

**Literature Review of Pharmacokinetics Information
Related to Silicone Gel-Filled Mammary Prostheses**

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There are two issues relevant to examining the pharmacokinetics of any substance of interest:

- 1) Absorption and distribution of the material throughout the body tissues; and
- 2) Metabolism and elimination of the substance from the body and its tissues.

With respect to materials such as the silicone polymers used in gel-filled mammary prostheses, there are limitations associated with traditional pharmacokinetics methodologies as well as a lack of validated methods to conduct such a study due to the nature of the material. As Dr. John Young, a pharmacokineticist with the National Center for Toxicological Research, stated at the 1991 FDA Conference on Silicone in Medical Devices, "*because of the extremely slow and limited movement of silicone from the initial site of administration, pharmacokinetics as a tool is really of limited usefulness*".

Nonetheless, a variety of studies (several using silicone gel) have examined some aspect of the Absorption, Distribution, Metabolism or Elimination ("ADME") of silicone materials or the potential metabolism and degradation of silicone in the body. In addition there are distribution studies of silicone fluid and low molecular weight silicones, evaluating species similar to those, which may be extracted from all silicone compounds using powerful, non-physiologic, hydrocarbon solvents. Pharmacokinetic studies of silicone were reviewed as part of the evaluation performed by the Committee on the Safety of Silicone Breast Implants, Institute of Medicine (IOM). Based on their findings, the IOM stated,

"Studies using whole fluids, gels, elastomers, or experimental implant models injected or implanted in ways that are directly relevant to the human experience with implants are also reassuring. These studies show that depots of gel, whether free or in implants, remain almost entirely where injected or implanted. Even low molecular weight cyclic and linear silicone fluids appear to have low mobility."

This conclusion is consistent with the findings of the Independent Review Group (IRG) which determined "*that the relevant studies have shown only local reactions to silicones. Systemic damage and dispersal of silicone polymers throughout the body has not been well demonstrated, despite various claims, even after rupture of gel-filled implants.*"

As indicated by both the IOM and IRG committees, a toxicity assessment requires evaluation of relevant scientific studies with respect to gel-filled breast implants. The portion of the available *in vivo* data on silicone materials that is not considered relevant to pharmacokinetic issues includes studies using oral, dermal, inhalation and intraperitoneal administration of silicone materials (with the exception of the low molecular weight silicones studies due to the virtually exclusive use of oral and inhalation exposure methodologies), or instances in which silicone gel

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remained within the capsule or moved in bulk. Additionally, studies describing particulate silicone (e.g., arising from significant wear of joint prostheses) were also excluded from the review (joint prostheses function mechanically whereas silicone gel-filled mammary prostheses function to create a breast mound). In all of these cases, due to the route of administration, confinement within the capsule, or source of material (bulk movement or mechanical wear), the data or observations are not relevant to a pharmacokinetic assessment regarding silicone gel-filled mammary prostheses.

A. Absorption, Distribution and Elimination of Silicone Materials

Studies have been identified that evaluated the absorption, distribution or elimination of silicone including silicon distribution into tissues from breast implants. Since precise measurements of silicone in tissues is difficult to obtain, studies that evaluate the level of elemental silicon in tissues have been performed. In addition, pharmacokinetic studies of silicone gel, fluid and low molecular weights species have been completed. A substantial amount of the work in this area has been sponsored by Dow Corning. Several studies were part of the pre-clinical technical information which supported Dow Corning's gel-filled mammary pre-market approval (PMA) application. In addition, beginning in the mid-1990s, a variety of studies have been performed as part of the Silicone Research Program. These reports from both the Dow Corning PMA application and Dow's Silicone Research Program are publicly available.

1. Elemental Silicon from Implants

Accurately determining the amount of silicone in clinically obtained tissues is analytically difficult. Therefore, methods have been developed to evaluate the levels of elemental silicon in tissues since, as described in the literature (Peters et al. 1996), *"available techniques do not easily allow precise measurements of silicone in tissues. However, all compounds containing silicon (which would include silicone) can be measured accurately"* in body fluids and tissues using a variety of techniques including electrothermal atomic absorption spectrometry, and direct-current plasma emission spectrometry.

Peters and his co-researchers evaluated capsule tissue for silicon using atomic absorption spectrometry with a graphite furnace. The capsule silicone levels were compared to the silicon levels of previously assayed blood samples. Capsule silicone levels were approximately 10 times higher than the blood silicon levels. No detectable silicone was found in blood samples analyzed using ^{29}Si nuclear magnetic resonance spectroscopy. Teubers and colleagues employed inductively coupled plasma emission spectroscopy for elemental silicon analysis to determine the amount of silicon in serum (Teubers et al. 1996). They reported that *"results suggest that elevations of serum silicone are seen in many women with silicone gel breast implants"* although there was no significant correlation to implant rupture or length of implantation.

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Both Evans and Barnard in association with their colleagues evaluated tissue samples from cadavers for silicon levels using inductively coupled plasma atomic emission spectroscopy and atomic absorption spectrometry, respectively (Evans and Baldwin 1997a and Barnard et al. 1997). Breast tissues as well as tissues from distant sites were evaluated. In addition, Evans and Baldwin evaluated tissue around silicone chemotherapeutic port-a-catheter devices (Evans and Baldwin, 1997b). Evans and Baldwin noted in each of their 1997 papers *"that there may be a progression of measurable tissue silicon levels based on the amount of environmental or device-related silicone exposure a person has."* Barnard et al. concluded *"that organosilicon polymers routinely migrate from the site of breast implantation to regional tissues near the implant site. Tissues from nonimplant cases often contained measurable amounts of organosilicon polymers"*.

The research was summarized in a review article by Peters et al., 1999. The authors noted that studies *"have shown that women with silicone gel implants have higher blood and serum silicon levels than control subjects, but their values were still within the range of control subjects."*

2. Silicone Gel

Four studies have examined some aspect of the absorption and distribution of silicone gel following injection in animals. One subchronic study described the fate of four different silicone gel formulations injected subcutaneously into monkeys and rats (Dow Corning 1975b). Four monkeys were injected with 5.0 g/kg of one of the following four prosthetic gel formulations: standard gel (88.6% Q1-0043, 8.5% DC-360), new production gel (80% DC-360, 19% XF1-0043), high fluid gel (84% DC-360, 13.5% E2-5057), or low cross-linker gel (79.1% DC-360, 19.8 % Q1-00543).

The treated monkeys were referred to as MG-1, MG-2, MG-3, and MG-4, respectively. Feces, urine and expired air were monitored for seven days. On day 15, the monkeys were sacrificed and tissue samples were analyzed for the presence of elemental silicon, as total silicon and as organosoluble silicon (i.e., the silicon levels extracted from tissue or excretion media using an organic solvent such as hexane, methylethyl ketone or toluene). Silicone, if present, would be detectable as organosoluble silicon. One monkey (MG-1) did have increased levels of total urinary silicon, but did not have increased levels of urinary organosoluble silicon. This same monkey also had elevated levels of fecal organosoluble silicon on days 6 and 7. One other monkey (MG-3) had very slightly elevated fecal organosoluble silicon in all post-dosage samples. No expired air samples contained toluene extractable silicon, except for two samples from MG-1 that were considered to be the result of system contamination.

Tissue analysis revealed that all treated monkeys had elevated levels of total silicon in the following organs or tissues: adrenals, axillary lymph node, bone marrow, inguinal

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lymph node, omental fat and perirenal fat. Two monkeys (MG-2 and MG-4) also had elevated levels of total silicon in the thymus. A confirmatory experiment was conducted with the new production gel (two monkeys) and the low cross-linker gel (one monkey). Organosoluble silicon was detectable in the inguinal lymph nodes of one monkey receiving the new production gel and in both the inguinal and axillary lymph nodes of the monkey receiving the low cross-linker gel.

In the companion studies in rats, one group of rats was subcutaneously injected with 1 g of the new production gel and sacrificed 15 days after dosage. As with the monkeys, tissue samples were analyzed for the presence of total silicon. The only significant increase in total silicon levels was detected in the axillary lymph nodes, although no organosoluble silicon was detected. A second group of rats was subcutaneously injected with either the new production gel or the standard gel and examined solely for the presence of silicon in the axillary lymph nodes. No elevated levels of total silicon were detected in this second group. A final group of rats was subcutaneously implanted with new production gel and sacrificed on days 1, 2, 4, 7, 10, or 12 to monitor the time course of silicon levels in the axillary lymph nodes. No elevated levels of total silicon were detected at any point during this final experiment. It should be noted that the gel used in this experiment was exposed to the atmosphere for two weeks, which the authors suggest may have allowed low molecular weight silicone compounds to volatilize (Dow Corning 1975b).

A study sponsored by McGhan Medical Corporation examined the fate of ¹⁴C-labeled PDMS gel (chemically and physically indistinguishable from the gel used in silicone gel-filled breast implants) following subcutaneous implantation in female rats. The final report was provided in the initial PMA application for McGhan Medical's gel-filled breast implants, submitted to FDA on July 9, 1991 (PMA P910022) in Volume 9, as Appendix 14. Expired air was sampled for the first 48 hours of the study, while urine and feces were collected daily for the first two weeks. Blood samples were taken throughout the course of the study. All rats were sacrificed at 30 days.

The silicone gel was poorly absorbed, as indicated by analysis of samples of the following tissues, which in total contained only 0.046% of the total implanted radioactivity: adipose, brain, gastrointestinal tract, heart, kidneys, liver, lungs, lymph nodes, muscle, ovaries, skin, spleen, uteri and remaining carcass. The highest concentration of radioactivity was detected in the liver (71 ug/g). The cumulative radioactivity found in air, feces, and urine samples accounted for 0.0195% of the total implanted activity. Blood levels remained low and peaked at Day 21 (78 ug/g). The low levels of detected activity in all tissues and excretions suggest that subcutaneously implanted silicone gel does not migrate or undergo significant biodegradation (Schulz et al. 1993).

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The absorption and distribution of silicone mammary gel has also been examined in mice. Groups of eight male and eight female mice were implanted with 0.50 ml of ^{14}C -labelled silicone gel and sacrificed at 4, 12, or 20 weeks. Tissue samples were analyzed for the presence of radioactivity. Overall, less than 0.01% of the administered dose was determined to have migrated from the implantation site and was found primarily in the lymph nodes, which is similar to the results of the rat and monkey studies already discussed (Dow Corning 1975b). Three of the ten pairs of lymph nodes analyzed (axillary, lateral axillary, and superficial inguinal) had detectable levels of radioactivity. No other consistent silicone distribution pattern was seen. To monitor the excretion of the silicone or silicone metabolites, a second set of four male and four female mice were implanted with 0.50 ml of the same silicone gel, but were placed in individual metabolism cages for 5 days post-dosage and at 4-week intervals thereafter, for a total of 21 weeks. Urinary excretion of ^{14}C peaked during the first week post-dosage. Radioactivity was detected in feces only during the first week post-dosage, except for a single fecal sample from one of the females at week 17. Because of the possibility of urine contamination of the feces, the levels of ^{14}C detected in feces may be an artifact of the urine levels (Dow Corning 1991b).

In a study of the long-term fate of injected silicone, 38 rats were subcutaneously injected with silicone gel (taken from a silicone gel-filled breast implant) and sacrificed at time intervals from 3 to 450 days. Histologic examination of the visceral organs (heart, kidneys, lungs, stomach, gonads, liver, pancreas, spleen and intestine) did not reveal the presence of silicone gel. The presence of silicone appeared to be limited to the subcutaneous space between the cutaneous and striated muscle. All animals demonstrated some kind of local inflammatory reaction and giant cell phagocytosis of silicone gel was observed in one animal sacrificed on Day 7 (do Amaral et al. 1993).

These findings indicate that there appears to be little movement of silicone gel in body tissues following subcutaneous implantation. In general, the distribution of the gel is restricted to the lymph nodes and the lymphatic system.

3. Silicone Fluid

Silicone gel consists of a crosslinked three-dimensional network of silicone polymer with entrapped polydimethylsiloxane (PDMS) species (Institute of Medicine 2000). Therefore, this literature discussion also reviews silicone fluid studies.

A group of studies was performed by Dow Corning Corporation on the absorption and distribution of silicone fluid (350 centistoke) after injection (Dow Corning 1968, 1972a, 1972b, 1975a; Truppman and Snyder 1966). The absorption of polydimethylsiloxane fluid was examined by subcutaneously injecting eight rats with ^{14}C -labeled DC 360 (Dow Corning medical grade silicone fluid). The rats were monitored in metabolism cages for 8, 30, 60, or 90 days, with feces and urine collected continuously during the

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study period. Expired air was monitored only for the first 48 hours, during which time the animals were partially restrained by a rubber dam separating the anterior and posterior sections of the chamber. Upon removal of these partial restraints, the study authors reported that three of the rats apparently ingested test fluid that had leaked from the needle entry site, based on high levels of fecal activity during the next 24-48 hours that reportedly later decreased to levels similar to the other rats. Cumulative fecal excretion, expressed as a percentage of the administered dose, ranged from 0.344 percent to 6.570 percent in these three rats, while the range in the remaining five rats ranged from 0.016 percent to 0.079 percent.

In the remaining five rats, the total activity excreted in urine, feces or expired air was less than 0.11 percent of the administered amount. Excretion via urine and expired air was comparable among all eight rats. The total activity from all (oxidized) tissues (excluding the muscle and skin at the dosage site) was less than 0.018% for all animals. Analysis of ¹⁴C in individual tissues and organs (lung, heart, spleen, kidney, liver, brain, muscle and salivary glands; axillary, cervical, thoracic and peritoneal lymph nodes; and fat stores in the thoracic, peritoneal and abdominal cavities) revealed low levels (0.02 to 0.3 ug/g tissue) of ¹⁴C activity in all tissues, with slightly higher levels (up to 1.255 ug/g) noted in the axillary and thoracic lymph nodes. No radioactivity was detected in blood samples from any treated animals (Dow Corning 1972a).

Another study examined the fate of injected PDMS fluid in mice. A total of 70 mice were subcutaneously injected with 1 cc of ¹⁴C-labelled PDMS. Following injection, groups of mice were sacrificed once each hour for 24 hours in order to determine the short-term kinetics of PDMS fluid. Other groups were followed for up to 140 days. Feces, urine, and tissue samples from the major organs (brain, kidney, heart, lungs, liver, spleen and intestines) were analyzed for the presence of ¹⁴C. A visible mass at the site of injection was seen in all mice. The peak ¹⁴C activity in the organs occurred on the third to fifth day and progressively decreased until only trace amounts were detectable. The highest percentage of original ¹⁴C activity (0.0095%) was recovered in heart tissue on Day 3. By day 140, only the lungs and spleen displayed detectable activity. Activity in feces and urine followed a similar pattern. The highest percent recovery in urine was 0.0006187% (on Day 3). The highest fecal activity, 0.01%, occurred on the first day (Truppman and Snyder 1966).

A study of the chronic effects of DC 360 included subcutaneous dosing of five male and five female rats with either 5 or 20 ml of DC 360 and monitoring for 401 days. Parallel control groups were dosed with sesame oil. Blood samples were taken monthly during the study and at sacrifice. No significant differences were detected in blood silicon levels in treated animals compared to controls. When administered subcutaneously, the test material tended to migrate to the ventral subcutaneous region (Dow Corning 1972b). A second study examining the absorption and distribution of

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DC 360 in rats included subcutaneous dosing. Rats were injected with 13 ml DC 360 and sacrificed at various intervals over an 18 month period. Histologic analysis revealed no significant pathology (Dow Corning 1975).

As part of a chronic general toxicity study of DC 360 in dogs, the absorption and distribution of DC 360 was studied. Three dogs each received a single subcutaneous injection of 1 ml ^{14}C -labeled DC 360 fluid and were sacrificed at 3, 6, and 12 months. Distribution of ^{14}C activity appeared to be ubiquitous at all time intervals, with no clear pattern of tissue concentration. It was apparent, however, that the silicone migrated from the initial site of injection. Although urine and feces were not monitored, the presence of radioactivity in the urinary and gastrointestinal tracts suggests that DC 360 was excreted through both urine and feces. In addition, the authors noted that the presence of radioactivity in the gastrointestinal tract indicated biliary recirculation, since the material was not administered orally (Dow Corning 1968).

These data, considered together, suggest that following subcutaneous injection, there is movement of the material away from the injection site, but only in very small amounts. Furthermore, there is no evidence of any pathophysiological effects attributed to migration of silicone fluid.

4. Low Molecular Weight Silicones

The IOM, as part of the assessment of gel-filled mammary implants, evaluated studies on low molecular weight silicones since they "*are found in breast implants, although in very low amounts*". A brief discussion of low molecular weight silicone pharmacokinetic studies follows.

In a study by Dow Corning, male rhesus monkeys orally received 50 mg/kg of radiolabeled D_4 . Urine and feces were collected for 10 days. Then the animals were sacrificed and tissues collected. The total urinary radiolabel recovery amount was 57% in urine; the total fecal radiolabel recovery amount was 13%. The urine did not contain intact D_4 . Instead, D_4 degradation products, including dimethylsilanediol, tetramethyl-1,3-disiloxanediol and hexamethyl-1,5-trisiloxanediol were detected which is suggestive of ring opening at the siloxane bond (Dow Corning 1980).

In a 28 day D_4 gavage study in rats (Dow Corning 1988a), urine and feces were collected for a 24 hour period between days 6 and 7. The urine and feces were assayed for dimethylsiloxane and methylsiloxane (Me_2SiO_2 and MeSiO_3 , respectively). Me_2SiO_2 and MeSiO_3 represented 23-33% and 0.18-0.26% of the silicone species in urine and feces, respectively. As with the previous study, the findings indicate that D_4 can undergo oxidative demethylation. Similarly in another study (Dow Corning 1988b), 400 mg/kg D_5 was administered to rats orally in a single dose. Me_2SiO_2 was predominately found in urine and feces. Urine also contained some Me_2SiO_3 ,

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indicative of oxidative methylation to a limited extent.

In addition, radiolabeled D₆ was orally administered to male rats in a single 600 mg/kg dose. The radiolabel recovery amounts were as follows: 75% feces, 13% expired air, 1.8% urine, 0.05% in lungs and liver. No radiolabel was recovered from the blood samples. The researchers estimated that approximately 85% of the administered dose was not absorbed (Dow Corning 1985a).

Two studies, one evaluating oligomeric linear dimethylsiloxanes and the other evaluating oligomeric cyclic dimethylsiloxanes, were also performed. (Dow Corning 1985b and Dow Corning 1985c, respectively). In the linear dimethylsiloxanes study, male rats were administered a 100 mg/kg oral dose of a radiolabeled L₈ and L₁₁ mixture. Within 2 days of dosing, approximately 95% of the radiolabel was recovered in feces. In the tissues, only about 0.02% of the radiolabel was recovered. Similarly, in the cyclics study, male rats received a single oral dose at 25 mg/kg body weight of a radiolabeled D₉, D₁₂ and D₁₅ mixture. Within the first 48 hours, approximately 98% of the radiolabel appeared in the feces. Only 0.36% of the radiolabel was recovered in urine, expired air and tissues. The plasma did not have a detectable level of radiolabel. These two studies demonstrate that linear siloxanes L₈ and above and cyclic siloxanes D₉ and above are not readily absorbed orally.

With respect to gel-filled mammary implants, these Dow Corning studies from the 1980s indicate that absorbed low molecular weight silicones may undergo oxidative demethylation to compounds with greater solubility in water and have relatively short half-lives. More recently, Dow Corning has performed additional studies on low molecular weight siloxanes as part of the Silicone Research Program. The work at Dow Corning has resulted in the publication of several papers in scientific journals (McKim et al. 1998, McKim et al. 1999, McKim et al. 2001, Plotzke et al. 2000, Varaprath et al. 1998, and Varaprath et al. 1999).

Four of the studies (Dow Corning 1995a, 1995b, 1995c, and 1996a) incorporated nose-only vapor inhalation of D₄. Two of the studies served as methods development for the subsequent studies. The results demonstrated that the primary route of excretion was urine, followed by expiration and feces. Furthermore, the reports indicated that the study animals had limited bioaccumulation of D₄.

In another Dow study, urine was collected from rats which were intravenously injected with radiolabeled D₄. The urine was then evaluated for D₄ metabolites with high pressure liquid chromatography (HPLC). The HPLC profile revealed two major and at least five minor radioactive metabolites but no D₄. The two major metabolites constituted 75-85% of the total components. These peaks were identified as dimethylsilanediol and methylsilanetriol. Formation of methylsilanetriol is indicative of

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D₄ ring opening and the occurrence of some demethylation (oxidation and hydrolysis). The minor metabolites were identified as: tetramethyldisiloxane-1,3-diol, hexamethyltrisiloxane-1,5-diol, trimethyldisiloxane-1,3,3-triol, dimethyldisiloxane-1,1,3,3-tetrol, and dimethyldisiloxane-1,1,3,3-pentol (Dow Corning 1997b). A urine analysis study evaluating the elimination of orally administered radiolabeled D₅ was also performed (Dow Corning 1999). As stated in the report, "*The profile for D₅ was essentially identical to that of octamethylcyclotetrasiloxane (D₄).*" Furthermore, the authors noted that "*formation of D₄D'OH and MeSi(OH)₃ clearly established some demethylation at the silicone-methyl bonds. No parent D₅ was present in urine.*"

Liver biochemical and morphometric studies have also been performed. Exposure to D₄ and D₅ have been evaluated and related to the effect of phenobarbital (Dow Corning 1996b, 1996c, 1996d and 1998a). Three of the studies were considered pilot studies. The results indicated that D₄ behaves similarly to phenobarbital regarding increased liver weight and enzyme activity but to a much lesser degree. With respect to the subfamily of cytochrome P450, which is specifically induced by phenobarbital, there is a dose and time related increase in enzyme activity, which essentially returns to normal after fourteen days of recovery. Exposure to D₄ results in an increase in the level of enzyme necessary to metabolize D₄. Furthermore, the expression of CYP2B enzymes is "*confined to the centrilobular regions, but expands across the hepatic lobule as exposure concentrations increase. These findings are consistent with those reported for phenobarbital*" (Dow Corning 1998a).

In a study using D₅ (Dow Corning 1997a), the results demonstrated that D₅ was associated with a similar enzyme induction profile but to a lesser magnitude. In a later study (Dow Corning 1998b), D₄ was evaluated for its ability to inhibit the major P450 enzymes in human liver microsomes and for its ability to inhibit CYP1A_{1/2} and CYP2B_{1/2} enzymes in rat liver microsomes. The results demonstrated that "*D₄ has little or no capacity to function as a metabolism-dependent (reversible or irreversible) inhibitor of any of the P450 enzymes examined, with the possible exception of rat CYP1A_{1/2} and human CYP3A_{4/5} which were weakly inhibited by D₄ in a reversible metabolism-dependent manner.*"

Two percutaneous absorption studies (Dow Corning 1995d and 1996e) were also performed with D₄ and D₅. The results showed that most of the test material volatilized at the site. The fraction which was absorbed remained at the dose site or was primarily eliminated either by expired air or urine.

The distribution of low molecular weight silicone mixtures has also been evaluated in CD-1 mice (Kala et al. 1998). Mice received a single subcutaneously injection of "*either breast implant distillate composed primarily of hexamethylcyclotrisiloxane [D₃], octamethylcyclotetrasiloxane [D₄], decamethylcyclopentasiloxane [D₅],*

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dodecamethylcyclohexasiloxane [D₆], and tetradecamethylcycloheptasiloxane [D₇] or a polydimethylsiloxane oil containing low molecular weight siloxanes". The animals were sacrificed at various time points and primary organs, including brain, heart, kidney, liver and lung, were evaluated for the presence of cyclosiloxanes. The authors indicated that low molecular weight siloxanes were detectable in various organs over a one year time period. However, as stated by Robert Meeks in his letter to a publishing journal (Meeks letter, 1999), "many of the values reported for tissue concentrations of cyclosiloxanes at 9 weeks and later appeared to be at or below the limit of detection of their analytical methodology and were well below what would be considered the limit of quantitation, making some of the conclusions misleading." Furthermore, Meeks reiterates results from Dow Corning's radiolabeled siloxane studies which demonstrated uniform distribution in the tissues "but with an elimination half-life of parent and metabolites of 50 – 200 hr., depending on the tissue".

Anderson and his colleagues evaluated tissue, plasma and excreta time-course data in Fischer 344 rats exposed to D₄ via inhalation. D₄ demonstrated high hepatic and exhalation clearance, which minimized retention time (Andersen et al. 2001).

Based upon review of the data for low molecular weight silicones, the IOM reported that the findings of the pharmacokinetic studies "*showed that these compounds are absorbed following oral administration or inhalation, but that skin penetration is very poor. Most of the compounds were excreted in the urine following intravenous administration.*" Furthermore the findings of distribution studies indicated that "*low molecular weight silicones which may be mobile to a small extent, are cleared from the body after relatively short half-lives.*"

B. Potential Metabolism and Degradation of Silicone Materials

The second issue relevant to examining the pharmacokinetics and assessing the safety of silicone gel-filled mammary prostheses is potential metabolism and degradation of the silicone gel and elastomer materials. As discussed above, there are no traditional methods for evaluating metabolism or degradation of silicone gel and elastomer materials. The following is a discussion of available studies that have examined some aspect of silicone degradation or metabolism for either silicone gel or elastomer. The pertinent data for silicone gel-filled mammary prostheses consist of observations of the device surface following long-term implantation in animals. The issue of availability of free silica derived from either breakdown of the silicone elastomer or release of the amorphous silica filler is also discussed.

1. Silicone Gel Biostability

The 1994 report by the Medical Devices Agency (MDA) reviewed toxicokinetic publications "*utilising nuclear magnetic resonance (NMR) techniques.*" In regard to the literature, the MDA concluded that a "*majority do not to date allow conclusions to*

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be drawn and have not been included in this review." The NMR based studies that were discussed by MDA describe the work performed during the 1990s at the laboratory of Dr. Leoncio Garrido and colleagues.

These researchers have applied nuclear magnetic resonance (NMR) spectroscopy techniques (^1H and ^{29}Si) to the evaluation of potential *in vivo* migration and biodegradation of silicone from silicone gel-filled implants (Garrido et al. 1993a,b; Pfeleiderer et al. 1993a-c; Garrido et al. 1994; Pfeleiderer and Garrido 1995, Garrido et al. 1996, Pfeleiderer et al. 1996 and Pfeleiderer et al. 1999). These investigators interpret their NMR findings as indicating that *in vivo* biodegradation of silicone gel occurs in both rats and humans, resulting in the formation of "*hydrolyzed silicone, silica, and highly coordinated silicon complexes*" (Pfeleiderer and Garrido 1995).

It is important to note, however, that the findings of Garrido and colleagues have not been confirmed by other investigators. As concluded in the 1994 MDA report, "*there is limited quantification and only indirect identification of the reported metabolites. The significance of the findings cannot yet be fully assessed.*" Indeed, Dr. Peter MacDonald and colleagues at the University of Toronto recently published data demonstrating that the ^{29}Si NMR signals observed by Garrido and coworkers were very likely an artifact of inappropriate application of the spectral baseline correction and phasing software routines that come standard on such machines (MacDonald et al. 1995).

Sensitivity calculations performed by MacDonald and coworkers further demonstrated that the ^{29}Si magic angle spinning NMR technique used by Dr. Garrido would be incapable (by several orders of magnitude) of detecting silicon at the levels reported present in Dr. Garrido's study. In addition, although Pfeleiderer et al. (1993c) report changes in T2 relaxation times during long-term implantation of silicone in rats, a recent study by Dorne et al. (1994) using proton magnetic resonance techniques reported no differences in T₁ and T₂ relaxation times for silicone from virgin and explanted (4 months to 17 years post-implantation) silicone gel-filled mammary prostheses from humans. Lastly there are no known *in vivo* mechanisms that would lead to the formation of silica from polydimethylsiloxane (*e.g.*, although superoxide anion could conceivably remove a methyl group from a silicon atom, such reactions on an elastomer shell would not produce silica or even an oxidized elastomer surface).

2. **Silicone Elastomer Biostability**

The effects of implantation have been studied on silicone elastomer taken from a mammary prosthesis. Disks (1 cm in diameter) were implanted in mice for up to 6 months. There was no degradation or surface modification of the elastomer surface or changes in the distribution of silica when compared to control, non-implanted discs. In

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addition, scanning electron microscopy after 6 months of implantation revealed no differences between the implanted versus non-implanted discs. This study produced no evidence suggesting that the silica filler becomes exposed or that the envelope surface degrades during implantation (Dow Corning 1991a).

In a second study, the effects of implantation on silicone elastomer were again addressed. Discs cut from a mammary prosthesis envelope were implanted in mice. At 1, 3, and 6 month intervals, sets of discs were removed and examined with transmission electron microscopy for any alterations or deterioration. No degradation or surface modification of the elastomer surface or changes in the distribution of silica were noted at any time period when compared to control non-implanted discs (Henrich et al. 1992).

Considered together, these data demonstrate that the surface of elastomer materials is not significantly degraded following implantation in animals for up to 6 months.

C. Conclusions and Summary

In general, review of the available data on the pharmacokinetics of silicone materials, with respect to silicone gel-filled mammary prostheses, suggests that the silicone elastomers of the devices neither distribute nor degrade *in vivo*. In addition, the data on silicone gel and fluids following subcutaneous injection into a variety of species demonstrate that the silicone gel of these devices typically do not distribute to any great extent in body tissues. Furthermore, low molecular weight species, which are absorbed, are primarily excreted in urine and are cleared after a relatively short half-life.

The IRG reported that "*looking with reliable, validated analytical techniques for the dissemination of silicones [including breakdown products of the polymers] from implants in the body have shown either no dissemination, or the presence of only very small amounts at distant sites following rupture of gel-filled implants, or after deliberate injection of the gel.*"

Therefore, based on review of the relevant published literature, there is no reason to believe that silicone materials from a silicone gel-filled mammary prosthesis would be absorbed, distributed, metabolized, or degraded in any appreciable amount following implantation.

Consistent with the findings of the pharmacokinetic literature, the report by the National Science Panel to the Honorable Sam C. Pointer Jr. "*reaffirmed the low systemic toxicity of silicone.*" The report reiterated that "*results of this review indicate that the silicones used in SBIs [silicone breast implants] are of very low toxicity to animals. Although there is documented evidence of local inflammatory reactions to silicone breast implant materials in animals, there is no convincing evidence for a significant systemic inflammatory response. The local reaction to silicone is similar to other 'foreign body reactions'*"

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described with other implanted materials.”

In its conclusion, the National Science Panel confirmed that “*the preponderance of evidence from animal studies indicates little probability that silicone exposure induces or exacerbates systemic disease in humans.*”

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