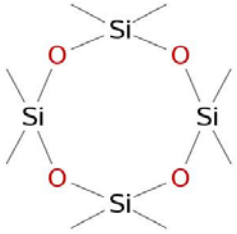
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

# Octamethylcyclotetrasiloxane (D4)(2014)

## I. IDENTIFICATION

Chemical Name: Octamethylcyclotetrasiloxane (D4)
Synonyms: D4; Cyclotetrasiloxane, octamethyl-; Octamethyltetracyclosiloxane; 2,2,4,4,6,6,8,8 octamethyl-1,3,5,7,2,4,6,8-tetroxatetrasilocane; Dow Corning 244; KF 994; cyclic dimethylsiloxane tetramer
CAS Number: 556-67-2 Molecular Formula: $C_8H_{24}O_4Si_4$
Structural Formula:




## II. CHEMICAL AND PHYSICAL PROPERTIES[1, 2, 3]

Physical State and Appearance: Clear fluid
Odor Description: Odorless
Molecular Weight: 296.61 g/mol
Conversion Factors: 1 ppm = 12 mg/m$^3$ at 22 °C (71.6 °F)
1 mg/m$^3$ = 0.0824 ppm at 22 °C (71.6 °F)
Melting Point: 17.7 °C (63.86 °F)
Boiling Point: 175 °C (347 °F)
Vapor Pressure: 0.99 mmHg at 25 °C (77 °F)
Flammability Limits: LEL: 0.75 % in air; UEL: 7.40 % in air
Flash Point: 61°C (open cup, measured); 51°C (closed cup, measured)
Autoignition Temperature: 384–387 °C (723.20 – 728.60 °F)
Specific Gravity: 0.95 at 25°C (77 °F)
Solubility in Water: 0.056 mg/l at 23°C (73.40 °F)
Stability: Stable
Reactivity and Incompatibilities: Silicone foam, particularly when quartz is used as filler, has good flammability characteristics.
Partition Coefficient: 6.49 at 20°C (68 °F)

## III. USES[4]

D4 is used as a monomer in the manufacture of polymeric materials, which are widely used in various industrial and consumer applications, topical pharmaceutical formulations and as breast implants. The polymers contain some residual monomers. Certain food products are processed using silicone antifoam containing D4, which is contained as impurity.

## IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

*1. Lethality Data*

| Species | Route | $LD_{50}$ or $LC_{50}$ |
|---|---|---|
| Rat | Oral | > 4,800 mg/kg[5] |
| Rat | Inhalation | 36,000 mg/m$^3$[6] |
| Rat[a] | Dermal | >2.1 ml/kg (>2000 mg/kg)[7] |
| Mouse | Oral | 1700 mg/kg[8] |
| Rabbit[a] | Dermal | >4640[9] |
| [a]Studies conducted according to OECD Guideline 402 | | |

*2. Eye Irritation*

Several *in vivo* eye irritation studies have been run with D4 in New Zealand White rabbits. These studies demonstrated no to very minimal eye irritation potential.[10, 11, 12]

*3. Skin Absorption*

D4 is not well absorbed systemically following dermal application based on studies of topically applied radiolabeled D4 in both *in vivo* and *in vitro* skin penetration studies. The majority of applied D4 appears to volatize directly or be initially absorbed with subsequent migration back to the skin surface for volatilization. Absence of significant dermal absorption observed in rats has been verified in *in vitro* tests using human skin. [13, 14, 15, 16, 17, 18]

*4. Skin Irritation*

A single group of six Albino rabbits were administered a dose of 0.5 ml undiluted D4 to 4 cm of intact and abraded skin for 24-hours. No skin reactions were observed for intact skin, but desquamation was observed initially, and was resolved by 72 hours for abraded skin. Based on these results, D4 would not be classified as a skin irritant.[8]

*5. Skin Sensitization*

An OECD Guideline 406 study was conducted using a group of 30 female albino guinea pigs (20 treated, 10 controls). The induction phase consisted of intradermal injection of 1% D4, followed by occlusive application of

100% D4 to the skin surface. For the challenge phase, guinea pigs were exposed to 10% and 100% D4 in paraffin oil on shaved flank skin for 24-hours under occlusive conditions. No positive reactions were noted upon challenge at the 48-, 72- or 96-hour observation. D4 was not sensitizing to the skin of guinea pigs under the conditions of this study.[19]

*6. Inhalation Toxicity*

The acute inhalation toxicity of D4 in Fischer 344 rats was evaluated by nose-only exposure to an aerosol (vapor and liquid phase) of D4 following OECD Guideline 403. Rats (5/sex/ group) were exposed to measured concentrations of D4 at 20,120, 30,030 or 54,370 mg/m$^3$ of D4 for 4 hours. Initial weight loss and slightly reduced food intake were observed in all exposed groups. Mortality following exposure was 0%, 30% and 90% at the low, medium and high concentrations, respectively. Effects such as hunched posture, stiff gait and ruffled fur were observed in all groups, while restlessness and or excitement during exposure were observed in animals that later died. All clinical signs were resolved by day 6 post-exposure. At necropsy, decedent animals' lungs showed red discoloration at the medium and high concentrations. The 4-hour $LC_{50}$ was determined to be 36,000 mg/m$^3$.[6] The $LC_{50}$ for D4 vapor is greater than the highest vapor concentrations that can be achieved at typical ambient temperatures.

B. Subacute Toxicity

*1. Inhalation*

In an inhalation OECD Guideline 412 study, Fischer 344 rats (10/ sex/group) were exposed by nose-only inhalation to D4 vapor at 0, 2500, 5000, 9000 or 16,000 mg/m$^3$ (days 1 to 5 and 12,000 mg/m$^3$ the remainder of study) for 4 weeks (6 hours/day, 5 days/ week). The measured vapor concentrations were 2780, 5130, 8620 and 14,210/13,250 mg/m$^3$; measured concentrations are equivalent to 229, 422, 720 and 1106/1187 ppm, respectively. Increased mortality in females, reduced body weight and body weight gain, decreased food consumption and minimal to slight degree of goblet cell proliferation in the nasal cavity were observed at the highest concentration of 1106/1187 ppm. Significant changes in several organ systems were observed including decreased relative thymus weights and increased adrenal weights in males at 1106/1187 ppm and in females at ≥720 ppm. At 720 ppm and above, clinical biochemistry changes indicative of a possible influence on adreno-cortical function were noted. At 422 ppm and above, clinical signs (hunched posture, stiff or abnormal gait, head tilt and ruffled fur) showed a dose-dependent increase, with sedation, tremor and excitement seen in some high dose animals. At all exposures, increased relative liver weights were observed and ultrastructural changes in hepatocytes were documented. Minimal to slight increased alveolar inflammation was also seen at all dose levels. The NOAEL for this study was determined to be 232 ppm (2780 mg/m$^3$, measured) based on dose-dependent effects observed at 422 ppm and above.[20]

A species comparison study was conducted to investigate liver effects. The study exposed (whole body) LVG Golden Syrian hamsters, Hartley guinea pigs, New Zealand White rabbits and CD-1 mice (5/sex/group for rabbits, 10/sex/group for other species) to 700 ppm nominal (697 ppm measured) of D4 vapor for 6 hours/day, 7 days/week for 28 days. No effects were seen in mortality, clinical signs, and body weight gain changes, organ weights for guinea pigs and rabbits. There was an increase in the relative liver weights of female hamsters and mice of both sexes; however, liver weights of guinea pigs, rabbits and male hamsters were comparable to controls. These liver changes were considered treatment-related, but in the absence of corresponding histopathology were considered adaptive, not toxicological in nature. The NOAEL for this study was ≥700 ppm nominal (697 ppm measured).[21]

In a five-week study (designed as follow-up to reference 21), Sprague-Dawley rats, CD-1 mice, Golden Syrian hamsters, New Zealand White rabbits and Hartley guinea pigs (numbers/ species/sex/group not specified) were exposed whole body to 10 or 700 ppm (nominal) D4 vapor for 6 hours/day, 5 days/ week for 5 weeks. At 700 ppm, increased liver weights were observed in rats, mice and hamsters, with females having a larger percent liver weight gain than their male counterparts. No increase in liver weight was observed in rabbits or guinea pigs. At both doses, demethylated D4 metabolites were detected in the urine of all species, with mice and hamsters > rat > rabbit and guinea pig. Animals exposed to 700 ppm D4 were evaluated for hepatocellular cell proliferation and metabolizing enzyme induction. An increase in hepatocellular proliferation was seen in female rats, but rapidly decreased after cessation of exposure. In male rats, the liver cell proliferation findings were mixed, with increased proliferation noted when based on BrdU incorporation, but unclear results when based on the presence of mitotic cells. At the concentration tested for liver enzyme induction (700 ppm), increased induction was reported for rats, but not guinea pigs. Overall there was a strong correlation between the metabolic induction observed in each species and the presence of liver weight changes. These findings reflect adaptive metabolic changes and the NOAEL was ≥700 ppm for all species.[22]

*2. Oral*

Subacute oral-dosing studies have been conducted in several species (Sprague-Dawley and F344 rats, Hartley guinea pigs and New Zealand White rabbits). The predominant findings involve the liver. Based on the pattern of effects and the mode of action for D4, observed liver weight changes are likely an adaptive effect involving up-regulation of cytochrome P450 (CYP)-dependent metabolism.[23, 24, 25]

*3. Dermal*

In a subacute dermal study New Zealand White rabbits (5/sex/ group) were exposed to 0.1, 0.3 or 1.0 ml/kg-day D4 5 days/ week for three weeks under open conditions with a two-week observation period. No signs of toxicity and no effects on mortality, body weight gain, food consumption, hematology, observed clinical chemistry, urinalysis, gross pathology or histopathology were observed during the study. Based on these

results, the NOAEL for dermal exposure to D4 was ≥ 1 mL/kg-day (950 mg/ kg-day).[26]

C. Subchronic Toxicity

*1. Inhalation*

Several subchronic inhalation studies have been conducted in rats. In addition, a study comparing effects at similar concentrations across multiple species has been conducted. The study results are consistent; effects occurring at the lowest concentrations were observed in the liver and at higher concentrations also affecting the respiratory tract. These studies provide evidence that suggests the liver changes observed are secondary to up-regulation of hepatic metabolism. Histopathologic evidence indicated that the ovary and vagina are also affected by inhalation exposures to D4. These effects occurred in the one study for which there was significant mortality at this same exposure level in which these effects were seen and that there was concern that the exposure was mixed vapor/aerosol and was conducted at a very low relative humidity. Stress as a consequence may have been a factor.

In an OECD Guideline 413 study, F344 rats (20/sex/group) were exposed to D4 vapor by nose-only inhalation for 6 hours/day, 5 days/week for 13 weeks. Additional animals (10/sex) were added to control and high doses to provide satellite groups for a 1-month recovery period. Target exposure concentrations were nominal 300, 1200, 5000 or 12,000 mg/m$^3$. Measured concentrations were 420, 1480, 5910 or 10,870 mg/m$^3$ which are equivalent to 35, 122, 487 or 896 ppm. Increased mortality (5/10) and clinical signs (hunched posture, still gait) were observed in females at the highest exposure concentration. Male rats had reduced body weight gain, decreased food intake, increased relative liver weights, female rats had markedly reduced ovary weights, vaginal mucification, increased incidence of ovarian atrophy, and increased incidence and severity of goblet cell proliferation (nasal cavity and nasopharyngeal duct) at 883 ppm. Slight to moderate increased adrenal weights (females), slightly reduced thymus weights (females), and minor changes in hematology indicative of a slight depression of erythropoesis (both sexes; decrease in erythrocyte count, hemoglobin, mean corpuscular hemoglobin concentration and increase in mean corpuscular volume) and increased relative liver weights (females) were seen at 122 ppm and above. The occurrence and severity (minimal to slight) of alveolar macrophage foci incidence increased with dose at all dose levels compared to controls. Chronic interstitial inflammation was observed in the lungs of all treated groups and increased in severity in females at 487 ppm and both sexes at 896 ppm (2 minimal in controls; 7 minimal at 34 ppm; 8 minimal at 120 ppm; 24 minimal to slight at 487 ppm; 34 minimal to moderate at 896 ppm). All effects proved to be completely reversible or showed a clear tendency for reversibility during the one-month post-exposure period. Based on reversible ovary hypoactivity and vaginal mucification, the systemic NOAEL was 487ppm (5.91 mg/l, measured). For local lung effects, the NOAEL is < 35ppm (0.42 mg/l, measured).[30]

In a second OECD Guideline 413 study, Sprague-Dawley rats (10/sex/group) were exposed (whole body) for 13 weeks (6 hours/day, 7 days/week) to D4 vapor at nominal concentrations of 50, 300 or 700 ppm (measured 51, 301 or 700 ppm) with a 28-day observation period for the control and high dose groups. No mortality or overt signs of toxicity were observed in either sex during the study. A reversible reduction (not statistically significant) in body weight gain was observed in females at the highest dose (700 ppm). No effects were seen in blood, clinical chemistry, urinary parameters, or gross necropsy and/or histopathology. Increased liver weights were seen in males in all treatment groups and in females in the 300 and 700 ppm dose groups. Liver weight increase was reversible in males, but not in females. The NOAEL was ≥700 ppm (>8.49 mg/l, measured) on the basis that the liver weight changes were adaptive not toxicological in nature[28]. A study of similar design but using lower concentrations was also conducted. Sprague-Dawley rats (10 to 50/sex/group) were exposed for 13 weeks (6 hours/day, 5 days/week) to D4 at measured concentrations of 0, 5, 10 or 300 ppm (0, 0.06, 0.12 or 3.588 mg/L measured). Increased liver weight was observed in females at the 300 ppm exposure; this change proved reversible within the four-week post-exposure period and was considered adaptive rather than toxicological in nature. Based on these results, the NOAEL was ≥300 ppm (3.6 mg/l) measured for both males and females.[29]

F344 rats (20/sex/group) were exposed 6 h/day, 5 days/week for 3 months to vapor concentrations of 0, 35, 122, 488, or 898 ppm D4 in a nose-only inhalation study. An additional 10/sex in the control and high-exposure groups were allowed a 4-week recovery period. A concentration-dependent increase in absolute and relative liver weights (488 and 898 ppm) and a significant decrease in ovarian weights (898 ppm) were observed in female rats. There were no histopathological findings noted in the liver. Histopathological evidence indicated the primary target organs following D4 inhalation exposure to be components of the female reproductive tract. Reversible histopathological changes were observed in the ovary (hypoactivity) and vagina (mucification) of female rats in the high-dose group only. Although an increase in macrophage accumulation, interstitial inflammation and eosinophil infiltration was observed in the lungs of male and female rats exposed to D4, the study authors considered the toxicological significance to be uncertain as other inhalation studies at similar concentrations failed to show these effects.[30] The study NOAEL was determined to be 488 ppm based on decreased ovarian weight at 898 ppm (liver effects were considered to be an adaptive, not an adverse toxicological effect).[30]

D. Chronic Toxicity

The effects of chronic whole body inhalation exposures to D4 were evaluated in Fisher 344 rats in a study similar to OECD Guideline 453. Rats (96/sex/group) were exposed to nominal concentrations of 10, 30, 150 or 700 ppm of D4 vapor for 6 hours/day, 5 days/week for up to 24 months. Subgroups of animals were sampled at 3, 6, 9 or 12 months to evaluate any potential effects from D4 exposure.

Effects of D4 exposure on survival, clinical signs and body weight were minimal for all females and for males exposed to 10, 30 or 150 ppm. Reduced 2-year survival, terminal body weight and body weight gain were observed in males exposed to 700 ppm during the last few months of the study when compared to controls. Lymphocytosis and leukocytosis were consistently in both sexes exposed to 700 ppm at all time points and therefore considered to be related to D4 exposure. With the exception of lactate dehydrogenase (LDH) in females at 3 months and alanine aminotransferase (ALT) in males at 12 months, there were consistently significant decreases in the mean aspartate aminotransferase (AST), ALT and LDH at 700 ppm in both sexes at all time points. Such decreases were sometimes also present at 150 ppm. After 6 months of exposure, D4 concentrations in plasma, liver and fat tissues increased with increasing D4 exposure concentration in both sexes for all time points. In general, female rats had consistently higher D4 concentrations in these tissues than male rats at all exposure concentrations. There was an observed increase in absolute and/or relative weights of liver, kidneys and uterus of D4-exposed rats at 700 ppm.

Histological examination indicated the primary target organs affected by D4 exposure included the uterus, respiratory tract, kidney and liver. An increased incidence of endometrial adenomas and endometrial epithelial hyperplasia was observed in the uteri of rats exposed to 700 ppm for 24 months. There was a significant increase and a significant positive trend in the incidence of minimal to mild goblet hyperplasia in sections of nasal cavity from both sexes of rats following 12 or 24 months of exposure to 700 ppm and to a lesser extent in males exposed to 150 ppm for 24 months. Minimal hyperplasia of squamous epithelium was present in the mucosa lining the atrioturbinates in the nasal vestibule of 19/20 rats (males and females combined) exposed to 700 ppm for 12 months. The incidence of this lesion was also statistically significant with a significant positive trend. There was an increased incidence of minimal or mild suppurative rhinitis compared to controls in both sexes of rats exposed to 700 ppm for 12 months. The incidence of rhinitis was significantly increased in males. At 24 months, the incidence or severity of suppurative rhinitis did not statistically increase from controls; however, the incidence in females was significantly increased compared to controls. There was a statistically significant and dose-related increase in the incidence and severity of eosinophilic globules in the nasal epithelium of both sexes exposed to 700 ppm, and in females exposed to 150 ppm for 12 or 24 months. There was a statistically significant increase in the severity of chronic nephropathy observed in both sexes exposed to 700 ppm for 24 months. After 12 or 24 months, there was an increased incidence of centrilobular hypertrophy of hepatocytes in male rats exposed to D4 at 700 ppm; this lesion was not present in males at any lower exposure concentrations or in females at any D4 concentrations.

A 51% increase in absolute and relative uterine weight was seen in the high dose female rats. Histopathologically the total incidence of cystic endometrial hyperplasia was 78% compared to 19% in the control group. Four of the 35 (11%) female animals in the high dose group that survived two years were diagnosed with endometrial adenomas. No uterine adenomas were diagnosed in the intercurrent mortality animals or in any of the other groups.

Overall, the NOAEL for non-neoplastic systemic toxicity was identified as nominal 150 ppm based on chronic nephropathy at 700 ppm. The NOAELs for carcinogenic effects were 150 and ≥700 ppm in females and males, respectively, based on uterine effects (increased uterine weight, increased incidence of endometrial cell hyperplasia and an increased incidence of endometrial adenomas at 700 ppm) in females and lack of effects in males. [31, 32]

E. Reproductive/Developmental Toxicity

In a two-generation reproductive toxicity study similar to OECD 416, Sprague-Dawley rats (30/sex/group) were exposed by whole-body vapor inhalation to D4. Rats were exposed 6 hours/day, 7 days/week to D4 at nominal concentrations of 70, 300, 500 or 700 ppm. The duration of the exposure period for the F0/F1 (F0, 16 weeks old; F1 starting PND 22) included at least 70 days prior to mating, throughout mating, through gestation (to day 20) and lactation (except lactations days 1-4). F1 parental animals were mated twice (offspring F2a, F2b), and F1 males were also mated to unexposed females (offspring F2c). For F0/F1 parental animals, no effects were seen on the estrous cycle (F0 only), male reproductive measures, the FOB (evaluated in F1 only) or gross pathology. For the F1/F2a offspring, no effects were observed for clinical signs, body weight, sexual maturation, developmental neurotoxicity (evaluated in F2a only), gross pathology or histopathology. Decreased body weight gain was observed during gestation in F0/F1 parental animals at 700 ppm, and in the first week of parental F0 exposure (at 500 ppm for females and at 700 ppm for both sexes). In parental animals, relative liver weights (interpreted by the study authors as an adaptive response) were increased in females at 300 and 500 ppm and in both sexes at 700 ppm, with relative kidney weights increased in males only at ≥500 ppm. Extended parturition and/or dystocia were observed in two and three F0 females in the 500 and 700 ppm groups, respectively, and in one F1 dam each in the 300, 500 and 700 ppm groups. Two of the three F0 700 ppm group dams and the one F1 500 ppm group female died as a result of the dystocia. For the F0 animals, statistically significant reductions in mean live litter sizes and mean number of pups born was observed at ≥500 ppm. For the first mating period in F1 animals, mean live litter size was reduced at ≥500 ppm, while the mean number of pups born was decreased in the 700 ppm group. When the F1 males were paired with unexposed females, no effects on reproductive performance were observed. In the F1 generation, mating indices were reduced in the 700 ppm group for the first (for females) and second (for both males and females) matings. Fertility indices were statistically significantly reduced in the 700 ppm group for the first F1 mating period. In the second F1 mating period, male and female fertility indices were statistically significantly reduced at ≥500 groups. Microscopic evaluation of the ovaries, uterus, vagina, mammary gland and pituitary gland from females in all D4-

exposed groups suggested a subtle non-exposure responsive effect characterized by perturbation of the estrous cycle and accelerated reproductive senescence in F1 (but not F0) females at 70, 300, and 500 ppm, with a more obvious effect at 700 ppm. The NOAEL for reproductive toxicity and general systemic toxicity (decreased parental body weight gains) was 300 ppm.[33, 34]

Female Sprague-Dawley rats were exposed by whole body inhalation for 6 hours/day, 7 days/week to D4 in another reproductive study with nominal concentrations of 70, 300, 500 or 700 ppm (measured at 72, 301, 503 or 696-702 ppm). In order to identify the critical window of exposure required for the effect on litter size, rats were exposed during different phases prior to mating, during the mating period and/or during gestation: an overall phase, 28 days prior to mating until GD 19 and four subphases at 700 ppm nominal only. The subphases included: ovarian phase, 31 days prior to mating until 3 days before mating; fertilization phase, 3 days prior to mating until GD 3; and implantation phase, GD0 through GD19. For the overall and implantation phases, the number of females/group was 24, with 60/group for the ovarian and fertilization phases. No treatment-related clinical signs or internal findings were observed for any of the four phases during the study. For the days between pairing and coitus, mating and fertility indices were not adversely affected by exposure to D4. Lower mean body weight gain was observed at 700 ppm for the overall phase (during gestation), during the fertilization phase and during the implantation phase. Organ weight changes were also seen at 700 ppm: increased mean absolute adrenal gland weight (overall phase), decreased mean uterine weight (overall phase; fertilization phase), and decreased mean ovarian weight (fertilization phase). The mean number of corpora lutea was also decreased: at ≥300 ppm in the overall phase (at 300 and 500 ppm) and at 700 ppm in the fertilization phase. In addition, indices of intrauterine survival (pre-/post-implantation loss and/or number viable fetuses) were affected during the overall and fertilization phases. At ≥500 ppm in the overall phase, pre-implantation loss was increased (not statistically significant at 500 ppm, but significant at 700 ppm) and the mean number of viable fetuses decreased (at 500 and 700 ppm). In the fertilization phase evaluated at 700 ppm, both implantation indices were increased (pre-implantation and post-implantation) and the mean number of viable indices decreased. A NOAEL of 300 ppm was reported for reproductive endpoints based on intrauterine survival.[35, 36]

Developmental toxicity studies have been conducted in rats and rabbits. Sprague-Dawley rats (30/group) were exposed to D4 by whole body inhalation for 6 hours/day from GD6 through GD15 at nominal concentrations of 100, 300 or 700 ppm in a study similar to OECD Guideline 414. Except for reduced food consumption (during the exposure period and over the entire gestation period) and reduced body weight gain (over the exposure interval and the entire gestation period) in parental females at 700 ppm, no treatment-related effects were observed. The NOAEL was 300 ppm for maternal toxicity and >700 ppm for teratogenicity.[37] In another study similar to OECD Guideline 414, New Zealand White female rabbits (20/group) were exposed to D4 by whole body inhalation during gestation (GD6 to GD18) for 6 hours/day at nominal concentrations of 100, 300 or 500 ppm. No substance-related embryotoxic or teratogenic effects were observed in the study. In the maternal animals, the only effect related to exposure was a decrease in food consumption at 500 ppm for GD6 to GD9 and for GD9 to GD12. The NOAEL was 300 ppm for maternal toxicity and ≥500 ppm for teratogenicity.[38]

Overall, effects of D4 on rat reproductive and development endpoints included prolonged estrous cycling, reductions in mating and fertility indices, extended parturition and dystocia, reductions in number of pups born and litter size observed in the F1 generation at both matings at exposures of 500 ppm and above. In addition, F1 males mated with unexposed females demonstrated the reproductive toxicity observed was not a result of effects on the males. No D4 developmental toxicity effects were observed in rat litters from rat dams exposed during major organogenesis up to 700 ppm or in rabbit litters from does exposed during major organogenesis up to 500 ppm. Together these data support a NOAEL of 300 ppm for these endpoints.

F. Genotoxicity/Mutagenicity

The genotoxicity of D4 has been evaluated using a variety of *in vitro* and *in vivo* test systems using guideline compliant protocols. The predominance of negative findings demonstrates that D4 is not genotoxic.

D4 was negative in bacterial mutagenicity tests in *S. typhimurium* (in a battery of standard tester strains).[39, 40, 41, 42, 43] D4 was also negative for mutagenicity in L5178Y mouse lymphoma cells in the presence and absence of metabolic activation, even at cytotoxic concentrations.[40, 41]

Studies for chromosome effects or DNA damage were also negative *in vitro* and *in vivo*. D4 was non-clastogenic when examined for chromosomal aberrations up to cytotoxic concentrations in Chinese hamster ovary cells.[43, 44] In L5178Y Fischer mouse lymphoma cells D4 was negative in the presence and absence of activation liver microsomes from un-induced CD-1 mice, but showed a positive response in the presence of microsomes from induced CD-1 mice, at the highest/cytotoxic dose (0.1 µl/ml).[40, 41]

For *in vivo* examination of genotoxic effects, Sprague-Dawley rats were exposed to 720 ppm D4 by whole body by inhalation for 6 hours/day for 5 days in a micronucleus test, with no increase in micronuclei observed.[43, 45] Sprague-Dawley rats were exposed to 100, 500 or 1000 mg/kg-day D4 by gavage for 5 days/week for 8 weeks in a dominant lethal assay (similar to OECD 478). No effects on body weight, mortality or clinical signs were noted during the study and D4 was not genotoxic in this assay.[46]

G. Metabolism/Pharmacokinetics

*1. Absorption*

No quantitative studies of inhalation or oral bioavailability were identified. The ability of D4 to be absorbed tissue levels demonstrate following inhalation measured post-exposure in rats as well as humans.[47, 48] D4 is not well absorbed through the skin.

*2. Distribution*

D4 (or its metabolites) is widely distributed to tissues following inhalation exposure. Fischer 344 and Sprague-Dawley IGS female rats were exposed to a $^{14}$C-D4 vapor concentration of 700 ppm for 6 hours in a single nose-only inhalation study. Total $^{14}$C body burden was determined in one group of animals immediately following the exposure; while the second group was placed in metabolism cages for 168 hours post exposure for collection of urine, feces and expired air. Radioactivity and parent D4 was measured in all samples. The concentration of radioactivity over time in blood and lung was similar over the 168-hour post exposure period, while differences were seen in fat, liver, feces and urine. D4-associated radioactivity supports the conclusion that D4 (or its metabolites) is widely distributed in tissues following inhalation exposure.[47] In another study focused on evaluating the effects of repeated inhalation exposure on hepatic microsomal induction, female Fischer 344 rats (4/group) were exposed to 0, 1, 7, 30, 70, 150, 300, 500, 700 or 900 ppm D4 for 6 hours/day for 5 days. D4 content in fat, liver and plasma increased proportionally with increasing exposure concentrations. The liver-to-plasma D4 ratio remained constant over the dose range.[49, 50]

*3. Metabolism*

Several studies have been conducted to evaluate the metabolism of D4 following inhalation and oral exposure for *in vivo* and *in vitro* studies, in part to more fully evaluate the mode of action for its effects in the livers of exposed rodents. Overall, the data indicate the D4 is an inducer of hepatic metabolism, and is itself metabolized extensively. D4 exposure induces microsomal CYP450 enzymes (CYP2B1, CYP2B2, CYP3A) in the liver. D4 is also biotransformed by CYP450 enzymes (CYP2B6 & CYP3A4) and D4 metabolites including dimethylsilanediol, methysilanetriol and five others are excreted in the urine.[47, 48, 49, 50, 51, 52, 53, 54, 55]

*4. Excretion*

D4 excretion pathways have been studied in Fischer 344 rats, Sprague Dawley rats and in human volunteers. Two groups of Fischer 344 rats (5/sex/group/subset combination) were exposed to two doses (7 or 700 ppm) of unlabeled D4 vapor by nose for 6 hours/day for 14 consecutive days, followed by a single 6-hour exposure to $^{14}$C-D4 vapor on day 15. At cessation of exposure, the retained total radioactivity ranged from 4.38 – 6.14% and was readily taken up by the tissues, especially by fat (the fat and liver had the highest % body burden). The recovery of radioactivity in excreta ranged from 89.2 to 92.8% of total recovered: urine (37.4–40.0%), feces (12.6–19.1%), expired volatiles (25.9–35.4%) and expired $^{14}CO_2$ (2.06–4.54). At the high exposure level significantly higher proportions of radioactivity were eliminated through the lung (as both volatiles and $^{14}CO_2$ ) and a significantly lower proportion was eliminated through the gastro-intestinal tract in the feces. Based on normalized values, the portion of radioactivity remaining in the carcasses at 168 hours post exposure ranged from 6.53–8.50%. The mean radioactivity $t^{1/2}$ ranged from 56 hours to 253 hours.[57, 58] A similar experiment with Sprague Dawley rats yielded basically the same results. Fischer 344 rats generally showed a lower percentage of total radioactivity present as parent D4. No parent D4 was found in the urine samples from either strain, indicating all radioactivity present in the urine was as metabolites. The major metabolite present in both strains was dimethylsilanediol. Fischer 344 rat urine contains a greater number of different metabolites and more of the metabolites that are demethylated when compared to the Sprague-Dawley rats, suggesting that Fischer 344 rats are better able to metabolize and excrete D4.[55]

In an *in vivo* toxicokinetics study in humans, 6 male human volunteers (24 to 52 years old) inhaled 10 ppm $^{14}$C-labeled D4 for one hour. At several time points before, during and after exposure, $^{14}$C activity was measured in blood and urine samples. In addition, respiratory uptake and elimination were measured. Metabolites were far more persistent in blood and plasma than parent D4 and were still present at 24-hours post-exposure. A rapid respiratory elimination of 28% of the D4 uptake was observed, with 25 to 30% found in urine.[48]

*5. PBPK Models*

Based on the studies that have been conducted to assess the dermal absorption of D4 through human skin *in vivo* and *in vitro*, a physiologically based pharmacokinetic (PBPK) model was developed. The compartment model for D4 dermal absorption included (1) volatilization of applied chemical from the skin surface, (2) a storage compartment in the skin tissue, (3) diffusion of absorbed chemical within the skin back to the skin surface, (4) evaporation of this chemical from the skin surface even though the applied dose was no longer present, and (5) uptake from the skin compartment into blood. Time course of blood and exhaled breath data from human volunteers were used to estimate model parameters. In volunteers exposed to D4, the maximum concentration of chemical in exhaled air was reached at or prior to 1 hour following administration of the test chemical. Based on model calculations, the percent of applied dose of D4 that was absorbed into systemic circulation for men and women was 0.12 and 0.30% respectively. Model calculations indicate that more than 83% of the chemical that reached systemic circulation was eliminated by exhalation within 24 hours.[58]

H. Other

*1. Immunotoxicity*

In a variety of *in vivo* and *in vitro* immunotoxicological studies D4 was not found to significantly affect systemic immune responses. D4 was not immunotoxic in an inhalation and oral gavage study with F344 rats, however thymus weight decreased in relation to D4 dosing.[59, 60, 61] D4 mixed with bovine serum albumin (BSA) in an intramuscular study with dark Agouti

rats[62] and subcutaneous study with A/J mice resulted in a moderate humoral adjuvant effect with intense inflammation evident at the site of injection.[63, 64] However, in an *in vitro* study D4 was not found to be associated with the production of TNF alpha.[66] D4 was not found to induce arthritis in female Sprague-Dawley rats.[66] In a 2-week study with human volunteers D4 ingestion was not found to be immunotoxic and no proinflammatory/adjuvant effect was found.[67] These data suggest some potential for local site effects where concentrated high doses are present, but do not identify a significant pattern of concern for suppression or increased immunologic response.

*2. Endocrine effects*

A series of experiments have been conducted to examine the ability of D4 to potentially disrupt endocrine pathways. These studies add to the evaluation of the mode of action and human relevance for the endometrial adenomas observed in the rat carcinogenicity study. Weak anti-estrogenic activity was observed in an oral gavage study with both F344 and Sprague-Dawley rats and in an *in vivo* uterotropic assay with F344 rats exposed via whole body inhalation exposure.[68, 69, 70, 71] In a study in human MCF-7 cells D4 expressed a dose-dependent estrogenic effect with no significant anti-estrogenic activity.[72] D4 did not show androgenic activity in the Herschberger assay with male F344 rats through whole body D4 inhalation.[71, 73]

In *in vitro* ligand binding assays, assessment of receptor binding to calf uterine progesterone receptor and to recombinant human progesterone receptor (alpha and beta forms) gave no indication for binding of D4 to the progesterone receptor. Also, assessment of D4 in the cell-based reporter gene assay gave no indication of progesterone receptor (recombinant human progesterone receptor-ß) activation.[78]

In the context of the reproductive toxicity studies, hormone release and ovulation were evaluated in female Sprague-Dawley rats exposed to nominal 700 or 900 ppm D4 through whole body inhalation 6 hours/day for 2 or 3 days. The results indicated that D4 at 900 ppm attenuated the preovulatory luteinizing hormone surge and at both 700 and 900 ppm significantly decreased the portion of female rats that ovulated. Additional hormonal effects at ≥700 ppm included reduced estrone on the morning of estrus, and increased follicle stimulating hormone. At 900 ppm, proestrus progesterone was increased and, in ovulating animals, prolactin was decreased.[75 76]

To study the effect of D4 on prolactin levels, F344 rats were pre-treated with reserpine and then exposed to D4 by nose-only inhalation. Serum prolactin levels were not decreased in reserpine-treated female F344 rats up to 8 hours post D4 exposure. Although serum prolactin was lower in the reserpine/ D4 exposed rats at 18 hours post D4 exposure, the significance of this finding was unclear as the effect of reserpine was diminishing by this time.[77] An earlier study found significantly decreased serum prolactin levels in reserpine pre-treated female F344 rats following exposure to D4. Pre-treatment of F344 rats with sulpiride, a dopamine receptor antagonist blocked the effect of D4 on the serum prolactin levels suggesting that D4 acts on the pituitary as dopamine D2-receptor agonist *in vivo*.[78] In another study in aged female F344 rats, D4 vapor nose-only inhalation (6 hours/day for 5 days) did not decrease prolactin blood levels immediately following exposure as would be consistent with the effects of a dopamine D2-receptor agonist. D4 treatment did increase prolactin levels on day 5 at 4 and 8 hours following exposure, but not at 18 hours post-exposure. With the exception of increased liver weights, no other effects of D4 exposure were observed.[79]

## V. HUMAN USE AND EXPERIENCE

No published studies examining exposure levels or health effects experience in workers handling D4 were identified.

## VI. RATIONALE

Octamethylcyclotetrasiloxane (D4) has a relatively low order of toxicity following acute administration via the oral, dermal and inhalation routes of exposure. D4 is not considered to be a dermal or eye irritant or to be a dermal sensitizer. There is no appreciable dermal absorption of D4 based on results from *in vivo* and *in vitro* studies. D4 has not been shown to be genotoxic/mutagenic when tested in a number of short-term *in vitro* and *in vivo* assays. Overall, studies have shown adverse effects on certain female reproductive endpoints at higher exposure concentrations; however, no D4 exposure-specific effects were noted with respect to developmental endpoints. 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 tract/lung effects either reversed or were tending towards reversal following cessation of exposure. Inhalation exposure of rats to 700 ppm D4 for up to 24 months produced effects in the liver, kidney and uterus (weight changes, hepatocellular hypertrophy, endometrial hyperplasia, nephropathy). Changes to the nasal epithelium (eosinophilic globules) were also noted at 150 and 700 ppm. Despite 24 months of exposure only mild to minimal inflammatory responses were found at 150 ppm and overall the basic integrity of the respiratory tract was unchanged at this dose. At 700 ppm, there was an increased incidence of endometrial adenomas in female rats.

Based on the adverse changes in the respiratory tract, kidney and female reproductive tract in the chronic inhalation study, 150 ppm was determined to be the NOAEL and selected as the point of departure for the derivation of the WEEL value. The inhalation NOAEL was adjusted to account for interindividual variability and residual uncertainty regarding upper respiratory tract changes still occurring at 150 ppm. A 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 D4.

## VII. RECOMMENDED WEEL GUIDE

8-Hour Time-Weighted Average: 10 ppm

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