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Office of Pollution Prevention and Toxics  
U.S. Environmental Protection Agency  
401 M Street S.W.  
Washington, D.C. 20460  
Attur TSCA Sections 8(d)/8(e) FYI Submission

pdCN 8896000065

Re: 49 FR 46741 (November 28, 1984) [OPPT-84013, FRL-2725-1]  
TSCA Section 8(d) Health and Safety Data Reporting and  
Supplemental Submission to 8EHQ-0296-13585  
TSCA Section 8(e) Notification: Octamethylcyclotetrasiloxane

Dear Sir:

The enclosed information is submitted on behalf of Dow Corning Corporation, Midland, Michigan 48686-0994, on a For-Your-Information (FYI) basis as (1) a follow-up to submissions made concerning octamethylcyclotetrasiloxane (OMCTS), which chemical substance was the subject of a health and safety data rule issued under Section 8(d) of the Toxic Substances Control Act (TSCA) and with an effective date of December 28, 1984 and a sunset date of December 28, 1994, and (2) a supplemental submission to our TSCA Section 8(e) Notification of Substantial Risk of February 13, 1996 (8EHQ-0296-13585). The information presented in this submission was generated as part of our Siloxane Research Program. This program was the subject of a memorandum of understanding, dated April 9, 1996, between Dow Corning and EPA.

**Chemical Substance:**

556-67-2 Octamethylcyclotetrasiloxane

**Manufacturer:**

Dow Corning Corporation  
2200 West Salzburg Road  
Midland, Michigan 48686-0994



8EHQ-96-13585

**Title of Recently Completed Assessment:**

ESTIMATION OF MARGINS OF EXPOSURE: A PRELIMINARY RISK ASSESSMENT FOR OCTAMETHYLCYCLOTETRASILOXANE (D4) BASED ON REPRODUCTIVE TOXICITY STUDIES IN SPRAGUE-DAWLEY RATS

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Dow Corning Corporation  
1999-I0000-46358  
April 26, 1999

**Background:**

As part of the Siloxane Research Program, octamethylcyclotetrasiloxane (OMCTS, D4), which is widely used as an ingredient in some cosmetics and some other commercial and consumer products, was evaluated in a series of reproductive toxicity studies in Sprague-Dawley rats. A pair of initial range-finding studies were conducted in which male and female rats were exposed to OMCTS by the inhalation route, followed by other studies in which only females or only males were exposed. The initial studies were designed to determine appropriate exposure levels for use in a two-generation reproduction study, while subsequent studies were included to determine if the effects in Sprague-Dawley rats could be attributed to females only, males only, or to both males and females. Another study was conducted to provide insights as to the phase of the reproductive cycle that may be affected as well as insights into the possible mode of OMCTS action on the reproductive system in the Sprague-Dawley rat.

The objective of this evaluation was to combine the results of the reproductive toxicity studies with estimates of OMCTS intake for purposes of estimating risk to selected workers, consumers, and the general public. Since the Siloxane Research Program is a United States-based program and as such is subject to regulation under TSCA, this interim risk assessment was conducted according to United States Environmental Protection Agency (USEPA) guidelines for reproductive toxicity risk assessments.

**Executive Summary:**

A series of reproductive studies has provided consistent evidence that OMCTS caused decreases in mean litter size, numbers of pups born, and numbers of uterine implantation sites in the Sprague-Dawley rat. The smallest lower statistical confidence bound on the benchmark dose (BMDL) estimated from these data was 51 mg/kg/day (323 ppm). Human exposures either in the workplace, through consumer products, or in the general environment that result in estimates of intake of at least 100-fold lower than the BMDL, i.e., a margin of exposure (MOE) of 100 or greater, are not expected to cause any adverse reproductive effects in those populations. All MOEs calculated for the selected receptors were greater than 100 and with few exceptions were greater than 1000. When the impact of assumptions regarding dermal absorption and route equivalence is considered, all MOEs for consumer use products are greater than 1000 and, for many products, greater than 10,000. MOEs of even greater magnitude are expected when the species extrapolation uses the delivered dose at the target

tissue rather than estimates of intake across the biological barrier. MOE's may be further increased when the species- and strain-specific modes of action can be considered.

This risk assessment is preliminary and will be refined when an ongoing two generation reproductive study is completed. However, given the several major assumptions that result in overestimates of intake and the assumptions with regard to route and species extrapolation, these preliminary MOEs are more likely to increase than to decrease. Conclusions with regard to the lack of potential for risk to reproduction in populations exposed, as described in the exposure assessment, are likely to remain unchanged in the final risk assessment.

**Actions:**

This risk assessment is preliminary in that there is ongoing research designed to address areas of uncertainty. Research into comparative pharmacokinetics across routes of exposure (inhalation versus dermal) and across species that will provide estimates of target tissue dose is ongoing. Studies as to the putative mode of action of OMCTS in the Sprague-Dawley rat will provide insight into any strain specificity that may influence extrapolation of these results to human populations. Therefore, until the two-generation reproductive study and additional studies evaluating the potential mode of action are completed, this review of the reproductive toxicity and this risk assessment should be considered preliminary. A copy of the final risk assessment will be provided to the Agency on completion.

For purposes of health and safety data reporting under TSCA Section 8(d) and supplemental notification under TSCA Section 8(e), the general INTERNAL designation on the attached preliminary risk assessment is waived by Dow Corning.

If you require further information regarding this submission, please contact Dr. Rhys G. Daniels, Senior Regulatory Compliance Specialist, Regulatory Compliance Group, HERA Americas, at 517-496-4222 or at the address provided herein.

Sincerely,

  
Michael P. Hill  
Executive Director of  
Environmental, Health and Safety  
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TECHNICAL REPORT

**Report No:** 1999-10000-46358  
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**Date:** 26 April 1999  
**Title:** Estimation of Margins of Exposure: A Preliminary Risk Assessment for Octamethylcyclotetrasiloxane (D4) Based on Reproductive Toxicity Studies in Sprague Dawley Rats

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**Report No:** 1999-10000-46358

**Authors:** The K.S. Crump Group, Inc., ICF Kaiser

**Department:** Health & Environmental Sciences, Environmental

**Supervisor:**

**Location:** Midland Corporate, Michigan USA

**Date:** April 19, 1999

**Title:** Estimation of Margins of Exposure: a Preliminary Risk Assessment for Octamethylcyclotetrasiloxane (D4) Based on Reproductive Toxicity Studies in Sprague Dawley Rats

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## ABSTRACT

The purpose of this investigation was to combine the results of reproductive toxicity studies conducted using octamethylcyclotetrasiloxane (D4) with estimates of D4 intake to conduct a preliminary evaluation of the potential for reproductive toxicity to selected workers, consumers, and the general public. In these studies male and/or female Sprague-Dawley rats were exposed by whole body inhalation to D4 at concentrations ranging from 70 to 700 ppm (mass/volume) for 6 hours/day. The general protocol for each study was similar and included exposure for at least 28 or 70 days prior to mating with exposure for females continuing in some studies throughout gestation and lactation. The major findings were both qualitatively and quantitatively consistent across these studies. In the male crossover studies, no alterations in any parameter evaluated were found. The suggested increase in the number of pups born dead in the first male crossover study was not statistically significant when evaluated using litter-based statistical analyses nor was it present in the confirmatory male crossover study. The major findings noted in females exposed to D4 at 700 ppm were statistically significant treatment-related decreases in the number of corpora lutea, the number of uterine implantation sites, the total number of pups born, the mean live litter size, and the mean number of viable fetuses.

In the study selected as the critical study, female Sprague-Dawley rats were exposed to 0, 70, 300, 500, or 700 ppm D4 by whole body inhalation for 6 hours/day for 70 days prior to mating, with exposure continuing through PND 20 (except for the interval from GD 20 through PND 4). The incidence of decreased mean live litter size, decreased number of pups born, and decreased number of uterine implantation sites were selected as the critical endpoints for dose-response modeling using the Benchmark Dose (BMD) modeling approach. A benchmark calculation was performed for all endpoints for which a significant dose-related trend ( $p < 0.05$ ) was present. In parallel with these and other toxicity studies, comprehensive analyses of potential exposures to D4 were conducted. These exposure assessments provided estimates of average daily intake (ADI) by both the dermal and inhalation routes (and in the case of lipstick, by the oral route) for personal care product users; the oral route for antifoams in food products; and by the inhalation route for workers and the general public. Workers engaged in the production of skin care products had the highest estimated ADIs (0.26 and 0.20 mg/kg/day for women and men, respectively), while workers in the hair care products industry had the lowest ADIs (0.0013 and 0.0010 mg/kg/day for women and men, respectively) for the worker populations assessed. Consumer use of antiperspirants/deodorants (AP/Ds), in particular the roll-on or aerosol types, followed by the use of hand and body lotions provided the highest estimates of intake for all the consumer products evaluated. Estimated ADIs for AP/Ds ranged from 0.0719 and 0.0737 mg/kg/day for women and men using roll-on APs to 0.0033 and 0.0042 mg/kg/day for women and men using the solid type. For a hypothetical woman who used several products and worked in either antiperspirant or silicone product manufacturing, the estimated ADIs were 0.158 or 0.145 mg/kg/day, respectively. ADIs for persons exposed to D4 in food products were highest for children one year of age or younger (approximately 0.002 mg/kg/day) and lowest in the 14- to 18-year-old age group (0.0006 and 0.0007 mg/kg/day for men and women, respectively). Margins of Exposure (MOEs), which are the ratios of the lowest BMDL (51 mg/kg/day) to the estimated intake, were calculated for all the selected receptors. Human exposures either in the workplace, through consumer products, or in the general environment that result in estimates of intake at least 100-fold lower than the BMDL, i.e., a MOE of 100 or greater, are not expected to cause any adverse reproductive effects in those populations. All MOEs calculated for the selected receptors were greater than 100 and with few exceptions were greater than 1000. When the impact of assumptions regarding dermal absorption and route equivalence was considered, all MOEs for consumer use products were greater than 1000 and for many products, greater than 10,000. MOEs of even greater magnitude are expected when the species extrapolation uses the delivered dose at the target tissue rather than estimates of intake. MOEs may be further increased when the species- and strain-specific modes of action can be considered.

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## EXECUTIVE SUMMARY

As part of the Siloxane Research Program, octamethylcyclotetrasiloxane (D4), a cyclic tetramer of dimethylsiloxane widely used as an ingredient in some cosmetics and some other commercial and consumer products, was evaluated in a series of reproductive toxicity studies in Sprague-Dawley rats. Two initial range-finding studies were conducted in which male and female rats were exposed to D4 by the inhalation route (DCC 8305, DCC 8306), followed by other studies in which only females (DCC 8463, DCC 8620) or only males (DCC 8462, DCC 8601) were exposed. The initial studies were designed to determine appropriate exposure levels for use in a two-generation reproduction study, while subsequent studies were included to determine whether the effects in Sprague-Dawley rats could be attributed to females only, males only, or to both males and females. Another study (DCC 8620) was designed to provide insights as to the phase of the reproductive cycle that may be affected as well as insights into the possible mode of D4 action on the reproductive system in the Sprague-Dawley rat.

The purpose of this investigation was to combine the results of the reproductive toxicity studies with estimates of D4 intake to conduct a preliminary evaluation of the potential for reproductive toxicity to selected workers, consumers, and the general public. To accomplish this, a preliminary quantitative risk assessment was conducted that is consistent with United States Environmental Protection Agency (USEPA) guidelines for reproductive toxicity risk assessments (USEPA 1996). This approach was selected because the Siloxane Research Program is a United States-based program and as such is subject to TSCA regulations. It should be noted that the approach taken may not be exactly the same applied by other regulatory agencies in other parts of the world. For example, we have applied dose-response modeling to estimate a Benchmark Dose (discussed below), while European agencies would use the No Observed Adverse Effect Level (NOAEL) approach. The technical approach to this risk assessment consisted of the following steps

- A review of the reproductive toxicity studies to evaluate the statistical and toxicological significance of the results and to identify the critical study(ies) and endpoints to be used in dose-response modeling (*Hazard/Toxicity Assessment*).

- Characterization of exposure scenarios and estimation of D4 intake for selected receptors (i.e., worker, consumer, general public) and routes of exposure (i.e., dermal, inhalation, oral) (*Exposure Assessment*);
- Selection of the appropriate measure of exposure (dose-metric) associated with the observed effects that is relevant for extrapolation across species and quantification of that dose-response relationship (*Dose-Response Assessment*); and
- Calculation of Margins of Exposures (MOEs), which describe the ratio of the estimated no effect level, expressed as the No Observed Adverse Effect Level (NOAEL) or the Benchmark Dose (BMD), with the estimated intake for each receptor and route of exposure; an assessment of the impact of underlying assumptions and uncertainties on the MOEs; and a discussion of the relative magnitude of the MOE that is considered to be health protective (*Risk Characterization*).

This risk assessment is preliminary in that there is ongoing research designed to address areas of uncertainty. Research into comparative pharmacokinetics across routes of exposure (inhalation versus dermal) and across species that will provide estimates of target tissue dose is ongoing. Studies as to the putative mode of action of D4 in the Sprague-Dawley rat will provide insights into any strain specificity that may influence extrapolation of these results to human populations. Therefore, until the two-generation study and additional studies evaluating the potential mode of action are completed, this review of the reproductive toxicity and this risk assessment based on that review, as reported in this document and discussed briefly in the following paragraphs, should be considered preliminary.

### ***Hazard/Toxicity Assessment***

A series of reproductive toxicity studies was conducted in which male and/or female Sprague-Dawley rats were exposed by whole body inhalation to D4 at concentrations ranging from 70 to 700 ppm (mass/volume) for 6 hours/day. The general protocol for each study was similar and included exposure for at least 28 or 70 days prior to mating with exposure for females continuing in some studies throughout gestation and lactation (Table E-1).

**Table E-1**  
**Summary of Experimental Protocols for Reproductive Studies**  
**in Sprague-Dawley Rats Exposed by Whole Body Inhalation to D4**

Protocol	8305	8306	8463	8620 (a)	8462	8601
Group size	20/sex/group	22/sex/group	22 females/ group	24 females/ group	22 males/ group	40 males/group
D4 concentrations (6 hrs/day, 7 days/week)	0, 70, 700 ppm (b)	0, 0, 700 ppm	0, 70, 300, 500, 700 ppm	0, 70, 300, 500, 700 ppm	0, 70, 300, 500, 700 ppm	0, 500, 700 ppm
Pre-mating exposure	28 days	28 days	70 days	28 days	70 days	70 days
Exposure regimen	Through mating, gestation, and lactation until PND 21, except for GD 21 to PND 4	Through mating and gestation through GD 20	Through mating, gestation, and lactation until PND 20, except for GD 20 to PND 4	Through mating through GD 19	Through mating	Through mating
Direct F <sub>1</sub> exposure	PND 21 through 28	None	PND 21 through 28	None	None	None
F <sub>0</sub> sacrifice	Males: After mating Females: PND 21	Males: After mating Females: PND 4	PND 21	GD 20	After mating or on PND 4	5 weeks after mating
F <sub>1</sub> sacrifice	PND 28	PND 4	PND 21 or 28	GD 20	PND 4	PND 21

PND Post-Natal Day

GD Gestation Day

(a) Overall Phase

(b) Doses are expressed as mass/volume

The major findings were both qualitatively and quantitatively consistent across these studies (Table E-2). There were minimal clinical signs of toxicity in all studies. No gross treatment-related findings were noted in either F<sub>0</sub> or F<sub>1</sub> males or females examined. With the exception of an increase in liver weights at 700 ppm (DCC 8463, 8462, 8601), no treatment-related increases in organ weights or organ histopathology were found in those studies in which these endpoints were evaluated.

Table E-2  
Summary of Major Findings in Sprague-Dawley Male and Female Rats Exposed to D4

PARAMETER	DCC 8305	DCC 8306	DCC 8463	DCC 8620	DCC 8462	DCC 8601
<b>Reproductive Parameters</b>						
Interval between paring and mating	NS (a).	NS	NS	NS	NS	NS
Male mating index	NS	NS	NS	NS	NS	NS
Female mating index	NS	NS	NS	NS	NS	NS
Gestation length	NS	Increased (b) (700 ppm)	NS	NS	NS	NS
Parturition duration	NS	NS	NS	NS	NS	NS
Number of corpora lutea	NE (c)	Decreased (700 ppm)	NE	Decreased (500 ppm)	NE	NE
Number of implantation						
PND 21	Decreased (700 ppm)	--	Decreased (700 ppm)	--	NS	NS
PND 4	--	Decreased (700 ppm)	--	--	--	--
GD 20	--	--	--	Decreased (500 ppm)	--	--
<b>Litter Effects Parameters</b>						
Number of total pups born	Decreased (700 ppm)	Decreased (700 ppm)	Decreased (700 ppm)	Decreased (500 ppm)	NS	NS
Number of pups born dead	NS	NS	NS	NE	NS (d)	NS
Mean live litter size	Decreased (700 ppm)	Decreased (700 ppm)	Decreased (700 ppm)	NE	NS	NS
Mean number of viable fetuses	NE	NE	NE	Decreased (500 ppm)	NE	NE
Pup viability indices (e)						
PND 1	NS	NS	NS	NE	NS	NS
PND 4	NS	NS	NS	NE	NS	NS

- (a) NS = not statistically significant by any statistical test.  
 (b) Indicates a statistically significant increase or decrease using relevant statistical test (Lowest Observed Adverse Effect Level - LOAEL)  
 (c) NE = not examined  
 (d) NS = not statistically significant using litter-based test (Jonckheere, Kruskal-Wallis), but significant trend using PHAT trend test.  
 (e) Fetuses counted following laparohysterectomy on GD 20

In all studies, except DCC 8306, exposure to D4 at any concentration tested did not result in any treatment-related alterations in any of the reproductive parameters measured to include: the interval between pairing and mating; mating and fertility indices, gestation length, or parturition duration. In study DCC 8306, the gestation length was statistically significantly increased compared to the concurrent control (21.7 days in the control and 22.3 days in the treatment group); however, the gestation length in the treated group was within the historical control range for the laboratory (21.5 to 22.8 days). Exposure to D4 did not have any treatment-related effects on pup viability as measured by the number of pups born dead or the pup viability indices on postnatal days (PNDs) 1 and 4.

The major findings noted in females exposed to D4 at 700 ppm in studies DCC 8305, DCC 8306, and DCC 8463 and at 500 and 700 ppm in study DCC 8620 (Overall Phase - see below) were statistically significant treatment-related decreases in:

- the number of corpora lutea (evaluated only in 8306 and 8620);
- the number of uterine implantation sites (8305, 8306, 8463, 8620);
- the total number of pups born (8305, 8306, 8463);
- the mean live litter size (8305, 8306, 8463); and
- the mean number of viable fetuses (evaluated only in 8620).

The mean live litter size was consistently 60% to 70% of control values. However, while the mean live litter size was decreased in the higher exposure groups only, the percentage of live births of the total number born was comparable to control values.

No effects on the number of uterine implantation sites, the litter size, or the mean live litter size were found in either of the male crossover studies. In the first male crossover study (DCC 8462), the suggested increase in the number of pups born dead was not statistically significant when evaluated using litter-based statistical analyses nor was it present in the confirmatory male crossover study (DCC 8601). Exposure to D4 did not affect sperm production, mobility, or morphology nor did it result in either weight changes or histopathology of male accessory organs. It can be concluded that the effects on litter size are not male-mediated effects.

In addition to the studies described above in which animals were exposed to D4 through pre-mating, mating, gestation, and, in all but DCC 8306 or 8620, through lactation, a study in which female rats were dosed during selected phases of the reproductive cycle was conducted. This study was designed to identify portions of the reproductive cycle where D4 may be exerting its effect on litter size in Sprague-Dawley rats. Knowledge of the timing of D4 action may provide insights into the potential mode of action of D4 on litter size in the Sprague-Dawley. In the phased study, four groups of female rats were exposed to D4 by whole body inhalation for 6 hours/day according to the following schedule:

- *Overall Phase.* Groups of 24 female Sprague-Dawley rats were exposed to D4 at target concentrations of 70, 300, 500, or 700 ppm (actual mean concentrations were 72, 301, 503, and 698 ppm) beginning at least 28 days prior to mating and continuing through gestation day (GD) 19;
- *Ovarian Phase.* Sixty female rats were exposed at 700 ppm beginning 31 days prior to mating and stopping 3 days prior to mating;
- *Fertilization Phase.* Sixty female rats were exposed at 700 ppm 3 days prior to mating and continuing through GD 3; and
- *Implantation Phase.* One group of 24 females was exposed at 700 ppm from GD 2 through GD 5.

In the Overall Phase, the following were the major observations: 1) a reduction in the number of corpora lutea (500 and 700 ppm exposure groups); 2) a reduction in the number of uterine implantation sites and viable fetuses (500 and 700 ppm exposure groups); 3) an increase in the mean pre-implantation loss (500 and 700 ppm exposure groups); and 4) an increased post-implantation loss (700 ppm exposure group only). In the Fertilization Phase, the number of corpora lutea, uterine implantation sites, and viable fetuses were reduced in the 700 ppm exposure group, the only dose tested, while the mean pre-implantation and post-implantation losses were increased. No significant effects were noted on the number of corpora lutea or indices of intrauterine survival in females exposed at 700 ppm in the Ovarian Phase and Implantation Phase.

The effects on corpora lutea and intrauterine survival were similar for the Overall Phase in which exposure began 28 days pre-mating and continued through GD 19 and for the Fertilization

Phase in which exposure began 3 days pre-mating and continued through GD 3. No effects were noted if exposure began after mating (Implantation Phase) or terminated 3 days prior to mating (Ovarian Phase), indicating either a lack of effect on earlier biological processes or a reversibility of a potential effect. Additional study may be required to assess fully the biological impact of these findings both for dose-response modeling and for species extrapolation to assess the potential for toxicity in humans.

### *Exposure Assessment*

In parallel with these and other toxicity studies, comprehensive analyses of potential exposures to D4 have been conducted [Everest Consulting Associates (ECA) (1997); DCC (1998a)]. These analyses evaluated the production, formulation, and use of D4 in the United States and estimated the potential exposure (intake) for:

- persons who work in the production of D4, in the formulation of this material into personal care products, 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;
- consumers who may be exposed to silicone antifoams used in food processing; 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 D4 released to the environment during manufacturing activities.

This exposure assessment provided estimates of intake by both the dermal and inhalation routes (and in the case of lipstick, by the oral route) for personal care product users; the oral route for antifoams in food products; and by the inhalation route for workers and the general public. The relative importance of these pathways differs for each exposure group. The dermal pathway accounts for the majority of consumer exposure, while the inhalation pathway is the most significant contributor to worker exposure and exposure to the general public. The oral pathway is the only pathway of exposure for D4 in silicone antifoams.

The estimates of intake reported in ECA (1997) and DCC (1998a) were based on a comprehensive review of the workplace for several exposure scenarios, as well as a review of the amount of D4 in selected consumer products and the use patterns for those consumer products

The information for workplace activities and usage patterns was based on industry-supplied data and represents a compilation of data across companies and products. As such, some unifying, and in some cases conservative, assumptions were made to provide generic exposure scenarios that characterized these exposures to the selected target populations.

Workers engaged in the production of SC products had the highest estimated average daily intakes (ADIs) (0.26 and 0.20 mg/kg/day for women and men, respectively), while workers in the HC products industry had the lowest ADIs (0.0013 and 0.0010 mg/kg/day for women and men, respectively) for the worker populations assessed (Table E-3a). In the ECA study (1997), workers were assumed to be exposed primarily by the inhalation route with limited dermal exposure. Therefore, the estimated ADIs shown in Table E-3a were based on the inhalation route only. ECA (1997) crafted two dermal exposure scenarios to estimate the amount of dermal absorption, under the assumption that, while infrequently, good manufacturing practices (GMPs) may not be followed. Under those scenarios, the dermal pathway contributed less than 1% to the total estimated exposure. The inhalation route of exposure was the only relevant route for the general public. Estimated ADIs for the general public were 0.0046 and 0.0036 mg/kg/day for women and men, respectively (Table E-3a).

The dermal route was the primary route of exposure for all consumer personal care products. Consumer use of AP/Ds, in particular the roll-on or aerosol types, followed by the use of hand and body lotions provided the highest estimates of intake for all the consumer products evaluated (Table E-3b). Estimated ADIs for AP/Ds ranged from 0.0719 and 0.0737 mg/kg/day for women and men using roll-on APs to 0.0033 and 0.0042 mg/kg/day for women and men using the solid type. These estimates included the contribution from both the dermal and inhalation pathways. Since it was assumed that 100% of the applied amount was retained and available for absorption by the dermal route, inclusion of an inhalation pathway, in which it was assumed that a percentage of that applied amount volatilized and was inhaled, results in an overestimation of intake. The magnitude of that overestimation depends on the amount and rate of volatilization.

**Table E-3a**  
**Estimates of ADIs (mg/kg/day) for Selected Populations Exposed to D4:**  
**Workers and the General Public**

Population	Women	Men
<b>Workers (a)</b>		
Antiperspirants	0.035	0.027
Skin care products	0.26	0.20
Hair care products	0.0013	0.0010
Silicone workers	0.022	0.017
Beauticians/Barbers	0.0071	0.0055
<b>General Public (a)</b>	0.0046	0.0036

(a) Inhalation route of exposure only.

**Table E-3b**  
**Estimates of ADIs (mg/kg/day) for Selected Populations Exposed to D4:**  
**Consumers Exposed Using Personal Care Products**

Population	Women	Men
<b>Consumers: Antiperspirants/Deodorants (a)</b>		
Solid	0.0033	0.0042
Roll-on	0.0719	0.0737
Aerosol	0.0329	0.0280
<b>Consumers: Skin Care Products (b,c)</b>		
Hand and body lotion	0.030	--
Lipstick	0.011	--
Nail care	0.00004	--
<b>Consumers: Hair Care Products (b,c)</b>		
Spray shine	0.0134	0.009
Cuticle coat	0.0095	0.0076
Shampoo	0.0002	0.00017

- (a) Dermal and inhalation routes of exposure.  
 (b) Represents the products with the two highest estimated intake and product with the lowest estimate intake for the group of products evaluated.  
 (c) Dermal route of exposure only.

Estimates of ADIs for HC/SC products were based on only the contribution from dermal exposure, which was assumed to be the primary route of exposure to consumers. Of the products evaluated, use of hand and body lotion resulted in the highest estimated ADIs (Table E-3b). Again, it was assumed that for most products 100% of the deposited amount was retained and available for absorption by the dermal route.

In the above estimates, intake was estimated separately for each product or type of exposure. However, it is recognized that an individual may use several products on a regular basis. Therefore, a hypothetical receptor who used several products was considered (Table E-3c). This receptor was assumed to be a woman who used roll-on antiperspirant, shampoo, leave-in conditioner, lipstick, hand and body lotion, and who worked in a plant manufacturing antiperspirants or silicone products. The total ADI for this receptor would be 0.158 or 0.145 mg/kg/day for a woman using these products and working in antiperspirant or silicone manufacturing, respectively.

**Table E-3c**  
**Estimate of ADI (mg/kg/day) for a Woman Who Used Multiple Products**

Source	ADI
Antiperspirant product worker or a silicone worker	0.035 or 0.022
Roll-on antiperspirant	0.719
Hand and body lotion	0.30
Lipstick	0.011
Moisturizer	0.0097
Leave-in conditioner	0.00084
Shampoo	0.0002
<b>TOTAL</b>	<b>0.158 or 0.145</b>

Persons may also be exposed to D4 by way of ingestion of food products processed using silicone antifoams (DCC 1998a). Estimates of exposure to D4 were based on the maximum allowable levels of silicone antifoams in food and assumed that 50% of all food ingested was processed with silicone antifoams. ADIs for this exposure were highest for children one year of age or younger (approximately 0.002 mg/kg/day) and lowest in the 14- to 18-year-old age group (0.0006 and 0.0007 mg/kg/day for men and women, respectively) (Table E-3d).

**Table E-3d**  
**Estimates of ADIs (mg/kg/day) for Selected Populations:**  
**Consumers Exposed to D4 in Food Products Processed with Silicone Antifoams**

Age (years)	Women	Men
<1	0.002063	0.001907
1-6	0.001630	0.001507
6-14	0.000844	0.000823
14-18	0.000723	0.000594
18-45	0.000841	0.000705
45-75	0.000699	0.000603

It is important to note that this exposure assessment provides estimates of *intake*, that is, the amount of material assumed to be absorbed following dermal application or oral or inhalation exposure. This exposure assessment does not consider or provide estimates of delivered *dose* of the active moiety (e.g., parent D4 or a metabolite) at the target tissue. Differences in the actual bioavailability and resulting dose to the target tissue due to route-specific (dermal and oral versus inhalation routes) delivery or species-specific metabolic differences were not considered.

#### *Dose-Response Assessment*

The dose-response assessment step in this preliminary risk assessment consisted of the following:

- Selection of the critical study and critical endpoints from that study to be used in dose-response modeling;
- Conversion of the applied dose (in ppm) to the appropriate dose-metric that can be used to extrapolate across species and routes of exposure and to provide estimates of intake for each of the selected receptors, products/activities, and routes of exposure; and
- Characterization of the dose-response relationship for the selected endpoints using the Benchmark model to estimate both the maximum likelihood estimate of the Benchmark Dose (BMD) and the 95% lower bound on that dose (BMDL).

The female crossover study (DCC 8463) was selected as the critical study. In this study, female Sprague-Dawley rats were exposed to 0, 70, 300, 500, or 700 ppm D4 by whole body

inhalation for 6 hours/day for 70 days prior to mating, with exposure continuing through PND 20 (except for the interval from GD 20 through PND 4). The incidence of decreased mean live litter size, decreased number of pups born, and decreased number of uterine implantation sites were selected as the critical endpoints for dose-response modeling.

The two range-finding studies (DCC 8305 and 8306) and the phased-female study (DCC 8620) provided supporting evidence for the findings reported in the female crossover study (DCC 8463). The range-finding studies were not selected for dose-response modeling because of the fewer number of doses tested (only 70 and 700 ppm in DCC 8305 and only 700 ppm in DCC 8306). The phased-female study was intended to provide insights into the phase of the reproductive cycle in the Sprague-Dawley rats during which D4 or a metabolite of D4 may be acting. In the phased-female study, only the Overall Phase segment exposed groups of animals to more than one concentration of D4, and the results were qualitatively and quantitatively similar to those reported in DCC 54041, the female crossover study.

As an alternative to the NOAEL, a benchmark calculation was performed for all endpoints for which a significant dose-related trend ( $p < 0.05$ ) was present. A BMD is a dose (or exposure) that corresponds to a specified level of response called the benchmark risk or benchmark response (BMR). A BMD is calculated by fitting a mathematical dose-response model to dose-response data. A lower statistical confidence bound on the BMD, termed the BMDL, has been proposed as an alternative to the NOAEL in determining acceptable human intakes of xenobiotics (Crump 1984, 1995).

Experimental NOAELs and BMDLs calculated are presented in Table E-4. Experimental NOAELs were 500 ppm for each endpoint evaluated. The BMDLs ranged from 323 to 390 ppm, or when expressed as an intake, from approximately 51 to 61 mg/kg/day. A BMDL of 51 mg/kg/day was selected for use in the calculation of the MOEs.

**Table E-4**  
**Results of Benchmark Dose-Response Analysis**  
**of Statistically Significant Endpoints from Study DCC 8463**

Endpoint	Experimental NOAEL (ppm)	Benchmark Doses in mg/kg/day (ppm)	
		BMD	BMDL
Total live births	500	83.2 (529)	61.2 (390)
Total number born (litter size)	500	82.5 (525)	60.2 (383)
Total implants	500	81.9 (521)	50.8 (323)

***Risk Characterization***

MOEs, which are the ratios of the BMDL to the estimated intake, were calculated for all the selected receptors. The MOEs for all of the worker populations as well as the three categories of AP/Ds evaluated are presented in Tables E-5a to E-5d. For both the HC/SC products, only the two products with the highest and the one product with the lowest estimates of D4 intake, and consequently, the largest and smallest MOEs for each category are reported in Table E-5. All MOEs were greater than 100, and with few exceptions, were greater than 1000.

A MOE of a specified magnitude indicates that exposure at the corresponding estimated intake level or below is not expected to result in adverse effects in populations so exposed. A MOE of 100 is typically considered of sufficient magnitude when the basis of the BMDL is animal data (USEPA 1994). A MOE of 100 indicates that the estimated intake is 100 times lower than the BMDL. The components of the MOE can be thought of as the typical factors of 10 for interspecies extrapolation (from animals to humans) and a factor of 10 for intrahuman variability, resulting in a MOE of 100. It could be argued, since this is a preliminary risk assessment, that applying an additional modifying factor of 3, because the two-generation study results are not yet available, would be prudent, thereby resulting in a MOE of 300. If only the data from the reproductive toxicity study used as the basis for the BMDL (DCC 8463) were considered and if it were assumed that the assumptions and parameter values used in the preliminary exposure assessment were correct, then a MOE of between 100 and 300 would be deemed acceptable.

As stated, at a MOE of 100, the estimated D4 intakes for all workers, the general public, and consumer product users evaluated are well below levels expected to be health protective

(Tables E-5a to E-5d). For those receptors with a MOE greater than 100 but less than 300, a closer look at the underlying assumptions used to develop those scenarios would be warranted. Only workers in the category designated as workers in the skin care products industry fell into that category.

**Table E-5a**  
**Estimates of MOE for Selected Populations Exposed to D4:**  
**Workers and the General Public**

Population	Women	Men
<b>Workers (a)</b>		
Antiperspirants	1457	1889
Skin care products	196	255
Hair care products	39231	51000
Silicone workers	2318	3000
Beauticians/Barbers	7186	9273
<b>General Public (a)</b>	11087	14167

(a) Inhalation route of exposure only.

**Table E-5b**  
**Estimates of MOE for Selected Populations Exposed to D4:**  
**Consumers - Personal Care Products**

Population	Women	Men
<b>Consumers: Antiperspirants/Deodorants (a)</b>		
Solid	15464	12232
Roll-on	709	692
Aerosol	1551	1821
<b>Consumers: Skin Care Products (b,c)</b>		
Hand and body lotion	1677	--
Lipstick	4602	--
Nail care	1436094	--
<b>Consumers: Hair Care Products (b,c)</b>		
Spray shine	3812	5655
Cuticle coat	5355	6746
Shampoo	251687	297727

- (a) Dermal and inhalation routes of exposure.
- (b) Represents the products with the two highest estimated MOEs and product with the lowest estimated MOE for the group of products evaluated.
- (c) Dermal route of exposure only.

**Table E-5c**  
**Estimate of MOE for a Woman Who Used Multiple Products**

Exposure Routes	MOE
Antiperspirant or silicone manufacturing worker who uses roll-on antiperspirant, hand and body lotion, moisturizer, lipstick, conditioner, and shampoo	323 or 352

**Table E-5d**  
**Estimates of MOE for Selected Populations Exposed to D4:  
Consumers - Silicone Antifoams in Food Processing**

Age (years)	Women	Men
<1	24720	26738
1-6	31291	33833
6-14	60394	61942
14-18	70571	85853
18-45	60612	72335
45-75	72966	84566

However, determination of the magnitude of the MOE considered adequate and health-protective should be based on a weight-of-evidence evaluation of all of the data and should consider the uncertainties (and in some cases, variability) inherent in either the extrapolation to the target population (e.g., consideration of species- or route-specific differences) or in the estimate of intake levels (e.g., consideration of underlying assumptions and parameter values). In each step in the calculation of each MOE, conservative, health-protective assumptions were made. Some of these assumptions are based on current practices in risk assessment, while other assumptions are based on preliminary data, e.g., with regard to dermal absorption. Refinement of these assumptions may lead to lower estimates of delivered dose to the target species and, hence, larger estimated MOEs for each scenario. The key considerations can be summarized as follows.

*Uncertainty due to route extrapolation*

A major source of uncertainty is the assumption of equivalent intake across routes of exposure. The air concentrations used in the whole body inhalation exposure in Sprague-Dawley rats in the reproductive toxicity study were converted to estimates of intake, expressed in

mg/kg/day in rats, which were subsequently used in the dose-response modeling to provide the BMDL. As described in the ECA (1997) exposure assessment, estimates of D4 intake, expressed in mg/kg/day, were calculated for the dermal route of exposure for the selected scenarios. A major assumption inherent in the calculation of MOEs is that once D4 crosses the initial biological barrier, i.e., the lung for inhalation exposure or the skin for the dermal exposure route, then delivery to the target tissue and hence the biologically relevant dose at the target tissue is independent of initial route of exposure.

Recent pharmacokinetic experiments and pharmacokinetic modeling have demonstrated that such an assumption greatly overestimates the delivered dose of D4 by the dermal route compared to the inhalation route of exposure (DCC 1998b). When absorbed through the lungs, D4 enters the arterial systemic circulation; where it is distributed throughout the body to potentially all organ systems. When absorbed by the dermal route, D4 enters the venous circulation, which moves directly to the heart and lungs, where the majority of D4 is then exhaled prior to being available systemically. The delivered dose to the target tissue is expected to be considerably less for an equivalent intake (amount that crosses the initial biological barrier) by the dermal route than the inhalation or oral routes of exposure.

A series of studies was conducted and a physiologically based pharmacokinetic (PBPK) model was constructed to evaluate the magnitude of that difference. As described more fully in the text, D4 dermal absorption was measured in Sprague-Dawley rats in which neat D4 was applied for 6 hours under an occluded dressing (DCC 1998b). The total amount absorbed and the amount excreted in expired air, urine, and feces were used to estimate the D4 body burden and to compare this body burden to that achieved following a 6-hour inhalation exposure at 700 ppm. The PBPK model developed using these and other data predicted that the area under the curve (AUC) of free D4 in blood for the 6-hour, occluded dermal exposure would be 60-fold lower than the AUC for free D4 following a 6-hour inhalation exposure at 700 ppm. Since absorption is considerably greater for rat skin than human skin, and since human skin would not be occluded, the 60-fold factor is likely to be an underestimate of the difference in delivered dose for different routes of exposure. However, even at a 60-fold difference, the MOEs as reported in Table E-5 would be 60 times greater. In such a case, all MOEs for consumer products would be greater than 1000 and most greater than 10,000.

\*

### *Uncertainties Due to Strain and Species Specificity*

One of the underlying assumptions in risk assessment is that animals and humans are equally sensitive in terms of risk when the dose is measured in the same unit for both species, i.e., the delivered dose to the target tissue. Two major considerations are inherent in this assumption. One assumption is similar in concept as discussed above for route-to-route extrapolation and presumes that for the same intake via the same route of exposure, the delivered dose to the target tissue is equivalent in humans and the animal model. Preliminary pharmacokinetic and metabolism studies indicate that not only would the metabolism and hence availability of D4 at the target tissue be different for rats and humans, but that this availability may be strain-dependent and be different between the Sprague-Dawley rat and the Fischer 344 rat. This suggests that prior to any dose-response modeling, the dose-metric should be the human equivalent dose to the target tissue rather than the estimated intake for the rat model. The MOEs should change in that event; however, the magnitude of that change will be assessed following completion of pharmacokinetic studies and PBPK modeling.

The second major consideration is the underlying assumption of species extrapolation in that, even when expressed as a human equivalent target dose, the human is as sensitive as the rodent and, therefore, in the absence of data to the contrary, it presumes the same mode of action in the human and the rodent. This currently is a major area of uncertainty.

### *Conclusions*

The series of reproductive studies has provided consistent evidence that D4 caused decreases in mean live litter size, numbers of pups born, and numbers of uterine implantation sites in the Sprague-Dawley rat. The smallest BMDL estimated from these data was 51 mg/kg/day (323 ppm). Human exposures either in the workplace, through consumer products, or in the general environment that result in estimates of intake at least 100-fold lower than the BMDL, i.e., a MOE of 100 or greater, are not expected to cause any adverse reproductive effects in those populations. All MOEs calculated for the selected receptors were greater than 100 and with few exceptions were greater than 1000. When the impact of assumptions regarding dermal absorption and route equivalence is considered, all MOEs for consumer use products are greater than 1000 and for many products, greater than 10,000. MOEs of even greater magnitude are expected when

the species extrapolation uses the delivered dose at the target tissue rather than estimates of intake across the biological barrier. MOEs may be further increased when the species- and strain-specific modes of action can be considered.

This risk assessment is considered preliminary and will be refined when the two-generation reproductive toxicity study is completed. However, given the several major assumptions that result in overestimates of intake and the assumptions with regard to route and species extrapolation, these preliminary MOEs are more likely to increase than to decrease. Conclusions with regard to the lack of potential for adverse reproductive effects in populations exposed, as described in the exposure assessment, are likely to remain unchanged in the final risk assessment.

## 1.0 INTRODUCTION

As part of the Siloxane Research Program, octamethylcyclotetrasiloxane (D4), a cyclic tetramer of dimethylsiloxane widely used as an ingredient in some cosmetics and other consumer products, was evaluated in a series of reproductive toxicity studies in Sprague-Dawley rats. Two initial range-finding studies were conducted in which male and female rats were exposed to D4 by the inhalation route (DCC 8305, DCC 8306), followed by other studies in which only females (DCC 8463, DCC 8620) or only males (DCC 8462, DCC 8601) were exposed. The initial studies were designed to determine appropriate exposure levels for use in a two-generation reproduction study, while subsequent studies were included to identify the affected sex in the  $F_0$ , to provide insights as to the phase of the reproductive cycle that may be affected, as well as insights into the possible mode of D4 action on the reproductive system in the Sprague-Dawley rat.

In parallel with these and other toxicity studies, a comprehensive analysis of the potential for exposure to D4 has been conducted [Everest Consulting Associates (ECA) 1997]. This analysis evaluated the production, formulation, and use of D4 in the United States and estimated the potential exposure (intake) for:

- persons who work in the manufacture of D4 and personal care products containing D4;
- consumers who use these personal care products, including antiperspirants/deodorants (AP/Ds) and hair care/skin care (HC/SC) products;
- consumers who may be exposed to silicone antifoams used in food processing; and
- the general public living in the vicinity of a plant that produces or processes these materials and who may be exposed to D4 released to the environment.

The purpose of this interim risk assessment was to combine the results of the rodent reproductive toxicity studies with the estimates of exposure in order to conduct a preliminary evaluation of the potential for reproductive toxicity to selected workers, consumers, and the general public who may be exposed to D4 either in the workplace or through the use of consumer products containing D4. To accomplish this, a quantitative risk assessment was conducted that is consistent with USEPA guidelines for reproductive toxicity risk assessments (USEPA 1996)

Risk 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 preliminary risk assessment for D4 consisted of the following steps:

- A review of the rat reproductive toxicity studies and other supporting data to evaluate the statistical and toxicological significance of the results and to identify the critical study(ies) and endpoints to be used in dose-response modeling (*Hazard/Toxicity Assessment*);
- Characterization of exposure scenarios and estimation of D4 intake for the selected receptors and modes of exposure (i.e., worker, consumer, general public) (*Exposure Assessment*);
- Selection of the appropriate measure of exposure (dose-metric) associated with the observed effects that is relevant for extrapolation across species and quantifying that dose-response relationship (*Dose-Response Assessment*); and
- Calculation of MOEs, which describe the ratio of the estimated no effect level, expressed as the NOAEL or the Benchmark Dose (BMD), with the estimated intake for each receptor and route of exposure (*Risk Characterization*).

The relative magnitude of these MOEs 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 is an integral part of any risk assessment. Therefore, 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 the risk assessment were identified, and, where possible, the impact on these assessments was quantified.

This risk assessment is preliminary in that there is ongoing research designed to address areas of uncertainty. Continuing research into comparative pharmacokinetics across routes of exposure (inhalation versus dermal) and species that may influence the target tissue dose is ongoing. Studies as to the putative mode of action of D4 in the Sprague-Dawley rat will provide insights into any strain specificity that may influence extrapolation of these results to human populations.

## 2.0 HAZARD/TOXICITY ASSESSMENT

D4 was evaluated in a series of reproductive toxicity studies in Sprague-Dawley rats in which males and females were exposed to D4 by the inhalation route (DCC 8305, DCC 8306), followed by other studies in which only females (DCC 8463, DCC 8620) or only males (DCC 8462, DCC 8601) were exposed. Exposure concentrations to D4 in these studies ranged from 70 to 700 ppm (all exposure concentrations are measures of mass/volume, not mass/mass). A review of these studies was conducted, as described in the following sections. The objectives of this review were to evaluate the effects of D4 on the reproductive function in the Sprague-Dawley rat, and if present, select the critical study and critical effects. Once the critical study was selected, then effects that were significantly increased and considered to be treatment-related in that study were retained for dose-response analysis (Section 4.0).

D4 is currently being evaluated in a two-generation reproduction study and other toxicological studies. Consequently, this Hazard/Toxicity Assessment is preliminary. When studies on the pharmacokinetics and potential mode of action of D4 in the Sprague-Dawley rat are completed, then the toxicological significance of these data can also be considered. The relevance of these data to human health and the applicability of using these data to extrapolate quantitatively in a human health risk assessment can then be assessed. These and other toxicological data for D4 can provide an initial basis to assess the uncertainties inherent in the use of rodent reproductive toxicity data in risk assessment, in particular as it affects the conversion of an animal-specific NOAEL or BMD to a human equivalent.

### 2.1 Male and Female Treatment Studies

Two range-finding studies were conducted in male and female Sprague-Dawley rats exposed to D4 by whole body inhalation. The initial study (DCC 8305) was conducted to assess the appropriate range of exposure levels to be used in a two-generation reproduction study. The second study (DCC 8306) was conducted to confirm the results found in the first study.

This preliminary review of the reproductive toxicity data discussed in this section and in subsequent sections focused more on statistical criteria than on toxicological relevance. In addition to the statistical tests conducted by the testing laboratory, nonparametric statistical tests

for dose-related trends were applied using the litter as the basic statistical unit. Litter-specific tests present significant advantages over using the fetus as the sampling unit when litter-specific effects are present. Moreover, litter-based statistics for certain endpoints were called for by the applicable guidelines. The nonparametric analysis of variance test, Kruskal-Wallis (Kruskal and Wallis 1952), was applied. In addition, the Jonckheere trend test (Hollander and Wolfe 1973) was applied to count data (e.g., on the total number of litter births in each litter), while the PHAT permutation test (Crump et al. 1991) was applied to data expressed as a ratio (e.g., the number of live births per total births). The PHAT test uses the same test statistic as the Cochran-Armitage trend test, but evaluates statistical significance by a permutation approach that uses the litter as the basic unit rather than the fetus. The results of statistical analyses reported in the text are those considered relevant for the endpoints under evaluation, as indicated. The data used for these analyses are discussed in the following sections.

#### 2.1.1 DCC Study 8305

In the first range-finding study, DCC 8305, groups of 20  $F_0$  male and 20  $F_0$  female Sprague-Dawley rats were exposed to vapor concentrations of 70 or 700 ppm of D4 via whole body inhalation. A third group served as the control and was exposed to filtered air. The animals were exposed 6 hours/day, 7 days/week, for 28 days prior to mating with exposure continuing in  $F_0$  males until necropsy at the end of the mating period. Exposure to  $F_0$  females continued through mating, gestation, and until PND 21, with the exception of the interval from GD 21 through PND 4. The interruption of female dosing in the periparturition interval was done to prevent the delivery of pups in the inhalation chamber. Some weanling offspring were exposed directly via inhalation for 6 hours/day at corresponding maternal exposure levels from PND 22 through 28. However, pups could have been exposed to the test substance indirectly *in utero* through placental transfer or through suckling and/or dermal contact with their mother during lactation.

All  $F_0$  animals were observed twice daily for behavior, appearance, moribundity, and mortality. Body weights and food consumption were recorded periodically. The reproductive

performance of the F<sub>0</sub> males and females was determined using mating and fertility indices<sup>1</sup>, as follows

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

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

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

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

The F<sub>0</sub> females from each exposure group were allowed to deliver naturally and rear their pups until weaning on PND 21, at which time F<sub>0</sub> females with viable pups were necropsied. The number of uterine implantation sites was recorded at this time. 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, including males necropsied at the end of the mating period, and tissues were preserved for a subsequent histopathological examination, if deemed necessary by the gross findings.

Each pup was examined daily for survival and adverse changes in appearance or behavior. All F<sub>1</sub> animals received a detailed physical examination and their body weights were recorded on PNDs 1, 4, 7, 14, 21, and 28. Mean live litter size and viability indices were calculated as follows:

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<sup>1</sup>In Europe, the Fertility Index (FI) is calculated as:

$$\text{FI (\%)} = \frac{\text{number of pregnant dams (or males siring a litter)}}{\text{number with evidence of mating}} \times 100$$

$$\text{Mean Live Litter Size} = \frac{\text{total viable pups on PND 0}}{\text{number of litters with viable pups on PND 0}}$$

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

On PND 21, 20 F<sub>1</sub> male and 20 F<sub>1</sub> female rats were randomly selected from each exposure group and necropsied. The animals were examined for developmental morphology and, in some cases tissue were preserved for histopathological evaluation. The remainder of the F<sub>1</sub> animals were started on direct exposure until PND 28 at exposure levels corresponding to maternal exposures.

There were no sustained, significant treatment-related effects on mean body weight, body weight gains, or food consumption in treated F<sub>0</sub> males or females. Reported exposure-related clinical signs, noted in the F<sub>0</sub> generation 1 hour post-exposure, included dried red material around the nose and dried clear material around both eyes in males and females at 700 ppm, with the incidence of these findings being greater in females. Another clinical finding was the increase in the incidence of ejaculatory plugs found on the cage paper of the male animals from day 16 of exposure until the day before euthanization.

The test substance did not produce any significant effects on reproductive performance (mean pre-coital interval, male and female mating and fertility indices) at any exposure concentration tested (Table 2.1-1). There were no significant effects on the gestation length (21.6 days in the control vs. 22.0 days in the 700 ppm exposure group) or on the duration of parturition of the treated females.

**Table 2.1-1  
Reproductive Parameters from Initial Range-Finding Study (DCC 8305)**

Parameter	Control	70 ppm	700 ppm
Mean Pre-Coital Interval (days)	2.3±1.15	2.5±1.23	3.5±3.15
Mating Index			
Males	19/20 (95%)	20/20 (100%)	19/20 (95%)
Females	19/20 (95%)	20/20 (100%)	20/20 (100%)
Fertility Index			
Males	19/20 (95%)	20/20 (100%)	18/20 (90%)
Females	19/20 (95%)	20/20 (100%)	19/20 (95%)

The mean number of uterine implantation sites (assessed at PND 21) and the total number of pups born were statistically significantly reduced in the 700 ppm dose group (Table 2.1-2). The mean number of uterine implantation sites was 17.2 in the controls compared to 13.5 in the 700 ppm dose group. The mean number of pups born per litter in the control group was 16.5 as compared to the mean number in the 700 ppm dose group of 12.0. No exposure-related findings were reported in the low-dose females.

Any difference between the number of uterine implantation sites found on PND 21 and the total number of pups born was termed an "unaccounted for" site and was presumed to represent a cannibalized pup. The number of unaccounted for sites was increased in the 700 ppm dose group, when compared to controls, but was not statistically significant (Table 2.1-2). The mean number of unaccounted sites per dam increased from 0.7 in the control group to 1.7 in the 700 ppm exposure group.

On PND 0, the mean live litter size was statistically significantly decreased in the 700 ppm group, when compared to the control group (Table 2.1-3). However, the reduction was only slightly below the historical control range (11.6 pups/litter compared to a range of 11.7 to 15.9 pups/litter) of the laboratory at which the study was conducted. No effects on live litter size were reported in the 70 ppm group. No significant increase in the number of pups born dead was found.

**Table 2.1-2**  
**Summary of Uterine Implantation Sites in Rats Following D4 Exposure (DCC 8305) (a)**

Dose (ppm)	Implantation Sites	Total Number Born	Unaccounted for Sites
0	17.2 ± 1.83 (19) (b)	16.5 ± 1.84 (19)	0.7 ± 0.82 (19)
70	17.0 ± 1.67 (20)	15.6 ± 1.81 (20)	1.3 ± 1.38 (20)
700	13.5 ± 4.22 (18) (c)	12.0 ± 4.04 (18) (c)	1.7 ± 2.08 (17)

- (a) Mean and Standard Deviation.
- (b) Total number of animals examined.
- (c) Statistically significantly different from the control group.

**Table 2.1-3**  
**Pup Viability Indices (PND 0) (DCC 8305)**

Dose (ppm)	Number Born Dead	Total Live Litter Size/Number of Dams	Mean Live Litter Size	Sex Ratio M:F
0	1	312/19	16.4	160:152
70	8	305/20	15.3	145:160
700	8	208/18 (a)	11.6 (a)	98:110

- (a) Statistically significantly different from control.

While the mean live litter size was significantly reduced in the high-dose group, the percentage of live births over total births on PND 0 was comparable to controls (99.7% in controls, 99.0% in the 70 ppm dose group and 98.5% in the 700 ppm dose group, excluding the dams with five losses each). In addition, the pup sex ratio of males to females was not affected by treatment with D4.

Postnatal pup viability was not reduced with D4 treatment (Table 2.1-4). The viability index for the high-dose group was reduced, when compared to controls only on PND 1 (Table 2.1-4); however, the value was not statistically significant and was within the range of the laboratory historical control data. No significant differences in pup survival were noted on any other days for the 700 ppm group and no treatment-related effects on viability indices were reported in the 70 ppm group.

**Table 2.1-4  
Pup Viability Index in Rats Following D4 Exposure (DCC 8305)**

Days		1	4	4 (a)	7	14	21	28
Dose (ppm)	Total live/ Total born	(Viability %)						
0	312/313 (99.7)	311/312 (99.7)	306/312 (98.1)				152/152 (100)	40/40 (100)
70	305/313 (99) (b)	302/305 (99)	298/305 (97.7)	160/160 (100)	160/160 (100)	160/160 (100)	159/160 (99.4)	38/40 (95)
700	208/216 (c) (96.3)	202/208 (97.1)	202/208 (97.1)	135/133 (101)	133/133 (100)	133/133 (100)	133/133 (100)	37/40 (92.5)

- (a) After selection on PND 4.
- (b) Excludes one dam with five losses.
- (c) Significantly different from control

There was a statistically significant increase in mean pup weights in the 700 ppm group on PNDs 1 and 4, when compared to controls. This is not unexpected, given the litter size effect. Pup weights in the high-exposure group were comparable to controls after PND 4, and alterations in initial pup weight in the 700 ppm group were not considered an adverse finding. No effects on pup body weight were reported in the 70 ppm group. Also, no significant clinical findings were reported following necropsy of pups that died before the scheduled necropsy. Following gross necropsy of pups on PNDs 21 and 28, no exposure-related effects were reported.

### 2.1.2 DCC Study 8306

The association of the findings in DCC 8305 of decreased litter size and number of implants with D4 exposure was unclear in the absence of other indicators of reproductive and developmental toxicity, such as decreased pup survival or morphological alterations. Therefore, a second range-finding study (DCC 8306) was conducted to determine if the effects observed in the previous study could be duplicated. In this second study, three groups of 22 male and 22 female Sprague-Dawley rats were used. One group was exposed to 700 ppm D4 via whole body inhalation, while two other groups served as controls and were exposed to clean, filtered air. The animals were exposed 6 hours/day, for a minimum of 28 days prior to mating. In males, exposure continued through mating, while in females, exposure continued through mating and during

gestation through GD 20. All animals were observed twice a day for behavior, appearance, morbidity, and mortality. F<sub>0</sub> male and F<sub>0</sub> female body weights and food consumption were recorded regularly.

The F<sub>0</sub> females were allowed to deliver naturally and rear the pups to PND 4. Each litter was examined daily for survival and adverse changes in appearance or behavior. Each pup received a detailed physical examination and pup body weights were recorded on PNDs 1 and 4.

All F<sub>0</sub> males were necropsied at the end of the mating period. All F<sub>0</sub> females with viable pups were necropsied on PND 4, and the numbers of uterine implantation sites and corpora lutea were recorded. F<sub>0</sub> females that did not deliver were sacrificed on post-mating day 25. 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<sub>0</sub> males, and the ovaries from all F<sub>0</sub> females were weighed and the absolute weights and weights relative to final body weights were recorded. The left testis and epididymis of all F<sub>0</sub> males were homogenized and the homogenization resistant spermatid count and sperm production rate were determined. The right testis and epididymis of all F<sub>0</sub> males and the ovaries of all the F<sub>0</sub> females were submitted for microscopic examination.

No significant, sustained changes in body weight or food consumption were reported in the F<sub>0</sub> males or females. There were minimal clinical signs of toxicity. In the 700 ppm group, there was an increased incidence of brown vaginal discharge during pre-mating exposure and a slightly increased incidence of dried red material around the nose. Another clinical finding was an increase in the incidence of ejaculatory plugs found on the cage paper of the male animals from day 16 of exposure until the day before euthanization.

No significant effects on reproductive performance (the number of days between pairing and mating, or male and female mating and fertility indices) were reported. The mean gestation length for the 700 ppm F<sub>0</sub> females was 22.3 days, which was statistically significantly greater than the control group values (21.5 and 21.8 days). However, the mean gestation length in the treated females was within the range of the historical controls (21.5 to 22.8 days).

As observed in DCC 8305, the mean number of uterine implantation sites and the total number of pups born were statistically significantly decreased in the treated females, when compared to the control group 1 (Table 2.1-5). The number of corpora lutea, which was not

counted in DCC 8305, was also statistically significantly reduced, when compared to control group 1. The mean numbers of uterine implantation sites, total number born, and corpora lutea were 10.8, and 9.2, and 15.7, respectively, in the treated females, and 15.8, 15, and 19.2 in control group 1 and 14.6, 13.8, and 17.7 in control group 2.

**Table 2.1-5**  
**Implantation Sites, Litter Size, Unaccounted for Sites, and Corpora Lutea [Mean±S.D. (n)]**  
**in Rats Following D4 Exposure (DCC 8306)**

Dose (ppm)	Implantation Sites	Total Number Born	Unaccounted for Sites	Corpora Lutea
0	15.8±2.22 (22)	15±2.23 (22)	0.8±0.96 (22)	19.2±2.22 (22)
0	14.6±2.39 (20)	13.8±2.45 (20)	0.9±0.79 (20)	17.7±2.13 (20)
700	10.8±4.31 (20) (a)	9.2±4.11 (20) (a)	1.5±1.28 (20) (a)	15.7±2.91 (20) (a)

(a) Significantly different from the control group.

The mean live litter size in the treated group was 8.7 pups/litter, which was statistically significantly reduced, when compared to a value of 14.6 pups/litter in control group 1 (see Table 2.1-6). The mean live litter size in the treated animals was also below the range of historical control values (11.7 to 15.9 pups/litter). However, the number of pups born dead and the ratio of the number of live pups to total pups born were not significantly different, when compared to the control groups. The percentages of live births over total born was 97.5% and 96.6% in the control groups and 94% in the treated groups. In the 700 ppm group, the viability indices for PNDs 1 and 4 were 92.5% and 91.3%, respectively, as compared to the control Group 1 indices of 98.8% and 98.6% for PNDs 1 and 4, respectively (Table 2.1-6). The values for the treated group were within the range of the historical control (83.6% to 100% for PND 1 and 80.4% to 99.4% for PND 4). Pup viability indices on PNDs 1 and 4 were not statistically significantly decreased. The pup viability index in the 700 ppm group was strongly influenced by two dams, one with two and the other with 11 pups, that had total litter loss on PND 1. The mean pup weights were statistically significantly increased in the treated animals, when compared to control group 1 on PNDs 1 and 4. The mean weight in the treated group at PND 1 was 7.4 grams as compared to the control, 6.7 grams. At PND 4 the mean pup weight in the treated group was 9.9 grams, as compared to the control mean pup weight of 8.9 grams.

**Table 2.1-6**  
**Live Litter Size/Total Born and Pup Viability Index in Rats Following Exposure**  
**(DCC 8306)**

Dose (ppm)	Lactation Day 0:		Viability (%)	
	Number Dead	Live Litter Size (Mean)	1	4
0	8	322/330 (14.6)	318/322 (98.8)	311/322 (98.6)
0	12	263/275 (13.2)	261/263 (99.2)	254/263 (96.6)
700	11	173/184 (8.7) (a)	160/173 (92.5)	158/173 (91.3)

(a) Significantly different from control group 1.

Lastly, no treatment-related histopathological alterations were found in any of the tissues examined in either the F<sub>0</sub> or the F<sub>1</sub> animals. There were no treatment-related findings in the testes or epididymides (Table 2.1-7). Testes and epididymides organ weights were comparable to controls and both sperm number and sperm production rates were unchanged. In F<sub>0</sub> females sacrificed on PND 4, there were no remarkable findings in the ovaries, and ovarian weights were comparable to controls (Table 2.1-7).

### 2.1.3 Summary of DCC 8305 and 8306

The results of DCC 8306 confirmed those found in DCC 8305. In both studies there were only minimal indications of toxicity to F<sub>0</sub> males and F<sub>0</sub> females. Body weights and food consumption were within normal values, and only minimal clinical signs were noted. There were no effects on the precoital interval, on male and female mating and fertility indices, or on the duration of gestation or length of parturition. There were no remarkable ovarian histological findings and no effects on testicular or epididymal histopathology or sperm numbers.

In the 700 ppm group only, there was a statistically significant reduction in the number of corpora lutea (examined in DCC 8306 only) and uterine implantation sites. A significant decrease (approximately 30%) in the total number of pups born and the mean live litter size was found for the 700 ppm group only. However, the proportion of pups born dead or live to the total number of pups born did not differ across exposure groups. Pup viability was unaffected, as measured on PNDs 1 and 4, and pup morphology was normal.

**Table 2.1-7**  
**Histological Results for F<sub>0</sub> Male and F<sub>0</sub> Female Rats (DCC 8306)**

Parameter	Control Group 1	Control Group 2	700 ppm
<b>Sperm Number (MM/g tissue)</b>			
Testis	91.5±19.6	106.4±18.3	98.2±14.2
Epididymides	520.4±111.5	519.6±69.4	523.6±116.9
<b>Sperm Production Rate (MM/g tissue/day)</b>	15.0±3.2	17.5±3.0	16.1±2.3
<b>Male Accessory Organ Weights</b>			
Right Testis	1.69±2.0	1.73±0.16	1.68±0.18
Left Testis	1.69±2.2	1.73±0.16	1.67±0.12
Right Epididymides	0.65±0.07	0.67±0.05	0.64±0.04
Left Epididymides	0.63±0.06	0.65±0.05	0.64±0.06
<b>Ovarian Weights (g)</b>			
PND 4	0.13±0.03	0.13±0.02	0.13±0.03
Nongravid (PND 25)	NA	0.13±0.05	0.08±0.02

Both DCC 8305 and 8306 were range-finding studies with the same protocol differing only in that DCC 8305 tested at concentrations of 70 and 700 ppm, while DCC 8306 only tested the 700 ppm exposure level. The data for these studies were combined and the same statistical analyses for the same endpoints as for the studies separately were evaluated for the combined data set (Table 2.1-8).

**Table 2.1-8**  
**Live Litter Size/Total Born and Pup Viability Index in Rats Following Exposure (DCC 8305, DCC 8306)**

Dose (ppm)	Lactation Day 0:		Viability (%)
	Number Dead	Live Litter Size (mean)	
0	21	897/918 (15.0)	871/897 (97.1)
70	6	305/313 (15.7)	298/305 (97.7)
700	19	318/400 (10.5) (a)	360/381 (94.5)

(a) Significantly different from control group.

## 2.2 Male Crossover Studies

Two studies were conducted in which male Sprague-Dawley rats were exposed by whole body inhalation to D4 and then mated with unexposed females (DCC 8462, DCC 8601). The purpose of these studies was to determine if the effects seen in studies DCC 8305 and 8306 were due to male treatment-related effects. In the first study (DCC 8462), four groups of 22 F<sub>0</sub> male Sprague-Dawley rats were exposed to 70, 300, 500, or 700 ppm D4 via whole body inhalation, while the fifth group of male rats served as a control group receiving only filtered air. The groups of female rats received only filtered air. Male rats were exposed to the test substance 6 hours/day, for a minimum of 70 days prior to mating and continuing until the end of the mating period. Females were exposed to filtered air for 21 days prior to mating and continuing until the end of the mating.

All animals were observed twice a day for behavior, appearance, moribundity, and mortality. Body weights and food consumption were recorded periodically. The reproductive performance of the F<sub>0</sub> males and females was determined using mating and fertility indices, which were calculated as indicated in Section 2.1.

Following the mating period, ten males from each group were euthanized and subjected to sperm motility/viability assessment, sperm morphology assessment, and enumeration of epididymal and testicular sperm numbers and sperm production rate. Following a 4-week recovery period, the remaining 12 male rats per dose group were necropsied on PND 4 at which time selected organs were weighed and examined.

The F<sub>0</sub> females from each dose group were allowed to deliver naturally and rear the pups to PND 4, at which time the F<sub>0</sub> females with viable pups were necropsied, 25 days after the breeding interval. The number of uterine implantation sites was recorded at this time. Females that did not deliver were sacrificed on post-mating day 25 (evidence of mating) or post-mating day 27 (no evidence of mating). Selected organs were weighed and examined microscopically.

Live litter size and pup viability indices were calculated as indicated in Section 2.1. All F<sub>1</sub> pups were sacrificed on PND 4.

The protocol for the second male crossover study (used International Genetic Standard rats) was the same as that for DCC 8462 with the following exceptions. There were 40 males per dose group exposed at either 500 or 700 ppm with 40 males in the air-exposed control group. F<sub>0</sub>

males had a 5-week recovery period after breeding to unexposed females prior to sacrifice and necropsy. F<sub>0</sub> females and F<sub>1</sub> pups were sacrificed on PND 21. Sperm motility and morphology as well as organ weights and organ histopathology were not reassessed in this study.

Consistent with earlier studies, there were minimal signs of toxicity in F<sub>0</sub> males. Several body weight and food consumption changes were noted; however, the effects were not sustained or dose-dependent. Clinical findings included an increase in the incidence of wet red material around the nose and eyes of the treated males and an increase in the incidence of ejaculatory plugs found on the cage paper of male animals in the 700 ppm exposure group. However, the plug production rate at 700 ppm did not exceed the rate reported in the literature for untreated Sprague-Dawley rats. There were also elevated plug counts in all exposure groups in DCC 8462 and at both the 500 and 700 ppm exposure groups in DCC 8601.

No remarkable, treatment-related gross findings at necropsy were noted. Also consistent with the previous study, DCC 8306, there was no effect on sperm motility (mean % mobile sperm) or sperm morphology (assessed in DCC 8462 only). Mean liver, kidney, and thyroid weights were increased at 700 ppm in the group sacrificed immediately after breeding, but were at control values in the recovery group. No effect was noted on the weights of any other organ. There were no remarkable, treatment-related histological findings in any organ examined.

No significant effects were reported for reproductive performance (number of days between pairing and mating, mating and fertility indices, gestation length, or duration of parturition) noted in either study. There were no effects on total number pups born (litter size) or the number of uterine implantation sites in either study.

Two findings that were noted in the first male crossover study (DCC 8462) were not duplicated in the larger, second male crossover study (DCC 8601). In DCC 8462, the number of pups dead at PND 0 in the 500 and 700 ppm groups was increased when compared to the control group (Table 2.2-1). The numbers of pups found dead in the two highest dose groups on PND 0 were 9 and 18, as compared to two pups found dead in the control group. Three dams in the high-dose group contributed 15 of 19 dead pups at PND 0. Pups from litter #44000 in the 700 ppm group were euthanized on day 1 due to maternal moribundity; these pups were not included in viability calculations on PNDs 1 or 4. Litter-based statistical results were mixed; there was no significant increase using the Kruskal-Wallis test, reflecting the large variability in the 700 ppm

group, but a significant trend using the PHAT permutation test was observed (Table 2.2-1). This observation was not reproduced in the larger repeat study, DCC 8601. In this larger study there were no effects on the number of pups born dead on PND 0 or on any other index of pup viability.

**Table 2.2-1**  
**Pup Viability in Rats Following D4 Exposure (DCC 8462)**

Dose (ppm)	Number Dead, Day 0	Viability Day 1 (%)	Viability Day 4 (%)
0	2	98.2	97.9
70	3	99.0	98.4
300	4	99.7	98.2
500	9 (a)	100.0	100.0
700	18 (a)	98.1	97.8

(a) Statistically significant trend using the PHAT permutation test but not significant using the Kruskal-Wallis test for litter-based statistical analyses.

The only other observation noted in DCC 8462 that differed in the 700 ppm treatment group compared to control was a decrease in  $F_1$  pup body weights at both PNDs 1 and 4. The pup weights in the 700 ppm group for PNDs 1 and 4 were 6.5 and 9.7 grams compared to the pup weight in the control groups of 7.4 and 10.6 grams, respectively. This observation was also not reproduced in the second study. In DCC 8601 on both PNDs 1 and 4, pup body weights were comparable to control values. In the second study, pup body weights in the 700 ppm group were 7.0 and 10.2 grams on PNDs 1 and 4 compared to values of 6.9 and 9.9 grams in the controls for the same days.

#### Summary of Male Crossover Studies

No biologically plausible, reproducible effects were seen in either male crossover study. No effects were noted on any of the reproductive performance parameters evaluated. An impact on pup viability in the 500 and 700 ppm groups was suggested in DCC 8463; however, this effect was not reproduced in the larger, second male crossover study. It can be concluded from these studies that any D4 impact on litter size seen in earlier studies did not occur through any male-mediated mechanism.

### 2.3 Female Crossover Study

The purpose of this study was to determine if the effects seen in the previous studies were due to female treatment-related effects. The protocol for this study was similar to previous studies. Four groups of 22 F<sub>0</sub> female Sprague-Dawley rats were exposed to 70, 300, 500, or 700 ppm D4 via whole body inhalation, while the fifth group of female rats served as a control group receiving only filtered air. The groups of male rats served as cage controls and were not exposed. Female rats were exposed to the test substance 6 hours/day, for a minimum of 70 days prior to mating. Exposure continued through necropsy on PND 21, with a suspension in the exposure from GD 20 through lactation day 4. Pups were exposed directly from PND 22 through 28 via whole body inhalation at corresponding maternal concentrations. Pups could also have been indirectly exposed to the test substance through placental transfer *in utero*, and through suckling and/or dermal contact during lactation.

As with the other studies, all animals were observed twice a day for behavior, appearance, moribundity, and mortality, and body weights and food consumption were recorded periodically. The reproductive performance of the F<sub>0</sub> males and females was determined using mating and fertility indices as indicated in Section 2.1.

The F<sub>0</sub> females from each exposure group were allowed to deliver naturally and rear the pups to PND 21. F<sub>0</sub> males were necropsied at the end of the mating period and discarded, and F<sub>0</sub> females with viable pups were necropsied on PND 21. The number of uterine implantation sites was recorded at this time. 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 from F<sub>0</sub> females in the 0 and 700 ppm groups underwent histopathological examination.

Live litter size and viability indices were calculated as indicated in Section 2.1. On PND 21, ten F<sub>1</sub> male and ten F<sub>1</sub> female pups were randomly selected from each group and necropsied. Selected organs of the F<sub>1</sub> generation were weighed.

The results of this study were consistent with the two initial range-finding studies (DCC 8305 and 8306). There were minimal signs of maternal toxicity in any exposure group. No sustained significant effects on body weight or food consumption were noted. As with the other studies, all F<sub>0</sub> females survived until scheduled euthanasia. Clinical observations in the F<sub>0</sub> females

were limited to wet yellow staining of the urogenital area, dried wet staining of the dorsal head, dried red material around the nose and eyes, and wet red material around the nose. Increased liver weights were noted in the 700 ppm F<sub>0</sub> group; however, no histopathological alterations in the liver were found. Organ weights and histopathology were normal in all other tissues examined, which included the adrenals, lungs, thymus, brain, mammary, uterus, kidney, pituitary, vagina, and spleen.

There were no significant changes in the reproductive performance (days between pairing and mating, mating and fertility indices, duration of gestation or length of parturition) among treated animals, when compared to controls. There were no effects on regularity or duration of estrous.

As with the previous studies, the mean number of uterine implantation sites (evaluated on PND 21), but not the number of unaccounted for sites, was statistically significantly decreased in the 700 ppm dose group, when compared to the controls (Table 2.3-1). The mean number of uterine implantation sites was 14.5 in the control group versus 12.3 in the 700 ppm treatment group. As in the previous range-finding study, DCC 8305, unaccounted for sites were defined as the difference in number of uterine implantation sites and total births.

**Table 2.3-1**  
**Implantation Sites, Total Number Born, and Unaccounted Sites [Mean±S.D.(n)] in Rats**  
**Following D4 Exposure (DCC 8463)**

Exposure Concentration (ppm)	Implantation Sites	Total Number Born	Unaccounted for Sites
0	14.5±2.14 (20)	13.6±2.14 (20)	0.9±1.10 (20)
70	15.0±1.41 (21)	13.9±1.74 (21)	1.1±1.24 (21)
300	14.1±2.65 (20)	13.5±2.74 (20)	0.6±0.75 (20)
500	13.8±1.89 (21)	12.7±2.15 (21)	1.1±1.96 (21)
700	12.3±3.27 (20) (a)	10.4±3.57 (20) (a)	1.9±1.83 (20)

(a) Significantly different from the control group.

As with the previous studies, there was a statistically significant decrease in the mean total number of pups born (Table 2.3-1) and the mean live litter size (Table 2.3-2) in the 700 ppm group only. The mean live litter size decreased from 13.5 pups/litter in the control group to 9.9

pups/litter in the 700 ppm group. The mean live litter size was reduced in the 500 ppm group, when compared to the control group, but was not statistically significantly different by any of the statistical tests conducted. As with the previous studies, while the mean live litter size was decreased, the percentage of live births over total births was comparable across exposure groups (99% in the control and 97%, 100%, 97%, and 96% in the 70, 300, 500, and 700 ppm dose groups, respectively). Pups in all groups appeared healthy, and pup viability as measured on PNDs 1 and 4 was comparable to controls. Pup viability indices were monitored until PND 21 and were comparable to controls. F<sub>1</sub> body weights were slightly increased compared to controls, but this was likely due to the smaller mean litter sizes. At necropsy, there were no treatment-related effects on organ weights for organs measured (liver, ovary) and no gross treatment-related findings were noted.

**Table 2.3-2**  
**Number Born Dead and Mean Live Litter Size in Rats Following D4 Exposure**  
**(DCC 8463)**

Dose (ppm)	Number Dead	Mean Live Litter Size
0	2	13.5
70	10	13.4
300	0	13.5
500	8	12.3
700	9	9.9 (a)

(a) Significantly different from the control group.

**Summary of DCC 8463**

The results of this female crossover study (exposed females mated to unexposed males) are consistent with the previous range-finding studies. Reproductive parameter values (mating and fertility indices, etc.) were not significantly different from control values. As with the two range-finding studies, intrauterine survival was significantly reduced in the 700 ppm exposure group. Both the number of uterine implantation sites and the mean live litter size were significantly reduced in the 700 ppm exposure group, when compared to controls. No treatment-related effects were seen in the other exposure groups. D4 administered by the inhalation route at a concentration of 700 ppm may produce these effects by pre-implantation or early post-

implantation loss, as suggested by the reduction in the number of corpora lutea (only evaluated in DCC 8306) and uterine implantation sites.

#### 2.4 Phased Female Study (DCC 8620)

A study in which groups of female Sprague-Dawley rats were exposed during different phases of their reproductive cycles was conducted to evaluate the effects of D4 on embryo-fetal survival and to provide insights as to the potential mode of action on litter size in Sprague-Dawley rats. Groups of female rats were exposed to D4 by whole body inhalation for 6 hours/day according to the following schedule:

- *Overall Phase.* Groups of 24 female Sprague-Dawley rats were exposed to D4 at concentrations of 70, 300, 500, or 700 ppm beginning 28 days prior to mating and continuing through GD 19;
- *Ovarian Phase.* Sixty female rats were exposed at 700 ppm beginning 31 days prior to mating and stopping 3 days prior to mating;
- *Fertilization Phase.* Sixty female rats were exposed at 700 ppm 3 days prior to mating and continuing through GD 3; and
- *Implantation Phase.* One group of 24 females was exposed at 700 ppm from GD 2 through GD 5.

With the exception of the duration of exposure post-mating, the Overall Phase was intended to duplicate the exposure protocol used for the female crossover study (DCC 8463), while the other phased studies were intended to isolate exposure to a portion of the reproductive cycle corresponding to those biological events in the designated time periods. In each phase, concurrent control groups were exposed to clean, filtered air on a comparable schedule for its corresponding phase. Males were not exposed to D4. All animals were observed twice daily for appearance and behavior with clinical observations, body weights and food consumption recorded prior to mating and during gestation.

All surviving pregnant females were euthanized on GD 20 for a scheduled laparohysterectomy. The uteri and ovaries were examined, and the number of fetuses, early and late resorptions, uterine implantations, and corpora lutea was recorded. Organ weights (brain,

ovaries, adrenal glands and thyroid glands) were recorded and mean gravid uterine weights and net body weight changes were calculated.

No treatment-related clinical signs were noted in any females in any phase; any clinical signs noted were seen infrequently and were similar to their respective control groups. All females in all phases survived to the scheduled necropsy, with the exception of one control female that died on GD 2 in the Implantation Phase. No cause of death was determined. One female in the Overall Phase delivered seven normal pups (no visible malformations) on GD 19, which was attributed to an error in detection of evidence of mating rather than to exposure to D4. The major findings for each phase are discussed in the following paragraphs

#### 2.4.1 Overall Phase

Statistically significantly reduced mean body weight gains with corresponding reductions in food consumption were recorded during the first week (week 0 to 1) of exposure in the 300, 500, and 700 ppm exposure groups. During week 1, mean body weights were significantly reduced in the 500 ppm exposure group only. All maternal mean body weights and body weight gains for all exposure groups were comparable to controls throughout the remainder of the pre-mating period.

Maternal mean body weights were comparable to control group values throughout gestation. However, on GD 20 mean body weights were reduced (not statistically significantly) in the 500 and 700 ppm groups. Reduced mean body weight gains were noted in the 500 and 700 ppm groups only during the last 7 to 10 days of gestation. This, along with the reduced mean gravid uterine weights observed at necropsy in the 500 and 700 ppm groups, was likely due to the decreased viable litter size seen in these groups.

All reproductive parameters measured (days between pairing and coitus, mating indices, and fertility indices) were comparable to controls in all exposed groups. Female mating indices were 100% in the control and 95.8% in each of the treated groups. Fertility indices were 95.8% in the control and 91.7%, 95.5%, 95.8%, and 91.7% in the 70, 300, 500, and 700 ppm groups, respectively.

The Overall Phase results with regard to interuterine survival were consistent with those found in previous studies in which female rats were exposed to D4. The results suggest that the

loss was primarily pre-implantation as indicated by a reduction in the number of corpora lutea, uterine implantation sites, and viable fetuses in the high-dose groups compared to control (Table 2.4-1). The mean numbers of corpora lutea in the 300, 500, and 700 ppm groups were reduced (14.6, 14.1, 14.7, respectively) compared to control values (16.2); however, no clear dose-response was noted and the effect was statistically significant only in the 500 ppm group, when evaluated using the Dunnett's test. The mean number of uterine implantations sites and mean live fetal number were significantly reduced in the 500 and 700 ppm groups, when compared to the control group. The mean live fetal number per litter was 13.7 in the control group and 10.4 and 8.7 in the 500 and 700 ppm groups, respectively. When evaluated on a proportional basis (live fetuses per litter), the viable fetal number was comparable to controls in the 70 and 300 ppm dose groups and, while reduced in the 500 and 700 ppm dose groups, the reductions were not statistically significant. The percentages of live fetuses per litter were 92.3%, 88.7%, and 83.4% in the control group, 500 and 700 ppm dose groups, respectively.

Table 2.4-1  
Overall Phase Results

Dose (ppm)	Mean Number of Corpora Lutea	Mean Number of Implantations	Mean Number of Live Fetuses per Litter	Mean Pre-Implantation Loss	Mean Post-Implantation Loss
0	16.2±2.1	14.7±1.7	13.7±2.3	1.5±1.6	1.1±1.2
70	15.8±1.8	14.9±1.9	13.9±1.7	1.0±1.1	1.0±1.1
300	14.6±2.0	13.5±2.9	12.8±3.5	1.0±2.1	0.7±1.1
500	14.1±2.7 (a)	11.6±3.7 (a)	10.4±3.8	2.6±2.6	1.1±1.4
700	14.7±2.5	10.0±4.0 (a)	8.7±4.7	4.6±4.1	1.3±1.3

(a) Statistically different from control.

#### 2.4.2 Ovarian Phase

The Ovarian Phase results indicated that the biological events occurring up to 3 days prior to mating are either unaffected by D4 exposure or fully reversible when D4 exposure ceases prior to mating (-3 days). Only two groups, the control and 700 ppm treatment group, were evaluated in this phase. There was a test article-related decrease in mean body weight and body weight gain with a corresponding decrease in food consumption during the first week of exposure; however,

these parameters were similar to control values for the remainder of the pre-mating period. No treatment-related effects on mean gestation body weights or body weight gains were found, and mean gravid uterine weights were unaffected by exposure to D4.

Reproductive performance (days between pairing and coitus, mating index, fertility index) was not adversely affected by exposure to D4. Female mating indices were 93.3% and 85% in the control and 700 ppm groups, while the female fertility indices were 86.7% and 83.3%.

The number of corpora lutea and indices of intrauterine survival (mean number of viable fetuses, uterine implantation sites, early/late resorptions) in the 700 ppm group were not statistically different from control values (Table 2.4-2). Absolute and relative organ weights (brain, ovary, adrenal gland, and thyroid gland) were unaffected by exposure to D4.

**Table 2.4-2**  
**Ovarian Phase**

Dose (ppm)	Mean Number of Corpora Lutea	Mean Number of Implantations	Mean Number of Live Fetuses per Litter	Mean Pre-Implantation Loss	Mean Post-Implantation Loss
0	17.0±2.3	15.0±1.8	14.6±2.1	2.0±2.3	0.4±0.64
700	16.5±2.4	14.4±2.8	13.8±2.9	2.1±2.4	0.6±0.81

### 2.4.3 Fertilization Phase

The results from exposure during this phase of the reproductive process (3 days prior to mating through GD 3) were similar to those observed during the Overall Phase in which exposure began 28 days prior to mating and continued to GD 19. Initially, mean body weight gains and food consumption were reduced in the 700 ppm group during the 3 days of exposure prior to mating. Mean body weight gains were reduced in early gestation (GDs 0 to 4) and significantly reduced the last week of gestation (GDs 14 to 20). Mean gravid uterine weight in the 700 ppm group was also significantly reduced, indicating that the reduced body weight gain and reduced gravid uterine weight were likely due to the decreased litter size.

As with the other studies, reproductive parameters (days between pairing and coitus, mating index, fertility index) were not affected by treatment with D4. Reductions in the mating

and fertility indices were noted, but were considered a function of the unusual study design rather than treatment-related. In the Fertilization Phase, females that did not show evidence of mating after 2 days of pairing were replaced, while control females were allowed a maximum of 5 days for mating.

As with the Overall Phase, statistically significant reductions in the numbers of corpora lutea, uterine implantation sites, and the mean live fetal number per litter were noted in the 700 ppm group compared to control values (Table 2.4-3). The mean number of corpora lutea was 17.1 in the control and 14.6 in the treated group, a 15% reduction. The mean number of uterine implantation sites was reduced from 15.1 in the control to 10.4 in the treated group, a 30% reduction. Mean pre-implantation losses and mean post-implantation losses, which were due entirely to early resorptions, were significantly increased over control values. Mean live fetal number, both the absolute number and the percentage per litter, was also significantly reduced compared to controls, when unadjusted for litter effects. The mean number of viable fetuses per litter in the treated group was 8.7, when compared to 14.2 in the control. The percentage of viable fetuses in the control group was 93.7%, while the percentage in the treated group was 82%.

Table 2.4-3  
Fertilization Phase

Dose (ppm)	Mean Number of Corpora Lutea	Mean Number of Implantations	Mean Number of Live Fetuses per Litter	Mean Pre-Implantation Loss	Mean Post-Implantation Loss
0	17.1±2.9	15.1±1.7	14.2±2.1	2.0±2.9	0.9±1.0
700	14.6±2.1 (a)	10.4±4.3 (a)	8.7±4.2 (a)	4.3±4.5 (a)	1.7±1.5

(a) Significantly different from control.

Absolute ovarian weight, but not relative ovarian weight, was significantly decreased in the 700 ppm group, when compared to controls. Absolute and relative adrenal gland weights were slightly increased compared to controls; however, a dose-response association was not clear. Other organ weights, both absolute and relative (brain and thyroid gland), were comparable to controls.

#### 2.4.4 Implantation Phase

Exposure to D4 at 700 ppm from GD 2 through 5 had no treatment-related effects on any parameter evaluated. Mean body weights were similar to control throughout gestation, and mean body weight gains, with the exception of GD 2 to 6, were similar to control. Significant reductions in food consumption were also noted on GD 2 to 6, but were at control values for the remainder of gestation.

As with all the other studies, no treatment-related effects were found for any of the reproductive parameters evaluated. In addition, the number of corpora lutea and indices of intrauterine survival (uterine implantation sites, live fetal numbers) were unaffected by exposure to D4 at 700 ppm (Table 2.4-4). Finally, all organ weights (brain, ovary, adrenal gland and thyroid glands) were comparable to control values.

Table 2.4-4  
Implantation Phase

Dose (ppm)	Mean Number of Corpora Lutea	Mean Number of Implantations	Mean Number of Live Fetuses per Litter	Mean Pre-Implantation Loss	Mean Post-Implantation Loss
0	16.7±2.0	15.5±1.6	14.6±1.9	1.1±1.2	0.9±1.2
700	15.3±2.1	14.7±2.4	13.4±2.7	1.5±1.7	1.3±1.5

#### 2.4.5 Summary of the Phased Female Study (DCC 8620)

In the Overall Phase, the following were the major observations: 1) a reduction in the number of corpora lutea (300, 500, and 700 ppm groups); 2) a reduction in the number of uterine implantation sites and viable fetuses (500 and 700 ppm groups); 3) an increase in the mean pre-implantation loss (500 and 700 ppm groups); and 4) an increased post-implantation loss (700 ppm group only). In the Fertilization Phase, the numbers of corpora lutea, uterine implantation sites, and viable fetuses were reduced, and the mean pre-implantation and post-implantation losses were increased in the 700 ppm group, the only exposure concentration tested. No effects were noted on the number of corpora lutea or indices of intrauterine survival in females exposed at 700 ppm in the Ovarian Phase and Implantation Phases.

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The effects on corpora lutea and intrauterine survival were similar for the Overall Phase in which exposure began 28 days pre-mating and continued through GD 19 and for the Fertilization Phase in which exposure began 3 days pre-mating and continued through GD 3. No treatment-related adverse effects were noted if exposure began after mating (Implantation Phase) or terminated 3 days prior to mating (Ovarian Phase).

### 3.0 EXPOSURE ASSESSMENT

An Exposure Assessment consists of multiple steps in which the population(s) that may be exposed are identified and pathways of exposure are evaluated, i.e., the potential for exposure via a particular pathway, such as ingestion, inhalation or dermal contact, is assessed. This information is then used to estimate *doses* that individuals would receive under the various exposure scenarios, and the uncertainty associated with those exposure estimates is considered. In an Exposure Assessment, the terms *exposure*, *intake*, and *dose* are often used imprecisely and, unfortunately, interchangeably. In this Exposure Assessment, these words are defined as follows:

- *Exposure* is defined as the amount of chemical which is presented to the relevant biological barrier, e.g., the concentration of chemical in air (inhalation exposure) and the amount of chemical applied to the skin (dermal exposure) or ingested (oral exposure).
- *Intake* is defined as the amount of chemical that crosses the first biological barrier into the blood stream, e.g., the amount of chemical absorbed across the lung, skin, or gastrointestinal tract.
- *Dose* is defined as the amount of the active form of the chemical (parent or metabolite) that reaches the target tissue.

DCC has conducted a comprehensive analysis of potential exposures for the relevant receptors and exposure pathways (ECA 1997, DCC 1998a). The ECA analyses evaluated the production, formulation, and use of D4 in the United States and estimated the potential exposure (intake) for:

- persons who work in the production of D4, in the formulation of this material into personal care products containing D4, or use these products in professional settings;
- consumers who use these personal care products, including antiperspirants/deodorants (AP/Ds) and hair care/skin care (HC/SC) products;
- consumers who may be exposed to silicone antifoams used in food processing; and
- the general public who may be exposed to D4 released into the environment.

The exposure assessments conducted by ECA (1997) and DCC (1998a) provided estimates of *intake* rather than estimates of *dose*. These intake estimates were based on a comprehensive review of the workplace for several exposure scenarios, as well as a review of the amount of D4 in selected consumer products and the use patterns for those products. The information for workplace activities and usage patterns was based on industry-supplied data and represents a compilation of data across companies and products. As such, some unifying and, in some cases, conservative assumptions were made to provide generic exposure scenarios that characterized these exposures to the selected target populations.

These exposure assessments provided estimates of intake by both the dermal and inhalation routes (and in the case of lipstick, by the oral route as well) for personal care product users; the oral route for antifoams in food products; and by the inhalation route for workers and the general public. The details of the ECA (1997) and DCC (1998a) assessments are not repeated in this chapter; however, a summary of the basis for each of the key assumptions and parameter values used is presented. For this preliminary risk assessment, the usage estimates and parameter values developed by DCC (ECA 1997; DCC 1998a) were used in this Exposure Assessment step without modification, with the exception of the D4 dermal absorption percentage (see Section 3.1.1.1). However, the underlying data and assumptions used to determine these estimates were reviewed. The relevant underlying assumptions, the data used, and the methods applied for quantifying exposure were identified. The purpose of this review was to assess the impact of alternative variables and assumptions in order to identify those that significantly contributed to estimates of intake and those that contributed significantly to uncertainty. The impacts of these uncertainties on the estimated MOEs are discussed in Section 5, Risk Characterization.

It is important to note that the exposure analysis conducted by ECA is a "work in progress." As newer data or information become available that can refine the definition of a parameter value or reduce uncertainty in an assumption made, then the estimates of intake can be refined. For example, more recent data to describe dermal absorption were available for use in this preliminary risk assessment (see Section 3.1.1.1) than that reported in the ECA (1997) document. It is expected that as these refinements are made, such as in the dermal absorption fraction or deposition fraction, estimates of intake will more likely be lower rather than higher compared to the current values used for this preliminary risk assessment. Consequently, use of

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these data, i.e., estimates of intake, is highly unlikely to result in an underestimation of intake but rather provide reasonable upper bounds that are likely to be overestimations of intake. In addition, exposure estimates for other receptors, such as adults and children who may use antigas products containing silicone antifoams, are under development. Consideration of these receptors will be included in the final risk assessment.

## PERSONAL CARE PRODUCTS

### 3.1 Exposures to Consumers via the Use of Personal Care Products

Due to their physical properties, cyclosiloxanes, a group of materials that include D4, have been widely used in consumer products as carriers, emollients, and lubricants. For this assessment, 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 all APs are formulated with cyclosiloxanes, this is not the case for HC/SC products. However, for this assessment it was assumed that cyclosiloxanes are used in all HC/SC products. Potentially relevant exposure pathways for all consumer products included inhalation and dermal contact. Each section below describes the methods used by ECA (1997) for conducting an exposure assessment for consumer products.

#### 3.1.1 Exposures of Consumers to D4 via the Use of AP/Ds

D4 is widely used in the formulation of many different consumer products including AP/Ds. Exposure occurs dermally through the direct application of the AP/Ds to the skin and via inhalation as the AP/D residue volatilizes. There are three principal forms of AP/Ds, solids, roll-ons, and aerosols. The D4 content and application rates vary with each form of AP/Ds; therefore, separate dermal and inhalation exposure analyses were conducted for consumers using each of the three principal forms of AP/Ds.

##### 3.1.1.1 Dermal Exposures to D4 from Use of AP/Ds

The dermal ADI s from the use of AP/Ds were calculated using the following equation:

$$\text{ADI (mg/kg/day)} = \frac{\text{AR} \times \text{CF} \times \text{AF} \times \text{Dep}_f \times \text{Res}_f \times \text{A} \times \text{D4}_f}{\text{BW} \times \text{DW}} \quad (3-1)$$

where

- AR = application rate (g/application)
- CF = conversion factor (1000 mg/g)
- AF = application frequency (applications/week)
- Dep<sub>f</sub> = deposition fraction (unitless)
- Res<sub>f</sub> = residue fraction (unitless)

- A = dermal absorption fraction (unitless)  
D4<sub>r</sub> = fraction of product applied that is D4 (unitless)  
BW = body weight (kg)  
DW = adjustment to daily intake (7 days/week)

Because the amount of D4 to which a consumer would be exposed following AP/D application varies, separate exposure assessments were conducted for solid, roll-on or aerosol use. Therefore, in the calculation of a dermal ADI for the use of APs, different exposure parameters were used for the different types of APs. A discussion of the values used by ECA (1997) for each of these parameters is provided below.

#### ***Application Rate (AR)***

The application rate of AP/Ds is the average number of grams of AP/D used each time it is applied. Information on application rates of the various forms of AP/Ds was available from numerous volunteer studies (ECA 1997). In these studies, groups of participants (n=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 by the participant, with average application amounts determined by dividing the amount used by the number of applications the participant reported that they used (Table 3.1-1). 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, the application rates for the various products followed the same order. Aerosols had the greatest average (1.54 g/application), followed by roll-ons (0.79 g/application), with solids having the smallest average application rates (0.65 g/application).

**Table 3.1-1**  
**Average Application Rates for AP/Ds (a)**

Product Form	Gender	Average Amount / Application		N (c)
		(grams)	(mg/cm <sup>2</sup> ) (b)	
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) Source: ECA (1997).  
 (b) Estimated amount per skin surface area for axillary area.  
 (c) N = number of studies with 30 to 50 participants per study.

***Application Frequency (AF)***

The application of AP/Ds is generally associated with a showering or bathing event. Approximately 70–75% of the American population bathes or showers every day, with 20–25% bathing or showering more than once a day (USEPA 1997). However, AP/Ds may be applied more often and applied in between a bath or shower, depending on a person's activity. Mediamark Research, Inc. (MRI 1995) conducted a consumer survey on the purchases and use of AP/Ds. The results of this survey are presented in Table 3.1-2. To determine the mean application frequency per group, the percentage of the population that fit into each range of application frequencies was multiplied by the midpoint of that range of frequencies (i.e., column 3 multiplied by column 4). These population-weighted frequencies were then added together to result in a mean for the group. These data indicated that the mean frequencies of AP/D application are 7.1 and 6.9 times/week for women and men, respectively.

***Deposition Fraction (Dep<sub>f</sub>)***

The deposition fraction of the AP/D is the fraction of product that is deposited onto the skin during a typical application. ECA (1997) assumed that 100% of the amount of product applied will be deposited onto the skin.

Table 3.1-2  
Usage Survey Data for AP/Ds for U.S. Population Age 18 or Older (a)

Reported AP/D Applications in Last 7 Days	Sex	Weighted # in Population (000)	Percent in Population	Mid-Point of Range	Extension
0	F	3,953	4.4	0	0.0
	M	3,686	4.6	0	0.0
1 - 3	F	3,287	3.6	2	0.1
	M	3,812	4.7	2	0.1
4 - 7	F	56,914	62.7	5.5	3.4
	M	51,431	63.6	5.5	3.5
8 - 11	F	10,320	11.4	9.5	1.1
	M	7,962	9.8	9.5	0.9
12 - 14	F	11,700	13.0	13	1.7
	M	10,727	13.3	13	1.7
15 or more (b)	F	4,498	5.0	16	0.8
	M	3,252	4.0	16	0.6
Subtotal	F	90,742	100.0	Mean of Group	7.1
	M	80,870	100.0		6.9

- (a) Source: MSI (1995) as reported in ECA (1997).  
 (b) No upper-bound given for those in application frequency group "15 or more." Mid-point of range arbitrarily set at 16.

**Residue Fraction ( $Res_f$ )**

The residue fraction of AP/Ds is the amount of material deposited onto the skin that is available for absorption. ECA (1997) assumed that 100% of the deposited D4 present in the AP/D was available for absorption; however, results of human skin studies indicate that this assumption will result in an overestimation of the D4 available for absorption. The University of Rochester conducted studies that evaluated the percutaneous absorption of D4 following the application of AP/Ds (Zareba et al. 1996a,b; 1997). These studies used the human skin/nude mouse model in which human fetal skin is grafted onto nude female BALB/C nu-nu mice. After the graft healed, the chemical of interest was applied at a level of 15.7 mg/cm<sup>2</sup> and the percutaneous absorption across human skin evaluated. Over a 24-hour period, approximately 76% of the applied D4 evaporated from the application site. ECA (1997) reported that results from other studies indicated residue fractions ranged from 25% to greater than 70%. However, for their exposure assessment, ECA (1997) assumed that 100% of the deposited amount remained as a residue, i.e., a residue fraction of 1.0.

### ***Dermal Absorption Fraction (A)***

The dermal absorption fraction (A) is the amount of D4 applied to the skin that is absorbed. In the University of Rochester studies (Zareba et al. 1996a,b;1997;1998) the dermal absorption of D4 following application of a typical roll-on AP formulation was examined in the human skin/nude mouse model. The roll-on formulation contained approximately 60% D4, with the remainder consisting of D5, D6, dimethicone 50 cs, and aluminum zirconium tetrachlorohydrate-gly. In an initial study, D4 dermal absorption was estimated to be approximately 3.5%, which is the value used to estimate intake by the dermal route in the exposure assessment conducted by ECA (1997). However, in a more recent study at the University of Rochester, the mean dermal absorption of D4 measured was approximately 1.09% (Zareba 1998). This is in agreement with other dermal absorption values obtained in *in vitro* studies using human skin, in which dermal absorption values of 0.5% (DCC 1998b) to 1% (Food and Drug Administration 1997) have been reported. The midpoint of this range, 0.75%, was assumed for this risk assessment.

### ***Fraction Applied That is D4 (D4<sub>f</sub>)***

The fraction of the AP/D applied that is D4 consists of two factors, the fraction of the formulation that consists of cyclic siloxanes combined with the fraction of cyclic siloxanes that consists of D4. Solid APs are estimated to contain 40-60% cyclosiloxanes (i.e., a blend of D4, D5, and D6), with the average or base case of 50% assumed by ECA (1997). It was then assumed that DC 345 Fluid containing 6% D4, the typical choice for this product, was used to make the AP. Therefore, ECA (1997) assumed the percent of AP/D applied that is D4 for solid AP/Ds to be 3%.

For roll-on APs, whose formulation is approximately 60% cyclosiloxanes (midpoint of 50-70%), the base fluid was assumed to be DC 344 Fluid. DC 344 Fluid consists of approximately 90% D4. Therefore, for roll-on APs, ECA (1997) assumed the percent of AP/D applied that was D4 to be 54%.

The base fluid for aerosol AP/D was also assumed to be DC 344 Fluid. The percentage of aerosol AP formulations that are cyclosiloxanes ranged from 5% to 20%. ECA (1997) assumed a midpoint of 12.5% for the amount of the formulation that consists of cyclics, and of that, 90%

was assumed to be D4. Thus, ECA assumed (1997) that 11.25% of the aerosol AP/D applied was D4.

### *Body Weight (BW)*

The body weights assumed by ECA (1997) for users of AP/Ds were based on data contained in the second National Health and Nutrition Examination Survey (NHANES II). This survey was conducted between 1976 and 1980 with 20,322 U.S. residents, ranging in age from 6 months to 74 years. For men, aged 19 to 75, body weights for the 5th and 95th percentiles were 57.7 and 101.7 kg, respectively. The median or 50th percentile body weight was 75.9 kg. For females, the 5th, 50th, and 95th percentile values were 45.6, 57.1, and 82.2 kg, respectively. For this assessment, the median values were used for men and women of 75.9 and 57.1 kg, respectively.

### *Estimation of Dermal ADIs*

The summary of the parameters used in the estimation of dermal ADIs for AP/D consumers is provided in Table 3.1-3. Using Equation 3-1 and the values reported in Table 3.1-3, dermal ADIs were calculated for consumers using each type of AP/D (solid, roll-on, aerosol) and are summarized in Table 3.1-4. The use of roll-on AP/Ds resulted in the highest estimated ADIs of approximately 0.064 and 0.057 mg/kg/day for men and women, respectively, followed by aerosols, which were estimated to have ADIs of approximately 0.022 and 0.023 mg/kg/day for men and women, respectively. Solid AP/Ds were estimated to have the lowest dermal ADIs, with 0.0038 and 0.0026 mg/kg/day for men and women, respectively. [Note: These estimates vary from those reported by ECA (1997) because of the use of a more recent dermal absorption value. ECA used a dermal absorption percentage of 3.6%, while this assessment used the more recent value of 0.75%.]

**Table 3.1-3**  
**Summary of Dermal Exposure Parameters – AP/D Consumers**

Parameter	Men	Women
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
AF	6.9 applications/week	7.1 applications/week
Dep <sub>f</sub>	100%	100%
Res <sub>r</sub>	100%	100%
A	0.75%	0.75%
D4 <sub>f</sub> Solid Roll-on Aerosol	3% 54% 11.25%	3% 54% 11.25%
BW	75.9 kg	57.1 kg

**Table 3.1-4**  
**Estimated ADI for D4 from Dermal Exposure to AP/Ds**

AP/D Type	ADI (mg/kg/day)	
	Men	Women
Solid	0.0038	0.0026
Roll-on	0.0642	0.0568
Aerosol	0.0218	0.0231

**3.1.1.2 Inhalation Exposures to D4 from Use of AP/Ds**

Through normal use of products that contain D4, consumers may be exposed to D4 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. ADIs of D4 from inhalation exposures to the different types of APs were calculated using the following equation:

$$\text{ADI (mg/kg/day)} = \frac{(\text{AC} \times \text{MW}/24.5) \times \text{ED} \times \text{AF} \times \text{INH} \times \text{A}_f}{\text{BW} \times \text{DW}} \quad (3-2)$$

where

- AC = air concentration (ppm)
- MW = molecular weight of D4 (296 g)
- ED = exposure duration (hours/application)
- AF = application frequency (applications/week)
- INH = inhalation rate (m<sup>3</sup>/hr)
- A<sub>f</sub> = absorption fraction (unitless)
- BW = body weight (kg)
- DW = adjustment to daily intake (7 days/week)

As discussed for dermal exposures, even though the same basic equation is used to calculate exposure to D4 via inhalation, different exposure parameters must be used for the different types of AP/Ds. A discussion of each of the parameters is provided below.

#### ***Air Concentration (AC)***

The air concentrations used for the estimation of the ADI from inhalation exposure were the estimated air concentrations in the room where the AP/D was applied. These concentrations varied with product form and were based on the amount of product that volatilized during the application of the product. ECA (1997) relied on information from a study conducted by DCC in which three different commercial cyclosiloxane-containing APs (a solid, a roll-on, and an aerosol) were applied by two male participants in a 30 m<sup>2</sup> room in which the air changes per hour were essentially reduced to zero. The products were applied at two levels, a typical application amount and a relatively heavy application. For the first 6 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 20 minutes. Twenty-minute, time-weighted average cyclosiloxane concentrations for each of the application amounts were measured. Following the application of 1.4, 1.0, and 4.3 g of solid, roll-on, or aerosol AP/Ds, respectively, the highest 20-minute, time-weighted average measured was for roll-on AP/Ds (1.90 ppm), followed by aerosol (1.20 ppm) and solid (0.38 ppm) AP/Ds. An average concentration for high rates of application across all AP/D forms was 1.16 ppm total

cyclics, and the corresponding average for low rates was 0.40 ppm total cyclics (Table 3.1-5). Based on these data and the assumed application rate and D4 content of each of the products, ECA (1997) estimated base case breathing zone concentrations of D4 to be 0.05, 1.15, and 0.75 ppm for solid, roll-on, and aerosol, respectively.

**Table 3.1-5  
Breathing Zone Concentration of Cyclosiloxanes During AP/D Use**

Product Form	Amount Applied (grams)	20-Minute TWA Cyclics (a) Concentration (ppm)
Solid	1.4	0.38
	0.5	0.16
Roll-on	1.0	1.90
	0.4	0.55
Aerosol	4.3	1.20
	1.6	0.50
Average (high application amount)		1.16 ppm
Average (low application amount)		0.40 ppm
Overall Average		0.78 ppm

(a) Includes D4, D5, and D6.

***Exposure Duration (ED)***

There are no consumer use data for the amount of time from the application of an AP/D product and subsequent dressing, e.g., putting on a shirt. It is during this time that D4 air concentrations would be expected to be highest, if bathing and dressing occurred in a closed-in bathroom. ECA (1997) relied upon information provided by USEPA (1989) on the average time that men and women spend washing or dressing per week as an indication of the length of time a consumer may spend exposed to D4 in air (i.e., the time when air concentrations of D4 would be expected to be the highest over the course of the day). USEPA (1989) reported that, on average, men and women spend approximately 4.33 and 5.43 hours/week (0.62 and 0.78 hours/day), respectively, washing or dressing. ECA (1997) indicated that the use of these averages as an estimate of time a consumer would spend in the room (bathroom or dressing room) with the

highest D4 concentration an overestimation, because it includes time spent in the bath or shower prior to the application of an AP/D.

***Application Frequency (AF)***

The mean AP/D application frequency was assumed to be 7.1 and 6.9 times/week for women and men, respectively, as discussed previously in Section 3.1.1.1 on dermal exposure of consumers to AP/Ds.

***Inhalation Rate (INH)***

Estimates of inhalation rates for men and women were obtained by ECA (1997) from USEPA (1989), which provides estimates of inhalation rates for both men and women during resting and during light, moderate, and heavy activities (Table 3.1-6). Inhalation rates for the average adult were reported to range from 0.5 m<sup>3</sup>/hour during resting periods to 3.9 m<sup>3</sup>/hour during heavy activity. For the consumer, inhalation rates corresponding with light activity, 0.8 m<sup>3</sup>/hour for men and 0.5 m<sup>3</sup>/hour for women, were assumed by ECA (1997).

**Table 3.1-6  
Summary of Human Inhalation Rates for Men and Women by Activity Level (m<sup>3</sup>/hour)**

	Resting (a)	Light (b)	Moderate (c)	Heavy (d)
Men	0.7	0.8	2.5 (e)	4.8
Women	0.3	0.5	1.6 (e)	2.9
Average adult	0.5	0.6	2.1	3.9

- (a) Includes watching television, reading, and sleeping.
- (b) Includes most domestic work, attending to personal needs and care, hobbies, and conducting minor indoor repairs and home improvements.
- (c) Includes heavy indoor cleanup, performance of major indoor repairs and alterations, and climbing stairs.
- (d) Includes vigorous physical exercise and climbing stairs carrying a load.
- (e) Derived by taking the mean of the man and woman values for each activity level.

***Absorption Fraction (A<sub>f</sub>)***

ECA (1997) estimated an absorption fraction (A<sub>f</sub>) for inhalation of D4 based on inhalation rates and the following equation.



$$A_f = \frac{0.74}{1 + 7.483 \text{ IR}}, \quad (3-3)$$

where IR is the relevant inhalation rate in m<sup>3</sup>/hour for men or women. Using inhalation rates of 0.8 m<sup>3</sup>/hour for men and 0.5 m<sup>3</sup>/hour for women, absorption percents of 10.59% and 15.61% for men and women, respectively, were estimated. This method for estimating A<sub>f</sub> is currently under investigation.

#### ***Body Weight (BW)***

As discussed previously, median body weight values of 75.9 kg for adult men and 57.1 kg for adult women were used by ECA (1997) in this assessment.

#### ***Estimation of Inhalation ADIs***

A summary of the parameters used in the estimation of inhalation ADIs for consumers using AP/Ds containing D4 is provided in Table 3.1-7. Using Equation 3-2 and the parameters in Table 3.1-7, inhalation ADIs were calculated for consumers using each type of AP/D (solid, roll-on, aerosol) and are summarized in Table 3.1-8. The inhalation ADIs resulting from the use of roll-on type AP/Ds were 0.0095 (men) and 0.0151 (women) mg/kg/day, followed by the ADI for aerosols of 0.0062 (men) and 0.0098 (women) mg/kg/day, with the lowest inhalation ADIs of 0.0004 (men) and 0.0007 (women) mg/kg/day estimated for consumers who use solid type AP/Ds.

**Table 3.1-7**  
**Summary of Inhalation Exposure Parameters - AP/D Consumers**

Parameter	Men	Women
AC		
Solid	0.05 ppm	0.05 ppm
Roll-on	1.15 ppm	1.15 ppm
Aerosol	0.75 ppm	0.75 ppm
ED	0.62 hours	0.78 hours
AF	6.9 applications/week	7.1 applications/week
INH	0.8 m <sup>3</sup> /hour	0.5 m <sup>3</sup> /hour
A <sub>r</sub>	10.59%	15.61%
BW	75.9 kg	57.1 kg

**Table 3.1-8**  
**Calculated ADIs from Inhalation Exposure to AP/D Users**

AP/D Type	ADI (mg/kg/day)	
	Men	Women
Solid	0.0004	0.0007
Roll-on	0.0095	0.0151
Aerosol	0.0062	0.0098

### 3.1.1.3 Estimates of Total ADIs from Dermal and Inhalation Exposures

Through the normal use of an AP/D product containing D4, the potential exists for an individual to be exposed through dermal contact and inhalation, with intake from these routes of exposure being additive. The total ADIs from dermal and inhalation exposure combined from use of the different types of AP/Ds ranged from 0.0042 to 0.0737 mg/kg/day for men and from 0.0033 to 0.0719 mg/kg/day for women (Table 3.1-9). The use of roll-on type AP/Ds resulted in the highest total ADIs of 0.0737 and 0.0719 mg/kg/day for men and women, respectively.

**Table 3.1-9  
Calculated Total ADIs from Inhalation and Dermal Exposure to AP/Ds**

AP/D Type	Total ADI (mg/kg/day)	
	Men	Women
Solid	0.0042	0.0033
Roll-on	0.0737	0.0719
Aerosol	0.0280	0.0329

### 3.1.2 Exposures to Consumers Via the Use of HC/SC Products

As stated previously, not all HC/SC products are formulated with cyclosiloxanes, but for this assessment it was assumed that cyclosiloxanes are used in all HC/SC products. Exposure to 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., mascara, moisturizer, nail care, foundation, hand/body lotion, sunscreen, under eye cover, after shave lotions and colognes, and lipstick) was evaluated by ECA (1997). As with AP/Ds, exposures were estimated for the dermal and inhalation pathways and the ingestion pathway (lipstick only).

#### 3.1.2.1 Dermal Exposures to D4 from the Use of HC/SC Products

The same equation used to estimate a dermal ADI for AP/Ds was used to estimate a dermal ADI for HC/SC products (Equation 3-1). For the different types of HC/SC products, different exposure parameters were used. A discussion of these parameters is provided below.

#### *Application Rate (AR)*

ECA (1997) used several sources of information in the estimation of application rates (g/application) of HC/SC products (Table 3.1-10), including the results of a study conducted by the Cosmetic, Toiletry, and Fragrance Association (CTFA 1983) that examined the safety of D&C Red No. 9, 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). Studies conducted by firms included in the Technical Steering Committee, who provided oversight for the exposure assessment conducted by ECA, were also considered. No gender-specific application rate estimates were available. If women and men both used an HC/SC

product, the application rate was an aggregate 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 cyclosiloxanes would likely result in an overestimation of exposure. Application rates ranged from a few hundredths of a g/application to greater than 11 g/application (Table 3.1-10).

#### *Application Frequency (AF)*

In estimating the number of applications of HC/SC products per week, ECA (1997) relied primarily on information from a Mediamark Research Product Summary Report (MRI 1996). The results of this survey were judged by ECA (1997) to be the most suitable for an exposure assessment because the data were the most recent of the available data (i.e., CTFA 1983; COLIPA 1981) and provided separate estimates of application frequency for men and women for most HC/SC products. The application frequencies were based on estimates for people who use the product. The estimates of AF are summarized in Table 3.1-11. The application frequencies are given in terms of number of applications per week and consider seasonal usage, such as with sunscreens.

**Table 3.1-10**  
**Application Rate Estimates for HC/SC Products**

Products	Estimated Application Rate (g/use)
<b><u>Hair Care:</u></b>	
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
<b><u>Skin Care:</u></b>	
Antiwrinkle, antiaging lotions/creams; alpha-hydroxy acid products; beauty lotions; bleaching, lightening lotions/creams; moisturizing lotions/creams; hormone lotions/creams; night lotions/creams	0.58
Eye lotions/creams; concealer; undereye cover	0.06
Foundation makeup	0.27
Suntan/sunscreen cream/lotion	6.1
Hand/body lotions	3.5
Nail polish driers	0.25
After-shave (gel)	0.95
Mascara	0.11
Lipstick	0.022

NOTE: Above estimates are believed to be averages. There is substantial individual variability about these averages.

***Deposition Fraction ( $Dep_f$ )***

For many of the HC/SC products, the deposition fraction ( $Dep_f$ ) or the fraction of product that is potentially available for absorption was assumed to be 1 (100%). However, for some of the products, especially leave-in HC products, only a small fraction of the product is deposited on the scalp. Therefore, for these types of HC products, specifically leave-in conditioner, hair spray, cuticle coat, brilliantine, promade, and spray shine, a deposition fraction of 0.05 (5%) was assumed by ECA (1997). This value was estimated by the Technical Steering Committee for the exposure assessment and was 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, the average diameter is 70 microns, and the average total area of the 100,000 hairs on the scalp is approximately 21,991 cm<sup>2</sup>. The use of the ratio of the surface area of the scalp to that of hair as an estimation of the deposition fraction assumes that the distribution of the HC product between the hair and the scalp is directly related to the relative surface areas.

For the remaining HC/SC products, a  $Dep_f$  of 1 (100%) was assumed, with the exception of nail products. ECA (1997) based its assumption of the  $Dep_f$  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 will contact the skin or cuticle and be available for absorption. Therefore, ECA (1997) assumed a  $Dep_f$  of 0.01 (1%) for nail care products.

***Residue Fraction ( $Res_f$ )***

Residue fractions were assumed to be 1 (100%) for all HC/SC products, with the exception of shampoo and rinse-off conditioner. ECA (1997) assumed a 1% residue for these two HC products. This  $Res_f$  is based on interviews with personnel from the HC industry, who indicated that the product residue remaining after the application of rinse-off products is typically small, ranging from 0.5% to 1.5%. Results of studies with anti-dandruff and antimicrobial agents were also discussed as providing conservative estimates of the  $Res_f$ . Results from residue studies with zinc pyrithione, an anti-dandruff component, indicated that when, in varying dilutions, it was

**Table 3.1-11  
Usage Frequencies by Gender for HC/SC Products**

MRI Category	Products Included	Consumer Gender	Average Frequency (times/week)
Shampoos	multifunctional shampoos	Men Women	5.77 5.11
Conditioners	rinse-off/leave-on conditioners, rinses	Men Women	4.57 4.46
Hair sprays	styling sprays/spritzes, finishing sprays/ spritzes, protective sprays, conditioning sprays, curl revitalizers, spray shines (does not include hair treatment serums)	Men Women	5.07 5.66
Hand/Body lotions	hand/body lotions	Men Women	5.05 6.43
After-shave lotions and colognes	after-shave lotions (gels)	Men	5.07
Hair tonics, dressings, styling gels, and lotions	curl activators, brilliantines, pomades, hair treatment serums, cuticle coats, setting lotions	Men Women	4.22 4.00
Foundation	foundation make-up, concealers/under-eye covers	Women	5.57
Mascara	mascaras	Women	5.44
Nail care products and polish	nail polish driers	Women	2.05
Suntan/Sunscreen	suntan or sunscreen lotion/cream	Adults	0.21
Lipstick	lipsticks	Women	8.27
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	Women	6.60

left on the scalp for 1 to 32 minutes, residual deposits were approximately 0.01 (1%) of the amount applied (Fed Reg. 1982, 1978). In a separate study evaluating dermal absorption for triclosan, an antimicrobial agent, from bar soap, USEPA used a value of 0.01 (1%) for residue fraction. Based on this information, ECA (1997) assumed a residue fraction of 0.01 (1%) for cyclosiloxanes contained in shampoo and rinse-off conditioner.

#### *Dermal Absorption Fraction (A)*

For HC/SC formulations, ECA (1997) assumed the same dermal absorption fraction (A) as that for AP/D formulations, based on studies conducted by the University of Rochester (Zareba et al. 1996a,b, 1997; 1998). Dermal absorption, as measured in the *in vitro* human skin/nude mouse model was approximately 1.09%. This is in agreement with other dermal absorption studies conducted using human skin in *in vitro* experiments. Dermal absorption ranged from 0.5% (DCC 1998b) to 1% (Food and Drug Administration 1997). The midpoint of this range, 0.75%, was used in this preliminary risk assessment.

#### *Fraction of Product Applied That is D4 (D4<sub>f</sub>)*

As with AP/Ds, the fraction of the HC/SC applied that is D4 consists of two factors: the fraction of the formulation that consists of cyclosiloxanes combined with the fraction of cyclosiloxanes that consists of D4. Information was available on the percentage of cyclosiloxanes in various HC/SC products (Table 3.1-12). The percentage of cyclosiloxanes (base case) ranged from 2% (hair rinse) to 60% (hair cuticle coat). This information was provided to ECA (1997) by industry experts and reviewed for accuracy by the members of the Technical Steering Committee. The majority of the products have cyclosiloxane concentrations that are less than those in AP/D formulations. The wide range of values for various products reflects the lack of standardization of 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.

In determining the fraction of the cyclosiloxane that is D4, for most HC/SC products, the cyclosiloxane used for a particular product was not standard as is the case with AP/Ds.

Therefore, two ADI calculations were conducted by: 1) assuming the base fluid was high in D4 (DC 344 Fluid or equivalent) and 2) assuming a base fluid high in D5 and low in D4 (DC 345 Fluid or equivalent). DC 344 base fluid contains approximately 90% D4, while DC 345 base fluid contains approximately 6% D4. This fraction of D4 in the formulation combined with the fraction of the formulation that consists of cyclosiloxanes resulted in the D<sub>4f</sub> used for each HC/SC product in this assessment (Table 3.1-12).

#### *Body Weight (BW)*

As discussed previously, median body weight values of 75.9 kg for men and 57.1 kg for women were used by ECA (1997) for this assessment.

#### *Estimation of Dermal ADIs*

Table 3.1-13 presents a summary of the parameter values used to estimate ADIs by the dermal route for HC/SC products. Table 3.1-14 contains the ADIs estimated for dermal exposure to HC/SC products, with the exception of the ADI for lipstick, which also contains the contribution from ingestion of lipstick. The ADIs estimated from dermal exposure to HC/SC products containing base fluid DC 344 ranged from 0.0001 mg/kg/day (sunscreen) to 0.009 mg/kg/day (spray shine) for men and from 0.00004 mg/kg/day (nail care) to 0.0304 mg/kg/day (hand/body lotion) for women. HC/SC products containing base fluid DC 345 had ADIs ranging from 0.00001 to 0.0043 mg/kg/day (women). The contribution of ingestion of lipstick to the dermal ADI reported in Table 3.1-15 is discussed in Section 3.1.2.2. The ADIs estimated based on exposure to HC products (base fluid DCC 344) indicated that exposures for men were similar as those for women, with those for women always greater. Therefore, additional ADIs were not estimated for men for HC products with DC 345 as the base fluid, and ADIs were only estimated for a limited number of SC products. The results indicate that dermal ADIs from exposure to D4 from HC/SC (Table 3.1-14) are much less than the dermal ADIs estimated from exposure to D4 in AP/Ds (Table 3.1-4). The highest ADIs overall for HC/SC products were estimated for women from the use of hand/body lotion (0.0304 mg/kg/day), and for men from the use of spray shine (0.009 mg/kg/day).

**Table 3.1-12  
Cyclosiloxane Content of HC/SC Products**

Products Included	Percent Cyclosiloxane		Percent D4 <sub>f</sub>	
	Range	Base Case	Base Fluid DC 344 (a)	Base Fluid DC 345 (b)
<b>Hair Care:</b> Spray shine	20 to 70	50	45	3
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 13	2	1.8	0.12
Cuicle coat	40 to 80	60	54	3.6
Brilliantine	25 to 30	25	25.2	1.7
Promade	3 to 35	19	17.1	1.14
Rinse	0 to 3	2	1.8	0.12
<b>Skin Care:</b> 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 30	15	13.5	0.9
Concealer/undereye cover; lipsticks	5 to 50	25	22.5	1.5
Mascara	0 to 30	15	13.5	0.9
Foundation	0 to 30	10	9	0.6
Hand/body lotion	5 to 12	8	7.2	0.48
Suntan/sunscreen cream/loion	8 to 12	10	9	0.6
Nail polish driers; after-shave (gel)	0 to 75	40	36	2.4

- (a) Assumes that 90% of cyclosiloxane is D4.  
(b) Assumes that 6% of cyclosiloxane is D4.

Table 3.1-13  
Summary of Exposure Parameters Used to Estimate ADIs from Dermal Exposure to HC/SC Products

HC/SC Type	ADIs										
	AR (g/use)	AF (times/week)		Dep (%)	Res (%)	A (%)	Total (%)	D4 Fraction		BW	
		Men	Women					DC 344	DC 345	Men	Women
<b>HC Products</b>											
Shampoo	11.7	5.77	5.11	100	1	0.75	2	1.8	0.12	75.9	57.1
Rinse-out conditioner	11.2	4.57	4.46	100	1	0.75	2	1.8	0.12	75.9	57.1
Leave-in conditioner	11.2	4.57	4.46	5	100	0.75	2	1.8	0.12	75.9	57.1
Hair spray	5.6	5.07	5.66	5	100	0.75	2	1.8	0.12	75.9	57.1
Cuticle coat	4.7	4.22	4	5	100	0.75	60	54	3.6	75.9	57.1
Brilliantine	4.7	4.22	4	5	100	0.75	28	25.2	1.7	75.9	57.1
Pomade	4.7	4.22	4	5	100	0.75	19	17.1	1.14	75.9	57.1
Spray Shine	5.6	5.07	5.66	5	100	0.75	50	45	3	75.9	57.1
<b>SC Products</b>											
Mascara	0.11	NA	5.44	100	100	0.75	15	13.5	0.9	75.9	57.1
Moisturizer	0.58	NA	6.6	100	100	0.75	15	13.5	0.9	75.9	57.1
Nail care	0.25	NA	2.05	1	100	0.75	40	36	2.4	75.9	57.1
Foundation	0.27	NA	5.57	100	100	0.75	10	9	0.6	75.9	57.1
Hand/body lotion	3.5	5.05	6.43	100	100	0.75	8	7.2	0.48	75.9	57.1
Sunscreen	6.1	0.21	0.21	100	100	0.75	10	9	0.6	75.9	57.1
Undereye cover	0.06	NA	5.57	100	100	0.75	25	22.5	1.5	75.9	57.1
Lipstick	0.022	NA	8.27	100	100	0.75	25	22.5	1.5	75.9	57.1
After-shave gel	0.95	5.07	NA	100	100	0.75	40	36	2.4	75.9	57.1

NA - Not Applicable

**Table 3.1-14**  
**Calculated ADIs from Dermal Exposure to HC/SC Products - Consumers**

HC/SC Type	ADI (mg/kg/day)			
	Base Fluid DC 344		Base Fluid DC 345	
	Men	Women	Men	Women
<b>Hair Care Products</b>				
Shampoo	0.00017	0.00020	NC	0.00001
Rinse-out conditioner	0.00013	0.00017	NC	0.00001
Leave-in conditioner	0.00065	0.00084	NC	0.00006
Hair spray	0.00036	0.00053	NC	0.00004
Cuticle coat	0.00756	0.00952	NC	0.00064
Brilliantine	0.00353	0.00445	NC	0.00030
Pomade	0.00239	0.00302	NC	0.00020
Spray shine	0.00902	0.01338	NC	0.00089
<b>Skin Care Products</b>				
Mascara	NC	0.00152	NC	0.00010
Moisturizer	NC	0.00970	NC	0.00065
Nail care	NC	0.00004	NC	0.00000
Foundation	NC	0.00254	NC	0.00017
Hand/body lotion	0.00120	0.03040	NC	0.00426
Sunscreen	0.00011	0.00216	NC	0.00030
Undereye cover	NC	0.00141	NC	0.00020
Lipstick	NC	0.01108	NC	0.00077
After-shave gel	0.00163	NC	NC	NC

NC - Not Calculated.

**Table 3.1-15**  
**Summary of Inhalation Exposure Parameters - HC/SC Consumers**

Parameter	Women
AC	0.338 ppm
ED	0.78 hours
AF	1 application/day
INH	0.5 m <sup>3</sup> /hour
A <sub>i</sub>	15.61%
BW	57.1 kg

### 3.1.2.2 Inhalation Exposures to D4 from the Use of HC Products

As with AP/Ds, through the normal use of HC/SC products that contain D4, consumers may be exposed to D4 vapors via inhalation. Compared to exposure via dermal contact, inhalation exposures would be expected to be relatively small in magnitude. Information was available regarding possible air concentrations following use of HC products. No information was available on the potential inhalation concentrations to which consumers may be exposed during the use of SC products; however, inhalation exposure to D4 from SC products was assumed to be comparable to that estimated for HC products. Inhalation ADIs were estimated for women consumers only. ADIs of D4 from inhalation exposures to HC products were calculated using the following equation:

$$\text{ADI (mg/kg/day)} = \frac{(\text{AC} \times \text{MW}/24.5) \times \text{ED} \times \text{AF} \times \text{INH} \times \text{A}_r}{\text{BW}} \quad (3-4)$$

where

AC	=	air concentration (ppm)
MW	=	molecular weight of D4 (296 g)
ED	=	exposure duration (hours/application)
AF	=	application frequency (applications/day)
INH	=	inhalation rate (m <sup>3</sup> /hr)
A <sub>r</sub>	=	absorption fraction (unitless)
BW	=	body weight (kg)

Separate analyses were not conducted for various HC products. A single inhalation ADI was estimated for women consumers and assumed to be representative of inhalation exposures to both HC and SC products. A discussion of the values used by ECA (1997) for each of the parameters involved in the estimation of the inhalation ADI is provided below.

#### *Air Concentration (AC)*

ECA (1997) relied on a study similar to the one conducted with AP/Ds to determine the air concentration of cyclosiloxanes following use of HC products. Six personal monitoring samples were taken while consumers were using shampoos, conditioners, and hair sprays containing cyclosiloxanes. Following application of the HC products, users remained in the room

where the products were applied for 17-40 minutes. Based on the monitoring information, a time-weighted average concentration of 0.338 ppm was determined for D4.

***Exposure Duration (ED)***

As with AP/Ds, no information was available on the length of time that a consumer would spend in the environment that would contain the highest concentrations of cyclosiloxane following application of HC products. ECA (1997) again relied upon information provided by USEPA (1989) on the average time that men and women spend washing or dressing per week as an estimate of D4 exposure duration. Women spend approximately 5.43 hours/week (0.78 hours/day) washing or dressing. This value is likely an overestimation of ED to cyclosiloxanes following use of HC products, because it includes time spent in the bath or shower prior to the use of an HC product (ECA 1997).

***Application Frequency (AF)***

ECA (1997) assumed an application frequency of one per day for all HC/SC products.

***Inhalation Rate (INH)***

The inhalation rate assumed for women in deriving an inhalation ADI following use of HC products was the same as the inhalation rate assumed in the exposure assessment for AP/Ds. An inhalation rate, corresponding with light activity, of 0.5 m<sup>3</sup>/hour was assumed by ECA (1997), based on information in USEPA (1989).

***Absorption Fraction (A<sub>f</sub>)***

As in the assessment of AP/Ds, ECA (1997) estimated an absorption fraction (A<sub>f</sub>) for inhalation of D4 based on inhalation rates and Equation 3-3, where IR is the relevant inhalation rate in m<sup>3</sup>/hour for women. Using the inhalation rate discussed previously, 0.5 m<sup>3</sup>/hour for women, the percent absorption for was 15.61.

**Body Weight (BW)**

As discussed previously, a median body weight value of 57.1 kg was assumed for women by ECA (1997) in this assessment.

**Estimation of Inhalation ADIs**

A summary of the parameters used in the estimation of inhalation ADIs for consumers using HC/SC products containing D4 is provided in Table 3.1-15. Using Equation 3-4 and the parameters in Table 3.1-15, inhalation ADIs were calculated for consumers using HC/SC products. The inhalation ADI estimated for women using HC/SC products was 0.00437 mg/kg/day. This value is based on the actual use of several HC products simultaneously and cannot be attributed to any one product individually. Therefore, ADIs were not estimated for the combined routes, dermal and inhalation, for each HC/SC product separately. Rather an upper bound can be assumed if all of this inhalation exposure resulted from the use of a single product with the highest estimated dermal exposure, i.e., hand/body lotion for women. Addition of the inhalation pathway for these products would increase the estimated ADI (for dermal pathway alone) by 15% for women. This was not considered a significant contribution to total exposure.

**3.1.2.3 Oral Exposures to D4 from the Ingestion of Lipstick**

Dermal and inhalation exposures are the pathways of potential concern for most of the HC/SC products. In the case of lipstick, ingestion is also a potential pathway of concern. Because the application rate of lipstick is relatively small, it is unlikely that the ADI for this exposure pathway would be substantial; however, ECA (1997) derived an ADI for ingestion of lipstick based on the following equation:

$$ADI \text{ (mg/kg/day)} = \frac{AR \times CF \times D4_f \times AF \times I_f \times A_f}{BW \times DW} \quad (3-5)$$

where

- AR = application rate (g/application)
- CF = conversion factor (1000 mg/g)
- D4<sub>f</sub> = fraction of product applied that is D4 (unitless)
- AF = application frequency (applications/week)
- I<sub>f</sub> = ingested fraction (unitless)

$A_r$  = absorption fraction (unitless)  
 $BW$  = body weight (kg)  
 $DW$  = adjustment to daily intake (7 days/week)

Many of the parameters ECA (1997) used in this equation were discussed in previous sections. The application rate assumed for lipstick was 0.022 g/application (Table 3.1-10), based on the results of the CTFA (1983) survey. The application frequency (AF) of lipstick was assumed to be approximately 8.3 times/week based on the results of the MRI (1996) report (Table 3.1-11). The D4 fraction was assumed to be 22.5%, if the base fluid was DC 344. ECA (1997) conservatively assumed the ingestion fraction of lipstick ( $I_r$ ) to be 0.5 (50%), based on the results of the CTFA (1983) analysis of D&C Red No. 9, with the absorption fraction assumed to be 0.12 (12%) (Crofoot et al. 1997), based on oral absorption of D4 in rats. These parameters resulted in an estimated ADI from ingestion of lipstick of approximately 0.006 mg/kg/day. Under these assumptions, ingestion of D4 from lipstick would increase the estimated intake by approximately 50%, from 0.0111 mg/kg/day for the oral route alone to 0.0176 mg/kg/day for both routes (Table 3.1-16). This is an overestimate because it was assumed that 100% of the lipstick applied was available for dermal absorption and 50% was available for oral absorption.

Table 3.1-16  
 Summary of Oral Exposure Parameters - Ingestion of D4 from Lipstick

Parameter	Women
AR (g/use)	0.022
D4	22.5
AF (times/week)	8.27
$I_r$ (%)	50
$A_r$ (%)	12
BW (kg)	57.1

### 3.2 Occupational Exposures

Occupational exposures to D4 may occur in individuals who work in D4 manufacturing plants, in workers who work in plants where consumer products containing D4 are formulated,

and in individuals who use D4-containing consumer products in their profession, such as beauticians and barbers. Occupational exposures also may occur via the dermal and inhalation routes.

### 3.2.1 Occupational Inhalation Exposure to D4

Inhalation exposures to D4 may occur in individuals in a plant that manufactures D4, in individuals who work in plants that formulate products that contain D4, or in professionals who use D4-containing products in their jobs. ECA (1997) estimated inhalation ADIs for six worker categories: 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 involved in silicone production facilities, 5) barbers, and 6) beauticians. The same basic equation was used to determine ADIs for the different occupations with varying assumptions based on occupation. Intake due to inhalation exposure was calculated using the following equation:

$$\text{ADI (mg/kg/day)} = \frac{(\text{AC} \times \text{MW}/24.5) \times \text{ED} \times \text{EF} \times \text{WY} \times \text{IR} \times \text{Dep}_f}{\text{BW} \times \text{DY}} \quad (3-6)$$

where

AC	=	air concentration (ppm)
MW	=	molecular weight of D4 (296 g)
ED	=	exposure duration (hours/application)
EF	=	exposure frequency (days/week)
WY	=	work year (weeks/year)
IR	=	inhalation rate (m <sup>3</sup> /hr)
Dep <sub>f</sub>	=	deposition fraction in the lung (unitless)
BW	=	body weight (kg)
DY	=	days/year (365)

A discussion of the values assumed by ECA (1997) for each of these parameters and the justification for the selection of these values is discussed below and the values used for each worker are summarized in Table 3.2-1.

### *Air Concentrations (AC)*

The estimated air concentrations to which workers could potentially be exposed vary depending on the job category or job description of the worker. For example, air concentrations at a plant where D4 is manufactured would be expected to be different from D4 air concentrations in a beauty or barber shop. Eight-hour time-weighted average air concentrations were calculated by ECA (1997) for AP, HC and SC workers using data collected from personal monitors from workers in various areas of each plant.

For silicone workers, based on the basic types of operations performed in the manufacture and processing of D4, ECA (1997) identified six basic job categories. These categories were primary polymer operators, secondary polymer operators, compounding and packaging operators, miscellaneous finishing operators, packaging, shipping, loading and warehouse personnel and auxiliary personnel. A total of 567 time-weighted average air concentrations were considered in order to estimate the mean D4 air concentrations associated with each job category. Arithmetic mean time-weighted average D4 air concentrations ranged from 0.0375 ppm in the auxiliary work areas to 0.3977 ppm in the primary polymer operations areas. ECA (1997) calculated the mean D4 air concentration for all silicone workers to estimate ADIs from inhalation.

For beauticians and barbers, personal 8-hour time-weighted average air concentrations were taken for six hair salon technicians. ECA (1997) used the arithmetic mean from these measurements as estimates of D4 air concentrations to which barbers or beauticians may potentially be exposed.

### *Exposure Duration (ED)*

For AP/Ds, HC and SC workers, ECA (1997) assumed a standard 8-hour work day. Due to the manner in which shifts are typically scheduled for silicone workers, ECA (1997) assumed an 8.75-hour day. For beauticians and barbers, ECA (1997) assumed a 6.32-hour work day based on U.S. Bureau of Labor Statistics for barbers. However, this assumption overestimates exposures for beauticians, who, according to U.S. Bureau of Labor Statistics, work an average of 28 hours/week or 5.6 hours/day.

Table 3.2-1  
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 <sup>3</sup> /hr)	Body Weight (kg)
Antiperspirant	0.33 (0.15)	8	5	50	2.5 (M) 1.6 (W)	75.9 (M) 57.1 (W)
Skin Care	2.44 (1.76)	8	5	50	2.5 (M) 1.6 (W)	75.9 (M) 57.1 (W)
Hair Care	0.012 (0.007)	8	5	50	2.5 (M) 1.6 (W)	75.9 (M) 57.1 (W)
Silicone	0.1908 (0.0950) (b)	8.74	5	50	2.5 (M) 1.6 (W)	75.9 (M) 57.1 (W)
Beauticians	0.085 (0.083)	5.6	5	50	2.5 (M) 1.6 (W)	75.9 (M) 57.1 (W)
Barbers	0.085 (0.083)	6.74	5	50	2.5 (M) 1.6 (W)	75.9 (M) 57.1 (W)

- (a) Values are reported as arithmetic mean (geometric mean)  
(b) Arithmetic and geometric mean concentrations from all types of silicone workers

**Exposure Frequency (EF)**

For all workers, ECA (1997) assumed a standard 5-day work week.

**Work Year (WY)**

For all workers, ECA (1997) assumed that workers would be off from work for vacation, sick leave, etc., for 2 weeks/year resulting in a 50-week work year.

**Inhalation Rate (IR)**

ECA (1997) assumed USEPA (1989) inhalation rates for moderate activity.

**Deposition Fraction (D<sub>sp</sub>)**

The deposition fraction was determined by using the following equation:

$$\text{Dep}_f = \frac{0.74}{(1 + 7.483 \times \text{IR})} \quad (3-7)$$

where IR is the inhalation rate. The calculated deposition fractions were 0.0375 and 0.057 for men and women, respectively.

**Body Weight (BW)**

Body weights were based on data from the National Health and Nutrition Survey (NHANES II). ECA (1997) assumed median body weights from NHANES II for men and women.

**Estimation of Inhalation ADIs for Workers**

Using these inhalation exposure parameters, ADIs were calculated and are summarized in Table 3.2-2. For men, the calculated inhalation ADIs ranged from 0.0010 to 0.2004 mg/kg/day with the highest ADI reported for SC workers. ADIs in women ranged from 0.0013 in HC workers to 0.2590 in SC workers.

**Table 3.2-2  
Calculated ADIs from Inhalation Exposure - Workers**

Worker	ADI (mg/kg/day)	
	Men	Women
Antiperspirant	0.0271	0.0351
Skin care	0.2004	0.2590
Hair care	0.0010	0.0013
Silicone	0.0171	0.0221
Barbers/beauticians	0.0055	0.0071

**3.2.2 Occupational Dermal Exposure to D4**

Workers in a manufacturing or processing plant could be exposed to D4 via dermal contact, for example, in the event of a spill or leakage from a container. However, dermal exposure in the workplace is expected to be small because of Good Manufacturing Practices

(GMPs) in the workplace. In estimating exposures to workers, two scenarios were assumed: 1) workers' hands were covered with a material equivalent in composition to a formulated roll-on AP (formulated with DC 344 fluid) during a spill event and workers wiped their hands off with a towel or rag after the spill, or 2) workers' entire forearm and hands were covered with neat DC 344 fluid (a highly unlikely event) during a spill event. Dermal ADIs were estimated for men and women. ADIs were calculated for dermal exposure using the following equation:

$$\text{ADI (mg/kg/day)} = \frac{\text{EF} \times \text{D4}_f \times \text{T} \times \text{D} \times \text{A}_f \times \text{SA}}{\text{BW} \times \text{DY}} \quad (3-8)$$

where

EF	=	frequency of spill events (events/year)
D4 <sub>f</sub>	=	fraction of D4 in product that is spilled onto skin (unitless)
T	=	thickness of liquid product that covers the skin (cm)
D	=	density of liquid product (mg/cc)
A <sub>f</sub>	=	fraction of material on skin that is absorbed (unitless)
SA	=	surface area of exposed skin (cm <sup>2</sup> )
BW	=	body weight (kg)
DY	=	days/year (365)

A discussion of the values assumed by ECA (1997) for each of these parameters and the justification for the selection of these values is discussed below.

#### *Frequency of Spill Events (EF)*

ECA (1997) assumed a frequency of one spill event per month or 12 events/year. This assumption was made for illustrative purposes and is expected to be a conservative assumption. Based on conversations with AP plant personnel and the members of the Technical Steering Committee, spill events are infrequent. The assumption of one event per month was considered reasonable by AP plant personnel and the Technical Steering Committee.

#### *Fraction of D4 in Silicone Liquid (D4<sub>f</sub>)*

As previously discussed in Section 3.1.1.1, the formulation for roll-on APs is approximately 60% cyclosiloxanes, if the base fluid is DC 344 Fluid, with DC 344 Fluid containing approximately 90% D4. Therefore, for roll-on APs (Scenario 1), ECA (1997)

assumed the fraction of D4 in the roll-on AP to which the worker is exposed was approximately 54%. For Scenario 2 (exposure to neat DCC 344 Fluid), the fraction of the silicone liquid that was D4 was assumed to be 90%.

#### *Thickness of Product that Covers the Skin (T)*

As an estimate of the thickness of the product that covers the skin, ECA (1997) relied on parameters used in an analysis of dermal exposure resulting from spills of polychlorinated biphenyls (PCBs) conducted by Versar, Inc. (1983, 1984). In that analysis, the average thickness of five test solutions on the skin (mineral oil, cooking oil, bath oil, 50% bath oil/50% water, and water) was reported. To determine the thickness, the hands were immersed into the test solution, followed by a partial wipe with a rag. The average thickness of the five test solutions was 0.0018 cm; therefore, ECA (1997) assumed that a thickness of 0.0018 cm of product would adhere to the skin.

#### *Density of Product (D)*

The density of D4 assumed by ECA (1997) is the typical value for cyclics of approximately 950 mg/cm<sup>3</sup>.

#### *Fraction of Product that is Absorbed (A<sub>r</sub>)*

The dermal absorption fraction (A<sub>r</sub>) is the amount of D4 remaining on the skin that is absorbed. As with dermal exposure of consumers to roll-on APs, a mean dermal absorption percentage of 0.75% of the applied amount was assumed for workers, as discussed previously (Section 3.1.1).

#### *Surface Area of Exposed Skin (SA)*

Direct dermal contact to D4 by workers is expected to be unlikely, because workers engaged in activities that might result in spills or in cleanup activities typically wear gloves. However, ECA (1997) evaluated dermal exposure using two scenarios, and assuming for each scenario that the surface area of the exposed skin was different. For Scenario 1, ECA (1997) assumed that the hands of the worker would be exposed, or a surface area of 840 cm<sup>2</sup> for men and

746 cm<sup>2</sup> for women, based on information provided in USEPA (1989). For Scenario 2, hands and arms of the workers were assumed to be exposed. This would assume a surface area of the skin of 3120 cm<sup>2</sup> for men and 2846 cm<sup>2</sup> for women (USEPA 1989).

#### *Body Weight (BW)*

As discussed previously, median body weight values of 75.9 kg for men and 57.1 kg for women were used by ECA (1997) in this assessment, based on NHANES II.

#### *Estimation of Dermal ADIs for Workers*

The values for these parameters and the assumptions used are provided in Table 3.2-3. Based on these assumptions, ADIs for dermal exposures were calculated for workers and are provided in Table 3.2-4. The ADI from dermal exposure for workers was estimated to be 0.0121 mg/kg/day (men) and 0.0142 mg/kg/day (women) for Scenario 1 and 0.0156 mg/kg/day (men) and 0.0189 mg/kg/day (women) for Scenario 2.

### 3.3 Exposures in the General Public

The general public, i.e., individuals who in the vicinity of a manufacturing plant, but do not work in a plant or a facility where D4 is manufactured or used in product formulation, could be exposed to D4 via inhalation released to ambient air. Exposures in the general public following inhalation were estimated according to the following equation:

$$\text{ADI (mg/kg/day)} = \frac{\text{AC} \times \text{ED} \times \text{EF} \times \text{WY} \times \text{IR} \times \text{Dep}_f}{\text{BW} \times \text{DY}} \quad (3-9)$$

where

AC	=	air concentration (mg/m <sup>3</sup> )
ED	=	exposure length (hours/day)
EF	=	exposure frequency (days/week)
WY	=	number of weeks exposed in a year (weeks/year)
IR	=	inhalation rate (m <sup>3</sup> /hr)
Dep <sub>f</sub>	=	deposition fraction (unitless)
BW	=	body weight (kg)
DY	=	365 days/year

**Table 3.2-3  
Summary of Dermal Exposure Parameters - Workers**

Parameter	Scenario 1		Scenario 2	
	Men	Women	Men	Women
EF (events/year)	12	12	12	12
D <sub>4f</sub> (%)	54	54	90	90
T (cm)	0.0018	0.0018	0.0018	0.0018
D (mg/cm <sup>3</sup> )	950	950	950	950
A <sub>f</sub> (%)	0.75	0.75	0.75	0.75
SA (cm <sup>2</sup> )	840	746	3120	2846
BW (kg)	75.9	57.1	75.9	57.1

**Table 3.2-4  
Calculated ADI from Dermal Exposure - Workers**

Average Daily Dose (mg/kg/day)		
Scenario	Men	Women
1	0.0121	0.0142
2	0.0156	0.0189

A discussion of each of these parameters and justification is provided below and each parameter is summarized in Table 3.3-1.

***Air Concentration (AC)***

ECA (1997) used the data reported by Shields et al. (1996), where 210 indoor and 210 outdoor air samples were collected from 70 facilities and analyzed for D4 content. The arithmetic mean of these data was used to estimate the ADI.

Table 3.3-1  
Summary of Inhalation Exposure Parameters – General Public

Parameter	Value
AC	0.12 mg/m <sup>3</sup>
ED	24 hours/day
EF	7 days/week
WY	52 weeks/year
IR	2.5 cm <sup>3</sup> /hour (M) 1.6 cm <sup>3</sup> /hour(W)
Dep <sub>f</sub>	0.0375 (M) 0.0570 (W)
BW	75.9 kg (M) 57.1 kg (W)

**Exposure Duration (ED), Exposure Frequency (EF) and Weeks per Year (WY)**

ECA (1997) assumed that exposure was continuous, i.e., 24 hours/day, 7 days/week, 52 weeks/year.

**Inhalation Rate (IR)**

ECA (1997) assumed USEPA (1997) inhalation rates with moderate activity.

**Deposition Fraction (Dep<sub>f</sub>)**

The deposition fraction was the same as was calculated for workers (See Section 3.2.1).

**Body Weight (BW)**

ECA (1997) assumed median body weights for men and women based on data from NHANES II.

*Estimates of ADIs for the General Public*

Based on these assumptions, ADIs for inhalation exposures for the general public were calculated and are provided in Table 3.3-2. The ADIs for men and women were 0.0036 and 0.0046 mg/kg/day, respectively

Table 3.3-2  
Calculated ADIs From Inhalation Exposure - General Public

ADI (mg/kg/day)	
Men	Women
0.003552	0.004591

3.4 Exposure by Multiple Routes

It is recognized that a person may use one or more of these products on a regular basis. Therefore, a hypothetical receptor was evaluated to construct an upper bound case. It was assumed that this receptor was a woman who worked in either an antiperspirant or silicone manufacturing facility. It was also assumed that this woman used roll-on antiperspirant, hand and body lotion, moisturizer, lipstick, leave-in conditioner, and shampoo. The roll-on antiperspirant provided the highest estimated ADI among the three AP/Ds considered (see Table 3.1-9). The other HC/SC products were also among those that provided the higher estimated ADIs of the products evaluated (see Table 3.1-14). (Note that it was assumed that the HC/SC products were formulated with Base Fluid DC 344.) The total ADI from the use of these products was 0.158 or 0.145 mg/kg/day (Table 3.4-1).

Table 3.4-1  
Estimate of ADI (mg/kg/day) for a Woman Who Used Multiple Products

Source	ADI
Antiperspirant worker or silicone worker	0.035 or 0.022
Roll-on antiperspirant	0.719
Hand and body lotion	0.30
Lipstick	0.011
Moisturizer	0.009
Leave-in conditioner	0.00084
Shampoo	0.0002
TOTAL	0.158 or 0.145

## SILICONE ANTIFOAMS

### 3.5 Exposure of Consumers to D4 Via Ingestion of Food Products

Silicone antifoams are used in the processing of a wide variety of food products, including soft drinks, potato chips, and canned fruit. As such, they are considered direct food additives. They are also added directly to food as process aids, and as such are termed secondary direct food additives. Exposure to workers or to the general public from the manufacture or use of these products in food processing is considered to be *de minimis* (DCC 1998a). Therefore, consumer exposure through the ingestion of food products containing or processed with silicone antifoams is considered in this exposure assessment.

Antifoams fall into three general types: nonpolar oils, such as polydimethylsiloxane (PDMS) fluid or mineral oil, hydrophobic silica or hydrophobic polymers, or mixtures of nonpolar oils and hydrophobic silica (DCC 1998a). Silicone antifoams contain PDMS, which contains residual quantities of D4 and silica.

The oral ADIs from consumption of food products containing trace amounts of D4 were calculated using the following equation. Age- and gender-specific estimates were made.

$$ADI_{(mg/kg/day)} = \frac{C \times D4_f \times (SI + LI) \times P_f \times A}{BW} \quad (3-10)$$

where

C	=	antifoam concentration (mg/kg)
D4 <sub>f</sub>	=	fraction of product that is D4 (unitless)
SI	=	solid food intake per day (kg/day)
LI	=	liquid food intake per day (kg/day)
P <sub>f</sub>	=	fraction of food processed with silicone antifoams (unitless)
A	=	absorption fraction (unitless)
BW	=	body weight (kg)

#### Concentration (C)

The amount of silicone antifoam and, consequently, the amount of PDMS and D4, vary with the food product. However, the level of PDMS allowed in food at the "ready-for-consumption-state" after the use of silicone antifoams is specified by the Food and Drug

**CONT:**

Administration (FDA) in 21 CFR 173.40 (DCC 1998a). The maximum allowable amount of PDMS is 10 ppm. Therefore, this was used as the default value for all foods.

***Fraction Applied That Is D4 (D4)***

According to DCC (1998a), chemical analyses of silicone antifoam, 4.9% of the product was identified as D4.

***Solid and Liquid Food Intake (SI and LI)***

Estimates of solid and liquid food intake were based on values given in USEPA (1995). Solid food was divided into nonmeat, meat, and dairy products categories and totaled for the solid food contribution. Nonmeat foods included produce, breads, cereals, and other grain, while the meat category included beef, pork, poultry, and fish. Dairy products excluded milk, since according to 21 CFR 173.340, no silicone antifoam levels are allowed in milk. Similarly, the liquid food intake excluded water and milk. The default assumptions for these food products, by age group, are listed in Table 3.5-1.

***Fraction Absorbed (A)***

Oral dosing studies conducted by DCC were conducted in Fischer 344 rats (Crofoot et al. 1997). Oral absorption of D4 administered in a PDMS vehicle was estimated to be 12.13%. The absorption fraction used in this exposure assessment was 0.12.

***Fraction of Food Consumed Processed With Silicone Antifoams (P<sub>f</sub>)***

It was assumed that 50% of the liquid (except water and milk) and solid food consumed had been processed with a silicone antifoam. Fifty percent was used as a conservative estimate based on the low market share for silicone antifoams in the overall antifoam food processing market, which is approximately 10-20% (DCC 1998a).

**Table 3.5-1**  
**Default Assumption for Age-Specific Food Consumption**

Age (years)	Solid and Liquid Food Intake (kg)				
	Nonmeat	Meat	Dairy Products	Total Solid Food	Liquid Food
<1	0.211	0.050	0.297	0.558	0.130
1 - 6	0.439	0.092	0.046	0.577	0.310
6 - 14	0.511	0.156	0.053	0.720	0.400
14 - 18	0.511	0.252	0.053	0.816	0.580
18 - 45	0.508	0.250	0.052	0.810	1.010
45 - 75	0.515	0.250	0.055	0.820	0.780

**Body Weight (BW)**

Because age-specific food consumption rates were used, age- and gender-specific body weights were also used in this assessment. The values used are taken from USEPA (1995) and are given in Table 3.5-2.

**Table 3.5-2**  
**Default Assumption for Age- and Gender-Specific Body Weights**

Age (years)	Body Weight (kg)	
	Men	Women
<1	10.6	9.8
1 - 6	17.3	16
6 - 14	40	39
14 - 18	69.1	56.8
18 - 45	75.9	63.9
45 - 75	78	67.3

**Estimation of Oral ADIs**

Using Equation 3-10 and the parameter values described above and listed in Tables 3.5-1 and 3.5-2, oral ADIs were calculated for consumers exposed to D4 from the consumption of food



products processed with silicone antifoams (Table 3.5-3). The ADIs ranged from approximately 0.002 mg/kg/day for infants and children (less than 6 years old) to 0.0008 mg/kg/day for adults (18 years and older).

**Table 3.5-3**  
**Estimates of ADIs (mg/kg/day) for Selected Populations:**  
**Consumers Exposed to D4 in Food Products Processed with Silicone Antifoams**

Age (years)	Men	Women
<1	0.001907	0.002063
1-6	0.001507	0.001630
6-14	0.000823	0.000844
14-18	0.000594	0.000723
18-45	0.000705	0.000841
45-75	0.000603	0.000699

## 4.0 DOSE-RESPONSE ASSESSMENT

The Dose-Response Assessment step in this preliminary risk assessment consisted of the following:

- Selection of the critical study and critical endpoints from that study to be used in dose-response modeling;
- Conversion of the applied dose (in ppm) to the appropriate dose metric that can be used to extrapolate across species and routes of exposure and to provide estimates of intake for each of the selected receptors, products/activities, and routes of exposure; and
- Characterization of the dose-response relationship for the selected endpoints using the benchmark model to estimate both the maximum likelihood estimate of the benchmark dose (BMD) and the 95% lower bound on that dose (BMDL).

### 4.1 Selection of the Critical Study

The female crossover study (DCC 8463) was selected as the critical study. In this study, female Sprague-Dawley rats were exposed to 0, 70, 300, 500, or 700 ppm (mass/volume) D4 by whole body inhalation for 70 days prior to mating, with exposure continuing until PND 20, except for the interval between GD 20 and PND 4. The incidences of decreased mean live litter size, decreased number of pups born, and decreased number of uterine implantation sites were selected as the critical endpoints for dose-response modeling.

The two range-finding studies (DCC 8305 and 8306) and the phased-female study (DCC 8620) provided supporting evidence for the findings reported in the female crossover study (DCC 8463). The range-finding studies were not selected for dose-response modeling because of the fewer number of exposure concentrations tested (only 70 and 700 ppm in DCC 8305 and only 700 ppm in DCC 8306). The phased-female study was intended to provide insights into the phase of the reproductive cycle in the Sprague-Dawley rats during which D4 or a metabolite of D4 may be acting. In the phased-female study, only the Overall Phase exposed groups of animals to more than one concentration of D4; however, the study was terminated prior to parturition.

#### 4.2 Conversion of Inhalation Concentration to Estimated Intake

The conversion of the ppm concentrations of exposure to mg/kg/day was done using the following formula:

$$\text{Intake (mg/kg/day)} = \text{Conc (ppm)} \times \left( \frac{Mw_{D4} \text{ mg/m}^3}{24450} \right) \times \text{VE (l/min)} \times \frac{\text{Time (min/day)}}{\text{BW (kg)}} \times A\% \quad (4-1)$$

The respiratory minute volume (VE) was calculated by an allometric scaling to the body weight (BW):

$$\text{VE (l/min)} = 0.492 \times [\text{BW (kg)}]^{0.75} \quad (4-2)$$

The average body weights used in Equations 4-1 and 4-2 were calculated for each exposure group. First, each animal's average body weight was calculated over the period from the beginning of exposure through the mating period (28 to 70 days). An overall average for each exposure group was then calculated from the average individual body weights.

#### 4.3 Benchmark Dose-Response Modeling

As an alternative to the NOAEL, a benchmark calculation was performed for all endpoints for which a significant dose-related trend ( $p < 0.05$ ) was present. A BMD is a dose (or exposure) that corresponds to a specified level of response called the benchmark risk or benchmark response (BMR). A BMD is calculated by fitting a mathematical dose-response model to dose-response data. A lower statistical confidence bound on the BMD, termed the BMDL, has been proposed as an alternative to the NOAEL in determining acceptable human intakes of xenobiotics (Crump 1984, 1995). The USEPA Science Advisory Board has endorsed the use of the benchmark approach, and the USEPA has recently used the benchmark approach to calculate a number of RfDs.

Several potential advantages of the benchmark over the NOAEL have been identified (Crump 1995):

- The benchmark makes better use of dose-response information. Whereas the determination of a NOAEL generally involves comparing responses at discrete doses to responses in control subjects, the benchmark approach involves fitting a dose-response model to all of the dose-response data.
- The benchmark reflects sample size more appropriately than a NOAEL. Smaller studies tend to result in smaller BMDLs, whereas the opposite is true for NOAELs.
- Although the NOAEL is constrained to be one of the experimental doses, this is not the case with the benchmark. One consequence of this is that the benchmark approach is less likely to involve difficult and argumentative decisions that often arise concerning whether a particular experimental group defines a NOAEL.
- A benchmark can be defined from a data set in which a NOAEL does not exist.
- The calculation of a NOAEL generally uses data that are categorized into distinct dose groups. However, in some studies, including most epidemiological studies, categorization of subjects into dose groups is an arbitrary process. Such categorizations are not required in the benchmark approach.

For these data, which are expressed as counts, with one count per litter (e.g., the total number of live births), the counts were assumed to be normally distributed and a power dose-response model was applied (Crump 1995; Crump and Van Landingham 1995). An abnormal count was defined as one in the lower 5% of counts from unexposed litters (based upon the assumed normal distribution), and the BMD was defined as the exposure that causes an additional 10% of litters to have an abnormal count (increase from 5% to 15%). The BMDL was defined as the 95% lower bound on the BMD. These definitions of the BMD and BMDL are in keeping with USEPA's use of a 10% increase in response to define a benchmark in several of its RfD documents recently published on its IRIS database, and are supported by the finding by Allen et al. (1994a) that using a 10% increase to define a benchmark, in conjunction with use of 95% lower bounds, results in an average ratio of the NOAEL to the BMDL of about 2 (i.e., this benchmark approach resulted in BMDLs that were lower - i.e., more health protective - on average than NOAELs.)

Experimental NOAELs and BMDLs calculated are presented in Table 4.3-1. Experimental NOAELs were 500 ppm for each endpoint evaluated. The BMDLs ranged from

323 to 390 ppm, or, when expressed as an intake, from approximately 51 to 61 mg/kg/day. A BMDL of 51 mg/kg/day was selected for use in the calculation of the MOEs.

**Table 4.3-1**  
**Results of Benchmark Dose-Response Analysis**  
**of Statistically Significant Endpoint: from Study DCC 8463**

Endpoint	Experimental NOAEL (ppm)	Benchmark Doses in mg/kg/day (ppm)	
		BMD	BMDL
Total live births	500	83.2 (529)	61.2 (390)
Total number born (Litter size)	500	82.5 (525)	60.2 (383)
Total implants	500	81.9 (521)	50.8 (323)

## 5.0 RISK CHARACTERIZATION

The final step of the risk assessment process involves the synthesis of the toxicity and exposure information to arrive at qualitative and quantitative evaluations of any potential health hazards. The potential for D4 under the defined exposure conditions to pose a reproductive health hazard will be evaluated by comparing the calculated BMDL with the estimated intake for each receptor for each exposure pathway. A MOE will result from that comparison.

MOEs, which are the ratios of the BMDL to the estimated intake, were calculated for all the selected receptors. The MOEs for all of the worker populations, as well as the three categories of AP/Ds evaluated, are presented in Tables 5.1-1 to 5.1-4. All MOEs were greater than 100, and with few exceptions, were greater than 1000.

**Table 5.1-1**  
**Estimates of MOE for Selected Populations Exposed to D4:**  
**Workers and the General Public**

Population	Women	Men
<b>Workers (a)</b>		
Antiperspirants	1457	1889
Skin care products	196	255
Hair care products	39231	51000
Silicone workers	2318	3000
Beauticians/Barbers	7186	9273
<b>General Public (a)</b>	<b>11087</b>	<b>14167</b>

(a) Inhalation route of exposure only.

**Table 5.1-2**  
**Estimates of MOE for Consumers Exposed to D4**  
**from the Use of Selected Personal Care Products**

Population	DCC 344		DCC 345	
	Men	Women	Men	Women
<b>Consumers: Antiperspirants/Deodorants (a)</b>				
Solid	12232	15464	NC	NC
Roll-on	692	709	NC	NC
Aerosol	1821	1551	NC	NC
<b>Consumers: Skin Care Products (b)</b>				
Mascara	NC	33628	NC	508617
Moisturizer	NC	5259	NC	79008
Nail care	NC	1436094	NC	24413595
Foundation	NC	20077	NC	301402
Hand/body lotion	42607	1677	NC	11979
Sunscreen	469492	23565	NC	168370
Undereye cover	NC	36168	NC	256985
Lipstick	NC	4602	NC	66522
After-shave gel	31259	NC	NC	NC
<b>Consumers: Hair Care Products (b)</b>				
Shampoo	297727	251687	NC	4068933
Conditioner (rinse out)	393768	701402	NC	4882719
Conditioner (leave in)	78500	630	NC	904207
Hair spray	141119	95366	NC	1436094
Cuticle coat	6746	5355	NC	80308
Brilliance	14454	11473	NC	171927
Pomade	21303	16907	NC	254308
Spray shine	5655	3812	NC	57175

NC - Not Calculated

(a) Dermal and inhalation routes of exposure.

(b) Dermal route of exposure only.

**Table 5.1-3**  
**Estimate of MOE for a Woman Who Used Multiple Products**

Exposure Routes	MOE
Antiperspirant or silicone manufacturing worker who uses roll-on antiperspirant, hand and body lotion, moisturizer, lipstick, conditioner, and shampoo	323 or 352

**Table 5.1-4  
Estimates of MOE for Persons Exposed to D4  
in Food Products Processed Using Silicone Antifoams**

Age (years)	Men	Women
<1	26738	24720
1-6	33833	31291
6-14	61942	60394
14-18	85853	70571
18-45	72335	60612
45-75	84566	72966

A MOE of a specified magnitude indicates that exposure at the corresponding estimated intake level or below is not expected to result in adverse effects in populations so exposed. A MOE of 100 is typically considered of sufficient magnitude when the basis of the BMDL is animal data (USEPA 1994). A MOE of 100 indicates that the estimated intake is 100 times lower than the BMDL, which is the equivalent of the NOAEL. If only the data from the reproductive toxicity study used as the basis for the BMDL (DCC 8463) were considered and if it was assumed that the assumptions and parameter values used in the preliminary exposure assessment were correct, then a MOE of between 100 and 300 would be deemed acceptable. The components of the MOE can be thought of as the typical factors of 10 for interspecies extrapolation (from animals to humans) and a factor of 10 for intrahuman variability, resulting in a MOE of 100. It could be argued, since this is a preliminary risk assessment, that applying an additional modifying factor of 3, because the two-generation study results are not yet available, would be prudent, thereby resulting in a MOE of 300. As stated, at a MOE of 100, the estimated D4 intake for all workers, consumer product users, and the general public evaluated would be well below levels expected to be health protective. For those receptors with a MOE greater than 100 but less than 300, a closer look at the underlying assumptions used to develop those scenarios would be warranted. Only workers in the category designated as SC workers fell into that category.

However, determination of the magnitude of the MOE considered adequate and health-protective should be based on a weight-of-evidence evaluation of all of the data and should consider the uncertainties (and in some cases, variability) inherent in either the extrapolation to the target population (e.g., consideration of species- or route-specific differences) or in the estimate of intake levels (e.g., consideration of underlying assumptions and parameter values). In

each step in the calculation of each MOE, conservative, health-protective assumptions were made. Some of these assumptions were based on current practices in risk assessment, while other assumptions were based on preliminary data, e.g., with regard to route-to-route extrapolation. Refinement of these assumptions may lead to lower estimates of delivered dose to the target species and, hence, larger estimated MOEs for each scenario. The key considerations can be summarized as follows.

### 5.1 Uncertainty Due to Route Extrapolation

A major source of uncertainty is the assumption of equivalent intake across routes of exposure. The air concentrations used in the whole body inhalation exposure in Sprague-Dawley rats in the reproductive toxicity study were converted to estimates of intake, expressed in mg/kg/day in rats, which were subsequently used in the dose-response modeling to provide the BMDL. As described in the ECA (1997) exposure assessment, estimates of D4 intake, expressed in mg/kg/day, were calculated for the dermal route of exposure for the selected scenarios. A major assumption inherent in the calculation of MOEs is that once D4 crosses the initial biological barrier, i.e., the lung for inhalation exposure or the skin for the dermal exposure route, then delivery to the target tissue and hence the biologically relevant dose at the target tissue is independent of initial route of exposure.

Recent pharmacokinetic studies and pharmacokinetic modeling have demonstrated that such an assumption greatly overestimates the delivered dose of D4 by the dermal route compared to the inhalation route of exposure (DCC 1998b). When absorbed through the lungs, D4 enters the arterial systemic circulation where it is distributed throughout the body to potentially all organ systems. When absorbed by the dermal route, D4 enters the venous circulation, which moves directly to the heart and lungs, where the majority of D4 is then exhaled prior to being available systemically. The delivered dose to the target tissue is expected to be considerably less for an equivalent intake (amount that crosses the initial biological barrier) by the dermal route than the inhalation or oral routes of exposure.

A series of studies were conducted and a physiologically based pharmacokinetic (PBPK) model was constructed to evaluate the magnitude of that difference (DCC 1998b). Dermal absorption of D4 was measured in Sprague-Dawley rats to which neat D4 was applied for 6 hours

under an occluded dressing. The total amount absorbed and the amount excreted in expired air, urine, and feces were used to estimate the D4 body burden and to compare this body burden to that achieved following a 6-hour inhalation exposure at 700 ppm. The PBPK model, developed using these and other data, predicted that the area under the curve (AUC) of free D4 in blood for the 6-hour, occluded dermal exposure would be 60-fold lower than the AUC for free D4 following a 6-hour inhalation exposure at 700 ppm. Since absorption across human skin is considerably less for the rat than human skin and human skin would not be occluded, the 60-fold factor is likely to be an underestimate of the difference in delivered dose for different routes of exposure. However, even at a 60-fold difference, MOEs based on the dermal route of exposure as reported in Table 5.1-2 would be 60 times greater, in which case, all MOEs for consumer products would be greater than 1000 and most greater than 10,000.

## 5.2 Uncertainties Due to Strain and Species Specificity

One of the underlying assumptions in risk assessment is that animals and humans are equally sensitive in terms of risk when the dose is measured in the same units for both species, i.e., the delivered dose to the target tissue. Two major considerations are inherent in this assumption. One assumption is similar in concept as discussed above for route-to-route extrapolation and presumes that for the same intake for the same route of exposure, the delivered dose to the target tissue is equivalent in humans and the animal model. Preliminary pharmacokinetic and metabolism studies indicate that not only would the metabolism and hence availability of D4 at the target tissue be different for rats and humans, but that this availability may be strain-specific and there may be differences between the Sprague-Dawley rat and the Fischer 344 rat. This suggests that prior to any dose-response modeling, the dose-metric should be the human equivalent dose to the target tissue rather than the estimated intake for the rat model. The MOEs may change in that event; however, the magnitude of that change will be assessed following completion of pharmacokinetic studies and PBPK modeling.

The second major consideration is the underlying assumption of species extrapolation in that, even when expressed as a human equivalent target dose, the human is as sensitive as the rodent and, therefore, in the absence of data to the contrary, it presumes the same mode of action in the human and the rodent. This currentl is a major area of uncertainty.

## 6.0 CONCLUSIONS

A series of reproductive studies provided consistent evidence that D4 caused decreases in mean live litter size, numbers of pups born, and numbers of uterine implantation sites in Sprague-Dawley rats. The lowest BMDL resulting from Benchmark dose-response modeling was 51 mg/kg/day (323 ppm). Exposures to humans either in the workplace, through consumer products, or in the general environment that result in estimates of intake at least 100-fold lower than the BMDL, i.e., a MOE of 100 or greater, are not expected to cause any adverse reproductive effects in those populations. All MOEs calculated for the selected receptors were all greater than 100 and with few exceptions were greater than 1000. When the impact of assumptions regarding dermal absorption and route equivalence is considered, all MOEs for consumer use products are greater than 1000 and for many products, greater than 10,000. MOEs of even greater magnitude are expected when the species extrapolation uses the delivered dose at the target tissue rather than estimates of intake across the biological barrier. MOEs may be further increased when the species- and strain-specific modes of action can be considered.

This risk assessment is considered preliminary and will be refined when the two-generation reproductive toxicity study is completed. However, given the several major assumptions that result in overestimates of intake and the assumptions with regard to route and species extrapolation, these MOEs are more likely to increase than to decrease. Conclusions with regard to the lack of potential for adverse reproductive effects in populations exposed, as described in this preliminary risk assessment, are likely to remain unchanged in the final risk assessment.

## 7.0 REFERENCES

- Allen B, Kavlock R, Kimmel C, Faustman E. 1994a. Dose-response assessment for developmental toxicity. II. Comparison of generic benchmark dose estimates with no observed adverse effect levels. *Fundam Appl Toxicol* 23:487-495.
- Allen B, Kavlock R, Kimmel C, Faustman E. 1994b. Dose-response assessment for developmental toxicity. III. Statistical models. *Fundam Appl Toxicol* 23:496-509.
- Cosmetic, Toiletry, and Fragrance Association (CTFA). 1983. Final Review and Analysis of Scientific Studies and Risk Assessments Supporting the Safety of D&C Red No. 9 for Use in (1) External Cosmetic and Drug Products that are not Subject to Incidental Ingestion at Levels Consistent with Good Manufacturing Practices and in (2) External Cosmetic and Drug Lipstick and Other Lip Products that are Subject to Incidental Ingestion at Levels Up to Two Percent. August 15, 1983 (as cited in ECA 1997).
- Crofoot SD, McMahon JM, Hubbell BG, Seaton MJ, Plotzke K. 1997. Absorption and disposition of octamethylcyclotetrasiloxane in female Fischer 344 rats following delivery in two carriers via gavage. *Toxicologist* 36, No. 1, Part 2, p. 143 (As cited in DOW 1998a).
- Crump K. 1984. A new method for determining allowable daily intakes. *Fundam Appl Toxicol* 4:854-871.
- Crump K. 1995. Calculation of benchmark doses from continuous data. *Risk Anal* 15:79-89.
- Crump K, Van Landingham C. 1995. *Bench\_C: A Fortran Program to Calculate Benchmark Doses from Continuous Data*. ICF Kaiser, K.S. Crump Group, Ruston, LA.
- Crump K, Howe R, Kodell R. 1991. Permutation tests for detecting teratogenic effects. In: Krewski D, Franklin C, eds. *Statistics in Toxicology*. Gordon and Breach Science Publishers, New York. Pp. 349-377.
- Dow Corning Corporation (DCC). 1998a. *Interim Exposure Assessment for Silicone Antifoams in Food Processing and Over-the-Counter (OTC) Antigas (AG) Products*. Prepared by Dow Corning Corporation, Midland, MI. September, 1998.
- Dow Corning Corporation (DCC). 1998b. Personal communications from Dr. Kathleen Plotzke.
- European Cosmetic, Toiletry, and Perfumery Association (COLIPA). 1981. Human Exposure to N-Nitrosamines, Their Effects, and a Risk Assessment for N-Nitrosodiethanolamine in Personal Care Products. Technical Report No. 41, European Chemical Industry Ecology and Toxicology Centre (ECETOC), Brussels, Belgium, August 1990 (as cited in ECA 1997).