

**Literature Review Update
of the Safety of
Silicone Gel-Filled
Breast Implants**

1999-2003

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- Appendix A.** Literature Review Tabulation of Long-Term Safety Information for Silicone Gel-Filled Breast Implants
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1. Scope

The Institute of Medicine (IOM) in 1998 assembled a Committee on the Safety of Silicone Breast Implants. This committee included scientific and medical experts from a wide range of fields, including: “preventive and internal medicine, nursing, family and women’s health, rheumatology, clinical and basic research, epidemiology, immunology, neurology, silicone chemistry, toxicology, breast and other cancer, plastic surgery, and radiology or mammography.” The work of this committee culminated in the generation of a full-length report entitled *Safety of Silicone Breast Implants* (Bondurant et al. 2000). This review conducted by the expert panel of the Institute of Medicine represents one of the most comprehensive examinations of the enormous body of published scientific and medical literature on the safety of silicone breast implants, including nearly 1200 cited references. The report was funded entirely by the agencies within the U.S. Department of Health and Human Services, including the U.S. Food and Drug Administration, and was first issued as a pre-print version in 1999, followed by a hardcover edition in 2000. As such, it covers the overwhelming majority of literature published over the more than 30 years that silicone breast implants have been available in this country. This very thorough and very critical evaluation of the available published data (through 1998) on the safety of silicone breast implants is reprinted with permission from *Safety of Silicone Breast Implants* (2000) by the National Academy of Sciences, courtesy of the National Academies Press, Washington, D.C., and included in the previous section of this Clinical PMA Module.

In the years subsequent to the publication of the IOM expert panel report, a number of additional studies have been published that provide additional information in several key areas related to the safety of silicone breast implants. In order to provide a supplemental review of such pertinent new information, a very broad and extensive search of the scientific and medical literature on silicone and silicone medical devices was conducted, including searches of MEDLINE and other online databases. A total of more than 5000 citations and/or abstracts of medical articles published from 1999 through 2003 were screened to identify those potentially relevant to the clinical safety of silicone gel-filled breast implants. The resulting full bibliography of more than 500 citations is included as an appendix to this updated literature review.

The citations included represent English language publications that address potential health effects of silicone gel-filled breast implants, and not publications that are focused solely or primarily on injectable silicone, other silicone medical devices, environmental silicone exposures, polyurethane coated breast implants, saline-filled breast implants, or other non-silicone gel-filled breast implants.

The IOM, in its review of the vast amount of available information noted that:

"... some of this material, although in peer-reviewed scientific publications, consisted of case reports, reviews, and other forms that the committee did not consider strong evidence. Case reports or case series reports are often essentially anecdotes or uncontrolled observational studies, which, lacking appropriate comparison or control groups, may not be helpful in determining rates of occurrence or accepting or rejecting causation."

Similar screening criteria were employed in assembling this literature review update. Thus, the focus of this review, wherever possible, is on results available from large, well-controlled, epidemiology studies, as opposed to less-representative individual case reports and/or case series (e.g., case series of explanted patients). The citations for such case reports and case series are, however, included in the full bibliography. A further emphasis of this literature review update, where possible, is on results from studies involving the current third generation of silicone breast implants, representative of the design of Mentor's silicone gel devices since the inception of the company. Lastly, those published studies deemed most pertinent to the key safety issues identified by the IOM and by the U.S. Food and Drug Administration are the primary focus within the narrative section of this report.

2. Introduction

A detailed review of the history of silicone and silicone breast implants was provided in the introduction of the IOM expert panel report (Chapter 1), along with a background history of the institute's Committee on the Safety of Silicone Breast Implants. The IOM expert panel estimated that as of 1997 somewhere between 1.5 to 2 million women in the U.S. had breast implants. Based on annual statistics of the number of breast augmentations and breast reconstructions performed by board-certified plastic surgeons since 1997 (National Clearinghouse of Plastic Surgery Statistics - American Society of Plastic Surgery), the current estimate would exceed 2 million U.S. women.

In evaluating health-related issues of women with silicone breast implants, it is important to identify potentially significant characteristics of this population that may differ from the general U.S. population and impact upon observed health outcomes. Three epidemiology studies published subsequent to the IOM expert report have described in significant detail a range of characteristics of women seeking breast augmentation (Brinton et al. 2000, Frycek et al. 2000, Kjoller et al. 2003).

Brinton et al. (2000) presented results from a larger U.S. study of 7,447 breast implant patients who were compared with 2,203 patients with other types of plastic surgery, rather than a general population of women. These patients were identified in a retrospective cohort study. The number of patients reflect questionnaire response rates of 70.7% and 71.1% for the two groups. Statistically significant differences observed in this study indicated that less implant patients had never been married or had advanced degrees. Implant patients were significantly more likely to:

- have been older at menarche
- have children
- have more pregnancies
- be younger at first birth
- use oral contraceptives
- use hormone replacement therapy
- weigh less.

With respect to mammography, implant patients were significantly more likely to have had a mammogram (Odds Ratio = 2.1, 95% CI 1.8-2.5), a difference that persisted even when mammograms performed two years or more prior to plastic surgery were excluded. Implant patients were also found to have a significantly greater family history of rheumatoid arthritis.

A Swedish study by Fryzek et al. (2000) compared 1,369 breast augmentation patients with 2,211 breast reduction patients and with a random sample of 49,262 women from the general population of Sweden. These numbers reflect response rates to a questionnaire of 65.1%, 71.9% and 51.3% among the three groups. As compared with breast reduction patients and with women from the general population, women with cosmetic breast implants were found to be significantly more likely to:

- be current smokers (Prevalence Odds Ratio = 2.8, 95% CI 2.4-3.2 vs. general population of Swedish women)
- have a lower body mass index
- have had an early pregnancy termination (induced abortion or miscarriage)
- have had fewer live births.

No significant differences were observed between 702 women with silicone gel implants and 288 women with saline breast implants in the study.

A Danish study by Kjoller et al. (2003) compared 423 breast augmentation patients with 231 control patients receiving other plastic surgery at the same clinics and with 4183 general population controls matched by age, sex and current residence. These numbers reflect response rates to the detailed self-administered questionnaire of 56%, 35% and 47% among the three groups. As compared with both control groups, women with cosmetic breast implants were found to be significantly more likely to:

- have a lower body mass index
- be current smokers (Odds Ratio = 2.6, 95% CI 1.8-3.8 vs. plastic surgery controls; OR = 2.1, 95% CI 1.4-3.1 vs. general population controls)
- have a greater number of full-term pregnancies.

Women with cosmetic breast implants were less likely to have had their first birth after age 30, and less likely to have hypertension (as compared with general population controls).

As noted in each of these studies, it is important to consider possible differences from the general population in demographic and other pre-surgery characteristics among breast augmentation patients when interpreting the health-based outcomes of any studies involving this patient population.

3. Chemistry of Silicone and Silicone Polymers

Although progressive improvements in manufacturing processes for silicone breast implants have been implemented over the years, the silicone polymer chemistry has remained substantially unchanged over the time period in which Mentor Corporation has manufactured these implants. The IOM report provided a background review of the chemistry of silicone materials used in the manufacture of silicone breast implants. No significant new literature published subsequent to the IOM report was identified on this topic.

4. Breast Implant Types

Silicone breast implants with a variety of different design variations have been provided by a range of manufacturers over the years. The IOM report (Chapter 3) provides a detailed cataloguing of the various implant types that have been available over the years, including Mentor silicone gel-filled breast implants. Mentor Corporation's silicone gel-filled breast implants incorporate a low-bleed elastomer shell. These devices are available in smooth and textured surfaces in a round design in varying sizes with three different profiles. The design of Mentor's silicone gel-filled breast implant has remained substantially identical since its introduction except for the introduction of new profiles and varying sizes. Manufacturing processes have been progressively refined over the years to ensure predictable manufacturing processes and consistent product quality. No significant new literature published subsequent to the IOM expert panel report was identified on this topic.

5. Toxicology of Silicone Materials Used in Silicone Breast Implants

The very extensive scientific information on the toxicology of silicone materials used in medical devices, including breast implants, is thought to represent the largest body of toxicology information available for any biomaterial. The IOM expert panel report (Chapter 4) reviewed this extremely large volume of data and concluded the following:

“Historically, silicone toxicology has tended to focus on short-term, acute and subacute studies and has suffered from a proportionate dearth of chronic, lifetime, and immunologic studies, as noted earlier in this chapter. Presumably, this reflects early conclusions that silicones were inert. Some silicones have clear biological effects. None can be said to be inert, if this implies an absence of tissue reaction, but the term has perhaps been used as a proxy to indicate that the toxicity of many silicones is of such low order that they comprise a useful class of biomaterials for medical implants.

Older silicone toxicology studies have deficiencies by current standards, but the body of toxicological information is substantial and improving. More chronic studies are being done, although modern regulatory requirements will undoubtedly generate a closer identification of silicones (and other substances) in implants and more specific toxicological studies of appropriate duration. Nevertheless, no significant toxicity has been uncovered by studies of individual compounds found in breast implants. Toxicology studies have examined carcinogenic, reproductive, mutagenic, teratologic, immunotoxic, and local and general toxic and organ effects by exposure routes that are varied and range to very high dose levels. Even challenges by doses that are many orders of magnitude higher than could be achieved on a relative-weight basis in women with silicone breast implants are reassuring. Toxic effects that have been found occur at very high, even extreme, exposure levels (e.g., D₄, D₅). The fact that some organic silicon compounds may have, as one would expect with any large family of chemical compounds, biologic or toxicologic effects is not relevant to women with breast implants since these compounds are not found in breast implants, as noted here and in Chapter 2.

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. Half-lives of low molecular weight silicones in body fluids and tissues have been measured infrequently, but known values appear to be on the order of 1 to 10 days. 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 detected by these animal experiments.

Some have speculated that platinum found in silicone gel and elastomer may be responsible for allergic disease in women with silicone breast implants. Very little platinum, microgram quantities, is present in implants, most investigators believe it to be in the zero valence state, and it likely diffuses through the shell at least over a considerable period of time. Evidence for resulting systemic disease at such exposures is lacking. Toxicological studies of tin compounds used in silicone breast implants are scarce, and generally not of parenterally administered tin. The data on organotins indicate that tin catalysts are among the less toxic, and they have not been extractable from implants shells by saline and some organic solvents. Based on the data available, the committee concluded that evidence is also lacking for tin toxicity at the very low amounts present in saline implants and at the virtually absent levels in gel filled implants.”

Since the completion of the IOM expert panel report, several additional studies in this area have been published. New physiologically-based pharmacokinetic (PBPK) models for D₄ have been reported, which, taken together, indicate rapid removal of free D₄ from the body with no accumulation from repeated exposures. Measurements of D₄, D₅, D₆ and platinum in a very limited sample of breast tissues was also reported. D₄ was identified in animal studies to exhibit weak estrogenic and antiestrogenic properties, but only at dose levels more than 200,000-fold greater than reasonable worst-case exposure levels from silicone breast implants. Results from state-of-the-art inhalation toxicology studies of D₄ and D₅ have also been published. Further published genotoxicity evaluations of D₄, both *in vivo* and *in vitro*, demonstrated no significant genotoxic potential. Lastly, updated estimates of D₄ exposures from personal care products have been provided in published communications. Details of these studies are provided below.

A state-of-the-art pharmacokinetic study of ¹⁴C-octamethylcyclotetrasiloxane (D₄) in Fischer 344 rats after single and multiple exposures to 7, 70 or 700 ppm was recently published by Plotzke et al. (2000). Data from this study formed the basis for development of a physiologically-based pharmacokinetic (PBPK) model for D₄ by Anderson et al. (2001) which concluded that “high pulmonary and hepatic clearance, coupled with induction of

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

Luu and Hutter (2001) published a different PBPK model for D₄ that challenges the Anderson et al. (2001) findings and predicted accumulation following multiple exposures. Numerous apparent flaws in the methodology of Luu and Hutter, however, have been asserted by Meeks (2002) and Anderson et al. (2002). Meeks (2002), in his critique, reported actual measured concentrations of D₄ in blood and fat from rats exposed to 700 ppm D₄ by inhalation (6hr/day, 5 days/week) for 15 days and 6 months, which “confirm that D₄ does not accumulate in the body.” An independent evaluation of the Luu and Hutter model by an internationally-recognized expert PBPK modeler to assess its validity was commissioned by Mentor Corporation. The evaluation identified very significant methodological shortcomings (including several key features of the model that are inconsistent with mammalian physiology) in the Luu and Hutter model that severely limit any interpretations of their findings. As such, the pharmacokinetic modeling of Anderson and colleagues that predicts no accumulation on multiple exposures represents the most reliable data currently available.

Flassbeck et al. (2003) applied GC-MS and ICP-HR-IDMS techniques to measure levels of D₄, D₅, D₆, and platinum in breast tissues from a total of 3 women with silicone breast implants and 3 controls. In women with silicone breast implants, D₄ levels ranged from 0.01 to 1.3 ppm, D₅ levels from 0.009 to 0.6 ppm, D₆ levels from 0.02 to 0.8 ppm, and platinum levels from non-detectable to 0.09 ppm. Given the known phenomenon of gel bleed, the low and well-defined toxicity profile of D₄-D₆ and platinum (present in its zero valence and least toxic form in catalysts used for breast implant materials), such findings do not raise any new safety issues.

The results from recently published state-of-the-art inhalation studies of D₄ and D₅ in experimental animals have provided the most sensitive toxicity endpoints as the basis for establishing the no-observable-adverse-effect levels for these materials.

For D₄, the most sensitive toxicity endpoint observed in rodent bioassays has been a dose-related increase in liver weights (reversible following removal of exposure). In the inhalation toxicity study of D₄ reported by Klykken et al. (1999), the lowest-observable-adverse-effect level (LOAEL) was found to be 0.24 mg/L and the no-observable-adverse-effect level (NOAEL) to be 0.085 mg/L for an exposure period of 6h/day, 5d/wk for 28 days in Fischer 344 rats. In a study evaluating the retention, distribution, metabolism and excretion of D₄ in Fischer 344 rats, Plotzke et al. (2000) reported that 5 to 6 percent of an inhaled dose is retained. Assuming a body weight of 350 g, a minute ventilation rate for rats

of 240 mL (Hayes 2001), and 5 percent retention (Plotzke et al. 2000), the NOAEL is equivalent to approximately 1.05 mg D₄/kg body weight/day.

For D₅, a similar 28-day inhalation toxicity study in Fischer 344 rats reported by Burns-Naas et al. (1998) identified a NOAEL (also based on reversible increase in liver weight) of 1.14 mg/L. The exposure regimen was the same as for the D₄ study described above, 6hr/d, 5d/wk for 28 days. Assuming a body weight of 350 g, a minute ventilation rate for rats of 240 mL (Hayes 2001), and 5 percent retention (based on the D₄ data of Plotzke et al. 2000), the NOAEL is equivalent to approximately 14 mg D₅/kg body weight/day.

McKim et al. (2001) recently reported results from their investigation of the potential estrogenic and antiestrogenic activity of D₄ and hexamethyldisiloxane (HMDS) 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 F-344 rats. The no-observable-adverse effect level (LOAEL) for D₄ identified in this study was 100 mg/kg. HMDS did not reveal any estrogenic activity at doses up to 1200 mg/kg; a small antiestrogenic effect at this high dose level of HMDS was observed when coadministered with ethinyl estradiol. Further elaboration of the mechanism by which D₄ exhibits weak estrogenic activity in mice was provided by He et al. (2003), who demonstrated such effects were mediated through estrogen receptor- α .

Vergnes et al. (2000) published a very thorough evaluation of the genotoxicity of D₄ (OMCTS, octamethylcyclotetrasiloxane). Their report included the results of both *in vitro* assays (bacterial mutagenicity, *in vitro* chromosomal aberration in CHO cells, sister chromatid exchange in CHO cells) and *in vivo* assays (*in vivo* chromosomal aberrations in rat bone marrow). The study 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.”

Shipp et al. (2000) provided an estimate of 158 ug/kg/day for the daily intake resulting from exposure to D₄ in a wide variety of personal care products. Owing to currently reduced use of D₄ in roll-on antiperspirants, a current conservative estimate of daily intake from personal care products is 78 ug/kg/day (Meeks 2002).

The IOM expert panel, in their report noted that “there has been considerable mention of silica as a component of breast implant elastomers,” however “the committee found no valid scientific evidence for the presence of or exposure to silica in tissues of women with breast implants.” A thorough search of recent literature has not identified any valid scientific

evidence of such presence or exposure to silica published subsequent to release of the IOM report.

A review of silicone toxicology information published subsequent to the IOM expert panel report reveals that the panel's original conclusions remain fully valid in light of the additional information.

6. Reoperations and Specific Local and Perioperative Complications

6.1 Introduction

Patients undergoing any surgical procedure may experience complications such as the effects of anesthesia, infection, swelling, redness, bleeding, and pain. The implantation of silicone gel-filled breast implants for augmentation and reconstruction of the breast may also result in complications specific to breast implants. The key complications that have been the focus of most clinical investigations of breast implants over the years include infection, capsular contracture, rupture, reoperation and explantation. Other possible complications identified in the IOM expert panel report included: gel migration, silicone granuloma, axillary adenopathy, silicone exudation through skin or nipple, hematomas, seroma, skin rashes, skin blistering and cysts, necrosis, extrusion, malposition, loss or change in sensation of the breast or nipple, chest wall skeletal changes, pneumothorax, peri-implant calcification, lactation and galactocele. Based on their extensive review of the available information, the IOM expert panel concluded in their report (Chapter 5) that:

“The frequency of local and perioperative complications has been substantial in both augmentation and reconstruction of the breast with either saline- or gel-filled silicone implants. These complications have safety implications, because they may have health consequences of their own and because they may result in further operative or medical interventions that may also have health consequences. The committee sees little justification for some of these interventions, for example, closed capsulotomies or the use of steroids.

Much information in this chapter may not apply to the present and may not provide a basis for decisions concerning future experiences because past reports of complications reflect experience with implants having physical and chemical characteristics that differ from current implants and surgical practices that differ from current practices. Although the present state of knowledge does not allow definite conclusions to be drawn about the prevalence or incidence of some complications, some of the more common complications such as rupture, deflation, and contracture may be becoming less frequent due to operative and technological improvements. Information to permit conclusions about the frequency, causes, and management of complications has to be gathered based on research on a stable population of standardized devices. Much remains to be learned about the basic

biology of foreign body, silicone, and other polymer interactions with tissue, although progress has been made recently.

The committee drew conclusions about ruptures and deflations, the role of silicone in contracture, saline versus gel implants, barrier shells and shell texturing, submuscular placement of implants, the roles of infection and hematomas, the use of adrenal steroid, pain and other outcomes that can affect reoperations and local and perioperative complications. In general, however, the frequency of reoperations and local complications is sufficient to be of concern to the committee and to justify the conclusion that this is the primary safety issue with silicone breast implants, and it is certainly sufficient to require very careful and thorough provision of the kind of information contained in this chapter to women considering breast implant surgery. The committee concludes that many of these risks continue to accumulate over the lifetime of a breast implant.”

6.2 Incidence Rates for Reoperations and Specific Local and Perioperative Complications

Consistent with the IOM panel’s identification of local and perioperative complications as the primary safety issue with silicone breast implants, manufacturers have collected and are reporting local and perioperative complication results from large prospective clinical studies of current silicone breast implants, including both saline-filled and gel-filled devices. Such data provide the best information relevant to current devices and surgical practices, allowing accurate estimation of incidence and prevalence rates in order to provide optimal informed consent.

Of the local and perioperative complication rate data reported in the published medical literature, the most extensive and complete information has been provided in two large epidemiological retrospective cohort studies conducted by Gabriel et al. (1997), Kjoller et al. (2001) and results from a nationwide breast implant registry reported by Henriksen et al. (2003). A subset of the population of the Kjoller et al. (2001) study was further evaluated by Holmich et al. (2003), focusing exclusively on MRI-diagnosed rupture. Such data represents the highest quality data available from the published literature for estimating complication rates among the general population of patients receiving silicone breast implants. Brief descriptions of the study populations are provided below and the observed incidence rates are summarized in Table 6.1.

Gabriel (1997) studied complications leading to surgery among 749 women from Olmstead County, Minnesota who had received a first breast implant at the Mayo Clinic between 1964 and 1991. The mean follow-up for these patients was 7.8 years.

Kjoller et al. (2001) reviewed the medical records of 754 women with cosmetic breast implants (52% single-lumen silicone gel implants; 32% double-lumen implants) who had received at least one cosmetic breast implant from private plastic surgery clinics in Denmark (>90% from two of the country's largest clinics). The mean follow-up for these patients was 7 years.

Henriksen et al. (2003) reported results from the nationwide Danish Registry for Plastic Surgery of the Breast for two-year complication incidence rates among a population of 971 patients who received initial cosmetic breast implant(s) between June 1999 and October 2002. The nationwide registry includes patient data from 31 private and public plastic surgery clinics representing 80% of those present in Denmark. The results for the 971 patients represents the subset of patients from clinics with follow-up data for 90 percent or more of their patients.

Holmich et al. (2003) evaluated the incidence of silicone breast implant rupture by repeated MRI imaging of a randomly selected cohort of Danish women with cosmetic silicone breast implants drawn from the Kjoller et al. (2001) study cohort.

Table 6.1. Reported Rates of Local and Perioperative Complications from Large Epidemiological Retrospective Cohort Studies

COMPLICATION	Complication Rate (per patient)			
	Gabriel et al. (1997) 749 patients (mean f/u = 7.8 yr)	Kjoller et al. (2002) 754 patients (mean f/u = 7 yr)	Henriksen et al. (2003) 971 patients (f/u = 2yr)	Holmich et al. (2003) 145 patients with 3 rd generation implants (mean f/u = 2 yr)
Capsular contracture	17.5%	7.9%	1.3%	-
Infection	2.5%	1.1%	0.8%	-
Rupture	5.7%	0.3%	0.0%	1.8%/year ^a
Explantation	-	7.6%	-	-
Reoperation	28%	10.1%	6.0%	-
Hematoma	5.7%	1.3%	1.1%	-
Seroma	2.1%	0.1%	0.1%	-
Erosion/Extrusion	1.9%	0.1%	0.0%	-
Breast pain	1.1%	-	1.1%	-
Necrosis	0.8%	0.1%	-	-
Herniation	-	0.4%	-	-
Malposition	-	2.6%	2.7%	-
Wound dehiscence	0.5%	0.4%	-	-
Change in Sensitivity	-	-	8.3%	-

^a MRI-assessed, 3rd generation implants (by shell type), age-adjusted rate

The rates of specific local and perioperative complication rates reported in the published medical literature over the past 12 years are summarized in Table 6.2 and detailed in Appendix Table LR-6. As the primary focus is on identifying rates relevant to the overall population of women receiving breast implants, data are not summarized from those studies involving highly selected subpopulations (e.g., explanted patients) that would not be expected to provide representative data.

Table 6.2. Complication Rates from the Published Literature

COMPLICATION	LITERATURE RATE
Infection	0 – 6.3%
Capsular Contracture	0 – 73 %
Rupture	0 – 69 %
Asymmetry	7.5%
Wrinkling	30 %
Breast Pain	1.1 – 20 %
Hypertrophic Scarring	4.1%
Inflammation	N/A
Delayed Healing	N/A
Seroma	0.0-2.1 %
Hematoma	0 – 5.7 %
Necrosis	0.1 – 5.0 %
Extrusion	0 – 5.4 %
Lymphadenopathy	0 – 0.3 %
Calcification	26 %
Reoperation	6 - 33%
Explantation	7.5 – 33 %

6.3 Infection

As with any invasive surgical procedure, particularly procedures involving placement of a medical device, the implantation of silicone breast implants presents an inherent risk of infection. Infections can occur at the site of the surgical incision, within the periprosthetic pocket, or as the result of bacterial colonization of the device surface.

Most infections occur immediately postoperatively; these infections may occur as the result of improper device handling, inadequate aseptic surgical technique, the extent of tissue manipulation, or a preexisting infection elsewhere in the body that was not clinically evident at the time of surgery. Proper surgical technique and device handling are thought to minimize such risks, and a great deal of experience has been gained over the approximately thirty years that silicone breast implants have been in use.

Delayed infections can also develop in breast implant recipients; these infections are thought to be the result of hematogenous seeding of bacteria from an infection elsewhere in the body resulting in bacteria entering the bloodstream and reaching the implant site. Some believe that the risk for this type of infection may be reduced by prophylactic administration of antibiotics prior to any medical procedures that could potentially introduce bacteria into the bloodstream (e.g., invasive dental procedures), although such prophylaxis is controversial.

The risk of infection in post-mastectomy reconstruction patients may be increased in patients undergoing radiation therapy or chemotherapy. Krueger et al. (2001), as part of the Michigan Breast Reconstruction Outcome Study, examined complications, including infection, among 81 breast cancer patients who underwent mastectomy followed by breast reconstruction with an expander/implant, with (n=19) or without (n=62) radiotherapy. The average follow-up in this study was 31 months (range = 12-162). After adjustment for smoking, diabetes, reconstruction type, chemotherapy, age and race, radiotherapy was associated with a significantly higher incidence of complications (odds ratio = 6.4, 95% CI 1.6-25.0). Infection was one of two most frequent complications, occurring in 37% (7/19) of those receiving radiotherapy, as compared with 19% (12/62) of those without exposure to radiotherapy. Vandeweyer et al. (2003) examined the potential impact of chemotherapy following immediate breast reconstruction with silicone breast implants among 27 patients receiving chemotherapy and 64 patients not receiving chemotherapy (mean follow-up = 44 months). A higher rate of implant infection, 10.7% versus 1.5% (p=0.0084) was observed in the chemotherapy patients following initiation of treatment.

In extremely rare instances, Toxic Shock Syndrome has been noted in women after breast implant surgery, and it is a life-threatening condition. Toxic shock syndrome is a nationally notifiable disease closely tracked by the Centers for Disease Control (Hajjeh et al. 1999). Symptoms include sudden fever, vomiting, diarrhea, fainting, dizziness, and/or sunburn-like rash. Cases of toxic shock syndrome have also been reported following breast reconstructions with transverse rectus abdominis (Cederna 1995) or latissimus dorsi musculocutaneous flaps (Gosain and Larson 1992), as well as following breast biopsy.

A final type of infection that has received growing attention with regard to silicone breast implants (as well as medical devices in general) is subclinical infection. Subclinical infection occurs when there is bacterial colonization, but there are no clinical signs of infection. (The infections described in the preceding paragraphs are all infections that are clinically evident, with such typical symptoms as fever, and swelling and warmth at the site of infection.) With subclinical infections, there are no outward signs of infection; symptoms, if there are any, consist mostly of vague, systemic symptoms (e.g., muscle ache, fatigue) that would be unlikely to be attributed to a specific cause. These infections are, for the most part, unique to medical devices. They are caused by microorganisms that are normally non-pathogenic and have low virulence. These organisms are able to adhere to medical devices (or normal host proteins coating the device surface), and produce a "biofilm" in which colonies of these organisms are able to slowly grow within a protective layer, protected from the body's defense mechanisms. Subclinical infection has been suggested as having a possible etiological role in the development of capsular contracture.

In a study published subsequent to the IOM expert panel report, Pajkos et al. (2003) conducted a comparative, prospective, blinded clinical investigation of 21 breast implants (15 gel, 6 saline) and 27 capsules removed from 16 revision augmentation patients with or without significant capsular contracture. The study employed very rigorous microbiological sampling procedures that included maceration, shaking and ultrasonication of samples to release bacteria tightly bound within biofilms (ordinary swab sampling techniques have previously been reported as generally ineffective in identifying subclinical infection of medical devices and surrounding tissues). Of 19 capsules with significant capsular contracture (III/IV), 17 (90%) tested positive for the presence of bacteria, whereas, only 1 of 8 capsules (12%) without significant contracture tested positive. Of 13 implants associated with significant contracture, 5 (38%) tested positive for bacteria, whereas, only 1 of 8 implants (12%) without significant contracture tested positive. No significant difference was observed in culture positivity between saline-filled and gel-filled implants. The most commonly identified organisms were coagulase-negative staphylococci, primarily *Staphylococcus epidermidis*.

6.4 Capsular Contracture

When the body's defense mechanisms are unable to eliminate any large, inert foreign body, a series of events occurs known as a nonspecific foreign body reaction. The result of this reaction is the creation of a fibrous tissue capsule around the object, which isolates it from surrounding tissue. As a normal physiologic response, such a capsule forms around an implanted breast prosthesis. In some instances the capsule contracts around the implant causing the implanted breast to become firm, and in severe cases, painful and distorted. Capsular contracture is generally the most often reported complication of breast implants. The degree of capsular contracture is typically evaluated using a subjective scale known as the "Baker Classification of Capsular Contracture," in which the criteria for classification are as follows:

- Grade I: The augmented breast feels as soft as an unoperated one.
- Grade II: The breast is less soft, the implant can be palpated, but is not visible.
- Grade III: The breast is more firm, the implant can be easily palpated and it (or distortion from it) can be seen.
- Grade IV: The breast is hard, tender, painful and cold. Distortion is often marked.

The degree of firmness may also be influenced by breast tissue thickness, density, and body position during evaluation. Grades III and IV are generally considered clinically significant. Although the etiology is not known – and a variety of hypotheses have been suggested – subclinical infection, as discussed above may be a significant factor.

Another potentially significant factor related to capsular contracture in post-mastectomy reconstruction patients appears to be exposure to radiation therapy. As shown in Table 6.3 below, a number of studies have reported increased incidence of capsular contracture in association with the use of radiation therapy.

Table 6.3 Effect of Radiation Therapy on the Incidence of Capsular Contracture

Study	Median Follow-Up	Incidence of Capsular Contracture (III/IV)	
		Patients w/ Radiotherapy	Patients w/o Radiotherapy
Ringberg et al. (1999)	43 mo.	71% (10/14)	N/A
Contant et al. (2000)	30 mo.	60% (9/15) prior radiotherapy 39% (5/13) post-reconstruction	11% (10/87)
Spear and Onyewu (2000) ^a	28 mo. (mean)	32.5% (13/40)	0% (0/40)
Vandeweyer & Deraimaecker (2000)	65 mo.	100% (6/6)	3.4% (4/118)
Krueger et al. (2001)	31 mo.	26% (5/19)	10% (6/62)
Tallet et al. (2003)	25 mo.	13% (7/55)	0% (0/22)

^a two-stage saline-filled breast implant reconstruction

Clinically significant capsular contracture may lead to additional surgery in cases where pain and/or firmness is severe. This surgery may involve removal of the implant capsule tissue or explantation and possible replacement of the implant itself. Capsular contracture may recur in such patients, and the incidence rate following revision procedures is generally higher than following initial implantation of a device.

6.5 Rupture

Device rupture is a long-recognized complication of silicone gel-filled breast implants. Bostwick (2000), in a detailed review of augmentation mammoplasty techniques and results noted that:

“Although breast implants are manufactured to specific standards requiring that they withstand breast compression as well as multiple and long-term physical stress, these devices are not indestructible. The outer shell of the implant can break if subjected to severe trauma such as pressure from a seat belt during a car accident, and certainly from a needle stick. Compression views taken during mammography are calibrated to avoid undue pressure that could rupture or deflate a breast implant.

The chance for rupture or deflation may increase with normal wear and tear and the length of time the device has been implanted. The incidence of rupture increases when the implant develops folds or rippling on the outer surface. Implants with thicker elastomer envelopes can develop more distinct folds and leak at a fold flaw point. Trauma or injury to the breast also increases the chance of rupture as may closed capsulotomy (a technique to correct capsular contracture in which strong pressure is applied to the breast to break up the scar tissue around the implant). This technique is less frequently used today and is not recommended by the manufacturers.”

A portion of breast implant ruptures are attributable to iatrogenic damage that may occur during the implantation procedure. Brandon et al. (2001) has provided a detailed characterization of the appearance of damage to the elastomer shell from a range of surgical instruments (e.g., forceps, suture scissors, scalpels, suture needles, hemostats) using scanning electron microscopy.

Determining an accurate estimate of device rupture has been a key element over the years of many clinical investigations of silicone gel-filled breast implants. Rupture can be categorized as overt rupture (definitively recognized by the patient and/or physician) or silent rupture (not recognized or externally apparent except through appropriate imaging techniques such as MRI). Device ruptures can be further grouped as intracapsular or extracapsular, depending upon whether the silicone gel remains within the fibrous capsule encircling the implant. The virtual elimination of closed capsulotomy as an accepted practice for treating capsular contracture is expected to result in a significant reduction in extracapsular ruptures. Although a very broad range of incidence rates for rupture have been published, most reports suffer from severe limitations in the underlying studies, particularly

reliance on highly selected – and therefore highly statistically biased – patient groups such as case series of explanted patients (e.g., Marotta et al. 2002), or a focus on device designs that pre-date the current third generation of silicone gel-filled breast implants that Mentor Corporation has manufactured since the inception of the company (e.g., Robinson et al. 1995). First and third generation devices incorporated a thicker gel and thicker elastomer shell than the second generation devices marketed in the United States between about 1972 to the mid-1980s. Second generation devices have been associated in a number of studies with substantially higher rates of rupture than either the first or third generation devices.

More reliable estimates of rupture rates are provided by population-based epidemiology studies, such as those published by Gabriel et al. (1997), Karlson et al. (1999), Kjoller et al. (2002), and Holmich et al. (2003). Gabriel et al. (1997) reported an overt rupture rate of 5.7% among 749 patients with an average follow-up of 7.8 years (up to a maximum of 26 years). Karlson et al. (1999) reported an overt rupture rate of 12% among a randomly selected subset women with silicone breast implants (median follow-up of 12 years) from the Nurse's Health Study. More recently, Kjoller et al. (2002) reported a 0.3% rate of overt rupture among 754 patients with an average follow-up of 7 years (up to a maximum of 23 years). Holmich et al. (2003) reported an MRI-based incidence rate of overt and silent rupture among a randomly selected subset of the Kjoller et al. (2002) study population. Consistent with previous reports in the literature, Holmich and colleagues observed a statistically significant 3- to 5-fold higher rate of rupture (definite and possible) amongst second generation devices as compared with third generation devices. The rupture (definite and possible) incidence rate for second generation devices was also higher than for first generation devices, also consistent with previous reports. The study authors reported that “for modern implants intact 3 years after implantation, we estimated rupture-free survival of 98% at five years and 83% to 85% at ten years.” A fifth epidemiology study, by Brown et al. (2000) also assessed rupture status of silicone breast implants with MRI, however, it included almost exclusively second generation implants (94%). The Brown et al. (2000) study included only twelve third generation implants (only one of which had ruptured), and therefore, does not provide pertinent rupture rate data for Mentor's third generation devices.

6.6 Potential Consequences of Device Rupture

Rupture of silicone breast implants generally leads to reoperation with explantation to replace the devices. Aside from the need for such operations, potential concerns have been raised over whether device rupture might be associated with the development of connective tissue or rheumatic diseases and/or symptoms. Well-designed, population-based epidemiology studies that have evaluated this issue do not, taken together, support such an association.

A study by Brown et al. (2001) evaluated the potential association between breast implant rupture and extracapsular silicone and various adverse health outcomes among 344 MRI-assessed patients with silicone gel breast implants. These authors noted a potential association between extracapsular rupture (MRI-assessed) and self-reported fibromyalgia. This study, however, was not able to assess whether the fibromyalgia was present prior to implant surgery. Wolfe and Anderson (1999) reported a similar, but not statistically significant, increase in prevalence of fibromyalgia among women with silicone breast implants in comparison to various control groups when the time of occurrence was not factored in. Importantly, though, when fibromyalgia that occurred prior to breast implantation was excluded, there was no significant difference in fibromyalgia occurrence. Furthermore, in the Brown et al. (2001) study, only when patients with non-ruptured and intracapsular ruptured devices were combined in the analysis, was a significant association noted. Comparison of patients with extracapsular rupture to patients with intracapsular rupture, or to patients without rupture, showed no significant association with fibromyalgia.

Of 28 symptoms (*e.g.*, joint pain, muscle pain, muscle weakness, headaches, neck aches, shoulder aches, backaches, fatigue, memory difficulties, hair loss) reported among 1280 cosmetic breast implant patients (average follow-up of 13 years) and 2,211 breast reduction patients in a study by Fryzek et al. (2001), no significant differences were observed between cosmetic breast implant patients with and without implant leakage. As compared with breast reduction patients, no significant differences were seen with cosmetic breast implant patients with implant leakage for 26 of the 28 symptoms. Only “other skin abnormalities” or “persistent or recurrent neck ache” were somewhat more likely (relative risk = 1.8) to be reported amongst patients with implant leakage.

A study by Berner et al. (2002) compared various symptoms among cancer patients with silicone breast implants (average follow-up of 7 years) with a control group, and reported that “positive correlation with implant rupture [assessed by MRI imaging] was given only for the numb feeling/tingling sensation in extremities.” There was no significant difference observed for 24 other symptoms. The study authors also noted that “there was no correlation between silicone implants and the symptoms of the ‘chronic-fatigue syndrome’ nor any other described silicone-induced disease,” and concluded that “according to our analysis many of the symptoms examined here are present in middle-aged women regardless of silicone implants and underlying disease.”

Holmich et al. (2003) examined a range of self-reported diseases or symptoms, as well as autoantibodies, among 238 randomly selected Danish women with cosmetic silicone breast implants. Patients in this study (average follow-up of 14 years) were categorized based on

the rupture status (MRI-assessed) of their implants (146 patients with intact implants, 92 patients with definite rupture, of whom 23 had extracapsular rupture). Based on their findings, the study authors concluded that “this study of unselected women with silicone breast implants could establish no association between silicone implant rupture and specific diseases or symptoms related to connective tissue disease or other rheumatic conditions, except for an excess of capsular contracture among women with extracapsular rupture.”

Overall, these studies with long-term follow-up provide considerable evidence that rupture of silicone breast implants is not associated with connective tissue or rheumatic diseases or symptoms.

6.7 Impact of Reoperations due to Local and Perioperative Complications

Reoperations may occur in 10-33% of patients receiving silicone breast implants (Gabriel et al. 1997, Brown and Pennello 2002, Kjoller et al. 2002). Despite these significant rates of reported reoperation, most patients who receive breast implants report that would have the surgery again, indicating a high level of satisfaction. The IOM expert panel, in addressing this issue, pointed out that although there have been significant limitations in previously published information on satisfaction levels among women with silicone breast implants::

“The high overall level of satisfaction of women in medical reports, if accurate and lasting, implies a low level of concern or at least a willingness to tolerate some complications. This may have an important moderating effect on the reported incidence of further operative or medical interventions.”

7. Immunology and Silicone Breast Implants

The potential for effects of silicone and silicone breast implants upon the immune system has been the subject of literally hundreds of scientific articles over the years. This very large body of literature was reviewed in detail by the IOM expert panel, which concluded in their report (Chapter 6) that:

“Based on the data available, the committee concludes that there is no convincing evidence to support clinically significant immunologic effects of silicone or silicone breast implants. This includes: insufficient evidence for an association of a particular HLA type in women with breast implants and health conditions; insufficient evidence for silicone as a super-antigen; insufficient or flawed evidence that silicone produces immune activation of cells of the immune system, silicone antibodies, delayed type hypersensitivity to silicone, cytokines as an immune response, antigen specific immune cellular infiltrates; and insufficient evidence for autoantibodies or T-cell self antigen activation. The paucity of significant, well-controlled studies examining these questions is responsible for these conclusions. The committee finds that there is conclusive evidence that some silicones have adjuvant activity, but there is no evidence that this has any clinical significance. The committee has also concluded that evidence from experimental studies of the immunology of silicone does not support, or lend biologic plausibility to, associations of silicone breast implants with immune related human health conditions.”

Although several additional studies in this area have been published since the IOM report, the conclusions stated by IOM remain fully applicable to the current information.

O'Hanlon et al. (2000), in a follow-up study to previous work reviewed by the IOM expert panel, examined patterns of T cell receptor beta-chain gene expression in silicone breast implant capsules and remote sites of tissue inflammation in order to assess whether “any immunological relationship exists between local inflammatory responses detected in silicone breast implant capsules and systemic sites of tissue injury.” This study focused primarily on evaluation of a total of three patients. The authors reported that overall, “the number and identity of TCR [T cell receptor] BV gene families detected varied considerably among tissues and patients” that they have evaluated. In a limited number of cases, however, identical T cell receptor gene transcripts were found in both left and right breast implant capsules as well as distant sites of inflammation, suggestive of a common, antigen-driven T cell response producing chronic inflammation. The authors noted, however, that they have previously observed such shared patterns of T cell receptor gene usage between capsules of

asymptomatic patients with silicone breast implants. Furthermore, it should be noted that the O'Hanlon and colleagues acknowledge that they have not identified the antigen, which could very well be microbial in origin (perhaps attributable to subclinical infection), rather than directly related to the silicone breast implants. Considerable additional progress in this research is required before any meaningful conclusions can be drawn.

Schaefer et al. (1999), in an extension of earlier work reviewed by the IOM expert panel, examined the potential influence in mice of long-term implantation of silicone (gel, oil, and elastomer) on the development of type II collagen-induced arthritis. A previous study of involving a 73-day exposure to silicone materials implanted by a different route revealed no adverse effect upon disease in this experimental model. In this study, the mice implanted with silicone elastomers nine months prior to immunization with Type II collagen and Freund's incomplete adjuvant developed a significantly increased incidence of arthritis. Interestingly, however, no increase in severity of the arthritis or shortening of the time to development of the collagen-induced arthritis were observed among the silicone-exposed animals, as might be expected if the silicone materials were directly responsible for the observed effects. As noted by the study authors, "the conclusions of this animal study must be related to findings with patients with silicone implants with great caution." No follow-up publications from this work, or reports of replication in other laboratories, have been identified in the literature from the past four years.

A second study published by this research group, Schaefer and Wooley (1999) evaluated the influence of silicone implantation on lupus in mice. The authors reported that although effects were observed on certain immune markers (*e.g.*, cytokines, autoantibodies), "no adverse influence of silicone gel or silicone oil on the clinical aspects of lupus was observed."

In a study with potentially significant implications for interpretation of earlier studies, Oliver et al. (2000) examined putative anti-silicone (IgG) antibodies among 20 women with silicone breast implants (some of which were ruptured, time since implantation ranging from 6 weeks to 20 years), 20 women without implants, 20 women with autoimmune disease and 20 anonymous blood donors. A previously used ELISA technique that had given positive results in an earlier uncontrolled series was employed. No differences were observed in antibody binding between women with silicone breast implants and women in the various control groups. Interestingly, samples that had been stored for the longest period of time, or had been frozen and thawed repeatedly, showed elevated levels of binding. The study authors concluded that "there is no demonstrable anti-silicone antibody formation in these patients with SBI and we would caution that the effect of storage may have been an important factor in previously published assay methods."

8. Antinuclear Antibodies and Silicone Breast Implants

Included among the literature addressing the potential for immune effects of silicone and silicone breast implants have been a number of studies in which antinuclear antibodies (ANA) were measured in patients' serum. These studies and the potential significance of their findings were reviewed by the IOM expert panel, which concluded in their report (Chapter 7) that:

"As noted at the outset, studies of ANAs in women with silicone breast implants are subject to a number of weaknesses. Results reported have varied from positive to negative in a number of experimental groups, including women with saline or gel implants and those with connective tissue disease, an array of symptoms and disabilities, fibromyalgia, or no symptoms. No differences between saline and gel implants emerge from these studies, but results are not always reported by type of implant. A number of different control groups have been reported including historical, concurrent, asymptomatic or healthy, with fibromyalgia, with soft tissue rheumatism, with connective tissue disease, and with diabetes, and they have been assessed using different ANA technologies and criteria for positivity. Studies with no controls at all are essentially case reports. Even though some may report large numbers of women, they offer only weak evidence. Different results of testing for defined antinuclear autoantibodies have also been reported. Even theoretically well designed, prospective studies (Miller et al., 1998) have problems, such as short follow-up, failure to include significant portions of the potential experimental group, and no description of the testing technology. The fact that a positive ANA test is not a disease diagnosis should also be kept firmly in mind.

The cohort studies, however, add strength to the evidence against an association between silicone breast implants and ANAs or other autoantibodies. The committee concludes that the data in support of a finding of increased prevalence, higher titers, or different profiles of antinuclear antibodies in women with gel- or saline-filled silicone breast implants compared to control women without breast implants are insufficient or flawed. The weight of the better-quality evidence suggests the lack of an association between silicone breast implants and positive ANAs. Although there are fewer data on specific autoantibodies, they also suggest no association and are insufficient to support a finding of increased prevalence or different profiles of specific autoantibodies in women with silicone breast implants."

Subsequent to release of the IOM expert panel report, further epidemiological studies have been published that reported rates for positive ANAs among women with silicone breast

implants. These studies have employed the optimal methodology identified by the IOM panel (indirect immunofluorescence in Hep-2 cells with a 1:160 dilution as a cut-off for positivity).

Karlson et al. (2001) conducted a serological evaluation of women randomly selected from amongst the 33,340 women in the large Women's Health Study from whom they had obtained blood samples. The frequency of ANA positivity was 8.4% (25/298) in women with breast implants, 8.7% (26/298) in women without implants, and 11.5% (6/52) in diabetic women.

Jensen et al. (2001) evaluated ANA positivity as part of an assessment of rheumatic disease profile among 188 Danish women identified through hospital and population registers. Their findings are summarized in Table 8.1.

Table 8.1 ANA Positivity Findings of Jensen et al. (2001)

Study Group	With Prior Diagnosis of Muscular Rheumatism	ANA Reactivity	
		Negative # pts.	Positive # pts. (%)
Women With Silicone Breast Implants	Y	26	2 (7%)
	N	19	2 (10%)
Breast Reduction Patients	Y	24	3 (11%)
	N	25	2 (7%)
Women With No Breast Surgery	-	20	6 (23%)
Central Population Register Controls	-	49	7 (13%)

Englert et al. (2001) conducted a population-based retrospective cohort study of Australian women that included 458 patients who received cosmetic breast implants and 687 patients who received other non-silicone related plastic surgery between 1979-1983 with a minimum 15 year follow-up,. A small elevation in "low titre positive" ANA occurred among women with breast implants (odds ratio = 1.29, 95% CI, 1.03-1.62). Comparable frequencies of higher titre ANA (1:320 dilution) were observed, leading the study authors to conclude that "the finding of elevations of low titre ANA is of dubious clinical significance.

Contant et al. (2002) conducted a prospective cohort study of 57 women undergoing mastectomy followed by immediate breast reconstruction with silicone breast implants.in which sera were tested for ANA positivity just before and one year following the surgery. No new cases of ANA positivity were identified one year after immediate breast reconstruction.

Holmich et al. (2003) reported ANA positivity status among 238 randomly selected Danish women with cosmetic breast implants drawn from the study population described by Kjoller et al. (2002). Patients in this study (average follow-up of 14 years) were categorized based on the rupture status (MRI-assessed) of their implants (146 patients with intact implants, 92 patients with definite rupture, of whom 23 had extracapsular rupture). No significant difference in the frequency of ANA positivity was observed between patients with intact implants (MRI-assessed) and those with any rupture (OR = 1.1, 95% CI, 0.4-2.6) or those with extracapsular rupture (OR = 0.7, 95% CI, 0.2-3.4).

The overall results from these predominantly population-based studies provide confirmatory evidence that there is no significant elevation of ANA among women with breast implants.

9. Epidemiological Investigations of Connective Tissue Disease or Rheumatic Disease and Silicone Breast Implants

The issue of a potential association between silicone breast implants and the development of connective tissue or rheumatic disease has received the greatest attention among the potential health risks of these devices. The IOM expert panel reviewed the very extensive body of information on this issue and focused in Chapter 8 of their report on the findings of epidemiological investigations of this issue. Their review addressed first the defined connective tissue or rheumatic diseases, and second, atypical connective tissue or rheumatic disease.

9.1 Defined Connective Tissue or Rheumatic Diseases

The IOM expert panel reviewed a number of epidemiological studies that examined the potential association between silicone gel-filled breast implants and individual or combined defined connective tissue diseases, primarily systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis/polymyositis and Sjogren's syndrome. The IOM expert panel focused on 17 epidemiological studies (mostly published, full-length, peer-reviewed studies), including 11 cohort studies, 5 case-control studies and 1 cross-sectional study. The panel also evaluated expert panel reviews prepared by the Independent Review Group (IRG 1998) and the National Science Panel (Diamond et al. 1998), as well as seven published meta-analyses. Based on their review of this large body of epidemiological evidence, the IOM expert panel concluded that:

“As noted earlier, the committee examined a number of comprehensive reviews and meta-analyses of epidemiological reports investigating associations of combined and individual connective tissue diseases with silicone breast implantation. The committee also reviewed published reports from 17 individual epidemiologic studies, which are discussed here, and took note of additional abstracts and letters. These reports and analyses generally examined connective tissue diseases combined. Of the 17 independent reports, from 6 to 12 – depending on the disease in question – looked specifically at one or more of the individual CTDs listed earlier (i.e., SSc, SS, RA, SLE and D/P). A number of these reports also provided data on “other” connective tissue diseases. In only one instance was a relative risk or odds ratio significantly elevated, however. That report, based on a large number of women, found a small association of implants with combined connective tissue diseases (Hennekens et al., 1996). However, among women who responded to the study questionnaire, the proportion reporting breast implants was more than twice the estimated national

frequency of these implants, which suggests selection bias. Moreover, the evidence for disease in these women consists of unverified self-reports. Thus, this study probably overstated the risk of connective tissue disease associated with silicone breast implants. If its results are valid, they rule out large increases of risk. Excluding this report, a very substantial body of evidence, consisting of a number of independent investigations and other analyses, does not provide evidence for an association of silicone gel- or saline-filled breast implants with defined connective tissue disease. Although others (e.g., Hulka, 1998) including authors of reports themselves, have pointed out problems with individual epidemiological studies, the consistency of results among many reports is impressive. As was the case with antinuclear antibodies (ANAs), data and results were rarely segregated by gel- or saline-filled implants, so no conclusions regarding associations with connective tissue disease by breast implant type are possible [see, however, Sánchez-Guerrero et al. (1995) data suggesting a lower relative risk with gel implants]. The committee concludes that there is insufficient evidence to support an association of silicone breast implants with defined connective tissue disease. That is, given the repeated finding of no elevated risk, the evidence supports the conclusion that there is no association, and therefore no justification for the use of resources in further epidemiological exploration of such an association.”

Since the release of the IOM report in 1999, a follow-up to the Hennekens et al. (1996) Women's Health Cohort Study has been published, along with an expansion of the Friis et al. (1997) study and an additional meta-analysis. The conclusions of the IOM expert panel regarding defined connective tissue diseases, as stated in their report, remain fully relevant, and in fact strengthened, with the addition of new information that has become available. The results from these additional epidemiological reports, along with the 17 cited by the IOM expert panel are presented in Table 9.1.

Table 9.1. Epidemiologic Findings Regarding Silicone Breast Implants and Defined Connective Tissue or Rheumatic Disease

REFERENCE	DISEASE(S)	RELATIVE RISK / ODDS RATIO
Cohort Studies		
Edworthy et al. (1998)	CTD	1.0 (95% CI, 0.45-2.22)
Friis et al. (1997)	CTD	1.1 (95% CI, 0.2-3.4) cosmetic 1.3 (95% CI, 0.5-3.6) reconstruction
Gabriel et al. (1994)	CTD	1.10 (95% CI, 0.37-3.23)
Giltay et al. (1994)	CTD	0.44 (no CI) ^a
Hennekens et al. (1996) ^b	CTD	1.17 (95% CI, 0.62-1.90) ^b
Kjoller et al. (2001)	CTD	1.1 (95% CI, 0.5-2.1)
Nyren et al. (1998)	CTD	1.10 (95% CI, 0.8-1.6)
Park et al. (1998)	RA	0.42 (95% CI, 0.1-15.63)
Sanchez-Guerrero et al. (1995)	CTD	0.6 (95% CI, 0.2-2.01)
Schusterman et al. (1993)	CTD (rheumatic disease)	1.08 (95% CI, 0.01-17.2)
Weisman et al. (1988)	Rheumatic symptoms	ND
Wells et al. (1994)	Arthritis	1.16 (95% CI, 0.15-9.04)
Case-Control Studies		
Burns et al. (1996)	SSc	0.95 (95% CI, 0.21-4.36)
Englert et al. (1996)	SSc	1.0 (95% CI, 0.16-6.16)
Hochberg et al. (1996)	SSc	1.07 (95% CI, 0.53-2.13)
Strom et al. (1994)	SLE	4.5 (90% CI, 0.2-27.3)
Williams et al. (1997)	CTD	0.74 (80% CI, 0.2-2.02) ^c
Cross-Sectional Study		
Goldman et al. (1995)	CTD	0.52 (95% CI, 0.27-0.92)

Adapted from IOM (2000). CTD = all connective tissue disease; SSc = systemic sclerosis; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; CI = Confidence Interval; ND = not done;

^a calculated by Perkins et al. (1995);

^b as adjusted by Karlson et al. 1999 based on validation study of self-reported CTD for Hennekens study population (see discussion below);

^c combined undifferentiated and defined CTD

The most recent meta-analysis, by Janowsky et al. (2000), coauthored by the lead epidemiologist of the National Science Panel, was published in the *New England Journal of Medicine*, and presented results from a new analysis of the relationship between silicone breast implants and the risk of connective tissue diseases. The new analysis considered eight new studies published since 1996 that were not included in previous meta-analyses. Janowsky and coworkers identified a total of nine cohort studies, nine case-control studies and two cross-sectional studies that met prestated inclusion criteria and were included in

their analysis. The summary adjusted relative risks reported by Janowsky are summarized in the table below. Based on these results, the study authors concluded that there was “no evidence of an association between breast implants in general, or silicone-gel-breast implants specifically, and any of the individual connective-tissue diseases, all definite connective-tissue diseases combined, or other autoimmune or rheumatic conditions.”

Table 9.2 Meta-Analyses of Silicone Breast Implants and CTD (Janowsky et al. 2000)

Connective Tissue Disease	Summary Adjusted Relative Risk	95% C.I.
rheumatoid arthritis	1.04	0.72-1.51
systemic lupus erythematosus	0.65	0.35-1.23
scleroderma or systemic sclerosis	1.01	0.59-1.73
Sjogren's syndrome	1.42	0.65-3.11
all definite CTDs combined	0.80	0.62-1.04
other autoimmune or rheumatic conditions	0.96	0.74-1.25

A follow-up study by Karlson et al. (1999) evaluated the validity of self-reports of connective tissue disease (CTD) among a subset of the Women's Health Cohort Study participants (Hennekens et al. 1996) that included 220 women with breast implants who self-reported CTD and a random sample of 879 women without breast implants. By comparing self-reports of CTD with medical records, the confirmation rate for women with breast implants was 22.7%, as compared with a confirmation rate of 24.0% for women without breast implants. Based on these findings, the authors adjusted their previously reported relative risk for connective tissue disease associated with breast implants, which was 1.24 (95% CI, 1.08-1.41), to an adjusted relative risk of 1.17 (95% CI, 0.62-1.90). The significance of this revised relative risk is that now, without exception, all of the well-conducted epidemiological studies identified in the original IOM report show no association between silicone breast implants and connective tissue diseases.

The population studied by Friis et al. (1997), which included only hospital cases of CTD, was expanded in a Danish study reported by Kjoller et al. (2001). In this study, the cohorts were expanded to include women who received either cosmetic breast implants or other plastic surgery procedures at private clinics in Denmark. The addition of these patients to the previous hospital-patient cohorts resulted in a total of 2,761 women with breast implants (average follow-up of 8.7 years) and 8,807 control subjects. No significant excess of definite CTD was observed in either the women with breast implants (8.8 cases expected, 10 observed; O/E ratio = 1.1, 95% CI, 0.5-2.1), or in the control cohort (35.9 cases expected, 42 observed; O/E ratio = 1.2, 95% CI, 0.8-1.6). A range of other and ill-defined rheumatic conditions were also evaluated. The only significant excess, which was observed in both

breast implant patients and controls, was in “unspecified rheumatism” (including fibromyalgia and myalgia), with 45.2 cases expected and 85 cases observed in the implant cohort (O/E ratio 1.9, 95% CI 1.5-2.3), and 152.0 cases expected and 238 cases observed in the controls (O/E ratio 1.6, 95% CI 1.4-1.8). The significant excess of unspecified rheumatism was not seen, however, in a direct comparison of implant patients versus controls (O/E ratio 1.2, 95% CI 0.9-1.5). The study authors previously concluded that the excess of muscular rheumatism (termed “unspecified rheumatism” in this study) was “related to breast surgery per se rather than to any systemic effect of silicone breast implants, owing to the fact that similar excesses were observed among women with breast implants and breast reduction.” This study significantly strengthens the findings of Friis et al. (1997) in demonstrating no increase in defined CTD among women with cosmetic breast implants.

9.2 Fibromyalgia

In their review of epidemiological investigations of connective tissue and rheumatic disease and breast implants, the IOM expert panel first addressed defined disease, and then a range of other atypical connective tissue and rheumatic disease signs and symptoms. Among the atypical connective tissue and rheumatic disease potentially associated with silicone breast implants, fibromyalgia has received considerable focus in recent years, and is discussed separately in this section.

As described in a previous section on the potential health consequences of device rupture, Brown et al. (2001, 2002) reported a higher rate of fibromyalgia among women with breast implant rupture and detectable extracapsular silicone (as assessed by MRI). Of 73 women with ruptured breast implants and extracapsular silicone, 18 (24.7%) self-reported fibrositis or fibromyalgia, compared with 29 of 271 women (10.7%) with breast implants not exhibiting extracapsular silicone (odds ratio 2.7, 95% CI, 1.3-10.5). Unfortunately, it was not possible within that study to ascertain whether the women had fibromyalgia prior to receiving breast implants. This may be a significant limitation, given the findings of other research in this area. Wolfe and Anderson (1999) reported a similar, but not statistically significant, increase in prevalence of fibromyalgia among women with silicone breast implants in comparison to various control groups (1228 control subjects overall, 464 patients with rheumatoid arthritis, 261 with osteoarthritis and 503 randomly selected community controls), when the time of occurrence was not factored in. The odds ratio for silicone gel-filled breast implants versus the control subjects overall was 2.45 (95% CI, 0.86-7.03). Importantly, though, when fibromyalgia that occurred prior to breast implantation was excluded, there was no significant difference in fibromyalgia occurrence (odds ratio 1.22, 95% CI, 0.30-4.89). A possible explanation of these results is provided by a third study by Lai et al. (2000) who investigated fibromyalgia, hypermobility and breast implants. Their

evaluation was based on review of medical records from 2500 women seen for the first time in a rheumatology practice in Atlanta, GA (1986-1992). Significant associations were found between hypermobility and fibromyalgia (adjusted odds ratio 2.20, 95% C.I. 1.73-2.80) as well as between hypermobility and breast implantation (adjusted odds ratio 1.80, 95% C.I. 1.19-2.69). No association was observed, however, between breast implantation and subsequent fibromyalgia (adjusted odds ratio 0.74, 95% C.I. 0.42, 1.32). The association between hypermobility and breast implantation would indicate that women with hypermobility are more likely to undergo breast augmentation than those without hypermobility. Given the widely recognized association between hypermobility and fibromyalgia, these findings may explain why some investigators have observed a higher incidence of fibromyalgia among breast implant patients.

Englert et al. (2001) conducted a population-based retrospective cohort study of Australian women that included 458 patients who received cosmetic breast implants and 687 patients who received other non-silicone related plastic surgery between 1979-1983 with a minimum 15 year follow-up. No difference in the prevalence of fibromyalgia was observed among women with cosmetic breast implants as compared with controls (relative risk = 0.38, 95% CI, 0.04-3.67).

9.3 Other Atypical Connective Tissue and Rheumatic Disease Signs and Symptoms

Based on their review of a large body of evidence regarding a potential association of other atypical connective tissue and rheumatic disease signs and symptoms with silicone breast implants, the IOM expert panel concluded that:

“The committee finds no convincing evidence for atypical connective tissue or rheumatic disease or a novel constellation of signs and symptoms in women with silicone breast implants. Case reports, of which there are many, do not provide evidence, although they may suggest hypotheses that can be tested, as has been possible for defined CTD. A defined and testable disease is a precondition for any type of study. Given the frequency of local complications in women with silicone breast implants and the frequency and subjective nature of the symptoms that have been proposed by some to characterize a hypothetical novel disease, a large group of women would meet the criteria for this disease if such a definition were accepted. The diagnosis would ultimately depend on conditions such as fatigue, cognitive dysfunction, arthralgia, and the like which are nonspecific and common. A new disease would then be created by the discovery of an implant and its common local complications in women who had signs and symptoms prevalent in the general population or in fibromyalgia, chronic fatigue syndrome, multiple chemical

sensitivities, or other less well-defined conditions. As noted earlier, silicone toxicity is conceptually more straightforward, although it is not supported by the toxicologic data reviewed in Chapter 4.

The evidence for an atypical disease or a novel syndrome is insufficient or flawed. It consists of selected case series, few of which describe a consistent and reproducible syndrome. The controlled epidemiological studies cited provide stronger, contrary evidence. In view of the paucity, weakness, and conflicting nature of the evidence, the committee concludes that there is no rigorous, convincing scientific support for atypical connective tissue or any new disease in women that is associated with silicone breast implants. In fact, epidemiological evidence suggests there is no novel syndrome.”

The conclusions of the IOM expert panel regarding atypical signs or symptoms of connective tissue or rheumatic disease, as stated in their report, remain fully relevant, and in fact strengthened, with the addition of further information from recently published epidemiological studies.

Fryzek et al. (2001) performed a retrospective cohort study by comparing individual symptoms and the constellation of symptoms in 2500 women who underwent breast augmentation surgery, with 3500 women who underwent breast reduction surgery, frequency matched to the implant subjects for age and calendar year of surgery. Although women with breast implants reported a multitude of symptoms more often than women with breast reduction surgery, there was no pattern of increasing relative risk with increasing time from implant surgery, and no increase in relative risk associated with an increase in implant size. Fryzek and colleagues concluded that the lack of specificity and absence of dose-response relationships suggest that the excess of reported symptoms was not causally related to the breast implants.

Jensen et al. (2001) investigated whether women with silicone breast implants develop a unique rheumatic symptomatology. Six groups of women were identified, and underwent a thorough clinical examination, blood tests, and a personal interview. Jensen et al. found no evidence of a rheumatic symptomatology unique to women with silicone breast implants. No significant differences in the frequencies of rheumatic diseases were observed among three groups of women without a prior hospital diagnosis of muscular rheumatism who had undergone surgery for: (a) silicone breast implant; (b) breast reduction; or (c) no breast surgery. In addition, women with a prior diagnosis of muscular rheumatism, but no prior breast surgery, had a significantly higher prevalence of soft-tissue rheumatism than those with a prior diagnosis of muscular rheumatism and breast implant or breast reduction

surgery. As expected, women with earlier rheumatism had significantly increased frequencies of rheumatic conditions than did those without. The authors emphasized the importance of determining prior rheumatic disease when evaluating rheumatic manifestations in women with silicone breast implants.

Berner et al. (2002) used a matched-pair analysis of 96 women with breast cancer, where 32 had silicone implants, and 64 had no implants. Athralgias and myalgias were not significantly more frequent in women with breast implants, and the Berner et al. conclude that many of the symptoms examined present in middle-aged women regardless of silicone implants.

Contant et al. (2002) conducted a prospective cohort study of 57 women undergoing mastectomy followed by immediate breast reconstruction with silicone breast implants. Contant et al. (2002) detected evidence of intracapsular rupture of the implant in three prostheses, but none of these women developed CTD-related complaints.

Most recently, Holmich et al. (2003) analyzed 238 women with silicone breast implants for implant rupture by MRI and adverse health effects. There were no differences in the occurrence of self-reported diseases or symptoms, or in the presence of autoantibodies between women with intact implants and women with ruptured implants, including extracapsular rupture. Holmich and colleagues concluded that there was no association between silicone implant rupture and specific diseases or symptoms related to CTD or other rheumatic conditions.

10. Cancer and Silicone Breast Implants

10.1 Introduction

Evidence continues to accumulate from a number of large well-controlled epidemiological studies that silicone gel breast implants are not associated with any elevated risk of breast cancer. Indeed, some of these studies have suggested that women with breast implants may actually be at lower risk of developing breast cancer. The IOM expert panel reviewed the body of scientific evidence on the overall issue of cancer and silicone breast implants and concluded in their report (Chapter 9) that:

“There is a consistent, substantial, long-term base of scientific evidence bearing on the experimental carcinogenicity and clinical breast or other cancer experience with silicone and silicone breast implants. Based on its review of this evidence, the committee concludes that the available evidence does not support an association of silicone or silicone breast implants with experimental carcinogenesis (other than rodent solid-state carcinogenesis), primary or recurrent breast cancer, breast sarcoma or other solid tumors, lymphoma, or myeloma. If anything, evidence (though limited) suggests a lower risk of breast cancer in women with silicone breast implants.”

Subsequent to the release of the IOM report, several additional large epidemiological studies on cancer have been published that report confirmatory data.

10.2 Breast Cancer

The recently published epidemiology studies further demonstrate that silicone breast implants do not increase the risk of breast cancer. Findings of these studies, reviewed in greater detail below, along with those discussed in the IOM report are presented in Table 10.1.

Table 10.1 Epidemiological Studies of Breast Cancer and Silicone Breast Implants

REFERENCE	# PATIENTS (w/ cancer or implants)	SIR / OR (adjusted)
Berkel et al. (1992)	11,676 (implant)	0.48 (no CI)
Brinton et al., (1996)	2,174 (cancer)	0.6 (95% CI, 0.4-1.0)
Brinton et al. (2000)	13,488 (implant)	0.9 (95% CI, 0.8-1.1)
Bryant and Brasher (1995)	10,835 (implant)	0.76 (95% CI, 0.6-1.0)
Deapen et al. (1997)	3,182 (implant)	0.63 (95% CI, 0.4-0.9)
Friis et al. (1997)	1,135 (implant)	1.0 (95% CI, 0.4-2.0)
Glasser et al. (1989)	4,742 (cancer)	1.0 (95% CI, 0.3-3.3)
Kern et al., 1997	680 (implant)	0.67 (95% CI, .02-2.17)
McLaughlin et al. (1998)	3,473 (implant)	0.7 (95% CI, 0.4-1.1)
Mellemkjaer et al. (2000)	2,740 (implant)	0.9 (95% CI, 0.5-1.5)
Park et al. (1998)	186 (implant)	No cancers observed
Pukkula et al. (2002)	2,171 (implant)	0.5 (95% CI, 0.2-1.0)

CI = confidence interval; OR = odds ratio; SIR = standardized incidence ratio

Brinton et al. (2000, 2001a,b) reported results from a large retrospective cohort of 13,488 women (mean follow-up = 12.9 years) who received cosmetic breast implantation at 18 plastic surgery practices and a group of 3936 women from the same practices who experienced other types of plastic surgery treatment. Comparison of the 136 observed breast cancer cases among cosmetic breast implantation patients with general U.S. population rates from the S.E.E.R. database (152.2 cases expected) revealed a standardized incidence ratio of 0.9 (95% CI 0.8-1.1). Comparison with the breast cancer incidence among other plastic surgery patients revealed a relative risk for cosmetic breast implant patients of 0.8 (95% CI 0.6-1.1). Both comparisons indicate no increase in breast cancer risk for cosmetic breast implant patients (Brinton et al. 2000).

A study by Mellemkjaer et al. (2000) expanded and updated the findings of the Friis et al. (1997) study reviewed by IOM. This report provided an additional two years follow-up (mean = 10.3 years) on the cosmetic breast implantation patients at public hospitals (1,114 patients), and also examined cancer incidence among 1,653 cosmetic breast implantation patients from private clinics (mean follow-up 6.0 years). There was no significant increase in the standardized incidence ratio for breast cancer among the private clinic cohort (SIR = 1.1, 95% CI, 0.5-2.2), the public hospital cohort (SIR = 0.9, 95% CI, 0.4-1.7) or the combined cohort (SIR = 0.9, 95% CI 0.5-1.5).

A further study of breast cancer incidence among cosmetic breast implant patients was reported by Pukkala et al. (2002). In this cohort study, a total of 2,171 Finnish women with

cosmetic breast implants were followed for up to 30 years (mean follow-up = 8.3 yr). A total of 7 cases of breast cancer were observed compared to an expected 13.9 cases (SIR 0.5, 95% CI 0.2-1.0). This study provided no evidence for increased risk of breast cancer.

10.3 Cancer at Other Sites

The incidence of cancer at other sites among the cohort detailed by Brinton et al. (2000) were reported by Brinton et al. (2001). Comparison of the 359 total cancer cases observed among cosmetic breast implantation patients with general U.S. population rates from the S.E.E.R. database (295.95 cases expected) revealed a standardized incidence ratio of 1.21 (95% CI 1.1-1.4). However, a comparison of overall cancer rate with other plastic surgery patients revealed a relative risk for cosmetic breast implant patients of 1.00 (95% CI 0.8-1.2), indicating no overall increased risk. In the comparison with the general U.S. population rates, significantly increased incidences of cervical (SIR 3.18) and vulvar (SIR 2.51) cancers were observed, consistent with previous findings of McLaughlin et al. (1998) and Deapen and Brody (1992), and considered attributable to documented reproductive and lifestyle factors, rather than silicone exposure. Statistically significant increases, not seen in other epidemiology studies of cosmetic breast implant patients, were also observed in comparisons with U.S. population rates for brain cancer (SIR 2.16) and leukemia (SIR 2.19). The observed increase in brain cancer, but not leukemia was also reported in a mortality analysis of the same cohort (Brinton et al. 2001). Given the histologic diversity of the observed leukemias, the study authors suggested that the excess "may be a chance finding." A statistically significant excess of lung cancer (relative risk = 2.23) was observed in comparison with the other plastic surgery patients, consistent with earlier findings of Deapen and Brody (1992), recent findings by Koot et al. (2003), a mortality analysis of the same cohort (Brinton et al. 2001) and a widely recognized higher incidence of smoking among cosmetic breast implant patients. In interpreting the Brinton et al. (2001) findings in light of the findings of other published cancer epidemiology studies, it is important to note, as the IOM committee did later in this chapter, that "occasional increases in a particular cancer are not consistent and are likely due to chance or confounding factors."

The study by Mellekjaer et al. (2000) above also looked at cancers at other sites. For private clinic patients, an elevated standardized incidence ratio of 1.65 (SIR = 1.17-2.27) for all cancers was observed, while for public hospital patients no such excess for all cancers was observed (SIR = 1.10, 95% CI 0.76-1.52). For the private clinic patients, the excess cancers were distributed amongst all major cancer sites, though the excess did not exceed two cases for any site other than non-melanoma skin cancer. Excluding non-melanoma skin cancer, the standardized incidence ratio for all cancers among the combined implant cohort was 1.31 (95% CI 0.88-1.52). The study authors concluded that "the overall findings of

these 2 implant cohorts and results from other investigations suggest that cancer risk is probably not increased among women receiving cosmetic breast implants.”

Pukkala et al. (2002) reported that for cancer overall among the cosmetic breast implant cohort described above, there were 30 cancers observed compared to an expected 33.7 cases (SIR 0.9, 95% CI 0.6-1.3). With respect to brain cancer, 2 cases were observed compared to an expected 2.0 cases (SIR 1.0, 95% CI 0.1-3.5). This study provided no evidence for increased risk of overall cancer or brain cancer.

10.4 Conclusions

An extensive review by Herdman and Fahey (2001) of silicone breast implants and cancer aptly summarizes the available data:

“We concluded from our review that, overall, medical and surgical oncologists have no reason for concern about possible relationships of silicone breast implants with any experimental or clinical malignancies. An impressive body of evidence has failed to find a convincing association of these implants with cancer in women.”

11. Neurological Disease and Silicone Breast Implants

Several well-designed epidemiological investigations have been conducted of neurological disease among women with silicone breast implants. The IOM expert panel reviewed three of these studies, as well as a host of case series and reports. Based on their review of this information the IOM concluded in their report (Chapter 10) that:

“The available studies suggesting neurologic disease, with the exception of obvious local problems due to the physical presence of silicone gel which can compress nerves following implant rupture and migration of the gel, have defects that limit any conclusions to be drawn from them. Furthermore, basic toxicological and animal experimental studies do not find pathology that would support a causation of human neurologic disease by silicone breast implants. Two epidemiological studies suggest that there is no elevated relative risk for neurological disease in large cohorts of women with silicone breast implants. The committee finds that the evidence for a general neurologic disease or syndrome caused by, or associated with, silicone breast implants is insufficient or flawed.”

These conclusions of the IOM report have been further strengthened by the full publication in 2001 of an updated and expanded Danish study by Winther et al. (2001) that found no causal association between silicone breast implants and neurological disease. Those results were consistent with the previously published large epidemiological study from Sweden. In this Danish study, neurologic disorders were examined in a new cohort of 1,653 women with cosmetic breast implants from private clinics (their previous study had examined women who received cosmetic breast implants in public hospitals) in comparison with a cohort of 1,736 who underwent other cosmetic surgery at the same clinics. Data from these two cohorts were compared with the Danish National Registry of Patients. Overall, the relative risk among the private clinic cosmetic breast implant cohort for any of the neurologic diseases was 0.8 (95% CI, 0.3-1.7), while for the comparison group the relative risk was 1.3 (95% CI, 0.7-2.2). These investigators also conducted an additional analysis in which two additional years of follow-up were added to the public hospital cohorts. The implant cohorts were then combined (2,761 women), and compared with the combined comparison cohorts (8,787 women). No significant excess risk of overall neurologic disease was observed in the combined breast implant cohort (relative risk = 1.3; 95% CI, 0.8-1.9), while a statistically significant relative risk of 1.7 (95% CI, 1.4-2.0) was observed in the combined comparison cohort. This expanded report more than doubled the population of Danish cosmetic breast implant patients studied, and provided sufficient statistical power to exclude excess relative risks of about twofold.

A full-length, peer-reviewed article by Vogel (1999) further detailed work previously reviewed by the IOM expert committee on pathologic findings based on light and electron microscopic evaluation of 47 consecutively received sural nerve and accompanying muscle biopsies from patients with silicone breast implants (most of whom were involved in litigation). Eight of the 47 nerves showed "pathologic changes likely to be symptomatic," primarily consisting of "an axonal neuropathy that was mild in degree." The study author concluded that "the pathologic data from this series do not support claims of an association of SBI with any unique neuropathologic entity."

These additional findings on silicone breast implants and neurological disease provide further confirmation of the original conclusions of the IOM report.

12. Silicone Breast Implants and Pregnancy, Lactation and Children

12.1 Introduction

The IOM expert panel, in their review of the safety of silicone breast implants, evaluated the body of available data on the issues of potential health effects on offspring, including possible interference with lactation, and concluded in their report (Chapter 11) that:

“The committee concludes on the basis of the studies reviewed in this chapter that evidence for an association of maternal silicone breast implants and children's health effects is insufficient or flawed. No biologically plausible causation has been suggested. Convincing evidence is available that silicon concentrations in breast milk are the same in mothers with and without breast implants, and thus there are no data to support transmission of silicone to infants in breast milk of mothers with implants. A modest number of normal mothers are positive for ANAs. Except for rare instances, as noted, evidence that this or similar situations in mothers with silicone breast implants have deleterious effects on children is lacking. Evidence for children's esophageal disease caused by maternal breast implants is insufficient or flawed.”

The conclusions of the IOM expert panel have been further strengthened by the subsequent publication of two additional, large, well-controlled, population-based epidemiological studies (one from Sweden and an expanded one from Denmark) that found no evidence to support an association of maternal silicone breast implants and adverse health outcomes in offspring. These studies are briefly reviewed below, followed by a discussion of potential effects of silicone breast implants on lactation.

12.2 Potential Health Effects on Offspring

Kjoller et al. (2002) updated and expanded their earlier study (Kjoller et al. 1998) that examined the occurrence of esophageal disorders, CTD and congenital malformations in children of mothers with silicone breast implants. In this latest study, the breast implant cohort was expanded to include 1,653 women who received cosmetic breast implants at private clinics in Denmark between 1973 and 1995, and the comparison cohort was expanded to include 1,736 women undergoing other types of plastic surgery procedures (or consultation only). This resulted in a cohort of 2,854 children of women with cosmetic breast implants (2106 born before the surgery, and 748 born afterwards), as well as a comparison cohort of 5,805 children of women undergoing other plastic surgery procedures

(2,596 born before the procedure and 3,209 born afterwards). Among the 748 children born to women with cosmetic breast implants after the surgery, 6 were diagnosed with an esophageal disorder, compared with 4.5 expected (relative risk = 1.3, 95% CI, 0.5-2.9). Among the 2,106 children born prior to cosmetic breast implant surgery, a larger and statistically significant excess of esophageal disorders were diagnosed, with 29 observed versus 14.9 expected (relative risk = 2.0, 95% CI, 1.3-2.8). A statistically significant excess of esophageal disorders was also observed amongst the children of the comparison cohort, both for those born after the comparison procedure (relative risk = 1.6, 95% CI, 1.1-2.3) and for those born prior (relative risk = 2.1, 95% CI, 1.5-2.8). The study also evaluated congenital malformations, for which there was a small but statistically significant overall excess among children born to women with cosmetic breast implants before, but not after surgery. This updated and expanded study addressed limitations of the earlier study by adding the population of private clinic patients, lengthening the follow-up period for the offspring, and incorporating data from outpatient visits. The average follow-up period for children born to women with cosmetic breast implants was 12.4 years for those born prior to surgery, and 6.0 years for those born subsequently. The results from the extended follow-up included in this study led the investigators to note that the outcomes were generally “manifest early in childhood and that longer follow-up is unlikely to change the findings appreciably.” Such findings provide strong evidence that there is no causal association between esophageal disorders and silicone breast implants.

Signorello et al. (2001) conducted a similar epidemiological study in Sweden to assess whether children born to women with cosmetic breast implants experience an increased risk of rheumatic disease or esophageal disorders. This retrospective cohort study included 5,874 children born to 2,910 women with cosmetic breast implants and 36,114 children born to 19,203 women who underwent breast reduction surgery, and used data from four national registers in Sweden. Compared to children of women who had breast reduction surgery, children of women with cosmetic breast implants did not show increased risk of rheumatic disease (relative risk [RR] = 1.1; 95% confidence interval [95% CI], 0.2-5.3), esophageal disorders (RR = 1.0; 95% CI, 0.7-1.6), cancer (RR = 0.3; 95% CI, 0.0-2.5), congenital malformations in total (RR = 1.0; 95% CI, 0.6-1.5), or specifically involving the digestive organs (RR = 0.5; 95% CI, 0.2-1.3) or perinatal death (RR = 0.9; 95% CI, 0.5-1.8). Furthermore, there were no significant differences in the incidence of these health outcomes for children born after versus before cosmetic implant surgery. These investigators concluded that “this study provides no evidence that certain hypothesized health outcomes are more likely among the children of women with cosmetic breast implants.”

12.3 Lactation

The IOM expert panel report detailed three studies that focused on augmentation mammoplasty and effects on lactation sufficiency (Neifert et al. 1990, Hurst 1996, Strom 1997). Each of these studies identified periareolar incisions as a significant risk factor for lactation insufficiency. The study by Neifert et al. (1990) included only five breast augmentation patients (Neifert et al. 1990), but identified periareolar incisions among breast surgery patients as five times more likely to be associated with lactation insufficiency. Similarly, in the survey study of Strom (1997) of women with saline-filled breast implants, seven out of eight women with lactation insufficiency had periareolar incisions. The third study, by Hurst (1996) reported that all eleven patients with periareolar incisions experienced lactation insufficiency. Such findings are not surprising, given that the transglandular trajectory typically associated with this surgical approach would be expected to disrupt ductal tissue. A modification of this approach to reduce the likelihood of subsequent lactation difficulties has been suggested by Brody (1998) who recommends that "the periareolar approach for augmentation should be directed subcutaneously around the lower pole of the breast to gain access to the retromammary space rather than risk disturbing the ductal system via a through-the-breast approach." Bostwick (2000), in a detailed review of augmentation mammoplasty techniques and results, noted that "The potential for lactation is not impaired by breast implants, especially when incisions within the breast parenchyma are avoided and when the implants are positioned behind the breasts and usually also behind the pectoral muscle layer." The available information, though limited, consistently indicates that surgical procedure, rather than the breast implants themselves, may represent a significant risk factor for lactation insufficiency.

With respect to the frequency of lactation insufficiency, the most often cited source is Hurst (1996) who reported insufficiency in 64 percent (27/42) of women with breast implants. Potential confounders that were not considered in the Hurst study were identified in a recently published community-based study of lactation by Dewey et al. (2003), who identified a multitude of risk factors for "suboptimal infant breast feeding behavior." Significant factors not controlled for in the Hurst (1996) study included: flat or inverted nipples, infant formula feedings, pacifier use, duration of labor, labor medications, and elevated maternal BMI. Failure to control for such factors, particularly in a relatively small study, limits the conclusions that should be drawn from this retrospective study. Furthermore, it should be noted that women receiving assistance from lactation consultants, as was the case in the Hurst study, generally represent a highly selected sample of those mothers having difficulty with breastfeeding. A substantial (and perhaps more representative) portion of women receives breastfeeding support, if needed, from other sources, e.g., La Leche League International mother-to-mother support groups. In addition, a

majority of the infants in the Hurst (1996) study were either ill or premature, requiring a 2-week or greater delay in the initiation of breastfeeding. As a result, the appropriateness of extrapolating the Hurst study results to the overall population of women with breast implants is further limited.

In a recent survey of more than 2000 women reported by Young et al. (2003), 93% of breast augmentation patients were noted to have had all their children prior to undergoing the procedure, so that nursing was not an issue. The survey also indicated that "of the small percentage who had children and nursed them after augmentation, there was essentially no difference in the rate of reported problems."

12.4 Conclusions

Further well-conducted epidemiological investigations of children of women with silicone breast implants provide further evidence of no association between breast implants and various adverse health outcomes in children.

Currently available information from the published literature identifies the periareolar surgical approach as a potentially significant risk factor for lactation insufficiency, but does not adequately characterize the incidence rate of this complication of breast surgery, which may only be an issue for a subset of augmentation mammoplasty patients.

13. Silicone Breast Implants and Breast Imaging

13.1 Introduction

The IOM expert panel reviewed a large body of studies addressing the issue of breast imaging for both cancer detection and implant integrity assessment. Based on their review of this information, the IOM panel in their report (Chapter 12) concluded that:

“The committee finds magnetic resonance imaging to be the most accurate imaging modality for the detection of intra- and extracapsular rupture. Mammography is of limited usefulness in detecting implant rupture in women with silicone implants. There is scant anecdotal evidence of rupture during mammography, and there are no data to support limiting screening or diagnostic mammography which would otherwise be indicated because of this concern. Implants placed in a subpectoral position do not interfere with mammography to the same extent as subglandular implants. Data on whether cancer detection is impaired by implants do not allow definite conclusions, although it is clear that implants do interfere with screening mammography by obscuring a variable part of breast tissue, distorting breast architecture, and especially in the presence of firm contractures, making a proper examination with proper compression of the breast more difficult and occasionally impossible.”

13.2 Imaging of Implant Rupture

A considerable number of studies on imaging of implant rupture, primarily involving use of MRI, have been published in the last several years (e.g., Beekman et al. 1999, Belli et al. 2002, Berg et al. 2002, Caskey et al. 1999, Cher et al. 2001, Goscin et al. 2001, Herborn et al. 2002, Ikeda et al. 1999, Lehman et al. 2000, Middleton et al. 2000, Murphy et al. 2002, and Peters et al. 1999). These studies, including two meta-analyses, confirm the superiority of MRI for rupture detection, consistent with the findings of the IOM expert panel report. The most recent meta-analysis, published by Cher et al. (2001) included 18 studies (mostly conducted by academic institutions) involving more than 1,000 women and 2,000 implants, and reported a summary sensitivity for MRI detection of rupture of 78% (95% CI, 71-83) and a summary specificity of 91% (95% CI, 86-94). More recently, Belli et al. (2002) concluded that “MRI plays a primary role as the gold standard diagnostic procedure in patients with breast implants for the diagnosis of ruptures (its sensitivity in the international literature varies from 90% to 95% and its specificity varies from 95% to 100%) ...”

13.3 Detection of Breast Cancer

Based on the information available at the time of their review, the IOM expert panel concluded that “data on whether cancer detection is impaired by implants do not allow definite conclusions.” Subsequent to completion of the IOM expert panel report, however, several large population-based epidemiological studies have been published which provide strong and consistent evidence that breast implants do not significantly delay the detection of breast cancer, nor adversely affect cancer survival.

Brinton et al. (2000) conducted a large retrospective cohort study of 13,488 women with cosmetic implants (average length of follow-up = 12.9 years) and 3,936 women receiving other types of plastic surgery from the same surgeons (average follow-up = 11.6 years). The study found no statistically significant difference in either stage of tumors at detection or in breast cancer mortality.

Similar findings were reported by Deapen et al. (2000) who reported on breast cancer stage at diagnosis and 5-year survival rates for a cohort of 3,182 breast implant patients from Los Angeles County, California with an average follow-up of 18.7 years. The study found that “the distribution of stage at diagnosis for cosmetic breast implant patients who subsequently developed breast cancer was virtually identical to that of all breast cancer patients in Los Angeles County who were of the same age and race, and were diagnosed during the same time period,” and that “the 5-year survival rate of the 37 patients did not differ from that which would be expected based on rates established by the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.”

A third epidemiological study by Pukkala et al. (2002) examined a cohort of 2,171 Finnish women with cosmetic breast implants (average length of follow-up = 8 years) and reported that “stage at breast cancer diagnosis did not differ from that expected.”

The above population-based epidemiology studies provide strong evidence that, compared to the general population, women with breast implants are not at an increased risk of delayed detection of breast cancer, nor do they suffer a poorer prognosis when breast cancer does occur.

13.4 Calcification and Breast Imaging

Calcification of a biomaterial occurs when calcium salts are deposited in the tissue capsule surrounding the implanted device. Calcification occurs in association with a wide variety of implanted prostheses, including breast implants, heart valves, vascular grafts, and soft

contact lenses, as well as in the mature breast tissue of women that have not undergone breast surgery.

Calcification of the fibrous capsule that may occur following implantation of breast prostheses is generally not of clinical significance, although it may exacerbate symptoms of capsular contracture. Concern has been raised, however, that calcification may interfere with tumor detection, because microcalcifications are considered a hallmark of malignant breast disease. Although clinicians have recommended pre- and post-surgical mammograms for augmentation patients to assist in distinguishing post-operative findings from calcification associated with malignancy, benign calcification resulting from surgery is generally considered distinguishable from malignant-type calcification. Further, no published reports were identified that document any actual occurrences of missed or delayed diagnoses attributable to capsular calcification.

Calcification is not a phenomenon unique to breast implants. It occurs in 11 to 53 percent of women who underwent breast reduction procedures (Abboud et al. 1995, Mitnick et al. 1990, Brown et al. 1987). In the breasts of women who have not undergone any breast surgery, the prevalence of benign calcifications increases progressively with age from 8 percent in women 25 to 29 years old up to 86 percent in women 75 to 79 years old (Stomper et al. 1996).

13.5 Potential Implant Rupture During Mammography

The IOM expert panel found that loss of implant integrity after mammography was a rare complication, as evidenced by scant anecdotal case reports in the medical literature. The panel noted that there was no data to support limiting screening or diagnostic mammography which would otherwise be indicated because of the concerns of rupture during mammography. Experience gained regarding mammography of augmented patients has led to improved techniques for imaging such patients such as displacement methods, improved compressive methods and use of special views during mammography. The panel concluded that a concern about implant rupture should definitely not discourage properly performed mammography.

13.6 Routine Mammogram Screening of Breast Implant Patients

While the IOM expert panel did not address whether augmented patients avoided routine mammogram screening for potential breast lesions, several recent reports in the medical literature have addressed this concern. Brinton et al. (2000) examined 13,488 patients from 18 plastic surgery practices in six geographic areas and observed that, with respect to

mammography, implant patients were significantly more likely to have had a mammogram (odds ratio = 2.1, 95% CI 1.8-2.5), a difference that persisted even when mammograms performed two years or more prior to plastic surgery were excluded. Additionally, breast implant patients were more likely to be vigilant regarding regular self breast exams (odds ratio = 1.2, 95% CI 1.0 – 1.4), thus supporting earlier studies which observed that women with breast augmentations performed breast self-examinations more often than nonaugmented women (Strom et al. 1997).

14. Silicone Breast Implants and Suicide

Subsequent to completion of the IOM expert panel report, three recently published studies of mortality among women who underwent augmentation mammoplasty with silicone breast implants have reported higher than expected rates of suicide (Pukkala et al. 2003, Koot et al. 2003, Brinton et al. 2002). Further details of these and other related studies are provided below.

A more recent study by an internationally recognized expert in the field of suicide (Joiner 2003), however, actually calculated somewhat higher expected suicide rates than those observed in these three mortality studies based upon demographic and other pre-surgery characteristics of breast augmentation patients. These characteristics, which have been documented to be associated with elevated rates of suicide, were summarized by Joiner (2003):

“The prototypical breast augmentation patient is white and aged 25 to 44 years. Although most breast augmentation patients are behaviorally and interpersonally stable, it appears that, before surgery, relative differences exist between these women and others with regard to divorce, heavy alcohol and cigarette use, and the symptoms of mood, eating, and appearance-related disorders. They may have more impulsive-personality features than other women. It is likely that other differences exist between breast augmentation patients and others, but the ones summarized above have received the most empirical attention.”

Thus, these data would strongly suggest that the recent reports of elevated suicide rates among breast augmentation patients are both to be expected and attributable to relatively small differences in demographic and other pre-surgery characteristics between these patients and the general population.

Further evidence that preexisting factors contribute to the observed elevation in suicide rates is provided by a 1987 study that included an evaluation of pre-operative psychiatric and psychosocial characteristics in a group of Swedish women prior to augmentation mammoplasty (Meyer and Ringberg 1987). In this study, attempted suicide (predating surgery) was reported in 18 percent of patients (7 of 38) preparing to undergo augmentation mammoplasty as compared with 3 percent of control group patients (1 of 33) preparing to undergo surgery for benign skin tumors of the face and neck.

The three aforementioned mortality studies sought to ascertain overall and specific causes of death among augmentation mammoplasty patients. The first study was published in 2002 in

the *Journal of Epidemiology* (Brinton et al. 2002). In this study, epidemiological data was reviewed in a retrospective cohort study of 13,488 women receiving breast implants and 3,936 with other types of plastic surgery. Mortality was compared with general population United States rates for both implant and comparison subjects. Findings indicated in general that patients seeking plastic surgery are healthier than their peers. Implant patients, however, experienced a higher risk of death compared with the general population for brain cancer and suicide. In their discussion, the authors suggested that, given the limited number of deaths from either brain cancer or suicide, the possibility that these were chance findings cannot be ruled out. They further indicated that suicide attempts had been correlated with a number of characteristics including marital difficulties, depression and emotional disorders, all of which have been noted among patients with breast implants. They further speculated that low self-esteem, which is commonly reported among breast implant patients, may have contributed to the higher suicide rates. They summarized their findings by noting that women with breast implants have slightly higher mortality risks than patients with other types of plastic surgery but that both groups have substantially better mortality rates than the general population.

In the second study, published in the *British Medical Journal* in 2003, the potential mortality risk among Swedish women with cosmetic breast implants was assessed (Koot et al. 2003). This was a prospective study assessing total and cause-specific mortality among 3,521 Swedish women who underwent augmentation mammoplasty between 1965 and 1993. This study was undertaken based on the premise that a desire for cosmetic surgery represents underlying psychopathology in some patients and therefore it was hypothesized that death due to suicide may be over represented (Hasan 2000). The results of this study indicated that 58.7 deaths (from all causes) were expected and 85 observed. Fifteen women committed suicide compared with an expected 5.2 deaths. Additional excess deaths were due to malignant disease, primarily lung cancer, and the number of deaths from all of the causes was close to that expected. The deaths due to lung cancer were linked to smoking, as was previously demonstrated in a cohort study (Fryzek et al. 2000). In their comments, the authors suggested that women who undergo cosmetic surgery for augmentation purposes are more likely to commit suicide than women from the general population. Koot and associates believe that the increased risk for death from suicide may reflect greater pre-existing psychopathology in a subset of patients rather than a causal association (Koot et al. 2003, Hasan 2000).

A third mortality study was published in the *British Medical Journal* in 2003 by Pukkala and colleagues. This study examined the potential mortality risk among 2,166 Finnish women with cosmetic breast implants (Pukkala et al. 2003). This was a retrospective cohort registry-linkage study assessing overall and cause-specific mortality among Finnish women who underwent augmentation mammoplasty between 1971 and 2001. The results of this study

indicated that 32.1 deaths (from all causes) were expected and 31 observed. No excess of cancer mortality was observed. Ten women committed suicide compared with an expected 3.1 deaths. The authors suggested that “underlying psychopathology represents a possible explanation for these observed excesses of suicide among women with breast implants.”

Sarwer et al. (2003) evaluated body image concerns of augmentation patients. They have hypothesized that breast augmentation candidates would report greater dissatisfaction with their breasts, greater avoidance of social situations, more frequent appearance-related teasing and lower self-esteem. Results indicated that breast augmentation patients reported a greater investment in their physical appearance. They also reported greater frequency of appearance-related teasing compared to controls and suggested that this may represent a variable that describes women who seek cosmetic surgery. The majority of breast augmentation patients (77 percent) reported a significant life change in the year prior to seeking the operation and 87 percent reported experiencing increased stress, anxiety or depressive symptoms during that time, suggesting that some breast augmentation candidates who may be experiencing psychological distress might benefit from pre-operative assessment and/or evaluation.

Anderson (1998) described characteristics of women seeking augmentation mammoplasty. She reported that preoccupation with breast size does not arise suddenly, but usually dates back to adolescence or after giving birth to a child. There is also a higher incidence of divorce, unhappy marriages, emotional discomfort, diminished feelings of femininity and higher levels of depression than in the general population. Goin and Goin (1981) in a comprehensive text regarding psychological issues in plastic surgery, reported that some augmentation mammoplasty patients have experienced depressive episodes and they identified three concerns. First, they felt that an unrecognized depression was often masked by the patient's fixation regarding her breasts. Second, they thought that these patients tended to think obsessively about their physical appearance and to view their self-worth in terms of the physical body. Third, they described these individuals as charming, attractive, outgoing, and socially secure, but noted that this demeanor may act as a protective shell to guard them against their underlying lack of self-esteem.

The relationship between depression and suicidal ideation among individuals with low self-esteem and body image concerns has been repeatedly demonstrated in the scientific literature (Dieserud et al. 2001, Van Gasteo et al. 1997). In an effort to explain a model for suicidal ideation and attempts, Dieserud et al. described a two-path model of suicide attempts. The first path began with low self-esteem, loneliness and separation or divorce, which advanced to depression and was mediated by hopelessness and suicidal ideation, which led to the suicide attempt. A second path developed from low self-esteem and a low sense of self-

empathy and advanced to a suicide attempt mediated by negative appraisal of one's own problem-solving capacity and poor interpersonal problem-solving skills (Dieserud et al. 2001). In an effort to predict suicidal intent in depressed patients Van Gasteo et al. (1997) determined that suicidal ideation was significantly related to severity of depression and that items with a strong predictive value for suicidal ideation were hopelessness, depressed mood, feelings of guilt, loss of interest and low self-esteem.

As previously mentioned, many of these factors associated with suicide are present prior to surgery in the augmentation mammoplasty patient, despite the fact that most augmentation mammoplasty patients report significant satisfaction with the outcome (Cash et al. 2002). Indeed, Joiner (2003) suggests that observed suicide rates among these patients might be higher if they had not undergone breast augmentation:

"... given the clear findings that, before surgery, breast augmentation patients are body-dissatisfied (at least with regard to their breasts); and that body dissatisfaction is a risk factor for mood and eating disorders, which, in turn, represent strong risk factors for suicide; and that breast augmentation appears to ameliorate body dissatisfaction for many patients, it stands to reason that the procedure may suppress suicidality by way of the protective effects of increased body image satisfaction against mental disorders that predispose individuals to suicide."

There may, however, be a subset of patients for which the surgery is too little too late. In the letter of response to the study regarding mortality in Swedish women with cosmetic breast implants, Klesmer (2003) described a subset of cosmetic surgery patients who might be at higher risk for suicide. He points out that body dysmorphic disorder, which is a form of somatoform disorder involves a preoccupation with a defect in appearance and the defect is either imagined or present but slight and the patient's concern is excessive. This disorder is estimated to occur in between six and fifteen percent of patients having cosmetic surgery or dermatological procedures. Klesmer (2003) recommends that cosmetic surgeons need to be alert to possible signs of body dysmorphic disorder during evaluation of patients seeking breast augmentation.

Additionally, an exhaustive review of the literature failed to identify any research suggesting that the suicide rate is elevated among breast cancer patients who have undergone reconstructive surgery with or without breast implants. This would suggest that patients who have been diagnosed with cancer, certainly a life-altering event, do not appear to present a risk for a higher rate of suicide, further giving weight to the notion that pre-existing demographic and other characteristics (including psychological issues) in augmentation

mammoplasty patients likely accounts for the observed increase in suicide rates among this population.

Appendix A.
Literature Review Tabulation
of Long-Term Safety Information
for Silicone Gel-Filled Breast Implants

Consistent with the Food and Drug Administration's "Guidance for Saline, Silicone Gel, and Alternative Breast Implants: Final Guidance for Industry and FDA," Mentor is providing as supplemental information a tabulation of certain outcomes that are addressed extensively in the published literature. The issues addressed include:

Table LR-1. Reported Cancer Rates Among Patients with Silicone Breast Implants;

Table LR-2. Reported Rates of Connective Tissue or Rheumatic Disorders (typical and atypical) Among Patients with Silicone Breast Implants;

Table LR-3. Reported Rates of Neurological Disorders Among Patients with Silicone Breast Implants;

Table LR-4. Reported Rates of Offspring Health Outcomes Among Patients with Silicone Breast Implants;

Table LR-5. Mammography Findings/Breast Cancer Stage at Diagnosis/Prognosis Among Patients with Silicone Breast Implants; and

Table LR-6. Complication Rates Among Patients with Silicone Breast Implants.

Screening criteria similar to those applied for the literature reviewed in the update narrative report have been applied for this tabulation. The citations included represent English language publications that address potential health effects of silicone gel-filled breast implants, and not publications that are focused solely or primarily on injectable silicone, other silicone medical devices, environmental silicone exposures, polyurethane coated breast implants, saline-filled breast implants, other non-silicone gel-filled breast implants or laboratory tests. Consistent with IOM criteria, "case reports or case series reports are often essentially anecdotes or uncontrolled observational studies, which, lacking appropriate comparison or control groups, may not be helpful in determining rates of occurrence or accepting or rejecting causation;" such reports are generally not included in these tabulations. The focus of these tabulations, where possible, is on results available from large, well-controlled, epidemiology studies (as opposed to less-representative individual case reports and/or case series, *e.g.*, case series of explanted patients and referral series), and on studies with patient populations of 100 or more. It should be noted that the citations for case reports, case series and smaller clinical series are, however, included in the full bibliography. A further emphasis, where possible, is on results from studies involving the current third generation of silicone breast implants, representative of the design of Mentor's silicone gel devices since the inception of the company. In those instances where both relative risk and standardized incidence data are included in a study, the relative risk data that allows comparison to a more relevant population are presented in the summary tables that follow. Lastly, those published studies deemed most pertinent to the key safety issues identified by the IOM and by the U.S. Food and Drug Administration are the primary focus within these tabulations.

Appendix B.
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Appendix C.
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of Recent Literature 1999-2003
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