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

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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/cm^2, 1.3 ng/cm^2, 0.9 ng/cm^2, and 0.08 ng/cm^2 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

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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