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Toxicology of decamethylcyclopentasiloxane (D5)

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ABSTRACT

Decamethylcyclopentasiloxane (D5) is a cyclic siloxane used in the formulation of consumer products as well as an industrial intermediate. A summary of the previous studies on the toxicology of D5 is provided. Toxicokinetic studies with D5 after dermal administration demonstrate a very low uptake of due to rapid evaporation. Following inhalation exposure, exhalation of unchanged D5 and excretion of metabolites with urine are major pathways for clearance in mammals. Due to this rapid clearance by exhalation, the potential for bioaccumulation of D5 is considered unlikely. The available toxicity data on D5 adequately cover the relevant endpoints regarding potential human health hazards. D5 was not DNA reactive or mutagenic in standard *in vitro* and *in vivo* test systems. D5 also did not induce developmental and reproductive toxicity in appropriately performed studies. In repeated studies in rats with subacute, subchronic and chronic inhalation exposure, mild effects on the respiratory tract typically seen after inhalation of irritating materials, increases in liver weight (28- and 90-day inhalation studies), and a small increase in the incidence of uterine adenocarcinoma (uterine tumor) in female rats (two-year inhalation chronic bioassay) were observed. The liver effects induced by D5 were consistent with D5 as a weak "phenobarbital-like" inducer of xenobiotic metabolizing enzymes and these effects are considered to be an adaptive response. Mechanistic studies to elucidate the mode-of-action for uterine tumor induction suggest an interaction of D5 with dopamine signal transduction pathways altering the pituitary control of the estrus cycle. The resulting estrogen imbalance may cause the small increase in uterine tumor incidence at the highest D5-exposure concentration over that seen in control rats. A genotoxic mechanism or a direct endocrine activity of D5 is not supported as a mode-of-action to account for the induction of uterine tumors by the available data.

1. Introduction

Decamethylcyclopentasiloxane (D5), CAS 541-02-6, is a cyclic siloxane used as an intermediate in the production of polydimethylsiloxanes and has a number of secondary uses as a component in consumer products. D5 has a low water solubility (17 ppb) and a boiling point of 211 °C. Due to the high volatility and low surface energy, D5 readily volatizes. Therefore, inhalation and dermal contact are the major expected routes of human exposures to D5 for consumers, the general public and manufacturing workers.

Extensive toxicity testing and experimental studies on D5 have been performed addressing the acute, subchronic and chronic effects of D5 in rodents via dermal, oral and inhalation routes of exposure. The very limited dermal absorption (due to volatility) and a specific toxicokinetic behavior after oral administration has resulted in the selection of inhalation as the preferred route of D5 administration for toxicity studies. Several experimental studies *in vitro* have also been performed with D5 to provide further information on the possible underlying mechanisms for the toxic effects observed with D5 and the relevance of these effects in rodents for human risk assessment.

This manuscript reviews and evaluates the results of the toxicity and mechanistically based studies with specific interest in understanding the mechanisms by which D5 induces liver enlargement and increases the incidence of the uterine adenocarcinomas after chronic exposure in rats.

2. Absorption, distribution, metabolism, and excretion of D5

The toxicokinetics of D5 are well characterized. Studies covering both single and repeated inhalation exposures to D5, and following

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dermal application and oral administration have been performed in experimental animals. In addition, human data on extent of dermal absorption of D5 and the disposition of systemically available D5 have been generated (DCC, 1996; Burns-Naas et al., 1998a, 1998b; DCC, 2002; DCC, 2003c; DCC, 2003d; DCC, 2003a; DCC, 2003b; Varaprath et al., 2003; DCC, 2005a; DCC, 2007; Jovanovic et al., 2008; Reddy et al., 2008; Tobin et al., 2008).

2.1. Absorption and distribution of D5 after inhalation exposures

The disposition of D5 was evaluated in male and female rats after single and repeated inhalation exposures using nose only inhalation (Tobin et al., 2008).

Rats were either exposed once for six hours to 7 or 160 ppm ^{14}C-D5 or, after 14 consecutive six hour nose-only exposures to 160 ppm of unlabeled D5 over two weeks, to a single six hour exposure to 160 ppm ^{14}C-D5 on day 15. D5-derived radioactivity and parent D5 were quantified in blood, plasma, selected tissues, expired air, urine, and feces collected at different time points. After both single and repeated inhalation exposures, less then three % of the delivered doses of D5 (calculation based on respiratory minute volume, exposure duration, and D5 vapor concentration) were retained in the animals. Significant accumulation of D5 on the fur was observed. Retained D5 was widely distributed from blood to tissues with maximum concentrations observed in the majority of the tissues three hours after exposure. In the plasma, liver and lung, the majority of radioactivity immediately following exposure represented unchanged D5. However, the contribution of D5 to the total radioactivity in tissues decreased over time and D5 represented only a small fraction of total radioactivity at time points >24 h after the end of the exposure. Elimination of D5 and presumed metabolites from fat was slower as compared to plasma and other tissues (DCC, 2001). Repeated exposure gave rise to higher concentrations of parent D5 in the lung and fat of both sexes and in the liver in female rats as compared to a single exposure.

Exhalation of unchanged D5 was the major pathway of elimination after both single and multiple inhalation exposures and accounted for app. 50% of the retained D5. Elimination of D5-derived radioactivity with urine in the form of metabolites accounted for approximately 12% and fecal elimination for approximately 16% of retained radioactivity. Fecal elimination of D5 may in part be due to oral ingestion of D5 deposited on the fur absorbed during grooming. Elimination of D5-associated radioactivity was multiphasic, but most of the radioactivity was eliminated within 24 h after the end of inhalation exposure. As with other lipophilic chemicals, fat may serve as a reservoir of D5 since little decrease of D5-associated radioactivity in fat was observed over an observation period of 168 h. Most of the radioactivity present in fat was attributed to unchanged D5, a minor fraction was presumed to represent a hydroxylated metabolite (Tobin et al., 2008).

Analysis of the fecal extracts by high-pressure liquid chromatography (HPLC) indicated that the majority of the radioactivity in feces was unchanged D5, a hydroxylated derivative of D5 was a presumed minor metabolite. HPLC-analysis of urine samples revealed the presence of seven metabolites. The two major metabolites were dimethylsilanediol and methylsilane triol with $[MeSi(OH)_2{-}O{-}Si(OH)_3]$, $[MeSi(OH)_2{-}O{-}Si(OH)_2Me]$, $[MeSi(OH)_2{-}O{-}Si(OH)Me_2]$, $[Me_2Si(OH){-}O{-}Si(OH)Me_2]$, and $[Me_2Si(OH){-}OSiMe_2{-}OSi(OH)Me_2]$ representing minor metabolites (Varaprath et al., 2003). The metabolite structures suggest that D5 is initially oxidized to a hydroxylated derivative, presumable by cytochrome P450 (Fig. 1). This initial metabolite appears to rearrange and downstream products are degraded by hydrolysis to the short-chain siloxanes, which are excreted (Fig. 1).

The toxicokinetics of D5 after inhalation exposure were also studied in human subjects (three males and two females) after inhalation of D5 at a single concentration of 10 ppm for one hour using a mouthpiece exposure system under a mixed rest/exercise scheme (DCC, 2004c). During exposure, D5 concentrations in exhaled air rapidly reach a steady state between 7 and 10 ppm; after the end of the exposures, D5 levels in exhaled air rapidly declined and reached concentrations of less than 1 ppm within 20 min in most of the subjects. Concentrations of D5 in plasma increased from a baseline level of 0.15–3.3 μg/L to between 31 and 70 μg/L at the end of the inhalation exposure and rapidly declined after the end of the exposure to reach the basal levels within 24 h after the termination of the inhalation exposure (DCC, 2004c).

2.2. Bioavailability and deposition of D5 after dermal administration

Toxicokinetics of D5 after dermal exposure were assessed in humans and in rats. In addition, the dermal absorption of D5 was studied in a number of *in vitro* studies (Jovanovic et al., 2008).

Three male and three female human subjects applied 1.4 g (males) or 1.0 g (female) of ^{13}C-D5 to the axilla under unoccluded conditions. Blood samples were collected for up to six hours and exhaled air samples were collected for up to 24 h after application (DCC, 2002). Peak concentrations of ^{13}C-D5 in the plasma were achieved within two hours after application and were 1.22 ng/g at one hour, 0.61 ng/g at six hour sampling, and were below the limit of detection of 0.03 ng/g in all samples taken later than six hours after ^{13}C-D5 application. Concentrations of ^{13}C-D5 in exhaled air were below one ng/L at all time points.

^{14}C-D5 was applied under semi-occluded conditions to human skin from six donors using a flow-through diffusion cell technique with provisions to collect material volatilized from the skin by absorption to charcoal traps. Skin samples were dosed either with neat D5 or with a generic antiperspirant formulation containing D5. After 24 h, only 0.04% of the applied dose of neat D5 and 0.022% of the D5 present in the formulation was absorbed. The majority of the applied D5 was volatilized from the skin samples and was recovered on the charcoal traps (DCC, 1999). The cumulative penetration for neat D5 was 0.1 μg/cm^2 and 0.3 μ/cm^2 for formulated D5.

To assess the fate of D5 absorbed from the skin in intact animals, ^{14}C-D5 was applied to the dorsal surface of male and female rats. Hair at the application site was clipped prior to application and the application site was covered with a non-occlusive elastic wrap. The study was designed to permit differentiation between D5 exhaled after absorption and D5 evaporating from the application site. After application of D5, the animals were transferred to metabolic cages for the collection of urine and feces. The majority (about 85%) of the applied ^{14}C-D5 volatilized from the skin. After 96 h, 0.35% of the administered D5 remained at the application site and less than 1% of the applied ^{14}C-activity was recovered in urine and carcass with trace levels of ^{14}C-activity recovered in feces, CO_2 traps, and tissues. The total amount of D5 absorbed was <1% (DCC, 2003c).

2.3. Toxicokinetics of D5 after oral administration

Toxicokinetic studies were performed in rats after dosing by gavage with ^{14}C-D5 (single dose of 1000 mg/kg bw) dissolved in different vehicles (corn oil and simethicone fluid) and as a neat material (DCC, 2003a). The carrier had a significant influence on the extent of absorption of ^{14}C-D5. After administration of neat D_5, approximately 10% of the dose was absorbed from the gastrointestinal tract. Based on blood area under the curve (AUC), absorption increased after administration of D5 in corn oil and decreased after administration in simethicone fluid. Elimination half-lives for D5-associated radioactivity in blood ranged from 45 (simethicone)

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