

ENVIRON

Health Sciences Institute

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Mentor Corporation
201 Mentor Drive
Santa Barbara, CA 93111

To Whom It May Concern:

My name is Joseph V. Rodricks. I am a consultant in toxicology and human health risk assessment and am employed as a Principal at ENVIRON Health Sciences Institute, a division of ENVIRON International Corporation. Before working as a consultant, I spent 15 years at the U.S. Food and Drug Administration (FDA), including two years as Deputy Associate Commissioner of Health Affairs, with special responsibility for risk assessment. My educational background includes a Bachelor of Science degree in chemistry from Massachusetts Institute of Technology, a Masters of Science degree in Organic Chemistry from the University of Maryland, and a Ph.D. in biochemistry from the University of Maryland. I am a diplomate of the American Board of Toxicology and have held that designation since 1982. I am also an Adjunct Professor at the Johns Hopkins University School of Public Health where I teach courses in toxicology and risk analysis. I have authored more than 120 scientific publications, edited and authored several books, and lectured on more than 200 occasions, in the United States and abroad, on matters of toxicology and product safety. I have served on 20 expert Committees of the National Academy of Sciences and the Institute of Medicine (IOM), all involving evaluation of potential threats to human health.

I have been retained by Mentor Corporation as an expert on toxicology and risk assessment. I have been asked to provide my scientific opinion on issues related to the toxicology of cyclic silicone compounds present in silicone gel-filled mammary implants. Specifically, I was asked to consider whether the results of studies completed since publication of the IOM expert panel report on the safety of silicone breast implants (IOM 1999) would alter the conclusions regarding these materials made by the panel at that time. In 1999, the panel concluded: "In general, there do not appear to be long-term systemic toxic effects from silicone gel implants or from unsuspected compounds in these gels or elastomers..." As will be discussed in more detail below, my opinion, after reviewing the results of recently completed studies on silicone materials, is that these studies add to the body of evidence confirming the safety of silicone materials as used in silicone gel-filled breast implants and lend further support to the conclusions drawn by the panel in 1999. The basis for my opinion is provided below.

Genotoxicity

Since the IOM expert panel review, Vergnes et al. (2000) have published a comprehensive evaluation of the genotoxicity of D₄ (octamethylcyclotetrasiloxane or OMCTS). This report includes the results of both *in vitro* assays (e.g., bacterial mutagenicity, chromosomal aberration in Chinese Hamster Ovary (CHO) cells, sister

chromatid exchange in CHO cells) and *in vivo* assays (chromosomal aberrations in rat bone marrow). The authors concluded that “the results of these studies indicate that OMCTS does not possess significant *in vitro* genotoxic potential” and that “no adverse genetic findings were seen in the *in vivo* screen for chromosome aberrations.”

Since the IOM expert panel review, additional genotoxicity studies have also been performed on D₅. An unpublished summary indicates that four genotoxicity studies, two *in vitro* and two *in vivo*, have recently been conducted by industry. The summary concludes that “Consistent with the existing genotoxicity data, all four studies confirmed that D₅ does not have the potential to cause changes in DNA” (GE Silicones 2004).

Chronic Toxicity/Oncogenicity

Since the IOM expert panel review, Dow Corning has conducted two-year chronic inhalation toxicity/oncogenicity studies on D₄ (octamethylcyclotetrasiloxane) and D₅ (decamethylcyclopentasiloxane) in Fisher 344 rats. Although final reports of these studies have not been released to the public, it is my understanding that Dow Corning has reported these results to FDA and EPA and that the results have provided the basis for quantitative risk assessments on D₄ and D₅. My review has been limited to preliminary Dow Corning summaries available in public dockets.

In the study on D₄, rats were exposed to vapor concentrations of 0, 10, 30, 150, or 700 ppm for 6 hr/day, 5 days/week for up to 24 months (Dow Corning 2002). Preliminary results showed effects in the kidneys (male and female) and uterus of rats exposed for 12 to 24 months. These effects included increased kidney weight, increased incidence of endometrial cell hyperplasia, and an increased incidence of endometrial adenomas. These effects were limited to the 700 ppm exposure group. Thus, a no-observed-effect level (NOEL) for this study was reported to be 150 ppm. This NOEL corresponds to an estimated daily dose of 16 mg/kg/day.¹

In the study on D₅, rats were exposed to vapor concentrations of 0, 10, 40, or 160 ppm for 6 hr/day, 5 days/week for up to 24 months (Dow Corning 2003). Results indicated an increase in uterine endometrial tumors for rats exposed to D₅ for 12 to 24 months. No precancerous lesions were reported, casting significant doubt on the question of whether the tumors were induced by D₅. Further mechanistic studies, reported in summary form in February 2004 (GE Silicones 2004), are said to further support the view that the effect is not D₅ related. No other adverse effects were reported, so that 40 ppm appears to be the NOEL. This NOEL corresponds to an estimated daily dose of 5.4 mg/kg/day.¹

As will be discussed further below, although this new information from long term inhalation studies on D₄ and D₅ shows potentially serious effects, these effects were seen at high systemic doses of D₄ and D₅ administered via inhalation. These doses are substantially in excess of the levels of D₄ and D₅ that would be expected to result from

¹ Assumes body weight of 350g, a minute retention ventilation rate for rats of 240mL (Hayes 2001), and 5 percent retention (based on D₄ data of Plotzke et al. 2000).

bleeding of small amounts of silicone gel from breast implants. As will be shown below, a risk assessment using the most sensitive toxicity endpoint for D₄ (reversible liver weight increases) and D₅ (endometrial tumors) as the basis for the no-observable-adverse-effect-level (NOAEL) demonstrates a wide margin of safety for these materials, considering the levels present in Mentor's silicone gel-filled mammary implants.

Reproductive Toxicity

Since the IOM expert panel review, Dow Corning has completed a two-generation reproduction and developmental neurotoxicity study on D₄ by inhalation exposure in Sprague-Dawley rats (Dow Corning 2001a). This study is available for review in the EPA docket and I have reviewed excerpts of the study. Rats were exposed to test article concentrations of 0, 70, 300, 500, or 700 ppm for 6 hr/day for at least 70 consecutive days prior to mating. Exposure of F₀ and F₁ males continued through mating and through the day prior to sacrifice. F₀ and F₁ females continued to be exposed throughout mating and gestation through gestation day 20. Exposure of the F₀ females was re-initiated on lactation day 5 and through the day prior to sacrifice. Exposure of F₁ females was re-initiated on lactation day 5 and continued throughout the second F₁ mating and gestation periods through gestation day 20. In the F₁ generation, mating indices were reduced in the 700 ppm group for the first and second 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 in the 500 and 700 ppm groups. Based on these results, the NOEL for reproductive effects (reduced mating and fertility indices) was 300 ppm. Dow Corning performed a follow-up study to evaluate the potential of D₄ to affect the preovulatory luteinizing hormone (LH) surge in ovariectomized female rats (Dow Corning 2001b). In this study, reduced LH levels were observed in the 700 and 900 ppm inhalation exposure groups. Because LH surge is required for ovulation to occur, it was suggested that the reduced fertility rate seen in rats exposed to D₄ at 700 ppm on the day of proestrus may have resulted from a reduction in peak serum LH levels.

While these new studies suggest an effect of D₄ on mating and fertility indices following inhalation exposure in rats, these effects were seen at systemic doses of D₄ equal to or greater than those causing the chronic effects discussed above. As will be shown below, a risk assessment using the most sensitive toxicity endpoint for D₄ (reversible liver weight increases) in rats as the basis for the no-observable-adverse-effect level (NOAEL) demonstrates a wide margin of safety for this material, considering the level of D₄ present in Mentor's silicone gel-filled mammary implants.

Other Toxicity Endpoints

For D₄, the most sensitive toxicity endpoint observed in animal studies was a dose-related increase in liver weights (reversible when exposure was discontinued for 14 days) observed in a 28-day inhalation study in Fisher 344 rats (Klykken et al. 1999). In this study, rats were exposed to D₄ at inhalation doses of 0, 7, 20, 60, 180, and 540 ppm for 6 hr/day, 5 days/week for 28 days. In addition to the usual endpoints measured, immune

function was assessed by splenic antibody-forming cell (AFC) assay and enzyme-linked immunoabsorbent assay (ELISA). The only adverse effect was a statistically significant increase in liver weight and liver-to-body weight ratio in male rats exposed to 540 ppm and females exposed to 20 – 540 ppm. This effect was not seen in the 14-day recovery group animals. No immune system changes were observed. The NOAEL for this study was 7 ppm. This NOAEL is equivalent to an estimated daily dose of 0.75 mg/kg/day D₄.¹

In a subsequent study of D₄ published by Burns-Naas et al. (2002), Fisher 344 rats were exposed to D₄ by nose-only inhalation at vapor levels of 0, 35, 122, 488, and 898 ppm for 6 hr/day, 5 days/week for 3 months. A dose-related increase in liver, thymus, and adrenal weights (488 and 898 ppm) and a significant decrease in ovarian weight ((898 ppm) were observed in female rats. These effects were not seen in the 1-month recovery group animals. Reversible histopathological changes were observed in the ovary (hypoactivity) and vagina (mucification) of female rats in the high-dose group (898 ppm).

For D₅, a 28-day inhalation toxicity study in Fisher 344 rats, similar to that described above for D₄, was published by Burns-Naas et al. (1998). In this study, rats were exposed to D₅ at inhalation doses of 0, 10, 25, 75, or 160 ppm for 6 hr/day, 7 days/week for 28 days. The authors identified a NOEL for systemic toxicity (based on a reversible increase in liver weight) of 75 ppm. This NOEL is equivalent to an estimated daily dose of 14 mg/kg/day D₅.¹

McKim et al. (2001) recently reported results from a study of the potential estrogenic and antiestrogenic activity of D₄ and hexamethyldisiloxane (HDMS) in a uterotrophic assay in immature rats. D₄ exhibited weak estrogenic activity, but was approximately 585,000 times less potent than ethinyl estradiol in Sprague-Dawley rats and 3.8 million times less potent than ethinyl estradiol in Fischer 344 rats. The LOAEL for D₄ identified in this study was 100 mg/kg. Further elaboration of the mechanism by which D₄ exhibits weak estrogenic activity in mice was provided by He et al. (2003), who demonstrated that such effects were mediated through estrogen receptor- α .

Pharmacokinetic Data

Since completion of the IOM expert panel review, several authors have published studies on the pharmacokinetics of D₄.

Plotzke et al. (2000) recently published a pharmacokinetic study of ¹⁴C-labelled D₄ in Fischer 344 rats following single and multiple inhalation exposures to 7, 70, or 700 ppm D₄. Based on these data, a physiologically-based pharmacokinetic (PB/PK) model was developed for D₄ by Andersen et al. (2001). It was concluded that “high pulmonary and hepatic clearance, coupled with induction of metabolizing enzymes at high exposure

¹ Assumes body weight of 350g, a minute retention ventilation rate for rats of 240 mL (Hayes 2001), and 5 percent retention (based on D₄ data of Plotzke et al. 2000).

concentrations, rapidly remove free D₄ from the body and ensure that there is no accumulation on multiple exposures.”

Luu and Hutter (2001) published an alternative PB/PK model for D₄, challenging the Andersen et al. (2001) model and predicting accumulation of D₄ following multiple exposures. However, flaws in the methodology used by Luu and Hutter (2001) have been asserted by Meeks (2002), Andersen et al. (2002), and Clewell (2003). Thus, the PB/PK model published by Andersen et al. (2001) which predicts no accumulation from multiple exposures remains the most reliable information currently available.

Exposure Estimates and Risk Assessment

Flassbeck et al. (2003) used GC-MS and ICP-HR-IDMS techniques to measure levels of D₄, D₅, and D₆ and platinum in breast tissues from a total of 3 women with silicone gel-filled breast implants and 3 controls. In women with silicone breast implants, D₄ levels ranged from 0.01 – 1.3 ppm, D₅ levels of 0.009 – 0.6 ppm, and D₆ levels of 0.02 - 0.8 ppm. Given the known phenomenon of gel bleed, the presence of small amounts of these materials in breast tissue adjacent to the implant site is not surprising. Since these levels do not represent levels of systemic exposure, they cannot be used in risk evaluation. It seems likely that any systemic exposure resulting from gel bleed would be only a small fraction of the levels observed in tissue adjacent to the implant site.

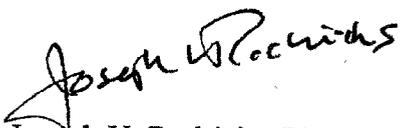
Information from Mentor Corporation indicates the current potential amount of D₄ in a whole device is 0.47 µg/g or 785 µg of D₄ per two devices, for an estimated reasonable worst-case daily exposure of 26 µg D₄.² As discussed earlier, a NOAEL of 0.75 mg/kg/day D₄ has been established based on the most sensitive toxic endpoint of reversible liver weight increases, based on a 28-day inhalation study in rats. This NOAEL is equivalent to a dose of 45,000 µg/day for a 60 kg human adult. Thus, this NOAEL is 1,700 higher than the estimated worst-case daily exposure from Mentor silicone gel-filled implants (i.e., assuming bioavailability of all of the D₄ present in two implants), demonstrating a wide margin of safety.

Information from Mentor Corporation indicates the current potential amount of D₅ in a whole device is 2.47 µg/g or 4,125 µg of D₅ per two devices, for an estimated reasonable worst-case daily exposure of 138 µg D₅.² As discussed earlier, a NOAEL of 5.4 mg/kg/day D₅ has been established for the most sensitive toxic endpoint of endometrial tumors, based on the chronic toxicity/oncogenicity inhalation study in rats. This NOAEL is equivalent to a dose of 324,000 µg/day for a 60 kg human adult. Thus, this NOAEL is 2,300 higher than the estimated worst-case daily exposure from Mentor silicone gel-filled implants (i.e., assuming bioavailability of all of the D₅ present in two implants), demonstrating a wide margin of safety.

² Assumes that all available D₄ and D₅ are released from the device over a 30-day period. A longer period of release of these materials would lead to a lower daily dose, and an even wider safety margin.

In conclusion, while substantial new data has become available since the completion of the IOM expert panel review, the findings do not affect the original conclusions made by the panel.

Sincerely,

A handwritten signature in black ink that reads "Joseph V. Rodricks". The signature is written in a cursive style with a large initial 'J'.

Joseph V. Rodricks, Ph.D., D.A.B.T
Principal
ENVIRON Health Sciences Institute

References

- Andersen M.E., Sarangapani R., Reitz R.H., Gallavan R.H., Dobrev I.D., and Plotzke, K.P. (2001). Physiological modeling reveals novel pharmacokinetic behavior for inhaled octamethylcyclotetrasiloxane in rats. *Toxicol. Sci.* 60(2):214-231.
- Andersen M.E., Dobrev I.D., Reddy M.B., Sarangapani R., Reitz R.H., and Plotzke, K.P. (2002). Further comments on the bioavailability of D₄. *Environ. Health. Perspect.* 110(8):A444-A445.
- Burns-Naas L.A., Mast R.W., Klykken P.C., McCay J.A., White K.L. Jr., Mann P.C., and Naas D.J. (1998). Toxicology and humoral immunity assessment of decamethylcyclopentasiloxane (D₅) following a 1-month whole body inhalation exposure in Fischer 344 rats. *Toxicol. Sci.* 43(1):28-38.
- Burns-Naas L.A., Meeks R.G., Kolesar G.B., Mast R.W., Elwell M.R., Hardisty J.F., and Thevenaz P. (2002). Inhalation toxicology of octamethylcyclotetrasiloxane (D₄) following a 3-month nose-only exposure in Fischer 344 rats. *Int. J. Toxicol.* 21(1):39-53.
- Clewell, H. (2003). Critical Evaluation of the Pharmacokinetic Model for D₄ Developed by Luu and Hutter. ENVIRON International Corporation. Ruston, LA 71270. 8 pp. (Unpublished).
- Dow Corning. (2001a). A two-generation inhalation reproductive toxicity and developmental neurotoxicity study of octamethylcyclotetrasiloxane (D₄) in rats. DC Study No. 8713. (Unpublished). pp 38-41 (Abstract).
- Dow Corning. (2001b). An inhalation study of the effects of octamethylcyclotetrasiloxane (D₄) on the preovulatory LH surge in ovariectomized female rats. DC Study No. 9377. (Unpublished). December 13, 2001. TSCA For Your Information Submission. (Excerpts).
- Dow Corning. (2002). 24-Month combined chronic toxicity and oncogenicity whole body vapor inhalation study of octamethylcyclotetrasiloxane (D₄) in Fischer 344 rats. DC Study No. 9106 (Unpublished). February 20, 2002. TSCA Section 8(e) Notification of Substantial Risk: Octamethylcyclotetrasiloxane. 4 pp. (Summary).
- Dow Corning. (2003). Decamethylcyclopentasiloxane (D₅): A 24-month combined chronic toxicity and oncogenicity whole body vapor inhalation study of Decamethylcyclopentasiloxane (D₅) in Fischer-344 rats. DC Study No. 9346. (Unpublished). February 3, 2003. TSCA Section 8(e) Notification of Substantial Risk: Decamethylcyclopentasiloxane. 6 pp. (Summary).

Flassbeck D., Pfeleiderer B., Klemens P., Heumann K.G., Eltze E., Hirner A.V. (2003). Determination of siloxanes, silicon, and platinum in tissues of women with silicone gel-filled implants. *Anal. Bioanal. Chem.* 375(3):356-362.

GE Silicones (2004). An update on the continuing research on decamethylcyclopentasiloxane (D₅). Jointly prepared by the Silicones Environmental, Health and Safety Council (SEHSC, USA), the Centre Europeen des Silicones, and the Silicone Industry of Japan (SIAJ, Japan). February 3, 2004. 1 pp. (Unpublished).

Hayes, A.W. (2001). *Principles and Methods of Toxicology*, 4th Edition, Taylor & Francis: Philadelphia. p. 206

He, B., Rhodes-Brower, S. Miller, M.R., Munson, A.E., Germolec, D.R., Walker, V.R., Korach, K.S., and Meade, B.J. (2003). Octamethylcyclotetrasiloxane exhibits estrogenic activity in mice via ER α . *Toxicol. Appl. Pharmacol.* 192:254-261.

Institute of Medicine (IOM). (1999). Safety of silicone breast implants. Bondurant, S., Ernster, V. and Herdman, R., Editors. Committee on the Safety of Silicone Breast Implants. 560 pp.

Klykken P.C., Galbraith T.W., Kolesar G.B., Jean P.A., Woolhiser M.R., Elwell M.R., Burns-Naas L.A., Mast R.W., McCay J.A., White K.L. Jr., and Munson A.E. (1999). Toxicology and humoral immunity assessment of octamethylcyclotetrasiloxane (D₄) following a 28-day whole body vapor inhalation exposure in Fischer 344 rats. *Drug Chem. Toxicol.* 22(4):655-677.

Luu H.M., and Hutter J.C. (2001). Bioavailability of octamethylcyclotetrasiloxane (D₄) after exposure to silicones by inhalation and implantation. *Environ. Health Perspect.* 109(11):1095-1101.

Luu H.M., and Hutter J.C. (2002). Rebuttal and critical review of Andersen et al.'s D₄ PBPK model. *Environ. Health Perspect.* 110(8):A445-A448.

McKim, J.M., Jr., Wilga, P.C., Breslin, W.J., Plotzke, K.P., Gallavan, R.H., and Meeks, R.G. (2001). Potential estrogenic and antiestrogenic activity of the cyclic siloxane octamethylcyclotetrasiloxane (D₄) and the linear siloxane hexamethyldisiloxane (HMDS) in immature rats. *Toxicol. Sci.* 63:37-46.

Meeks, R.G. (2002). Bioavailability of D₄ after inhalation and implantation exposure to silicones. *Environ. Health Perspect.* 110(8):A442-A443.

Plotzke K.P., Crofoot S.D., Ferdinandi E.S., Beattie J.G., Reitz R.H., McNett D.A., and R.G. Meeks (2000). Disposition of radioactivity in Fischer 344 rats after single and multiple inhalation exposure to [¹⁴C]octamethylcyclotetrasiloxane ([¹⁴C]D₄). *Drug Metab. Dispos.* 28(2):192-204.

Vergnes JS, Jung R, Thakur AK, Barfknecht TR, Reynolds VL. (2000). Genetic toxicity evaluation of octamethylcyclotetrasiloxane. *Environ. Mol. Mutagen.* 36(1):13-21.