Toxicology Letters 279S (2017) 42–53

Contents lists available at ScienceDirect

Toxicology Letters

journal homepage: www.elsevier.com/locate/toxlet

Biological relevance of effects following chronic administration of octamethylcyclotetrasiloxane (D4) in Fischer 344 rats

Wolfgang Dekant[a,*], Anthony R. Scialli[b], Kathy Plotzke[c], James E. Klaunig[d]

[a] University of Würzburg, Germany
[b] Scialli Consulting LLC and George Washington University, USA
[c] Dow Corning, USA
[d] Indiana University, USA

HIGHLIGHTS

- Inhalation of octamethylcyclotetrasiloxane (D4) induces uterine adenomas in rats.
- Biological relevance of this effect for human risk characterization is assessed.
- Alterations in the estrous cycle in the aging F344 rat is the most likely mode of action.
- Cycle alterations likely induced indirectly via a dopamine-like mechanism.

ARTICLE INFO

Article history:
Received 19 October 2016
Received in revised form 13 January 2017
Accepted 15 January 2017
Available online 18 January 2017

Keywords:
Octamethylcyclotetrasiloxane
D4
Silicones
Uterine adenoma
F344 rats

ABSTRACT

Octamethylcyclotetrasiloxane (D4) is a cyclic siloxane primarily used as a monomer or intermediate in the production of silicone polymers resulting in potential exposure of workers, and potential low level inhalation or dermal exposure for consumers and the general public. Following a two-year inhalation toxicity study with D4 in rats, increases in uterine endometrial cystic hyperplasia and adenomas were observed at the highest concentration of D4 administered (700 ppm). No other neoplasms were increased with D4 treatment. In addition, chronic inhalation exposure of rats to D4 induced changes in relative liver and kidney weights, and produced a chronic nephropathy.

This manuscript examines the biological relevance and possible modes of action for the effects observed in the F344 rat following chronic inhalation exposure to D4. D4 is not genotoxic and appears to exert its effects through a nongenotoxic mode of action. An alteration in the estrous cycle in the aging F344 rat was the most likely mode of action for the observed uterine effects following chronic inhalation exposure. Data support the conclusion that D4 acts indirectly via a dopamine-like mechanism leading to alteration of the pituitary control of the estrous cycle in aging F344 rats with a decrease in progesterone and an increase in the estrogen/progesterone ratio most likely induced by a decrease in prolactin concentration. D4 also inhibited the pre-ovulatory LH surge causing a delay in ovulation, persistent follicles and thus a prolonged exposure to elevated estrogen in the adult Sprague Dawely rat. A lengthening of the estrous cycle in the F344 rat with an increase in endogenous estrogen was also induced by D4 inhalation. Although the mode of action responsible for induction of uterine adenomas in the female F344 rat has not been clearly confirmed, the subtlety of effects on the effects of D4 on cyclicity may prevent further assessment and definition of the mode of action. The occurrence of uterine endometrial adenoma in the rat is not relevant for human risk characterization because (1) there are differences in ovulatory cycle regulation in rats compared to humans, (2) cystic hyperplasia without atypia in women is not a cancer precursor, and (3) there is no endometrial lesion in women that is directly analogous to endometrial adenoma in the rat. The effects of D4 on liver are due to a phenobarbital-like mechanism that results in induction of cytochrome P450 and other enzymes of xenobiotic

* Corresponding author at: Department of Toxicology, University of Würzburg, Versbacher Str. 9, 97078 Würzburg, Germany.
E-mail address: dekant@toxi.uni-wuerzburg.de (W. Dekant).

http://dx.doi.org/10.1016/j.toxlet.2017.01.010

biotransformation. The liver effects are adaptive and not adverse. Kidney findings included chonic progressive nephropathy, a rat lesion that has no counterpart in the human and that should not be used in human risk assessment.

1. Introduction

Octamethylcyclotetrasiloxane (D4) is a cyclic siloxane primarily used as a monomer or intermediate in the production of silicone polymers. Potential human exposure includes workers, consumers, and the general public. D4 is highly lipopilic (log K_{ow} of 6.5) with very low water solubility (50 ppb) and a boiling point of 175 °C and is highly volatile. Inhalation of D4 vapor and dermal contact with D4-containing formulations are the major expected routes of human exposures (SCCS, 2010). However, dermal absorption of D4 is very limited and most of the D4 applied to skin rapidly evaporates due to the high volatility (DCC, 2000d, 2000c; Jovanovic et al., 2008). Because D4 does not have a potential for bioaccumulation (Andersen et al., 2008), dietary exposures of humans are considered of little relevance.

Toxicity studies on D4 have been performed addressing the acute, subchronic, and chronic effects of D4 in rodents (Franzen et al., 2017). Most of these studies used inhalation as the route of exposure due to the high volatility of D4, the very limited dermal absorption (DCC, 1998a, 2000c), and the unique toxicokinetics of D4 after oral administration (Sarangapani et al., 2003; DCC, 2006a; Andersen et al., 2008). Inhalation studies following established study protocols have been performed to address most endpoints relevant to risk characterization (Burns-Naas et al., 2002; Batelle, 2004; Meeks et al., 2007; Siddiqui et al., 2007). In addition, mechanistic studies have been performed with D4 both *in vivo* and *in vitro* to provide information on the underlying mechanisms of the effects observed in the hazard assessment studies and the relevance of the D4 effects observed in rodents for human risk characterization.

This manuscript summarizes the results of the D4 experimental studies with regard to the understanding of those mechanisms by which D4 elicited effects including the increases in liver weight, nephropathy, and the incidence of proliferative uterine endometrial lesions after chronic exposure in F344 rats.

2. Absorption, distribution, metabolism, excretion of D4

The toxicokinetics of D4 are well characterized, and studies investigating both single and repeated inhalation, dermal application, and intravenous (i.v) administration have been performed in experimental animals and, for some routes of administration, in human subjects. Toxicokinetics following single oral exposures also have been assessed in humans and rats (Utell et al., 1995, 1998; DCC, 1996b, 1997b, 1997c, 2000b, 2001c, 2006a; Kala et al., 1998; Varaprath et al., 1999; Plotzke et al., 2000; Dobrev et al., 2008). The biotransformation of D4 was investigated in experimental animals after inhalation and intravenous administration. Initial oxidation of D4 occurs by cytochromes P450 to give heptamethylcyclotetrasiloxanol (DCC, 1997a, 1997b, 2006b) (Fig. 1); this cyclic siloxanol is then further hydrolyzed to dimethylsilanediol ($Me_2Si(OH)_2$), methylsilanetriol ($MeSi(OH)_3$), and a number of other minor metabolites (DCC, 2001c). These polar metabolites are excreted in urine (Fig. 1).

In human subjects exposed to a D4 concentration of 10 ppm in air, absorption of D4 from the lung after inhalation is limited and exhalation of absorbed parent D4 is rapid. In addition, D4 not exhaled is cleared by biotransformation to polar metabolites and excretion in urine (DCC, 1996b, 1996c, 2000b, 2000a, 2002a; Utell et al., 1998; Plotzke et al., 2000; Reddy et al., 2003). Systemically

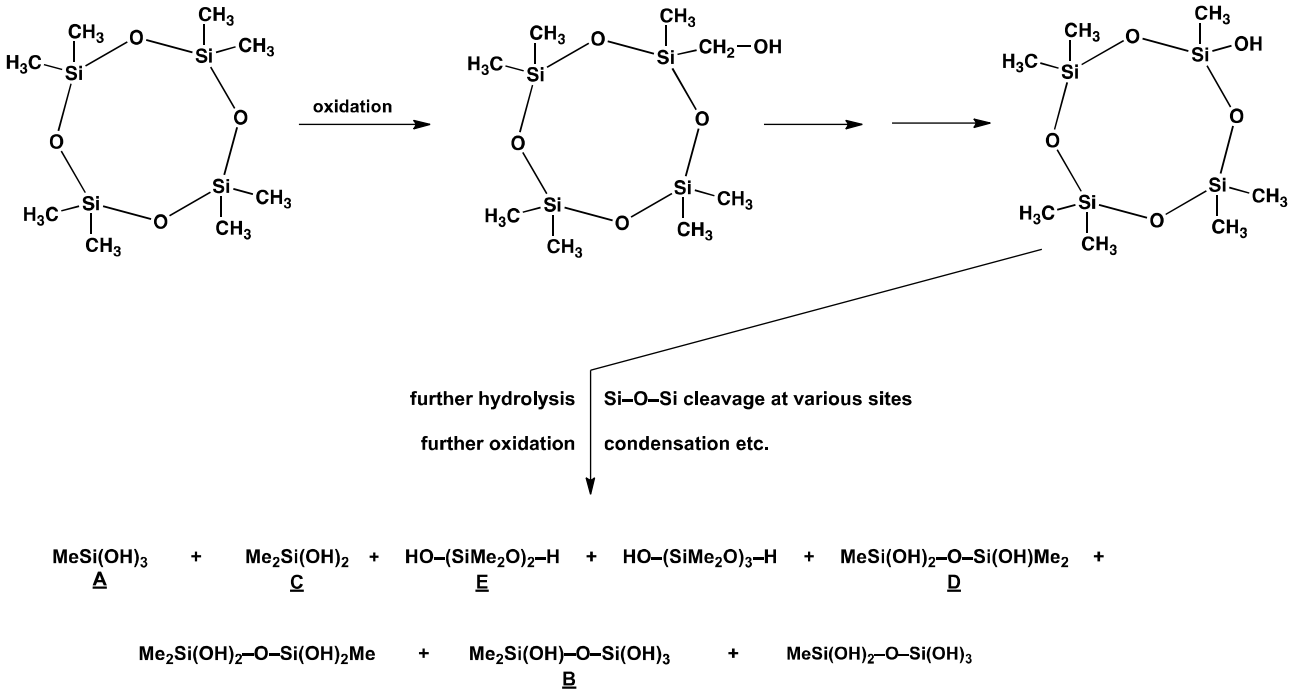

Fig. 1. Biotransformation of D4 in rodents.