



## Review

Platinum in silicone breast implants<sup>☆</sup>Michael A. Brook<sup>\*,1</sup>*Department of Chemistry, McMaster University, 1280 Main Street W., Hamilton, Ont., Canada L8S 4M1*

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**Abstract**

Silicone elastomers are widely used in implantable devices, including silicone breast implants. These rubbers are generally formed/cured using platinum-catalyzed hydrosilylation. The current scientific literature on the chemistry of platinum is reviewed, as it applies to the use of platinum catalysts for cure of silicone elastomers destined for use in silicone breast implants. These discussions serve as a basis to examine the recent literature describing release of platinum into tissues adjacent to silicone breast implants, the chemical nature of the platinum present in breast implants and the possible association between platinum and clinical outcomes.

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*Keywords:* Silicone elastomer; Breast implant; Hydrosilylation; Platinum catalysis; Biological consequences

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<sup>☆</sup> *Editors Note:* This review covers a controversial aspect of the clinical consequences of the use of silicone gel based breast implants and relates to matters that have been subject to product liability litigation. The Editor-in-Chief wishes it to be known that for a number of years he was involved with, and received compensation for testimony in, this litigation. On receipt of this unsolicited review, the Editor-in-Chief selected two highly qualified referees, both well known for their robust and impartial scientific work on silicone breast implants, who both submitted extensive, constructive but critical reports on the manuscript. The paper was substantially revised in the light of these reports and the Editor-in-Chief believes that the published version is a scientifically valid, academically sound review of this subject. Readers should note that the format of this review, especially in the citations, deviates slightly from normal practice (for example with the use of some web-site sourced information) which we believe is appropriate in this situation but should not be taken as a precedent.

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<sup>1</sup>The author provided information on the chemical nature of the platinum in silicone breast implants at the FDA panel hearing on breast implants April 2005 on behalf of Inamed Corporation. He was also a member of a Health Canada regulatory advisory panel considering applications by Mentor Corporation and Inamed Corporation for new breast implant models in March and September 2005.

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## 1. Introduction

Platinum is a metal that is broadly used in a variety of manufacturing processes. As noted below, there are many environmental sources, with ingestion and inhalation as the primary routes of exposure. The silicone industry uses platinum widely as a catalyst for the crosslinking of silicones by a hydrosilylation reaction (also known as addition cure). Silicone elastomers are also constituents of a variety of commercial products, such as baby bottles nipples [1], and a variety of biomedical applications, e.g., in intraocular lenses [2], as coatings for the outer sheath of pacemaker leads [3] and in silicone breast implants, the focus of this article.

Silicone breast implants (SBIs) have been available since the 1960s, but gained notoriety in the early 1990s when they were the subject of mass tort litigation and much attention in the press [4]. Particularly since then, the fundamental science of silicone breast implants has been extensively studied with respect to chemistry, materials properties and medical outcomes through epidemiological studies. Three exhaustive reviews of the literature up to about 1999 have appeared, each of which have examined all aspects of silicone breast implants and the possibility of a link to disease [5–7].

Traditionally, platinum metal has been considered to be a very innocuous material biologically [8]. Platinum salts are much more biologically active: they are potent allergens [9] and some platinum (II) compounds serve as effective anticancer drugs, such as cisplatin [10]. Recently, several papers have examined the amounts of platinum that bleed from silicone breast implants in vitro [11], or during implantation in vivo [12,13]. In one of these papers, it was proposed that the platinum contained in silicone-based breast implants is associated with unusual, high oxidation states, which may be highly toxic [13].

The objective of this review is to summarize the scientific literature on platinum as it applies to crosslinked silicone materials used in biomedical devices, especially silicone breast implants. To do so, an introduction to the chemistry of platinum, particularly in the context of silicone elastomer cure, is followed by a simplified description of the fabrication process for silicone breast implants. A comparison of exposure to platinum from the environment and from silicone breast implants is then provided. Finally, the recent papers describing in vivo platinum release from breast implants, and the biological conse-

quences arising from the presence of platinum, are discussed.

One challenge in writing this review is the paucity of published data. A significant fraction of the available knowledge about platinum in SBIs resides in internal company documents that have been published either as a consequence of litigation or applications by companies to regulators for new device designs. In general, peer reviewed publications were used in preparing this review. However, interested readers are also referred to selected company data, which are generally available on the internet at regulatory agency sites, and left to make their own conclusion about the data’s relative importance.

## 2. Platinum species

There is a voluminous literature on the organometallic chemistry of platinum because of the metal’s broad utility, particularly as catalysts [14]. Platinum compounds may be distinguished by the degree to which they form aggregates or clusters, the ligands used to stabilize the platinum centres, the coordination number (number of ligands around the metal centre) and the metal oxidation state. For convenience, a very brief summary of platinum chemistry, including oxidation state, is provided along with some simple rules of reactivity.

### 2.1. Normal oxidation states and coordination numbers of platinum

Platinum is normally found in three different oxidation states: Pt(IV), Pt(II) and Pt(0) [15,16]. These three states are all relevant to the discussion of the hydrosilylation reaction used to form silicone elastomers, as will be discussed below. The latter two oxidation states (0 and II) are normally found with coordination numbers of 4 [17] (four ligands on platinum, e.g.,  $\text{H}_2\text{PtCl}_4$ , 16) although depending on the nature of the ligands, Pt(0) compounds of coordination number three are relatively common, as with Karstedt’s catalyst (Fig. 1A) [18,19].

Pt(IV) is normally found with six ligands at the apices of an octahedron [20]. Thus, the oxidation state is distinct from the coordination number: chloroplatinic acid  $\text{H}_2\text{PtCl}_6$ , for example, has a coordination number of 6 (six ligands bonded to Pt), but an oxidation state of +4. In the crystal structure, only octahedral platinum(IV) is seen,

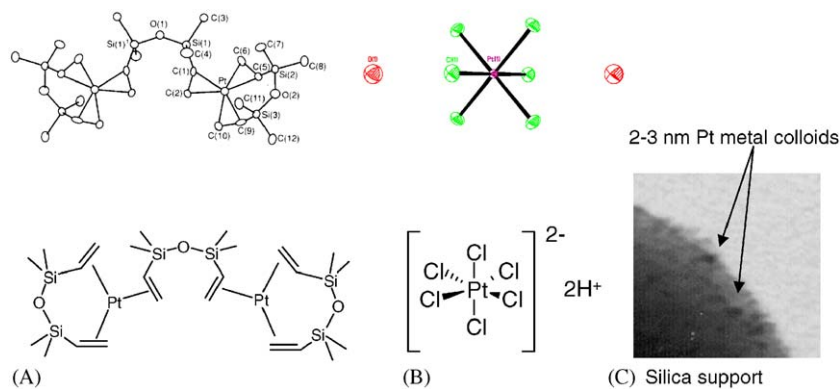


Fig. 1. Crystal structures of (A) a three co-ordinate Pt(0) complex (Karstedt's catalyst) [26]; (B) a six co-ordinate Pt(IV) complex ( $\text{H}_2\text{PtCl}_6 \cdot 2\text{H}_2\text{O}$  (redrawn from coordinates provided in Ref. [21], Hs not displayed for clarity); (C) TEM micrograph showing 2–3 nm Pt nanoparticles supported on silica particles, resulting from the reduction of Karstedt's catalyst [27].

with two outriding cations ( $\text{H}_3\text{O}^+$ ) that provide overall charge neutrality [21] (Fig. 1B).

Many stable Pt(IV) and Pt(II) compounds are known. However, the thermodynamically favoured oxidation state for platinum is Pt(0) [22]. As a result, the reduction cascade from Pt(IV) to Pt(II) to Pt(0) is well known to occur in the presence of a variety of mild reducing agents. For example, chloroplatinic acid ( $\text{H}_2\text{PtCl}_6$ , Pt(IV)) is converted by vinyl groups ( $\text{H}_2\text{C}=\text{CHR}$ ) to Pt(0) compounds. A particularly relevant example of this reduction is Karstedt's catalyst—the current platinum catalyst of choice for curing silicone elastomers—which is formed from the reduction of  $\text{H}_2\text{PtCl}_6$  by  $\text{H}_2\text{C}=\text{CHSiMe}_2\text{OSiMe}_2\text{CH}=\text{CH}_2$  (Fig. 1A) [23,24]. Hydrosilanes, the other constituent of hydrosilylation reactions, are even more effective in reducing Pt(IV) to Pt(0) [25].

In the absence of stabilizing ligands, particularly in any reducing medium and during silicone cure (see below), platinum atoms at the zero oxidation state begin to aggregate. Ultimately colloidal platinum metal particles are nucleated. As the concentration of available stabilizing ligands is reduced, aggregation of these particles leads to very large clusters with typical dimensions of 1–5 nm in diameter, which are comprised of several hundred to several thousand platinum atoms (Fig. 1C).

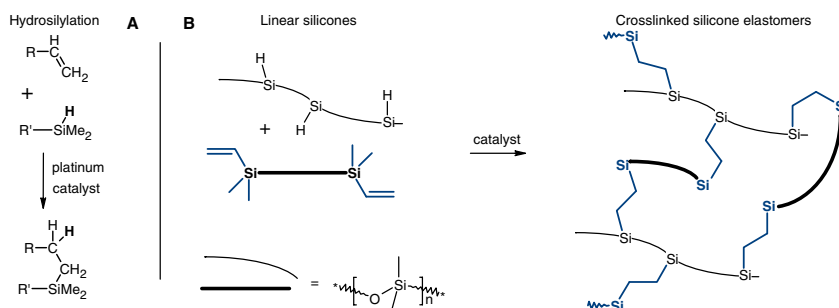
The thermodynamic stability of metallic platinum over platinum salts is exemplified by the reaction conditions necessary to convert platinum metal to higher oxidation state materials. Strong acids such as nitric acid are normally insufficient this process. Conversion of platinum metal to platinum salts requires extremely aggressive oxidative and acidic conditions [16,28]. The normal reagent to convert platinum metal to Pt(II) or Pt(IV) salts, e.g. when one wishes to digest platinum species to permit analysis by atomic absorption (AA), inductively coupled plasma-mass spectrometry (ICP-MS) or related techniques, is aqua regia, a mixture of nitric and hydrochloric acids [29].

## 2.2. Atypical oxidation states: Pt(V) and Pt(VI)

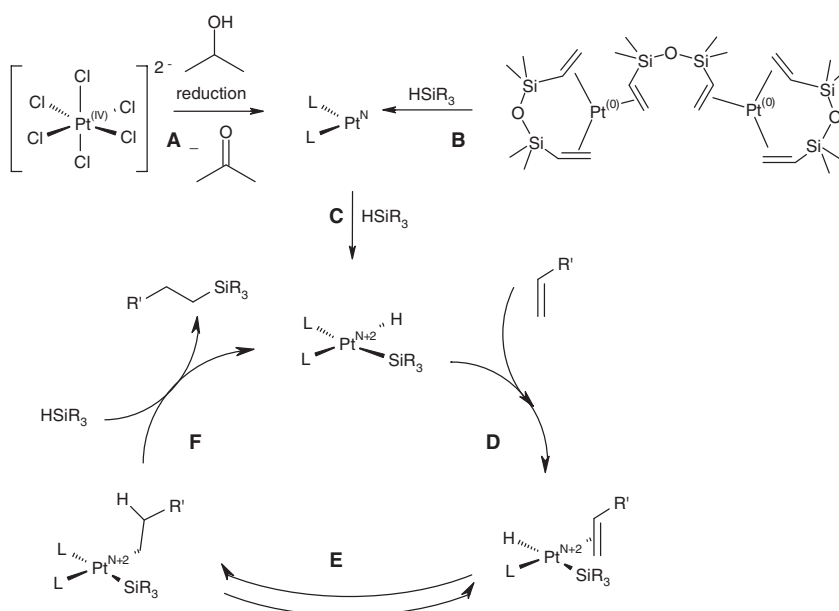
Platinum compounds with oxidation states greater than 4 are extremely rare. The best known is  $\text{PtF}_6$ , which is “extraordinarily reactive” [30] and one of the strongest oxidizing agents known, able even to oxidize oxygen. The pentafluoride  $\text{PtF}_5$  (Pt(V)) is also very reactive. Only strongly stabilizing fluoride ligands support Pt(V) and Pt(VI) compounds; high oxidation state Pt complexes of other ligands either do not form, or are quickly reduced to lower oxidation states. Thus, Pt(V) and Pt(VI) compounds can only be formed in an inert atmosphere, as they are not stable in an oxygen (or air) atmosphere or in contact with water. Such compounds cannot be present in physiological conditions, as they rapidly undergo reduction to more stable oxidation states.

## 3. Platinum catalysts for silicone crosslinking by hydrosilylation

Hydrosilylation, the addition of an “Si–H” residue across a  $\pi$ -bond—which in silicone chemistry is generally an alkene ( $\text{C}=\text{C}$ )—is one of the most effective ways to crosslink silicone polymers to give elastomeric networks (Scheme 1A) [31]. The process is not effectively catalyzed by supported, heterogeneous platinum metal catalysts. However, Speier [23] demonstrated that homogenous catalysis with soluble platinum compounds ( $\text{H}_2\text{PtCl}_6$ , now known in the silicone industry as Speier's catalyst) led to highly efficient crosslinking reactions, for which the cure temperature can be very moderate (25–75 °C) [32] and for which very little platinum was required (< 50  $\mu\text{g/g}$  Pt) [23]. Speier's catalyst became the workhorse of the silicone industry for hydrosilylation until it was supplanted by a catalyst that benefits from a more predictable reactivity profile, Karstedt's catalyst. The latter catalyst (Fig. 1A) is an organosoluble Pt(0) complex.



Scheme 1. (A) Hydrosilylation to give (B) crosslinked silicones.

Scheme 2. Chalk–Harrod model for hydrosilylation.  $N$ —starting oxidation state (e.g.,  $N = 4$  or  $0$ ).

### 3.1. Mechanism of hydrosilylation

The details of platinum-catalyzed hydrosilylation have been extensively examined and reviewed [33–35]. These studies provide information about the mechanism of the reaction and the species of platinum present before, during and after the hydrosilylation reaction [27,36,37].

The most commonly invoked mechanism for platinum-catalyzed hydrosilylation is that of Chalk and Harrod, who made an analogy between the proposed reactive platinum catalyst species and isolated Ir complexes [38,39]. Their mechanism accounts for most experimental observations in hydrosilylation reactions catalyzed by  $\text{H}_2\text{PtCl}_6$ : (i)  $10^{-7}$ – $10^{-8}$  equiv.  $\text{H}_2\text{PtCl}_6$  are enough, in perfect conditions, to catalyze the reaction; (ii) there is an induction period followed by a very fast reaction; (iii) platinum is reduced in the process first to Pt(0) complexes and aggregates, and then to Pt(0) colloids; (iv) the rate determining step is the decomplexation of good ligands from the catalyst; (v) the reaction is stereoselective, with retention at silicon [40]; and (vi) *cis* addition of  $\text{R}_3\text{Si-H}$  to the alkene occurs.

Although several alternative mechanisms have been proposed over the years, convincing experimental results support the original mechanism with only minor changes [41]. First, an active catalyst is formed by the reduction of platinum. When starting from a Pt(IV) complex, reduction from Pt(IV) to Pt(0) is mediated by an alkene, a vinylsiloxane in the case of silicone crosslinking (Scheme 2A) [24]. In the case of platinum already at the zero oxidation state, such as Karstedt's catalyst, the catalytic process is initiated by the reduction of the ligands (hydrosilylation of one of the ligands by an Si–H compound), which liberates a coordination site on platinum (Scheme 2B)—the vinyl ligands on Pt are very labile.

In either Pt(IV) or Pt(0) catalysis of hydrosilylation, there is an induction time before the reaction proceeds efficiently (Scheme 2C). The induction time associated with  $\text{H}_2\text{PtCl}_6$  catalysis may be related to the reduction process that must occur to form the active Pt(0) catalyst; the induction time for Karstedt's Pt(0) catalyst is associated with activation of the catalyst by removal of the vinyl ligands [41].

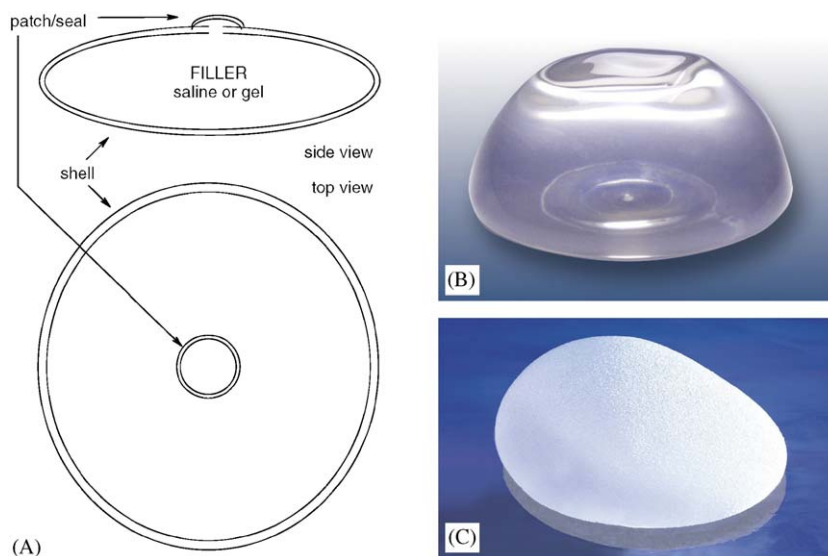


Fig. 2. Structural features of breast implants. (A) General characteristics. (B) Round/responsive implant (smooth surface). (C) Cohesive/contoured implant (textured surface, photos provided courtesy of Inamed Corporation).

Once the active catalyst is formed, oxidative addition by a hydrosilane (Scheme 2C), formation of an alkene  $\pi$ -complex (Scheme 2D), transfer of “H” from the Pt  $\pi$ -complex to create a  $\sigma$ -complex (Scheme 2E) and reductive elimination (Scheme 2F) comprise the catalytic cycle. In normal commercial applications, catalyst loadings of  $< 10 \mu\text{g/g}$  are generally used. Under ideal circumstances, even less platinum is required. Only in the presence of excellent ligands (L, e.g., phosphines, cyclooctadiene [41], naphthoquinone [42]) do monomeric platinum species remain at the end of the hydrosilylation process. Much more common is the formation of colloidal platinum metal particles during hydrosilylation.

Catalysts, by definition, are recovered in their original form at the end of a reaction [43]. However, as noted above, the active platinum catalyst in hydrosilylation reactions is constantly removed from the reaction mixture by ‘side reactions’. ‘Poisons’ for platinum, such as sulphur, lead and tin compounds react with and deactivate platinum catalysts. Other processes, including those that deprive the metal centres of ligands, lead to the aggregation of Pt(0) atoms until crystalline or partly crystalline colloidal platinum metal particles are formed (Fig. 1C).

Conversion to platinum nanoparticles is particularly facilitated by an excess of Si–H groups but can also occur in recipes that have an excess of vinyl groups. Such nanoparticles of platinum metal are the common product of hydrosilylation to generate silicone elastomers. Irrespective of the exact mixtures of platinum aggregates and particles, careful experiments using a broad spectrum of techniques including X-ray crystal structure analysis, NMR ( $^{195}\text{Pt}$ ,  $^{29}\text{Si}$ ,  $^{13}\text{C}$ ,  $^1\text{H}$ ), cyclic voltametry, transmission electron microscopy (TEM) and X-ray absorption experiments (SAXS, XANES) have demonstrated that the

platinum reaction products at the end of hydrosilylation are in the zero oxidation state [22,25,36,37].

Seminal studies by Lewis [37,44,45] of hydrosilylation using Karstedt’s Pt(0) catalyst demonstrated the reaction mechanisms were the same as with  $\text{H}_2\text{PtCl}_6$ . Although it was initially suggested that platinum metal colloids were the primary hydrosilylation catalytic species, a series of extremely elegant and sophisticated experiments using SAXS (small-angle X-ray scattering) measurements with neutrons showed that catalytic activity is inversely proportional to colloid particle size. That is, monomeric platinum species, rather than small colloidal platinum particles, are the active catalysts in hydrosilylation [45].

### 3.2. Crosslinking of silicone elastomers in SBIs by platinum-catalyzed hydrosilylation

The crosslinking process can be understood by considering ropes (analogous to uncrosslinked linear polymer chains) that are knotted/woven into a fishnet (analogous to a crosslinked elastomer, Scheme 1B). Junctions must link at least three polymer chains to form a network. Silicone elastomers are generally prepared by combining two types of polymer chains: one polymer with two functional groups and a second polymer chain that has several functional groups (Scheme 1B). Crosslinking dramatically changes the physical properties of a polymer, leading to an increase in viscosity, cohesivity and a reduction in the ability to be swollen by solvents [46].

Elastomer shells and gels for silicone gel breast implants [47,48] are made by platinum-catalyzed [31] hydrosilylation [6,49] of silicone polymers: note that silicones crosslinked by other processes, including room temperature vulcanization and radical cure, play minor roles in silicone gel-filled breast implants (e.g., patch and patch adhesive) [6]. Most

silicone polymers are comprised of methylsiloxane fragments ( $\text{Me}_3\text{SiO}$ ,  $\text{Me}_2\text{SiO}$ ,  $\text{MeSiO}_{3/2}$ ).<sup>2</sup> The requisite functional groups for addition cure can be located at the termini of linear silicone chains (e.g.,  $\text{HMe}_2\text{SiO}$ ,  $(\text{Me})\text{H}_2\text{C}=\text{CHSiO}$ ) or interspersed along a dimethylsilicone chain (e.g.,  $(\text{Me})\text{HSiO}$ ,  $(\text{Me})\text{H}_2\text{C}=\text{CHSiO}$ ) (Scheme 1B). To prevent adventitious cure, silicone elastomers are made from two different polymers, one part containing the vinyl groups ( $\text{H}_2\text{C}=\text{CHR}$ ) and the platinum catalyst, and the other part containing the Si-H groups [47,50,51]—the two parts are kept separated until curing is desired. The properties of the final rubber are dependent upon the lengths of the starting linear silicones, the spacing and number of crosslinks introduced between the chains and the presence of silicone polymers that are not crosslinked [47].

After cure of silicone elastomers, the platinum catalyst is mostly transformed into Pt(0) metal nanoparticles [25,36,37]. It is not uncommon to observe the development of a yellow or brown hue within silicone elastomers resulting from the presence of the nanoparticles, particularly when prepared using high platinum concentrations. Silicone polymers tend to stabilize platinum nanoparticles [52].<sup>3</sup> The ability of platinum nanoparticles to catalyze hydrosilylation is affected by the ligands at their external surface [53] and is low when those ligands are silicone constituents [27].

## 4. Silicone breast implants

### 4.1. Simple design characteristics for SBIs

A simplified description of breast implant construction is shown in Fig. 2. A thin silicone elastomer shell surrounds a core of saline or silicone gel [6,54]. The shells of saline implants are frequently prepared by a room-temperature vulcanization process (RTV) catalyzed by tin esters [55]. By contrast, silicone gel implants are generally prepared using platinum-catalyzed addition cure (hydrosilylation) of two linear silicone polymers; one containing vinyl groups ( $\text{Si}-\text{CH}=\text{CH}_2$ ) and the other Si-H groups [6]. The shells are prepared by repeated dipping of a mandrel (a mold) into mixtures of silicones diluted with solvent. The shell elastomers are usually reinforced with hydrophobically modified (usually by  $(\text{Me}_3\text{Si})_2\text{NH}$ ) amorphous silica to

<sup>2</sup>Note that the external elastomer on current silicone breast implants is constitutionally different from the gel. The gel is typically derived from dimethylsilicone elastomers swollen with dimethylsilicone oil, while the shells generally contain up to about 85% or more dimethylsilicones that are modified with differently substituted silicone monomer units, such as  $\text{Ph}_2\text{SiO}$  or  $(\text{F}_3\text{CCH}_2\text{CH}_2)\text{MeSi}$ .

<sup>3</sup>Personal experience in our laboratory. Following hydrosilylation of silicone oils, it is necessary to filter the reaction mixture through surface active media to remove colloidal platinum. Extraction of silicone elastomers by organic solvents such as hexanes or dichloromethane leads to platinum-rich fractions that also contain siloxanes.

improve strength and tear resistance [32,54,56,57].<sup>4</sup> When the shell is removed from the mandrel, the resulting hole is ‘patched’ with a piece of silicone elastomer. In the case of silicone gel implants, the empty shell is filled with gel by injection through the patch before implantation; in the case of saline implants, the physician fills the shell with saline after implantation in the patient using a filltube, which is then removed.

The core of a silicone gel implant—the gel—is made up of lightly crosslinked silicone elastomers (ca. 15–50%), cured using platinum-catalyzed hydrosilylation in the presence of non-functional silicone oil (ca. 50–85%, 30,000–80,000 MW [6,58]) to produce a swollen elastomer gel [59].

The differences in the silicone chemistry of implants manufactured by different companies include the specific molecular weights of the silicone starting materials, crosslink densities of the final products, the presence of smooth or textured outer surface and the chemical nature of the silicones in the barrier layer on the shell (see next section) used to reduce the magnitude of bleed. The specific details are known only by manufacturers and regulators. However, the silicone chemistry across all manufacturers, and the gross characteristics of the implants, are all very closely related [6,60].

#### 4.1.1. Implant generations

Different generations of silicone gel breast implants were produced between the 1960s and 2005 [61], which exhibit subtle variations in the characteristics of both the shell and gel core [6,62]. Currently, two types of silicone gel breast implants are available outside of North America [62,63].<sup>5</sup> Starting about 1988, these devices were made with thicker shells and more cohesive gels than previous generations. In addition, the chemical nature of the shells were modified starting with generation 3 to reduce bleed [64], which is the name for the migration of silicone oil from the gel to the outer surface of the shell, and release to the local environment. Bleed is significantly reduced when the dimethylsilicone gel is surrounded by silicone elastomers other than pure dimethylsilicones, including diphenyl/dimethylsilicone or fluorosilicone layers [6].<sup>6</sup> Generation 2 devices had thin shells, while generation 1 devices had thicker shells but poorly cohesive gels.

<sup>4</sup>Silica is the most abundant compound in the Earth’s crust (e.g., beach sand). Certain particle sizes of crystalline silica can be problematic, leading to pulmonary fibrosis (silicosis) [59]. The silica used to reinforce silicone elastomers is amorphous, which is considered to be of lower toxicity than crystalline silica [6].

<sup>5</sup>At the time of writing, both Mentor and Inamed [64] had received ‘‘approvable letters’’ from the FDA for ‘‘responsive’’ gels. Canada is jointly considering responsive/flexible gels and formed/shaped cohesive gels from both companies [65]. Mentor considers both types of implants to be generation 3, while Inamed considers the shaped implants to be a fourth generation device.

<sup>6</sup>Bleed is an issue of contention associated with breast implants that is beyond the scope of this review, which focusses on platinum chemistry.

Early generations of implants used the Pt(IV) catalyst  $\text{H}_2\text{PtCl}_6$  (Speier's catalyst [23]) to promote cross-linking, whereas more recent implants are made using Pt(0) catalysts derived from divinylsiloxanes, (e.g.,  $\text{Pt}_2(\text{H}_2\text{C}=\text{CHSiMe}_2\text{OSiMe}_2\text{CH}=\text{CH}_2)_3$ , Karstedt's catalyst, Fig. 1A) [18,26].

#### 4.2. Platinum in breast implants

Silicone elastomer shells can contain up to 6–8  $\mu\text{g}$  of platinum per gram of silicone [6]. Depending on manufacturer, and on whether the shell is smooth or textured, the shell comprises approximately 2–15% of the total implant weight [6]. Silicone gels, with much lower crosslink densities also contain less platinum, typically up to about 5  $\mu\text{g}/\text{g}$  although some commercial products have used levels as low as 0.1  $\mu\text{g}/\text{g}$  [6]. The total amount of platinum found in implants will, of course, depend on the size of the implants. Implants are sold by volumes ranging from about 80–800  $\text{cm}^3$ . Simple calculations for the recent generation of implants suggest the total platinum weight contained in two implants will range from about 0.1–10 mg.

### 5. Sources of environmental exposure to platinum

Platinum, one of the noble metals, costs about twice as much as gold [65]. The metal is well known for its useful properties, which include a very high melting point [16,66], high resistance to corrosion (including in vivo) and the ability to catalyze a wide variety of reactions [8,16]. In the latter category, platinum is used to reform petroleum to increase the octane rating of gasoline, to hydrogenate alkenes and to catalyze conversion of hydrocarbons and CO in automobile exhausts into the much more innocuous compounds  $\text{CO}_2$  and water [66].

One consequence of the utility of platinum in many industrial processes is subsequent human exposure; the main routes are inhalation, ingestion and topical contact. Platinum is ubiquitous in developed societies, in particular because of the broad utilization of platinum in automobile catalytic converters since the mid-1980s. Widely differing values for the total release of platinum from automobile exhaust pipes have been made, ranging from 6–8 ng/km of Pt at the low end [67], to 120 ng/km at the high end [68,69]. Approximately 10% of the Pt released in this form is soluble [70]. Platinum dust or platinum black (finely divided platinum metal) can be solubilized by organic complexing agents, among which the amino acid methionine is particularly effective [71]. The dust found on plants adjacent to highly travelled roads (measured in 1986) has been measured to contain as much as 0.7  $\mu\text{g}/\text{g}$  platinum [72]. The main routes to human exposure to platinum in this form are inhalation and ingestion.

Platinum is found in humans even in relatively unpolluted locales away from significant exposure to automobiles—a study found comparable concentrations of platinum in city and country dwellers [73]. It has been

reported that the average Australian diet contains up to approximately 1.44  $\mu\text{g}$  Pt/day, which was ascribed as the primary source of in vivo platinum [71,73,74]. The quantity of platinum found in diverse foods is quite varied. For example, the level of Pt in liver (8.1 ng/g) was measured to be much higher than in cream (0.13 ng/g) [71]. Humans are also exposed to platinum topically. For example, jewelry often contains platinum. In some cases, this is added to reduce the “allergic response” to jewelry (although some have claimed an enhanced biological response to platinum jewelry [75]). Platinum is permitted in food grade wrapping materials (the residual levels of platinum that may be contained in food contacting coatings of paperboard were increased by the FDA to 200 ppm) [76]. Platinum may also be directly implanted, e.g., in the form of platinum metal or platinum alloys in pacemaker leads, in related devices such as vagus nerve stimulators for epilepsy patients [77], or as constituents of dental implants [66].

Workers in the platinum industry have platinum urine concentrations approximately 1000 times that of the general population (6270 ng/g creatinine [78]) due to their significantly higher exposure: typical concentrations in urine in the general population are found to be about 5 ng/g creatinine. The half-life of platinum in vivo is relatively short (<3 days) [79], although there is some evidence that workers with these very high exposures take considerably longer to rid the Pt from their system than the average population.

Several studies have shown that platinum is found in blood, urine [71] and tissues, particularly the kidney [80], of the general population [81,82]; cadaver studies on the general population indicate that concentrations of platinum in tissues can vary from 3 to 1460 ng/g wet tissue [66,82]. Little data is available on the concentration of Pt in breast tissue of the non-implanted control female population. A report on platinum in muscular tissue found concentrations on the order of 2 ng/g [83].

### 6. Migration of platinum from SBIs

#### 6.1. Gel “bleed”

Silicone fluids bleed from silicone elastomer shells in silicone gel breast implants [5–7]. Platinum, another constituent of the shell and gel in silicone gel breast implants, similarly has the possibility to “bleed” or leach from the implant. A few studies have examined the potential for platinum release using in vitro tests [11], and the examination of explanted tissues from implanted women [12,13].

#### 6.2. In vitro release

Lykissa et al. [11] examined in vitro platinum bleed from explanted SBIs. The devices at time of measurement contained about 700  $\mu\text{g}/\text{kg}$  of platinum in explanted breast implants, as determined by ICP–MS. The devices used in

the study were intact, weighed 240–260 g, and had been implanted from 2 to 5 yr—the concentrations of platinum in the devices before implantation were not reported. Extraction of the implants by an aqueous solution did not lead to detectable platinum [84–86].<sup>7</sup> By contrast, extractions of platinum into ‘lipid rich’ (soybean oil) and 10% lipid/90% aqueous media, respectively, over 24 h at 37 °C were calculated to give a “release rate” of 25 µg/day of platinum into the lipid and 20 µg/day into the soy oil/water mixture based on a 250 g implant.

These reported release values from explanted implants correspond to a loss of 10–15% of available platinum from the implant in one day, which establishes that these *in vitro* tests do not mimic physiological conditions. If platinum were lost *in vivo* at similar rates to the *in vitro*, 1 day measurement, all the platinum would have been released *in vivo* from the implants over a few weeks and there would be no residual platinum in the SBI. As noted in the National Science Panel report [87].

“Since the whole implant used in these studies would only contain 175 µg of Pt, it suggests that all of the Pt would diffuse from the gel into the media within 7 days. This is not logical. There are no data available that address the level of Pt in blood or tissues of animals or humans who have SBIs. However, if a worst case exposure scenario was calculated based on the value published by Lykissa, wherein all of the Pt in two 300 ml implants was released into the body of a 50 kg woman, the Pt dose would be 8.4 µg/kg (8.4 ng/g). This concentration of Pt is approximately equivalent to the 5 ng/g level found naturally in the environment.”

The ICP–MS is designed to run with samples of 5% nitric acid [29,88]. Matrix effects (effects of the media in which the sample is dissolved) can affect the efficiency of the nebulization process (forming droplets [89]) and, as a result, the overall quantities of metal determined. Thus, it is extremely important to use identical conditions to calibrate the instruments with standards and to measure the samples; otherwise, “chemical matrix effects and loss of analysis accuracy can occur” [90,91]. Positive control experiments, demonstrating that there were no matrix effects associated with the lipids used for extraction were not reported. Such experiments are necessary, as the platinum must move in these experiments from soybean oil to 0.1 N nitric acid, a medium in which the oil is not soluble. Negative control experiments demonstrating that there was no platinum in the lipids prior to extraction were similarly not reported. The authors noted that they cannot

determine the particular species of platinum quantitated with the technique they used.

This experiment demonstrates a direct correlation between the oil fraction in the receiving material and the magnitude of platinum release. However, the lipid-rich media experiments do not represent a physiologically relevant model. First, as noted above, it is illogical that rapid release *in vitro* are related to *in vivo* release—if platinum was lost *in vivo* at the reported ‘rates’, the explanted implants would have contained essentially no platinum. Concentration measurements at only two proximal time points are insufficient to permit a valid kinetic rate to be established. Second, the constituents of the human breast cavity have been reported to be primarily aqueous fluid containing proteins [85], consistent with the low bleed from SBIs of platinum into aqueous fluid. Of course fatty tissue is also present in the breast cavity and this study is useful, as it shows a correlation between platinum bleed and the hydrophobicity of the medium. Platinum nanoparticles are stabilized by silicones, and migration of a silicone-bound platinum particle will be significantly easier when the receiving medium is, like silicones, hydrophobic rather than aqueous. It is thus of interest to further refine this model to better correlate it with the type of fatty tissue found *in vivo* and to better mimic the lower bleed rates observed *in vivo*.

### 6.3. Platinum in explanted tissues

Hirner’s group performed experiments to examine the quantity of platinum found in tissue adjacent to breast implants that had been explanted after 16, 8 and 7 yr, respectively [12]. Fat and muscle tissue samples were taken from the areas in direct contact with the capsular tissue. In addition, capsular tissue and the “fibrin layer” (undefined) were also examined for platinum. Tissues from three explanted women were compared with those of three women that had never had implants, who served as the control group. As with Lykissa’s work, and noted by the authors, ICP-MS does not permit speciation of the metal.

ICP-MS with spiked standards (two methods: detection limit 2–6 ng/g and 50 pg/g, respectively) was used to measure the total platinum content. The control group tissue samples showed values of 0.3, 1 and 0 ng/g of platinum, respectively. Selected tissue samples adjacent to the explants of three women were studied. Fat tissue showed 90 ng/g in one case and less than 2 ng/g in another; capsular tissue showed 2 ng/g in one case and 0 (not detectable) in a second subject; and, muscle tissue showed no Pt in one sample (not detectable) and 25 ng/g in a fibrin layer. It was not possible to estimate the total amount platinum released from the implants, as total sample sizes (e.g., fraction of fatty tissue excised, weight of fatty tissue excised) were not reported.

This is an important and carefully done study that shows platinum can, in some cases, be found in higher concentrations in tissues adjacent to SBIs. With further refinement, it

<sup>7</sup>As noted above, there is a paucity of data on peer-reviewed literature on platinum release from SBIs. For interested readers, non-peer-reviewed data provided by Mentor to the FDA as part of their submission for approval of a new implant design is available [86]. Platinum release profiles into the biological medium porcine serum, a system that may approximate the constitution of the human breast cavity [87], showed Pt loss over 120 days of 4.1 µg of a total of 529 µg in a 125 cm<sup>3</sup> implant silicone. The oxidation state of the platinum was shown by X-ray absorption to be Pt(0) [88].

should be possible to better quantify total platinum release in the region of breast implants as a function of tissue type in a broader population base. Such a study would allow one to better understand the migratory aptitude and mechanism of platinum from breast implants and to compare those values with the migratory aptitude and mechanism of platinum from other environmental sources.

Maharaj [13] has also examined platinum in explanted silicone breast implants and in tissues found adjacent to the implants (16 samples chosen from 64 available). The author notes the samples were selected, “so that each type of encasing material would be represented, without knowledge of patient age, implant residence time, fixative used, or diagnosis.” However, no information is provided about the manufacturer of the implant or the year of manufacture, which would provide information about the generation of implant.

Microwave digestion followed by ICP-MS, techniques previously used to determine platinum in tissue samples [92], found platinum concentrations ranging from 260 to 48,900 ng/g ( $n = 15$ ) for gel, 3050–28,780 ng/g ( $n = 7$ ) for shell and 3–272 ng/g ( $n = 15$ ) for capsular tissue. Some questions are raised about the reported results, because the concentrations of platinum found in the shells and gels were significantly higher than the concentrations used to prepare the devices in the first place. The IOM report described values of platinum in devices ranging from about 0.1–10 µg/g [6]. The reported concentrations are at least five times higher than would be expected to be found in a device even with a highest platinum concentration. This discrepancy is not discussed. Previous analyses of silicone breast implants by ICP-MS found platinum levels in implants that were comparable to the amount of platinum initially used to form the implant [6]. The platinum values found in capsular tissue samples in this study were higher than in one study of the muscular tissue of the general population, 2 ng/g [83] and than those found in the Flassbeck study [12]. However, no data was provided from a control group, which makes comparison difficult.

ICP-MS does not permit platinum speciation, as noted by Flassbeck [12] and Lykissa, who comments, “Our ICP-MS analyses do not allow direct determination of whether platinum in implant gels is present as inorganic metal as opposed to organic or silicone-based complexes” [11]. However, Maharaj posits while referring to Lykissa that, “Platinum most likely occurs in implant material as hexavalent platinum ( $\text{Pt}^{+6}$ ) compounds, along with other ionized forms of Pt, and organoplatinum or silicon–Pt complexes.” This suggestion is completely inconsistent with known platinum chemistry, described above, and not supported by any experimental data.

Both of the tissue studies discussed indicate that platinum migrates from the SBI into adjacent tissue. A partition mechanism, between silicone/platinum particles in a silicone shell and in biological lipids, would be accompanied by a gradually decreasing concentration of platinum as one moves to tissues located further from the

implant, whereas biological mechanisms of migration would be expected to lead to migration from the implant to the normal site of platinum concentration, the kidney [71,80]. Implanted women are reported to have platinum urine concentrations similar to those of unimplanted women [79], suggesting migration in the women studied may be primarily based on local partition at the shell/biology interface. In this case, it will be very important to develop platinum assays that are able to distinguish platinum concentrations radially from the implant shell surface. This would provide the opportunity to estimate total platinum release and may account for the large differences in the platinum tissue concentrations reported in these studies.

## 7. Biological consequences of platinum

Platinum salts can have significant biological activity. They can be potent allergens [93,94]. Long-term exposure can lead to platinosis, a disease with rhinitis, conjunctivitis, asthma, bronchitis and contact dermatitis as its symptoms. Platinosis is explicitly defined as the effect of soluble platinum salts on occupationally exposed people [95].

Some platinum salts are very effective anti-cancer agents. Antitumorogenicity is associated with inhibition of DNA replication and mitosis by the platinum/DNA adducts formed [66]. For example, cisplatin and related analogues such as carboplatin are used as chemotherapeutic agents for ovarian and testicular cancer (Fig. 3) [96]. By contrast, transplatin is not an active antitumor agent [97], which exemplifies the hypothesis that even closely related compounds can have very different (bio)reactivity profiles [98]. Large, partially soluble platinum particles (250–500 nm) derived from automobile exhaust can form DNA adducts with alveolar epithelial cells [66,99]. Thus, when discussing potential biological outcomes, it is quite important to establish exposure levels to particular chemical species.

There is a direct correlation between solubility of platinum species and toxicity [70]. Compared to soluble platinum salts, platinum metal is non-soluble (except under very aggressive conditions, see above) and considered to be relatively non-toxic [100]: it is relatively common to find the descriptor “inert” associated with the metal [101]. The general consensus is that the metal is an acceptable constituent of materials for both topical (e.g., food grade wrapping materials [78]) and internal contact. Thus, platinum is used in dental implants [66], in electrodes in pacemakers (in some cases, in order to harden the material, a Pt–Ir alloy is used [102]), in vagus nerve stimulators for epilepsy patients (Teflon-coated platinum wires) [77] and in other implantable materials such as catheters as a marker, as the metal is radio-opaque. Although the degradation of Pt is facilitated under electrical current (i.e., when electrochemistry is facilitated) [103,104], this has not been an encumbrance to the use of this metal both because the magnitude of the degradation is small and any resulting

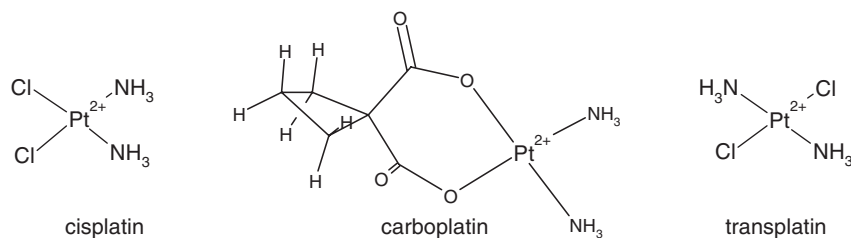


Fig. 3. Structures of cisplatin, transplatin, carboplatin.

bi-products are judged not to be problematic in the concentrations formed.

### 8. Platinum in breast implants: consequences

The foregoing discussion makes clear that all humans are in contact with environmental sources, and thus contain measurable quantities of platinum. When ascribing specific biological responses to platinum derived from silicone elastomers in breast implants, it is critical to do so in the context of control groups with known exposure to platinum from normal environmental sources. It is also important to provide specific data about structures and concentrations (dose) of putative bioactive platinum compounds before making inferences about possible toxicities.

Attempts have been made to associate negative biological consequences with the platinum catalyst used in breast implants. For example, Harbut and Churchill inferred that women with implants have a higher incidence of asthma than the background population as a consequence of the platinum to be found in implants [105]. The study has been considered incomplete by the UK Medical Devices Bureau, “in the absence of controls one could not speculate that these women might not have developed asthma anyway. Furthermore, given the absence of a proper controlled study it is impossible to quantify any risks” [5]. Similarly, Maharaj suggests, “some women with breast implants develop the signs, symptoms, and diseases consistent with toxicity from and allergy to Pt salts.” True, but the absence of proper studies, such symptoms could have many other origins than SBIs.

SBIs, some saline and all silicone gel, contain platinum used to crosslink the shell; the gel in the latter style is also formed using platinum. The platinum exists in a reducing environment, provided both by the vinyl and Si-H containing silicone polymers, and the monomeric Pt(0) species ultimately undergo aggregation. Speculation that the platinum in breast implants undergoes oxidation to toxic, higher oxidation state species, particularly Pt<sup>6+</sup>, is unsupported by data, or by the well known chemistry of platinum in the literature. By contrast, the papers that have examined the species of platinum in silicone breast implants have found no evidence of any species not at the zero oxidation state.

The studies described above suggest that some fraction of the platinum present migrates to the adjacent tissue. The prevailing understanding based on exhaustive analysis of the chemical and medical/epidemiological literature is that: the platinum found in silicone breast implants is at the zero oxidation state—a markedly less bioactive state than platinum salts; and, that epidemiological studies do not provide evidence linking platinum in SBIs with symptoms [94], symptoms which could have other origins [5–7].

The scientific world is increasingly ‘going nano’ and determining the specific mechanisms of interaction between nanoparticles and local biology is an important area of current research. It is extremely important that the scientific and medical community continue to examine in detail the consequences of compounds, chemicals, fabrication processes, and device designs and design performance on the health of patients who use the devices. This includes the small platinum nanoparticles formed during hydrosilylation which, it is hoped, will be the subject of such studies.

### 9. Conclusions

Platinum at the zero oxidation state is found in parts per million levels in silicone breast implants. Recent papers based on small cohort sizes show that implanted women may, in some cases, have elevated levels of platinum in breast tissues when compared to the non-implanted control group and to the general population, which contains platinum due to various forms of environmental exposure. The experimental evidence supports the conclusion that there are no clinical consequences of the platinum in silicone breast implants [6,94], which is to be expected based on the known toxicity of this metal in this oxidation state.

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