

AMENDMENT TO PANEL PACKAGE

October 4, 2003

Dear Panel Member:

FDA has reviewed additional information since we sent you the Panel package on September 12th. Because this information will be referred to in FDA's discussion, we are providing it to you as an amendment to your Panel package.

There are two topics:

1. Additional information on ongoing Dow Corning animal studies regarding the toxicity of PDMS D5 found in breast implants
2. Update on recent literature studies regarding mortality after cosmetic augmentation with breast implants.

If you have any questions, please contact me at 301-594-3090, ext. 139 or by email at snx@cdrh.fda.gov.

Sincerely,

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1. D5 TOXICOLOGY RISK ASSESSMENT

As noted on p.8 of the Summary Panel Memo (Tab 2 in the Panel Package), D5 is a cyclic decamethylcyclotrisiloxane component which may be present at low levels in the Inamed gel implant. Dow Corning is conducting inhalation toxicology studies on the D5 in rats. FDA reviewed an interim carcinogenicity report from Dow Corning. In this study, the rats in the highest dosage group were exposed to D5 by the inhalation route for 6 hours a day, 5 days a week, for up to 24 months. An increased risk of uterine adenocarcinomas was observed following inhalation exposure to D5 for 24 months. Under these conditions, assuming all the D5 was absorbed at the highest exposure (160 ppm), the dose was 158 mg/kg/day.

Inamed reported that D5 was not detected in their silicone gel, but the limit of detection was 6 ppm, or 6 µg per gram. Therefore, a 60 kg woman with two 800 ml implants could potentially be exposed at most to a total of 9.6 mg of D5, or an exposure of 0.16 mg/kg. If we assume that all the D5 is absorbed and the risk is over a period of 30 years, the daily exposure would be 0.015 µg/kg/day. This allows a safety factor greater than 1 million fold over the dose causing the adenocarcinomas in animals. The cancer risk in humans is likely to be minimal.

The study will not be completed until the spring of 2004. The interim Dow Corning report can be found at the EPA web site: <http://www.epa.gov/opptintr/tsca8e/doc/8ehq/2003/february03/8EHQ-0203-15273A.pdf>. A similar study on D4 has shown uterine adenomas, but no adenocarcinomas. We will continue to follow both studies.

To evaluate the risk more systematically, FDA has developed two risk assessments. One uses a low dose linear model. The other uses a nonlinear dose response model to estimate the benchmark dose and applied uncertainty factors to estimate the dose associated with a 10^{-6} risk. Both of these assessments follow below.

Linear Model Risk Assessment

Subject: Toxicology Consult
Dow Corning Carcinogenicity Study of Decamethylcyclotrisiloxane (D5)

A review was requested of the results of a study conducted by Dow Corning (Study No. 9346 submitted to OPPT/EPA) in which an increased incidence of uterine adenocarcinomas was observed in F344 rats following inhalation exposure to D5 for 24 months. Using Petos' test and the Fisher's Exact test, Dow Corning found a statistically significant difference in the incidence of adenocarcinomas in control rats vs. those in the high dose group (160 ppm). However, they note that the "statistical significance was reduced or eliminated when the adenomas and adenomatous polyps were combined with the adenocarcinomas." Dow Corning further notes that no endometrial hyperplasia was observed in any of the treatment group females and that this lesion is considered an essential precursor lesion associated with uterine adenoma/carcinoma. Nevertheless, the potential exists that the increased incidence of uterine adenocarcinomas in the high dose group females could be associated with exposure to D5.

It is interesting to note that exposure of F344 rats to 160 ppm of D5 for 28 days results in hepatomegaly and induction of a number of hepatic enzymes.¹ Similar findings were observed by Burns-Naas et al.², with the NOAEL and LOAEL for these effects being 75 and 160 ppm, respectively. Hepatic enzyme

¹ McKim JM Jr, Choudhuri S, Wilga PC, Madan A, Burns-Naas LA, Gallavan RH, Mast RW, Naas DJ, Parkinson A, Meeks RG (1999) Induction of hepatic xenobiotic metabolizing enzymes in female Fischer-344 rats following repeated inhalation exposure to decamethylcyclotrisiloxane (D5) *Toxicol Sci.* 50(1):10-9.

² Burns-Naas LA, Mast RW, Meeks RG, Mann PC, Thevenaz P. (1998) Inhalation toxicology of decamethylcyclotrisiloxane (D5) following a 3-month nose-only exposure in Fischer 344 rats. *Toxicol Sci.* 43(2):230-40.

induction has also been observed in rats following oral administration of D4 and D5.³ The potential exists for hepatic enzyme induction to alter the metabolism of endogenous hormones, which in turn, could lead to the development of neoplasia. The development of uterine adenocarcinomas in at least some strains of rats is associated with hormonal imbalance, notably, a high serum estrogen:progesterone (E2:P) ratio.⁴ Imbalances in estrogen metabolism are also associated with an increased risk of breast cancer in women.⁵ Although it is not known whether D5 exposure induces the metabolic enzymes that would result in an altered E2:P ratio, the potential exists for hormone imbalances to occur following enzyme induction. If this is the case, then carcinogenic effects in hormone-sensitive tissues such as the endometrium are not likely to occur at doses of D5 that do not result in hepatomegaly and enzyme induction.

Although the above argument suggests a nonlinear dose-response relationship for the development of adenocarcinomas in rats (and presumably humans) exposed to D5, one can alternately and conservatively assume low-dose linearity for these effects. The dose of D5 received by animals in the high dose group is:

$$160 \text{ ppm} \times 15.1 \text{ mg/m}^3/\text{ppm} \times 0.11 \text{ m}^3/\text{day} \times 6/24 \times 5/7 \div 0.3 \text{ kg} = 158 \text{ mg/kg/day}$$

assuming 100% absorption of D5. Using a simple low-dose linear extrapolation approach, the unit risk based on the incidence of adenocarcinoma in the high dose group in the Dow Corning study is:

$$\frac{0.083 - 0}{158 \text{ mg/kg/day}} = 5.25 \times 10^{-4} \text{ (mg/kg/day)}^{-1}$$

Based on this unit risk value, the dose of D5 associated with various excess cancer risk values is summarized in the table below.

Excess Cancer Risk	Human Equivalent D5 dose (mg/kg/day)	
	BW scaling	BW ^{2/3} scaling
10 ⁻⁴	0.19	0.012
10 ⁻⁵	0.019	0.0012
10 ⁻⁶	0.0019	0.00012

If the dose of D5 released from various medical devices is known or can be estimated, then the excess cancer risk associated with this D5 dose can be estimated. Estimates in the above table suggest that D5 doses less than 1.9 µg/kg/day (0.12 µg/kg/day based on surface area scaling) are associated with *de minimis* risk. In general, doses less than 0.19 mg/kg/day are associated with an acceptable cancer risk, based on the medical benefits conferred by the device. However, it is important to keep in mind that these excess cancer risk estimates are based on the highly conservative assumption of low dose linearity of the dose-response curve for D5-induced uterine adenocarcinomas. As discussed above, the potential exists for the development of this tumor to be hormonally mediated and, consequently, for the effect to only occur at doses at which a hormonal imbalance occurs. If hormonal imbalance occurs as a result of enzyme induction, then the tumors are only likely to occur at doses of D5 equal to or greater than those that produce enzyme induction (160 ppm in earlier Dow Corning studies).

³ Zhang J, Falany JL, Xie X, Falany CN. (2000) Induction of rat hepatic drug metabolizing enzymes by dimethylcyclodioxanes. *Chem Biol Interact.* 15;124(2):133-47.

⁴ Nagaoka T, Onodera H, Hayashi Y, Maekawa A. (1995) Influence of high-fat diets on the occurrence of spontaneous uterine endometrial adenocarcinomas in rats. *Teratog Carcinog Mutagen.* 15(4):167-77.

⁵ Rogan EG, Badawi AF, Devanesan PD, Meza JL, Edney JA, West WW, Higginbotham SM, Cavalieri EL. (2003) Relative imbalances in estrogen metabolism and conjugation in breast tissue of women with carcinoma: potential biomarkers of susceptibility to cancer. *Carcinogenesis* 24(4):697-702.

Nonlinear Model Risk Assessment

Subject: Toxicology Consult (Revised)
Dow Corning Carcinogenicity Study of Decamethylcyclopentasiloxane (D5)

The previous analysis used a simple, linear extrapolation approach to estimate the excess cancer risk for low doses of D5. However, the uterine adenocarcinoma data in the Dow Corning study are decidedly nonlinear. Therefore, a series of nonlinear dose-response models was used to derive values for a benchmark dose (BMD) and the lower limit of a one-sided 95% confidence interval on the BMD (BMDL). A BMD₁₀ was selected as the point of departure for this analysis. The dose of D5 corresponding to a 10⁻⁶ excess cancer risk in humans was then derived from the BMDL using the approach suggested by Gaylor et al.⁶, specifically, to divide the BMDL by 100,000.

The results of the benchmark dose modeling exercise are provided in table below.

Model	BMD (mg/kg/day)	BMDL (mg/kg/day)
Logistic	143.83	120.06
Quadratic	140.49	106.51
Gamma	151.76	87.96
Probit	141.29	114.06
Weibull	154.45	87.95

Based on the value of the lowest model-derived BMDL (87.95 mg/kg/day), the 10⁻⁶ cancer risk in humans is equivalent to a D5 dose of 8.8 x 10⁻⁴ mg/kg/day.

⁶ Gaylor DW, et al. (1999) A unified approach to risk assessment for cancer and noncancer endpoints based on benchmark doses and uncertainty/safety factors. Regul Toxicol Pharmacol. 29(2 Pt 1):151-7.

2. UPDATE ON LITERATURE MORTALITY STUDIES

FDA reviewed additional literature on mortality studies related to breast implants. There are two new studies, one published in March, 2003 and the other published in early October 2003, that describe increased mortality due to suicide in women after cosmetic augmentation with breast implants. FDA reviewed these studies and a previous study on mortality in women with cosmetic implants. These studies are not specific to the Inamed silicone gel breast implants that are under consideration at the panel meeting.

Three studies evaluated mortality from various causes in women with cosmetic breast augmentation. Table 1 shows the standardized mortality ratio (SMR) and 95% confidence limits of the implant population versus the comparison population for positive findings. In the Brinton et al. study⁷, death from all causes was significantly reduced in women with breast implants compared to the general U.S. population rates. This reduction was attributed to the generally healthier status of patients seeking plastic surgery. However, there was a significantly increased mortality rate for both suicide and brain malignancy in women with implants despite a decreased mortality for malignancies overall. Similar studies performed in Sweden⁸ and Finland⁹ found either slightly increased risk for mortality from all causes or no difference. However, both studies also found an increase in death by suicide in women with cosmetic breast implants. The reason for this increased mortality is not clear. Pukkala et al.⁹ suggested that this may be due to underlying psychopathology in women seeking cosmetic augmentation, but studies seeking to characterize women desiring cosmetic augmentation have been seriously flawed making conclusions difficult.¹⁰

Table 1. Mortality in women with cosmetic breast implants, SMR (95% Confidence Interval)

All Causes	Suicide	Accidents (and Violence)*	Brain Malignancy	Study and Country
0.68 (0.6-0.8)	1.54 (1.0-2.4)	0.95 (0.6-1.4)	2.45 (1.4-4.2)	Brinton et al ⁷ , 2001 US
1.5 (1.2-1.8)	2.9 (1.6-4.8)	1.8 (0.9-3.3)	n.d.**	Koot et al ⁸ , 2003 Sweden
1.01 (.67-1.44)	3.19 (1.53-5.86)	2.14 (1.17-3.58)	n.d.	Pukkala et al ⁹ , 2003 Finland

*Accidents reported by Brinton, unintentional injury by Koot, and accidents and violence reported by Pukkala.

** not done

⁷ Brinton LA, Lubin JH, Burich MC, Colton T, Hoover RN. Mortality among augmentation mammoplasty patients. *Epidemiology* 2001;12:321-326.

⁸ Koot VCM, Peeters PHM, Granath F, Grobbee DE, Nyren O. Total and cause specific mortality among Swedish women with cosmetic breast implants: prospective study. *BMJ* 326;527-528.

⁹ Pukkala E, Kulmala I, Hovi S-L, Hemminki E, Keskimäki I, Lipworth L, Boice JD, McLaughlin JK. Causes of death among Finnish women with cosmetic breast implants, 1971-2001. *Ann Plast Surg* 2003;51:339-342.

¹⁰ Sarwer DB. Invited discussion: Causes of death among Finnish women with cosmetic breast implants. *Ann Plast Surg* 2003;343.