Evaluation of Exposure to Decamethylcyclopentasiloxane (D_5) for Consumers, Workers, and the General Public

Final

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January, 2006

Table of Contents

List of Tables

List of Figures

EXECUTIVE SUMMARY

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. Consequently, persons who may be exposed to D_5 include: workers in the manufacture of D_5 or personal care products containing D_5; workers in dry cleaning establishments that use D_5 as a replacement for other cleaning solvents; consumers who use personal care products containing D_5, including antiperspirants/deodorants (AP/Ds) and hair care/skin care (HC/SC) products; and the general public living in the vicinity of a plant that produces or processes these materials. Because of the widespread use of D_5 and the potential for human exposure, the toxicity of D_5 in laboratory animals and the kinetics of D_5 in both laboratory animals and humans by relevant routes of exposure have been assessed.

The purpose of this investigation was to conduct a safety assessment to evaluate the potential hazard of D_5 to these populations by defining a level at which no effects would be expected and then comparing that to the amount of D_5 to which workers, consumers or the general public may be exposed. The technical approach to this assessment for D_5 was consistent with approaches used by the United States Environmental Protection Agency (USEPA) and other regulatory agencies.

The experimental data for D_5, including an oncogenicity study, were reviewed and discussed as part of the hazard assessment. The review of these and other supporting data, in particular those studies designed to elucidate the mode of action (MoA) for observed effects in laboratory animals, was considered as part of a weight-of-evidence evaluation. This evaluation used a framework proposed by USEPA and Health Canada.

Following the hazard assessment, a dose-response assessment was performed to identify the dose associated with any observed effects that were relevant for extrapolation across species and for quantifying the dose-response relationship in order to define the Point of Departure (POD), as defined by the USEPA. The relevance of the MoA of the key findings was a significant determinant of the approach for the dose-response assessment. The dose-response assessment was completed using a physiologically based pharmacokinetic model (PBPK) to

convert the experimental concentrations in the bioassay to human equivalent exposures, defined as the internal dose-metric, Area Under the Curve (AUC), in blood.

An exposure assessment was conducted using this PBPK model 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 and modes of exposure (i.e., worker, consumer, general public) were conducted.

Finally, Margins of Safety (MOS) were developed, which compared the AUC for the POD to the AUC for the estimated internal dose metric estimated for each receptor and exposure scenario. The relative magnitude of the MOS estimated for selected receptors exposed by different routes of exposure was evaluated. A discussion of the relevance of such estimates and of the uncertainties associated with these estimates was an integral part of this safety assessment. Sources of uncertainty were considered. Assumptions or parameter values (i.e., variables, pathways, or parameter values) contributing most to estimates of risk or to the uncertainty in this assessment were identified, and, where possible, the impact on these assessments was quantified. Numerical estimates were put into context and an interpretation of those estimates made and conclusions drawn as to the safety to persons who manufacture D_5 or D_5-containing products, work in dry cleaning establishments, use products containing D_5, or live in the vicinity of a plant making or using D_5 in products.

HAZARD ASSESSMENT

The experimental data for D_5 were reviewed. The main focus of that review was the 2-year oncogenicity bioassay of D_5 in male and female Fisher 344 (F344) rats. However, other studies that provided insights into the potential for toxicity of D_5 were reviewed to include toxicokinetic data, mutagenicity and genotoxicity, reproductive/developmental toxicity, and immunotoxicity studies, and studies designed to elucidate the MoA for observed effects in laboratory animals. These data were used to assess the relevance of those observations to human health outcomes.

Summary of Experimental Studies

The major findings of this review were:

- D_5 was absorbed by the oral, dermal, and inhalation routes of exposure, and was rapidly distributed and excreted without bioaccumulation. Dermal absorption, which is most relevant for the use of consumer products, was small (approximately 0.05% of the applied amount). The majority of the dermally absorbed D_5 (90%) was rapidly eliminated through exhalation. A PBPK model provided estimates of the most relevant internal dose-metric, which is an internal dose, termed the area under the curve (AUC) in blood by way of the dermal and inhalation routes of exposure. This PBPK model was used to estimate the internal dose in the animal bioassays and the internal dose corresponding to each of the identified human exposure scenarios.

- In subacute and subchronic repeated exposure studies by the oral (at doses up to 1600 mg/kg/day) and inhalation (up to the highest concentration that remains a vapor, 160 ppm) routes of exposure, the only effects observed in rodents were adaptive, non-adverse transient phenobarbital-like changes in liver weight, and, by the inhalation route, irritation in the nose and lungs consistent with adaptive responses to mild, non-specific irritants.

- D_5 was not mutagenic or genotoxic in *in vitro* assays in bacterial or mammalian cells or *in vivo* in genotoxicity tests both with and without metabolic activation.

- D_5 was not immunotoxic when exposure occurred for 28 days at concentrations up to 160 ppm.

- No parental toxicity or reproductive toxicity was noted in adult male or female rats, nor was there neonatal toxicity or developmental neurotoxicity in their offspring in a 2-generation reproductive toxicity test at concentrations up to 160 ppm.

- There were no treatment-related, adverse non-neoplastic effects seen in the 2-year bioassay in male and female F344 rats at doses up to 160 ppm. The only neoplastic lesion noted was an increase in uterine endometrial adenocarcinomas in the high exposure group females, found primarily on terminal sacrifice.

- D_5 did not demonstrate estrogenic, anti-estrogenic, or androgenic activity in several assays designed to assess estrogen agonist/antagonist potential. D_5 did demonstrate dopamine agonist activity in that D_5 decreased the amount of circulating prolactin in reserpine-treated female F344 rats.

Weight-of-Evidence Evaluation

Because there was a positive finding in an oncogenicity study, a weight-of-evidence assessment was conducted to include consideration of the MoA of the only carcinogenic

response observed in animals following chronic exposure to D_5. The relevance of these tumors for human health safety assessment was considered using a framework proposed by the USEPA and others. The evidence in the scientific literature indicates that uterine adenocarcinomas can form in aging female F344 rats in response to estrogen dominance caused by exogenous chemicals either directly, as an estrogen agonist, or indirectly, as a dopamine agonist. There are several lines of evidence to support the conclusion that D_5 induced uterine adenocarcinomas in female rats indirectly by this non-genotoxic mechanism. This evidence includes studies that have shown that D_5: 1) is not mutagenic or genotoxic; 2) tumors in D_5-treated rats were histologically indistinguishable from untreated control tumors; 3) D_5 did not bind to estrogen receptors and was not an estrogen agonist; and, 4) D_5 demonstrated dopamine agonist activity. Dopamine agonists, such as bromocriptine, act at the level of the pituitary to inhibit prolactin release in aged female rats, thereby, resulting in a reduction in progesterone synthesis and secretion by the ovary and producing an increased estrogen:progesterone ratio and estrogen dominance. These changes do not occur in other species, including humans. The MoA of dopamine agonist-induced tumors is not relevant to humans because dopamine agonists do not lead to estrogen dominance in women. There is sufficient evidence that tumors formed in aging female F344 rat by a dopamine agonist MoA are not relevant to humans.

DOSE-RESPONSE ASSESSMENT

As noted above, uterine adenocarcinomas formed in response to a dopamine agonist occur in aging rats by a MoA that is not operative in humans. According to USEPA guidelines and those used by other regulatory agencies, incidence data for tumors identified in rodents that occur by a MoA not relevant to humans would not be used quantitatively to determine a POD. Rather, noncarcinogenic effects or precursor lesions would be used to derive the POD either from the NOAEL (No Observed Adverse Effect Level) or by using a Benchmark model with all of the dose-response data to define the lower bound on dose at a specified level of risk, typically termed the $BMDL_{10}$. However, exposure to D_5 did not produce significant, treatment-related noncarcinogenic effects relevant to human health outcomes in either the 2-year bioassay or in the reproductive or immunotoxicity studies nor were there precursor lesions, such as uterine hyperplasia, found in the 2-year bioassay. Consequently, there were no relevant chronic effects

that would provide data for Benchmark modeling. Therefore, 160 ppm, the highest concentration tested, represented the NOAEL.

The POD was estimated two ways: 1) use of the NOAEL of 160 ppm based on the lack of relevant, treatment-related adverse effects in any toxicity study; and 2) use of a LED_{10} based on the incidence of female rat uterine adenocarcinomas data, which was significantly increased in only the highest exposure concentration following 2 years of exposure. While not considered relevant to human health, dose-response modeling using the tumor data was conducted only as a point of comparison to the experimentally-derived NOAEL and to provide a conservative lower bound on the POD. A PBPK model, using female rat parameters, simulated the D_5 exposure pattern in the bioassay to derive human equivalent dose(s), expressed as the internal dose-metric, in this case the AUC in arterial blood, for each experimental concentration. The AUC based on the highest concentration tested, 160 ppm, was identified as the internal dose-metric at the NOAEL. The PBPK-derived AUCs for each exposure concentration was used along with the incidence data in a dose-response model (in this case, the Multistage model) to estimate the AUC at the LED_{10} (the lower bound on the dose corresponding to a 10% increase in risk), which is the typical POD when using animal bioassay data in dose-response modeling. The AUC based on the evaluation of the tumor data was 23.5 mg-hrs/L/day, while the AUC derived based on the NOAEL was 28.5 mg-hrs/L/day.

In the case of D_5, if low-dose extrapolation were to be conducted, then a non-linear extrapolation is indicated based on the available data for the following reasons: 1) D_5 has no mutagenic or genotoxic potential; and, 2) the MoA for the development of the observed tumors in rats is a non-genotoxic mechanism involving indirect hormonal perturbation by way of altered prolactin levels. According to the USEPA, when tumors arise through a nonlinear mode of action, such as the case with D_5, an oral Reference Dose (RfD) or an inhalation Reference Concentration (RfC) is derived. Typically, when deriving an RfD/RfC, the POD, defined as either an experimentally-derive NOAEL or the $BMDL_R$[1], is adjusted (divided) by uncertainty factors to account for species extrapolation, human variability, and confidence in the data base. Application of these factors requires judgment and may not be universally applied by all regulatory agencies.

[1] Then BMDL is the lower bound on dose/concentration at a specified level of risk (R), which is typically 10% but can be lower, such as 5%, depending on the data and the endpoint.

In this assessment, the POD was not adjusted by safety or uncertainty factors. Determination of safe levels for the groups considered in this exposure assessment fall to different regulatory agencies and the choice of which factors to use and the magnitude of those factors may differ among these various regulatory agencies (i.e., OSHA, USEPA, CalEPA, etc.). Rather, a comparison of the internal dose metric associated with the NOAEL or LED_{10} to the internal dose metric estimated for each exposure scenario was conducted to derive exposure-specific MOS. The magnitude of the MOS can then be evaluated for the different exposure groups in the context of what would be deemed an acceptable margin by various regulatory agencies for the particular exposure group.

EXPOSURE ASSESSMENT

The exposure scenarios considered were designed to emulate the exposure from the production, formulation, and use of D_5 and attempted to characterize the persons who may be exposed; the pathways or routes by which that exposure could occur; and the frequency, duration, and intensity (amount) of that exposure. The populations considered were:

- Occupational - persons who work in the production of D_5 or in the formulation of this material into personal care products; persons working in the dry cleaning industry who are using D_5; or persons who use these products in professional settings;
- Consumers – individuals who use personal care products, including antiperspirant/deodorants (AP/Ds) and hair care/skin care (HC/SC) products; and
- General Public – individuals living in the vicinity of a plant that produces or processes these materials and who may be exposed to ambient levels of D_5 released to the environment during manufacturing activities.

The frequency, duration and amount of that exposure were all exposure-scenario specific. The values for these parameters differed for each of the populations considered and for each personal care product considered. The duration varied from continuous inhalation exposure for a person living near a plant to intermittent or infrequent exposure through the use of some personal care products. Numerical values for each of the parameters required to characterize and quantify exposure for each receptor, route, or product were defined. For consistency, parameter values that described the average or typical user were selected to describe estimates of exposure. These

parameter values were used with the PBPK model to determine the internal dose metric, the AUC, in arterial blood that were receptor- and exposure scenario-specific.

Occupational Exposures

In estimating dermal exposures to workers (men and women), only one scenario was considered - barbers and beauticians whose hands could come in contact with hair care products over the course of a work day. It was assumed that such exposure occurred approximately every 30 minutes during a work day. Using the dermal PBPK model with parameter values based on human data and assumptions, dermal exposure for barbers and beauticians from the application of HC products was simulated. The AUCs estimated for dermal exposure to D_5 from this occupational scenario ranged from 4.2×10^{-5} mg-hrs/L/day to 4.7×10^{-5} mg-hrs/L/day, for women and men, respectively.

Other workers, as well as barbers and beauticians, could be exposed to D_5 that has volatilized. Exposure was estimated for the inhalation route using varying assumptions for the duration and frequency of exposure and amount of D_5 measured in air in the work environment. These varied with the type of work performed. The AUCs estimated for occupational inhalation exposure to D_5 ranged from 2.0×10^{-5} mg-hrs/L/day to 4.5×10^{-2} mg-hrs/L/day. The AUCs estimated for dry cleaner workers were 2.9×10^{-3} mg-hrs/L/day for men and 1.4×10^{-3} mg-hrs/L/day for women. The largest estimated AUC, indicating the highest exposure, was derived using exposure assumptions for men who work in a plant that produced antiperspirants containing D_5 at the conservative levels assumed. Determination of the AUC was based on the expected years of exposure specific to the type of worker.

Consumer Exposure

The consumer products evaluated included AP/Ds, HC products (shampoo, rinse-out conditioner, leave-in conditioner, and hair spray) and SC products (moisturizer, body lotion, and foundation). For AP/Ds, both the inhalation and dermal pathways were considered for three formulations of AP/Ds - solids, aerosols and roll-ons. Estimates of the AUC for dermal exposure were simulated using the PBPK model with human parameter values, and considered the amount of D_5 applied over a specified skin area and the frequency of application (assumed to be once daily). Rather than define a specific number of years of use of these products, it was assumed that exposure occurred for an entire lifetime and, therefore, exposures are likely to be

overestimated for most of these scenarios. The daily average AUC from the use of AP/Ds ranged from 5.5×10^{-5} mg-hrs/L/day to 2.8×10^{-3} mg-hrs/L/day. The largest estimated AUC for the dermal route was derived based on the use of roll-on antiperspirants by men. The inhalation exposure pathway considered the potential air concentration resulting from volatilization of D_5 during the use of these products. The AUC based on the possible inhalation exposure from the use of AP/Ds ranged from 4.9×10^{-4} mg-hrs/L/day to 6.0×10^{-3} mg-hrs/L/day with the largest AUC derived based on the use of roll-on antiperspirants by women.

Exposures were modeled for specific HC products (e.g., shampoo, conditioners, hair spray, cuticle coat, brilliantine, pomade, and spray shine) and specific types of SC products (e.g., moisturizer, foundation, hand/body lotion, sunscreen, under-eye cover, aftershave lotions and colognes, and lipstick). As with AP/Ds, exposures were estimated for the dermal and inhalation pathways. PBPK simulations for products containing various amounts of D_5 were assumed to occur once per day for a various number of days per week for both men and women. The exceptions were for exposures from the use of moisturizer, lipstick and sunscreen. Moisturizer exposure was simulated to occur twice per day (once every twelve hours); lipstick exposure was simulated to occur every four hours for a total of three exposures per day; and sunscreen exposures were assumed to occur for eleven consecutive days once per year. As with AP/D products, exposure was assumed to occur over an entire lifetime, hence, exposure is likely to be an overestimate for most products. The AUCs estimated for dermal exposure to D_5 from the use of HC/SC products ranged from 6.9×10^{-7} mg-hrs/L/day to 8.3×10^{-4} mg-hrs/L/day. The largest AUC was derived for the use of moisturizer by women. For inhalation exposures, PBPK model simulations were conducted in the same manner as the exposures from AP/D applications using air concentrations assumed for HC/SC products. The air concentration used was an estimate based on the use of many HC/SC products and represented the combined exposure from the use of these products. The AUCs estimated for inhalation exposure to D_5 from the use of HC/SC products were 6.3×10^{-4} mg-hrs/L/day for women and 4.3×10^{-4} mg-hrs/L/day for men.

General Public Exposures

Exposure to persons who may live near a facility that manufactures or formulates products containing D_5 was considered. It was assumed that residents, both adults and children, were at their residence 24 hours per day for a lifetime. Data were available from outdoor air

samples that were collected from 70 facilities and analyzed for D_5 content. The average value reported in the ambient air was used to estimate the exposure for the general public.

The AUCs estimated for inhalation exposure to D_5 by the general public ranged from 7.8×10^{-6} mg-hrs/L/day to and 2.2×10^{-5} mg-hrs/L/day. The largest AUC was estimated for adult men.

RISK CHARACTERIZATION

In the Risk Characterization step, Margins of Safety (MOSs) were estimated. A MOS was defined as the ratio of the internal dose metric (AUC) associated with either the LED_{10} or the NOAEL to the internal dose metric estimated for each relevant exposure scenario. Further, uncertainties associated with this evaluation were considered and, where possible, the impact of the assumptions made on these MOS was considered.

Estimated Margins of Safety

For occupational inhalation exposures, the estimated AUCs were largest for workers involved in the production of antiperspirants. Comparison of the AUC for this worker to either the LED_{10} or the NOAEL resulted in a MOS of 500 to 600 (Table ES-1). Because the carcinogenic effects observed in rats were not considered relevant to human health, comparing the AUC at the NOAEL to the AUC for these exposure scenarios is the more appropriate comparison. This results in a MOS of at least 600, which is greater than the factor of 30 to 100 that would typically be applied to the NOAEL for a noncarcinogenic assessment for the worker. The MOS for workers in the dry cleaning industry were approximately 10000 or greater. These MOS would indicate that D_5 does not pose a significant hazard to workers in the production of D_5 or D_5-containing products or to workers in the dry cleaning industry, based on the exposure scenarios defined. The MOS determined for dermal exposure for barbers and beauticians were approximately 500000 or greater, regardless of comparison of the AUCs to the LED_{10} or the NOAEL, indicating that occupational dermal exposures to D_5 does not pose a significant hazard to persons in these professions who may use D_5-containing products in the manner described in the exposure assessment.

For consumer products use, all of the MOS were greater than approximately 4000 based on inhalation exposure from the use AP/D (Table ES-2). Dermal exposure from the use of AP/D

resulted in AUCs that were estimated to be 12000 or greater (Table ES-2). The data used and the assumptions made in the generation of these exposures for AP/D resulted in conservative estimates, as discussed in the uncertainty section.

In general, AUCs estimated for the use HC/SC products were smaller than those for AP/D products for both the dermal and inhalation pathways (Table ES-2). All MOS were approximately 30000 (based on the use of moisturizers by women or the use of after-shave gels by men) or larger for any HC/SC product for the dermal route. The next largest MOS for HC/SC products by either the dermal or inhalation routes were 40000 or greater (inhalation exposure for men and women) but were more typically greater than approximately 350000 or greater for other products. Given some of the conservative assumption used in these assessments, it is not anticipated that any of the inhalation or dermal exposures resulting from typical consumer use of these products would pose an unacceptable hazard.

For the general public, exposure to D_5 was assumed to be limited to inhalation of ambient air. The ambient air concentrations were based on concentrations measured near manufacturing facilities. The MOS determined for this scenario for men, women and children were all greater than 1000000, regardless of comparison to either the AUCs for the LED_{10} or the NOAEL (Table ES-3). This indicates that residential inhalation exposure to D_5 does not pose a significant hazard to human health.

Consideration of Uncertainties

As part of the Risk Characterization, uncertainties in the assessment were considered and were classified into two major categories, PBPK model uncertainties and uncertainties associated with assumptions, data, and judgments made in the exposure assessment. If alternative assumption or data had been used, in some cases, exposures would be under- or overestimated. In balance, the data used and the assumptions made tended to overestimate rather than underestimate exposure. Consequently, use of average or central tendency values present reasonable estimates for this assessment.

SUMMARY AND CONCLUSIONS

The purpose of this investigation was to conduct a safety assessment to evaluate the potential hazard to selected workers, consumers, and the general public who may be exposed to

D_5 either in the workplace, through the use of consumer products containing D_5 or exposed to D_5 in ambient air. This involved a critical review of the available toxicity and oncogenicity studies, as well as supporting information, including toxicokinetic data, mutagenicity and genotoxicity, reproductive/developmental toxicity, and immunotoxicity studies. In addition, studies designed to elucidate the mode of action (MoA) for observed effects in the animal were reviewed. Based on this review, potential endpoints for consideration as part of a human health risk assessment were limited to one neoplastic finding of uterine endometrial adenocarcinomas in female rats. Changes in liver weights and enzyme induction and non-specific effects on the nasal passages were also observed; however, these effects were not considered adverse and were consistent with an adaptive response identical to the classical response observed following phenobarbital treatment or exposure to mild respiratory irritants, respectively.

The studies conducted to evaluate the potential MoA of the uterine response observed in female rats indicated that D_5, at high concentrations, was likely functioning as a dopamine agonist in rats, leading to the development of the observed uterine tumors. The changes that occur in the uteri of female rats treated with dopamine agonists result from the effects of prolonged estrogen dominance resulting from reduced prolactin secretion superimposed on the waning endocrine system characteristic in aging rats. These changes do not occur in other species, including humans. Therefore, the production of dopamine agonist-induced uterine tumors in female rats is not relevant to humans.

There are several lines of evidence to support that D_5 is inducing uterine adenocarcinomas in a non-genotoxic, indirect, hormonally-mediated mechanism in rats that is not relevant to humans. This evidence includes studies that have shown that: 1) D_5 is not mutagenic or genotoxic, 2) tumors in D_5-treated rats were histologically indistinguishable from untreated control tumors; 3) D_5does not bind to estrogen receptors and is not an estrogen agonist or antagonist, and, 4) experimental evidences indicates that D_5 exhibits dopamine agonist activity.

However, if the incidence of uterine adenocarcinomas were to be used for a safety assessment, based on the available data on the MoA, a nonlinear extrapolation to low doses would be appropriate. Based on the most recent USEPA Guidelines for Carcinogenic Risk Assessment, an LED_{10} was derived using the incidence/concentration data from the 2-year bioassay, to be used as a POD. A PBPK model was also used to estimate the internal dose

metric associated with the LED_{10} in the rat, assumed to be the human equivalent dose metric and POD.

More appropriately, because no other significant, treatment-related adverse effects relevant to human exposures were observed in the experimental studies reviewed, the highest NOAEL in the toxicity studies was also selected as the POD. The PBPK model was also used to estimate the internal dose metric associated with the NOAEL.

The estimated human equivalent doses, defined as the AUC corresponding to either the NOAEL or to the LED_{10} derived using dose-response modeling, were compared with those based on the receptor-, route-, exposure scenario-specific estimates of the AUC. Three populations were considered in the exposure assessment:

- persons who work in the production of D_5, in the formulation of this material into personal care products, in the dry cleaning industry, or in the use of these products in professional settings;
- consumers who use these personal care products, including antiperspirant/deodorants (AP/Ds) and hair care/skin care (HC/SC) products; and,
- the general public living in the vicinity of a plant that produces or processes these materials and who may be exposed to ambient levels of D_5 released to the environment during manufacturing activities.

Exposure for all three populations was considered to occur via dermal and/or inhalation exposure. As with the dose-response assessment, a PBPK model was used to estimate the internal dose metric associated with dermal or inhalation exposures for each population. These dose metrics were then compared to that derived for the LED_{10} or the NOAEL resulting in a MOS. A MOS is the ratio of the internal dose metric or AUC associated the POD to the internal dose metric estimated for each relevant exposure scenario.

Regardless of the POD considered for conducting a safety assessment, the MOS estimated for each exposure scenario was not larger than those values that would be deemed acceptable by the appropriate regulatory agency (i.e., OSHA for occupational exposure). Therefore, it can be concluded that, under the exposure scenarios defined in this assessment, typical exposure to D_5, whether occupationally, or to consumers, or to the general public, would not result in a significant human health hazard.

Table ES-1
Margins of Safety (MOS) Estimated for Workers Following Occupational Exposure to D_5

Type of Exposure	Industry	Margin of Safety			
		LED_{10}		NOAEL	
		Men	Women	Men	Women
Inhalation	Antiperspirant	$5.2\times10^{+2}$	$1.1\times10^{+3}$	$6.3\times10^{+2}$	$1.3\times10^{+3}$
	Skin Care	$1.1\times10^{+3}$	$2.2\times10^{+3}$	$1.3\times10^{+3}$	$2.7\times10^{+3}$
	Hair Care	$5.8\times10^{+5}$	$1.2\times10^{+6}$	$7.0\times10^{+5}$	$1.4\times10^{+6}$
	Dry Cleaner	$8.1\times10^{+3}$	$1.7\times10^{+4}$	$9.8\times10^{+3}$	$2.0\times10^{+4}$
	Silicone	$1.8\times10^{+4}$	$3.7\times10^{+4}$	$2.2\times10^{+4}$	$4.5\times10^{+4}$
	Barbers and Beauticians	$2.7\times10^{+5}$	$5.6\times10^{+5}$	$3.3\times10^{+5}$	$6.8\times10^{+5}$
Dermal	Barbers and Beauticians	$5.0\times10^{+5}$	$5.5\times10^{+5}$	$6.1\times10^{+5}$	$6.7\times10^{+5}$

Table ES-2
Margins of Safety (MOS) Estimated for Consumers Following Use of Products Containing D_5

Type of Exposure	Product	Type	Margin of Safety			
			LED_{10}		NOAEL	
			Men	Women	Men	Women
Dermal	AP/D	Solid	$1.2\times10^{+4}$	$3.7\times10^{+4}$	$1.5\times10^{+4}$	$4.6\times10^{+4}$
		Roll-on	$8.2\times10^{+3}$	$1.9\times10^{+4}$	$1.0\times10^{+4}$	$2.4\times10^{+4}$
		Aerosol	$2.2\times10^{+5}$	$4.3\times10^{+5}$	$2.6\times10^{+5}$	$5.2\times10^{+5}$
	HC/SC	Shampoo	$2.7\times10^{+7}$	$2.5\times10^{+7}$	$3.3\times10^{+7}$	$3.0\times10^{+7}$
		Rinse-out conditioner	$3.4\times10^{+7}$	$3.2\times10^{+7}$	$4.1\times10^{+7}$	$3.9\times10^{+7}$
		Leave-in conditioner	$6.8\times10^{+6}$	$6.5\times10^{+6}$	$8.2\times10^{+6}$	$7.9\times10^{+6}$
		Hair spray	$1.4\times10^{+7}$	$8.6\times10^{+6}$	$1.6\times10^{+7}$	$1.0\times10^{+7}$
		Cuticle coat	$6.7\times10^{+5}$	$5.1\times10^{+5}$	$8.2\times10^{+5}$	$6.2\times10^{+5}$
		Brilliantine	$1.4\times10^{+6}$	$1.1\times10^{+6}$	$1.7\times10^{+6}$	$1.3\times10^{+6}$
		Pomade	$2.1\times10^{+6}$	$1.6\times10^{+6}$	$2.6\times10^{+6}$	$2.0\times10^{+6}$
		Spray shine	$5.4\times10^{+5}$	$3.5\times10^{+5}$	$6.6\times10^{+5}$	$4.2\times10^{+5}$
		Moisturizer	$3.7\times10^{+4}$	$2.8\times10^{+4}$	$4.5\times10^{+4}$	$3.4\times10^{+4}$
		Foundation	N/A	$2.6\times10^{+5}$	N/A	$3.2\times10^{+5}$
		Hand/body lotion	$5.2\times10^{+5}$	$2.9\times10^{+5}$	$6.4\times10^{+5}$	$3.5\times10^{+5}$
		Sunscreen	$4.3\times10^{+5}$	$3.3\times10^{+5}$	$5.2\times10^{+5}$	$4.0\times10^{+5}$
		Under-eye cover	N/A	$4.7\times10^{+5}$	N/A	$5.7\times10^{+5}$
		Lipstick (3 times/day, 6 days/week)	N/A	$1.9\times10^{+6}$	N/A	$2.3\times10^{+6}$
		Lipstick (3 times/day, 5 days/week)	N/A	$2.3\times10^{+6}$	N/A	$2.8\times10^{+6}$
		After-shave gel	$2.9\times10^{+4}$	N/A	$3.6\times10^{+4}$	N/A
Inhalation	AP/D	Solid	$4.8\times10^{+4}$	$3.3\times10^{+4}$	$5.9\times10^{+4}$	$4.0\times10^{+4}$
		Roll-on	$5.7\times10^{+3}$	$3.9\times10^{+3}$	$6.9\times10^{+3}$	$4.7\times10^{+3}$
		Aerosol	$1.5\times10^{+4}$	$1.0\times10^{+4}$	$1.8\times10^{+4}$	$1.2\times10^{+4}$
	HC/SC		$5.4\times10^{+4}$	$3.7\times10^{+4}$	$6.6\times10^{+4}$	$4.5\times10^{+4}$

Table ES-3
Margins of Safety (MOS) Estimated for the General Public Following Exposure to D_5 in Ambient Air

Age Group	Margin of Safety			
	LED_{10}		NOAEL	
	Male	Female	Male	Female
Adult (18-75)	$1.1\times10^{+6}$	$1.5\times10^{+6}$	$1.3\times10^{+6}$	$1.8\times10^{+6}$
Children				
Ages 1-2	$2.6\times10^{+6}$	$3.0\times10^{+6}$	$3.2\times10^{+6}$	$3.7\times10^{+6}$
Ages 3-5	$2.4\times10^{+6}$	$2.7\times10^{+6}$	$2.9\times10^{+6}$	$3.3\times10^{+6}$
Ages 6-8	$2.0\times10^{+6}$	$2.4\times10^{+6}$	$2.4\times10^{+6}$	$2.9\times10^{+6}$
Ages 9-11	$1.7\times10^{+6}$	$2.0\times10^{+6}$	$2.0\times10^{+6}$	$2.4\times10^{+6}$
Ages 12-14	$1.4\times10^{+6}$	$1.7\times10^{+6}$	$1.7\times10^{+6}$	$2.1\times10^{+6}$
Ages 15-17	$1.2\times10^{+6}$	$1.6\times10^{+6}$	$1.4\times10^{+6}$	$2.0\times10^{+6}$

1.0 INTRODUCTION

Decamethylcyclopentasiloxane (D_5) is a clear, odorless, synthetically derived silicone fluid. Chemically, D_5 consists of alternating silicon-oxygen bonds connected in a ring (cyclic) arrangement with two methyl groups covalently bonded to each silicon atom $(Me_2SiO)_5$ (Figure 1). It is a member of a family of low-molecular-weight cyclic siloxanes, whose hydrophobic and low surface energy properties provide a unique basis for some of its selected uses.

D_5 is primarily used as an intermediate in the production of some widely-used industrial and consumer products (Burns *et al.* 1996). In recent years, D_5 has been used or proposed for use in the dry cleaning industry as a replacement for other organic cleaning solvents. D_5 is also found in some household care products and in selected personal care products, such as antiperspirants and shampoos. D_5 is used in cosmetics and toiletries as a vehicle, as an end blocking agent in antiperspirants, and in aerosol products containing insoluble powders. Consequently, persons in the manufacture of D_5 and personal care products containing D_5; workers in the dry cleaning industry who use D_5 as a substitute for other organic solvents; consumers who use these personal care products, including antiperspirants/ deodorants (AP/Ds) and hair care/skin care (HC/SC) products; and the general public living in the vicinity of a plant that produces or processes these materials may be exposed to D_5 released during production or use. Because of the widespread use of D_5 and the potential for human exposure, the toxicity of D_5 in laboratory animals and the kinetics of D_5 in both laboratory animals and humans by relevant routes of exposure have been assessed.

The purpose of this investigation was to conduct a safety assessment to evaluate the potential hazard to selected workers, consumers, and the general public who may be exposed to D_5 either in the workplace, through the use of consumer products containing D_5, or to D_5 release to the environment. Safety assessment is defined as the scientific evaluation of potential health impacts that may result from exposure to a particular substance or mixture of substances under specified conditions. The technical approach to this assessment for D_5 was consistent with the final Human Cancer Risk Assessment Guidelines (USEPA 2005) and consisted of the following steps:

- *Hazard Assessment*: The experimental data for D_5 was reviewed and discussed. The oncogenicity study was reviewed, as well as other supporting data, to include toxicokinetic data, repeated exposure studies, mutagenicity and genotoxicity, reproductive/developmental toxicity, and immunotoxicity studies. In addition, studies designed to elucidate the mode of action (MoA) for observed effects in the animal were reviewed. The potential MoA for key observations and the relevance of those to human health outcomes was considered using a framework proposed by the USEPA and Health Canada (Cohen *et al.* 2004, Meek *et al.* 2003, USEPA 2005). A weight-of-evidence narrative of the key finding is presented.

- *Dose-Response Assessment:* This step involved the selection of the appropriate measure of exposure (dose-metric) associated with the observed effects, which is assumed to be relevant for extrapolation across species and for quantifying that dose-response relationship. The relevance of the MoA of the key findings was a significant determinant of this approach. As part of the final USEPA (2005) guidelines, when the MoA is species-specific and not relevant in humans either qualitatively or quantitatively, then the tumor data are not considered further. Rather, a noncarcinogenic endpoint is selected to serve as to Point of Departure (POD), which is either the study-determined No Observed Adverse Effect Level (NOAEL) or a model-derived Benchmark Dose at a specified Benchmark Risk to derive a Reference Dose/Concentration (RfD/RfC). A physiologically based, multi-route route pharmacokinetic model (PBPK) was used to derive the internal dose-metric to serve as the POD.

- *Exposure Assessment:* A conceptual model was formulated that identified the potential receptors and routes of exposure. Estimates of intake were also assessed using this PBPK model 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 and modes of exposure (i.e., worker, consumer, general public) were conducted; and

- *Risk Characterization:* This step usually presents numerical estimates of risk or hazard that are derived by comparing the estimated intake with some measure of a toxicity value, i.e., the POD adjusted by uncertainty factors to reflect interspecies and intraspecies variability as well as the confidence in the data base for noncarcinogenic endpoints and cancer endpoints deemed to be non-linear or having a threshold in the low dose region, or linear extrapolation to the target risk level for assumed linear, non-threshold agents. However, when multiple populations are to be evaluated that may be considered by multiple regulatory agencies, rather than decide appropriate uncertainty factors *a priori*, a more versatile approach is to calculate Margins of Safety (MOS), which compares the estimated POD to the estimated intake, both of which are expressed as the internal dose-metric, defined as the Area Under the Curve (AUC) in blood. The relative magnitude of the MOS estimated for selected receptors exposed by different routes of exposure were evaluated. A discussion of the relevance of such

estimates and of the uncertainties associated with these estimates is an integral part of any safety assessment. Therefore, sources of uncertainty were considered. Assumptions or parameter values (i.e., variables, pathways, or parameter values) contributing most to estimates of AUC or to the uncertainty in the risk assessment were identified, and, where possible, the impact on these assessments was quantified. Lastly, numerical estimates must be put into context and an interpretation of those estimates made and conclusions drawn as to the safety for persons who manufacture or use products containing D_5.

2.0 HAZARD NARRATIVE

2.1 Carcinogenicity Studies

Male and female F344 rats (96 rats/sex/group) were exposed to vapor concentrations of 0, 10, 40, or 160 ppm D_5 for 6 hours per day, 5 days per week for up to 2 years via whole body inhalation (Dow Corning Corporation 2005a). The animals were divided into 4 subgroups based on the time of sacrifice. Interim sacrifices were performed at 6 months (6 rats/sex/group) and 1 year (10 rats/sex/group) in subgroups A and B, respectively. In subgroup C, 20 rats/sex/group were treated for 1 year and taken off exposure for 1 year and then sacrificed. In subgroup D, 60 rats/sex/group were exposed for 2 years and sacrificed at the end of the exposure period. Rats in the control group and rats in the recovery group (group C) during the 2nd year of the study were exposed to filtered air according to the same schedule. For males in all subgroups, the overall mean nominal chamber concentrations were 10.46, 41.32, and 160.45 ppm D_5 (0.16, 0.63, and 2.44 mg/L, respectively). For females, in all subgroups, the overall mean nominal chamber concentrations were 10.47, 41.45, and 161.65 ppm D_5 (0.16, 0.63, and 2.45 mg/L, respectively) (Dow Corning Corporation 2005a).

Biological parameters recorded during the study included mortality, clinical signs, ophthalmoscopic changes and body weights. Hematology, clinical biochemistry, and urinalysis investigations were performed after 3, 6, and 12 months, and hematology after 14 months of treatment. Blood, perirenal fat, abdominal fat, brown fat and liver from subgroup A animals were analyzed for D_5 content. Gross necropsy was performed on all animals, organ weights were recorded, and tissues prepared for histopathological examinations. Table 1 describes the histopathology performed for each treatment group.

Survival analyses indicated that there was no difference in the mortality observed when comparing exposed groups with controls (Dow Corning Corporation 2005a). No treatment-related clinical signs of toxicity or changes in body weight were noted in any group. No treatment-related findings were noted in the ophthalmoscopic examination. The only significant organ weight change considered to be treatment-related was increased liver weights in females at 6 and 12 months exposed to 10 and 160 ppm D_5 and

in males exposed to 160 ppm for 2 years. As discussed in Section 2.3.1, these changes in liver weight were likely an adaptive change and were not considered adverse.

Hematological results in treated male rats were not considered to be treatment-related. Hematological analysis of the females indicated decreased urea concentrations at 3 and 12 months, increased cholesterol at 3, 6, and 12 months, increased triglycerides at 12 months, increased total protein at 3 and 6 months, and increased gamma glutamyl transferase at 3 and 12 months. These changes were considered to be treatment-related and suggest metabolic adaptive changes in the liver. No significant changes in urinalysis results seen were considered to be indicative of renal pathology.

A number of nonneoplastic findings were observed; however, with the exception of nonneoplastic findings in the nasal cavity, the type, incidence, and severity of these effects did not differ significantly between the exposed and control rats (Dow Corning Corporation 2005a). Increases in hyaline inclusions in the nasal cavity in the high exposure group were considered by the authors to represent a non-specific, exposure-related effect consistent with chronic inhalation of some mildly irritating chemicals and are also commonly seen in aging rats. No other effects indicative of irritation (e.g., inflammatory cell infiltration or degenerative changes in the epithelium) were noted and the finding was considered non-specific.

Neoplastic findings were limited to the uterus of female rats. A significant increased incidence of endometrial adenocarcinomas in the uterus was reported in the high-dose female rats after 2 years of exposure (Table 2). There were no endometrial adenocarcinomas reported in control rats. There were significant decreasing trends in the incidence of fibroadenoma, C-cell adenoma, and C-cell carcinomas in the 24-month group rats, with the controls having the highest incidences. All other microscopic findings were considered to be incidental findings that commonly occur in rats of this age and strain. Additional studies have been performed to further evaluate the mechanism by which endometrial adenocarcinomas were formed. These studies are discussed in the following sections.

In summary, this chronic inhalation toxicity/oncogenicity study conducted in rats showed a significant increase in the incidence of uterine endometrial adenocarcinomas in female rats administered the highest concentration (160 ppm). No other toxicologically

significant neoplastic or nonneoplastic findings were reported. There were significant increases in liver weights in the female rats exposed to 10 and 160 ppm for 6 and 12 months, and in the male rats exposed to 160 ppm for 2 years. In addition, hematological analysis indicated significant treatment-related increases in cholesterol, triglycerides, total proteins, and gamma glutamyl transferase, which are suggestive of metabolic non-adverse, adaptive changes related to the liver. The only treatment-related non-neoplastic finding reported was increased hyaline inclusions in the nasal cavity in the high exposure group. This finding was considered to be a non-specific, exposure-related effect consistent with chronic inhalation of some mildly irritating chemicals and is also commonly seen in aging rats.

2.2 Analysis of Other Key Data

2.2.1 Toxicokinetics

Because of the potential for multi-route exposure, the pharmacokinetics of D_5 has been investigated by inhalation, oral, and dermal routes of exposure. Five main studies have been conducted in animals: two single-exposure inhalation studies (Battelle Northwest Toxicology 2001, Dow Corning Corporation 2003b) and a multiple-exposure inhalation study (Dow Corning Corporation 2005b), a single-exposure oral study (Dow Corning Corporation 2003a), and single exposure *in vivo* and *in vitro* dermal studies (Dow Corning Corporation 2003d). In humans, a single-exposure inhalation study (Utell 2004) and single-exposure *in vivo* and *in vitro* dermal studies (Dow Corning Corporation 1999, Plotzke *et al.* 2002) have been conducted. Overall, studies in both animals and humans indicated that only a relatively small amount of inhaled D_5 was retained. The absorption of neat D_5 was about 10% following oral exposure in rats. Only a small amount (~0.05%) of D_5 applied to human skin was absorbed into the blood and only a fraction of that was retained with the vast majority (approximately 90% of the absorbed amount) exhaled on first pass. A description of the results of these studies is provided below.

2.2.1.1 Absorption, Distribution, and Elimination by Route

2.2.1.1.1 *Inhalation*

Human Studies

The toxicokinetics of D_5 in humans were evaluated following a 1-hour exposure to 10 ppm D_5 using a mouthpiece exposure system (Utell 2004). During the hour of exposure, 3 male and 2 female volunteers rested for 10 minutes, exercised for 10 minutes, rested for 20 minutes, exercised for 10 minutes, and then rested for 10 minutes. D_5 concentrations in the inhaled and exhaled air were monitored regularly during the exposure period and the D_5 concentration in the exhaled air was monitored up to 20 minutes after the exposure ended. Blood samples were drawn from the forearms of each subject during, immediately after, and at 1, 6, and 24 hours post-exposure, and D_5 plasma concentrations were determined. Exhaled air concentrations increased rapidly to steady state and remained relatively constant during exposure (Table 3). Slight changes were observed in the concentration of D_5 exhaled, with increases observed during the exercising periods. For the majority of the subjects, no D_5 was detected in the exhaled air by 20 minutes post-exposure. Plasma concentrations of D_5 increased during exposure and had returned to baseline by 24 hours post-exposure (Table 4).

Animal Studies

Studies were conducted in rats to evaluate the toxicokinetics of D_5 following single or multiple nose-only inhalation exposures to [^{14}C]-D_5 (Battelle Northwest Toxicology 2001, Dow Corning Corporation 2003b, 2005b). In the Battelle Northwest study, groups of male and female Fischer 344 (F344) rats were exposed for a single, 6-hour period to air containing 7 or 160 ppm [^{14}C]-D_5. Subset groups of 4 to 5 male and female animals for a total of at least 8 per group were designated to evaluate body burden, distribution, or elimination. Samples of blood, fat, liver, lung, urine, feces and expired air were processed for parent D_5. In addition, 2 males and 2 females were used as controls and confined in restraining tubes for the same length of time as the treated rats to establish background matrix effects on radioactivity measurements. Other groups

received 14 6-hour nose only exposure to unlabeled D_5 at a concentration of either 7 or 160 ppm, followed on the 15th day by a 6-hour exposure to radiolabeled D_5.

In the body burden subgroup (Battelle Northwest Toxicology 2001), immediately following the 6-hour exposure period, each rat was removed from the exposure system, given a lethal intraperitoneal (ip) injection of sodium pentobarbital, and then placed back in the exposure system. Half of these animals were solubilized *in toto* and the remaining half were pelted and the pelt and carcass were solubilized and counted separately. The mean body burden, as a percentage of achieved dose[2] for male and female rats in the 7- and 160-ppm single exposure groups, was 1.86 ± 0.29%, including that present on the pelt, indicating only approximately 2% of the inhaled test material was retained in either dose group. Animals receiving multiple inhalation exposures to D_5 retained 7.7% to 9.5% of the achieved dose in females and males, respectively, including the pelt. When compared to the body burdens for animals with the pelt attached, the carcasses of the animals with the pelt removed had 20.3% (males) and 30.8% (females) of the total body burden of animals with the pelt attached. Therefore, approximately 80 % and 70% for the males and females, respectively, of the body burden could be attributed to deposition on the fur following repeat exposure. If the body burden were adjusted to exclude the pelt, this would result in approximately 2% retained in animals receiving multiple exposures of D_5 by the inhalation route of exposure.

Rats in the distribution subgroups were removed from the exposure tubes and anesthetized with carbon dioxide (CO_2) at 3 hours after the start of exposure or at 0, 1, 3, 12, 24, 48, 72, 96, 120, or 168 hours post-exposure. Blood and tissues were collected from 4 rats/sex/time point at all times except 168 hours post-exposure at which time blood and tissues from 5 rats/sex/group were collected. Radioactivity was widely distributed to tissues in both males and females, with the maximum concentration of radioactivity found in the majority of the tissues by 3 hours post-exposure. The main exceptions were the fat and the thyroid gland. In the 7 ppm group, the maximum concentration in the fat was observed at 168 hours post-exposure in males and at 24 hours

[2] Achieved dose (μCi) was calculated by multiplying the normalized minute volume (L/min-kg) by the body weight (kg), exposure duration (min), achieved mean [^{14}C]-D_5 vapor concentration (mg/L), and specific gravity of [^{14}C]-D_5 solution (μCi/mg).

in females (Table 5). In the 160 ppm group, the maximum concentrations in the thyroid were observed in both males and females at 120 hours post-exposure.

One to three hours following a single exposure to 7 ppm, the highest concentrations (microgram equivalents of D_5 per gram of tissue) were found in the small and large intestines, stomach, thyroid (male only), lung, and adrenal gland (Table 5). In both the single and multiple exposures in the 160 ppm groups (Tables 5 and 6), the highest concentrations were found in the small and large intestines, the adrenal gland, and the lung. While this study was a nose-only inhalation study, significant amounts of D_5 adhered to the fur. After removal from the exposure tubes, this D_5 was available for ingestion by the animals during grooming. This probably contributed to levels of radioactivity observed in the gastrointestinal tract of the animals immediately following exposure.

In the distribution subset following single exposure to 160 ppm, samples of blood, fat, liver, lung, urine, feces and expired air also were processed for parent D_5 analysis. Results of these analyses indicated that almost all the radioactivity present in the plasma up to 12 hours post-exposure was parent D_5. In the fat, approximately 50% of the radioactivity present could be attributed to the parent up to 12 hours post-exposure; the percentage increased with increasing time post-exposure. In the liver and the lung, the majority of the radioactivity immediately following exposure could be attributed to the parent, with this decreasing over the 24 hours post-exposure. No parent was detected in the liver at the 48-hour post-exposure sampling or at later time points. Similar results were seen in the lung, with less than 5% of the radioactivity present attributed to the parent from 24 to 168 hours post-exposure.

Following single exposures to 7 ppm or 160 ppm D_5, most of the radioactivity retained was excreted in the urine and the feces within the first 24 hours post-exposure (Battelle Northwest Toxicology 2001). There appeared to be a dose-dependence in the relative importance of these two major elimination routes. As exposure increased from 7 to 160 ppm, relatively higher amounts of radioactivity were recovered in the feces of both male and female rats, with relatively lower amounts reported in the urine. However since deposition was higher in the repeat exposure it can not be ruled out that this difference

was due to grooming. In both male and female rats, some radioactivity was recovered in expired air and CO_2 traps.

As mentioned previously, despite the nose-only exposure design, a significant amount of D_5 was deposited on the fur of the animals following either single or multiple exposures to D_5. This, in combination with the distribution to the gastrointestinal tract suggesting ingestion of the compound, led to an additional experiment.

It was discovered during the procedure of processing the body burden animals that there was a lag time between removal of the animals from the exposure chamber and the time of euthanasia. This lag time has an impact on the measurement of expired volatiles, as well as the characterization of body burden and mass balance. A separate experiment (Dow Corning Corporation 2003b) was conducted to address this question. Groups of 4 to 5 male and female animals were exposed to air containing 160 ppm [^{14}C]-D_5 for 6 hours. Immediately following exposure, one group of males and one group of females were euthanized while still loaded in the exposure chamber, then transferred to metabolism cages for 6 hours, and used to determine levels of [^{14}C]-D_5 off-gassed from the pelt. The total body burden of both radioactivity and parent chemical from these animals was compared with the results from two additional groups of males and females that were not sacrificed and moved immediately following the exposure period into individual Roth style glass metabolism cages. Urine, feces and expired air were collected from each live animal at various time points up to 168-hours post-exposure. As close as possible to the 168-hour post-exposure time point, animals were euthanized, tissues collected, and the remaining carcasses were solubilized.

In the animals that were euthanized before removal from the exposure chambers, significant amounts of D_5 were measured in the cages and the volatile traps for both males and females, indicating volatilization of D_5 from the animals' fur. However, the deposition rate of D_5 collected in the expired air via volatile traps was greater for the euthanized rats than for the live rats. It was noted that after the rats were moved to metabolism cages, routine grooming could result in ingestion of D_5 from the fur, reducing the amount of D_5 available for evaporation from the fur of the live animals that could contribute to continued post-exposure inhalation of D_5. This ingestion of D_5 during grooming is also supported by the amounts of radioactivity measured in the

gastrointestinal tract of the animals exposed to [^{14}C]-D_5 via inhalation. The mass balance, as a percentage of total recovered amounts, in the live animals measured in this experiment (Dow Corning Corporation 2003b) was different than that noted in the initial single exposure study (Battelle Northwest Toxicology 2001), with a higher fraction of the recovered radioactivity in the expired air. This could be attributed to the immediate transfer of the animals to metabolism cages increasing the capture of expired volatiles from exhalation and volatilization from the pelt.

Following multiple exposures to 160 ppm [^{14}C]-D_5 (Dow Corning Corporation 2005b), most of the radioactivity was recovered in the expired volatiles, which is consistent with the results from the additional single exposure study in which the animals were immediately transferred to metabolism cages. Also, as with the single exposure studies, the majority of the radioactivity was eliminated with the first 24 hours following exposure (Table 6).

In summary, overall, studies in both animals and humans indicated that only a relatively small amount of inhaled D_5 was retained. Although blood and the majority of tissues achieved steady state concentrations rapidly during exposure, some tissues, such as the fat, did not appear to achieve steady state during exposure. Therefore, any continued uptake of inhaled D_5, following the achievement of steady state concentrations in the major tissues, would be related to metabolism or loading into fat. However, as discussed in Section 2.2.1.3, tissue concentrations, even in fat, did not increase with repeated exposures up to 6 months duration.

2.2.1.1.2 *Oral*

Animal Studies

A study was performed to evaluate the pharmacokinetics of D_5 following oral administration (Dow Corning Corporation 2003a). In order to determine whether the vehicle or carrier had an effect on the disposition of D_5, the test substance was administered as a neat material, in corn oil, or in a simethicone fluid. D_5 was administered as a single gavage dose of 0 or 1000 mg [^{14}C]-D_5 in corn oil/kg to groups of males and females (4/sex/group for controls and 16/sex/group for treated) F344 rats. In addition, groups of female rats (4/group controls and 20/group treated) were administered D_5 as either a neat material or in simethicone at 0 or 1000 mg/kg. The volume of

administered dosing solutions in corn oil and simethicone fluid was targeted at 10 mL/kg body weight to deliver a nominal dose of 1000 mg D_5/kg body weight. Animals were housed in glass metabolism cages for collection of urine, feces, and expired volatiles. Sacrifice occurred 168 hours after exposure and selected tissues were collected for radioactivity analysis. Blood was collected from 6 males and 6 females in the corn oil groups and 6 females from both the neat and simethicone groups at 6, 12, 24, 48, 72, 96, 120, 144, or 168 hours post-dose. Six males and 6 females in the corn oil group were sacrificed at 3, 12, 24, 96, or 168 hours post-exposure and prepared for whole body autoradiography.

The absorption of D_5 following administration in various carriers was evaluated by two methods, one based on the radioactivity collected in the urine, expired volatiles, expired CO_2, tissues and carcass over 168 hours post-exposure and the other based on the area under the blood concentration time curve (AUC) for the parent compound. Based on the first method, a mass balance of radioactivity approach, absorption of [^{14}C]-D_5 in corn oil was estimated to be approximately 20% of the administered dose for both males and females. Absorption of D_5 in female rats was estimated to be approximately 26% and 10% in the simethicone fluid or neat material, respectively.

In contrast, based on the second method, blood curve analyses, comparisons of area under the blood concentration time-curves (AUCs) indicated the highest absorption of D_5 occurred following administration in corn oil (879.50 µg D_5 x hr/g), followed by neat (188.00 µg D_5 x hr/g), and the lowest following administration in simethicone fluid (54.70 µg D_5 x hr/g). The authors suggested that some of the discrepancy between absorption assessed by blood curve analysis and mass balance data analysis may have been caused by evaporation of [^{14}C]-D_5 from excreted fecal matter, contributing to the radioactivity trapped on charcoal tubes (used to measure expired volatiles). Animals dosed with corn oil and simethicone, but especially simethicone, had a higher incidence of loose feces that adhered to the sides of the metabolism cages.

Whole body autoradiography of male and female rats in the corn oil group showed that radioactivity was systemically available and distributed to major organs including the bone marrow, liver, kidney, and fat. The majority of the administered D_5 was excreted in the feces regardless of the sex of the animals or the carrier. Total

radioactivity found in feces, GI tract contents, and cage rinses, was determined to be 80.03%, 68.31%, and 84.95% for females administered D_5 in corn oil, simethicone, or neat D_5, respectively. The radioactivity eliminated in the urine consisted entirely of polar metabolites of D_5. Elimination half lives ($t_{1/2}$) in blood ranged from 45.45 hours (simethicone) to 240.36 hours (corn oil) for radioactivity, and between 116.77 (neat) and 242.21 hours (simethicone) for parent D_5.

Overall, this study indicated that oral absorption of D_5 could be influenced by the carrier used for delivery. With neat D_5, absorption was approximately 10%; however, this increased with administration in corn oil or simethicone fluid. The majority of D_5 administered was not absorbed but excreted, regardless of carrier, in the feces. The other routes of elimination (i.e., urine, exhalation) accounted for approximately 15% of the administered dose, with less than 5% remaining in the tissues.

2.2.1.1.3 *Dermal*

Human Studies

A study to evaluate the dermal absorption of D_5 in human volunteers (3 men and 3 women) has been conducted (Plotzke *et al.* 2002). In this study, [^{13}C]-D_5 was used so that D_5 absorbed during this experiment could be differentiated from that present from other sources, such as personal care products. Subjects were asked not to shave their underarms for several days prior to the study. Subjects were provided two separate syringes containing a total of 1.4 g (male) or 1.0 g (female) [^{13}C]-D_5. Subjects were positioned on their sides and the contents of one syringe administered to the indent of the axilla. The subjects remained still for approximately 5 minutes, allowing the test material to absorb and evaporate. The subjects then changed sides and the second half of the dose was administered to the other axilla. The area of application site was measured and recorded. To measure exhaled air following administration of [^{13}C]-D_5, subjects breathed 40 (pre-exposure) or 5 (post-exposure) liters of air, as determined using a dry test meter, into a specially adapted 40 liter or 5 liter Tedlar® bag using a Hans Rudolf non-rebreathing valve. Exhaled air samples were obtained before exposure and at 15, 30, 45, 60, 75, 90, 105, 120, 240, 360, and 1440 minutes post-exposure. Blood samples were drawn before the exposure and at 30 minutes and 1, 2, 4, and 6 hours post-exposure.

Measured concentrations of D_5 in the plasma were very low in both men and women with concentrations of less than 2 µg/L at every time point (Table 7), indicating very low absorption of D_5 by the dermal route of exposure. Peak concentrations in the plasma were achieved within 2 hours post-exposure, and had decreased to below the detection limit (approximately 0.03 ng/gm) by 6 hours post-exposure. Exhaled air concentrations were also very low (i.e., less than 1 ng/L at all time points), with levels approaching baseline by 24 hours post-exposure (Table 8). These data indicated that approximately 90% of the absorbed D_5 was eliminated in the exhaled air (Reddy *et al.* 2005b).

An *in vitro* experiment was conducted with human cadaver skin to evaluate dermal absorption following application of neat D_5 or an antiperspirant formulation containing D_5 (Dow Corning Corporation 1999). With appropriate consent, the skin samples used were human cadaver abdominal skin (24 sq. in/sample), obtained from six donors (4 men, 40 to 66 years of age and 2 women, 46 and 74 years of age) within approximately 24 hours of death. On the day of dosing, blemish-free, circular pieces of skin approximately 2 cm in diameter were cut from one of the skin samples from each donor. The dermis was separated from the epidermis and the samples were placed epidermis side up in the diffusion cell. The skin area available for test article application after mounting into the diffusion cell was 0.64 cm^2. Absorption was evaluated in skin samples from all 6 individuals. Four epidermal skin samples were prepared from each of the 6 donors. In experiment one, neat D_5 was applied to 2 samples from 3 donors (Group A) and the antiperspirant formulation was applied to 2 samples from the remaining 3 donors (Group B). In experiment two, 2 samples from each donor in Group A were dosed with the antiperspirant formulation and two samples from each donor in Group B were dosed with the neat D_5 formulation. This design allowed absorption of each formulation to be tested in duplicate in each donor to control for tissue sample variability. Neat D_5 was delivered via a syringe while the antiperspirant was administered with a dosing rod. Immediately after application, charcoal baskets were placed above the skin and secured into a custom designed cap to capture any volatilized material. The average neat applied dose was 6.18 mg D_5/cm^2, and the average antiperspirant formulation

applied dose was 7.68 mg D_5/cm^2. The final content of D_5 in the antiperspirant formulation was calculated to be 54.59%.

An average of 0.040% (SEM = 0.007%) of the applied dose of neat D_5 and 0.022% (SEM = 0.005%) of the D_5 in antiperspirant formulation was absorbed after 24 hours of exposure The largest percentage of the "absorbed" dose was found in the skin compartment, 93.8% for neat and 86.5% for formulated treatment group. The majority of applied D_5 was volatilized from the skin surface and was recovered in the charcoal traps. The percent of applied dose recovered from all analyzed samples for neat D_5 and D_5 formulated in an antiperspirant ranged between 91% and 99%. No significant differences in absorption between neat D_5 and antiperspirant formulated D_5 were found, and no significant vehicle-related effect on either the percent of applied dose in the charcoal baskets or the total percent of applied dose recovered was found. In both cases (charcoal and recovery), the sample means for the formulated treatment group exceeded the sample means for the neat treatment group. The cumulative penetration over 24 hours for neat D_5 was 0.098 ± 0.01 μg/cm2 in experiment 1 and 0.15 ± 0.01 μg/cm2 in experiment 2. The cumulative penetration over 24 hours for formulated D_5 was 0.22 ± 0.00 μg/cm2 in experiment 1 and 0.31 ± 0.02 μg/cm2 in experiment 2.

Animal Studies

An *in vivo* study was also conducted in F344 female rats to measure the amount of dermal absorption of D_5 neat and formulated in an antiperspirant (Dow Corning Corporation 2003d). This study consisted of four exposure groups (4 females/group) and one control group (2 females). Two exposure groups were exposed to D_5 for 6 hours or 24 hours. An additional exposure group of rats (wash group) were exposed for 24 hours after which the application site was washed (1 dry swab, followed by 3 soapy water swabs and a final dry swab) and the rats returned to the metabolism cages for collection of urine, feces and exhaled/escaped volatiles for an additional 6 days. In order to differentiate expired air from [^{14}C]-D_5 that had escaped the skin depot, an additional group of rats (no expired air group) were euthanized immediately prior to application of D_5 to the skin for 24 hours during which time the animals were placed in metabolism cages for collection of volatiles escaping the application site apparatus.

Rats were acclimated to the metabolism cages for a day one day prior to dosing. The hair was removed from the dorsal surface and a skin depot attached. A single dose of D_5 was applied with a syringe to the skin surface (~2.5 cm^2) inside the attached skin depot. The average amount applied for groups 2, 3, 4 and 5 was 10.8, 10.3, 11.7, and 10.7 [^{14}C]-D_5 /cm^2 (mg/cm^2), respectively. Immediately after application of D_5, rats (including the euthanized dose-group) were placed into individual Roth-style glass metabolism cages for a maximum of 24 hours except for animals in wash group, which were followed for 168 hours post-dosing. All animals were observed at least twice daily in their cages for mortality, morbidity, and moribundity, and were euthanized by CO_2 asphyxiation at the appropriate time points (0 hours in no expired air group; 168 hours in wash group and 6 hours or 24 hours in remaining exposure groups). Samples of expired/escaped volatiles (charcoal tubes), CO_2, feces, and urine, were collected at scheduled times.

For all treatment groups, most (66% to 92%) of the applied D_5 volatilized from the skin at the application site and was trapped in an activated charcoal basket placed above the exposure site. In the wash group, the majority of D_5 (~67%) that remained in the skin and skin depot (excised skin) after the skin had been washed, continued to evaporate and was trapped in the charcoal basket rather than being absorbed. In the 24-hour exposure group, excluding the D_5 retained in the skin, the amount absorbed (D_5 in the feces, urine and carcass), was less than 0.1% of the applied dose after 24 hours. In the wash group, 0.056% was retained after 24 hours exposure, a washing protocol, and 6 days of non-exposure. The reduction in the amount penetrating the skin (feces, urine and carcass) after the washing procedure is consistent with the migration of D_5 in the epidermis to the skin surface and volatilization over the 144 hour post-application/washing period.

These studies demonstrate that during dermal exposure, D_5 is rapidly absorbed into the outer layers of the skin, but can evaporate back out of the skin before systemic absorption can occur. The results of the *in vivo* studies in both the rat and the human are consistent with the *in vitro* results, in that only a small amount of siloxane applied to the skin is actually absorbed into the blood (~0.05%).

2.2.1.2 Metabolism

Animal Studies

Metabolism of D_5 yields a wide range of biotransformation products, including short chain linear silanols (Varaprath *et al.* 1999, 2003) (Figure 2). Two major metabolites and five minor metabolites have been identified in the urine of female rats administered [^{14}C]-D_5 orally, with no parent D_5 measured. The major metabolites were dimethylsilanediol ($Me_2Si(OH)_2$) and methylsilanetriol ($MeSi(OH)_3$). The minor metabolites included: [$MeSi(OH)_2$-O-$Si(OH)_3$], [$MeSi(OH)_2$-O-$Si(OH)_2Me$], [$MeSi(OH)_2$-O-$Si(OH)Me_2$], [$Me_2Si(OH)$-O-$Si(OH)Me_2$], and [$Me_2Si(OH)$-$OSiMe_2$-$OSi(OH)Me_2$]. In addition, the presence of nonamethylcyclopentasiloxanol ($D_4D'OH$) and hydroxymethylnonamethylcyclopentasiloxane ($D_4D'CH_2OH$) also were detected in the urine. The formation of $D_4D'OH$ and ($MeSi(OH)_3$) clearly shows demethylation at the silicon-methyl bonds (Varaprath *et al.* 2003).

2.2.1.3 Bioaccumulation

With most lipophilic compounds, because of their physical/chemical properties, there is the possibility of bioaccumulation. This is typically observed with lipophilic compounds that are cleared very slowly from the body. While D_5 is a very lipophilic compound, the studies discussed previously demonstrate it also has a high rate of clearance, both by metabolism and exhalation. Comparison of blood and tissue concentrations following 15-day (Dow Corning Corporation 2005b) and 6-month exposures indicates a lack of bioaccumulation of this compound (Table 9).

No appreciable increase in any tissue examined was observed between the 15-day and 6-month exposures (Andersen *et al.* 2005). Because D_5 is rapidly eliminated by pulmonary and metabolic clearance, tissue concentrations, even in fat, do not increase with repeated exposures.

2.2.1.4 Physiologically Based Pharmacokinetic Multi-Route Model

The multi-route model for D_5 used in this assessment was based upon three models previously developed (Reddy *et al.* 2005b) for rat inhalation, human inhalation, and human dermal exposure. These three models were combined into a single model,

described below (Dow Corning Corporation 2005e). The multi-route model was coded and run in the Advanced Continuous Simulation Language (ACSL®) (AEgis Technologies Group).

2.2.1.4.1 *Rat Inhalation Model*

Because a previously published inhalation model structure for octamethylcyclotetrasiloxane (D_4) (Andersen *et al.* 2001) had been used successfully to describe the behavior of hexamethyldisiloxane (HMDS) (Dobrev *et al.* 2003), Reddy *et al.* (2005a) based the initial rat inhalation model for D_5 upon the same model structure. The Andersen *et al*. model included compartments for the lung, liver, fat, and rapidly and slowly perfused tissues that were connected by arterial and venous blood compartments. These compartments were described with perfusion-limited kinetics with the exception of the fat compartment, which was described with diffusion-limited kinetics. Also included in the Andersen *et al*. model were deep compartments in both the lung and the liver in order to simulate storage of the highly lipophilic D_5 in the tissue lipids, and two separate fat compartments to more adequately describe differences in storage between different types of fat.

Several modifications were made to the initial D_5 model (Reddy *et al.* 2005a). Due to the tri-phasic nature of the blood, liver, and lung data, additional deep compartments were added to each of these in order to obtain adequate fits. Deep compartments were added to both the arterial and venous blood compartments and flow-limited transfer between these two deep compartments was included. The model was also modified to allow the mobile lipid pool to transfer from the liver to the venous blood and to allow for transfer of the lipid pool between the venous and arterial blood until it left the arterial blood to go into the larger of the two fat compartments. The kinetics for the slowly perfused tissues were also changed from perfusion-limited to diffusion-limited in order to more adequately fit the exhaled air and body burden data. The metabolism description was changed to be linear rather than saturable due to the relatively small blood concentrations resulting from the low exposure concentrations and the small blood:air partition coefficient.

Due to the availability of additional data on the metabolite concentrations following exposure to D_5, a sub-model was added to the rat inhalation model to describe the pharmacokinetics of lipophilic metabolites (Reddy *et al.* 2005a). The lipophilic metabolite sub-model was a simplified version of the parent D_5 model. The lung had only a single deep compartment and the blood and liver compartments had no deep compartments. The two fat compartments of the parent model were combined into a single compartment that was still described with diffusion-limited kinetics; however, the slowly perfused tissue compartment in the metabolite sub-model was described with perfusion-limited kinetics rather than diffusion-limited. Fecal excretion of the lipophilic metabolite from the liver compartment was added. As in the Andersen *et al*. model, this model also described urinary excretion of short chain linear silanols from the blood, where blood concentration was calculated by using a volume of distribution. The urinary excretion differed from the Andersen *et al*. model in that the short chain linear silanols were a product of the metabolism of the lipophilic metabolites rather than the parent.

Model parameters were fit using the data from either a single exposure or repeated exposures to 160 ppm of D_5. Data from a single exposure to 7 ppm could not be used since parent levels were too low to analyze; therefore the 7 ppm data was used to validate the parameters fit to the data from 160 ppm single and repeated exposure. Parameter values were fit separately for male and female rats to account for any sex-specific differences that might exist.

2.2.1.4.2 *Human Inhalation Model*

The human version of the inhalation model (Reddy *et al.* 2005a) was much simpler than the rat version due to the more limited data. No metabolite sub-model was included in the human inhalation model and some of the deep compartments were not included. There was only a single deep compartment used for the lung and liver compartments and the blood compartments no longer had deep compartments. There was also only a single fat compartment that was still described with diffusion-limited kinetics, but, as with the metabolite sub-model for the rat, the slowly perfused tissue compartment was described with perfusion-limited kinetics. Urinary and fecal excretion was not described in the human inhalation model. The human model was also modified from the

rat inhalation model to allow for the effects of exercise. Alveolar ventilation and cardiac output were allowed to change as well as the blood flow to the fat and slowly perfused tissue compartments. Resting cardiac output was described as a function of age, and was described during exercise as a fixed increase of the resting value. All of the increase in cardiac output was directed to increases in blood flow to these two tissue compartments.

Experimentally measured values were available for body weight and alveolar ventilation rate. Values from the rat inhalation model were used for the tissue:blood partition coefficients and for the metabolism rate. Remaining parameters were estimated based upon fitting the available data.

2.2.1.4.3 *Human Dermal Exposure Model*

The human dermal exposure model (Reddy *et al.* 2005b) was created by adding a dermal absorption model to the existing human inhalation model (Reddy *et al.* 2005a). Dermal exposure was described to occur until the entire applied dose had either absorbed into the skin or evaporated from the surface of the skin. During this time, evaporation and absorption were described as zero-order processes. After this point, the chemical was only allowed to move back to the skin surface for evaporation via a first-order rate constant. Once the chemical was absorbed into the skin, it could transfer into and out of a deep skin compartment or transfer into the blood. It was assumed that the blood concentration remained relatively low compared to the amount in the skin and, therefore, it was considered that simulation of the return of the chemical from the blood to the skin was unnecessary (Reddy *et al.* 2005b). The dermal absorption model was set up with two separate skin compartment models to simulate the exposure scenario of the available *in vivo* human dermal data where one-half of the total amount of D_5 was applied to one axilla and the remaining amount was applied 5 minutes later to the other axilla. The model parameters were defined to assume that, while the second dose was being applied, evaporation could not occur from the first application site. These two dermal absorption models served as input functions to the existing human inhalation model; the chemical could only enter the blood from the skin at the exposed sites, whereas, the skin itself was considered a part of the slowly perfused tissue compartment (Reddy *et al.* 2005b).

Because data were not available for the amount of chemical evaporated per area of application, the evaporation rate was calculated based upon data on the amount of D_5 evaporated from filter paper. The timing for complete evaporation (approximately 5 minutes) was consistent with observations during the human dermal exposure studies (Reddy *et al.* 2005b). Although it is expected that the rate of evaporation might decrease over time, it was assumed that over a period of 5 minutes the rate would remain constant (Koini *et al.* 1999, Reddy *et al.* 2005b) and the rate was, therefore, calculated as the amount evaporated divided by the area of application divided by the time for evaporation to occur. The remaining parameters for the dermal portion of the model were fit to the existing data (Plotzke *et al.* 2002). All other parameters were the same as those used for the human inhalation model with the exception of the rate of transfer into the mobile lipid pool from the liver. A value approximately 10-fold higher was necessary to adequately fit the dermal data.

This model has been applied, using the available information on plasma and exhaled air concentrations of D_5 (Plotzke *et al.* 2002), to estimate the systemic absorption and elimination of D_5 following dermal application (Reddy *et al.* 2005b). Model calculations indicated that approximately 0.05% of the applied dose was absorbed systemically in both men and women volunteers. Exhalation was the most important route of elimination, with approximately 90% of the absorbed dose eliminated via exhaled air.

2.2.1.4.4 *Multi-Route Model*

The three separate models discussed above were converted from Berkeley-Madonna code to the Advanced Continuous Simulation Language (ACSL®) (AEgis Technologies Group), modified to be in the same units, and then combined into a single model (Dow Corning Corporation 2005e). Additional code was then added to the model to allow for simulation of the various exposure scenarios described in Section 4. Specific application and assumptions used in the model to describe each exposure scenario are given in Section 4. The models were used to provide the area under the curve (AUC) values for each exposure scenario using route-, age-, and gender-specific parameters.

2.2.2 Animal Toxicity Studies

Oral and inhalation subacute and subchronic studies have been conducted in rats and dermal subacute studies in rabbits have been conducted. The following sections summarize the subacute oral, dermal, and inhalation studies and subchronic 3-month oral and inhalation studies.

2.2.2.1 Oral

2.2.2.1.1 *Subacute Studies*

An oral subacute study was conducted to evaluate the potential effects of D_5 in rats. Ten groups (8/sex/group) of Charles River CDE Sprague Dawley rats were administered D_5 by gavage at doses of 0, 25, 100, 400, or 1600 mg/kg/day, 5 days per week for 2 weeks (Dow Corning Corporation 1990a). The rats were observed daily for signs of toxicity, general appearance, behavioral abnormalities, and incidence of mortality. Body weights and organ weights were recorded. Gross pathological evaluation revealed 6 rats scattered among dose groups with liver lesions; however the incidence of these lesions was not considered treatment-related. Results indicated that subacute oral doses of up to 1600 mg/kg/day produced no adverse effects in male and female Sprague Dawley rats.

A second oral gavage study was conducted in rats (6 per sex) given 1500 mg/kg/day, 5 days per week for 4 weeks (Dow Corning Corporation 1990b). No overt signs toxicity or changes in general appearance or behavior were noted. No treatment-related changes in body weight or food consumption were seen and mortality was not increased. A significant increase in absolute but not relative liver weight was observed in females; however, no gross pathological changes were noted in the liver or in any of the organs or tissues in either the controls or treated animals.

2.2.2.1.2 *Subchronic Studies*

In a 13-week study, male and female Wistar rats were administered by gavage neat D_5 at doses of 100, 330, or 1000 mg/kg/day (Jager and Hartmann 1991), as cited in (Dow Corning Corporation 2005c). No changes in cage-side observations, body weight or body weight gain, food consumption, or ophthalmologic effects were noted at any

dose. Increases in liver weight were seen at all dose levels (statistical significance not given) in both males and females. However, no gross or histopathological changes were seen in the livers of treated rats of either sex and none were seen in the other tissues examined grossly and microscopically.

In summary, the results of oral subacute and subchronic studies with D_5 in male and female rats indicated there were no treatment-related adverse effects at doses up to 1600 mg/kg/day following 14 and 28 days of exposure. Changes in liver weight in these oral studies were not accompanied by any gross or histopathological changes in the liver and were considered adaptive responses that would be expected to be transient

2.2.2.2 Inhalation

2.2.2.2.1 *Subacute Studies*

Inhalation studies have been conducted to evaluate the potential systemic toxicity of D_5 (Burns-Naas *et al.* 1998, Dow Corning Corporation 2000a, Experimental Pathology Laboratories 1996a, 1996b, RCC 1995a, 1995b). In a subacute 1-month study, D_5 was administered to F344 rats of both sexes by whole body inhalation at concentrations of 0, 10, 25, 75, or 160 ppm for 6 hours/day, 7 days/week for 4 weeks (Burns-Naas *et al.* 1998). At the end of the last exposure 10 rats/sex/group were sacrificed and 5 rats/sex/group were retained for a 2-week recovery period. Body weights and consumption of food were measured twice weekly, and animals were monitored daily for signs of exposure-related effects including respiratory, dermal, behavioral, nasal, or ocular changes. Necropsies were performed on day 29 (10 rats/group/sex) and, after the 2-week recovery period, the final 5 rats/group/sex were necropsied. Organ weights were obtained and tissues were collected from the liver, spleen, testes, heart, lung, thymus, ovaries, kidneys, adrenals, and brain for histopathological examinations.

A significant increase in lung weight was seen in male rats in the 160 ppm dose group following the 28-day exposure period. A significant increase in relative liver weight, but not absolute liver weight, in the males in the 160 ppm dose group was observed. Significant increases were also seen in female rat liver weights in the 160 ppm

dose group. However, none of these effects were seen following the 2-week recovery period.

No treatment-related lesions in any organs were found with gross necropsies, including groups evaluated after the 28-day exposure period and following the 2-week recovery period. The results of the statistical analyses were not reported; however, an increase in goblet cell proliferation in Level 1 of the nasal cavity was seen in male and female animals at the 160 ppm concentration. An increase in incidence at 75 and 10 ppm was also seen when compared to controls. However, this was not seen in groups exposed to 25 ppm. Males (75 ppm) and females (160 ppm) were noted as having increased incidence and severity of submucosal inflammation in the lung. After the recovery period, no submucosal inflammation was observed in any of the animals and increases in the incidence of goblet cell proliferation was only seen in the high exposure females (160 ppm) leading the authors to conclude that the submucosal inflammation and goblet cell proliferation were reversible following cessation of exposure

In another subacute study, rats were exposed to D_5 by inhalation for one month (28d)[3] (RCC 1995b). Groups of 10 male and 10 female F344 rats were exposed to D_5 at concentrations of 0 (Group 1), 28 (Group 2), 42 (Group 3), 96 (Group 4), or 151 (Group 5) ppm in air (nose-only) for 6 hours per day, 5 days per week for a total of 20 (males) or 21 (females) exposures over a 27- or 28-day period. The highest concentration of D_5 was expected to produce adverse effects; however, when no marked signs of toxicity were observed at this exposure level by day 11, the high exposure concentration was increased to 224 ppm (3.4 mg/L of air) for an average over the exposure duration of 197 ppm. The saturated vapor concentration of D_5 was experimentally evaluated to be 139 ppm (2.1 mg/L) of air. D_5 should have been in the vapor phase at all exposure levels, with the exception of the highest exposure group. At this concentration, approximately 40% of the test atmosphere was expected to be a liquid aerosol, which affected the amount of D_5 that was respirable, as well as the potential response in the lung.

[3] Both the one-month and three-month studies were conducted by RCC. A re-evaluation of the pathology data was conducted by Experimental Pathology Laboratories (EPL) to assure consistency in terminology, diagnosis criteria, and interpretation across several studies. A Pathology Working Group (PWG) consisting of six pathologists resolved any differences. This discussion and that for the subchronic, 90-day inhalation study contains the consensus findings.

No treatment-related results were reported for survival, body weight changes, or food consumption; and no clinical signs of toxicity were reported. Significant changes in hematology included increased total leukocyte count and increased lymphocytes of the differential leukocyte count for males in the two highest dose groups, which the authors stated could reflect a stimulated immunological response. No other treatment related hematological results were reported. Significant clinical biochemistry results included increased glucose concentration in all treated males; increased creatinine concentration in high dose group males; increased triglyceride concentrations for males and females in Groups 4 and 5; decreased alkaline phosphatase activity in females in Groups 4 and 5; decreased calcium concentration in females in Groups 3, 4, and 5; increased phosphorous concentrations in all treated male groups; and increased globulin concentration and decreased albumin to globulin ration in high dose group females. The clinical biochemistry results suggest metabolic adaptations or stress related changes in response to treatment

Absolute liver weights and liver-to-body and brain weight ratios were significantly increased in Group 5 females. Mean lung absolute weights and lung to brain weight ratios were significantly increased in males and female in Group 5. Pathology results were evaluated by RCC, EPL, and PWG (Experimental Pathology Laboratories 1996a, 1996b, RCC 1995a, 1995b). In the nasal cavity there was a significant increase in the incidence and severity of goblet cell proliferation in males and females in the high dose group. The incidence of focal macrophage accumulation and interstitial inflation of the lung was significantly increased in males and females in the high dose group. In addition, RCC reported a significantly increased incidence of heptocellular hypertrophy in females in the high dose group. Histopathologic changes in the liver were not reported by EPL and the PWG.

2.2.2.2.2 *Subchronic Studies*

In a 3-month inhalation study, five groups of Fischer 344 rats (20/sex/group) were exposed to D_5 via nose-only inhalation at concentrations of 0 (Group 1), 26.4 (Group 2), 46.1 (Group 3), 85.7 (Group 4), or 224 (Group 5) ppm for 6 hours/day, 5 days/week for

13 weeks[4] (RCC 1995a). In addition, 2 groups of 10 animals were exposed to D_5 under the same conditions at concentrations of 0 (Group 1 recovery) or the high concentration (Group 5 recovery), and allowed to recover for 1 month following treatment.

No treatment-related changes were noted for survival or food consumption, and there were no clinical signs of toxicity. The mean body weight gains for males and females in Group 5 were reduced during the treatment period; however, body weight gains returned to normal during the second week of the recovery period. No treatment related hematological, clinical biochemistry, or urinalysis results were considered treatment-related.

A significant increase in the mean absolute and relative lung weights in males and females of Group 5 was reported. Only Group 5 females showed a similar finding in the recovery group. There was also a significant increase in the absolute and relative liver weights of male rats in Group 5 and female rats in Groups 3, 4, and 5 at the end of the treatment period. However, there was no evidence of similar changes in liver weights for males or females in the recovery group.

Pathology results were reported by RCC, EPL, and PWG (Experimental Pathology Laboratories 1996b, 1996c, RCC 1995a). RCC (1995a) reported an increased incidence of goblet cell hyperplasia in the nasal cavity of male and female rats in Group 5. No evidence of this finding was reported following the 1-month recovery period. No findings in the nasal cavity of main test or recovery animals were reported by EPL (1996c) or the PWG (Experimental Pathology Laboratories 1996b).

In the lungs, there was an increase in the incidence of subacute/chronic focal or multifocal alveolitis reported in Group 4 and Group 5 male and female rats, when compared to controls (RCC 1995a). Following the 1-month recovery period, the incidence of alveolitis was still evident in Group 5 males and females. An increase in the incidence and severity of focal interstitial inflammation in the lungs was reported in Group 5 male and female rats and in male and female recovery Group 5 rats

[4] Both the one-month and three-month studies were conducted by RCC. A re-evaluation of the pathology data was conducted by Experimental Pathology Laboratories (EPL) to assure consistency in terminology, diagnosis criteria, and interpretation across several studies. A Pathology Working Group (PWG) consisting of six pathologists resolved any differences. This discussion and that for the subacute, 28-day inhalation study contains the consensus findings.

(Experimental Pathology Laboratories 1996b, 1996c, RCC 1995a). An increase in the incidence and severity of alveolar macrophages within the lungs of Group 4 (Experimental Pathology Laboratories 1996c) and Group 5 (Experimental Pathology Laboratories 1996c, RCC 1995a) male and female rats was reported, and the increase was still evident in the recovery groups. The incidence of pleural fibrosis in the lungs of male and female rats in Group 5 was also increased; however, the incidence decreased in Group 5 recovery animals (RCC 1995a).

RCC (1995a) reported an increased incidence of interstitial gland hyperplasia within the ovaries of Group 5 females that was still evident following recovery. In addition, Group 5 female rats exhibited an increased incidence of vaginal mucification and atrophy of the vaginal mucosa (RCC 1995a). No vaginal mucification was reported following the 1-month recovery period. EPL (1996c) reported no interstitial gland hyperplasia of ovaries in control or treated female rats; however, PWG (Experimental Pathology Laboratories 1996b) reported similar findings to RCC of the "prominence of interstitial glands related to a decrease in the number of follicles and corpora lutea in the ovaries" of female rats in the control group and Group 5. PWG (Experimental Pathology Laboratories 1996b) also reported this finding in female control and Group 5 rats following the 1-month recovery period.

In summary, the histopathological changes observed which appeared to be associated with D_5 1- or 3-month inhalation exposure were limited to the lungs, nasal cavity, and liver (1-month). In the 1-month study, in both males and females in the high-concentration group, an increase in the incidence and the severity of focal alveolar macrophage accumulation and focal interstitial inflammation in the lungs, and goblet cell proliferation in the nasal cavity and the nasopharyngeal duct was reported. Similar effects were observed in the lungs of both male and female rats following 3 months of exposure to D_5 via inhalation. These effects are likely a response to irritation by D_5. Localized effects, such as those observed in the lungs of rats treated with D_5, are not usually observed following exposure to a vapor. These types of effects are generally observed following exposure to an aerosol. RCC (1995b) reported that the saturated vapor concentration of D_5 was experimentally evaluated to be 2.1 mg/L of air. The test atmosphere was expected to be saturated vapor only, without liquid particles, at the three

lower concentrations. For the highest concentration, approximately 4–40% of the test atmosphere was expected to be liquid aerosol. Therefore, the histopathological changes observed both in the lung and the nasal cavity of rats exposed to the high concentration of D_5 are probably the result of localized irritation from aerosol deposition.

Increases in absolute and relative liver weights were observed in female rats in the 1-month (Group 5 only) and 3-month studies (Groups 3 to 5) and in male rats in the 3-month study (Group 5). Although slight hypertrophy was noted in Group 5 females in the 1-month study, there were no histopathological changes observed in the liver in males or females in the 3-month study related to exposure to D_5. Foci of inflammation, comprised primarily of macrophages and lymphocytes, were randomly distributed throughout the liver of most rats in both treated and control groups. Therefore, the liver findings were considered to be incidental.

Many other histopathological changes, such as atrophy of the seminiferous tubules and oligospermia in the epididymis in male rats, were also observed in both the 1-month and the 3-month studies. These changes, however, are probably related to the method of treatment, rather than a direct effect of D_5. Many of these changes have been reported to be secondary effects to the restraint methods used for nose-only inhalation exposures.

In conclusion, the only histopathological changes that may be directly related to D_5 subacute or subchronic exposure were histopathological changes observed in the lungs and nasal cavity of Group 5 males and females. However, as discussed previously, the histopathological changes observed in the lungs may be related to aerosol formation, rather than a chemical effect of D_5.

2.2.2.3 Dermal

Two 21-day dermal toxicity studies have been reported by Dow Corning (Huntingdon Research Center 1979, Krötlinger 1988). In one of the studies, D_5 (1000 mg/kg/day) was applied to abraded and non-abraded skin of New Zealand white rabbits (3/sex/group abraded skin; 3/sex/group non-abraded skin) for 6 hours per day under occlusive dressing for 21 consecutive days (Huntingdon Research Center 1979). Skin reactions were scored for edema and erythema. No changes in body weight, organ

weights, including the heart, lungs, liver, kidneys, spleen, testes, epididymides, ovaries, and urinary bladder, or gross pathology findings were recorded at necropsy. No signs of skin irritation were noted.

In another 21-day study, D_5 was applied dermally to male and female New Zealand white rabbits (number per group not given) at doses of 0, 96, 288, or 960 mg D_5/kg/day, 5 days per week, for 3 weeks followed by a 2-week recovery period (Krötlinger 1988). No clinical signs of toxicity were noted during exposure or by the end of the recovery period. No increase in mortality occurred between treated groups and controls. No alterations in hematological or clinical biochemistry parameter evaluated were found. Further, no changes in body weights were noted and no treatment-related gross or microscopic effects were seen.

The potential effects of D_5 by the dermal route were evaluated in a 28-day study in Charles River CD Sprague Dawley rats (Dow Corning Corporation 1990c). Male and female rats (10/sex/group) were exposed to 0, 200, 800, or 1600 mg/kg/day of D_5 applied to the skin under occlusive conditions for 6 hours per day, 7 days per week, for 28 days. In addition, two satellite groups were exposed to 0 or 1600 mg D_5/kg/day in the same manner with a 28-day recovery period. There were no treatment-related overt signs of toxicity, or changes in behavior, body weight, food consumption or hematological parameters measured. Changes in some of the clinical chemistry parameters evaluated were within normal biological variation. Based on the results of these studies, D_5 did not produce any significant toxicological effects following up to 28 days of dermal exposure to doses as high as 1600 mg/kg/day.

In summary, following dermal exposure, D_5 did not produce any significant toxicological effects after 21 to 28 days of exposure to doses as high as 1600 mg/kg/day.

2.2.3 Mutagenicity and Genotoxicity Studies

Studies conducted with D_5 indicate it is neither mutagenic or genotoxic in bacterial or in mammalian test systems. These studies are summarized in the following sections.

2.2.3.1 Mutagenicity Studies

A series of studies were conducted to assess the potential for mutagenicity using *Salmonella typhimurium, Saccharomyces cerevisiae,* and *Escherichia coli* (Litton Bionetics Inc 1978). D_5 was incubated with *S. typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98, and TA 100, *S. cerevisiae* D4 and *E. coli* strains W3110/polA$^+$ and P3478/polA$^-$ with and without S9 metabolic activation (S9 was prepared from Sprague-Dawley adult male rat liver administered Aroclor 1254 five days prior to sacrifice). Plates containing *S. typhimurium* and *E. coli* were incubated with D_5 at doses of 0, 0.001, 0.01, 0.1, 1.0, or 5.0 µL per plate for 48 hours at 37ºC, while *S. cerevisiae* D4 plates were incubated with D_5 at doses of 0, 0.001, 0.01, 0.1, 1.0, or 5.0 µL per plate at 30ºC (nonactivation) and 37ºC (activation) for 3 to 5 days. Results of the tests with and without metabolic activation systems indicated that D_5 was not mutagenic. Tests using *S. typhimurium* strain TA 98 were repeated because of increased revertants observed at the lowest concentrations tested, both with and without metabolic activation. The results of the repeat tests were negative. Since the initial results could not be reproduced, D_5 was not considered mutagenic in strain TA 98.

An additional battery of mutagenicity studies was performed in strains TA 1535, TA 1537, TA 98, and TA 100 and the *E. coli* strain WP2 uvrA both with and without liver microsomal activation (Dow Corning Corporation 2003c). Phenobarbital/β-Naphthoflavone-induced rat liver S9 homogenate was used as the metabolic activation system. The D_5 assays were performed in triplicate for each strain at D_5 concentrations of 0, 33, 100, 333, 1000, 2500, or 5000 µg/plate prepared using absolute ethanol as the solvent. The plates incubated with D_5 showed normal background growth up to 5000 µg/plate both with and without metabolic activation in all strains tested. No substantial increase in revertant colony numbers of any of the five tester strains was observed at any dose level.

These results indicated that D_5 was not mutagenic and no gene mutations occurred either by base pair changes or frameshift in the strains used in these experiments. Further, mutations as a result of oxidative stress did not occur, as indicated by the negative results in *E. coli* strain WP2 uvrA, a strain sensitive to oxidative stress (Wilcox *et al.* 1990).

2.2.3.2 Genotoxicity Studies

In a study using L5178Y mouse lymphoma cells, D_5 was evaluated with and without metabolic activation for its ability to induce point mutations, sister chromatid exchanges (SCE), chromosome aberrations or primary DNA damage (Litton Bionetics Inc 1978). A number of positive controls were used to test the responsiveness of the lymphoma cells in the absence and presence of microsomal activation, including ethylmethanesulfonate (0.5 µL/mL), dimethylnitrosamine (0.3 µL/mL), methylmethanesulfonate (0.1 µL/mL), and benzo(a)pyrene (0.1 mg/mL). The mouse lymphoma cells were incubated with D_5 at concentrations of 0, 0.8, 1.6, 3.2, 6.4, 12.5, or 25 µL/mL. The solvent used to dissolve the test compound, ethanol, was also used as the negative control. The solvent or negative control did not result in any genotoxic effects, and positive control responses were within the expected ranges. The results of all three tests (point mutation, chromosomal events, and primary DNA damage) were all negative, indicating that D_5 does not exhibit genetic toxicity potential.

In an *in vitro* chromosomal aberrations assay, D_5 was dissolved in ethanol and assessed for its potential to induce structural chromosome aberrations in Chinese hamster V79 lung cells (CHL) (Dow Corning Corporation 2004b). Negative, solvent, and positive control substances were tested and the treated groups and positive controls were evaluated both with and without phenobarbital-induced metabolic activation. The solvent used in the experiments was absolute ethanol at a final concentration of 0.5% (v/v) in the culture medium. Experiments at D_5 concentrations from 0.001 to 0.2 µL/mL (without activation) and 1 to 5 µL/mL (with activation) showed that D_5 did not induce significant increases in structural chromosome aberrations in V79 cells at any of the doses tested both with or without metabolic activation. In addition, there were no significant increases in the percentage of polyploidy cells in treated cultures as compared to negative and solvent control values.

The genotoxic potential of D_5 was assessed using the *in vivo* hepatocyte unscheduled DNA synthesis (UDS) test and the mammalian bone marrow erythrocyte micronucleus test (Dow Corning Corporation 2004f). Six male and 6 female F344 rats per group were exposed via whole body inhalation to D_5 at a concentration of 160 ppm for 7 consecutive days. Six male and 6 female rats were assigned to the negative and

positive control groups. Filtered air was used for the negative control group. The positive control groups were also given filtered air but, following the last exposure to D_5, these groups were given either a gavage dose of either 2-acetylaminofluorene (2-AAF; 100 mg/kg) for the UDS test or cyclophosphamide (CPA 40 mg/kg) for the micronucleus test. During treatment, all animals were observed for mortality, clinical signs, and changes in body weights. For the UDS test, the animals were sacrificed 5 or 16 hours following treatment and the livers were perfused to obtain primary hepatocytes. The primary hepatocytes were established and exposed for 4 hours to ^{3}HTdR (methyl-^{3}H-thymidine) and occurrence of UDS was quantified by the amount of radioactive incorporation. No UDS induction in the hepatocytes was noted in the treated animals when compared to controls and the viability of the hepatocytes was not significantly affected by D_5. In the micronucleus analysis, bone marrow cells were collected 24 hours following the last treatment. Results indicated that the number of polychromatic erythrocytes (PCE) was not decreased compared to the control, indicating D_5 did not exert cytotoxic effects on the bone marrow cells. In addition, there was no biologically relevant or significant enhancement in the frequency of the detected micronuclei after administration of D_5. It was concluded that D_5 was nongenotoxic in the UDS and micronucleus assays.

In summary, D_5 was not mutagenic or genotoxic in *in vitro* assays in bacterial or mammalian cells or *in vivo* genotoxicity tests both with and without metabolic activation.

2.2.4 Reproductive/Developmental Studies

No exposure-related adverse effects have been observed in any of the reproductive or developmental toxicity studies conducted with D_5. An inhalation range-finding reproductive study was conducted to determine appropriate exposure levels of D_5 that produced toxicity with less than 10% lethality in the adult, and to determine a concentration that was a potential NOAEL for reproductive and developmental effects (WIL 1996). Three groups of 22 F_0 male and 22 F_0 female Sprague-Dawley Crl:CDBR rats were used in the study. Two groups were exposed to 26 or 132 ppm D_5 via whole body inhalation. The third group served as the control and was exposed to clean, filtered air. The animals were exposed for 6 hours a day, for a minimum of 28 days prior to mating and continuing through

necropsy, with the exception of the F_0 females whose exposure was suspended from gestation day 21 through lactation day 4. Dosing of female animals was suspended to prevent the delivery of pups in the exposure chambers. The offspring were directly exposed to the test substance on lactation days 21 to 28; therefore, the F_1 pups could have been exposed to D_5 indirectly *in utero* through placental transfer, through suckling and/or dermal contact during lactation, or directly via 6-hour exposures from weaning through sacrifice.

All F_0 animals were observed twice a day for behavior, appearance, moribundity, and mortality; and food consumption and body weight were recorded weekly. The reproductive performance of the F_0 males and females was determined using mating and fertility indices which were calculated as follows:

$$\text{Female Mating Index}(\%) = \frac{\text{number of females with evidence of mating}}{\text{total number of females used for mating}} \times 100 \quad (1)$$

$$\text{Male Mating Index}(\%) = \frac{\text{number of males with evidence of mating}}{\text{total number of males used for mating}} \times 100 \quad (2)$$

$$\text{Female Fertility Index}(\%) = \frac{\text{number of females with confirmed pregnancy}}{\text{total number of females used for mating}} \times 100 \quad (3)$$

$$\text{Male Fertility Index}(\%) = \frac{\text{number of males siring at least 1 litter}}{\text{total number of males used for mating}} \times 100 \quad (4)$$

The F_0 females from each dose group were allowed to deliver naturally and rear the pups to postnatal day 21. F_0 females with viable pups were necropsied on lactation day 21, at which time the number of implantation sites was recorded. Females that did not deliver were sacrificed on post-mating day 25 (evidence of mating) or post-mating day 27 (no evidence of mating). Gross necropsy was performed on all animals that were sacrificed and tissues were preserved for histopathological examination when deemed necessary by the gross findings. The testes and epididymides from all F_0 males, and the ovaries from all F_0 females were weighed and the absolute weights and weights relative to final body weights were recorded.

Pups received a detailed physical examination and pup body weights were recorded on postnatal days 1, 4, 7, 14, 21, and 28. Each litter was examined daily for survival,

adverse changes in appearance or behavior. Live litter size and viability indices were calculated as follows:

$$\text{Live Litter Size} = \frac{\text{total viable pups on day 0}}{\text{number of litters with viable pups on day 0}} \quad (5)$$

$$\text{Viability Index (\%)} = \frac{\text{pups viable on day 1 or 4}}{\text{pups viable on day 0}} \times 100 \quad (6)$$

Eight F1 pups (of equal sex distribution) from each litter were randomly selected on postnatal day 4. The remaining pups were euthanized and discarded. When the selected pups reached an age of 21 days, a minimum of one male and one female per litter were selected to obtain 20 males and 20 females for each group. The pups were examined for developmental morphology and in some cases; tissues were preserved for histopathological evaluation. Non-gravid animal data were not included in the statistical analyses following the mating period. The statistical tests used were the Chi-square test with Yates correction factor (pup sex ratios, pup survival indices, mean number of stillborn and dead pups, and parental fertility indices) and the ANOVA (two-tailed) with the Dunnett's test (F_0 body weights and weight gains, gestation and lactation body weights and weight gains, parental food consumption, mean litter weights, length of gestation, and live litter sizes).

Clinical observations of the F_0 males and females showed no significant treatment-related effects when compared to control animals. There were no significant differences in treated and control F_0 animals when reproductive performance (male and female mating and fertility indices) was compared. No sustained changes in the food consumption or body weights of the F_0 males or females were reported.

The gross necropsy of the F_0 males and females also showed no treatment-related findings. There were no significant effects on the mean ovarian weights, absolute or relative ovarian weights, or testicular or epididymal weights (absolute or relative).

No significant effects were reported for the mean number of implantation sites, number of pups born, or the number of sites unaccounted for (the number of implantation sites minus the number of pups born).

The general physical condition of the F_1 generation was reported to be similar to the controls. There was no significant treatment-related effect on pup sex ratios, live litter size or pup weights. No significant treatment-related effects were reported following gross necropsy of selected F_1 generation pups on postnatal days 21 and 28.

On postnatal day 0, the numbers of dead pups in any treated group was not significant when compared to the control group. No significant differences were noted in survival in the exposed groups on postnatal days 1, 4, and 7; however, the viability indices were significantly decreased in the 132 ppm group on postnatal days 14 and 21, when compared to controls. The viability indices at both the 14 and 21 day reading were 94.3% as compared to 100% in the control group which was within the range of the historical control. Most of the pup loss in the high exposure group occurred in two litters, female numbers 53128 and 25342 with total litter loss. Consequently, pup survival was considered comparable to controls. The NOAEL for maternal toxicity and reproductive/developmental effects was 132 ppm.

A two-generation inhalation reproductive and developmental neurotoxicity study of D_5 was conducted in Crl:CD®(SD)BR rats (WIL 1999). Male and female rats were exposed to D_5 at concentrations of 0, 30, 70, or 160 ppm. The F_0 and F_1 animals were exposed to D_5 for 6 hours a day for 7 days per week for a minimum of 70 days prior to mating. The F_0 and F_1 males were exposed through the mating process and up to the day before euthanization. Exposure of the F_0 and F_1 females continued throughout mating and through gestation day 20. The female groups were re-exposed to D_5 on lactation day 5, and exposure continued up to the day of euthanization (PND 21).

All animals were observed twice daily for appearance, behavior, mortality, and morbidity. F_0 and F_1 male body weights were recorded on a weekly basis from initiation of exposure until euthanization. Female F_0 and F_1 body weights were measured weekly from the beginning of exposure until observation of copulation and on gestation days 0, 7, 10, 14, and 20 and on lactation days 1, 4, 7, 14, and 21. F_0 and F_1 females also underwent daily vaginal smears to determine the stage of the estrous cycle, beginning 21 days prior to pairing and continuing until evidence of copulation.

The F_1 generation was selected from the offspring of the F_0 animals, and the F_2 generation pups were selected from the F_1 generation rats. The F_1 and F_2 animals were

observed for onset of puberty (balanopreputial separation and vaginal patency). Parental animals from the F_0 and F_1 generations as well as F_1 and F_2 pups underwent a detailed gross necropsy. Microscopic examinations were conducted on selected tissues from all F_0 and F_1 parental animals in the control and 160 ppm dose groups and in F_2 pups selected for neuropathological evaluation.

Thirty pups per sex per dose group were selected from the F_2 generation for developmental landmarks, neurobehavioral testing, neuropathology, brain weights, and/or brain dimension measurements.

Five F_0 animals died (two in the 30 ppm dose group and three in the 160 ppm dose group) between weeks 2 and 18. In addition, one F_0 female in the 70 ppm group was euthanized at the point of death during week 15. All other F_0 and F_1 parental animals were necropsied after scheduled euthanization. No clear exposure-response relationship was evident for the six deaths mentioned above, and no consistent target organs were identified at the gross and microscopic examinations of these animals. In addition, there were no exposure-related clinical signs noted at any D_5 concentration in any of the F_0 and F_1 parental animals.

Reproductive endpoints evaluated in the F_0 and F_1 parental generations for adverse effects related to D_5 exposure were negative. Endpoints evaluated included: days between pairing and coitus, mating indices, fertility indices, duration of gestation, and parturition. Ovarian primordial follicle counts were evaluated in the F_0 and F_1 animal groups at a concentration of 160 ppm and found to be unaffected by exposure to D_5. Spermatogenic characteristics (testicular and epididymal sperm numbers, sperm production rate, sperm motility, and sperm morphology) of F_0 and F_1 parental rats were unaffected by exposure to D_5. Other endpoints including mean pre-mating weights, gestational and lactational body weights, body weight gains, and food consumption were not adversely affected by exposure to D_5 at concentrations of 30, 70, or 160 ppm in F_0 and F_1 parental animals.

Endpoints evaluated in F_1 and F_2 litters (mean live litter sizes, numbers of pups born, percentage of males per litter at birth, postnatal survival, and anogenital distance) were not affected by exposure to D_5 at concentrations of 30, 70, or 160 ppm. A total litter loss on lactation day 0 was seen in one F_0 female in the 160 ppm group. However, the

authors noted that this female delivered only one pup and concluded that because no exposure-related decreases in postnatal survival of the F_1 and F_2 litters were noted at any concentration, the single occurrence of total liter loss was not attributed to D_5 exposure (WIL 1999). Developmental landmarks (balanopreputial separation and vaginal patency) in F_1 and F_2 groups, and F_2 neurobehavioral endpoints (motor activity, startle response, Biel maze, and functional observational data were unaffected by exposure to D_5.

Macroscopic evaluations were conducted on F_0 and F_1 adults with no gross internal findings related to exposure to D_5 seen at any concentration. Gross necropsies were also performed on the F_1 and F_2 litter groups. No gross internal findings were found at any concentration in the litter groups. Organ weights for all litter groups were unaffected following D_5 exposure. Tissues from selected F_2 rats were evaluated on post-natal days 11 or 70. No microscopic findings or differences in mean brain weights and brain measurements related to parental exposure to D_5 were noted.

No parental toxicity, reproductive toxicity, neonatal toxicity, or developmental neurotoxicity was evident at any concentration of D_5. The NOAEL from this two generation study was considered to be >160 ppm.

In summary, no exposure-related adverse effects have been observed in any of the reproductive or developmental toxicity studies conducted with D_5. In an inhalation range-finding reproductive study in which rats were exposed to concentrations of 26 or 132 ppm via whole body inhalation for 6 hours per day for a minimum of 28 days, the NOAEL for maternal toxicity and reproductive/developmental effects was 132 ppm. In a two-generation inhalation reproductive and developmental neurotoxicity study in which rats were exposed to air concentrations of 0, 30, 70, or 160 ppm, the NOAEL from this two generation study was considered to be >160 ppm.

2.2.5 Immunological Studies

In a study conducted to assess the immunotoxicity of D_5 (Burns-Naas *et al.* 1998), male and female F344 rats were exposed by whole body inhalation to 0, 10, 25, 75, or 160 ppm D_5 for 6 hours per day, 7 days a week for 28 days. Ten rats per sex per dose group were intravenously administered sheep erythrocytes (sRBC) (1 mL) 4 days prior to euthanasia. Cyclophosphamide was administered to 5 male and 5 female rats (25 mg/kg

ip) on days 24 through 28 of exposure to serve as immunosuppressive controls. Animals were euthanized on day 29 and spleens were removed, weighed, and placed on ice. The anti-sRBC antibody-forming cell (AFC) assay was conducted within 24 hours to determine the immune status of the exposed animals. An anti-sRBC enzyme linked immunosorbant assay (ELISA) was conducted on serum samples to confirm the antibody response to sRBC, as measured in the spleen.

No differences were observed in the AFC response between animals exposed to D_5 and the control group, indicating that D_5 did not alter humoral immunity. The anti-sRBC ELISA yielded results consistent with the antibody response to sRBC measured in the spleen. Rats treated with cyclophosphamide were examined and found to exhibit significant immunosuppression, confirming that the laboratory could detect immunosuppression in these assays. The authors concluded that under the conditions of the study, D_5 did not affect the immune system in rats.

2.3 Evaluation of Potential Modes of Action

2.3.1 Mode of Action for Hepatic Effects

As noted in the previous sections, only minimal changes in the liver were reported following subacute or subchronic exposure to high concentrations of D_5 by the oral and inhalation routes of exposure. These changes included increased liver weights and hematological changes (decreased urea concentration, increased cholesterol, increased triglycerides, increased total proteins, and increased gamma glutamyl transferase). Such increases in liver weight or other measures of metabolic function, all of which were negative in a chronic 2-year bioassay, would suggest an adaptive response. Such adaptive changes, in the absence of histopathological changes, are not considered adverse (USEPA 1994), and unlikely to be relevant to human health. Hepatic adaptive responses in rodents have been seen for a number of chemicals, including phenobarbital (Williams and Iatropoulos 2002). According to Williams and Iatropoulos, these adaptive changes are an attempt to maintain homeostasis in response to chemically-induced stress and when moderate, reversible and do not effect survival, are not considered adverse. Several studies were conducted in order to further examine the reversible effects of D_5 on

hepatocytes in male and female rats following subchronic oral and inhalation exposure (Dow Corning Corporation 2000b, McKim *et al.* 1999, Zhang *et al.* 2000).

Zhang *et al.* (2000) conducted a study to characterize the ability of D_5 to induce drug metabolizing enzymes in rats in a "phenobarbital-like" manner. Male and female Sprague-Dawley rats in groups of 3 or 4 were treated by gavage with corn oil or 1, 5, 20, or 100 mg/kg D_5 dissolved in corn oil for 4 consecutive days. Male and female rats in the positive control group received 50 mg/kg phenobarbital in phosphate buffered saline by ip injection for 4 days. At the end of exposure the rats were weighed and sacrificed. The livers were removed, weighed, and homogenized. The cytochrome-P450 (CYP) content of the liver homogenates was estimated using a spectrofluorometric method. Induction of CYP1A1/2 was determined by measuring microsomal 7-ethoxyresorufin O-deethylase (EROD) and immunoreactive CYP1A1/2 protein. Induction of CYP2B1/2 was determined by assaying microsomal 7-pentoxyresorufin O-depentylase (PROD) activity as well as CYP2B1/2. CYP3A1/2 immunoreactive protein levels and changes in NADPH cytochrome P-450 were also measured by immunochemical analysis.

Results of this study showed significant increases in the liver-to-body weight ratios of male rats in the 100 mg/kg group and in female rats at doses of 20 mg/kg and higher. Treatment with 100 mg/kg D_5 produced a 41% and 33% increase in liver-to-body weight ratios in male and female rats, respectively. In the positive control group, phenobarbital induced 38% and 27% increases in the liver-to-body weight ratios in male and female rats, respectively. No significant changes in body weight gain were noted between D_5 treated rats and control rats.

The quantitative results of the EROD and PROD analysis are presented in Table 10. Significant increases in EROD activity were observed in male and female rats administered D_5 at doses of 5 mg/kg and greater, while CYP1A1/2 immunoreactive protein levels were not significantly affected by D_5 treatment. Significant increases in PROD activity were noted in male rats at doses of 20 mg/kg and greater and in female rats at doses of 5 mg/kg and greater. The PROD activity increases noted in the male rats were dose-related; however, in the females the maximum increases in PROD were noted at 20 mg/kg and remained constant in the highest dose group. Immunoreactive CYP2B1/2 increased in a similar pattern as that for PROD activity.

Slightly significant increases in CYP3A1/2 immunoreactive protein were noted in the male rats treated with 100 mg/kg. However, a dose-dependent increase in CYP3A1/2 immunoreactive protein levels was observed at doses of 5 mg/kg and greater in female rats. NADPH cytochrome P-450 reductase immunoreceptive protein was significantly increased in male and females rats treated with doses of 5 and 20 mg/kg and greater, respectively.

In the positive control male and female rats treated with phenobarbital at 50 mg/kg, there was significant induction of CYP2B1/2, CYP3A1/2 and NADPH cytochrome P-450 reductase. The authors concluded that D_5 induced CYP2B1/2 in the adult rat liver in a similar manner as that observed with phenobarbital; and female rats were more sensitive to this induction than were male rats.

McKim *et al.* (1999) performed a study to investigate the effects of D_5 on the expression and activity of selected rat hepatic phase I and phase II metabolizing enzymes in F344 rats. Female rats were exposed to vapors concentrations of 0 or 160 ppm D_5 via whole body inhalation for 6 hours per day, 7 days per week for 28 days. Two groups of rats were treated for 28 days (0 or 160 ppm D_5) and allowed to recover for 14 days. Female rats were chosen for this study because, according to the authors, preliminary data indicated they were more sensitive to liver enlargement than males (McKim *et al.* 1999). Daily clinical observations and body weights were noted and liver samples were collected from control and D_5-exposed rats following exposure or recovery. A separate group of female rats, serving as positive controls, were administered phenobarbital at 80 mg/kg/day or 3-methylcholanthrene at 30 mg/kg/day via ip injections once a day for 3 days. Microsomes were prepared from frozen liver samples and microsomal protein concentration was determined by the bicinchoninic acid (BCA) method. Total hepatic P450, NADPH-cytochrome c reductase activity, EROD and PROD activity, testosterone 6β-hydroxylase activity, hydroxylation of lauric acid, epoxide hydrolase activity, immunoreactive CYP proteins, and UDP-glucuronosyltransferase activity toward 4-nitrophenol and chloramphenicol were determined.

Liver size in the D_5-treated rats was significantly higher (16%) than controls at day 28. Liver size decreased during the14-day recovery period, but remained significantly higher than controls. No significant changes were noted in hepatic P450

enzymes. However, there was a significant (1.4-fold) increase in NADPH-cytochrome c reductase and a significant (1.8 fold) increase in EROD, but no change in CYP1A1/2 immunoreactive protein. EROD activity returned to normal in 14-day post-exposure rats. D_5 exposure produced a significant (4.2-fold) increase in PROD and a corresponding significant (3.3-fold) increase in CYP2B1/2 immunoreactive protein, when compared to controls. In rats examined 14-days post-exposure, PROD activity had returned to control levels. There was a significant (2.4-fold) increase in hepatic microsomal CYP3A1/2 activity and a corresponding increase in CYP3A1/2 immunoreactive protein, as indicated by changes in testosterone 6β-hydroxylase levels.

Treated rats also showed a significant increase (1.2 fold and 1.1 fold) in 11- and 12-hydroxylation of lauric acid, respectively. Lauric acid is hydroxylated by CYP4A, which is a biomarker for peroxisome proliferation. However, western blot analysis showed no increase in immunoreactive CYP4A protein. In treated rats, epoxide hydrolase (EH) was significantly increased (1.6-fold) with a corresponding increase (1.4-fold) in EH immunoreactive protein. Using chloramphenicol as a substrate, UDPGT activity was significantly increased (1.8-fold).

In summary, the moderate changes in liver weight in rats exposed to high doses or concentrations of D_5 and the enzyme induction profile in rats treated with D_5 is consistent with the classical response observed following phenobarbital treatment indicating that D_5 was a weak phenobarbital-type inducer the rat liver. The liver weight and enzyme induction were transient and no effects on liver weight or metabolic indicators of function or altered liver histopathology was seen in the 2-year bioassay in male and female rats exposed to vapor concentrations of D_5 up to 160 ppm, the highest concentration that remains a vapor and not a mixed aerosol. These hepatic adaptive changes are not considered adverse and are not relevant or predictive of human health outcomes.

2.3.2 Mode of Action for Uterine Adenocarcinomas in Rats

2.3.2.1 Background

Significant scientific advances in recent decades have prompted the revision of Human Health Cancer Risk Assessment guidelines to incorporate knowledge about the carcinogenic MoA in the animal model and a determination of whether that MoA is

relevant or likely to occur in humans (USEPA 2005). A working group formed under the sponsorship of the USEPA and Health Canada developed a simple, broadly applicable framework for evaluating the human relevance of MoAs defined in animals (Cohen *et al.* 2004, Meek *et al.* 2003, USEPA 2005). This framework is summarized as the following three questions:

1. Is the weight of evidence sufficient to establish the MoA in animals?
2. Are key events in the animal MoA plausible in humans?
3. If the answer to Question 2 is yes, taking into account kinetic and dynamic factors, is the animal MoA plausible in humans?

Within this framework, when the MoA in the animal model is known and is not plausible in humans, then the tumor data are not used further in any subsequent dose-response analyses. Noncarcinogenic data are then used and either a Reference Dose or Reference Concentration (RfD or RfC) is estimated using the appropriate methods. This framework was applied to examine the MoA for the production of uterine adenocarcinomas in female F344 rats, which were only seen in the high exposure group and only after 2 years of exposure.

Studies have revealed that uterine adenocarcinomas appear to be caused in rats by altered endocrine functions (Nagaoka *et al.* 2000). Uterine adenocarcinomas and endometrial carcinomas have been observed in rats as a result of chronic over-stimulation by estrogen (Nagaoka *et al.* 1990, 1994). Although hormones such as estrogen are not genotoxic, they can induce tumors in target tissues in various species (Neumann 1991). A MoA involving endogenous estrogen over-stimulation is believed to occur in aging rats and in rats treated with certain chemical or pharmaceutical agents; however, such tumors have not been observed in other species [Burek *et al.*(1988), as reported in Alison *et al.* (1994)]. The evidence suggests that uterine adenocarcinomas arise in response to endogenous estrogen dominance in aged rats that can be exacerbated by administration of exogenous chemicals by two primary pathways: 1) **directly** by estrogenic agonists, and, 2) **indirectly** by dopamine agonists that initiate a biological cascade ultimately resulting in changes in the estrogen:progestrogen ratio (Alison *et al.* 1994) . As discussed in the following sections, research has been conducted to evaluate which of these provides the

most plausible MoA for the development of uterine adenocarcinomas in aging female F344 rats exposed to high concentrations of D_5 for 2 years.

2.3.2.2 Evaluation of the Potential Estrogenicity and Androgenicity

A series of studies have been conducted to determine the potential estrogenic and androgenic activity of D_5 (Dixon and Brown 1979, Dow Corning Corporation 2004c, 2004d, 2004e). The rat uterotrophic assay (RUA) (USEPA 1998) was used as an indicator of the ability of D_5 to mimic the action of 17β-estradiol. Groups of adult, ovariectomized Fischer 344 (F344) and Sprague-Dawley (SD) rats were used to evaluate the potential estrogenic and anti-estrogenic activity of D_5 (Dow Corning Corporation 2004d, 2004e) (Table 11). Animals were exposed to D_5 at a concentration of 160 ppm via whole body inhalation for 16 hours per day for 3 consecutive days with and without co-administration of 3.0 mg ethinyl estradiol (EE)/kg/day subcutaneously (sc) in corn oil for the corresponding 3 days to test for estrogenic and anti-estrogenic effects, respectively. Two negative control groups were included: one for the inhalation route of exposure using filtered air, and the other for the subcutaneous route using a corn oil vehicle. Additional groups of animals were administered either EE sc at doses of 0.0003, 0.001, or 0.003 mg/kg/day or geninstein sc at doses of 10, 25, or 50 mg/kg/day for 3 consecutive days to serve as positive controls. A final group of positive control animals were given a combination of the estrogen receptor antagonist, ICI 182,780 (3.0 mg/kg/day) and EE (0.003 mg/kg/day) sc also for 3 days.

All groups of rats not administered D_5 were sacrificed 6 hours after the final sc dose. The groups exposed to filtered air or D_5 were sacrificed following the end of the exposure period on day 3. The uterus of each rat was weighed and re-weighed after the uterine fluid was blotted. After being weighed, the uteri were stained with hematoxylin and eosin and a histological evaluation was conducted to determine uterine glandular and luminal epithelial cell heights. In addition, for animals that were exposed by the inhalation route to D_5, blood, uterus, and brain tissue were harvested at necropsy and analyzed for parent D_5.

Positive control groups (groups 2 to 8) and the EE/D_5 combined group (group 9) were compared to the group 1 control animals with respect to all of the endpoints

evaluated (Tables 12 and 13). Exposure to EE and genistein (groups 2 to 7) increased estrogenic endpoints. Results following administration of anti-estrogen ICI 182,780, the positive control (group 8), demonstrated complete antagonism of the estrogenic effects of EE. In contrast, exposure to D_5 did not result in any changes in the estrogenic endpoints in either strain, including absolute or relative (wet or blotted) uterine weight, luminal and glandular epithelial cell height, or uterine fluid increases leading the authors to conclude that D_5 had no significant estrogenic or anti-estrogenic activity. In an analysis of D_5 parent material, brain and uterine tissues, as well as blood were found to contain D_5 at levels reflective of the exposure conditions ranging from 2.48 to 10.07 μg D_5/g tissue (Table 14). In conclusion, D_5 exposure did not result in any estrogenic or anti-estrogenic effects in SD or F344 rats.

A study was conducted in male F344 rats using the Hershberger assay to evaluate the potential androgenic and anti-androgenic activity of D_5 (Dow Corning Corporation 2004c). Castrated F344 male rats were divided into 10 treatment groups, as shown in Table 15. To evaluate the androgenic activity of D_5, one animal group was exposed via whole body inhalation to 160 ppm D_5 for 16 hours per day for 10 consecutive days. Five groups of rats were treated sc with testosterone propionate (TP) at doses of 0.1, 0.2, 0.4, 0.8, or 1.6 mg/kg/day (0.04, 0.08, 0.16, 0.32, or 0.64 TP/mL) for 10 consecutive days. To evaluate the anti-androgenic potential of D_5, animals were treated with a combination of TP (0.54 mg/kg/day) and D_5 (160 ppm). A negative inhalation control group was exposed to filtered air and another negative control group was treated with corn oil subcutaneously. As an anti-androgen positive control, a final group of animals were treated with a combination of TP (0.54 mg/kg/day) and flutamide (4 mg/kg/day).

Rats treated sc (groups 1 to 8) were sacrificed 24 hours after administration of the final dose. The two groups exposed by whole body inhalation (filtered air and D_5 groups 9 and 10) were sacrificed immediately following the 16 hours of exposure on day 10. The following organs were weighed: ventral prostate, seminal vesicle, levator ani/bulbocavernosus (LABC) muscle, glans penis, Cowper's (bulbourethral) gland, and liver. Once weighed, the ventral prostate was placed in 10% buffered formalin and re-weighed 24 hours later as a fixed weight. In addition, blood and brain tissue were collected and analyzed for D_5 content in the groups exposed via inhalation.

Positive control groups (2 to 8) were compared to the group 1 control animals. Significant effects on body weight changes were observed in groups exposed to TP in concentrations ranging from 0.2 mg/kg/day to 1.6 mg/kg/day (groups 3 to 6). No statistical differences in absolute or relative liver weights were seen in any groups. Significant weight increases were seen in absolute and relative organ weights at 0.2 mg/kg/day in ventral prostate (fresh and fixed), seminal vesicle, and levator ani/bulbocavernosus (LABC) muscle. The Cowper's gland absolute and relative organ weight was significantly increased at 0.8 mg/kg/day dose group.

The filtered air control group was used to determine the effect of D_5 (group 10) exposure. No significant dose-related increases in the weights of any tissues examined were seen when compared to the negative control group tissues. The investigators concluded that significant androgenic effects were not observed as a result of exposure to D_5, nor were there any significant anti-androgenic effects.

In vitro experiments were conducted to evaluate the ability of D_5 to interact with the estrogen receptor subtypes alpha (Dow Corning Corporation 2004a). The assay utilizes purified estrogen receptors alpha and beta from the Panvera Corporation (Madison, WI). The human receptor was recombinantly expressed from baculovirus-infected insect cells, and had been shown by the manufacturers to exhibit the binding characteristics of the endogenous receptor (Dow Corning Corporation 2004a). A set of competition experiments was conducted in which the ability of D_5 to displace a radiolabeled ligand from the estrogen receptor alpha was evaluated. Mixtures containing ^{3}H-estradiol (3.4 nM), estrogen receptor alpha (0.2 nM) and 160 ppm D_5 were prepared. Estradiol in concentrations ranging from 100 pM to 100 nM served as positive controls. A set of saturation binding assays was included for each experiment conducted to ensure that the receptor was performing as expected. Mixtures containing a constant amount of estrogen receptor alpha and concentrations of ^{3}H-estradiol ranging from 5 pM to 50 nM were incubated in a sealed 2 mL reaction vial at 37°C with gentle inversion. The authors concluded that D_5 did not displace the radiolabeled estradiol, indicating that D_5 does not interact with the estrogen receptor alpha. The β-receptor subtype was also negative for any D_5 binding.

In summary, D_5 is not a direct acting estrogenic, anti-estrogenic, androgenic, or anti-androgenic compound. The above evidence provides support for an indirect MoA for the increased incidence of uterine adenocarcinomas in aging F344 rats.

2.3.2.3 Studies to Evaluate the Potential for Dopamine Agonist Activity

The potential for D_5 to act as a pituitary dopamine agonist was analyzed in female F344 rats (Dow Corning Corporation 2005d). However, to understand this potential MoA, it is important to consider the normal events in the aging female F344 rat.

2.3.2.3.1 *Mode of Action of Uterine Tumor Formation in the Aging Rat*

Studies have reported that the aged rats exhibit spontaneous tumors of the uterine endometrium, which are believed to be the result of estrogen-related hyperplasia (Nagaoka *et al.* 1994, 2000, Tang and Tang 1981, Tang *et al.* 1982). This process appears to be related to a decline in reproductive function, which occurs during the middle third of the lifespan of rats (Cooper *et al.* 1986). This decline has been attributed to age-dependant changes in the hypothalamic-pituitary-gonadal complex, which leads to a disruption of the hormonal balance.

Rodents exhibit a particularly sensitive positive feedback mechanism between prolactin secretion and estrogen levels in that estrogen inhibits the hypothalamic secretion of dopamine, resulting in the stimulation of prolactin release (Neumann 1991). With normal aging in the female rat, dopaminergic inhibition of prolactin secretion from the pituitary via the hypothalamic tuberoinfundibular dopaminergic neurons decreases, resulting in increased blood prolactin levels (Demarest *et al.* 1982, 1985)**.** Prolactin maintains corpora lutea function and stimulates the synthesis of progesterone (Alison *et al.* 1994)**.** As a consequence, aging female F344 rats enter a state of pseudopregnancy where the corpora lutea persist and continue to secrete progesterone rather than regress, as occurs in a rat that is cycling normally (Demarest *et al.* 1982, Meites *et al.* 1978, Peluso 1992). The result of this is a decrease in the estrogen:progesterone ratio and can lead to progesterone dominance as the primary signal to the endometrium. A pseudopregnancy episode usually lasts about 2 weeks and animals that become pseudopregnant usually do so multiple times (Demarest *et al.* 1982, Peluso 1992). As with pregnancy, pseudopregnancy is associated with low levels of estrogen, luteinizing

hormone (LH), and follicle stimulating hormone (FSH). Ovariectomy results in increased serum LH and FSH and a reduction of prolactin in both young and old female rats (Cooper *et al.* 1986). However, in the aged female rat, neither LH nor FSH levels rise as high as they do in young animals and serum prolactin levels in old rats do not decrease as much as that observed in the young. The high prolactin secretion observed in rats is believed to contribute to the increased incidence of mammary fibroadenomas and pituitary tumors (Meites *et al.* 1978, Neumann 1991).

Dopamine serves as a key regulator of serum prolactin by activating dopamine D2-receptors on the pituitary to inhibit the secretion of prolactin. Reproductive senescence in old female rats leads to a reduction in dopamine secretion, which is different than the loss of ovarian responsiveness observed in human menopause (Alison *et al.* 1994). Chronic administration of dopamine receptor agonists to aged female F344 rats results in decreased serum prolactin levels by acting at the level of the pituitary to inhibit prolactin release. In response to the decrease in serum prolactin, there is a reduction in progesterone synthesis and secretion by the ovary, resulting in an increased estrogen:progesterone ratio. This estrogen dominance leads to persistent endometrial stimulation and hyperplasia, which ultimately may lead to endometrial tumors. This carcinogenic effect has not been demonstrated in any other species (Burek *et al.* 1988, Neumann 1991).

2.3.2.3.2 *Mechanism of Dopamine Agonist-Induced Uterine Adenocarcinomas: An Example with Bromocriptine*

Bromocriptine is an ergot-derived dopamine agonist that is used to treat a condition called hyperprolactinemia because it can inhibit pituitary prolactin secretion. It is marketed as Parlodel for treating Parkinson's disease, amenorrhea, and female infertility. Bromocriptine inhibits prolactin release from rat and human pituitaries and reduces neurotransmitter turnover in rat hypothalamic and neostriatal dopamine neurons, indicating that it is a centrally acting dopaminomimetic agent (Richardson *et al.* 1984). Bromocriptine is characterized as a dopaminomimetic drug and the various clinical indications that it is used for are linked to this pharmacodynamic property. Although it has been in use as a pharmaceutical agent since 1975, bromocriptine has been shown to

cause uterine hyperplasia, adenomas, and carcinomas in female rats (Richardson *et al.* 1984). However, treatment with bromocriptine does not result in uterine tumor production in mice (Richardson *et al.* 1984). In addition, because of their effect on prolactin levels, the rate of spontaneously occurring pituitary and breast tumors in rats can actually be reduced with dopamine agonists such as bromocriptine (Neumann 1991).

Uterine adenocarcinomas were observed in rats following treatment with bromocriptine in a chronic carcinogenicity study; however, a series of experiments showed that the hyperplastic and metaplastic lesions were the result of the drug's inhibitory effect on prolactin secretion and prolonged estrogen dominance superimposed on the waning endocrine system of the aging female rat (Richardson *et al.* 1984). The aging female rat normally exhibits hyperprolactinemia in concert with decreased circulating levels of LH; treatment with bromocriptine results in a decrease in prolactin levels resulting in estrogen dominance leading to the development of uterine tumors (Burek *et al.* 1988). Studies have been conducted to elucidate the mechanism by which chronic bromocriptine administration induces a state of estrogen dominance. Experiments in ovariectomized rats showed that bromocriptine lacked estrogenic activity but that it does function as a dopamine receptor agonist (Burek *et al.* 1988, Richardson *et al.* 1984).

Women taking bromocriptine do not exhibit an endocrine imbalance like that observed in rats. Further, several million patients have received bromocriptine since it was introduced in 1975 and there is no evidence that bromocriptine causes any tumors in humans (Burek *et al.* 1988, Richardson *et al.* 1984). The effects of bromocriptine observed in rats are considered to be a species-specific exaggerated pharmacological effect that does not pose a risk to humans (Burek *et al.* 1988).

2.3.2.3.3 *Evaluation of the Potential for D_5 to be a Dopamine Agonist*

In an initial experiment, the potential of D_5 to off-set the effects of reserpine, was evaluated. Reserpine acts by depleting brain dopamine levels thereby blocking dopamine's inhibitory influence on the lactomorphs in the pituitary and causing an elevation in prolactin levels in blood. Dopamine agonist, such as bromocriptine, act in such a manner. In this initial experiment, female F344 rats were acclimated over four

days by placing animals in exposure cones in the absence of treatment for 1.0, 2.0, 4.0, or 6.0 hours per day. Reserpine (2 mg/kg intraperitoneally, ip) was administered on day 5 to two groups of animals one of which was also exposed on day 6 to D_5 by the inhalation route at a concentration of 160 ppm for 6 hours, while the other group received filtered air only. Ovariectomized rats were used as a second control group and were not administered reserpine. Animals were decapitated immediately following inhalation exposure and trunk blood samples were collected. Treatment with reserpine resulted in a 6.5-fold increase in serum prolactin levels compared to a non-reserpine-treated, ovariectomized control group, demonstrating the effectiveness of reserpine treatment (Table 16). Exposure to D_5 off-set the dopamine-inhibiting action of reserpine resulting in a significant decrease of 49% in serum prolactin levels compared to reserpine-treated rats not exposed to D_5.

Dow Corning Corporation (2005d) conducted another experiment to confirm the prolactin-lowering effect of D_5 and to evaluate the potential of pretreatment with 6 mg/kg sulpiride to block the actions of D_5. Sulpiride is a dopamine receptor antagonist, which would block the inhibitory action of endogenous dopamine or the actions of a dopamine agonist on prolactin serum levels when administered prior to a dopamine agonist. Animals were acclimated to the nose-only chamber for four days prior to reserpine treatment. Ovariectomized rats that did not receive reserpine were used as a control group to determine if reserpine was effective in elevating serum prolactin. This group did not receive reserpine pretreatment. Approximately 24 hours after the animals were treated with reserpine, two groups were treated with sulpiride at a dose of 25 mg/kg. Approximately 15 minutes later animals were exposed to a 6-hour nose only inhalation exposure to filtered air (control) or 160 ppm D_5. Immediately following the inhalation exposure, trunk blood was collected.

Treatment with reserpine resulted in a 12-fold increase in serum prolactin levels compared to the non-reserpine-treated ovariectomized control group. Serum prolactin decreased 34% following exposure to D_5 compared to the reserpine-treated group exposed to filtered air (Table 17). Sulpiride pre-treatment blocked the D_5 effect on serum prolactin further illustrating that D_5 is acting at the dopamine-D2 receptor. When the data from the two experiments were pooled together to increase statistical power in

analyzing the effects of D_5 on serum prolactin levels, a significant decrease (44%) in the levels of serum prolactin were reported. The investigators concluded that these observations provided support for their hypothesis that D_5 is a dopamine receptor agonist.

2.3.2.4 Weight of Evidence for a Dopamine Agonist Mode of Action

There are several lines of evidence to support that D_5 is inducing uterine adenocarcinomas indirectly in a non-genotoxic mechanism in rats that is not relevant to humans. This evidence includes studies that have shown that D_5: 1) is not mutagenic or genotoxic, 2) tumors in D_5-treated rats were histologically indistinguishable from untreated control tumors; 3) does not bind to estrogen receptors and is not an estrogen agonist, and, 4) functions as a dopamine agonist. The results of the studies described below support the non-relevance to humans of the mode of action of D_5 in rats.

1. *Lack of Mutagenicity or Genotoxicity*

Several assays conducted with D_5 revealed that it is not genotoxic or mutagenic (Dow Corning Corporation 2003c, 2003d, 2004f). D_5 was not mutagenic in *in vitro* tests with several bacteria strains or genotoxic in mammalian cells with or without metabolic activation at any dose tested. I*n vivo* tests for genotoxicity were also negative when conducted in rats exposed to D_5 by the inhalation route at concentrations up to 160 ppm.

2. *Lack of unique histopathology*

The National Toxicology Program's (NTP) database was queried for all diagnoses of adenoma, adenocarcinomas, or carcinoma in the uterus of untreated control F344 rats to compare their histopathology to the uterine adenomas and adenocarcinomas observed in rats treated with D_5 (Experimental Pathology Laboratories 2003). Tissues from untreated control groups of animals from 107 studies in the NTP database were evaluated, including a total of 158 tumors (40 adenomas and 118 adenocarcinomas or carcinomas). These tumors were likely the result of the normal aging process as described above. An evaluation of the D_5-induced uterine tumors (2 adenomas, 8 adenocarcinomas) indicated that they were histomorphologically identical to the adenomas and adenocarcinomas present in the control animals in the NTP studies (EPL 2003). In addition, there were many fewer non-neoplastic changes such as cystic endometrial hyperplasia and epithelial hypertrophy in the uteri of the D_5-treated rats than

in the NTP control animals (Experimental Pathology Laboratories 2003). The fact that the histopathological and morphological characteristics of the tumors in D_5-treated rats were indistinguishable from untreated control tumors raises the question of whether this response could be due to exacerbation of age-related changes and inhibitory effect of D_5 on prolactin secretion and prolonged estrogen dominance superimposed on the declining endocrine system of the aging female rat.

3. Lack of Estrogenic or Anti-estrogenic Activity

D_5 was negative for estrogenic activity in rat uterotrophic assays conducted in F344 rats and SD rats that were exposed to 160 ppm (Dow Corning Corporation 2004d, 2004e). There were no treatment-related increases in any of the estrogenic endpoints in either strain of rat. D_5 (160 ppm) did not compete for binding at the estradiol receptor in an *in vitro* estrogen receptor binding assay and it did not activate the reporter gene for estrogen receptor when evaluated in an *in vitro* luciferase reporter gene assay using MCF-7 cells that were transiently transfected with 0.2nM of a plasmid for estrogen receptor alpha (Dow Corning Corporation 2004a). Therefore, D_5 has not been shown to be an estrogen agonist and does not bind to estrogen receptors. Further, D_5 was not anti-estrogenic, androgenic, or anti-androgenic in rats.

4. Evidence for Dopamine Agonist Activity

The more likely mode of action responsible for D_5-induced uterine adenocarcinomas is by its ability to bind to dopamine D2 receptors and function as a dopamine agonist, in a way similar to that observed with bromocriptine. Studies were conducted to evaluate whether D_5 functions as a dopamine agonist *in vitro* and *in vivo* (Dow Corning Corporation 2005d, Jean *et al.* 2005). D_5 was shown to cause a significant reduction of pituitary prolactin secretion both *in vitro* in a rat pituitary tumor cell line and *in vivo* in F344 rats. Utilizing an *in vitro* cell line derived from a rat pituitary tumor (MMQ), 10 μM of D_5 was shown to decrease maitotoxin-induced prolactin release by 55% without affecting viability of the cell line (Jean *et al.* 2005) In addition, an *in vivo* study was conducted to evaluate the ability of D_5 (160 ppm) to bind to dopamine D2 receptors and effect prolactin levels in rats (Jean *et al.* 2005). A model test system has been developed to investigate the potential of chemical substances to act as dopamine

D2-receptor agonists/antagonists (Horowski and Graf 1976)). The premise of this method is based on the observation that serum prolactin is secreted from the pituitary under the control of pituitary dopamine D2-receptors. Dopamine D2-receptor agonists decrease secretion of prolactin in rats, which may be measured following treatment. In addition, pretreatment of rats with reserpine, which disrupts storage of dopamine in the brain, would lead to dopamine depletion and increased prolactin levels. Subsequent treatment with a dopamine agonist (e.g., D_5) would stimulate dopamine secretion and reduce prolactin levels. However, pretreatment of rats with sulpiride, a dopamine receptor antagonist, would reduce the ability of a dopamine agonist (e.g. D_5) to decrease prolactin levels.

Female F344 rats were pretreated with reserpine or sulpiride and subsequently treated with 160-ppm D_5 for up to 6 hours (Dow Corning Corporation 2005d). Exposure to 160-ppm of D_5 caused a 44% decrease in serum prolactin levels relative to the reserpine-treated control group. Exposure of reserpine-pretreated rats to D_5 resulted in a 34% decrease in serum prolactin. In addition, sulpiride pretreatment blocked the ability of D_5 to reduce prolactin levels. These findings indicate that D_5 acts on the pituitary to function as a dopamine D2 receptor agonist. However, because it is important to use ovariectomized rats to ensure that the elevated estrogen is not the result of ovarian stimulation, a control group of rats was ovariectomized and treated with 160 ppm D_5. D_5 reduced prolactin levels in ovariectomized rats not pretreated with reserpine, strengthening the conclusion that D_5 is a dopamine agonist and induced uterine adenocarcinomas in an estrogen receptor-independent mode of action.

2.3.2.5 Relevance to Human Health

The hyperplastic, metaplastic, and inflammatory changes that occurred in the uteri of female rats treated with dopamine agonists, such as bromocriptine, were shown to result from the effects of prolonged estrogen dominance resulting from the reduced prolactin secretion superimposed on the waning endocrine system, which is characteristic of aging rats (Richardson *et al.* 1984). These changes do not occur in other species, including humans (Richardson *et al.* 1984). The mechanism of dopamine agonist-induced tumors is not relevant to humans, because prolactin is not luteotropic in primates

and dopamine agonists do not lead to estrogen dominance in women (Neumann 1991). In humans and other primates, reproductive senescence is the result of ovarian follicular depletion causing menopause (Huang *et al.* 1976). This is not related to aging of the hypothalamus. At the time of menopause, ovarian follicles are essentially depleted and estrogens and progestins are severely reduced, but the capacity of the hypothalamus is normal. Prolactin secretion, which is driven by ovarian estrogens, decreases after menopause begins. Thus, in humans, the post-menopausal period is associated with elevated LH and FSH secretion, and reduced secretion of estrogens, progestins, and prolactin. Women that have taken bromocriptine do not exhibit any endocrine imbalances (e.g., no effect on FSH, LH, estradiol, progesterone levels, or endometrial histology) and they do not develop uterine tumors (Burek *et al.* 1988). Based on the hormonal differences between rats and humans and the lack of effects seen in the clinical studies, the tumorigenic effects of dopamine agonists in female rats is considered a species-specific effect with no relevance to human health.

The available scientific evidence supports that D_5 at very high concentrations is functioning as a dopamine agonist in rats, indirectly leading to the development of uterine tumors. Therefore, the answer to the first question in the MoA framework , "Is the weight of evidence sufficient to establish the MoA in animals?" is **yes**. The answer to the second question of the framework, "Are key events in the animal MoA plausible in humans?" is **no** because the mode of action of D_5-induced uterine adenocarcinomas in rats is by functioning as a dopamine agonist, an effect regarded as species-specific. Therefore, the answer to the third question, "If the answer to Question 2 is yes, taking into account kinetic and dynamic factors, is the animal MoA plausible in humans?" is also **no**.

In conclusion, the tumorigenic effect of D_5 in female rats exposed to very high concentrations (160 ppm) for two years is related to a rodent-specific imbalance in the normal hormonal milieu that occurs in aging female F344 rats. These changes are common in rodents and are not relevant to humans.

3.0 DOSE-RESPONSE ASSESSMENT

It has been recognized in the scientific community that many chemicals may exert their effects in animal models by a nonlinear mode of action, produce an effect by a mode of action that has a threshold, or be a carcinogen in rodents by a mode of action that is not relevant to humans (Alison *et al.* 1994, USEPA 2005). The most recent USEPA guidance on human health cancer risk assessment recommends a weight-of-evidence assessment of the mode of action by which a chemical may be producing the observed tumors in the animal model and the relevance of these tumors for human health risk assessment (USEPA 2005). A framework for this assessment has been proposed by USEPA and IARC (Cohen *et al.* 2003, 2004, Meek *et al.* 2003, Sonich-Mullin *et al.* 2001, USEPA 2005). When the mode of action in the animal model is known and not likely to occur in humans, the tumor data are not used in hazard assessment and relevant noncarcinogenic endpoints are evaluated using other USEPA guidelines for derivation of either a Reference Dose or Reference Concentration (RfD or RfC). If the response in rodents is deemed relevant to humans, then pharmacokinetic and pharmacodynamic differences between the animal model and humans should be considered in the derivation of the appropriate human equivalent dose or concentration. According to the new guidelines, appropriate dose-response modeling is applied to derive a point of departure (POD), defined as the lower bound on dose or concentration at a specific level of risk, typically a 10% risk (LED_{10}) (USEPA 2005). Depending on the weight of evidence assessment, extrapolation from the POD is either linear (estimate a slope factor and risk-specific doses) or non-linear. When the evidence supports a threshold or non-linear mode of action in the low dose region, the POD serves as the basis for development of a Reference Dose (RfD) or Reference Concentration (RfC) by application of relevant uncertainty factors.

3.1 Selection of Data for Dose-Response Modeling

As discussed in detail above, D_5 was administered by the inhalation route for two years to groups of male and female F344 rats at air concentrations 0, 10, 40 or 160 ppm. The only tumor response noted was in female rats and was an increase in incidence of uterine adenocarcinomas. 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. As noted above, the historical background range for these uterine adenocarcinomas in female F344 rats ranges from approximately 0.5%, depending on the route of exposure, up to 2% or approximately 1.2 per 60 animals (Experimental Pathology Laboratories 2003). Survival was not affected in any treatment group; the first uterine adenocarcinoma was 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. Moreover, the tumors in the treated groups were histologically indistinguishable for those found in control rats in other NTP studies (Experimental Pathology Laboratories 2003).

As described in Section 2.3.2, uterine adenocarcinomas can occur in aging rats by a mode of action not operative in humans, namely, indirect-acting, dopamine agonist-mediated alterations in hormone balance (Burek *et al.* 1988, Richardson *et al.* 1984). Studies with D_5 support this dopamine-mediated pathway as the mode of action in the production of uterine adenocarcinomas in the high exposure group receiving D_5 at a concentration of 160 ppm for 2 years. Consequently, according to these new USEPA guidelines, this uterine effect would not be used in dose-response modeling and other, noncarcinogenic effects would be used. However, administration of D_5 did not produce significant, treatment-related effects relevant to human health outcomes in the 2-year bioassay, nor were effects noted in reproductive or immunotoxicity studies that were clearly relevant, treatment-related adverse effects. Therefore, consistent with the newest USEPA guidelines, 160 ppm represents the NOAEL and should be used as the POD in the derivation of a human equivalent concentration and RfC. However, while not considered relevant to human health, dose-response modeling was conducted using these tumor data to provide a lower bound on a dose and as a comparison to the NOAEL.

3.2 Estimation of the Human Equivalent Dose

When data from animal studies are extrapolated to humans to provide estimates of lifetime cancer risks, then potential differences in pharmacokinetics (metabolism) and pharmacodynamics (sensitivity) between the animal species and humans should be considered in the estimation of human equivalent doses. Toxicokinetic data were sufficient to develop a pharmacokinetic model for D_5 that was used to develop the human

equivalent dose, expressed as the Area Under the Curve (AUC), as described below. Consequently, the default scaling factor for animal-to-human kinetic differences is not necessary. Pharmacodynamic differences should also be considered when extrapolating from the animal species to humans. For this assessment, no adjustment was made to account for these potential differences in sensitivity, since the pathway is not relevant.

A PBPK model, described in Section 2.2.1.3 was used to estimate a human equivalent concentration. Because the proposed mode of action involves activation of the dopamine receptor rather than a direct effect on the uterus, the AUC of the parent compound, D_5, in the blood was considered to be the relevant dose-metric for use in dose-response modeling and for the relevant exposure scenarios (see Section 4). The AUC provides a more consistent and stable internal dose metric than the peak concentration when exposure is chronic. First, simulations were run using the female rat parameters to simulate exposure for 6 hours per day, 5 days per week, for 2 years to 10, 40 or 160 ppm D_5 to derive the AUC in the rat for each experimental concentration. These internal dose metrics are shown in Table 18. Second, the AUC based on exposure at the NOAEL of 160 ppm was developed using the same female rat parameters and assuming 6 hours per day, 5 days per week, for 2 years. As with the application of other PBPK models and consistent with USEPA guidance (USEPA 2005), it was assumed that the resulting AUC is the human equivalent dose. The human PBPK model was then used to provide the AUCs for each of the exposure scenarios considered in Section 4.0.

3.3 Estimation of Point of Departure

The POD was estimated two ways: 1) use of the NOAEL of 160 ppm based on the lack of relevant, treatment-related adverse effects in any toxicity study; and 2) use of the female rat uterine adenocarcinomas data, which was significantly increased in only the highest exposure concentration following two years of exposure, as input for dose-response modeling. As indicated below, dose-response modeling was only conducted as a point of comparison to the experimentally-derived NOAEL and to provide a conservative lower bound on the POD. Because human exposures are often much lower than those selected for animal studies, the USEPA (2005) uses appropriate dose-response models to estimate a dose in the observable experimental range that serves as the POD

for extrapolation to low doses. The PBPK-derived AUCs for each exposure concentration were used along with the incidence data, as indicated in Table 18. Because of uncertainty around the estimate of the LED_{10} or lower bounds for other risk levels, values for the maximum likely estimate (ED_{10}) and the upper bound (UED_{10}) can be derived along with the lower bound. However, the lower bound is used as the POD for extrapolation to lower doses.

Because there were no survival differences among control and treated females, dose-response modeling for the uterine adenocarcinomas was conducted for the selected data set using the multistage model, which has the form:

$$p(d) = 1 - e^{-(q_0 + q_1 \times d + q_2 \times d^2 \cdots + q_k \times d^k)} \qquad \text{Equation 1}$$

where P(d) is the probability of developing cancer from a lifetime continuous exposure at that dose, q_1 is the fitted dose coefficient 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. The multistage dose-response model results were estimated using TOX_RISK Version 5.3 (ICF Consulting) and the output is provided in Appendix. The results of the dose-response modeling are given in Table 18. The AUC at the LED_{10} or POD based on the evaluation of the tumor data was 23.5 mg-hrs/L/day, while the AUC derived based on the NOAEL was 28.5 mg-hrs/L/day.

3.4 Choice of Approach for Low-Dose Extrapolation

Based on USEPA (2005) guidelines, the method used to characterize and quantify cancer risk or acceptable doses for a chemical depends on what is known about the mode of action of carcinogenicity for that chemical. The mode of action information can suggest the likely shape of the dose-response curve at lower doses.

Two approaches can be considered: a linear or a nonlinear extrapolation. Linear extrapolation should be used when there is mode of action data to indicate that the dose-response curve is expected to have a linear component below the POD. The guidelines indicate that agents typically considered to be linear in the low-dose region are DNA-reactive and have direct mutagenic activity, or human exposures or body burdens are high

and near doses associated with key precursor events in the carcinogenic process. A non-linear extrapolation (according to the guidelines) is used when the shape of the dose-response curve has either a threshold below which the effects are not expected to be seen or the curve is expected to be non-linear in the low dose region, i.e., the response is not proportional to dose.

In the case of D_5, if low-dose extrapolation were to be conducted, a non-linear extrapolation is indicated based on all the available data. That is, D_5 has no mutagenic or genotoxic potential. In addition, the MoA for the development of the observed tumors in rats is a non-genotoxic mechanism involving indirect hormonal perturbation (Section 2.3.2). The formation of uterine endometrial tumors in rats is contingent on altered endocrine status over a chronic duration and occurs by an mode of action that is not relevant to human health (Burek *et al.* 1988, Richardson *et al.* 1984). This type of mode of action in rats would not be linear at low doses and is reflected in the tumor response observed in the chronic bioassay (Dow Corning Corporation 2005a).

For cases when tumors arise through a nonlinear mode of action, such as the case for D_5, and if such tumors were considered relevant to human health outcomes, an oral RfD or an inhalation RfC is derived (USEPA 2005). The RfD/RfC are developed using the same methodology as that adapted for noncarcinogenic risk assessment (USEPA 1994). Extrapolation to the low-dose is conducted by the application of uncertainty factors as applied in the noncarcinogenic risk assessment (USEPA 1994). The uncertainty factors are applied to account for extrapolation across species, human variability, and confidence in the data base. These uncertainty factors would be applied to either the NOAEL of the $BMDL_{10}$ to derive the RfD/RfC, to which estimates of exposure would be compared to assess the potential hazard associated with specific exposure scenarios.

It should be noted, however, that selection of these uncertainty factors (typically multiples of 3 to 10) requires judgment and may not be uniformly applied by all regulatory agencies. As discussed in Section 4, several populations were considered to include workers, consumers, and the general public and the responsibility for regulating exposure to a chemical for these populations would fall to different agencies, i.e., to OSHA for worker safety or to USEPA for exposures to the general public. The

uncertainty factors that may be applied could be different because of the population under consideration.

In this assessment, rather than attempting to derive factors that may be used by the various regulatory agencies (i.e. OSHA, USEPA) to adjust the POD for low-dose extrapolation, a comparison of the internal dose metric associated with the LED_{10} or the NOAEL to the internal dose metric estimated for each exposure scenario was conducted. The use of these ratios or Margins of Safety (MOS) are consistent with previous guidelines for cancer risk assessment (USEPA 1999) for assessing whether an existing exposure to a chemical might present potential risk.

In evaluating each MOS for different exposure scenarios, different MOS may be protective of human health. For occupational exposures under OSHA guidelines for example, a risk of $1x10^{-4}$ or less may be considered acceptable using a linear approach, which is OSHA's standard approach. Since the POD is the internal dose associated with a $1x10^{-1}$ risk, an acceptable MOS for an occupational scenario under a linear approach would be approximately a factor of 1000. Recognizing that the mode of action for D_5 in the rodent is nonlinear and not relevant to human health, noncarcinogenic effects would be considered and a smaller MOS would be deemed acceptable. OSHA does not have a nonlinear approach for cancer risk assessment; however, if a noncarcinogenic-type assessment were conducted by OSHA for D_5, as would be more appropriate, uncertainty factors applied to the POD 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. Based on the anticipated factor of 30 for noncarcinogenic effects, a MOS of greater than 30 would be deemed acceptable.

For environmental exposures or exposures through the use of consumer products, composite factors of up to 3000 have been applied in practice by the USEPA to the LED_{10} (POD) when the chemical in question resulted in tumors in rodents by a non-linear MOA that was considered relevant to humans. These typically included factors of up to 10 applied to the POD to 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. If the uterine adenocarcinomas in the rat were considered relevant to humans, it is likely that a factor of approximately 1000 could be

derived. This would include a factor of 10 for 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 2-year bioassay in multiple species. Therefore, it is anticipated that any MOS greater than 1000 should indicate no significant risk of adverse effects due to the exposure scenarios being considered.

Since the mode of action for the carcinogenic effects observed in female rats is not relevant to humans, then a noncarcinogenic assessment should be conducted based on the results from the 24-month inhalation bioassay. However, there were no significant changes in any noncarcinogenic endpoint evaluated in this study, resulting in a NOAEL of 160 ppm. Use of the NOAEL as the POD is the more appropriate choice. In this case, a MOS of greater than 100 (3 for interspecies extrapolation, 10 for intraspecies variability, and perhaps a factor of 3 for any data base limitation) would be adequately protective of human health outcomes if exposure occurred as indicated.

4.0 EXPOSURE ASSESSMENT

The Exposure Assessment was intended to characterize the persons who may be exposed, the pathways or routes by which that exposure could occur, and the frequency, duration, and intensity (amount) of that exposure. The populations considered were:

- persons who work in the production of D_5, in the formulation of this material into personal care products, in the dry cleaning industry, or in the use of these products in professional settings;
- consumers who use these personal care products, including antiperspirant/deodorants (AP/Ds) and hair care/skin care (HC/SC) products; and,
- the general public living in the vicinity of a plant that produces or processes these materials and who may be exposed to ambient levels of D_5 released to the environment during manufacturing activities.

Both the dermal and inhalation routes of exposure were considered for personal care product users. The major route of exposure was via inhalation for workers and the general public. The dermal route was also considered for barbers/beauticians. The contribution from the oral route was expected to be a negligible contributor to exposure for workers, consumers, and the general public and was not considered quantitatively (Maxim *et al.* 1998). The relative importance of these pathways differs for each exposure group.

The frequency (number of applications in a given time period, e.g., per day or per week), the duration (the period of time over which exposure would be expected to occur), and the amount of that exposure were exposure-scenario specific. The values for these parameters differed for each of the populations considered and for each personal care product considered. For example, residential exposure may be continuous under the conservative assumption that a person could be at home all day, every day at a given address. In contrast, some personal care products may be used intermittently or infrequently.

A numerical value for each of the parameters required to characterize and quantify exposure for each receptor, route, or product was defined. Sources used to define these parameters included:

- Exposure Factors Handbook (USEPA 1997);
- The NHANES Study (NHANES 1999-2002);
- Toxicology and Hair Dyes (Kalopissis 1986);
- Report of the Task Group on Reference Man (International Commission on Radiological Protection (ICRP) 1992);
- Mediamark Research Project Summary Report (MRI 1996);
- Exposure data for cosmetic products: lipstick, body lotion and face cream (Loretz *et al.* 2005); and,
- D_4, D_5, and D_6 Exposure in the Manufacture and Use of Personal Care Products (Maxim *et al.* 1998).

For some of parameters, such as body weight, a measure of central tendency, i.e., the mean or average value for the designated population, is typically used. For some parameters, such as the amount of time spent showering, a distribution of values for which the average and upper bound values were defined was available. However, for most of the parameters, only a single, average value was available. For consistency and, in particular for exposure scenarios involving consumer products, parameter values that described the average or typical user were selected to describe estimates of exposure. The impact on the estimated intake and subsequent MOS due to the use of an average value rather than an upper bound value is discussed in the uncertainty section.

In this Exposure Assessment, rather than use external measures of exposure, such as an air concentration, the parameters that defined the scenarios are used with the PBPK model to determine the internal dose metric, AUC in mg-hrs/L/day. The parameter values described in this section were used with the PBPK model to determine the internal dose metric, the AUC in the blood.

4.1 Occupational Exposures

Occupational exposures to D_5 may occur in individuals who work in D_5 manufacturing plants, in workers in plants where consumer products containing D_5 are

formulated; in individuals who use D_5-containing consumer products in their profession, such as beauticians and barbers; and in individuals that work in a dry cleaning establishment that use GreenEarth solvent. Occupational exposures may occur via the dermal and inhalation routes.

4.1.1 Occupational Dermal Exposure to D_5

Workers in a manufacturing or processing plant could be exposed to D5 via dermal contact, e.g. in the event of a spill or leakage from a container. However, dermal exposure in the workplace is not expected because of Good Manufacturing Practices (GMPs). Exposure to D_5 dermally is also not expected for workers in the dry cleaning industry because D_5 is used in closed systems with little or no opportunity for dermal contact with D_5.

The only occupations that were considered to have the potential for dermal exposure were barbers and beauticians. A variety of hair care (HC) products may be used by barbers and beauticians over the course of a work day. To determine the product that would provide an upper bound estimate of the amount of D_5 to which these workers could be exposed, data on application rates, the fraction of product deposited on skin, the fraction of residue left by rinse-off products on skin, and the amount of D_5 in hair care products were collected.

Application rates (g/application) of hair care products were found in studies conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA 1983) and a study of the usual application practices of several personal care products in Europe conducted by the European, Cosmetic, Toiletry, and Perfumery Association (COLIPA 1981). Application rates ranged from 4.7 grams/application to 11.7 grams/application (Table 19).

For some of the products, especially the leave-on HC products, only a small fraction of the product is deposited on the scalp, as opposed to being distributed on the individual hairs, and, therefore, available to be absorbed into the systemic circulation. For these types of HC products, specifically leave-on conditioner, hair spray, cuticle coat, brilliantine, pomade, and spray shine, a deposition fraction of 0.05 (5%) was assumed. This value was estimated based on the ratio of the surface area of the scalp to that of the

hair on the head. Based on the average length of one hair of 10 cm for men and 15 cm for women (International Commission on Radiological Protection (ICRP) 1992), 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. The ratio of the surface area of the scalp to the surface area of the hair and scalp was less than 0.05, so a deposition fraction of 5% was used for the leave-on hair care products. For the remaining HC products, a deposition fraction of 1 (100%) was assumed.

Shampoos and rinse-off conditioners were assumed to leave only a fraction of the product as residue on the skin. Results from residue studies with zinc pyrithione, an anti-dandruff component, indicated that when, in varying concentrations, it was left on the scalp for 1 to 32 minutes, residual deposits were approximately 1% of the amount applied (Food and Drug Administration (FDA) 1978, 1982). In a separate study that evaluated the dermal absorption of triclosan, an antimicrobial agent, from bar soap, USEPA used a value of 0.01 (1%) for residue fraction (USEPA 1996). These values agree with that reported in Maxim *et al.* (1998) who, based on interviews with personnel from the HC industry, reported that the product residue remaining after the application of a rinse-off product, was typically small, ranging from 0.5% to 1.5%. Based on this information, a residue fraction of 0.01 (1%) for shampoos and rinse-off conditioners was used in this assessment.

The percentage of D_5 in HC products varied with the formulation of the product and ranged from 0.2% (hair rinse) to 6% (hair cuticle coat) (Maxim *et al.* 1998) (Table 19). Based on the information in Table 19, use of hair cuticle coat products could provide the largest amount of exposure. This was determined by multiplying the grams of application by the percentage of D_5 in the product and the deposition or residue fraction.

Dermal exposures were estimated for both men and women barbers and beauticians. A discussion of the remaining values assumed for each of the exposure parameters and the justification for the selection of these values is provided below.

4.1.1.1 Frequency of Occurrence

For barbers and beauticians, the frequency of some hair product being applied was assumed to occur once every 30 minutes during the work day. Occupational tenure was used to define the number of years over which exposure might occur. According Carey (1988), as cited in the USEPA Exposure Factors Handbook (1997), 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 median tenure, in years for full-time workers, was 8.4 years for men and 5.9 years for women. Considering a lifetime to be 75 years (USEPA 1997), the occupational exposures were adjusted by 8.4/75 for men and 5.9/75 for women.

4.1.1.2 Amount of D_5 in Product

For the barber and beautician scenario, it was assumed one of the hair care products would be used. To get a conservative estimate of exposure, the data for cuticle coat 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.

4.1.1.3 Surface Area of Exposed Skin

For barbers and beauticians, the surface area exposed was assumed to be the hands (840 cm^2 for men and 746 cm^2 for women based on information provided in the Exposure Factors Handbook (USEPA 1997).

4.1.1.4 Body Weight

For this analysis the body weights assumed for users of consumer products that contain D_5 were based on data from the National Health and Nutrition Examination Survey (NHANES 1999-2002). The NHANES 1999-2000 and 2001-2002 surveys were combined and the 4-year sampling weights then were used to produce unbiased estimates of the body weights for men and women in the United States between the ages of 18 and 75. The combined data set had sample sizes of 4396 for men and 4869 for women. For men, the 5th and 95th percentiles were 60.2 and 121.5 kg, respectively. The median or

50th percentile body weight was 83.6 kg. For women, the 5th, 50th, and 95th percentile values were 50.3, 70.8 and 111.4 kg, respectively. For this assessment, the median values of 83.6 and 70.8 kg were used for men and women, respectively

4.1.1.5 PBPK Simulations for the Occupational Dermal Exposure to D_5

The U.S. Department of Labor Bureau of Labor Statistics (2005) 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 of 1995 through 2005. An average of 28 hours per week or 5.6 hours per day was used for this analysis. A 5-day work week and a 50-week work year were assumed for both barbers and beauticians.

Alveolar ventilation rates used were equivalent to pulmonary ventilation rates of 1.6 m^3/hour during work hours and 1.0 m^3/hour for non-work hours. 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. 2005b). Application times were adjusted to reflect differences between the specific exposure scenario and the *in vivo* human study in which D_5 was applied to both underarms of volunteers (Plotzke et al. 2002).

Using the parameters defined in Table 20, the AUC estimated for dermal exposure to D_5 for barbers and beauticians were 4.2×10^{-5} mg-hrs/L/day for a female barber or beautician and 4.7×10^{-5} mg-hrs/L/day for a male barber or beautician (Table 21).

4.1.2 Occupational Inhalation Exposure to D_5

Inhalation exposures to D_5 also may occur in individuals who work in plants that manufacture D_5 or formulate products that contain D_5, or in professionals, such as dry cleaners, who us D_5-containing products in their jobs. D_5 air concentrations were measured using personal monitors for the following workers: 1) workers involved in the formulation of APs; 2) workers involved in the manufacture of HC products; 3) workers involved in the manufacture of SC products; 4) workers in dry cleaning establishments that use GreenEarth solvent; 5) workers in a D_5 production facility; and, 6) barbers and beauticians. The same basic process was used to determine the exposure for each of the

occupations with varying assumptions as to the duration, frequency, and amount of D_5 exposure, depending on the type of work performed. Values for the parameters used to estimate exposure by the inhalation route and the rationale for the selection of these values is discussed below and the values used are summarized in Table 22.

4.1.2.1 Air Concentrations

The estimated air concentrations to which workers could potentially be exposed varied depending on the job category or job description of the worker. .In a study of workers in the production of D_5 (silicone worker), a total of 567 time-weighted average air concentrations were measured for each of six job categories and were averaged to estimate the mean D_5 air concentrations associated with each job category in a silicone production plant (Maxim *et al.* 1998). Arithmetic mean, time-weighted average D_5 air concentrations ranged from 0.0124 ppm in the shipping, loading and warehouse work areas to 0.1219 ppm in the secondary polymer operations areas (Maxim *et al.* 1998). From this study, the mean D_5 air concentration (Table 22) for all silicone workers was 0.0587 ppm, and this value was used to estimate exposure from inhalation.

For workers in plants that produced consumer products containing D_5, data from various AP and HC/SC plants were used. Specifically, the average D_5 concentrations were obtained from personal time-weighted average measurements taken at various plants and reported by Maxim *et al.* (1998). The averages were based on 89 samples taken at an AP plant, 16 samples at a plant that produced mostly SC products, and 16 samples at a plant that produced HC products. These estimated concentrations were 2.21 ppm for AP workers, 1.06 ppm for SC workers, and 0.002 ppm for HC workers (Table 22).

For dry cleaners, eight-hour time-weighted average air concentrations were calculated by Severn Trent Laboratories (2001) from samples taken by California Industrial Hygienist Services at GreenEarth sites using data collected from personal monitors on workers doing various tasks in the plant. The time-weighted averages were 0.05 ppm for the worker assembling, bagging and finishing the garments; 0.071 for the worker who did only the dry cleaning finishing; and 0.31 ppm for the operator who

loaded and unloaded machines, did prespotting and garment hanging. An average of these values (0.143 ppm) was used for dry-cleaner workers (Table 22).

For beauticians and barbers, personal eight-hour time-weighted average air concentrations were based on measurements for six hair salon technicians (Maxim *et al.* 1998). The arithmetic mean from these measurements (0.006 ppm) was used as estimates of D_5 air concentrations to which barbers or beauticians may potentially be exposed (Table 22).

4.1.2.2 Exposure Duration

For most workers, a standard 8-hour work day was assumed (workers in antiperspirant, skin care and hair care plants and dry cleaner workers). However, due to the manner in which shifts were typically scheduled for silicone workers (Maxim *et al.* 1998), an 8.75-hour day was used. For beauticians and barbers, the value used was a 28 hours/week or 5.6 hours work day, based on U.S. Bureau of Labor Statistics (2005).

As with the dermal exposure, occupational tenure was again used to define the number of years of exposure. The median tenure in years for full-time workers is 8.4 years for men and 5.9 years for women (USEPA 1997). Considering a lifetime to be 75 years (USEPA 1997), the inhalation occupational exposures were adjusted by 8.4/75 for men and 5.9/75 for women.

4.1.2.3 Exposure Frequency

For all workers, a standard 5-day work week was assumed. For all workers, it was assumed that workers would be away from work for vacation, sick leave, etc., for 2 weeks per year resulting in a 50-week work year.

4.1.2.4 Inhalation Rate

An inhalation rate of 1.6 m^3/hour was used for all workers during the work day. This value is the inhalation rate for moderate activity (Table 23) taken from the USEPA Exposure Factors Handbook (USEPA 1997). After the work day (i.e., the exposure period) was over, a rate of 1.0 m^3/hour, the value for light activity, was assumed for the remainder of the day.

4.1.2.5 Body Weight

Body weights were based on data from the National Health and Nutrition Survey (NHANES 1999-2002), as described above. The median body weight values of 83.6 kg for adult men and 70.8 kg for adult women were used in this assessment.

4.1.2.6 PBPK Simulations for the Occupational Inhalation Exposure to D_5

Model simulations were conducted to simulate occupational exposure to men and women at various exposure concentrations and hours per day (Table 22). As with the occupational dermal exposures, the AUC estimated was representative of the exposure pattern (hours/day, days/year) over a given year. These simulations used alveolar ventilation rates equivalent to a pulmonary ventilation rate during work hours of 1.6 m^3/hour. A rate equivalent to 1.0 m^3/hour was used for non-work hours. The alveolar ventilation rates were changed to reflect the change in activity levels (moderate vs. light) that would occur between work (i.e., exposure) periods and non-work periods when exhalation of the chemical would still be an important route of elimination. Cardiac output rates were calculated in the same manner as for the previous simulations from Clewell *et al.* (2004). It was assumed that the increase in cardiac output due to the increase in alveolar ventilation was distributed among the various tissue compartments in the same manner as at rest (i.e., increase in cardiac output did not go only to the fat and slowly perfused tissue compartments). At the end of each simulation, the internal dose metric (AUC) was the output.

Using the parameters defined in Table 22, the AUCs estimated for occupational inhalation exposure to D_5 ranged from 2.0×10^{-5} mg-hrs/L/day to 4.5×10^{-2} mg-hrs/L/day. AUCs for dry cleaner workers were 1.4×10^{-3} mg-hrs/L/day for women and 2.9×10^{-3} mg-hrs/L/day for men. The largest AUC was seen for men who worked in plants that produced antiperspirants. All the results for men and women are reported in Table 24.

4.2 Personal Care Products

Due to its physical properties, D_5 has been widely used in consumer products as a carrier, emollient, and lubricant. Consumer products evaluated included AP/Ds, HC products (shampoo, rinse-out conditioner, leave-in conditioner, and hair spray) and SC

products (mascara, moisturizer, nail care, and foundation). While most AP/Ds are formulated with D_5, this is not the case for HC/SC products. However, D_5 is present in small amounts in materials that are used to make HC/SC products. Potentially relevant exposure pathways for all consumer products included, primarily, dermal contact with some inhalation exposure. Each section below describes the data used in conducting an exposure assessment for individuals using these consumer products.

4.2.1 Exposure to D_5 When Using Antiperspirants or Deodorants

D_5 has been widely used in the formulation of many different consumer products including AP/Ds. Exposure could occur dermally through the direct application of the AP/D to the skin and via inhalation as the AP/D residue on the skin volatilizes. There are 3 major forms of AP/Ds, solids, roll-ons, and aerosols. The D_5 content and application rates vary with each form of AP/D; therefore, separate dermal and inhalation exposure analyses were conducted for consumers using each of the 3 major forms of AP/Ds.

4.2.1.1 Dermal Exposure via the Use of Antiperspirants or Deodorants

The key considerations in estimating exposure from the use of AP/D products was the amount of D5 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 described in the following sections.

4.2.1.1.1 *Application Rate*

The application rate used for the AP/Ds was the average number of grams of AP/D applied each time. Information on application rates of the various forms of AP/Ds was available from numerous volunteer studies (Maxim *et al.* 1998). In these studies, groups of participants (with group sizes of 30 to 50) were provided with one or more AP/D products and asked to apply these products as they would in normal use for a defined period of time, such as 1 to 2 weeks. The amount that each participant used in the defined period of time was determined from the difference in container contents before and after use, with average application amounts determined by dividing the amount used by the number of applications reported by the participant (Table 25). For men, the average application rate ranged from 1.99 g/application for aerosols to 1.22 and

1.29 g/application for roll-ons and solids. For women, aerosols had the highest average (1.54 g/application), followed by roll-ons (0.79 g/application), with solids having the lowest average application rate (0.65 g/application).

4.2.1.1.2 *Percent of D_5 in Amount Applied*

The fraction of the AP/D applied that is D_5 differed depending on the type of AP/D being applied. For this assessment the percent of D_5 applied was assumed to be 34% for solid AP/Ds, 54% for roll-on AP/Ds, and 1.25% for aerosol AP/D formulations (Meeks 2005).

4.2.1.1.3 *Application Frequency*

Mediamark Research, Inc.(MRI 1995) conducted a consumer survey of the purchases and use of AP/Ds by approximately 90000 men and 80000 women (Table 26). To determine the mean application frequency per group, the percentage of the population in each range of application frequencies was multiplied by the midpoint of that range of frequencies (i.e., column 4 multiplied by column 5). These population-weighted frequencies were then added together to result in a mean for the group. The mean frequencies of AP/D application (regardless of type) were 7.1 and 6.9 times/week for women and men, respectively. For this exposure assessment, the frequency of use for AP/D was set at once a day or 7 times a week. For the majority of the population surveyed (approximately 63%), the mid-point of the range of uses was 5.5 times/week.

4.2.1.1.4 *Surface Area*

The surface area of the axillary vault to which the AP/D is applied was measured by a major AP/D marketer in 49 adult males and 33 adult females (Maxim *et al.* 1998). Measurements of the length and width of the axilla was taken to the nearest 0.25 inch. The axillary vault areas were calculated assuming that the axilla could be represented by an ellipse defined by the major and minor axes (e.g. the length and width). The average areas calculated by this method were 119.5 cm^2 and 60.9 cm^2 for men and women, respectively. These values were used as the surface area to which the AP/D was applied.

4.2.1.1.5 *Body Weight*

Body weights were based on data from the National Health and Nutrition Survey (NHANES 1999-2002), as described above. The median body weight values of 83.6 kg for adult men and 70.8 kg for adult women were assumed in this assessment.

4.2.1.1.6 *Summary of Dermal Exposure Parameters*

The dermal exposure parameters used in the assessment of exposure to D_5 contained in AP/D products are presented in Table 27.

4.2.1.1.7 *PBPK Simulations for the Dermal Exposure to D_5 from Use of Antiperspirants or Deodorants*

PBPK model simulations were conducted to estimate dermal exposure to men and women from the application of solid, roll-on, or aerosol antiperspirants/deodorants. Exposures to a given amount of D_5 over a given skin area (Table 27) were simulated to occur once daily for one year. The data upon which the model was built (Plotzke *et al.* 2002) were for only 24 hours post-exposure; however, it did not seem that such a short simulation would adequately capture the chronic nature of the exposure scenarios of interest. Therefore, the model was run to simulate 1 year, which, from a dose-metric perspective, would be more representative of chronic exposure. Alveolar ventilation rates used were equivalent to pulmonary ventilation rates of 1.0 m^3/hour and were constant over the course of the day. Alveolar ventilation rates are a necessary parameter for the PBPK model and, as mentioned previously, exhalation is the primary route of elimination from dermal exposure (Reddy *et al.* 2005b). Cardiac output rates were calculated based on an equation relating alveolar ventilation and cardiac output (Clewell *et al.* 2004). It was assumed that each AP/D was applied under the second arm approximately 10 seconds after application under the first arm. The parameters for the time to allow evaporation and absorption were set for each scenario to be consistent with the dose and exposure duration for a given scenario. At the end of each simulation, the internal dose metric of daily AUC for arterial blood was the model output.

The AUCs estimated for dermal exposure to D_5 from the use of AP/Ds ranged from 5.5×10^{-5} mg-hrs/L/day to 2.8×10^{-3} mg-hrs/L/day. The largest AUC was seen

based on the use of roll-on antiperspirants by men. Results for dermal exposure in men and women are reported in Table 28.

4.2.1.2 Inhalation Exposures to D_5 from Use of Antiperspirants or Deodorants

Through normal use of products that contain D_5, consumers may be exposed to D_5 via inhalation. However, compared to exposure via dermal contact, inhalation exposures would be expected to be relatively small in magnitude and of limited duration because they will occur primarily when the AP/D is first applied. Once the consumer is dressed, volatilization rates will be lowered, because the AP/D container will be closed and AP/D-coated skin surfaces will be covered with clothing. Since the AP/Ds are applied in different ways, different exposure parameters must be used for the different types of AP/Ds. A discussion of each of the exposure parameters is provided below. The application rate, percentage of D_5 in the product, the surface area to which the product is applied and body weights are the same as those described above for the dermal scenario for AP/Ds. In this inhalation scenario, the key parameters that differed the resulting air concentration from the use of these products and the duration of time that a person would spend in the room, typically a bathroom or dressing room, in which the product was applied. These are described below.

4.2.1.2.1 *Air Concentration*

The air concentrations used were based on a study conducted by Dow Corning (Andersen and Weaver 1989) in which each of 3 different commercial D_5-containing AP/Ds (a solid, a roll-on, and an aerosol) were applied by two male participants in a 30 m^3 room in which the air changes per hour were essentially reduced to zero, and the concentration of total cyclosiloxanes measured for each type of product. The estimated concentrations varied with product form and were based on the amount of product that volatilized during the application of the product. The products were applied at two levels, a typical application amount and a relatively heavy application. For the first 4 minutes after application of each product, the subjects did not put on shirts and moved their arms in a manner to simulate the combing of hair and brushing of teeth. The subjects then put on undershirts and remained in the test room for 2 minutes. Six-minute, time-weighted average cyclosiloxane concentrations in room air for each of the

application amounts for each type of AP/D were measured. Following the relatively heavy application of 1.93, 1.05, and 2.6 g of solid, roll-on, or aerosol AP/Ds, respectively, the highest 6-minute, time-weighted average concentration of the cyclics measured in air was greatest for the roll-on AP/Ds (2.9 ppm), followed by the aerosol (1.0 ppm) and the solid (0.3 ppm) AP/Ds. For the lower application amounts of 0.96, 0.45, and 2.4 g of solid, roll-on, or aerosol AP/Ds, respectively, the 6-minute, time-weighted average concentration of the cyclics measured in the air was 0.9 ppm for roll-on AP/Ds, 0.9 ppm for aerosol and 0.3 ppm for solid AP/Ds. Based on these data and the D_5 content (Table 27) in the mixture of cyclics of each of the products applied, 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 calculated as the average of the high application and lower application time-weighted average concentration of cyclics measured times the percent D_5 in that product.

4.2.1.2.2 *Exposure Duration*

There were no consumer use data for the amount of time that elapses between the application of an AP/D product and subsequent dressing, e.g., putting on a shirt or top. It is during this time that D_5 air concentrations would be expected to be highest, particularly if bathing, application, and dressing occurred in a closed bathroom. The Exposure Factors Handbook (USEPA 1997) reported that the number of minutes spent in a bathroom immediately following a bath ranges from 0 to 121 minutes with the 50^{th} percentile (median) of 5 minutes for men and 10 minutes for women. 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 gives a weekly time of 0.58 hours/week for men and 1.17 hours/week for women.

4.2.1.2.3 *Application Frequency*

The mean AP/D application frequency was assumed to be 7 times/week for both women and men, as discussed previously in the section on dermal exposure of consumers to AP/Ds.

4.2.1.2.4 *Inhalation Rate*

The Exposure Factors Handbook (USEPA 1997), recommends inhalation rates for short-term exposures, as given in Table 23. Inhalation rates for the average adult were reported to range from 0.4 m^3/hour during resting periods to 3.2 m^3/hour during heavy activity. For the consumer, inhalation rates corresponding with light activity, 1.0 m^3/hour for men and women, were assumed.

4.2.1.2.5 *Body Weight*

As discussed previously in the dermal contact section, median body weight values of 83.6 kg for adult men and 70.8 kg for adult women obtained from NHANES 1999-2002 were used in this assessment.

4.2.1.2.6 *Summary of Inhalation Exposure Parameters*

The exposure parameter values used in the assessment of inhalation exposure to D_5 contained in AP/D products is presented in Table 30.

4.2.1.2.7 *PBPK Simulations for the Inhalation Exposure to D_5 from Use of Antiperspirants or Deodorants*

The PBPK model simulated the inhalation exposure that was assumed to occur following dermal application of AP/Ds. The simulations used the same alveolar ventilation rates and cardiac outputs as the dermal simulations with the frequency of application and other parameters as described in the above sections. The air concentrations and length of exposure varied by type of product and are summarized in Table 30. As with the dermal simulations, these simulations were also for one year of exposure. The internal dose metric was again the AUC.

Using the parameters defined in Table 30, the AUCs estimated for inhalation exposure to D_5 from the use of AP/Ds ranged from 4.9×10^{-4} mg-hrs/L/day to 6.0×10^{-3} mg-hrs/L/day (Table 31). The largest estimated AUC was for women who used roll-on antiperspirants.

4.2.2 Exposures to Consumers via the Use of Hair Care/Skin Care Products

As stated previously, most HC/SC products are not formulated with D_5, but for this assessment it was assumed that D_5 was present in HC/SC products. Exposure to D_5 from specific types of HC products (e.g., shampoo, conditioners, hair spray, cuticle coat, brilliantine, pomade, and spray shine) and specific types of SC products (e.g., moisturizer, foundation, hand/body lotion, sunscreen, under-eye cover, aftershave lotions, and lipstick) was evaluated. As with AP/Ds, the amount of exposure was estimated for both the dermal and inhalation pathways.

4.2.2.1 Dermal Exposures to D_5 from Use of Hair care/Skin Care Products

For the different types of HC/SC products, different exposure parameters were used. A discussion of these parameters is provided below.

4.2.2.1.1 *Application Rate*

Application rates (g/application) of HC/SC products were estimated from data from studies conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA 1983) and a study of the usual application practices of several personal care products in Europe conducted by the European, Cosmetic, Toiletry, and Perfumery Association (COLIPA 1981) (Table 32). No gender-specific application rates were available in these studies. If women and men both used an HC/SC product, the application rate was a combination of the application rate for each. Because men typically have a greater skin surface area than women, the use of these application rates may underestimate the average application rates for men. However, the assumption that all HC/SC products contain a small amount of D_5 would likely result in an overestimate of exposure. Application rates for HC/SC products ranged from a few hundredths of a g/application to greater than 11 g/application.

In a more recent study, Loretz *et al*. (2005) provided exposure estimates for lipstick, body lotion, and face cream. This study included 360 women from the ages of 19 to 65 years who regularly used these products. The mean and median usage per application from this study were 1.22 g and 0.84 grams for face cream, 10 and 5 mg for lipstick and 4.42 and 3.45 g for body lotion, respectively. Again the assumption that all these products contain a small amount of D_5 would likely result in an overestimation of

exposure. The median values from the distributions reported by Loretz *et al*. (2005) were used for lipstick, body lotion and face cream because the distributions were all highly skewed indicating a small number of heavy users with the majority using much smaller amounts. Under these conditions, the median is a better measurement of central tendency than is the mean. Values used for amount per application are given in Table 32 and ranged from 0.005 grams to 11.7 grams.

4.2.2.1.2 *Application Frequency*

Selection of the number of applications of HC/SC products per week relied primarily on information from a Mediamark Research Product Summary Report (MRI 1996). The results of this survey were judged to be the most suitable for an exposure assessment because the data were the most recent of the available data (i.e., (COLIPA 1981, CTFA 1983)) and provided separate estimates of application frequency for men and women for most HC/SC products. The Loretz *et al.* study (2005) also provided use frequencies for lipstick, face cream and body lotion. The estimates of application frequency (AF) are summarized in Table 33. The AFs are given in terms of number of applications per week and considered seasonal usage, such as with sunscreens. In each case, the number of applications per week (or per year in the case of sunscreen) is rounded to integers for use in the PBPK model.

4.2.2.1.3 *Deposition Fraction*

For many of the HC/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 products, especially the leave-on HC products, only a small fraction of the product is deposited on the scalp and, therefore, available to be absorbed into the systemic circulation. For these types of HC products, specifically leave-on conditioner, hair spray, cuticle coat, brilliantine, pomade, and spray shine, a deposition fraction of 0.05 (5%) was assumed. This value was estimated based on the ratio of the surface area of the scalp to that of hair, assuming the average length of one hair is 10 cm for men and 15 cm for women (International Commission on Radiological Protection (ICRP) 1992), the average diameter is 60 microns (Kalopissis 1986), then the average total area of the 115000 hairs (Kalopissis 1986) on the scalp is approximately 22000 cm^2

for men and 33000 cm^2 for women. The ratio of the surface area of the scalp to the surface area of the hair and scalp is less than 0.05 so a deposition fraction of 5% was used for the leave-on hair care products.

For the remaining HC/SC products, a deposition fraction of 1 (100%) was assumed, with the exception of nail products. The estimate of the deposition fraction for nail products was based on the results of an analysis of D&C Red No. 9 conducted by CTFA (1983). In this analysis, CTFA (1983) made the assumption that a maximum of 1% of material intended for application to the nails would contact the skin or cuticle and be available for absorption. This amount is so small and the surface area of the skin affected is also so small that the exposure from this pathway was considered to be negligible and was not calculated in this assessment.

4.2.2.1.4 *Residue Fraction*

Residue fractions were assumed to be 1 (100%) for all HC/SC products, with the exception of shampoo and rinse-off conditioner. Results of studies with anti-dandruff and antimicrobial agents were reviewed as providing conservative estimates of the residue fraction. Results from residue studies with zinc pyrithione, an anti-dandruff component, indicated that when, in varying concentrations, it was left on the scalp for 1 to 32 minutes, residual deposits were approximately 1% of the amount applied (Food and Drug Administration (FDA) 1978, 1982). In a separate study that evaluated the dermal absorption of triclosan, an antimicrobial agent, from bar soap, USEPA used a value of 0.01 (1%) for residue fraction (USEPA 1996). These values agree with that reported in Maxim *et al.* (1998) who, based on interviews with personnel from the HC industry, reported that the product residue remaining after the application of a rinse-off product, is typically small, ranging from 0.5% to 1.5%. Based on this information, a residue fraction of 0.01 (1%) for shampoo and rinse-off conditioner was used in this assessment.

4.2.2.1.5 *Fraction of Product Applied that is D_5*

As with AP/Ds, the fraction of the HC/SC applied that is D_5 varies with the formulation of the product. The percentage D_5 (base case) ranged from 0.2% (hair rinse) to 6% (hair cuticle coat) (Maxim *et al.* 1998) (Table 34). The majority of the products have smaller amounts of D_5 than those in AP/D formulations. The wide range of values

for various products reflects the lack of standardization in the formulation of HC/SC products, compared to AP/Ds. For some of the products, reasonable base case estimates were available that were applicable to the majority of the products. Where this information was lacking, the midpoint of the range was used as the base case estimate.

4.2.2.1.6 *Surface Area*

The surface area to which the HC/SC is applied differs depending on the product. Using mean values reported by the USEPA in the Exposure Factors Handbook (1997), the surface areas were estimated. Table 35 gives these values and how those data were used in determining the surface areas for the areas of application. It was assumed that that moisturizers and foundations would be applied to the face; after-shaving gel to only the lower portion of the face; and hair care products (shampoo, conditioners, hair spray, etc.) would be applied to the scalp. The surface area of the lips and undereye area were both assumed to be fractions of the surface area of the head.

Kalopissis (1986) estimated the surface area of the scalp to be 700 cm^2, which is approximately 60% of the surface area of the head for men and 64% of the surface area of the head for women (USEPA 1997). Based on that information, the face was assumed to be 40% of the surface area of the head for men and 36% of the surface area of the head for women.

For hand/body lotion and sunscreen, the total surface area was assumed to be the sum of the average surface area of the legs, feet, hands, arms and trunk with neck. The surface area of the skin for both mascara and nail care products was considered to be negligible and those items were not considered in the overall dermal exposure scenario.

4.2.2.1.7 *Body Weight*

As discussed previously, median body weight values of 83.6 kg for adult men and 70.8 kg for adult women obtained from NHANES 1999-2002 are used in this assessment.

4.2.2.1.8 *Summary of Dermal Exposure Parameters*

The exposure parameter values used in the assessment of exposure from the dermal contact with D_5 contained in HC/SC products are presented in Table 36.

4.2.2.1.9 *PBPK Simulations for the Dermal Exposure to D_5 from Use of Hair care/Skin Care Products*

The PBPK model was used to simulate dermal exposure in the same manner as for the AP/D dermal exposures. Exposures to various products containing various amounts of D_5 were simulated to occur once per day for a various number of days per week for both men and women (Table 36). The exceptions were for exposures from the use of moisturizer, lipstick and sunscreen. Moisturizer exposure was simulated to occur twice per day (once every twelve hours); lipstick exposure was simulated to occur every four hours for a total of 3 exposures per day. Sunscreen exposures were assumed to occur for eleven consecutive days once per year. Constant alveolar ventilation rates, equivalent to pulmonary ventilation rates of 1.0 m^3/hour, were used, and cardiac outputs were calculated as described above. As with the AP/D dermal exposures, the time over which the evaporation and absorption occurred were calculated for each product based on the amount of D_5 and application area. Application times were adjusted to reflect the differences between these exposure scenarios and the *in vivo* human study (Plotzke *et al.* 2002). As with the AP/D dermal exposure scenarios, the model simulated exposure for one year, and the internal dose metric was output at the end of each simulation.

Using the parameters defined in Table 36, the AUCs estimated for dermal exposure to D_5 from the use of HC/SC products ranged from 6.9×10^{-7} mg-hrs/L/day to 8.3×10^{-4} mg-hrs/L/day. The largest AUC was seen for the use of women's moisturizer. Model estimated AUC values for men and women from dermal exposure to HC/SC products are reported in Table 37.

4.2.2.2 Inhalation Exposures to D_5 from the Use of Hair Care/Skin Care Products

As with AP/Ds, consumers may be exposed to D_5 vapors via the inhalation pathway through the normal use of HC/SC products that contain D_5. Compared to exposure via dermal contact, inhalation exposures would be expected to be insignificant in magnitude. Information was available regarding possible air concentrations following use of HC products. However, no information was available on the potential D_5 air concentrations to which consumers may be exposed during the use of SC products;

therefore, inhalation exposure to D_5 from SC products was assumed to be comparable to that estimated for HC products.

Separate analyses were not conducted for various HC products. Maxim *et al.* (1998) estimated a single inhalation air concentration (AC) for women consumers that were assumed to be representative of inhalation exposures to both HC and SC products. For this assessment, we assumed that men would have the same inhalation exposure to both HC and SC products. Since men use less of these products, this is an overestimation of the inhalation exposure for men. A discussion of the values used for each of the parameters involved in the estimation of the inhalation exposure estimates is provided below.

4.2.2.2.1 *Air Concentration*

The air concentrations were based on a study in which six personal monitoring samples were taken while the six volunteers were using shampoos, conditioners, and hair sprays containing D_5 (Maxim *et al.* 1998). Following application of the HC products, users remained in the room where the products were applied for 17 to 40 minutes. Based on the monitoring information, a time-weighted average concentration of 0.178 ppm was determined for D_5.

4.2.2.2.2 *Exposure Duration*

As with AP/Ds, no information was available on the length of time that a consumer would be exposed to D_5 vapor following application of HC/SC products. As with AP/D products, it was assumed that exposure to HC/SC products by inhalation would be highest when they were applied in a closed bathroom after bathing. Therefore, the 50^{th} percentile of the distribution for the number of minutes spent in a bathroom immediately following a bath (USEPA 1997), 5 minutes for men and 10 minutes for women, was used as the exposure duration.

4.2.2.2.3 *Application Frequency*

The assumed application frequency for all HC/SC products was once a day.

4.2.2.2.4 *Inhalation Rate*

The inhalation rate assumed for men and women was the same as the inhalation rate assumed in the exposure assessment for AP/Ds. An inhalation rate, corresponding with light activity, of 1.0 m^3/hour was assumed based on information in the Exposure Factors Handbook (USEPA 1997).

4.2.2.2.5 *Body Weight*

As discussed previously, median body weight values of 70.8 kg for adult women and 83.6 kg for men obtained from NHANES 1999-2002 are used in this assessment.

4.2.2.2.6 *Summary of Inhalation Parameters*

A summary of the exposure parameter values used in the assessment of inhalation exposure to D_5 contained in HC/SC products is presented in Table 38.

4.2.2.2.7 *PBPK Simulations for the Inhalation Exposure to D_5 from Use of Hair Care/Skin Care Products*

PBPK model simulations were conducted to simulate inhalation exposure in women and men and were conducted in the same manner as the exposures from AP/D applications. The air concentration was assumed to be 0.178 ppm D_5 and the duration of exposure for any given application was assumed to be 5 minutes for men and 10 minutes for women. The internal dose metric was output at the end of each simulation.

Using the parameters defined in Table 38, the AUCs estimated for inhalation exposure to D_5 from the use of HC/SC products is 6.3×10^{-4} mg-hrs/L/day for women and 4.3×10^{-4} mg-hrs/L/day for men (Table 39).

4.3 Exposures in the General Public

The general public, i.e., individuals who reside in the vicinity of a manufacturing plant but do not work in a plant or a facility where D_5 is manufactured or used in product formulation, could be exposed to D_5 via the inhalation pathway due to the release of D_5 to ambient air. A discussion of each of these parameters and justification for the values used is provided below with a summary of the selected values presented in Table 40.

4.3.1 Air Concentration

Air samples (210 indoor and 210 outdoor) were collected from 70 facilities and analyzed for D_5 content. The average values from these samples were reported by Shields *et al.* (1996) as cited in (Maxim *et al.* 1998). The majority of the samples taken had values below the limit of detection and the overall average value of 0.5 $\mu g/m^3$ was reported as the amount in the ambient air. This value was used to estimate the exposure for the general public.

4.3.2 Exposure Duration, Exposure Frequency and Weeks per Year

The individual residing in the vicinity of the plant was assumed to be continuously exposed, i.e., 24 hours per day, 7 days per week, 52 weeks per year, to ambient air levels of D_5.

4.3.3 Inhalation Rate

USEPA (1997) inhalation rates for long-term exposure of 0.47 m^3/hour for women and 0.63 m^3/hour for men were used in the evaluation for the adults (ages 18-75). Long-term exposures inhalation values from the Exposure Factors Handbook (USEPA 1997) were also used for children and the values ranged from 0.28 to 0.71 m^3/hour (Table 40).

4.3.4 Body Weight

Body weights were based on data from the National Health and Nutrition Survey (NHANES 1999-2002). The median body weight values of 83.6 kg for adult men and 70.8 kg for adult women were used in this assessment. In addition, median body weights for children in the age ranges of 1 to 2 years, 3 to 5 years, 6 to 8 years, 9 to 11 years, 12 to 14 years and 15 to 17 years were obtained from the NHANES data. Values used in this assessment are provided in Table 40.

4.3.5 PBPK Simulations for the Inhalation Exposure to D_5 for the General Public

These model simulations were similar to the occupational simulations except that inhalation exposure to 0.5 $\mu g/m^3$ was continuous (i.e., 24 hours per day, 7 days per week, 52 weeks per year). The model was again run to simulate 1 year of exposure 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 AP/D application simulations. The internal dose metric was the output at the end of each run.

Using the parameters defined in Table 40, the AUCs estimate for inhalation exposure to D_5 for the general public ranged from 7.8×10^{-6} mg-hrs/L/day to 2.2×10^{-5} mg-hrs/L/day. The largest values seen were for adult men. Table 41 gives all the inhalation exposure AUC values computed for the general public.

5.0 RISK CHARACTERIZATION

5.1 Results

As discussed previously (Section 3), regulatory agencies have different approaches to safety assessment. Assumptions about low-dose extrapolation or the type and magnitude of uncertainty factor to apply in that extrapolation differ among agencies because of the different mandates for those agencies, i.e., worker safety to OSHA and safety of the general population by USEPA. Different uncertainty factors could have been applied to the POD derived in this assessment and then the resulting value, whether defined as the RfD/RfC using methods employed by the USEPA or the Permissible Exposure Limit (PEL) using methods applied by OSHA, could have been to the estimated exposure for the various populations considered. That was not done in this assessment. Rather, a MOS was calculated. A MOS was the ratio of the internal dose metric or AUC associated with either the LED_{10} or the NOAEL to the internal dose metric estimated for each relevant exposure scenario. The magnitude of that MOS could then be assessed to evaluate the potential hazard to the selected populations for the defined exposure scenarios.

For occupational exposures, a MOS of greater than 30 would indicate that the estimated exposure would not pose an unacceptable hazard. This is based on the assumption that OSHA would conduct a noncarcinogenic-type assessment for D_5. For this type of assessment, the uncertainty factors applied to the POD would be 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, resulting in a total factor of 30.

For environmental exposures or exposures resulting from use of consumer products, a MOS of greater than 1000 would indicate that the exposure to D_5 would not pose an unacceptable risk to persons exposed as described, if the tumors observed in rats were considered relevant to human health. The factor of 1000 would likely be based on the application of factors of up to 10 applied to the POD to account for one or more of the following uncertainties: intrahuman variability, interspecies extrapolation, lack of

precursor data, and remaining sources of uncertainty in the database. In the case of these uterine effects, a factor of 1 could be argued for uncertainties in pharmacodynamics, because humans may be less sensitive than the rodent to modifications in hormone balance. However, if the assessment were based on the NOAEL, rather than the LED_{10} this argument would not be appropriate.

Because the MoA for the carcinogenic effects observed in the rat is not relevant to human health (Section 2.3.2), noncarcinogenic effects should be relied upon to determine a critical endpoint for this safety assessment. However, no significant noncarcinogenic effects were observed in the available 24-month bioassay or were seen in the genotoxicity, reproductive toxicity or immunotoxicity tests. Consequently, a NOAEL of 160 ppm, the highest dose tested, would be selected. When based on the NOAEL for noncarcinogenic effects, a MOS of greater 100 to 300 would indicate that exposure by way of the pathways described would not pose a hazard to human health.

As stated, MOS for each exposure scenario were calculated by comparing the AUC for the NOAEL to the AUC for the specific exposure scenario. As a comparison, and to serve as a lower bound on the NOAEL, MOS were also calculated using the LED_{10},

5.1.1 Occupational Exposure

Occupational exposures to D_5 were assumed to occur in individuals working in D_5 manufacturing plants, in workers employed in plants where consumer products containing D_5 are formulated, in individuals using D_5-containing consumer products as part of their profession (i.e., beauticians, barbers), and in individuals working in dry cleaning establishments using GreenEarth solvent. For inhalation exposures, six types of workers (Table 42) were considered for which air concentrations from the workplace had been measured. For workers in the dry cleaning industry, MOS were approximately 100 to 20000, 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 either the LED_{10} or the NOAEL resulted in an MOS of approximately 500-600. Because the carcinogenic effects observed in rats are not considered relevant to human health, the comparison of the AUC for these exposure scenarios to the NOAEL is the most appropriate comparison. This results in an MOS of 600, which is greater than the factor of 30 that would be expected to be applied to the NOAEL for a noncarcinogenic assessment for an occupational population. This would indicate that exposure does not pose a significant hazard to workers.

For barbers and beauticians, it was assumed that some hair product would be used approximately every 30 minutes during the work with the hands being exposed. The MOS determined for any of these scenarios, either by the inhalation pathway (Table 42) or the dermal pathway (Table 43), were approximately 400000 or greater, regardless of comparison of the AUCs to the LED_{10} or the NOAEL, indicating that occupational dermal exposures to D_5 in these professions does not pose a significant hazard to human health.

5.1.2 Consumer Products

AUCs were estimated for average usage scenarios of AP/D (Tables 44 and 45) and HC/SC products (Tables 46 and 47). Exposure was assumed to occur via inhalation and dermal routes for all products.

For AP/Ds, when the AUCs estimated for each type of AP/D resulting from inhalation or dermal exposure were compared to the AUC for the LED_{10} or the NOAELs, the smallest MOS was 3900 and 4700, respectively and was based on inhalation exposure from the use of roll-on products in women. The smallest MOS based on dermal exposure was 8200 to 10000 based on the use of roll-on products by men. However, because the MOS is greater than 3000, it is not anticipated that any of the inhalation or dermal exposures resulting from typical consumer usage of AP/Ds would pose a hazard. As noted in the uncertainty section, estimates of the air concentration for D_5 was based on air concentrations for all cyclosiloxanes and assumed that a certain percentage of the total was D_5. However, the presumed percentage of D_5 was that considered likely in products

currently manufactured. The percentage of D_5 in the product tested and used to derive these air concentrations may have differed.

For HC/SC products, one inhalation exposure scenario for all HC/SC products was considered for women consumers (Table 46). Maxim *et al.* (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-minute exposure to this air concentration (0.178 ppm D_5) to that associated with the LED_{10}, resulted in a MOS of 37000. Comparison with the AUC associated with the NOAEL resulted in a larger MOS (45000). Both of 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 (Section 4.1.4.1). Comparison of the AUCs associated with exposure to one of sixteen HC/SC products to the AUC associated with either the LED_{10} or the NOAEL resulted in MOS of approximately 28000 or greater (Table 47). The lowest MOS (28000) was associated with moisturizer usage in women. Therefore, dermal exposure to D_5 from the usage of HC/SC products would not pose a significant health hazard.

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 moisturizer, 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.

5.1.3 General Public Exposure

For purposes of this assessment, the general public was considered to be individuals who reside in the vicinity of a D_5 manufacturing plant, but do not work in a plant or facility where D_5 is manufactured or used in product formulation. Exposures to this group were assumed to occur by inhalation only. Air concentrations were based on 210 indoor and 210 outdoor air samples collected at 70 facilities. The MOS determined for this scenario for men, women and children residents were all greater than 1000000,

regardless of comparison of the AUCs to the LED_{10} or the NOAEL (Table 48). This indicates that residential inhalation exposures to D_5 do not pose a significant hazard to human health for the general public

5.2 Uncertainties

5.2.1 Uncertainties in Model Parameters

In evaluating the potential uncertainties in the estimation of the internal dose metrics with the PBPK model, it is important to focus on the most sensitive parameters or those that may have the most impact on the determination of acceptable doses. For this assessment, the model parameters having the largest effect upon dose metric predictions were the blood:air partition coefficient, the rates into and out of the mobile lipid pool, and several of the dermal absorption parameters.

For the rat inhalation, human inhalation and human dermal simulations, the blood:air partition coefficient had the largest impact upon the simulated dose metric of daily average AUC in arterial blood. The blood:air partition is directly related to the dose metric estimates (i.e., increase in parameter results in increase in dose metric). Although an *in vitro* value was available for the blood:air partition coefficient, this value was unable to adequately simulate the rat kinetic data following inhalation exposure. With the limited amount of available data, it was not possible to get a better estimate of the blood:air partition than the one obtained from re-parameterizing the model. The selection of the value to be used for the blood:air partition is very critical. This can have a significant impact on estimated blood concentrations of D_5 because exhalation is a major route of excretion following dermal absorption. If the current value within a given species decreases, this results in a direct decrease in the internal dose metric or AUC in that species. The relationship of human and rat values for this parameter also has a significant effect on the animal-to-human extrapolation using the PBPK model. The relationship between the animal and the human blood:air partition coefficient can be critical in the determination of the amount of D_5 that is available in the blood for distribution. As the rat to human ratio of blood:air partition coefficients increases or decreases, the air concentration to which the human can be exposed that would achieve

similar blood concentrations as that estimated in the rat increases or decreases, respectively.

The rate of D_5 into the mobile lipid pool and the rate of D_5 from the mobile lipid pool to the diffuse fat also have a significant effect on the dose metric estimates. Like the blood:air partition coefficient, the rate into the mobile lipid pool is directly related to the dose metric estimates. The rate from the mobile lipid pool into the diffuse fat is inversely related with the dose metric or AUC indicating that as the rate increases, the amount of D_5 available in the blood decreases. In contrast, the rate into the mobile lipid pool is directly related with the dose metric or AUC indicating that as this rate increases, the D_5 concentration in the blood increases. These values for the rate of movement of D_5 into and out of the mobile lipid pool were estimated by fitting simulations to the available blood concentrations measured following inhalation or dermal exposures. Different assumptions for the value of the rate would directly impact the estimated blood concentration of D_5. It would be extremely difficult, if not impossible, to actually get measurements upon which to base these rates; therefore, the best available estimates will come from fitting data. Additional data for fitting might provide more certainty in the estimated values.

The rates used in the PBPK model for dermal evaporation and absorption have almost as significant an effect upon the dose metrics as the blood:air partition coefficient, and, as with the mobile lipid pool, there are limited data upon which to base some of these parameters. The initial rate of evaporation from the skin surface was estimated from published data (Reddy *et al.* 2005b), and the initial absorption rate into the skin was estimated by fitting the data using this estimated initial evaporation rate. Both estimates for these parameters are based upon the fact that D_5 appeared to be gone from the surface after 5 minutes. The time at which to stop evaporation and absorption from skin surface for the various dermal exposures were determined based upon the values of these parameters; increases in these parameters without re-adjustment of the time setting would allow for more D_5 to be absorbed than was applied and would thus increase the dose metric. The rate of evaporation from inside the skin back to the surface (inversely related to dose metric) and the rate of absorption from the skin into the blood (directly related to dose metric) were fit to the data upon which the model was built (Reddy *et al.* 2005b).

As is typical, these parameters have some of the largest impacts upon the dose metric estimates, but are the most uncertain since the only way to estimate them with the limited amount of data is to fit them. These 2 parameters are time dependent and inversely related. This would indicate that as the dermal evaporation rate is increased, the dermal absorption rate should decrease.

5.2.2 Uncertainties Associated with Exposure Parameters

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. The following uncertainties were considered.

- Most parameter estimates were based on the average or median values for that parameter. In many cases, the upper bounds on these estimates were not available (e.g. inhalation concentrations for AP/Ds and HC/SC products). Since averages and medians 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 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.

- Not all AP/Ds or HC/SC products contain D_5, although this assessment assumed that they do. This assumption will overestimate the exposure for both dermal and inhalation exposure from AP/Ds and HC/SC products, if a person more typically used products that did not contain D_5..

- Gender-specific data were not available for the application rates of most HC/SC. It is likely that men may use less of a hair care product than a woman who uses the same product due both to the relative length of hair and frequency of application. It is also more likely that a woman will more consistently use a body lotion than will a man. For moisturizers, the information on frequency and amount of used was based on studies in women. It is highly likely that the amount of use and frequency of use is less for men. Therefore, the estimates from exposure to those HC/SC products for men are likely to be overstated.

- 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 D_5.
- The percentage of D_5 in the product used may not have been the same as that assumed for today's AP/D products.

These would result in an overestimation of the inhalation exposure to D_5 in AP/Ds.

- The 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.

- For occupational exposure the median number of years worked at a particular occupation was used to adjust the lifetime exposure which results in factors of 0.11 for males and 0.072 for females being applied to the average AUC. It is possible that a worker could work 45 years at the same job. If a person worked 45 years at the same occupation with the same exposure pattern, the estimates of exposure would be 5 to 8 times higher; however, still within the acceptable range. However, estimates of the AUC were not adjusted for the years of usage. For those products not used for an entire lifetime or a significant portion of that lifetime, the AUC based on lifetime usage would be overestimated and the MOS underestimated.

- 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 skin care product 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

- 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 (USEPA 1997), respectively.

- Each exposure scenario was treated independently (i.e., consumer product, occupational, general public), however, there is the possibility an individual could be a D_5 production worker, who lives near the plant and uses consumer products containing D_5. This would be a "worst case" exposure scenario. However, because of the orders of magnitude difference between the dose metrics estimated for each exposure scenario, it is likely that the occupational scenario would dominate in a combined scenario situation.

6.0 SUMMARY AND CONCLUSIONS

As discussed previously, the purpose of this investigation was to conduct a safety assessment to evaluate the potential hazard to selected workers, consumers, and the general public who may be exposed to D_5 either in the workplace or through the use of consumer products containing D_5. This involved a critical review of the available toxicity and oncogenicity studies, as well as supporting information, including toxicokinetic data, mutagenicity and genotoxicity, reproductive/developmental toxicity, and immunotoxicity studies. In addition, studies designed to elucidate the mode of action (MoA) for observed effects in the animal were reviewed. Based on this review, potential endpoints for consideration as part of a human health safety assessment were limited to one neoplastic finding of uterine endometrial adenocarcinomas in female rats. Changes in liver weights and enzyme induction were also observed; however, these effects were not considered adverse and were consistent with the classical adaptive response observed following phenobarbital treatment indicating that D_5 was a weak phenobarbital-type inducer the rat liver.

Consideration of the studies conducted to evaluate the potential MoA of the uterine response observed in female rats indicated the likelihood that D_5 at very high concentrations is functioning as a dopamine agonist in rats, leading to the development of observed uterine tumors. There are several lines of evidence to support that D_5 is inducing uterine adenocarcinomas indirectly in a non-genotoxic mechanism in rats that is not relevant to humans. This evidence includes studies that have shown that D_5: 1) is not mutagenic or genotoxic, 2) tumors in D_5-treated rats were histologically indistinguishable from untreated control tumors; 3) does not bind to estrogen receptors and is not an estrogen agonist or antagonist, and, 4) demonstrated dopamine agonist activity. The changes that occur in the uteri of female rats treated with dopamine agonists result from the effects of prolonged estrogen dominance resulting from the reduced prolactin secretion superimposed on the waning endocrine system, which is characteristic of aging rats (Richardson *et al.* 1984). These changes do not occur in other species, including humans (Richardson *et al.* 1984). Therefore, the mechanism of dopamine agonist-induced tumors observed following exposure of female rats to D_5 is not relevant to humans.

While a dose-response assessment and risk characterization were conducted as part of this effort based upon the uterine effects observed in female rats following chronic administration of D_5, the most appropriate approach for a human health safety assessment would rely upon other effects observed. In this case, there were no treatment-related adverse effects noted in the toxicity studies. Consequently, the NOAEL should serve as the POD. If the incidence of uterine adenocarcinomas were to be used for a safety assessment, based on the available information on the MoA, it would be a nonlinear process. Therefore, based on the most recent USEPA (USEPA 2005) Guidelines for Carcinogenic Risk Assessment, an LED_{10} was derived to be used as a POD to provide a lower bound to a POD based on the NOAEL. A PBPK model was also used to estimate the internal dose metric associated with the LED_{10} or the NOAEL, assumed to be the human equivalent dose metric.

The internal dose-metric, the AUC, based on the LED_{10} or the NOAEL were compared with those based on the various exposure scenarios to determine if typical exposure to D_5 might represent a hazard to human health. Three populations were considered in the exposure assessment:

- persons who work in the production of D_5, in the formulation of this material into personal care products, in the dry cleaning industry, or in the use of these products in professional settings;

- consumers who use these personal care products, including antiperspirant/deodorants (AP/Ds) and hair care/skin care (HC/SC) products; and,

- the general public living in the vicinity of a plant that produces or processes these materials and who may be exposed to ambient levels of D_5 released to the environment during manufacturing activities.

Exposure for all 3 populations was considered to occur via dermal and/or inhalation exposure. As with the derivation of the AUC for the LED_{10} or the NOAEL, a PBPK model was used to estimate the internal dose metric associated with the dermal or inhalation exposures for each population. These dose-metrics were then compared by deriving a MOS. A MOS is the ratio of the internal dose metric or AUC associated the POD to the internal dose metric estimated for each relevant exposure scenario.

Regardless of the POD considered for conducting a safety assessment, the MOS estimated for each exposure scenario was not greater than values that would be deemed

acceptable by the appropriate regulatory agency (i.e., OSHA for occupational exposure). Therefore, it could be concluded that typical exposure to D_5, whether occupationally, or through the use of D_5-containing consumer products, or to the general public, would not result in a significant human health hazard.

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Table 1

Description of Exposure Groups and Histopathology in a 24-Month Inhalation Oncogenicity Study of D_5 in Fischer 344 Rats (Dow Corning Corporation 2005a)

Exposure Group (ppm)	Sub-group	Males	Females	Sacrifice	Histopathology
0 or 160 ppm	A	6	6	6 months	nasal cavity, paranasal sinuses, nasal vestibule, and Zymbal's glands
	B	10	10	1 year	adrenal glands, aorta, bone(sternum, femur with joint), bone marrow (femur, sternum), brain (cerebellum, pons, medulla oblongata), cervix, clitoral glands, common bile duct, epididymis, esophagus, exorbital lacrimal glands, eyes, heart, kidneys, large intestine (cecum, colon, rectum), larynx, liver, lungs, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland area, nasal cavity with paranasal sinuses, optic nerves, ovaries, oviducts, pancreas, parathyroid glands, penis, pharynx/nasal vesibule, prepuce, preputial glandspituitary gland, prostate, salivary glands (mandibular, sublingual), sciatic nerve, seminal vesicles, skeletal muscle, skin, small intestine (duodenum, jejunum, ileum), spinal cord (cervical, midthoracic, lumbar), spleen, stomach, testes, thymus, thyroid gland, trachea, urinary bladder, uterus, vagina, Zymbal's glands, and all gross lesions and tissue masses
	C	20	20	Recovery	
	D	60	60	2 year	
10 or 40 ppm	A	6	6	6 months	nasal cavity, paranasal sinuses, nasal vestibule, and Zymbal's glands
	B	10	10	1 year	liver, lungs, kidneys, nasal cavity, uterus (including cervix and vagina), Zymbal's glands, gross lesions and tissue masses were examined microscopically
	C	20	20	Recovery	
	D	60	60	2 year	

Table 2

Neoplastic Findings with a Significant Positive Trend and Significant Differences between One or More Dosed Groups and Control (Dow Corning Corporation 2005a)

Sub-Group	Sex	Organ/ Tissue	Finding	Control (0 ppm)		10 ppm		40 ppm		160 ppm	
24-Month Exposure Group	Female	Uterus	Endometrial Adenocarcinoma	0/60	[a]	1/60		0/60		5/60	*

[a] Significant positive trend test ($p < 0.05$) by the Peto test

* Significantly higher ($p < 0.05$) than control by the Fisher's Exact test

Table 3

Expired Air Data from a Single D_5 Inhalation Exposure in Humans (Utell 2004))

Minutes	D_5 Expired Air Concentration (ppm)				
	Subject 1 (M)	Subject 2 (F)	Subject 3 (M)	Subject 4 (M)	Subject 5 (F)
2	4.84	4.31	4.08	4.06	3.36
4	6.28	6.43	7.17	6.35	5.47
6	6.32	5.86	7.55	7.21	6.33
8	6.76	6.35	7.83	6.96	6.64
10	7.31	7.07	8.04	7.64	7.19
12	7.87	8.17	8.51	8.26	7.85
14	7.97	7.65	8.83	8.45	8.19
16	8.53	7.66	8.66	9.01	8.9
18	8.64	8.36	8.73	9.1	8.96
20	8.24	8.25	8.85	9.27	9.28
22	8.24	8.32	8.58	7.84	9.17
24	7.87	7.24	8.43	8.36	9.01
26	7.99	7.47	8.24	8.23	8.69
28	8.01	6.71	8.49	8.11	8.35
30	7.82	7.05	8.66	8.11	8.34
32	8.11	7.19	8.4	8.32	8.47
34	7.96	7.37	8.5	8.6	8.96
36	7.23	7.81	8.44	8.99	8.97
38	7.5	7.34	8.37	8.48	8.85
40	7.92	7.1	8.44	8.19	8.71
42	7.86	8.47	8.91	8.87	9.25
44	8.01	8.48	8.91	8.92	9.27
46	7.95	8.42	8.54	9.25	9.41
48	8.08	8.55	8.68	9.08	9.65
50	8.73	8.42	8.77	8.89	9.58
52	8.68	7.76	8.62	8.93	9.49
54	8.06	8	8.49	8.63	8.88

Table 3 (continued)

Expired Air Data from a Single D_5 Inhalation Exposure in Humans (Utell 2004)

Minutes	D_5 Expired Air Concentration (ppm)				
	Subject 1 (M)	Subject 2 (F)	Subject 3 (M)	Subject 4 (M)	Subject 5 (F)
56	8.03	7.55	8.64	8.62	
57					8.69
58	8.06	7.96	8.71	8.69	8.99
60	7.97	7.41	8.71		8.93
60.5				8.76	
62	8.16	2.88	3.09		4.27
62.6				3.62	
64	2.18	2.13	1.22		
64.5				1.64	2.49
66	1.37	1.23	0.85		
66.5				1.52	1.81
68	1	1.71	0.79		
68.5				1.12	1.61
70	1.06	1.25	0.95		
70.5				1.15	1.34
72	0.96	1	0.72		
72.5				1.07	1.42
74		0.74	0.7		
74.5				1.12	1.29
76		0.8	0.66		
76.5				1	0.85
78			0.67		
78.5				1.77	0.75
80			0.54		
80.5				2.28	0.68

Table 4

D_5 Plasma Concentration Data from a Single Inhalation Exposure in Humans (Utell 2004)

Minutes	D_5 Plasma Concentration (µg/L)				
	Subject 1 (M)	Subject 2 (F)	Subject 3 (M)	Subject 4 (M)	Subject 5 (F)
0	3.3	0.56	1.73	0.15	3.21
30	37.57	21.55	36.66	25.42	49.34
60	66.22	30.72	55.3	37.65	70
120	25.13	15.47	26.69	17.09	33.46
420	13.6	4.34	13.47	5.11	16.69
1500	5.74	1.99	3.86	1.09	8.26

Table 5

Pharmacokinetic Parameters for Total Radioactivity in Plasma and Tissues After a Single Inhalation Exposure to D_5 in Rats

(Battelle Northwest Toxicology 2001)

Dose	Tissue	t_{Max} (hours)		C_{Max} (µg eq/g)		$AUC_{0\text{-}168}$ (µg eq hr/g)		$t_{1/2}$ (hours)	
		Male	Female	Male	Female	Male	Female	Male	Female
7 ppm	Plasma	0	0	0.158 ± 0.0253	0.0713 ± 0.025	3.05	1.49	123	50.5
	Perirenal Fat	168	24	0.343 ± 0.13	0.235 ± 0.108	37.8	30.5	b	495
	Liver	0	0	0.918 ± 0.174	0.637 ± 0.268	30.7	28.9	147	78.8
	Lung	0	0	2.05 ± 0.267	1.05 ± 0.336	83.7	45.9	143	80.8
	Small Intestine[a]	0	0	4.31 ± 0.776	1.8 ± 0.81	33.5	19.8	146	78.2
	Large Intestine[a]	3	1	5.57 ± 2.23	2.26 ± 1.11	88.5	45.9	282	64.6
	Stomach[a]	1	0	3.1 ± 2.98	1.38 ± 0.938	17.6	17.8	148	155
	Adrenal Gland	0	0	1.15 ± 0.173	1.01 ± 0.343	49.2	48.5	b	114
	Thyroid	0	0	2.91 ± 3.87	0.595 ± 0.309	39.8	45.7	113	198
	Ovaries		12		0.304 ± 0.24		29.5		106
	Uterus		0		0.099 ± 0.0337		8.22		b
	Vagina		0		0.112 ± 0.047		7.52		b
	Testes	0		0.102 ± 0.0173		4.86		198	

Table 5 (continued)

Pharmacokinetic Parameters for Total Radioactivity in Plasma and Tissues After a Single Inhalation Exposure to D_5 in Rats

(Battelle Northwest Toxicology 2001)

Dose	Tissue	t_{Max} (hours)		C_{Max} (µg eq/g)		AUC_{0-168} (µg eq hr/g)		$t_{1/2}$ (hours)	
		Male	Female	Male	Female	Male	Female	Male	Female
160 ppm	Plasma	0	0	3.33 ± 0.233	2.23 ± 0.803	54.9	35.7	68.5	52
	Perirenal Fat	3	12	8.16 ± 1.22	8.08 ± 1.45	946	1020	371	111
	Liver	0	0	31.8 ± 1.27	31.5 ± 12.6	775	766	85.2	59.3
	Lung	0	0	61.2 ± 7.34	49.8 ± 18.9	2030	1330	375	216
	Small Intestine[a]	0	0	176 ± 44	82.1 ± 32.8	1320	723	135	79.7
	Large Intestine[a]	3	3	253 ± 12.7	114 ± 41	3070	1830	98.5	51.9
	Stomach[a]	0	0	62.6 ± 30.7	32.1 ± 8.35	441	389	75.2	57.2
	Adrenal Gland	0	0	59.9 ± 4.79	70.7 ± 31.8	1470	1650	136	360
	Thyroid	120	120	33.3 ± 57.3	22.6 ± 27.8	2020	1760	78.5	76.8
	Ovaries		0		14 ± 6.02		673		95.3
	Uterus		0		4.11 ± 1.23		218		121
	Vagina		0		3.97 ± 1.95		219		99.7
	Testes	3		2.01 ± 0.121		107		173	

[a] Includes contents

[b] Data does not show a linear apparent terminal phase

Table 6

Pharmacokinetic Parameters for Total Radioactivity in Plasma and Tissues After Repeated Inhalation Exposure to 160 ppm D_5 in Rats (Battelle Northwest Toxicology 2001)

Tissue	t_{Max} (hours)		C_{Max} (µg eq/g)		AUC_{0-168} (µg eq hr/g)	
	Male	Female	Male	Female	Male	Female
Plasma	0	0	4.21 ± 0.366	4.82 ± 0.451		
Fat	12	3	11.5 ± 6.36	15 ± 2	1176.8	1922.53
Liver	0	0	26.6 ± 5.87	44.4 ± 5.69	780.69	1195.05
Lung	0	0	125 ± 14.4	90.6 ± 6.51	1465.04	1354
Small Intestine	0	0	223 ± 133	184 ± 80.8	803.99	784.66
Large Intestine	1	1	129 ± 102	91 ± 66.8	1547.58	1811.72
Stomach	0	0	42 ± 24.9	56.5 ± 49	175.27	220.24
Adrenal Gland	1	0	93 ± 62.1	1671 ± 3118		
Thyroid	0	24	23.8 ± 4.37	268 ± 527		
Ovaries		3		54.9		
Uterus		0		6.7 ± 0.761		
Vagina		12		8.68 ± 4.21		
Testes	1		1.78 ± 0.366			

Table 7

D_5 Plasma Concentration Data from Dermal Exposure in Humans (Plotzke *et al.* 2002)

Hours	D_5 Expired Air Concentration (µg/L)							
	Males				Females			
	Subject			Average	Subject			Average
	1	2	3		1	2	3	
0	ND	ND	ND	ND	ND	ND	ND	ND
0.5	1.2	0.25	1.1	0.86 ± 0.53	0.53	1.4	0.65	0.87 ± 0.49
1	1.7	0.70	1.2	1.2 ± 0.5	0.95	2.0	0.77	1.2 ± 0.66
2	1.6	0.97	0.90	1.1 ± 0.4	0.92	1.8	0.50	1.1 ± 0.66
4	1.2	0.61	0.62	0.79 ± 0.31	0.90	1.5	0.34	0.91 ± 0.58
6	0.88	0.51	0.47	0.62 ± 0.23	0.75	0.82	0.21	0.59 ± 0.33

ND – No D_5 was detected

Table 8

D_5 Expired Air Data from Dermal Exposure in Humans (Plotzke *et al.* 2002)

Hours	D_5 Expired Air Concentration (ng/L)							
	Males				Females			
	Subject			Average	Subject			Average
	1	2	3		1	2	3	
0	0.38[a]	0.65[a]	1.9[a]	0.98 ± 0.82[a]	2.2[a]	3.0[a]	2.3[a]	2.5 ± 0.5[a]
0.25	702	150	1000	620 ± 430	320	710	350	460 ± 220
0.5	1700	140	1000	930 ± 770	260	700	91	350 ± 310
0.75	1600	680	210	830 ± 700	420	370	260	350 ± 80
1	2300	220	230	920 ± 1200	120	360	150	210 ± 130
1.25	520	280	180	330 ± 170	150	320	91	190 ± 120
1.5	740	360	270	460 ± 250	220	180	47	150 ± 90
1.75	670	300	98	350 ± 290	170	120	29	110 ± 70
2	620	250	58	310 ± 280	350	110	36	160 ± 160
4	120	24	22	55 ± 55	96	49	16	53 ± 40
6	26	17	7.4	17 ± 9	64	15	7.5	29 ± 31
24	3.9	13	6.3	7.6 ± 4.4	18	5.6	5	9.6 ± 4.5

[a] The air samples had a small, variable background level due to the re-used Rudolph valve despite efforts to decontaminate in between uses.

Table 9
Tissue Concentrations in Female Rats Immediately Following Single or Repeat Inhalation Exposures to 160 ppm [^{14}C]-D_5, μg/g [a] (Dow Corning Corporation 2005b)

Tissue	Single	15-Day	6-Month
Plasma	2.50±1.28	3.48±0.57	3.19±0.76
Liver	27.14±11.66	32.74±4.68	32.76±2.97
Perirenal fat	3.32±1.84	190.3±10.9	176±58
Abdominal fat			115±42
Brown fat			141±22.9

[a] Values are mean ± one SD for n = 3 to 6.

Table 10

Effect of D_5 and Phenobarbital on PROD and EROD Activity in Male and Female Sprague-Dawley Rats (Zhang *et al.* 2000)

Dose (mg/kg)	PROD (pmol/min per mg)		EROD (pmol/min per mg)	
	Male	**Female**	**Male**	**Female**
0	12.7 ± 1.9	1.6 ± 0.5	47.4 ± 9.8	36.8 ± 6.2
1	19.4 ± 5.8	1.9 ± 0.1	44.9 ± 9.6	41.3 ± 10.7
5	37.8 ± 16.6	2.8 ± 0.2*	126 ± 48.4*	48.3 ± 5.1*
20	69.1 ± 26.7*	10.7 ± 4.8*	114 ± 36.2*	63.2 ± 18.5*
100	99.4 ± 25.9*	10.4 ± 5.1*	141 ± 9.8*	51.8 ± 7.2*
Phenobarbital 50 mg/kg	1053 ± 60.4*	172 ± 59.1*	222 ± 8.5*	109 ± 6.4*

* - Significant difference from control at $P \leq 0.05$ as determined by Dunnett's test.

Table 11

Description of Test Groups in an Evaluation of D_5 with the Rat Uterotrophic Assay in Adult Fischer 344 Rats and Adult Sprague-Dawley Rats (Dow Corning Corporation 2004d, 2004e)

Group	Treatment	Dose	Dosing Route	Duration of Exposure	Number of Rats per Group
1	Vehicle control (corn oil)	0	sc	3 days	6
2	EE	0.0003 mg/kg/day	sc	3 days	6
3		0.001 mg/kg/day	sc	3 days	6
4		0.003 mg/kg/day	sc	3 days	6
5	Gen	10 mg/kg/day	sc	3 days	6
6		25 mg/kg/day	sc	3 days	6
7		50 mg/kg/day	sc	3 days	6
8	ICI 182,780 and EE	3.0 mg/kg/day ICI and 0.003 mg/kg/day EE	sc	3 days	6
9	EE and D_5	0.003 mg/kg/day EE and 160 ppm D_5	EE - sc D_5 - WBI	EE – 3 days D_5 – 16/hours/day for 3 days	6
10	Filtered air control	0	WBI	3 days	10
11	D_5	160 ppm	WBI	16 hours/day for 3 days	10

EE – ethinyl estradiol
Gen - genistein
ICI – estrogen receptor agonist ICI
WBI – whole body inhalation
sc – subcutaneous

Table 12

Comparison of Positive Control Groups to Control Groups in Ovariectomized Adult Sprague-Dawley Rats (Dow Corning Corporation 2004d)

Group	Treatment	N	Mean Initial Body Wt. (g)	Mean Terminal Body Wt. (g)	Mean Change in Body Wt. (g)	Mean Uterine Wt. (g)		Mean Uterine Wt. Relative to Body Wt. (g) ($x10^{-3}$)		Luminal and Glandular Epithelial Cell Heights (um)	
						Wet	Blotted	Wet	Blotted	Glandular	Luminal
1	Control	6	262.3	258.3	-4.0	0.0642	0.0627	0.2500	0.2333	11.686	14.161
2	EE 0.0003 mg/kg/day	6	264.3	260.7	-3.7	0.1791[2]	0.1706[2]	0.7000[3]	0.6500[3]	18.067[4]	24.651[4]
3	EE 0.001 mg/kg/day	6	261.1	251.6	-9.5	0.2835[2]	0.2240[2]	1.1333[3]	0.9000[3]	18.406[4]	30.922[4]
4	EE 0.003 mg/kg/day	6	268.2	256.1	-12.1[1]	0.4142[2]	0.2546[2]	1.6000[3]	0.9833[3]	20.471[4]	33.603[4]
5	Gen 10.0 mg/kg/day	6	271.7	269.3	-2.5	0.0874	0.0846	0.3333	0.3333	13.025[4]	14.250
6	Gen 25.0 mg/kg/day	6	279.9	276.4	-3.5	0.1483[2]	.01413[2]	0.5333[3]	0.5167[3]	15.551[4]	15.042
7	Gen 50.0 mg/kg/day	6	270.8	269.2	-1.7	0.1497[2]	0.1424[2]	0.5667[3]	0.5500[3]	16.866[4]	18.194[4]
8	EE + ICI	6	277.9	267.9	-10.0	0.0801	0.0773	0.2980	0.2880	12.883[4]	14.562
9	EE + D_5	6	262.1	253.4	-8.7	0.3635[2]	0.2548[2]	1.4333[3]	1.0167[3]	19.439[4]	36.321[4]
10	Filtered air control	10	264.8	251.3	-13.6	0.0687	0.0668	0.2800	0.2700	11.477	13.220
11	D_5	10	271.7	258.4	-13.3	0.0670	0.0641	0.2700	0.2700	11.347	12.853

g = grams; Gen = genistein; EE = ethinyl estradiol; ICI = 3 mg/kg/day

[1] = statistically decreased from Group 1 control ($p=0.0295$)

[2] = statistically increased over Group 1 control ($p\leq0.0184$)

[3] = statistically increased over Group 1 control ($p\leq0.0368$)

[4] = statistically increased over Group 1 control ($p\leq0.0006$)

Table 13

Comparison of Positive Control Groups to Control Groups in Ovariectomized Adult Fischer Rats (Dow Corning Corporation 2004e)

Group	Treatment	N	Mean Initial Body Wt. (g)	Mean Terminal Body Wt. (g)	Mean Change in Body Wt. (g)	Mean Uterine Wt. (g)		Mean Uterine Wt. Relative to Body Wt. (g) ($x10^{-3}$)		Luminal and Glandular Epithelial Cell Heights (um)	
						Wet	Blotted	Wet	Blotted	Glandular	Luminal
1	Control	6	150.9	147.3	-3.6	0.0458	0.0445	0.3167	0.3167	11.7732	13.6739
2	EE 0.0003 mg/kg/day	6	156.8	151.6	-5.2	0.1259[1]	0.1196[1]	0.8333[2]	0.8000[2]	19.6488[3]	27.9664[3]
3	EE 0.001 mg/kg/day	6	159.1	152.3	-6.8	0.2598[1]	0.1831[1]	1.7000[2]	1.2000[2]	21.5275[3]	34.3496[3]
4	EE 0.003 mg/kg/day	6	159.0	153.9	-5.1	0.2621[1]	0.1930[1]	1.7167[2]	1.2500[2]	19.9548[3]	38.3061[3]
5	Gen 10.0 mg/kg/day	6	154.1	150.6	-3.5	0.0661	0.0628	0.4500	0.4333	12.9878[3]	14.5450
6	Gen 25.0 mg/kg/day	6	152.2	148.8	-3.4	0.0769	0.0725	0.5167	0.5000	14.0944[3]	14.4092
7	Gen 50.0 mg/kg/day	6	162.4	161.0	-1.5	0.0978[1]	0.0929[1]	0.6000[2]	0.5667	15.5596[3]	16.6933[3]
8	EE + ICI	6	158.1	154.6	-3.6	0.0472	0.0458	0.3000	0.3000	12.0356	13.8210
9	EE + D_5	6	155.9	149.0	-6.9	0.2471[1]	0.1710[1]	1.6667[2]	1.1500[2]	21.5433[3]	39.8907[3]
10	Filtered air control	10	157.9	146.9	-11.0	0.0497	0.0478	0.3300	0.3300	12.4067	13.3832
11	D_5	10	154.1	144.8	-9.2	0.0472	0.0472	0.3400	0.3400	11.32618	12.8140

g = grams; EE = ethinyl estradiol; Gen = genistein; ICI = 3 mg/kg/day

[1] = statistically increased ($p \leq 0.0192$)

[2] = significantly increased over the Group 1 control ($p \leq 0.0322$)

[3] = statistically increased over Group 1 control ($p \leq 0.0108$)

Table 14

Summary of Levels of D_5 Found in Ovariectomized Adult Sprague-Dawley Rats and Ovariectomized Adult Fischer 344 Rats (Dow Corning Corporation 2004d, 2004e)

D_5 Analysis	µg D_5/g tissue	
	Sprague-Dawley Rats	Fischer 344 Rats
Blood	2.68	2.48
Brain	5.34	4.62
Uterus	10.07	7.39

Table 15.

Description of Test Groups in an Evaluation of D_5 with the Hershberger Assay Using Castrated Adult Male Fischer 344 Rats (Dow Corning Corporation 2004c)

Group	Treatment	Dose	Dosing Route	Duration of Exposure	Number of Rats per Group
1	Vehicle control (corn oil)	0	sc	10 days	6
2	Testerone propionate (TP)	0.1 mg/kg/day	sc	10 days	6
3		0.2 mg/kg/day	sc	10 days	6
4		0.4 mg/kg/day	sc	10 days	6
5		0.8 mg/kg/day	sc	10 days	6
6		1.6 mg/kg/day	sc	10 days	6
7	TP and flutamide (FLUT)	0.54 mg/kg/day TP and 4 mg/kg/day FLUT	TP – sc FLUT – oral	10 days	6
8	TP and D_5	0.54 mg/kg/day TP and 160 ppm D_5	TP – sc D_5 – WBI	TP – 10 days D_5 – 16 hours/day for 10 days	6
9	Filtered air control	0 ppm	WBI	10 days	10
10	D_5	160 ppm	WBI	16 hours/day for 10 days	10

sc – subcutaneous

WBI – whole body inhalation

Table 16

Effect of D_5 Vapor Inhalation Exposure on Serum Prolactin Levels in Reserpine Pretreated Female Fischer 344 Rats (Dow Corning Corporation 2005d)

Treatment	Serum Prolactin (ng/ml)
Ovariectomized Control[a]	11
Reserpine Control[b]	72[*]
Reserpine + 160 ppm D_5	37[**]

[a] Ovariectomized Fischer 344 rats not treated with reserpine.

[b] Fischer 344 rats treated with reserpine (2.0 mg/kg) only

[*] Statistically different from ovariectomized control ($p<0.05$).

[**] Statistically different from respective reserpine control ($p<0.05$).

Table 17

Dose-Dependent Effect of Sulpiride on the D_5-Induced Decrease of Serum Prolactin Levels in Reserpine Pretreated Female Fischer 344 Rats (Dow Corning Corporation 2005d)

Treatment	Serum Prolactin (ng/ml)
Ovariectomized Control[a]	5
Reserpine Control[b]	58*
Reserpine + 160 ppm D_5	38
Reserpine + 160 ppm D_5 + Sulpiride	395**

[a] Ovariectomized Fischer 344 rats not treated with reserpine.

[b] Fischer 344 rats treated with reserpine (2.0 mg/kg).

* Statistically different from ovariectomized control ($p<0.05$).

** Statistically different from respective reserpine/siloxane treated group ($p<0.05$).

Table 18

Dose-Response Model Predicted LED_{10}

Exposure Dose (ppm)	Incidence of Uterine Endometrial Adenomas	Human Equivalent Doses (HED)
		AUC (mg-hrs/L/day)
0	0/60	0
10	1/60	1.77
40	0/60	7.20
160	5/60	28.49
	LED_{10}	23.47

Table 19

Hair Care Products Containing D_5 – Application Rates, Deposition and Residue Amounts

Hair Care Products	Application. Rate (g/use)	Deposition (%)	Residue (%)	D_5 (%)
Shampoo	11.7	100	1	0.2
Rinse-out conditioner	11.2	100	1	0.2
Leave-in conditioner	11.2	5	100	0.2
Hair spray	5.6	5	100	0.2
Cuticle coat	4.7	5	100	6.0
Brilliantine	4.7	5	100	2.8
Pomade	4.7	5	100	1.9
Spray Shine	5.6	5	100	5.0

Table 20

Summary of Dermal Exposure Parameters – Barbers and Beauticians

Parameter	Barbers and Beauticians		Sources
	Men	**Women**	
Amount of product applied (g)	4.7	4.7	Mediamark Research(1996) as cited in Maxim *et al* (1998)
Amount of D_5 (%)	6.0	6.0	Maxim *et al.*(1998)
Exposure frequency (applications per day)	12	12	Personal judgment
Days per week	5	5	
Weeks per year	50	50	
Surface Area (cm^2)	840	746	USEPA (1997)
Body Weight (kg)	86.3	70.8	NHANES (1999-2002)

Table 21

Area Under the Curve (AUC): Dermal Exposure – Barbers and Beauticians

Worker	AUC (mg-hrs/L/day)	
	Men	**Women**
Barbers and Beauticians	4.7×10^{-5}	4.2×10^{-5}

Table 22

Summary of Inhalation Exposure Parameters - Workers

Worker	Parameter					
	Air Concentration (ppm) [a]	Daily Exposure (hours/day)	Exposure Frequency (days/week)	Work Year (weeks/ year)	Inhalation Rate (m^3/hr)	Body Weight (kg)
Antiperspirant	2.23 (1.07)	8	5	50	1.6	83.6 (M) 70.8 (W)
Skin Care	1.06 (0.83)	8	5	50	1.6	83.6 (M) 70.8 (W)
Hair Care	0.002 (0.001)	8	5	50	1.6	83.6 (M) 70.8 (W)
Dry Cleaner	0.143 (0.103)	8	5	50	1.6	83.6 (M) 70.8 (W)
Silicone	0.0587 (0.0286)[b]	8.75	5	50	1.6	83.6 (M) 70.8 (W)
Barbers and Beauticians	0.006 (0.006)	5.6	5	50	1.6	83.6 (M) 70.8 (W)

See text for sources.

[a] Values are reported as arithmetic mean (geometric mean)

[b] Arithmetic and geometric mean concentrations from all types of silicone workers

Table 23

Summary of Human Inhalation Rates for Men and Women by Activity Level (m^3/hour) (USEPA 1997)

	Resting	Sedentary Activity	Light Activity	Moderate Activity	Heavy Activity
Average adult	0.4	0.5	1.0	1.6	3.2

Table 24

Area Under the Curve (AUC): Occupational Inhalation Exposure

Worker	AUC (mg-hrs/L/day)	
	Men	**Women**
Antiperspirant	4.5×10^{-2}	2.2×10^{-2}
Skin Care	2.1×10^{-2}	1.0×10^{-2}
Hair Care	4.0×10^{-5}	2.0×10^{-5}
Dry Cleaner	2.9×10^{-3}	1.4×10^{-3}
Silicone	1.3×10^{-3}	6.3×10^{-4}
Barbers and Beauticians	8.6×10^{-5}	4.2×10^{-5}

Table 25

Average Application Rates for Antiperspirant/Deodorants (Maxim *et al.* 1998) (a)

Product Form	Gender	Average Amount/Application		N [b]
		(grams)	(mg/cm^2) [a]	
Solid	Men	1.29	10.8	17
	Women	0.65	10.7	11
Roll-on	Men	1.22	10.2	4
	Women	0.79	13.0	4
Aerosol	Men	1.99	16.7	3
	Women	1.54	25.2	3

[a] Estimated amount of application per skin surface area for axillary area.

[b] N = number of studies with 30 to 50 participants per study.

Table 26

Usage Survey Data for Antiperspirant/Deodorants for U.S. Population Age 18 or Older (MRI 1995)

Reported AP/D Applications in Last 7 Days	Sex	Weighted # in Population (×1000)	Percent in Population	Mid-Point of Range	Computed Usage
0	F	3953	4.4	0	0.0
	M	3686	4.6	0	0.0
1 - 3	F	3287	3.6	2	0.1
	M	3812	4.7	2	0.1
4 - 7	F	56914	62.7	5.5	3.4
	M	51431	63.6	5.5	3.5
8 - 11	F	10320	11.4	9.5	1.1
	M	7962	9.8	9.5	0.9
12 - 14	F	11700	13.0	13	1.7
	M	10727	13.3	13	1.7
15 or more [a]	F	4498	5.0	16	0.8
	M	3252	4.0	16	0.6
Subtotal	F	90742	100.0	Mean of Group	7.1
	M	80870	100.0		6.9

[a] No upper-bound was given for those in application frequency group "15 or more." Mid-point of range arbitrarily set at 16.

Table 27

Summary of Dermal Exposure Parameters – Antiperspirant/Deodorant Consumers

Parameter	Men	Women	Source
Application Rate (AR) Solid Roll-on Aerosol	 1.29 g/application 1.22 g/application 1.99 g/application	 0.65 g/application 0.79 g/application 1.54 g/application	Maxim *et al.*(1998).
Application Frequency (AF)	7 applications/week	7 applications/week	(MRI 1995) as cited in (Maxim *et al.* 1998)
Surface Area (SA)	119.5 cm^2	60.9 cm^2	Maxim *et al.*(1998)
Percent D_5 per gram Product Solid Roll-on Aerosol	 34% 54% 1.25%	 34% 54% 1.25%	Meeks (2005)
Body Weight (BW)	83.6 kg	70.8 kg	NHANES (1999-2002)

Table 28

Area Under the Curve (AUC): Dermal Exposure – Antiperspirant/Deodorant Consumers

Type of AP/D	AUC (mg-hrs/L/day)	
	Men	Women
Solid	1.9×10^{-3}	6.3×10^{-4}
Roll-on	2.8×10^{-3}	1.2×10^{-3}
Aerosol	1.1×10^{-4}	5.5×10^{-5}

Table 29

Breathing Zone Concentration of Cyclics During Antiperspirant/Deodorant Use

(Andersen and Weaver 1989)

Product Form	Amount Applied (grams)	6-Minute Time-Weighted Average Cyclics [a] Concentration (ppm)
Solid	1.93 0.96	0.3 0.3
Roll-on	1.05 0.45	2.9 0.9
Aerosol	2.6 2.4	1.0 0.9

[a] Includes D_4, D_5, and D_6.

Table 30

Summary of Inhalation Exposure Parameters - Antiperspirant/Deodorant Consumers

Parameter	Men	Women	Source
Air Concentration (AC) Solid Roll-on Aerosol	 0.2 ppm 1.7 ppm 0.65 ppm	 0.2 ppm 1.7 ppm 0.65 ppm	Meeks (2005)
Exposure Duration (ED)	5 minutes	10 minutes	USEPA (1997)
Application Factor (AF)	7 applications/week	7 applications/week	Professional Judgment
Inhalation Rate (INH)	1.0 m^3/hour	1.0 m^3/hour	USEPA (1997)
Body Weight (BW)	83.6 kg	70.8 kg	NHANES (1999-2002)

Table 31

Area Under the Curve (AUC): Inhalation Exposure - Antiperspirant/Deodorant Consumers

	AUC (mg-hrs/L/day)	
	Men	**Women**
Solid	4.9×10^{-4}	7.1×10^{-4}
Roll-on	4.1×10^{-3}	6.0×10^{-3}
Aerosol	1.6×10^{-3}	2.3×10^{-3}

Table 32

Application Rate Estimates for Hair Care/Skin Care Products (Maxim *et al.* 1998)

Products	Estimated Application Rate (g/use)
Hair Care:	
Spray shine; finishing spritz; finishing spray; styling spritz; styling spray; curl revitalizer; conditioning spray; protective spray	5.6
Cuticle coat; brilliantine; pomade; curl activator; setting lotion	4.7
Shampoo	11.7
Rinse-off conditioner; leave-in conditioner	11.2
Skin Care:	
Antiwrinkle, antiaging lotions/creams; alpha-hydroxy acid products; beauty lotions; bleaching, lightening lotions/creams; moisturizing lotions/creams; hormone lotions/creams; night lotions/creams	0.84[(a)]
Eye lotions/creams; concealer; under-eye cover	0.06
Foundation makeup	0.27
Suntan/sunscreen cream/lotion	6.1
Hand/body lotions	3.45[(a)]
Nail polish driers	0.25
After-shave (gel)	0.95
Mascara	0.11
Lipstick	0.005[a]

NOTE: Above estimates are averages or medians. There is substantial individual variability about these averages. Source CTFA (1983) and COLIPA as cited in (Maxim *et al.* 1998) unless otherwise noted

[a] Taken from Loretz *et al.* (2005). Medians were used due to the highly skewed distributions of average amount used per application.

Table 33

Usage Frequencies by Gender for Hair Care/Skin Care Products

MRI Category	Products Included	Consumer Gender	Average Frequency (times/week)[a]
Shampoos	multifunctional shampoos	Men Women	6 5
Conditioners	rinse-off/leave-on conditioners, rinses	Men Women	5 4
Hair sprays	styling sprays/spritzes, finishing sprays/ spritzes, protective sprays, conditioning sprays, curl revitalizers, spray shines (does not include hair treatment serums)	Men Women	5 6
Hand/Body lotions	hand/body lotions	Men Women	5 7[(b)]
After-shave lotions and colognes	after-shave lotions (gels)	Men	5
Hair tonics, dressings, styling gels, and lotions	curl activators, brilliantines, pomades, hair treatment serums, cuticle coats, setting lotions	Men Women	4 4
Foundation	foundation make-up, concealers/under-eye covers	Women	6
Mascara	mascaras	Women	5
Nail care products and polish	nail polish driers	Women	2
Suntan/Sunscreen	suntan or sunscreen lotion/cream	Adults	0.21 or 11 days/year
Lipstick	lipsticks	Women	16[b] 3 times/day for 5 or 6 days
Facial moisturizers	alpha-hydroxy acid lotions/creams; anti-wrinkle/antiaging; beauty lotions/creams; eye lotions; bleaching/lightening lotions/creams; moisturizing lotions/creams; hormone lotions/creams; night lotions/creams	Men[(c] Women	12[b] 2 times/day for 6 days

[a] Source Mediamark Research Product Summary Report (1996) unless otherwise noted
[b] Taken from Loretz *et al.* (2005), with the body lotion being the average over all body parts.
[c] Assumed men would use the same amount that women use

Table 34

D_5 Content of Hair Care/Skin Care Products (Maxim *et al.* 1998)

Products Included	Percent D_5	
	Range	**Base Case**
Hair Care: Spray shine	2 to 7	5
Finishing spritz; finishing spray; styling spritz; styling spray; curl revitalizer; conditioning spray; protective spray; curl activator; setting lotion; multifunctional shampoo; wash-off conditioner; leave-in conditioner	0 to 1.3	0.2
Cuticle coat	4 to 8	6
Brilliantine	2.5 to 3	2.8
Pomade	0.3 to 3.5	1.9
Rinse	0 to 0.3	0.2
Skin Care: Antiwrinkle, antiaging lotions/creams/ alpha-hydroxy acid products; beauty lotions; bleaching, lightening lotions/creams/moisturizing lotions/creams; hormone lotions/creams; night lotions/creams/eye lotions/creams	0 to 20	10
Concealer/undereye cover; lipsticks	3 to 34	17
Mascara	0 to 20	10
Foundation	0 to 20	6.8
Hand/body lotion	3.4 to 5.5	3.7
Suntan/sunscreen cream/lotion	5.4 to 8	6.8
Nail polish driers; after-shave (gel)	0 to 51	27.2

Table 35

Surface Area of Application

Product	Area of Application		From Exposure Factors Handbook (1997)					Surface Area (m^2)	
	Men	Women	Body Part	Mean Surface Area (m^2)		% of Body Part to which Product is Applied		Men	Women
				Men	Women	Men	Women		
Shampoo	Scalp		Head	0.118	0.11	60	64	0.0708	0.0704
Rinse-out conditioner			Head	0.118	0.11	60	64	0.0708	0.0704
Leave-in conditioner			Head	0.118	0.11	60	64	0.0708	0.0704
Hair spray			Head	0.118	0.11	60	64	0.0708	0.0704
Cuticle coat			Head	0.118	0.11	60	64	0.0708	0.0704
Brilliantine			Head	0.118	0.11	60	64	0.0708	0.0704
Pomade			Head	0.118	0.11	60	64	0.0708	0.0704
Spray Shine			Head	0.118	0.11	60	64	0.0708	0.0704
Moisturizer	Face		Head	0.118	0.11	40	36	0.0472	0.0396
Foundation	N/A	Face	Head	N/A	0.11	NA	36	N/A	0.0396
Hand/body lotion	Sum of hands, arms, legs, feet, and trunk			Men	Women				
			Feet	0.112	0.0975	100	100	1.498	1.4121
			Legs	0.505	0.488				
			Hands	0.084	0.0746				
Sunscreen			Arms	0.228	0.21	100	100	1.498	1.4121
			Trunk w/neck	0.569	0.542				
Undereye cover	N/A	Undereye areas	Head		0.11	N/A	1	NA	0.0011
Lipstick	N/A	Lips	Head		0.11	N/A	1	NA	0.0011
After-shave gel	Lower portion of face	N/A	Head	0.118	0.11	25	N/A	0.0295	NA

See text for sources.

Table 36

Summary of Parameters Used to Estimate Exposure from Dermal Exposure to Hair Care/Skin Care Products

HC/SC Type	App. Rate (g/use)	Frequency (times/week)		Surface Area (m^2)		Dep (%)	Res. (%)	D_5 (%)	Body Weight	
		Men	Women	Men	Women				Men	Women
Shampoo	11.7	6	5	0.059	0.055	100	1	0.2	83.6	70.8
Rinse-out conditioner	11.2	5	4	0.059	0.055	100	1	0.2	83.6	70.8
Leave-in conditioner	11.2	5	4	0.059	0.055	5	100	0.2	83.6	70.8
Hair spray	5.6	5	6	0.059	0.055	5	100	0.2	83.6	70.8
Cuticle coat	4.7	4	4	0.059	0.055	5	100	6.0	83.6	70.8
Brilliantine	4.7	4	4	0.059	0.055	5	100	2.8	83.6	70.8
Pomade	4.7	4	4	0.059	0.055	5	100	1.9	83.6	70.8
Spray Shine	5.6	5	6	0.059	0.055	5	100	5.0	83.6	70.8
Mascara	0.11	NA	5	NA	NG	100	100	10.2	83.6	70.8
Moisturizer	0.84	NA	12	NA	0.055	100	100	10.2	83.6	70.8
Nail care	0.25	NA	2	NA	NG	1	100	27.2	83.6	70.8
Foundation	0.27	NA	6	NA	0.055	100	100	6.8	83.6	70.8
Hand/body lotion	3.45	5.05	7	1.498	1.4121	100	100	0.42	83.6	70.8
Sunscreen	6.1	0.21	0.21 11 d/yr	1.498	1.4121	100	100	6.8	83.6	70.8
Undereye cover	0.06	NA	6	NA	0.0011	100	100	17.0	83.6	70.8
Lipstick	0.005	NA	16	NA	0.0011	100	100	17.0	83.6	70.8
After-shave gel	0.95	5.07	NA	0.0295	NA	100	100	27.2	83.6	70.8

See text for sources.
NA - Not Applicable.
NG - Negligible

Table 37

Area Under the Curve (AUC): Dermal Exposure - Hair Care/Skin Care Consumers

Product	AUC (mg-hrs/L/day)	
	Men	Women
Shampoo	8.7×10^{-7}	9.5×10^{-7}
Rinse-out conditioner	6.9×10^{-7}	7.3×10^{-7}
Leave-in conditioner	3.5×10^{-6}	3.6×10^{-6}
Hair spray	1.7×10^{-6}	2.7×10^{-6}
Cuticle coat	3.5×10^{-5}	4.6×10^{-5}
Brilliantine	1.6×10^{-5}	2.1×10^{-5}
Pomade	1.1×10^{-5}	1.4×10^{-5}
Spray shine	4.3×10^{-5}	6.8×10^{-5}
Moisturizer	6.4×10^{-4}	8.3×10^{-4}
Foundation	N/A	8.9×10^{-5}
Hand/body lotion	4.5×10^{-5}	8.2×10^{-5}
Sunscreen	5.5×10^{-5}	7.1×10^{-5}
Under-eye cover	N/A	5.0×10^{-5}
Lipstick (3 times a day, 6 days a week)	N/A	1.2×10^{-5}
Lipstick (3 times a day, 5 days a week)	N/A	1.0×10^{-5}
After-shave gel	8.0×10^{-4}	N/A

Table 38

Summary of Inhalation Exposure Parameters - Hair Care/Skin Care Consumers

Parameter	Women	Men	Sources
Air Concentration	0.178 ppm	0.178 ppm	(Maxim *et al.* 1998)
Exposure Duration	10 minutes	5 minutes	(USEPA 1997)
Application Frequency	1 application/day	1 application/day	Personal judgment
Inhalation Rate	1.0 m^3/hour	1.0 m^3/hour	(USEPA 1997)
Body Weight	70.8 kg	83.6 kg	(NHANES 1999-2002)

Table 39

Area Under the Curve (AUC): Inhalation Exposure - Hair Care/Skin Care Consumers

AUC (mg-hr/L/day)	
Men	**Women**
4.3×10^{-4}	6.3×10^{-4}

Table 40

Summary of Inhalation Exposure Parameters - General Public

Parameter	Value			Source
Air Concentration	0.5 μg/m^3			Shields *et al.* (1996) as cited in Maxim *et al* (1998)
Exposure Duration	24 hours/day			Personal judgment
Exposure Frequency	7 days/week			Personal judgment
Year	52 weeks/year			Personal judgment
Inhalation Rates (m^3/hour)	Ages	Males	Females	(USEPA 1997)
	1-2	0.28	0.28	
	3-5	0.35	0.35	
	6-8	0.42	0.42	
	9-11	0.58	0.54	
	12-14	0.63	0.50	
	15-17	0.71	0.50	
	18-75	0.63	0.47	
Body Weights (kg)	Ages	Males	Females	(NHANES 1999-2002)
	1-2	12.4	12.3	
	3-5	17.8	17.4	
	6-8	26.1	24.9	
	9-11	37.3	39.3	
	12-14	53.8	53.9	
	15-17	69.4	59.2	
	18-75	83.6	70.8	

Table 41

Area Under the Curve (AUC): Inhalation - General Public

AUC (mg-hrs/L/day)		
Ages	**Male**	**Female**
1-2	8.9×10^{-6}	7.8×10^{-6}
3-5	1.0×10^{-5}	8.6×10^{-6}
6-8	1.2×10^{-5}	9.7×10^{-6}
9-11	1.4×10^{-5}	1.2×10^{-5}
12-14	1.7×10^{-5}	1.4×10^{-5}
15-17	2.0×10^{-5}	1.4×10^{-5}
18-75	2.2×10^{-5}	1.6×10^{-5}

Table 42

Margins of Safety (MOS): Occupational Inhalation Exposure

Worker	AUC (mg-hr/L/day)		MOS			
			LED_{10}		NOAEL	
	Men	Women	Men	Women	Men	Women
Antiperspirant	4.5×10^{-2}	2.2×10^{-2}	$5.2\times10^{+2}$	$1.1\times10^{+3}$	$6.3\times10^{+2}$	$1.3\times10^{+3}$
Skin Care	2.1×10^{-2}	1.0×10^{-2}	$1.1\times10^{+3}$	$2.2\times10^{+3}$	$1.3\times10^{+3}$	$2.7\times10^{+3}$
Hair Care	4.0×10^{-5}	2.0×10^{-5}	$5.8\times10^{+5}$	$1.2\times10^{+6}$	$7.0\times10^{+5}$	$1.4\times10^{+6}$
Dry Cleaner	2.9×10^{-3}	1.4×10^{-3}	$8.1\times10^{+3}$	$1.7\times10^{+4}$	$9.8\times10^{+3}$	$2.0\times10^{+4}$
Silicone	1.3×10^{-3}	6.3×10^{-4}	$1.8\times10^{+4}$	$3.7\times10^{+4}$	$2.2\times10^{+4}$	$4.5\times10^{+4}$
Barbers and Beauticians	8.6×10^{-5}	4.7×10^{-5}	$2.7\times10^{+5}$	$5.6\times10^{+5}$	$3.3\times10^{+5}$	$6.8\times10^{+5}$

Table 43

Margins of Safety (MOS): Occupational Dermal Exposure

Worker	AUC (mg-hr/L/day)		MOS			
			LED_{10}		NOAEL	
	Men	Women	Men	Women	Men	Women
Barbers and Beauticians	4.7×10^{-5}	4.2×10^{-5}	$5.0\times10^{+5}$	$5.5\times10^{+5}$	$6.1\times10^{+5}$	$6.7\times10^{+5}$

7

Table 44

Margins of Safety (MOS): Inhalation - Exposure from Antiperspirant/Deodorant Use by Consumer

	AUC (mg-hr/L/day)		MOS			
			LED_{10}		NOAEL	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Solid	4.9×10^{-4}	7.1×10^{-4}	$4.8\times10^{+4}$	$3.3\times10^{+4}$	$5.9\times10^{+4}$	$4.0\times10^{+4}$
Roll-on	4.1×10^{-3}	6.0×10^{-3}	$5.7\times10^{+3}$	$3.9\times10^{+3}$	$6.9\times10^{+3}$	$4.7\times10^{+3}$
Aerosol	1.6×10^{-3}	2.3×10^{-3}	$1.5\times10^{+4}$	$1.0\times10^{+4}$	$1.8\times10^{+4}$	$1.2\times10^{+4}$

Table 45

Margins of Safety (MOS): Dermal Exposure from Antiperspirant/Deodorant Use by Consumer

	AUC (mg-hr/L/day)		MOS			
			LED_{10}		NOAEL	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**
Solid	1.9×10^{-3}	6.3×10^{-4}	$1.2\times10^{+4}$	$3.7\times10^{+4}$	$1.5\times10^{+4}$	$4.6\times10^{+4}$
Roll-on	2.8×10^{-3}	1.2×10^{-3}	$8.2\times10^{+3}$	$1.9\times10^{+4}$	$1.0\times10^{+4}$	$2.4\times10^{+4}$
Aerosol	1.1×10^{-4}	5.5×10^{-5}	$2.2\times10^{+5}$	$4.3\times10^{+5}$	$2.6\times10^{+5}$	$5.2\times10^{+5}$

Table 46

Margins of Safety (MOS): Inhalation Exposure from Hair Care/Skin Care Use by Consumer

Overall for Combined HC/SC Products	AUC (mg-hr/L/day)	MOS	
		LED_{10}	NOAEL
Women	6.3×10^{-4}	$3.7\times10^{+4}$	$4.5\times10^{+4}$
Men	4.3×10^{-4}	$5.4\times10^{+4}$	$6.6\times10^{+4}$

Table 47

Margins of Safety (MOS): Dermal Exposure from Hair Care/Skin Care Use by Consumer

Product	AUC		MOS			
			LED_{10}		NOAEL	
	Men	Women	Men	Women	Men	Women
Shampoo	8.7×10^{-7}	9.5×10^{-7}	$2.7\times10^{+7}$	$2.5\times10^{+7}$	$3.3\times10^{+7}$	$3.0\times10^{+7}$
Rinse-out conditioner	6.9×10^{-7}	7.3×10^{-7}	$3.4\times10^{+7}$	$3.2\times10^{+7}$	$4.1\times10^{+7}$	$3.9\times10^{+7}$
Leave-in conditioner	3.5×10^{-6}	3.6×10^{-6}	$6.8\times10^{+6}$	$6.5\times10^{+6}$	$8.2\times10^{+6}$	$7.9\times10^{+6}$
Hair spray	1.7×10^{-6}	2.7×10^{-6}	$1.4\times10^{+7}$	$8.6\times10^{+6}$	$1.6\times10^{+7}$	$1.0\times10^{+7}$
Cuticle coat	3.5×10^{-5}	4.6×10^{-5}	$6.7\times10^{+5}$	$5.1\times10^{+5}$	$8.2\times10^{+5}$	$6.2\times10^{+5}$
Brilliantine	1.6×10^{-5}	2.1×10^{-5}	$1.4\times10^{+6}$	$1.1\times10^{+6}$	$1.7\times10^{+6}$	$1.3\times10^{+6}$
Pomade	1.1×10^{-5}	1.4×10^{-5}	$2.1\times10^{+6}$	$1.6\times10^{+6}$	$2.6\times10^{+6}$	$2.0\times10^{+6}$
Spray shine	4.3×10^{-5}	6.8×10-5	$5.4\times10^{+5}$	$3.5\times10^{+5}$	$6.6\times10^{+5}$	$4.2\times10^{+5}$
Moisturizer	6.4×10^{-4}	8.3×10^{-4}	$3.7\times10^{+4}$	$2.8\times10^{+4}$	4.5×10+4	$3.4\times10^{+4}$
Foundation	N/A	8.9×10^{-5}	N/A	$2.6\times10^{+5}$	N/A	$3.2\times10^{+5}$
Hand/body lotion	4.5×10^{-5}	8.2×10^{-5}	$5.2\times10^{+5}$	$2.9\times10^{+5}$	$6.4\times10^{+5}$	$3.5\times10^{+5}$
Sunscreen	5.5×10^{-5}	7.1×10^{-5}	$4.3\times10^{+5}$	$3.3\times10^{+5}$	$5.2\times10^{+5}$	$4.0\times10^{+5}$
Undereye cover	N/A	5.0×10^{-5}	N/A	$4.7\times10^{+5}$	N/A	$5.7\times10^{+5}$
Lipstick (3 times a day 6 days a week)	N/A	1.2×10^{-5}	N/A	$1.9\times10^{+6}$	N/A	$2.3\times10^{+6}$
Lipstick (3 times a day, 5 days a week)	N/A	1.0×10^{-5}	N/A	$2.3\times10^{+6}$	N/A	$2.8\times10^{+6}$
After-shave gel	8.0×10^{-4}	N/A	$2.9\times10^{+4}$	N/A	$3.6\times10^{+4}$	N/A

Table 48

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

Residential	AUC (mg-hr/L/day)		MOS			
			LED_{10}		NOAEL	
	Male	Female	Male	Female	Male	Female
Adult (18-75)	2.2×10^{-5}	1.6×10^{-5}	$1.1\times10^{+6}$	$1.5\times10^{+6}$	$1.3\times10^{+6}$	$1.8\times10^{+6}$
Children						
Ages 1-2	8.9×10^{-6}	7.8×10^{-6}	$2.6\times10^{+6}$	$3.0\times10^{+6}$	$3.2\times10^{+6}$	$3.7\times10^{+6}$
Ages 3-5	1.0×10^{-5}	8.6×10^{-6}	$2.4\times10^{+6}$	$2.7\times10^{+6}$	$2.9\times10^{+6}$	$3.3\times10^{+6}$
Ages 6-8	1.2×10^{-5}	9.7×10^{-6}	$2.0\times10^{+6}$	$2.4\times10^{+6}$	$2.4\times10^{+6}$	$2.9\times10^{+6}$
Ages 9-11	1.4×10^{-5}	1.2×10^{-5}	$1.7\times10^{+6}$	$2.0\times10^{+6}$	$2.0\times10^{+6}$	$2.4\times10^{+6}$
Ages 12-14	1.7×10^{-5}	1.4×10^{-5}	$1.4\times10^{+6}$	$1.7\times10^{+6}$	$1.7\times10^{+6}$	$2.1\times10^{+6}$
Ages 15-17	2.0×10^{-5}	1.4×10^{-5}	$1.2\times10^{+6}$	$1.6\times10^{+6}$	$1.4\times10^{+6}$	$2.0\times10^{+6}$

Figure 1 Chemical structure of D_5.

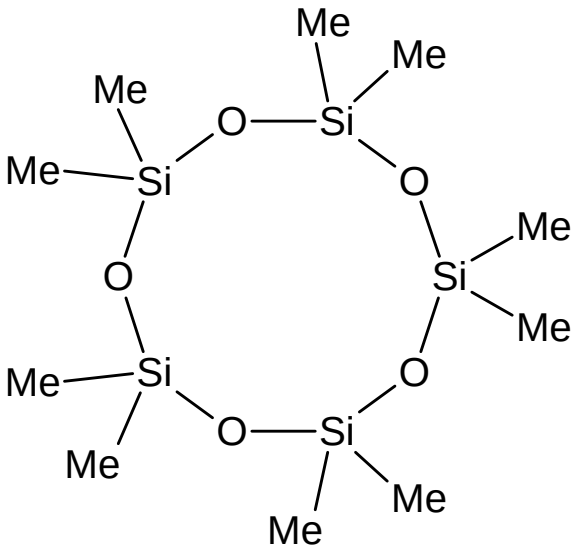
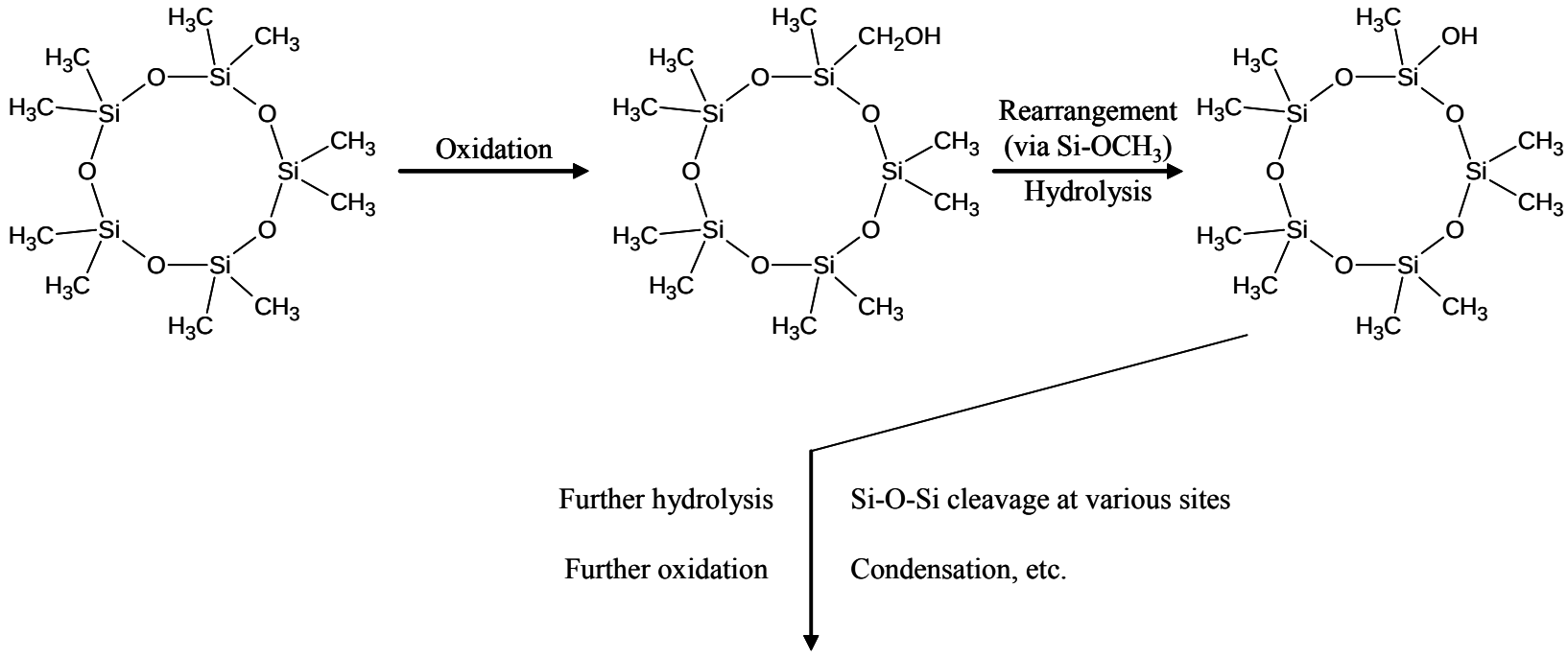


Figure 2 Possible pathways for the formation of the metabolites of D_5 in the Fischer 344 R



$MeSi(OH)_3$ + $Me_2Si(OH)_2$ + $HO\text{-}(SiMe_2O)_2\text{-}H$ + $HO\text{-}(SiMe_2O)_3\text{-}H$ + $MeSi(OH)_2\text{-}O\text{-}Si(OH)Me_2$

$Me_2Si(OH)_2\text{-}O\text{-}Si(OH)_2Me$ + $Me_2Si(OH)\text{-}O\text{-}Si(OH)_3$ + $MeSi(OH)_2\text{-}O\text{-}Si(OH)_3$