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A global human health risk assessment for Decamethylcyclopentasiloxane (D_5)

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ABSTRACT

Decamethylcyclopentasiloxane (D_5) is a low-molecular-weight cyclic siloxane used primarily as an intermediate in the production of several widely-used industrial and consumer products and intentionally added to consumer products, personal products and some dry cleaning solvents. The global use requires consideration of consumer use information and risk assessment requirements from various sources and authoritative bodies. 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 and various independent scientific committees of the European Commission, as well as provide guidance for chemical safety assessments under REACH in Europe, and other relevant authoritative bodies. 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 to estimate internal dose metrics, benchmark modeling to determine a point of departure (POD), and a margin of safety (MOS) evaluation to compare the estimates of intake with the POD. Because of the specific pharmacokinetic behaviors of D_5 including high lipophilicity, high volatility with low blood-to-air partition coefficients and extensive metabolic clearance that regulate 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_5 using a MOS approach based on an internal dose metric removes the subjective application of uncertainty factors that may be applied across various regulatory agencies and allows examination of the differences between internal dose metrics associated with exposure and those associated with adverse effects.

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1. Introduction

Decamethylcyclopentasiloxane (D_5), a low-molecular-weight cyclic siloxane, is primarily used as an intermediate in the production of some widely-used industrial and consumer products and intentionally added to personal care products, cosmetics and in GreenEarth solvent used in dry cleaning. Consequently, its widespread use can result in the potential for exposure in workers (occupational exposure), consumers and the general public. The potential for human exposure has resulted in the identification of D_5 as a compound of interest to various authoritative bodies and scientific committees worldwide (e.g., United States Environmental Protection Agency (USEPA), Health Canada, and the Scientific Committee on Consumer Safety (SCCS)). However, the methods used, endpoints relied upon, and assumptions applied in assessing the potential for human risk across assessments have varied.

Rather than attempt to account for or justify differences in approaches and assumptions, a "globally harmonized" risk assessment was conducted that addresses the requirements for substance-specific risk assessments conducted by these various global agencies and committees. Based on the potential for exposure, this harmonized human health risk assessment considered the potential hazard from exposure to D_5 in workers, consumers, and the general public who may be exposed to D_5 either in the

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workplace, through the use of consumer products containing D_5, or to D_5 released to the environment.

In addition to consideration of the available exposure and toxicity data that are typically used in a standard risk assessment, an integrated multi-route multi-species physiologically based pharmacokinetic (PBPK) model for both the rat and the human was incorporated (McMullin et al., 2015). Rather than relying only on external air or dietary concentrations, 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_5 is a volatile cyclic methyl siloxane that has specific pharmacokinetic behaviors including high lipophilicity, high volatility with low blood-to air-partition coefficients and extensive hepatic metabolism (Battelle Northwest Toxicology, 2001; Dow Corning Corporation, 2003; Reddy et al., 2008; Xu and Kropscott, 2007). These properties lead to rapid systemic clearance of the parent material in the blood by exhalation and metabolism following inhalation, dermal and oral exposure. Because these multiple pharmacokinetic processes regulate tissue dose following D_5 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 exposure assessment that reflect these processes.

The results of a risk assessment or the risk characterization are typically numerical estimates of risk or hazard that are derived by comparing the estimated exposure or 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 for this assessment by comparing the estimated POD to the estimated intake. In addition to using this comparison for the MOS, both the POD and the estimated intake were expressed as the internal dose-metric using the results of a PBPK model, which incorporates species differences in physiology and pharmacokinetics. The magnitude of the MOS was then evaluated for the different potentially exposed populations (workers, consumers and the general public) 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 (Dekant and Klaunig this issue) as well as the application of studies in other hazard assessments conducted worldwide were considered (Environmental Control Center Co. 2011; Health Canada, 1994, 2008; REACH, 2011; REACH Registration Dossier, 2011; SCCS, 2010). All of the available toxicological literature was used in drawing conclusions regarding the potential for hazard following exposure to D_5 and determine which endpoints were the most sensitive or were observed following exposure to the lowest concentrations.

2.2. Dose-response assessment

Dose-response assessments have been conducted for D_5 by Health Canada (2008), the European Commission's Scientific Committee on Consumer Safety (SCCS, 2010) and under REACH (2011). The methodologies used globally are all similar in that they determine a Point of Departure (POD) and apply a form of safety/uncertainty factors to the POD to determine an acceptable dose/concentration. However, differences do remain due to the subjectivity and variability in the choice and application of uncertainty factors, not only in different countries, but also in different regulatory agencies within each country. 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 was made between the internal dose metric associated with the lower bound on the benchmark dose (BMDL) and the internal dose metric estimated for each relevant exposure scenario.

2.2.1. Estimation of the human equivalent concentration

When data from animal studies are extrapolated to humans to provide estimates of lifetime cancer risks, potential differences in pharmacokinetics (absorption, distribution, metabolism and excretion) and pharmacodynamics (sensitivity) between the animal species and humans should be considered in the estimation of human equivalent doses. A multi-route, multi-species PBPK model (McMullin et al., 2015) was used to estimate a internal dose metric associated with each of the animal exposure concentrations for use in dose–response modeling. For this assessment, the internal dose metric relied upon is the Area Under the Curve (AUC) of free D_5 (parent compound) in the blood. This assumption is justified based on the pharmacokinetic behavior and fate of D_5

Upon absorption, D_5 is either exhaled as parent D_5 or undergoes hepatic metabolism primarily to water soluble silanol metabolites that are rapidly removed from circulation and excreted by the kidney into the urine. A more polar yet still lipophilic metabolite (hydroxylated D_5) was also detected in fat and feces. This metabolite partitions primarily into the fat tissue and as it partitions back out into the blood it is further metabolized to the same water soluble silanol metabolites (that are rapidly eliminated) or is eliminated through enterohepatic circulation in the feces (Andersen et al., 2001; Reddy et al., 2003, 2007). Due to the uncertainty in the mode of action for the uterine tumor endpoint relied upon this assessment, the choice of using the free concentration of D_5 in the blood is the most reasonable moiety available for distribution to target tissues. The free concentration of parent D_5 in blood also provides a reasonable surrogate for target tissue dose because it partitions fairly equally between blood and tissues, with the exception of the fat tissue (McMullin et al., 2015). In addition, the use of an AUC as the most appropriate dose metric has been considered to be an appropriate dose metric for assessment to health risk related to lifetime exposure of systemically acting chemicals (USEPA, 2006a).

2.2.2. Estimation of point of departure

In conducting the dose–response modeling, two dose-metrics were considered. The first was the external animal exposure concentration in ppm adjusted from 6 hours per day and 5 days per week to continuous exposure. The second was the PBPK-derived animal internal dose metric (AUCs) for each exposure concentration. If there were no survival differences in treated animals, 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 typical models applied in BMD modeling, and the model with the best fit was chosen. Best 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.

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 an absolute 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

Estimates of exposure were based on measurements or models of existing conditions for the potentially exposed populations (workers, consumers and the general public).

Several populations that might be exposed to D_5 through various pathways included: occupational exposure to workers, consumers, and the general public. Occupational workers consist of persons who work in the production of D_5, in the formulation of this material into personal care products, individuals in the dry cleaning industry that use GreenEarth solvent, or in the use of these products in professional settings, such as beauticians and barbers. Primary exposure to D_5 in the occupational setting was considered to occur through the inhalation route, with beauticians and barbers also being exposed through the dermal route.

Consumers consist of persons who use personal care products, 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, lipstick). While potential exposure to consumer products occurs by all routes of exposure (dermal, oral or inhalation), the primary exposure 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.

General public consists of persons who may be exposed to ambient levels of D_5 released to the environment during manufacturing activities and to predicted levels of D_5 in soil, water, and food such as meat, vegetables, milk and breast milk. The primary routes of exposure for the general public considered were inhalation of D_5 in both indoor and outdoor air and oral exposure from the consumption of water, fish, vegetables, meat, milk, soil, anti-foam in food, and breast milk containing D_5. In general, monitoring programs have not been conducted to detect D_5 in food and water and it is uncertain if D_5 is present in any of the foods mentioned above or in drinking water.

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 highest potential for large exposure were included in the PBPK analysis. This involved the various exposure scenarios for dermal uptake from contact with the skin, inhalation from ambient air, or oral consumption of environmental media (water) or consumer/food products and identifies those pathways providing the greatest contribution of potential exposure. As the only exposure scenarios considered for the worker receptors were inhalation and dermal contact for barbers and beauticians, Monte Carlo analysis was not conducted for these receptors and the exposure for occupational receptors was evaluated directly by the PBPK analysis.

The Monte Carlo analysis produced an estimate of the intake of D_5 in mg/kg of body weight (bw)/day from each consumer item and from general sources (air, water, food and soil) using distributions for the parameters in order to prioritize the exposure to consumer products and to general sources; as well as assist in the identification of Consumer and General Public exposure pathways that provided the greatest potential for exposure to D_5. Only those exposure pathways that were associated with specific product usage that had the largest estimates for intake based on the results of the Monte Carlo analysis were then used with the PBPK model 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_5 included the following age-dependent and exposure-route-dependent scenarios with each product being evaluated independently:

Children.

- **Dermal route**: body lotion, conditioner (leave in), conditioner (rinse off), diaper cream, shampoo, soothing vapor, spray detangler, and sunscreen.
- **Ingestion route:** antifoam, baby bottle nipple, fish (general population), fish (subsistence population), breast milk, leafy vegetables (greens), meat, cow's milk, pacifier, root vegetables, sipper tube, soil, straws, water, and over-the-counter (OTC) antigas medication.
- **Inhalation route:** indoor air, outdoor air, 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**: antifoam, fish (general population), fish (subsistence population), leafy vegetables (greens), lipstick, meat, milk, root crops, soil, and water, as well as OTC antigas 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 were 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_5/kg bw/day. The mean reported intake for each pathway within each gender age group were then compared to evaluate which of the exposure pathways resulted in the higher estimates of intake and which would be considered to have a negligible contribution to overall intake.

A second Monte Carlo analysis was subsequently performed to estimate the total oral intake of D_5 per day (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, antifoam, 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 in grams per application (grams per application)
Freq = frequency of application (applications per day)
Conc = concentration of D_5 in the product as a percentage (%)
Abs = absorption fraction (fraction)
KF = kinetic factor (fraction)
Conv = conversion factor from g to mg (1000)
BW = body weight (kg)

Application rates of D_5 from the use of consumer products are typically provided as either grams/application (AppR) or grams per day (GD). If the application rate (AppR) is provided in units of grams/day, the equation is modified because the usage for a product, the Freq is assumed to be once per day, effectively replacing the AppR × Freq variables with GD.

Estimating exposure to D_5 from the use of hair care products requires modification to Equation (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 in grams per application (grams per application)
Freq = frequency of application (applications per day)
Conv = conversion factor from g to mg (1000)
Conc = concentration of D_5 in the product (%)
Abs = absorption fraction (fraction)
KF = kinetic factor (fraction)
Res = product (residue) left on hands and scalp after rinsing (fraction)
Dep = fraction deposited on hands and scalp versus the hair (fraction)
BW = body weight (kg)

Body weight distributions for males and females in the European nations that were considered are presented in Supplementary Table S-6. The mean values were obtained from the ECETOC Exposure Factors Sourcebook (ECETOC, 2001) while the standard deviations were taken from Eurostat (2002). 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 encompass the default body weight values used globally for risk assessment. Additionally, the distribution of body weights assumed in the Monte Carlo analysis from the NHANES data encompasses the body weights available for other populations.

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 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 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 was estimated based on the ratio of the surface area of the scalp to that of the hair on the head (<0.05). Based on the average length of one hair of 10 cm for men and 15 cm for women (ICRP, 2002), an average diameter of each hair of 60 microns (Kalopissis, 1986), and an average of 115000 hairs on the scalp (Kalopissis, 1986), the surface area of hair over which a HC product could be distributed was approximately 22000 cm^2 for men and 33000 cm^2 for women. 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 deposited on the skin. These residue fractions do not take into consideration the volatility of D_5. 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 interview 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 products (USEPA, 1997; USFDA, 1982; USFDA, 1978). For the remaining products, a conservative residue fraction of 1 (100%) was assumed.

A study performed by Reddy et al. (2007), indicated that 83% of the dermally applied D_5 (0.94 g for women, 1.34 g for men) that reaches the systemic circulation was eliminated by exhalation within 24 hours. The 17% (0.17) that reached the systemic circulation and was not exhaled was considered representative of the kinetic factor. A value of 0.0004 (0.04%) was used as the dermal absorption factor as described in Jovanovic et al. (2008). The 0.045 was determined by the average amount of neat D_5 absorbed after 24 hours of exposure to cadaver skin *in vitro*. 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_5 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; Horii and Kannan, 2008; Health Canada, 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 (2.35 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_5 in various consumer products (Supplementary Table S-9) was used as the amount of D_5 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_5 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_5 via inhalation, the following general equation can be used:

$$Intake(mg/kg/day) = \frac{Conc \times Conv \times BR \times KF}{BW} \quad (3)$$

where:

Conc = concentration of D_5 in the air (μg/m3)
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_5 following the application of soothing vapor, the following equation must be used:

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

where:

AppR = application rate of soothing vapor in grams per application (grams per application)
Freq = frequency of soothing vapor use (applications per day)
Conv = conversion factor from g to mg (1000)
Conc = concentration of D_5 in soothing vapor (%)
FV = fraction of product volatizing (fraction)
BR = breathing rate (m3/day)
KF = kinetic factor (fraction)
BW = body weight (kg)
Room = area of the room in cubic meters (m^3)

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. Inhalation rates used in the Monte Carlo analysis were obtained from USEPA (2011) and are provided in Supplementary Table S-10.

2.3.1.2.1. General public. Indoor air concentrations used for the Monte Carlo analysis were derived from the NYIEQ (2005) assessment. NYIEQ (2005) reported a median D_5 concentration in indoor air of 34.5 μg/m^3 with a range of 2.3–1560 μg/m^3. These data were relied upon to determine a triangular distribution using the median value of 34.5 μg/m^3 as the most likely value with a minimum of 0.05 μg/m^3 and a maximum of 1560 μg/m^3. This distribution includes the ranges of indoor air concentrations seen in other studies (Hodgson and Levin, 2003; Norden, 2005; Shields et al., 1996; Wu et al., 2011; Yucuis et al., 2013).

For the outdoor air concentrations used in the Monte Carlo analysis, values from all the available studies that reported outdoor air concentrations were combined to determine a lognormal distribution with a mean of 1.4 μg/m^3 and a standard deviation of 8.34 (Boehmer et al., 2001; Kaj et al., 2005; Norden, 2005; Shields et al., 1996; Yucuis et al., 2013). The distribution was truncated at 20 μg/m^3, the largest value reported.

2.3.1.3. Ingestion. Intake of D_5 for ingestion scenarios (e.g., ingestion of water, soil, fish, and other food, OTC anti-gas medication, etc.) was determined using the following equations:

For water or soil:

$$Intake(mg/kg/day) = \frac{Amt \times Conc \times Conv \times Bio}{BW} \quad (5)$$

where:

Amt = amount consumed per day (L/day or mg/day)
Conc = concentration of D_5 in the product (mg/L or μg/kg)
Conv = conversion factor (for soil from μg to mg in conc and mg to kg in amt (1/1000000) or for water the conv is 1)
Bio = bioavailability fraction
BW = body weight (kg)

For intake of D_5 contained in food:

$$Intake(mg/kg/day) = Amt \times Conc \times Conv \times Bio \quad (6)$$

where:

Amt = amount consumed (g/kg BW/day)
Conc = concentration of D_5 in the food (mg/kg)
Conv = conversion factor from g to kg (1/1000)
Bio = bioavailability fraction
BW = body weight (kg)

For intake of D_5 contained in fish by a subsistence fisherman:

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

where:

Amt = amount consumed per day (g/day)
Conc = concentration of D_5 in the fish (mg/kg)
Conv = conversion factor (g to kg (1/1000)
Bio = bioavailability fraction
BW = body weight (kg)

For intake of OTC medications:

$$Intake(mg/kg/day) = \frac{Amt \times Freq \times Conc \times Conv \times Bio}{BW} \quad (8)$$

where:

Amt = amount consumed per use (g)
Freq = frequency of use (times/day)
Conc = concentration of D_5 in the product (μg/g)
Conv = conversion factor (μg to mg (1/1000)
Bio = bioavailability fraction
BW = body weight (kg)

Intakes due to the ingestion of antifoam present in processed

food and the incidental ingestion of lipstick were calculated using alternate ingestion equations. The antifoam equation considers how much food is consumed per day as well as the percentage that contains antifoam.

$$Intake(mg/kg/day) = Amt \times AF \times Conc \times Frac \times Conv \times Bio \quad (9)$$

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_5 in the antifoam
Conv = conversion factor from g to kg (1/1000)
Bio = bioavailability fraction

For lipstick, multiple applications could be possible during a day so the equation was adjusted to account for that difference.

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

where:

Amt = amount of lipstick (g/application)
Conc = concentration of D_5 in the product (mg/g)
Freq = frequency of usage (applications/day)
Bio = bioavailability fraction
BW = body weight (kg)

Intakes due to the use of baby bottle nipples, pacifiers, and sipper tubes were calculated using the ingestion equations as presented below:

$$Intake(mg/kg/day) = \frac{Wgt \times Conc \times MF \times Conv \times Bio}{BW} \quad (11)$$

where:

Wgt = weight of product (grams)
Conc = concentration of D_5 in the product (mg/g)
MF = the fraction of D_5 in the product that can migrate per day (%)
Conv = conversion factor from g to kg (1/1000)
Bio = bioavailability fraction
BW = body weight (kg)

The migration fraction (MF) is an estimate of the amount of D_5 that can migrate out of the nipple, pacifiers, and sipper tubes into formula, milk, salvia, 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 factor of 0.0046% per day was used for the amount of D_5 that could migrate from baby bottle nipples, pacifiers, sipper tubes and straws 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, including silicone nipples and silicone cookware and 2) to determine the potential migration of siloxanes from products to milk, formula, and liquid simulants. Concentrations of D_5 determined in silicone nipples ranged from 0.5 to 269 μg/g of product with a median value of 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 cake pans, with an average D_5 concentration of 3451 mg/kg, as surrogates for silicone nipples. After 24 hours, only trace amounts of D_5 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. Using the concentration of D_5 in the product tested (3451 mg/kg), the amount of the product placed into solution (2 g) and the amount of solution tested for D_5 (10 ml), a conservative estimate of the fraction of migration of D_5 is 0.000046. This was considered a conservative assumption, as it assumes that the amount of D_5 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. 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_5 in food was determined from a study reported in Jovanovic et al. (2003) to evaluate the absorption of [^{14}C]-D_5 by various carriers after a single oral dose (i.e., corn oil, simethicone fluid, and neat [^{14}C]-D_5). Doses of D_5 in each carrier were administered to female Fischer 344 rats. The mass balance data obtained showed that 19.62%, 25.81%, and 9.94% of the administered [^{14}C]-D_5 was absorbed when delivered in the corn oil, simethicone fluid, and neat [^{14}C]-D_5, respectively. These percentages were used as the bioavailability fractions for all food products. A normal distribution with a mean of 19.62% and a standard deviation of 0.042 was used. For OTC medications and antifoam in food, the absorption reported for D_5 in simethicone fluid was used as a normal distribution with mean of 25.81% and a standard deviation of 0.044.

2.3.1.3.1. General public. The various consumption rates of environmental media/food for the General Public receptor for water, soil, fish, milk, meat and vegetables was based on information from USEPA (2011), Health Canada (2008), CSFII 1994–96 (USDA, 1998) and Kitakanto Branch of the Environmental Control Center Co. of Japan (Environmental Control Center Co. 2011). Concentrations of D_5 in the various media ranging from 8.30×10^{-6} to 1 mg D_5/kg of food were based upon data, either measured or predicted, provided in Brooke et al. (2009), Health Canada (2008), Boehmer and Gerhards (2003), Norden (2005), NILU (2007), and Kitakanto Branch of the Environmental Control Center Co. of Japan (Environmental Control Center Co. 2011). This included concentrations of D_5 for water, fish, meat, milk, and vegetables. Concentrations of D_5 in breast milk were obtained from Kaj et al. (2005).

Concentrations of D_5 from antifoam in food were provided in two Dow Corning Corporation internal reports (Dow Corning Corporation, 2004, 2007) and varied from 0 to 10 ppm. The percentage of antifoam in food is consistent with the USFDA code of regulations (USFDA, 2012) for the maximum concentration of defoaming agents in processed foods of 10 ppm and the EU (European Commission, 2011) database on Food Additives (European Commission, 2011). It was assumed that 50% of the food consumed would contain antifoam which is a very conservative estimate as antifoam is only contained in some processed food (excluding 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 antifoam. For the child receptor, a subsistence fish consumption rate and consumption rates for breast milk were obtained from USEPA (2006b).

2.3.2. Application of PBPK model

The final step of the exposure assessment was conducted using the PBPK model (McMullin et al., 2015). This model was executed with human parameter values (for both physiological parameters, such as ventilation rate or cardiac output, and for D_5-specific parameters, such as partition coefficients) to develop estimated internal dose-metrics that were unique to the receptor, route of exposure, and exposure pattern.

Characterization of exposure scenarios and estimation of D_5 intake for the selected receptors (i.e., worker, consumer, general public) were conducted. These parameter values were used with the PBPK model to determine 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 the triangular distribution, the midpoint of the uniform distribution, or the mean value for 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_5 from the combined oral sources of food, water, soil, antifoam and lipstick. The individual consumption of D_5 taken in with root crops, greens, meat, milk, water, antifoam, soil, and fish were summed for males and females with the addition of D_5 in lipstick for females. For the subsistence fisherman, the distribution of amount of fish consumed was obtained from USEPA (2006a). One hundred thousand iterations were run in the Monte Carlo analysis which provided distributions of daily intakes. The mean and 90^{th} 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_5 from the oral route.

2.3.2.1. Occupational. As stated earlier no analysis of potential oral exposure to D_5 for a worker was conducted in the Monte Carlo analysis and no exposure to D_5 through the oral (ingestion) scenario was expected to occur during occupational exposure; therefore, exposure to workers was limited to the dermal and inhalation scenarios only. Barbers and Beauticians were the only occupation workers considered to have the potential for dermal exposure through the application of HC products containing D_5.

Data on application rates, the fraction of product deposited on the skin, the fraction of residue left by rinse-off products on skin, and the amount of D_5 in hair care products were collected to determine the product that would provide an upper bound estimate of the amount of D_5 to which the workers could be exposed. Based on information provided in Table 1, the use of conditioner products would provide the largest amount of exposure to D_5 to a barber/beautician. This was determined by multiplying the grams of application by the percentage of D_5 in the product and the deposition and residue fraction. Therefore, to get the most conservative estimate of exposure and therefore the highest internal dose metric using the PBPK model, the data for conditioner products were used because it was the HC product that would result in the highest exposure to D_5, when the application rate, the percentage of D_5 in the product, and the deposition and residue fractions were considered. This information is considered a conservative representative exposure for HC products because the amount of D_5 in conditioners is four times higher than any other product considered and approximately 60 times higher than shampoo (the most used HC product). Other PBPK input parameters used are provided in detail in Table 2.

D_5 air concentrations were measured in the workplace using personal monitors for the following groups of workers that may be exposed to D_5 via inhalation during the performance of their job: 1) workers involved in the formulation of AP/Ds; 2) workers involved in the manufacture of HC/SC products; 3) workers in dry cleaning establishments that use GreenEarth solvent; 4) workers in a D_5 production facility; and, 5) barbers and beauticians. For workers involved in the production of D_5, an arithmetic mean, time-weighted average D_5 air concentration of 0.0587 ppm was estimated (Maxim, 1998). For workers in plants that formulated consumer products containing D_5, Maxim (1998) reported average concentrations of 2.23 ppm for AP workers, 1.06 ppm for SC workers, and 0.002 ppm for HC workers (Table 3). Representative air concentration of 0.143 ppm and 0.008 ppm were obtained for dry cleaners (Severn Trent Laboratories, 2001) and beauticians and barbers (Maxim, 1998), respectively (Table 3). Several indoor air data concentrations were also evaluated to represent the range of exposures to a general office worker. The value of 9.7 $\mu g/m^3$ (Norden, 2005) (Table 10) was used within this assessment to represent the mean exposure to a resident which could be representative of someone working out of their home. The value of 39 $\mu g/m^3$ (Shields et al., 1996) was used to represent the mean exposure to an office worker (Table 10). A concentration of 120 $\mu g/m^3$ (Wu et al., 2011) was used as the upper bound on indoor air exposure as this was larger than most of the ranges given. An inhalation rate for moderate activity of 1.6 and 1.4 m^3/hour for males and females, respectively, were used for workers during the work day (USEPA, 2011) (Table 3).

The U.S. Department of Labor's Bureau of Labor Statistics (2012) reported the range of hours in the annual average work week for barber shops and beauty salons to be from 26.3 hours to 28.3 hours for the years 1995 through 2012. An average of 28 hours per week or 5.6 hours per day for 50 weeks out of the year was used for both the dermal and inhalation analysis.

For most workers exposed to D_5 (e.g., workers in antiperspirant, skin care and hair care plants and dry cleaner workers), a standard 8 hour work day was assumed. However, due to the manner in which shifts were typically scheduled for silicone workers, an 8.75 hour day was used (Maxim, 1998) and is consistent with other recently published data (US Bureau of Labor Statistics, (2013)).

For all occupational exposures analyses, 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 (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 for men and 6.4/80 for women.

For the dermal exposure scenario for barbers and beauticians, the frequency of a hair product being applied was assumed to occur once every 30 min during the work day for a 5 day work week and every 27 min for a 4 day work week. Therefore, the number of applications of HC products in a day was assumed to be 12 to 15 over a 5 or 4-day work week for 50 weeks per year. The HC products used by barbers and beauticians were assumed to contact both sides of the hands which represent a surface area of 890 cm^2 in females and 1070 cm^2 in males.

Alveolar ventilation rates used for the inhalation exposure analysis were equivalent to pulmonary ventilation rates of 1.6 and

Table 1
Hair care products used by barbers/beauticians containing D_5.

Hair care products	Application rate (g/use)	Midpoint D_5 (%)	Amount of exposure to D_5 (g/use)
Shampoo	6[e]	0.02[f]	0.0012
Rinse-out Conditioner	13.77[b]	44.5[f]	6.1277
Leave-in Conditioner	13.77[b]	44.5[f]	6.1277
Hair Spray	5.8[d]	27[c]	1.3986
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 form Loretz et al., 2008.
[c] Maximum midpoint of ranges presented in studies (see Tables 4 and 5).
[d] Mean value form 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)	13.77	13.77	Loretz et al., 2008
Amount of D_5 (%)	56	56	Johnson et al. (2011); Median value from D_5 in other noncoloring hair products
Residue Fraction	0.01	0.01	See Section 2.3.1.1
Exposure Frequency (applications per day)	12	12	Professional Judgment
Days per week	5	5	
Weeks per year	50	50	
Surface Area[a] (cm^2)	1070	890	USEPA 2011
Body Weight (kg)	87	73	CDC (2007–2010)

[a] Surface area of the hands.

Table 3
Summary of inhalation exposure parameters – workers.

Worker	Air concentration[a] (ppm)	Daily exposure[e] (hours/day)	Parameter exposure frequency[e] (days/week)	Work year[e] (weeks/year)	Inhalation rate[f] (m3/hr)	Body weight[g] (kg)
Antiperspirant	2.23 (1.07)	8	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Skin Care	1.06 (0.83)	8	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Hair Care	0.002 (0.001)	8	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Dry Cleaner	0.143 (0.103)	8	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Silicone	0.0587 (0.0286)[b]	8.75[c]	5	50	1.6 (M) 1.4 (F)	86.9 (M) 73.4 (W)
Barbers and Beauticians	0.008[h]	5.6[d]	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 are reported in Maxim (1998).
[d] Based upon The US 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 (2007–2010) data.
[h] Value based on sample from Wu et al. (2011). Similar value of 0.006 ppm presented in Maxim (1998).

1.4 m^3/hour for males and females, respectively, during work hours and 0.8 and 0.7 m^3/hour for non-work hours for males and females. Cardiac output rates were calculated based on an equation relating alveolar ventilation and cardiac output (Clewell et al., 2004). The evaporation rate of D_5 from the site of application and the absorption rate into the skin were adjusted based on the available data (Reddy et al., 2007).

2.3.2.2. Consumers. The key considerations in estimating internal dose metrics associated with dermal exposure from the use of consumer products were the amount of D_5 in the product, the amount applied, the surface area over which the product was applied, and the frequency of that application. The values for these parameters are presented in 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_5, the surface area is estimated based upon a percentage of the body part to which the product is applied. The surface areas used to derive the application areas used in the PBPK analysis are summarized in the Supplementary Table S-8. Median axilla surface areas were reported for females and males in Cowan-Elsberry et al. (2008) (64.5 cm^2 and 135.5 cm^2,

Table 4
Application parameter values for consumer user.

Product	Application rate (gms/day)	Application frequency (application/day)[h]	Midpoint D_5 (%)[b]
Antiperspirant/Deodorant gel or roll-on	1.22 (male)[c] 0.898 (female)[c]	1.3	40.5
Antiperspirant/Deodorant stick or solid	0.79 (male)[f] 0.61 (female)[f]	1.3	40.5
Antiperspirant/Deodorant aerosol	3.478[c]	1.3	40.5
Shampoo	6[c]	1	0.02
Conditioner (Leave-in)	13.77[e]	1	44.5
Conditioner (Rinse-out)	13.77[e]	1	44.5
Hair Care – Hair Spray			
Aerosol	3.57[f]	1	18.1
Pump	5.18[f]	1	18.1
Cosmetic Foundation	0.33[g]	1	50
Cosmetic Under-eye Cream	0.06[a]	1	11.2
Cosmetic Mascara	0.11[a]	1	16.8
Cosmetic Lipstick	0.025[c]	1	28.5
Skin Care – After Shave Gel	0.95[a]	1	11.5
Skin Care – Lotion (Hand/Body)	8.69[c]	1	44.2
Skin Care – Moisturizer	0.91[c]	1	47
Skin Care – Nail Care	0.25[a]	1	47
Skin Care – Sunscreen	6.1[a]	1	24.6
Soothing Vapor	5[d]	2	0.03

[a] For Maxim (1998), maximum application rates were selected as those having greater than a 1% response for those numbers of days.
[b] Midpoints calculated from Johnson et al. (2011).
[c] Hall et al. 2007.
[d] Meeks 2005.
[e] Loretz et al. 2008.
[f] Loretz et al. 2006.
[g] Hall et al. 2011.
[h] Personal judgment.

Table 5
Surface 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	USEPA 2011
Cosmetic – foundation Skin Care – Moisturizer	NA	570	½ head	USEPA 2011
Cosmetic – under-eye cream	NA	11.4	1% of head	USEPA 2011
Skin Care – after shave gel	340,535	NA	¼ head ½ hands	USEPA 2011
Skin Care – lotion (hand/body), sunscreen	20,670	17,000	Body – Head	USEPA 2011
Skin Care – nail care	NA	11		SCCS 2003

Table 6
Summary of inhalation exposure parameters for consumer product exposure.

Parameter	Men	Women	Source
Air Concentration (AC)			
AP/C Solid	0.2 ppm	0.2 ppm	Andersen and Weaver 1989
AP/D Roll-on	1.7 ppm	1.7 ppm	
AP/D Aerosol	0.65 ppm	0.65 ppm	Maxim 1998
HC/SC Products	0.178 ppm	0.178 ppm	
Exposure Duration (ED)	5 min	10 min	USEPA 2011 [a]
Application Factor (AF)			
AP/D Products	9.1 apps/week	9.1 apps/week	Loretz et al. 2006
HC/SC Products	7 apps/week	7 apps/week	Professional judgment
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.

respectively). The surface area reported in Table 5 is doubled the values reported in Cowan-Ellsberry to take in consideration of application of antiperspirants/deodorants to both axilla.

Exposures to various products containing various amounts of D_5 were assumed to occur once per day for various numbers of days per week for both men and women (Table 4). Consumer products for which there were exceptions to this exposure scenario included moisturizer exposure, which was simulated to occur twice per day (once every 12 hours), and sunscreen exposures, which were assumed to occur for eleven consecutive days once per year.

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_5. Therefore, the PBPK modeling was conducted using air concentration data that was available for selected consumer products.

The average case breathing zone concentrations of D_5 were estimated to be 0.2, 1.7, and 0.65 ppm for solid, roll-on, and aerosol, respectively. These values were based on data obtained from a

Table 7
Summary of inhalation exposure parameters for general public.

Parameter	Value	Source
Air Concentration		
Indoor	34.5 μg/m^3 (0.00227 ppm) or 393 μg/m^3 (0.0259 ppm)	Health Canada 2008; NYIEQ 2005
Outdoor	0.5 μg/m^3 (0.00003 ppm)	Shields et al. 1996
Exposure Duration		
Indoor	24 h/day	Professional judgment
Outdoor	24 h/day	Professional judgment
Exposure Frequency	7 days/week	Professional judgment
Year	52 weeks/year	Professional judgment
Inhalation Rates (m^3/hour)	0.8 (male) 0.7 (female)	USEPA 2011
Body Weights (kg)	86.9 (male) 73.4 (female)	CDC (2007–2010)

[a] since the PBPK model is not set up for accounting for varying inhalation exposure during the day, 24 h exposure to either indoor and outdoor air was assumed.

Table 8
Dose-response model predicted $BMDL_{10}$.

Incidence of uterine endometrial adenomas	Exposure dose (ppm)	Adjusted exposure doses (ppm) adjusted to continuous from 6 h per day and 5 days per week	Human equivalent doses (HED)
			AUC (mg-hrs/L/day)
0/60	0	0	0
1/60	10	1.79	0.35
0/60	40	7.14	1.39
5/60	160	28.57	5.57
$BMDL_{10}$	131	23.43	4.57

Table 9
Results of BMDS Modeling for the incidence of Uterine Adenocarcinomas 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	52.801	0.156	0	166.2	135.5	29.67	24.19	5.79	4.72
Logistic	51.173	0.301	0.043	173.7	141.0	31.02	25.18	6.05	4.91
LogLogistic	52.801	0.156	0	163.6	135.1	29.21	24.11	5.70	4.71
LogProbit	52.801	0.156	0	167.1	132.5	29.82	23.65	5.82	4.61
Multistage	50.947	0.354	0.035	175.3	131.3	31.31	23.43	6.11	4.57
Multistage-Cancer	50.947	0.354	0.035	175.3	131.3	31.31	23.43	6.11	4.57
Probit	51.251	0.295	0.063	177.4	137.3	31.68	24.52	6.18	4.78
Weibull	52.801	0.156	0	163.5	134.8	29.19	24.05	5.70	4.69
Quantal-Linear	52.010	0.275	0.291	224.0	117.4	39.98	20.95	7.80	4.09

[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 per day, and 5 days per week 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_5 in arterial blood.

study conducted by Dow Corning (Andersen and Weaver, 1989) in which three different commercial D_5-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. These values were calculated as the average of the high application and lower application time-weighted average concentration of cyclics measured multiplied by the percent D_5 in that product.

A time-weighted average D_5 concentration of 0.178 ppm was determined for general HC products. This value was based on a study in which six personal monitoring samples were taken while six volunteers were using shampoos, conditioners, and hair sprays containing D_5. Following application of the HC products, users remained in the room where the products were applied for 17–40 min. Since no studies were identified related to SC products, 0.178 ppm was also assumed as representative of these products and was assumed applicable to both men and women.

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_5 vapor during this time D_5 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_5 in the air. Using the median percentile from the time spent in the bathroom after a bath or shower reported from the Exposure Factors Handbook (USEPA, 2011) gives a weekly time of 0.58 hours/week for men and 1.17 hours/week for women.

The frequency of use for AP/D for this exposure assessment was set at 1.3 applications per day or 9.1 times a week (Loretz et al.,

Table 10
Area under the curve: Occupational Exposure.

Worker	AUC (mg-hrs/L/day)	
	Men	Women
Dermal Exposure		
Barbers and Beauticians		
5 days	3.6×10^{-4}	3.6×10^{-4}
4 days	3.7×10^{-4}	3.7×10^{-4}
Inhalation Exposure		
Antiperspirant	9.6×10^{-2}	9.4×10^{-2}
Skin Care	4.6×10^{-2}	4.5×10^{-2}
Hair Care	8.6×10^{-5}	8.5×10^{-5}
Dry Cleaner	6.1×10^{-3}	6.0×10^{-3}
Silicone	2.8×10^{-3}	2.7×10^{-3}
Barbers and Beauticians	2.4×10^{-4}	2.4×10^{-4}
Office Worker		
9.7 μg/m^3	2.6×10^{-5}	2.5×10^{-5}
39 μg/m^3	1.0×10^{-4}	1.0×10^{-4}
120 μg/m^3	3.2×10^{-4}	3.1×10^{-4}

2006). This information is from a study in 360 women ages 19–65, in 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). No reported information was available in the study for aerosols and roll-on antiperspirants, and their application frequency was assumed to be similar. Additionally, this value is expected to be suitable for a man's use of antiperspirant. This value differs from the application frequency used in the dermal contact evaluation since that evaluation had an application rate based on a gram per day basis indicating an implied application frequency of once per day.

Soothing vapor was identified as a consumer product of interest based upon the potential volatilization of D_5 into air. The air concentration for soothing vapor was estimated by multiplying the percent of D_5 in soothing vapor (0.03%) by the grams applied (5 g per day) multiplied by two applications per day. This result was then divided by an estimated room volume of 10 m^3 resulting in a D_5 air concentration of 0.3 mg/m^3 (or 0.02 ppm). This was assumed to be a consistent dose in the room in which the person applying the soothing vapor stayed.

The PBPK simulations for the inhalation exposure of consumers used the same alveolar ventilation rates and cardiac outputs as the dermal simulations with the frequency of application and other parameters as described above. As with the dermal simulations, the AUC was determined following one year of exposure.

2.3.2.3. General public. NYIEQ (2005) identified a value of 34.5 μg/m^3 as representative of the indoor air concentration to which an individual would be exposed. As a conservative bounding estimate a value of 393 μg/m^3 representing the 90th percentile from all available data was estimated by Health Canada (2008) and was also used to predict the amount of exposure from indoor air. A value of 0.5 μg/m^3 was identified (Health Canada, 2008) as representative of the typical exposure to D_5 in outdoor air to estimate D_5 exposure for the general public. Although the general public would be assumed to be exposed to a combination of concentrations of D_5 in indoor air for a certain number of hours and to outdoor air for the remainder of the day simulating this was not possible with the current PBPK model. For this evaluation, estimates of exposure for the general public were estimated under the assumption that a person would be indoors 24 hours per day or outdoors 24 hours per day. This bounds the potential for exposure with outdoor exposure representing the minimum and indoor exposure representing the maximum, while the exposure from being present both indoors and outdoors during the day falls somewhere between. Other required parameters used in the PBPK model 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 same alveolar ventilation rates and cardiac outputs were used for these simulations as were used for the consumer simulations.

The PBPK simulations for the oral exposure of the general public and subsistence fisherman used a modified version of the oral PBPK model. The existing version of the model (McMullin et al., 2015) only allows for a single bolus dose or intake to be applied per day. As the oral intake of D_5 from either food or lipstick products is anticipated to be episodic based on the standard of multiple meals per day for food intake and multiple applications of lipstick per day (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_5 for adults was estimated using a Monte Carlo analysis. This intake was a combination resulting from the consumption of D_5 in root crops, greens, meat, milk, water, antifoam, soil, lipstick and seafood determined by the MC analysis. The intake was divided into fifths, allowing for episodic equal intakes of one-fifth of the total daily consumption of D_5, spaced out over the day at 8 AM, 10 AM, 12 AM, 4 PM and 7 PM.

2.4. Risk characterization

In this assessment, rather than attempting to derive uncertainty factors that may be used by the various regulatory agencies and programs (i.e. Health Canada, REACH, SCCS, OSHA, USEPA) to adjust the POD for low-dose extrapolation, a comparison of the internal dose metric associated with the POD to the internal dose metric estimated for each exposure scenario was conducted. The use of these ratios or Margins of Safety (MOS) removes the need to consider various uncertainty factors that may be applied across various regulatory agencies globally.

In evaluating each MOS for different exposure scenarios, different MOS may be protective of human health. For occupational exposures, OSHA considers a risk of 1×10^{-4} or less as acceptable. In applying uncertainty factors to the POD, OSHA may include a factor of 10 for intrahuman variability and a factor of 3 for extrapolation from animal-to-human allowing for uncertainties in pharmacodynamics across species. In comparison, the highest uncertainty factor applied in the REACH Chemical Safety Report (REACH, 2011) in the derivation of occupation DNELs for D_5 was 3 for intraspecies differences. Based on the highest anticipated factor of 30 for noncarcinogenic effects, a MOS of greater than 30 would be acceptable.

For environmental exposures or exposures through the use of consumer products, the highest uncertainty factor applied by REACH in the D_5 assessment was 10. For USEPA in the derivation of RfC or RfD values, the factors typically applied to the POD would include factors of up to 10 and would account for one or more of the following uncertainties: intrahuman variability, interspecies extrapolation, use of precursor data, and remaining sources of uncertainty in the database. This would include a factor of 10 for intrahuman variability, 3 for extrapolation from animal-to-human allowing for uncertainties in pharmacodynamics across species (although it could be argued that a factor of 1 is appropriate because 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, based on the uncertainty factors that could be applied by regulatory agencies or authoritative bodies

globally, 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 data for D_5 (Dekant and Klaunig this issue) and regulatory reviews of these data (Environmental Control Center Co. 2011; Health Canada, 2008; Lassen et al., 2005; REACH, 2011; REACH Registration Dossier, 2011; SCCS, 2010) have identified the liver as a potential target organ following repeated-dose oral exposure and liver, lungs and uterus as potential target organs following repeated-dose inhalation exposure. No significant toxicological effects were observed following repeated-dose dermal exposure to D_5 following exposure to doses as high as 1600 mg/kg bw/day. Based on the literature D_5 is not genotoxic. The only treatment-related endpoint identified following inhalation exposure to D_5 was the statistically significant increase in uterine adenocarcinomas observed in female rats following 24 month exposure to 160 ppm D_5. The incidence of these tumors was 0/60 in the control and 1/60, 0/60 and 5/60 in the low, mid- and high treatment groups, respectively. Survival was not affected in any treatment group, with the first uterine adenocarcinoma found in an animal in the low dose group after approximately 1.5 years of exposure, while those noted in the high exposure group were found at or near terminal sacrifice. The tumors in the treated groups were also histologically indistinguishable from those found in control rats in other NTP studies (Experimental Pathology Laboratories, 2003).

Following both oral and inhalation exposure (14 days–3 months) to D_5, increases in liver weights were reported. Because no accompanying histopathological changes were observed in these studies and no liver effects were reported in the chronic inhalation toxicity/carcinogenicity study, these effects have been suggested to be adaptive, non-adverse transient effects in the rodent. Further, enzyme induction studies conducted in rats indicate induction of Cytochrome P450 pathways that are consistent with the classical response observed following phenobarbital treatment. This indicates that D_5 was a weak phenobarbital-type inducer in the rat liver. However, it has also been noted that there may be important mechanistic differences between rodents and humans in phenobarbital-type inducers (Health Canada, 2008; Zhang et al., 2000). While these changes have been assessed as relevant to human health, it is also unclear as to whether they would represent "adverse" changes, due to the lack of accompanying histological changes in the rodent and the lack of liver effects at the terminal sacrifice in the chronic inhalation toxicity/carcinogenicity study. In summary, D_5 is a not a genotoxic carcinogen and while the results of mode of action studies are not clear, the tumorogenic effects observed in Fischer 344 female rats may be species-specific with no risk or relevance to human health.

3.2. Dose-response assessment

3.2.1. Selection of data and approach for dose-response modeling

Based on the review of the toxicological literature on D_5, dose–response modeling was conducted relying upon the incidence of uterine adenocarcinomas in female rats after inhalation exposure to 160 ppm of D_5 for two years (Experimental Pathology Laboratories, 2003). Administration of D_5 did not produce other significant, treatment-related carcinogenic or noncarcinogenic effects in the chronic inhalation toxicity/carcinogenicity study, nor were any clearly relevant, treatment-related adverse effects noted in reproductive or immunotoxicity studies.

The incidence of uterine adenocarcinomas (0/60, 1/60, 0/60 and 5/60 in the control, low, mid- and high treatment groups, respectively) does not increase with increasing exposure concentration, with no statistically significant increase in tumor incidence only observed at the highest concentration tested (160 ppm). While the mode of action of D_5 in the production of uterine tumors is unknown, there is some evidence that the tumors are occurring by a nonlinear mode of action. Based on the literature D_5 is not genotoxic. Carcinogens acting by a linear mode of action are generally considered to be DNA reactive and have direct genotoxic activity. In general, a nongenotoxic carcinogen that exhibits a threshold response has a POD that is either the externally derived no observed adverse effect level (NOAEL) or the benchmark dose (BMD). Uncertainty or safety factors are then applied to the POD to develop permissible exposure levels at which no relevant human cancer risk are anticipated. However, there are limitations to the NOAEL approach, which have been used in prior risk assessments conducted for D_5 (Health Canada, 2008; REACH, 2011; SCCS, 2010).

These 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/C/LOAEL/C approach for determining the POD, the BMD approach was chosen as the method for derivation of a POD for D5 in this assessment.

3.2.2. Estimation of the human equivalent dose

Simulations were run with the rodent PBPK model using the female rat parameters to simulate exposure for 6 h per day, 5 days per week, for 2 years to 10, 40 or 160 ppm D_5 to derive the AUC of the free D_5 in the blood in the rat for each experimental concentration applied in the Experimental Pathology Laboratories (2003) study (Table 8). It was assumed that the resulting AUC in the rat is the AUC for estimating the human equivalent concentration (HEC), which is 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). The human PBPK model was then used to provide the human AUCs for each of the exposure scenarios considered (Section 4.0) for comparison to the estimated POD from the dose–response modeling. Since the POD is in terms of the rat AUC, and the rat AUC is assumed to be equivalent to the human AUC or the relevant

target tissue concentration associated with the endpoint of concern, the human AUCs for each exposure scenario can be used to determine MOS using the ratio of these values.

3.2.3. Estimation of point of departure

The BMDs and BMDLs derived using the BMDS software are presented in Table 9 including the goodness-of-fit criteria. The model chosen as the "best fit" to the incidence of uterine adenocarcinomas was the Multistage model, which has the form:

$$p(d) = \gamma + (1-\gamma) \times \left(1 - e^{-q_1 \times d + q_2 \times d^2 \ldots q_k d^k}\right)$$

where P(d) is the probability of developing cancer from a lifetime continuous exposure at that dose, $q_i = 1, \ldots k$ are the fitted dose coefficients of the model, and k is the number of stages selected through the best fit of the model, typically not greater than one less than the number of dose groups. Using the continuous animal exposure doses in the evaluation of the tumor data, the estimate of the exposure in ppm at a BMR of 10%, the $BMDL_{10}$ or POD is 23.43 ppm. Using the internal dose-metrics (AUC of free D_5 in the blood), the $BMDL_{10}$ is 4.57 mg-hrs/L/day.

3.3. Exposure assessment

3.3.1. Estimates of exposure based on 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 provided information as to exposure to which consumer products would result in the highest potential for D_5 exposure (e.g., food, consumer products, etc.). It was determined from the Monte Carlo analysis that in adults in all cases, consumer product use provided the highest contribution to potential D_5 exposure, with use of body lotion, hair spray, foundation, after shave and APs providing the highest estimated intakes in adults. Estimates of intake determined by the Monte Carlo analyses for remaining pathways for both adults were $\leq$55% than the estimated intake of D_5 from use of body lotion in females. These results demonstrate that it is not likely that these pathways would represent a significant contribution to the potential exposure to D_5 that could occur via multiple pathways.

Results of common exposure scenarios from the Monte Carlo analysis in children resulted in similar estimates of intake as the adults. For example, in general, diaper cream was the driving exposure scenario for children under 4 years of age and body lotion for children 4–11 years old. Comparison of the values indicated that child exposure was no more than 2 times higher than that of adults. Comparisons of other exposure scenarios between adults and children produced results where the intakes were close to the same or the child slightly greater than the adult. The current PBPK model (PBPK model, in press) is not designed to estimate internal dose metrics for children. Therefore, these scenarios were not evaluated in the PBPK analysis, but were qualitatively related to the PBPK results from 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. As stated earlier no analysis of potential oral exposure to D_5 for a worker was conducted in the Monte Carlo analysis and no exposure to D_5 through the oral (ingestion) scenario was expected to occur during occupational exposure; therefore, exposure to workers was limited to the dermal and inhalation scenarios only. Barbers and Beauticians were the only occupation workers considered to have the potential for dermal exposure through the application of HC products containing D_5.

The maximum AUC estimated for dermal exposure to D_5 for barbers and beauticians were 3.7×10^{-4} mg-hrs/L/day for male and female barber or beautician for 4 days of exposure and 3.6×10^{-4} mg-hrs/L/day for a male and female barber or beauticians exposed for 5 days (Table 10). The maximum AUC estimates from inhalation exposure to D_5 was 2.4×10^{-4} mg-hrs/L/day for a barber or beautician (Table 10) using the parameters defined in Table 3. Workers involved in the formulation of AP/D were identified as having the highest AUC values from inhalation exposure at 9.6×10^{-2} mg-hrs/L/day followed closely by working in facilities manufacturing SC products at a value of 4.6×10^{-2} mg-hrs/L/day and finally office workers and workers in HC facilities had the smallest values ranging between 3.2×10^{-4} mg–hrs/L/day to 2.5×10^{-5} mg-hrs/L/day (Table 10) based on inhalation exposure.

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_5 in environmental media (e.g., ingestion of soil, water, etc.). Therefore, the PBPK analysis for personal care products was limited to the products identified as contributing the most exposure to the consumer. Products within two orders of magnitude exposure of the product providing the highest estimate of intake (body lotion) were selected for evaluation, and included moisturizer, solid deodorant, roll-on deodorant, sunscreen, nail care, foundation, after shave, and hair spray for dermal exposure and soothing vapor for inhalation exposure. Additional information is provided in detail in the supplementary material, specifically Supplementary Tables S-1 through S-5.

The AUCs estimated for dermal exposure to D_5 from the use of HC/SC products ranged from 3.3×10^{-10} mg-hrs/L/day for female exposure to shampoo products to 5.2×10^{-3} mg-hrs/L/day for female exposure to hand/body lotion. Model estimated AUC values for men and women resulting from dermal exposure to HC/SC products are reported in Table 11. Using the parameters defined in Table 6, the AUCs estimated for inhalation exposure to D_5 from the use of the selected consumer products ranged from 2.0×10^{-3} to 3.5×10^{-5} (Table 11).

Table 11
Area under the curve (AUC) (mg-hrs/L-day): Selected consumer products.

Product	Dermal		Inhalation[a]	
	Men	Women	Men	Women
Solid Deodorant	6.0×10^{-4}	4.1×10^{-4}	1.2×10^{-4}	2.4×10^{-4}
Roll-on Deodorant	1.2×10^{-3}	6.0×10^{-4}	1.0×10^{-3}	2.0×10^{-3}
Aerosol Deodorant	5.3×10^{-4}	1.8×10^{-3}	4.0×10^{-4}	7.7×10^{-4}
Shampoo	1.5×10^{-8}	3.3×10^{-10}		
Conditioner (Rinse-out)	7.7×10^{-5}	7.8×10^{-5}		
Conditioner (Leave-in)	3.8×10^{-4}	3.9×10^{-4}		
Hair Spray (aerosol)	2.3×10^{-5}	2.3×10^{-5}	1.1×10^{-4}	2.1×10^{-4}
Hair Spray (pump)	3.3×10^{-5}	3.4×10^{-5}	1.1×10^{-4}	2.1×10^{-4}
Moisturizer	1.1×10^{-3}	1.1×10^{-3}	1.1×10^{-4}	2.1×10^{-4}
Foundation	N/A	1.4×10^{-4}	N/A	2.1×10^{-4}
Under eye cover	N/A	7.3×10^{-6}		
Lipstick (6 days)	N/A	2.3×10^{-5}		
Lipstick (5 days)	N/A	1.9×10^{-5}		
Mascara	N/A	4.2×10^{-5}		
Hand/Body Lotion	5.0×10^{-3}	5.2×10^{-3}	1.1×10^{-4}	2.1×10^{-4}
Sunscreen	7.0×10^{-5}	6.5×10^{-5}	1.1×10^{-4}	2.1×10^{-4}
Nail Care	N/A	3.6×10^{-7}	N/A	2.1×10^{-4}
After Shave Gel	9.8×10^{-5}	N/A	1.1×10^{-4}	N/A
Soothing Vapor	N/A	N/A	3.5×10^{-5}	3.5×10^{-5}

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

3.3.2.3. General public. The PBPK analysis for the general public considered both inhalation of indoor and outdoor air as well as exposure to D_5 in environmental media (e.g., ingestions of soil, water, food). 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_5 determined from the MC analysis ranged from 0.005 mg/kg/day for males and females in the general public ages 60 and older to 0.008 mg/kg/day for male and female subsistence fishermen ages 12–19 years of age. The 90th percentile of oral intake to D_5 was approximately 0.011 mg/kg/day for males in the general public or subsistence fisherman 20–59 years of age.

The AUCs estimated following inhalation exposure to D_5 for the general public ranged from 5.6×10^{-6} to 5.8×10^{-6} mg-hrs/L/day for outdoor air (Table 12). The AUC estimated due to exposure to an indoor air concentration of 34.5 μg/m^3 was approximately of 4×10^{-4} mg-hrs/L/day and when the value of 393 μg/m^3 was used as the indoor air concentration, the estimated AUC ranged from 4.4×10^{-3} to 4.6×10^{-3} mg-hrs/L/day. The mean AUCs for exposure from food, water and soil ranged from 1.7×10^{-7} to 3.0×10^{-7} mg-hrs/L/day, and the 90th percentiles ranged from 2.8×10^{-7} to 4.0×10^{-7} mg-hrs/L/day (Table 13).

3.4. Risk characterization

As noted previously, for this assessment, rather than attempting to derive uncertainty factors that may be used by the various regulatory agencies and programs (i.e. Health Canada, REACH, SCCS, OSHA, USEPA) to adjust the POD for low-dose extrapolation, 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. The use of these MOS removes the need to consider various uncertainty factors that may be applied across various regulatory agencies globally.

3.4.1. Occupational exposure

For inhalation exposures, seven types of workers (Table 14) were considered for which air concentrations from the workplace had been measured. For workers in the dry cleaning industry, MOS were approximately 5500 to 9500; indicating that exposure to D_5 as described for these workers would not pose a hazard to health. For workers in facilities that produced D_5 or manufactured consumer products containing D_5, the estimated AUCs were highest for the workers involved in the production of antiperspirants, and, consequently, the lowest MOS was associated with antiperspirant production workers, in particular men. Comparison of the AUC for this worker to the $BMDL_{10}$ resulted in an MOS of approximately 350. Therefore, based on the fact that the MOS is greater than 30 (the highest anticipated factor for noncarcinogenic effects) occupational exposures to D_5 are deemed acceptable and would not be expected to pose a significant hazard to humans.

For barbers and beauticians, it was assumed that some hair product would be used approximately every 27–30 min during the work day with the hands being exposed. The MOS determined for any of these scenarios, either by the inhalation pathway (Table 13) or the dermal pathway (Table 13), were approximately 78,000 or greater, when the AUCs were compared to the $BMDL_{10}$, indicating that occupational dermal exposures to D_5 in these professions does not pose a significant hazard to human health. Finally, potential exposure to D_5 through indoor air for office workers was evaluated at three concentrations of D_5 (9.7, 39, 120 μg/m3) and even at the highest concentration simulated the MOS for office workers was >14,000 (Table 13).

3.4.2. Consumer products exposure

AUCs were estimated for average usage scenarios of consumer products providing the greatest potential for exposure (Table 15) as identified based on the results of the Monte Carlo analysis. Exposure was assumed to occur via inhalation and dermal routes for all products.

The smallest MOS for AP/Ds was 2300 and was based on inhalation exposure from the use of roll-on products in women, 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 for dermal exposure was 2500 and was based on the use of aerosol products by women. However, because the MOS for either is greater than 1000, it is not anticipated that any of the inhalation or dermal exposures resulting from typical consumer usage of AP/Ds would pose a hazard.

For HC/SC products, one inhalation exposure scenario for all HC/SC products was considered for female and male consumers (Table 15). 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_5) to that associated with the $BMDL_{10}$, resulted in a MOS of 22,000 in women and an MOS of 42,000 in men. The estimated MOS indicated that exposure to D_5 by this route would not pose a significant health hazard.

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. Comparisons of the AUCs associated with exposure to one of seventeen HC/SC products to the AUC associated with the $BMDL_{10}$ resulted in MOS of approximately 880 or greater (Table 15). The lowest MOS (880) was associated with hand and body lotion usage in women. Although slightly less than 1000, these MOS are likely overestimates in that estimation of the AUC did not consider the duration of exposure over a lifetime. For example, some products, such as body lotion, 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_5 from the usage of HC/SC products would not be expected to pose a significant health hazard.

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_5 in outdoor or indoor air or through environmental media (food, water and soil). A value of 35.4 μg/m^3 was identified as representative of the indoor air concentration to which an individual would be

Table 12
Area under the curve (AUC): Inhalation – general public.

Ages	Male			Female		
	Outdoor	Indoor		Outdoor	Indoor	
	0.5 μg/m^3	34.5 μg/m^3	393 μg/m^3	0.5 μg/m^3	34.5 μg/m^3	393 μg/m^3
19–59 years	5.8×10^{-6}	4.0×10^{-4}	4.6×10^{-3}	5.6×10^{-6}	3.8×10^{-4}	4.4×10^{-3}

Table 13
Margins of safety (MOS): Oral exposure for the general public and subsistence fishermen.

Gender	Age group	General public			Subsistence fishermen		
		Exposure (mg/kg body weight/day)	AUC (mg-hr/L/day)	MOS LED_{10}e	Exposure (mg/kg body weight/day)	AUC (mg-hr/L/day)	MOS LED_{10}e
Mean Exposure							
Female	12–19 years	0.007	2.1×10^{-7}	19,000,000	0.008	2.3×10^{-7}	19,000,000
	20–59 years	0.006	1.9×10^{-7}	23,000,000	0.006	2.0×10^{-7}	21,000,000
	60 and older	0.005	1.7×10^{-7}	15,000,000	0.006	3.0×10^{-7}	24,000,000
Male	12–19 years	0.007	2.3×10^{-7}	21,000,000	0.008	2.3×10^{-7}	20,000,000
	20–59 years	0.006	2.1×10^{-7}	24,000,000	0.007	2.1×10^{-7}	22,000,000
	60 and older	0.005	2.1×10^{-7}	27,000,000	0.006	1.8×10^{-7}	21,000,000
90^{th} Percentile of Exposure							
Female	12–19 years	0.011	3.3×10^{-7}	14,000,000	0.010	3.2×10^{-7}	14,000,000
	20–59 years	0.010	3.4×10^{-7}	13,000,000	0.010	3.2×10^{-7}	14,000,000
	60 and older	0.009	3.3×10^{-7}	14,000,000	0.009	2.8×10^{-7}	16,000,000
Male	12–19 years	0.013	4.0×10^{-7}	11,000,000	0.013	3.9×10^{-7}	11,000,000
	20–59 years	0.011	3.7×10^{-7}	12,000,000	0.011	3.6×10^{-7}	12,000,000
	60 and older	0.009	3.1×10^{-7}	15,000,000	0.009	2.9×10^{-7}	15,000,000

Table 14
Margins of safety (MOS): Occupational inhalation exposure.

Worker	AUC (mg-hr/L/day)		MOS	
	Men	Women	Men	Women
Barbers and Beauticians				
5 days	3.6×10^{-4}	3.6×10^{-4}	92,000	160,000
4 days	3.7×10^{-4}	3.7×10^{-4}	90,000	156,000
Inhalation				
Antiperspirant	9.6 × 10-2	9.4 × 10-2	350	600
Skin Care	4.6 × 10-2	4.5 × 10-2	740	1280
Hair Care	8.6 × 10-5	8.5 × 10-5	393,000	679,000
Dry Cleaner	6.1 × 10-3	6.0 × 10-3	5500	9500
Silicone	2.8 × 10-3	2.7 × 10-3	12,200	21,000
Barbers and Beauticians	2.4 × 10-4	2.4 × 10-4	138,000	239,000
Office Worker:				
9.7 μg/m^3	2.6×10^{-5}	2.5×10^{-5}	178,000	185,000
39 μg/m^3	1.0×10^{-4}	1.0×10^{-4}	44,000	46,000
120 μg/m^3	3.2×10^{-4}	3.1×10^{-4}	14,300	15,000

Table 15
Margins of safety (MOS): Exposure from selected consumer products.

Product	AUC (mg-hr/L/day)		MOS	
	Men	Women	Men	Women
Dermal				
Solid Deodorant	6.0×10^{-4}	4.1×10^{-4}	7600	11,200
Roll-on Deodorant	1.2×10^{-3}	6.0×10^{-4}	3800	7600
Aerosol Deodorant	5.3×10^{-4}	1.8×10^{-3}	8600	2500
Hair Spray (aerosol)	2.3×10^{-5}	2.3×10^{-5}	203,000	199,000
Hair Spray (pump)	3.3×10^{-5}	3.4×10^{-5}	140,000	137,000
Moisturizer	1.1×10^{-3}	1.1×10^{-3}	4300	4200
Foundation	N/A	1.4×10^{-4}	N/A	32,000
Hand/body Lotion	5.0×10^{-3}	5.2×10^{-3}	920	880
Sunscreen	7.0×10^{-5}	6.5×10^{-5}	66,000	71,000
Nail Care	N/A	3.6×10^{-7}	N/A	1.3×10^{7}
After-Shave Gel	9.8×10^{-5}	N/A	47,000,	N/A
Inhalation				
Solid Deodorant	1.2×10^{-4}	2.4×10^{-4}	37,000	19,000
Roll-on Deodorant	1.0×10^{-3}	2.0×10^{-3}	4400	2300
Aerosol Deodorant	4.0×10^{-4}	7.7×10^{-4}	11,500	5900
Hair Spray (aerosol)	1.1×10^{-4}	2.1×10^{-4}	42,000	22,000
Hair Spray (pump)	1.1×10^{-4}	2.1×10^{-4}	42,000	22,000
Moisturizer	1.1×10^{-4}	2.1×10^{-4}	42,000	22,000
Foundation	N/A	2.1×10^{-4}	N/A	22,000
Hand/body Lotion	1.1×10^{-4}	2.1×10^{-4}	42,000	22,000
Sunscreen	1.1×10^{-4}	2.1×10^{-4}	42,000	22,000
Nail Care	N/A	2.1×10^{-4}	N/A	22,000
After-Shave Gel	1.1×10^{-4}	N/A	42,000	N/A
Soothing Vapor	3.5×10^{-5}	3.5×10^{-5}	131,000	131,000

exposed and a value of 0.5 μg/m^3 was identified as representative of the typical exposure to D_5 in outdoor air to estimate D_5 exposure for the general public. The MOS determined for indoor and outdoor inhalation using these estimates for men, women and children residents were all greater than 11,000 (Table 16). In addition, a conservative upper bound on the indoor air of 393 μg/m^3, identified by Health Canada (2008) representing the 90th percentile from all available indoor air concentrations was considered. The MOS's calculated for continuous exposure to this upper bound was 1000 for males and 1050 for females. All estimates of inhalation exposure for the general public were estimated under the assumption that a person would be indoors 24 hours per day or outdoors 24 hours per day. This bounds the potential for exposure with outdoor exposure representing the minimum and indoor exposure representing the maximum, while the exposure from being present indoors and outdoors during the day falls somewhere between.

Intakes of 0.005–0.0076 mg/kg body weight/day were estimated to represent the intake resulting from consumption of D_5 from food, water and soil combined. These intakes also include D_5 from antifoam used in processing of food, and the consumption of D_5 from the use of lipstick. The MOS determined for the mean oral consumption for men, women and teens in both the general public and the subsistence fishermen population were all greater than 15,000,000 (Table 16). In addition, an upper bound using the 90^{th} percentile of consumption of 0.008–0.013 mg/kg/day resulted in MOS values of greater than 11,000,000.

4. Discussion

As with any exposure assessment, a number of assumptions must be made and judgment used when selecting values for parameters, 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 95^{th} percentile was less than an order of magnitude (Supplementary table S-13b) in all cases. Therefore, if the upper

Table 16
Margins of safety (MOS): Inhalation exposure for the general public.

Residential	Indoor (34.5 μg/m^3)				Indoor (393 μg/m^3)				Outdoor (0.5 μg/m^3)			
	AUC (mg-hr/L/day)		MOS LED_{10}		AUC (mg-hr/L/day)		MOS LED_{10}		AUC (mg-hr/L/day)		MOS LED_{10}	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
19–59 years	5.8×10^{-6}	3.8×10^{-4}	11,500	11,900	4.6×10^{-3}	4.4×10^{-3}	1000	1050	5.8×10^{-6}	5.6×10^{-6}	790,000	820,000

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 uncertainty 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 these siloxanes. This multi-purpose siloxane model was used for this risk assessment (McMullin et al., 2015).

D_5 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 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_5 required two deep-tissue compartments in the lung and liver to account for this kinetic behavior (Reddy et al., 2008). Although adequate for modeling this kinetic behavior of D_5, 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_5 in the blood is sequestered as a bound, unavailable pool of D_5, resulting in both free and bound D_5 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_5 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_5 in the particle to fat stores in the body without allowing D_5 to be available to the blood. Although the modeling of the kinetic data drove these model descriptions of the behavior of D_5, 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 axilla and a deep tissue storage compartment likely representing the stratum corneum that slowly releases D_5 into the viable epidermis and bloodstream upon termination of exposure (Reddy et al., 2007). In addition to evaporation of D_5 from the skin surface following application, the model also describes diffusion of D_5 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_5 following dermal application, this process for D_5 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 could also introduce some uncertainty. We chose to use the US average body weight but as a check of the effect of body weight on the PBPK model results, we also ran the model using a body weight of 60 kg which is the recommended body weight in the SCCS (2012) guidance. This change in the body weight, without changing the application rates or concentrations of D_5 in the products, increased the estimated PBPK dose metrics of no more than a factor of 2.

4.1. Occupational

The median number of years worked 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). 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_5 for the workers in HC product plants was obtained from a single set of 16 personal time-weighted samples taken in one plant. Similarly, the average air concentration of D_5 for workers in personal care production plants was also obtained from a single set of 16 personal time-weighted average samples taken in one plant. No information is given about the variation in the samples. Without additional information, it is impossible to predict whether the estimates of inhalation from HC/SC products over or underestimates the exposure.

4.2. Consumers

For dermal exposure of consumers not all AP/Ds or HC/SC products contain D_5, although this assessment assumed they do. This assumption will overestimate the exposure for exposure from AP/Ds and HC/SC products, if a person more typically used products that did not contain D_5. This would result in an overestimation of the dermal exposure to D_5 in AP/Ds.

Another uncertainty in consumer dermal exposure is using the most conservative estimate of exposure and therefore the highest internal dose metric using the PBPK model. The data for conditioner products were used because it was the HC product that would result in the highest exposure to D_5 when the application rate, the percentage of D_5 in the product and the deposition and residue fractions were considered. This would be considered a conservative but not representative exposure for HC products because the

amount of D_5 in conditioners is four times higher than any other product considered and approximately 60 times higher than shampoo (the most used HC product).

For consumer inhalation exposure not all AP/Ds or HC/SC products contain D_5, although this assessment assumed they do. This assumption may overestimate the exposure for exposure from AP/Ds and HC/SC products. The inhalation values 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. The study did not report the amount of D_5 in the products being applied. The authors of the study state that they expected the exposures measured would represent the high-end of exposure due to the study design because: the room was sealed to air-exchange unlike most bathrooms which have an exhaust fan or window; a single brand of each type of antiperspirant was used. Different formulations of antiperspirant could contain ingredients that could retard or enhance the evaporation of D5; and the percentage of D_5 used in the product may not have been the same as that assumed for today's AP/D products. This would result in an overestimation of the inhalation exposure to D_5 in AP/Ds.

Other uncertainties include that inhalation values for the 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_5. No information was available about the ventilation of the room, the size of the room, the exact products being used or the amount of D_5 in those products. Only the time-weighted average of the samples was available. Without additional information, it is impossible to predict whether the estimates of inhalation from HC/SC products over- or underestimates the exposure.

Recently, the Scientific Committee on Consumer Safety (SCCS, 2015) provided an opinion on the safety of D_5 in consumer products, estimating MOS of less than 100. In contrast to the current assessment, SCCS relied upon PODs observed following oral or inhalation subchronic exposure to D_5 (90 days) that may not be considered adverse or directly related to exposure. SCCS (2015) relied upon changes in liver weights observed following oral exposure to D_5, in the absence of histopathological changes or changes in two or more liver enzymes as per USEPA (2002) Health Effects Division Guidance and noted by SCCS (2015). SCCS (2015) further notes the uncertainty as to whether these effects are adverse or adaptive.

Following inhalation exposure, SCCS (2015) relied upon endpoints associated with local toxicity in the lung observed following exposure to higher concentrations. Dekant et al. (2015) note that the physicochemical properties of D_5 limit the maximum vapor exposure concentrations achievable in inhalation exposures (Burns-Naas et al., 1998) and results obtained in studies using higher concentrations of D_5 in air have to be evaluated with caution due to the potential formation of aerosols and associated issues with doses delivered. SCCS (2015) further noted that the histopathological changes observed both in the lung and the nasal cavity of rats exposed to the high concentrations of D_5 may be due to the localized irritation from aerosol deposition and were not considered as systemic toxicity of the test substance.

The difference in PODs combined with a lack of incorporation of a PBPK model to estimate a systemic dose and consideration of only the maximum concentration of D_5 as representative of the concentration in products resulted in the estimation of smaller MOS. Longer term studies with D_5 do not provide results that support that the endpoints relied upon by SCCS (2015) would be considered adverse (Dekant et al. 2015). The use of a POD from a chronic study, in combination with Monte Carlo analyses and a PBPK model, allow for a comparison based on an internal dose metric (decreasing the uncertainties with route-to-route extrapolation) and considering the distribution of potential parameters in estimating exposure. The current approach for estimating an MOS should incorporate the most available science and be more representative of population exposure.

4.3. General public

Inhalation exposures to the general public were assumed to be for a lifetime. These values were not adjusted for the length of residency. This would overstate the risk by a factor of 8.3 to 2.3 based on the median and 95th percentile of the residency time being 9 years and 30 years, respectively.

The migration factor of 0.0046% 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_5 were determined to range from 0.5 to 269 μg/g of in baby bottle nipples with a median value of 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_5 of 3451 mg/kg – about 13 times higher than the largest value that was seen in baby bottle nipples. Migration from food containers was assumed to be a per day amount but there is little evidence that this amount could be repeatedly extracted from the same product or that a new product would be used each day. Therefore, this is a very conservative estimate of the daily exposure and would provide an overestimation of D_5 exposure.

It was also assumed that 50% of all food consumed from the general public would contain antifoam, which is a very conservative estimate as antifoam is only contained in some processed food and is excluded from use in milk and milk products. This assumption would overestimate the amount of antifoam consumed from the general public.

MOS's were estimated for oral intake only for teens and adults. The results from the Monte Carlo analysis indicate oral intakes in children are up to 10 times higher than intakes estimated for adults (Supplemental Tables S12a and S13a). However, the large MOS values computed for teens and adults (Table 13) would suggest that even for children, the MOS values should be greater than 1 million.

5. Conclusions

Based on the global approaches for conducting risk assessments, it is anticipated that any MOS greater than 1000 indicates no significant risk of adverse effects. Depending upon the regulatory body, a MOS of greater than 100 may be acceptable. MOS for three scenarios were less than 1000 (Occupational inhalation of D_5 in the production of antiperspirants, (MOS = >350), Occupational: Inhalation of D_5 in the production of skin care products, Consumers: Use of body lotion (MOS = 880). While there is some uncertainty remaining for the human relevance of the endpoint that is relied upon for the MOS (possible rat-specific and rat strain-specific increase in the development of spontaneous adenocarcinomas), the MOS results are large enough to increase confidence that the concentrations of D_5 evaluated for this assessment in consumer products, the workplace and the environment suggest no significant risk of adverse effects.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.yrtph.2015.10.023.

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