Articles

Total Platinum Concentration and Platinum Oxidation States in Body Fluids, Tissue, and Explants from Women Exposed to Silicone and Saline Breast Implants by IC-ICPMS

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Ion chromatography-inductively coupled plasma-mass spectrometry was used to determine the total platinum concentration and platinum oxidation states in samples from women exposed to silicone and saline breast implants. Samples included the following: whole blood, urine, hair, nails, sweat, brain tissue, breast milk, and explants. Mean Pt concentration in samples from women exposed to silicone breast implants were as follows: whole blood, 568.1 \pm 74.77 pmol/L (n = 9); urine, 1.77 \pm 0.847 μ g/g of creatinine (n = 10); hair, 2.13 \pm 2.984 ng/g (n = 9); nails, 0.88 ± 0.335 ng/g (n = 9); sweat, 1.90 ± 1.691 ng/g (n = 9); breast milk, 1.09 ± 0.316 $\mu g/L$ (n = 6). Pt in explanted silicone breast implant gel (n = 9) occurred mainly in the +2, +4, and +6 oxidation states. Pt in whole blood (n = 7) and breast milk samples (n = 6) from women exposed to silicone breast implants occurred mainly in the +2 and +4 oxidation states. Saline breast implant fluid (n = 2) did not contain detectable levels of Pt. This is the most comprehensive report, to date, to show that women exposed to silicone breast implants have Pt levels that exceed that of the general population, and the first report, to date, to document the various Pt oxidation states present in samples from women exposed to silicone breast implants.

Considerable debate exists regarding the health risks of breast implants. Approximately 200 000 reports of adverse health effects from breast implants have been reported to the U. S. Food and Drug Administration since 1985. Previous work in the field has focused on investigating the toxicity and immunogenicity of silicones as possible causes for some of the reported diseases. To date, there is no clear explanation for the diseases reported by women with breast implants.

Medical grade silicone or poly(dimethysiloxane) (PDMS) is used as the gel in silicone breast implants and as the envelope in

10.1021/ac0514016 CCC: $33.50\ @$ 2006 American Chemical Society Published on Web 04/01/2006

silicone and saline breast implants. A complex platinum salt, hexachloroplatinate, has been used in silicone gel-filled breast implants as the catalyst for the cross-linking of the PDMS chains in both gels and envelopes. Pt salt exposure has been associated with positive skin-patch tests,^{1,2} contact dermatitis,^{3,4} asthma,^{5–7} immunogenicity,⁸ inhibitory effects on brain enzymes,⁹ neurotoxicity,¹⁰ mutagenicity,¹¹ carcinogenicity,¹² and anaphylactic reactions.^{13,14}

Recent studies have shown that significant amounts of Pt occur in silicone breast implant gel^{15–17} and envelopes.¹⁷ Platinum has also been shown to leak out of intact implants¹⁶ and accumulate in the tissue^{17,18} of women exposed to silicone breast implants. No study to date has investigated the fate of total Pt from leached implants. A complete understanding of the amount of residual Pt present in women with silicone and saline breast implants is therefore warranted.

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Pt in compounds that occur in oxidation states other than zero may be harmful to human health. In the compound hexachloroplatinate, H₂PtCl₆, (used in silicone gel-filled breast implants), the oxidation state of Pt is +4 (or Pt⁴⁺). [The H ion has a +1 charge, with a total H charge of +2; the Cl ion has a -1 charge, with a total Cl charge of -6. Neutrality is obtained, therefore, with a Pt charge of +4. The (+) charge means that a loss of electrons (e⁻) has occurred, and the Pt has been oxidized.] The greater the number of electrons lost, the higher the oxidation state of the Pt. Pt +1 through +6 are reactive forms, with the higher oxidation states more reactive, as is the case in other metals, e.g., Cr^{3+} versus Cr^{6+} . Pt⁶⁺ is an unstable oxidation state that is easily reduced to Pt⁴⁺ or Pt²⁺. Oxidized forms of Pt have significant biological activity, as has been demonstrated, for example, in cancer chemotherapy and occupational medicine.

Previous work¹⁹ (and references therein) has been used²⁰ to indicate that Pt in silicone breast implants would only be present in the [0] oxidation state. However, no previous study ever actually analyzed a breast implant or explant for the various forms of Pt. The determination of the oxidation states of Pt in silicone and saline breast implants, and in the body fluids, and tissue of exposed women is vital for gauging the health risks of breast implants.

Therefore, we present the following: (1) the first report of Pt concentrations in whole blood, urine, hair, nails, sweat, and/or breast milk of women exposed to silicone or saline breast implants, and (2) the first report of the detection, separation, and analysis of Pt oxidation states in silicone explants, whole blood, urine, and/or brain tissue from explanted women. This study may be useful for risk assessment of Pt exposure in women that have had, or currently have, silicone or saline breast implants.

MATERIALS AND METHODS

Subjects. A total of 23 subjects were studied. Subjects consisted of 18 cases and 5 controls (Table 1). Cases 1–18 were women that have been exposed to breast implants. Cases 1–11 represent the first 11 consecutive women that volunteered to participate in the study. Cases 1–18 (except 2 and 4) were exposed to silicone breast implants. Cases 2 and 4 were exposed to saline breast implants only. Case 11 was exposed to both silicone and saline breast implants (Table 1). Limited information was available for cases 12–18, but all women were exposed to silicone breast implants only. Cases 12 and 13 implants are still in situ. Controls were women that have not been exposed to breast implants and ranged in age from 22 to 45 years old; two were Hispanic and three were Caucasian Americans.

Residence time of implants before removal and the number of years subjects were explanted before analyses were among the demographics collected (Table 1). Residence time of implants was available for cases 1–11, 13, and 18. The total amount of time subjects were implanted with silicone or saline breast implants was 14.6 ± 4.98 years (range 3–25; n = 13). The number of years subjects were explanted before analyses was available for cases 1–11 and was 6.0 ± 2.00 years (range 1–8; n = 10).

Three women (cases 3, 9, and 11) had multiple implants (Table

1). These women were tested once after explantation of their last

implants, and one silicone explant per case was analyzed. The sum of the number of years each individual was implanted for was used in the above calculations; for example, case 3 was implanted for a total of 18 years (3 + 13 + 2 yrs; Table 1). However, when the amount of time women were implanted with silicone breast implants was considered (see the section Total Platinum), only the number of years women were implanted specifically with silicone prostheses was used in calculations; for example, case 11 was implanted with breast implants for a total of 13 years but was implanted with silicone breast implants for a total of 12 years (Table 1).

Manufacturer, type, model, and catalog/lot/serial no. of implants were among the implant information collected (Table 1). Four generations of silicone breast implants are commonly recognized. Silicone explants in this study were all secondgeneration implants, except for case 3's last explant, which was a third-generation "low-bleed" implant. Third- and fourth-generation silicone implants are currently on the market.

Questionnaires completed by cases 1–11 were used to determine possible past platinum exposure. Subjects were asked questions regarding whether they, for example, had been treated with platinum-based chemotherapy drugs, had worked in various occupational settings where exposure may have occurred, or had platinum-containing dental amalgams. Cases 1–11 were not exposed to any such traditionally known source(s) of Pt. Breast implants represent the only known source of Pt for cases 1–11.

Reagents. All acids and solvents (ACS grade minimum) were purchased from J. T. Baker Inc. (Phillipsburg, NJ). Cisplatin (Platinol) was purchased from Bristol Laboratories Ltd. (Hertfordshire, UK). Platinum, platinum oxide, chloroplatinic acid, transplatinum diamine dichloride, and hexachloroplatinate were purchased from Sigma Chemicals (Perth, Western Australia). Metalfree (18 M Ω /cm, and by ICPMS all metals <0.01 μ g/mL) or type I water was used.

Samples. Standard laboratory procedures for the analysis of trace metals were followed. All plasticware was certified metal-free or acid-washed. All stainless steel surgical instruments were precleaned in organic solvents. Sample envelopes were paper and unused. Samples not collected at the laboratory were shipped via airborne courier service under strict chain of custody procedures.

Blood samples were collected in royal blue (metal-free) Vacutainer blood collection tubes, mixed with 4% HNO₃, and centrifuged, and the supernatant was analyzed. Urine samples from the first morning voiding were collected in sterile vials, shipped on blue ice, and stored at 4 °C until analyzed. Blood and urine samples were 1-5 mL.

Hair samples 1-2 in. long were cut with stainless steel scissors from the nape of the neck area (hair samples longer than 2 in. were adjusted to 1.5 in. in length from the root end) and stored in paper envelopes. Fingernail, toenail samples, or both, were collected using stainless steel scissors or nail clippers (depending on the subject's preference) and stored in paper envelopes. Hair and nail samples were thoroughly washed using the following sequence: methanol, type I water, 0.1% sodium dodecyl sulfate, and type I water. Samples were washed for 5 min, each step. Hair, nails, and other tissue samples weighed 0.10-0.50 g. Hair, nails, and other tissue samples were hydrolyzed in warm 6 N HNO₃. After hydrolysis, samples were diluted with metal-free water to a final concentration of 4% HNO₃.

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ir subject ^b	$\inf_{(yrs)}$	reason ^d	implantation age (yrs)	explantation age (yrs)	yrs explanted before testing	present age (yrs) ^e	ethnicity	occupation/ degree/ other	manu- facturer	type ^g	model/ style	catalog no.	lot no.	serial no.
control no.	0	46.4	46 4			96	hienanio	5						5
	00	n.ap	n.ap	n.ap	n.ap	37	hispanic		n.ap	ur.ap	n.ap	n.ap	n.ap	n.ap
	0	n.ap	n.ap	n.ap	n.ap	45	white	na	n.ap	n.ap	n.ap	n.ap	n.ap	n.ap
	0	n.ap	n.ap	n.ap	n.ap	22	white	na	n.ap	n.ap	n.ap	n.ap	n.ap	n.ap
0	0	n.ap	n.ap	n.ap	n.ap	31	white	na	n.ap	n.ap	n.ap	n.ap	n.ap	n.ap
case 110. 1	16	aug	38	54	6	65	white	small business	McGhan	double lumen	na	25-76240	na	S02-1361B
	18	aug	32	50	7	62	white	owner small business	Heyer Schulte	saline	1300	na	na	na
	ŝ	mast.	34	37	n.ap	62	hispanic	former mortgage	Heyer Schulte	double lumen	na	350/3120	144184	na
	$\frac{13}{2}$	mast. mast.	37 50	50 52	n.ap 5	= =			McGhan Mentor H S Siltev	double lumen low bleed	na na	25/76/260 354-4007	S-04-122831 65789	na na
	က	aug	19	22	1	28	white	college	Mentor	saline	1600 round	350/1640-50	145406/145521	na
	10	aug	32	42	па	50^{ℓ}	white	homemaker	Heyer	double lumen	7000 round	360-7425	225676	na
	16	aug	31	47	9	58	white	B.A.	Surgitek	single elast	na	na	1553-77-B	15260
	15	aug	21	36	7	48	white	M.A.	Dow	na	soft, low profile	na	na	na
	13	mast.	45	58	8	71	na	animal rights	Dow	silastic	round, low profile	na	na	na
	4	aug	20	24	n.ap	47	white	activist fitness	Dow	silastic	na	na	na	na
	10	aug	24	34	8	=	=	"	McGhan 3M	double lumen	76	25-76220	AE3580	na
	14	aug	39	53	9	64	white	M.A.	McGhan	double lumen	na	na	na	na
	1	aug	35	36	n.ap	58	white	B.A. B.A. arts (cum laude)	Cox- Uphoff	double lumen	220:40 cc round	SCR-220:40	G41138/42290	na
	11	aug	36	47	n.ap	=	=	=	Heyer Schulte	single elast	na	na	$4516880 \times 2-350$	na
	1	aug	47	48	9	-	=	=	McGhan	textured saline	BM-3 STL.713 TS1	8263	na	na
	na	na	na	in situ	na	na	na	na	na	silicone	na	na	na	na
	C7.	na	na	in situ	na	na	na	na	na	silicone	na	na	na	na
	na	na	11a 11a	na	na	na	na	na	na na	silicone	na	na	na	na
	na	na	na	na	na	na	na	na	na	silicone	na	na	na	na
	na	na	na	na	na	na	na	na	na	silicone	na	na	na	na
	15	na	na	na	na	na	na	na	na	silicone	na	na	na	na
	15	na	na	na	na	na	na	na	na	silicone	na	na	na	na

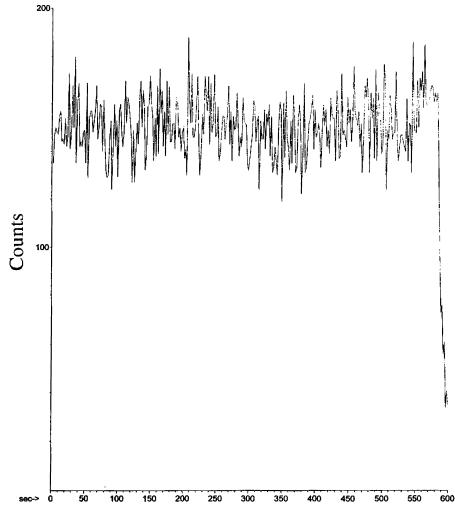


Figure 1. IC-ICPMS chromatogram of a typical blank run shown at an expanded scale, showing no signal greater than background.

Sweat (sebum) samples were collected with alcohol wipes around the base of the neck area and stored in paper envelopes. Sweat samples were eluted off with 4% HNO₃. Breast milk samples (\sim 5 mL) were collected by the lactating mothers in plastic containers and stored at 4 °C. Breast milk samples were mixed with 4% HNO₃ and centrifuged, and the supernatant was analyzed. Explants were digested using standard analytical chemistry techniques.¹⁶

Quality Assurance/Quality Control. Blanks, along with internal and external standards, were used for quality assurance. Blanks and internal standards were subjected to the same preparatory conditions as samples. Blanks contained 5% HNO₃. Internal standards contained 100 μ g/L yttrium or thallium added to samples as spikes or 100 μ g/L platinum in 5% HNO₃. External standards contained 1, 25, 50, 250, 1000, and 2500 ng/L Pt in 5% HNO₃.

Blanks were run prior to each ion chromatography-inductively coupled plasma-mass spectrometry (IC–ICPMS) analysis. Standards do not exist for Pt oxidation states other than 0, +2, and +4. Platinum was used as the standard for Pt oxidation state 0. Cisplatin, platinum oxide, and trans-platinum diamine dichloride was used as standards for Pt oxidation state +2. Hexachloroplatinate was used as the standard for Pt oxidation state +4. Oxidation states in samples that did not have standards were calculated from a graph of counts versus retention time. **Instrumentation.** All analyses were carried out with an Agilent Technologies (Palo Alto, CA) 7500 ICPMS equipped with a cross-flow-type nebulizer. A radio frequency forward power of 1.3 kW was used. Argon flow rates for the plasma and auxiliary gas were 15 and 1.2 L/min, respectively. Samples were delivered at 1.0 mL/min by a peristaltic pump and aspirated into the ICPMS for platinum analysis. Platinum isotope ions monitored were m/z 190, 192, 194, 195, 196, and 198. Quantitation was performed at m/z 195. All analyses were repeated in duplicate or triplicate. The detection limit was calculated at 1-2 pg/g using three times the standard deviation of multiple blanks.

Silicone gel (n = 9), saline fluid (n = 2), body fluids (n = 8), and tissue (n = 1) from cases 1–11 were subsequently analyzed by IC–ICPMS in order to determine the ionization state of the platinum. An Agilent Technologies liquid chromatograph equipped with an Agilent Technologies speciation column and guard column was used. The Pt was eluted with a gradient from 20% 0.001 M HNO₃, 80% 0.01 M NH₄OH to 80% 0.001 M HNO₃, 20% 0.01 M NH₄OH.

Data Analysis. Descriptive statistics are the most appropriate statistical tool for data analysis in this study. The number of observations (*n*), arithmetic means, ranges, and standard deviations are given. Statistical analyses were performed with STATA 9.0 (StataCorp LP, College Station, TX). Data were evaluated using

two nonparametric methods: the Spearman rank correlation test and the Mann–Whitney test. Some correlations, for example, between manufacturer and implant type with total Pt or Pt oxidation states in body fluids, tissue, or explants, were not appropriate given the small number of samples in each subgroup.

Correlations (and corresponding negative values) of 0-0.25indicate little or no relationship; 0.26-0.50 indicate a fair relationship; 0.51-0.75 indicate a moderate to good relationship; >0.75indicate a very good to excellent relationship or a strong correlation. A correlation of 1.00 represents a perfect correlation. Spearman's ρ or r_s was further evaluated with a test of significance of rank correlation for a two-tailed test at the 0.05 significance level.

RESULTS AND DISCUSSION

Quality Assurance/Quality Control. The percentage relative standard deviation for all measured internal spiked standards was 10% of known concentrations and shows very good accuracy for all sample types. Method linearity was established (i.e., correlation coefficient of \geq 0.999) between external standards. Recovery of added Pt was complete, i.e., between 93 and 100.8% (includes all sample types). Sample standard deviations were small and show very good precision for each sample. The very low detection limit also shows the precision of the analytical methods used. Blank concentrations were very low, i.e., 10–75 pg/g Pt (includes all sample types) and show contamination was minimal. All IC–ICPMS blank runs showed no peaks discernible above background, indicating no standard or sample carryover (Figure 1).

Total Platinum. Platinum concentration results for whole blood, urine, hair, nails, sweat, and breast milk samples are reported in Table 2. Mean Pt concentration in whole blood samples from control subjects was 506.4 \pm 112.64 pmol/L (range, 346–616; n = 5). Mean Pt concentration in whole blood samples from women exposed to silicone breast implants was 568.1 \pm 74.77 pmol/L (range, 470–688; n = 9). The Pt concentration in a whole blood sample from a woman exposed to saline breast implants was 412 pmol/L. Mean Pt concentration in urine samples from control subjects was 0.37 \pm 0.233 μ g/g of creatinine (range, 0.20–0.53; n = 2). Mean Pt concentration in urine samples from women exposed to silicone breast implants was 1.77 \pm 0.847 μ g/g of creatinine (range, 0.40–2.95; n = 10).

Mean Pt concentration in hair samples from women exposed to silicone breast implants was $2.13 \pm 2.984 \text{ ng/g}$ (range, 0.6-10.0; n = 9). Mean Pt concentration in nail samples from women exposed to silicone breast implants was $0.88 \pm 0.335 \text{ ng/g}$ (range, 0.6-1.4; n = 9). Mean Pt concentration in sweat samples from women exposed to silicone breast implants was $1.90 \pm 1.691 \text{ ng/g}$ (range, 0.3-5.4; n = 9). Mean Pt concentration in breast milk samples from women exposed to silicone breast implants was $1.09 \pm 1.691 \text{ ng/g} \pm 0.316 \mu \text{g/L}$ (range, 0.78-1.64; n = 6).

A comparison of the Pt concentration in blood, urine, tissue, hair, nails, and breast milk samples from groups not exposed to, and exposed to Pt, are reported in Table 3. Higher Pt values than those listed in Table 3 have been reported, e.g., ref 36, in a normal population and are most likely a result of population differences,²⁹

Table 2. Platinum Concentration Results^a

	samples								
subject	whole blood (pmol/L)	urine $(\mu g/g \text{ of creatinine})$	hair (ng/g)	nails (ng/g)	sweat (ng/g)	breast milk (µg/L)			
control									
1	501	na	na	na	na	na			
2	346	na	na	na	na	na			
3	459	na	na	na	na	na			
4	610	0.20	na	na	na	na			
5	616	0.53	na	na	na	na			
case									
1	688	2.00	10.0	1.2	5.4	na			
2	412	na	na	na	na	na			
3	585	0.76	1.5	0.6	2.2	na			
4	na	na	na	na	na	na			
5	na	na	na	na	na	na			
6	578	0.95	2.1	0.9	2.4	na			
7	470	2.34	1.2	0.6	0.8	na			
8	602	2.81	0.6	1.3	0.8	na			
9	na	1.69	1.0	0.7	0.8	na			
10	608	1.83	0.9	0.6	0.8	na			
11	494	0.40	na	na	na	na			
12	470	1.95	0.7	0.6	0.3	na			
13	618	2.95	1.2	1.4	3.6	na			
14	na	na	na	na	na	1.25			
15	na	na	na	na	na	1.06			
16	na	na	na	na	na	0.84			
17	na	na	na	na	na	0.78			
18L	na	na	na	na	na	1.64			
18R	na	na	na	na	na	0.98			
^{<i>a</i>} na,	not available.								

due to, for example, different geochemical environments, consumption of foodstuffs, and lifestyle factors. Another report of Pt values that is not included in Table 3 is a non-peer-reviewed Letter to the Editor.³⁷

Mean Pt concentration in whole blood samples of women exposed to silicone breast implants and that of control subjects did not show a statistically significant difference. Mean Pt concentration in whole blood samples from women exposed to

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Table 3. Comparison of Platinum Concentration in Nonexposed and Exposed Groups

group	mean ^a	$range^b$	п	method ^c	country of residence	reference	comments
blood (pmol/L)							
no known Pt exposure	na	<4-35	13	AV	Germany	Messerschmidt et al. ²¹	whole blood
" occupationally exposed " precious metal workers cisplatin therapy patients	506 415 872 1263 12205128	346-616 164-923 487-1436 780-2170 7948718-	5 11 5 7 5	ICPMS AV AV ICPMS DCP-AES	USA Germany Germany UK USA	this study Messerschmidt et al. ²¹ Messerschmidt et al. ²¹ Farago et al. ²² Belliveav et al. ²³	or plasma whole blood whole blood plasma whole blood plasma
exposed to silicone breast implants	568	$13948718 \\ 470-688$	9	ICPMS	USA	this study	whole blood
urine $(\mu g/L)$,	
no known Pt exposure " " "	0.0010 0.0012 0.00172 0.0035 0.37	< 0.0009 - 0.0138 < 0.0009 - 0.0066 0.0005 - 0.0076 0.0005 - 0.0143 0.20 - 0.53	$32 \\ 20 \\ 16 \\ 14 \\ 2$	AV AV ICPMS AV ICPMS	Germany Germany Germany Germany USA	Herr et al. ²⁴ Philippeit and Angerer ²⁵ Begerow et al. ²⁶ Messerschmidt et al. ²¹ this study	values in $\mu g/g$
occupational workers not exposed	0.0062	0.0034 - 0.0078	42	AV	Germany	Schierl ²⁷	creatinine values in $\mu g/g$
" exposed to Au dental alloys	$0.0063 \\ 0.0119$	$\substack{0.0021-0.0174\\0.0056-0.0189}$	12 50	AV AV	Germany Germany	Schierl et al. ²⁸ Schierl ²⁷	creatinine values in $\mu g/g$ creatinine
normal population	< 0.03	< 0.03	2465	ICPMS	USA	CDC ²⁹	values in $\mu g/g$
working with precious metal salts	0.47	0.210 - 1.180	7	ICPMS	UK	Farago et al. ²²	creatinine values in $\mu g/g$
occupationally exposed cisplatin therapy patients	0.68 9.65	$0.021 - 2.90 \\ 0.74 - 77.24$	27 23	AV AV	Germany Germany	Messerschmidt et al. ²¹ Schierl et al. ³⁰	creatinine values in $\mu g/g$ creatinine
cisplatin therapy patient exposed to silicone breast implants	4466 1.77	$740-23390 \\ 0.40-2.95$	7 10	AAS ICPMS	USA USA	Aggarwal et al. ³¹ this study	values in $\mu g/g$ creatinine
tissue (µg/g)							
no known Pt exposure cisplatin therapy patients	$\begin{array}{c} 0.0004 \\ 0.51 \end{array}$	nd-0.001 0.25-1.10	$\frac{3}{4}$	ICPMS NAA	Germany Denmark	Flassbeck et al. ¹⁸ Krarup-Hansen et al. ³²	breast tissue dorsal root ganglia tissue
"	1.48	na	21	AAS	Canada	Gregg et al. ¹⁰	dorsal root
" " exposed to silicone breast implants	$1.78 \\ 3.22 \\ 0.020$	1.25-2.50 1.45-6.59 nd-0.090	$\begin{array}{c} 4\\10\\6\end{array}$	NAA AAS ICPMS	Denmark France Germany	Krarup-Hansen et al. ³² Troger et al. ³³ Flassbeck et al. ¹⁸	ganglia tissue liver tissue tumor tissue capsule, fat, or
"	0.035	0.003-0.272	15	ICPMS	USA	Maharaj ¹⁷	muscle tissue capsular tissue
hair (ng/g)							
no known Pt exposure exposed to silicone breast implants	0.15 2.1	$\begin{array}{c} 0.02 {-} 0.61 \\ 0.6 {-} 10.0 \end{array}$	$^{114}_{9}$	ICPMS ICPMS	Sweden USA	Rodushkin and Axelsson ³⁴ this study	
nails (ng/g)							
no known Pt exposure exposed to silicone breast implants	0.31 0.88	0.02 - 1.1 0.6 - 1.4	96 9	ICPMS ICPMS	Sweden USA	Rodushkin and Axelsson ³⁴ this study	
sweat (ng/g)							
exposed to silicone breast implants	1.9	0.3-5.4	9	ICPMS	USA	this study	
breast milk (μ g/L)							
no known Pt exposure exposed to silicone breast implants	<0.01 1.09	$< 0.01 - 0.04 \\ 0.78 - 1.64$	27 6	ICPMS ICPMS	Austria USA	Krachler et al. ³⁵ this study	
^{<i>a</i>} na, not available. ^{<i>b</i>} nd, not detect	table. ^c AV,	adsorptive voltam	netry; I	CPMS, indu	ctively coupl	ed plasma-mass spectromet	ry; AAS, atomic

^{*a*} na, not available. ^{*b*} nd, not detectable. ^{*c*} AV, adsorptive voltammetry; ICPMS, inductively coupled plasma-mass spectrometry; AAS, atomic absorption spectrometry; DCP-AES, direct current plasma-argon emission spectrometry; NAA, neutron activation analysis.

silicone breast implants was higher than for individuals with no known Pt exposure.²¹ However, mean Pt concentrations in whole blood samples from women exposed to silicone breast implants and control subjects from this study were within the range for occupationally exposed individuals.¹⁹

Mean Pt concentration in urine samples from women exposed to silicone breast implants and that of control subjects did not show a statistically significant difference. Mean Pt concentration in urine samples from women exposed to silicone breast implants was approximately 60 to >1700× higher than for individuals with no known Pt exposure.^{21,24–26,29} The mean Pt concentration in urine samples from women exposed to silicone breast implants was within the range for occupationally exposed individuals.^{21,22}

Mean Pt concentration in hair samples from women exposed to silicone breast implants was $\sim 14 \times$ higher than for individuals with no known Pt exposure.³⁴ In addition, there is nearly no overlap in the Pt ranges of hair samples between exposed and nonexposed groups (Table 3). Mean Pt concentrations in nail

Table 4. Platinum Oxidation State Results

			0	xidatio	n stat	es (%) ^t	,	
subject	sample ^a	0	+1	+2	+3	+4	+5	+6
control								
1	whole blood	100.0	nd	nd	nd	nd	nd	nd
2	whole blood	98.0	nd	nd	nd	nd	nd	nd
3	whole blood	100.0	nd	nd	nd	nd	nd	nd
4	whole blood	95.0	nd	nd	nd	nd	nd	nd
5	whole blood	95.0	nd	nd	nd	nd	nd	nd
case								
1	explant	nd	nd	78.0	nd	22.0	nd	nd
	whole blood	nd	nd	48.5	nd	51.5	nd	nd
2	explant	nd	nd	nd	nd	nd	nd	nd
3	explant	nd	15.0	28.0	nd	45.0	nd	12.0
	whole blood	nd	nd	42.8	nd	55.6	nd	2.6
4	explant	nd	nd	nd	nd	nd	nd	nd
5	explant	56.0	nd	42.0	nd	2.0	nd	nd
	brain tissue	15.0	nd	45.0	nd	40.0	nd	nd
6	explant	nd	24.0	29.0	4.0	14.0	nd	18.0
	whole blood	nd	nd	46.0	nd	50.0	nd	4.0
7	explant	10.0	nd	75.0	nd	15.0	nd	nd
	whole blood	3.0	nd	55.0	nd	42.0	nd	nd
8	explant	4.0	nd	23.0	nd	35.0	nd	38.0
	whole blood	nd	nd	44.0	nd	48.0	nd	7.0
9	explant	nd	nd	25.0	nd	nd	65.0	10.0
	urine	nd	nd	39.0	nd	58.0	nd	3.0
10	explant	nd	nd	22.0	8.0	nd	32.0	38.0
	whole blood	nd	nd	45.0	nd	54.0	nd	1.0
11	explant	43.0	nd	20.0	nd	37.0	nd	nd
	whole blood	46.0	nd	18.0	nd	36.0	nd	nd

^{*a*} Cases 3 and 9 explant = last explant; case 11 explant = second explant (see Table 1). ^{*b*} nd, not detectable; converted to 0.0 in calculations (see text).

samples from women exposed to silicone breast implants were $\sim 3 \times$ higher than for individuals with no known Pt exposure.³⁴

As far as we know, this is the only published report on Pt concentrations in sweat samples. A comparison between the Pt concentration in sweat samples from women exposed to silicone breast implants and that of the general population is, therefore, not possible at this time. Mean Pt concentration in breast milk samples from women exposed to silicone breast implants was $\sim 100 \times$ higher than for individuals with no known Pt exposure.³⁵

The amount of time women were implanted with silicone breast implants was not strongly correlated with the amount of Pt in blood ($r_s = 0.3952$; n = 8), urine ($r_s = 0.2353$; n = 9), or nail samples ($r_s = 0.1605$; n = 8). A good to very good correlation existed between the amount of time women were implanted with silicone breast implants and the amount of Pt in hair ($r_s = 0.7273$; n = 8), and sweat ($r_s = 0.7959$; n = 8) samples.

The total Pt concentration in whole blood samples from women exposed to silicone breast implants was not strongly correlated with the amount of Pt in urine ($r_s = 0.3347$; n = 9), hair ($r_s = 0.2711$; n = 8), nails ($r_s = 0.6252$; n = 8), or sweat ($r_s = 0.6872$; n = 8) samples.

No clear correlation was apparent between the amount of time subjects exposed to silicone breast implants were explanted for before testing and the total Pt concentration in samples. For example, some samples showed an inverse correlation (i.e., as the time before testing decreased, total Pt concentration in samples increased): blood ($r_s = -0.1576$; n = 7); hair ($r_s = -0.5988$; n = 7); sweat ($r_s = -0.6400$; n = 7). While other samples showed positive correlations (i.e., as the time before testing

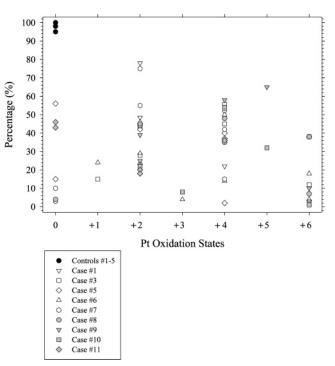


Figure 2. Pt oxidation states in samples from control subjects (\bullet), and all subjects exposed to silicone breast implants (e.g., \triangle , gray box), showing that Pt occurs only in the 0 oxidation state in samples from controls but may occur in all oxidation states (0 to +6) in samples from exposed subjects (see Table 4 for samples).

increased, total Pt concentration in samples increased): urine ($r_s = 0.6257$; n = 8); nails ($r_s = 0.4078$; n = 7).

Statistically significant (P < 0.05) positive correlations were established between the amount of time women were implanted with silicone breast implants and the amount of Pt in hair (p = 0.0409) and sweat (p = 0.0181) samples. Correlations indicative of little or no relationships, to those indicating moderate relationships, may be reflective of individual differences in Pt dose, accumulation, and elimination.

Pt Oxidation States. Platinum oxidation state results are reported in Table 4. All oxidation states in samples totaled $100 \pm 5\%$ except for one explant (case 6) that totaled 89% due to a low signal-to-noise ratio. Pt in explanted silicone breast implant gel occurred mainly in the +2, +4, and +6 oxidation states: [0] = 12.6% (range, nd-56.0; n = 9); [+1] = 4.3% (range, nd-24.0; n = 9); [+2] = 38.0% (range, 20.0–78.0; n = 9); [+3] = 1.3% (range, nd-8.0; n = 9); [+4] = 18.9% (range, nd-45.0; n = 9); [+5] = 10.8% (range, nd-65.0; n = 9); [+6] = 12.9% (range, nd-38.0; n = 9). This differed significantly from that of saline breast implant fluid where Pt was not detectable for oxidation states [0] through [+6], (n = 2), reflecting the differences in starting materials used in silicone gel and saline fluid.

Mean Pt oxidation states in whole blood samples from control subjects shows 97.6% (range 95–100; n = 5) in the [0] oxidation state (Figure 2); oxidation states +1 through +6 were not detectable (Table 4). Mean Pt oxidation states in whole blood samples from women exposed to silicone breast implants occurred mainly in the +2 and +4 oxidation states: [0] = 7.0% (range, nd–46.0; n = 7); [+1] = nd (n = 7); [+2] = 42.8% (range, 18.0–55.0; n = 7); [+3] = nd (n = 7); [+4] = 48.2% (range, 36.0–55.6; n = 7); [+5] = nd (n = 7); [+6] = 2.1% (range, nd–7.0; n = 7); (Figure

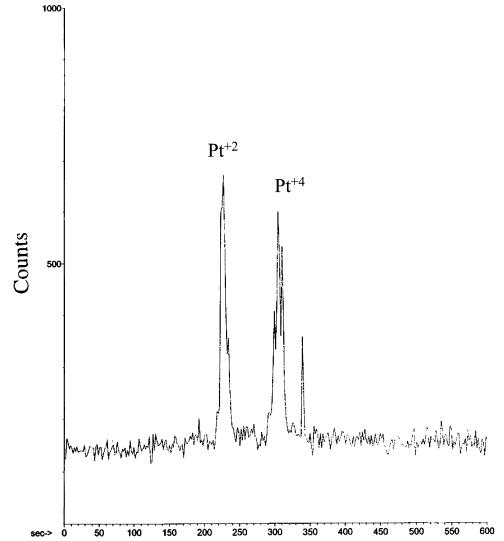


Figure 3. IC-ICPMS chromatogram of a typical whole blood sample from a subject exposed to silicone breast implants, showing that Pt occurs in the +2 and +4 oxidation states.

3). As whole blood samples from control subjects did not contain Pt oxidation states +1 through +6, and whole blood samples from exposed women did, this large difference in Pt oxidation states between the two groups was most likely due to exposure of the latter group to silicone breast implants.

Pt in urine, brain tissue, and breast milk samples from women exposed to silicone breast implants occurred mainly in the +2 and +4 oxidation states. For example, Pt oxidation states in a urine sample from a woman exposed to silicone breast implants was as follows: [0] = nd; [+1] = nd; [+2] = 39.0%; [+3] = nd; [+4] = 58.0%; [+5] = nd; [+6] = 3.0%. Pt oxidation states in a brain tissue sample from a woman exposed to silicone breast implants was as follows: [0] = 15%; [+1] = nd; [+2] = 45.0%; [+3] = nd; [+4] = 40.0%; [+5] = nd; [+6] = nd. Pt oxidation states in breast milk samples (n = 6) consistently yielded Pt²⁺ and Pt⁴⁺ (quantification of free Pt in breast milk samples was not possible due to interferences from lactalbumin, which strongly bound the ionized platinum).

Pt oxidation states between silicone breast explants and whole blood samples (n = 7) showed very strong positive correlations in three cases (i.e., cases 1, 3, and 8), and perfect correlations in two cases (i.e., cases 7 and 11): case 1 ($r_s = 0.9444$); case 3 (r_s

= 0.8383); case 6 ($r_s = 0.5169$); case 7 ($r_s = 1.000$); case 8 ($r_s = 0.8179$); case 10 ($r_s = 0.0818$); case 11 ($r_s = 1.000$) and indicates that the various forms of Pt leached from implants. A very good to excellent positive correlation also existed between Pt oxidation states in an explant and the subject's brain tissue (case 5; $r_s = 0.8696$). Little or no correlation existed between Pt oxidation states in an explant and the subject's urine (case 9; $r_s = 0.1196$).

Statistically significant (P < 0.05) positive correlations were established between Pt oxidation states in silicone breast explants and blood or tissue samples for cases 1 (p = 0.0014), 3 (p = 0.0185), 5 (p = 0.0110), 7 (p = 0.0000), 8 (p = 0.0246), and 11 (p = 0.0000). Again, correlations indicative of little or no relationships, to those indicating moderate relationships, may be reflective of individual differences in Pt dose, accumulation, and elimination.

Pt Chemistry and Fate. The platinates utilized in the manufacture of the silicone gels of silicone breast implants were neutralized with vinyl binding that detached in the reactive, hot organosilicone oil mixture. In this transitional state, the freed Pt⁴⁺ initiated the cross-linking of the low molecular weight organosilicones, which are oily in nature, into heavier molecules that possessed more cross-linking and, thus, the higher viscosity of the gel.

Our results indicate that the possible fate of Pt is as follows: migration from silicone implants¹⁶ via the lymphatic and blood systems \rightarrow urine, sebaceous secretions, and breast milk \rightarrow deposition and accumulation in hair and nails. Silicones in biological tissue³⁸ have been shown to be widely distributed after a single subcutaneous injection³⁹ and to persist in organs over an extended period.³⁹ Pt and ionized forms of Pt may, likewise, persist after years of explantation as Pt-silicone complexes¹⁶ and Ptprotein complexes. Pt may also persist for years after explantation in bone tissue. Like lead, Pt may accumulate in bone tissue by interfering with calcium deposition. Our recent (unpublished) data show unusually high amounts of Pt in extracted teeth from women with silicone breast implants. After deposition in bone tissue, the fate of Pt is dependent on the desorption and absorption rates of calcium.

All heavily cross-linked organosilicone envelopes (used in silicone and saline breast implants and in testicular implants) catalyzed with ionized Pt would be expected to undergo degradation and depolymerization with aging. Depending on the amount of ionized Pt that is liberated by the degradation process, proteins may become vulnerable to denaturation. Denaturation most likely occurs primarily through binding of ionized Pt by the sulfhydryl bridges that control the folding of the protein molecules.

This report is limited by the number of cases studied. Additional work on a large number of cases by independent researchers is needed to corroborate and extend the results of this study. Future work should concentrate on the identification and quantification of the platinum compounds present.

CONCLUSIONS

This is the most comprehensive report, to date, to show that women exposed to silicone breast implants have Pt levels that exceed that of the general population and the first report to show Pt in various oxidation states present in samples from exposed women. Women exposed to silicone breast implants had higher Pt levels by approximately 60 to >1700× for urine, $14\times$ for hair, $3\times$ for nails, and $100\times$ for breast milk samples than individuals with no known Pt exposure. Pt in explanted silicone breast implant gel, whole blood, urine, brain tissue, and breast milk samples from women exposed to silicone breast implants occurred mainly in reactive forms. Saline breast implant fluid did not contain detectable levels of any form (reactive or nonreactive) of Pt. Silicone breast implants are the most likely source of the elevated total Pt levels and the reactive forms of Pt in women exposed to these devices.

ACKNOWLEDGMENT

We thank the women that volunteered to participate in this study. We are grateful to the Editor for comments, and three anonymous reviewers (65–67) for their critiques. We extend a special thank you to reviewer 65 for his/her obviously large investment of time and for providing numerous helpful suggestions that significantly improved the manuscript. Dr. C. Lutmar (Princeton University) provided assistance with STATA 9.0. The corresponding author's interest in this subject is scientific and medical and has not consulted for breast implant manufacturers or plantiffs' attorneys. Partial support for this study was provided by Chemically Associated Neurological DisOrders (CANDO).

Received for review August 4, 2005. Accepted February 17, 2006.

AC0514016

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