

Decamethylcyclopentasiloxane (D5) (2015)

I. IDENTIFICATION^(1,2)

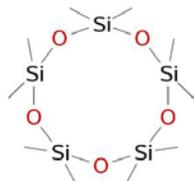
Chemical Name: 2,2,4,4,6,6,8,8,10,10-decamethylcyclopentasiloxane

Synonyms: D5; Cyclic dimethylsiloxane pentamer; Cyclomethicone; Volasil™ 245; Cyclopentasiloxane, decamethyl-; Cyclopentasiloxane, 2,2,4,4,6,6,8,8,10,10-decamethyl-; Decamethylcyclopentasiloxane (cyclic monomer); Dimethylsiloxane pentamer; Dow Corning 345 fluid; Dow Corning 9040 Silicone Elastomer Blend; KF 995; MolPort-000-153-808; NUC silicone VS 7158; Silicon SF 1202; Siloxane F-222; UNII-0THT5PCI0R; Union Carbide 7158 silicone fluid; VS 7158

CAS Number: 541-02-6

Molecular Formula: C₁₀H₃₀O₅Si₅

Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES⁽³⁻⁵⁾

Physical State: Synthetically derived oily, clear to grayish silicone fluid

Molecular Weight: 370.85

Conversion Factors: 1 ppm = 15.1 mg/m³

1 mg/m³ = 0.0645 ppm

Boiling Point: 210 °C (410 °F)

Melting Point: -38 °C (-36.40 °F)

Vapor pressure: 0.2 mm Hg at 25 °C (77 °F)

Saturated Vapor Concentration: 263 ppm (3.2 mg/L) at 25 °C (77 °F)

Odor Description and Threshold: Odorless

Vapor Density: 6.8

Flash Point: 82.7 °C (180.86 °F) at 101.3 kPa

Flammability Limits: non-flammable

Autoignition Temperature: 372 °C (701.60 °F) at 101.3 kPa

Specific Gravity: 0.959 g/cm³ at 20 °C (68 °F)

Solubility: 17µg/l at 23 °C (73 °F) in water; soluble in ethanol, ether, acetone, and benzene; very soluble in pyridine.

Partition Coefficient: (log Kow) 8.02 at 25.3 °C

Stability: Stable

Reactivities and Incompatibilities: Oxidizing agents

III. USES

D5 is a precursor in the production of siloxane polymers for the industry and medical field. It is a carrier ingredient in many toiletries and cosmetics. It is also used in dry cleaning, electronics, and lubricants.⁽⁵⁾

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity

1. Lethality Data

Species	Route	LD ₅₀ or LC ₅₀
Rat	Oral	>5,000 mg/kg ⁽⁶⁾
Rat	Oral	>20,000 mg/kg ⁽⁷⁾
Rat	Oral	>64 mL/kg ⁽⁸⁾
Rat	Inhalation	6.7 mg/L (4-hr) ⁽⁹⁾
Rat	Inhalation	8.67 mg/L (4-hr) ^(10,11)
Rabbit	Dermal	>2000 mg/kg ⁽¹²⁾
Rabbit	Dermal	>15,360 mg/kg ⁽⁷⁾

It should be noted that, for the inhalation studies, the reported LC₅₀ values were in excess of the saturated vapor concentration (~3 mg/L), meaning that animals were exposed to a mix of vapor and aerosol. There were no deaths following acute exposures at or below the saturated vapor concentration.

2. Eye Irritation

Four studies (two guideline-compliant, two unknown) evaluating the eye irritation potential of undiluted D5 in rabbits were identified. Results showed minimal or no irritancy.⁽¹³⁻¹⁶⁾

3. Skin Absorption

D5 is not well absorbed systemically following dermal application based on studies of topically applied radiolabeled D5 (14^C-D5) in both *in vivo* and *in vitro* skin penetration studies. In studies where 14^C-D5 was applied to dorsal, clipped areas of male and female rat skin, under non-occlusive wrap, it was noted that the majority of applied 14^C-D5 (approximately 85%) volatilized from the skin.⁽¹⁷⁾ After 96 hours, very little (0.35%) of the applied 14^C-D5 remained at the site and less than 1% of the applied 14^C-D5 radioactivity was recovered in feces, CO₂ traps and tissues. Overall, it was determined that less than 1% of the applied D5 was absorbed.

Normal healthy volunteers (3/sex) were exposed to a single dose of approximately 1.3 g (male) or 1.0 g (female) of [^{13}C]-D5, by applying the compound to axilla (underarms), since D5 has applications topically applied in consumer products (including antiperspirants) and the characteristics of this region of the human skin are expected to favor absorption. When adjusted for surface area, this corresponds to doses of 13.5 mg/cm² (men) and 15.4 mg/cm² (women). Blood samples were obtained prior to exposure and at 0.5, 1, 2, 4 and 6 hours after application. Exhaled air samples were obtained prior to exposure and approximately every 15 minutes up to 360 minutes and 24 hours after application. D5 levels were statistically significantly elevated above baseline in blood, plasma, and in exhaled air at all time points after application. This result is indicative of fairly rapid absorption rate, but the total percentage of the applied dose absorbed was very low suggesting that the degree of absorption is limited. Peak plasma D5 levels were 1.2 µg/L at 1 hour and 0.5 µg/L at 6 hours post-exposure. Peak amounts of D5 in exhaled air were 930 ng/L in men at 30 minutes, and 430 ng/L in women at 15 minutes. Based on analysis of the study results using a compartmental PBPK model, it was estimated that about 0.05% of the applied dose was absorbed for both men and women.⁽¹⁸⁾

4. Skin Irritation

D5 was not considered to be a skin irritant when applied undiluted under semi-occlusive or occlusive bandage in rabbits.⁽¹⁹⁻²¹⁾

5. Skin Sensitization

D5 was not shown to be a skin sensitizer in experimental animals (murine local lymph node assay; LLNA) or in humans.^(17,22)

6. Acute Inhalation Toxicity

In the key, well-conducted acute inhalation toxicity study carried out under OECD Guideline No. 403 (Klimisch = 1; reliable without restrictions), male and female Fischer 344 rats (5/sex/group) were exposed nose-only for 4 hours to measured concentration of D5 (vapor/aerosol) at 4.62, 6.73, 9.82 or 15.37 mg/L.^(10,11) Clinical observations were made during exposure and during the 14-day post-exposure period.

There was no mortality (either during exposure or during the 14-day post-exposure observation period) in the rats exposed to either 4.62 mg/L or 6.73 mg/L. During exposure, an exposure-related increase in both incidence and intensity of restlessness was noted; some rats in both the 4.62 and 9.82 mg/L exposure groups also exhibited tachypnea. During the post-exposure period, stiff gait, hunched posture and restlessness were observed in most or all of the rats; these observations started immediately following exposure and lasted up to post-exposure day 13. Tachypnea was observed for one to four days post-exposure in a few females and males from the 4.62 and 9.82 mg/L exposure groups. There were no remarkable effects upon gross necropsy in surviving animals; the lungs from the animals that died were reddish or dark red and incompletely collapsed. The study 4-hr LC₅₀ was determined to be 8.67 mg/L.

B. Subacute Toxicity

1. Inhalation

Groups of male and female Fisher 344 rats (25/sex/group) were exposed to undiluted D5 vapor by whole-body inhalation for 6 hr/day and for 28 days, in order to investigate the immunological effects of D5. Measured concentrations were 154, 385, 1156 or 2466 mg/m³ (10, 25, 75 or 160 ppm). There were no adverse effects on body weight, food consumption, or urinalysis parameters. At 160 ppm, decreased serum alkaline phosphatase activity (females), increased relative liver (males and females), and thymus (males) weights were seen, along with increased incidence and severity of nasal goblet cell proliferation and focal macrophage accumulation in the lung (males and females). These changes were essentially reversible during the 14 day recovery period. There was no indication of alteration of humoral immunity based on measurements of an antibody-forming cell response via standard plaque assay and ELISA. The study No-Observed-Adverse-Effect Level (NOAEL) was 75 ppm, based on reversibly increased liver weights at the highest dose.⁽²³⁻²⁵⁾

A follow-up study examined the mode of action for D5-induced effects on liver (proliferation and hypertrophy) and thyroid cell (proliferation). A single group of 10 female Fisher F344 rats were exposed to undiluted D5 vapor by whole-body inhalation 6 hr/day, 5 day/week for 28 days. The exposure concentration was 160 ppm. A phenobarbital control group was included in the study to compare effects of D5 to a well-characterized cytochrome P450-inducing agent. No overt signs of toxicity were observed. There was a transient increase in liver weights (approximately 11%) that was present after one and two 5-day exposure periods with a return to control levels by the end of the fourth 5-day exposure period. These reversible, liver weight changes were not accompanied by histopathological changes. Based on the pattern of changes, the authors concluded that the liver changes were an adaptive effect involving up-regulation of metabolic enzymes. Results also demonstrated that thyroid weight was only minimally affected by D5 exposure, and therefore the NOAEL was ≥160 ppm.⁽²⁶⁾

2. Oral Toxicity

Male and female Sprague-Dawley rats were dosed by gavage with D5 at doses of 0.25, 100, 400 or 1600 mg/kg-day, 5 days/week for 28 days. Absolute liver weight in both males and females was observed at doses >100 mg/kg; slight, but non-statistically-significant increases in liver weight was also noted in females. An increased incidence, along with a dose-related increase of periportal lipidosis, was also observed in females. The NOAEL for males in this study was determined to be 100 mg/kg-day; no NOAEL for females was able to be determined.⁽¹⁶⁾

2. Dermal Toxicity

Groups of Sprague-Dawley rats (10/sex/dose in main study groups) were exposed to undiluted D5 under occlusive cover, 6 hours/day for 28 days at 0, 200, 800, or 1600 mg/kg/day. No adverse effects were observed on survival, body weight, food consumption, clinical observations, clinical pathology,

hematology, ophthalmoscopy, organ weights, or gross or microscopic pathology. The NOAEL was ≥ 1600 mg/kg/day.⁽²⁷⁾

A single group of New Zealand white rabbits (6/sex/dose) was exposed under occlusive cover to 1000 mg/kg/day undiluted D5 for 21 days. The skin of 3 animals/sex was abraded. There were no clinical signs, effects on body or organ weight, signs of skin irritation, or mortality, and no treatment-related gross pathology findings. The NOAEL was ≥ 1000 mg/kg/day.⁽²⁸⁾

C. Subchronic Toxicity

1. Inhalation

In a study conducted according to OECD Guideline 413, groups of male and female Fisher F344 rats (control and high dose – 30/sex/concentration; all other doses – 20/sex/concentration) were exposed to undiluted D5 vapor by nose-only inhalation for 6 hours/day, 5 days/week, for 90 days. There was a post-exposure recovery period of one month for a subgroup of 10 animals for the control and high dose groups. The exposure concentrations were 28.6, 49.2, 87.7, or 233.0 ppm (target concentrations 26, 46, 86, or 224 ppm). There were no dose-related effects on body weights, food consumption, mortality, and hematology or urinalysis parameters. Serum gamma glutamyl transferase (GGT) activity was increased in males at 233 ppm and in females at ≥ 49.2 ppm. GGT levels had returned to baseline at the end of the recovery period in males, but not in females; furthermore, although elevated GGT is considered a sensitive indicator of liver damage, it was not accompanied by changes in ALP, an event which typically accompanies elevations in GGT. There were no accompanying histopathological changes in the liver. Therefore, the toxicological relevance of this effect is unclear.^(29,30)

Other findings in this study included a decrease in lactate dehydrogenase activity (which did not resolve after recovery) and a slight decrease in serum calcium concentration, both of which occurred in females at ≥ 87.7 ppm. Absolute and relative lung weights were increased in both sexes at 233 ppm. Absolute and relative liver weights were increased in females at ≥ 49.2 ppm and higher, and in males at 233 ppm, and had resolved by the end of the recovery period. Non-statistically significant increases in focal macrophage accumulation and interstitial inflammation were observed in the lungs of males and females at 87.7 and 233 ppm, respectively. The NOEL for male and female rats was determined to be 49.2 ppm, and the NOAEL was ≥ 233 ppm.^(29,30)

In a study conducted in a manner similar to OECD Guideline 413, groups of male and female Sprague-Dawley rats (10/sex/group) were exposed 6 hr/day for 90 days by whole body vapor inhalation to 0, 20, 60, or 120 ppm D5 vapor. Satellite groups were included in the study to evaluate effects after a 28-day no-exposure recovery period. There were no significant differences found for body weight, clinical signs, ophthalmologic changes, clinical biochemistry, hematology, and gross or microscopic pathology. Increased liver weights in high-dose females (but not males) were reported, which

resolved by the end of the recovery period. The NOAEL was ≥ 120 ppm.⁽³¹⁾

2. Oral Toxicity

In an OECD Guideline 408 study, groups of male and female Wistar rats (10/sex/group) were administered undiluted D5 at 0, 100, 330 or 1000 mg/kg/day for 13 weeks. There were no clinical signs and no substance-related deaths. There were no effects on body weight and weight gain, or on food or water consumption. There were no substance-related ophthalmologic effects at any dose, and no effects on clinical chemistry or urinalysis. The high-dose group showed significantly lower hemoglobin concentrations after 14 weeks. Female rats in all dose groups showed significantly increased liver weights of up to 62% compared to the control group. At necropsy, lung nodules (hard, glassy/gray) of varying size which were predominantly located in the apical or cranial parts of the diaphragmatic lobes close to the bronchi were reported. The combined incidence for either sex was 0 / 1 / 14 / 12 (0, 100, 330 or 1000 mg/kg/day, respectively). Microscopically, an increase in granulomatous pneumonia was observed in males (incidence 0 / 0 / 9 / 8) and in females (incidence 0 / 1 / 7 / 6). An accompanying goblet cell hypertrophy of larger bronchi occurred in males at 330 mg/kg/day and in females at ≥ 100 mg/kg/day. The lesions were restricted to lung lobes involved macroscopically; other parts of the lungs demonstrated no relevant histopathologic alterations. The localization, morphologic pattern and resorptive character of the pneumonic changes are presumed to be the result of the test compound unintentionally reaching the lungs by the airways (e.g., by the methods of administration), most likely by aspiration. They are not considered to be systemic alterations caused by the test material reaching the lungs by the bloodstream. Histiocytosis was found in almost all males and females at 100 mg/kg and above. The sinus of affected lymph nodes contained foci of macrophages loaded with foamy material. These changes were not associated with leukocytic infiltration or necrosis. Frequency and severity scores were not dose-dependent in males, but in females, the most severe lesions were observed at 1000 mg/kg/day. Less severe, but comparable lesions were observed in females of the low- and mid-dose groups. Histiocytosis of the mesenteric lymph node can be explained by absorption of test compound or metabolites by intestinal mucosal transfer to the local lymph node, where it is phagocytized by sinusoidal macrophages/histiocytes. There were no corresponding inflammatory reactions. Several animals receiving 1000 mg/kg/day had hepatocytic cytoplasmic changes which were interpreted as morphological signs of an increased metabolic activity. These liver cell changes were not considered adverse in nature. Based on localized lung and lymph node effects at all doses, a NOEL was not established in this study. However, for the purposes of human hazard assessment, the NOAEL is considered to be >1000 mg/kg/day.⁽³²⁾

D. Chronic Toxicity/Carcinogenicity

The effects on chronic inhalation exposures to D5 were evaluated in Fisher F344 rats.^(33,34) In a study conducted according to EPA OPPTS 870.4300, groups of male and female

Fisher 344 rats were exposed for up to 2 years by whole-body inhalation to D5 vapor for 6 hr/day, 5 days/week at nominal concentrations of 10, 40 or 160 ppm (highest vapor concentration that could be reliably generated without appreciable aerosol or condensation). The exposure groups were further divided into subgroups: subgroup A (interim sacrifice after 6 months); subgroup B (interim sacrifice after 12 months exposure); subgroup C (12 month exposure/12 month recovery; Recovery); and subgroup D 24-month exposure; oncogenicity phase).

There were no treatment-related effects on survival, clinical signs, or body weights. There were no ophthalmological effects or major effects of toxicological significance on hematology, clinical biochemistry or urinalysis findings. Statistically significant, but non-dose related increases/decreases in organ weights were noted for brain, pituitary, heart, lungs, liver, kidneys, adrenals, spleen, testes, epididymides, ovaries and uterus in all exposure groups. Exposure-related histopathological observations were limited to the upper respiratory tract (see below) and the uterus.

A statistically significant increased incidence of hyaline inclusions in the nasal respiratory/olfactory epithelium was noted in high-dose animals sacrificed after 6, 12 and 24 months and are considered to represent a non-specific exposure-related effect. An increased incidence of hyaline inclusions was also noted in high-dose males after the recovery period. It was not clear from this study whether or not this increase was exposure-related. Histomorphologic changes in the nasal cavity were consistent with chronic inhalation of some mildly irritating chemicals, but are also commonly observed in aging rats. Since there were no other changes indicative of an irritant response, such as an inflammatory cell infiltration or degenerative changes to the epithelium, the finding was considered to be nonspecific and of low toxicological importance. Local effects on the nasal cavity and adaptive increases in liver weights (with no microscopic findings) in females were observed at 160 ppm. The NOAEL for general toxicity was ≥ 160 ppm.

Neoplastic findings were not different from controls for any tissues except for the uterus. Except for endometrial adenocarcinoma, these findings were not different between exposed rats and controls. In subgroup C, the incidence of endometrial adenocarcinomas was 1 / 1 / 0 / 2 (incidence at 0, 10, 40 or 160 ppm, respectively). In subgroup D, the incidence of endometrial adenocarcinomas was 0 / 1 / 0 / 5. In addition, endometrial adenoma was noted in one rat in subgroup D at 10 ppm. Adenomatous polyps were noted in one rat from subgroup D at 0 and 40 ppm, and in one subgroup C rat at 160 ppm. The increased incidence of endometrial adenocarcinomas in high-dose rats might be treatment-related, since there were no such neoplasms in the control rats of subgroup D. However, the relationship to exposure is unclear since these neoplasms also occur occasionally in control rats, and a clear dose-response trend was not observed. The apparent NOAEL for carcinogenic effects was 40 ppm, though a further detailed investigation showed that a NOAEL of 160 ppm is scientifically-defensible (see Section I – Biological Relevance).

E. Reproductive/Developmental Toxicity

A range-finding, single-generation reproductive toxicity study involving whole-body inhalation exposure of male and female Sprague-Dawley rats (22/sex/group) to D5 vapor at 26 or 132 ppm, 6 hr/day for a minimum of 28 days prior to mating and through the day of necropsy (female exposure was suspended from gestation day 21 through post-natal day (PND) 4 to prevent parturition from occurring within the inhalation chamber and to avoid separating the dams from their offspring during early neonatal life. All of the females were allowed to deliver and rear their pups to weaning on PND 21. The offspring were euthanized on PND 28. The surviving dams were necropsied on lactation day 21. The males were necropsied after the breeding period. In these animals, reproductive parameters (fertility, mating, days between pairing and coitus, gestation and parturition), mean body weights, body weight gains and food consumption, mean numbers of implantation sites and mean live litter size were not adversely affected by treatment. No clinical signs were noted in the pups for either exposure group. Pup viability (through lactation), pup sex ratios, and mean pup weights were not affected at any exposure level. No internal findings related to the test material were noted at either exposure level in females necropsied on post-mating day 25. The NOAEL for this study was ≥ 132 ppm.⁽³⁵⁾

A two-generation reproductive toxicity study (per study guidelines EPA OPPTS 870.3800 and EPA OPP 83-6) was conducted in Sprague-Dawley rats (30/sex/group) involving whole-body inhalation exposure to undiluted D5 at concentrations of 0, 30, 70, or 160 ppm (nominal). F0 and F1 males and females were exposed at least 70 days prior to mating and through lactation, with the exception of lactation days 0-4, until scheduled euthanasia. F1 pups were exposed from weaning through sexual maturity, breeding, and gestation. The pups were culled at 21 days of age. The age at mating of the mated animals in the study was 13-15 weeks. No parental toxicity in the F0 and F1 generations was observed at exposure concentrations of 30, 70, or 160 ppm. F0 and F1 reproductive performance was not affected at any concentration. F2 pups were randomly selected on PND 4 for neuropathological and/or neurobehavioral evaluations. No test-substance-related total litter losses occurred, and no neonatal toxicity was evident in the offspring of the F0 and F1 generations at concentrations of 30, 70, or 160 ppm. On PND 1, there was a slight, but statistically significant, increase in the mean F1 male pup AGD (absolute and relative to cube root of body weight) in the 160 ppm group; however, there was no change in the mean F1 female pup AGD or across all exposure groups in the F2 generation. If prenatal D5 exposure causes an increase in PND 1 male pup AGD, the authors stated that this alteration should have been evident in both the F1 and F2 generations of prenatally exposed pups. Since the more conclusive F2 generation AGD data were virtually identical across all exposure groups, the alteration in the F1 male AGD was not considered related to D5 exposure. Based on the results of this study, the NOAEL for parental and developmental toxicity is ≥ 160 ppm.^(36,37)

F. Genotoxicity/Mutagenicity

D5 was negative in bacterial mutagenicity tests in *S. typhimurium* (standard tester strains) and *E. coli* (WP2 uvrA), with and without S9 metabolic activation.⁽³⁸⁻⁴²⁾ It was also negative for mutagenicity in L5178Y TK+/- mouse lymphoma cells, both in the presence and absence of metabolic activation.^(40,41) It was non-clastogenic when examined for chromosomal aberrations up to cytotoxic concentrations in Chinese hamster V79 cells.⁽⁴³⁾ In *in vivo* studies, male and female Fisher F344 rats were exposed by whole-body inhalation to 0 or 160 ppm D5 vapor, 6 hr/day for 7 days, in a combined micronucleus/unscheduled DNA synthesis (UDS) test (conducted according to OECD Guidelines 474 and 486). There was no statistically significant or biologically relevant increase in the frequency of the detected micronuclei. D5 did not induce UDS in the hepatocytes of the treated animals.⁽⁴⁴⁾

G. Metabolism/Pharmacokinetics

1. Absorption

Data on oral and inhalation absorption kinetics for D5 were not identified. Following oral administration, D5 appears to enter the blood via the lymphatics within the lipid core of chylomicrons and other lipoproteins, which is in a form different from that for inhalation or dermal routes of exposure. Given the route-specific nature of D5 pharmacokinetics, data collected using the oral route of exposure does not give a meaningful understanding of the tissue kinetics of D5 by relevant routes of human exposure.⁽⁵⁾

As described in Section A3, D5 is not well absorbed systemically following dermal application.⁽⁴⁵⁾ Studies with rats and humans have shown that it is rapidly absorbed into the outer layers of skin, but evaporates back out of the skin before significant systemic absorption can occur.⁽⁵⁾

2. Distribution

Fischer F344 rats (53/sex/group) were exposed via nose-only inhalation for a single 6-hour period to 0, 7 or 160 ppm of [¹⁴C]-D5 as part of a toxicokinetics study. Body burden was counted in total and for pelt and carcass separately. Approximately 2% of the inhaled test article was retained. D5 was found to distribute widely to tissues. The highest concentrations of radioactivity (>1 µg equivalent/g) immediately following exposure to 7 ppm were in the small and large intestines, stomach, thyroid (male only), lung, and adrenal gland. The highest concentrations of radioactivity (>30 µg equivalent/g) immediately following exposure to 160 ppm were in the small and large intestines, stomach, lung, adrenal gland, and liver.⁽⁴⁶⁻⁴⁸⁾

The comparative toxicokinetic profile of D5 following single versus 14-day inhalation exposures was evaluated. Overall, retention of radioactivity following single and repeated exposures was relatively low (approximately 1–2%). Maximum concentrations of radioactivity were observed in most tissues 3 hours post-exposure. Fat was a depot for D5, with elimination

occurring at a slower rate than observed for plasma and other tissues.^(47,49)

In a generic PBPK volatile compound (VC) model for humans and a more detailed PBPK model specifically developed for D5, inhalation in rats exposed daily for 6 hr/day to D5 for periods up to 6 months was used to assess bioaccumulation. The more detailed PBPK model for D5 predicted that this highly lipophilic VC does not accumulate in blood. Instead, it slowly partitions into and out of fat and lipid compartments.^(50,51)

3. Metabolism

Varaprath (2003) evaluated the urinary metabolites of D5 in Fischer F344 rats administered [¹⁴C]-D5 orally and via intravenous injection. Major metabolites found in urine were dimethylsilanediol (Me₂Si(OH)₂) and methylsilanetriol (MeSi(OH)₃). No parent D5 was detected. Demethylation at the silicon-methyl bonds was identified as a metabolic pathway.⁽⁵²⁾

4. Excretion

Following: 1) single, 6-hour, nose-only exposures of male and female Fischer 344 rats to 7 ppm or 160 ppm ¹⁴C-D5 and 2) fourteen, 6-hour nose-only exposures to unlabeled D5 followed, on day 15, by a 6-hour nose-only exposure to ¹⁴C-D5, retention of D5 was found to be low (approximately 1–2% of the dose).^(46,49) Distribution of radioactivity was found to be highest in fat, lung, intestines, and adrenal glands; the maximum concentration of radioactivity was found in most tissues within 3 hours, post-exposure. Significant deposition on the fur was demonstrated; the intestinal D5 content was postulated to be a function of grooming D5 from the fur after exposure. In all groups, the primary route for elimination of systemically-absorbed radioactivity was through expired air. Analyses for parent D5 indicated that essentially all the radioactivity in the expired volatiles was unchanged D5. After exhalation, the most prevalent elimination routes were through the urine and feces. Urinary elimination was entirely polar metabolites, while fecal elimination was primarily D5 and a putative hydroxylated D5.

In the comparative toxicokinetics study described previously, the primary route for elimination of radioactivity in all groups was through expired air, and D5 was found to be unchanged. Repeated exposures gave rise to higher levels of parent D5 in the lung and fat of both sexes and in female livers relative to the single exposure. Immediately after sacrifice, approximately 50% of the radioactivity in fat was attributed to parent material. In urine, five polar metabolites were identified with no parent material detected. Radiochromatograms demonstrated two peaks in feces corresponding to parent and hydroxylated D5.^(47,49)

Regarding the potential for the accumulation of D5 following repeated exposure, Dekant and Klaunig state the following: “PBTK [physiologically based toxicokinetic] models also predict that D5 has no tendency to accumulate after repeated dosing. Absence of a potential for bioaccumulation is also indicated by an absence of an increase in D5-tissue concentrations after a 6-month inhalation exposure performed

as a segment of the chronic bioassay [see section D of this Documentation]. While D5 is very lipophilic with fat:blood partition coefficients between 500 and 1,000, it is readily eliminated by exhalation or by biotransformation to polar metabolites.”⁽¹⁷⁾

H. Other

1. Endocrine-Disrupting Potential

A series of experiments have been conducted to examine the ability of D5 to disrupt endocrine pathways to further examine the mode of action for the uterine tumors observed in female F344 rats in the two-year chronic bioassay. No significant activity was observed in any of these studies. D5 did not show estrogenic or androgenic activity in rats at whole-body inhalation exposures as high as 160 ppm.⁽⁵³⁾ This result is consistent with the absence of D5 binding to human estrogen receptors (ERs) or progesterone receptors (PRs) using a reporter gene assay and other *in vitro* methodologies.⁽⁵⁴⁾ An uterotrophic assay conducted in Sprague-Dawley and F344 rats exposed by inhalation to D5 was negative for estrogenic endpoints.⁽⁵⁵⁾

2. Dopamine Agonist Potential

The ability of D5 to impact prolactin levels through action as a dopamine agonist has been investigated in several studies. Although there is some evidence for and against this hypothesis, the most robust studies did not indicate significant activity. An investigative study was conducted to evaluate the potential for D5 to act as a dopamine D2 receptor agonist.^(17,56) Reserpine-pretreated female F344 rats were exposed by nose-only vapor inhalation to 160 ppm D5 for 6 hours. A subgroup of 8 animals was administered sulpiride, a dopamine receptor antagonist, just prior to D5 exposure. Serum prolactin levels were decreased in the D5 group by 34% 8 hours post-exposure, as compared to reserpine controls (not statistically significant). Sulpiride administration just prior to D5 exposure blocked the observed D5 prolactin-lowering activity. This finding was considered supportive of dopamine D2 receptor agonist potential, and is further supported by *in vitro* evaluations conducted to evaluate the potential of D5 to modulate pituitary prolactin secretion secondary to dopamine D2 receptor agonism. 10 μ M D5 decreased maitotoxin- induced prolactin release by 55% without affecting viability in a cell line derived from a rat pituitary tumor, suggesting activity on the dopamine pathway.⁽³⁴⁾

A study was conducted to evaluate the effect of D5 on circulating prolactin levels in aged female Fischer F344 rats and the influence of the timing of blood sample collection relative to D5 exposure.⁽⁵⁷⁾ Jugular-cannulated aged female rats were exposed to 160 ppm D5 by vapor inhalation, 6 hr/day for 5 days. 160 ppm was chosen because this dose level gave rise to uterine tumors in the two-year chronic bioassay and is the highest vapor concentrations which can be generated reliably. The positive control group received 0.2 mg/kg pergolide mesylate (a dopamine agonist) by oral gavage on exposure days 1 and 5 to demonstrate dopamine D2 receptor-mediated suppression of circulating prolactin. Blood levels of prolactin were determined the day prior to test substance exposure, immediately following exposure on days 1 and 5, and 4, 8 and

18 hours post-exposure day 5. One or five days of nose-only exposure did not decrease prolactin blood levels immediately following exposure as would be consistent with the effects of a dopamine D2 receptor agonist. D5 treatment did not significantly change prolactin levels at any of the time points evaluated. However, the average prolactin levels in the D5 group tended to be higher 4 and 8 hours post-exposure on day 5.

The duration and effect of D5 on circulating prolactin levels following exposure was also evaluated in reserpine-treated female Fischer F344 rats.⁽⁵⁸⁾ On day 1, reserpine was given by oral (gavage) to all animals except those in the control group. On day 2, another dose of reserpine or vehicle was given to the same animals. Immediately thereafter, pergolide was given to the animals of group 3 (positive control), while the remaining animals received the corresponding vehicle. Immediately following the pergolide administration, the animals were exposed for 6 hours, by nose-only inhalation, to air or 160 ppm D5. Pergolide reduced circulating prolactin levels in reserpine-treated rats as expected. However, serum prolactin levels were not decreased in reserpine-treated 344 rats immediately following D5 exposure. The prolactin-lowering effect of D5 at the 18-hour time point post-exposure remains insufficiently characterized to provide an unequivocal interpretation of the potential for direct/indirect dopamine agonism in this model.

3. Biological Relevance of Uterine Adenocarcinomas

An in-depth, evidence-based analysis of the biological relevance of the D5-induced adenocarcinomas seen in the chronic inhalation study with Fischer F344 rats was performed.⁽⁵⁵⁾

Based on the results of this study, the authors⁽⁵⁵⁾ concluded that “Taken as a whole, the mode of action data of D5 indicates that it is acting possibly via a dopamine receptor agonist-like mechanism to alter the pituitary control of the estrous cycle. Like dopamine receptor agonists, pharmacology studies show that D5 decreases pituitary lactotroph release of prolactin *in vitro* and decreases circulating prolactin levels *in vivo* in specific animal models designed to optimize the release of prolactin, an effect that can be competed for by a dopamine receptor agonist. Further studies *in vitro* confirmed the effect but suggest it may be an effect on one or more downstream components of the dopamine signal transduction pathway. Studies in aged animals show that the effects of D5 on estrous cyclicity are consistent with a dopamine-like effect and further suggest that D5 might be accelerating the aging of the reproductive endocrine axis in this strain of rat. These results are consistent with a mode of action for uterine endometrial adenocarcinoma tumorigenesis that is not relevant for humans.”

Consequently, the WEEL Committee also concluded that the uterine endometrial adenocarcinomas seen in the D subgroup of the 2-year bioassay, at the highest dose, are not considered to be biologically relevant for human risk assessment purposes (including OEL development), and a more scientifically-defensible NOAEL in the 2005 combined chronic toxicity/carcinogenicity study would be 160 ppm.

V. HUMAN USE AND EXPERIENCE

No published studies examining exposure levels or health effects experience in workers handling D5 were identified. Epidemiology studies of medical applications of low-molecular-weight silicones are not directly relevant to occupational exposures.

VI. RATIONALE

Decamethylcyclopentasiloxane (D5) has a relatively low order of toxicity following acute administration via the oral, dermal and inhalation routes of exposure. It is not considered to be a dermal or eye irritant or a dermal sensitizer. There is no appreciable dermal absorption of D5 based on results from *in vivo* and *in vitro* studies. It has not been shown to be genotoxic/mutagenic when tested in a number of short-term *in vitro* and *in vivo* assays, and did not cause reproductive or developmental toxicity in rats. Findings from subacute and subchronic inhalation studies in rats and other species have, in general, shown evidence of effects on both the liver (i.e., weight changes) and respiratory tract/lungs (i.e., inflammatory responses). The liver effects were determined to be adaptive responses; in many cases, both the liver and respiratory/pulmonary effects either reversed or were tending towards reversal following cessation of exposure. Inhalation exposure of rats to 160 ppm D5 for up to 24 months produced effects in the liver (weight changes and hepatocellular hypertrophy) and uterus (increased incidence of endometrial adenocarcinoma, endometrial adenoma, and adenomatous polyps in several animals). However, the results of recent mode of action studies are consistent with a mode of action of D5 uterine tumorigenesis that is not relevant for humans. Moreover, this finding might be the result of hormonal dysregulation from interaction of D5 with the dopamine D2 receptor; the relevance of this possible mode of action to humans is questionable. Changes to the nasal epithelium, which were indicative of a chronic inflammatory response, were also noted at 160 ppm. However, only mild to minimal effects were seen after 24 months of exposure, and overall the basic integrity of the respiratory tract was unchanged at this exposure dose.

Based on the results of the chronic inhalation study, 160 ppm was determined to be the NOAEL and was selected as the point of departure for the derivation of the WEEL value. This chronic inhalation NOAEL was adjusted to account for inter-individual variability and residual uncertainty regarding upper respiratory tract changes still occurring at 160 ppm. The resulting WEEL value of 10 ppm is expected to provide a significant margin of safety against the production of any potential adverse health effects in workers exposed to airborne D5.

VII. RECOMMENDED WEEL

8-hour Time-Weighted Average (TWA): 10 ppm

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