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Toxicology of octamethylcyclotetrasiloxane (D_4)

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ABSTRACT

Octamethylcyclotetrasiloxane (D_4) is a volatile cyclic siloxane used primarily as a monomer or intermediate in the production of some silicon-based polymers widely used in industrial and consumer applications and may be present as a residual impurity in a variety of consumer products. A robust toxicological data set exists for D_4. Treatment-related results from a chronic inhalation study conducted in rats are limited to mild effects on the respiratory tract, increases in liver weight, increases in the incidence of uterine endometrial epithelial hyperplasia, and a dose-related trend in the incidence of endometrial adenomas. The observed increases in liver weight appear to be related to the induction of hepatic metabolizing enzymes, similar to those that are induced in the presence of phenobarbital. D_4 is not mutagenic or genotoxic in standard *in vitro* and *in vivo* tests; therefore, the benign uterine tumors observed likely occur by a non-genotoxic mechanism. Results from mechanistic studies suggest that D_4 has very weak estrogenic and antiestrogenic activity, as well as dopamine agonist-like activity. In rats, D_4 exposure delays ovulation and hypothesized to prolong exposure of the uterine endometrium to endogenous estrogen. Though this mode of action may play a role in the development of benign uterine tumors in the rat, it is considered unlikely to occur in the human due to the marked differences in cycle regulatory mechanisms. Reproductive effects were observed following D_4 exposure in female rats. These effects appear to be related to a delay of the luteinizing hormone (LH) surge, which fails to induce complete ovulation in the rat. However, based on differences in ovulatory control in rats and humans, it appears these effects may be species-specific with no risk or relevance to human health. Results from pharmacokinetic studies indicate that dermal absorption of D_4 is limited, due to its high volatility and, if absorbed via dermal, oral or inhalation exposure, the majority of D_4 is rapidly cleared from the body, indicating bioaccumulation is unlikely.

1. Introduction

Octamethylcyclotetrasiloxane (D_4), CAS RN 556-67-2, is a low-molecular-weight volatile cyclic siloxane used primarily as a monomer or intermediate in the production of silicon-based polymers for industrial and consumer applications and may be present as a residual impurity in a variety of consumer products. The low boiling point of D_4 (175 °C) results in its high volatility, and limited exposure via inhalation is possible in occupational settings. It also displays a rather low water solubility (56 µg/L) and high lipophilicity. As such, there are potential dermal and inhalation routes of exposure to consumers, the general public, workers involved in the manufacture of D_4, and workers involved in the production of polymers and products containing D_4.

This manuscript summarizes the results of the toxicity and mechanistic studies available for D_4, with specific focus on two primary effects seen in animal studies (liver enlargement and reproductive effects). The pharmacokinetics of D_4 are also discussed. Companion manuscripts (Jean and Plotzke, 2017; Jean et al., 2017; Dekant et al., 2017) further review the uterine results reported in rats following chronic exposure (dose-related increased incidences of uterine endometrial epithelial hyperplasia and a dose-related trend in the incidence of endometrial adenomas) and explore the mechanisms by which D_4 exposure may contribute to these reported results.

2. Absorption, distribution, metabolism, elimination of D_4

The pharmacokinetics of D_4 are well characterized. Single exposure inhalation (Utell et al., 1995, 1998) and dermal (Powell et al., 1996; Jovanovic et al., 2008) pharmacokinetic studies have been performed in humans, with single and repeated dose inhalation (Plotzke et al., 2000; Dow Corning Corporation 1995c,d, 1996c) and dermal (Jovanovic et al., 2008; Zareba et al., 2002; Reddy et al., 2007) pharmacokinetic studies performed in experimental animals. Studies to investigate pharmacokinetics following single oral exposures have also been conducted in rats (Dobrev et al., 2008; Sarangapani et al., 2003; Domoradzki et al., 2017). These studies are discussed in more detail in

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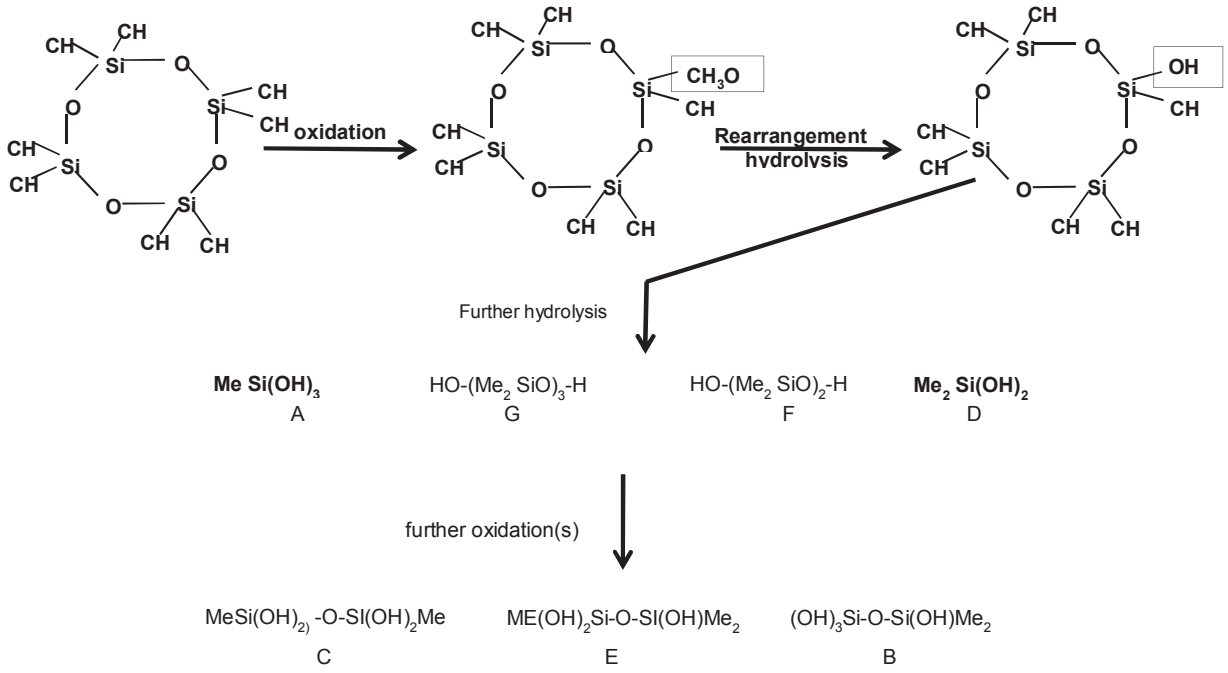

Major metabolites A and D indicated in bold, minor metabolites C, E and B can be produced by multiple pathways (Modified from Varaprath et al. 1999).

Fig. 1. Adapted from Varaprath et al. (1999) – Possible pathways for formation of D_4 metabolites in rat urine.

the following sections.

The metabolism of D_4 was investigated in humans following single inhalation exposure (Utell et al., 1998) and in animals following single or repeated inhalation (Plotzke et al., 2000; Dow Corning Corporation 2000a, 2002), single or repeated intravenous (iv) administration (Varaprath et al., 1999) and single oral exposure (Domoradzki et al., 2017). Based on the metabolite profiles reported in blood, tissues and excreta of rats following exposure to D_4, a metabolic pathway was proposed (Fig. 1) by Varaprath et al. (1999). D_4 is initially oxidized, which leads to ring-opening followed by simple hydrolysis, and eventually two major metabolites (dimethylsilanediol, $Me_2Si(OH)_2$) and methylsilanetriol, $MeSi(OH)_3$ and five minor metabolites are formed, based on analyses of compounds present and identified in urine (Varaprath et al., 1999).

2.1. Inhalation[1]

2.1.1. Humans

Utell et al. (1995, 1998) conducted four double-blind, crossover inhalation studies in humans (single 1-h exposure to 10 ppm D_4) to investigate the pharmacokinetics of inhaled D_4 and one nose-piece exposure system study to compare the deposition of D_4 in the lung during nasal and oral inhalation exposures. The mean D_4 intake, determined from continuously-measured inspiratory and expiratory D_4 concentrations, ranged from 122 to 154 mg (Utell et al., 1995, 1998) and absorption of D_4 was reported to range from 12% to 17% at rest, decreasing with exercise to 10%. Utell et al. (1995) reported that 95% of D_4 absorbed was eliminated in 10 min through post-exposure exhalation. Comparison of nasal breathing (nose-only) to mouth breathing (mouthpiece) exposures indicated that the average total intake of D_4 was 11.5 mg (mouthpiece) and 14.8 mg (nose-only). The estimated uptake of D_4, determined by the product of the mean intake concentration of D_4 and the estimated deposition fraction, was 1.1 mg and 2.0 mg for mouthpiece and nose-only, respectively. D_4 was not found in the urine of exposed volunteers, but three to five minor D_4 metabolites were detected (Utell et al., 1998).

Table 1
Range of Concentrations from studies in ppm and mg/L.

5 ppm	60 mg/L
7 ppm	84.9 mg/L
10 ppm	121.3 mg/L
20 ppm	242.6 mg/L
30 ppm	363.9 mg/L
35 ppm	424.6 mg/L
60 ppm	727.9 mg/L
70 ppm	849.2 mg/L
122 ppm	1480.1 mg/L
150 ppm	1819.7 mg/L
180 ppm	2183.7 mg/L
226 ppm	2741.7 mg/L
300 ppm	3639.5 mg/L
417 ppm	5058.8 mg/L
488 ppm	5920.2 mg/L
500 ppm	6065.8 mg/L
540 ppm	6551 mg/L
700 ppm	8492.1 mg/L
898 ppm	10894.1 mg/L
900 ppm	10918.4 mg/L
1000 ppm	12131.5 mg/L
1076 ppm	13053.5 mg/L
1154 ppm	13999.8 mg/L
2975 ppm	36091.3 mg/L

2.1.2. Rodents – single exposure

Two single-exposure nose only inhalation studies in Fischer 344 (F344) rats (Plotzke et al., 2000) (Dow Corning Corporation, 1995c,d, 1996c); Dow Corning Corporation, 2002) and one in Sprague-Dawley (SD) rats (Dow Corning Corporation, 2002) have been conducted.

[1] Throughout the manuscript, discussion of concentrations in inhalation studies will be reported as ppm and will be the nominal concentrations planned for administration by the study authors. Table 1 provides all concentrations tested as mg/L.