

Executive Summary

In House Report 104-659, which accompanied a 1997 appropriations bill, Congress asked the U.S. Department of Health and Human Services (DHHS) to sponsor a study of the safety of silicone breast implants by the Institute of Medicine (IOM) of the National Academy of Sciences. Funds were committed from several sources in DHHS, and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) was designated as the lead agency. In late 1997, the IOM agreed to carry out a comprehensive evaluation of the evidence for the association of silicone breast implants, both gel and saline filled, with human health conditions, assemble a comprehensive list of scientific references on this subject, and to consider recommendations for further research.

Chapter 1 recounts this history and the steps taken by the IOM to form the committee on the Safety of Silicone Breast Implants and to arrange for the preparation of a report with national public and scientific input, standards for evaluating evidence, and appropriate committee deliberations. Data and evidence for an association or for no association of a health condition with breast implants were ranked as either conclusive/convincing, limited/suggestive, insufficient, flawed or lacking. A finding of insufficient or absent data was not meant to imply that more information was needed. When this was desirable, and only then, the committee so noted. Chapter 1 also includes a brief description of the history of cosmetic breast surgery, cosmetic silicone injections, and the early development of silicone implants and continues with a discussion of women's satisfaction with breast implants.

Satisfaction is important, both inherently and because women's tolerance for complications influences their demand for medical and surgical interventions to correct implant problems, which in turn has safety implications. Yet surveys of satisfaction are often administered by plastic surgeons, which may bias results and influence women's reporting, and surveys are also often carried out before the likely appearance of some complications. The response rate itself may be influenced by the degree of satisfaction or other personal considerations.

The committee arrived at an estimate of 1.5 million to 1.8 million U.S. women with breast implants in 1997, the year the IOM study began. The committee estimates that about 70% of these implants were performed for augmentation, (i.e., enlarging or changing the appearance of the breast), and 30% for reconstruction, (i.e., restoring the form of the breast after mastectomy for cancer, fibrocystic disease, or other indications). The committee also noted that more than 10 million persons in the United States have some type of implant, such as finger joints or pacemakers, and many of these implants are made, at least in part, from silicone. A short review of regulation by the Food and Drug Administration (FDA) explains why current breast implantation is primarily with saline-filled implants, and describes the effects of government actions on gel-filled, polyurethane-coated, and other implants and on the companies that manufactured them.

Silicon is a semimetallic element, and silicone is a family of silicon-based organic compounds, of which the poly(dimethylsiloxanes) (PDMS) are prominent members. PDMS compounds are polymers, and the length and cross-linking of the polymer chain(s) affect the physical properties of these substances. Implant shells are made from an elastomer, that is, a high molecular weight, cross-linked rubbery substance, and they are filled with silicone gel, a less cross-linked spongy substance permeated with lower molecular weight silicone fluids. Other fillers are possible and include primarily saline. Chapter 2 describes in summary fashion the chemical steps in the manufacture of breast implants; Chapters 2 and 4 discuss the extensive presence of, and wide exposure of citizens in developed countries to silicones in foods, cosmetics, lubricants for machinery, hypodermic syringes and other products, insulators, and a wide array of consumer products.

Many kinds of implants with very different characteristics, made by various manufacturers, are described in Chapter 3. The committee was struck by the great number of changes in silicone breast implants since they were introduced in 1962. These changes have created different "generations" of gel-filled implants, which may have very different effects. The changes were introduced with little or no pretesting for biological or clinical effects as far as the committee could determine. Varying control of the diffusion of silicone fluid through gel implant shells, shell strength,

and therefore durability of both gel- and saline-filled implants, and polyurethane coating were among the changes that affected the clinical performance of silicone breast implants in ways that were not predicted in many instances. The history and implications of polyurethane coating of breast implants were reviewed, although polyurethane implants have not been available from U.S. manufacturers since 1991. On the other hand, changes have been made that have improved implants, as plastic surgeons and manufacturers have learned from reports of problems with existing implant models. Barrier shells, texturing, better valves in saline implants, and stronger shells that are more resistant to rupture or deflation have been some of these changes.

Study of the toxicology of silicones began in the 1940s. Although these studies were consistent with the standards of the day, in hindsight they fall short of current regulatory requirements; in particular, more chronic, long-term studies would have been desirable. As would be expected for any large family of organic compounds, some silicones have toxic or biologic effects, but PDMS fluids, gels, and elastomers were generally well tolerated on injection or implantation. Like other polymers, silicone can induce "solid state" carcinogenesis in rodents, but there is no evidence that this occurs in humans. Studies of the reproductive toxicology of PDMS have been negative. Several studies of the distribution of silicones from depots of experimental gel implantation or fluid injection have shown that silicones remain localized where deposited and that low molecular weight silicones which may be mobile to a small extent, are cleared from the body after relatively short half-lives.

Since the evidence is lacking or flawed that amorphous silica in breast implant shells is available to, or found in tissues of experimental animals or humans, or that crystalline silica is formed or present at any time in women with implants, the toxicology of silica has not been reviewed, although literature on silica is included in the references. Some investigators have asserted that platinum catalysts in breast implants may diffuse through the implant shell, be present in multivalent states, and provoke toxic reactions. The evidence currently available suggests that platinum is present only in the zero valence elemental state. Evidence does not suggest there are high concentrations in implants, significant diffusion of platinum out of implants, or platinum toxicity in humans. In general, the committee has concluded that a review of the toxicology studies of silicones known to be used in breast implants does not provide a basis for concern at expected exposures.

Local complications and reoperations have significant implications for the safety of silicone breast implants, because they may involve risks themselves and may lead to medical and surgical interventions that have risks. Local complications were not extensively reviewed in other recent,

important reports such as those of the Independent Review Group in the United Kingdom or the National Science Panel appointed by the court to examine systemic diseases and silicone breast implants. The committee considered local complications an important aspect of the story of breast implantation—historically, now, and in the future—for women considering these implants.

Chapter 5 approaches local complications both from the standpoint of overall reoperation and complication frequency and during reconstruction and augmentation. It then examines specific complications. In general, the committee concludes that complications are frequent. Specific complications discussed include implant rupture and deflation, contracture of the fibrous tissue capsule around implants, and elevated silicone concentrations in peri-implant tissues. Results with saline versus gel implants, barrier implants, textured implants, steroid-treated implants and implants in different positions are discussed. The infections, hematomas, and pain that may accompany implants are also considered.

A number of factors affect the integrity of the silicone elastomer implant shell. These include: shell thickness and strength which can vary considerably; untoward events such as needle sticks and other trauma associated with the vagaries of daily life, including closed capsulotomies, which the committee concludes should be abandoned; and the abrasion and wear of the implant shell in the body enhanced by wrinkling and fold flaws. Precise frequencies of the rupture of gel-filled, or the deflation of saline-filled, implants are not available. The properties of these devices that can affect rupture or deflation have changed markedly over time, and particularly in the case of gel implants, it has not been possible to reliably diagnose and study rupture in an unbiased cross section of implanted women. It is safe to say however that, like any device, breast implants have a finite life span. Rupture frequencies, in the past, have been considerable, and the rupture rate of current models has yet to be measured over the relevant periods of time. The deflation of saline implants is more easily diagnosed, but 100% discovery of deflations does not occur, and deflation frequencies of current models remain to be measured reliably.

Breast implants, like any foreign body, incite a surrounding fibrous tissue reaction. This fibrous capsule may contract, distorting the appearance of the implanted breast and causing pain. Contracture may be apparent as early as a few months after implantation, and the committee finds that it most likely continues over prolonged periods of time. As with any biologic reaction, some variation in contracture may be expected. The severity of contracture can differ in the breasts of the same woman. The exact frequency of contracture is not known because it has varied from 100% with pre-silicone implants to much lower prevalences, depending

on a number of factors, as modern silicone implants have evolved. Few studies that have measured contracture have controlled all except one study variable.

Silicon or silicone levels are elevated in capsular and sometimes breast tissue around implants, and this may contribute to capsular contracture. The committee has found suggestive evidence that contracture frequency is lessened by saline implants and barrier shells that, among other things, diminish the exposure of peri-implant breast tissue to silicone. Construction of an implant shell with projections, known as texturing, also appears to control contracture. The committee reviewed the evidence on the effects of adrenal corticosteroids on capsular contracture. Although some data suggest that they may reduce contractures, steroids also cause damage to surrounding breast tissue, are not an FDA approved or manufacturer-recommended usage, and may weaken elastomer implant shells.

A number of studies have shown that bacteria can be cultured from normal breast tissue, even at some depth below the surface of the skin. These bacteria are skin flora that reside in the lactiferous ducts of the normal breast, and often can be cultured from implants, where they may contribute from time to time to infections. There is suggestive evidence that the presence of bacteria correlates with contracture. A few investigators have reported finding an association between the presence of bacteria around implants and systemic symptoms or breast pain, although this evidence is limited. Hematomas, or collections of blood around implants, have also been proposed as causes of contracture. Evidence for this is insufficient. Significant contractures are reported considerably more frequently than clinically observable hematomas. Pain is also a problem in some women with implants. A number of studies report pain that has resulted in considerable discomfort and led to the removal of implants.

The committee reached three major general conclusions regarding local and perioperative complications. First, these complications occur frequently enough to be a cause for concern and to justify the conclusion that they are the primary safety issue with silicone breast implants. Among others, these include overall reoperations, ruptures or deflations, contractures, infections, hematomas, and pain. Second, risks accumulate over the lifetime of the implant, but quantitative data on this point are lacking for modern implants and are deficient historically for a number of reasons that have been noted in this report. Among these are lack of data from representative samples of the population, lack of information on implant characteristics that affect complications, and lack of precise and reliable detection of complications. Third, information concerning the nature and relatively high frequency of local complications and reoperations is an essential element of adequate informed consent for women undergoing breast implantation.

Chapters 6 through 8 evaluate the immunology of silicone, the relationship of antinuclear and other autoantibodies to breast implants, and the association of breast implants with classic connective tissue disease, undifferentiated connective tissue disease, and proposed new signs, symptoms, or novel disease. Studies in experimental animals have reported modest adjuvant effects of silicone gel and some silicone fluids, but no clinical implications of adjuvant effects have been discovered. Human adjuvant disease is not a defined disease, and the term should be abandoned. Other animal studies have not elucidated a role for silicone in immune disease. Cytokine assays have not provided conclusive evidence of immune activation. Evidence for silicone as a superantigen is insufficient. Modest decreases in natural killer cell activity have been reported after exposure to silicone, but no clinical roles or biological effects on resistance to infection, tumor surveillance or immune responses have been demonstrated in these studies.

Evidence for a particular HLA (human lymphocyte antigen) class I or class II haplotype associated with symptomatic women with silicone breast implants, or for specific T-cell activation or delayed hypersensitivity to silicone is insufficient and often flawed, and there is limited evidence that HLA haplotypes of symptomatic women with implants resemble those of symptomatic women without implants and that there is no T-cell activation or delayed hypersensitivity from silicone. Studies addressing these issues are limited and technical problems substantial, providing the committee with no support for a role of silicone as a T-cell antigen or in creating T-cell autoantigens. The committee also finds no evidence for antisilicone antibodies. The clinical significance of a recently described antipolymer antibody test is unclear, although the polymer in question is not silicone or silicon containing, and it is extremely unlikely that it measures an antisilicone antibody. The committee also noted several reports suggesting that women with breast implants might have elevated serum immunoglobulin levels. A few case reports also suggested that there might be an increased frequency of multiple myeloma in women with breast implants. These data are insufficient and a number of current epidemiological studies do not report an increase in immunoglobulin levels or multiple myeloma in such women.

Reports of antinuclear antibodies and epidemiological studies of classical and atypical connective tissue or rheumatic disease in women with breast implants also do not provide any support for immunologic or autoimmune responses or diseases associated with silicone breast implants. The committee reviewed 30 studies of antinuclear antibodies and other autoantibodies in women with silicone (primarily gel-filled) breast implants. These reports were often conflicting; many used differing technologies to assay antinuclear antibodies or differing criteria to determine

a positive test. Lack of controls and other design problems hampered the interpretation of some studies. No pattern of association of antinuclear antibodies with silicone breast implants emerged from these data. Several epidemiological studies suggested support for the conclusion that there is no association of antinuclear or other autoantibodies with breast implants.

A review of 17 epidemiological reports of connective tissue disease in women with breast implants was remarkable for the consistency in finding no elevated relative risk or odds ratio for an association of implants with disease. Studies of breast implants and undifferentiated connective tissue disease or atypical signs and symptoms were much fewer in number. Several high-quality studies of classical connective tissue disease in women with implants were available, but this was not the case with atypical signs and symptoms or unusual presentations. Nevertheless, many of the studies focusing on classical disease had also collected data on rheumatic and related signs and symptoms, and in general, no association with implants was found.

A novel syndrome or disease associated with silicone breast implants has been proposed. Evidence for this proposed disease rests on case reports and is insufficient or flawed. The disease definition includes, as a precondition, the presence of silicone breast implants, so it cannot be studied as an independent health problem. The committee finds that the diagnosis of this condition could depend on the presence of a number of symptoms that are nonspecific and common in the general population. Thus, there does not appear to be even suggestive evidence for the existence of a novel syndrome in women with breast implants. In fact, epidemiological evidence suggests that there is no novel syndrome.

Silicone like many polymers (and other substances) can cause solid state carcinogenesis. Implantation of a material formulated with appropriate size, shape, and surface characteristics causes infrequently metastasizing sarcomas in susceptible rodent species. This phenomenon is not believed to occur in humans, and no increases in human breast sarcomas have been observed. Epidemiological studies have not found elevated relative risks for breast cancer in women with implants. In fact, some of these studies, now evaluating women two decades or more after implantation, have found fewer breast cancers than expected, and some animal studies have suggested that breast implants might be associated with lower frequencies of breast cancer. The committee cannot find that evidence for a lower risk of breast cancer in women with breast implants is conclusive, but the committee does conclude that there is no increase in primary or recurrent breast cancer in these women.

Occasional reports of cancer occurring in the breasts of women injected with silicone for breast augmentation have been noted (see Chapter 1), but these are uncontrolled case reports or anecdotes, and do not consti-

tute useful evidence of any carcinogenic effect of silicone in humans. Several cohort studies have examined the risk for all cancers combined in women with breast implants, and all have reported numbers of cases similar to or lower than the number expected based on rates in the general population. The committee concludes that evidence is lacking for a relationship of breast implants to any specific cancers.

Neurologic disease, symptoms, and pathological and physical findings have been reported in case series of women with breast implants by a few groups. Other investigators have not found neurological problems and have criticized the experimental design used in reports of such an association. Experimental animal studies do not lend support to silicone as a cause of neurologic disease. Some case reports describe silicone gel deposits that migrate from ruptured breast implants, causing scarring and constriction around peripheral nerves. However, reports that silicone might be associated with autoantibodies to nerve components, that silica might be present in the nerves of women with implants, or that multiple sclerosis-like or other neurologic syndromes might be associated with implants have been found to have design and methodological problems that limited any conclusions. Two epidemiological studies of neurologic disease in women with implants provide limited support for a conclusion that there is no elevated relative risk for any association, and the committee concludes that with the exception of local problems caused by the migration of gel from ruptured implants, evidence that silicone breast implants cause neurologic signs, symptoms, or disease is lacking or flawed.

In an overall consideration of the epidemiological evidence, the committee noted that because there are more than 1.5 million adult women of all ages in the United States with silicone breast implants, some of these women would be expected to develop connective tissue diseases, cancer, neurological diseases, or other systemic complaints or conditions. Evidence suggests that such diseases or conditions are no more common in women with breast implants than in women without implants.

A few investigators have proposed that women with silicone breast implants might transmit silicone or some immunological factor via breast milk or across the placenta to their children. There is limited evidence that implantation, especially through a periareolar incision, may interfere with lactation and breast feeding, but no differences are observed in milk or blood silicon (and thus presumably silicone) levels in lactating women with implants compared to lactating control women without implants. Much higher levels of silicon have been measured in cows' milk at the retail level and commercially available infant formula. It is likely that some of this silicon is organic. Infants are also exposed to other sources of silicone, for example, pacifiers, nipples, and widely available drops for

colic. Antinuclear antibodies are reported in normal women without implants, and no untoward effects on their children have been observed. The committee can find no evidence of elevated silicone in breast milk or of any other substance that would be deleterious to infants. Because there is conclusive evidence that breast feeding is beneficial to infants, the committee strongly recommends a trial of breast feeding by mothers with implants.

A single group of investigators examined children at about 5 years of age who had been breast fed by mothers with implants and reported abnormalities of esophageal motility that they hypothesized might have been caused by exposure to silicone. These investigators did not carry out any silicon or silicone measurements in either the children or their mothers. A number of problems with the reports of this group have been identified, and an epidemiological study of esophageal disease in the children of mothers with implants found no elevated relative risk for esophageal disease. As noted, breast milk silicon concentrations in implanted women are normal. Also, an experimental animal study found no esophageal silicone or abnormalities in rat pups breast-fed by mothers with silicone implants, and toxicological studies of the reproductive and teratologic effects of silicone (PDMS) reviewed in Chapter 4 were negative. The committee concludes that evidence for health effects in children related to maternal breast implants is insufficient or flawed.

Breast implants interfere with diagnostic and screening imaging examinations of the breast by compressing and distorting breast tissue, by making compression of the breast in a mammographic examination difficult and obligating special views, and by interposing (particularly with gel-filled implants) a radiopaque mass in the middle of the breast that obscures some breast tissue. These problems are fewer with submuscular placement of the implant and can be at least partially overcome with special views. Data on whether cancer detection is impaired by implants do not allow definite conclusions, but no studies have shown increases in cancer mortality in women with implants because of diagnostic delays. Mammographic screening for cancer in women with implants under the same conditions as recommended for women without implants should be encouraged. The imaging techniques described in Chapter 12 have varying sensitivities and specificities for the diagnosis of implant rupture and varying advantages or disadvantages. Magnetic resonance imaging is the most sensitive and specific technology for rupture diagnosis. The committee did not find direct evidence on the cost/benefit of screening for rupture, however. Relevant screening data and analysis might allow a firmer conclusion on screening in general or in women with implants with known high prevalence of rupture or in other specific circumstances. Only if such data showed reduced morbidity as a result of screening and

a screening driven intervention, would routine screening of the general population of asymptomatic women with breast implants be justified.

Appendix A describes a scientific workshop sponsored by the IOM to bring presentations and discussions of the work and experiences of academic, governmental, and industry physicians and scientists to the committee. Appendix B describes a public meeting sponsored by the Institute of Medicine primarily to hear the experiences of women with breast implants, although other interested parties spoke as well. Appendix C reviews two recent important, related reports from the Independent Review Group of the United Kingdom and the National Science Panel appointed by the judge for the U.S. multidistrict litigation.

CONCLUSIONS AND RESEARCH RECOMMENDATIONS

The committee wishes to highlight the following conclusions from this Summary:

- There is extensive presence of, and wide exposure of citizens of developed countries to silicones in foods, cosmetics, lubricants for machinery, hypodermic syringes and other products, insulators and a wide array of consumer products.
- The committee concludes that a review of the toxicology studies of silicones and other substances known to be in breast implants does not provide a basis for health concerns.

The committee has reached three major conclusions regarding local and perioperative complications. First, reoperations and local and perioperative complications are frequent enough to be a cause for concern and to justify the conclusion that they are the primary safety issue with silicone breast implants. Complications may have risks themselves, such as pain, disfigurement and serious infection and they may lead to medical and surgical interventions, such as reoperations, that have risks. Second, risks accumulate over the lifetime of the implant, but quantitative data on this point are lacking for modern implants and deficient historically. Third, information concerning the nature and the relatively high frequency of local complications and reoperations is an essential element of adequate informed consent for women undergoing breast implantation.

The committee has also come to the following conclusions:

- Studies addressing the immunology of silicones are limited and technical problems substantial, providing the committee with no support for an immunologic role of silicone.
- A novel syndrome or disease associated with silicone breast im-

plants has been proposed by a small group of physicians. Evidence for this proposed disease rests on case reports and is insufficient and flawed. The disease definition includes, as a precondition, the presence of silicone gel breast implants, so it cannot be studied as an independent health problem. The committee finds that the diagnosis of this condition could depend on the presence of a number of symptoms that are nonspecific and common in the general population. Thus, there does not appear to be even suggestive evidence of a novel syndrome in women with breast implants. In fact, epidemiological evidence suggests that there is no novel syndrome.

- There is no increase in primary or recurrent breast cancer in implanted women.
- In an overall consideration of the epidemiological evidence, the committee noted that because there are more than 1.5 million adult women of all ages in the United States with silicone breast implants, some of these women would be expected to develop connective tissue diseases, cancer, neurological diseases or other systemic complaints or conditions. Evidence suggests that such diseases or conditions are no more common in women with breast implants than in women without implants.
- The committee finds no evidence of elevated silicone in breast milk or any other substance that would be deleterious to infants; the committee strongly concludes that all mothers with implants should attempt breast feeding.
- The committee concludes that evidence for health effects in children related to maternal breast implants is insufficient or flawed.

RECOMMENDATIONS FOR RESEARCH

1. Reliable techniques for the measuring of silicone concentrations in body fluids and tissues are needed to provide established, agreed-upon values and ranges of silicone concentrations in body fluids and tissues with or without exposure to silicone from an implanted medical device. Such developments could improve the study of silicones and silicone distribution in humans, could help with regulatory requirements, and might in some circumstances resolve questions by providing quantitative data on the presence or absence of silicones.

2. Ongoing surveillance of recipients of silicone breast implants should be carried out for representative groups of women, including long-term outcomes and local complications, with attention to, or definition of the following:

- implant physical and chemical characteristics,
- tracking identified individual implants,

- using appropriate, standardized, and validated technologies for detecting and defining outcomes,
- carrying out associated toxicology studies by standards consistent with accepted toxicological standards for other devices; and
- ensuring representative samples, appropriate controls and randomization in any specific studies, as required by good experimental design.

3. The development of a national model of informed consent for women undergoing breast implantation should be encouraged, and the continuing effectiveness of such a model should be monitored.