Toxicology Letters xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Toxicology Letters

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

A global human health risk assessment for octamethylcyclotetrasiloxane (D_4)

Robinan Gentry[a], Allison Franzen[*,a], C. Van Landingham[a], Tracy Greene[a], Kathy Plotzke[b]

[a] Ramboll Environ US Corporation, 3107 Armand Street, Monroe, LA 71201, United States
[b] Dow Corning Corporation Health and Environmental Sciences, 22000 West Salzburg Road, Auburn, MI 48611, United States

ARTICLE INFO

Keywords:
Octamethylcyclotetrasiloxane
D_4
Human health risk assessment

ABSTRACT

Octamethylcyclotetrasiloxane (D_4) is a low-molecular-weight volatile cyclic siloxane, primarily used as an intermediate in the production of some widely-used industrial and consumer silicone based polymers and may be present as a component in a variety of consumer products. A global "harmonized" risk assessment was conducted to meet requirements for substance-specific risk assessments conducted by regulatory agencies such as USEPA's Integrated Risk Information System (IRIS), Health Canada's Chemical Management Program (CMP) and various independent scientific committees of the European Commission (e.g. the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER)), as well as to provide guidance for chemical safety assessments under REACH in Europe. This risk assessment incorporates global exposure information combined with a Monte Carlo analysis to determine the most significant routes of exposure. Utilization of a multi-species, multi-route physiologically based pharmacokinetic (PBPK) model was included to estimate internal dose metrics, benchmark modeling was used to determine a point of departure (POD), and a margin of safety (MOS) evaluation was used to compare the estimates of intake with the POD. Because of the specific pharmacokinetic behaviors of D_4 including high lipophilicity, high volatility with low blood-to-air partition coefficients and an extensive metabolic clearance that regulates tissue dose after exposure, the use of a PBPK model was essential to provide a comparison of a dose metric that reflects these processes. The characterization of the potential for adverse effects after exposure to D_4 using a MOS approach based on an internal dose metric removes the subjective application of varying uncertainty factors from various regulatory agencies and allows examination of the differences between internal dose metrics associated with exposure and those associated with adverse effects.

1. Introduction

Octamethylcyclotetrasiloxane (D_4) is a low-molecular-weight volatile cyclic siloxane, primarily used as an intermediate in the production of some widely-used industrial and consumer silicone based polymers and may be present as a component in a variety of consumer products. Although the direct use in personal care products is included here, the use of D_4 as a direct ingredient in personal care products has declined significantly over the past 20 years. It may remain as residual monomer in these polymers at less than 1000 ppm. Persons who may be exposed include occupational exposure for workers, consumers and the general public. The purpose of this investigation was to develop a globally representative human health risk assessment, or a "harmonized" risk assessment for D_4, that incorporates the requirements of risk assessments conducted by authoritative bodies worldwide including the US Environmental Protection Agency's (USEPA) Integrated Risk Information System (IRIS) Program and Health Canada Chemical Management Program (CMP) in North America; various independent scientific committees working on behalf of the European Commission (e.g. the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER), as well as guidance for chemical safety assessments under the REACH Regulation in Europe.

This human health risk assessment has been conducted to evaluate the potential hazard to workers, consumers, and the general public who may be exposed to D_4 either in the workplace, through the use of consumer products containing D_4, or to D_4 released in the environment. As an initial step, all information available and relevant to the project were reviewed, including effects on mammals, PBPK models, exposure data, and previous risk assessments conducted by the Scientific

* Corresponding author.
E-mail addresses: rgentry@ramboll.com (R. Gentry), afranzen@ramboll.com (A. Franzen), cvanlandingham@ramboll.com (C. Van Landingham), tgreen@ramboll.com (T. Greene), kathy.plotzke@dowcorning.com (K. Plotzke).

http://dx.doi.org/10.1016/j.toxlet.2017.05.019
Received 7 November 2016; Received in revised form 5 May 2017; Accepted 15 May 2017

Committee on Consumer Products (SCCP, 2005), Health Canada (2008), and Environmental Control Center Co. Ltd. (2011) of Japan and as part of a REACH (2011) dossier. In addition, a literature search was conducted to obtain any publicly available information on use (quantities and patterns of use, types of consumer products), prevalence and concentrations in various environmental media (e.g. water, soil, air fish, other foods), and consumer products (including OTC anti-gas medications, etc.)

This assessment considered risk assessment approaches used globally, including North America (Canadian Environmental Protection Act, 1999; IPCS, 2010; USEPA, 2005) and others (Brooke et al., 2009; Environmental Control Center Co. Ltd., 2011; Health Canada, 2008; REACH, 2011; SCCP, 2005), following the standard risk assessment paradigm: hazard assessment, dose-response assessment, exposure assessment and risk characterization. A unique component of this risk assessment involves the incorporation of a harmonized multi-route physiologically-based pharmacokinetic (PBPK) model for both the rat and the human. The dose-response and exposure assessments were conducted using both an external exposure concentration and an internal dose metric estimated using the PBPK model. D_4 has an unusual pharmacokinetic behavior that includes high lipophilicity and extended tissue half-lives in lipophilic tissues, high volatility with low blood-to-air partition coefficients that lead to exhalation of parent material following inhalation exposure, and extensive evaporation following dermal exposure. In addition, a rapid metabolic transformation of the substance must be considered. Because multiple pharmacokinetic processes regulate tissue dose following D_4 exposure, the use of a PBPK model in the risk assessment allows for the development of internal dose metrics for use in dose-response modeling and an exposure assessment that reflect these processes.

A risk characterization usually presents numerical estimates of risk or hazard that are derived by comparing the estimated intake with some measure of a toxicity value, i.e. the point of departure (POD) adjusted by uncertainty factors to reflect interspecies and intraspecies variability. However, when multiple populations are to be evaluated globally by multiple regulatory agencies, rather than decide appropriate uncertainty factors a priori, Margins of Safety (MOS) were determined comparing the estimated POD to the estimated intake. The MOS and POD were expressed as the internal dose-metric, which incorporates species differences in physiology and pharmacokinetics. The magnitude of the MOS can then be evaluated for the different exposure groups in the context of what would be deemed an acceptable margin by various global regulatory agencies.

2. Methods

2.1. Hazard identification

The available toxicological literature as cited in Dekant et al. (2017), Domoradzki et al. (2017), Franzen et al. (2017), Jean and Plotzke (2017), Jean et al. (2017) as well as the studies described in other hazard assessments conducted worldwide were considered (Environmental Control Center Co. Ltd., 2011; Health Canada, 2008; REACH, 2011; REACH Registration Dossier, 2011; SCCS, 2010). The conclusions reached by Franzen et al. (2017), which is a review of the available toxicological literature for D_4, were relied upon in drawing conclusions regarding the potential for hazard following exposure to D_4 and to determine which endpoints were the most sensitive or were observed following exposure to the lowest concentrations.

2.2. Dose-Response assessment

2.2.1. Selection of data for dose-response modeling

Dose-response assessments have been conducted for D_4 by Health Canada (2008), the European Commission Scientific Committee on Consumer Safety (European Commission, 2011) and as part of the EU REACH Chemical Safety Report (REACH 2011). While similar conclusions on the toxicity of D_4 were reached, different methodologies were used, as well as different Derived No Effect Levels (DNELs) and No Observed Adverse Effect Levels (NOAEL) requiring the application of adjustment factors to account for uncertainty in the estimated levels. In each case, however, the point of departure (POD) utilized in the dose-response assessments was the NOAEL. While the methodologies used globally are all similar in some aspects, differences do remain. In particular, there is a high degree of subjectivity and variability in the choice and application of uncertainty factors, not only in different countries but also in different regulatory agencies within a country. Therefore, for this assessment, rather than attempting to derive factors that may be used by the various regulatory agencies worldwide to adjust the POD for low-dose extrapolation, a comparison of the internal dose metric associated with the lower bound on the benchmark dose (BMDL) to the internal dose metric estimated for each relevant exposure scenario was conducted. The use of these ratios or MOS removes the need to consider various uncertainty factors that may be applied by various regulatory agencies.

2.2.2. Estimation of the human equivalent concentration

Prior to conducting dose-response modeling, the relevant dose metric in the human must be determined. When data from animal studies are extrapolated to humans to provide estimates of lifetime cancer risks or non-cancer hazard, potential differences in pharmacokinetics (metabolism) and pharmacodynamics (sensitivity) between the animal species and humans should be considered in the estimation of human equivalent concentrations. This can be done by applying adjustments to the external exposure concentrations, or when data are available, deriving an internal dose metric associated with the target tissue dose. Pharmacokinetic data for D_4 are sufficient for the development of a multi-route pharmacokinetic model (McMullin et al., 2016) that can be applied to estimate the human equivalent concentration rather than relying on an external dose for the BMD modeling.

2.2.3. Estimation of point of departure

In conducting the dose-response modeling, three dose-metrics were considered. The first was the external animal inhalation exposure concentration in ppm. The second was the external exposure concentrations adjusted to continuous inhalation exposure from 6 h per day for 7 days per week in the 2-generation study (Franzen et al., 2017). The third was the PBPK-derived internal dose metric (area under the curve (AUCs)) for each exposure concentration. The parent compound was assumed to be the relevant toxic moiety and the AUC of the free D_4 in the blood was considered to be the relevant dose-metric for use in benchmark dose (BMD) dose-response modeling. Although the use of an internal dose metric (Human Equivalent Concentration, HEC) to conduct the dose-response modeling is considered to be the more relevant dose metric for D_4, the dose-response modeling was also conducted using the external exposure concentrations for comparative purposes. Because of uncertainty around the estimate of the lower bound on the benchmark dose (BMDL) values for the maximum likely benchmark dose (BMD) can be derived along with the lower bound. However, the BMDL is used as the POD for extrapolation to lower doses because it accounts for uncertainty in the estimate of the dose-response that may be due to characteristics of experimental design (Setzer and Kimmel, 2003). If there were no survival differences in treated animals compared to concurrent controls, the dose-response modeling was conducted using USEPA's Benchmark Dose Software (BMDS) Version 2.3.1, an available free software program providing all of the standard models applied in BMD modeling. The model with the best fit was selected for the determination of the POD. The fit of a model to the data was determined using three different goodness-of-fit criteria: the Akaike Information Criteria (AIC), a p-value, and the scaled residual of interest (USEPA, 2015).

The AIC is a function of the maximum log-likelihood and the number of parameters in the model. It can be used to compare the fit

of different models for a single dataset and the smallest AIC indicates the "best" fit. The p-value is from a Chi-Square goodness-of-fit test and has values between 0 and 1. A minimum value of 0.1 is needed for an adequate fit of the model to the data and the larger the value (e.g. closer to 1), the better the fit. The scaled residual of interest is an indication of the fit of the model at the observed dose closest to the BMD and indicates how well the model fits the data at that point on the dose-response curve. A zero is the ideal scaled residual with a value of 2 or greater indicating an unacceptable fit, so a scaled residual with a smaller value indicates a better fit.

2.3. Exposure assessment

An exposure assessment was conducted to characterize the groups of persons who may be exposed to D_4, the pathways or routes by which that exposure could occur, and the frequency, duration and intensity (amount) of that exposure. Several populations that might be exposed to D_4 through various pathways included: occupational workers, who work in the production of D_4 or in the formulation of this material into personal care products as well as those that use these products in professional settings, such as beauticians and barbers, and office workers who might be exposed to D_4 in the air. Primary exposure to D_4 in the occupational setting was considered to occur through the inhalation route, with beauticians and barbers also being exposed through the dermal route.

Consumers were also considered and consisted of persons who use personal care products containing D_4, including antiperspirant/deodorants (AP/Ds) (aerosols, solids, and roll-ons) and hair care/skin care (HC/SC) products (i.e. shampoo, conditioners, hair spray/hand or body lotion, sunscreen, mascara, and lipstick). While potential exposure to consumer products occurs by all routes of exposure (dermal, oral or inhalation), the primary exposure based on the products containing D_4 would be through the dermal route. Dermal exposure occurs through the intentional, direct application of the product to the skin, with potential for inhalation exposure as the product residue on the skin volatilizes.

Potential exposure for the general public included exposure to ambient levels of D_4 released to the environment during manufacturing activities. Some of the potential exposure pathways considered were soil, water, and food (such as meat, fish, vegetables, milk, breast milk, etc.). These potential pathways of exposure were developed based on typical pathways of exposure to the general public as discussed in the Exposure Factors Handbook (USEPA, 2011). In conducting an exposure assessment, standard equations can be used to estimate exposure from possible exposure routes for each population that could be exposed to D_4. These equations are route-specific and include exposure-scenario specific parameters. The values for these parameters differed for each of the populations considered and for each exposure media considered. Many of the D4 concentrations used in this assessment were obtained from publications that are 10–20 years old (e.g., Boehmer and Gerhards, 2003; Hall et al., 2007; Maxim, 1998). Values obtained from these publications may be considered conservative due to the decreasing concentrations of D4 in personal care products over the past 20 years.

2.3.1. Monte Carlo analysis

Because of the large number of potential exposure pathways for the consumer and the general public, a Monte Carlo probabilistic analysis was conducted to prioritize those scenarios that would potentially result in the greatest exposure. Those scenarios with the largest potential exposure estimate were included in the PBPK analysis. The various exposure scenarios evaluated in the Monte Carlo analysis included dermal uptake from contact with the skin, inhalation from ambient air, or oral consumption of environmental media, personal care, hair care/skin care products, or consumer/food products and identify those pathways providing the greatest contribution of potential exposure. Inhalation was the only exposure scenario of relevance for the workers involved in the manufacture of D_4, production of silicone polymers or formulation of D_4 containing industrial products. For barbers and beauticians, the exposure routes considered were inhalation and dermal contact. Therefore, Monte Carlo analysis was not conducted for the barber and beautician receptors; the exposure for occupational receptors was evaluated directly by the PBPK analysis.

The Monte Carlo analysis produced a distribution of estimates of the intake of D_4 in mg/kg of body weight (bw)/day for each consumer product and from general sources (air, water, food and soil) using distributions for the parameters in order to identify those exposure scenarios for the Consumer and General Public exposure pathways that provided the greatest potential for exposure to D_4. Only those exposure pathways associated with specific product usage that had the largest mean and upper bound estimates for intake based on the results of the Monte Carlo analysis, were then used for the PBPK analysis to obtain an estimate of the internal dose for comparison to the internal dose associated with the POD.

The Monte-Carlo-based probabilistic assessment for D_4 included the following age-dependent and exposure-route-dependent consumer or general population scenarios with each product type evaluated independently:

Children

- **Dermal route**: body lotion, conditioner (leave-in), conditioner (rinse-off), diaper cream, shampoo, soothing vapor, spray detangler, and sunscreen.
- **Ingestion route**: residual antifoam in some processed foods, baby bottle nipples and pacifiers, and drinking straws manufactured from silicone polymers, fish (general population), fish (subsistence population), breast milk, leafy vegetables (greens), meat, cow's milk, root vegetables, sipper tube, soil, (potable) water, and over-the-counter (OTC) anti-gas medication.
- **Inhalation route**: indoor air, outdoor air, and soothing vapor.

Adults

- **Dermal route**: after shave, body lotion, conditioner (leave-in), conditioner (rinse-off), foundation, hair spray, mascara, moisturizer, nail care, shampoo, antiperspirant (gel/solid, roll-on and spray), soothing vapor, sunscreen, and under-eye cream.
- **Ingestion route:** residual antifoam in some processed foods, fish (general population), fish (subsistence population), leafy vegetables (greens), lipstick, meat, cow's milk, root vegetables, soil, and drinking (potable) water, as well as OTC anti-gas medication.
- **Inhalation route**: indoor air, outdoor air, and soothing vapor.

Separate route-specific estimates were made for males or females for the following subpopulation: children 0–6 months, 6 months – 4 years, 4–11 years, teens from 12 to 19 years, and adults 20–59 years and 60+ years. In addition, combined males and females for the ages of 0–6 months, 7–11 months and 1–2 years was stratified by breastfed versus non-breastfed. A non-gender-specific population, children ages 2–4 years was also considered.

Input parameter distribution values used for each of the variables presented below in the dermal, inhalation and oral equations are summarized in Supplementary Tables S-1 through S-5 and are based on a conservative choice from all of the relevant data available. For each product evaluated, the intake from each pathway was estimated with the results provided in units of mg D_4/kg bw/day. The mean reported intake for each pathway within each gender age group was then compared to evaluate which of the exposure pathways resulted in the higher estimates of intake and which pathways would be considered to have a negligible contribution to overall intake.

A second Monte Carlo analysis was subsequently performed to estimate the total daily oral intake of D_4 (mg/kg/day) for use in

estimating internal dose-metrics using the PBPK model. For this analysis, the estimated intakes for each oral exposure scenario (water, food, residual antifoam in food, soil and lipstick) were summed. Bioavailability factors were not considered for this analysis in the estimates of intake, as the PBPK model accounts for the bioavailability by the oral route. Because the PBPK model is only an adult model, oral consumption for children was not considered in the PBPK modeling analysis.

2.3.1.1. Dermal. For dermal exposures, the following general equation was used, with specific parameters used for each exposure scenario documented in the Supplemental material.

$$Intake\,(mg/kg/day) = \frac{AppR \times Freq \times Conc \times Abs \times KF \times Conv}{BW} \quad (1)$$

where:

AppR = application rate of the product (grams per application)
Freq = frequency of application (applications per day)
Conc = concentration of D_4 in the product as a percentage (%)
Abs = absorption fraction (fraction)
KF = kinetic factor (fraction)
Conv = conversion factor from g to mg (1000 mg per g)
BW = body weight (kg)

Application rates of D_4 from the use of consumer products are typically provided as either grams/application (AppR) or grams per day (GD). If the application rate (AppR) was provided in units of grams/day, the equation was modified because the usage for a product, the frequency (Freq), is assumed to be once per day, effectively replacing the AppR × Freq variables with GD.

Estimating exposure to D_4 from the use of hair care products required modification to Eq. (1) to include parameters to characterize the application of the product (e.g., shampoo, conditioner, etc.), as well as the potential removal of product due to rinsing.

$$Intake\,(mg/kg/day) = \frac{AppR \times Freq \times Conv \times Conc \times Abs \times KF \times Res \times Dep}{BW} \quad (2)$$

where:

AppR = application rate of the product (grams per application)
Freq = frequency of application (applications per day)
Conv = conversion factor from g to mg (1000 mg per g)
Conc = concentration of D_4 in the product (%)
Abs = absorption fraction (fraction)
KF = kinetic factor (fraction)
Res = product (residue) left on hands and scalp after rinsing (fraction)
Dep = amount deposited on hands and scalp versus the hair (fraction)
BW = body weight (kg)

To develop a global distribution of body weight, multiple sources were considered. For Europe, mean values were obtained from the ECETOC Exposure Factors Sourcebook (ECETOC, 2001) while the standard deviations were taken from Eurostat (2002) (Supplementary Table S-6). For the United States, mean body weights for men, women and children from the National Health and Nutrition Examination Study (NHANES) for the years 2007/2008 and 2009/2010 were used. These estimates, including the minimum and maximum body weights are presented in Supplementary Table S-7. The results from the NHANES 2007 to 2010 were considered as most suitable for use in this assessment because they represent the most current values available. The distributions of adult body weight values provided in the NHANES data are consistent with default body weight values used globally for risk assessment (Environmental Control Center Co. Ltd., 2011; Health Canada, 2008; SCCS, 2012; USEPA, 2011). Additionally, the distribution of body weights assumed in the Monte Carlo analysis from the NHANES data encompasses the body weights available for other populations, such as Scotland, France, Germany, Spain, Great Britain, and Denmark (Hall et al., 2007, 2011).

One of the key parameters for estimating potential dermal exposure is the skin surface area to which a product is applied. Information on the receptor skin surface area for occupational workers was obtained from the Exposure Factors Handbook (USEPA, 2011) and is summarized in Supplementary Table S-8. Since the majority of application rates were defined for the US population, use of the USEPA surface areas should provide the correct proportioning of product to surface area. For the skin care (SC) products, the deposition fraction (Dep) or the fraction of product that is potentially available for absorption was assumed to be 1 (100%). However, for some of the hair care (HC) products, especially the leave-on HC products, only a small fraction of the product is deposited on the scalp and available to be absorbed into systemic circulation. For these types of HC products, a deposition fraction of 0.05 (5%) was used. This value of deposition (DEP) was estimated based on the ratio of the surface area of the scalp (SA_{scalp}) to that of the hair on the head (SA_{hair}) (< 0.05) using an approach reported by Van Landingham et al. (2004).

$$DEP = \frac{SA_{scalp} + 0.5xSA_{hands}xCF_{cm}}{SA_{scalp} + 0.5xSA_{hands}xCF_{cm} + SA_{hair}} \quad (3)$$

Based on the average length of one hair of 10 cm for men and 15 cm for women (ICRP, 1992), an average diameter of each hair of (Kalopissis, 1986), and an average of 115,000 hairs on the scalp (Kalopissis, 1986), the surface area of hair (SA_{hair}) over which a HC product could be distributed was approximately 22000 cm^2 for men and 33000 cm^2 for women. The average surface area of the hands (SA_{hands}) for males and females was 1070 cm^2 and 890 cm^2, respectively (USEPA, 2011). CF_m is the conversion factor from m^2 to cm^2 (10,000). For the remaining HC and other personal care products, a deposition fraction of 1 (100%) was assumed.

Residue fractions were used in the Monte Carlo analysis to account for the amount of a product that could be retained on the skin after product washing. These residue fractions do not take into consideration the volatility of D_4. Residue fractions were assumed to be 1 (100%) for all HC/SC products, with the exception of any rinse-off products such as shampoo and rinse-off conditioner. Shampoos and rinse-off conditioners were assumed to leave only a fraction of the product as residue on the skin. Maxim (1998) reported that the product remaining after the application of a rinse-off product was typically small, ranging from 0.5% to 1.5% based on interviews with personnel from the HC industry. A residue fraction of 0.01 (1%) was used for shampoos and rinse-off conditioners. This residue fraction is consistent with the fractions proposed by the American Cleaning Institute (SDA, 2005) for screening dermal exposure to consumer products in Europe and residue studies conducted in similar consumer products (USEPA 1997; USFDA 1978, 1982).

A dermal absorption value of 0.005 (0.5%) was used as the dermal absorption factor, as described in Jovanovic et al. (2008). The 0.5% was determined by the average amount of neat D_4 absorbed after 24 h of exposure to cadaver skin *in vitro*. A study performed by Reddy et al. (2007) to determine the absorption fraction of neat D_4 indicated that 83% of the dermally applied D_4 that reaches the systemic circulation was eliminated by exhalation within 24 h. The 17% (0.17) that reached the systemic circulation and was not exhaled was considered representative of the kinetic factor. Both the kinetic fraction and the absorption fraction were used in the evaluation of dermal exposure to consumer products.

The application frequencies for consumer products containing D_4 used in the Monte Carlo analysis are presented in Supplementary Tables S-1 through S-4 and include information from multiple sources (Hall et al., 2007, 2011; Health Canada 2008; Horii and Kannan 2008; Loretz et al., 2005, 2006, 2008; Maxim 1998; McNamara et al., 2007). The application rate used for the consumer products was the number of

grams of product applied each time (grams/application) or over the entire day (grams/day). In this case, the maximum amount of the product applied during the day was indicated and, therefore, the application frequency was assumed to be once per day, although some of these products could be applied multiple times per day. For most of the products the use of grams per day was sufficient since the products would only be expected to be used once per day. However, there were exceptions such as lipstick (2.4 times during the day (Loretz et al., 2005)) and there were products for which an application rate in grams per day was not available. In these instances the grams per application and application frequencies were obtained from Maxim (1998).

A uniform distribution over the ranges of percent of D_4 in various consumer products (Supplementary Table S-9) was used as the amount of D_4 in consumer products for the Monte Carlo analysis. The data provided from Johnson et al. (2011) was typically used as these were the most recent published data and in general the ranges encompassed the reported concentrations of D_4 from other sources (Boehmer and Gerhards, 2003; COLIPA report pre-2000; Horii and Kannan 2008; Maxim 1998; Wang et al., 2009).

2.3.1.2. Inhalation. For the majority of the exposure scenarios that present the potential for exposure to D_4 via inhalation, the following general equation was used:

$$Intake\,(mg/kg/day) = \frac{Conc \times Conv \times BR \times KF}{BW} \quad (4)$$

where:

Conc = concentration of D_4 in the air (μg/m^3)
Conv = conversion factor from μg to mg (1/1000)
BR = breathing rate (m^3/day)
KF = kinetic factor (fraction)
BW = body weight (kg)

For the evaluation of inhalation due to volatilization of D_4 following the application of soothing vapor, the following equation was used:

$$Intake\,(mg/kg/day) = \frac{AppR \times Freq \times Conv \times Conc \times FV \times BR \times KF}{BW \times Room} \quad (5)$$

where:

AppR = application rate of soothing vapor (grams per application)
Freq = frequency of soothing vapor use (applications per day)
Conv = conversion factor from g to mg (1000 mg per g)
Conc = concentration of D_4 in soothing vapor (%)
FV = fraction of product volatizing (fraction)
BR = breathing rate (m^3/day)
Room = area of the room in cubic meters (m^3)
KF = kinetic factor (fraction)
BW = body weight (kg)

Body weight distributions were assumed to be the same for all exposure routes and a detailed description of body weight data relied upon has been provided previously in Section 2.3.1.1. Inhalation rates used in the Monte Carlo analysis were obtained from USEPA (2011) and are provided in Supplementary Table S-10.

Indoor air and outdoor air concentrations used for the Monte Carlo analysis were derived from measured concentrations of D_4 (Beohmer et al., 2001; Kaj et al., 2005; Maxim 1998; Norden 2005; NYIEQ 2005; Shields et al., 1996; Yucuis et al., 2013). For both the indoor and outdoor air concentrations used in the Monte Carlo analysis, the distribution of values was determined using a triangular distribution. A triangular distribution was used as it is a conservative approximation for a lognormal distribution since the parameters of a triangular distribution can be determined even when individual sample data are not available. The minimum and the maximum concentrations were taken from across all the reported studies. The triangular distribution used for indoor and outdoor air concentrations in the Monte Carlo analysis had a most likely value of 10 μg/m^3 (0.000766 ppm) and 0.2 μg/m^3 (0.0000153 ppm), respectively. A minimum concentration of 0.005 and a maximum of 173 μg/m^3 was reported for outdoor air concentrations and a minimum of 0.1 and a maximum of 51.2 μg/m^3 was reported for indoor air concentrations.

2.3.1.3. Ingestion. Intake of D_4 in the general population and consumers resulting from ingestion included multiple scenarios (e.g. ingestion of water, soil, fish, and other food, OTC anti-gas medication, etc.) and was evaluated using the following equations:

Water:

$$Intake\,(mg/kg/day) = \frac{Amt \times Conc \times Conv \times Bio}{BW} \quad (6)$$

where:

Amt = amount consumed per day (L/day)
Conc = concentration of D_4 in water (mg/L)
Bio = bioavailability fraction (unitless)
BW = body weight (kg)

Soil:

$$Intake\,(mg/kg/day) = \frac{Amt \times Conc \times Conv \times Bio}{BW} \quad (7)$$

where:

Amt = amount consumed per day (mg/day)
Conc = concentration of D_4 in soil (μg/kg)
Conv = conversion factor from μg to mg in conc (1 mg/1000 μg and mg to kg in amt (1 kg/1000 mg or a total conversion factor of (1/1000000)
Bio = bioavailability fraction (unitless)
BW = body weight (kg)

Diet:

$$Intake\,(mg/kg/day) = Amt \times Conc \times Conv \times Bio \quad (8)$$

where:

Amt = amount consumed (g/kg BW/day)
Conc = concentration of D_4 in the food (mg/kg)
Conv = conversion factor (1/1000 kg per gram)
Bio = bioavailability fraction (unitless)

Fish consumption by a subsistence fisherman:

$$Intake\,(mg/kg/day) = \frac{Amt \times Conc \times Conv \times Bio}{BW} \quad (9)$$

where:

Amt = amount consumed per day (g/day)
Conc = concentration of D_4 in the fish (mg/kg)
Conv = conversion factor (1/1000 kg per gram)
Bio = bioavailability fraction (unitless)
BW = body weight (kg)

Over the counter medications:

$$Intake\,(mg/kg/day) = \frac{Amt \times Freq \times Conc \times Conv \times Bio}{BW} \quad (10)$$

where:

Amt = amount consumed per use (g/use)
Freq = frequency of use (use/day)
Conc = concentration of D_4 in the product (μg/g)
Conv = conversion factor (1/1000 mg per μg)
Bio = bioavailability fraction (unitless)
BW = body weight (kg)

Intakes due to the ingestion of residual antifoam present in processed food and the incidental ingestion of lipstick were calculated using two alternate ingestion equations as presented below:

Food containing Antifoam:

$$Intake\,(mg/kg/day) = Amt \times AF \times Conc \times Frac \times Conv \times Bio \quad (11)$$

where:

Amt = amount of food consumed (g/kg BW/day)

AF = Fraction of food that contains antifoam (assuming 50%)
Conc = concentration of antifoam in food (mg/kg)
Frac = fraction of D_4 in the antifoam
Conv = conversion factor from g to kg (1/1000 g per kg)
Bio = bioavailability fraction (unitless)
Use of Lipstick:

$$Intake\,(mg/kg/day) = \frac{Amt \times Conc \times Freq \times Bio}{BW} \quad (12)$$

where:
Amt = amount of lipstick (g/application)
Conc = concentration of D_4 in the product (mg/g)
Freq = frequency of usage (applications/day)
Bio = bioavailability fraction (unitless)
BW = body weight (kg)
Use of baby bottle nipples, pacifiers, and sipper tubes manufactured from silicone polymers:

$$Intake\,(mg/kg/day) = \frac{Wgt \times Conc \times MF \times Conv \times Bio}{BW} \quad (13)$$

where:
Wgt = weight of product (grams)
Conc = concentration of D_4 in the product (mg/g)
MF = the fraction of D_4 in the product that can migrate per day (%)
Bio = bioavailability fraction (unitless)
BW = body weight (kg)
The migration fraction (MF) is an estimate of the amount of D_4 that can migrate out of the nipple, pacifiers, and sipper tubes into formula, milk, saliva, or other media with which they are in contact. The migration amount used here is assumed to be a per day amount but there is little evidence that this amount could be repeatedly extracted from the product or that a new product would be used each day, so this is a very conservative estimate of the daily exposure.

A migration fraction of 0.0045 per day was used for the amount of D_4 that could migrate from baby bottle nipples, pacifiers, sipper tubes and drinking straws manufactured from silicone polymers, based on results from an experiment on the migration of siloxanes from silicone rubber products into milk, formula and liquid dietary simulants (Zhang et al., 2012). This study had two purposes: 1) to determine the concentrations of siloxanes in silicone products manufactured from silicone polymers, including silicone nipples and silicone cookware and 2) to determine the potential migration of siloxanes from products manufactured from silicone polymers, to milk, formula, and liquid simulants. Concentrations of D_4 determined in silicone nipples ranged from 0.6 to 49 μg/g of product with a median value of 2.4 μg/g. Due to the irregular shape of silicone nipples, the authors noted difficulty in conducting migration tests with nipples; and silicone plaques from bakeware were determined to be good surrogates for silicone nipples. Therefore, the migration tests were performed using silicone-coated cake pans as surrogates for silicone nipples, with an average D_4 concentration of 23 mg/kg, After 24 h, only trace amounts of D_4 were detected that had migrated from the silicone cake pans into the milk or formula, indicating insignificant migration of the siloxanes to milk or infant formula. Based on the conditions described in this study, an estimate of the fraction of migration of D_4 is 0.0045. This was considered a conservative assumption, as it assumes that the amount of D_4 that could migrate out of the product per day (baby bottle nipple, pacifier, etc.) can continue for an unlimited duration. However, the amount available for migration from the product would be limited, with the fraction anticipated to decrease per day with continued use.

Body weight distributions were assumed to be the same for all exposure routes and detailed description of body weight data relied upon has been provided previously in section 2.3.1.1 Inhalation rates used in the Monte Carlo Analysis were obtained from USEPA (2011) and are provided in Supplementary Table S-10.

The bioavailability fraction for D_4 in the diet, water, or consumer products was determined from a study that was conducted to evaluate the absorption of D_4 by various carriers (i.e. corn oil, a simethicone fluid, and neat ^{14}C D_4) (Dow Corning Corporation 1998; Franzen et al., 2017). Doses of each carrier were administered to female Fischer 344 rats. The mass balance data obtained showed that 51.95% (SD 4.97%), 12.11% (SD 1.21%), and 28.14% (SD 5.78%) of the administered ^{14}C D_4 was absorbed when delivered in the corn oil, simethicone fluid, and neat ^{14}C D_4, respectively. For the Monte Carlo analysis, the absorption reported for corn oil was assumed for all food products. A normal distribution with a mean of 51.95% and a standard deviation of 4.97 was used for these analyses. For OTC anti-gas medications and residual antifoam in processed food, the absorption reported for D_4 in simethicone fluid was used as a normal distribution with a mean of 12.11% and a standard deviation of 1.21%.

The general public exposure population includes persons who may be exposed to ambient levels of D_4 released to the environment during manufacturing activities and to levels of D_4 potentially in food, soil, water, meat, fish, vegetables, milk and breast milk. The various consumption rates of environmental media for the general public receptor along with the measured or predicted concentrations in that media included consumption rates of water, soil, fish, milk, meat and vegetables provided by USEPA (2011), Health Canada (2008), USDA (1998) and Environmental Control Center Co. Ltd. (2011). Median concentrations of D_4 in various foods and water ranged from 5.6×10^{-7} to 40 mg D_4/kg of food based upon either measured data or predicted values, provided in Brooke et al. (2009), Norden (2005), NILU (2007), or Environmental Control Center Co. Ltd. (2011). As noted, the data relied upon reflect a mixture of measured and predicted values. Those data that are based on predicted effect concentrations (PEC) are based on food chain modeling that relies upon a worse-case assessment of soil and water (Brooke et al., 2009), so therefore represents the potential upper-bounds of exposure. The actual measured concentrations, such as those measured in fish (Norden, 2005), were below the limit of for many samples. Therefore, the combination of measured and predicted values provides a potential range of exposures that might not be captured in the measured values.

Concentrations of D_4 in food from residual antifoam from processed food use were based on the percentage of D_4 in a representative antifoam product (4.9%) reported by Dow Corning Corporation (1999). The amount of residual antifoam in food ranges from 0 and 10 ppm. This amount is consistent with the USFDA code of regulations (USFDA, 2012) and the EU (European Commission, 2011) database on the allowable levels of Food Additives (European Commission, 2011). It was assumed that 50% of the food consumed would contain residual antifoam, which is a very conservative estimate as antifoam is only used to process some food and is not used to process milk and milk products. A triangular distribution with a most likely value of 5 ppm and a maximum value of 10 ppm was used in the Monte Carlo analysis to determine the intake of residual antifoam.

2.3.2. Application of PBPK model

For the final step in the exposure assessment, the published PBPK model (McMullin et al., 2016) was applied. The model was executed with human parameter values for both physiological parameters (such as ventilation rate or cardiac output) and for D_4-specific parameters to develop estimated internal dose-metrics that were unique to the receptor, route of exposure, and exposure pattern.

Using the basic equations provided previously for various exposure scenarios including inhalation and dermal exposure (i.e. worker, consumer, general public), intake estimates to use with the PBPK model were calculated after excluding any parameters related to absorption or bioavailability from the equations, as the PBPK model already includes data related to these parameters. These intake estimates were used as inputs to the PBPK model to estimate the AUC, the internal dose metric in arterial blood that was receptor- and exposure scenario-specific. The values for the parameters used within

the PBPK model were the most-likely values from those parameters with a triangular distribution, the mid-point for those with a uniform distribution, or the mean value for those parameters with a lognormal or normal distribution as described in the Monte Carlo analysis.

For the analysis of oral intake for the PBPK model, the output from the second Monte Carlo analysis was used to estimate the amount of intake of D_4 from the combined oral sources of food, water, soil, residual antifoam and lipstick. The individual consumption of D_4 ingested from root crops, greens, meat, milk, water, residual antifoam, soil, and fish were summed for males and females with the addition of D_4 in lipstick for females. For the subsistence fisherman, the distribution of amount of fish consumed was obtained from USEPA (2006). One hundred thousand iterations were run in the Monte Carlo analysis, which provided distributions of daily intakes. The mean and 90th percentiles of the distributions for teens and adults both for the general public and for subsistence fishermen were used for input in the PBPK model as estimates of the daily intake of D_4 from the oral route.

2.3.2.1. Occupational. A Monte Carlo analysis of potential exposure to D_4 for an occupational worker was not conducted and exposure to D_4 through the oral (ingestion) scenario was not assumed to occur in the workplace. Exposure to occupational workers was limited to the dermal and inhalation routes of exposure, therefore, a Monte Carlo analysis was not needed to assist in prioritizing those exposures that would present the greatest potential for intake. The equations described in the Monte Carlo analysis for estimating inhalation and dermal intake were used for PBPK modeling of occupational exposure, excluding parameters related to absorption or bioavailability as the model already includes data to adjust for these parameters.

Barbers and beauticians were considered to have the potential for dermal exposure through the application of HC products containing D_4. To determine the product that would provide the highest amount of exposure to D_4 to which these workers could be exposed, data on application rates, the fraction of product deposited on skin, the fraction of residue left by rinse-off products on skin, and the amount of D_4 in hair care products were considered.

To determine a conservative (maximal) estimate of exposure, it was assumed that all exposure during a given work day for barbers/beauticians would be to a single product that would provide the largest potential exposure to D_4. This would likely overestimate exposure, as barbers/beauticians would likely be exposed to multiple products during the day, many of which would have less or no concentration of D_4. The data for cuticle coat products were determined to provide the greatest exposure to D_4 for barber/beauticians from typical use because it had the highest percentage of D_4 reported for the various HC products. In addition, considering the assumed application rate (4.7 g), the median percentage of D_4 in the product (6%), the deposition (5%) and residue fractions (100%), the use of these products resulted in the greatest possible exposure (Table 1). This would be considered a conservative representative exposure for HC products, since the amount of exposure to D_4 from any of the remaining HC products considered is less than or equal to the exposure calculated for cuticle coat (14.1 mg of D_4 exposure per application). This was determined by multiplying the grams of application by the percentage of D_4 in the product and the deposition and residue fractions. Other input parameters necessary for running the PBPK model to estimate internal dose metrics associated with exposure to these products are detailed in Table 2.

D_4 air concentrations were measured in the workplace for 1) workers involved in the formulation of AP/Ds; 2) workers involved in the manufacture of HC/SC products; 3) workers in a D_4 production facility; and 4) barbers and beauticians. Maxim (1998) reported average concentrations of D_4 as follows: 2310 μg/m^3 (0.1908 ppm) for workers involved in the production of D_4, 4000 μg/m^3 (0.33 ppm) for AP/D workers, 29,600 μg/m^3 (2.44 ppm) for SC workers, and 150 μg/m^3 (0.012 ppm) for HC workers (Table 3). A representative air concentration of 0.085 ppm (0.001 μg/m^3) was estimated for beauticians and barbers (Maxim, 1998) (Table 3).

Several reported indoor air concentrations of D_4 were considered to represent the range of potential inhalation exposures for office workers. The value of 5 μg/m^3 (0.000383 ppm) (Shields et al., 1996) was used in this assessment to represent the mean exposure to an office worker and was calculated by estimating the weighted average of the geometric means reported and the number of each type of office, with the weight being the number of samples of each type being reported in the office. The value of 10.2 μg/m^3 (0.000781 ppm) (Shields et al., 1996) was the highest mean concentration reported for any office type and was used to represent the upper bound exposure to an office worker. Inhalation rates of 1.6 and 1.4 m^3/h were used for males and females, respectively, based on moderate activity during the work day (USEPA, 2011).

For all occupational exposures, tenure was used to define the number of years over which exposure might occur. According to Carey (1988), as cited in the USEPA Exposure Factors Handbook (USEPA, 2011), occupational tenure was defined as the "cumulative number of years a person works in his or her current occupation, regardless of the number of employers, interruptions in employment, or time spent in other occupations." The weighted average of the median tenure, in years for full-time workers between the ages of 16 and 59, was 10.2 years for men and 6.4 years for women (USEPA, 2011). Considering a lifetime to be 75 years for men and 80 years for women (USEPA, 2011), the occupational exposures were adjusted by 10.2/75

Table 1
Hair care products used by barbers/beauticians containing D_4.

Hair Care Products	Application. Rate (g/use)	Midpoint D_4 (%)	Amount of Exposure to D_4 (g/use)
Shampoo	6[e]	0.002 [f]	0.00012
Rinse-out conditioner	13.77[b]	1.0 [f]	0.1377
Leave-in conditioner	13.77[b]	1.0 [f]	0.1377
Hair spray	5.8[d]	0.001[c]	0.000058
Coloring Sprays	5.8[d]	3	0.174
Cuticle coat	4.7[a]	6[a]	0.282
Brilliantine	4.7[a]	2.8[a]	0.1316
Pomade	4.7[a]	1.9[a]	0.0893
Spray Shine	5.6[a]	5[a]	0.28

[a]Maxim (1998).
[b]Mean value from Loretz et al. (2008).
[c]Wang et al. (2009).
[d]Mean value from Loretz et al. (2006).
[e]Mean value from Hall et al. (2007).
[f]Midpoint from range in Johnson et al. (2011).

Table 2
Summary of dermal exposure parameters – barbers and beauticians.

Parameter	Barbers and Beauticians		Sources
	Men	Women	
Amount Hair Product applied (g)	4.6	4.6	Loretz et al., 2008; Maxim, 1998
Amount of D_4 (%)	6	6	Median value for Cuticle Coat Maxim (1998)
Deposition Fraction	0.05	0.05	Van Landingham et al., 2004
Residue Fraction	1	1	Van Landingham et al., 2004
Exposure frequency (applications per day)	12 or 15	12 or 15	Professional judgment
Days per week	5 or 4	5 or 4	
Weeks per year	50	50	
Surface Area a (cm2)	1070	890	USEPA, 2011
Body Weight (kg)	86.9	73.4	CDC (2007–2010)

[a]Surface area of the hand.

Table 3
Summary of inhalation exposure parameters – workers.

Worker	Parameter					
	Air Concentration[a] (ppm/μg/m^3)	Daily Exposure[e] (hours/day)	Exposure Frequency[e] (days/week)	Work Year[e] (weeks/year)	Inhalation Rate[f] (m^3/h)	Body Weight[g] (kg)
Antiperspirant	0.33/4000 (0.15)	8	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Skin Care	2.44/29,600 (1.76)	8	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Hair Care	0.012/150 (0.007)	8	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Silicone	0.1908/2310 (0.0950)[b]	8.75c	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Barbers and Beauticians	0.085[a]/1000	5.6 or 7d	4 or 5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Office workers	0.000383/5 0.000781/10.2	8	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)

[a]Values are reported as arithmetic mean (geometric mean). The arithmetic mean was used in the assessment. Results from Maxim (1998) unless otherwise specified.
[b]Arithmetic and geometric mean concentrations from all types of silicone workers.
[c]Based upon results for silicone workers as reported in (Maxim, 1998).
[d]Based upon The U.S. Department of Labor Bureau of Labor Statistics (2012).
[e]Defaults based upon professional judgment.
[f]Inhalation rates as reported in USEPA (2011).
[g]Body weights based upon NHANES (CDC 2007–2010) data.

years for men and 6.4/80 years for women for all occupational exposures.

For most workers (e.g. workers in antiperspirant, skin care and hair care plants), a standard 8-h work day was assumed. However, due to the manner in which shifts are reported to be scheduled for silicone workers (Maxim, 1998), an 8.75-h day was used for workers involved in the production of consumer products containing D_4. This is consistent with data from the US Bureau of Labor Statistics (2013) which reports that in the chemical manufacturing sector, production and nonsupervisory employees averaged a 43 h week. For beauticians and barbers, the work week was assumed to be 28 h/week (US Bureau of Labor Statistics, 2012) which results in a 5.6 h work day for a 5 day work week and 7 h work day for a 4 day work week. Workers were assumed to be present on the job 50 weeks out of the year.

2.3.2.2. Consumers. The PBPK analysis for personal care products was limited to the products identified as contributing the most to potential consumer exposure based on the Monte Carlo analysis results. Products with estimated exposure levels from the Monte Carlo analysis that were estimated to have an exposure of at least 1% of the body lotion exposure for adults (the product representing the greatest exposure) were selected for evaluation and included moisturizer, solid deodorant, roll-on deodorant, sun screen, nail care, foundation, after shave, hair spray for dermal exposure and soothing vapor for inhalation exposure. Specific parameters and the results of the PBPK modeling are reported in the supplemental material (Tables S-11 through S-13b). This approach identified the largest potential contributors to exposure and with application of the PBPK model provides the estimated internal dose metrics associated with exposure to these products, which could then be used to determine MOS.

The key considerations in estimating internal dose metrics associated with dermal exposure from the use of consumer products was the amount of D_4 in the product, the amount applied, the surface area over which the product was applied, and the frequency of the application (Tables 4 and 5). The surface area to which a consumer product is applied differs based upon the product and the receptor to which the product is being applied. For many of the products that contain D_4, the surface area is estimated based upon a percentage of the body part to

Table 4
Application parameter values for consumer user.

Product	Application rate (gms/day)	Application Frequency (application/day)[h]	Midpoint D_4 (%)[b]
Antiperspirant/ Deodorant gel or roll-on	1.22 (male)[c] 0.898 (female)[c]	1.3	9.5
Antiperspirant/ Deodorant stick or solid	0.79 (male) [f] 0.61 (female)[f]	1.3	9.5
Antiperspirant/ Deodorant aerosol	3.478 [c]	1	9.5
Shampoo	6[c]	1	0.002
Conditioner (Leave-in)	13.77[e]	1	1.0
Conditioner (Rinse-out)	13.77[e]	1	1.0
Hair care-hair spray			
Aerosol	3.57[f]	1	41.2[i]
Pump	5.18[f]	1	41.2[i]
Cosmetic foundation	0.33[g]	1	19
Cosmetic night cream/ under eye cream	0.06[a]	1	9.5
Cosmetic mascara	0.11[a]	2	6.5
Cosmetic lipstick	0.025[c]	3	14
Skin care-after-shave gel	0.95[a]	1	11.5
Skin care-lotion (hand/body)	8.69[c]	1	5.52
Skin care-Moisturizer	0.91[c]	1	2.0
Skin care-nail care	0.25[a]	1	10
Skin care-sunscreen	6.1[a]	1	0.31
Soothing Vapor	5[d]	2	0.45

[a]Maxim (1998).
[b]Midpoints calculated from Johnson et al. (2011).
[c]Hall et al. (2007).
dMeeks (2005).
[e]Loretz et al. (2008).
[f]Loretz et al. (2006).
[g]Hall et al. (2011).
[h]Personal judgment.
[i]Wang et al. (2009).

Table 5
Surface area for dermal evaluation of consumer exposure to antiperspirant/deodorant, hair care, and skin care products.

Product Type	Surface Area (cm^2)		Area Description	Basis
	Male	Female		
Antiperspirant/Deodorant – gel/roll-on, stick/solid, and aerosol	271	129	Both axillae	Cowan-Ellsberry et al., 2008
Hair care – hair spray (aerosol and pump)	680	570	½ head (hair sprays)	SCCS, 2012; USEPA, 2011
	1215	1015	½ area head + ½ hands (conditioners)	
	1750	1460	½ area head + total area of hands (shampoo)	
Cosmetics – foundation Skin Care – moisturizer	NA	570	½ head	SCCS, 2012; USEPA, 2011
Cosmetics – night cream/under-eye cream	NA	24	Assume is same as area for eye shadow	SCCS, 2012
Cosmetics – Mascara	NA	1.6		SCCS, 2012
Skin Care – after shave gel	340	NA	¼ head	USEPA, 2011
	535		½ hands	
Skin Care – lotion (hand/body), sunscreen	20,670	17,000	Body − head	USEPA, 2011
Skin Care – nail care	NA	11	Estimate of skin around nail	SCCS, 2003
Soothing Vapor	4175	3270	½ of Trunk	USEPA, 2011

which the product is applied. The surface area of the axillary vault to which the AP/D is applied was identified in Cowan-Ellsberry et al. (2008) to have median values of 64.5 cm^2 and 135.5 cm^2 for a single axilla for females and males, respectively. These values were doubled for use as the surface area to which the AP/D was applied to account for application to both underarms.

Exposures to products containing D_4 were assumed to occur once per day for specified number of days per week for both men and women (Table 4). The exceptions were for exposures from the use of moisturizer and sunscreen. Moisturizer exposure was simulated to occur twice per day (once every twelve hours) while sunscreen exposures were assumed to occur for eleven consecutive days once per year (Maxim, 1998).

For the consumer inhalation analysis, no specific information on resulting air concentrations in areas following use of consumer products was available for all of the products containing D_4. Therefore, the PBPK modeling was conducted using air concentration data that were available for selected consumer products. For deodorants, the breathing zone concentrations of D_4 were estimated to be 290 μg/m^3 (0.024 ppm), 22,080 μg/m^3 (1.82 ppm), and 11,400 μg/m^3 (0.94 ppm) for solid, roll-on and aerosol AP/Ds, respectively. These values were obtained from a study conducted by Dow Corning (Anderson and Weaver, 1989) in which three different commercial D_4-containing AP/Ds (solid, roll-on and aerosol) were applied by two male participants in a 30 m^3 room using a typical application amount and a relatively heavy application and air concentrations for cyclomethicone were measured (Table 6). Concentrations of D_4 were estimated based on the average concentration of cyclomethicone measured following a high application and lower application amount for each type of deodorant multiplied by the percent D_4 measured in the headspace above each type of deodorant. The average concentrations were determined over a 6 min period and were assumed to be representative of the average exposure time spent in the bathroom following application.

There were no consumer use data for the amount of time that elapses between the application of an AP/D, HC, or SC product and subsequent dressing, e.g. putting on a shirt or top, during which time a consumer would be exposed to D_4 vapor. It is during this time that D_4 air concentrations would be expected to be highest, particularly if bathing, application, and dressing occurred in a closed bathroom. For this assessment, the time spent in the bathroom following a bath or shower was used as an estimate of the length of time that a consumer would be exposed to D_4 in the air. The median percentile from the time spent in the bathroom after a bath or shower reported by USEPA (2011) was used for AP/D, HC and SC products: 5 min/day (0.58 h/week) for men and 10 min/day (1.17 h/week) for women.

A time-weighted average D_4 concentration of 4100 μg/m^3 (0.338 ppm) was determined for the use of general HC products. This value was based on an experiment in which personal monitoring samples were taken while six volunteers were using shampoos, conditioners, and hair sprays containing D_4 (Maxim, 1998). Following application of the HC products, users remained in the room where the products were applied for 17 to 40 min. Although the USEPA (2011) values for time spent in the bathroom following a bath or shower were used for the PBPK modeling, the air concentration relied upon for each HC product was measured during the use of multiple products (shampoo, conditioners and hair sprays) and is likely an overestimate. Therefore, no adjustment was made for the time differences between the time-weighted average air concentrations reported following use of HC products (Maxim, 1998). Since no studies were identified related to SC products, the 4100 μg/m^3 (0.338 ppm) was also assumed as representative of these products and was assumed applicable to both men and women.

The frequency of use for AP/D was assumed to be 1.3 applications per day or 9.1 times a week based on information reported by Loretz et al. (2006). This study was conducted in 360 women, ages 19–65, from ten different geographical locations in the US who were asked to keep a diary of use of a solid antiperspirant for two weeks (Loretz et al., 2006). The results from this study are consistent with other recent exposure assessments (SCCS 2012). No information was available in the study for aerosols and roll-on antiperspirants, therefore the application frequency for these products was assumed to be similar to that for solid antiperspirants. Additionally, this value was assumed to be

Table 6
Summary of Inhalation Exposure Parameters for Consumer Product Exposure.

Parameter	Men	Women	Source
Air Concentration (AC)			
AP/D Solid	0.024 ppm (290 μg/m^3)	0.024 ppm (290 μg/m^3)	Anderson and Weaver (1989)
AP/D Roll-on	1.82 ppm (22,000 μg/m^3)	1.82 ppm (22,000 μg/m^3)	
AP/D Aerosol	0.94 ppm (11,400 μg/m^3)	0.94 ppm (0.0114 μg/m^3)	
HC/SC Products	0.338 ppm (4000 μg/m^3)	0.338 ppm (4000 μg/m^3)	
Exposure Duration (ED)	5 min/day	10 min/day	USEPA (2011a,b)
Inhalation Rate (INH)	0.8 m^3/hour	0.7 m^3/hour	USEPA (2011)
Body Weight (BW)	86.9 kg	73.4 kg	CDC (2007–2010)

[a]Median time spent in bathroom following a shower or bath.
[b]Due to the limitations of the PBPK model, the inhalation times were run for 7 days per week for an exposure duration equal to ED * AF/7 min per day.

relevant for a man's application frequency of antiperspirant in the absence of other data.

Soothing vapor was identified as a consumer product of interest based upon the potential volatilization of D_4 into air following dermal application. The air concentration resulting from volatilization of D_4 from soothing vapor was estimated by multiplying the percent of D_4 in soothing vapor (0.05%) by the grams applied (5 g/application) times the number of applications per day, which was assumed for this assessment to be 2 applications/day. This result was then divided by an estimated room volume of 10 m^3 (assumed to be the average size of a small room, 6 ft. by 6 ft. by 10 ft.) resulting in a D_4 air concentration of 5 $\mu g/m^3$ (or 0.00798 ppm). This was assumed to be a consistent dose in the room in which the person applying the soothing vapor stayed. This was a conservative assumption, as a smaller room size would result in the most conservative estimates of exposure.

The PBPK simulations for the inhalation exposure of consumers used the same alveolar ventilation rates and cardiac outputs as the dermal simulations (Supplementary Table 1). As with the dermal simulations, the AUC was determined following one year of exposure.

2.3.2.3. General public. The results of the Monte Carlo analysis identified those pathways with the greatest potential intake and target tissue concentrations and therefore, those pathways with the greatest potential contribution to hazard or risk. The results indicated that ingestion of fish, root crops or ingestion of food containing residual antifoam, and indoor air exposure resulted in the greatest intake (Supplementary Table 2).

The PBPK simulations for the oral exposure to the general public and subsistence fisherman required a modification to the published version of the oral PBPK model (McMullin et al., 2016). The existing version of the model only allows for a single bolus dose or intake per day. As the oral intake of D_4 from either food or lipstick products is anticipated to be episodic (Loretz et al., 2005), the PBPK model was modified to allow for episodic rather than bolus or continuous intake. The estimated mean and the 90th percentile of total daily oral intake of D_4 for adults were estimated using a Monte Carlo analysis. This intake was a combination resulting from the consumption all potential sources of D_4, which included root crops, greens, meat, milk, water, residual antifoam, soil, lipstick and fish determined by the Monte Carlo analysis. The intake was divided into fifths, allowing for episodic equal intakes of one-fifth of the total daily consumption of D_4, spaced out over the day at 8 AM, 10 AM, 12 AM, 4 PM and 7 PM.

A value of 10 $\mu g/m^3$ (0.000766 ppm) D_4 in indoor air was identified from the New York Indoor Environmental Quality Center study (NYIEQ, 2005) and was assumed to be representative of the indoor air concentration to which an individual in the general public would be exposed. A value of 0.2 $\mu g/m^3$ (0.0000153 ppm) was identified as representative of the typical exposure to D_4 in outdoor air, and was used to estimate D_4 exposure for the general public. This value was estimated using the average of the median or midpoint of the reported outdoor air concentration ranges from all the available published studies (Boehmer et al., 2001; Kaj et al., 2005; Norden 2005; Shields et al., 1996). Although an individual in the general public would be assumed to be exposed to concentrations of D_4 in indoor air and outdoor air for a specific number of hours per day, the conduct of this type of simulation (contribution of inhaled D_4 from multiple sources) was not possible with the current PBPK model. Therefore, for this evaluation, estimates of exposure for the general public were estimated under the assumption that the person would be indoors 24 h per day or outdoors 24 h per day. This provided bounds for potential exposure, considering that a person could be both indoors and outdoors over the course of a day and assuming that exposure would be expected to be within those bounds. Other required input parameter values are identified in Table 7. The PBPK simulations were run to simulate 1 year of exposure and were assumed to be representative of any given year. The alveolar ventilation rates and cardiac outputs that were used for these simulations were the same as those used for the consumer simulations (Table 6).

Table 7
Summary of Inhalation Exposure Parameters for General Public.

Parameter	Value	Source
Air Concentration		Boehmer et al., 2001; Kaj et al., 2005; Norden 2005; Shields et al., 1996; Yucuis et al., 2013
Indoor	10 $\mu g/m^3$ (0.000766 ppm)	
Outdoor	0.2 $\mu g/m^3$ (0.0000153 ppm)	
Exposure Duration[a]		
Indoor	24 h/day	Professional Judgment
Outdoor	24 h/day	
Frequency	7 days/week	Professional Judgment
Year	52 weeks/year	Professional Judgment
Inhalation Rates		
Male	0.8 m^3/hour	USEPA (2011)
Female	0.7 m^3/hour	
Body Weights		
Male	86.9 kg	CDC (2007–2010)
Female	73.4 kg	

[a]Since the PBPK model is set up for accounting for varying inhalation exposure during the day, 24 h exposure to either indoor and outdoor air was assumed.

2.4. Risk characterization

A comparison of the internal dose metric associated with the $BMDL_{10}$ to the internal dose metric estimated for each exposure scenario was conducted. The use of these ratios or MOS removes the need to consider various uncertainty factors that may be applied across regulatory agencies.

Acceptable MOS vary by different exposure scenarios. For example, for occupational exposures under OSHA guidelines, a risk of 1×10^{-4} or less is considered acceptable using a linear approach. Since the POD is the internal dose associated with a 0.1 risk, an acceptable MOS for an occupational scenario under a linear approach would be approximately a factor of 1000. In comparison, the highest uncertainty factor applied in the REACH Chemical Safety Report (REACH 2011) in the derivation of occupational DNELs for D_4 was 6. This reflects differences between ECHA and other agencies, such as OSHA, in the application of default uncertainty factors. For the USEPA, uncertainty factors of up to 10 are applied to the POD to account for intra-human variability, interspecies extrapolation, use of precursor data, and/or remaining sources of uncertainty in the database of studies on D_4. If the uterine adenomas in the rat were considered relevant to humans, it is likely that a factor of approximately 1000 could be derived. This would include a factor of 10 for intra-human variability, 1 for extrapolation from animal-to-human allowing for uncertainties in pharmacodynamics across species (it is expected that women would be less sensitive than the rodent to modifications in hormone balance), 10 for the use of tumor rather than precursor data, and 3 for remaining sources of uncertainty related to the database. This last factor may be applied due to lack of a chronic inhalation toxicity/carcinogenicity study in multiple species. Therefore, it is anticipated that any MOS greater than 1000 should indicate no significant risk of adverse effects due to the exposure scenarios being considered.

3. Results

3.1. Hazard identification

The available toxicological literature as described in Franzen et al. (2017), as well as the studies described in other hazard assessments conducted worldwide were considered (Environmental Control Center Co. Ltd., 2011; Health Canada 2008; REACH, 2011; REACH Registration Dossier, 2011; SCCS, 2010). In these assessments, the lung

and liver have been identified as potential target organs following repeated inhalation exposure, the uterus as the potential target organ following repeated oral or inhalation exposure, and effects on fertility as a critical endpoint in a two-generation inhalation exposure reproductive study. No significant toxicological effects were observed after single or repeated oral exposure to D_4 at concentrations as high as 2400 mg/kg bw or 960 mg/kg bw, respectively.

The liver effects reported after subchronic and chronic inhalation exposure have been attributed to a "phenobarbital-like" induction of rat hepatic cytochrome P450 enzymes (Varaprath et al., 1999; Zhang et al., 2000; McKim et al., 2001). The changes noted in the liver following exposure to D_4 were reversible and not associated with overt hepatotoxicity, and the mild enzyme induction observed was considered an adaptive response. The changes noted in the lung after subchronic inhalation exposure to D_4 were considered to be an adaptive response to a mild, non-specific irritant and are supported by no significant adverse change in the respiratory tract reported after a 2-year chronic inhalation study with D_4 (Jean and Plotzke, 2017).

Reproductive effects have been observed in female rats in one-generation studies (Franzen et al., 2017; Meeks et al., 2007) following inhalation exposure to D_4 at concentrations of 500 ppm and greater. These effects included decreases in the number of corpora lutea, number of uterine implantation sites, total number of pups born and the mean live litter size. Similar effects were noted in exposed female rats in a two-generation study (Franzen et al., 2017; Siddiqui et al., 2007), in addition to increased estrous cycle length, increased pituitary gland weights, and histopathological changes in the ovaries and mammary glands in the F1 generation. Based on these results of a 2-generation study (Franzen et al., 2017; Siddiqui et al., 2007), a reproductive no observed adverse effect concentration (NOAEC) of 300 ppm was identified.

Additional studies conducted to assess the potential endocrine activity of D_4 suggest that although D_4 has been found to have very weak estrogenic and antiestrogenic activity, the reproductive effect was not related to estrogenic activity. The proposed mechanism for the observed reproductive toxicity of D_4 in rats is the induction of a delay or blockage of the LH surge necessary for optimal timing of ovulation. This mechanism is supported by mechanistic studies (Quinn et al., 2007) and is discussed in more detail in Dekant et al. (2017) and Franzen et al. (2017) as it related to the observation of uterine adenomas in the rat. An insufficient or blocked pre-ovulatory LH surge fails to induce complete ovulation in the rat and results in the fertility effects observed. However, the current understanding of estrous cyclicity and neural/hormonal regulation of ovulation in humans suggests that the effects of D_4 on fertility as observed in the rat are unlikely to be relevant to humans (Plant, 2012).

The remaining treatment-related endpoint identified following inhalation exposure to D_4 was the statistically significant increase in the incidence of uterine endometrial cystic hyperplasia and the increase in trend in the incidence profile across dose groups for uterine adeonmas in female rats exposed to 700 ppm in a chronic study (Jean and Plotzke, 2017). Based on the increase in uterine weight, increased incidence of endometrial cystic hyperplasia and increased trend in endometrial adenoma and a low historical incidence of uterine adenomas in F344 rats, the uterus was identified as a target organ. Uterine adenomas occur in aging rats by a mode of action not relevant to humans (Dekant et al., 2017). Studies with D_4 suggest that there may be a rat-specific mechanism involved in the formation of these benign adenomas, but it is unlikely to be a direct acting dopamine agonist effect. It should also be noted that the incidence of endometrial cystic hyperplasia was observed only in the highest concentration tested and only a significant positive trend was noted for the incidence of endometrial adenomas, but the incidence of adenomas was not significantly increased relative to the incidence in concurrent control, so it cannot be fully excluded that this observation is an artefact and not related to D_4.

Although the mode of action for the induction of uterine adenomas in the female F344 rat has not been well-defined, the available data support the conclusion that the observed endometrial adenomas are not relevant to human health, as discussed further in Dekant et al. (2017). D_4 has not been shown to be mutagenic or genotoxic in *in vitro* and *in vivo* experimental models, indicating the observed tumors occur by a non-genotoxic mechanism. In addition, no tumors were observed in male F344 rats and no tumors were observed in organs other than the uterus of female F344 rats following chronic D_4 exposure.

3.2. Dose-response assessment

3.2.1. Selection of data for dose-response modeling

Previous assessments have focused on the reproductive effects observed following inhalation exposure to D_4, (Health Canada, 2008; REACH 2011; SCCP, 2005); however in a recent assessment by SCCS (2010), a NOAEL of 150 ppm for D_4 determined for the uterine endometrial adenomas and hyperplasia in female rats exposed to 700 ppm D_4 for two years (Jean et al., 2017). The incidence of uterine adenomas was not increased compared to concurrent controls and are a common tumor in aging female Fischer 344 rats. No other toxicologically significant neoplastic or non-neoplastic findings were reported in this chronic inhalation toxicity study.

Reproductive effects have been observed in one-generation inhalation studies with female rats (Franzen et al., 2017; Meeks et al., 2007) at D_4 concentrations of 500 ppm and greater. These effects included decreases in the number of corpora lutea, number of uterine implantation sites, total number of pups born and the mean live litter size. Similar effects were noted in exposed female rats in a two-generation study (Franzen et al., 2017; Siddiqui et al., 2007), in addition to increased estrous cycle length, increased pituitary gland weights, and histopathological changes in the ovaries and mammary glands in the F1 generation. Based on these results, identified from the one-generation reproductive studies and a two-generation reproductive study, a NOAEC of 300 ppm was identified from the two-generation reproductive study.

Based on the results of mode of action studies, the most relevant explanation for the reproductive toxicity of D_4 is the induction of a delay or blockage of the LH surge necessary for optimal timing of ovulation. An insufficient or blocked pre-ovulatory LH surge fails to induce ovulation in the rat and results in the fertility effects. However, the current understanding of estrus cyclicity and neural/hormonal regulation of ovulation in humans suggests that the effects of D_4 on fertility as seen in the rat are not relevant to humans (Plant, 2012).

The development of a POD for this assessment is focused on the results from the two-generation study, which provided the lowest NOAEC (300 ppm). The results from the carcinogenicity study suggest a lower NOAEC (150 ppm) due to the spacing of dosing compared to the reproductive studies; however, the incidence of uterine benign tumors is not statistically significant, although greater than historical controls. Since D_4 is negative in assays for mutagenicity and genotoxicity, it can affect cancer-related endpoints only via non-genotoxic modes of action. Therefore, a non-genotoxic mode of action should be considered. Carcinogens acting by a linear mode of action are generally considered to be agents that are DNA reactive and have direct mutagenic activity (Bolt and Degen, 2004), which D_4 does not. Second, the incidence of uterine adenomas (0/59 in the control and 0/59, 0/59, 0/60 and 4/60 in the 10, 30, 150 or 700 ppm treatment groups) does not increase with increasing exposure concentration, suggesting a threshold for response between 150 and 700 ppm for a lifetime exposure.

While the mode of action for the observed uterine adenomas in F344 rats is not known, it has been suggested that the occurrence of these adenomas is not relevant for human risk assessment (Dekant et al., 2017). The proposed mode of action is likely related to effects on cyclicity in the rat that are subtle in nature and may prevent further assessment. In addition, there is no endometrial lesion in women that is

directly analogous to endometrial adenoma in the rat. Therefore, because of the potential lack of relevance to human health of the uterine adenomas reported in F344 rats and the reliance upon reproductive endpoints to classify D_4 in Europe as a category 2 reproductive toxicant under REACH, the POD for the development of MOS will be based on the reproductive effects observed in rats. A discussion of the comparison of a POD based on the incidence of uterine adenomas is also provided in the discussion section.

In general, a POD is either the externally derived NOAEL/C or the BMD with uncertainty or safety factors applied to the POD to develop permissible exposure levels, or levels at which no relevant human risk are anticipated. In prior risk assessments conducted for D_4, NOAELs were used as the PODs (Health Canada, 2008; REACH 2011; SCCS, 2010). Limitations to the NOAEL approach have been summarized in the 1995 USEPA Benchmark Dose Approach guidance (USEPA, 1995) and include: 1) Whether or not a given experimental dose actually constitutes a NOAEL is subject to scientific judgment and is often a source of controversy; 2) Larger NOAELs can result from experiments involving fewer animals, that is, a poorly designed study may be "rewarded"; 3) The shape and slope of the dose-response is not considered in the determination of the NOAEL; 4) The NOAEL (if one exists) must be one of the experimental doses; and 5) Use of a NOAEL does not provide estimates of potential risk at any exposure level. As an alternative, the BMD approach (i.e. the maximum likelihood estimate of the dose associated with a specified increase in risk or change in response) has been proposed for determining a POD for development of a toxicity value that can be used in setting exposure limits and has several advantages over the NOAEL approach. These advantages include: 1) The BMD approach, unlike the NOAEL, takes into account the dose-response information (i.e., the shape of the dose-response curve); 2) The BMD approach does not involve sometimes argumentative "all or nothing" decisions, such as determining whether or not a NOAEL was defined at a particular dose; 3) The BMDL, a lower confidence limit, appropriately reflects the sample size of a study (smaller studies tend to result in wider confidence limits and lower PODs, whereas the opposite is true for NOAELs); and 4) A POD from the BMD approach can be determined even when a NOAEL has not been identified in a study. Therefore, taking into account the limitations of the NOAEL/LOAEL approach for determining the POD, the BMD approach was chosen as the method for derivation of a POD for D_4 in this assessment.

3.2.2. Estimation of the human equivalent concentration

A multi-route PBPK model (McMullin et al., 2016) was used to estimate a human equivalent concentration associated with each of the animal exposure concentrations for use in dose-response modeling. Because the mode of action is not known, the parent compound was assumed to be the relevant toxic moiety. Volatile cyclic siloxanes, including D_4, have unusual pharmacokinetic behaviors that include high lipophilicity with a fat:blood partition coefficients in excess of 500, high volatility with low blood to air partition coefficients that lead to exhalation of parent material following inhalation exposure and extensive evaporation following dermal exposure. Following exposure of rats to D_4, hepatic responses were reported to be more closely related to time course concentrations of free parent compound in the target tissue rather than total liver D_4. Based on these observations, the AUC of the free parent compound, D_4, in the blood was considered to be the relevant dose-metric for use in dose-response (BMD) modeling and for the relevant exposure scenarios. The AUC provides a more consistent and stable internal dose metric than the peak concentration when exposure is chronic. In addition, the change in AUC corresponds to the change in reproductive endpoints reported in the two-generation study (Table 8). While alternative dose-metrics could be considered, such as peak concentration (Cmax), use of Cmax as the dose metric is very sensitive to changes in exposure, requiring more specific information regarding exposure patterns, which are usually lacking in the D_4 animal studies and for exposure in the human. In addition, the use of the AUC, in general, results in more conservative estimates of acceptable intake and therefore will be used for this assessment.

Because these multiple pharmacokinetic processes regulate tissue concentration following D_4 exposure, the use of a PBPK model to estimate internal dose metrics for use in dose-response modeling is more appropriate than using an external concentration. Simulations were run with the rodent PBPK model using the female rat parameters to simulate exposure for 6 h per day, 7 days per week, for 70 days to 70, 300, 500 or 700 ppm D_4 to derive the AUCs of the free D_4 in the blood in the rat for each experimental concentration. These internal dose metrics are shown in Table 8. Consistent with the application of other PBPK models (Clewell and Andersen 1985; Clewell and Clewell 2008; Clewell et al., 2001a, 2001b; Gentry et al., 2011; Reddy et al., 2008), it was assumed that the resulting AUC in the rat is the HEC. The human PBPK model was then used to estimate the AUCs for each of the exposure scenarios considered for comparison to the estimated POD, which is the result of the dose-response modeling.

3.2.3. Estimation of point of departure

The BMDs and BMDLs derived using the BMDS software are presented in Table 9 which also includes the goodness-of-fit criteria. The endpoint chosen as the most sensitive was the live litter size in the F1 generation of the two generation study. The model chosen as the "best fit" for the endpoint was the Linear continuous model (Table 9) with a constant variance over the dose groups. This model has the form:

$$\mu(d) = \beta_0 + \beta_1 \times d \quad (14)$$

where:

μ(d) = mean response at dose d

β0 and β1 = fitted dose coefficients of the model.

The BMR for this continuous model was chosen to be 1.1 standard deviations with the BMD being the dose at which the mean response was expected to be 1.1 standard deviations less than the response seen in the control group. The selected results of the dose-response modeling are provided in Table 9. Using the continuous animal exposure doses in the evaluation of the reproductive data, the estimate of the exposure in ppm at which a BMR of a change in the mean response equal to 1.1 times the standard deviation results in a BMDL or POD of approximately 125 ppm. Using the internal dose-metrics (AUC of free D_4 in the blood), the BMDL is approximately 30 mg-hrs/L/day.

3.3. Exposure assessment

3.3.1. Monte Carlo analysis

The results of the Monte Carlo analysis were used to prioritize the potential pathways for adults in which internal dose metrics would be estimated for the development of MOS. The results from the Monte Carlo analysis identified which consumer products would result in the highest potential for D_4 exposure (e.g. food, personal care products, etc.). It was determined from the Monte Carlo analysis that in all cases, specific personal care product use (body lotion, hair spray, foundation, after shave and APs) by adults provided the highest contribution to potential D_4 exposure. For example estimates of intake for the remaining consumer products (for adults (male and female) were 33% or less than the estimated intake of D_4 from use of body lotion in adult females. These results demonstrate that it is not likely that consumer products beyond these products would represent a significant contribution to the potential exposure to D_4.

Results of common exposure scenarios from the Monte Carlo analysis resulted in similar estimates of intake for children as the adults. The intake of D_4 from body lotion in 4 to 11 year olds was the largest intake estimated from the Monte Carlo analysis but it was within a factor of 1.5 of the mean estimate of intake for adult females in the 20–59 year old group for exposure from body lotion. Other estimated intakes ranged from < 0.1% to 27% of the 95th percentile estimated

Table 8
Dose-Response Model Predicted BMDLs from Reproductive Endpoints.

Endpoints considered from 2-Gen Study (Siddiqui et al., 2007) Mean ± Std (N)				Exposure Dose (ppm)	Adjusted Exposure Doses (ppm) Adjusted to continuous from 6 h per day	Human Equivalent Concentration (HEC)
F_1 Generation		F_2 Generation				AUC (mg-hrs/L/day)
Pups Born	Live Litter Size*	Pups Born	Live Litter Size			
13.7 ± 3.1 (27)	13.3 ± 3.3 (27)	13.4 ± 3.2 (29)	13.1 ± 3.4 (29)	0	0	0
13.5 ± 3.8 (24)	13.4 ± 3.8 (24)	12.5 ± 3.9 (26)	12.0 ± 3.9 (26)	70	17.5	4
12.2 ± 3.3 (27)	11.9 ± 3.1 (27)	12.5 ± 3.6 (25)	12.0 ± 3.7 (25)	300	75	17.6
10.8 ± 3.7 (23)**	10.4 ± 3.8 (23)**	11.2 ± 3.3 (26)	10.5 ± 3.4 (26)**	500	125	29.8
10.0 ± 3.9 (23)***	9.7 ± 3.8 (23)**	9.0 ± 3.9 (17)***	8.6 ± 3.7 (17)***	700	175	42.1
BMDL* (1.1std)				497.36	124.34	29.91

*BMDLs reported are for the live litter size in the F_1 generation – which was determined to be the most sensitive endpoint in the reproductive endpoints modelled.
**$p \leq 0.05$.
***$p \leq 0.01$.

Table 9
Results of BMDS Modeling of data in Table 8 for the Significant Reproductive Endpoints from a 2-Generation study in Fischer 344 Rats.

Endpoint	Model Name	p-value Test 1	p-value Test 2	p-value Test 3	p-value for fit	AIC	Scaled residual of Interest	BMD[a] (ppm)	BMDL (ppm)	BMD[b] (ppm)	BMDL (ppm)	BMD[c] (mg-hrs/L/day)	BMDL (mg-hrs/L/day)
Number pups born in F_1 generation	Exp. 2	0.0060	0.7599	0.7599	0.9847	439.35	0.0428	696.36	476.20	174.09	119.05	41.82	28.60
	Exp. 3	0.0060	0.7599	0.7599	0.944	441.32	0.1383	695.32	478.04	173.83	119.51	41.79	28.67
	Exp. 4	0.0060	0.7599	0.7599	0.9847	439.35	0.0428	696.36	438.19	174.09	109.55	41.82	26.02
	Exp. 5	0.0060	0.7599	0.7599	0.9274	443.21	0.0093	767.60	445.15	191.90	111.29	46.20	26.38
	Hill	0.0060	0.7599	0.7599	0.8975	443.22	0.0197	754.79	341.01	188.70	85.25	45.43	20.01
	Linear	0.0060	0.7599	0.7599	0.9847	439.35	0.1590	691.05	503.05	172.76	125.76	41.56	30.25
	Polynomial	0.0060	0.7599	0.7599	0.9847	439.35	0.1590	691.05	503.05	172.76	125.76	41.56	30.25
	Power	0.0060	0.7599	0.7599	0.9847	439.35	0.1590	691.41	503.08	172.85	125.77	41.56	30.25
Live Litter Size in F_1 generation	Exp. 2	0.0060	0.7724	0.7724	0.9259	439.63	0.0874	684.65	469.13	171.16	117.28	41.10	28.16
	Exp. 3	0.0060	0.7724	0.7724	0.8283	441.54	0.2284	683.81	472.88	170.95	118.22	41.08	28.32
	Exp. 4	0.0060	0.7724	0.7724	0.9259	439.63	0.0874	684.65	434.97	171.16	108.74	41.10	25.81
	Exp. 5	0.0060	0.7724	0.7724	0.8591	443.20	0.0000	NA	NA	NA	NA	NA	NA
	Hill	0.0060	0.7724	0.7724	0.8915	443.18	−0.0105	807.11	334.51	201.78	83.63	48.71	19.62
	Linear	0.0060	0.7724	0.7724	0.9271	439.63	0.2120	680.68	497.36	170.17	124.34	40.93	29.91
	Polynomial	0.0060	0.7724	0.7724	0.9271	439.63	0.2120	680.68	497.36	170.17	124.34	40.93	29.91
	Power	0.0060	0.7724	0.7724	0.7954	441.62	0.2390	682.07	497.74	170.52	124.44	40.98	29.91
Number pups born in F_2 generation (first mating)	Exp. 2	0.0045	0.8134	0.8134	0.3946	439.08	−1.0370	793.80	523.26	198.45	130.82	47.47	31.32
	Exp. 3	0.0045	0.8134	0.8134	0.6407	438.99	−0.0152	689.78	575.77	172.45	143.94	41.47	34.43
	Exp. 4	0.0045	0.8134	0.8134	0.3946	439.08	−1.0370	793.80	523.26	198.45	130.82	47.47	31.32
	Exp. 5	0.0045	0.8134	0.8134	0.3454	440.99	−0.0152	689.78	518.68	172.45	129.67	41.47	34.43
	Hill	0.0045	0.8134	0.8134	0.3482	440.98	−0.0092	689.07	575.23	172.27	143.81	41.43	34.39
	Linear	0.0045	0.8134	0.8134	0.4687	438.64	−0.8670	747.30	527.54	186.83	131.89	44.73	31.61
	Polynomial	0.0045	0.8134	0.8134	0.6914	438.84	−0.0139	683.53	570.91	170.88	142.73	41.08	34.17
	Power	0.0045	0.8134	0.8134	0.6441	438.98	−0.0091	689.03	575.15	172.26	143.79	41.42	34.38
Live Litter Size in F_2 generation (first mating)	Exp. 2	0.0110	0.9477	0.9477	0.4771	442.40	−0.8078	758.04	503.03	189.51	125.76	45.37	30.13
	Exp. 3	0.0110	0.9477	0.9477	0.5304	443.18	−0.0048	689.30	550.73	172.33	137.68	41.44	32.85
	Exp. 4	0.0110	0.9477	0.9477	0.4771	442.40	−0.8078	758.04	503.03	189.51	125.76	45.37	30.13
	Exp. 5	0.0110	0.9477	0.9477	0.2601	445.18	−0.0048	689.30	550.73	172.33	137.68	41.44	32.85
	Hill	0.0110	0.9477	0.9477	0.2629	445.16	−0.0045	687.93	543.17	171.98	135.79	41.35	32.38
	Linear	0.0110	0.9477	0.9477	0.553	442.00	−0.6320	720.46	513.66	180.12	128.42	43.17	30.80
	Polynomial	0.0110	0.9477	0.9477	0.5903	442.96	0.0180	679.22	546.55	169.81	136.64	40.82	32.67
	Power	0.0110	0.9477	0.9477	0.5345	443.16	−0.0046	687.83	542.69	171.96	135.67	41.35	32.37

p-value Test 1: Lack dose response? P-values below 0.05 indicate that there is a sufficient dose-response for modeling
p-value Test 2: Constant variance? P-values above 0.05 indicate that the variance is homogeneous across dose groups.
p-value Test 3: Good variance model? P-values above 0.05 indicate that the variance model is adequate for the data.
p-value for fit: Does the model for the mean fit? P-values above 0.1 indicate an adequate fit of the model to the data.
Exp, Exponential.
[a]The dose-response models were fit to the data using the animal exposure doses unadjusted.
[b]The dose-response models were fit to the data using the animal exposure doses adjusted from 6 h/day to continuous (i.e. multiplying by 6/24 and 5/7).
[c]The dose-response models were fit to the data using the internal dose-metrics for average daily area under the curve (AUC) of the concentration of free D_4 in arterial blood.

for 20–59 year old females for exposure from the use of body lotion. The current PBPK model (McMullin et al., 2016) is not designed to estimate internal dose metrics for children. Therefore, child scenarios were qualitatively related to the PBPK results from adult scenarios evaluated in the PBPK analysis. The Supplementary Tables S-11 through 13b provide results from the Monte Carlo analysis.

3.3.2. Application of PBPK model

3.3.2.1. Occupational. Exposure to workers was limited to the dermal and inhalation scenarios. Barbers and Beauticians were the only workers considered to have the potential for dermal exposure through the application of HC products containing D_4. The largest AUCs estimated for dermal exposure to D_4 for barbers and beauticians were

Table 10
Area under the curve: Occupational Exposure.

Workers	AUC (mg-hrs/L/day)	
	Men	Women
Dermal Exposure		
Barbers and Beauticians		
5 day work week	8.98×10^{-4}	2.16×10^{-3}
4 day work week	1.14×10^{-3}	2.73×10^{-3}
Inhalation Exposure		
Antiperspirant	1.95×10^{-2}	1.07×10^{-2}
Skin Care	1.44×10^{-1}	7.88×10^{-2}
Hair Care	7.09×10^{-4}	3.88×10^{-4}
Silicone	1.23×10^{-2}	6.74×10^{-3}
Barbers and Beauticians		
5 day work week	3.63×10^{-3}	2.03×10^{-3}
4 day work week	3.60×10^{-3}	2.01×10^{-3}
Office Worker:		
5 μg/m^3 (0.000383 ppm)	2.26×10^{-5}	1.24×10^{-5}
10.2 μg/m^3 (0.000781 ppm)	4.61×10^{-4}	2.50×10^{-5}

2.73×10^{-3} mg-hrs/L/day for a female barber or beautician and 1.14×10^{-3} mg-hrs/L/day for a male barber or beautician (Table 10). The consideration of the worker having a 4-day workweek and performing 15 applications per day compared to a 5-day workweek with 12 applications per day did not greatly affect the calculated AUC as seen from the results presented in Table 10, with the difference between the 4- and 5-day work weeks being approximately a 25% increase in the AUC for the 4-day work week over the 5-day work week. The largest AUC estimate from inhalation exposure to D_4 for a barber or beautician was 3.63×10^{-3} mg-hrs/L/day (Table 10) for a male barber or beautician working 5 days per week. Workers involved in the formulation of SC products were identified as having the highest AUC values at 1.44×10^{-1} mg-hrs/L/day followed closely by workers in facilities manufacturing AP/D products at a value of 1.95×10^{-2} mg-hrs/L/day. Office workers and workers in HC facilities had the smallest values ranging between 4.61×10^{-4} mg-hrs/L/day to 1.24×10^{-5} mg-hrs/L/day.

3.3.2.2. Consumers. The Monte Carlo analysis indicated that consumer product use resulted in much greater exposure than that obtained through exposure to D_4 in environmental media. Therefore, the PBPK analysis for personal care products was limited to the products identified as contributing the most exposure to the consumer. Consumer products with estimates of intake within two orders of magnitude of the product providing the highest estimate of intake (dermal exposure to body lotion) were selected for evaluation. Additional information is provided in detail in the Supplementary material (Supplementary Tables S-1 through S-5).

The AUCs estimated for dermal exposure to D_4 from the use of HC/SC products ranged from a low of 6.02×10^{-9} mg-hrs/L/day for male dermal exposure to shampoo up to the highest exposure of 3.14×10^{-3} mg-hrs/L/day for female exposure to hand/body lotion. Model estimated AUC values for men and women from dermal exposure to HC/SC products are reported in Table 11. The AUCs estimated for inhalation exposure to D_4 from the use of the selected consumer products ranged from 1.55×10^{-6} for soothing vapor inhalation exposure in women up to 2.31×10^{-3} from roll-on deodorant inhalation exposure for women (Table 11).

3.3.2.3. General public. The PBPK analysis for the general public considered both inhalation of indoor and outdoor air in the home environment, exposure to D_4 in environmental media (e.g. ingestion of water, soil, air, fish, and other foods) and ingestion of anti-gas medication etc. Exposure to environmental media was also considered for subsistence fishermen where the consumption of fish was assumed to be the main source of protein. The mean reported oral intake of D_4 determined from the Monte Carlo analysis ranged from 0.005 mg/kg/day for males and females in the general public ages 60 and older to 0.007 mg/kg/day for male and female subsistence fishermen ages 12 to 19 years of age. The 90th percentile of oral intake to D_4 was approximately 0.009 mg/kg/day for males in the general public or subsistence fisherman 20 to 59 years of age. The AUCs estimated for inhalation exposure to D_4 for the general public ranged from 2.15×10^{-6} to 3.8×10^{-6} mg-hrs/L/day for the female and male receptors, respectively, from exposure to outdoor air (Table 12). A range of AUCs of 1.08×10^{-4} to 1.9×10^{-4} mg-hrs/L/day was estimated for the females and males respectively, from exposure to indoor air.

Table 11
Area Under the Curve (AUC) (mg-hrs/L-day): Selected Consumer Products.

Product	Dermal		Inhalation[a]	
	Men	Women	Men	Women
Solid Deodorant	4.15×10^{-4}	3.97×10^{-4}	2.68×10^{-5}	3.04×10^{-5}
Roll-on Deodorant	4.82×10^{-6}	2.58×10^{-6}	2.04×10^{-3}	2.31×10^{-3}
Aerosol Deodorant	9.17×10^{-4}	1.19×10^{-3}	1.05×10^{-3}	1.16×10^{-3}
Shampoo	6.02×10^{-9}	1.51×10^{-8}		
Conditioner (Rinse-out)	7.14×10^{-6}	1.74×10^{-5}		
Conditioner (Leave-in)	3.57×10^{-5}	8.71×10^{-5}		
Hair spray (aerosol)	9.01×10^{-9}	2.24×10^{-8}	4.16×10^{-4}	4.71×10^{-4}
Hair spray (pump)	1.31×10^{-8}	3.26×10^{-8}	4.16×10^{-4}	4.71×10^{-4}
Moisturizer	9.53×10^{-5}	2.32×10^{-4}	4.16×10^{-4}	4.71×10^{-4}
Foundation	N/A	5.41×10^{-4}	N/A	4.71×10^{-4}
Night cream/Under eye cream	N/A	6.14×10^{-5}		
Lipstick (6 days)	N/A	7.56×10^{-5}		
Lipstick (5 days)	N/A	3.12×10^{-5}		
Mascara	N/A	1.44×10^{-4}		
Hand/body lotion	2.49×10^{-3}	3.14×10^{-3}	4.16×10^{-4}	4.71×10^{-4}
Sunscreen	1.31×10^{-7}	3.15×10^{-7}	4.16×10^{-4}	4.71×10^{-4}
Nail care	N/A	8.93×10^{-7}	N/A	4.71×10^{-4}
After-shave gel	4.05×10^{-4}	N/A	4.16×10^{-4}	N/A
Soothing vapor	7.54×10^{-9}	1.77×10^{-8}	2.74×10^{-6}	1.55×10^{-6}

[a]Non-deodorant inhalation exposure were based upon results reported in a single study.

3.4. Risk characterization

A comparison of the internal dose metric associated with the POD to the internal dose metric estimated for each exposure scenario was conducted to develop MOS.

3.4.1. Occupational exposure

For inhalation exposures, seven types of workers (Table 13) were considered for which air concentrations from the workplace had been measured. Note that the MOS values for occupational exposure are adjusted by the median tenure in years for full-time workers (10.2 years for men and 6.4 years for women (USEPA, 2011)) over the expected lifetime (75 years for men and 80 years for women (USEPA, 2011)).

The estimated AUCs were highest (and the MOS lowest) for the workers involved in the production of skin care products, particularly in men. Comparison of the AUC for this worker to the $BMDL_{10}$ resulted in

Table 12
Area Under the Curve (AUC): Inhalation – General Public.

Ages	AUC (mg-hrs/L/day)			
	Male		Female	
	Outdoors (0.2 μg/m^3)	Indoors (10 μg/m^3)	Outdoors (0.2 μg/m^3)	Indoors (10 μg/m^3)
20–59 years	3.80×10^{-6}	1.90×10^{-4}	2.15×10^{-6}	1.08×10^{-4}

Table 13
Margins of Safety (MOS): Occupational Inhalation Exposure.

Worker	AUC (mg-hr/L/day)		MOS	
	Men	Women	Men	Women
Dermal				
Barbers and Beauticians				
5 days	8.98×10^{-4}	2.16×10^{-3}	245,000	173,000
4 days	1.14×10^{-3}	2.73×10^{-3}	193,000	137,000
Inhalation				
Antiperspirant	1.95×10^{-2}	$1.07 \times 10-2$	11,000	35,000
Skin Care	1.44×10^{-1}	7.88×10^{-2}	1500	4700
Hair Care	7.09×10^{-4}	3.88×10^{-4}	311,000	967,000
Silicone	1.23×10^{-2}	6.74×10^{-3}	17,000	55,000
Barbers and Beauticians				
5 days	3.63×10^{-3}	2.03×10^{-3}	60,000	184,000
4 days	3.60×10^{-3}	2.01×10^{-3}	61,000	186,000
Office Worker				
5 μg/m^3 (0.000383 ppm)	2.26×10^{-5}	1.24×10^{-5}	1,300,000	2,400,000
10.2 μg/m^3 (0.000781 ppm)	4.61×10^{-4}	2.50×10^{-5}	65,000	1,200,000

an MOS of approximately 1500. A MOS between 30 and 1000 for occupational exposures is generally considered acceptable by regulatory agencies and would not be expected to pose a significant risk to humans.

For barbers and beauticians, it was assumed that some hair products would be used approximately every 27 to 30 min during the work day, with the hands being exposed. The MOS determined for any of these scenarios, either by the inhalation pathway or the dermal pathway (Table 13), were approximately 60,000 or greater, when the AUCs were compared to the BMDL10. Occupational dermal exposures to D_4 in these professions do not pose a significant risk to human health.

Finally, potential exposure to D_4 in indoor air for office workers was evaluated at two concentrations, 5 and 10.2 μg/m^3 (0.000383 and 0.000781 ppm). Even at the highest concentration, the MOS for office workers was 65,000 or greater (Table 13); exposures to D_4 in these professions are not expected to pose a significant risk to human health.

3.4.2. Consumer products exposure

AUCs were estimated for average usage scenarios of consumer products providing the greatest potential for inhalation and dermal exposure (Table 14) based on the results of the Monte Carlo analysis.

When the AUCs estimated for each type of AP/D resulting from inhalation or dermal exposure were compared to the AUC for the $BMDL_{10}$, the smallest MOS from inhalation exposure was 13,000 (roll-on products in women) and the smallest MOS for AP/Ds based on dermal exposure was 180,000 (solid deodorant in women). It is not anticipated that any of the inhalation or dermal exposures resulting from typical consumer usage of AP/Ds would pose a risk

For HC/SC products, one inhalation exposure scenario for all HC/SC products was considered for women consumers (Table 14). Maxim (1998) estimated a single air concentration that was assumed to be representative of inhalation exposure to both HC and SC products. Comparison of the estimated AUC associated with a 10-min exposure to this air concentration (0.178 ppm D_4) to that associated with the $BMDL_{10}$, resulted in a MOS of 63,000 Exposure to D_4 by this route would not pose a significant health risk.

For dermal exposure to HC/SC products, multiple exposure scenarios were considered related to average application rates and usage frequencies for multiple hair care and skin care products. Comparison of the AUCs associated with exposure to each of the seventeen HC/SC products to the AUC associated with the $BMDL_{10}$ resulted in MOS of approximately 9500 or greater (Table 14). The lowest MOS (9500) was associated with the use of body lotion by women. These MOS are likely overestimates in that estimation of the AUC because they consider

Table 14
Margins of Safety (MOS): Exposure from Selected Consumer Products.

Product	AUC (mg-hr/L/day)		MOS	
	Men	Women	Men	Women
Dermal				
Solid Deodorant	4.15×10^{-4}	3.97×10^{-4}	2.4×10^{6}	1.8×10^{5}
Roll-on Deodorant	4.82×10^{-6}	2.58×10^{-6}	1.8×10^{6}	1.2×10^{6}
Aerosol Deodorant	9.17×10^{-4}	1.19×10^{-3}	2.1×10^{6}	2×10^{5}
Shampoo	6.02×10^{-9}	1.51×10^{-8}	4×10^{9}	1×10^{9}
Conditioner (Rinse-out)	7.14×10^{-6}	1.74×10^{-5}	4.1×10^{6}	1.4×10^{5}
Conditioner (Leave-in)	3.57×10^{-5}	8.71×10^{-5}	8.3×10^{5}	3.4×10^{5}
Hair spray (aerosol)	9.01×10^{-9}	2.24×10^{-8}	3×10^{9}	1.3×10^{9}
Hair spray (pump)	1.31×10^{-8}	3.26×10^{-8}	2×10^{9}	9×10^{8}
Moisturizer	9.53×10^{-5}	2.32×10^{-4}	3.1×10^{5}	1.2×10^{5}
Foundation	N/A	5.41×10^{-4}	N/A	55,000
Night cream/Under eye cream	N/A	6.14×10^{-4}	N/A	4.8×10^{5}
Lipstick (6 days)	N/A	7.56×10^{-5}	N/A	3.9×10^{5}
Lipstick (5 days)	N/A	3.12×10^{-5}	N/A	9.6×10^{5}
Mascara	N/A	1.44×10^{-4}	N/A	2×10^{5}
Hand/body lotion	2.49×10^{-3}	3.14×10^{-3}	12,000	9500
Sunscreen	1.31×10^{-7}	3.15×10^{-7}	2.2×10^{8}	9.5×10^{7}
Nail care	N/A	8.93×10^{-7}	N/A	3.3×10^{6}
After-shave gel	4.05×10^{-4}	N/A	74,000	N/A
Soothing vapor	7.54×10^{-9}	1.77×10^{-8}	3.9×10^{9}	1.6×10^{9}
Inhalation				
Solid Deodorant	2.68×10^{-5}	3.04×10^{-5}	1.1×10^{6}	9.8×10^{5}
Roll-on Deodorant	2.04×10^{-3}	2.31×10^{-3}	14,000	13,000
Aerosol Deodorant	1.05×10^{-3}	1.16×10^{-3}	28,000	25,000
Hair spray (aerosol)	4.16×10^{-4}	4.71×10^{-4}	72,000	63,000
Hair spray (pump)	4.16×10^{-4}	4.71×10^{-4}	72,000	63,000
Moisturizer	4.16×10^{-4}	4.71×10^{-4}	72,000	63,000
Foundation	N/A	4.71×10^{-4}	N/A	63,000
Hand/body lotion	4.16×10^{-4}	4.71×10^{-4}	72,000	63,000
Sunscreen	4.16×10^{-4}	4.71×10^{-4}	72,000	63,000
Nail care	N/A	4.71×10^{-4}	N/A	63,000
After-shave gel	4.16×10^{-4}	N/A	72,000	N/A
Soothing vapor	2.74×10^{-6}	1.55×10^{-6}	1×10^{7}	1.9×10^{7}

lifetime exposure in comparing the AUC to the POD and are not adjusted if the exposures are expected to be less than lifetime. For example, some products, such as soothing vapor, may be used beginning in childhood or infancy and continuing throughout adulthood, while others may only be used during adult years. The estimated AUCs were for an average daily exposure and not an average daily lifetime exposure. Therefore, dermal exposure to D_4 from the usage of HC/SC products would not be expected to pose a significant health risk.

3.4.3. General public exposure

For purposes of this assessment, the general public was considered to be individuals who could be exposed to levels of D_4 in outdoor or indoor air. Exposure to the general public from environmental media or to subsistence fisherman were not carried further in the evaluation to develop a MOS because during the MC analysis they were determined to be two orders of magnitude less than the product representing the greatest exposure to D_4 through consumer use (e.g. body lotion for adults). A value of 10.0 μg/m^3 (0.000766 ppm) was identified as representative of the indoor air concentration to which an individual would be exposed. A value of 0.2 μg/m^3 (0.0000153 ppm) was identified as representative of the typical exposure to D_4 in outdoor air to estimate D_4 exposure for the general public. The smallest MOS determined for indoor and outdoor inhalation for men and women residents was 150,000 and 278,000, respectively so D_4 would not be considered a significant health risk. (Table 15).

4. Discussion

To perform a risk assessment hazard and exposure must be defined. As with any exposure assessment, a number of assumptions must be

Table 15
Margins of Safety (MOS): Inhalation Exposure for the General Public.

Location	Residential 20–59 yr olds			
	AUC (mg-hr/L/day)		MOS LED_{10}	
	Men	Women	Men	Women
Indoor (10 μg/m^3)	1.9×10^{-4}	1.08×10^{-4}	150,000	278,000
Outdoor (0.2 μg/m^3)	3.8×10^{-6}	2.15×10^{-6}	7.8×10^{5}	1.3×10^{6}

made and judgment used when selecting values for dose metrics, such as the body weight, or the duration of exposure, etc. This introduces uncertainty into the assessment. Most parameter estimates used in the PBPK analysis were based on the average, mean, or midpoint in a range of values for that parameter. Since means are measurements of central tendency, there are values for those parameters both larger and smaller than the ones used. Different choices for these parameters could result in larger/smaller estimates of exposure. Depending on the magnitude of the differences between the upper bound or lower bound for a parameter and the median, it is possible that with the interactions of several parameters, a significant difference in the estimated dose metrics may be observed if upper bounds were considered, as is the case also with the lower bounds. The difference between the mean and the 95th percentile was less than an order of magnitude (Supplementary table S-13b) in all cases. Therefore, if the upper bounds were used instead of the means in the model, the effect should increase the exposure by no more than a factor of 10. On this basis, the variability in dose metrics is not considered to be significant.

The different compartmental structures in various PBPK models produced challenges when extrapolating between rodents to humans for risk assessments. To overcome these difficulties, a common model structure with consistent parameters between cyclic siloxanes, routes and species was developed to simulate exposures to D_4. This multi-purpose siloxane model was used for this risk assessment (McMullin et al., 2016). D_4 has an unusual set of physical chemical properties, including low blood:air and high fat:blood partitioning. These characteristics lead to exhaled breath and tissue time-course concentration profiles that could not be described without kinetically distinct storage compartments within these tissues that account for tissue-lipid fractions where the cyclic siloxanes are transferred to these compartments and slowly released from these compartments into the blood. The process of fitting a PBPK model to the rat inhalation studies with D_4 required two deep-tissue compartments in the lung and liver to account for this kinetic behavior (Andersen et al., 2001; Reddy et al., 2003, 2007). Although adequate for modeling this kinetic behavior of D_4, the model description of these deep compartments as well-defined compartments equivalent to the percentages of lipid within a tissue is a simplified representation of the physiological distribution of lipids within these tissues. Similarly, fat was represented as two distinct diffusion limited fat compartments, diffuse and distributed fat.

The blood description in the model also includes diffusion-limited deep compartments in the arterial and venous blood similar to the liver and lung (Reddy et al., 2008). The kinetic behavior of cyclic siloxanes in the blood over multiple day exposures in the rat required an additional description where a portion of D_4 in the blood is sequestered as a bound, unavailable pool of D_4, resulting in both free and bound D_4 represented in the experimentally measurable blood compartment (Andersen et al., 2001; Reddy et al., 2003, 2007). This blood compartment is modeled as a portion of D_4 bound to blood lipids that were formed by transport of a mobile lipid pool from a shallow-liver compartment to blood and from blood to the diffuse-fat compartment. Conceptually, this compartment likely represents the production and transport of possibly chylomicron-like structures that carry D_4 in the particle to fat stores in the body without allowing D_4 to be available to the blood. Although the modeling of the kinetic data drove these model descriptions of the behavior of D_4, the validity of these model assumptions and the associated model derived parameters have yet to be experimentally evaluated.

Based on a variety of data following dermal exposures from *in vitro* and *in vivo* human skin studies and *in vivo* rodent studies, the skin compartment in the human siloxane model described uptake and evaporation from the skin assuming a two compartment model that includes a skin surface and a deep tissue storage compartment, likely representing the stratum corneum, that slowly releases D_4 into the viable epidermis and bloodstream upon termination of exposure (Reddy et al., 2007). In addition to evaporation of D_4 from the skin surface following application, the model also describes diffusion of D_4 from the deep compartment back to the surface followed by evaporation from the skin. While this description was essential to accurately describe the time-course behavior of D_4 following dermal application, this process for D_4 is still not well understood. Additionally, the model parameters for dermal absorption were set using data from axilla skin. Axilla skin absorbs chemicals more rapidly that other skin areas. It is possible, therefore, that model predictions of internal dose following dermal absorption could be overestimated (Reddy et al., 2007).

A general uncertainty that would apply to all populations and scenarios is the choice of the body weight to use in the PBPK modeling. We chose to use the NHANES US average body weight of 86.9 kg for men and 73.4 kg for women (CDC 2007–2010) rather than the body weight of 60 kg (SCCS 2012 guidance). The difference in the body weight considered, without changing the application rates or concentrations of D_4 in the products, increased the estimated PBPK dose metrics no more than a factor of 2.

4.1. Occupational

The median number of years worked (10.2 years for men and 5.6 years for women) was used to adjust the lifetime occupational exposure (results in factors of 0.136 for males and 0.08 for females applied to the average AUC) (USEPA, 2011). It is possible that a worker could work more than the median number of years at the same job. For example, if a person worked 45 years at the same occupation with the same exposure pattern, the estimates of exposure would be 5 to 7 times higher than predicted using a median value.

The average air concentration of D_4 assumed for workers involved in the production of HC products containing D_4 was obtained from a single set of 16 personal time-weighted samples taken in one plant (Maxim, 1998). Similarly, the average air concentration assumed for workers involved in the production of skin care products containing D_4 was also obtained from a single set of 16 personal time-weighted average samples taken in one plant (Maxim, 1998). No information was provided in these studies regarding the variation in the samples. Without additional information, it is impossible to predict whether the estimates of AUC resulting from inhalation of D_4 in the production of HC/SC products is an over- or underestimate.

4.2. Consumers

In estimating dermal or inhalation exposure to D_4 by consumers using AP/Ds or HC/SC products, it was assumed that all available products in these categories contain D_4. This assumption will likely result in an overestimate of both dermal and inhalation exposure of consumers to D_4 from use AP/Ds and HC/SC products, as all AP/Ds or HC/SC products do not contain D_4. The air concentrations relied upon for the consumer using antiperspirants or deodorants were calculated from the measurements taken in a single unpublished study in which only two sets of samples were taken for each type of antiperspirant (roll-on, solid, and aerosol). This study used one brand of antiperspirant and the measurements were taken in a 30 m^3 room with the vents sealed to prevent air exchange; as such the exposures measured would likely represent the high-end of exposure (Maxim, 1998). Different

formulations of antiperspirant could contain ingredients that could retard or enhance the evaporation of D_4 and the percentage of D_4 used in the product may not have been the same as that assumed for AP/D products that are currently on the market. This would result in an overestimation of the inhalation exposure to D_4 resulting from use of AP/Ds.

The air concentrations assumed for inhalation exposure to HC/SC products were also calculated from a single unpublished study in which 6 personal monitoring samples were taken for consumers using hair products containing D_4 (Maxim, 1998). No specific information was available about the ventilation of the room, the size of the room, the exact products being used or the amount of D_4 in those products. Only the time-weighted average of the samples was reported by Maxim (1998). Without additional information, it is impossible to predict whether the estimates of AUC resulting from inhalation exposure to HC/SC products are over- or underestimated.

A recent assessment by SCCS (2010) relied upon a NOAEL of 150 ppm for D_4, based on the incidence of uterine endometrial adenomas and hyperplasia in female rats exposed to 700 ppm D_4 for two years (Jean and Plotzke, 2017). The incidence of uterine adenomas was not statistically significantly increased (4/60), compared to concurrent controls (0/59) but a significant increase in trend was reported and endometrial adenoma is a common tumor in aging female Fischer 344 rats. No other toxicologically significant neoplastic or non-neoplastic findings were reported in this chronic inhalation toxicity study. For comparison purposes, a POD based on results of the bioassay study (Jean and Plotzke, 2017) was developed for comparison to the POD based on the reproductive effects reported in multiple studies following exposure to D_4 (Franzen et al., 2017; Siddiqui et al., 2007), incorporating BMD and PBPK modeling into the estimation. Because there were no statistically significant survival differences among control and treated females in the Jean and Plotzke (2017) study, dose-response modeling for the uterine adenomas, as with the reproductive toxicity endpoints, was conducted using a BMR of 10% extra risk for quantal data and the USEPA's Benchmark Dose Software (BMDS) Version 2.3.1. All of the available models were applied, and the model with the best fit was chosen for comparison.

The BMDs and BMDLs derived using the BMDS software relying upon the incidence of uterine adenoma are presented in Table 16, including the goodness-of-fit criteria. Multiple models provided the same fit to the data, with estimated BMDLs ranging from approximately 109 to 119 ppm, using the continuous animal exposure concentrations. Incorporation of dose metrics using the PBPK model resulted in PODs expressed in the internal dose metric (AUC of free D_4 in the blood) of approximately 26 to 29 mg-hrs/L/day. These PODs are consistent with the POD relied upon from the reproductive endpoints of approximately 30 mg-hrs/L/day. Therefore, reliance upon the incidence of uterine adenomas from the Jean and Plotzke (2017) chronic bioassay study in the estimation of the POD would have provided similar results to those obtained from the current assessment relying upon the more conservative approach, the incidence of reproductive effects (Franzen et al., 2017; Siddiqui et al., 2007) observed following inhalation exposure to D_4.

4.3. General public

Estimates of exposure to the general public from inhalation of D_4 were assumed to be for a lifetime at a single location or residency. If the exposure in other locations were lower, this would overstate the risk by a factor of 8.3 to 2.3 based on the assumption of a median and 95th percentile of residency time at any location being 11.7 years and 33 years, respectively (USEPA, 2011). In addition, the exposures were calculated for continuous indoor or continuous outdoor exposure. The actual inhalation exposure would likely be an air concentration somewhere between the two concentrations estimated for indoor or outdoor air (These values were not adjusted for length of residency).

Estimates for exposure of children to D_4 through the use of silicone rubber products, such as pacifiers, is dependent on the migration rate of the siloxanes from the product into saliva or other fluids. The migration factor of 0.0045 used in this assessment was based on results from an experiment on the migration of siloxanes from silicone rubber products into milk, formula and liquid dietary simulants (Zhang et al., 2012). Concentrations of D_4 were determined to range from 0.6 to 49 μg/g of D_4 in baby bottle nipples with a median value of 2.4 μg/g. However, due to the irregular shape of the silicone nipples, migration tests were performed using silicone cake pans, which was demonstrated to be an appropriate surrogate for the nipples. These cake pans had an average concentration of D_4 of 23 mg/kg − about 4 times higher than the largest value that was reported in baby bottle nipples (Supplemental Table S-2). Migration from food containers was assumed to be an amount per day over the duration of exposure, but there is little evidence that this amount could be repeatedly extracted from the same product each day or that a new product would be used each day. Therefore, this is a very conservative estimate of the daily exposure and would result in an overestimation of D_4 exposure.

It was also assumed that 50% of all food consumed by the general public would contain residual antifoam (formulated with D_4), which is a very conservative estimate as antifoam is only used to process some foods and is excluded from use in milk and milk products. This assumption would result in an overestimate the amount of antifoam containing D_4 consumed by the general public.

MOS were estimated for oral intake only for teens and adults, as the PBPK model cannot conduct simulations for infants. The results from the Monte Carlo analysis indicated that oral intakes in children are up to 10 times greater than intakes estimated for adults (Supplemental Tables S12a and S13a). However, the large MOS values computed for

Table 16
Results of BMDS Modeling for the incidence of Uterine Adenomas in Female Rats.

Model Name	AIC	P-value	Scaled Residual of Interest	BMD[a] (ppm)	BMDL (ppm)	BMD[b] (ppm)	BMDL (ppm)	BMD[c] (mg-hrs/L/day)	BMDL (mg-hrs/L/day)
Gamma	33.39	1.0000	0.0000	749.06	624.07	133.93	111.44	32.23	26.72
Logistic	33.39	1.0000	0.0000	714.32	667.71	127.56	119.23	30.68	28.67
LogLogistic	33.39	1.0000	0.0000	728.42	627.60	130.14	112.07	31.32	26.86
LogProbit	33.39	1.0000	0.0000	756.68	610.71	135.13	109.06	32.57	26.12
Multistage	31.47	0.9998	0.0200	808.85	628.77	144.44	112.28	34.72	26.90
Multistage-Cancer	31.47	0.9998	0.0200	808.85	628.77	144.44	112.28	34.72	26.90
Probit	33.39	1.0000	0.0000	727.53	656.27	129.92	117.19	31.26	28.17
Weibull	33.39	1.0000	0.0000	727.62	630.34	129.93	112.56	31.28	26.98
Quantal-Linear	33.37	0.8908	0.4930	1368.30	663.58	244.36	118.50	58.12	28.18
Gamma	33.39	1.0000	0.0000	749.06	624.07	144.44	112.28	34.72	26.90

[a]The dose-response models were fit to the data using the animal exposure doses unadjusted.
[b]The dose-response models were fit to the data using the animal exposure doses adjusted from 6 h/day to continuous (i.e., multiplying dose by 6/24 and 5/7).
[c]The dose-response models were fit to the data using the internal dose-metrics for average daily area under the curve (AUC) of the concentration of free D4 in arterial blood.

teens and adults (Table 13) would suggest that even for children, the MOS values resulting from ingestion of food containing D_4 should be greater than 1 million.

5. Conclusions

MOS were greater than 1000 for workers, consumers, and the general public who may be exposed to D_4 either in the workplace, through the use of consumer products containing D_4, or to D_4 released in the environment, indicating no anticipated significant risk of adverse effects.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.toxlet.2017.05.019.

References

Andersen, M.E., Sarangapani, R., Reitz, R.H., Gallavan, R.H., Dobrev, I.D., Plotzke, K.P., 2001. Physiological modeling reveals novel pharmacokinetic behavior for inhaled octamethylcyclotetrasiloxane in rats? Toxicol. Sci. 60 (2), 214–231.

Anderson, D., Weaver, M., 1989. Dimethylcyclosiloxane Inhalation Exposure Levels During the Use of Anti-perspirant Products. Report No: H-0-0000-27, Series I-0008-730. Industrial Hygiene Department, Corporate Medical Department, Dow Corning Corporation.

Boehmer, T., Gerhards, R., 2003. Presence of Volatile Siloxanes in Cosmetics – European Product Survey (Essen: Degussa Goldschmidt AG), Report for Study, Draft. SEHSC CES Project 2003/18.

Boehmer, T., Gerhards, R., Koerner, M., 2001. Presence of volatile siloxanes in ambient air samples. (Essen: Degussa Goldschmidt AG). Centre European Des Silicones, Brussels.

Bolt, H.M., Degen, G.H., 2004. Human carcinogenic risk evaluation: part II: Contributions of the EUROTOX specialty section for carcinogenesis. Toxicol. Sci. 81 (1), 3–6.

Brooke, D.N., Crookes, M.J., Gray, D., Robertson, S., 2009. Environmental Risk Assessment Report: Decamethylcyclopentasiloxane. Environment Agency, Bristol, UK.

CDC (2007–2010). National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. http://www.cdc.gov/nchs/nhanes/nhanes_questionnaires.htm.

COLIPA (pre 2000). Maximum Concentration Range of D_4 and D_5 in Various Product Types (Result of Colipa AP 304).

Canadian Environmental Protection Act, 1999. Canadian Environmental Protection Act, 1999. Retrieved June 18, 2013, from: http://canlii.ca/en/ca/laws/stat/sc-1999-c-33/105826/sc-1999-c-33.html.

Carey, M.L., 1988. Occupational Tenure in 1987: Many Workers Have Remained in Their Fields. pp. 3–12 Monthly Labor Review (October 1, 1988).

Clewell 3rd, H.J., Andersen, M.E., 1985. Risk assessment extrapolations and physiological modeling? Toxicol. Ind. Health 1 (4), 111–131.

Clewell, R.A., Clewell 3rd, H.J., 2008. Development and specification of physiologically based pharmacokinetic models for use in risk assessment? Regul. Toxicol. Pharm. 50 (1), 129–143.

Clewell, H.J., Gentry, P.R., Gearhart, J.M., Allen, B.C., Andersen, M.E., 2001a. Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model? Sci. Total Environ. 274 (1–3), 37–66.

Clewell, R.A., Merrill, E.A., Robinson, P.J., 2001b. The use of physiologically based models to integrate diverse data sets and reduce uncertainty in the prediction of perchlorate and iodide kinetics across life stages and species? Toxicol. Ind. Health 17 (5–10), 210–222.

Cowan-Ellsberry, C., McNamee, P.M., Leazer, T., 2008. Axilla surface area for males and females: measured distribution. Regul. Toxicol. Pharm. 52 (1), 46–52 (Abstract).

Dekant, W., Scialli, A.R., Klaunig, J.E., 2017. Biological Relevance of Effects Following Chronic Administration of Octamethylcyclotetrasiloxane (D_4) in Fischer 344 Rats. (Submitted to Toxicology Letters as companion paper).

Domoradzki, J., Sushynski, C., McNett, D.A., Van Landingham, C., Plotzke, K., 2017. Metabolism and Disposition of 14C-Octamethylcyclotetrasiloxane ([14C]D_4) or 14C-Decamethylcylopentasiloxane ([14C]D5) Following Oral Gavage Administration in Fischer 344 Rats. (Submitted to Toxicology Letters as companion paper).

Dow Corning Corporation, 1998. An Oral Gavage Study to Compare the Absorption Potential of ^{14}C- Octamethycyclotetreasiloxane (D_4) in Fischer 344 Rats when Delivered in Various Carriers. Dow Corning Corporation, Midland, Michigan (Report No: 1998-I0000-44815. Study Number: 8546. Sponsor).

Dow Corning Corporation, 1999. Interim Exposure Assessment for Silicone Antifoams in Food Processing and Over-the-counter (OTC) Antigas (AG) Products. Report No: 1999-I0000-47945. Location: Midland Corporate, Michigan, Dow Corning Coporation.

ECETOC, 2001. Exposure factors sourcebook for European populations (with focus on UK data), Technical Report No. 79. European Centre for Ecotoxicology & Toxicology of Chemicals (As cited in Hall et al., 2007).

Environmental Control Center Co. Ltd., (2011). Investigation of cyclic volatile methylsiloxanes (cVMS) materials in sediment and fish samples 2010, Calculation of margin of exposure due to fish consumption, and risk evaluation RS065202001D. Kitakanto Branch.

European Commission, (2011). REGULATIONS – Commission Regulation (EU) No 1129/2011 of 11 November 2011 amending Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council by establishing a Union list of food additives. European Union: 1–177.

Eurostat, (2002). European Social Statistics – Demography 2002. Statistical Office of the European Communities. ISBN 10: 9289443243 (As cited in Hall et al., 2007).

Franzen, A., Greene, T., Van Landingham, C., Kinslow, C., Gentry, R., 2017. Toxicology of Octamethylcyclotetrasiloxane (D_4). (Submitted to Toxicology Letters as companion paper).

Gentry, P.R., Clewell 3rd, H.J., Clewell, R.A., Campbell, J., Van Landingham, C., Shipp, A.M., 2011. Challenges in the application of quantitative approaches in risk assessment: a case study with di-(2-ethylhexyl)phthalate. Crit. Rev. Toxicol. 41 (S2), 1–72.

Hall, B., Tozer, S., Safford, B., Coroama, M., Steiling, W., Leneveu-Duchemin, M.C., McNamara, C., Gibney, M., 2007. European consumer exposure to cosmetic products: a framework for conducting population exposure assessments. Food Chem. Toxicol. 45 (11), 2097–2108.

Hall, B., Steiling, W., Safford, B., Coroama, M., Tozer, S., Firmani, C., McNamara, C., Gibney, M., 2011. European consumer exposure to cosmetic products: a framework for conducting population exposure assessments Part 2. Food Chem. Toxicol. 49 (2), 408–422.

Health Canada (2008). Screening Assessment for Octamethylcyclotetrasiloxane (D_4). Chemical Abstracts Service Registry Number 556-67-2. Environment Canada.

Horii, Y., Kannan, K., 2008. Survey of organosilicone compounds including cyclic and linear siloxanes, in personal-care and household products. Arch. Environ. Contam. Toxicol. 55 (4), 701–710.

ICRP, 1992. Report of the Task Group on Reference Man. ICRP Publication 23. International Commission on Radiological Protection. Pergamon Press, Oxford, England, pp. 58–61.

IPCS, 2010. WHO Human Health Risk Assessment Toolkit: Chemical Hazards. International Programme on Chemical Safety. World health Organization.

Jean, P., Plotzke, K., 2017. Chronic Toxicity and Oncogenicity of Octamethylcyclotetrasiloxane (D_4) in the Fischer 344 Rat. (Submitted to Toxicology Letters as companion paper).

Jean, P., Sloter, E.D., Plotzke, K.P., 2017. Effect of Chronic Exposure to Octamethylcyclotetrasiloxane Decamethycyclopentasiloxane, and Pergolide on Hormonal Status and Estrous Cyclicity in the Aging Female Fischer 344 Rat. (Submitted to Toxicology Letters as companion paper).

Johnson Jr, W., Bergfeld, W.F., Belsito, D.V., Hill, R.A., Klaassen, C.D., Liebler, D.C., Marks Jr, J.G., Shank, R.C., Slaga, T.J., Snyder, P.W., Andersen, F.A., 2011. Safety assessment of cyclomethicone, cyclotetrasiloxane, cyclopentasiloxane, cyclohexasiloxane, and cycloheptasiloxane. Int. J. Toxicol. 30 (Suppl. 6), 149S–227S.

Jovanovic, M.L., McMahon, J.M., McNett, D.A., Tobin, J.M., Plotzke, K.P., 2008. In vitro and In vivo percutaneous absorption of 14C-octamethylcyclotetrasiloxane (14C-D_4) and 14Cdeca-methylcyclopentasiloxane (14C-D5). Regul. Toxicol. Pharm. 50 (2), 239–248.

Kaj, L., Andersson, J., Palm Cousins, A., Remberger, M., Brorström-Lundén, E., Cato, I., 2005. Results from the Swedish National Screening Programme 2004. Subreport 4: Siloxanes. Swedish Environmental Research Institute, Stockholm.

Kalopissis, G., 1986. Chapter 9: toxicology and hair dyes. In: Zviak, C. (Ed.), The Science of Hair Care. Marcel Dekker, New York, pp. 287–308.

Loretz, L.J., Api, A.M., Barraj, L.M., Burdick, J., Dressler, W.E., Gettings, S.D., Han Hsu, H., Pan, Y.H., Re, T.A., Renskers, K.J., Rothenstein, A., Scrafford, C.G., Sewall, C., 2005. Exposure data for cosmetic products: lipstick: body lotion and face cream. Food Chem. Toxicol. 43 (2), 279–291.

Loretz, L., Api, A.M., Barraj, L., Burdick, J., Davis de, A., Dressler, W., Gilberti, E., Jarrett, G., Mann, S., Laurie Pan, Y.H., Re, T., Renskers, K., Scrafford, C., Vater, S., 2006. Exposure data for personal care products: hairspray spray perfume, liquid foundation, shampoo, body wash, and solid antiperspirant. Food Chem. Toxicol. 44 (12), 2008–2018.

Loretz, L.J., Api, A.M., Babcock, L., Barraj, L.M., Burdick, J., Cater, K.C., Jarrett, G., Mann, S., Pan, Y.H., Re, T.A., Renskers, K.J., Scrafford, C.G., 2008. Exposure data for cosmetic products: facial cleanser hair conditioner, and eye shadow. Food Chem. Toxicol. 46 (5), 1516–1524.

Maxim, L., 1998. D_4, D_5, and D_6 Exposure in the Manufacture and Use of Personal Care Products: an Interim Assessment. Dow Corning Corporation Report No: 1998-I000-45430.

McKim Jr., J.M., Kolesar, G.B., Jean, P.A., Meeker, L.S., Wilga, P.C., Schoonhoven, R., Swenberg, J.A., Goodman, J.I., Gallavan, R.H., Meeks, R.G., 2001. Repeated inhalation exposure to octamethylcyclotetrasiloxane produces hepatomegaly transient hepatic hyperplasia, and sustained hypertrophy in female Fischer 3244 rats in a manner similar to phenobarbital. Toxicol. Appl. Pharmacol. 172 (2), 83–92.

McMullin, T.S., Yang, Y., Campbell, J., Clewell, H.J., Plotzke, K., Andersen, M.E., 2016. Development of an integrated multi-species and multi-dose route PBPK model for volatile methyl siloxanes – D_4 and D_5. Regul. Toxicol. Pharm. 74 (Supplement), S1–S13.

McNamara, C., Rohan, D., Godlen, D., Gibney, M., Hall, B., Tozer, S., Safford, B., Coroama, M., Leneveu-Duchemin, M.C., Steiling, W., 2007. Probabilistic modeling of European consumer exposure to cosmetic products? Food Chem. Toxicol. 45 (11), 2086–2096.

Meeks, R.G., Stump, D.G., Siddiqui, W.H., Holson, J.F., Plotzke, K.P., Reynolds, V.L., 2007. An inhalation reproductive toxicity study of octamethylcyclotetrasiloxane (D_4)

in female rats using multiple and single day exposure regimens. Reprod. Toxicol. 23 (2), 192–201.
Meeks, B., 2005. Personal Communication from Dow Corning Corporation.
NILU, 2007. Siloxanes in the Environment of the Inner Oslofjord. Norsk Institutt for Luftforskning. Rapport 986/2007. Kjeller (NO) Norvegian Institute of Air Research.
NYIEQ, 2005. Indoor Environmental Quality: Assessing and Mitigating the Impact of Exposure to Multiple Indoor Contaminants. Phase I: Collection of Multiple Pollutants from Indoor and Laboratory Evaluated Sources (COMPILES). Final Report. New York Indoor Environmental Quality Center, Syracuse, New York Project No. R828605-01.
Norden, 2005. Siloxanes in the Nordic Environment. Nordic Council of Ministers. TemaNord 2005:593. ISBN 92–893-1268-8.
Plant, T.M., 2012. A comparison of the neuroendocrine mechanisms underlying the initiation of the preovulatory LH surge in the human, old world monkey and rodent. Front. Neuroendocrinol. 33 (2), 160–168.
Quinn, A.L., Dalu, A., Meeker, L.S., Jean, P.A., Meeks, R.G., Crissman, J.W., Gallavan Jr., R.H., Plotzke, K.P., 2007. Effects of octamethylcyclotetrasiloxane (D_4) on the luteinizing hormone (LH) surge and levels of various reproductive hormones in female Sprague-Dawley rats? Reprod. Toxicol. 23 (4), 532–540.
REACH Registration Dossier (2011). RECONSILE HPV (DRAFT) octamethylcyclotetrasiloxane (IUC4 DSN 147). Retrieved 06-08, 2011, from file:///J:/SEHSC/RefDocs/D4/D4%20Dossier%20June%2008%202011.html.
Chemical Safety Report – Octamethylcyclotetrasiloxane, D_4 Name: Octamethylcyclotetrasiloxane CAS Number: 556-67-2. Peter Fisk Associates Ltd.
Reddy, M.B., Andersen, M.E., Morrow, P.E., Dobrev, I.D., Varaprath, S., Plotzke, K.P., Utell, M.J., 2003. Physiological modeling of inhalation kinetics of octamethylcyclotetrasiloxane in humans during rest and exercise? Toxicol. Sci. 72 (1), 3–18.
Reddy, M.B., Looney, R.J., Utell, M.J., Plotzke, K.P., Andersen, M.E., 2007. Modeling of human dermal absorption of octamethylcyclotetrasiloxane (D_4) and decamethylcyclopentasiloxane (D_5)? Toxicol. Sci. 99 (2), 422–431.
Reddy, M.B., Dobrev, I.D., McNett, D.A., Tobin, J.M., Utell, M.J., Morrow, P.E., Domoradzki, J.Y., Plotzke, K.P., Andersen, M.E., 2008. Inhalation dosimetry modeling with decamethylcyclopentasiloxane in rats and humans? Toxicol. Sci. 105 (2), 275–285.
SCCP, (2005). Opinion on octamethylcyclotetrasiloxane (D_4) cyclomethicone (INCI name) SCCP/0893/05. Scientific Committee on Consumer Products, European Commission, Health & Consumer Protection Directorate.
SCCS, (2003). The SCCNFP's notes of Guidance for the testing of cosmetic ingredients and their safety evaluation 5th revision. SCCNFP/0690/03 Final. The Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers.
SCCS, (2010). Opinion on cyclomethicone octamethylcyclotetrasiloxane (cyclotetrasiloxane, D_4) and decamethylcyclopentasiloxane (cyclopentasiloxane, D_5). Scientific Committee on Consumer Safety European Commission. Directorate-General for Health & Consumers.
SCCS, (2012). The SCCS'S notes of guidance for the testing of cosmetic substances and their safety evaluation 8th Revision. SCCS/1501/12. Scientific Committee on Consumer Safety, European Commission.
SDA, 2005. Exposure and Risk Screening Methods for Consumer Product Ingredients. Soap and Detergent Association, Washington DC.
Setzer Jr., R.W., Kimmel, C.A., 2003. Use of NOAEL benchmark dose, and other models for human risk assessment of hormonally active substances. Pure Appl. Chem. 75 (11–12), 2151–2158.
Shields, H.C., Fleischer, D.M., Weschler, C.J., 1996. Comparisons among VOCs measured in three types of U: S. commercial buildings with different occupant densities. Indoor Air 6 (1), 2–17.
Siddiqui, W.H., Stump, D.G., Plotzke, K.P., Holson, J.F., Meeks, R.G., 2007. A two-generation reproductive toxicity study of octamethylcyclotetrasiloxane (D_4) in rats exposed by whole-body vapor inhalation? Reprod. Toxicol. 23 (2), 202–215.
US Bureau of Labor Statistics, (2012). Employment, Hours, and Earnings from the Current Employment Statistics Survey (National): Barber Shops and Beauty Salons. United States Department of Labor.
US Bureau of Labor Statistics, (2013). Chemical Manufacturing: NAICS 325. United States Department of Labor. Retrieved November 2013, from: http://www.bls.gov/iag/tgs/iag325.htm#earnings.
USDA, (1998). Continuing Survey of Food Intakes by Individuals 1994-96, 1998 and Diet and Health Knowledge Survey 1994-96: Documentation (csfii9498_documentationupdated.pdf) or Data Files (csfii9498_data.exe). United States Department of Agriculture, Agricultural Research Service, Beltsville Human Nutrition Research Center, Food Surveys Research Group (Beltsville, MD). Retrieved January 2005, from USDA Agricultural Research Service, Food Surveys Research Group website: http://www.ars.usda.gov/Services/docs.htm?docid=14531.
USEPA, (1995). The use of the benchmark dose approach in health risk assessment. United States Environmental Protection Agency, Risk Assessment Forum. Washington, DC.EPA/630/R-94/007.
USEPA, (1997). Carcinogenicity peer review of vinclozolin (3rd). United States Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances. Washington, DC,A pril.
USEPA (2005). Guidelines for carcinogen risk assessment. United States Environmental Protection Agency, Risk Assessment Forum. Washington, DC, M arch. EPA/630/P-03/001B.
USEPA (2006). Child-specific exposure factors handbook. External Review Draft, September. United States Environmental Protection Agency. EPA/600/R/06/096A.
USEPA (2011). Exposure Factors Handbook: 2011 Edition. September. United States Environmental Protection Agency, Office of Research and Development, Washington, DC.EPA/600/P-95/002Fa.
USEPA (2015). Benchmark Dose (BMD) Methods. Selecting the Model. September. https://www.epa.gov/bmds/benchmark-dose-bmd-methods.
USFDA, (1978). General comment applicable to all ingredients in Category III Food and Drug Administration. Federal Register: 1231–1233.
USFDA, 1982. Proposed Rule for Zinc Pyrithione Food and Drug Administration Federal Register. pp. 54664–54668.
USFDA, (2012). Title 21 — Food and Drugs, Chapter I – Food and Drug Administration, Subchapter B – Food and Human Consumption, Part 173 – Secondary Direct Food Additives Permitted in Food for Human Consumption, Subpart D – Specific Usage Additives. 21. U.S. Food and Drug Administration Department of Health and Human Services.
Van Landingham, C.B., Lawrence, G.A., Shipp, A.M., 2004. Estimates of lifetime-absorbed daily doses from the use of personal-care products containing polyacrylamide: a Monte Carlo analysis. Risk Anal. 24 (3), 603–619.
Varaprath, S., Salyers, K.L., Plotzke, K.P., Nanavati, S., 1999. Identification of metabolites of octamethylcyclotetrasiloxane (D_4) in rat urine. Drug Metab. Dispos. 27 (11), 1267–1273.
Wang, R., Moody, R.P., Koniecki, D., Zhu, J., 2009. Low molecular weight cyclic volatile methylsiloxanes in cosmetic products sold in Canada: implication for dermal exposure? Environ. Int. 35 (6), 900–904.
Yucuis, R.A., Stanier, C.O., Hornbuckle, K.C., 2013. Cyclic siloxanes in air: including identification of high levels in Chicago and distinct diurnal variation. Chemosphere 92 (8), 905–910.
Zhang, J., Falany, J., Xie, X., Falany, C., 2000. Induction of rat hepatic drug metabolizing enzymes by dimethylcyclosiloxanes? Chem. Biol. Interact. 124 (2), 133–147.
Zhang, K., Wong, J.W., Begley, T.H., Hayward, D.G., Limm, W., 2012. Determination of siloxanes in silicone products and potential migration to milk: formula and liquid simulants. Food Addit. Contam. 29 (8), 1311–1321.