Statistical Office; SI, Supplementary Information; U.S. EPA, United States Environmental Protection Agency

[☆] The authors received funding from the Swiss Federal Office of Public Health.

The authors declare they have no conflict of interests.

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<https://doi.org/10.1016/j.envint.2018.05.047>

Received 15 September 2017; Received in revised form 24 May 2018; Accepted 27 May 2018

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Table 1
Typical isothiazolinone concentrations used in products and corresponding regulation in EU and Switzerland.

Product	Typical concentration	EU/Swiss regulation
Cosmetics	MI < 133 ppm ^a CMI < 4.8 ppm ^a	MCI/MI < 15 ppm (forbidden in leave-on). MI < 100 ppm (forbidden in leave-on). BIT forbidden (allowed in US and Canada). OIT forbidden.
Paints, glues, detergents	CMI/MI < 15 ppm ^b MI < 300 ppm ^b BIT < 360 ppm ^b OIT: insufficient data ^b	No regulatory restrictions regarding the concentration. For paints and glues no labelling required. For detergents, labelling required.
Industrially used biocides	CMI, MI, BIT: potentially high concentrations (e.g. > 5000 ppm) ^b OIT: insufficient data ^b	No regulatory restrictions regarding the concentration. Labelling is legally required.

^a Garcia-Hidalgo et al. (2017b).

^b Friis et al. (2014).

efficacy against a broad spectrum of bacteria, fungi, and yeasts (Lundov et al., 2009). The isothiazolinones methylchloroisothiazolinone (CMI) and methylisothiazolinone (MI) are used as a mixture with 3:1 ratio (CMI/MI; CAS no.: 55965-84-9) or MI as single substance in HC&PCPs, do-it-yourself products, and indoor water-based paints (Friis et al., 2014). In consumer products other than personal care products (PCPs), further isothiazolinones are used, including benzisothiazolinone (BIT) and octylisothiazolinone (OIT) (for an overview of the concentrations and regulations of isothiazolinones used in products available in the EU and Switzerland see Table 1).

BIT, OIT, MI, and CMI are all classified as skin sensitizers in the harmonized classification according to the Regulation European Commission (EC) No. 1272/2008 (Regulation European Commission EC, 2008) and known to cause allergic contact dermatitis (ACD; Aerts et al., 2016; Mose et al., 2013). ACD is the manifestation of an allergic response caused by contact with a sensitizing agent. ACD develops in two key stages: an induction phase, which primes and sensitizes the immune system for an allergic response, and an elicitation phase, in which this response is triggered. Once the sensitization has occurred, any events of re-exposure trigger the rash. Isothiazolinones have low molecular weights allowing for an easy penetration of the epidermis, followed by a reaction with the skin macromolecules. Owing to an increasing number of reported cases of contact allergy to isothiazolinones, the international regulation of isothiazolinones has been reinforced: The use of the mixture CMI/MI in leave-on PCPs was prohibited starting from the 16th of April 2016 (Regulation EC. No. 1003/2014), whereas the same ban was applied to MI alone from the 12th of February 2017 (Regulation EC, 2014, 2016). While CMI/MI and MI alone are still allowed in rinse-off PCPs, BIT and OIT are not. In 2012, BIT was classified as unsafe for use in PCPs due to its sensitizing potential (SCCS, 2004) and according to Annex V in Regulation EC. No. 1223/2009 BIT and OIT are not allowed in PCP formulations (Regulation EC, 2009). However, some illegal cases of isothiazolinones' occurrence in PCPs were reported by Meysman and Goossens (2017). The growing number of isothiazolinone-related ACD cases among the general public raised concerns among dermatologists (Bruze et al., 2015), because between 2009 and 2012 in many European countries the incidences of ACD caused by MI or CMI increased 2- to 5-fold (SCCS, 2013). Therefore, more data on the risk of ACD caused by isothiazolinones are required (Madsen and Andersen, 2016). Currently, there are no restrictions for isothiazolinones in household care products (HCPs) and other consumer products: In fact, concentrations are sometimes > 100 ppm, which was the maximum value permitted in rinse-off PCP until the change of regulation in July 2017 (Garcia-Hidalgo et al., 2017b) and it is unclear whether these substances are safe (Garcia-Hidalgo et al., 2017b). For sensitizing fragrances, the 'Quantitative Risk Assessment (QRA)' approach was developed (Api

et al., 2008), which was recently used for geraniol (Nijkamp et al., 2015) and octocrylene (Manová et al., 2015). Nonetheless, the approach is still under discussion (SCCS, 2017a, 2017b; SCCP, 2008).

To determine the risk from using HC&PCPs, it is necessary to estimate consumer exposure (Van Leeuwen et al., 1996). Exposure can be direct or indirect. Indirect exposure may be especially relevant for children who may be exposed to cleaning or personal care products used by others or applied on surfaces. However, the focus of this study was on direct exposure. In the case of simultaneous use of different products by the same person the aggregate exposure needs to be calculated (Manová et al., 2013; Lorenz et al., 2011; Von Goetz et al., 2010). However, only higher tier tools for calculating aggregate consumer exposure are available. Lower tier screening models such as ECETOC TRA (European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), 2017) or A.I.S.E. REACT (International Association for Soaps Detergents and Maintenance Products (A.I.S.E.), 2017) can only aggregate exposure in a very simplified way leading to an overly conservative and unrealistic aggregate exposure. In recent years, higher tier probabilistic models like Crème RIFM (McNamara et al., 2007; Safford et al., 2015), SHEDS-HD (Isaacs et al., 2014) and PACEM (probabilistic aggregate consumer exposure) (Delmaar et al., 2015; Dudzina et al., 2015) were developed. These models use different approaches for calculating uptake into the skin: Crème RIFM (Safford et al., 2015) normally assumes 100% dermal absorption, whereas SHEDS-HT estimates dermal absorption fraction distributions scaled via predicted dermal permeability coefficients (k_p) across chemicals (Isaacs et al., 2014). Skin permeability coefficients were also used in the dermal exposure models of ConsExpo (Delmaar et al., 2006) and PACEM (Delmaar et al., 2015; Dudzina et al., 2015). Currently the available models do not allow dermal aggregation of exposure for a particular body part in the consistent manner that is necessary for sensitizers. The only model that has already been used to determine consumer exposure to a sensitizing substance in HC&PCPs is PACEM (Nijkamp et al., 2015), but here external exposure was calculated for comparison with external toxicity values, internal exposure was not in the focus.

The aim of this project was to probabilistically assess the population exposure to isothiazolinones via HC&PCPs with an extended version of PACEM. Our probabilistic model PACEM-KD (Probabilistic Aggregated Consumer Exposure Model–Kinetic, Dermal) calculates exposure inside the skin at an individual level (as suitable for sensitizing substances) and contains a new approach to calculate dermal uptake based on uptake kinetics.

2. Materials and methods

PACEM-KD was developed based on the established structure of

Table 2

General overview of the selected product categories included in PACEM-KD.

Category	Product
Household cleaning products	All-purpose cleaner liquid/spray/wipes, bleach, hand-dishwashing detergent, kitchen cleaner liquid/spray, bathroom cleaner liquid/spray, toilet cleaner, glass cleaner, carpet cleaner, fungicide spray
Personal care products	Rinse-off: Shampoo, conditioner, shower gel, bubble bath, liquid hand soap, toothpaste Leave-on: Hand cream, body lotion, face cream, facial cleansing, cosmetic/baby wet wipes, shaving products, aftershave, perfume/eau de toilette/cologne, deodorant, lipstick/lip gloss/lip balm, nail polish, make-up remover, eye shadow, powder or rouge, foundation

PACEM, by incorporating new data on use patterns for HC&PCP for the Swiss population from a survey across several regions of Switzerland (Garcia-Hidalgo et al., 2017a) and extending the model concept to meet the specific requirements associated with exposure to sensitizing agents present in HCPs and rinse-off PCPs. Even if the focus of this work is on isothiazolinones, we included in the model the most important additional HC&PCP categories (also those, which do not contain isothiazolinones), in order to allow dermal internal exposure assessments for other sensitizing agents occurring in HC&PCP products. Table 2 gives a general overview of the selected product categories included in PACEM-KD.

2.1. Model background

The mechanisms of skin sensitization are not yet fully understood. There is qualitative understanding of the skin sensitization process (AOP 40) but to date there are still many open issues, which make it difficult e.g. to identify the exposure site relevant for risk assessment. For instance, it is still unclear which lymph node is involved after absorption of an antigen: Whether it is the closest lymph node or whether many lymph nodes are acting together and which exposure values trigger a reaction in humans. Furthermore, it is still not entirely clear how the exposure in the animal test (normally the LLNA) can easily be related to human exposure levels. Quite certain is that skin sensitization is induced following dermal exposure to a sensitizing substance with a dermal load exceeding the sensitization threshold. It is currently assumed that no aggregation across different body locations is necessary. The individual exposure varies across the body locations, depending on the use and type of HC&PCPs used (Garcia-Hidalgo et al., 2017a), therefore we divided the body in relevant areas of exposure similar to Comiskey et al., 2015 (i.e. head, face/lips/eyes, neck, trunk, arms, underarms, back of hands, palms, intimate parts, legs, feet). Important factors affecting the development of ACD are duration and type of exposure, concentration and potency of the allergen, genetic susceptibility as well as existing polysensitization to contact allergens (Schnuch et al., 2011, 2008).

Frasch et al. (2014) have underlined that dermal absorption is a chemical-specific process, but depends on other factors like skin permeability and exposure duration. To account for this, in this work we adopt the more mechanistic approach that was proposed by the United States Environmental Protection Agency (U.S. EPA) and which describes the dermal exposure to chemicals after dilution in water (E_{it} over one day per unit area of skin, [ng/cm² d]) as described in Eq. (1) (EPA, 2007). Taking into consideration the respondents' self-reported use-patterns, we calculated the exposure inside the skin, according to Eq. (1):

$$E_{it} = C_{CP} \times f_{event} \times t_{event} \times k_p \quad (1)$$

C_{CP} : concentration of isothiazolinone in the consumer product used by the respondent [ng/cm³], f_{event} : product application frequency [day⁻¹], t_{event} : duration of the event/application of the consumer product [h], and k_p : chemical-dependent skin permeability coefficient [cm/h]. In case of individual product dilution (i.e. specific amount (g) of water added to the product during its usage), the concentration was recalculated.

If the respondent was exposed via more than one HC&PCP category,

the aggregate exposure was defined as the sum of the exposures to the same isothiazolinone across the different product categories. At the small time-scales considered in this paper, E_{it} will always be smaller than the theoretical highest dermal exposure (i.e. E_{max}). For longer time-scales, E_{it} must be limited by E_{max} .

2.2. Study design and data collection

Firstly, to establish a list of HC&PCPs that often contain isothiazolinones, a market survey was conducted in Switzerland in 2015 (Garcia-Hidalgo et al., 2017b). After the label screening of 1948 products, it was found that 239 household care products (HCPs) (42.9% of 557), 97 PCPs for adults (7.7% of 1266), and eight PCP baby products (6.4% of 125) were preserved with at least one isothiazolinone.

Secondly, the HC&PCP use-patterns were collected among the Swiss population by postal questionnaire (Garcia-Hidalgo et al., 2017a). Special emphasis was placed on including children and adolescents, and, in response to the market survey, on incorporating the product categories that are likely to contain isothiazolinones. Thus, the main focus of this work was on water-based rinse-off PCPs and cleaning products, but some leave-on products were included as well (see Table 1). Since exposure from laundry products is considered to be very low (Corea et al., 2006), they were not incorporated in the model. After exclusion of incomplete, ineligible, and contradictory responses, the final input dataset included 669 respondents of the French-, German- and Italian-speaking regions of Switzerland (age ≤ 1–91 y). The overall adjusted response rate was 18% (Garcia-Hidalgo et al., 2017a).

Thirdly, on the basis of the questionnaire study the most frequently used product brands were identified among the most relevant product categories that can contain isothiazolinones. Of these, a sample of 69 HCPs and 19 PCPs was selected and analyzed by liquid chromatography–high-resolution mass spectrometry (HPLC-MS) after ultrasonic extraction (Garcia-Hidalgo et al., 2017b). In this study, the measured concentration ranges in HCPs were 4.3–10, 3.5–279, 3.8–186 and 7.9 ppm (one product only) for CMI, MI, BIT, and OIT, respectively. Of the 69 HCPs analyzed, eight (12%) were mislabelled. For PCPs, these were 1.3–133 and 4.8 ppm (one product only) for MI and CMI, respectively. Although 16 PCPs were labelled as containing isothiazolinones, they could not be detected in four products, owing either to the LOD (limit of detection) or faulty declaration (Garcia-Hidalgo et al., 2017b).

2.3. PACEM-KD description

PACEM is a person-oriented consumer exposure model, which was already used to model aggregate exposure to parabens (Gosens et al., 2014), diethyl phthalate (Delmaar et al., 2015), and cyclic siloxanes (Dudzina et al., 2015). These PACEM applications targeted systemic human exposure to chemicals (internal exposure in the blood), which is expressed in mass of chemical per body weight. Lately, PACEM was also used to predict dermal aggregated exposure to the skin sensitizing fragrance geraniol in HC&PCPs (Nijkamp et al., 2015) for which it was modified to calculate external dermal exposure as mass of chemical per unit surface area.

The newly developed PACEM-KD is a refinement of PACEM that follows a kinetic approach regarding substance uptake instead of the

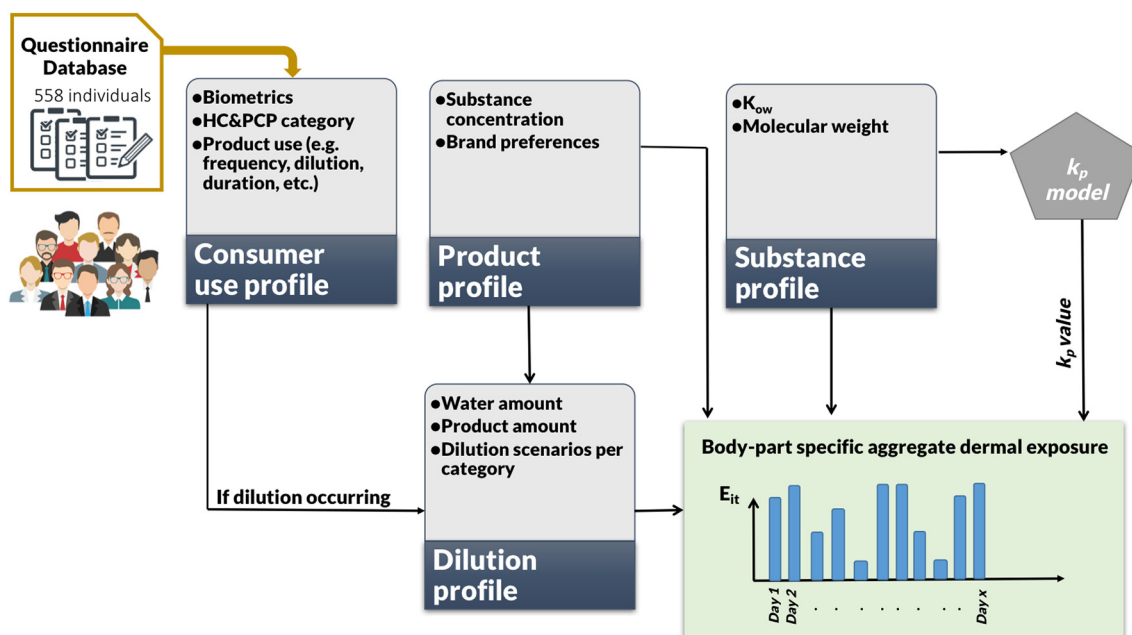


Fig. 1. Workflow scheme for PACEM-KD for adults (N = 558) and children (N = 111). For children PACEM-KD was used without HCP.

PACEM-approach of assuming a fixed fraction. The exposure estimates are expressed as amount absorbed per skin surface area ($\text{ng}/\text{cm}^2\text{d}$) for different body locations and represent internal concentrations inside the skin. The workflow of PACEM-KD is shown in Fig. 1: The core of PACEM-KD consists of a relational database of biometric details (i.e. body weight, body height, age, and gender) and HC&PCPs use data. The model calculates exposure by repeated sampling of 1) person-specific product use (frequency and amount), 2) person data from the biometric data base, and 3) randomly sampled concentrations of the chemical in the products (Delmaur et al., 2015). The model input data are based on the information provided in Section 2.2. The following parameters were used for calculating the aggregate consumer exposure to isothiazolinones. Those marked with an asterisk are the most variable and uncertain parameters, which were treated probabilistically:

1. Frequency of product use*
2. Skin locations of application of the products
3. Exposure time to the products*
4. Amount per use of each product (only used if a dilution occurred) *
5. Chemical concentration of isothiazolinones in the product*
6. Permeability coefficient (also very uncertain, but not treated probabilistically)

The model has been implemented in the language R (version 3.3.1).

2.4. Model parameter values: Origin and variability/uncertainty

2.4.1. Concentration C_{CP}

The concentrations of isothiazolinones in HC&PCP (C_{CP}) were measured by HPLC-MS (Garcia-Hidalgo et al., 2017b). Further, a survey on HC&PCP use-patterns (Garcia-Hidalgo et al., 2017a) served to derive for each product category the fraction of the population that uses a specific brand of HC&PCP. Since only a limited number of products could be analyzed, it was assumed that the isothiazolinone concentrations of a brand are the same within a product category. In the Monte Carlo approach, the brand-specific product concentrations were then sampled proportional to the respective fraction of the population that uses that brand. In the case that no product of that brand had been analyzed, the use fractions of these missing brands were reallocated equally to the analyzed brands within their HC&PCP category.

2.4.2. Dilution

PACEM-KD accounts for dilution if indicated by the respondent for a specific HCP category. For PCPs, no data on dilution was available. Therefore, we always assumed dilution for the following categories: Shampoo, liquid hand soap, bathing foam, and toothpaste. In the questionnaire, the water volume used for dilution was not inquired; therefore, a small study was conducted to measure the water absorbing capacity of sponges and wipes (results shown in Section 1 of the Supplementary Information (SI)). HCP dilution in sinks, buckets, or bathtubs was also considered. For HC&PCP volume estimates and distributions see SI Section 2 Table S1.

2.4.3. Amount m_{CP}

The applied/used amount is necessary to recalculate the diluted concentration. The PCP amount applied was assessed in our person-oriented questionnaire based on photographs, while the use amount for HCPs was not (Garcia-Hidalgo et al., 2017a). Therefore, the data collected in the EPHECT project (i.e. European household survey on domestic use of HCPs) was used (EPHECT, 2012). For extrapolation to the Swiss population, the data of the three neighboring countries (i.e. France, Germany, and Italy) were selected by adjusting for socio-demographical status (i.e. gender, age-groups, and region) (see SI Table S2-3). Some HCPs were not included in the EPHECT study. Therefore, uniform distributions were chosen by expert judgment (see SI Table S4).

2.4.4. Frequency f_{event}

f_{event} was obtained for every questionnaire participant (Garcia-Hidalgo et al., 2017a). When participants did not indicate the f_{event} , we assumed that they did not use that HC&PCP category. The ranges of f_{event} were modelled as follows: i) For choice selections such as 'X-Y times per day' the frequency was represented by a uniform distribution with minimum X and maximum Y per day; ii) For precise information (e.g. Z times per day), a single value for that parameter was used; iii) For $f_{event} < 1$ (i.e. < 1 per day), a Bernoulli probability distribution with probability = f_{event} determined whether the event was happening on a specific modelled day. For HCP, the treatment of the data is described in the SI Section S3.

2.4.5. Duration of contact/exposure t_{event}

Duration of exposure was inquired only for HCPs. The same procedure for modelling ranges was applied as explained for frequency (see Section 2.4.4), for data treatment see SI Section S4. For PCPs, we estimated for each product category the ranges for duration of contact between product and skin by using either literature data or expert judgment (see SI Table S5). The calculated/estimated duration ranges were modelled by assigning uniform (for ranges) or point distributions (for point values).

2.4.6. Skin permeability coefficient k_p

The k_p is a key parameter in estimating dermal absorption and a measure of the skin conductance of a specific chemical in a specific vehicle. To our knowledge, k_p values for isothiazolinones have not yet been measured. Hence, they need to be predicted by models, which are constructed based on physicochemical characteristics such as the octanol-water partitioning coefficient (K_{ow}) and/or molecular weight/size. k_p estimates vary widely between the respective estimation methods: In the literature, a small number of distinct models are available to estimate the k_p through *stratum corneum* from an aqueous vehicle (Mitragotri, 2002; Frisch, 2002; Potts and Guy, 1992; and Robinson as modified by Wilshut et al. 1995) and the comparison of the predictions arising from four of these models are given in SI Table S6. For PACEM-KD, the model provided by Mitragotri (2002) and rewritten by Lian et al. (2008) was selected (Eq. (2)). According to Lian et al. (2008) this model performed best among several dermal mathematical permeability models for a large experimental dataset of skin permeability (124 chemical compounds).

$$\log k_p = 0.7 \log K_{ow} - 0.0722 \text{ MW}^{\frac{2}{3}} - 5.27 \quad (2)$$

where MW is the molecular weight of the solute [g/mol], K_{ow} the octanol-water partitioning coefficient, and k_p is given in cm/s (estimated for all four isothiazolinones using EPI Suite™, Version 4.11).

2.5. Modelled population and days

On the basis of the use patterns and corresponding socio-demographics for 558 Swiss adult persons, 20,000 individuals were simulated within PACEM-KD: 9899 males and 10,101 females respecting the gender ratio of the Swiss population (Swiss Federal Statistical Office (SFSO), 2015). For the 111 children and adolescents, the survey did not inquire about HCP usage; thus, for children and adolescents only the exposure to MI and CMI was estimated and 1485 male and 1515 female children were simulated respecting the questionnaire ratio between children and adolescents (16.6% of 669) and adults. Aggregated dermal exposure to isothiazolinones was modelled for 7 independent days. For each individual in the population, the maximum exposure day in this 7-day set was determined. The values presented in the Results section are based on a modelled population constructed from the unique maximum day of exposure for each individual within the population.

2.6. Uncertainty analysis

The aggregate exposure distributions for each isothiazolinone were generated probabilistically using Monte Carlo Simulations (MCSs) at an individual level to integrate parameter variability and uncertainty. Additionally, the model was run for 1000 times (since no significant difference was noticed when 5000 iterations were used for MI) on the basis of the 558 Swiss adults, each time varying the input parameters within their defined distribution described in the Section 2.4. For each run (representing the whole original population), the P5, P50, and P95 were calculated and for each quantile ($N = 1000$) a cumulative distribution function was drawn. The importance of an individual input parameter for the aggregated dermal exposure was determined by variance-based global sensitivity analysis (GSA) using Sobol's variance

decomposition method (Zhang et al., 2015). This GSA describes the sensitivity pattern of a model depending on the uncertain input parameters and their interactions (Saltelli et al., 2010), which is done by MCS estimation of first-order and total Sobol's indices simultaneously (Pujol et al., 2017). They were calculated for PACEM-KD input parameters by using the package *sensitivity* in the language R (Pujol et al., 2017) and represent their individual (1st order Sobol) and total contributions (total Sobol) to the variance of calculated exposure (see SI Section S6).

2.7. Risk assessment

Recently, QRA (Quantitative Risk Assessment) has been proposed as an approach for the risk assessment of sensitizing fragrances (Api et al., 2008; Nijkamp et al., 2015; WHO, 2012), but has also been applied to other skin sensitizers, e.g. a UV-filter (Manová et al., 2014), hair dye chemicals (Goebel et al., 2012), and preservatives (Basketter, 2010). QRA of sensitizing substances is aimed to assess the risk of induction (sensitization) in the general population (Nijkamp et al., 2015) and currently consists of three main parts (Api et al., 2008):

1. The determination of No Expected Sensitization Induction Level (NESIL).
2. The implementation of Sensitization Assessment Factors (SAFs).
3. Consumer exposure level (CEL) determination through individual product use data.

The NESIL is a threshold value derived from in vitro or in vivo experiments. SAFs are defined as safety factors that account for inter-individual variability (e.g. genetics, metabolic activity, age), matrix effects (e.g. penetration enhancers), and use considerations (e.g. exposed body part, skin integrity) (Api et al., 2008). NESIL and SAFs are used to derive the Acceptable Exposure Level (AEL), which is then compared to CEL. If the AEL is higher than the CEL it is presumed that there is no significant risk of sensitization for the general public (Api et al., 2008). In this work, a QRA was performed for BIT using the models PACEM-KD and PACEM in order to compare the obtained results for validation purposes. However, the combined risk assessment for a mixture of isothiazolinones was not performed in this study because to date it is not clear whether their effects are additive.

3. Results

3.1. Aggregate exposure assessment

The aggregate exposure distributions of BIT, OIT, MI, and CMI are shown in Table 3. Fig. 2 shows the histogram frequency of the aggregate exposure distributions for BIT, OIT, MI, and CMI on palms for palms. The highest aggregate exposure was calculated for BIT on palms with 15.4 ng/cm² as the P99, but no exposure to body parts other than palms, back of hands or arms was observed. At least 10% of the Swiss population was not exposed to BIT on any body part, because they do not use products preserved with BIT. No statistically significant difference was observed between the two genders. The predicted aggregate dermal exposure to OIT for most body parts was zero, but for both palms and back of hands the P99 was 1.28 ng/cm². Only 5% of the Swiss population was exposed to OIT. The highest MI exposure was calculated for palms (P99 = 0.9 ng/cm²), followed by back of hands (P99 = 0.5 ng/cm²). Regarding the median on palms, men had lower exposure than women. Fig. 2 shows that there were only few individuals who were highly exposed to MI (max values > 1.5 ng/cm² on palms). For CMI the predicted aggregate dermal exposure ranged between 0 and 0.35 ng/cm². For CMI, the highest aggregate exposure was found on palms and back of hands with 0.08 ng/cm² as the P99. We did not see a statistically significant difference across genders.

For children and adolescents, PACEM-KD was used to perform

Table 3Percentiles of the BIT, OIT, MI, and CMI aggregate exposure distributions (including zeros) for specified body parts for the total population in ng/cm².

Percentile	P5	P25	P50	P75	P95	P99
BIT						
Face, lips, eyes	0	0	0	0	0	0
Head	0	0	0	0	0	0
Neck	0	0	0	0	0	0
Trunk	0	0	0	0	0	0
Arms	0	0.0619	0.607	1.97	7.12	15.4
Underarms	0	0	0	0	0	0
Back of hands	0	0.0827	0.628	1.98	7.12	15.4
Palms	0	0.0991	0.663	2.05	7.26	15.4
Intimate parts	0	0	0	0	0	0
Legs	0	0	0	0	0.268	2.02
Feet	0	0	0	0	0.268	2.02
OIT						
Face, lips, eyes, head	0	0	0	0	0	0
Head	0	0	0	0	0	0
Neck	0	0	0	0	0	0
Trunk	0	0	0	0	0	0
Arms	0	0	0	0	0.00132	0.625
Underarms	0	0	0	0	0	0
Back of hands	0	0	0	0	0.00784	1.28
Palms	0	0	0	0	0.00784	1.28
Intimate parts	0	0	0	0	0	0
Legs	0	0	0	0	0.00132	0.625
Feet	0	0	0	0	0.00132	0.625
MI						
Face, lips, eyes	0	0	0	0	2.23×10^{-5}	6.28×10^{-5}
Head	0	0	0	0	1.91×10^{-5}	6.18×10^{-5}
Neck	0	0	0	0	3.45×10^{-5}	6.54×10^{-5}
Trunk	0	0	0	0	3.54×10^{-5}	6.54×10^{-5}
Arms	0	3.96×10^{-7}	0.00262	0.0272	0.18	0.291
Underarms	0	0	0	0	3.55×10^{-5}	6.54×10^{-5}
Back of hands	0	3.45×10^{-7}	0.0156	0.0752	0.276	0.549
Palms	1.14×10^{-7}	0.00585	0.0362	0.111	0.423	0.949
Intimate parts	0	0	0	0	3.42×10^{-5}	6.54×10^{-5}
Legs	0	0	0	0	6.33×10^{-5}	0.0267
Feet	0	0	0	0	6.35×10^{-5}	0.0267
CMI						
Face, lips, eyes	0	0	0	0	2.95×10^{-6}	1.22×10^{-5}
Head	0	0	0	0	6.65×10^{-6}	2.44×10^{-5}
Neck	0	0	0	0	4.06×10^{-6}	1.38×10^{-5}
Trunk	0	0	0	0	3.97×10^{-6}	1.31×10^{-5}
Arms	0	0	0	2.78×10^{-5}	0.0317	0.0835
Underarms	0	0	0	0	4.12×10^{-6}	1.37×10^{-5}
Back of hands	0	0	0	3.35×10^{-5}	0.0317	0.0835
Palms	0	0	0	3.35×10^{-5}	0.0317	0.0835
Intimate parts	0	0	0	0	4.06×10^{-6}	1.32×10^{-5}
Legs	0	0	0	0	2.84×10^{-4}	0.0477
Feet	0	0	0	0	2.84×10^{-4}	0.0477

In bold, the highest values for the range of percentile is given.

dermal exposure assessments for the chemicals MI and CMI. Generally, their exposure was lower than that of adults. The P99 was zero for both chemicals, and the maximum exposure calculated on the basis on 3000 individuals was 1.15×10^{-4} ng/cm², 1.54×10^{-4} ng/cm², for MI and CMI, respectively. The only sources of exposure were shampoo and shower gel.

3.2. Contribution of product categories to aggregate exposure

To identify the contributions to isothiazolinones' aggregate exposure, the relative average contributions of each HC&PCP category were calculated for palms for male and female adults (see Fig. 3). Regardless of the gender, the highest source of BIT exposure was all-

purpose cleaner liquid, with contributions of 34% and 35% for males and females, respectively, followed by all-purpose cleaner spray (M = 30%; F = 18%). The only two HCP categories contributing to the aggregate exposure of OIT were fungicide spray and floor cleaner liquid. For both genders, dishwashing detergent was the major source of MI exposure, with contributions of 57% and 51% for males and females, respectively, followed by all-purpose cleaner wipes (M = 21%; F = 17%). For CMI, the highest contribution to aggregate exposure on palms came from all-purpose cleaner liquid (M = 64%; F = 67%), followed by floor cleaner liquid (M = 32%; F = 29%), carpet cleaner liquid (M = 2%; F = 3%) and shampoo (M = 2%; F = 1%). Owing to recent enforcements of the cosmetics regulation only four PCP categories contributed to the aggregate exposure of MI and CMI.

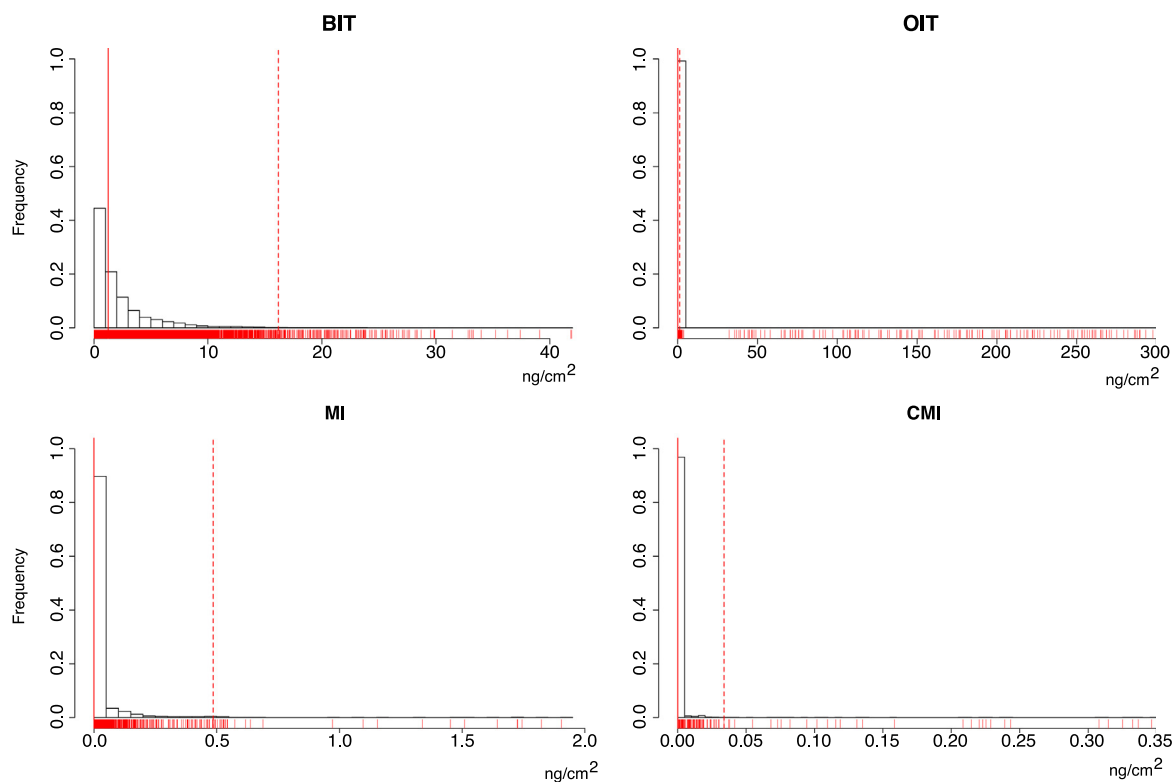


Fig. 2. Histogram frequency distribution for BIT, OIT, MI, and CMI on palms. P50 and P99 are indicated with full red and dashed red lines, respectively. For OIT these lines are overlapping. Red vertical bars under the histogram represent the modelled individuals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.3. Uncertainty/variability and sensitivity analysis

Qualitative assessments of uncertainty and variability for the input parameters in PACEM-KD are listed in Table S7 of SI. Fig. 4 shows the uncertainty and variability analysis for BIT ($N = 756$) by Monte Carlo simulation (1000 runs) for palms excluding the non-exposed individuals (all other chemicals gave a similar pattern, see SI Figs. S3–S5). Furthermore, for BIT the importance of each individual parameter for the aggregate exposure estimate was additionally assessed using the Sobol's variance decomposition method (SI Table S8). This analysis was only performed for BIT, because for the other isothiazolinones the number of zeros in the matrix used for the Sobol analysis was very high (i.e. many products did not contain isothiazolinones). This is problematic for such an analysis, because the few positive values would relate to only few participants' use-patterns, so that the result is meaningless. Generally, the total indices, which sum the effect of input parameters and interactions' effects of any order, exceeded the corresponding first-order indices, which assess only the effect of the independent input variable. The difference between the total index and first order index represents all the possible (synergistic) interactions between the input parameters, which consequently results in higher output variance. For example, in the case of kitchen cleaner spray, the sum of all first-order indices for each input parameter was 0.89 with the concentration sharing mostly the total contribution. This means that 89% of the variance of the exposure in the skin stemming from kitchen cleaner sprays was determined by the variance of four parameters (frequency, amount, duration, and concentration), while the other 11% of the variance was explained by interactions of the input parameter variances and by uncertainties. Regardless of HCP category, the concentration parameter had the largest first-order Sobol indices (0.615–0.878), meaning that the calculated exposure variance was mainly governed by the variance of the BIT concentration in the product.

3.4. Quantitative Risk Assessment (QRA)

Historically, the Human Repeat Insult Patch Test (HRIPT), a test conducted in healthy individuals, has been widely used to establish the sensitizing potency of chemicals, because human data are the most relevant information for risk assessment (European Executive Agency for Health and Consumers (EEAHC), 2009) and is also mainly used as a basis for QRA. Nowadays, for ethical reasons, HRIPT has been replaced in many countries by the local lymph node assay (LLNA) which uses an animal model.

The HRIPT derives a threshold level of no sensitization by testing different doses (Api and Vey, 2008). The HRIPT study on BIT described by Stotts (1980) and reported by Basketter et al. (1999, 2005) showed that at 360 ppm none of 54 tested individuals showed any sensitization symptoms. Afterwards, each volunteer was challenged using the concentration of 725 ppm and five out of 58 individuals (8.6%) were sensitized (Basketter et al., 1999, 2005). From this study, it is possible to estimate the (external) $NESIL_{ext}$ of $45 \mu\text{g}/\text{cm}^2$ (Novick et al., 2013). In our approach, we deviated from the classical QRA approach in terms of the location where the risk is calculated. QRA calculates the risk by comparing the external estimates of exposure (CEL_{ext}) and effect ($AE-L_{ext}$). We, however, estimate exposure inside the skin. Therefore, we needed to adjust the NESIL, which was originally calculated based on external exposure. The adjusted internal NESIL (i.e. $NESIL_{int}$) value was calculated based on the original data from Basketter et al. (1999, 2005) using Eq. (1). Knowing that BIT (360 ppm) was applied by dermal patches 9 times for 24 h during the course of 3 weeks and that BIT k_p equals $0.000505 \text{ cm}/\text{h}$, the resulting $NESIL_{int}$ was $4.37 \mu\text{g}/\text{cm}^2$ (using frequency = 1/day with an exposure duration of 24 h, see SI Section S8). SAFs were applied to the $NESIL_{int}$ to cover uncertainty for (1) inter-individual differences, (2) vehicle effects, and (3) use considerations. Since the NESIL value was derived by human test studies, no inter-species SAF was applied, but the recommended intraspecies SAF of 10

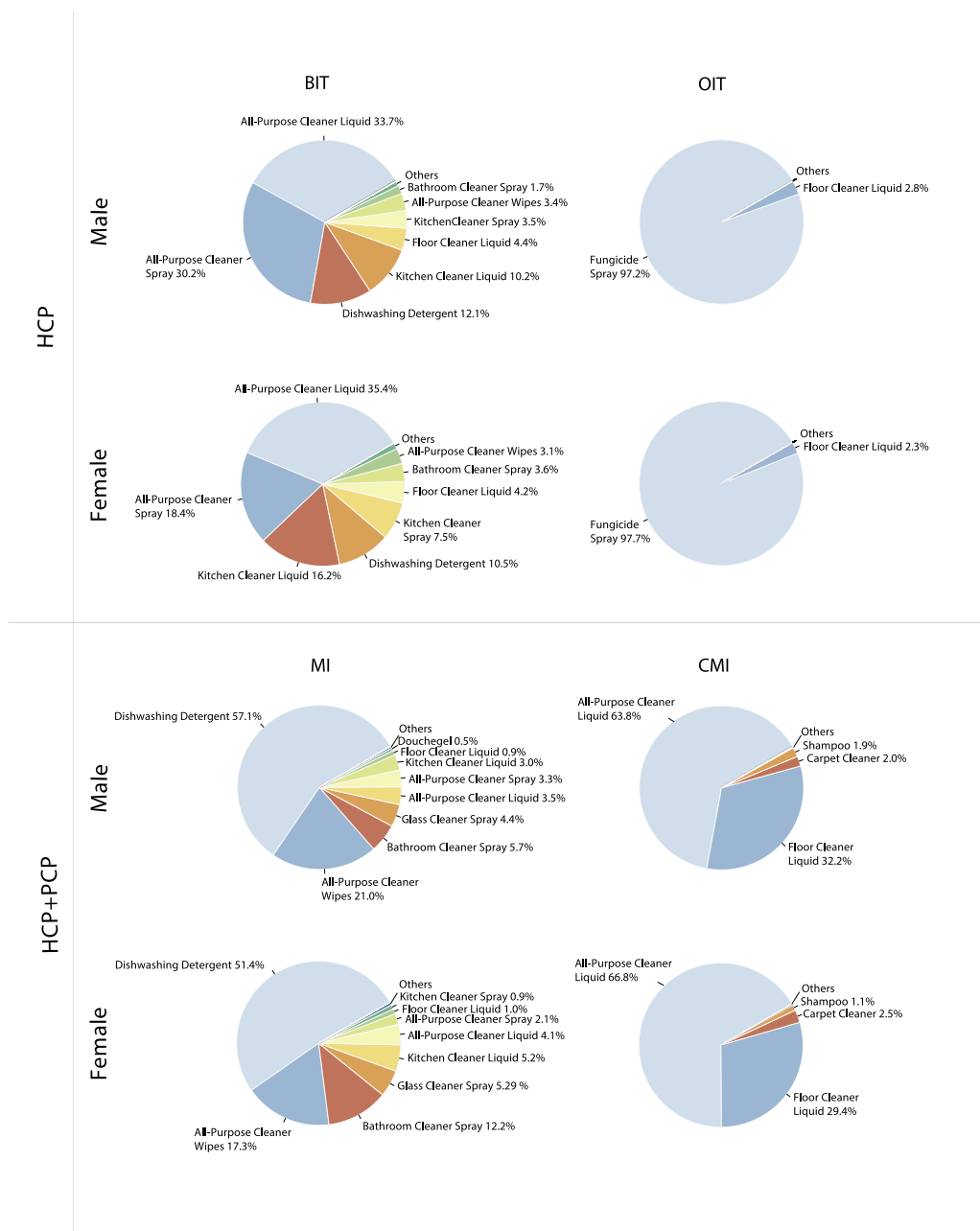


Fig. 3. Exposure to the isothiazolinones BIT, OIT, MI, and CMI for palms of male and female adults: Contributions of product categories.

(WHO, 2012) was used. A matrix factor of 3 was chosen for all HCPs because they likely contain additional irritants (due to aggregation a common matrix factor has to be used for all HCPs). A SAF of 10 for use considerations was also implemented to account for the delay of sensitization in the HRIPT studies, i.e. the case that a person is sensitized but does not show any symptoms during the test (Nijkamp et al., 2015), for regional skin differences, and barrier integrity (Api et al., 2008). Thus, the most conservative SAF that is suggested in the QRA approach (300) was used.

Dividing the $NESIL_{int}$ by the overall SAF of 300 resulted in an AEL_{int} for BIT of 14.6 ng/cm^2 . The modelled mean and median exposure to BIT via HCP on palms (largest exposure) did not exceed this predicted AEL_{int} of 14.6 ng/cm^2 . At the upper end percentiles ($P99 = 15.4 \text{ ng/cm}^2$), the BIT aggregate exposure on arms, back of hands, and palms was higher than the AEL_{int} . In total, for 1.14% of the modelled individuals, an exposure higher than AEL_{int} on their palms, back of hands, and arms was reached. The majority of them were females (63%) and

the median age was 61 years. The major product contributors were all-purpose cleaners, dishwashing detergent, bathroom and kitchen cleaners.

3.5. PACEM and PACEM-KD comparison for BIT

For BIT, the performance of PACEM-KD was evaluated by comparing its results with the results from the original PACEM version, which is based on exposure fractions. Since the model structure is the same for both models, this comparison serves to evaluate the influence that the new KD-approach has on the model results. The comparison has to be done based on the population at risk, because both models calculate different types of exposures: PACEM calculates the external aggregate dermal load using a default retention factor for rinse-off products and for detergents, whereas PACEM-KD calculates an aggregate internal exposure inside the skin, i.e. absorbed through the *stratum corneum*. Thus, the percentage of modelled individuals

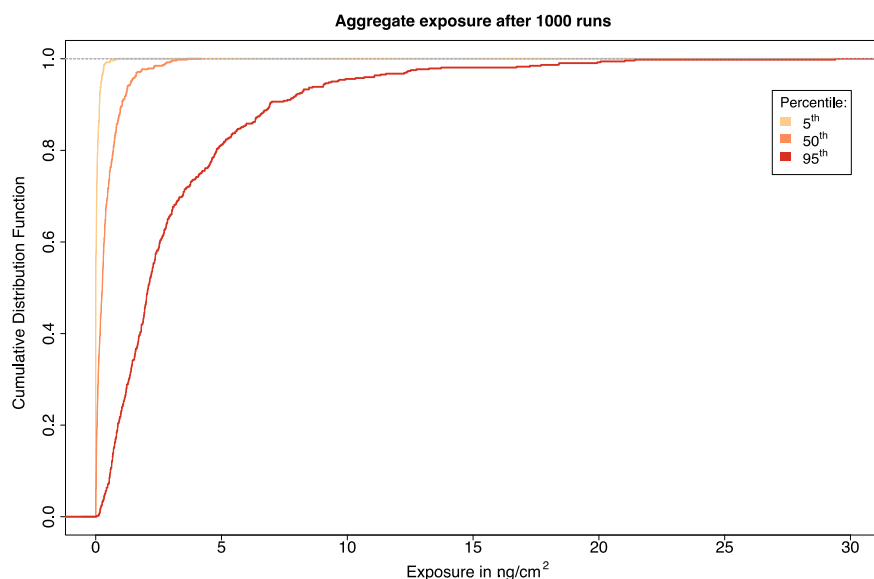


Fig. 4. Uncertainty and variability analysis for BIT excluding the non-exposed individuals ($N = 756$) with a Monte Carlo simulation for palms (all other chemicals gave a similar pattern, see SI). Cumulative distribution functions for the P5, P50, and P95 of each run ($N = 1000$).

exceeding the AEL on hands (palms are not separately represented in PACEM) was the metric selected for this comparison. Exposure calculation with PACEM-KD is described in the [Materials and methods](#) section. The calculation performed with the original PACEM is described by [Nijkamp et al. \(2015\)](#). The use data of the PACEM model was obtained from two different population surveys: The Dutch population ($n = 516$; [Biesterbos et al., 2013](#)) and the EPHECT surveyed population ($n = 1629$ from UK, Germany, Denmark, and Sweden; [EPHECT, 2012](#)). 10,000 modelled persons were sampled from this constructed database combined with the BIT concentrations measured by [Garcia-Hidalgo et al. \(2017b\)](#). With PACEM we obtained a P99 for the external dermal load of 15 ng/cm^2 over 7 days. Applying the same SAF of 300 to the normal 'external' $\text{NESIL}_{\text{ext}}$ derived by [Basketter et al. \(1999, 2005, NESIL = \$45 \mu\text{g/cm}^2\$ \), we obtained an \$\text{AEL}_{\text{ext}}\$ of \$15 \text{ ng/cm}^2\$. This \$\text{AEL}_{\text{ext}}\$ was compared to the calculated \$\text{CEL}_{\text{ext}}\$ and we found that PACEM predicts that 0.01% of the PACEM modelled population exceed the given \$\text{AEL}_{\text{ext}}\$.](#)

4. Discussion

4.1. Exposure to isothiazolinones

A substantially smaller number of consumer product categories contain BIT and/or OIT in comparison to CMI/MI or MI also owing to the fact that BIT and OIT are not allowed in PCPs ([Regulation EC, 2009](#)). However, the results showed a lower consumer exposure for CMI/MI than for BIT and OIT. This is explained by the isothiazolinone concentrations in products: BIT and OIT are used in much higher concentrations than CMI/MI and MI in HCP ([Garcia-Hidalgo et al., 2017b](#)), also because for HCP and biocides no upper concentration limits apply. Although research has focused more on MI and the mixture CMI/MI, also BIT and OIT can cause ACD ([Aerts et al., 2016; Mose et al., 2013; Schwensen et al., 2016](#)), and apart from workers also the general public can be affected. For all isothiazolinones, the major contributors to consumer exposure were the product categories dishwashing detergent, all-purpose cleaner (liquid, spray, and wipes), and fungicide spray (which is a biocide, implying higher weight fractions of isothiazolinones).

Currently, the Annex V of Regulation EC. No. 1223/2009 ([Regulation EC, 2009](#)) was revised to restrict the use of MI to 15 ppm in rinse-off products and impose labelling of MI. In our assessment, the

contribution of PCPs to the aggregate consumer exposure to MI and CMI/MI was $< 2\%$ due to the last limiting regulations: 100 ppm rinse-off and 0 ppm leave-on ([Regulation EC, 2014, 2016](#)). Already with the introduction of that regulation the risk of sensitization to MI from PCPs seems to be low and becomes lower with the prospect of even stricter regulation. [Garcia-Hidalgo et al. \(2017b\)](#) have raised the issue that, in contrast to PCPs, HCPs are largely unregulated. HCPs constitute an important source of allergens, in particular the chemicals MI and BIT, which were found in relatively high concentrations by [Garcia-Hidalgo et al. \(2017b\)](#) and [Alvarez-Rivera et al. \(2012\)](#). For this reason, future risk assessments for isothiazolinones should include HCPs in the exposure assessment and eventually restrict their use. It is important to bear in mind that also other products can contribute to the aggregate consumer exposure. Isothiazolinones can be used as biocidal substances or preservatives in many other industrial applications like wood preservatives, fungicides, and insecticides. In fact, recent studies reported several ACD cases caused by various consumer products containing isothiazolinones such as belts, shoes ([Aerts et al., 2016](#)), and paints ([Amsler et al., 2017](#)). However, to include these products into a model like PACEM or PACEM-KD, a number of use and release parameters have to be determined that are not yet available.

Previously, ACD in children was considered rare. Only lately, due to an increase of ACD cases among this population group, patch testing in children has become a more common practice ([Jacob et al., 2017](#)). In 2014, Madsen and Andersen described a case report of a 3-year-old girl with a severe facial ACD caused by MI. Thus, for many chemicals it is especially important to include children in the exposure and risk assessment. Overall, children and adolescents were the lowest exposed in our population. This is explained mainly by the fact that the questionnaire designed by [Garcia-Hidalgo et al. \(2017a\)](#) inquired only about the PCP use-patterns of this age category, assuming that children are exempt from house cleaning tasks. Since our study showed that HCP use may significantly enhance exposure to isothiazolinones, HCP usage among under-aged should be further investigated. However, the survey conducted by [Garcia-Hidalgo et al. \(2017a\)](#) included questions about the use-patterns of cosmetic wet wipes and some do it yourself products (i.e. art supply, finger paint, and glue) among children and adolescents since these may be the most relevant product categories that contribute to isothiazolinones exposure.

A qualitative characterization of uncertainty and variability of the exposure parameters in PACEM-KD is given in SI Table S7. Uncertainty

and variability are associated with the parameters chemical product concentration, use frequencies, use durations, etc. GSA of this higher-tier model indicated that concentration in product is the largest contributor to the variability (and uncertainty) of the predicted dermal exposure.

4.2. QRA for BIT

In 2013, Novick et al. reported a QRA for BIT for a pilot study, aiming to determine a safe use concentration in HCPs and sunscreens. In their conclusion, they claimed that their study was a screening level assessment with many limitations and, therefore, a higher tier evaluation was desirable. This study with PACEM-KD provides such a higher tier assessment and is the first QRA comparing the BIT AEL_{int} for the induction of sensitization to CEL_{int} assessed in a probabilistic way by using realistic consumer habits. Moreover, we considered aggregate exposure resulting from concurrent use of multiple BIT-containing HCPs on the same body part. Aggregation of exposure is not commonly included in QRA studies (SCCP, 2008), but only performed in selected recent studies (Manová et al., 2014; Nijkamp et al., 2015). 1.14% of our study population was exposed to BIT via HCP exceeding the AEL_{int} value. Only very few dermatological studies exist that can be used to compare this comparatively high level of sensitization: Patch testing with a concentration of 1000 ppm reported an incidence of 0.8% in dermatological patients (Andersen and Veien, 1985), whereas Schnuch et al. (1998) observed a sensitization rate in patients of 1.2%. However, these studies represent an overestimation (patients with ACD, not general population) and are quite old. Recent literature on sensitization to BIT is rare, probably because BIT is not included in the baseline patch test series that dermatologists use to test their patients in case of a suspected ACD.

This QRA includes conservative choices regarding the choice of AEL and the SAFs. In the HRIPT study reported by Basketter et al. (1999, 2005), the author discussed that the true no effect level may be > 360 ppm. In fact, a twofold higher BIT concentration (725 ppm) was tested and this affected 9% of tested individuals (Basketter et al., 1999, 2005) meaning that the no effect level can be > 360 ppm but lower than 725 ppm. In addition, the BIT solution applied on the participants' skin contained ethylene diamine, which is also a skin sensitizer. As to the SAFs, a SAF of 10 was chosen regarding the selected use. The 'selected use' comprises two components, which are the difference in frequency of exposure between HRIPT and real-life, and the delay of sensitization. The former we judge to be potentially significant, the latter less, because it is rather rare. Thus, the SAF may likely be smaller than 10, for instance, 3. Both AEL and SAFs are therefore on the conservative side and may have led to a moderate overprediction of the actual risk. We have to acknowledge, however, that the original data reported by Basketter et al. (1999) are not available for critical evaluation.

In 2008, QRA was severely criticized by SCCP, who nonetheless admitted that with some improvements, namely by including aggregate exposure and validation, QRA might be a useful tool in the future (SCCP, 2008). Lately, the International Dialogue for the Evaluation of Allergens (IDEA) project was established to improve the risk assessment of fragrance substances with experts coming from academia, hospital, and industry (IDEA, 2017). The QRA2 (SCCS, 2017b) is the outcome of this project (Basketter and Safford, 2016), which addressed uncertainty factors and dermal aggregate exposure for fragrance ingredients. In October 2017, the SCCS decided that QRA2 is still not adequate to establish a concentration at which induction of sensitization by a fragrance ingredient is unlikely to occur and further scientific rationale behind QRA2 needs to be provided since scientific reasoning and explanation of certain approaches and assumptions is lacking (SCCS, 2017b).

Note that QRA and QRA2 were developed for fragrances and not preservatives, but for preservatives the same risk assessment principles apply.

4.3. Comparison between PACEM-KD and PACEM

PACEM-KD and PACEM were compared based on the fractions of the population at risk of developing ACD according to the respective QRA calculation: The results differ by two orders of magnitude. To better illustrate the differences, single aggregate exposures were calculated for a male and a female adult and reported in SI Table S9. The most important differences are the treatment of dilution and the approach to determine the fraction of substance available for uptake. PACEM uses exposure fractions to account for dilution and assumes that a fixed thickness of the product layer (0.01 cm) is available for exposure. The dilution volume is fixed to 5 L for each HCP with the exception of cleaning wipes. PACEM-KD uses individual dilution patterns assessed by Garcia-Hidalgo et al. (2017a) who observed that several HCPs were used undiluted. In PACEM-KD the dilution volume was treated probabilistically (using volume distributions; see Fig. S6 of the SI) and it includes several dilution scenarios which are specific to the HCP categories (e.g. for dishwashing detergent dilution only with max 133 g of water contained in a sponge). The other important difference between the models is that in PACEM the exposure fraction depends on a fixed thickness of the product layer, whereas PACEM-KD uses a kinetic approach. The thickness of the product layer was necessary to derive the exposure fraction of all liquid/gel/powder/tablet cleaning products, but represents an assumption and therefore is very uncertain and at the same time very influential. On the other hand, PACEM-KD uses a kinetic approach, which is mechanistically better justified, but based on k_p , which is also associated with large uncertainties (discussed below).

Two more aspects might be responsible for differences between the two models: i) only six HCP categories were included in PACEM instead of ten in PACEM-KD; ii) the input populations have slightly different use-patterns (Garcia-Hidalgo et al., 2017a; Nijkamp et al., 2015).

4.4. Study limitations

PACEM-KD calculates aggregate dermal exposure with a mechanistic approach for dermal uptake, incorporating the exposure duration as a parameter and using the skin permeability coefficient instead of default exposure fractions. Despite the prominence of the fractional approach in exposure assessment, it is not backed up by experimental studies and presents limitations for dermal risk assessment (Frasch et al., 2014). However, the approach presented here is comparatively new and has not yet been evaluated against experimental data such as biomonitoring data for chemicals inside the skin. Recently, Schettgen and Kraus (2017) developed a new method for investigating the metabolism of MI and CMI by biomonitoring. According to this study, it may be possible to apply radiolabelled isothiazolinones on the skin, and, by their newly developed method, investigate the urine concentration in comparison to the applied concentration in order to assess which variables influence the metabolism. The study of Schettgen and Kraus (2017) provides the first insight into human metabolism of the biocidal active substances MI and CMI. Further studies are needed on the metabolism of isothiazolinones, not only for CMI and MI, but also for BIT and OIT, for which there is even less information available.

The largest parameter uncertainty is associated with k_p , for which only computational data was available for the four isothiazolinones. Furthermore, different skin sites may have different characteristics and the composition of HCPs may contain substances acting as permeability enhancers/inhibitors. Likewise, the pH of the product (for HCPs in particular) can influence the K_{ow} and thus also the k_p .

Another uncertainty is linked to the aggregation time. The exposure was aggregated for one day. However, it is still unknown which the relevant measure is in terms of activating the immune system. It may be that allergens are aggregated in the skin over a different duration than one day.

PACEM-KD was mainly designed for rinse-off products. During the

exposure time (max 1.5 h), it is assumed that the concentration layer in contact with the outmost skin layer is not depleted. For HCPs, this is a realistic assumption, but for leave-on PCPs this aspect may lead to an overestimation of the exposure (not relevant for this assessment since no leave-on PCPs were included). In particular, for PCPs it is unclear how washing hands influences the exposure time on palms/back of hands.

The effect of gloves was not taken into account in this study. Gloves are particularly useful for already sensitized persons who need to avoid further contact with the allergen by wearing protective clothing (such as gloves), using barrier creams, or complete avoidance of a product (Rycroft et al., 2013). Nevertheless, gloves should be used cautiously since, in some cases, they can enhance allergic reactions if the allergen can migrate through the gloves (Espasandín-Arias and Goossens, 2014; Uter et al., 2013). Even if data on the usage of the gloves was provided by the questionnaire's respondents, this aspect was not included in the model PACEM-KD because depending on the glove material (unspecified by the respondents) this could enhance or prevent exposure to isothiazolinones.

Questionnaire respondents were asked to recall their usage of HC&PCPs retrospectively, and therefore recall bias has to be assumed. Not all product categories that contain isothiazolinones were included, so that the predicted dermal exposure might be slightly underestimated. For example, consumers might be occasionally exposed to water-based paints in which isothiazolinones are widely used as preservatives (Aerts et al., 2015; Schwensen et al., 2015). It has been reported that exposure to isothiazolinones from paint emission has led to severe ACD reactions (Bohn et al., 2000; Bregnbak and Johansen, 2013; MD Lundov et al., 2011; Wright and Cahill, 2016). Aerts et al. (2015) analyzed four paints in Belgium and found that three of them contained BIT at concentration up to 35 ppm. Schwensen et al. (2015) showed the distribution of measurements of MI, CMI, and BIT in wall paints across five European countries (Denmark, France, Germany, Sweden, and UK). MI was found in 93.0% (n = 66) of the paints, with concentrations ranging from 0.7 to 180.9 ppm, MCI in 23.9% (n = 17) ranging from 0.26 to 11.4 ppm, and BIT in 95.8% (n = 68) ranging from 0.1 to 462.5 ppm. Nevertheless, there is currently no EU regulation defining maximum isothiazolinone concentrations permitted in water-based paints (Aerts et al., 2015) and it is possible that isothiazolinone concentrations in paint products sold on the Swiss market can exceed those reported for the EU market. However, even if this might lead to an underestimation of the aggregate exposure, the use frequency of certain do-it-yourself products such as water paint, furniture polish, anti-rust products, etc. is normally around once per year or less (Garcia-Hidalgo et al., 2017a). Moreover, for paints, it is currently not understood how the ACD mechanism works. Therefore, only dermal exposure from direct contact with consumer products was estimated in this study.

Switzerland follows the same regulations for cosmetics and household cleaning products as the EU. Moreover, about 80% of the products sold in Switzerland are also sold in other EU-countries. On the other hand, HC&PCPs products sold e.g. on the US market are substantially different. Therefore, whereas our study can be largely extrapolated to other European countries, especially those neighboring Switzerland, the results can only give a qualitative indication about the situation in the US and other regions of the world.

5. Conclusion

It is essential to understand the hazards and risks associated with exposure to potential skin sensitizers. The described QRA for the sensitizer BIT showed that one person out of 100 (1.14%) may exceed the adjusted acceptable exposure level, i.e. is at risk to be sensitized by BIT. Therefore, we consider it desirable that the safety of BIT in HCP be re-evaluated.

PACEM-KD extends the original PACEM by calculating dermal uptake based on exposure duration, product dilution, and skin permeability. This new model can be used for any other sensitizer used in HC & PCPs and ideally should be validated against biomonitoring data for

substances inside the skin. As the sensitivity analysis showed, concentration of the substance in the product is always the most sensitive factor in the calculation of aggregate exposure: In this context, a freely accessible online database containing reliable ingredient information for consumer products would be beneficial.

Acknowledgment

The authors received funding from the Swiss Federal Office of Public Health. We thank all our participants for their contribution to the survey. Special thanks to codecheck.info for providing access to their database. We further acknowledge Janine Ezendam of the National Institute of Public Health and the Environment (RIVM), Bilthoven, The Netherlands, for important discussions.

Funding

This work was supported by the Swiss Federal Office of Public Health.

Appendix A. Supplementary data

Supplementary data associated with this article and extracts of the model-code can be found, in the online version, at <https://doi.org/10.1016/j.envint.2018.05.047>.

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Supplemental Information

for

Aggregate consumer exposure to isothiazolinones via household care and personal care products: probabilistic modelling and BIT risk assessment

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Table of Contents

Section S1. Small pilot study to measure the water absorbing capacity of sponges and wipes

Section S2. Supplementary Tables and Figures

Section S3. Data treatment for HCP frequency f_{event}

Section S4. Data treatment for HCP duration of use (t_{event})

Section S5. Skin permeability coefficient k_p : model choice

Section S6. Sobol's variance decomposition method

Section S7. Supplementary Results Tables and Figures

Section S8. NESIL calculation

Section S9. Comparison between PACEM and PACEM-KD

Section S1. Small pilot study to measure the water absorbing capacity of sponges and wipes

Due to the great variability in size/material composition/saturation state of sponges and wipes, we conducted a small sub-study to measure the difference in water absorbing capacity. The absorbing water ability of three types of saturated/squeezed out sponges (A-C) and three types saturated/squeezed of wipes (D-F) were measured. All the products were purchased in the Supermarket Coop Oerlikon (CH). For each sponge/wipe type, two (C, F) to three (A, B, D, E) repetitions were conducted (Figure S 1). The differences between masses of dry, saturated and hand-squeezed sponges/wipes were calculated. The results are shown in Figure S 2.



Figure S 1 Sponges and wipes used for the experiment.

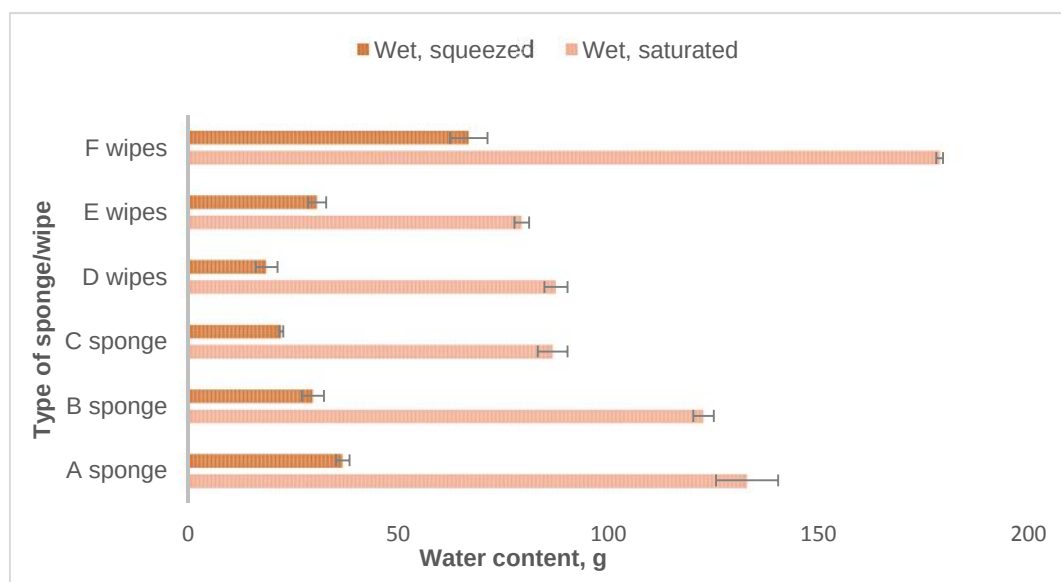


Figure S 2. Mean of the mass of water absorbed by different types of sponges and wipes. Standard deviation is presented by the bars.

Section S2. Supplementary Tables and Figures

Table S 1. Mass of dilution-water under different dilution scenarios. The dilution-water mass is an average between non-diluted (time=0) and diluted product by rinsing/mixing afterwards (time=X min).

Dilution medium	Volume distribution	Water content parameters, g	Applied to these HC&PCP categories
Sponge	Uniform	22.2-133.1	All Purpose Cleaner (Liquid and Spray) Bathroom Cleaner (Liquid and Spray) Bleach Carpet Cleaner Floor Cleaner (Liquid) Glass Cleaner (Spray) Kitchen Cleaner (Liquid and Spray) WC Cleaner Dishwasher Fungicide (Spray)
Wipe	Uniform	30.7-178.9	All Purpose Cleaner (Liquid and Spray) Bathroom Cleaner (Liquid and Spray) Bleach Carpet Cleaner Floor Cleaner (Liquid) Glass Cleaner (Spray) Kitchen Cleaner (Liquid and Spray) WC Cleaner Dishwasher detergent Fungicide (Spray)
Sink	Triangular	5000, 20000, 105000	All Purpose Cleaner (Liquid) Bathroom Cleaner (Liquid) Floor Cleaner (Liquid) Kitchen Cleaner (Liquid) WC Cleaner Dishwasher
Bucket	Triangular	2000, 5000, 10000	All Purpose Cleaner (Liquid) Bathroom Cleaner (Liquid) Bleach Carpet Cleaner Floor Cleaner (Liquid) Kitchen Cleaner (Liquid) WC Cleaner Dishwasher detergent
Extra water for wet wipes	Uniform	1-10	All Purpose Cleaner (Wipes)
Water for bathtub	Uniform	80000-160000	Bathing foam
Water for handwashing	Uniform	80-1000	Liquid hand soap
Water for shampooing	Uniform	50-2000	Shampoo
Water for tooth brushing	Uniform	20-150	Toothpaste

Table S 2. Amount data: assignment criteria between the Swiss database and the EPHECT database (2012) for HCPs.

Swiss database		EPHECT database
Product-specificity		
All Purpose Cleaner (Liquid) All Purpose Cleaner (Spray) Bathroom Cleaner (Liquid) Bathroom Cleaner (Spray) Kitchen Cleaner (Liquid) Kitchen Cleaner (Spray) Glass Cleaner (Spray) Floor Cleaner (Liquid)	←	All Purpose Cleaner (Liquid) All Purpose Cleaner (Spray) Bathroom Cleaner (Liquid) Bathroom Cleaner (Spray) Kitchen Cleaner (Liquid) Kitchen Cleaner (Spray) Glass Cleaner (Spray) Floor Cleaner (Liquid)
Gender-specificity		
Female Male	←	Female Male
Age-specificity		
<18 years 18-39 years 40-54 years 55-71 years ≥72 years	←	18-39 years 18-39 years 40-54 years 55-71 years ≥72 years
Region-specificity		
Swiss-German Swiss-French Swiss-Italian	←	Germany (DE) France (FR) Italy (IT)

Because the EPHECT data characteristics of the product category all-purpose cleaning wipes further assignment considerations were needed and the age and region criteria were adjusted as shown in Table S3.

Table S 3. Amount data assignment criteria for all-purpose cleaning wipes.

Swiss database		EPHECT database
Age & region-specificity		
<55 (region-specific) ≥55 years (all three regions)	←	<55 (region-specific) ≥55 years (DE + FR + IT)

Table S 4. Uniform amount distributions for the HCP categories not included in the EPHECT study.

HCP category	Amount distribution, g
Dishwasher	2-15
Bleach	30-90
Fungicide spray	30-90
Carpet cleaner	15-60

Section S3. Data treatment for HCP frequency f_{event}

For HCPs, questions included the usage, frequency, and duration of cleaning tasks at different home sites (i.e. floor, windows, etc.). If a respondent indicated to have used one product per home site, we processed it as for PCPs. For any respondent using more than one product per home site (e.g. products A, B, and C used to clean the bathroom), we assigned the frequency selected for that specific site (e.g. bathroom 1 per day), divided by the total number of products used for cleaning that specific site (e.g. 1 per day/ "number of products"), for every HCP used. Although this might not be completely realistic, we assumed that all HCPs are used together during that specific cleaning event and that consumers can use only one product per cleaning event.

$$\text{Eq. S1: } C_2 = \frac{C_1 \times M_1}{M_2} = \frac{C_1 \times M_1}{M_1 + M_{H_2O}} \quad [\text{ng/mL}]$$

where C_1 is the isothiazolinones concentration in the product [ng/mL], C_2 is the (recalculated) diluted concentration of isothiazolinones [ng/mL], M_1 is the amount of undiluted product applied/used [g] and M_2 is the amount of diluted product, which is the sum of the amounts of undiluted product and water used for dilution [g].

Section S4. Data treatment for HCP duration of use (t_{event})

Duration was inquired (Elena Garcia-Hidalgo et al. 2017a) only for HCPs. For example, a respondent used the glass cleaner to clean bathroom and windows with a duration of 1-10 min and 60-90 min, respectively. If both home places would be cleaned with the same frequency, for the glass cleaner an average of the two durations could be used, i.e. 30.5-50 min. However, if the windows are cleaned only once per month, whereas the bathroom is cleaned once per week, the bathroom cleaning duration should be 4 times greater than that of the windows. Thus, in this case, the previous approach of calculating HCP-use duration as an average of durations of cleaning different parts of the house, cannot be applied. To calculate then frequency-weighted lower boundary for the HCP duration (similar process for the parameter 2) the following formula was used:

$$\text{Duration parameter } 1_x = \frac{\sum_{i=1}^9 (\text{Frequency parameter } 2_i \times \text{Duration parameter } 1_i)}{\sum_{i=1}^9 \text{Frequency parameter } 2_i} \quad [\text{min}]$$

where x is a cleaning product and i is the number of the house compartment (max 9). Duration parameter 1 refers to the duration lower bound and duration parameter 2 to the duration upper bound, respectively. In a similar manner, the upper boundary was also calculated.

Table S 5. Duration ranges for PCPs.

Product	Lower bound [min]	Upper bound [min]	Reference
Shampoo	1	10	Bremmer et al. 2006
Conditioner	1	10	Bremmer et al. 2006
Shower gel	2	8	Bremmer et al. 2006
Bathing foam	5	45	Estimate
Liquid hand soap	2	10	Garcia-Hidalgo et al. 2017a
Shaving product	5	20	Estimate
Hair dye	20	45	Bremmer et al. 2006
Toothpaste	1.2	2.2	Bremmer et al. 2006
Nail polish	1	7	Bremmer et al. 2006

Section S5. Skin permeability coefficient k_p : model choice

To our knowledge, k_p values for isothiazolinones have not yet been measured. Hence, they need to be predicted by models, which are constructed based on physicochemical characteristics such as the octanol-water partitioning coefficient (K_{ow}) and/or molecular weight/size. k_p estimates are subject to great variability due to different methods used to generate them: In the literature few distinct models are available to estimate the *stratum corneum* k_p from an aqueous vehicle (Mitragotri et al. 2002; Frasch et al. 2002; Potts and Guy 1992; and Robinson as modified by Wilshut et al. 1995) and the comparison of their predictions for isothiazolinones are given in Table S6. All four models listed have strengths and weaknesses. In this work, the mechanistic explanation of the diffusion mechanism was adopted and such assumption was supported by Frasch (2002). In this work, to estimate the k_p the model proposed by Mitragotri et al. (2002) and rewritten by Lian et al. 2008) was used. This model was found to give the best results in an evaluation of several dermal permeability models (Lian et al. 2008).

Table S 6. Characteristics of four isothiazolinones: molecular weight (MW), octanol-water partitioning coefficient (K_{ow}), permeability coefficient (k_p) through stratum corneum (cm/h).

Chemical	MW, g/mol	LogKow	k_p (cm/h)			
			Mechanistic	Mechanistic	Empirical	Empirical
			Mitragori (2002)	Frasch (2002)	Potts and Guy (1992)	Robinson as modified by Wilshut et al. 1995
MI	115.15	-0.83	0.000103	0.0000219	0.0000933	0.000191
CMI	149.6	0.04	0.000199	0.0000692	0.00024	0.000339
BIT	151.18	0.64	0.000505	0.000263	0.000617	0.000741
OIT	213.34	2.61	0.00358	0.008913	0.00646	0.00447

Section S6. Sobol's variance decomposition method

The importance of an individual input parameter for the aggregated dermal exposure was determined by variance-based global sensitivity analysis (GSA) using Sobol's variance decomposition method (Zhang et al. 2015). This GSA describes the sensitivity pattern of a model depending on the uncertain input parameters and their interactions (Saltelli et al. 2010), which is done by Monte Carlo Simulation (MCS) estimation of first-order and total Sobol's indices simultaneously (Pujol et al. 2017). The first order Sobol's indices assess only the effect of the independent input variable, while the total index sums the effect of individual parameters and interactions' effect of any order. The interaction effect among the two model parameters describes the part of the output variance that cannot be explained by the sum of the individual contributions of these two parameters (Dudzina, 2014). The difference between the total index and the first order index thus represents all the possible (synergistic) interactions between the input parameters. However, if both indices are equal, then there are no interactions present between the input parameters.

Section S7. Supplementary Results Tables and Figures

Table S 7. Parameter representation and qualitative characterization of uncertainty and variability of the model parameters in PACEM-KD. The source of uncertainty/variability can be either the data itself, data changes during process of data conversion and/or modelling, or both. These are ranked based on their impact on the model output: Letters in the brackets indicate whether the importance of uncertainty/variability reason is low (l), medium (m) or high (h). The symbols (▼)(▲) indicate the direction of this impact: i.e. leads to under- or overestimation, respectively. Ranges of uncertainty and variability are provided where possible.

Exposure factor	Representation in the model	Uncertainty	Variability
Substance concentration in the product	A set of discrete values	Data: 1) analytical errors (l; ▼/▲) (For HCP LOQs were 3.1 ppm for MCI, 3.5 ppm for MI, 3.8 ppm for BIT, and 3.4 ppm for OIT; for PCP were 1.3 ppm for MCI and 1.4 ppm for MI) 2) limited number of products tested (h; ▼) (79 products tested in Swiss market) Process: assumption that product market is represented only by surveyed products (h; ▲)	Data: spatial and temporal variability among different products and their labels (m; ▼/▲) (concentration ranges: 0 – 500 ppm (OIT), 0 – 186.2 ppm (BIT), 0-133 (MI), 4.8 (CMI; one value measured)) Process: discrete distributions assigned to each product category in the model (m; ▼/▲)
Product use frequencies reported by survey respondents	Distribution and parameter values describing the distribution	Data: limited number of answers with specified broad ranges (e.g. 3-6 times per week) (m; ▼/▲) Process: 1) data conversion from frequency of cleaning sessions into frequency of product use (m-h; ▲) 2) uniform distributions assigned to each individual, who specified a range in the questionnaire (m; ▼/▲)	Data: natural inter-individual variability (m; ▼/▲) (frequency range: of 1.8 times/year – 10.3 times/day) Process: point values drawn from personal distributions for every simulated individual (l; ▼/▲)
Product amounts assigned from the questionnaire or the EPHECT study (used only in case of dilution event)	Distribution and parameter values describing the distribution	Data: 1) amount parameters for HCP were assigned from different European populations (m; ▼/▲) 2) subjectively assigned amounts for products not included in EPHECT questionnaire (m-h; ▼/▲) 3) the analytical errors of weighing the product amounts in the source EPHECT data (l-m; ▼/▲) 4) amount parameter for PCPs were extrapolated from the questionnaire which used photographs for the assessment: uncertainty in the estimation by photographs plus the measurement error while weighing the product amounts (m; ▼/▲) Process: 1) For HCPs: uniform distributions assigned to each individual, who specified a range in the questionnaire (l-m; ▼/▲) 2) For HCPs: the assignment based on gender, age and region (l-m; ▼/▲) 3) For HCPs: Estimate of the amount ranges missing in the EPHECT study (l-m; ▼/▲) 4) For PCPs: determination of the ranges corresponding to each photograph (l-m; ▼/▲) and uniform distributions assigned to each modelled individual (l)	Data: natural inter-individual variability (m; ▼/▲) Process: point values drawn from personal distributions for every simulated individual (l; ▼/▲)
Water amounts used to dilute the products (used only in case of dilution event)	Distribution and parameter values describing the distribution	Data: 1) analytical errors (l; ▼/▲) 2) uncertainty in the estimation of the volumes (l-m; ▼/▲) Process: 1) limited number of dilution scenarios provided (m; ▼/▲) 2) subjective assignment of potential dilution scenarios for different product categories (m-h; ▼/▲) 3) the assignment of the same probability for all dilution scenarios to occur (m-h; ▼/▲)	Data: 1) variability among different dilution scenarios (m; ▼/▲) 2) natural inter-individual variability (m; ▼/▲) Process: point values drawn from dilution distribution assigned to each product category in the model (m; ▼/▲)
Durations of use	Distribution and parameter values describing the distribution	Data: For HCPs, limited number of answers with specified broad ranges (e.g. up to 10 minutes) (l-m; ▼/▲) For PCPs, uncertainty in the estimation (m-h; ▼/▲) Process: 1) for HCPs, conducted data treatment to convert duration of cleaning sessions into duration of product use (m-h; ▲) 2) for HCPs, uniform distributions assigned to each individual, who specified a range in the questionnaire (m; ▼/▲) 3) for PCPs, uniform distributions assigned to each individual PCP category (m; ▼/▲)	Data: natural inter-individual variability (m; ▼/▲) (duration range: 1 min – 90 min) Process: point values assigned from personal distributions for every simulated individual (l; ▼/▲)

Permeability coefficient k_p	Single point value	Data: 1) measurement/prediction errors of molecular weight and K_{OW} (l; ▼/▲) 2) uncertainty in the selected k_p model (i.e. Mitragori et al. 2002) (m; ▼/▲) 3) uncertainty around the real measure of the k_p value (h; ▼/▲) Process: choice of k_p model (m-h; ▼/▲) (max 2.5 times difference between different models)	Data: natural variability of different skin sites (l-m; ▼/▲) Process: a single point value used for every person and all body parts (m; ▼/▲)
Uncertainties associated with the model		1) Equation 1 is only valid for very low absorption (i.e. small k_p or short durations) (l; ▲) 2) Aggregation time used (i.e. 24 h) (m; ▲) 3) Exposure time (i.e. stopped when the cleaning task is completed) (m; ▼) 4) Treatment of leave-on products (h; ▲) 5) Decreasing of the percutaneous absorption (i.e. saturation) (m; ▼) 6) Surface renewal assumption (l; ▲) 7) Well-mixes bulk region assumption (l; ▲) 8) Assumption of intact skin barrier (m; ▼)	-

* LOQ – limit of quantification

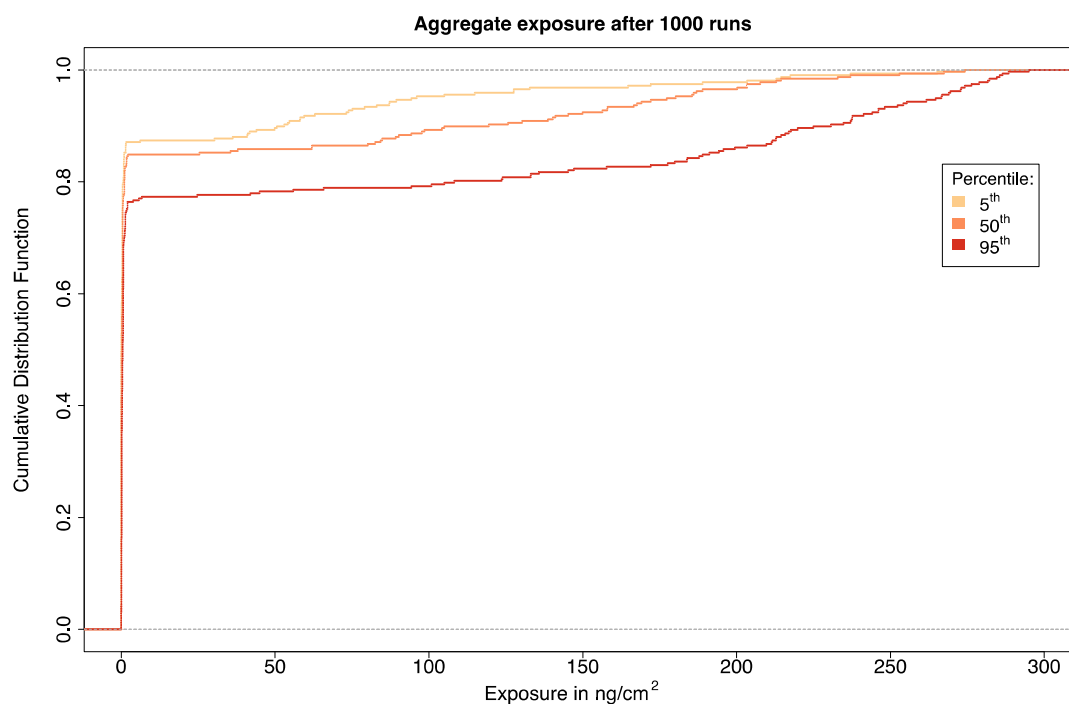


Figure S 3. Uncertainty and variability analysis for OIT excluding the non-exposed individuals (N=756) with the Monte Carlo simulation. Cumulative distribution functions for the P5, P50, and P95 of each run (N=1'000).

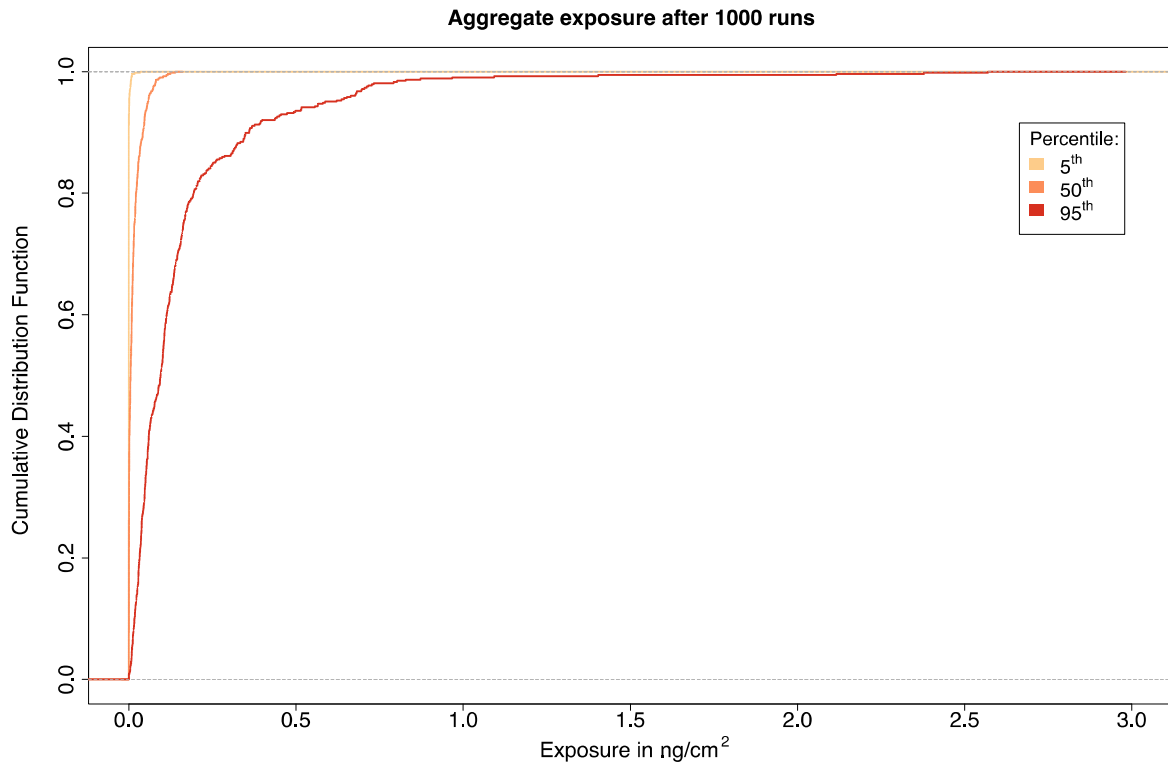


Figure S 4. Uncertainty and variability analysis for MI excluding the non-exposed individuals (N=756) with the Monte Carlo simulation. Cumulative distribution functions for the P5, P50, and P95 of each run (N=1'000).

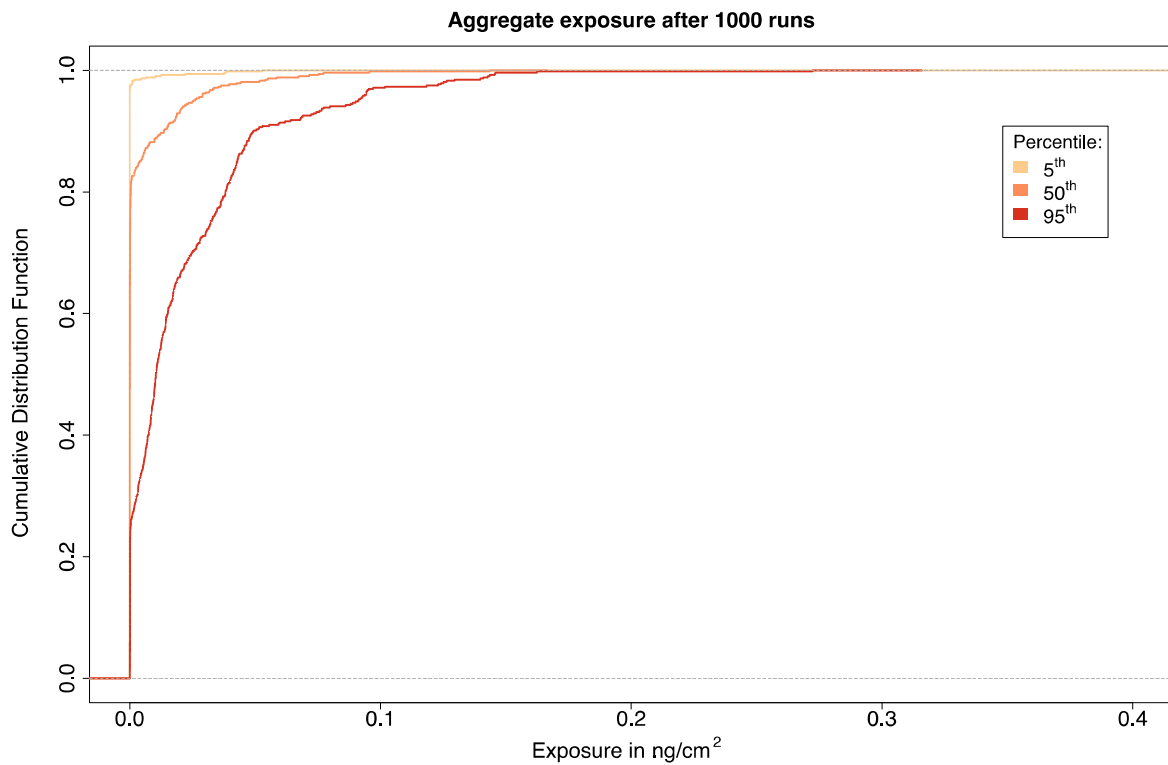


Figure S 5. Uncertainty and variability analysis for CMI excluding the non-exposed individuals (N=756) with the Monte Carlo simulation. Cumulative distribution functions for the P5, P50, and P95 of each run (N=1'000).

Table S 8. Sobol's first-order sensitivity indices (first SI) and total sensitivity indices (total SI) for the main HCP

Product	N	Frequency		Amount		Duration		Concentration	
		first SI	total SI	first SI	total SI	first SI	total SI	first SI	total SI
Kitchen Cleaner Spray	78200	0.00876	0.0564	0.00	0.00001	0.0163	0.0822	0.782	0.883
Kitchen Cleaner Liquid	109000	0.0278	0.0667	0.00	0.00007	0.0229	0.0855	0.716	0.754
All Purpose Cleaner Liquid	143500	0.0287	0.0412	0.00142	0.00354	0.0343	0.0795	0.646	0.725
All Purpose Cleaner Spray	65800	0.0202	0.0615	0.00008	0.00079	0.0352	0.09452	0.642	0.748
All Purpose Cleaner Wipes	55900	0.00138	0.0172	0.00001	0.00023	0.00916	0.0741	0.857	0.9
Bathroom Cleaner Spray	99000	0.0149	0.0551	0.00003	0.00001	0.0335	0.0632	0.636	0.712
Floor Cleaner Liquid	139000	0.0162	0.0489	0.00008	0.000676	0.00321	0.0643	0.615	0.788
Glass Cleaner Spray	181000	0.00819	0.0507	-0.00005	0.000456	0.00889	0.039	0.719	0.902
Dishwashing detergent	232000	0.0128	0.0471	0.00049	0.00256	0.00976	0.0635	0.771	0.904
Carpet Cleaner	32000	0.000009	0.00118	0.00001	-0.00008	0.00398	0.0436	0.878	0.982

categories contributing * to the aggregate dermal consumer exposure to BIT calculated by PACE M-KD.

* Products that do not contain BIT and thus do not contribute to aggregate dermal consumer exposure to BIT include bathroom cleaner liquid, bleach, fungicide spray, WC cleaner, and all PCPs.

Section S8. NESIL calculation

To allow a comparison of CEL generated by PACEM-KD with AEL it is necessary to adjust the NESIL, because PACEM-KD is based on an internal dermal dose. Therefore, an adjusted NESIL value was calculated based on the data from Basketter et al. (1999, 2005) using Eq. S2.

$$\text{Eq. S2} \quad \text{NESIL} = C_{\text{HRIPT}} \times f_{\text{event}} \times t_{\text{event}} \times k_p \quad [\mu\text{g}/\text{cm}^2]$$

C_{HRIPT} : HRIPT concentration [$\mu\text{g}/\text{cm}^3$], f_{event} : application frequency [day^{-1}], t_{event} : duration of the application t [h], and k_p : chemical-dependent skin permeability coefficient [cm/h].

Knowing that 360 ppm aq. BIT (i.e. $360 \mu\text{g}/\text{cm}^3$) was applied on the skin 9 x 24 hours during the course of 3 weeks and that BIT k_p equals $0.000505 \text{ cm}/\text{h}$, we decided to use $f_{\text{event}} = 1/\text{day}$ because the patch stays on the skin 24 hours and then it is removed and replaced after few days. The calculation of the NESIL was performed as follows:

$$\text{NESIL} = 360 \mu\text{g}/\text{cm}^3 \times 1 \text{ day}^{-1} \times 24 \text{ h} \times 0.000505 \text{ cm}/\text{h} = 4.37 \mu\text{g}/\text{cm}^2$$

Section S9. Comparison between PACEM and PACEM-KD

In PACEM, a unique fix dilution volume of 5L was used for each HCP product (i.e. for liquid/gel/powder/tablet cleaning products) with the exception of the cleaning wipes. In PACEM-KD the dilution volume was treated probabilistically using volume distributions (see Figure S6) and it includes four different dilution scenarios.

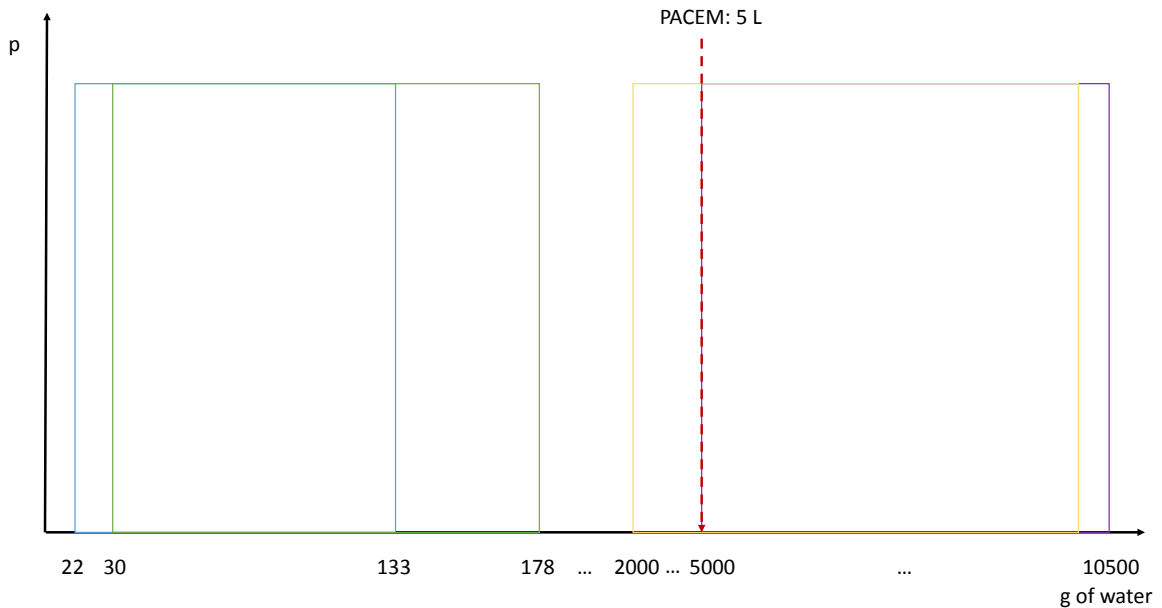


Figure S 6. Uniform distributions of the four dilution scenarios (i.e. sponge, wipe, sink, and bucket) considered in PACEM-KD compared to the unique dilution scenario of 5L used for PACEM. Each color corresponds to a new uniform distribution.

Table S9. Comparison of the results obtained by the models PACEM and PACEM-KD for a male and a female participant regarding BIT (consideration of HCP only)

BIT												
1° Example: Female, 51y												
	Amount [g]	Freq [1/d]	Ex. Time [h]	Dilution	Amount dilution H ₂ O [g]	k _p BIT [cm/h]	Exposure fractions	Surface area hands [cm ²]	Conc [ug/mL]	Weight fraction in the product	PACEM-KD [ug/cm ²]	PACEM [ug/cm ²]
All-purpose cleaner spray	2	7	0.3	No	0	0.000505	0.0018	900	30	0.00003	0.3	0.0008
Dishwasher detergent	15	3	0.2	Yes	22	0.000505	0.0018	900	8	0.000008	0.02	0.0007
Bathroom cleaner spray	40	1	0.5	No	0	0.000505	0.0018	900	0	0	0	0
Floor cleaner liquid	40	3	0.5	Yes	22	0.000505	0.0018	900	8.3	0.0000083	0.01	0.002
Glass cleaner liquid	4	1	0.2	No	0	0.000505	0.0018	900	2	0.000002	0.0002	0.00002
TOT on hands [ug/cm ²]:											0.33	0.007
2° Example: Male, 49y												
	Amount [g]	Freq [1/d]	Ex. Time [h]	Dilution	Amount dilution H ₂ O [g]	k _p BIT [cm/h]	Exposure fractions	Surface area hands [cm ²]	Conc [ug/mL]	Weight fraction in the product	PACEM-KD [ug/cm ²]	PACEM [ug/cm ²]
All-purpose cleaner liquid	40	1	0.5	Yes	22	0.000505	0.0018	900	30	0.00003	0.3	0.0008
Dishwasher detergent	15	2	0.3	Yes	22	0.000505	0.0018	900	8	0.000008	0.02	0.0007
Bathroom cleaner spray	6	1	0.5	Yes	22	0.000505	0.0018	900	6	0.000006	0.02	0.00007
WC cleaner	9	1	0.5	No	0	0.000505	0.0018	900	0	0	0	0
Glass cleaner liquid	4	1	1.5	No	0	0.000505	0.0018	900	2	0.000002	0.0002	0.00002
All-purpose cleaner wipes	6	1	0.1	No	0	0.000505	1	900	11	0.000011	0.006	0.07
TOT on hands [ug/cm ²]:											0.35	0.007

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