M E M O R A N D U M

TO: Robert Barham, Ph.D.
Assistant Chief, Stationary Source Division
Air Resources Board

FROM: George Alexeeff, Ph.D.
Deputy Director for Scientific Affairs

DATE: September 13, 2007

SUBJECT: REVIEW OF TOXICITY INFORMATION ON D5

We are forwarding our review of available information on the toxicity and persistence of decamethylcyclopentasiloxane (D5), a proposed alternative for perchloroethylene in dry cleaning. The review was conducted to provide ARB with information on which to base a determination of whether D5 could be considered a non-toxic alternative to perchloroethylene for dry cleaning under AB 998 (Lowenthal, Chapter 821, Statutes of 2003), pursuant to contract number 05-414. In response to your request to evaluate available information on the toxicity of D5 under the statutory mandate, OEHHA staff have reviewed information submitted by the Silicones Environmental Health and Safety Council (SEHSC), including studies evaluating acute and subchronic toxicity, neuroendocrine activity, estrogenicity, genotoxicity, chronic toxicity and carcinogenicity and related mode of action studies, and pharmacokinetics. In addition, we evaluated an SEHSC white paper summarizing the toxicity of D5, and an exposure assessment conducted by Environ Corporation for SEHSC. We also searched the open literature for additional information, including government documents from other countries, and identified additional information on human exposure, environmental persistence and accumulation in biota. As requested by ARB, we focused on evaluating the applicability of the SEHSC-proposed mechanism of action of tumor formation in rodents to human health risk assessment. Our review of the available information is attached.

In the process of reviewing the information, we met three times with the SEHSC representatives, including their toxicologists. We sought outside expertise from the University of California, Davis, regarding the merits of the proposed mode of action of D5 induced tumors in rodents. We also spoke with U.S.EPA scientists, who reviewed materials on D5 toxicity under

their own regulatory program, particularly with regard to the proposed mode of action of D5 induced rodent tumors.

OEHHA has several concerns about the toxicity and persistence of D5. In evaluating the information on the mode of action of D5 tumorigenesis in rodents, we used similar criteria to those laid out by U.S. EPA for determining whether a mode of carcinogenic action in animals is applicable to humans. The materials presented by SEHSC argue that D5 mode of action involves a pathway not applicable to humans – in acting as a dopamine agonist in the brain, the hormonal milieu of the rodent becomes estrogen-dominated, thus stimulating uterine tumors. Although the argument that the uterine tumors in rats due to D5 exposure occur by a mechanism not applicable to humans appears plausible, OEHHA has determined that the data presently in hand are insufficient to conclude definitively that this is the MOA for tumorigenesis and that the information is irrelevant to human risk assessment. In making this determination, OEHHA is consistent with the judgment of U.S. EPA's scientists, who reported a similar conclusion to SEHSC in December 2006. Furthermore, additional non-carcinogenic effects, associated with altered dopamine and prolactin levels, have been reported in humans and animals. Systems affected include the nervous system, fat tissue, the liver (bile formation), and the immune system. Thus, more widespread exposure to D5, a dopamine agonist, has potential public health impacts. Further, D5 appears to have significant bioaccumulative potential, has been measured in several aquatic species at ppm concentrations, and appears to have a long half-life in humans. Thus, D5 persistence in the environment and in animal and human tissues is a concern. OEHHA cannot conclude at this time that D5 is non-toxic.

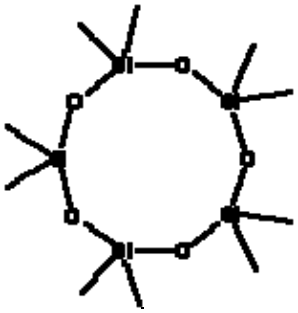
We hope the review of this material is useful in your implementation of AB 998. Should you have any questions or concerns, please call me at (916) 322-2067, or Dr. Melanie Marty at (510) 622-3150.

Attachment

cc: Robert Krieger, ARB
Melanie A. Marty, Ph.D.
Andrew Salmon, Ph.D.

TOXICITY DATA REVIEW

Decamethylcyclopentasiloxane (D5)



CAS Registry Number: 541-02-6

Summary

Decamethylcyclopentasiloxane (D5) is a low molecular weight cyclic siloxane used for industrial (silicone fluids and elastomers) and consumer product (cosmetics and toiletries) applications. It is also being developed as an alternative to perchloroethylene in dry cleaning and is currently in use in California under the Green Earth trademark. Under the Non-toxic Dry Cleaning Program established by AB 998 (Lowenthal, Chapter 821, Statutes of 2003), dry cleaners who currently use perchloroethylene are eligible to apply for $10,000 demonstration grants to assist them in switching to non-toxic and non-smog forming cleaning technologies. This evaluation discusses whether there is a scientific basis for considering D5 to be non-toxic. Concerns for possible toxic effects of D5 were raised following the discovery that D5 exposure causes uterine cancer in female rats. At the request of the California Air Resources Board, staff of the Office of Environmental Health Hazard Assessment (OEHHA) evaluated information on D5 toxicity, including a proposed mode of action for the formation of rodent tumors, and the relevance of this mechanism to cancer in humans. This review includes data in the open literature or made available by the Silicones Environmental Health and Safety Council (SEHSC) through June 2007.

D5 is an oily liquid that boils at 210°C. It has low solubility in water and high lipid solubility; the logarithm of its octanol water partition coefficient (log K_{ow}) is between 5 and 6 (Table 1). Thus it has a 100,000 times greater preference for lipids than water. Based on this log K_{ow}, OEHHA concludes that D5 could accumulate in the environment and may bioconcentrate. Estimations of the bioconcentration factor (BCF) for D5 range from 2000 (HSDB, 2007) to 46,774 (Environment Canada, 2007). (For comparison, the range of BCF for perchloroethylene, for which D5 is a proposed substitute, is 26-76 (HSDB, 2007).) A chemical with a BCF of > 1000 is considered by U.S. EPA (1998) to be a potentially persistent pollutant, while a BCF > 5000 is characteristic of highly persistent substances such as DDT and polychlorinated biphenyls. D5 has been detected in human adipose tissue and breast milk, and in fish. Animal experiments have also shown that siloxane residues, including unchanged D5, are persistent in a

variety of tissues for extended periods after exposure. Based on the log K_{ow}, BCF, detection in biota and experimental data showing residues, OEHHA considers D5 to be a persistent substance.

Table 1. Chemical and physical properties (HSDB[a], 2007; Environment Canada[b], 2007)

Description	oily liquid
Molecular formula	$C_{10}H_{30}O_5Si_5$
Molecular weight	370.8 daltons
Boiling point	210°C
Melting point	-38°C
Density/Specific gravity	0.9593 at 20°C/4°C
Vapor pressure	0.2 torr (mm Hg) at 25°C
Solubility	0.017[a] – 0.05[b] mg/L at 25°C
Log Kow	5.2[a] – 5.71[b]
Log Koc (organic carbon/water partition coefficient)	5.16
Henry's law constant	0.306 atm-m^3/mole at 25°C
Hydroxyl radical reaction rate constant	1.55 x 10^{-12} cm^3/molec-sec at 25°C
Conversion factor	1 ppm = 15.1 mg/m^3

Inhalation of 160 ppm D5 for 12 or 24 months by female rats led to uterine endometrial adenocarcinomas (Dow Corning, 2005a). The structural analog octamethylcyclotetrasiloxane (D4) is estrogenic in rats, but D5 is not positive in the assays conducted to date for estrogenicity. The SEHSC has proposed that the mode of action for rodent carcinogenicity, involving action as a dopamine agonist causing suppression of prolactin (and thus of progesterone) that leads to tumor formation in the female rat, is not relevant to humans. Although the proposed mode of action is plausible, additional study is necessary to make a definitive conclusion that this is the mode of action for tumorigenesis and that it has no relevance to human risk assessment. OEHHA also has concerns about other health implications of the effects of D5, including impacts on the various human physiological systems that are regulated or influenced by prolactin (e.g., reproductive system, adipose tissue, bile production, immune system), and the potential for effects on the nervous system subsequent to disruption of normal dopaminergic neurotransmission (e.g., possible psychological imbalance). Based on these health concerns, and the evident potential for bioaccumulation, OEHHA is not prepared to recommend that D5 be considered non-toxic.

D5 Environmental Effects

Environmental Fate and Transport

D5 exhibits high vapor pressure, Henry's law constant, log Kow (octanol:water partition coefficient) and log Koc (organic carbon:water partition coefficient) values. These data indicate that D5 will partition into air, soil and sediments. Fugacity modeling indicates that if this substance is released equally to the three major environmental compartments (air, water, and soil), it will partition into all compartments including air, water, soil, and sediments, with the

latter two compartments being predominant (Environment Canada, 2007). D5 released only to air will generally remain in air, with little partitioning to other compartments. D5 released to water will adsorb to suspended solids and sediment because of its high log Koc value, which will reduce the potential for volatilization. Therefore, D5 can be expected to remain mainly in water and primarily partition into sediments. D5 released to soil is expected to remain mostly in soil, since it will adsorb to and be relatively immobile in soil, thus reducing its potential for volatilization.

Environmental Occurrences

Air

US EPA (1992) reported detecting D5 in 29 indoor air samples (0.3-12.4 µg/m3) from office buildings located in 7 cities and in three outdoor air samples (0.21-0.9 µg/m3).

Indoor air measurements of siloxanes were performed in children's bedrooms in 400 Swedish households as part of a siloxanes screening study performed for the Swedish Environmental Protection Agency by the IVL Swedish Environmental Research Institute (IVL SERI). D5 was detected in 250 homes at concentrations of 0.5 - 79.4 µg/m^3, with a mean concentration of 9.7 µg/m^3 (personal communication, Norbert Schmidbauer, Norwegian Institute for Air Research, 2005, as cited in Kaj et al. 2005).

An environmental monitoring study of volatile methylated siloxanes in the Nordic countries was sponsored by the Council of Nordic Ministers (Norden, 2005). This study found D5 in air, water, sediment, sewage sludge and biota samples, and D5 was noted to be the dominating siloxane in most samples. The average air concentration of siloxanes [D4 (Octamethylcyclotetrasiloxane), D5 and D6 (dodecamethylcyclohexasiloxane)] was in the\range of 0.01 - 5 µg/m^3 in urban areas, landfills, and other point sources. Samples taken inside sewage treatment plants (STPs) were significantly higher (up to approximately 20 µg/m^3).

Water

D5 has been detected in drinking water concentrates obtained from water supplies in new Orleans, LA and Cincinnati, OH (Lucas, 1984).

In wastewater treatment plants in Canada, levels of organosiloxanes, principally D4 and D5, have been reported to be up to 710 µg/L and up to 13 µg/L in the influent and effluent, respectively (Maguire, 2001; as cited in Hydromantis et al., 2005).

D5 was not detected in any of six water samples analyzed in the Swedish siloxane screening study (Kaj *et al*., 2005). D5 was also not detected in background or urban water in the Nordic screening study (Norden, 2005), but was detected in substantial amounts in sewage treatment plant (STP) intakes (approximate concentrations 1 – 25 µg/L), and in sewage treatment plant outfalls (approximately < 1 – 5 µg/L) and landfill leachates (approximately 0 - 5 µg/L).

Sediments

The Swedish siloxane screening study (Kaj et al. 2005) did not find D5 in analyzed lake or marine sediments. However, D5 was the predominant cyclosiloxane detected in sediments in the Nordic screening study (Norden, 2005). Concentrations ranged from <5 - 130 ng/g dry weight (dw), with one Danish sample having a concentration of 2,000 ng/g dw.

Aquatic Organisms

The Swedish siloxane screening study (Kaj *et al*., 2005) did not find D5 in analyzed fish muscle. However, in the Rhine River in Germany, D5 has been detected in fish up to 1 mg/kg (1 ppm) and in eels up to 2.6 mg/kg (Mait, 2005).

D5 was also detected in aquatic organisms in the Nordic siloxane screening study (Norden, 2005). D5 was the predominant cyclosiloxane found in both fish livers and marine mammals. D5 concentrations in freshwater and marine fish from urban areas and near STPs ranged from < 5 - 84 ng/g wet weight (ww). One sample of cod liver (9 pooled livers) collected near a Norwegian city center had a D5 concentration of 2,200 ng/g ww. D5 was also detected in the blubber of seals and pilot whales at concentrations ranging from <5 - 24 ng/g ww. Environment Canada (2007) concluded that since concentrations of D5 in Nordic waters were <5 μg/L, except for STP influents, the detection of D5 in biota indicated that D5 has the potential to bioaccumulate.

<u>Environmental Persistence</u>

D5 appears to be relatively persistent in air, water, soil and sediments. The fugacity modeling done by Environment Canada (2007) indicates that D5 will partition to air, where it will be oxidized by photochemically produced hydroxyl radicals. The half-life for D5 in this reaction is 6.9 days (Atkinson, 1989), indicating that this substance is persistent in air (half-life > 2 days). This reaction is expected to be the most important fate process in the atmosphere for D5, as it is not expected to degrade via direct photolysis or react appreciably with other photo oxidative species in the atmosphere (Atkinson, 1991).

Environment Canada (2007) noted that no D5 empirical persistence data for water, sediment and soil were available, and therefore proceeded to make an environmental persistence evaluation based on comparisons with other cyclic siloxanes and persistence modeling data. D5 is structurally similar to D3 (hexamethylcyclotrisiloxane) and D4 (octamethylcyclotetrasiloxane); Environment Canada considered it to be likely that D5 would have a biodegradation potential similar to that of D3 and D4. D3 did not undergo biodegradation over 28 days in a ready-biodegradation test (SEHSC 2005b), suggesting that it is persistent in water, sediment and soil. Additionally, D4 did not biodegrade in an aerobic water/sediment system (Silicones Health Council 1991, as cited in Environment Canada, 2007). Environment Canada (2007) modeled D5 biopersistence using BIOWIN v4.02 and found that the probability of biodegradation of D5 occurring in water or soils was essentially zero.

Based on the above data, Environment Canada (2007) categorized D5 as persistent in air based on empirical data, and also likely to be persistent in soil, sediment and water based on the weight-of-evidence from the behavior of similar chemicals and modeled data. Environment Canada (2007) concluded that D5 meets the persistence criteria for soils, sediments and water (half-lives in soil and water > 182 days; in sediments > 365 days) as set out in the *Persistence and Bioaccumulation Regulations* (Government of Canada, 2000).

Potential for Bioaccumulation

Empirical bioaccumulation data is not available for D5. Bioaccumulation can be estimated from the octanol:water partition coefficient K_{ow}. The higher the Kow (or its logarithm), the more likely a chemical will bioaccumulate in fatty tissue. The empirical and modeled log K_{ow} values for D5 (Table 1) suggest that this substance has the potential to bioaccumulate in the environment (log K_{ow} > 5). D5 has been reported to have the potential to be taken up by fish in a laboratory bioconcentration study where particles were not present to which D5 could bind and where D5 was not allowed to evaporate (SEHSC 2004). The Nordic siloxane environmental screening data also indicates that D5 has the potential to accumulate in fish livers and marine mammals (Norden, 2005). Environment Canada (2007) used D4 exposure data in fathead minnows (*Pimephales promelas*) (Annelin and Frye, 1989) to generate an experimental bioconcentration (BCF) factor for D4 of 12,400 L/kg.

Environment Canada (2007) also generated modeled fish BCF and bioaccumulation factor (BAF) data for D5. A BAF of 34,670 L/kg was derived using a Gobas BAF T2MTL model (Arnot and Gobas, 2003) and BCF values of 1995, 7244 and 46,774 L/kg were derived using BCFWIN v2.15, OASIS 2005 and Gobas BCF T2MTL (Arnot and Gobas, 2003) models, respectively. Environment Canada noted that the BCFWIN model may underestimate the BCF value for cyclosiloxanes, since the BCFWIN modeled D4 BCF (1,698 L/kg) was much lower than an experimentally derived D4 BCF (12,400 L/kg). These modeled bioaccumulation values do not take into account any potential metabolism of D5 to other compounds. However, an experimental BCF study with D4 (Fackler *et al*., 1995) suggests that metabolism of D4 in fish is probably not significant, and therefore D5 may also not be significantly metabolized in fish. Environment Canada (2007) found the weight of evidence indicated that D5 meets the bioaccumulation criterion (BCF, BAF > 5,000) as set out in the *Persistence and Bioaccumulation Regulations* (Government of Canada 2000).

Environmental Toxicity

D5 environmental toxicity study data are not available. However, D4 is both acutely and chronically toxic to fish and daphnia (crustaceans) (Hobson *et al*., 1997). Acute No Observable Effect Levels (NOELs) for fish and daphnia were 4.4 and 15 µg/L, respectively. A chronic NOEL for daphnia was 7.9 µg/L. Based on their similarity in structure and physical-chemical properties, the modes of action and toxicities to aquatic organisms of D5 would be expected to resemble those of D4. Environment Canada (2007) developed modeled data (ECOSAR v.0.99h) suggesting that D5 would be capable of causing harm to aquatic organisms at relatively low concentrations. Concentrations causing a 50% effect (EC50) in green algae and daphnia were

96 µg/L (96 hour exposure) and 32 µg/L (16 day exposure), respectively. Environment Canada (2007) noted that these values were close to or below the D5 solubility limit, and concluded that D5 has the potential to cause ecological harm in Canada.

D5 Human Exposure

In addition to detection in the breathing space of people working with D5, this compound has been detected in the fat of members of the general population, in human breast milk and in women with breast implants.

A national survey of human adipose tissue in 1982 found D5 in 28 of 46 people sampled (US EPA, 1987). Kaj *et al*. (2005) reported levels of D5 as high as 4.5 µg/L in samples of human breast milk in Sweden. Neither D5 nor any other siloxane was measured for the recent Second National Report on Human Exposure to Environmental Chemicals released in January 2003 by the National Center for Environmental Health. D5 and its structural analog D4, which has one less dimethylsiloxane group than D5, occur together in breast implants and are often investigated together because of their structural similarities. However, D4 has some activity mimicking the female hormone estrogen, so any contamination of D5 by D4 is cause for concern.

Flassbeck *et al*. (2001) analyzed plasma and blood of women exposed to silicone gel-filled implants (n = 14) and of control subjects (n = 2) for low molecular weight silicones. D5 and its structural analogs D3, D4, and D6 were not detectable in control plasma or blood. The numbers of patient samples were limited, but the data showed an increase in the amount of low molecular weight cyclic siloxanes in the bodies of women with silicone implants. Many years after the removal of ruptured silicone implants, siloxanes were still in blood samples from several women. D3 varied from 6 to 12 ng/mL in plasma and from 20 to 28 ng/mL in blood. The range of D4 was 14-50 ng/mL in plasma and 79-92 ng/mL in blood. D5 (28 ng/mL) and D6 (17 ng/mL) were detected in the plasma of one patient. Possible shortcomings in the data, which were noted by Smith (2002), included only two controls, possible inadvertent contamination, and some values near or at the limit of detection.

Flassbeck *et al*. (2003) used a sophisticated combination of mass spectrometry and gas chromatography to analyze siloxanes (D4, D5, D6) in prosthesis capsule, muscle, and fat of 3 women who had silicone gel-filled breast implants and in breast tissue of 3 control women. In all tissues of women with breast implants, D4, D5 and D6 were identified. Depending on the siloxane species and type of tissue analyzed, siloxane levels in the range of 10-1,400 ng/g were detected. The highest level of D5 was 637±100 ng/g (637 ppb) in the fat tissue of one woman. This investigation shows that siloxanes leak from prostheses and accumulate in surrounding tissues.

In addition to its presence in cosmetics and toiletries, D5 is emitted from some furnishings, such as urethane cushions (Schaeffer *et al*. (1996). Otson and Fellin (1992) [cited in HSDB (2007)] report that the average value for 25 different locations in the United States was 0.206 ppb in air. No site exceeded 1 ppb.

Environ (2006) reported several measurements of occupational exposure to D5 in workplace air. Mean values included 0.0587 ppm for silicone workers, 2.21 ppm for antiperspirant products workers, 1.06 ppm for skin care products workers, 0.002 ppm for hair care product workers, and 0.143 ppm for dry cleaners.

D5 Health Effects Information

OEHHA staff reviewed published literature on D5 toxicity, and information submitted by the Silicones Environmental Health and Safety Council (SEHSC). These materials included studies evaluating acute and subchronic toxicity, neuroendocrine activity, estrogenicity, genotoxicity, chronic toxicity and carcinogenicity and related mode of action studies, and pharmacokinetics. In addition, we evaluated an SEHSC white paper summarizing the toxicity of D5.

Metabolism/pharmacokinetics/pharmacodynamics

Varaprath *et al*. (2003) reported that Fischer 344 rats metabolize D5 to at least ten metabolites identifiable by GC-MS analysis. The metabolites of D5 were: $(CH_3)_2Si(OH)_2$, $CH_3Si(OH)_3$, $CH_3Si(OH)_2OSi(OH)_3$, $CH_3Si(OH)_2OSi(OH)_2CH_3$, $CH_3Si(OH)_2OSi(OH)(CH_3)_2$, $(CH_3)_2Si(OH)OSi(OH)(CH_3)_2$, $(CH_3)_2Si(OH)OSi(CH_3)_2OSi(OH)(CH_3)_2$, nonamethyl-cyclopentasiloxanol, and hydroxymethylnonamethylcyclopentasiloxane. No parent D5 was detected in the urine. Thus metabolism of D5 in the rat is extensive, and it is likely that the distribution, excretion, and toxic effects reported after D5 exposure are influenced by the properties of its metabolites.

McKim *et al*. (1999) investigated the effects of exposure to 160 ppm D5 for 28 days on the expression and activity of selected rat hepatic phase I and phase II enzymes. Exposure to D5 resulted in a 1.4-fold increased activity of hepatic NADPH-cytochrome c reductase, a 1.8-fold increase in 7-ethoxyresorufin O-deethylase (EROD) activity (CYP1A1 and CYP1B1 activity), a 4.2-fold increase in both 7-pentoxyresorufin O-depentylase (PROD) activity and immunoreactive CYP2B1/2 protein (3.3-fold), a 2.4-fold increase in testosterone 6-beta-hydroxylase activity and in CYP3A1/2 immunoreactive protein, a small increase in 11- and 12-hydroxylation of lauric acid (CYP4A activity), no change in immunoreactive CYP4A levels, and increases of 1.7- and 1.4-fold, respectively, in liver microsomal epoxide hydrolase activity and immunoreactive protein. The authors suggested that the profile for enzyme induction following inhalation exposure of female Fischer-344 rats to D5 vapors is similar to that reported for phenobarbital, and therefore described D5 as a weak "phenobarbital-like" inducer. D5 also induced some of these activities in male and female Sprague-Dawley rats administered 1, 5, 20, or 100 mg/kg D5 in corn oil daily by gavage for 4 days (Zhang *et al*., 2000). Thus D5 exposure alters the activity of several liver enzymes involved in metabolism of other foreign compounds (xenobiotics) and of endogenous chemicals that have hormone activity (see also Table 3 below).

In experiments in CD-1 female mice, a mixture of cyclosiloxanes (i.e., breast implant distillate), which included D5, was shown after a single subcutaneous injection of 250 mg to be widely distributed in the ten organs examined and to persist for at least a year, with highest levels in mesenteric lymph nodes, abdominal fat, ovaries and uterus (Kala *et al*., 1998). In

mesenteric lymph nodes, D5 levels at one year (~5.4 ppm) were similar to those 9 weeks after injection. In the ovaries and uterus, D5 levels at one year were half or less of those at 9 weeks after injection. D5 was selectively retained in tissues compared to D4. According to these animal experiments, siloxane residues, including unchanged D5, are persistent in a variety of tissues for extended periods after exposure.

The physical properties of D4 and D5 are unusual in combining both moderate volatility and very high lipophilicity (solubility in fats), which necessarily impacts the pharmacokinetic properties. D4 and D5 are cleared from the circulation by exhalation and methyl-group oxidation. High lipophilicity, i.e., fat:blood partition coefficients of 1000-2000, usually leads to bioaccumulation. Andersen and colleagues have developed a multi-dose route (including inhalation), multi-species physiologically based pharmacokinetic (PBPK) model for D4 and integrated physical chemical, metabolic and partitioning information to provide an understanding of the expected time course of D4 concentrations in tissues, including fat, during various scenarios (Andersen *et al*., 2001; Sarangapani *et al*., 2002).

PBPK models for D5 dermal absorption and inhalation have been under development for several years but have not been fully published (Reddy *et al*., 2005a, b, submitted). Reddy *et al*. (2004) used extensive data on D5 distribution in the rat following inhalation to develop a PBPK model, similar to that for D4. The rat D5 model incorporated deep compartments in lung and liver and had two fat compartments and an unusual combination of low blood:air and high fat:blood partitioning. For D5 in humans, a PBPK model was based on the rat model but was simplified since less human data are available. In spite of this, a similar model structure described D5 pharmacokinetics in both rats and humans. An important component of both models was a sequestered pool of D5, presumably in lipoproteins. This bound D5 was released from the liver, distributed by the blood, and "cleared" into fat. D5 metabolism is essentially flow-limited, due to its low blood:air partition coefficient (0.2 in rats and 0.5 in humans in vivo). However, the primary mechanism of D5 elimination was exhalation.

Andersen *et al*. (2005) simplified the model(s) for D4 and D5 to evaluate the time course of their concentrations in plasma and fat during periodic daily exposures. The model(s) was calibrated with blood and tissue levels in rats due to 6 hr/day exposures for 1 day, 14 days, and 6 months. The model had a central compartment with first-order metabolic clearance and either one or two fat compartments with variable limitations for uptake by diffusion. At steady state, D5 levels were equal to those expected for a continuous exposure multiplied by the ratio of the daily exposure duration/24 hours. As stated by the authors, the approach to steady state and persistence after cessation for all exposure scenarios depended on the characteristic clearance by diffusion from the deeper fat compartment.

The authors of these PBPK modeling studies (Reddy *et al*., 2005a; 2005b; Andersen *et al*., 2005) stated that, despite high fat:blood partitioning, they did not expect D5 to accumulate due to rapid clearance by exhalation and metabolism. However, this expectation is not consistent with the reported occurrence of measurable levels of siloxanes (including D5 and metabolites) in plasma and tissues of women who had received implanted silicone prostheses, including those where the prostheses had been later removed (Flassbeck *et al.,* 2001; 2003). It

is also difficult to reconcile with reportedly substantial levels of D5 in breast milk (Kaj et al., 2005). The percentage of inhaled D5 which is retained in fat may be small under the conditions examined by Reddy *et al.* and Andersen *et al*. (which may actually imply that the model in question is not suited to examining the question of long-term persistence). However, that portion retained in fat seems to be persistent, both in animal studies (Kala *et al*., 1998), and in humans in the case of D5 leaking from silicone breast implants. Thus, OEHHA remains concerned about the empirical data indicating a long half-life in humans and animals, and the chronic effects of this persistent compound.

Hormonal effects

Hormonal effects are of interest and concern because of the finding of malignant tumors (adenocarcinomas) due to chronic D5 exposure in a hormone sensitive organ, the rat uterus (Dow Corning, 2005a). A similar exposure study of D4 in rats found benign uterine tumors (adenomas) at the highest concentration tested (700 ppm) (Plotzke *et al*., 2005). D4, a structural analog of D5, has one less dimethylsiloxane group, and has been shown to have direct (estrogenic) hormonal effects on the uterus. Such direct estrogenic effects would be relevant to humans. The indirect hormonal effect on the rat uterus by D5 via prolactin would not be relevant to humans, because prolactin affect the corpus luteum in rats, but not in humans..

Hayden and Barlow (1972) reported that several siloxanes are estrogenic in animals and that the cyclic compounds are more active than the linear compounds. Hayden and Barlow (1972) did not examine D5 but did find weak (not statistically significant) estrogenic activity in its structural analog D4 in the ovariectomized (to reduce endogenous estrogen), immature female rat uterus following oral administration. Some cyclic siloxanes with phenyl groups (rather than methyl groups as in D5) had stronger estrogenic activity in the assay.

In mice dosed orally for 3 days He *et al*. (2003) reported that D4 at 250, 500 and 1000 mg/kg body weight was estrogenic using the uterine wet weight test in ovariectomized animals but that D5 was not estrogenic using the assay.

In a recent peer-reviewed paper, Quinn *et al*. (2007) used receptor-binding experiments and a luciferase reporter gene assay to determine if D5 was able to bind and activate either the estrogen receptors (ERs) or the progesterone receptors (PRs). They used the rat uterotrophic assay (RUA) for estrogenic activity and the Hershberger assay for androgenic activity as in vivo assays. In the ER-binding studies, D5 did not bind to either ER- α or ER- ß. D5 was also negative in the estrogen reporter gene assay and was not a ligand for the progesterone receptors. Both the RUA and Hershberger assays were conducted using whole-body inhalation of 160 ppm D5 for 16 h/day for 3 and 10 days, respectively. D5 was negative in both rat strains (Sprague-Dawley and Fischer-344), indicating that D5 does not possess estrogenic activity. D5 also did not possess any significant antiestrogenic activity. D5 was negative in the Hershberger assay indicating that it did not have any significant androgenic activity. The structural analog D4 had a low affinity for ER- α *in vitro* and was weakly estrogenic in vivo. D4 had no androgenic activity. As noted later in the section on developmental toxicity, Siddiqui *et al.* (2007) observed

a significant increase in male pup anogenital distance. This may indicate an anti-estrogenic or androgenic effect.

Neuroendocrine activity

Dopamine acts both as a hormone in regulating prolactin release from the pituitary gland and as a transmitter of nerve impulses. Thus it can affect both the endocrine and nervous systems. Jean *et al*. (2005) evaluated the potential for D5 (and D4) to modulate pituitary prolactin secretion as dopamine D2-receptor agonists. In an *in vitro* cell line, derived from a rat pituitary tumor (MMQ, American Type Culture Collection #: CRL-10609), 10 μM (3.7 μg/mL), D5 decreased maitotoxin-induced prolactin release by 55% without affecting cell viability. An *in vivo* model was used to assess serum prolactin levels in reserpine-treated female Fischer 344 rats following 6-h vapor inhalation exposure to 160 ppm D5. In this model, serum prolactin levels were decreased 50% by 160 ppm D5 relative to the reserpine control. Pretreatment with sulpiride, an antagonist of the dopamine receptor, blocked the effect of D5 suggesting that D5 is a dopamine D2-receptor agonist on pituitary cells (Table 2). However, as discussed further below (D5 Cancer risk evaluation, section 2), some desirable controls were missing and no attempt to determine a dose-response relationship was reported.

Table 2. Effect of D5 on dopamine receptor regulation of serum prolactin (Dow Corning, 2005b)

	Serum prolactin (ng/ml)	
	Experiment 1	Experiment 2
Untreated control Fischer 344 rats	Not reported	Not reported
Ovariectomized control rats	11 ± 6 (10)	5 ± 3 (9)
Reserpine (2 mg/kg) controls	72 ± 36 (9)	58 ± 34 (7)
Reserpine + 160 ppm D5 exposure	37 ± 20 (7)	38 ± 37 (8)
Reserpine + 160 ppm D5 + 6 mg/kg sulpiride	Not done	395 ± 200 (8)

* mean ± SD (number of rats)

Acute and subchronic toxicity

There are few published reports evaluating D5 toxicity. OEHHA staff obtained a copy of the "Siloxane Product Stewardship Program" 2002 Annual Progress Report of Dow Corning Corporation to the U.S. EPA. Dow Corning tested D5 for various effects, including organ effects and reproductive effects, by the inhalation, oral, and dermal routes of exposure for up to 13 weeks, and for potential genetic activity. The acute inhalation LC_{50} in rats was calculated to be 8.67 mg/liter (8670 mg/m^3), *i.e*., relatively nontoxic. The results of other tests are presented in publications reviewed in this report.

Burns-Naas *et al*. (1998a) assessed potential toxic consequences and immune system modulation of inhalation exposure to D5 in male and female Fischer 344 rats exposed by whole body inhalation to 0, 10, 25, 75, or 160 ppm D5 6 h/day, 7 days/week for 28 days. D5 inhalation exposure did not alter humoral immunity (as measured by an anti-sRBC (sheep red blood cell)

antibody-forming cell response) and caused only minor, transient changes in hematological, serum chemistry, and organ weight values. Histopathological changes were confined to the respiratory tract and appeared to be reversible. The no-observed-adverse-effect-level (NOAEL) for systemic toxicity, based primarily on the liver weight changes, was 75 ppm for this 28 day study.

Burns-Naas *et al*. (1998b) evaluated the subchronic toxicity of D5 using a 3-month, nose-only inhalation exposure. Control and high dose groups were also allowed a 4-week recovery period to observe reversibility, persistence, or delayed occurrence of any potential adverse effects. Male and female Fischer 344 rats were exposed for 6 h/day, 5 days/week for 3 months to target concentrations of 0, 26, 46, 86, and 224 ppm D5. There were several minor changes observed in clinical biochemistry parameters; the most notable was an increase in gamma glutamyl transferase (gamma-GT) in both sexes at the high dose (Table 3). In females, this effect was dose-related between 46 and 224 ppm and did not return to control levels upon cessation of exposure. Additionally, there was a decrease in serum lactate dehydrogenase (LDH) observed in females at 86 and 224 ppm, which did not resolve during recovery. There was an increase in absolute and/or relative liver weight in rats of both sexes. Taken together, these data suggest that the female rat is more sensitive to the actions of D5 on the liver. Exposure-related increases in absolute and relative lung weights were observed in both sexes at terminal necropsy. This observation was not noted in males in the recovery phase, but was still present in females. Histopathology indicated that the lung is a target organ following D5 inhalation, with an increase in focal macrophage accumulation and interstitial inflammation in the lungs of male and female rats exposed to 224 ppm D5. This observation did not appear to resolve at the end of a 1-month period of non-exposure. The incidence of these changes was also slightly increased in rats of both sexes exposed to 86 ppm D5. The authors however characterized the changes in the lung following nose-only D5 vapor inhalation as minimal. The authors report no histopathological findings noted in the livers, despite the observed changes in organ weight and serum chemistry parameters shown in Table 3.

Table 3. Effects of inhalation of D5 for 3 months in female rats

D5 level	*Liver wt (g)*	*Serum triglycerides (mg/dL)*	*Serum γ-glutamyl tranferase (U/L)*	*Serum LDH (U/L)*
0 ppm	3.71±0.46[#]	42.88±7.88	0.70±0.15	229.2 ± 29.4
26 ppm	3.94±0.26	39.38±4.38	1.10±0.34	206.4 ± 83.4
46 ppm	4.26±0.60**	33.25±3.5**	1.49±0.37**	171.6 ± 84.6
86 ppm	4.02±0.50	31.50±3.5**	1.56±0.53**	147.0 ± 33.6*
224 ppm	4.31±0.59**	35.00±3.5	3.35±0.51**	97.8 ± 22.8**
Recovery	3.74±0.29	35.00±3.5	1.80±0.26**	181.8 ±30.0**

[#] mean ± standard deviation ($n \geq 10$); * $p<0.05$; ** $p<0.01$ compared to controls

Lieberman *et al*. (1999a) injected female CD-1 mice intraperitoneally with different doses (3.5-35 g/kg body weight) of breast implant distillate containing D3, D4, D5, and D6. The distillate was lethal at high doses and all the mice injected with 35 g/kg died within 5-8 days. The median lethal dose (LD_{50}) for distillate was approximately 28 g/kg. The mice developed inflammatory lesions of the lung and liver as well as liver cell necrosis with elevated serum

levels of alanine aminotransferase, aspartate aminotransferase, and lactic acid dehydrogenase. Administration of D4 alone produced lethality with an LD_{50} of 6-7 g/kg. D4-treated mice exhibited pulmonary and hepatic lesions and elevated serum enzymes. The authors stated that analysis of LD_{50} data indicated that D4 is about as acutely toxic as carbon tetrachloride or trichloroethylene. The authors measured hydroxyl radical formation in D4-treated mice and found increases of approximately 20-fold in liver and approximately 7-fold in lung on day 4 following injection. They believe that the findings are significant because experiments *in vitro* have demonstrated that cyclosiloxanes can migrate out of breast implants. However, chemicals requiring a dose of greater than 15 g/kg to exert lethality are generally considered to be of low toxicity. Five commenters (Carlton, 1999; Meeks, 1999; Witschi, 1999; Burin, 1999; and Dost, 1999) noted this point and were critical of the author's conclusions. They pointed out (1) the low toxicity classification of the chemicals based on the LD_{50}s reported by Lieberman *et al*., (2) the likelihood that the distillation pretreatment of the chemicals by the investigators altered the chemicals including opening of the cyclosiloxane ring structure, and (3) the lack of mass balance calculation in the study of distribution of the chemical. On the other hand, Lukasiak et al. (1999) were complimentary and pointed out that related chemicals were used to treat intestinal gas in humans. Lieberman *et al*. (1999b) defended their study and said that it was the first time an LD_{50} had been reported for cyclic siloxanes. In addition, they reported effects at doses below the LD_{50}. They state that effects similar to those obtained with the distillate were seen with commercial D4; thus heat treatment of the distillate did not cause the effects.

Developmental/reproductive toxicity

Siddiqui *et al*. (2007) carried out a two-generation reproduction study of D5. Sprague-Dawley rats (30/sex/group) were exposed by whole-body inhalation to 30, 70, or 160 ppm D5 or filtered air for 6 h/day. Exposures for the F0 and F1 generations started at least 70 days prior to mating and lasted through weaning of the pups on postnatal day 21. Female exposures were interrupted from gestation day 21 through postnatal day 4 to allow for parturition and continuous maternal care for the pups. F2 pups were not directly exposed to D5. The authors found no exposure-related mortalities, no clinical signs of toxicity, no effects on body weight or food consumption, and no treatment-related gross findings or organ weight effects at the F0 and F1 necropsies. However, in F0 females the 10% increase in liver weight at 160 ppm was significantly different from controls. The only noteworthy microscopic finding to the authors was minimal alveolar histiocytosis in all exposed groups (Table 4).

Table 4. Alveolar histiocytosis (minimal) in F_0 and F_1 rats

	Control	30 ppm	70 ppm	160 ppm
F_0 males	5/30	5/29	7/30	6/28
F_0 females	0/30	5/29	4/29	10/29*
F_1 males	2/30	4/30	6/30	7/30
F_1 females	3/30	10/30	8/30	13/30*

$p < 0.05$ vs. controls by the Kolmogorov-Smirnov test, one-tailed

No significant changes between D5-treated and control groups were noted in reproductive parameters (specifically number of days between pairing and mating, mating and

fertility indices, gestation length, and parturition), spermatogenic parameters (sperm number, production rate, motility, morphology), ovarian primordial follicle counts, and numbers of corpora lutea in the F_0 and F_1 parental animals. Mean live litter sizes, number of pups born, sex ratios, pup body weights, postnatal pup survival, and the general physical condition of offspring in each generation were not affected. There was a slight, but statistically significant, increase in the mean F_1 male pup anogenital distance (AGD; the distance between the anus and the male genitalia) at the highest concentration (5.5 ± 0.50 mm in the controls versus 6.1 ± 0.77 mm at 160 ppm; the AGD was not measured in F_1 male pups exposed to 30 and 70 ppm D5). The authors did not consider this effect to be related to treatment, but did not explain why they reached this conclusion. Vaginal patency and balanopreputial separation were unchanged compared to controls. The authors suggested a NOAEL of 160 ppm D5 for parental and reproductive toxicity. However, OEHHA considers the statistically significant increase in AGD at 160 ppm an effect of concern, possibly reflecting an anti-estrogenic (female hormone) or androgenic (male hormone) property of D5.

Genotoxicity

Isquith *et al*. (1988) evaluated D5 and 11 other organosilicon compounds for genotoxic potential in vitro. Microbial assays included the Ames test (reverse mutation assay in five *Salmonella typhimurium* his^- tester strains), mitotic gene conversion in *Saccharomyces cerevisiae* strain D4, and DNA repair in *E. coli* pol A +/-. The assays were conducted with and without an S-9 metabolic activation system that contains the soluble fraction of Aroclor 1254-induced rat-liver homogenate. The range of D5 tested in the microbial assays was 0.001 to 5 microliters (1 microgram to 5 mg) D5 per plate. Forward gene mutation, sister-chromatid exchange, DNA alkaline elution, and chromosome aberration potential were evaluated in mouse lymphoma L5178Y tissue culture cells. The tissue culture assays were performed with and without metabolic activation mixture utilizing uninduced mouse-liver S-9. D5 was tested in the range of 0.8 to 25 microliters D5 per milliliter of culture medium (2 to 65 mM). D5 showed no activity in gene mutation. D5 also did not have in vitro clastogenic activity. Although the existing data do not suggest that D5 is genotoxic, no studies evaluating oxidative DNA damage have been reported.

Chronic toxicity/carcinogenicity

A 24 month combined chronic toxicity and carcinogenicity study was conducted in male and female Fischer 344 rats exposed to 0, 10, 40, or 160 ppm D5 6 hr/day, 5 days per week (96 rats/sex/dose). The concentration of 160 ppm is the highest that can be maintained as a vapor. Above 160 ppm some D5 aerosol is formed. Dow Corning's Environment, Health and Safety Office reported preliminary results to the U.S. EPA's Office of Pollution Prevention and Toxics in a letter dated February 4, 2003 (Dow Corning, 2003) and a final report was later released (Dow Corning, 2005a; Crofoot *et al*., 2005). The experiment was conducted with 4 groups (Table 5):

Table 5. Scheme of chronic toxicity and oncogenicity study

Group	*Rats*	*Exposure*	*Recovery*	*Analysis*
A	6/sex/dose	6 months	None	D5 levels in liver, fat, plasma
B	10/sex/dose	12 months	None	Necropsy and organ/tissue analysis
C	20/sex/dose	12 months	12 months	Necropsy and organ/tissue analysis
D	60/sex/dose	24 months	None	Necropsy and organ/tissue analysis

All animals were monitored for mortality, clinical signs, food consumption, and body weights. Laboratory tests included hematology, clinical biochemistry, and urinalysis.

D5 was measured in rats in Group A at necropsy. D5 levels in fat and plasma increased with increasing levels of exposure (Table 6). D5 levels in the fat of females were three to six times higher than in male rats.

Table 6. D5 levels in plasma and fat of Group A animals (µg/g or ppm).

D5 exposure (ppm)	Plasma	Abdominal fat	Perirenal fat	Brown fat
Males				
0	0.122	0.205	0.091	0.177
10	0.189	2.09	2.04	0.970
40	0.471	5.93	9.36	7.42
160	2.20	23.0	54.5	32.0
Females				
0	0.048	0.128	0.081	0.192
10	0.169	7.83	7.26	5.83
40	0.625	27.3	40.2	42.8
160	3.19	115	176	141

Crofoot *et al*. (2005) found no mortality, clinical signs or palpable masses related to D5 exposure. They reported slight increases in female body weights of 0.7 to 9.2% at 40 and 160 ppm after 24 months of exposure and in the recovery group, and in all males exposed to D5 for 24 months (1.4 to 4.3%) but they did not find a dose-response relationship. Increased liver weights in males after 24 months at 160 ppm and females after 6 and 12 months at 10 and 160 ppm showed no dose-response. Crofoot *et al*. (2005) also reported histological changes in the nasal cavity at 160 ppm in both males and females. They considered the changes to be consistent with changes due to the chronic inhalation of a mild irritant.

After both 12 and 24 months of exposure, female rats showed an increase in tumors of the uterine endometrium. No uterine tumors were seen in groups A and B. Results in group C females (12 months exposure plus 12 months recovery in air) were (Table 7):

Table 7. Uterine tumors after 12 months exposure to D5 plus 12 months recovery in air

Tumor	*0 ppm*	*10 ppm*	*40 ppm*	*160 ppm*
Endometrial adenocarcinoma	1	1	0	2
Endometrial adenomatous polyp	0	0	0	1
Total tumors	*1*	*1*	*0*	*3*
Number rats in group	20	20	20	20

In group D, after 24 months of exposure to D5, the results in female rats were (Table 8):

Table 8. Uterine tumors after 24 months exposure to D5

Tumor	*0 ppm*	*10 ppm*	*40 ppm*	*160 ppm*
Endometrial adenocarcinoma	0	1	0	5
Endometrial adenoma	0	1	0	0
Endometrial adenomatous polyps	1	0	1	0
Total tumors	*1*	*2*	*1*	*5*
Number of rats in group	60	60	60	60

The authors note that the progression of hyperplasia (abnormal increase in the number of cells) to adenoma to adenocarcinoma was not observed in the experiments, but some hyperplasia was found in a later analysis of the pathology slides (Environ, 2006). For adenocarcinomas alone, the authors reported a p value for trend < 0.05. The authors found a statistically significant increase in adenocarcinomas alone using the Peto test ($p < 0.05$). OEHHA staff also found a significant increase in adeno-carcinomas in the 160 ppm D5 group using the Fisher exact test (one-sided) ($p = 0.029$).

Interim D5 Reference Exposure Level Determination

In experiments with rats, D5 has shown adverse effects on the liver, the lung, and the uterus. The most sensitive non-cancer effects were seen in the liver in a three month study (Table 3). The No Observed Adverse Effect Level (NOAEL) was 26 ppm and the Lowest Observed Adverse Effect level (LOAEL) was 46 ppm (Burns-Naas et al., 1998b). Dose response effects included increases in liver weight and serum gamma-glutamyl transferase, and decreases in serum triglycerides and lactate dehydrogenase. An interim chronic Reference Exposure Level (cREL) is estimated below based mainly on the liver effects. The cancer effects in the uterus and the noncancer effects on the lung were reported in a lifetime study but were significant only at the highest concentration of 160 ppm. The experiments on hormonal effects which bear on the uterine tumors were only studied at 160 ppm. Because there is still uncertainty about whether the uterine tumors are or are not relevant to humans, it was considered premature to calculate a cancer potency for D5.

Interim D5 inhalation chronic REL estimate

A chronic REL is a level at or below which adverse noncancer health effects would not be expected to occur even in sensitive subpopulations. An interim chronic REL for D5 can be estimated from the spleen and liver changes reported by Burns-Naas *et al*. (1998a).

Study	Burns-Naas *et al*. (1998a)
Study population	Male and female Fischer 344 rats
Exposure method	Discontinuous whole-body inhalation to 0, 26, 46, 86, and 224 ppm
Critical effects	Spleen and liver changes
LOAEL	46 ppm
NOAEL	26 ppm
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	3 months
Average experimental exposure	4.6 ppm for NOAEL group (26 x 6/24 x 5/7)
Human equivalent concentration	4.6 ppm for NOAEL group
LOAEL uncertainty factor	1
Subchronic uncertainty factor	3 (NOAEL is based on a 3 month study in rats)
Interspecies uncertainty factor	3 (see below)
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	100
Interim Reference Exposure Level	46 ppb; 700 $\mu g/m^3$

The NOAEL from the 3 month (subchronic) study of Burns-Naas *et al*. (1998a) was 26 ppm. The NOAEL was time adjusted to an equivalent continuous exposure of 4.64 ppm. OEHHA's methodology for developing a chronic Reference Exposure Level (REL) entails division of the NOAEL by a series of uncertainty factors (UFs). A subchronic UF of 3 was used since the study lasted only 3 months. An interspecies UF of 3 was used to account for residual susceptibility differences in rats not accounted for by U.S. EPA Human Equivalent Concentration (HEC) approach. Finally, an intraspecies UF of 10 was used to account for variability in susceptibility in the human population). This results in a chronic inhalation REL of 46 ppb (700 $\mu g/m^3$). This value is an estimate based on our approved procedure (OEHHA, 2000), but it has not been reviewed by the state's Scientific Review Panel for Toxic Air Contaminants. Thus, OEHHA considers this to be an interim guidance value.

Margin-of-safety (MOS) calculations were made by Environ for the SEHSC based on a NOAEL of 160 ppm (Environ, 2006). However, there are several statistically significant effects seen at 160 ppm that OEHHA considers adverse including:

- At the end of the two year study a "statistically significant increase of hyaline inclusions in the respiratory/olfactory epithelium was noted in high dose (160 ppm) males and females" when all levels of the nasal cavity were considered. At 40 ppm, females exposed for 24 months and males exposed for 12 months with 12 months recovery showed significantly increased hyaline inclusions.
- In the two year study a statistically significant effect was increased lung foci, presumably sites of macrophage accumulation, in 13% of the females (8/60) at 160 ppm after 24 months (controls = 0%).

- In a two-generation reproduction study of D5 by inhalation, Siddiqui *et al*. (2007) reported increased alveolar histiocytosis (minimal) in the F_0 and F_1 rats (Table 7). The increase was statistically significant in F_0 and F_1 females exposed to 160 ppm D5.
- In newborn rats the external genitalia are undeveloped, but both sexes have a genital tubercle. The AGD is the distance from the anus to the insertion of this tubercle. The AGD is androgen dependent and is about twice as long in males as in females (Swan *et al*., 2005). Siddiqui *et al*. (2007) reported a small, but statistically significant, increase in the mean F_1 male pup anogenital distance (AGD) at 160 ppm (6.1 ± 0.77 mm vs. 5.5 ± 0.50 mm in the controls; the AGD was not measured in the 30 and 70 ppm D5 pups.
- Finally, as discussed above, the proposed mode of action of D5 involves central dopamine agonism. Thus production of tumors at 160 ppm indicates dopamine agonism at this dose level.

These data indicate that selection of 160 ppm as a NOAEL is inappropriate.

D5 cancer risk evaluation

A statistically significant increase in a malignant tumor (uterine adenocarcinoma) due to D5, a chemical that may be bioconcentrated and is a candidate to replace perchloroethylene in dry cleaning, indicates a potential hazard for workers in the dry cleaning industry and perhaps for the general public. Dow Corning has proposed that the tumors in rats are due to a mechanism not applicable to humans (Environ, 2006). Dow Corning postulates that D5 acts as a dopamine agonist, i.e., D5 mimics the effects of dopamine by binding to dopamine receptors in the body and causing effects like dopamine. Dow Corning has done a variety of experiments to test this hypothesis. In the human female the release of luteinizing hormone (LH) from the pituitary gland results in an increase in progesterone which favors maturation of the corpus luteum. In female rats, however, the LH mechanism does not operate; instead, prolactin (PRL) acts as the luteotrophic hormone. In rats, dopamine (or a dopamine agonist such as bromocriptine) binds to dopamine D2 receptors in the pituitary and causes inhibition of pituitary prolactin release. It has been suggested that the lower prolactin levels cause an increased estrogen/progesterone (E/P) ratio, leading to estrogen dominance over progesterone in the rat ovary. Estrogen dominance would then result in endometrial stimulation followed by endometrial hyperplasia and finally uterine endometrial adenomas and adenocarcinomas in the rat. In aged rats experiencing lower levels of dopamine, prolactin is released which leads to progesterone dominance (pseudopregnancy) which does not cause endometrial stimulation. This mode of action would indicate that the uterine adenocarcinomas observed in the rat after D5 exposure would not be relevant to human cancer risk assessment.

This hypothesized mode of action for D5 rat uterine carcinogenicity is plausible, but a substantial amount of uncertainty remains due to contradictions and information gaps in the available data. The main points of concern regarding the proposed mode of action for D5 carcinogenicity are listed below:

1. The proposed mode of action for D5 carcinogenicity involves an increase in the estrogen/progesterone (E/P) ratio (estrogen dominance). However, no direct data, such as estrogen and progesterone blood, plasma or uterine levels, have been provided to indicate that this action is actually happening.

2. Some experimental design deficiencies are apparent in the studies used to characterize the dopamine agonist activity of D5 (Dow Corning, 2005b):

   First, it is not clear if all the experiments were performed in an animal from which the ovaries had been removed (ovariectomized, OVX). The comparison of prolactin (PRL) levels between intact animals treated with reserpine (a dopamine antagonist) and OVX control animals is inappropriate (the comparison should be to levels in OVX + reserpine animals or in untreated intact control animals).

   Second, the authors in the experiment that uses reserpine interpreted the result of D5 inhibiting the action of reserpine as an effect on the dopamine receptor (DR). There was no analysis of other possible mechanisms than a direct action of D5 on reserpine (e.g., changes in metabolism, or D5 blocking the reserpine effect by other means than at the DR). In summary, these experiments showed only that D5 decreased the action of reserpine but do not provide evidence for a possible MOA.

   Third, the experiments with sulpiride (DR antagonist) also lack the appropriate control groups. If sulpiride were to directly increase PRL, then the D5 effect (lower PRL) would not necessarily demonstrate an interaction with the DR but could simply be an inhibition of sulpiride action by any mechanism (including, but not limited to, an effect at the DR). In summary, this experiment only demonstrated that sulpiride increases PRL and does not demonstrate the interaction of D5 and DR that the author suggests.

3. Studies that have been cited in support of the proposed mode of action for D5 carcinogenicity include studies that compare spontaneous uterine endometrial tumor incidences and E/P ratios in Donyru and F344 rats. The Donryu rats experienced substantially greater E/P ratios, endometrial hyperplasia and spontaneous uterine endometrial tumor incidences compared to the F344 rats (Nagaoka *et al*., 1990, 1994; Ando-Lu *et al*., 1998). These studies have been cited as evidence for the proposed D5 carcinogenicity mode of action; that is, D5 dopamine agonist activity causes a decrease in PRL release, leading to an increased E/P ratio which results in increased endometrial hyperplasia, and thence endometrial tumors. However, the D5-exposed rats in the 2-year carcinogenicity study did not demonstrate increased endometrial hyperplasia (Dow Corning, 2005a). An increase in endometrial hyperplasia would be expected if D5 was causing an increased E/P ratio. The lack of endometrial hyperplasia exposed in the D5-exposed rats calls into question how well the D5 carcinogenicity data fit the Donyru rat estrogen dominance endometrial cancer model. Also, dopamine agonists such as cabergoline which induce uterine tumors in rats also tend to induce endometrial hyperplasia (FDA, 1996).

   Additionally, Environmental Pathology Laboratories, Inc. (EPL) performed a review and comparison of uterine adenomas, adenocarcinomas, and carcinomas from

untreated control animals (107 studies) in the National Toxicology Program (NTP) database at the request of Dow Corning Corporation (EPL, 2003). EPL did not find a substantial amount of endometrial hyperplasia in the untreated control rats, either with or without tumors. EPL also found fewer non-neoplastic changes (cystic endometrial hyperplasia, epithelial hypertrophy) in the uteri of the rats with adenomas or adenocarcinomas after treatment with D5 compared to the NTP study animals. It has been suggested that spontaneous tumors in untreated animals may result from factors such as errors in DNA replication and repair, and accumulation of DNA damage from endogenous generation of reactive oxygen species (Jackson and Loeb, 2001). The lack of rat endometrial hyperplasia seen after D5 treatment, and the similarity of uterine tumor and non-tumor histopathology to that in untreated control animals that develop spontaneous tumors, suggest that D5 may have an adverse effect on the processes that are involved in the generation of spontaneous tumors.

4. Cytochrome P450 CYP1B1 enzyme converts 17β−estradiol to the carcinogenic 4−hydroxyestradiol, which forms adducts with DNA and undergoes redox cycling to generate reactive oxygen species that can damage DNA, protein and lipids (Husbeck and Powis 2002). Cytochrome P450 CYP1B1 mRNA is expressed in rat uterine tissue (Desaulniers *et al*., 2005). D5 has been observed to induce a variety of cytochrome P450 isozymes (McKim *et al*., 1999; Zhang *et al*., 2000), and was present in the uteri of rats exposed to 160 ppm D5 at levels 3-4-fold greater than the levels observed in blood. This suggests the possibility that D5 might induce uterine cytochrome P450 which then could metabolize estrogen to the carcinogenic metabolite 4−hydroxyestradiol.

5. According to the SEHC submission, D5 is a dopamine agonist, and the proposed mode of action for the induction of the rat uterine tumors seen after D5 exposure depends on the indirect effects of dopamine receptor activation. Dopamine agonists such as cabergoline and mesulergine have been observed to have adverse effects on male and female reproductive function in rats (FDA, 1996; Dirami and Cooke, 1998). These effects include inhibition of female fertility (prolactin is essential in rats for maintaining corporea lutea formation and progesterone production, which are necessary for conception), and induction of Leydig cell hyperplasia and adenomas. However, female fertility was unaffected by D5 treatment, and D5 did not induce Leydig cell hyperplasia or adenomas in male rats. It would be anticipated that these effects would occur if D5 was a dopamine agonist.

6. D5 has not been adequately tested for genotoxicity. As described above, D5 has been tested and generally found to not cause gene mutations resulting from bulky DNA adduct formation, or chromosomal damage (Environ, 2006). However, D5 has not been adequately tested for oxidative DNA damage. It has been claimed that the negative results which occurred when D5 was tested for mutagenicity using *E. coli* strain WP2 uvrA indicate that D5 does not cause mutations due to oxidative DNA damage. However, the parent *E. coli* strain WP2 uvrA has been demonstrated to be relatively insensitive to oxidative DNA damage (Blanco *et al*., 1998; Martinez *et al*., 2000). This suggests the need for further testing to determine if D5 is capable of causing oxidative DNA damage. Such testing could include bacterial mutagenicity

testing using *Salmonella* strains TA102 and TA104, and the OxyR deficient strain of *E. coli* WP2 uvrA, as well as the COMET single-cell gel electrophoresis DNA damage assay using a suitable cell type.

Other human health concerns

Even if the uterine adenocarcinomas seen at 160 ppm in the 2-year study are due to a carcinogenic mechanism which is rodent specific, there is still concern that D5 could be a dopamine agonist and result in other adverse effects in humans.

- Dopamine is a major neurotransmitter, involved in many brain functions and downstream physiological processes. Dopamine has been demonstrated to affect brain neural architecture during development (Todd, 1992; Swarzenski *et al*., 1994; Song *et al*., 2002). Data described above indicate that brain levels of D5 in rats exposed to 160 ppm D5 were approximately twice as high as corresponding blood levels. This raises the possibility that *in utero* exposure to D5 could result in adverse effects on brain neural development. Dopamine D2 receptors, with which D5 interacts, have a role in neurological disorders and mental illness (Ben-Jonathan and Hnasko, 2001; Seeman *et al*., 2006). For example, administration of the dopamine agonist bromocriptine may exacerbate schizophrenia (Ben-Jonathan and Hnasko, 2001) or it may produce improvements in negative symptoms (Lindenmayer, 1995).
- Dopamine acts on the endocrine system by inhibiting prolactin release (Ben-Jonathan and Hnasko, 2001). In humans prolactin induces and maintains the secretion of milk (lactation) and during lactation decreases reproductive function and suppresses sexual drive in the mother. Drugs used to treat hyper-prolactinemia, such as cabergoline and bromocriptine, are dopamine receptor agonists (Melmed and Jameson, 2005).
- Dopamine can activate dopaminergic receptors in normal human T-cells, and trigger the selective secretion of IL-10 and/or TNFα (Besser *et al*., 2005). Assuming D5 has dopamine agonist properties, this could have detrimental consequences in various immunological diseases, injuries and cancers.
- Prolactin has been reported to affect a variety of other cells including human adipocytes (Asai-Sato *et al.*, 2006; Nilsson *et al.*, 2005), mouse adipocytes (Flint *et al.*, 2006) rat cholangiocytes (Bogorad *et al.*, 2006a, b), rat chondrocytes (Zermeno *et al.*, 2006), human natural killer (NK) cells (Sun *et al.*, 2004), developing human thymocytes (Carreno *et al.*, 2005), and rat pancreatic islet cells (Amaral *et al.*, 2004).
- *In vivo*, in rodents, prolactin has a synergistic relationship with the glucocorticoids and adrenal function, possibly acting to determine adrenal size and function (Silva *et al.*, 2004). A recent report that alactogenesis resulting from an inherited defect in prolactin secretion also has an adrenal component in humans (Saito *et al.*, 2006) raises the possibility that adrenal function and carbohydrate metabolism could be adversely affected by chronic suppression of prolactin in humans.

Thus, even if D5 does not induce uterine or other tumors in humans, if D5 acts as a dopamine agonist it may therefore have other adverse health impacts.

Finally, there are several data gaps:

- Although there is information that D5 does not adversely effect reproduction, developmental toxicity data are limited; in one study a possible effect (on anogenital distance) was identified but was dismissed as not being treatment related without sufficient justification. There also is no information on toxicity due to exposure in very young animals. OEHHA has a mandate to protect infants and children in its risk assessments.
- The PBPK model for D5 is not final. Results from the model might address some of OEHHA's concerns about possible D5 bioaccumulation in humans. However, data indicate that D5 bioaccumulates in fish, a negative ecological effect and a source of additional exposure to humans via fish consumption. Detailed analysis by Environment Canada indicates potential for bioaccumulation in biota. Further, biomonitoring data indicate a long half-life of D5 in humans.

Conclusions

(1) The MOA for tumor induction in rodents is plausible, but there are at present insufficient data to conclusively determine the relevance or otherwise of these tumors to humans. Measurement of a sustained, dose-dependent increase in the ratio of estrogen to progesterone levels in chronically D5-treated animals would strengthen the evidence supporting the proposed MOA. Clarity on whether or not D5 induces sustained uterine endometrial hyperplasia would also strengthen the proposed MOA.

(2) D5 might have effects other than cancer in humans due to dopaminergic activity. For example, although prolactin is not the luteinizing hormone in humans, it has important roles in human reproduction. Thus, there is substantial concern that D5 would produce other toxicities by virtue of its impacts on prolactin via the dopamine agonist properties (e.g., on adipose tissue, bile production, and the immune system). Further, dopamine is a major neurotransmitter in the central nervous system. Disruption of dopaminergic pathways by D5 could have adverse health impacts on the nervous system (e.g., possible psychological imbalance).

(3) Several data gaps are present both for the cancer mode of action analysis and for the general toxicity of D5, including limited data on developmental toxicity, lack of toxicity data in young animals, and incomplete genotoxicity data.

(4) Concerns exist for the environmental persistence of D5, which is highly lipophilic, has been measured in aquatic species in a number of environments, and has a long half-life in human tissues.

For these reasons, OEHHA cannot make a finding at this time that D5 is non-toxic.

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