



## Comments on the safety assessment of decamethylcyclopentasiloxane (D5) published in regulatory toxicology and pharmacology, 2017, 83:117–118



### Keywords:

Safety assessment  
Decamethylcyclopentasiloxane  
Uterine tumors  
Mode of action  
Inhalation toxicology

Dear Dr. Gori,

This letter is in response to the summary of the safety assessment of the Scientific Committee on Consumer Safety (SCCS) on decamethylcyclopentasiloxane (D5) in cosmetic products published (SCCS & Rousselle, 2017) and the opinion (SCCS, 2017). We have been asked by the Silicones Environmental, Health and Safety Center of the American Chemistry Council to provide comments given that SCCS (2017) references our publication in this journal (Dekant and Klaunig, 2015; Klaunig et al., 2016). In reviewing the SCCS assessment, we noted that these manuscripts may have been unclear regarding description of some important information that would have assisted SCCS in their conclusions.

### 1. Lung effects and risk characterization

For assessment of inhalation exposures to D5, the NOAEC for local changes in the respiratory tract in a 90-day inhalation study in rats was used by SCCS (2017). Alveolar macrophage accumulation and focal interstitial inflammation in the lung with increased lung weights, goblet cell proliferation, and submucosal inflammation in the nose were observed in a number of inhalation studies with D5. These changes are consistent with a response of the airways to repeated exposure to a mild irritant. Consequently, SCCS previously stated that the respiratory changes were "... considered to be of little/no relevance for consumer exposure to much lower concentrations of D5". SCCS now concludes that "D5 is not safe in hair styling aerosols and sun care spray products ..." suggesting that SCCS has changed its opinion and considers the airway effects as relevant. No reason for rejecting the previous conclusion of little/no relevance for consumer exposure is given.

If the NOAEC for the mild airway irritation is used as a point of departure for risk characterization, the exposure assessment requires refinement. Such an exposure pattern is unlikely for consumers and the NOAEC used is therefore highly conservative. For calculation of the margin of safety (MoS), SCCS compares the

predicted air concentration of D5 from aerosol applications to the NOAEC. SCCS apparently assumes that all D5 aerosol particles are able to penetrate into the airways. Since dose to the target tissue is relevant for the local effect, the MoS calculation needs to be compared with the dose of D5 received/unit of lung weight under the conditions of the inhalation toxicity studies and doses of D5 received/unit of lung weight from the consumer exposure considering rat and human alveolar ventilation rates. In addition, particle size distribution of the inhaled aerosols needs to be integrated since only particles <10 μm may penetrate into the airways. Only a fraction of the D5 is present as a respirable aerosol and SCCS in 2010 referenced the mean particle sizes as approximately 38 μm for aerosol spray and as > 80 μm for pump sprays. Particles of these sizes do not penetrate beyond the uppermost regions of the respiratory tract. Therefore, the present approach by SCCS widely underestimates the MoS. Not considering particle sizes and the respirable fraction of the aerosol particles is inconsistent with previous assessments for D4 (and D5) and the guidance developed by SCCS.

### 2. Uterine effects

In Klaunig et al. (2016), we detailed the reasons why the reported marginal increase in rat uterine tumors detected in the two-year bioassay of D5 was not relevant to humans. We noted "the slight increase in uterine endometrial adenocarcinomas observed in the D5 chronic bioassay might not be the result of D5 exposure but may be related to variability of the spontaneous tumor incidence in this strain of rat." We further indicated "if the uterine endometrial adenocarcinomas are related to D5-exposure, a plausible mode of action exists in the rat that involves alteration in the estrous cycle in the aging F344 rat". A dopamine-like mode-of-action was the explanation for the observed effects on the uterus in rats (Klaunig et al., 2016). Our analysis considered genotoxicity, direct estrogenic activity of D5 on the uterus, oxidative stress, alterations in the metabolism of endogenous estrogens, and alterations in pituitary control of the estrous cycle as possible modes of action for the uterine tumor effect. The only mode of action supported by the data was altered estrous cyclicity, for which there is ample literature support, some of which was not specifically delineated in our paper (Klaunig et al., 2016).

In the rodent, prolactin is required for maintenance of the corpus luteum. In the absence of adequate prolactin, the rodent corpus luteum will regress, resulting in resumption of follicle recruitment and growth and an increase in endogenous estrogen exposure. D5 has not been shown to alter LH, but D5 exposure of rats from 11 to 25 months of age results in an increased cumulative

number of days in estrus or proestrus with a consequent increase in endogenous estrogen exposure of the uterus. Dopamine is an endogenous inhibitor of the pituitary release of prolactin. Dopamine-like activity of D5 was demonstrated in a rat pituitary tumor cell line (Jean, 2005a) and D5 produced a concentration-dependent decrease in forskolin-stimulated cAMP accumulation in this cell line, consistent with dopamine-like activity. This activity was not mediated by the dopamine receptor (Domoradzki, 2011). In female Fischer 344 rats treated with reserpine to deplete dopamine, inhalation of D5 partially inhibited the serum prolactin elevation seen in reserpinized control animals (Jean, 2005b). Pharmaceutical dopamine agonists such as bromocriptine decrease pituitary prolactin secretion in rats with consequent luteolysis and an increase in estrogen exposure (Alison et al., 1994).

A dopamine-like mode of action is not relevant to ovulatory disturbance in humans due to independence of the human corpus luteum from prolactin (NDA 17-962; Bachelot and Binart, 2007). Uterine tumors in rats secondary to inhibited prolactin are not relevant to human risk assessment, because inhibition of prolactin is not a mechanism of uterine tumor induction in women (Burke et al., 1988). We also reviewed the well characterized mechanisms of uterine tumor induction in humans. Most of the uterine tumors seen in humans are due to anovulation or oligo-ovulation with consequent excessive exposure to estrogen. Based on the irrelevance of the dopamine-like mode of action to humans, the rat uterine tumor findings with D5 are not relevant to human risk assessment. We respectfully disagree with SCCS that mechanisms of uterine tumor production in rats or in women have not been inadequately characterized.

#### Acknowledgement

Preparation of this letter was supported in part through an honorarium to the authors from the Silicones Environmental, Health and Safety Center of the American Chemistry Council. This letter represents the individual professional views of the authors and not necessarily the views of the American Chemistry Council.

#### References

Alison, R.G., Capen, C.C., Prentice, D.E., 1994. Neoplastic lesions of questionable

- significance to humans. *Toxicol. Pathol.* 22, 179–186.
- Bachelot, A., Binart, N., 2007. Reproductive role of prolactin. *Reproduction* 133 (2), 361–369.
- Burke, J.D., Patrick, D.H., Gerson, R.J., 1988. Weight-of-biological evidence approach for assessing carcinogenicity. In: Grice, H.C., Cimino, J.L. (Eds.), *Carcinogenicity*. Springer-Verlag, New York, pp. 83–85.
- Dekant, W., Klaunig, J.E., 2015. Toxicology of decamethylcyclopentasiloxane (D5). *Regul. Toxicol. Pharmacol.* 74S, S67–eS76.
- Domoradzki, J.Y., 2011. *In Vitro* MMQ Cell-based Evaluation of the Potential for Dopamine Receptor Activation by Octamethylcyclotetrasiloxane (D4) and Decamethylcyclopentasiloxane (D5). Dow Corning Corporation Health & Environmental Sciences Technical Report, Study, pp. 11256–12102.
- Jean, P.A., 2005a. Effect of Cyclic Siloxanes on Dopamine Receptor Regulation of Prolactin Release from Rat Pituitary Tumor-derived Transformed Cell Lines. Dow Corning Corporation Health & Environmental Sciences Technical Report, Study, pp. 9872–10102.
- Jean, P.A., 2005b. Effect of Cyclic Siloxanes on Dopamine Receptor Regulation of Serum Prolactin Levels in Female Fischer 344 Rats. Dow Corning Corporation Health & Environmental Sciences Technical Report, Study, pp. 9939–10102.
- Klaunig, J.E., Dekant, W., Plotzke, K., Scialli, A.R., 2016. Biological relevance of decamethylcyclopentasiloxane (D5) induced rat uterine endometrial adenocarcinoma tumorigenesis: mode of action and relevance to humans. *Regul. Toxicol. Pharmacol.* 74, S44–S56.
- NDA 17-962. Parlodel (bromocriptine mesylate) Tablets New Drug Application submitted to FDA November 15, 1976 and closed on May 15, 1978.
- Scientific Committee on Consumer Safety (SCCS), Rousselle, C., 2017. Opinion of the Scientific Committee on Consumer Safety (SCCS) – final version of the opinion on decamethylcyclopentasiloxane (cyclopentasiloxane, D5) in cosmetic products. *Regul. Toxicol. Pharmacol.* 83, 117–118.
- SCCS, 2017: [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/sccs\\_o\\_174.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_174.pdf).

James Bridges  
University of Surrey, United Kingdom

Wolfgang Dekant\*  
University of Würzburg, Germany

James E. Klaunig  
Indiana University, USA

Anthony R. Scialli  
Reproductive Toxicology Center, George Washington University, USA

\* Corresponding author.  
E-mail address: [dekant@toxi.uni-wuerzburg.de](mailto:dekant@toxi.uni-wuerzburg.de) (W. Dekant).

14 June 2017  
Available online 2 August 2017