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Medical Device Material Performance Study

Siloxane Safety Profile

Prepared for
U.S. FDA Center for Devices and Radiological Health

Submitted to

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Executive Summary

Project Overview

The FDA engaged ECRI to perform a comprehensive literature search, systematic review, and analysis of ECRI surveillance data to identify the current state of knowledge with regard to biocompatibility of siloxane used in medical devices. Five key questions were provided by FDA and are summarized below. If data did not exist to sufficiently address these questions, a gap was noted in this report, which could represent areas of further research. Literature searches identified 2,740 articles and 122 of these met inclusion criteria for the systematic review.

1. What is the typical/expected local host response to Siloxane?

a. Can that response vary by location or type of tissue the device is implanted in or near?

Local host responses to siloxane vary depending on the device (implant or injection) and the target location or tissue type:

i. For silicone gel-filled breast implants the primary local responses reported in the literature were capsular contracture and rupture.
ii. For silicone injections, the primary local response is granuloma formation.
iii. For silicone oil used for tamponade in retinal surgery, local responses include visual loss, cataracts, elevated intraocular pressure, emulsification, inflammation, and retinal detachment.
iv. For neuromodulatory systems we found no evidence from human studies, but in animal studies the primary local response was fibrous tissue growth.
v. We found no evidence on local host responses to penile implants or implanted continence devices.
vi. The quality of evidence supporting these findings is moderate for breast implants and neuromodulatory systems, and low for silicone injections and silicone oil tamponade in retinal surgery.

ECRI's surveillance data for siloxane found the following:

i. Surveillance data are consistent with the clinical literature for breast implants with infection, rupture, or deflation as the most common complications.
ii. The majority of penile implant complications consist of infection or malfunction, with lower associated harm than breast implant events.
iii. The majority of neuromodulatory system complications were infection and malfunction, and the most serious complications (2 reports with harm score G) were infection and paralysis.
iv. There are very few reports on urinary continence devices and injectables.

b. Over what time course does this local host response appear?

i. The risk of breast implant responses increases over time, with events occurring up to 7 years post-implant.
ii. Granuloma formulation after silicone injection occurred between 1 to 15 years post-injection.
iii. Events involving silicone oil response occurred between 1 week and 2 years after tamponade.

2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?

a. What evidence exists to suggest or support this?

The majority of evidence evaluated silicone gel-filled breast implants and silicone injections; however, the quality of evidence supporting the association between silicone and systemic manifestations is low for breast implants and very low for injections.

b. What are the likely systemic manifestations?

Silicone gel-filled breast implants: Sjögren syndrome, scleroderma, rheumatoid arthritis, melanoma, myositis, multiple sclerosis, systemic sclerosis, multiple sclerosis, fibromyalgia/chronic fatigue syndrome, sarcoidosis, hyperthyroidism, psoriasis, hypothyroidism, ASIA, lymphoma (including ALCL), lymphadenopathy, siliconomas, interstitial lung disease, and systemic inflammatory reaction.

Silicone injections: Pneumopathy, pneumonitis, hypercalcemia, renal failure (related to hypercalcemia), non-thrombotic pulmonary embolism, hepatitis, and serositis.

c. What is the observed timeline(s) for the systemic manifestations?

Systemic manifestations associated with breast implants occurred during a period from 1 to 42 years following implantation. Manifestations associated with injections occurred during a period from 3 months to 28 years after injection.

d. Have particular cellular/molecular mechanisms been identified for such manifestations?

We did not find evidence concerning cellular/molecular mechanisms of systemic manifestations.

3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

i. A cohort study of autoimmune/inflammatory disease induced by adjuvants (ASIA) cases reported that the risk of developing autoantibodies was significantly increased in vitamin D deficient and/or insufficient patients.
ii. Another study of ASIA cases reported pre-existing allergies present in 75% of cases
iii. Implants may cause systemic symptoms in patients with atopy or a hyperimmune state.

4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?

i. One systematic review and one case series reported an association between textured breast implants and development of anaplastic large cell lymphoma (ALCL).
ii. One case series noted that implant rupture or silicone bleed may cause lymphadenopathy.
iii. One cohort study noted that semi-acute onset of ASIA symptoms may be explained by implant rupture or silicone gel bleeding.
iv. Two cohort studies reported that explantation reduced ASIA symptoms in 50% to 69% of cases.

5. What critical information gaps/research are needed to better understand this issue?

i. Local response to silicone injections and silicone oil tamponade
ii. Local response to penile implants and urinary continence devices.
iii. Nueromodulatory biocompatibility studies addressing "clinical manifestation" and pain, as reported in the PSO database
iv. Systemic manifestations for all devices. The quality of evidence for all reported systemic manifestations was either low (breast implants) or very low (injections and other devices). Breast implants was the only device category with several studies reporting systemic responses, but the quality of evidence was low. All of the reported systemic manifestations require further research to determine whether they are truly associated with silicone.
v. With the exception of the literature concerning silicone breast implants, the literature for silicone/siloxane generally lacked data on patient-related or material-related factors that influence the likelihood and/or severity of sustained, exaggerated systemic responses.

Project Overview

FDA engaged ECRI to perform a comprehensive literature search and systematic review to identify the current state of knowledge with regard to medical device material biocompatibility. Specific materials were selected by FDA based on current priority. For 2020, the following six materials were chosen:

1. Siloxane (Si)
2. Polypropylene (PP)
3. Polyether ether ketone (PEEK)
4. Poly(lactic-co-glycolic acid) (PLGA)
5. Polyurethane (PUR)
6. Polyethylene terephthalate (PET)

The systematic review was guided by key questions mutually agreed upon by FDA and ECRI. Data were extracted from literature articles and ECRI surveillance databases accordingly.

Key Questions:

1. What is the typical/expected local host response to the material?
    - Over what time course does this local host response appear?
    - Can that response vary by location or type of tissue the device is implanted in or near?
2. Does the material elicit a persistent or exaggerated response that may lead to systemic signs or symptoms – beyond known direct toxicity problems?
    - What evidence exists to suggest or support this?
        - In-vivo/clinical studies/reports?
        - Bench or in-vitro studies?
    - What are the likely systemic manifestations?
    - What is the observed timeline(s) for the systemic manifestations?
    - Have particular cellular/molecular mechanisms been identified for such manifestations?
3. Are there any patient-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
4. Are there any material-related factors that may predict, increase, or decrease the likelihood and/or severity of an exaggerated, sustained immunological/systemic response?
5. What critical information gaps/research are needed to better understand this issue?

If data did not exist to sufficiently address these questions, a gap was noted in this report. These gaps could represent areas of further research.

Safety Profiles were written for the six materials listed above to include the summary of key findings from the systematic review and surveillance search and are included in this report.

Literature Search and Systematic Review Framework

The ECRI-Penn Evidence-based Practice Center (EPC) conducts research reviews for the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program. ECRI's scientific staff within our Center for Clinical Excellence has authored hundreds of systematic reviews and health technology assessments on 3,500+ technologies/interventions for ECRI's public- and private-sector clients. In addition to this work, ECRI staff have coauthored several methods papers on evidence synthesis published on the AHRQ Effective Health Care website and peer-reviewed journals.

For this project, the clinical and engineering literature was searched for evidence related to biocompatibility of each material. Searches of PubMed/Medline and Embase were conducted using the Embase.com platform. Scopus was used initially to search non-clinical literature however it was determined that the retrieved citations did not meet inclusion criteria and that database was subsequently dropped from the search protocol. Search limits included publication date 2010 – 2020 and English as the publication language. ECRI and FDA agreed on appropriate host and material response search concepts as follows:

- **Material Response**
    - Strength
    - Embrittlement
    - Degradation
    - Migration
    - Delamination
    - Leaching

- **Host Response**
    - Local
        - Inflammation
        - Sensitization
        - Irritation
        - Scarring/fibrosis
            - *Keloid formation*
            - *Contracture*
        - Ingrowth
        - Erosion
    - Systemic
        - Cancer
        - Inflammation
        - Immune Response
        - Fatigue
        - Memory Loss
        - Rash
        - Joint Pain
        - Brain Fog

Search strategies were developed for each concept and combined using Boolean logic. Several search approaches were used for comprehensiveness. Strategies were developed for devices of interest as indicated by the FDA as well as the material-related strategies. Each of these sets were combined with the material and host response strategies. Detailed search strategies and contextual information are presented in Appendix B. Resulting literature was screened by title review, then abstract review, and finally full article review. Data were extracted from the articles meeting our inclusion criteria to address the key questions for each material.

ECRI Surveillance Search Strategy

There are four key ECRI sources for medical device hazards and patient incidents. These databases were searched by key terms and device models. Relevant data were extracted to address the key questions agreed upon by FDA and ECRI. Patient demographics were extracted when available. All data presented were redacted and contain no protected health information (PHI).

ECRI PSO

ECRI is designated a Patient Safety Organization by the U.S. Department of Health and Human Services and has collected more than 3.5 million serious patient safety events and near-miss reports from over 1,800 healthcare provider organizations around the country. Approximately 4% of these reports pertain to medical devices. Most of these reports are acute (single event) reports and do not include patient follow-up. These data were filtered by complication, and relevant reports were included in the analysis. "Harm Score" refers to the National Coordinating Council Medication Error Reporting and Prevention (NCC MERP) taxonomy of harm, ranging from A to I with increasing severity (see Figure 1). The entire PSO database was included in the search, with reports ranging from year 2004 through March 2020, unless otherwise noted.

Figure 1. NCC MERP "harm score," which is now regularly used by patient safety organizations.

Category A (No Error)
Circumstances or events that have the capacity to cause error.

Category B (Error, no harm)
An error occurred, but the error did not reach the patient (an "error of omission" does reach the patient).

Category C (Error, no harm)
An error occurred that reached the patient but did not cause patient harm.

Category D (Error, no harm)
An error occurred that reached the patient and required monitoring to confirm that it resulted in no harm to the patient and/or required intervention to preclude harm.

Category E (Error, harm)
An error occurred that may have contributed to or resulted in temporary harm to the patient and required intervention.

Category F (Error, harm)
An error occurred that may have contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization.

Category G (Error, harm)
An error occurred that may have contributed to or resulted in permanent patient harm.

Category H (Error, harm)
An error occurred that required intervention necessary to sustain life.

Category I (Error, death)
An error occurred that may have contributed to or resulted in patient death.

Definitions
Harm: Impairment of the physical, emotional, or psychological function or structure of the body and/or pain resulting therefrom.
Monitoring: To observe or record relevant physiological or psychological signs.
Intervention: may include change in therapy or active medical/ surgical treatment.
Intervention necessary to sustain life: includes cardiovascular and respiratory support (eg CPR, defibrillation, intubation).

Accident Investigation

ECRI has performed thousands of independent medical-device accident investigations over more than 50 years, including on-site and in-laboratory investigations, technical consultation, device testing and failure analysis, accident simulation, sentinel event and root-cause analyses, policy and procedure development, and expert consultation in the event of litigation. Our investigation files were searched by keywords, and the search was limited to the past 10 years unless we found landmark investigations that are particularly relevant to biocompatibility.

Problem Reporting Network (PRN)

For more than 50 years, ECRI's Problem Reporting Network (PRN) has gathered information on postmarket problems and hazards and has been offered as a free service for the healthcare community to submit reports of medical device problems or concerns. Each investigation includes a search and analysis of the FDA MAUDE database for device-

specific reports. Based on our search findings, we may extend our analysis to all devices within that device's FDA-assigned product code. The PRN database was searched by keywords, and the search was limited to the past 10 years.

Healthcare Technology Alerts

We regularly analyze investigation and PRN data to identify trends in use or design problems. When we determine that a device hazard may exist, we inform the manufacturers and encourage them to correct the problem. ECRI publishes the resulting safety information about the problem and our recommendations to remediate the problem in a recall-tracking management service for our members. The Alerts database contains recalls, ECRI exclusive hazard reports, and other safety notices related to Medical Devices, Pharmaceuticals, Blood Products, and Food Products. This database was searched by keywords and specific make and model, and the search was limited to the past 10 years.

Safety Profile - Siloxane

Full Name: Siloxanes and Silicones, polyether-

CAS Registry Number: 94469-32-6

Search Overview

The systematic review included clinical and engineering literature on biocompatibility (i.e. host response and material response) of siloxane used in medical devices. In addition to fundamental material biocompatibility, we focused on specific devices known to be made of siloxane. The devices in Table 1 were recommended by FDA CDRH to guide ECRI in searching this literature and ECRI's surveillance data. Only devices in Table 1 are included in ECRI surveillance searches, with exception of an antireflux prosthesis device found in ECRI's accident investigation files.

Table 1: Medical devices containing siloxane provided by FDA to guide ECRI

Regulatory Description	Pro Code	Class
Breast Implant, Sizer Breast Implant – Saline Filled Breast Implant – Gel Filled	MRD FTR FWM	III
Implanted mechanical/hydraulic urinary continence device	EZY	III
Prosthesis, penis, inflatable / Penile inflatable implant	JCW	III
Neuromodulatory systems Stimulator, spinal-cord, totally implanted for pain relief Peripheral nerve stimulator Implanted spinal cord stimulator, for pain relief	 LGW GZF GZB	 III
Silicone, liquid, injectable	KGM	III

Systematic Review Safety Brief

The Safety Brief summarizes the findings of the literature search on toxicity/biocompatibility of siloxane/silicone. Inclusion/exclusion criteria and quality of evidence criteria appear in Appendix A in the Appendices document. Quality of evidence ratings reflected a combination of the quality of comparative data (study designs), quantity of evidence (number of relevant studies), consistency of evidence, magnitude of effect, directness of evidence, and evidence for a dose or time response. The search strategy appears in Appendix B, and a flow diagram documenting inclusion/exclusion of studies appears in Appendix C. Summary evidence tables with individual study data appear in Appendix D, and a reference list of studies cited in the Safety Brief appears in Appendix E.

A summary of our primary findings is shown in Table 2. We then turn to a detailed discussion of research on siloxane/silicone as a material as well as research on the five device categories.

Table 2: Summary of primary findings from our systematic review

Application	**Local host responses**	**Quality of evidence (local responses)**	**Systemic responses***	**Quality of evidence (systemic responses)**
Siloxane/silicone as a material 1 human study, 34 animal studies	Local inflammation, Foreign body response	Moderate	Pulmonary toxicity Anti-drug antibody responses	Low
Silicone breast implants 25 human studies, 4 animal studies	Capsular contracture and rupture	Moderate	Sjögren syndrome, scleroderma, rheumatoid arthritis, melanoma, myositis, multiple sclerosis, systemic sclerosis, multiple sclerosis, fibromyalgia/chronic fatigue syndrome, sarcoidosis, hyperthyroidism, psoriasis, hypothyroidism, ASIA, lymphoma (including ALCL), lymphadenopathy, siliconomas, interstitial lung disease, systemic inflammatory reaction	Low
Silicone injections 12 human studies, 1 animal study	Granuloma	Low	Pneumopathy, pneumonitis, hypercalcemia, renal failure, non-thrombotic pulmonary embolism, hepatitis, serositis	Very low
Neuromodulatory systems 6 animal studies	Fibrous tissue growth	Moderate	No issues reported in included studies	Low

Application	Local host responses	Quality of evidence (local responses)	Systemic responses*	Quality of evidence (systemic responses)
Silicone oil for opthamologic uses 42 human studies	Visual loss, Cataracts, Elevated intraocular pressure, Emulsification, Inflammation, Retinal detachment	Low	No issues reported in included studies	Low
Penile implants and implanted continence devices 0 studies	No studies	Very low (no evidence)	No studies	Very low (no evidence)

*The quality of evidence was low for all systemic responses; ASIA = autoimmune/inflammatory disease induced by adjuvants; ALCL = anaplastic large cell lymphoma.

Siloxane/silicone as a material: 35 studies (1 human study, 34 animal studies)[1-34]. The human study was a case series[1]; the animal studies included 1 systematic review[8], 4 randomized controlled trials (RCTs)[5,17,20,29], and 29 non-randomized controlled studies[1-4,6,7,9-16,18,19,21-28,30-34]. For further information, see Tables 1 and 2 in Appendix D.

Local and systemic responses (human study). In the human case series (39 individuals)[1], accidental industrial exposure to non-fluorinated alkylsiloxanes in a tile-coating product caused tachycardia and severe respiratory symptoms in 38% and 7% of exposed individuals, respectively. Other symptoms included coughing (100%), shortness of breath (74%), chest pain (20%), general malaise (49%), headache (46%), tachypnea (51%), and fever (66%). The onset of symptoms occurred within 1 to 12 hours of exposure (all patients began having respiratory symptoms within the first hour). All patients had recovered by 72 hours after exposure. Although the authors stated that no delayed symptoms were observed, some patients reported having shortness of breath during hard physical work 2 months later. The study did not rule out the possibility that the toxic effects were related to the solvents used to suspend the alkylsiloxanes.

Patient-related or material-related factors associated with systemic response: Patient characteristics that may have been related to more severe symptoms include smoking, ischemic heart disease, and older age, but there were too few patients with severe symptoms to statistically determine associations. The study did not provide sufficient evidence for or against a dose-response association.

Local host responses (animal studies): The animal studies involved a variety of silicone or siloxane formulations either injected or implanted; most studies evaluated subcutaneous implants. The most common reaction was mild local inflammation (14 studies; 2 studies described the inflammation as "chronic"); another common reaction was a foreign body response (reported in 12 studies).

Systemic responses (animal studies): The only animal studies evaluating systemic reactions were 6 studies evaluating subcutaneous injections of silicone oil microdroplets. Five non-randomized controlled studies reported that silicone oil microdroplets can act as an adjuvant to increase anti-drug antibody responses[30-34]. The remaining study was an RCT that did not find an increased anti-drug antibody response associated with silicone oil microdroplets[29]. No serious systemic responses were noted in any animal study.

Overall quality of evidence: The evidence for local responses in animal studies was based on a large number of studies, and the findings were relatively consistent across studies. Although this is indirect evidence with respect to humans, the findings are consistent with findings from other silicone devices (injections, breast implants) used in humans. Therefore, the quality of evidence supporting local host responses is moderate.

Few studies evaluated systemic responses, and only one was a human study. Although alkylsiloxanes may have pulmonary toxicity in humans, the study was small and conclusions were hindered by the possibility that toxic effects may have been at least partly related to the solvent used to suspend the alkylsiloxanes and the lack of accurate exposure information from the workplace. Thus, the quality of evidence for systemic responses is low.

Silicone breast implants: 25 human studies (4 systematic reviews[37,41,43,46], 21 observational studies [cohort studies and case series][35,36,38-40,42,44,45,47-56]); 4 animal studies (2 RCTs[57,58] and 2 case series[59,60]). For further information, see Tables 3 and 4 in Appendix D.

Local host responses: 9 human studies reported whether there were local host reactions related to silicone gel-filled breast implants; the most common were capsular contracture (reported in 4 studies, including the largest study), rupture (2 studies, including the largest study), and breast pain (2 studies, including the largest study). The largest study was a retrospective cohort analysis of U.S. FDA breast implant postapproval studies in the large postapproval study (LPAS) database (Coroneos et al. 2019)[35]. This study analyzed data from 41,342 Allergan silicone breast implants and 41,975 Mentor silicone breast implants, and thus represented more patients than all of the other included studies combined. The two manufacturers' studies did not report all the same outcomes at the same time points, so they are not directly comparable. Allergan reported the following event rates at 2 years: capsular contracture (5%) and rupture (0.5%); at 5 years, rupture ranged from 1.4% to 2.6%. Mentor reported the following adverse event rates at 7 years: Grade III/IV capsular contracture (7.2% to 18.3%), rupture (8.2% to 15.6%), and breast pain (19.6% to 29.6%). Longer contact duration was associated with higher incidence of adverse events. The 4 animal studies reported local responses such as fibrous capsule formation and local inflammatory reactions.

Systemic responses: 16 human studies reported systemic responses that may be related to silicone breast implants. The 3 largest studies were the FDA database study noted above[35], a systematic review of longitudinal studies with a total of 42,973 patients with silicone breast implants (Balk et al. 2016)[46], and a cross-sectional study of a healthcare database in Israel (Watad et al. 2018)[45] that included 24,651 patients with silicone breast implants.

The FDA database study reported standardized incidence ratios (SIRs) and found incidence ratios greater than 2 (more than double the risk in the general population) for Sjögren syndrome (8.14 [95% confidence interval (CI) 6.24–10.44]), scleroderma (7.00 [5.12–9.34]), rheumatoid arthritis (5.96 [5.35–6.62]), and melanoma (3.71 [2.87–4.73]) associated with Mentor silicone breast implants. The study found incidence ratios less than 2 (but still statistically significant) for myositis (1.88 [1.09–3.00]), multiple sclerosis (1.72 [1.26–2.29]), neurological disorder (1.59 [1.44–1.76]), and overall cancer diagnosis (1.54 [1.42–1.68]) associated with Mentor silicone breast implants. Allergan descriptively reported that silicone implants for revision reconstruction have SIRs over 2.0 for scleroderma, Sjögren syndrome, and myositis compared with normative at 7-year follow-up[35].

Balk et al. reported possible increased risk of rheumatoid arthritis (3 study meta-analysis): effect size (ES) (95% CI): 1.42 (1.04–1.95) and Sjögren syndrome (1 study): risk ratio (RR) (95% CI): 6.64 (2.01–21.9). For lung cancer and Raynaud's phenomenon, they noted possible associations (odds ratios [ORs] 1.5 and 1.42, respectively) but neither ES reached statistical significance[46].

Watad et al. reported that patients with silicone implants were more likely to be diagnosed with the following: any autoimmune/rheumatic disorder (OR 1.22 [95% CI: 1.18–1.26]; HR 1.45 [1.21–1.73]), sarcoidosis (OR 1.98 [1.50–2.60]), systemic sclerosis (OR 1.63 [1.26–2.11]), Sjögren syndrome (OR 1.58 [1.26–1.97]), MS (OR 1.41 [1.11–1.80]), fibromyalgia/chronic fatigue syndrome (OR 1.37 [1.29–1.45]), RA (OR 1.19 [1.03–1.38]), hyperthyroidism (OR 1.16 [1.07–1.26]), psoriasis (OR 1.13 [1.05–1.21]), hypothyroidism (OR 1.10 [1.05–1.16])[45]. We note that all the ORs reported by Watad et al. are small (<2), and although the authors adjusted for several potential confounding factors (age, socioeconomic status, smoking status, and breast cancer history), the increased event rates still could be related to confounding factors not included in the analysis. In spite of elevated event rates compared to controls without implants, all systemic harms reported in these studies were considered rare events.

The remaining studies had far fewer patients and merely reported systemic adverse events rather than comparing event rates to a control group without implants. Six studies reported on cases with silicone breast implants with symptoms believed to represent autoimmune/inflammatory disease induced by adjuvants (ASIA)[40,52-56]. Other studies reported events including lymphoma (2 studies[48,49], both report anaplastic large cell lymphomas [ALCLs] as the most common type associated with breast implants), lymphadenopathy[38,50], siliconomas[50], interstitial lung disease[44], systemic sclerosis[47] and systemic inflammatory reaction[51]. Again, all these were considered rare events.

Patient-related or material-related factors associated with systemic response: The FDA database study noted that longer contact duration was associated with higher event incidence. Balk et al.[46] reported that for lung cancer, 1 study found a higher association with breast implants after longer follow-up. For Sjögren syndrome, there was higher

outcome incidence when the outcome was self-reported. Neither Balk nor Watab[45] found significant differences in systemic adverse events between breast augmentation and breast reconstruction procedures.

One systematic review of 83 cases of lymphoma reported an association between textured implants (both silicone and saline) and ALCL[48]. A case series similarly noted that implant rupture or chronic irritation by the textured implant surface may trigger ALCL proliferation[49]. Another case series also noted that implant rupture or silicone bleed may cause lymphadenopathy[50].

Four cohort studies reported on factors that may be related to ASIA. A controlled cohort study of patients with silicone breast implants and symptoms of ASIA reported that explantation reduced symptoms in 50% of cases[53]. Another cohort study of ASIA cases reported that the risk of developing autoantibodies was significantly increased in vitamin D deficient and/or insufficient patients (RR [95% CI] 3.14 [1.24–7.95], $p = 0.009$)[54]. A third study of ASIA cases reported pre-existing allergies present in 75% of cases; implants may cause systemic symptoms in patients with atopy or a hyperimmune state. The study also noted that semi-acute onset of symptoms may be explained by implant rupture or silicone gel bleeding and that explantation reduced symptoms in 69% of cases[40]. The remaining study speculated that implant aging or rupture may result in immune dysregulation and the development of autoimmune diseases[55].

Overall quality of evidence: Several studies (including systematic reviews and very large database studies) support the susceptibility of silicone breast implants to capsular contracture and rupture. The quality of evidence supporting these outcomes is moderate.

Although 3 large studies provide evidence concerning several systemic adverse events, there is some inconsistency among studies regarding the significance of their potential associations with silicone implants. The risk of bias from unadjusted confounding factors means that the quality of evidence for systemic responses is low.

Silicone injections: 13 studies (12 human[61-72], 1 animal[73]). Of the 12 human studies, 3 were systematic reviews[63,71,72] and 9 were case series[61,62,64-70]. The animal study was a case series[73]. The human studies evaluated silicone injected for cosmetic purposes. For further information, see Tables 5 and 6 in Appendix D.

Local host responses: 9 human studies reported local host responses, of which the most common was granuloma (reported in 6 studies). Other events included inflammation (2 studies), silicone mastitis, fibrosis, and palpable nodules (1 study each).

Systemic responses: 2 systematic reviews[71,72] and 1 case series[73] reported systemic responses. All of these responses are relatively uncommon but the reviews did not provide a denominator by which to determine incidence or prevalence. The most serious acute response was pneumopathy, which is usually self-limiting but has led to death in some cases[72]. The most serious late systemic reactions included 23 cases of hypercalcemia related to granulomas (10 cases in patients who received silicone injections) that led to renal failure in 14 cases (unclear how many of these had received silicone). Two patients died due to renal failure[71]. Other reported serious systemic reactions included pneumonitis, non-thrombotic pulmonary embolism, hepatitis, and serositis.

Overall quality of evidence: The systematic reviews and case series had small numbers of patients and lacked comparison groups. The only consistently reported outcome across studies was granuloma, and the overall quality of evidence for this outcome is low.

For other events, particularly systemic events that require more evidence to determine whether they are associated with silicone, the quality of evidence is very low.

Neuromodulatory systems: 6 animal studies (1 RCT[79], 4 controlled studies[74-77], and 1 case series[78]) reported adverse events related to neuromodulatory systems containing silicone. No human studies were identified that met inclusion criteria. The studies evaluated silicone electrodes (3 studies), nerve implants (1 study), silicone-coated platinum wire (1 study), and silicone particles (1 RCT). Electrodes and nerve implants were implanted in sciatic nerves (3 studies), 1 electrode microarray was implanted on cortical surface via craniotomy, the platinum wire was implanted in scala tympani (1 study), and the silicone particles were implanted in lumbar spinal dura. For further information, see Table 7 in Appendix D.

Local host responses: All 6 studies reported local responses, the most common of which was fibrous tissue growth (reported in 5/6 studies).

Systemic responses: The RCT[79] was the only study that reported systemic data (related to silicone particles), in which a histopathological analysis of lymph nodes and several organs revealed no significant pathological changes.

Overall quality of evidence: The 6 animal studies, 5 of which had control groups, were consistent in showing fibrous tissue growth in response to neuromodulatory implants containing silicone. Although the evidence is indirect with respect to humans, the quality of evidence is moderate. The quality of evidence for systemic responses was based on a single small animal RCT and is therefore low.

Silicone oil for ophthalmic uses: 42 human studies (1 systematic review[101], 2 RCTs[110,116], 5 controlled cohort studies[82,84,91,97,109], 1 case-control study[99], 2 single-arm cohort studies[80,88], and 31 case series[81,83,85-87,89,90,92-96,98,100,102-108,111-115,117-122]) evaluated adverse events associated with silicone oil tamponade used in retinal surgery. For further information, see Table 8 in Appendix D.

Local host responses: All the studies reported local adverse events that occurred in the eyes that received silicone oil tamponade. Vision loss was the most frequently reported event across studies; other common events included cataract, elevated intraocular pressure, emulsification, and inflammation, but a range of other events were reported including re-detachment of the retina and glaucoma. One controlled cohort study of moderate size that compared silicone oil tamponade to gas tamponade found a much higher risk of visual loss associated with silicone oil tamponade[109]. Longer duration of silicone oil tamponade was the only factor significantly associated with visual loss. Another moderate size controlled cohort study of patients with cytomegalovirus retinitis and AIDS reported that history of retinal detachment was associated with higher risk of cataract if repaired with silicone oil vs. without silicone oil (adjusted hazard ratio (AHR) 10.37, 95% CI: 6.51 to 16.52 with silicone oil, AHR 2.90, 95% CI: 1.73 to 4.87 without silicone oil)[114].

Systemic responses: We did not identify any studies reporting systemic responses to silicone oil tamponade in retinal surgery.

Overall quality of evidence: The evidence base was large, but the bulk of the studies were uncontrolled case series. Although visual loss appears to be associated with silicone oil tamponade, the available evidence is not sufficient to determine whether this is due to silicone toxicity or some other factor related to silicone oil in the eye. Therefore, the overall quality of the data is low.

Penile implants and implanted continence devices: Our literature searches did not identify any studies of these devices that met inclusion criteria.

ECRI Surveillance Data

ECRI surveillance data comprise ECRI PSO event reports, accident investigations, user problem reports (PRNs), and alerts. The PSO, investigations, and problem reporting network (PRN) reports included in this report mostly include acute patient events. We rarely find chronic conditions or patient follow up reports, which are more prevalent in the clinical literature. Complications are reported directly by clinical staff, thus there is inherent variability in the reports. For example, breast implant rupture could be a result of capsular contracture, indicative of potential inadequate biocompatibility. Rupture could also be iatrogenic and noticed immediately during surgery. We extracted these differentiating factors where possible.

The surveillance data for siloxane are consistent with the clinical literature with regard to reported complications. Material failures such as rupture, deflation, and retained foreign bodies are particularly concerning as the mechanism is not always clear and they result in direct siloxane contact with tissue potentially for a long duration. Excluding infection from breast implant complications, rupture or deflation was reported in 55% of the remaining breast implant PSO event reports. The majority of penile implant complications consist of infection or malfunction, with lower associated harm than breast implant events. The majority of neuromodulatory system complications were infection and malfunction, and the most serious complications (2 reports with harm score G) were infection and paralysis. There are very few reports on urinary continence devices and injectables in our surveillance data.

Patient Safety Organization

Search Results: ECRI PSO identified 1,373 reports that involved siloxane materials that occurred between 4/2004 and 3/2020. 349 of these involved complications (see Table 3). The top 5 complications were 1) infection - 110 (32%), 2) rupture - 50 (14%), 3) hematoma - 35 (10%), 4) iatrogenic injury - 25 (7%), and 5) deflation - 19 (5%) and malfunction - 19 (5%). Harm occurred in 40% of the events, and the majority of events were associated with harm scores ranging from C through F (see
Table *4*). Harm scores C and D refer to errors that did not cause harm to the patient. E and F resulted in patient harm, where F required initial or prolonged hospitalization.

All individual PSO event reports are redacted and included in Appendix F.

Table 3: Complications in siloxane-related PSO event reports.

Complication	Breast Implant (MRD/FTR/FWM)	Penile Implant (JCW)	Neuro (LGW/GZF /GZB)	Urinary Continence (EZY)	Injectable (KGM)	Total
Infection	49	12	49			110
Rupture	50					50
Hematoma	23	4	8			35
Iatrogenic Injury	2	4	17	1	1	25
Deflation	18	1				19
Malfunction		10	7		2	19
Paralysis			10			10
Lead issue			9			9
Retained foreign body		3	6			9
Pain		2	6			8
Clinical manifestations		1	6			7
Unsatisfactory Style/Size	7					7

Complication	Breast Implant (MRD/FTR/FWM)	Penile Implant (JCW)	Neuro (LGW/GZF /GZB)	Urinary Continence (EZY)	Injectable (KGM)	Total
Fall			6			6
Migration		3	3			6
Malposition/Displacement	5					5
Delayed Wound Healing	4					4
Inflammation/Irritation	3					3
Necrosis	2					2
Wrong site/side/level			2			2
Asymmetry	2					2
Implant erosion		2				2
Seroma	2					2
Cerebritis			1			1
Chest Wall Deformity	1					1
Extrusion	1					1
Wrinkling/Rippling	1					1
Calcification/Calcium Deposits	1					1
Capsular Contracture	1					1
Lymphedema or Lymphadenopathy	1					1
Total	**173**	**42**	**130**	**1**	**3**	**349**

Table 4: Harm Score associated with siloxane-related event reports.

Harm Scores (NCC-MERP)

Category	Severity	Breast Implant (MRD/FTR/ FWM)	Penile Implant (JCW)	Neuro (LGW/GZF /GZB)	Urinary Continence (EZY)	Injectable (KGM)	Total
A	No Error	10	4	17	--	--	31
B1	Error, No Harm	--	--		--	1	1
B2	Error, No Harm	1	--	2	--	--	3
C	Error, No Harm	18	9	16	--	--	43
D	Error, No Harm	15	7	19	--	--	41
E	Error, Harm	43	11	40	1	--	95
F	Error, Harm	19	2	16	--	--	37
G	Error, Harm	4	--	2	--	--	6
H	Error, Harm	--	--	--	--	--	--
I	Error, Death	--	--	--	--	--	--
NULL*		63	9	18	--	2	92
Total		**173**	**42**	**130**	**1**	**3**	**349**

**Harm score was not reported*

Accident Investigations

Search Criteria: Breast implant, penile implant, neuromodulatory systems, urinary continence devices, injectables. Antireflux prostheses were added for historical reference and guidance. Investigation files were searched as far back as 1985 to recover cases pertaining to the above devices.

Search Results: 28 investigations were recovered as summarized in Table 5. Reported patient incidents were associated, in part, with implant deflation, rupture, and leaking – all of which increase the likelihood of a host response. There were no investigations of neuromodulatory systems or injectables.

All individual investigations are redacted and included in Appendix F.

Table 5: Accident investigations of patient incidents involving siloxane devices.

Device Type	# Investigations	Reported Problem and Findings (number of investigations)
Breast Implant (FTR/FWM)	9	*Deflation (3)* – needle perforation in subsequent procedure *Capsular Contracture (1)* – crease-fold failure, overpressurization *Rupture / Tear (5)* – iatrogenic at implantation, manufacturing defect, design defect
Penile Implant (JCW)	5	*Leaking (1)* – iatrogenic at implantation *Inflation Deficiency (1)* – design defect *Deflation (2)* – crease failure, incorrect sizing
Urinary Continence (EZY)	1	*Deflation (1)* – material alteration from contact with povidone-iodine
Antireflux prosthesis	13	*Migration* *Erosion* *Leaching*

ECRI Problem Reports

Search Criteria: Breast, Mammary, Breast Implant, Breast Prosthesis, Penile Implants, Penile Prosthesis, Urinary, Neuro, DBS, Deep Brain Stim, Neuromodulation, and Injectables

Search Results: The search returned 23 reports submitted by ECRI members (

Table *6*). The reports include device ruptures, erosions, leaking, causing pain, malfunctioning, and unintentional shocking. All reports, with exception of one neuromodulatory system report, specified that patients required additional surgeries for device removal.

All problems reports are redacted and included in Appendix F.

Table 6: ECRI Problem Report Summary

Device Type	# Problem Reports	Reported Problem (number of problem reports)
Breast Implant (FTR)	10	*Leaking / Rupture / Deflation (6)* *Infection/ Cellulitis (3)* *Malfunction (1)*

Device Type	# Problem Reports	Reported Problem (number of problem reports)
Penile Implant (JCW)	9	*Leaking* *Pain* *Malfunction* *Erosion*

Device Type	# Problem Reports	Reported Problem (number of problem reports)
Neuromodulatory systems (LGW)	2	*Failure (1)* *Short with Repeated Shocking (1)*
Urinary Continence (EZY)	2	*Leaking /Failure (2)*
Injectables (KGM)	0	NA

Alerts

Search Criteria: Breast Implants, Penile Implants, AMS 800, Urinary Prosthesis, Neuromodulatory Systems, NMS

Search Results: The search returned 81 alerts related to siloxane implants, summarized in Table 7.

Table 7: Summary of regulatory and manufacturer alerts

Device Type	# Alerts	Problems
Breast Implant (FTR, FWM)	35 7 issued by regulatory agencies 28 manufacturer-issued	• Unapproved composition • Manufacturing errors • Labeling errors • Contamination with particles, Increased risk of developing anaplastic large cell lymphoma (ALCL)
Penile Implant (JCW)	4 All manufacturer-issued	• Component may break • Labeling • Manufacture validation
Neuromodulatory systems (LGW/GZF/GZB)	35 All manufacturer-issued	• Unexpected stimulation • Damaged materials • Labeling • Loss of communication • High impedance of components • Implant site may become warm

Device Type	# Alerts	Problems
Urinary Continence (EZY)	7 All manufacturer-issued	• Unintended activation • Manufacturer quality compliance • Packaging problems • IFU update
Injectables (KGM)	1 Manufacturer-issued recall	NA

Potential Gaps

ECRI surveillance searches reflect mostly acute patient incidents that involved medical devices made of the material of interest, in this case siloxane. Areas of particular concern involve incidents that result in direct tissue exposure to the material if there is moderate to high-quality evidence of acute or systemic reaction to this exposure, as determined by the systematic review. Topics with very low or low quality of evidence represent areas of potential gaps in the literature. In addition if the literature revealed areas of new concern (e.g., systemic response to long-duration contact) and there is little supporting evidence, these are considered gaps.

With the exception of the literature concerning silicone breast implants, the literature for silicone/siloxane generally lacked data on patient-related or material-related factors that influence the likelihood and/or severity of sustained, exaggerated systemic responses.

Siloxane/silicone as a material: Only one human study reported systemic response of siloxane material and its relevance to medical device applications is questionable. This study was related to accidental inhalation of alkylsiloxanes in an industrial setting. The few animal studies for systemic response reported no serious adverse outcomes.

Breast implants: There is sufficient evidence in the literature and surveillance search addressing risk of local host response including capsular contracture, rupture, and pain. The systemic response literature, however, has low-quality evidence when potential confounding factors and rarity of the reported responses in large population studies are considered. In addition, there was only one human study on systemic response for siloxane material, which was unrelated to medical device applications. Additional research is indicated to address systemic response to breast implants.

Silicone injectables: The overall quality of evidence was low and was very low for systemic response. One study reporting hypercalcemia related to granulomas could indicate further research. The surveillance search produced very few reports and only one manufacturer recall. Additional research in FDA's databases may be indicated to determine the risk associated with silicone injectables and thus the need for additional studies.

Neuromodulatory systems: No human studies on neuromodulatory systems met inclusion criteria. The animal studies were consistent in showing fibrous tissue growth in response to neuromodulatory implants containing silicone, with moderate quality of evidence. Systemic response data were limited to one animal study, thus quality of evidence was low. The amount of data in the surveillance searches for neuromodulatory systems was considerable; however, most data were associated with device malfunction, which can result in significant harm, rather than inadequate biocompatibility. There were some reports in the PSO data of "clinical manifestation" and pain, both of which could indicate the need for further biocompatibility research.

Silicone oil for ophthalmic uses: The quality of evidence was low for ophthalmic oil risk given that the majority of the studies were uncontrolled case series. Further research is indicated to determine whether vision loss associated with silicone oil tamponade is due to silicone toxicity or another mechanism related to silicone oil in the eye.

Penile implants and urinary continence devices: No studies met inclusion criteria for penile implants and urinary continence devices. There were very little data in these categories from the surveillance searches as well. These devices are of less concern with regard to biocompatibility.

Appendix A. Inclusion/Exclusion Criteria and Quality of Evidence Criteria

Inclusion Criteria

1. English language publication
2. Published between January 2010 and July 2020
3. Human and animal studies
4. Systematic reviews, randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, case series
5. Studies that evaluate toxicity/biocompatibility of siloxanes/silicone or priority devices that include this material

Exclusion Criteria

1. Foreign language publication
2. Published before January 2010
3. Not a study design of interest (e.g., in vitro lab study, case report, narrative review, letter, editorial)
4. Off-topic study
5. On-topic study that does not address a key question
6. No device or material of interest
7. No relevant outcomes (adverse events or biocompatibility not reported)
8. Study is superseded by more recent or more comprehensive systematic review

Quality of Evidence Criteria

1. **Quality of comparison** – is there evidence from systematic reviews including randomized and/or matched study data and/or randomized or matched individual studies?
2. **Quantity of data** – number of systematic reviews and individual studies (human and animal) providing relevant data.
3. **Consistency of data** – are the findings consistent across studies that report relevant data?
4. **Magnitude of effect** – in human and animal studies, what is the likelihood of adverse effects compared to controls (with no device, lower dosage, shorter exposure time), and possibly number of patients likely to have harms.
5. **Directness of evidence** – do human studies isolate the effect of the device (i.e. can the adverse effects be attributed to the device)? Animal studies are indirect but may provide the best evidence for the material itself.
6. Is there evidence of a **dose response or time response** (e.g. adverse effects increase with longer exposure time)?

Appendix B. Search Summary

Strategies crafted by ECRI's medical librarians combine controlled vocabulary terms and free-text words in conceptual search statements that are joined with Boolean logic (AND, OR, NOT).

Most medical bibliographic databases such as Medline and Embase include detailed controlled vocabularies for medical concepts accessible through an online thesaurus. Controlled vocabularies are a means of categorizing and standardizing information. Many are rich ontologies and greatly facilitate information transmission and retrieval. Frequently seen examples of controlled vocabularies include ICD-10, SNOMED-CT, RxNorm, LOINC, and CPT/HCPCS.

Citations in PubMed are indexed with MeSH terms and those in Embase are indexed with terms from EMTREE. These terms are assigned either by a medical indexer or an automated algorithm. Several terms are selected to represent the major concept of the article – these are called "major" headings. This "major" concept can be included in search strategies to limit search retrieval. The syntax in Embase for this is /mj. We have used this convention in our strategies sparingly since indexing is subjective and we are using a sensitive search approach which errs in the direction of comprehensiveness.

Database providers build functionality into their search engines to maximize the usefulness of indexing. One of the most frequently used shortcuts is term explosion. "Exploding" in the context of hierarchical controlled vocabularies means typing in the broadest (root or parent) term and having all the related more specific terms included in the search strategy with a Boolean OR relationship. We use term explosions whenever feasible for efficiency. Feasibility depends on whether you wish to include all of the related specific terms in your strategy. For example, in one of our approaches we explode the Emtree concept mechanics. This explosion automatically added the all the following terms (n = 174) and their associated entry terms (lexical variants and synonyms) to the strategy using an "OR" without the searcher having to type them in. That's one of the major advantages to searching using controlled vocabularies. We don't rely exclusively on controlled vocabulary terms since there are possible limitations such as inconsistent indexing and the presence of unindexed content. That's why we also include free text words in our strategies.

Material: Siloxanes

Set Number	Concept	Search statement
1	**Siloxanes**	'dimethyl polysiloxan' OR 'dimethyl polysiloxane' OR 'dimethylpolysiloxan*' OR 'dimethylpolysiloxane' OR 'dimethylpolysiloxanes' OR 'dimethyl siloxane' OR 'dimethylsiloxane' OR 'polydimethyl siloxane' OR 'polydimethylsiloxane' OR 'poly dimethyl siloxane' OR 'polysilan*' OR 'polysilane' OR 'sentry dimethicone' OR polysiloxan*
2		silicone* OR siloxane* OR siloxone* OR 'silicone gel' OR 'silicone elastomer*' OR 'silicone polymer*' OR 'silicone*shell'
3		dimeth* NEAR/3 (polysilox* OR siloxan* OR siloxon*)
4		silastic
5		'organosilicon derivative'/exp
6		'silicone oil'
7	**Combine sets**	**#1 OR #2 OR #3 OR #4 OR #5 OR #6**

Set Number	Concept	Search statement
8	Exclude concepts	#7 NOT (simethicone OR dimeticone OR biosensor* OR immunosensor*)
9	Limit by language and publication date	#8 AND [english]/lim AND [2010–2020]/py
10	Limit by publication type	#9 NOT ('book'/it OR 'chapter'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'erratum'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it OR 'tombstone'/it)

Material Response

Set Number	Concept	Search statement
11		'biocompatibility'/de OR biocompat* OR tribolog* OR 'bio compat*' OR 'biological* compat*' OR 'biological* evaluation'
12		'degradation'/exp OR degradation OR degrad* OR split OR splitting OR split* OR wear OR deteriorat* OR atroph* OR migrat* OR movement OR shift* OR transfer* OR 'delamination'/exp OR delamina* OR leach* OR filtrate OR filter* OR seep*
13		Leachable* OR extractable*
14		(swell* OR shrink* OR contract* OR stretch* OR retract* OR extension OR extend* OR deform* OR creep OR plasticity OR degrad* OR disintegrat*) NEAR/3 (implant* OR mesh* OR sling* OR tape* OR suture*)
15		‘mechanics’/exp [see Emtree explosions section at the end of the strategy]
16		‘device material’/exp/mj
17		‘Biomedical and dental materials’/exp/mj
18	**Combine sets**	**#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17**

Devices

Set Number	Concept	Search statement
19	Neurostimulators	‘implantable neurostimulator’/exp

Set Number	Concept	Search statement
20		('nerve' OR 'ac powered nerve' OR 'battery powered nerve' OR 'neuromuscular' OR 'peripheral nerve' OR 'spinal cord' OR 'spinal ganglion' OR 'neuro' OR nerv* OR neural) NEAR/5 (implant* OR stimulator*)
21		'electrostimulation'/exp OR 'nerve stimulator'/exp
22		(electric OR electrode* OR electronic OR lead OR leads) NEAR/5 (implant* OR stimulator*)
23		'implant'/exp OR implant OR implantation OR implanted OR implant* OR stimulator*
24		'penis prosthesis'/exp
25		(penis OR penile) NEAR/2 (prosthes* OR prosthet* OR implant*)
26	**Combine sets**	**#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25**
Note: A search filter was created for breast implants but ultimately was not used for this search. The results from the materials response and host response searches captured the relevant breast implant citations.		

Host Response

Set Number	Concept	Search statement
27		Host NEAR/2 (reaction* OR response*)
28		'toxicity'/exp OR toxic*:ti OR cytotox* OR teratogenic* OR genotox* 'carcinogenicity'/exp OR carcinogen*:ti
29		('fibrosis'/exp OR fibrosis OR fibrotic) AND ('postoperative complication'/exp OR implant* OR mesh* OR sling* OR tape*)
30		'immune response'/exp OR 'immunity'/exp/mj OR 'hypersensitivity'/exp OR 'immunopathology'/exp/mj
31		Immun*:ti OR autoimmun*:ti OR hypersens*:ti
32		'inflammation'/exp OR inflamm*:ti

Set Number	Concept	Search statement
33		‘foreign body reaction’ OR granuloma*
34		('adhesion'/exp OR 'tissue adhesion'/exp OR 'biomechanics'/exp OR biocompat*)
35		('tissue adhesion'/exp OR adhes*) AND ('postoperative complication'/exp OR implant* OR mesh* OR sling* OR tape*)
36		(‘erosion’/exp OR ‘mesh erosion’/exp OR eros* OR erod*)
37		Expos* AND (implant* OR mesh* OR sling* OR tape* OR suture*)
38		(protrude* OR protrus*) NEAR/3 (implant* OR mesh* OR sling* OR tape* OR suture*)
39		Migrate OR migration
40	**Combine sets**	**#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39**

Alternate Approaches

Set Number	Concept	Search statement
41	By periodical title	(material* OR biomaterial*):jt
42		(‘physical parameters’/exp/mj OR ‘mechanics’/exp/mj) AND ([humans]/lim OR [animals]/lim)
43	**Combine sets**	**#41 AND #42**

Other combinations

Set Number	Concept	Search statement
#44	**Siloxanes AND Material Response AND Alternate Approaches**	**#10 AND #18 AND #43**
#45	**Siloxanes AND Host Response**	**#10 AND #40**
#46	**Devices AND (Material Response OR Host Response OR Alternate Approaches)**	**(#26 AND (#18 OR #40 OR #43)**
#47	**Combine all**	**#44 OR #45 OR #46**

Emtree term explosions

Mechanics/exp

- Biomechanics
- Compliance (physical)
    - Bladder compliance
    - Blood vessel compliance
        - Artery compliance
        - Vein compliance
    - Heart muscle compliance
        - Heart left ventricle compliance
        - Heart ventricle compliance
    - Lung compliance
- Compressive strength
- Dynamics
    - Compression
    - Computational fluid dynamics
    - Decompression
        - Explosive decompression
        - Rapid decompression
        - Slow decompression
    - Gravity
        - Gravitational stress
        - Microgravity
        - Weight
            - Body weight
                - Birth weight
                    - High birth weight
                    - Low birth weight
                        - Small for date infant
                        - Very low birth weight

        - Extremely low birth weight
    - Body weight change
        - Body weight fluctuation
        - Body weight gain
            - Gestational weight gain
        - Body weight loss
            - Emaciation
        - Body weight control
        - Fetus weight
        - Ideal body weight
        - Lean body weight
        - Live weight gain
    - Dry weight
    - Fresh weight
    - Molecular weight
    - Organ weight
        - Brain weight
        - Ear weight
        - Heart weight
        - Liver weight
        - Lung weight
        - Placenta weight
        - Spleen weight
        - Testis weight
        - Thyroid weight
        - Uterus weight
    - Seed weight
    - Tablet weight
    - Thrombus weight
- Weightlessness
- Hydrodynamics
    - Hypertonic solution
    - Hypotonic solution
    - Isotonic solution
    - Osmolality
        - Hyperosmolality
        - Hypoosmolality
        - Plasma osmolality
        - Serum osmolality
        - Urine osmolality
    - Osmolarity
        - Blood osmolarity
        - Hyperosmolarity
        - Hypoosmolarity
        - Plasma osmolarity
        - Serum osmolarity
        - Tear osmolarity
        - Urine osmolarity
    - Osmosis
        - Electroosmotic
        - Osmotic stress
            - Hyperosmotic stress
            - Hypoosmotic stress
- Photodynamics
    - Photoactivation

                - Photoreactivation
            - Photodegradation
            - Photoreactivity
                - Photocytotoxicity
                - Photosensitivity
                - Photosensitization
                - Phototaxis
                - Phototoxicity
            - Photostimulation
        - Proton motive force
        - Shock wave
            - High-energy shock wave
        - Stress strain relationship
        - Thermodynamics
            - Adiabaticity
            - Enthalpy
            - Entropy
- Elasticity
    - Viscoelasticity
    - Young modulus
- Force
- Friction
    - Orthodontic friction
- Hardness
- Kinetics
    - Adsorption kinetics
    - Flow kinetics
        - Electroosmotic flow
        - Flow rate
        - Gas flow
        - Laminar airflow
        - Laminar flow
        - Powder flow
            - Angle of repose
            - Hausner ration
        - Pulsatile flow
        - Shear flow
        - Thixotropy
        - Tube flow
        - Turbulent flow
        - Vortex motion
        - Water flow
    - Motion
        - Coriolis phenomenon
        - Rotation
        - Vibration
            - Hand arm vibration
            - High frequency oscillation
            - Oscillation
            - Oscillatory potential
            - Whole body vibration
    - Velocity
        - Acceleration
        - Deceleration
        - Processing speed

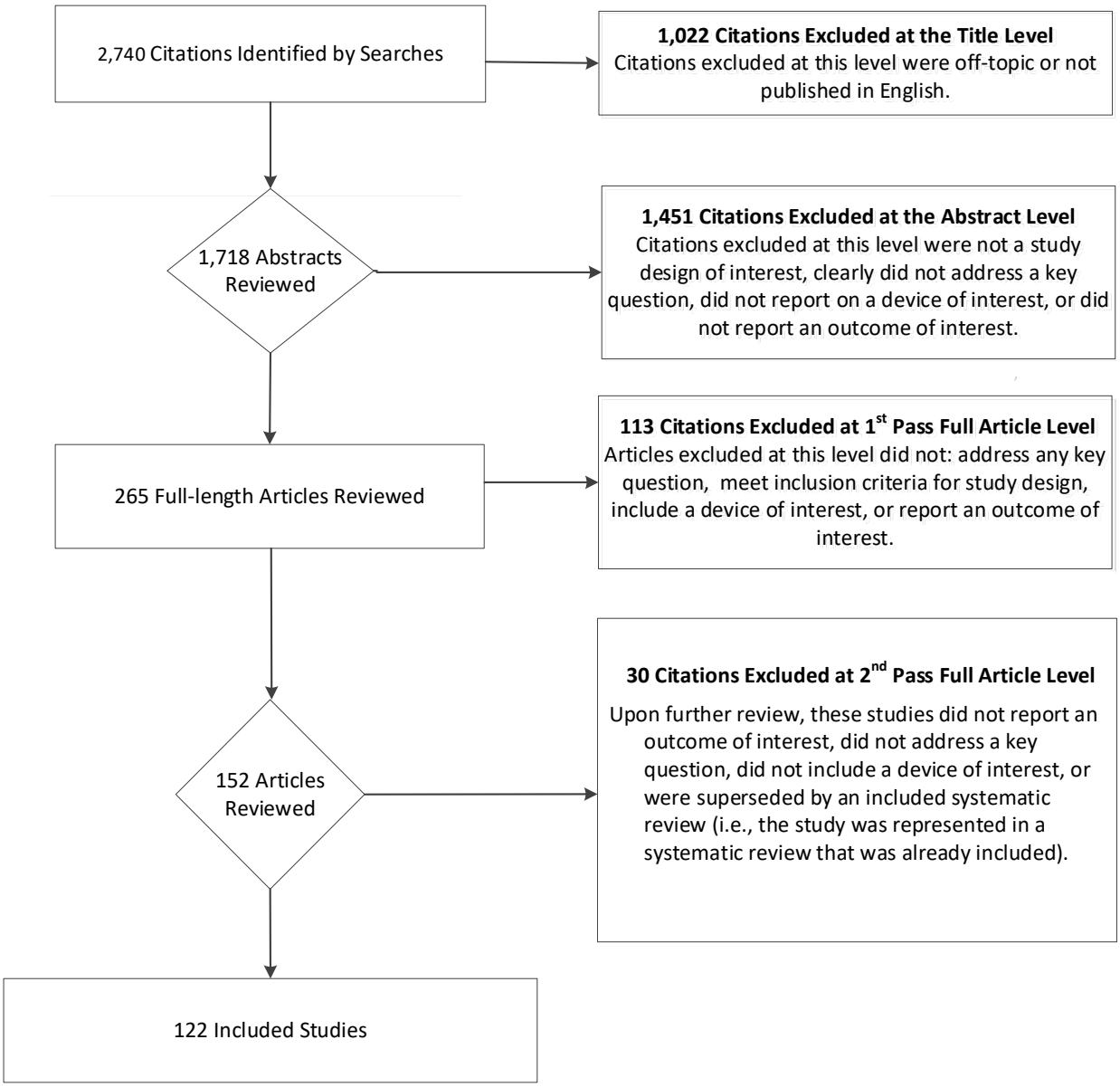
        - Wind speed
- Mass
    - Biomass
        - Fungal biomass
        - Immobilized biomass
        - Microbial biomass
    - Body mass
    - Bone mass
    - Dry mass
    - Fat free mass
    - Fat mass
    - Heart left ventricle mass
    - Kidney mass
- Materials testing
- Mechanical stress
    - Contact stress
    - Contraction stress
    - Shear stress
    - Surface stress
    - Wall stress
- Mechanical torsion
- Molecular mechanics
- Plasticity
- Pliability
- Quantum mechanics
    - Quantum theory
- Rigidity
- Torque
- Viscosity
    - Blood viscosity
        - Plasma viscosity
    - Gelatinization
    - Shear rate
    - Shear strength
    - Shear mass
    - Sputum viscosity

Viscoelasticity Organosilicon derivative/exp

- 1 ethoxysilatrane
- 2 (2 trimethylsilylethylthio)ethylamine
- 2 [2 (dimethylphenylsilyl)ethylthio]ethylamine
- 3 aminopropyltriethoxysilane
- 3 decyldimethylsilyl n [2 (4 methylphenyl) 1 phenylethyl]propionamide
- 5 fluoro 3,4 dihydro 2,4 dioxo n (4,4 dimethyl 4 sila 5 hexenyl) 1(2h) pyrimidinecarboxamide
- abil b 8843
- allyltrimethylsilane
- amsilarotene
- chlorotrimethylsilane
- cyclohexyl(phenyl)(2 piperidinoethyl)silanol
- Dimeticone
- Dirocaftor
- ethylmethyl(1 silatranylmethyl)sulfonium iodide
- fluorosilicone
- flusilazole

- hexahydrosiladifenidol
- hexahydrosiladifenidol derivative
- hexamethyldisiloxane
- hydrotalcite plus simethicone
- loperamide plus simethicone
- n [2 [2 (dimethylphenylsilyl)ethylthio]ethyl] 5 fluoro 3,4 dihydro 2,4 dioxo 1(2h) pyrimidinecarboxamide
- organically modified ceramic
- para fluorohexahydrosiladifenidol
- polysiloxane
- silahexocyclium
- silane
- silane derivative
- silanol
- silastic
- silastic 382
- silatrane derivative
- silicone
- silicone derivative
- silicone gel
- silicone oil
- silorane
- siloxane
- Silperisone
- Simethicone
- Tetraethoxysilane
- Tetramethoxysilane
- Trimethoxymethylsilane
- Trimethoxyoctadecylsilane
- trimethylsilyl derivative

Appendix C: Study Flow Diagram



Appendix D. Evidence Tables

Table 8: Silicone or Siloxane as a Material – Health Effect (In Vivo) Human Studies

Local and Systemic Response/Toxicity

Source Citation: Duch et al. 2014[1]

Study Design: Case series

Device or Material: Non-fluorinated alkylsiloxanes

Contact Duration: 10 to 150 minutes

Dose: 30 L of tile-coating product Stain Repellent Super (SRS), about 3.2 g/m^3 (22,800 g in 7220 m^3)

Frequency/Duration: One industrial exposure. SRS aerosols were visible for hours

Response: Bilateral perihilar infiltrates, Chest pain, Coughing, Elevated CRP, Fever, General malaise, Headache, Leukocytosis, Shortness of breath, Tachycardia, Tachypnea

Patient characteristics (gender, mean age): 29 males, median age 33 years.

Number per group: 39

Observations on adverse effects (brief): Exposure to non-fluorinated alkylsiloxanes in a tile-coating product caused tachycardia and severe respiratory symptoms in 38% and 7% of exposed individuals, respectively. Symptoms included coughing (100%), shortness of breath (74%), chest pain (20%), general malaise (49%), headache (46%), tachycardia (38%), tachypnea (51%), and fever (66%). Radiographs of 66% individuals with severe respiratory symptoms indicated bilateral perihilar infiltrates, leukocytosis, and elevated CRP levels. The patients generally recovered within 72 hours. No delayed effects but 15 patients still had shortness of breath during hard physical work 2 months later.

Timing of adverse effects: Within 1 to 12 hours.

Factors that predict response: Smoking (median pack years: 7, range 1 to 40), ischemic heart disease (NYHA II), increased age were associated with a few cases with severe symptoms. Dose-response was not straightforward, as only 1 of 5 patients with high-dose exposure had severe symptoms. None of the workers reported any sensory irritation in the eyes or airways related to the spraying event. This is important in relation to risk assessment, because workers may be exposed to even very high concentrations without feeling discomfort, that is the product does not provide a 'warning signal.'

Other Toxicity/Carcinogenicity

No Studies

CRP = C-reactive protein; NYHA = New York Heart Association

Table 9: Silicone or Siloxane as a Material – Health Effect (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Chen et al. 2019[2]

Study Design: Controlled study

Device or Material: Polydimethyl-siloxane (PDMS) (co-polymer modified or untreated – untreated used as control group)

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 1 month

Response: Local FBR to implant

Species (strain): Nude mouse

Gender: Female

Number per Group: 3

Observations on adverse effects (brief): Capsule thickness was 270 ± 49 μm in untreated PDMS group compared with 142 ± 23 μm in co-polymer modified PDMS group.

Timing of adverse effects: 1 month

Data Quality: NR

Source Citation: Lee et al. 2019[3]

Study Design: Controlled study

Device or Material: PDMS treated or untreated (control group)

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 2 to 8 weeks

Response: FBR

Species (strain): Sprague-Dawley rat

Gender: male

Number per Group: NR

Observations on adverse effects (brief): Untreated PDMS had highest inflammation markers, macrophage number, and collagen density.

Timing of adverse effects: 2 to 8 weeks

Factors that predict response: NR

Data Quality: NR

Source Citation: Bae et al. 2018[4]

Study Design: Controlled study

Device or Material: Silicone implants

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 8 weeks

Response: Capsular contracture, Inflammation, Fibrosis

Species (strain): Mice

Gender: Male

Number per Group: 6

Observations on adverse effects (brief): FBR

Timing of adverse effects: 8 weeks

Factors that predict response: NR

Data Quality: NR

Source Citation: Colak et al. 2018[5]

Study Design: Randomized controlled study

Device or Material: Silicone block implants (untreated control group, saline-injection control group, IV dexamethasone group, IV plus intraperitoneal dexamethasone group)

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 70 days

Response: FBR

Species (strain): Sprague Dawley rat

Gender: Female

Number per Group: 8

Observations on adverse effects (brief): Untreated control had thickest capsule, myofibroblast proliferation was significantly increased in controls.

Timing of adverse effects: Within 70 days

Factors that predict response: TLR4 system suppression reduces capsule thickness and myofibroblast proliferation.

Data Quality: NR

Source Citation: Li et al. 2018[6]

Study Design: Controlled study

Device or Material: Poly(citrate-siloxane) (PCS) elastomer

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 2 to 4 weeks

Response: Inflammation

Species (strain): Rat

Gender: Male

Number per Group: NR

Observations on adverse effects (brief): Indicators of inflammation were highest in the untreated PCS.

Timing of adverse effects: 2 to 4 weeks

Factors that predict response: NR

Data Quality: NR

Source Citation: Yoo et al. 2018[7]

Study Design: Controlled study

Device or Material: PDMS

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 2 to 8 weeks

Response: FBR, capsular contracture

Species (strain): Sprague-Dawley rat

Gender: NR

Number per Group: 18

Observations on adverse effects (brief): Indicators of inflammation were higher in the bare PDMS implant. Higher number of fibroblasts and higher collagen density.

Timing of adverse effects: NR

Factors that predict response: NR

Data Quality: NR

Source Citation: Dekant et al. 2017[8]

Study Design: Systematic review

Device or Material: Octamethyl-cyclotetrasiloxane (D4), a cyclic siloxane primarily used as a monomer or intermediate in the production of silicone polymers

Route: Chronic inhalation

Dose: Male and female F344 rats (60 rats/sex/dose) were exposed to 0, 10, 30, 150, or 700 ppm D4 vapor for 6 hr/day, 5 days/week for up to 104 weeks in whole-body inhalation chambers.

Frequency/Duration: 2-year chronic toxicity

Response: Increases in liver weight, Nephropathy, Incidence of proliferative uterine endometrial lesions

Species (strain): F344 and Sprague-Dawley rat

Gender: Male and Female

Number per Group: 60

Observations on adverse effects (brief): Increases in uterine endometrial cystic hyperplasia and adenomas were observed at the highest concentration of D4 administered (700 ppm).

Timing of adverse effects: During 2-year period.

Factors that predict response: NR

Data Quality: XXX

Source Citation: Huang et al. 2017[9]

Study Design: Controlled study

Device or Material: Silicone implant

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: Implant collected at 7, 8, 9, 10, 11, and 14 days

Response: Localized immune response

Species (strain): Sprague-Dawley rat.

Gender: Male

Number per Group: 18 silicone implant (3 at each time point) and 3 sham control.

Observations on adverse effects (brief): Silicone implants are responsible for triggering a localized immune response.

Timing of adverse effects:

Factors that predict response: 5 genes (Fes, Aif1, Gata3, Tlr6, Tlr2) were identified as hub genes that are most likely related to the silicone-induced immune response, 4 of which (Aif1, Gata3, Tlr6, Tlr2) have been associated with autoimmunity as target genes or disease markers.

Data Quality: NR

Source Citation: Lei et al. 2016[10]

Study Design: Controlled study

Device or Material: Silicone rubber

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 7, 15, and 30 days

Response: FBR

Species (strain): Sprague Dawley rat

Gender: Female

Number per Group: 16 total

Observations on adverse effects (brief): Inflammatory reaction was greatest in untreated implants. Fibrous capsules were thicker in untreated implants.

Timing of adverse effects: 30 days

Factors that predict response: NR

Data Quality: NR

Source Citation: Zhou et al. 2016[11]

Study Design: Controlled study

Device or Material: Carbon ion silicone rubber

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 7, 30, 90, and 180 days after implantation

Response: Local inflammation, FBR

Species (strain): Sprague-Dawley rat

Gender: Female

Number per Group: 16 total, 4 per group

Observations on adverse effects (brief): Silicone rubber implants are associated with local inflammation, foreign body response. At 7 days after implantation, silicone rubber had the thinnest tissue capsules, and carbon ion silicone rubber (C1, C2, and C3) had thicker ($p > 0.05$) and weaker tissue capsules. Carbon ion silicone rubber had obviously lower collagen deposition than silicone rubber.

Timing of adverse effects: NR

Factors that predict response: NR

Data Quality: NR

Source Citation: Dearth et al. 2015[12]

Study Design: Controlled study

Device or Material: Silicone membranes

Route: Abdominal implant

Dose: NR

Frequency/Duration: 4, 8, 12 weeks

Response: Silicone-induced capsule formation and contracture

Species (strain): Sprague Dawley rat

Gender: Female

Number per Group: 5

Observations on adverse effects (brief): Decreased thickness of the collagenous tissue layer at biologic scaffold/silicone interface compared to the abdominal wall/silicone interface.

Timing of adverse effects: 4 to 12 weeks.

Factors that predict response: NR

Data Quality: NR

Source Citation: Gellynck et al. 2015[13]

Study Design: Controlled study

Device or Material: PDMS

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 1 and 3 months

Response: FBR

Species (strain): Goat

Gender: Female

Number per Group: 6

Observations on adverse effects (brief): Response was limited.

Timing of adverse effects: Within 3 months.

Factors that predict response: : Implants were doughnut shaped.

Data Quality: NR

Source Citation: Kim et al. 2015[14]

Study Design: Controlled study

Device or Material: Silicone implant with smooth surface

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 2 months

Response: FBR

Species (strain): Sprague Dawley rat

Gender: Female

Number per Group: 52 divided into 3 groups: 16, 18, and 18.

Observations on adverse effects (brief): Capsule formation in control group was 188.5 µm.

Timing of adverse effects: 2 months

Factors that predict response: Increase in blood flow decreased inflammatory response.

Data Quality: NR

Source Citation: Bergmann et al. 2014[15]

Study Design: Controlled study

Device or Material: Silicone gel-filled implant, textured versus smooth

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 60 days

Response: Acute and chronic inflammation, Fibrotic capsule tissue formation, Capsule contraction

Species (strain): Wistar rat

Gender: Female

Number per Group: 20

Observations on adverse effects (brief): NR

Timing of adverse effects: Within 60 days.

Factors that predict response: NR

Data Quality: NR

Source Citation: Duch et al. 2014[1] Animal study

Study Design: Controlled study

Device or Material: Alkylsiloxanes

Route: Breathing of aerosol

Dose: 59 mg/m3 to 5,700 mg/m3

Frequency/Duration: 10 to 60 minutes

Response: Concentration- and time-dependent decrease in the tidal volume

Species (strain): BALB/cA mice.

Gender: Male

Number per Group: 10

Observations on adverse effects (brief): NR

Timing of adverse effects: Within 60 minutes

Factors that predict response: NR

Data Quality: NR

Source Citation: Hosseinpour et al. 2014[16]

Study Design: Controlled study

Device or Material: Silicone versus latex catheters

Route: Catheters placed in the urethra, hypospadias-like defect was created by a 1 cm long excision of the ventral urethra

Dose: NR

Frequency/Duration: 10 days

Response: No urinary tract infections in silicone group, silicone not responsible for cystitis development

Species (strain): Rabbit with hypospadias.

Gender: Male

Number per Group: 20

Observations on adverse effects (brief): Silicone not responsible for inflammation or cystitis.

Timing of adverse effects: 10 days

Factors that predict response: NR

Data Quality: NR

Source Citation: Hsueh et al. 2014[17]

Study Design: Randomized controlled with sham control

Device or Material: Medical grade silicone tube, treated and untreated

Route: Sciatic nerve transection model

Dose: NR

Frequency/Duration: 6 weeks

Response: Inflammation

Species (strain): Sprague-Dawley rat.

Gender: Male

Number per Group: NR

Observations on adverse effects (brief): Untreated silicone tubes had increased inflammatory reaction and less nerve growth.

Timing of adverse effects: 6 weeks

Factors that predict response: NR

Data Quality: NR

Source Citation: Park et al. 2014[18]

Study Design: Controlled, each animal received a treated and non-treated implant

Device or Material: Polydimethyl-siloxane silicone elastomer implant

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 4 and 12 weeks

Response: Local inflammation

Species (strain): Sprague-Dawley rat

Gender: Female

Number per Group: 24

Observations on adverse effects (brief): Capsule formation was thicker and number of inflammatory cells were greater in the non-treated group. Other indicators of inflammation were greater in non-treated group.

Timing of adverse effects: Within 4 weeks.

Factors that predict response: NR

Data Quality: NR

Source Citation: Steiert et al. 2014[19]

Study Design: Controlled study

Device or Material: Silicone disks

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 12 weeks

Response: Local inflammation

Species (strain): C57/BL6 mice

Gender: Female

Number per Group: 5

Observations on adverse effects (brief): Untreated silicone implants showed more local inflammatory response.

Timing of adverse effects: within 12 weeks.

Factors that predict response: Demonstrated that the activation of a silicone surface with a vectored antibody influences the surrounding tissue.

Data Quality: NR

Source Citation: Vijayalakshmi et al. 2013[20]

Study Design: Randomized controlled study

Device or Material: Polydimethylsiloxane (PDMS), silicone, and silicone plus silica, each was extracted into saline for injection

Route: Intraperitoneal injection

Dose: Normal saline control, cyclophosphamide positive, control, and unknown amount of PDMS, silicone, and silicone plus silica

Frequency/Duration: 24 and 48 hours

Response: PDMS and silicone did not induce oxidative stress responses

Species (strain): Swiss albino mice

Gender: Male and female

Number per Group: 12 each for 5 groups.

Observations on adverse effects (brief): Liver tissue homogenates showed no increased oxidative stress except for cyclophosphamide positive control.

Timing of adverse effects: NR

Factors that predict response: NR

Data Quality: NR

Source Citation: Bergmann et al. 2012[21]

Study Design: Controlled study

Device or Material: Silicone implants, smooth vs. titanium-coated

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 12 and 36 weeks

Response: Chronic inflammation

Species (strain): Wistar rat

Gender: Female

Number per Group: 17 smooth saline-filled implant and 14 saline-filled titanium-coated silicone implants.

Observations on adverse effects (brief): Chronic inflammatory reaction seen for both implants. No significant differences between capsule thickness, signs of inflammation, or presence of blood vessels.

Timing of adverse effects: Within 36 weeks.

Factors that predict response: Increased cellular infiltration with conventional silicone implants.

Data Quality: NR

Source Citation: Fleckman et al. 2012[22]

Study Design: Controlled study

Device or Material: Silicone implants, each mouse was implanted with 1 porous/solid poly(HEMA) rod and 1 porous/solid silicone rod

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 14 days, 1, 3, and 6 months

Response: Mild inflammation

Species (strain): C57BL/6 mice.

Gender: Female

Number per Group: 32

Observations on adverse effects (brief): Silicone implant showed greater skin contraction, but both showed little inflammation.

Timing of adverse effects: Within 6 months.

Factors that predict response: NR

Data Quality: NR

Source Citation: Jensen et al. 2012[23]

Study Design: Controlled study

Device or Material: Polydimethyl-siloxane implant with and without water vapor plasma treatment

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 2 and 4 weeks

Response: Capsule formation, Mild inflammation

Species (strain): Wistar rat.

Gender: Female

Number per Group: 20 total

Observations on adverse effects (brief): Thin fibrotic capsules and mild inflammatory reactions were noted surrounding the implants.

Timing of adverse effects: Inflammatory response.

Factors that predict response: : Capsule thickness was less around treated implants.

Data Quality: NR

Source Citation: Kolb et al. 2012[24]

Study Design: Controlled study

Device or Material: Silicone granule coated polypropylene scaffold

Route: Each pig was implanted with 12 grafts (3 strips each silicone granule, freeze-dried acellular human dermis, cross-linked acellular porcine dermis, and polytetra-fluoroethylene

Dose: NR

Frequency/Duration: 7, 21, 90, 180 days

Response: FBR

Species (strain): Pig

Gender: NR

Number per Group: 5

Observations on adverse effects (brief): Silicone implant showed mild to moderate inflammation at day 7, robust foreign body reaction was persistent at 180 days.

Timing of adverse effects: Started at 7 days and persisted to 180 days.

Factors that predict response: NR

Data Quality: NR

Source Citation: Tuncel et al. 2012[25]

Study Design: Controlled study

Device or Material: Silicone implants

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 3 months

Response: Local inflammation, Capsule formation

Species (strain): Rabbit.

Gender: Male

Number per Group: 8

Observations on adverse effects (brief): Inflammatory response and capsule formation were greater in the untreated implant, fibroblast cell count was higher in untreated implant.

Timing of adverse effects: Within 3 months

Factors that predict response: Fascia tissue barrier effectively prevented silicone rod reaction and foreign body reaction developing against silicone prosthesis.

Data Quality: NR

Source Citation: Auquit-Auckbur et al. 2011[26]

Study Design: Controlled study

Device or Material: Disks from silicone breast implant coated with fibrinogen

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 14 days

Response: FBR, Inflammation

Species (strain): C57BL wild-type mice and TLR4 knockout mice

Gender: NR

Number per Group: NR

Observations on adverse effects (brief): Significant decrease in the number of polymorphonuclear cells in the surrounding prosthesis tissue in TLR4-negative mice.

Timing of adverse effects: Within 14 days.

Factors that predict response: TLR4 is a key receptor that plays a role in the foreign body reaction to silicone implants.

Data Quality: NR

Source Citation: Peters et al. 2011[27]

Study Design: Controlled study

Device or Material: Silicone ring catheters, medical grade

Route: Intraperitoneal implant

Dose: NR

Frequency/Duration: 1 to 5 weeks

Response: FBR / inflammation

Species (strain): C57BL mice

Gender: Female

Number per Group: 28 implanted, 12 sham with no catheter

Observations on adverse effects (brief): Progressive increases in submesothelial thickening and ongoing angiogenesis over the 5 weeks of exposure to the silicone catheters.

Timing of adverse effects: Starting at 1 week.

Factors that predict response: NR

Data Quality: NR

Source Citation: Lynn et al. 2010[28]

Study Design: Controlled study

Device or Material: Medical grade silicone implant compared with hydrogel implants

Route: Subcutaneous implant

Dose: NR

Frequency/Duration: 28 days

Response: FBR

Species (strain): Wild-type mice (c57bl/6).

Gender: Male

Number per Group: Each mouse received all implants, number not reported.

Observations on adverse effects (brief): "Well-healed" FBR. Thin layer of inflammatory cells at the material surface, but very few of the cells stained positive for activated macrophages.

Timing of adverse effects: : 28 days

Factors that predict response: NR

Data Quality: NR

Source Citation: Joh et al. 2020[29]

Study Design: Randomized controlled trial

Device or Material: Silicone oil used to lubricate prefilled syringes

Route: Subcutaneous

Dose: Up to ~50,000 particles/mL of spherical silicone oil particles

Frequency/Duration: 6, 9, 11 weeks

Response: No increased immunogenicity with silicone oil

Species (strain): Xeno-het mouse model

Gender: Male and female

Number per Group: 13 groups, 11 animals per group.

Observations on adverse effects (brief): Silicone oil particles were associated with no antidrug antibodies or significant cytokine production in transgenic Xeno-het mice, regardless of whether mAb1 or polysorbate 80 was present.

Timing of adverse effects: NR

Factors that predict response: NR

Data Quality: NR

Source Citation: Krayukhina et al. 2019[30]

Study Design: Controlled study

Device or Material: Silicone oil

Route: Subcutaneous

Dose: NR

Frequency/Duration: Injected on days 0, 7, and 14

Response: Anti-drug antibody response

Species (strain): BALB/c mice

Gender: NR

Number per Group: 4 groups, 7 per group

Observations on adverse effects (brief): A slight increase in the plasma concentrations of antidrug antibodies over 21 days in response to silicone oil-containing antibody samples compared to the absence of silicone oil. SO droplets form complexes with pharmaceutical proteins that can potentially invoke early- and late-stage immune responses.

Timing of adverse effects: Blood samples taken on days 0, 7, 14, and 21.

Factors that predict response: NR

Data Quality: NR

Source Citation: Chisholm et al. 2017[31]

Study Design: Controlled study

Device or Material: Silicone oil droplets from syringes

Route: Subcutaneous injections

Dose: NR

Frequency/Duration: Injected days 1 and 15

Response: Antibody titer was higher with silicone oil in injection.

Species (strain): Wild-type C57BL/6 and sHEL-transgenic mice.

Gender: Female

Number per Group: NR

Observations on adverse effects (brief): Adsorption of proteins to silicone oil can perturb protein structure. Lysozyme readily adsorbed to silicone oil droplets that change lysozyme conformation. Silicone oil microdroplets acted as an adjuvant to boost the immune response.

Timing of adverse effects: NR

Factors that predict response: NR

Data Quality: NR

Source Citation: Uchino et al. 2017[32]

Study Design: Controlled study

Device or Material: Silicone oil droplets from syringes

Route: Subcutaneous injections with shaken siliconized or non-siliconized syringes

Dose: NR

Frequency/Duration: Blood collected 1, 7, 14, and 21 days

Response: Anti-drug antibody response

Species (strain): BALB/c mice

Gender: Male

Number per Group: 28

Observations on adverse effects (brief): Induced antibody production due to silicone oil-induced protein aggregation.

Timing of adverse effects: NR

Factors that predict response: Protein aggregates containing silicone oil were more immunogenic than those generated without silicone oil.

Data Quality: NR

Source Citation: Chisholm et al. 2016[33]

Study Design: Controlled study

Device or Material: Silicone oil microdroplets

Route: Subcutaneous injections

Dose: Silicone oil microdroplets at a higher concentration of 3.7 ± 0.5 mg/mL, or rmGH that contained a lower concentration of 0.12 ± 0.04 mg/mL silicone oil microdroplets extracted from commercial syringes

Frequency/Duration: 11 and 29 days

Response: Antibody response

Species (strain): CB6F1 mice

Gender: Female

Number per Group: 8

Observations on adverse effects (brief): Silicone oil microdroplets can act as an adjuvant to promote a break in immunological tolerance and induce antibody responses against a recombinant self-protein. Mice exhibited a small IgG1 response against rmGH when silicone oil-containing rmGH formulations were administered daily.

Timing of adverse effects: NR

Factors that predict response: Silicone oil microdroplets may act as adjuvants to induce an immune response.

Data Quality: NR

Source Citation: Chisholm et al. 2015[34]

Study Design: Controlled study

Device or Material: Silicone oil microdroplets

Route: Subcutaneous injections

Dose: Injected days 1 and 15; injection of 200 µL contained 50 µg of OVA; emulsified silicone oil microdroplets at 3.2 ± 0.5 mg/mL

Frequency/Duration: Day 11 and 29

Response: Antibody response

Species (strain): CB6F1 mice

Gender: Female

Number per Group: 5 to 8

Observations on adverse effects (brief): When administered with high concentrations of silicone oil microdroplets, ovalbumin (OVA) formulations elicited strong anti-OVA IgG1 and IgG2a antibody responses.

Timing of adverse effects: NR

Factors that predict response: The anti-OVA antibody response was dependent on the concentration of silicone oil microdroplets in OVA formulations.

Data Quality: NR

Other Toxicity/Carcinogenicity

No Studies

FBR = foreign body response; NR = not reported; rmGH = recombinant murine growth hormone

Table 10: Silicone Breast Implants – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Coroneos et al. 2019[35]

Study Design: Cohort study

Device or Material: Silicone breast implant

Route: 2 to 7 years

Dose: Allergan: 300-399c Mentor: NR

Frequency/Duration: Single and repeat administration

Response: Capsular contracture, Rupture, Breast pain

Patient characteristics (gender, mean age): Female, Allergan cohort: mean age 35 years; Mentor cohort: 78.2% over 30 years.

Follow up: 2 to 7 years

Number per group: Allergan: 41,342; Mentor: 41,975

Observations on adverse effects (brief): Incidence of local complications: Allergan at 2 years: Capsular contracture (5%), rupture (0.5%); Allergan at 5 years: rupture (1.4% to 2.6%); Mentor at 7 years: Grade III/IV capsular contracture (7.2% to 18.3%), rupture (8.2% to 15.6%), breast pain (19.6% to 29.6%).

Timing of adverse effects: NR

Factors that predict response: Higher incidence associated with longer contact duration.

Source Citation: Glicksman et al. 2019[36]

Study Design: Prospective histological cohort study

Device or Material: Silicone breast implant

Route: 3 to 8 years

Dose: NR

Frequency/Duration: Single administration

Response: Double capsule formation, Capsule adhered to surrounding tissue

Patient characteristics (gender, mean age): Female, mean age 41 years (range 32 to 70), with breast implants requiring revision surgery.

Follow up: NR

Number per group: 8 double capsules

Observations on adverse effects (brief): The double capsule had 2 distinct capsular layers divided by an intercapsular space, with the outer portion of the capsule adherent to the surrounding soft tissue; all capsules showed evidence of granulation tissue, α-SMA positive myofibroblasts due to repeated cycles of microtrauma, and capsular folds with embedded implant silicone.

Timing of adverse effects: 3 to 8 years

Factors that predict response: Shearing may cause delamination and lead to partial or complete double capsule formation due to micro-fractures merging from multiple locations over time. Double capsule formation is more often associated with macrotextured implants.

Source Citation: Labadie et al. 2018[37]

Study Design: Systematic review of case reports and case series

Device or Material: Silicone breast implant

Route: NR

Dose: NR

Frequency/Duration: NR

Response: Cutaneous hypersensitivity-like reactions

Patient characteristics (gender, mean age): Female, age NR

Follow up: NR

Number per group: 14 cases (13 silicone; 1 saline) in 10 case reports and case series.

Observations on adverse effects (brief): 14 patients presented with skin findings of erythematous pruritic papules, patches, and/or pustules overlying the skin of the implanted breast with varying involvement of other body sites; other reactions included Red Breast Syndrome (n=4), reaction of the cervix after implant rupture from mammogram (n=1), fever (n=3), arthritis (n=1), seroma (n=1), breast edema (n=2).

Timing of adverse effects: Immediately to 43 months post-op; 86% in the first 5 months post-op.

Factors that predict response: Patch testing with nonpolyurethane-textured silicone implants found patients to be sensitive to the textured outer silicone surface and not the smooth inner layer (n=2). Patients who underwent explantation (n=9) experienced significant or complete symptom relief.

Source Citation: Ryu et al. 2018[38]

Study Design: Cohort study

Device or Material: Silicone breast implants, free silicone injections

Route: NR

Dose: NR

Frequency/Duration: NR

Response: Localized deformity and mass/nodules in breast or chest wall, Painful nodules in buttocks or thigh

Patient characteristics (gender, mean age): Female, median (IQR) 64 (13.5) years.

Follow up: NR

Number per group: 79 patients with silicone breast implant leakage (n=71; 28 with history of breast cancer) or related to free silicone injections (n=7).

Observations on adverse effects (brief): Inflammatory response to leakage in breast implants included 31 breast and chest wall complications. Inflammatory response to free silicone injections included painful nodules in the buttocks/thighs. Localized silicone-related complications: 31 breast or chest wall

complications: 18 localized deformity, 13 mass/nodules; 3 buttocks or thigh complications: painful nodules.

Timing of adverse effects: Median 22 years, range 1 to 40

Factors that predict response: 28 (39%) with history of breast cancer

Source Citation: Lund et al. 2016[39]

Study Design: Cohort study

Device or Material: Allergan Natrelle 410 textured silicone gel breast implants

Route: NR

Dose: 165 to 740 cc

Frequency/Duration: Single administration

Response: Skin sensitivity changes, Nipple sensitivity changes, Lactation issues

Patient characteristics (gender, mean age): Female, inframammary cohort: median age 36 years (range 18 to 72 years); Periareolar cohort: median age 36 years (range 18 to 82 years); data collected through the 410 Continued Access study.

Follow up: 4 weeks, 6 months, annually up to 10 years.

Number per group: 4,927 patients; inframammary implants (n=9,217), periareolar implants (n=610).

Observations on adverse effects: Inframammary cohort: Nipple sensation changes (n=19), loss of nipple sensation (n=12); risk of first occurrence of nipple sensation changes was 0.3% (95% CI: 0.2–0.5) at 4 weeks, 0.3% (0.2–0.5) at 6 months, and 0.4% (0.3–0.7) annually from 1 to 10 years; risk of losing nipple sensation was 0.2% (0.1–0.4) at 4 weeks, 6 months, and 1 year, 0.3% (0.1–0.4) at 2 and 3 years, and 0.3% (0.2–0.5) at all remaining time points; median time to resolution for nipple sensation changes was 241 days (ranging from 6 to 406 days). Skin sensation changes (n=5), risk of skin sensation changes was 0.0% (0.0–0.2) at 4 weeks, 0.1% (0.0–0.2) at 6 months, and 0.1% (0.0–0.3) annually from 1 to 10 years.

Periareolar cohort: No changes to nipple or skin sensation observed. For both types of incision, the incidence of lactation issues was similar to the general population.

Timing of adverse effects: NR. BIOCELL textured breast implants and tissue expanders have been recalled as of July 24, 2019.

Factors that predict response: Greater risk of nipple and skin sensation changes with inframammary incision.

Source Citation: Maijers et al. 2014[40]

Study Design: Cohort study

Device or Material: Silicone breast implant

Route: 2 to 42 years

Dose: NR

Frequency/Duration: Single administration

Response: Pain, Capsular contracture, Lymphadenopathy, Loss of sensation

Patient characteristics (gender, mean age): Female, median age 47 years (range 22 to 78), with unexplained systemic symptoms.

Follow up: Median follow-up after explantation: 7 months (range 1 month to 18 years).

Number per group: 80

Observations on adverse effects (brief): Pain (51%), capsular contracture (50%), lymphadenopathy (35%), loss of sensation (11%).

Timing of adverse effects: Mean exposure time 14.5 years (range 2 to 42); median time to symptom onset 4.5 years (range 1 month to 30 years).

Factors that predict response: Semi-acute onset of symptoms may be explained by implant rupture or silicone gel bleeding. Explantation reduced symptoms in 69% of cases.

Source Citation: Wazir et al. 2014[41]

Study Design: Systematic review

Device or Material: PIP silicone breast implant

Route: NR

Dose: NR

Frequency/Duration: Single administration

Response: Rupture

Patient characteristics (gender, mean age): NR

Follow up: NR

Number per group: 1,351 total patients in 7 studies; number of patients NR for 1 study.

Observations on adverse effects (brief): Overall rupture rate for PIP implants is 14.5% (382/2635) and ranged 4.2% to 35.2%. The rate of rupture is higher compared to the 7.7% 10-year rupture rate of current generation implants (Allergan Natrelle).

Timing of adverse effects: 5 to 10 years; PIP implants off market since March 2010.

Factors that predict response: PIP implants are related to an increased rate of rupture. The textured silicone shells of PIP implants had a minimum thickness lower than specified, weaker mechanical strength compared to controls, lack of cohesiveness, and changes suggestive of degradation. Rupture rates may be due to problems of quality control of the shell or may be due to the industrial grade silicone filler. There was no evidence that the high levels of siloxanes in the industrial grade silicone genotoxic, immunotoxic, or carcinogenic. No clear evidence that those with ruptured PIP implants have a higher risk of adverse health events compared to those who had rupture of non-PIP silicone implants.

Source Citation: Britez et al. 2012[42]

Study Design: Prospective cohort study

Device or Material: Silicone breast implant

Route: NR

Dose: NR

Frequency/Duration: Single administration

Response: Capsular contracture, Inflammation

Patient characteristics (gender, mean age): Female, median age 36.5 (range 22 to 45) at time of implant replacement due to capsular contracture Baker grades 1 to 4.

Follow up: NR

Number per group: 40 cases; 80 capsules.

Observations on adverse effects (brief): Inflammation was present in 92.5% of cases (27/40), with a statistically significant higher proportion in textured implants (97%) compared to smooth implants (60%) ($p = 0.036$). Low profile implants were significantly associated with a higher proportion of Baker grades 3 and 4 capsular contracture compared to high profile implants ($p = 0.002$). Siliconomas were present in 40% of cases (16/40), primarily in textured implants (15/16). The majority of inflammatory cells present in the implant capsules were T cells. A significantly higher

mean percentages of CD3 positive cells were found in textured implants compared to smooth implants (57 vs. 29 %, p = 0.003).

Timing of adverse effects: NR

Factors that predict response: Low-profile implants may be associated with more severe capsular contracture. Silicone may induce a local T cell immune response, and textured implants showed a stronger response compared to smooth implants. Rate of contracture was not associated with implant type or location.

Source Citation: Schaub et al. 2010[43]

Study Design: Systematic review of prospective studies

Device or Material: Silicone breast implant

Route: Mean: Range 1 to 6 years

Dose: Implants range 125 to 390 g

Frequency/Duration: Single administration

Response: Capsular contracture

Patient characteristics (gender, mean age): Female, mean age ranging from 28 to 35, who underwent elective cosmetic breast augmentation.

Follow up: Mean ranging from 1 to 6 years.

Number per group: 2,404 patients in 11 studies

Observations on adverse effects (brief): Subglandular position: One study reported incidence of Baker grade III/IV capsular contracture at 1 year: smooth: 58% vs. textured: 8% ($p < 0.0001$) and at 3 years: smooth: 59% vs. textured: 11% ($p < 0.001$). Another study reported incidence of Baker grade III capsular contracture at 1 year: smooth: 44% vs. textured: 0%. Submuscular/dual plane position: One study reported incidence of capsular contracture at 1 year and found a nonsignificant trend toward less capsular contracture in textured implants compared to smooth implants. Across studies, capsular contracture rate for textured cohesive silicone gel implants ranged from 0% at 3 years to 28% at a median of 5 years.

Timing of adverse effects: 1 to 5 years.

Factors that predict response: Textured implants had a tendency for less contracture compared to smooth implants. Implants in the submuscular plane had a decreased contracture rate compared to those in the subglandular position.

Source Citation: Coroneos et al. 2019[35]

Study Design: Cohort study

Device or Material: Silicone breast implant

Route: 2 to 7 years

Dose: Allergan: 300 cc to 399 cc Mentor: NR

Frequency/Duration: Single and repeat administration

Response: Sjögren syndrome, Rheumatoid arthritis, Scleroderma, Melanoma, Myositis, MS, Neurological disorder, Cancer, Still birth

Patient characteristics (gender, mean age): Female, Allergan cohort: mean age 35 years; Mentor cohort: 78.2% over 30 years.

Follow up: 2 to 7 years.

Number per group: Allergan: 41,342; Mentor: 41,975.

Observations on adverse effects (brief): Incidence compared to the general population event rate (SIR [95% CI]): Systemic harms: Mentor: Sjögren syndrome (8.14 [6.24–10.44]), scleroderma (7.00 [5.12–9.34]), rheumatoid arthritis (5.96 [5.35–6.62]), melanoma (3.71 [2.87–4.73]), myositis (1.88 [1.09–3.00]), multiple sclerosis (1.72 [1.26–2.29]), neurological disorder (1.59 [1.44–1.76]), and overall cancer diagnosis (1.54 [1.42–1.68]). Allergan descriptively reported silicone implants for revision reconstruction have SIRs over 2.0 for scleroderma, Sjögren syndrome, and myositis compared with normative at 7-year follow-up. Reproduction: Mentor: Stillbirth (4.50 [3.59–5.56]), preterm birth (1.32 [1.15–1.50]), and neonatal intensive care (1.77 [1.53–2.03]).

Timing of adverse effects: NR

Factors that predict response: Higher incidence associated with longer contact duration. Event rates higher for reconstruction compared to augmentation, and revision compared to primary surgery.

Source Citation: Fireman et al. 2018[44]

Study Design: Case series

Device or Material: Silicone gel breast implant

Route: 5 to 13 years

Dose: NR

Frequency/Duration: Single and repeat administration

Response: Interstitial lung disease

Patient characteristics (gender, mean age): Female, age: Case 1: 61 years; Case 2: 31 years; Case 3: 47 years; diagnosed ILD.

Follow up: NR

Number per group: 3 cases

Observations on adverse effects (brief): Case 1: History of pulmonary and allergic diseases; implants removed due to leakage; presented with persistent cough and nonlocalized chest pain 2 years postexplantation; hilar and mediastinal lymphadenopathy with enlarged lymph nodes and multiple pulmonary nodules in the lungs; sarcoidosis; non-necrotizing granulomatous inflammation; diagnosed with granulomatous lung disease; Case 2: Single implant, no relevant clinical history, symptoms presented 5 years post-implantation and included weakness, diffuse chest, abdominal pain, nausea, diarrhea, and weight loss; and implant leak was confirmed, the implant was replaced, and the replacement removed again due to leakage; diagnosed with nonspecific interstitial pneumonia; Case 3: Progressive cough and dyspnea beginning 10 years postimplantation; history of celiac disease and esophageal dysmotility with Raynaud's phenomenon; diagnosed with COPD.

Timing of adverse effects: 5 to 13 years.

Factors that predict response: Systemic symptoms followed implant rupture in all cases. A wide range of metals (cadmium, molibden, zirconium, tungsten, aluminum, zinc, nickel, iron, and cuprum) were identified in all samples. Interstitial lung disease may be associated with the metal content in silicone gel-filled breast implants. Silicone leakage may become a chronic stimulus to the immune system.

Source Citation: Ryu et al. 2018[38]

Study Design: Cohort study

Device or Material: Silicone breast implants, free silicone injections

Route: NR

Dose: NR

Frequency/Duration: NR

Response: Severe hypercalcemia, Lymphadenopathy in axilla, mediastinum, neck, Silicone pneumonitis

Patient characteristics (gender, mean age): 94% female, median age (IQR) 63 (13.2) years

Follow up: NR

Number per group: 79 patients with silicone breast implant leakage (n=71) or free silicone injections (n=7).

Observations on adverse effects (brief): 16 complications involving distant migration or embolization were mostly due to leaking breast implants. 11 (69%) responses were silicone lymphadenopathy. Silicone pneumonitis and severe hypercalcemia (due to injection) occurred in 1 patient each.

Timing of adverse effects: 1 patient with severe hypercalcemia received silicone injections in the buttocks 25 years before. Overall timing of systemic adverse effects was median 17.5 years (range 3 to 40).

Factors that predict response: 28 (39%) with history of breast cancer.

Source Citation: Watad et al. 2018[45]

Study Design: Cross-sectional study

Device or Material: Silicone breast implant

Route: Up to 20 years

Dose: NR

Frequency/Duration: Single administration

Response: Autoimmune diseases, Rheumatic disorders

Patient characteristics (gender, mean age): Female, median age 47 (range 40 to 58); data from Maccabi Healthcare Services (MHS) database (Israel) (2 million patients, 25% of Israeli population).

Follow up: Up to 20 years.

Number per group: Silicone breast implants: 24,651; no silicone breast implant: 98,604 (frequency matched by age and socioeconomic status).

Observations on adverse effects (brief): Patients with silicone implants were more likely to be diagnosed with the following: any autoimmune/rheumatic disorder (OR 1.22 [95% CI: 1.18–1.26]; HR 1.45 [1.21–1.73]), sarcoidosis (OR 1.98 [1.50–2.60]), systemic sclerosis (OR 1.63 [1.26–2.11]), Sjögren syndrome (OR 1.58 [1.26–1.97]), MS (OR 1.41 [1.11–1.80]), fibromyalgia/chronic fatigue syndrome (OR 1.37 [1.29–1.45]), RA (OR 1.19 [1.03–1.38]), hyperthyroidism (OR 1.16 [1.07–1.26]), psoriasis (OR 1.13 [1.05–1.21]), hypothyroidism (OR 1.10 [1.05–1.16]).

Timing of adverse effects: NR

Factors that predict response: No significant differences found between breast augmentation and breast reconstruction.

Source Citation: Balk et al. 2016[46]

Study Design: Systematic review of longitudinal studies

Device or Material: Silicone gel breast implant

Route: Mean: Ranging from 4 to 12 years

Dose: NR

Frequency/Duration: Single administration

Response: Lung cancer, Rheumatoid arthritis, Sjögren syndrome, Raynaud's phenomenon

Patient characteristics (gender, mean age): Female, mean age at implant ranging 30 to 42, mean age at study ranging 34 to 53 (not all included studies reported mean age).

Follow up: NR

Number per group: Implant group: 42,973, Comparator group: 2,701 in 8 studies.

Observations on adverse effects (brief): Studies of 100% silicone breast implants showed a possible increased risk for the following conditions: Rheumatoid arthritis (3 study meta-analysis): ES (95% CI): 1.42 (1.04–1.95); Sjögren syndrome (1 study): RR (95% CI): 6.64 (2.01–21.9); lung cancer (3 studies): Adjusted RR 2.6; SMR 0.2; OR (95 % CI): 1.50 (0.21–10.7), not statistically significant, and only the first study adequately controlled for predictors of cancer; Raynaud's phenomenon (5 study meta-analysis): ES (95% CI): 1.42 (0.23–8.74), not statistically significant.

Timing of adverse effects: Ranging from 4 to 12 years.

Factors that predict response: For lung cancer, 1 study found a higher association after longer follow-up. For Sjögren syndrome, there was higher outcome incidence when the outcome was self-reported. No significant differences found between breast augmentation and breast reconstruction.

Source Citation: Saigusa et al. 2016[47]

Study Design: Cohort study

Device or Material: Silicone breast implant

Route: NR

Dose: NR

Frequency/Duration: NR

Response: Systemic sclerosis

Patient characteristics (gender, mean age): Female, age NR

Follow up: NR

Number per group: 262 patients with systemic sclerosis; 6 with silicone breast implants.

Observations on adverse effects (brief): 2.3% of 262 patients with systematic sclerosis had a history of silicone breast implants; patients with breast implants and anti-RNAP III antibody developed systemic sclerosis at a higher frequency (16%) compared with Topo-I antibody (0%) or anti-centromere antibody (1.2%).

Timing of adverse effects: Median 20 years, range 8 to 50.

Factors that predict response: Patients with anti-RNAP III antibody may be at higher risk of developing systemic sclerosis compared to those with anti-Topo-I antibody or anti-centromere antibody.

Source Citation: Rupani et al. 2015[48]

Study Design: Systematic review of case studies

Device or Material: Silicone breast implant

Route: 1 to 32 years

Dose: NR

Frequency/Duration: Single and repeat administration

Response: Lymphomas, Anaplastic large cell lymphoma

Patient characteristics (gender, mean age): Female, mean age at presentation of ALCL 51.4 years (range 28 to 87).

Follow up: NR

Number per group: 83 cases

Observations on adverse effects (brief): Although rare, 83 cases of lymphomas were reported, the most common being ALCL, including ALK-negative ALCL (n=66), ALK-positive (n=1), and ALCL subtype unknown (n=4). Since the FDA's 2011 report that identified 34 cases of breast implant-associated ALCL, 37 additional cases have been reported. Overall, 30/71 of these cases were in patients with silicone implants; 24/71 patients had textured implants. The other types of lymphomas reported in

patients with silicone implants include multiple myeloma (n=3), cutaneous T-cell lymphoma (n=3), follicular lymphoma (n=2), marginal zone B-cell lymphoma plus follicular lymphoma (n=1), lympho-plasmacytic lymphoma (n=1), and primary effusion lymphoma (n=1).

Timing of adverse effects: Ranging 1 to 32 years.

Factors that predict response: There is an association between textured implants (both silicone and saline) and ALCL. No association found between age group, duration since implantation, or type of implant.

Source Citation: Laurent et al. 2014[49]

Study Design: Retrospective case series

Device or Material: Silicone breast implant

Route: Median 9 years

Dose: Single administration

Frequency/Duration: Single administration

Response: Lymphoma

Patient characteristics (gender, mean age): Female, mean age 61 years; lymphomas registered in the French Lymphopath network (database totals: 43,830 lymphomas, 300 breast lymphomas, 25 peripheral T-cell lymphomas, 19 ALK-negative ALCL).

Follow up: 18 months (range 2 to 60 months).

Number per group: : 19 cases (16 silicone, 2 saline, 1 NR).

Observations on adverse effects (brief): 76% of PTCL in the database were ALK-negative ALCL that were associated with breast implants in all cases (n=19); 39% of implants were ruptured at the time of diagnosis; 26% of patients presented with erythematous skin eruption before i-ALCL diagnosis. There were two distinct presentations: in situ i-ALCL (anaplastic cell proliferation confined to the implant capsule) presenting with seroma (n=11) and infiltrative i-ALCL (pleomorphic cells diffusely infiltrating adjacent tissue) presenting with palpable breast tumor mass (n=8). At 18-month follow-up, 3 patients had died, 2 from lymphoma progression and 1 from relapsed breast cancer.

Timing of adverse effects: Median time to diagnosis 9 years (range 1.5 to 20).

Factors that predict response: Implant rupture or chronic irritation by the textured implant surface may trigger ALCL proliferation. Patients with infiltrative i-ALCL subtype have a significantly shorter 2-year overall survival rate compared with those with in situ i-ALCL subtype (52.5% vs. 100%).

Source Citation: Zambacos et al. 2012[50]

Study Design: Case series and systematic review

Device or Material: Silicone breast implant

Route: NR

Dose: NR

Frequency/Duration: Single administration

Response: Lymphadenopathy, Siliconomas

Patient characteristics (gender, mean age): Female, age NR.

Follow up: NR

Number per group: 14 cases in case series; 174 cases in SR.

Observations on adverse effects (brief): Case series: Implantation before 2000 (4 cases): lymphadenopathy or siliconoma (n=4), enlarged axillary nodes (n=1), rupture (n=3); Implantation after 2000 (10 cases, all PIP implants): palpable lump in the axilla or breast (n=8), siliconoma (n=10); rupture or

silicone bleeding (n=9). SR: A literature search identified 175 cases of lymphadenopathy related to silicone implants included in case reports or case series from 1978 to 2012. 164 cases had extractable data. Mean age of implant at presentation or explanation was 10.8 years (ranging 1 to 31 years). 159 cases (97%) had implants implanted before 2000. The remaining cases 5 were implanted after 2000, two of which were PIP implants.

Timing of adverse effects: Mean age of implants at presentation or explantation 10.56 years.

Factors that predict response: Implant rupture or silicone bleed may cause lymphadenopathy. Silicone implants implanted before 2000 have a higher risk of rupture and migration compared current devices, with the exception of PIP implants.

Source Citation: Silva et al. 2011[51]

Study Design: Prospective controlled cohort study

Device or Material: Textured silicone breast implant

Route: NR

Dose: Mean: 258 mL

Frequency/Duration: Single administration

Response: Systemic inflammatory reaction

Patient characteristics (gender, mean age): Female, BMI = 18.5 to 30 kg/m2, Silicone breast implant group: mean age (SD) 23.9 (3.9) years, mean prosthesis size (SD) 258 (21 ml); Abdominal liposuction group: mean age (SD) 25.9 (3.8) years, mean aspirate of liposuction (SD): 1972 (499) ml.

Follow up: 2 and 6 months

Number per group: Silicone breast implant: 20; Liposuction: 24

Observations on adverse effects (brief): Systemic inflammation, measured by C-reactive protein concentration (SD), was significantly increased 2 months postoperatively and remained elevated at 6 months for breast implants (pre-op: 1.3 [1.2] mg/l, 2 months: 4.8 [3.0]; 6 months: 4.3 [6.4]) compared to liposuction (pre-op: 3.5 [2.7] mg/l, 2 months: 3.5 [2.1]; 6 months: 2.2 [2.2]).

Timing of adverse effects: NR

Factors that predict response: Results for C-reactive protein concentration had a wider dispersion at 6 months, for some patients elevated levels returned to normal and for others levels increased further.

ASIA Syndrome

Source Citation: Pavlov-Dolijanovic and Stupar 2017[52]

Study Design: Case series

Device or Material: Silicone breast implant

Route: 1 to 15 years

Dose: NR

Frequency/Duration: Single administration

Response: ASIA syndrome

Patient characteristics (gender, mean age): Female, Age: Case 1: 28 years; Case 2: 37 years; Case 3: 55 years.

Follow up: NR

Number per group: 3 cases

Observations on adverse effects (brief): Case 1: 1 year postimplantation: Fatigue; progressive pain in the temporomandibular joints, proximal interphalangeal joints hands, wrists, and left ankle; morning stiffness; tenderness and swelling in the affected joints; high C-reactive protein values (18.9, normal range <5); positive cryoglobulin test; patient experienced miscarriage and stillbirth; active smoker. Case 2: 10 years postimplantation: Raynaud's phenomenon; 15 years postimplantation: pain in wrists and shoulders, heartburn, difficulty swallowing solids, mild dyspnea, puffiness of fingers and toes; progressive tightening of the skin of hands, feet and face; examination showed telangiectasia of the hands and face, and fibrotic skin changes, and lung fibrosis; active scleroderma pattern; active smoker. Case 3: 4 years postimplantation: Fatigue, pain in legs, sleep disturbances and severe Raynaud's phenomenon. SR: A literature search identified 215 cases of ASIA related to silicone implants included in case reports or case series from 2011 to 2016.

Timing of adverse effects: Range 1 to 10 years.

Factors that predict response: Aging or rupture may cause migration of silicone out of the breast and result in substantial the development autoimmune disease or immune deficiencies. Risk of ASIA includes adjuvant exposure, previously diagnosed autoimmune disorders, history of allergic conditions, and predisposition to develop autoimmunity (genetic or environmental triggers).

Source Citation: Colaris et al. 2017[53]

Study Design: Comparative cohort study

Device or Material: Silicone breast implant

Route: 1 to 39 years

Dose: NR

Frequency/Duration: Single administration

Response: ASIA syndrome

Patient characteristics (gender, mean age) Maastricht cohort: Female, median age at time of implantation 33 years (range 14 to 56); median age at onset of symptoms 41 years (range 20 to 68); fulfilled Shoenfeld's criteria for the diagnosis of ASIA after receiving silicone breast implants.

Baylor College cohort: Female, median age at time of implantation 32 years (range 19 to 52); median age at onset of symptoms 38 years (range 23 to 57); with human adjuvant breast disease due to silicone incompatibility.

Follow up: NR

Number per group: 100 per cohort (Maastricht cohort: 2014, Netherlands; Baylor College cohort: 1985 to 1992, USA).

Observations on adverse effects (brief):): Fatigue (97%), arthralgia and/or arthritis (85%), cognitive impairment (80%), myalgia or muscle weakness (73%), dry eyes or dry mouth (73%), pyrexia (58%), neurological manifestations (26%). Other frequently present symptoms include Raynaud's phenomenon, headache, alopecia or hair loss, skin abnormalities, gastrointestinal symptoms (IBS), night sweats, and lymphadenopathy. This study found that ASIA due to SIIS has a nearly identical typical clinical manifestation as the previously described adjuvant breast disease.

Timing of adverse effects: Median time to symptom onset 4 to 6 years.

Factors that predict response:

Source Citation: Colaris et al. 2017[54]

Study Design: Cohort study

Device or Material: Silicone breast implant

Route: NR

Dose: NR

Frequency/Duration: Single administration

Response: ASIA syndrome

Patient characteristics (gender, mean age): Female; ASIA syndrome in relation to SIIS.

Follow up: NR

Number per group: 132

Observations on adverse effects (brief): 100% of patients met clinical diagnostic criteria for ASIA syndrome in relation to SIIS; 25% presented with vitamin D deficiency and 28% with vitamin D insufficiency.

Timing of adverse effects: NR

Factors that predict response: The risk of developing autoantibodies was significantly increased in vitamin D deficient and/or insufficient patients (RR [95% CI] 3.14 [1.24–7.95], p = 0.009).

Source Citation: Maijers et al. 2014[40]

Study Design: Cohort study

Device or Material: Silicone breast implant

Route: 2 to 42 years

Dose: NR

Frequency/Duration: Single administration

Response: ASIA syndrome

Patient characteristics (gender, mean age): Female; median age 47 years (range 22 to 78), with unexplained systemic symptoms.

Follow up: Median follow-up after explantation 7 months (1 month to 18 years).

Number per group: 80

Observations on adverse effects (brief): All patients had at least two major ASIA criteria and 79% fulfilled at least 3 typical clinical ASIA manifestations: fatigue (89%), neurasthenia (74%), joint pain (69%), muscle pain (65%), morning stiffness (65%), night sweats (63%), dyspnea (45%), cognitive problems (35%), dermatological symptoms (31%), gastrointestinal symptoms (30%), and alopecia (23%).

Timing of adverse effects: Mean exposure time 14.5 years (range 2 to 42); median time to symptom onset 4.5 years (range 1 month to 30 years); median time to diagnosis of autoimmune disease 7 years (range 3 to 30) from implantation (14% of cases).

Factors that predict response: Pre-existing allergies present in 75% of cases; implants may cause systemic symptoms in patients with atopy or a hyper-immune state. Semi-acute onset of symptoms may be explained by implant rupture or silicone gel bleeding. Explantation reduced symptoms in 69% of cases.

Source Citation: Cohen Tervaert and Kappel 2013[55]

Study Design: Cohort study

Device or Material: Silicone breast implant

Route: 2 to 24 years

Dose: NR

Frequency/Duration: Single administration

Response: ASIA, Immunodeficiency, Autoimmune diseases

Patient characteristics (gender, mean age): Female, median age 49 years (range 18 to 64), with silicone implant incompatibility syndrome and complaints fulfilling the diagnostic criteria of ASIA.

Follow up: NR

Number per group: 32

Observations on adverse effects (brief): ASIA (n=32), enlarged lymph nodes (n=10; non-Hodgkin lymphoma [n=2], silicosis n=8]), systemic auto immune disease (n=17; connective tissue diseases [n=6] including Sjögren's syndrome, anti-phospholipid syndrome, systemic sclerosis, and systemic lupus erythematosus), systemic necrotizing vasculitis (n=6), organ-specific autoimmune disease (n=7; pernicious anemia [n=4], autoimmune thyroiditis, [n=3]), systemic granulomatous disease (n=4), MS (n=1), immunodeficiency (n=15; hypogammaglobulinemia [n=8], IgG subclass deficiency [n=7]).

Timing of adverse effects: Median time to symptom onset 10 years (range 2 to 24) postimplantation; median time between implantation and diagnosis of ASIA was 16 years (range 2 to 40).

Factors that predict response: Implant aging or rupture may result in immune dysregulation and the development of autoimmune diseases.

Source Citation: Kappel et al. 2013[56]

Study Design: Case series

Device or Material: Silicone breast implant

Route: 3 to 5 years

Dose: 150 cc - 390 cc

Frequency/Duration: Single administration

Response: ASIA

Patient characteristics (gender, mean age): Female, BRCA-1 gene mutation, reconstruction post-mastectomy with round, textured, silicone implant.

Follow up: 2.5 years

Number per group: 3 cases

Observations on adverse effects (brief): 3 sisters with symptoms consistent with ASIA due to SIIS including fatigue, arthralgia, and myalgia.

Timing of adverse effects: 3 to 5 years

Factors that predict response: Susceptibility of ASIA due to SIIS maybe be genetically determined. Explantation reversed symptoms in all 3 cases.

Table 11: Silicone Breast Implants – Health Effect (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Silva et al. 2019[57]

Study Design: RCT

Device or Material: Silicone

Route: Implanted on the back, below the panniculus carnosus

Dose: NR

Frequency/Duration: Single administration

Response: Extrusion, Fibrous capsule formation, Increased myofibroblast concentration , Intense mast cell expression

Species (strain): Rat (Wistar)

Gender: Female

Number per Group: 64 (32 polyurethane foam, 32 textured surface).

Observations on adverse effects (brief): Significantly higher concentrations of myofibroblasts (e.g., α-SMA) were reported at 70 days in the capsules formed around polyurethane implants (vs. textured). A more intense expression of mast cells was reported with polyurethane. Extrusion was noted in 7 rats (4 polyurethane, 3 textured).

Timing of adverse effects: Extrusion was noted at 50 days (4), 70 days (2), and 90 days (1). Myofibroblasts and mast cells were measured at 30 days to 90 days.

Factors that predict response: NR

Data Quality: NR

Source Citation: França et al. 2013[58]

Study Design: RCT

Device or Material: Silicone (Silimed®)

Route: Upper medium dorsal region

Dose: 1 cm x 1 cm x 0.5 cm

Frequency/Duration: Single administration

Response: Fibrous capsule formation, Foreign body cells, Decrease in macrophages

Species (strain): Rat (Wistar).

Gender: NR

Number per Group: 30 (6 groups of 5 animals each).

Observations on adverse effects (brief):

Timing of adverse effects: While silicone gel caused an inflammatory process slightly higher than other groups, the rare presence of foreign body giant cells and decrease in other several cell types (e.g., lymphocytes, plasma cells) at 30 days indicated an acceptable chronic inflammatory response.

Factors that predict response: NR

Data Quality: NR

Source Citation: Joseph et al. 2010[59]

Study Design: Case series

Device or Material: Silicone

Route: Implanted in gluteus muscle

Dose: 1.5 x 1.5 cm

Frequency/Duration: Single administration

Response: Thick fibrous capsule formation, Persistent myofibroblasts, lymphocytes, and macrophages

Species (strain):): Rat (Wistar).

Gender: Female

Number per Group: 48

Observations on adverse effects (brief): The silicone expander implants were surrounded by a thick collagenous fibrous capsule at 180 days. Myofibroblasts, lymphocytes, and macrophages were persistent at follow-up (30 days, 90 days, 180 days).

Timing of adverse effects: 30 days to 180 days

Factors that predict response: NR

Data Quality: NR

Source Citation: Vieira et al. 2010[60]

Study Design: Case series

Device or Material: Silicone

Route: Implanted on the back, 1 cm below the scapula

Dose: 2.5 cm pocket

Frequency/Duration: Single administration

Response: Disrupted collagen layer around the capsule, Secretion of inflammatory mediators, Thick capsule formation

Species (strain): Rat (Wistar)

Gender: Female

Number per Group: 32 (16 polyurethane-coated silicone implant, 16 texture-surface silicone implant).

Observations on adverse effects (brief): A more intense inflammatory response was displayed with polyurethane-coated silicone implants by significantly thicker capsules around the implants, and a disrupted collagen layer around the capsules. Secretions of inflammatory mediators such as higher levels of TGF-B in the capsules, and an intense VEGF expression in capsules around the implants was also noted.

Timing of adverse effects: 30 to 90 days

Factors that predict response: NR

Data Quality: NR

NR = not reported; RCT = randomized controlled trial; TGF-B = transforming growth factor beta; VEGF = vascular endothelial growth factor; α-SMA = alpha-smooth muscle actin

Table 12: Silicone Injections – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Harlim et al. 2018[61]

Study Design: Case series

Device or Material: Industrial silicone injection in chin

Contact Duration: Mean time of onset of granuloma was 12.5 years

Dose: Silicone levels in the granulomas was 4.1 to 10,430 ug/g

Frequency/Duration: Received silicone injections 3 to 25 years previously

Response: Granulomatous reactions (inflammatory response followed by mild fibrosis); 22.6% severe fibrosis

Patient characteristics (gender, mean age): Female, 20 to 55 years old, mean age 40.1 years

Number per group: 31

Observations on adverse effects (brief): Granulomas; inflammatory activity peaked at 10 to 19 years and tended to decrease after 19 years.

Timing of adverse effects: Mean 12.5 years.

Factors that predict response: NR

Source Citation: El-Khalawany et al. 2015[62]

Study Design: Case series
Device or Material: Injected silicone

Contact Duration: Mean onset of complications was 14.6 ± 5.27 months after injection but this included silicone and other injections

Dose: NR

Frequency/Duration: NR

Response: Foreign body granuloma

Patient characteristics (gender, mean age): Female, mean age 47 years

Number per group: 20

Observations on adverse effects (brief): Mostly skin granulomas, 7 cases, infectious granuloma 2 cases, dermal pseudocysts with chronic inflammatory infiltrate but without granuloma formation 9 cases, dermal fibrosis 1 case, eosinophilic panniculitis 1 case.

Timing of adverse effects: Mean 14.6 ± 5.27 months after injection, NR separately for silicone.

Factors that predict response: NR

Source Citation: Moragas et al. 2015[63]

Study Design: Systematic review specific to lip enhancement fillers

Device or Material: Silicone, polydimethyl-siloxane

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: Silicone associated with 3.1% granuloma rate.

Patient characteristics (gender, mean age): NR

Number per group: NR

Observations on adverse effects (brief): 6 studies reported high complication rates with silicone implants (references provided).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Requena et al. 2015[64]

Study Design: Case series

Device or Material: Injected silicone

Contact Duration: Time between injection and symptoms: 3, 5, 13, and 15 years

Dose: NR

Frequency/Duration: One injection

Response: Granulomas

Patient characteristics (gender, mean age): Female, ages 65, 68, 75, and 72 years.

Number per group: 4

Observations on adverse effects (brief): Granulomatous reaction in deep dermis and/or hypodermis simulated orofacial granulomatosis, a chronic disorder with intermittent diffuse enlargement of the lips or facial swelling, which eventually become persistent.

Timing of adverse effects: : 3, 5, 13, and 15 years.

Factors that predict response: NR

Source Citation: Echo et al. 2013[65]

Study Design: Case series

Device or Material: Free silicone breast injection

Contact Duration: Mean 21.1 years, range 1 to 35 years

Dose: NR

Frequency/Duration: NR

Response: Silicone-induced mastitis in all 14 patients, silicone granulomas in 9 patients

Patient characteristics (gender, mean age): Female, mean 58.8 years.

Number per group: 14

Observations on adverse effects (brief): Silicone mastitis; most patients were symptomatic with pain and inflammation and presented with obscured mammograms and palpable masses.

Timing of adverse effects: 1 to 35 years.

Factors that predict response: NR

Source Citation: Eversole et al. 2013[66]

Study Design: Case series

Device or Material: Liquid medical grade silicone

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: Foreign body granuloma

Patient characteristics (gender, mean age): Female, ages 53, 54, and 69 years.

Number per group: 3

Observations on adverse effects (brief): Granuloma.

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Kadouch et al. 2013[67]

Study Design: Case series

Device or Material: Liquid injectable silicone

Contact Duration: Mean 38 months before reaction

Dose: NR

Frequency/Duration: 1 injection, mean 38 months

Response: Low grade inflammation (3/4 patients) and migration from injection site (2/4 patients)

Patient characteristics (gender, mean age): NR

Number per group: 4

Observations on adverse effects (brief): Local inflammation.

Timing of adverse effects: Mean of 38 months before reaction.

Factors that predict response: NR

Source Citation: Sánchez et al. 2012[68]

Study Design: Case-control study

Device or Material: Medical grade silicone

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: Late-onset adverse reactions (18/44 patients)

Patient characteristics (gender, mean age): NR

Number per group: 44 (with injected silicone)

Observations on adverse effects (brief): Late-onset adverse reactions include edema, angioedema, skin induration, swelling/tender nodules with or without fistula formation or discharge of sterile pus or filler material. Systemic symptoms include slight fever, arthralgia, arthritis, skin lesions, dry eyes and mouth, and any other sign or clinical complaint, depending on the organ involved. However, the study did not report which of these reactions occurred in the silicone-injected patients who experienced late-onset adverse reactions. No cases had either local or systemic infection when the blood samples were taken. All patients suffering adverse reactions had at least 1 marker of biochemical inflammatory activity when blood samples were drawn.

Timing of adverse effects: : >6 months post-injection.

Factors that predict response: Plasma myeloperoxidase, chitotriosidase, and human cartilage glycoprotein-39 levels were significantly higher in patients bioimplanted with silicone. Elevated levels of these substances in the blood indicate risk of chronic immune system activation and development of adverse events or pathological processes.

Source Citation: Wortsman et al. 2012[69]

Study Design: Case series

Device or Material: Silicone oil

Contact Duration: 2 to 10 years

Dose: NR

Frequency/Duration: NR

Response: Inflammation (69 patients), Palpable nodules (43/69), Cheilitis (inflammation of the lips)(28/69)

Patient characteristics (gender, mean age): NR

Number per group: 69

Observations on adverse effects (brief): In patients who had received injections in the lips, the silicone infiltrated the orbicularis muscle; and in patients injected in the gluteal and calf regions, it also reached into the local muscles (gluteal and anterior tibial groups).

Timing of adverse effects: 2 to 10 years.

Factors that predict response: Injected by cosmetologists, likely off label use.

Source Citations: Alijotas-Reig et al. 2018[70]

Study Design: Case series

Device or Material: Silicone medical grade used as skin filler (6 of 45 cases described in the publication)

Contact Duration: After 3 months

Dose: NR

Frequency/Duration: NR

Response: Angioedema, Sarcoidosis, Arthritis

Patient characteristics (gender, mean age): NR

Number per group: 6

Observations on adverse effects (brief): All patients in the study suffered from late-onset, non-infectious inflammatory/autoimmune disorders that were considered possible cases of ASIA.

Timing of adverse effects: All after 3 months.

Factors that predict response: NR

Source Citation: Tachamo et al. 201871

Study Design: Systematic review

Device or Material: Cosmetic injection of silicone, polymethylmethacrylate or paraffin oil (23 patients identified in 20 articles)

Contact Duration: Hyper-calcemia was diagnosed from a few months to 28 years after initial cosmetic injection

Dose: NR

Frequency/Duration: NR

Response: Hypercalcemia (elevated serum calcium) in all cases. 14 of 23 cases had renal failure which led to 2 deaths

Patient characteristics (gender, mean age): 78% female, 49.83 ± 14.70 years (group of 23 patients).

Number per group: 10/23 injected with silicone.

Observations on adverse effects (brief): Cosmetic injection-associated granuloma caused hypercalcemia. Recurrence of hypercalcemia following treatment occurred in 45% of cases. The study does not specify what percentage of silicone-injected cases developed renal failure.

Timing of adverse effects: 7.96 years (SD 7.19) not specific to silicone patients.

Factors that predict response: NR

Source Citation: Alijotas-Reig et al. 2013[72]

Study Design: Systematic review

Device or Material: Silicone medical grade, polydimethyl-siloxane

Contact Duration: Longer than 24 months

Dose: NR

Frequency/Duration: NR

Response: Acute response: pneumopathy; late-onset inflammatory reactions local and systemic

Patient characteristics (gender, mean age): NR

Number per group: NR

Observations on adverse effects (brief): The review did not report specific numbers of patients with silicone injections who experienced systemic adverse reactions, it just provided a list of systemic adverse reactions reported in the literature. These include flu-like symptoms, lymphadenitis, pneumonitis, non-thrombotic pulmonary embolism, serositis, hepatitis, panniculitis, angioedema, bone erosion, amyloidosis, siliconosis, distant nodules, renal failure, human adjuvant disease, sarcoidosis, scleroderma, inflammatory myopathy, Sjögren syndrome, fibromyalgia, Hand's syndrome, undifferentiated connective tissue disease, and ASIA.

Timing of adverse effects: : Typically longer than 24 months.

Factors that predict response: : Improper injections of large volumes of industrial silicone always result in an exaggerated inflammation reaction, also tends to migrate more.

ASIA = autoimmune/inflammatory syndrome induced by adjuvants; NR = not reported;

Table 13: Silicone Injections – Health Effect (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Hizal et al. 2014[73]

Study Design: Case series, each rat received the same treatment

Device or Material: Liquid injectable medical grade silicone oil (LIS); "We aimed to compare the effect of the viscosity of LIS on long-term inflammatory response and found that there was no difference between 1,000 cSt and 5,000 cSt LIS injections in terms of the degree of inflammation."

Route: Subdermal injection

Dose: (1) autogenous auricular cartilage graft, (2) silicone sheet implantation, (3) 1,000 centistokes (cSt) LIS injection using a 1-mL insulin syringe with a 26-gauge needle, (4) 1,000 cSt LIS injection using an insulin pen with a 30-gauge fine needle, (5) 5,000 cSt LIS injection using a 1 mL insulin syringe with a 26- gauge needle, and (6) 5,000 cSt LIS injection using an insulin pen with a 30- gauge fine needle

Frequency/Duration: Once / followed for 6 months

Response: Low-grade, well-tolerated long-term inflammatory response to microdroplet injections of 1,000 cSt and 5,000 cSt LIS that is comparable to autogenous cartilage graft in rats

Species (strain): Adult Sprague-Dawley rat.

Gender: NR

Number per group: 17

Observations on adverse effects (brief): Low-grade long-term inflammation. Standard dose delivery devices such as insulin pens can be used for controlled LIS injections.

Timing of adverse effects: 6 months

Data Quality: NR

NR = Not Reported

Table 14: Neuromodulatory Systems – Health Effect (In Vivo) Animal Studies

Local Response/Toxicity

Source Citation: Zheng et al. 2019[74]

Study Design: Controlled study

Device or Material: Soft wire (SW) peripheral nerve electrodes made of silicone/PEDOT-PEG interwoven with carbon nanotubes

Route: Implanted in the sciatic nerves

Dose: Not applicable

Frequency/Duration: Implanted for 1 month

Response: Fibrous encapsulation thickness; reduced axon size and density

Species (strain): Adult rat (Sprague-Dawley).

Gender: NR

Number per group: 5

Observations on adverse effects (brief): Fibrous encapsulation thickness. Reduced axon size and density.

Timing of adverse effects: 1 month.

Factors that predict response: Wire stiffness.

Data Quality: NR

Source Citation: Gonzalez-Gonzalez et al. 2018[75]

Study Design: Controlled study

Device or Material: Silicone nerve cuff electrode compared to thiol-ene/acrylate nerve cuff electrode

Route: Implanted in the sciatic nerves

Dose: Not applicable

Frequency/Duration: Implanted for 30 days

Response: Fibrous tissue growth, and increased number of activated macrophages

Species (strain): Adult rat (Lewis)

Gender: Female

Number per group: 9

Observations on adverse effects (brief): Fibrous tissue growth and increased number of activated macrophages. Gross evaluation of the explanted nerves showed that the segments with the silicone cuff were on average twice the diameter of those in the multi-electrode softening cuff electrodes made of

thiol-ene/acrylate soft memory polymer.

Timing of adverse effects: 30 days

Factors that predict response: Flexural force

Data Quality: NR

Source Citation: FitzGerald 2016[76]

Study Design: Controlled study

Device or Material: Microchannel nerve implants made of plain silicone or silicone doped with dexamethasone

Route: Implanted in right sciatic nerve

Dose: Not applicable

Frequency/Duration: Implanted for 3, 6, or 12 months

Response: Fibrous scar tissue growth

Species (strain): Adult rat (Lewis).

Gender: Male

Number per group: 6

Observations on adverse effects (brief): Fibrous tissue thickness increased with time. Number of axons tended to decrease over time, but the change was not significant.

Timing of adverse effects: 3 to 12 months.

Factors that predict response: Elution of steroids.

Data Quality: NR

Source Citation: Kopelovich et al. 2015[77]

Study Design: Controlled study

Device or Material: Silicone-coated platinum wire

Route: Implanted in scala tympani via minimally invasive dorsal cochleostomy

Dose: Not applicable

Frequency/Duration: Implanted for 22 weeks

Response: Fibrosis

Species (strain): Mice (C57Bl/6J)

Gender: NR

Number per group: 14

Observations on adverse effects (brief): Fibrosis (no quantification).

Timing of adverse effects: Within 22 weeks.

Factors that predict response: Presence of silicone. No fibrosis observed with titanium implant or sham.

Data Quality: NR

Source Citation: Barrese et al. 2013[78]

Study Design: Case series

Device or Material: Silicon microelectrode arrays with silicone insulation, some with Silastic wire coating

Route: Implanted on cortical surface via craniotomy

Dose: 1 or 2 MEAs per monkey

Frequency/Duration: Max 8 years

Response: Skin irritation, Meningeal encapsulation

Species (strain): Rhesus monkeys (Macaca mulattar).

Gender: 18 male, 9 female.

Number per group: 27m

Observations on adverse effects (brief): Meningeal encapsulation in 8 monkeys, 9 arrays.

Timing of adverse effects: Mean 160 days.

Factors that predict response: NR

Data Quality: "The research goals of the implants did not include failure mode analysis or a planned path of continuous improvement. Thus, this retrospective study required searching through records with substantial differences in the degree and detail of information gathered by many individuals over many years, sometimes making it difficult to report the same data for each case."

Source Citation: Cunningham et al. 2013[79]

Study Design: RCT

Device or Material: Silicone particles; particles of 10 other materials were also tested

Route: Implanted in lumbar spinal dura

Dose: 4 mg at 7*106 particles/mg

Frequency/Duration: 3 and 6 months

Response: Fibrosis, although metallic materials resulted in greater fibrosis than polymeric materials; activated TNF-α levels down regulated from 3 to 6 months (42.0 ± 37.0 vs 0 ± 0, p=0.035)

Species (strain): Skeletally mature rabbits (Harlan Sprague-Dawley New Zealand white).

Gender: NR

Number per group: 10

Observations on adverse effects (brief): See Response.

Timing of adverse effects: Within 6 months.

Factors that predict response: NR

Data Quality: NR

Source Citation: Cunningham et al. 2013[79]

Study Design: RCT

Device or Material: Silicone particles; particles of 10 other materials were also tested

Route: Implanted in lumbar spinal dura

Dose: 4 mg at 7*106 particles/mg

Frequency/Duration: 3 and 6 months

Response: Histopathological analysis of 9 structures (axillary, periaortic, and mesenteric lymph nodes; liver; lung; kidney; spleen; pancreas; and heart) demonstrated no significant pathological changes

Species (strain): Skeletally mature rabbits (Harlan Sprague-Dawley New Zealand white).

Gender: NR

Number per group: 10

Observations on adverse effects (brief): See Response.

Timing of adverse effects: Not applicable.

Factors that predict response: NR

Data Quality: NR

MEA = microelectrode array; NR = not reported; RCT = randomized controlled trial; TNF-α = tumor necrosis factor-alpha

Table 15: Silicone Oil in Eyes – Health Effect (In Vivo) Human Studies

Local Response/Toxicity

Source Citation: Cebeci et al. 2020[80]

Study Design: Cohort study

Device or Material: HSO tamponade

Contact Duration: Mean months: 12.63 ± 4.87 (range 7-26

Dose: 5,000 cSt

Frequency/Duration: Single administration

Response: Emulsification. ERM Flare, Elevated IOP, Leakage

Patient characteristics (gender, mean age): 68% male, 52.75±16.06 years

Number per group: 19 with RRD and emulsified silicone particles

Observations on adverse effects (brief): Emulsified SO particles continued to cause inflammation after long-term SO tamponade removal.

SO in situ: significant increase in mean IOP

Post-SOR (followup 3 months): 21% ERM, leakage (57.9% peripheral vascular leakage, 36.8% optic disk leakage), mean flare value in eyes with emulsified silicone was significantly higher vs. fellow eyes (31.41 ± 19.27 vs. 5.43 ± 2.09), 21% ERM at the macula

Timing of adverse effects: NR.

Factors that predict response: NR.

Source Citation: Dormegny et al. 2020[81]

Study Design: Case series

Device or Material: SO

tamponade

Contact Duration: Range 35 to 287 days (no macular cysts)

43 to 644 days (macular cysts)

Dose: NR.

Frequency/Duration: NR.

Response: Macular cysts

Patient characteristics (gender, mean age): 72% male; 57.4 and 61.6 years

Number per group: 41 (43 eyes)

Observations on adverse effects (brief): SO tamponade duration was not associated with macular cyst presence.

SO in situ: macular cysts occurred in 7 eyes.

Post-SOR (mean followup 15.9±10.76 months): macular cysts occurred in 18 eyes

Timing of adverse effects: macular cysts occurred at mean 4.9±4.8 months post-SOR

Factors that predict response: NR.

Source Citation: Eibenberger et al. 2020[82]

Study Design: Comparative cohort study

Device or Material: SO

tamponade

Contact Duration: Mean months: 9 ± 4 PRD, 12 ± 11 RRD

Dose: NR.

Frequency/Duration: Single administration

Response: Cataracts, CME, ERM, EZ disruption, Elevated IOP, INL cysts, Macular hole, Re-detachment, Secondary glaucoma, Tear detachment, Visual loss

Patient characteristics (gender, mean age): 60% male; 57±14 years PRD, 53±13 years RRD

Number per group: 35 eyes PRD, 40 eyes RRD

Observations on adverse effects: SO tamponade duration was significantly correlated with poor postoperative VA in PRD arm ($r=0.395$, $p = 0.02$). The most commonly reported SO in situ complaints were ERM, EZ disruption, and CME. The most commonly reported post-SOR complaints were ERM, cataracts, and EZ disruption. SO in situ: 19 CME, 37 ERM, 5 macular hole, 36 EZ disruption. Post-SOR: 4 eyes acute rise in IOP, 26 cataracts, 11 CME, 38 ERM, 23 EZ disruption, 15 INL cysts, 3 macular hole (all PRD), 8 eyes retinal re-detachment, 1 secondary glaucoma (RRD), 1 unexplained visual loss (PRD)

Timing of adverse effects (f/u after SOR: mean months 28 ± 15 PRD, 22 ± 23 RRD): Unexplained visual loss in both eyes in 1 PRD patient occurred after an SO duration of 5 and 7 months.

Factors that predict response: NR.

Source Citation: Hu et al. 2020[83]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: Mean months: 7.99(range 2 to 16)

Dose: NR.

Frequency/Duration: Repeat administration 5%

Response: Cataract, emulsification, Hypotony, Elevated IOP, Macular hole, New break formation, PVR, Retinal re-detachment, Secondary glaucoma, Visual loss

Patient characteristics (gender, mean age): 61% male, 57.82 ± 11.9 years.

Number per group: 57.

Observations on adverse effects: SO tamponade duration was significantly associated with cataract development, emulsified eyes, and glaucoma.
SO in situ: 47.3% cataract, 22.8% emulsification, 12.2% secondary glaucoma, increase by 5.35 mmHg in mean IOP.
Post-SOR: 19.2% visual loss, 8.77% retinal re-detachment (due to unhealed macular hole, new break formation, and PVR), 7% hypotony (<8 mmHg).

Timing of adverse effects: Cataract occurred with SO in situ for >6 months.
Emulsification occurred in 10 eyes with SO in situ for ≥6 months and in 3 eyes <6 months.
Re-detachment in 5 eyes presented ≤15 days, <30 days (2 cases), <2 months, and 6 months and 10 days post-SOR, with a mean SO tamponade duration of 7.61 ± 2.82 months.

Factors that predict response: NR.

Source Citation: Inan et al. 2020[84]

Study Design: Comparative cohort study

Device or Material: SO and gas tamponade

Contact Duration: Mean weeks: 15.85 ± 3.14

Dose: 1,000 cSt (silicone)

12% C3F8 (gas)

Frequency/Duration: Single administration

Response: Decrease in inner retinal thickness, Elevated IOP, Visual loss.

Patient characteristics (gender, mean age): 62% male, 60.7 ± 11.2 years.

Number per group: 58 (116 eyes) w/ RRD.

Observations on adverse effects: Despite significantly more thinning of the outer nuclear layer (ONL) with SO, there was no statistically significant difference in BCVA between arms at 12 months.
Post-SOR (follow-up 1 year): elevated IOP: 3 SO, 5 gas; significantly more thinning of retinal layers was reported in the SO arm vs. gas arm; ONL thickness was significantly associated with reduced visual acuity. BCVA was significantly better in fellow control eyes vs. treated eyes.

Timing of adverse effects: elevated IOP occurred at 1 week post-SOR.

Factors that predict response: NR.

Source Citation: Issa et al. 2020[85]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean months: 9.46

Dose: 5,000 cSt (99%)

Frequency/Duration: Single administration

Response: Band keratopathy (BK), Cataract progression, CME, Corneal decompensation, Corneal edema, Corneal stromal haze, Failed PKP graft, Hypotony, Non-healing epithelial defects, Ocular hypertension, SO in AC, Retinal re-detachment.

Patient characteristics (gender, mean age): 65% male, 47.2 ± 15 years.

Number per group: 99 (101 eyes) undergoing RD repair. Observations on adverse effects: Cataract progression occurred in 68% of patients.
SO in situ: 4 eyes w/ corneal abnormalities (failing PKP graft, moderate corneal stromal haze with oil in the AC, mild BK from oil in the AC, and a nonhealing epithelial defect).
Post-SOR: 6.9% retinal re-detachment, 8% hypotony, 12.9% ocular hypertension, 9.9% corneal decompensation, 2% CME, 68% cataract progression, 4.9% oil in AC, 11% corneal complications (corneal edema, BK [all 3 eyes had SO in the AC], failed graft and non-healing epithelial defects).

Timing of adverse effects: 4 corneal abnormalities at an SO duration of 20.4 months.

Factors that predict response: NR

Source Citation: Kars et al. 2020[86]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: Mean months: 12.07 ± 10.52 (range 3 to 38)

Dose: 1,000 cSt

Frequency/Duration: Repeat administration due to RRD (10%)

Response: Elevated IOP, Emulsification, Recurrent RD, Visual loss

Patient characteristics (gender, mean age): 75% male, 58.52±12.15 years.

Number per group: 29 with RRD.

Observations on adverse effects: Decrease in postoperative BCVA (logMAR) was significantly associated with SO contact (p=.021, rs=0.441).
SO in situ: 55% SO emulsification.
Post-SOR: 10% recurrent RD, mean IOP significantly increased vs. SO in situ (22.4 vs. 13.9 mmHg, p<.001), visual loss.

Timing of adverse effects: BCVA was measured 1 month post-SOR.

Factors that predict response: Aging.

Source Citation: Lee et al. 2020[87]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: Mean months: 4.46 ± 1.19

Dose: NR.

Frequency/Duration: Single administration

Response: Enlargement of FAZ, Elevated IOP, Reduction of VD, Visual loss.

Patient characteristics (gender, mean age): 63.2%, 57.68 ± 12.68 years.

Number per group: 38 with RRD.

Observations on adverse effects: SO duration was significantly correlated with changes in the foveal microvascular structures (larger FAZ and lower VD in the DCP); however, these changes did not correlate with LogMAR BCVA.
SO in situ: 36.8% elevated IOP.
Post-SOR:

Mean FAZ area in the DCP was significantly larger and the parafoveal mean VD in the DCP was significantly lower in study eyes vs. fellow eyes.

Multivariate regression analyses indicated that SO duration was significantly correlated with the enlargement of FAZ and reduction of VD in the DCP.

While BCVA was significantly lower in study eyes vs. fellow eyes, FAZ area of the DCP (p=0.381) and VD of the DCP (p=0.528) did not correlate with the LogMAR BCVA.

Timing of adverse effects: 3 month follow-up.

Factors that predict response: NR.

Source Citation: Mimouni et al. 2020[88]

Study Design: Cohort

Device or Material: SO tamponade

Contact Duration: NR.

Dose: 1,000 cSt

Frequency/Duration: Single administration

Response: Hypotony, OHT

Patient characteristics (gender, mean age): 56.7% males, 61.7 ± 14.3 years.

Number per group: 307.

Observations on adverse effects: Stepwise multivariate analysis indicated that SOR was significantly associated with early postoperative hypotony (R2=16.34, OR 13.45; p <0.001).
SO in situ: 27% OHT.
Post-SOR (follow-up 1 month): 5.8% hypotony.

Timing of adverse effects: hypotony was identified at day 1 (n=16) and week 1 (n=2).

Factors that predict response: Pseudophakia (OR = 3.65, p = 0.03) and younger age (OR = 0.96, p = 0.04) were significantly associated with hypotony.

Source Citation: Oliveira-Ferreira et al. 2020[89]

Study Design: Case series

Device or Material: HSO and SO tamponade

Contact Duration: mean months: 7.27 ± 5.21 (range 3 to 30)

Dose: 5000 mPa.s (89.1%)3000 mPa.s (10.9%)

Frequency/Duration: Single administration (41 eyes)

Response: Cataract, Emulsification, Glaucoma, Keratopathy, Membrane proliferation, Migration, OHT, PVR, Retinal re-detachment, Visual loss, Vitreous hemorrhage

Patient characteristics (gender, mean age): 67.4% male, 61.39 ± 19.99 years.

Number per group: 46 eyes.

Observations on adverse effects: OHT during SO tamponade and silicone emulsification were significantly associated with unexplained visual loss after SOR. The most commonly reported SO in situ AEs were OHT, SO emulsification, and SO migration. The most commonly reported post-SOR AEs were unexplained visual loss and visual loss due to retinal re-detachment and proliferative vitreoretinopathy.
SO in situ: 47.8% OHT, 30.4% SO emulsification, 17.4% anterior chamber SO migration, 15.2% membrane proliferation, 10.9% glaucoma, 8.7% subconjunctival SO migration, 8.7% keratopathy, 6.5% cataract.
Post-SOR: 34.8% visual acuity loss (10.9% unexplained loss, 23.9% explained loss).

Timing of adverse effects: duration of SO tamponade was 8.25 ± 3.11 months in 4 (80%) patients with unexplained visual loss.

Factors that predict response: OHT with SO in situ (p=0.046) and silicone emulsification (p=0.001) were significantly associated with unexplained visual loss after SO removal (occurred in 10.9%). 63% of patients were hypertensive.

Source Citation: Pichi et al. 2020[90]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: 3 to 4 months

Dose: 5000 cSt (2 cases)

Frequency/Duration: Single administration (2 cases). Multiple administrations (1 case)

Response: Central scotoma, Re-detachments, Visual loss

Patient characteristics (gender, mean age): 66% male, 51 years. Number per group: 3 (2 RRD, 1 macular-off RD).

Observations on adverse effects: Complications reported in 3 patients included visual loss (100%), central scotoma (66%), and multiple re-detachments in 1 patient.
SO in situ: 1 visual loss, 1 retinal re-detachment.
Post-SOR: 100% visual loss, 66% central scotoma, 2 re-detachments (1 patient).

Timing of adverse effects:
Visual loss occurred in 1 patient with SO in situ for 3 months.
Retinal re-detachments occurred in 1 patient with SO in situ for 3 to 4 months.
Visual loss and central scotoma occurred in 1 patient one week post-SOR.

Factors that predict response: NR.

Source Citation: Poulsen et al. 2020[91]

Study Design: Comparative cohort study

Device or Material: SO vs gas tamponade

Contact Duration: NR.

Dose: 1,000 cSt

Frequency/Duration: Single administration

Response: Elevated IOP, PVR, Visual loss

Patient characteristics (gender, mean age): 65.5% male, 63.3±9.9 years.

Number per group: 84 (38.1% SO, 61.9% gas).

Observations on adverse effects: Multiple logistic regression analysis indicated that SO was not a significant predictor of poor visual outcome. Significantly more individuals with SO (vs. gas) had increases in IOP, and more severe cases of PVR.
Post-SOR: More severe grades of PVR (B or C) occurred with SO; elevated IOP (>22 mmHg) occurred in 46.4% SO, 13.3% gas; p = 0.04.

Timing of adverse effects: Elevated IOP occurred within 2 months of SOR.

Factors that predict response: Female gender was significantly associated with poor visual outcome (OR 8.5, 95% CI: 1.8 to 39.8; p = 0.007)

Source Citation: Rabina et al. 2020[92]

Study Design: Case series

Device or Material: HSO and SO tamponade

Contact Duration: Mean days: 151±54

Dose: 5,500 cSt (68%), 1,300 cSt (32%)

Frequency/Duration: Single administration

Response: Optic nerve neuropathy, Significant cataract, Visual loss

Patient characteristics (gender, mean age): 48.7% male, 56.1 ± 15.2 years.

Number per group: 41 with RRD.

Observations on adverse effects: Significant cataracts and visual loss occurred in 5 and 1 patient, respectively.
Pre- and post-SOR: 5 significant cataracts.
Post-SOR: visual loss: 1 patient with optic nerve neuropathy.

Timing of adverse effects: Visual loss occurred ≥1 month post-SOR.

Factors that predict response: NR.

Source Citation: Shin et al. 2020[93]

Study Design: Case series

Device or Material: HSO and SO

tamponade

Contact Duration: Mean months: 6.0 ± 6 (range 2 to 25)

Dose: 1,000 cSt or 5,000 cSt

Frequency/Duration: Single administration

Response: Increase in internal optic higher-order aberrations (HOAs), Visual loss

Patient characteristics (gender, mean age): 52.5% male, 52.0 ± 14.6 years.

Number per group: 58 (59 eyes) with RRD, PDR, PVR, and MH.

Observations on adverse effects: Increased internal optic HOAs from SO in situ caused a reduction in visual acuity especially in pseudophakic eyes.
SO in situ: Increase in internal optic HOAs caused a reduction in visual acuity, particularly in pseudophakic eyes.
Post-SOR: 1 phakic eye showed an increase in total HOAs, and decreased BCVA

Timing of adverse effects: NR.

Factors that predict response: NR.

Source Citation: Tsui et al. 2020[94]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean months: 26.89 ± 25.45

Dose: 5,000 cSt

Frequency/Duration: Single administration

Response: Capsular opacity, Cataract progression, Elevated IOP, Emulsification, FIbrin clot, FTMH, OHT, Retinal re-detachment, VH.

Patient characteristics (gender, mean age): 48% male, 44.1 ± 10.2 years.

Number per group: 64 (74 eyes) with PDR.

Observations on adverse effects: Vitreous hemorrhage occurred in 5.4% of patients; recurrent hyphema in 2.7% of patients. Authors noted no correlation between SO duration and incidence of re-detachments.
SO in situ: Extensive fibrin clot in 1 eye, 8.7% IOP elevation, 31.1% significant SO emulsification.
Post-SOR: 4.1% retinal re-detachment (1 MHRD), 10.8% late-onset IOP elevation, 2.7% immediate IOP elevation, 4.1% de novo long-term OHT (no visible SO emulsification in the AC), 2% cataract progression, 33.3% posterior capsular opacity (1 eye w/ transient choroidal detachment), 2.7% FTMH, 5.4% VH (2.7% recurrent hyphema).

Timing of adverse effects:
SO in situ: fibrin clot, mean 3 months; OHT at mean 36.2 months, significant SO emulsification in AC at mean 40.9 months; macular hole at mean 13.5 months; macular pucker causing structural changes at mean 31.3 months.
Post-SOR: FTMH occurred immediately after SOR, and 2 weeks after SOR. VH occurred immediately after SOR. 66% of retinal re-detachments occurred within 1 month of SOR.

Factors that predict response: 86% type 2 diabetes mellitus, 6% type 1 diabetes mellitus, 67% hypertension, 22% kidney disease, 12.5% heart disease; comorbidities were not analyzed as possible risk factors for re-detachment.

Source Citation: Wang et al. 2020[95]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean days: 101.3 ± 8.4

Dose: 5,000 csT

Frequency/Duration: Single administration

Response: Cataract, Increase in RPC vessel density, Retinal re-detachment, Subfoveal PFCL retention.

Patient characteristics (gender, mean age): 68% male, 52.2 ± 12.3 years.

Number per group: 31 (included AEs for 9 excluded patients).

Observations on adverse effects: A mild increase in peripapillary capillary vessel density was identified post-SOR.
SO in situ: 13.6% cataract, 4% macular hole, 4% subfoveal PFCL retention.
Post-SOR (follow-up at 3 months): significant increase in RPC vessel density vs. SO in situ.

Timing of adverse effects: <4 months SO in situ.

Factors that predict response: NR.

Source Citation: Xiang et al. 2020[96]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: Mean months:5.56 ± 2.17

Dose:NR.

Frequency/Duration: NR.

Response: Decrease in inner retinal thickness

Patient characteristics (gender, mean age): 74% male, 46.57 ± 15.64 years.

Number per group: 23.

Observations on adverse effects: SO tamponade significantly reduced the thickness of the inner retina by 3 months.
SO in situ: Significant reductions in arafovea, superior-hemi, inferior-hemi, tempo, superior, and nasal inner retinal thickness were reported.

Timing of adverse effects: ≤3 months.

Factors that predict response: NR.

Source Citation: Zhou et al. 2020[97]

Study Design: Comparative cohort study

Device or Material: SO and gas tamponade

Contact Duration: ~4 months

Dose:NR.

Frequency/Duration: Single administration

Response: Inflammation, Decrease in inner retinal thickness

Patient characteristics (gender, mean age): 38% male, 53.86 ± 8.25 years.

Number per group: 21 (21 eyes)(14 gas, 7 SO).

Observations on adverse effects: The negative effect of SO tamponade on fundus vasculature (e.g., fovea, parafovea) and structure (e.g., NFL, ONL) may lead to visual loss.
Post-SOR (follow-up 3 months): Increase in choroidal blood flow may indicate more severe postoperative choroidal inflammation, significantly more loss in fovea and parafovea vs. gas, significantly more loss in ONL thickness vs. gas, significantly more loss in thickness of NFL and GCL+IPL inner retinal layers vs. gas.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source Citation: Keilani et al. 2019[98]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean months:4.18 ± 2.56 Densiron 68, 3.5 ± 2.2 Oxane HD

Dose: 5,000 cSt to 5,700 cSt

Frequency/Duration Single administration:

Response: Emulsification, Glaucoma, Increased IOP, inflammation, Retinal re-detachment

Patient characteristics (gender, mean age): 43% male, 65 ± 12 years.

Number per group: 23 (16 Densiron 68, 7 Oxane HD).

Observations on adverse effects: Chronic glaucoma occurred in 1 patient with Densiron. 10 re-detachments occurred with Oxane (3 in situ, 4 post-SOR) and Densiron (3 post-SOR).
SO in situ: 3 re-detachments (Oxane), 1 chronic glaucoma (Densiron), intraocular inflammation (grade 2 inflammation in ~10% in both groups), elevated IOP, emulsification (range 12.5 to 25% Densiron, range 14.3 to 16.6% Oxane).
Post-SOR (mean follow-up at 9 ± 4 months): 7 re-detachments (4 Oxane, 3 Densiron).

Timing of adverse effects:
SO in situ:
3 re-detachments occurred at 1 week (1 eye) and 1 month (2 eyes).
Intraocular inflammation, increases in IOP, and emulsification were measured at week 1, and 1 and 3 months.
Post-SoR: 3 re-detachments occurred at 5 months.

Factors that predict response: NR

Source Citation: Melo et al. 2019[99]

Study Design: Case control

Device or Material: SO-coated syringes

Contact Duration: 1 to 5 days

Dose: NR

Frequency/Duration: Single administration

Response: Anterior uveitis, Blurred vision, Visual loss, Vitreous cells

Patient characteristics (gender, mean age): 42.4% male, 69.42 ± 2.01 years.

Number per group: 33 with intravitreal injection of aflibercept.

Observations on adverse effects: Saldanha Rodrigues (SR) syringes (with inner surface coating of dimethylsiloxane and polydimethylsiloxane) were significantly associated with inflammation (OR 21.66, 95% CI: 1.10–425.06; p=0.043).
SO in situ: inflammation (anterior uveitis (n=3), vitreous cells (n=5) occurred in 6 patients, blurred vision in 3 patients, incomplete visual acuity recovery in 1 patient.

Timing of adverse effects: 1 to 5 days post-injection with SR syringes.

Factors that predict response: NR

Source Citation: Semeraro et al. 2019[100]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: Mean weeks: 12.8 ± 4.8 HSO, 12.3 ± 6.2 PDMS

Dose: 1,000 cSt (15 eyes), 1,200 cSt (20 eyes)

Frequency/Duration: Single administration

Response: Emulsification, Elevated IOP, Posterior synechiae, Retinal re-detachments

Patient characteristics (gender, mean age): 74% males, 59 years to 62 years.

Number per group: 35 (20 HSO, 15 PDMS) with complicated RD.

Observations on adverse effects: After a mean duration of SO in situ of 12 weeks, re-detachments occurred more frequently with PDMS, while IOP requiring treatment, emulsification in the AC, and posterior synechiae occurred more frequently with HSO.
Post-SOR: 5 (14%) re-detachments (10% HSO, 20% PDMS), 29 (83%) IOP requiring treatment, 30 (85%) emulsification in AC, 22 (63%) posterior synechiae between iris and IOL.

Timing of adverse effects: NR.

Factors that predict response: NR

Source Citation: Russo et al. 2018[101]

Study Design: Systematic review

Device or Material: HSO tamponad

Contact Duration: <3 months to 4 months Oxane HD, 27 days to 4,000 days Densiron 68

Dose: 5,000 and 5,700 mPa.

Frequency/Duration: NR.

Response: AC shallowing, Capsular fibrosis, Cataract progression/clinically significant cataract, Choroidal detachment, Corneal edema and rubeosis iridis, Corneal opacification, Dispersion, Emulsification, ERM formation, Fibrin accumulation, Glaucoma, Granulomatous uveitis, Ocular hypotension, Hyphema and endothelial corneal dystrophy, Hypotony, Elevated IOP, Inflammation, Marked AC inflammation, PC inflammation with preretinal membranes w/o traction, Pupillary block, Posterior synechiae, PVR, Retinal hemorrhage, Sterile hypopyon, Suspected intraretinal gliosis, Veitis.

Patient characteristics (gender, mean age): NR.

Number per group: Mean 32 (range 5 to 94) with RRD.

Observations on adverse effects: Of the 14 studies included in this review, most authors noted complications were similar with HSO vs. conventional SO. Individual study authors noted concerns with granulomatous uveitis with Oxane HD; and fibrin accumulation in the AC and early emulsification with Densiron 68.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source Citation: Tanaka et al. 2018[102]

Study Design: Case series.

Device or Material: HSO tamponade.

Contact Duration: Mean months 10.6 +/- 7.1

Dose: 5,000 cSt.

Frequency/Duration: Single administration.

Response: Emulsification, inflammation, thicker fovea centralis.

Patient characteristics (gender, mean age): 66% male, 61.3 +/- 9.9 years.

Number per group: 9 with ERMs treated for RRD.

Observations on adverse effects (brief): Emulsified SO formed granulomatous lesions and a fragile sponge-like layer that caused retinal inflammation.
SO in situ: 8 (89%) granulomatous lesions with emulsified SO and severe retinal edema.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source Citation: Banerjee et al. 2017[103]

Study Design: Case series

Device or Material: SO or gas tamponade

Contact Duration: 3 to 5 months

Dose: NR

Frequency/Duration: Single administration

Response: Cataract, Elevated IOP, Glaucoma, Inflammation, Retinal re-detachment, Visual loss.

Patient characteristics (gender, mean age): 91% male, ~46 years.

Number per group: 64 with fovea-sparing RDs: 49 SO, 15 gas.

Observations on adverse effects: SO-treated eyes resulted in significantly more visual loss and more postoperative complications including cataracts and uveitis vs. gas.
Post-SOR: Visual loss (49% SO – 20% unexplained, 13.3% gas), 7 re-detachments with SO, 22 cataracts (4 gas, 18 SO), 10 uveitis (2 gas, 8 SO), 17 prolonged elevated IOP/glaucoma (1 gas, 16 SO).

Timing of adverse effects: NR.

Factors that predict response: NR.

Source Citation: Hussain et al. 2017[104]

Study Design: Case series.

Device or Material: HSO tamponade.

Contact Duration: Mean months 6.8 (range 3 to 12).

Dose: 5,000 cSt.

Frequency/Duration: Repeat administration n 39%.

Response: Cataract, emulsification, ERM, migration, phthisis bulbi, visual loss.

Patient characteristics (gender, mean age): 61% male, 53.7 years.

Number per group: 28 with complex retinal detachments.

Observations on adverse effects: SO migration in the AC, phthisis bulbi, ERM, and cataracts each occurred in less than 10% of the population. Unexplained visual loss occurred in 1 patient post-SOR.
SO in situ: 1 anterior chamber SO migration, 1 emulsification, extensive lymphomatous changes and inflammation in 1 patient with lymphoma, 2 phthisis bulbi, 2 ERM, 3 cataracts.
Post-SOR: 1 unexplained visual loss.

Timing of adverse effects: NR.

Factors that predict response: NR

Source Citation: Jin et al. 2017[105]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: NR

Dose: NR

Frequency/Duration Repeat administration 1.8%:

Response: Atrophy, Emulsification, Hypotony, Inflammation, OHT, Phthisis bulbi, Retinal re-detachments.

Patient characteristics (gender, mean age): 65.4% male, 7.84 ± 2.31 years.

Number per group: 107 with post-traumatic endophthalmitis.

Observations on adverse effects: At 13 months follow-up, the most common complications in situ were OHT and hypotony. Re-detachments occurred in 2 children with post-traumatic endophthalmitis.
SO in situ: 6.5% inflammation (1.8% uncontrolled inflammation), 11.2% transient OHT, 2.8% SO emulsification, 1.8% re-detachment, 7.5% hypotony, 1.8% phthisis bulbi, 0.9% atrophy.

Timing of adverse effects: NR.

Factors that predict response: NR.

Source Citation: Liu et al. 2017[106]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: Mean months: 10.8 ± 7.1 (with secondary glaucoma);11.5 ± 7.1(without secondary glaucoma)

Dose: NR

Frequency/Duration: Single administration

Response: Elevated IOP, Emulsification, Increased expression of IL-17, IL-6, and TNF-α, Inflammation, Peripheral anterior synechiae, Pupillary block, Secondary glaucoma, SO in the AC.

Patient characteristics (gender, mean age): 60% male, mean 51 years.

Number per group: 58 with retinal detachment (19 with secondary glaucoma).

Observations on adverse effects: Significant differences between individuals with glaucoma vs. without glaucoma were the significantly higher expression levels of IL-17 (and its effector molecules IL-6 and TNF-α) in the aqueous humor.
SO in situ: 27 (46.6%) SO particles in the AC, 9 (15.5%) peripheral anterior synechiae, 4 (6.9%) pupillary block, 17 (29%) SO emulsion, significantly higher levels of inflammatory mediator levels (e.g., IL-17, IL-6, and TNF-α) in the aqueous humor (IL-17 levels showed a significantly positive correlation with IL-6 and TNF-α). ROC curves indicated that aqueous humor levels of IL-17, IL-6, and TNF-α could be applied for the diagnosis of secondary glaucoma.
Post-SOR: 19 elevated IOP.

Timing of adverse effects: Elevated IOP occurred at 2 days to 2.1 years post-op.

Factors that predict response: NR

Source Citation: Antoun et al. 2016[107]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: Mean months:5.12 ± 2.37 (range 2 to 12)

Dose: 1.000 cSt

Frequency/Duration: Single administration

Response: Cataract, CME, Elevated IOP, Keratopathy, Macular pucker, OHT, PVR, SO in AC, Visual loss.

Patient characteristics (gender, mean age): 66% male, 57.6 ± 10.5 years.

Number per group: 62 with uncomplicated RRD living in high altitude (>1.000 m).

Observations on adverse effects: Post-SOR, 11.4% of patients had elevated IOP that was not medically controlled. Visual loss occurred in 3.2 patients.

Post-SOR: 88% transient OHT, 80% cataract formation, 56.5% elevated IOP (11.4% not medically controlled), 3.2% macular pucker, 3.2% SO in AC, 4.8% PVR, 1.6% CME, 1.6% keratopathy, 3.2% loss in visual acuity.

Timing of adverse effects (followup 6 to 70 months): OHT occurred at 1 month; cataract surgery was performed at 2 to 13 months; PVR occurred at 4 weeks in 2 eyes, and at 6 weeks in 1 eye; elevated IOP occurred mostly during first month.

Factors that predict response: History of glaucoma

Source Citation: Dooley et al. 2016[108]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean months: 4.5 ± 1.5 temporary

Dose: 5.700 cSt

Frequency/Duration: Single administration

Response: BK, Corneal ulcer, Emulsification, Keratopathy, Retinal re-detachment, Secondary glaucoma, Visual loss.

Patient characteristics (gender, mean age): NR, 54 to 59 years.

Number per group: 75 (39 temporary HSO, 36 indefinite HSO) with RRD.

Observations on adverse effects: Keratopathy and re-detachments were higher with indefinite HSO. Final logMAR BCVA was significantly worse with indefinite HSO.
SO in situ:Temporary tamponade: 2 (5.3%) corneal pathology (corneal ulcer, BK), 15% re-detachments, 17.9% secondary glaucoma.
Indefinite tamponade: 14 (38.8%) re-detachments, 11.1% secondary glaucoma, 5 (13.9%) corneal pathology (3 BK, 2 bullous keratopathy), 3 (8.3%) anterior segment emulsification.
Temporary vs. indefinite tamponade: significantly worse final logMAR BCVA with indefinite HSO.

Timing of adverse effects: NR.

Factors that predict response: NR

Source Citation: Scheerlinck et al. 2016[109]

Study Design: Comparative cohort study

Device or Material: SO and gas tamponade

Contact Duration: Median months:16 weeks

Dose: Gas: C3F8 (58%), SF6 (40%), air (1%), SO: NR

Frequency/Duration: Single administratio

Response: Cataract, CME, Scotoma, Secondary capsular opacification, VH, Visual loss

Patient characteristics (gender, age): SO: 76% male, median 59 years. Gas: 58% male, median 60 years.

Number per group: 37 eyes SO, 151 eyes gas; indication: macula-on RRD.

Observations on adverse effects: Significantly more unexplained visual loss occurred with SO (30% SO, 0.7% gas); SO duration was significantly associated with visual loss. A small scotoma in the central 2° was identified on microperimetry in 10 of 10 patients examined for unexplained visual loss.
SO in situ: Visual loss in 9 eyes was due to cataract formation, secondary capsular opacification (5 eyes), CME, and VH. Unexplained visual loss occurred in 8 (22%) eyes during tamponade.
Post-SOR (median f/u 52 to 55 days): Unexplained visual loss occurred in 3 (8%) eyes post-SOR.

Timing of adverse effects: NR.

Factors that predict response: NR

Source Citation: Stalmans et al. 2015[110]

Study Design: RCT

Device or Material: HSO and SO tamponade

Contact Duration: 6 months

Dose: 2,000 cSt, 5,000 cSt

Frequency/Duration: Single administration

Response: Blepharitis, Branch retinal vein occlusion, Change in contract sensitivity, Conjunctivitis, Corneal edema/epitheliopathy, Elevated IOP, Emulsification, Endothelial deposits, PVR, Retinal hemorrhage, SO in AC, Visual loss.

Patient characteristics (gender, mean age): 22% male, 68.2 ± 7.5 years.

Number per group: 36 with full-thickness macular hole.

Observations on adverse effects: Overall serious AEs (SAEs) and AEs including PVR and Goldmann visual field loss occurred at a similar rate between Siluron2000 and Siluron5000.
SO in situ: 31 SAEs (44% 2,000 cSt, 42% 5,000 cSt) and 38 AEs (50% 2,000 cSt, 56% 5,000 cSt).
Post-SOR (follow-up 3 months): 19 SAEs (25% 2,000 cSt, 28% 5,000 cSt), 22 AEs (36% 2,000 cSt, 31% 5,000 cSt).

Timing of adverse effects: NR

Factors that predict response: NR

Source Citation: Prazeres et al. 2014[111]

Study Design: Case series

Device or Material: SO tamponade

Contact Duration: Mean months: 26.55 ± 21.38 11 eyes,11.07 ± 7.44 14 eyes

Dose: 3,800 cSt 25 eyes; retreated eyes initially received 1,000 cSt (10 eyes), 5,000 cSt (2 eyes), and gas (5 eyes)

Frequency/Duration: Repeat administration 17 eyes

Response: Cataracts, Elevated IOP, Emulsification, ERM development, Inflammation, Retinal re-detachment, SO in the AC.

Patient characteristics (gender, mean age): 76% male, 49 ± 18.2 years.

Number per group: 25 with complicated retinal detachments by PVR.

Observations on adverse effects: Inflammation in the AC and emulsification occurred in 40% and 52% of patients, respectively. Approximately 50% of patients were being retreated with SO after re-detachments.
SO in situ: 13 (52%) emulsification, 1 (4%) ERM development, 16% elevated IOP, 1 (4%) SO in the AC, 1 (4%) superior persistent retinal detachment.
Post-SOR (mean follow-up 21.44 ± 15.28 months): 10 (40%) inflammation in the AC, 1 (4%) re-detachment, 1 (4%) persistent tractional retinal detachment; re-detachment in all 12 eyes retreated with SO, 2 cataracts.

Timing of adverse effects: Inflammation in the AC occurred within 1 month of SOR.

Factors that predict response: NR.

Source Citation: Schwarzer et al. 2014[112]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean weeks: 20.2 ± 19.0 (82%) retained until final f/u (18%)

Dose: HSO, Densiron 68 (73%), Oxane HD (27%)

Frequency/Duration: Single administration

Response: Cystoid macular edema, Emulsification, Elevated IOP, Inflammation (prolonged and recurrent), Persistent corneal erosion, Recurrent RD,

Patient characteristics (gender, mean age): NR. Number per group: 100.

Observations on adverse effects: IOP increased during tamponade and post-SOR.
SO in situ: 37 SO emulsification (29 eyes elevated IOP), 3 persistent corneal erosions, 29 prolonged AC inflammation.
Post-SOR (follow-up mean 35.9 ± 51.8 weeks): 13 recurrent RD, 15% elevated IOP, 20 recurring AC inflammation, 2 cystoid macular edema.

Timing of adverse effects: IOP increase occurred at 7.8 ± 4.5 weeks with tamponade, and within the first few days post-SOR in 15 (15%) patients, recurrent AC inflammation occurred at 6 weeks post-SOR (n=20), and a 2nd reoccurrence ≤2 weeks postoperatively in 9 patients.

Factors that predict response: NR.

Source Citation: Levasseur et al. 2013[113]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean weeks: 7.2 ± 3.3 (range 3 to 44)

Dose: Lc5000

(Densiron-68)

Frequency/Duration: Single administration

Response: Capsular opacification, Cataract , Choroidal effusion, Elevated IOP, Emulsification, ERM, Fibrin accumulation, Hyphema, Inflammation, Ocular hypotension, OHT, PVR, Recurrent RD, Visual loss.

Patient characteristics (gender, age): 60% male, median 65.6 ± 13.4.

Number per group: 42 with inferior RRD; 39 at 6-month follow-up.

Observations on adverse effects: In-situ complications were equally distributed when comparing patients with SO duration <4, 5 to 8, and >8 weeks. Visual loss occurred in 6 patients.
SO in situ: 15% elevated IOP, 26% cataract formation, 5% ERM, 5% emulsification, 6/27 (22%) posterior capsular opacification, 6 recurrent RDs.
Post-SOR (f/u range 26 to 133 weeks): 2% ERM, 10% moderate intraocular inflammation of the AC, 1 fibrin grade 2+, 10% PVR development, 5% ocular hypotension (3% associated with choroidal effusion), 3% hyphema, 15% OHT, 6/38 (16%) visual loss.

Timing of adverse effects:
Emulsification with SO in situ for 8 weeks and 12 weeks
Elevated IOP occurred at day 1 with SO in situ
Recurring RD ≤3 months in situ
ERM occurred in situ, and at 53 weeks post-SOR
Inflammation occurred ≤1 post-SOR

Factors that predict response: NR

Source Citation: Kempen et al. 2012[114]

Study Design: Comparative cohort study

Device or Material: SO tamponade

Contact Duration: NR

Dose: NR

Frequency/Duration: NR

Response: Cataract

Patient characteristics (gender, age): 81% male, median 41 (IQR 36, 46).

Number per group: 489 (729 eyes) with cytomegalovirus retinitis and AIDS.

Observations on adverse effects: History of retinal detachment was associated with higher risk of cataract if repaired with SO vs. without SO (adjusted hazard ratio [AHR] 10.37, 95% CI: 6.51 to 16.52 with SO, AHR 2.90, 95% CI: 1.73 to 4.87 without SO).

Timing of adverse effects: NR.

Factors that predict response: History of retinal detachment.

Source Citation: Moisseiev and Barak 2012[115]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: 1 day

Dose: 5,500

Frequency/Duration: Single administration

Response: Fibrin accumulation, Toxic anterior segment syndrome (TASS), Elevated IOP, Hyphema in the AC, Retinal re-detachment.

Patient characteristics (gender, mean age): 100% male, 63 years.

Number per group: 4 with retinal detachment and PVR

Observations on adverse effects: A TASS outbreak in 4 patients was resolved after exchange of the SO batch.
SO in situ: 4 TASS with fibrin accumulation, 1 elevated IOP, hyphema in the AC, and re-detachment

Timing of adverse effects: within 1 day

Factors that predict response: NR

Source Citation: Avitabile et al. 2011[116]

Study Design: RCT

Device or Material: SO and HSO tamponade

Contact Duration: 12 weeks

Dose: 5,000 cSt (Densiron), 1,000 cSt (standard)

Frequency/Duration: Single administration

Response: Cataract progression, Elevated IOP, Emulsification, Fibrin accumulation, Keratopathy, Inflammation, Tyndall effect, Retinal re-detachment.

Patient characteristics (gender, age): 43% male, median 60 to 64 years.

Number per group: 30 with high myopia and RD.

Observations on adverse effects: Inflammation (e.g., keratopathy, fibrin accumulation, Tyndall effect) and elevated IOP were more frequent with HSO tamponade in situ.
SO in situ: 7 significant emulsifications (5 SO, 2 HSO), 6 emulsifications (4 SO, 2 HSO), 6 elevated IOP (2 SO, 4 HSO), 10 cataract progression (3 SO, 7 HSO), 8 inflammation including fibrin accumulation, keratopathy, and Tyndall effect (2 SO, 6 HSO).
Post-SOR (median follow-up 11.9 months (HSO), 12.7 months (SO)): re-detachment 13% Densiron, 47% SO; 2 elevated IOP (1 eye each group).

Timing of adverse effects: Significant emulsification within 12 weeks of surgery.

Factors that predict response: NR.

Source Citation: Duan et al. 2011[117]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean weeks: 10.7 ± 3.9

Dose: 5,000 cSt (Densiron 68) 33 eyes, reinjection with standard SO in 2 eyes.

Frequency/Duration: Repeat administration 6%

Response: Aqueous flare , Cataract , Conjunctival congestion, Elevated IOP, Emulsification, Hypotony, Localized posterior synechia, Posterior capsular opacification, Recurrent RD, Visual loss.

Patient characteristics (gender, mean age): 33% male, 58.6 ± 17.8 years.

Number per group: 33 with complicated RD.

Observations on adverse effects: Elevated IOP occurred in 10 (30%) patients with HSO in situ, and remained in 2 patients after HSO removal. 1 patient had decreased BCVA due to cataract.
SO in situ: 32 cataract/posterior capsular opacification, 14 (42.4%) HSO emulsification, 10 (30.3%) elevated IOP, 13 (39.4%) aqueous flare and cells, 4 (12.1%) recurrent RD, 3 (9.1%) hypotony, 5 (15.2%) localized posterior synechia, 8 (24.2%) conjunctival congestion
Post-SOR (followup mean 8.1 ± 5.3 months): 1 decreased BCVA due to cataract, 2 elevated IOP

Timing of adverse effects:
SO in situ:

elevated IOP occurred at 1-7 days (6), 1 month (3) and 2 months (1)

aqueous flare and cells occurred at 1-7 days (13)

emulsification occurred at 2 weeks (3), 1 month (8), 2 months (1), and 3 months (2)

cataract/PCO occurred at 1 month (8), 2 months (17), and 3 months (7)

recurrent RD occurred at 2 weeks (1), and 1 month (3)

hypotony occurred at 1-7 days (3)

conjunctival congestion was prominent at 2 weeks (8)

Post-SOR: elevated IOP remained at 1 month

Factors that predict response: NR

Source Citation: Nashed et al. 2011[118]

Study Design: Case series

Device or Material:

Contact Duration: NR

Dose: Oxane 5700

Frequency/Duration: Single administration

Response: Cataract, Endophthalmitis, Keratopathy, Phthisis bulbi, PVR, Retinal re-detachment.

Patient characteristics (gender, mean age): 82% male, 50 ± 20 years.

Number per group: 88.

Observations on adverse effects: Endophthalmitis, keratopathy, and cataracts occurred in ≤10% of patients. PVR developed in 44% of patients.
SO in situ: 39 (44%) PVR, 33 (38%) re-detachment, 3 (3.4%) endophthalmitis, 9 (10%) keratopathy, 7 (8%) cataract, 7 (8%) phthisis bulbi.
Post-SOR (mean follow-up 22 ± 23 months): NR

Timing of adverse effects: re-detachment occurred in mean 94 ± 36 days.

Factors that predict response: NR.

Source Citation: Ozdek et al. 2011[119]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean months: 5.7 (range 3 to 34)

Dose: Oxane HD (73%), Densiron (24%)

Frequency/Duration: Repeat SO

53%, repeat HSO 29%

Response: BK, Cataract, Corneal edema, Emulsification, Fibrosis, Glaucomatous optic atrophy, Hypotony, Elevated IOP, Inflammation, Recurrent PVR, Retinal re-detachment, SO in the AC, Subretinal hemorrhage.

Patient characteristics (gender, mean age): 73% male, 38.6 ± 2.03 years (range 5 to 73).

Number per group: 41 with retinal detachment complicated with PVR.

Observations on adverse effects: Subretinal hemorrhage and significant inflammation resembling granulomatous uveitis occurred in one (2.4%) patient each. Corneal complications (e.g., BK, persistent edema) occurred in 14% of patients.
SO in situ: 1 glaucomatous optic atrophy (patient refused HSO removal), 29.2% intraretinal/subretinal fibrosis (30% Densiron, 29% Oxane), 1 (2.4%) significant anterior segment inflammation with large pigmented keratic precipitates and 3(+) AC cellular reaction, 4 (9.7%) significant emulsification, 3 (7.3%) persistent corneal edema, 3 (7.3%) BK, 57.1% cataract, 1 (2.4%) hypotony, 4 (9.7%) elevated IOP, 7 (17%) SO in the AC, 7 (17%) re-detachment due to recurrent PVR, 2 (4.8%) subretinal hemorrhage.
Post-SOR: 3 recurrent RD.

Timing of adverse effects:
SO in situ: Glaucomatous optic atrophy secondary to emulsification at 34 months postoperatively. 7 re-detachments (due to recurring PVR) occurred <1 month (2), and 3 months (5).

Factors that predict response: NR

Source Citation: Ang et al. 2010[120]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean weeks: 27 ± 38

Dose: 5,700 cSt

Oxane HD

Frequency/Duration: Single administration

Response: Corneal decompensation, Emulsification, ERM, OHT, Posterior capsular opacification, Pseudohypopyon, Retinal re-detachment, Severe uveitis.

Patient characteristics (gender, mean age): 66% male, 57.6 ± 21.6 years.

Number per group: 18 undergoing RD repair.

Observations on adverse effects: Emulsification occurred in 33.3% of patients.
SO in situ: 5 (27.8%) re-detachments, 33.3% emulsification, 27.8% ERM, 22.2% posterior capsular opacification, 11.1% OHT, 5.6% severe uveitis, 5.6% pseudohypopyon, 5.6% corneal decompensation.

Timing of adverse effects: SO in situ: 1 emulsification occurred at 36 months, 1 corneal decompensation occurred at 22 months.

Factors that predict response: NR

Source Citation: Er H 2010[121]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean days: 87 (range 60 to 180)

Dose: 5,000 cSt

Densiron 68

Frequency/Duration: Single administration

Response: Adherence of residual bubble(s), Corneal decompensation, Early cataract, Elevated IOP, Emulsification, ERM, Fibrin reaction, Intraocular inflammation, Retinal re-detachments, Temporary lens opacities.

Patient characteristics (gender, mean age): 64% male, 54 years.

Number per group: 67 with inferior primary RRD.

Observations on adverse effects: Authors were concerned with removal time causing early cataract formation and corneal decompensation in phakic and aphakic patients, respectively.
SO in situ: 3 re-detachments, 7 (10.4%) intraocular inflammation or fibrin reaction, 6 (8.9%) elevated IOP, 8 (11.9%) emulsification, 14 temporary lens opacities, 9 (60.4%) early cataract, 6 (8.9%) ERM, 2 corneal decompensation.
Post-SOR (mean follow-up 110±41 days): 6 adherence of residual bubble(s).

Timing of adverse effects: 2 corneal decompensations occurred at 4 and 5 months.

Factors that predict response: NR

Source Citation: Meng et al. 2010[122]

Study Design: Case series

Device or Material: HSO tamponade

Contact Duration: Mean days: 87.9 ± 10.4

Dose: 5,700 cSt Oxane HD

Frequency/Duration: Single administration

Response: Cataract, Elevated IOP, Emulsification, Fibrin accumulation, HSO in the subretina, Inflammation, Lens opacity, Retinal re-detachment, Retinal proliferative membranes, Temporary synechia.

Patient characteristics (gender, mean age): 58% male, 51.3 ± 11.7 years.

Number per group: 40 with complicated RD.

Observations on adverse effects: Lens opacity occurred in 77.8% of patients; most developing nuclear cataract. Inflammation in the AC occurred within 1 day of tamponade placement.
SO in situ: 3 re-detachments, 18 (45%) mild-to-moderate inflammation in the AC, 17 fibrin accumulation, 6 temporary synechia in pupillary zone, 7 (17.5%) elevated IOP, 9 (22.5%) emulsification (some droplets in the AC), 21 (77.8%) lens opacity – most developing nuclear cataract, 12 (30%) retinal proliferative membranes, 1 HSO droplet in the subretina.
Post-SOR (mean followup 438.1 ± 153.7 days): 2 re-detachments.

Timing of adverse effects:
SO in situ: 3 re-detachments at 1 month (1), at 3 months (2); droplet in the subretina at 1 day, inflammation within 1 day.
Post-SOR: 2 re-detachments ≤1 month.

Factors that predict response: NR.

Note: Similar number of patients and eyes in "Number per group" unless noted otherwise.

AC = anterior chamber; AE = adverse event = AIDS = acquired immune deficiency syndrome = BCVA = best-corrected visual acuity; CME = cystoid macular edema; cSt = centistokes; DCP = deep capillary plexus; ERM = epiretinal membrane; EZ = ellipsoid zone; f/u = follow-up; FAZ = foveal avascular zone; FTMH = full-thickness macular hole; GCL = ganglion cell layer; HSO = heavy silicone oil; INL = inner nuclear layer cysts; IOP = intraocular pressure; IPL = inner plexiform layer; MH = macular hole; MHRD = macular hole with retinal detachment; mmHg = millimeter of mercury; mPa.S = millipascal-second; NFL = nerve fiber layer; NR = not reported; OHT = ocular hypertension; ONL = outer nuclei layer; OR = odds ratio; PDMS = polydimethylsiloxane; PDR = proliferative diabetic retinopathy; PFCL = perfluorocarbon liquid; PKP = penetrating keratoplasty; PRD = primary rhegmatogenous retinal detachment; PVR = proliferative vitreoretinopathy; RD = retinal detachment; RPC = radial peripapillary capillaries; RRD = rhegmatogenous retinal detachment; SAE = serious adverse event; SO = silicone oil; SOR = silicone oil removal; VA = visual acuity; VD = vascular density; VH = vitreous hemorrhage

Appendix E. References

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Appendix F. Surveillance Event Reports – PSO and Accident Investigation

Provided with this report as separate Excel spreadsheet.

Appendix G. Regulatory and Manufacturer Safety Alerts

Provided with this report as a separate PDF.

Appendix H. ECRI Accident Investigations of Antireflux Prosthesis and Urinary Continence Devices

Case Summary: Angelchik Antireflux Prosthesis (AAP)

The FDA approved AAP was a c-shaped "hotdog-" like silicone shell filled with silicone gel and having a reinforced silicone tie strap affixed to its outer circumference by silicone RTV. Unfortunately, prior to its market release, the Heyer-Schulte Company changed the tie strap design from a single circumferential strap to two separate straps each of which was bonded into the ends of the silicone shell by the use of small rectangular vulcanization pads. According to company documents, the change was made to decrease production costs and facilitate assembly of the device. Without informing the FDA of the design change, the two strap design was sold. Different from the PMA results for the 101 trial patients with the single strap design, the two strap design exhibited strap failure almost always by avulsion of one of the strap attachment vulcanization pads in the shell. The prostheses would be found in the floor of the peritoneal cavity. Eventually, the manufacturer reverted to the single strap design. Even so, patients experienced complications related to erosion of the prosthesis through the stomach wall or diaphragm. In some cases, radiographs during follow up visits showed the prosthesis to be absent from the patient's body. The only explanation for the finding was that the AAP eroded through the stomach wall and passed out through the intestinal system.

ECRI's involvement with the AAP was entirely through review of 13 cases for various attorneys representing patients injured by it. The litigation took place in the mid 1980s. Because the case materials for these cases was deemed no longer needed and discarded, it is not possible to provide the specifics of the cases. Nevertheless, there were issues common to these cases that are germane to silicone materials compatibility:

- Silicone gel exposure and potential for leachable PDMS
- Dense adhesions
- Erosion
- Surface contamination
- Mechanical Irritation

Silicone Gel Exposure

The AAP was a thin walled silicone elastomer shell filled with silicone gel. Thus, it inherently had the capacity for lower molecular weight silicone components to migrate through its shell by diffusion through an intact shell. In the event that one of the strap vulcanization pads avulsed, the underlying gel was then directly exposed to the surrounding tissue making for easier diffusion of lower molecular weight components out of the prosthesis. From a clinical diagnostic standpoint, no testing was performed in any of the cases to identify or quantify silicon or silicone in the tissues biopsied, if any, from the implant site.

ECRI had the opportunity to examine several explanted AAPs. After cleaning and drying them for photodocumentation, we noticed that they would leave an "oil stain" imprint on the graph paper used as a photographic background. From this, we concluded that the shell of the AAP was permeable to the lower molecular weight silicone components within the gel lattice structure.

Mechanical Irritation

The AAP was secured around the GE junction by manually tying the straps. The recommended method was four throws of square knots. The straps with imbedded mesh reinforcement and radiopaque strip were ribbon-like and not supple resulting in a final hard knot about one half inch long with rough edges. When the knot tails were cut, those also presented pointed corners. The AAPs that we examined always had at least six throws and often had the cut tails clipped together with ligation clips. Presumably, the physician wanted to guarantee that the knot would remain secure for the duration. However, in so doing, they created a larger than recommended securement with multiple presenting rigid surfaces capable of producing mechanical irritation and possibly acting as a nidus for adhesion development.

Surface Contamination

Review of the operative records in many of the cases revealed that Avitene powder, a microcrystalline collagen, was applied in the operative site after the AAP had been tied in place. In a few of the cases, other procedures in which transmural incisions of the gut were performed in addition to the AAP placement. The AAP instructions for use warned against performing other such procedures to avoid contaminating the AAP with bacteria from the gut.

Dense Adhesions

All of the patients had some degree of adhesions. In the cases of erosion, the adhesions were dense and thick. In some instances, the diaphragm was "bonded" to the superior stomach wall by the adhesions, leaving the GE junction anatomy unidentifiable. ECRI believed the adhesions resulted from multiple factors including low molecular weight silicone leaching from the AAP, collagen adsorbed to the AAP shell, mechanical irritation, and possibly infection. We were particularly concerned about the hemostatic agent, Avitene, and wrote to Baxter Healthcare suggesting that they warn against its use during implantation.

Erosion

The complete disappearance of the prosthesis sometimes within a year of implantation was shocking. Ruling out dissolution of the device *in situ*, erosion into stomach and elimination via the alimentary tract was the only explanation. Due to the soft nature of the device (except for the knot), it could pass without the patient realizing it. In addition to reports of strap failure, cases of erosion began to be reported in the clinical literature. In one such report, a radiograph showed the AAP in a transmural position. Notably, the patients often felt bad and ran a low grade fever, but did not develop peritonitis. The absence of acute peritonitis was best explained by adhesions overlying and "sealing" the erosion site. ECRI believed that the mechanism of erosion was likely pressure necrosis in which the contraction of the adhesions pressed the AAP into stomach wall.

Case Summary: AMS 800 Urinary Control System (FDA Pro Code EZY)

A male patient with spina bifida had placement of an AMS 800 implantable, inflatable, urinary sphincter device to control congenital incontinence. The device is comprised of a hand-pump placed in the scrotum, a saline reservoir placed anterior to the pubic bone, and one or two cuffs place around the urethra. The physician assembles these components using tubing segments cut to the appropriate length and various types of coupling unions provided with the device kit. In this case, two new cuffs were placed and a prior cuff remained in place unused. She functionally tested the device and examined the connections for leaks and after determining that the device was intact closed the patient. The device is not used for a period of 6 weeks post implantation to permit the insertion sites for the cuff(s), pump, and reservoir bulb to heal. On the first attempted use, the device did not work. The surgeon believed that the device was leaking and, upon surgical exploration found that the reservoir was now under-filled and appeared to contain blood.

The explanted device was sent to ECRI for independent inspection. When the surgeon removed it, she had to cut the tubes between the pump and cuffs; however, she plugged the four ends to prevent the fluid contents from leaking any further. Upon examination, the fluid in the reservoir appeared reddish and had a fine precipitate. It did not appear to be blood. Minor pressure applied to the fluid filled components resulted in no obvious leaks. After each component was drained and flushed with water, they were then individually air pressurized to 250 mm Hg while submerged in water. None of the components manifested leaks. Notably, the thin silicone shell of the reservoir component was stained uniformly orange. The ECRI investigator applied a drop of the drained solution to corn starch, which immediately turned black indicating the possible presence of iodine. At this point, we suspected that reddish color was possibly from povidone-iodine.

After reviewing the note and talking with the surgeon, we confirmed that she had irrigated the tissue pocket for the reservoir with a 1:1 mixture of Betadine and hydrogen peroxide, which she claimed to have irrigated out with antibiotic solution. Given that the reservoir was stained orange and that the device had no perforations or leaking connections, we concluded that the doctor likely failed to adequately, if at all, flush the mixture form the implant pocket. The mixture affected the material properties of the silicone such that the thin reservoir shell acted as a semi-permeable membrane. The outer mixture was likely hypertonic relative to the inner saline, which allowed the water

in the saline to diffuse out, resulting in the reduced volume. The povidone-iodine (or more likely iodine freed from it based on the starch test,) diffused through the shell, coloring the saline.

Lesson: This is another instance in which an implantable silicone device has failed because the material properties of silicone have been altered by contact with commonly used substances in surgery.