

## Confirmation of the systematic presence of tin particles in fallopian tubes or uterine horns of Essure implant explanted patients: A study of 18 cases with the same pathological process

M. Catinon<sup>a</sup>, E. Roux<sup>a</sup>, A. Auroux<sup>b</sup>, A.M. Trunfio-Sfarghiu<sup>c</sup>, C. Lauro-Colleaux<sup>d</sup>, E. Watkin<sup>e</sup>, G. Sournies<sup>f</sup>, M. Vincent<sup>a,\*</sup>

<sup>a</sup> Minapath Développement, Insavalor CS : 52132, 69603, Villeurbanne, France

<sup>b</sup> IRCELYON UMR 5256, CNRS, Université Claude Bernard Lyon 1, 69626, Villeurbanne, France

<sup>c</sup> Univ Lyon, INSA-Lyon, CNRS UMR5259, LaMCoS, F-69621, Villeurbanne, France

<sup>d</sup> Laboratoire Technipath, 41 allée des Cyprès, 69760, Limonest, France

<sup>e</sup> Laboratoire Cypath, 201 Route de Genas, 69100, Villeurbanne, France

<sup>f</sup> Natecia Service de gynécologie, 28 Avenue Rockefeller, 69008, Lyon, France

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### ABSTRACT

**Objective:** To examine associations between local and systemic symptoms and the wear of the tin weld of Essure implants.

**Design:** study of a series of cases.

**Settings:** Two French hospitals.

**Participants:** Eighteen patients explanted by hysterectomy and salpingectomy for removal of their Essure implants between September 2019 and July 2020, have had a common anatomopathological process.

**Main outcome measures:** anatomopathological examination by optical microscopy and mineralogical analysis of the fallopian tube or uterine horn with scanning electron microscopy coupled with energy dispersive X-ray (SEM-EDX). Evaluation of local and systemic symptoms with a questionnaire. Examination of blood metal assays (nickel, chromium, and tin).

**Results:** anatomopathological examination highlights foreign body granulomas, fibrosis, adenomyosis, non-specific inflammation, cysts and myomas in the Fallopian tubes, uterine horns, or both and mentions the presence of foreign bodies in seven cases. SEM-EDX analyses showed, systematically, the presence of tin particles integrated in the wall near the weld, generally in clusters, and with a size ranging from about one micron to several dozen microns. The questionnaire shows that the most frequent local symptoms were pelvic pain, urinary disorders, bleeding, and pains during intercourse. The most common systemic symptoms were: asthenia, visual disturbances, amnesia, giddiness, dorsal pains, headaches, and joint pains. The majority of local and systemic symptoms decreased after explantation, but sometimes incompletely. Before explantation, high levels of nickel, tin and chromium were observed in 11/17, 1/7 and 2/17 patients. After explantation, tin levels were high in 3/11 patients.

**Conclusions:** our new anatomopathological process systematically demonstrates the presence of tin particles in tissue near the weld. These particles could be responsible for granulomatous inflammations as well as local symptoms. Many of the systemic symptoms are consistent with chronic organotin poisoning but further studies are needed to find out whether tin from the solder can be converted to organotin in the patients' bodies.

### 1. Introduction

In 2002, a novel hysteroscopic sterilization device was put on the market after review and premarketing approval by the US Food and

Drug Administration (FDA): the ESSURE System (initially marketed by Conceptus, a start-up later bought by Bayer Healthcare, Whippany, New Jersey, in 2013). The ESSURE device is made of an internal spring made of steel (iron, chromium and nickel) associated with terephtha-

\* Corresponding author at: MINAPATH Développement, 56 Boulevard Niels Bohr, CEI2, CS : 52132, 69603, Villeurbanne Cedex, France.  
E-mail address: [mvincent@minapath.com](mailto:mvincent@minapath.com) (M. Vincent).

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late polyethylene (Dacron) and an external spring made of Nitinol (nickel and titanium) to help maintain the device in the fallopian tube. Polyethylene fibers were used to produce a fast inflammatory response with macrophages, fibroblasts, foreign body giant cells and lymphoplasmocytes, designed to induce fibrosis and tubal occlusion in each fallopian tube, to prevent fertilization [1,2]. Three months after placement of the device, women underwent hysterosalpingography to confirm implant placement and occlusion, before discontinuing use of other contraceptive methods.

The device offered clear advantages, namely the absence of incision and the possibility to insert intravaginally the implant without general anesthesia and in an ambulatory setting. The outer coil and inner coil were linked by a tin solder. Some incidents of nickel allergy were rapidly noticed [3–5], and pain [6–8], migration [9–11], contraceptive failure [12] have also been noted, but at the same time studies comparing hysteroscopic versus laparoscopic sterilization were in favor of micro-implantation [13–15].

In 2015 a sudden increase of patient-reported adverse effects surrounding the ESSURE implant was observed [1,16]. The driving forces for the sudden increase in adverse event reporting starting in 2013 remain unclear. Pharmacovigilance through online community outreach and mobile reporting applications may have played a role [17]. In France, which was the largest market among European countries with about 200 000 women, three associations of patients have been created and represent more than three thousand women. There is a marked tendency towards salpingectomy or hysterectomy treatment of many affected women. In 2018 a retrospective French study based on data from hospitals and the health safety agency compared 71,303 women sterilized by Essure implant and 34 054 sterilized by tubal ligation [18]. The Essure implant technique was associated with a higher risk of gynecological complications one and three years after implantation; however there was no difference for systemic symptoms. A September 2019 FDA report about biological responses to metal implants includes a discussion about ESSURE implants [19], principally centered on nickel hypersensitivity as a proposed explanation for ESSURE intolerance [3–5].

We recently published in 2020 a study based on ten explanted cases, discussing a dysfunction of the implant at the level of the tin weld [20]. We made four proposals: 1/ to always perform a hysterectomy with salpingectomy because we frequently found tin particles in the uterine horns, 2/ to systematically look for tissue lesions at the weld level during anatomopathological examination, 3/ to perform a mineralogical analysis by SEM-EDX for chemical identification of the particles in fallopian tubes and/or horns, and 4/ to monitor tin blood levels. The purpose of our study is to examine associations between local and systemic symptoms and the wear of the tin weld of Essure implants. Each patient have systematically a new anatomopathological protocol specially designed to search for mineral particles in their fallopian tube or uterine horn with a mineralogical analysis by SEM-EDX, correlated with a clinical questionnaire before and after explantation and, sometimes, a blood metal assays.

## 2. Patients and methods

### 2.1. Study design

This is a retrospective study of a series of 18 cases.

### 2.2. Patient population

Eighteen women aged 36–56 years (median and mean: 49 years old), implanted for a duration of 44–178 months (median: 89, mean: 94), who requested removal of their ESSURE implant and underwent salpingectomy and hysterectomy. All the patients having benefited from the anatomopathological protocol designed to study the effects of

wear on the tin solder were systematically included in the study between September 2019 and July 2020.

Every woman gave an informed consent agreeing to the observation of her specimen in an individual research context with SEM-EDX analysis (MC, ER, and AMS) and to a grouping of cases for publication.

### 2.3. Patient and public involvement

Patients participated in the research but were not involved in the design, conduct, reporting or dissemination plans of the research.

### 2.4. Anatomopathological protocol

The process has been elaborated by our pathologist partners (EW, CL). Seventeen analyses were made by the same medical and pathologist team (GS, and CL); one other center received the anatomopathological protocol beforehand. For the preparation of biopsies, it was recommended that the Essure implant not be removed by the surgeon, so as to make it possible during the macroscopic anatomopathological examination to locate the Essure implant within the fallopian tube, and to open longitudinally the tube and horn without altering the implant and ablate it without stretching it if possible. A longitudinal fallopian tube and/or uterine horn section was prepared in front of the implant, as well as a transversal section at the weld level and at the distal extremity of the implant, in addition to classical sampling of horn and uterus tissue. Finally the implants were put into a dry flask, with identification of each side. The pathologist sent a paraffin block for mineralogical analysis of the specimen showing the most granulomatous inflammation and if possible foreign bodies identification.

### 2.5. Preparation for scanning electron microscopy coupled with energy dispersive X-ray (SEM-EDX) study

Two 5 µm thick histological sections were made from the paraffin block. The first one was subjected to HES coloring and placed on an optical slide. The second was deposited on a double-sided adhesive carbon disc (diameter 25 mm) as described in our recent article [20], which also describes the SEM analysis conditions.

### 2.6. Particle analysis protocol

The goal of the mineralogical analysis was to look for any mineral particles coming from the Essure implant weld in the tube or horn samples. All the histological sections were firstly observed with a low magnification (x50) for identifying high density clusters of particles. Field analyses were then performed on these clusters and as well possibly on granulomatous inflammation lesions. For each biopsy, at least 30 particles were analyzed on at least three fields. On each field, the analyzed particles were sampled by the operator and classified into different particle families based on the EDX spectra.

### 2.7. Clinical data

All patients were interviewed by one or two clinicians (GS, MV). Patients were solicited with an evaluation form to assess the level of tolerability of each local or systemic symptom on a scale from 0 to 10, before explantation and after at least three months from explantation. One patient did not respond to the questionnaire.

**Blood metal measurements** were not systematically performed. The levels were measured by ICP-MS for nickel in plasma, for chromium in total blood, and generally for tin initially in plasma before explantation and total blood after explantation.

3. Results

3.1. A/ Pathological analysis by optical microscopy and SEM-EDX (Fig. 1 and Table 1 and 2)

The pathological study by optical microscopy (Table 1) shows that all women presented some granulomas (17/18 patients) or fibrosis (1/18) identified in the fallopian tube (9/18), uterine horn (6/18) or both (3/18). We also observed uterine adenomyosis (14/18), nonspecific inflammatory signs (10/18) and foreign bodies (7/18 patients). Various other lesions such as cysts and myomas were observed. Mineralogical analysis showed for each patient some particles of size between one and several dozen microns, often in clusters, in the fallopian tube or horn

not far from the wall (Fig. 1). Table 2 shows that the presence of tin-based particles was observed in all samples by EDX analysis. Tin was sometimes associated with silver. Some calcium particles were also found, corresponding most often to calcium phosphate and more rarely to calcium oxalate. We observed also some particles of titanium, platinum, silver, and steel (FeCrNi).

3.2. B/ Clinical results (Tables 3 and 4, Figs. 2 and 3)

Seventeen patients responded to the questionnaire. The most frequent local symptoms before explantation, irrespective of perceived intensity, were: pelvic pains (13/17 patients), urinary sphincter disorder (12/17), bleeding (11/17), pains during intercourse and genital pruritus

Table 1

Description of the patients, the different biopsies analyzed and details of the histological study. ft: fallopian tube; uh: uterine horn.

Patient number	Age	Biopsy	Time before removal (months)	Granuloma	Fibrosis	Non-specific inflammation	Foreign bodies	Uterine adenomyosis	Others
1	49	ft + uh	127	X				X	Cervical epidermal dystrophy
2	52	uh	90	X		X	X	X	Dystrophic endometrium
3	49	uh	73	X				X	Myomas
4	56	ft	114	X				X	Calcifications
5	52	ft	66	X		X	X	X	Cystosteanonecrosis
6	43	ft	80	X				X	Paratubar cysts
7	46	ft	60	X		X		X	Myomas
8	48	ft	103	X				X	
9	36	ft	44	X		X	X		
10	54	uh	178	X		X	X	X	Ovarian and paratubar cysts
11	38	ft + uh	55	X		X		X	Paratubar cyst
12	51	ft	80	X					Myomas
13	45	ft	61		X				Paratubar cysts
14	56	uh	121	X				X	Myomas
15	49	uh	107	X		X	X	X	
16	50	uh	91	X		X	X	X	Paratubar cyst
17	56	ft	162	X		X			Myomas
18	55	ft + uh	89	X		X	X	X	

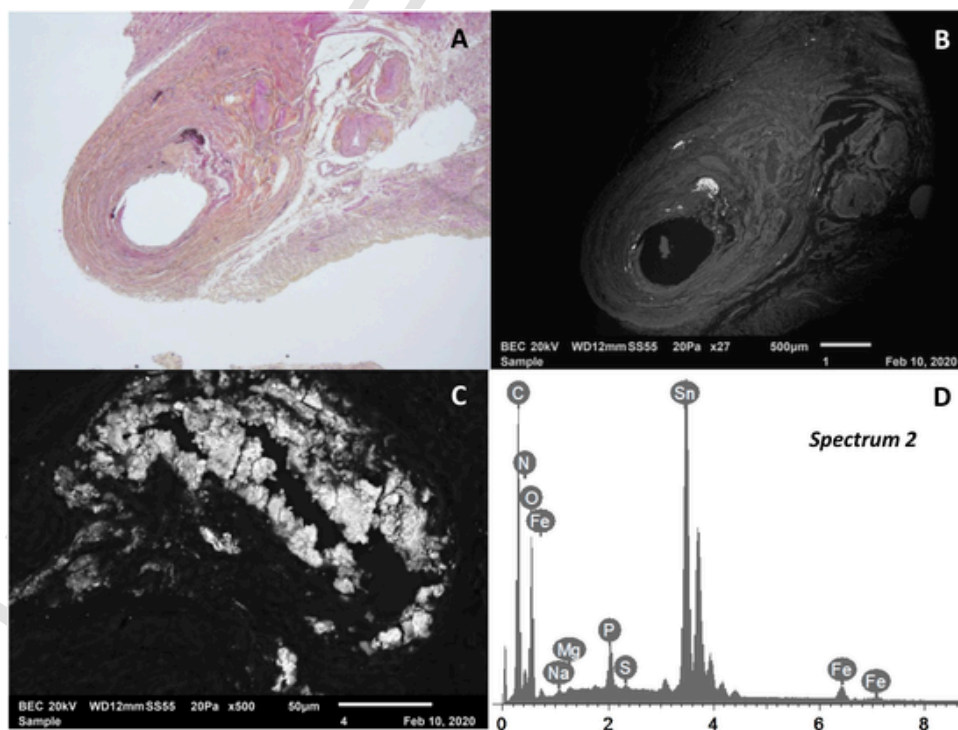


Fig. 1. Correlative observation by light microscopy (A) and scanning electron microscopy (B) of the histological section of the fallopian tube of patient no. 6 at x25 and x27 magnification. A cluster was observed at x500 magnification (C) and an EDX analysis was performed. In this field, the 10 particles analyzed have a spectrum similar to the spectrum n°2 presented in figure (D).

**Table 2**

Results of the mineralogical analysis of the biopsies. + + + + : 75 to 100 %; + + + : 50 to 75 %; + + : 25 to 50 %; + : 0 to 25 %. ft: fallopian tube; uh: uterine horn.

Patient number	Sample	tin-based	calcium-based	silicon-based	Steels	Fe comp	Ti comp	Pt comp	AgO	number of particles analyzed
1	ft + uh	++++							+	96
2	uh	++++	+		+					133
3	uh	++++	+							30
4	ft	++++								59
5	ft	++++								40
6	ft	++++								45
7	ft	+++					+	+		40
8	ft	++++	+				+			50
9	ft	++++			+					30
10	uh	++++								30
11	ft + uh	++++								45
12	ft	++				+++				70
13	ft	++++	+		+					32
14	uh	++++								30
15	uh	+++	++	+						47
16	uh	++++								30
17	ft	++	++	+	+		+	+		42
18	ft + uh	++++								45

(9/18), and symptoms linked to microbial urinary infection (8/18). For 17 patients there was a global improvement in the intensity of symptoms after explantation (Fig. 2). The most frequent systemic symptoms were asthenia, visual disturbances (15/17), dizziness and back pains (14/17), headaches and joint pains (13/17). Fig. 3 shows a significant decrease of all systemic symptoms after implant removal. Regarding the questionnaire scoring for each patient, in the majority of cases there was a decrease in the total scores, sometimes modest. Three patients had unchanged total systemic symptom scores (among them patients 10 and 11 who had no symptoms before explantation). The eight patients who had urinary infections had a mean systemic score of 88.5 whereas the 9 patients without infection had a mean score of 44.8 (Mann and Whitney test;  $p = 0.0037$ ).

3.3. C/ Metal blood level measurements (Table 5)

Before explantation, the plasmatic nickel levels were above the superior limit (SL) in 11/17 patients, and so were the plasmatic tin level in 1/9 patient and the total blood chromium level for 2/17 patients. After explantation the total blood tin level was still higher than SL in 3/11 patients, and in three cases we observed a higher total blood tin level after explantation compared to the plasma level before explantation.

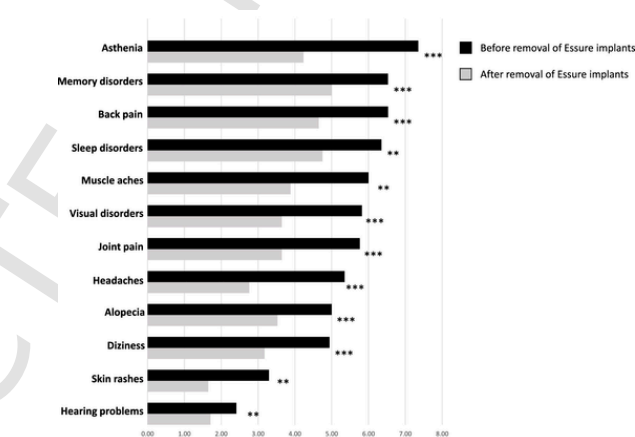


Fig. 3. Histogram representing the score for each systemic symptom before (black histograms) and after implant removal (grey histograms). The results are expressed as an average. A Wilcoxon signed rank test for paired samples was performed for each symptom.  $0.01 < p < 0.05$  (\*\*);  $p \leq 0.01$  (\*\*\*)

4. Discussion

We pre-established and applied an anatomopathological protocol to a series of 18 patients who underwent surgery to remove their Essure implants. The use of this protocol followed by a mineralogical analysis of uterine biopsies enabled us to systematically detect tin-based particles in the fallopian tubes and uterine horns. These results are correlated with an anatomopathological examination, a questionnaire and, sometimes, a blood metal assays in order to examine associations between local and systemic symptoms and the wear of the tin weld of Essure implants.

4.1. Limitations

The results of blood tests are incomplete due to the retrospective nature of our study. In fact, the patients did not systematically carry out this type of examination. For symptom collection, the intensity scale from 0 to 10 is filled in by the patients. There may be a bias in the perception of pain that may be dependent on the patient. As our study was a retrospective study, it was unfortunately not possible to compare these results with a group of women having hysterosalpingectomy for reasons other than Essure device removal. One patient did not respond to the questionnaire.

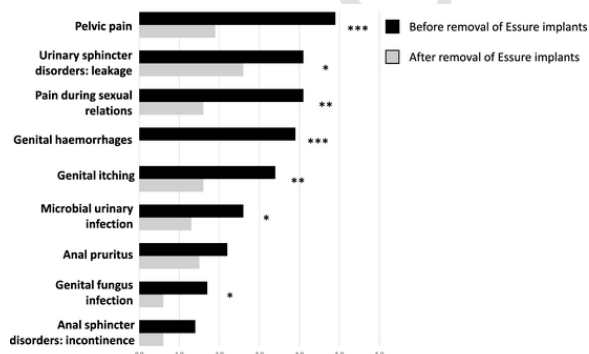


Fig. 2. Histogram representing the score for each local symptom before (black histograms) and after implant removal (grey histograms). The results are expressed as averages. A Wilcoxon signed rank test for paired samples was performed for each symptom.  $0.05 < p < 0.1$  (\*);  $0.01 < p < 0.05$  (\*\*);  $p \leq 0.01$  (\*\*\*)

**Table 3**

Intensity of local symptoms contracted by patients before and after removal of their ESSURE implants. The intensity is measured with a score ranging from 0 (no symptoms) to 10 (very strong symptoms). Patient N°12 lost of follow up.

		1	2	3	4	5	6	7	8	9	10	11	13	14	15	16	17	18	Total score
Genital haemorrhages	Before	0	0	8	0	10	5	0	8	10	0	1	4	8	10	1	0	1	66
	After	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pelvic pain	Before	4	3	0	8	6	8	10	9	10	3	0	2	0	9	6	6	0	84
	After	0	0	0	10	0	0	10	3	6	0	0	0	0	0	0	3	0	32
Pain during sexual relations	Before	0	0	0	7	5	8	10	8	10	0	0	0	0	7	4	10	0	69
	After	0	0	0	10	0	0	0	2	10	0	4	0	0	0	0	0	1	27
Microbial urinary infection symptoms	Before	1	0	0	9	0	4	2	5	10	0	0	0	0	0	8	6	0	45
	After	0	0	0	10	0	0	1	0	10	0	0	0	0	0	0	0	1	22
Genital fungus infection symptoms	Before	6	0	0	0	0	0	5	10	0	0	2	0	0	0	6	0	29	
	After	0	0	0	0	0	0	0	0	10	0	0	1	0	0	0	0	11	
Urinary sphincter disorders	Before	0	2	0	8	0	7	3	10	7	0	0	2	7	5	7	6	6	70
	After	0	2	0	9	0	3	10	3	5	0	0	0	4	2	3	2	2	45
Anal sphincter disorders	Before	0	0	0	2	0	0	10	2	0	0	0	0	0	0	0	0	9	23
	After	0	0	0	2	0	0	9	0	0	0	0	0	0	0	0	0	0	11
Genital itching	Before	0	0	0	6	0	4	9	8	9	0	0	0	3	6	7	6	0	58
	After	0	0	0	7	0	0	7	2	9	0	0	0	0	2	0	1	0	28
Anal itching	Before	0	0	10	4	0	0	10	8	0	0	0	0	0	0	6	0	38	
	After	0	0	0	4	0	0	10	2	8	0	0	0	0	0	0	1	0	25
Total score	Before	11	5	18	44	21	36	54	63	66	3	1	10	18	37	33	46	16	
	After	0	2	0	52	0	3	48	12	58	0	4	1	4	4	3	7	4	

**Table 4**

Intensity of systemic symptoms contracted by patients before and after removal of their ESSURE implants. The intensity is measured with a score ranging from 0 (no symptoms) to 10 (very strong symptoms). Patient N°12 lost of follow up.

		1	2	3	4	5	6	7	8	9	10	11	13	14	15	16	17	18	Total score
headaches	Before	9	0	0	8	3	9	9	9	10	0	1	0	8	8	3	8	6	91
	After	0	0	0	6	0	3	9	3	5	0	1	0	2	5	2	8	3	47
asthenia	Before	10	9	9	10	7	8	10	10	10	0	0	3	6	9	8	9	7	125
	After	3	7	5	9	1	7	10	2	6	0	0	1	0	5	7	6	3	72
alopecia	Before	4	8	0	10	3	0	10	7	9	0	0	7	5	9	10	3	0	85
	After	1	7	0	8	1	0	10	3	9	0	0	6	2	1	10	2	0	60
skin rash	Before	7	0	7	3	3	0	7	5	9	0	0	0	5	8	1	1	0	56
	After	0	0	2	3	0	0	7	2	7	0	0	0	4	1	0	2	0	28
muscle pains	Before	10	0	7	8	8	6	10	9	10	0	0	0	8	9	9	1	7	102
	After	6	0	4	10	7	3	10	3	10	0	0	0	4	0	6	1	2	66
back pains	Before	10	5	10	9	0	8	10	7	10	0	1	0	8	10	8	9	6	111
	After	8	5	9	10	0	5	10	3	10	0	1	0	5	1	3	7	2	79
joint pains	Before	10	0	2	8	4	7	10	10	9	0	0	0	9	5	9	8	7	98
	After	8	0	2	10	1	3	10	3	6	0	0	0	3	1	5	8	2	62
visual disorders	Before	8	6	2	5	3	6	10	10	8	0	0	2	6	9	10	9	5	99
	After	3	6	0	5	1	2	10	2	5	0	0	1	0	9	8	8	2	62
memory disorders	Before	8	9	1	6	8	7	10	10	10	0	0	5	8	8	8	9	4	111
	After	6	4	0	6	7	5	10	3	10	0	0	5	3	8	8	8	2	85
sleep disorders	Before	9	9	5	8	0	3	10	9	10	0	1	7	8	9	5	9	6	108
	After	0	7	5	7	0	2	10	9	10	0	1	9	3	5	3	7	3	81
hearing problems	Before	6	0	0	7	6	0	8	8	0	0	0	0	3	0	1	2	0	41
	After	5	0	0	6	1	0	8	7	0	0	0	0	0	0	1	1	0	29
dizziness	Before	5	5	2	6	5	4	10	6	2	0	0	4	8	8	6	9	4	84
	After	2	2	1	5	5	0	10	2	0	0	0	4	4	4	6	7	2	54
Total score	Before	96	51	45	88	50	58	114	100	97	0	3	28	82	92	78	77	52	
	After	42	38	28	85	24	30	114	42	78	0	3	26	30	40	59	65	21	

4.2. A/ anatomopathological and mineralogical analysis by SEM-EDX

These results confirm those of our preliminary study in which there was no specific anatomopathological examination [20]. In that study, the reason why half of the specimens did not show tin particles is probably because the biopsies studied were far from the implant weld. The sampling made in the present study, at the implant weld level, explains the systematic observation of (most often) granulomatous inflammation or (in one instance) fibrosis lesions. Indeed, a 2001 preliminary study of pathological effects of implants on fallopian tube and uterine tissue on 33 women [2] showed that there were foreign body granulomatous reactions in 26 of 47 fallopian tubes studied and a chronic inflammatory reaction in 42 of them.

However, a US retrospective study on 126 explanted women observed an inflammatory aspect in only 59 cases, of which 31 were in association with giant cells and a chronic lympho-plasmacytic reaction [21]. Finally, a French study on 90 explanted patients found that 28 had fibrosis signs, and only 14 had inflammatory salpingitis and 10 had a macrophagic reaction [22]. A preclinical animal study on pigs by Conceptus Inc. showed by optical microscopy the presence of foreign bodies in fallopian tubes, without chemical identification [23].

Indeed SEM-EDX analysis was necessary for identifying particles coming from worn tin solder. The identification of foreign body granulomas at the uterine horn level for nine women suggests a diffusion of particles from the fallopian tubes or a partial implant migration, justifying the recommendation for systematically associating a hysterectomy to salpingectomy. This diffusion of particles is confirmed with the ob-



**Table 5**

Nickel, tin and chromium concentrations ( $\mu\text{g/L}$ ) in plasma (p) and whole blood (wb) of patients before and after explantation of their ESSURE implants. Plasma nickel  $< 1.3 \mu\text{g/L}$  (95th percentile) (Cesbron A, 2013); Whole blood tin  $< 0.6 \mu\text{g/L}$  (95th percentile) (Cesbron A, 2013); Whole blood chromium  $< 0.87 \mu\text{g/L}$  (95th percentile) (Cesbron A, 2013).

	nickel		tin		chromium	
	Before (p)	After (p)	Before (p)	After (wb)	Before (wb)	After (wb)
1	4.8	<0.5	<0.7	0.23	<0.87	
2	2		<0.1	0.31	0.74	
3	2.6		0.1		0.5	
4	1.2			0.34	1.36	
5	1.4				0.65	
6	1.2			0.25	0.68	
7	1		0.17	0.23	0.5	
8	1.4				<0.5	
9	1.2			0.35	<0.5	
10	0.6				2.65	
11	2.3				<0.5	
12	1.8				0.88	
13	0.3		<0.5	0.85	3.2	
14	1.2			0.66	<0.5	
15	3.5		0.32		<0.5	
16		1.4		0.37		<0.5
17	2.3		1.34	0.73	<0.5	
18	1.6			0.33	0.69	

servation (unpublished) by our team of an implanted patient with a rectovaginal inflammatory granulomatosis nodule for which SEM-EDX analysis identified granulomatous inflammation with some tin particles.

Adenomyosis, observed in the myometrium, was an associated condition in 15/18 cases. This pathology, easily identified by Magnetic Resonance Imagery and linked to a uterine traumatism [24], could have been induced by the Essure implants. SEM-EDX observation allowed the identification of particles for all patients whereas optical microscopy only identified foreign bodies in 7/18 cases. This proves the interest of SEM-EDX use to identify foreign body granulomatosis. The other identified particles come from other Essure implant parts: the steel internal spring (iron, chromium and nickel) or the nitinol external spring (nickel and titanium). However, steel particles were rarely observed. It is possible that the nickel is associated with nanoparticles or is solubilized and cannot be observed by our SEM with the magnification used for analysis. Indeed an inductively coupled plasma mass spectrometry (ICP-MS) tissue study [25] of the elements chromium and nickel showed the presence in fallopian tube and uterine tissue of a density gradient between the juxta implant zone and the more distal zone, suggesting that a release of these two metals did occur. Unfortunately, no study of the presence of tin in the same tissues was performed, either by ICP-MS or by SEM-EDX analysis. Chromium, nickel and titanium particles coming from joint prostheses are considered biocompatible. This is the case for example with hip prostheses, even if some particles are observed in loco-regional nodes [26]. Similarly, the nitinol implants widely used in vascular endoprotheses are considered to be well tolerated despite a long term leaching [27,28]. The calcium particles frequently observed in our study could be linked to a beginning of endogenous calcification from uterine inflammatory tissues. Thus it seems possible that an important part of the inflammatory and fibrosis process observed in the fallopian tubes and uterine horns could be attributed to tin particles coming from tin weld wearing [20], even though one cannot eliminate a possible role for chromium and nickel nanoparticles.

#### 4.3. B/ clinical data

For the studied patients, the median time between implantation and explantation was about 90 months, i.e. seven and a half years. In previous studies, the frequency and importance of symptoms have been

found to increase with the time elapsed since implantation [29]. After a median follow up time of 29 months, 689 implanted women out of 924 (74 %) responded to a satisfaction questionnaire about symptoms. Of those, only 100 (15 %) reported disabling symptoms, most often local. The same questionnaire sent to 577 patients after a median follow up time of 144 months (12 years) resulted in 157 out of 317 respondents (49.5 %) reporting disabling symptoms, and 51 (16 %) undergoing implant removal.

An improvement in clinical data and quality of life has been reported in all explantation studies [30–33]. The screening questionnaire with scores between 0 and 10 about the level of symptoms before and after explantation was completed after an individual interview about symptoms by at least one clinician for all patients. It took into account the most frequently reported local and systemic symptoms. One patient did not respond to the scoring questionnaire. Two patients signaled that they had no symptoms but asked for implant removal in relation to information found on social networks. However the placebo hypothesis for explaining the regression of local symptoms on the great majority of patients (14/17) can be eliminated in light of the large-scale French data analysis comparing Essure implant and tubal ligation cohorts [18]. The difference between the two cohorts has been studied for the incidence of new local surgery procedures, but also systemic symptoms such as auto-immune disease, thyroid disorders, allergies, antalgic, antimigraine, antidepressant or benzodiazepine treatments, medical check-ups, death, new disease, suicide attempts. More than 5 % of Essure implanted women (5.6 %) needed another local surgery, compared to only 1.8 % of the patients treated by ligation.

In our experience, local symptoms with pelvic pains were the most frequently reported ones, ahead of urinary sphincter troubles and intercourse pain; all of these were significantly improved by explantation. If the pains and bleeding can be linked to local inflammation and adenomyosis, the frequency of urinary leaks (12/17), associated in four cases with troubles of the anal sphincter, suggest a neurogenic factor independent of uterine inflammation. Among the four cases with anal sphincter troubles, one patient needed a neurostimulation and was completely cured after explantation. However, it also seems plausible that the tin weld corrosion inducing inflammatory granulomatosis could also be responsible on a non-exclusive basis, along with adenomyosis, for the pelvic and intercourse pains and bleeding.

About systemic symptoms, the median follow up time between implantation and explantation of more than 7.5 years confirms the need to have a new large-scale study on the French data [18] with a minimal follow-up time of five years. It is interesting to compare the total screening results of patients with or without urinary infections and systemic symptoms: the mean systemic symptom score of patients with infection was 88 whereas the other patients without infection had a mean score of 44. One other patient has been diagnosed with multiple sclerosis after two neurologic symptoms, diplopy followed by abnormal movements of the arm, signs which are compatible with organotin intoxication [34].

Finally about systemic symptoms all patients could be considered as having an ASIA syndrome [35]. Besides siliconosis, golf war and macrophage myofasciitis syndromes, and post vaccination phenomena, systemic symptoms associated with Essure implant could be a fifth condition with ASIA syndrome.

#### 4.4. C/ metal measurements

The measurements were realized by ICPMS dosage, taking into account 100 healthy control subjects [36]. For nickel dosage, the frequency of levels higher than SL was important compared with studies on nickel-rich stainless steel. A first study on nickel alone, 9–15 years after implantation of hip prostheses, did not show any significant difference for 12/13 patients compared to 30 healthy subjects. In this study, the mean nickel levels reported were  $0.28 \mu\text{g} \pm 0.24 \mu\text{g/l}$ . Only one pa-

tient, a 78 year old man with two hip prostheses, had a high level of 3.1 µg/l but related to a renal insufficiency [37]. On the other hand, a chromium and nickel level study on 20 patients who had hip prostheses for more than ten years and 20 controls showed a significant difference for those two elements, but without levels that exceeded the SL [38]. The nickel values were between 0.26 and 0.33 µg/l. If some neurologic symptoms have been observed related to chromium-cobalt intoxication in patients with metal-metal prostheses [39], we do not know of systemic symptoms linked to stainless steel hip implants. In some studies nickel and chromium are found to have a low risk of neurotoxic symptoms [40,41]. However other studies discuss a possibility of nickel neurotoxicity [42,43]. The frequent occurrence of high levels of nickel in the blood for Essure implants, compared to their very rare occurrence for hip prostheses, is probably linked to the high vascularization of the uterine horn tissue, in sharp contrast with the bone support of hip prostheses.

Partial tin dosages confirm the higher sensitivity on the total blood specimen rather than in plasma, due to a large portion of micro or nanoparticles being positioned within blood cells. Based on this, we recommend looking for tin overloading by performing dosage on total blood. At the present time we were unable to locate, in France, a biological laboratory able to study organotin levels, which could help to explain some systemic symptoms. Eleven out of seventeen patients agreed to realize a new dosage of tin in total blood after explantation, and in 3/11 the tin level was higher than SL. In our recent experience, tin dosage on total blood before explantation can be very high, up to four to five times the superior limit.

In addition to blood metal level measurements, it would be interesting to measure hypersensitivity to the various elements that make up Essure implants, such as nickel, chromium, titanium, platinum and silver by carrying out, for example, lymphoblastic transformation tests.

#### 4.5. *D the hypothesis of a chronic organotin intoxication*

Regarding this hypothesis, which seem plausible, three points have to be discussed: 1/ an incorrect estimation in preclinical studies of the importance of tin leaching by the implant weld; 2/ a possible transformation in the body of inorganic tin into organotin; and 3/ the similarity of some symptoms of implanted patients and organotin intoxication victims.

#### 4.6. *1/ An underestimation of the importance of tin release by the weld into the body compared to oral diet intake*

Tin may be found in the body in three principal forms: in ionic form, in the form of metal particles and in organic form (also called organotin).

Inorganic tin is widely used in fruit or vegetable juice cans, in the form of tin chloride salt, as an antioxidant and color-preserving additive (E512). Some cases of intoxication have been reported in the literature, involving a contamination of the steel can with tin [44,45]. Inorganic tin tolerance has been reviewed in 2018 by the European agency for food safety [46]. The maximum tolerable daily dose (MTD) was decreased from 140 mg a day to 40 mg, a level above which patients begin having gastric symptoms. It was estimated that the daily diet intake from additives was under 1.3 µg/day and that the 95 percentile maximum exposure could be 11 µg/day. At the same time, the daily intake of inorganic tin from the diet, outside of canned juice additives, was estimated in various studies to be 1–8 mg/day [34]; 0.2 to 1 mg according to Rudel and Shaeffer [47,48]; and 0.18 mg in the United Kingdom according to Winship [49]. Moreover it is established that the proportion of mineral tin absorbed from the gastro-intestinal tract is very low, about 1–2% [34]. So the approximate penetration of inorganic tin in the body is about 25 µg/day. A Conceptus document submitted to the French medical safety agency in 2004 (Annex 1) showed that the im-

plant weld observed by SEM after immersion for six months in a salted serum bath had a very important corrosion on 25–50 % of the surface at 3 months and 100 % at six months whereas no implant rupture was observed. The report's authors considered that the absence of rupture after six months was sufficient to achieve fallopian tube fibrosis and sterilization. In the same study, chemical tests measuring implant corrosion were made for tin, chromium and nickel in salt baths over a six months survey. The release of tin ions was up to 25 µg/day, two hundred times more than for nickel and one thousand times more than chromium. The importance of tin release had to be minimized according to the report's authors if we compare this release to the daily diet tin intake "of 100 mg/day per os". However this daily tin intake of 100 mg does not correspond to the usual daily intake which is only about one mg, and the comparison ignores the very low absorption of tin by the gastrointestinal tract. In fact the release of tin into the body by the Essure implant was at least of the same order of magnitude as that arising from the diet daily intake. The corrosion of the tin weld has recently been confirmed by Aslam [50] by a galvanic corrosion study in a bath with phosphate buffer saline (PBS) and formol. Nickel release was 10 ppb after 1000 h, with a stabilization over time, whereas tin release increased from 200 ppb to 300 ppb between 500 and 1000 h without apparent stabilization. The weld corrosion was also shown in SEM.

#### 4.7. *2/ The hypothesis of a transformation of inorganic tin into organotin after ionic corrosion*

Tin in ionic form can combine with carbon atoms to form organotin compounds. Those compounds are largely used in the industry for plastics, but also insecticides, wood preservatives, antifouling paints for boat hulls and repulsives. The industrial process for organotin synthesis requires high temperatures (about 200 °C) and special reagents [44]. However organotin may also be produced without such high temperatures from inorganic tin within ecosystems in relation with microbiota [50–52]. Moreover, redox reactions at normal temperature have been described to allow the transformation of inorganic tin into organotin by contact between tin coming from corrosion and organic molecules such as acetylcholine, via a methylation process [53]. The probability that inorganic tin absorbed by the gastrointestinal tract could be transformed into organotin was considered as impossible by Blunden [44]. Indeed, the very low digestive absorption of inorganic tin, which is rapidly eliminated with feces, and the transformation process of inorganic tin into organotin by microbes is very slow seems to this author impossible to complete during the short amount of time spent by the inorganic tin in the body. However, in the case of the Essure implant, the tin mineral particles observed in the uterine tissue are present for several years in contact with the uterine biotope [54], and further subjected to infections [55], as attested by the frequency of genito-urinary infections among our cases. Such a mechanism of transformation of inorganic metal into more toxic organometal compounds by the biotope has also been described for mercury [56]. The fact that patients having had urinary infections have a higher score on symptom intensity than patients without infections is a result in favor of this hypothesis. Finally if we take in count this possibility of inorganic tin transformation into organotin in the body, over a period of several years during which the implant weld slowly undergoes corrosion, we can suspect that some systemic and local symptoms, (such as sphincter troubles) observed on patients could correspond to the symptoms of organotin intoxications.

#### 4.8. *3/ Organotin toxicity*

has been known since 1954, following the French sanitary scandal of Stalinon [57]. This organotin based medication was prescribed in France for treating furunculosis. Animal and human clinical trials had been largely insufficient and led to the sale of highly toxic organotin capsules, resulting in about 100 deaths and more than 100 cases of se-

vere injuries. Patients presented cerebral and meningeal edemas and intracranial hypertension. Several survivors had severe paraplegias with motor and sphincter troubles. Another cluster of organotin intoxication cases was observed in the 1990s in South China where more than a thousand were poisoned by misusing organotin contaminated industrial lard as cooking oil [58]. Other observations have been reported more often in an occupational context [59–61], sometimes with psychiatric symptoms. Brain Magnetic Resonance Imaging (MRI) noted defects in the white matter [62,63]. Cima [34] details neurologic symptoms linked to organotin toxicity: hearing loss, visual disturbances, headaches, involuntary hand movement episodes, diplopia, giddiness, amnesia, polyneuropathy, calculation ability impairment, delayed sensorimotor polyneuropathy. Many of these symptoms are frequently mentioned in the complaints of Essure implanted patients. Among the 18 cases in our study, one patient was diagnosed with multiple sclerosis after two types of symptoms: diplopia and involuntary unilateral hand movements, both of which occur with organotin toxicity. Finally, the neurologic bladder signs could be interpreted as organotin toxicity symptoms. Another physiopathological hypothesis of toxicity linked with tin weld corrosion, despite the small ponderal level of tin (1.9 mg in each solder according to Bayer) is the possibility of nano-toxicity mechanisms. Indeed the persistent wear of tin particles over the years could induce the production of nanoparticles. We know that the toxicity of nanoparticles is not directly linked to the weight of metal, but rather proportional to the exchange surface between metal particles and biological tissue, with an increase of toxicity level by factors of up to a thousand for the same weight [64].

Of course these results have to be confirmed by other SEM-EDX analyses conducted by other teams. Some patients report continuing symptoms after explantation, which could be linked to a dissemination of particles in the body before explantation. We recall the case of a patient with a rectovaginal granulomatosis nodule within which tin particles were identified, confirming the transport of such particles outside the uterus. The persistence of a high tin blood level, as was the case for three patients of our study, could form the basis to propose a prospective clinical trial with treatment by a chelating agent [65].

## 5. Conclusion

The development of an anatomopathological process specially designed for the mineralogical analysis of uterine tissue near the weld zone of Essure implants has enabled us to demonstrate the systematic presence of tin-based particles (sometimes associated with silver) embedded in the tissue of the fallopian tubes and/or uterine horn biopsies analyzed. The risk of toxicity related to the corrosion of the weld, carried out in 2004, seems to us underestimated. Moreover, the chemical nature of the particles observed in the wall of the tubes during animal experiments and preliminary clinical studies has not been determined. The presence of foreign body granulomas in contact with the weld zone is, in our opinion, related to wear of the implant weld. This wear phenomenon could explain the high frequency of adenomyosis in the patients we followed (77.8 %), but also some local signs of pain and bleeding.

Some systemic symptoms, which appear gradually and reach 50 % of patients after 5 years, are consistent with symptoms of chronic organotin poisoning. Further studies are needed to look for tin and organotin in the patients' bodies as well as other components of Essure implants such as nickel, chromium, titanium, platinum or silver. It also seems interesting to work on the phenomena of hypersensitivity to these metals with, for example, the realization of lymphoblastic transformation tests.

On a broader scale, this study confirms the interest of SEM-EDX analysis, which is a precious tool in preclinical biomaterial studies as well as in the search for identifying the causal agent of many inflammatory granulomatosis diseases often considered as idiopathic. It is thanks

to SEM-EDX analysis, which had not been previously used in preclinical trials and explanted tissue analysis, that tin imputation could have been evoked.

## Authorship

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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## Author contributions

**M Catinon:** Methodology, Software, Formal analysis, Investigation, Writing - Original Draft. **E Roux:** Methodology, Validation, Writing - Review & Editing. **A Auroux:** Writing - Review & Editing. **AM. Trunfio-Sfarghiu:** Methodology, Writing - Review & Editing. **C Lauro-Colleaux:** Methodology, Writing, Review & Editing, Resources. **E Watkin:** Methodology, Writing, Review & Editing, Resources. **G Sournies:** Methodology, Validation, Writing - Review & Editing. **M Vincent:** Conceptualization, Validation, Writing - Original Draft, Project administration.

## Declaration of Competing Interest

"All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organisation for the submitted work; *Michel Vincent is Chief Executive Officer of Minapath Développement. Mickaël Catinon and Elisabeth Roux are employees of Minapath Développement*; no other relationships or activities that could appear to have influenced the submitted work."

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