Environment International 74 (2015) 231–239

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Aggregate dermal exposure to cyclic siloxanes in personal care products: Implications for risk assessment

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ARTICLE INFO

Article history:
Received 27 May 2014
Received in revised form 26 September 2014
Accepted 17 October 2014
Available online 5 November 2014

Keywords:
Octamethylcyclotetrasiloxane
Decamethylcyclopentasiloxane
D4
D5
Human biological monitoring
End-exhaled air

ABSTRACT

Consumers who use personal care products (PCPs) are internally exposed to some of the organic components present of which some may be detected in exhaled air when eliminated. The aim of this study was the quantitative determination of octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5) in end-exhaled air to study dermal absorption of substances in PCPs. We exposed the forearm of fifteen healthy volunteers for 60 min to pure D4 or D5 and to commercial products containing D4 and D5. Inhalation uptake was kept to a minimum by keeping the forearm in a flow cabinet during dermal exposure and supplying filtered air to the breathing zone of the volunteer during the post-exposure period. End-exhaled air was collected using a breath sampler (Bio-VOC), transferred to carbograph multi-bed adsorbent tubes and analyzed by thermal desorption gas chromatography mass spectrometry (TD-GC-MS). In the end-exhaled air of non-exposed volunteers background concentrations of D4 (0.8–3.5 ng/L) and D5 (0.8–4.0 ng/L) were observed. After exposing the volunteers, the level of D4 and D5 in end-exhaled air did not or barely exceed background concentrations. At t = 90 min, a sharp increase of the D4/D5 concentration in end-exhaled air was observed, which we attributed to the inhalation of the substances during a toilet visit without using inhalation protection devices. When this visit was taken out of the protocol, the sharp increase disappeared. Overall, the results of our study indicate that dermal absorption of D4 and D5 contributes only marginally to internal exposure following dermal applications. As in our study inhalation is the primary route of entry for these compounds, we conclude that its risk assessment should focus on this particular exposure route.

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1. Introduction

Consumers use personal care products (PCPs) to clean, refresh and decorate their bodies. Some products are used on a daily basis, whereas others are used less frequently (Biesterbos et al., 2013; Wu et al., 2010). When multiple products are used simultaneously, consumers may be exposed to the same substance through different sources and routes, also referred to as aggregate exposure (Lorenz et al., 2011; von Goetz et al., 2010). Cyclic siloxanes, such as octamethylcyclotetrasiloxane (D4) and decamethylcyclopentasiloxane (D5), are added to PCPs as emollients or solvents (Johnson et al., 2011; Scientific Committee on Consumer Safety (SCCS), 2010) in many different products throughout the world (Dudzina et al., 2014; Horii and Kannan, 2008; Lu et al., 2011; Wang et al., 2009). D5 and to a lesser extent D6 were observed to be the predominant substances, whereas D4 was found in smaller amounts. The use of PCPs is the primary source of exposure to cyclic siloxanes (Health Canada, 2008). Therefore, the Scientific Committee on Consumer Safety in Europe and the Cosmetic Ingredient Review Expert Panel in the US assessed the health implications of the use of cyclic siloxanes processed in PCPs (Johnson et al., 2011; Scientific Committee on Consumer Safety (SCCS), 2010). Both committees concluded that cyclic siloxanes are safe with regard to the present practices of use and their concentrations in PCPs.

Abbreviations: D4, octamethylcyclotetrasiloxane; D5, decamethylcyclopentasiloxane; EI, electron impact; LOQ, limit of quantification; PBPK model, physiologically based pharmacokinetic model; PCPs, personal care products; TD-GD-MS, thermal desorption gas chromatography mass spectrometry.

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http://dx.doi.org/10.1016/j.envint.2014.10.017
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The substance specific properties of D4 and D5 (e.g. high vapor pressure) and the fact that PCPs are mainly applied to the skin, point towards inhalation and dermal uptake as the dominant determinants of the internal dose. The retention of inhaled labeled D4 was 5–6%, when rats were exposed to single and multiple dosages of ^{14}C-D4 (7, 70, 700 ppm) (Plotzke et al., 2000a). A physiologically based pharmacokinetic (PBPK) model was developed and successfully described the data presented above (Andersen et al., 2001). The PBPK model was extended with a pharmacodynamic model for hepatic enzyme induction by D4 (Sarangapani et al., 2002) and used to describe the tissue dosimetry, plasma concentration, and clearance in the rat following inhalation, dermal, oral, and intravenous exposure (Sarangapani et al., 2003). Furthermore, 12 healthy volunteers inhaled 122 μg/L D4, resulting in a mean intake of 137 ± 25 mg (Utell et al., 1998).

When male and female rats were exposed to single or repeated doses of 7 or 160 ppm ^{14}C-D5, lung retention was rather low (4–5% for single exposure and 8–10% for repeated exposures) (Tobin et al., 2008). Reddy and co-workers developed an inhalation PBPK model, using human and rat exposure data (Reddy et al., 2008). An additional compartment was added to describe the presence of D5 bound to blood proteins, indicating that not all D5 is freely available for biotransformation and elimination.

Zarebra and co-workers investigated the dermal absorption of neat D4 in human skin, using the human skin/nude mouse model (Zareba et al., 2002). Under semi-occluded conditions, only 1.1% of the applied dose was absorbed while a large fraction of D4 (95%) evaporated from the skin. A PBPK model was developed to determine the dermal uptake of D4 and D5 after application of these substances to the skin of axilla of human volunteers (Reddy et al., 2007). The percentages of the applied dose that reached the systemic circulation were calculated to be 0.12% and 0.30% for D4 in men and women, respectively, and 0.05% for D5 in both sexes. In a study on the *in vitro* and *in vivo* dermal absorption of ^{14}C-D4 and ^{14}C-D5, the majority of the applied substances volatilized before being absorbed (Jovanovic et al., 2008). Only small percentages of the applied dose were absorbed (0.5% D4 and 0.04% D5 *in vitro* and <1.0% D4 and 0.2% D5 *in vivo*). Despite these low absorption fractions, dermal exposure cannot be considered insignificant as dermal application of PCPs is the primary source of consumer exposure (Health Canada, 2008) and the applied products contain large quantities of D4/D5 (Dudzina et al., 2014; Horii and Kannan, 2008; Lu et al., 2011; Wang et al., 2009).

Assuming dermal absorption fractions of 0.5% for D4 and 0.04% for D5, Dudzina and co-workers calculated theoretical maximum internal doses after dermal application of PCPs that amount to 0.054 and 0.49 mg/capita/day, respectively, in a European population (Dudzina et al., 2014). Furthermore, the internal doses of D4 and D5 were determined in blood and exhaled air after dermal application of ^{13}C-labeled D4 and D5 to the axilla of human volunteers (Plotzke et al., 2000b, 2002). The average D4 concentrations ranged from 0.57 to 5.67 ng/g in blood and corresponded to values in exhaled air of 111 ng/L (women) and 30 ng/L (men). The D5 levels ranged from 0.61 to 1.41 ng/g in blood and from 347 to 2315 ng/L in exhaled air. Plotzke and colleagues (Plotzke et al., 2000b, 2002) investigated the internal dose after a single application of D4 or D5, but in reality consumers tend to use several products simultaneously, leading to aggregate exposure.

The concentration of a component in end-exhaled air reflects the blood concentration, which is considered to be the most reliable estimate of the internal dose for many substances (Angerer et al., 2007). However, sampling of blood is invasive and should be limited to a minimal number of samples. In contrast, the collection of end-exhaled air samples, using canisters, bags or glass tubes, is non-invasive. Because of easy accessibility repeated end-exhaled air samples can be obtained in a short period of time without causing much of a burden to the study participant (Alonso and Sanchez, 2013). D4 and D5 are excellent candidates for detection in end-exhaled air, because of their high vapor pressure and low blood:air partition coefficients. Therefore, we aimed to quantify the dermal uptake of D4 and D5 after dermal application of two PCPs (i.e. night cream and deodorant) and to subsequently investigate the internal consumer exposure to both D4 and D5 using end-exhaled air as a biological medium for sample collection.

2. Materials and methods

2.1. Chemicals and test substances

Octamethylcyclotetrasiloxane (98% D4; CAS 556-67-2) and decamethylcyclopentasiloxane (97% D5; CAS 541-02-6) were obtained from Sigma-Aldrich (St. Louis, MO, United States). A commercially available night cream (50 mL) and deodorant (40 mL) were purchased from an online retailer. According to the manufacturer, the night cream contained approximately 25% of D5 and 0.3% of D4. The deodorant contained approximately 30% D5 and 0.3% D4. ^{13}C-labeled D4 and ^{13}C-labeled D5, used as internal standards, were purchased from Dow Corning (Midland, MI, United States). Methanol (99.9%; CAS 67-56-1) supplied by Boom (Meppel, The Netherlands) was used to dissolve ^{13}C-labeled D4 or D5 and unlabeled D4 or D5 for the preparation of standards.

2.2. Study design

Fig. 1 provides an overview of the study design. We recruited 15 volunteers using information folders, bulletin boards and word of mouth. We included volunteers above 18 and not older than 70 years of age, with good general health. Volunteers were excluded from the study when they were using prescribed medication, were suffering from a skin disease (e.g. psoriasis or eczema) or worked occupationally with PCPs. Several animal studies showed that exposure to D4 may lead to a disruption of the reproductive cycle of a female rat (Johnson et al., 2011). Therefore, D4 was classified as a reprotoxic substance (Scientific Committee on Consumer Safety (SCCS), 2010). We decided to exclude female volunteers who were pregnant or not taking birth control measures.

The volunteers participated in a series of experiments, during which the forearm was exposed to D4 or D5 as a pure substance or as ingredient of a PCP (i.e. night cream and deodorant) for one hour. When the substance was removed, the volunteer provided several end-exhaled air samples over a time period of five hours to monitor the internal D4 or D5 concentration. A more detailed description of the experiments is provided below.

2.2.1. Baseline

Before the start of the study, all volunteers (N = 15) completed a questionnaire and a 24 h diary, which were used to assess their PCP usage pattern prior to the baseline experiment. Subsequently, the volunteers visited our laboratory. During this first visit, we collected duplicate samples of end-exhaled air to study the baseline (normal) excretion of D4 and D5. At this point in the study, the volunteers were not restricted regarding their PCP use.

2.2.2. Control experiments

To study the contribution of a background exposure to D4 and D5, we performed control experiments for some volunteers (N = 6). The experiment was executed as if it was an exposure experiment, but we did not administer D4 or D5 to the forearm of the volunteer. Instead, D4 or D5 was applied to an artificial arm (graduated cylinder wrapped with filter paper), placed next to the arm of the volunteer to determine the presence of D4 and D5 in end-exhaled air, without a dermal source. The participants were asked to refrain from the use of PCPs 24 h prior to the start of the experiments. However, they were allowed to brush their teeth using toothpaste provided by us. According to the ingredients list, this toothpaste was free of D4 and D5.

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