Les enjeux de la Miéralopathologie
Silice, amiante et métaux
De la pollution aérienne à celle de certains implants

Présentation Faculté Pharmacie

Le 17/02/2022

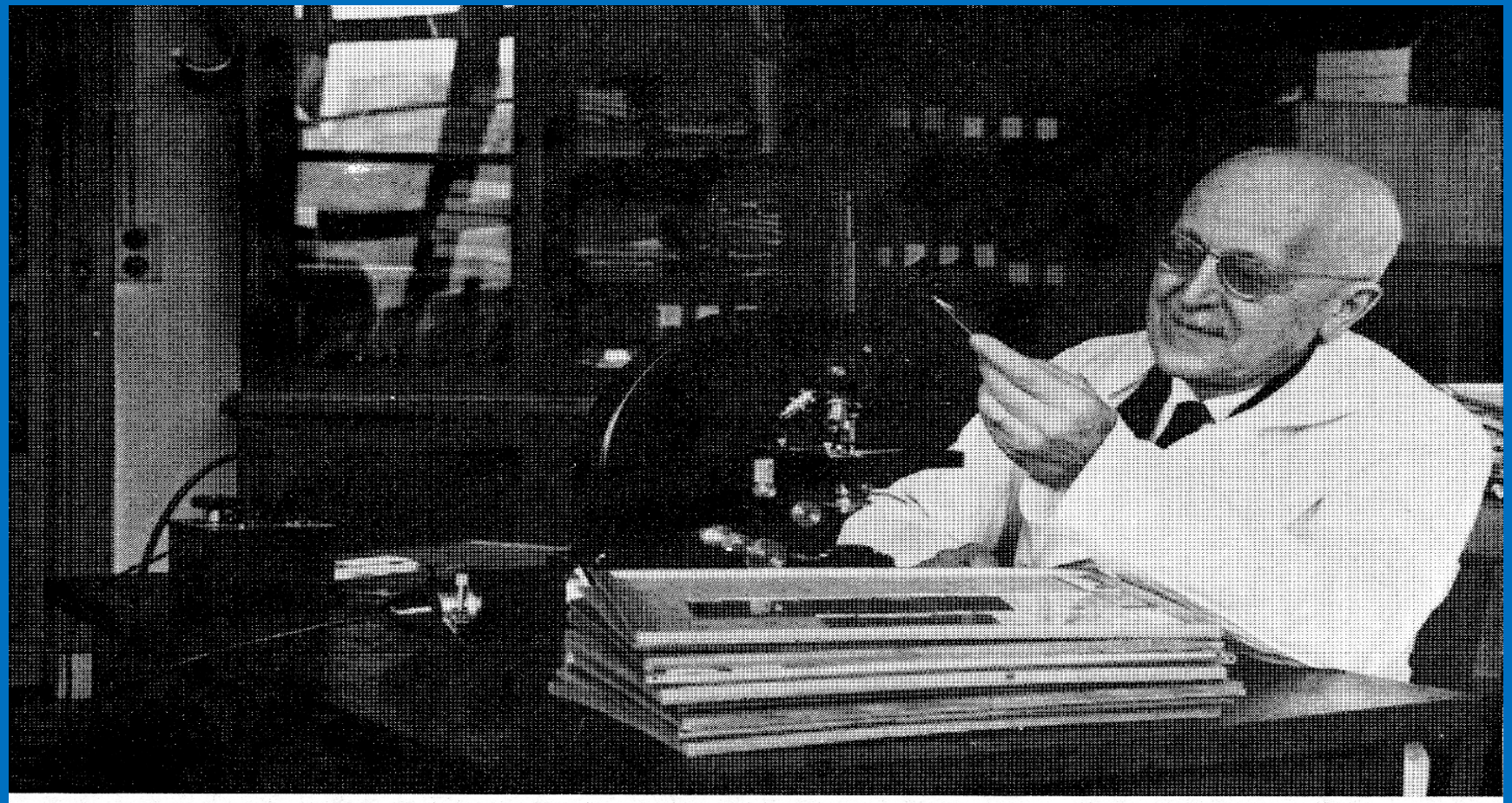
Dr Michel Vincent

Ancien chef de service pneumologie et cancerologie thoraçique au CH St Joseph et St Luc

Créateur de Minapath en 2014 , biotek de recherche médicale au statut ESS et reconnue d'utilité sociale

Le mur des sciences

Albert Policard (1881-1972): Le créateur de l'anatomopathologie moderne : plus de 72 ans consacré à la science et à la médecine



Le professeur Albert Policard

A. POLICARD P. GALY

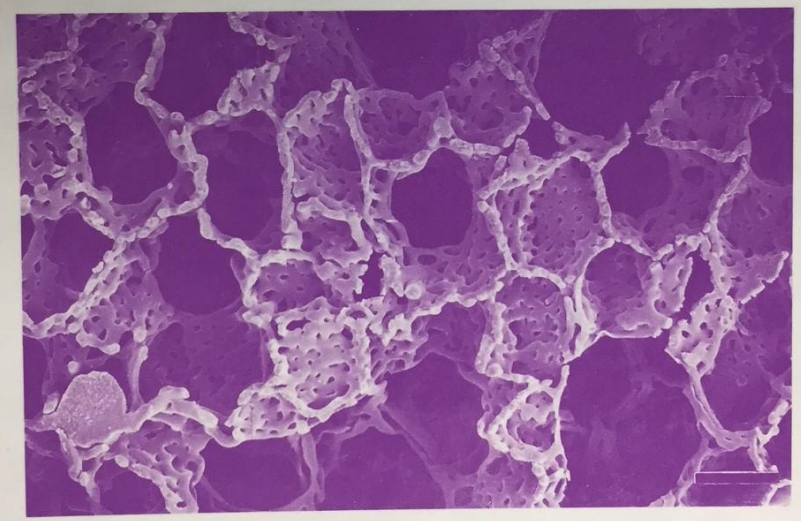
L'APPAREIL BRONCHO-PULMONAIRE

structures et mécanismes à l'état normal et pathologique

MASSON & CIE

Lung Biology in Health and Disease Volume 48
Executive Editor: Claude Lenfant

Electron Microscopy of the Lung



edited by
Dean E. Schraufnagel

ELECTRON MICROSCOPY OF THE LUNG

Edited by

Dean E. Schraufnagel

College of Medicine
University of Illinois
at Chicago
Chicago, Illinois

MARCEL DEKKER, INC.

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INTRODUCTION

> Pour le médecin qui veut éssayer de comprendre le "comment" des troubles qu'il observe . . . histopathologie est d'un intérêt capital.
>
> Comme on pourra s'en convaincre . . . l'histopathologie pulmonaire est encore por mal connue.
>
> *A. Policard, 1955*

A. Policard is credited by the French to be the master, if not the creator, of pulmonary histopathology. In 1929, he published the first edition of *Poumon* [*The Lungs*]. The quotation above is from the introduction to the second edition; it says that if we want to understand lung pathology we must understand lung structure.

Contexte MINAPATH

Discussion ALDES

Brevet avec Lamcos

IFFSTAR

Bureau Hygiène ville de Lyon

Travaux Master Lamcos Qualité air Lyon

Analyse d'air ou de poussière ou d'implant….

Environnement

La Minéralo-pathologie

Analyse des poussières minérales dans les tissus malades

Santé Maladie

Minapuih Région

Minapild Europe

MinaEssure

Minasarc BTP

Cas Louvain

Montpellier

Pediasarc

Cancer vessies Rennes


JEOL
JSM-6010PLUS/LV
Scanning Electron Microscope

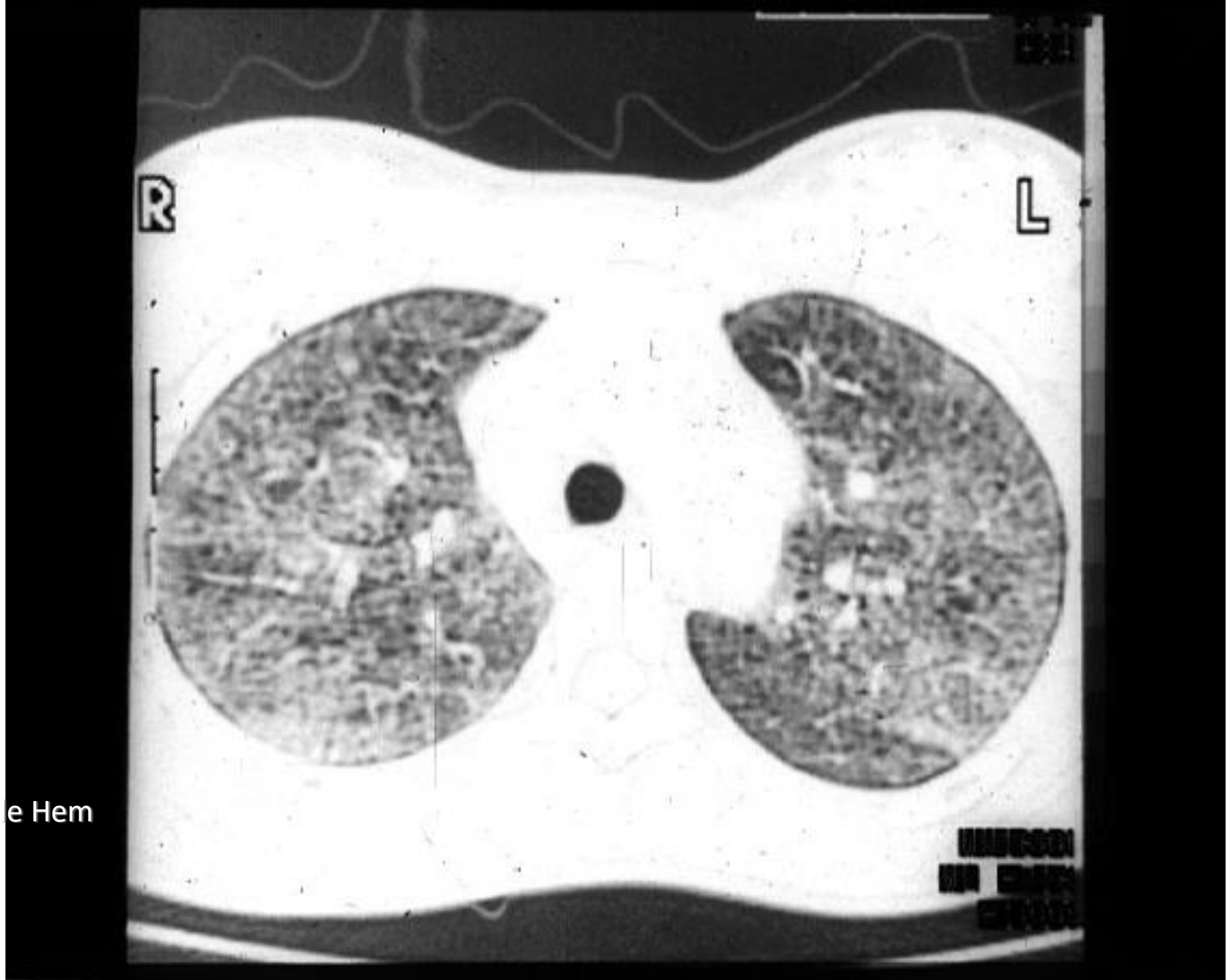
Minapath Présentation

- Innovations
  - Un questionnaire élaboré suite projet Européen Silicosis
  - Un savoir faire avec MEB et EDX mais aussi MET in situ
  - Un projet brevet : valise itinérante

- Disruption:
  - Changement de paradigme pour les pathologies idiopathiques: Questionnaire et MEB-EDX avant d'évoquer une maladie « idiopathique » Démonstration Essure
  - Le concept nanotoxicité : une nouvelle approche de la toxicologie


TALCO PROFUMATO
FELCE AZZURRA
PAGLIERI
AJAX
POUDRE
DEGRAISSE ET FAIT BRILLER


Mlle Hem



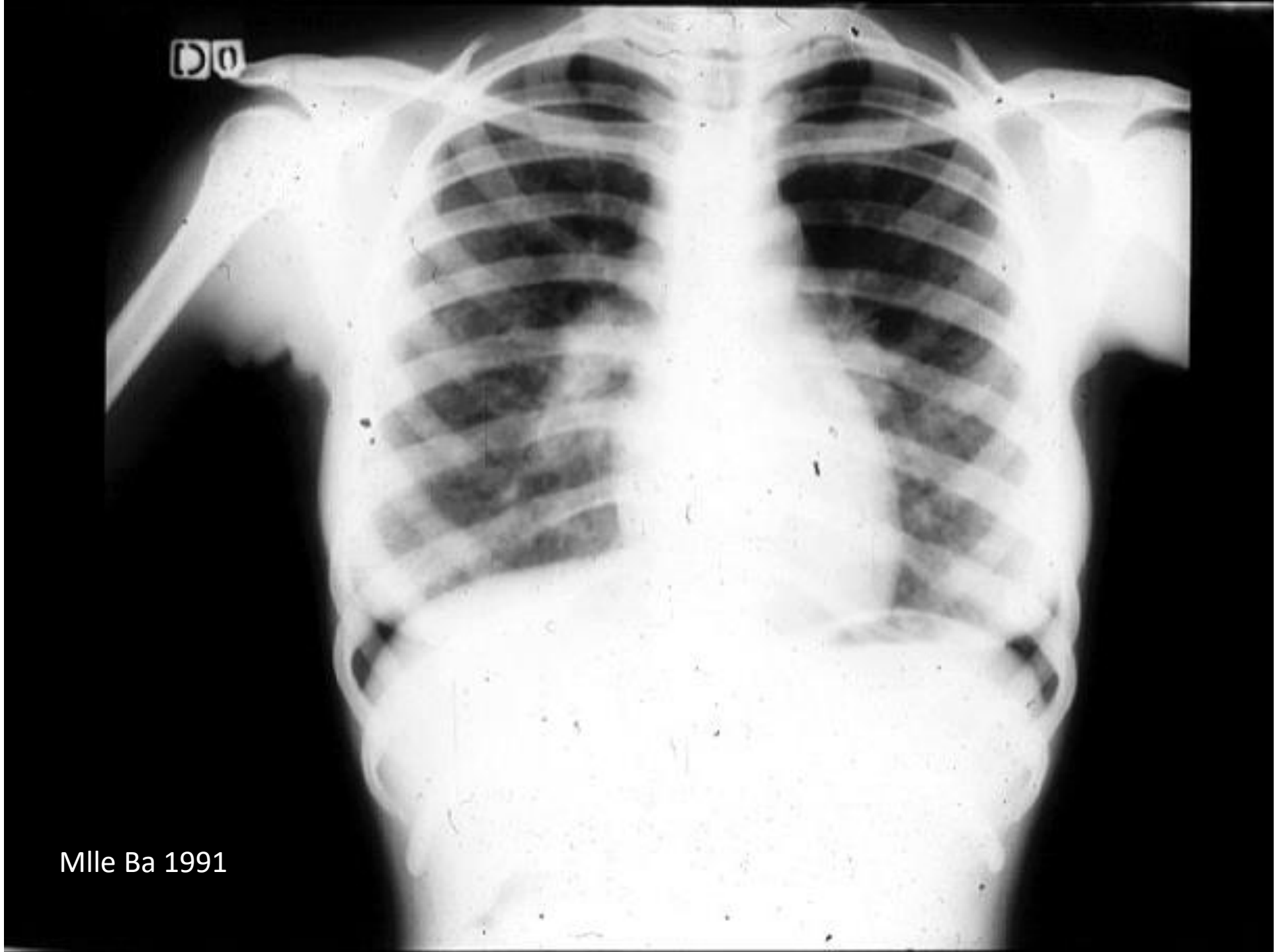
Mlle Hem

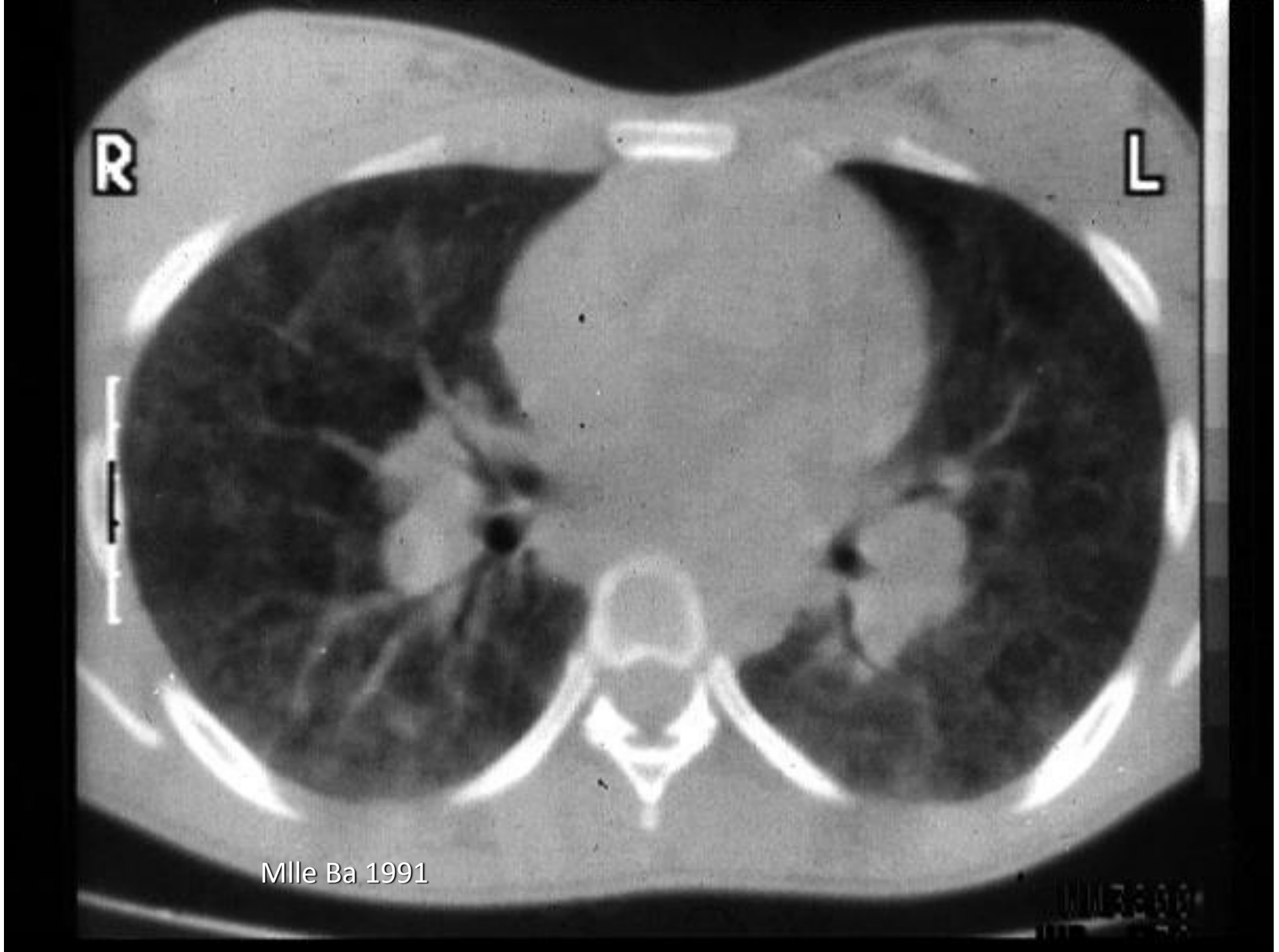
Acute silicosis due to inhalation of a domestic product

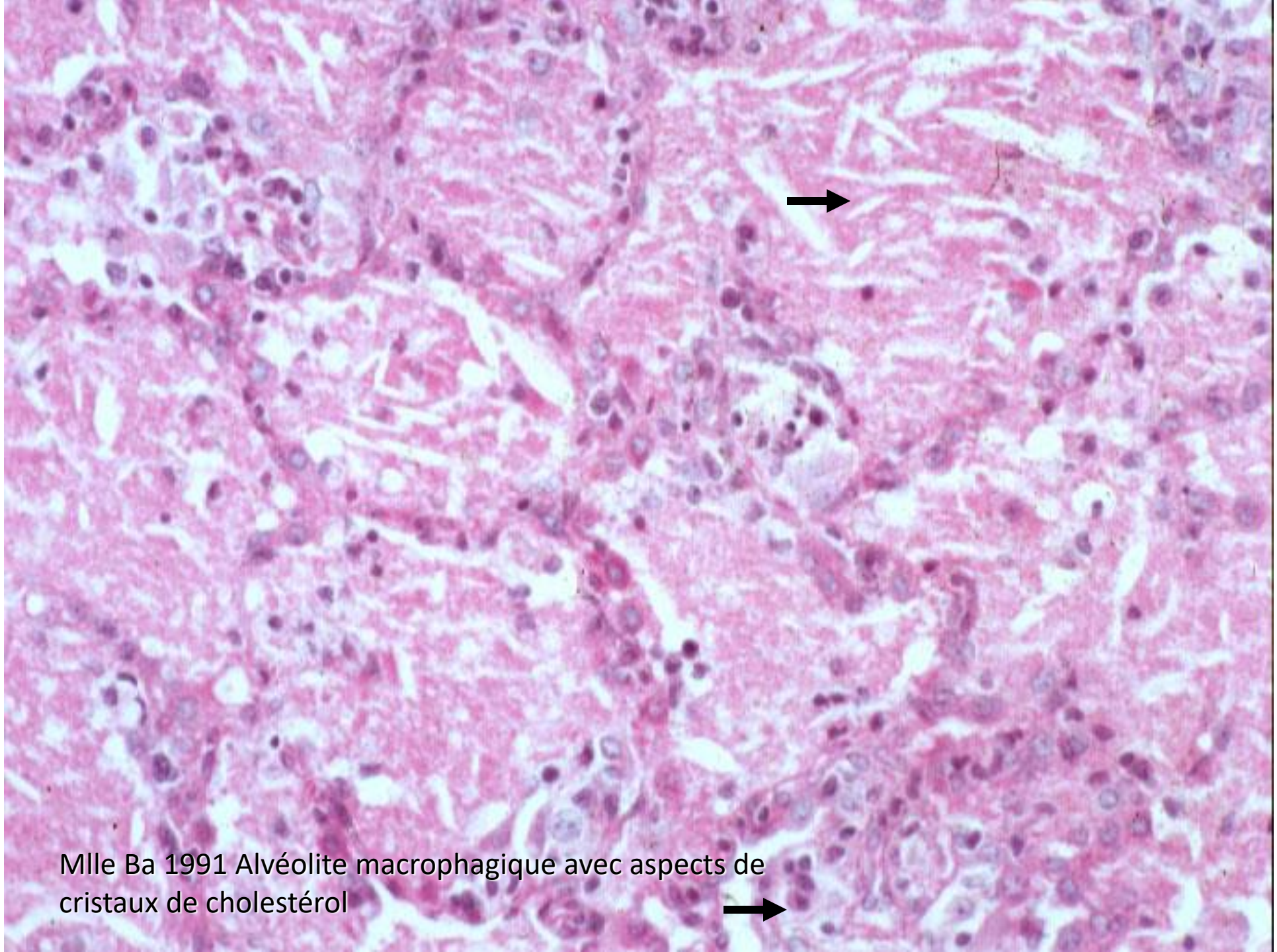
Dumontet Ch, Biron F, Vitrey D, Guérin JC,
Vincent M, Jarry O, Meram D, Peyramond D

Am Rev Resp Dis 1991 ; 143 : 880 - 2

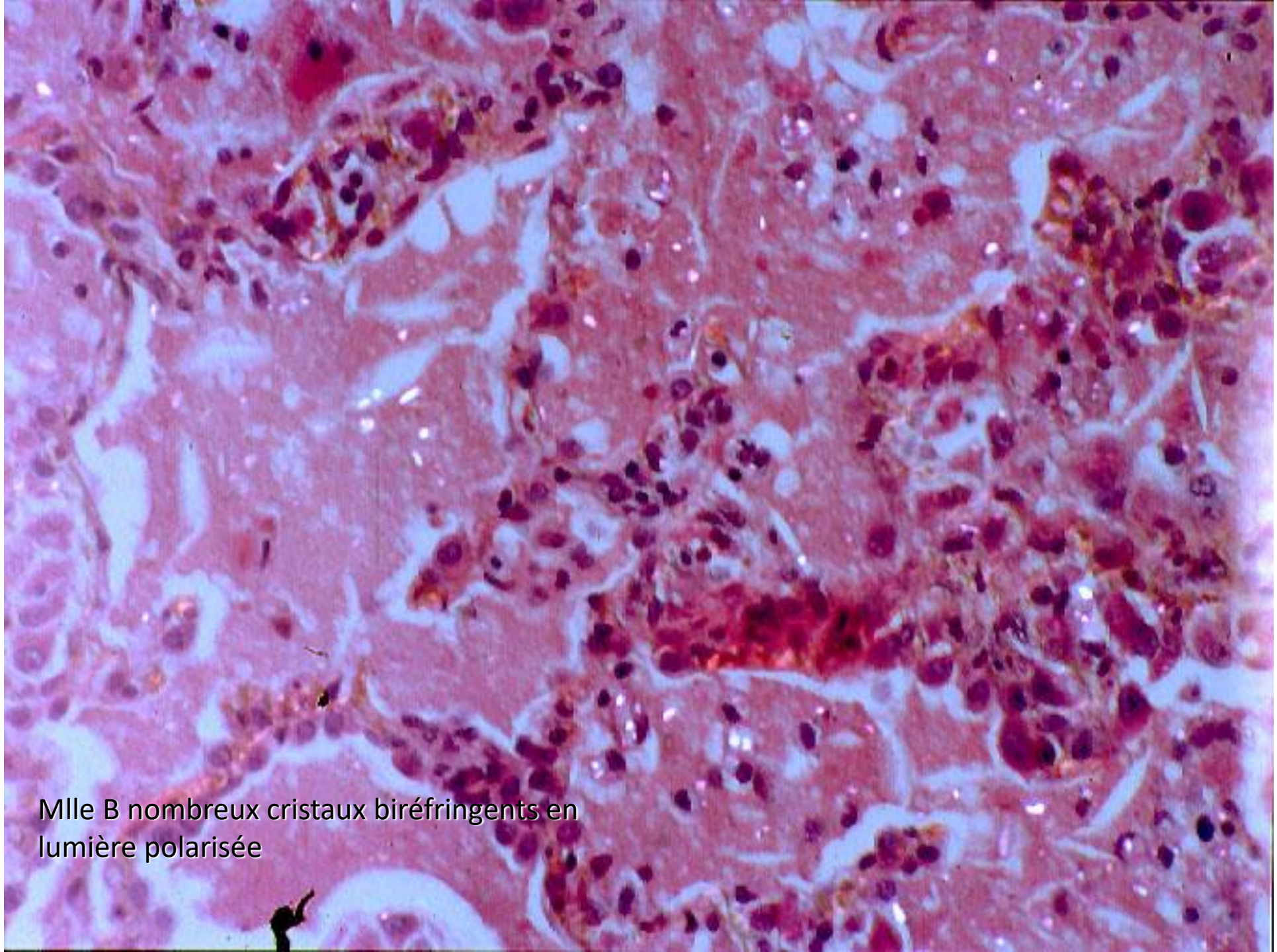
"This is the first report of acute pulmonary silicosis developping after exposure to a common house hold product"


Mlle Ba 1991


R
L
Mlle Ba 1991

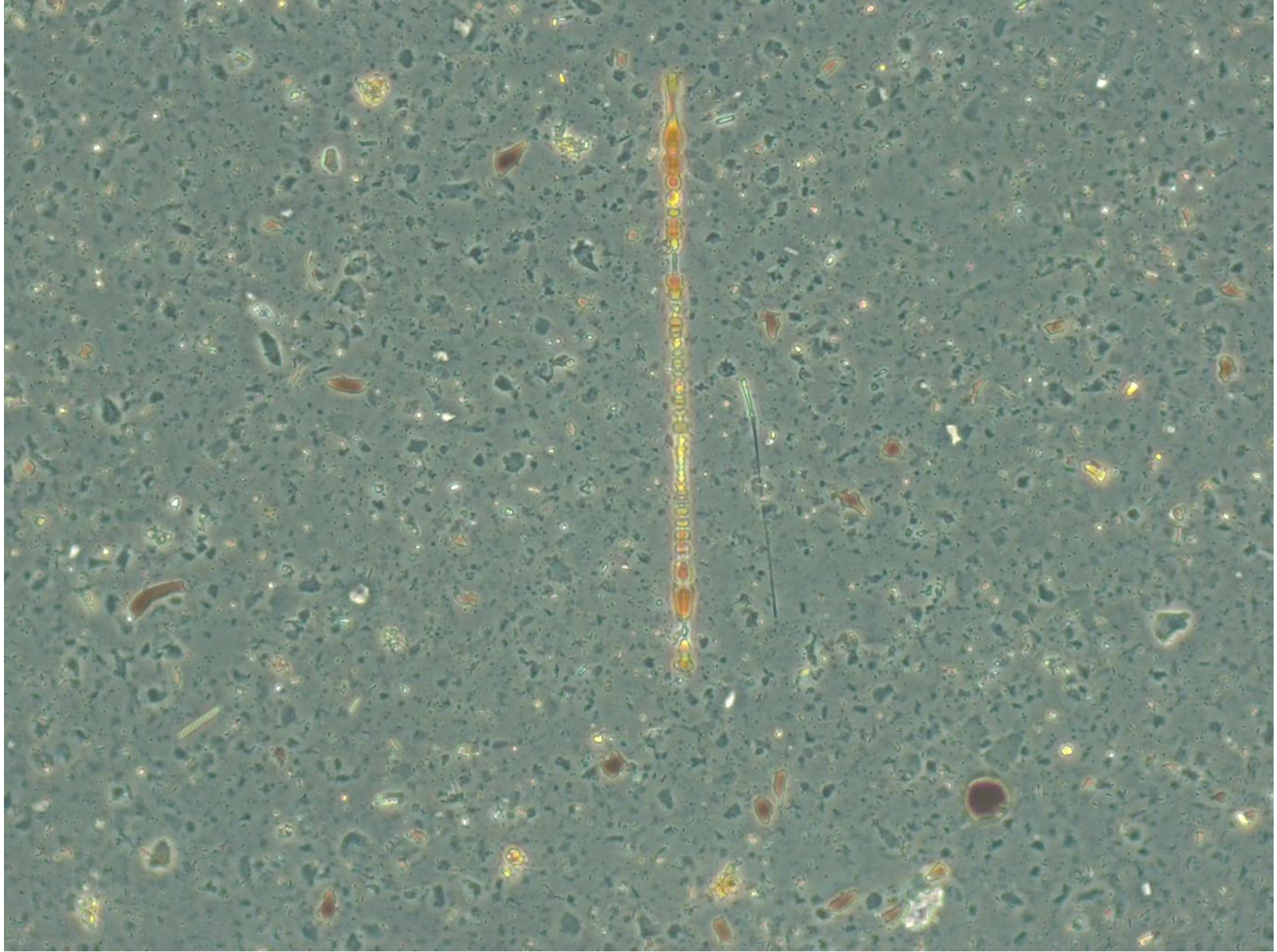


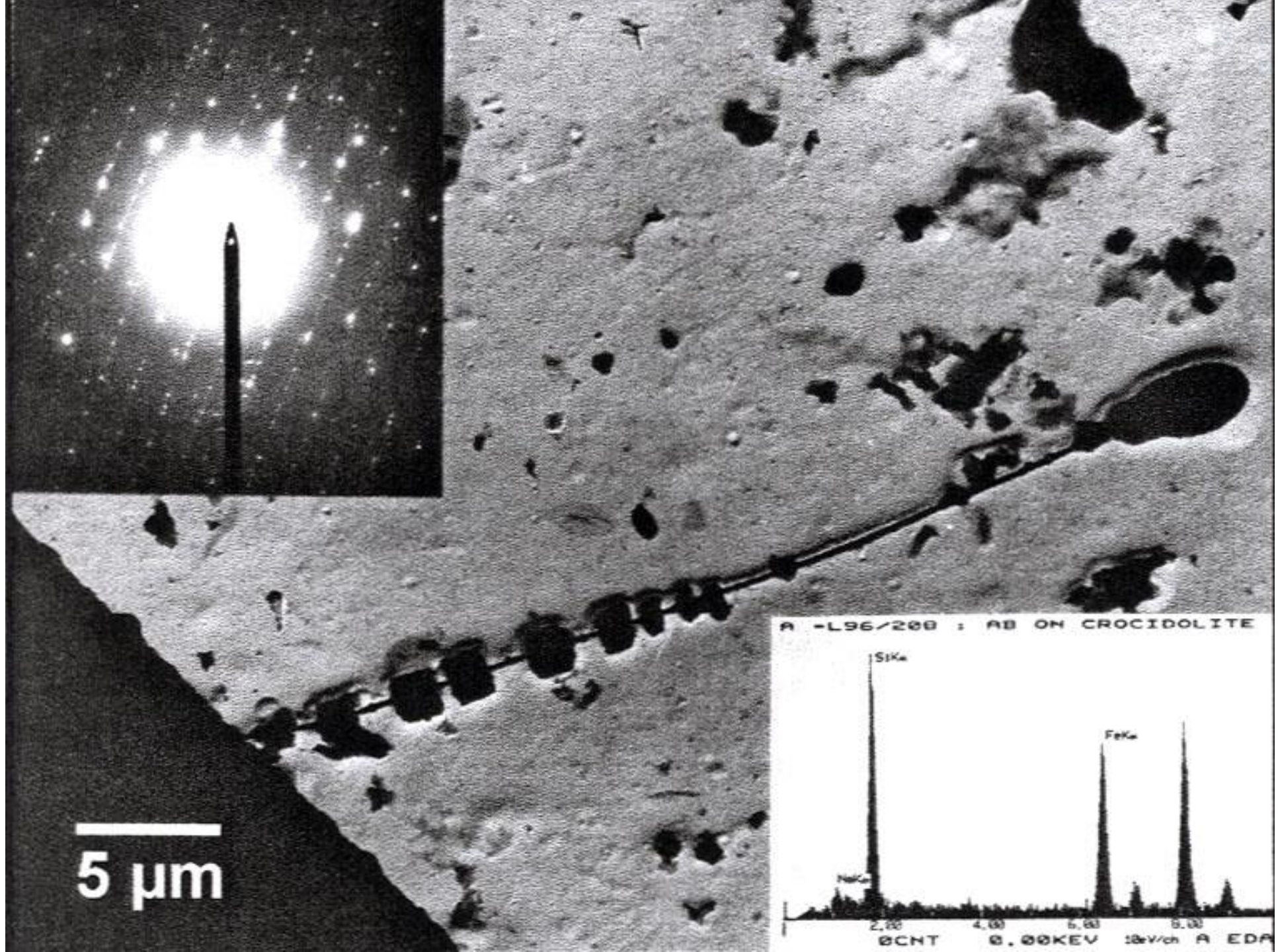
Mlle Ba 1991 Alvéolite macrophagique avec aspects de cristaux de cholestérol



Mlle B nombreux cristaux biréfringents en lumière polarisée

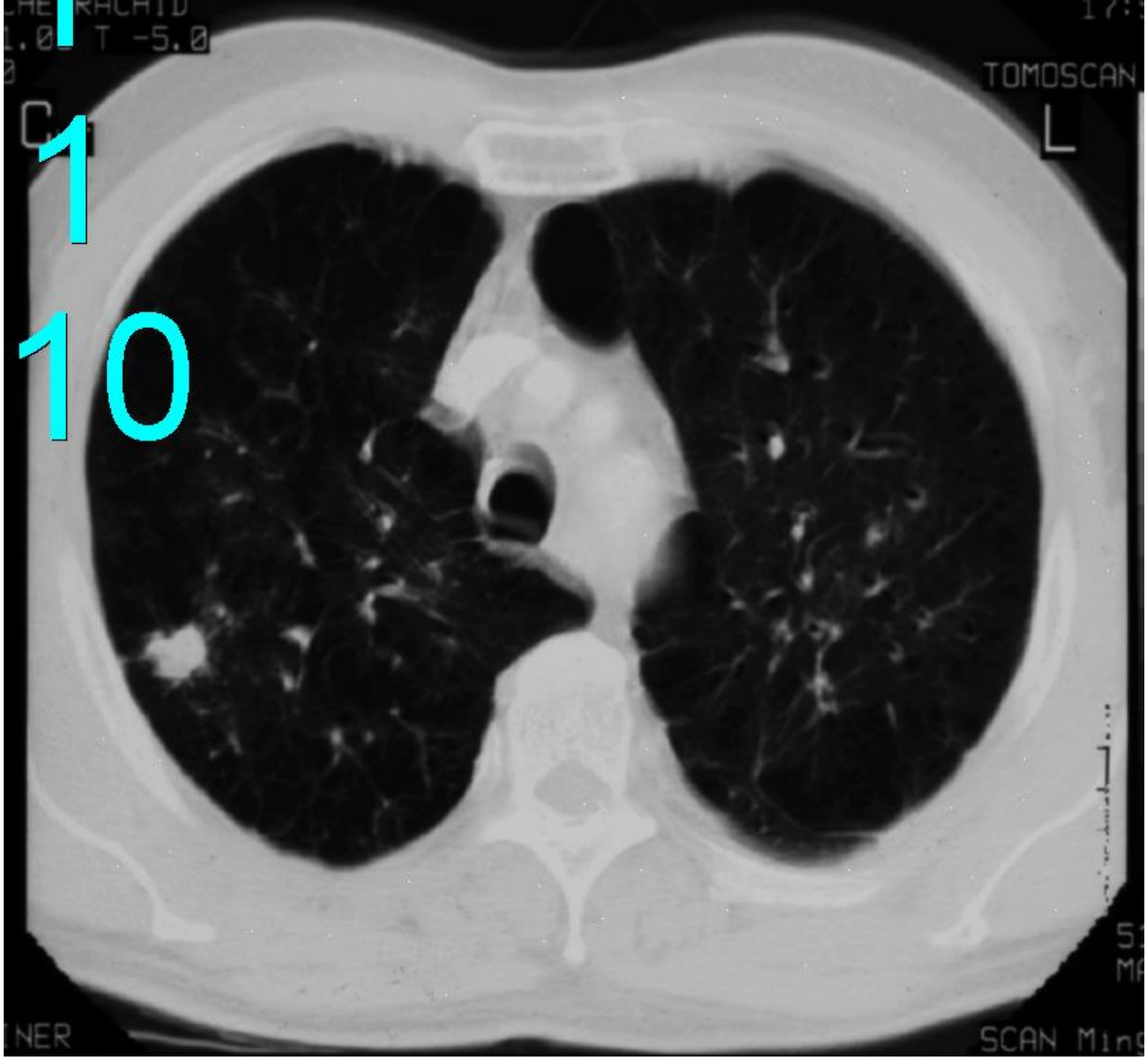

50 µm




5 µm
A -L96/200 : AB ON CROCIDOLITE
SiKa
FeKa
MgKa
2.00
4.00
6.00
8.00
0CNT 0.00KEV 10eV/ch A EDA

Métrologie tissulaire de l'amiante

- **Les corps asbestosiques en optique**
  - Sujet normaux : médiane : 67 CA/g
    Min : 15, Max : 648
  - Cancers du poumon : 15 à 20 % sup à 1000 CA/g
  - Mésothéliome : de l'ordre de 6 000 CA/g
  - Fibrose asbestosique : plus de 100 000 CA/g


1
1
10
TOMOSCAN
L

Cancer du poumon avec exposition significative à l'amiante

Les critères d'Helsinki

- **Taux de CA > 1 000 CA/g ou > 1 CA/ml LBA**
- **M électronique : FN amphibole > 5 µ > 100 000**
  FN amphibole > 1 µ > 1 million

Nécessité pour chaque laboratoire d'avoir ses propres valeurs de références

Cancer du poumon
Le choix Français

La présomption d'imputabilité prédomine

- en cas de stigmate radiologique d'exposition amiante : plaques pleurales, pachypleurite…
- en cas de profession exposée pendant plus de 10 ans (cf questionnaire)
- en cas d'élévation CA > 1 000 CA / gr poumon sec
  CA > 1 / ml au LBA

**Même si le patient fume 2 paq/jr depuis 40 ans (RR > 20),
il doit bénéficier de la présomption d'imputabilité et
bénéficier d'une déclaration en maladie professionnelle
et / ou au F I V A**

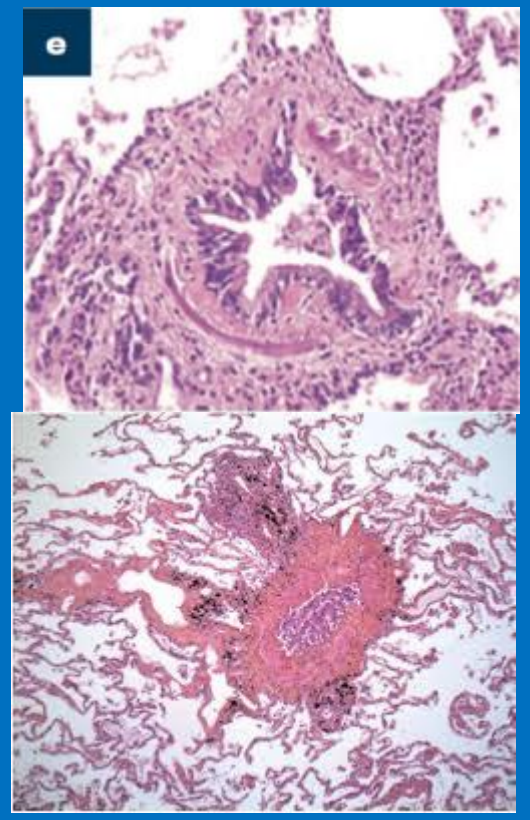
International Silicosis Conference, Johannesburg, 13th to 27th August, 1930

Revisiting the 1930 Johannesburg conference in Paris, September 2013

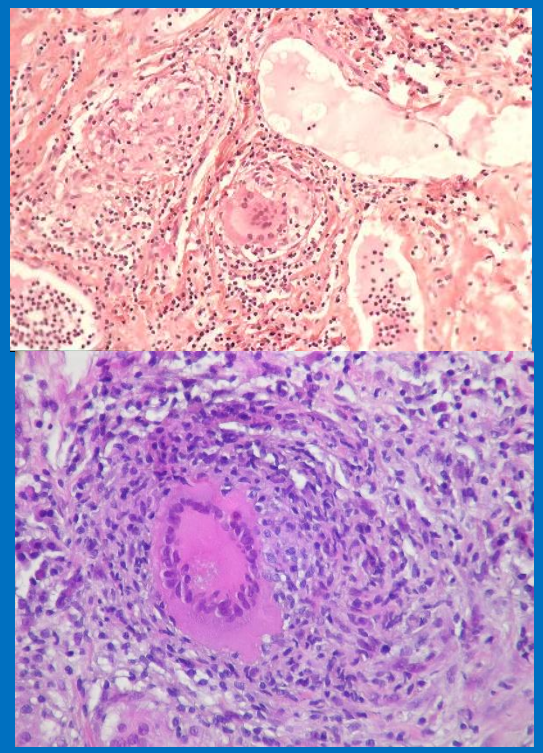
http://www.sciencespo.fr/silicosis/content/colloquium-2013

Une maladie définie à un stade avancé de manière tronquée: seul le nodule définit la maladie.

Bronchiolite

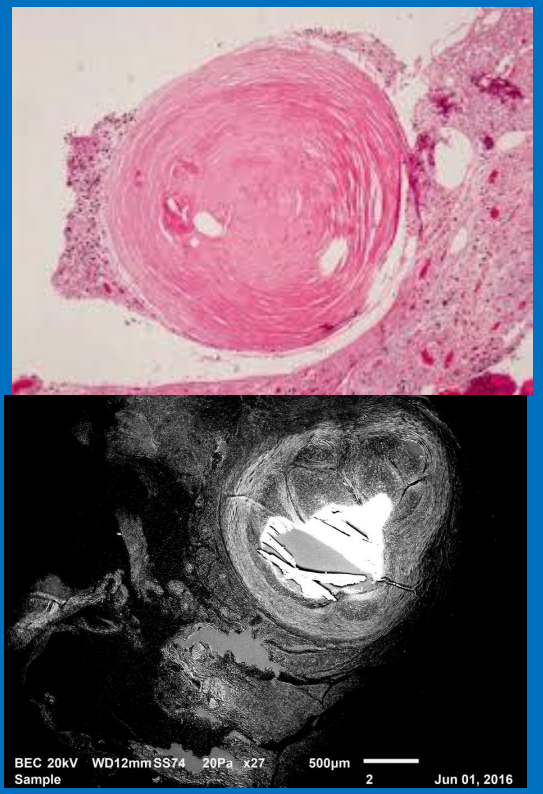


Granulome

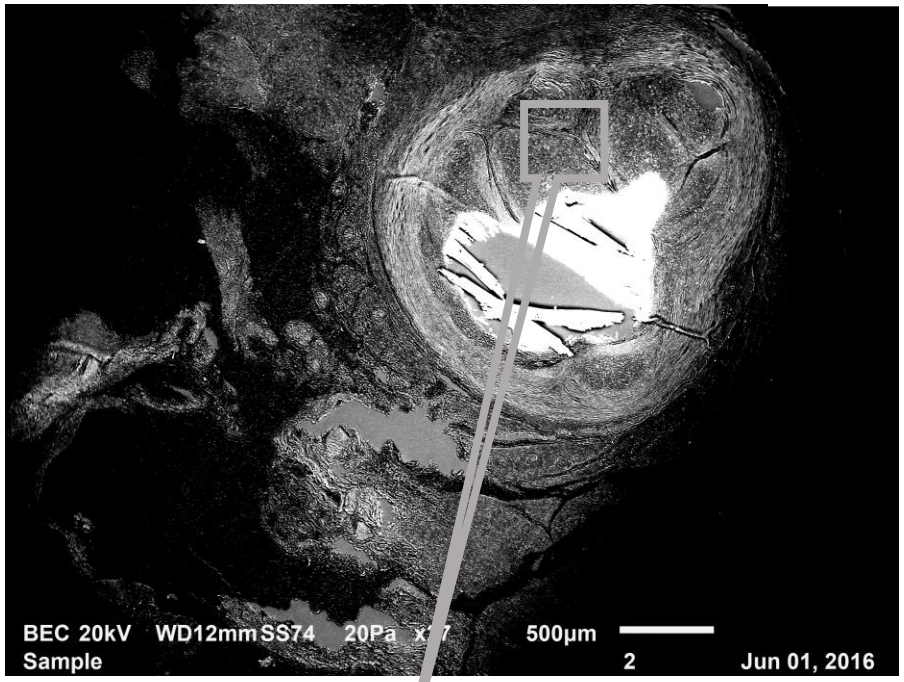


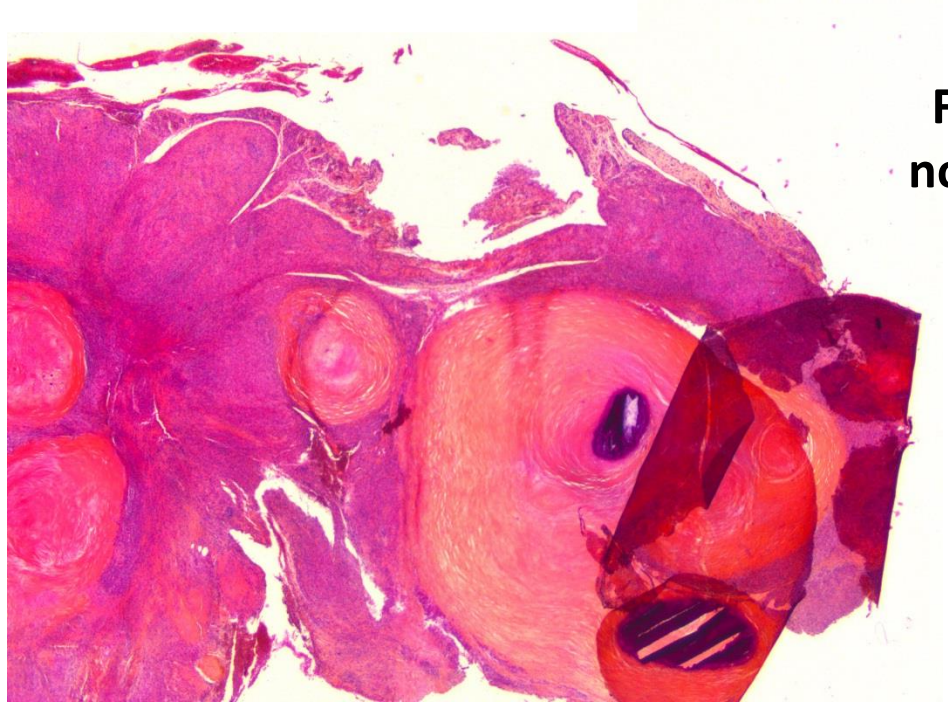
Silicose

Nodule silicotique

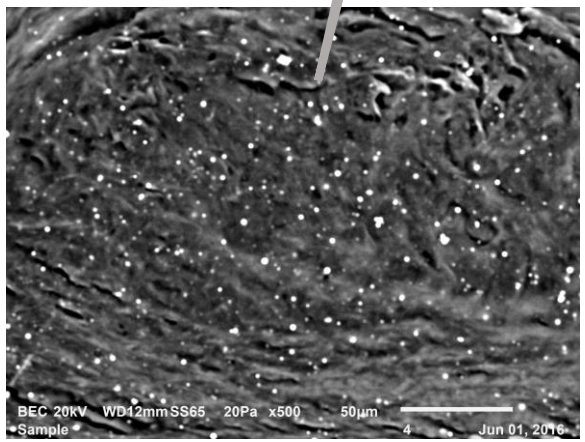


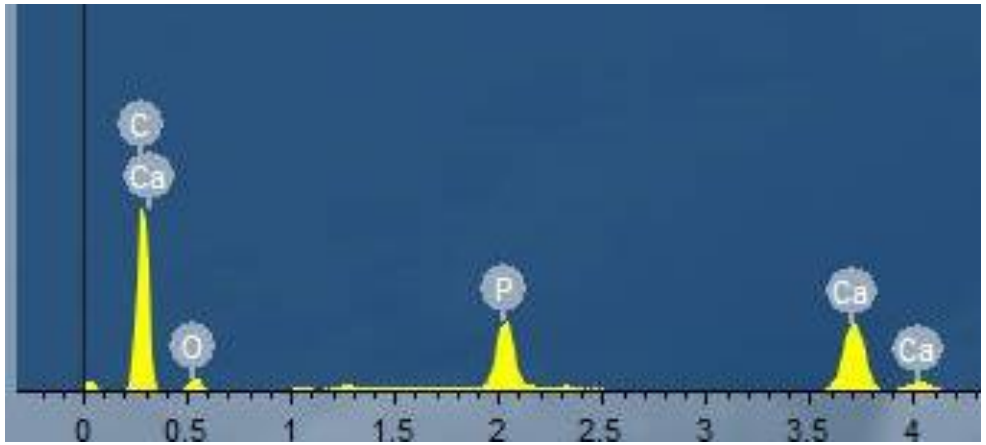
In situ mineralogical analysis on silicotic lesions

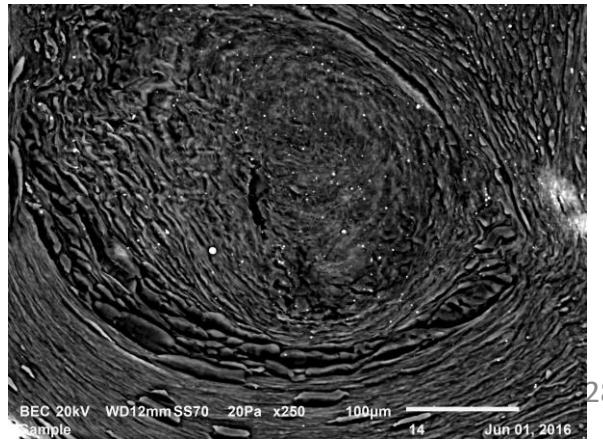




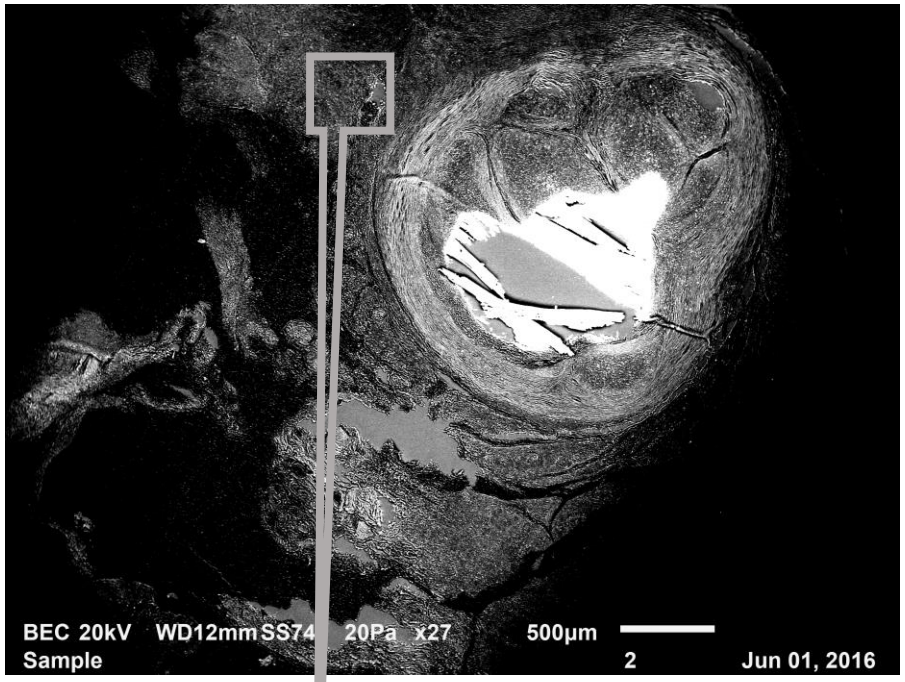
Feasability study : silicotic nodules, dental technician – inside nodule
Only Calcium phosphate

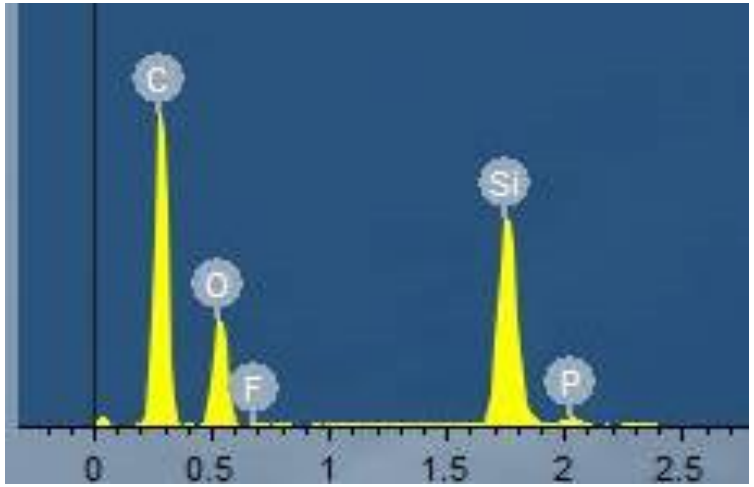




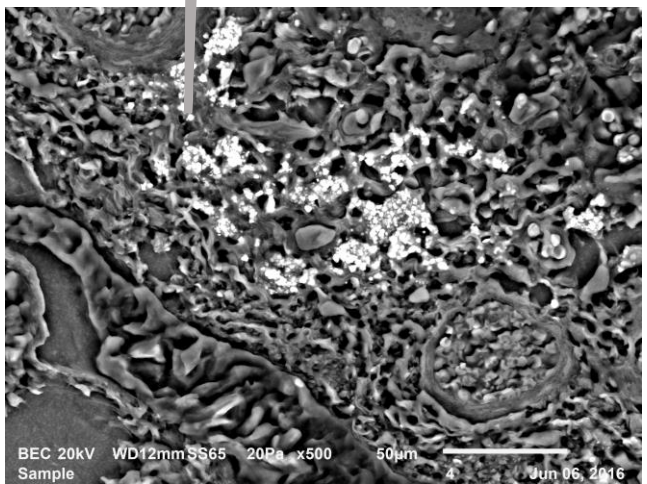


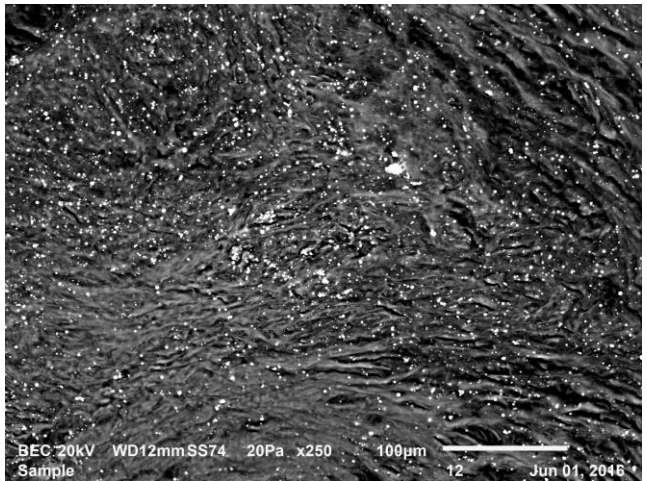
In situ mineralogical analysis on silicotic lesions

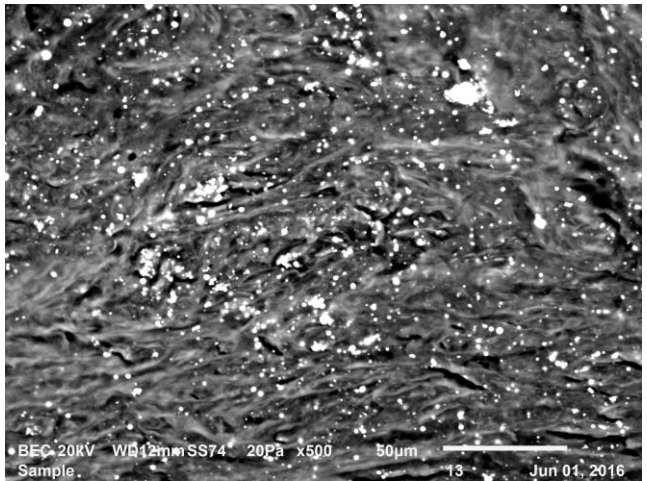


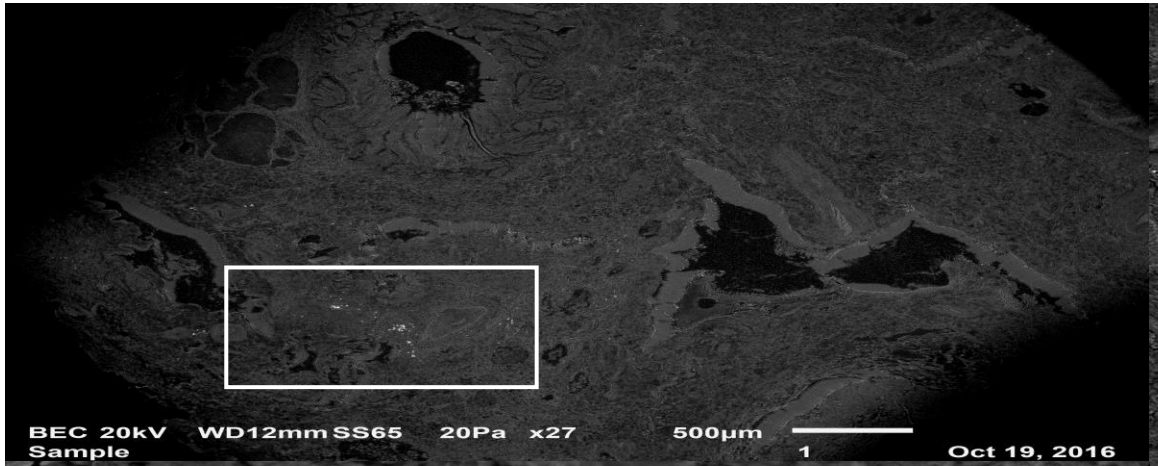


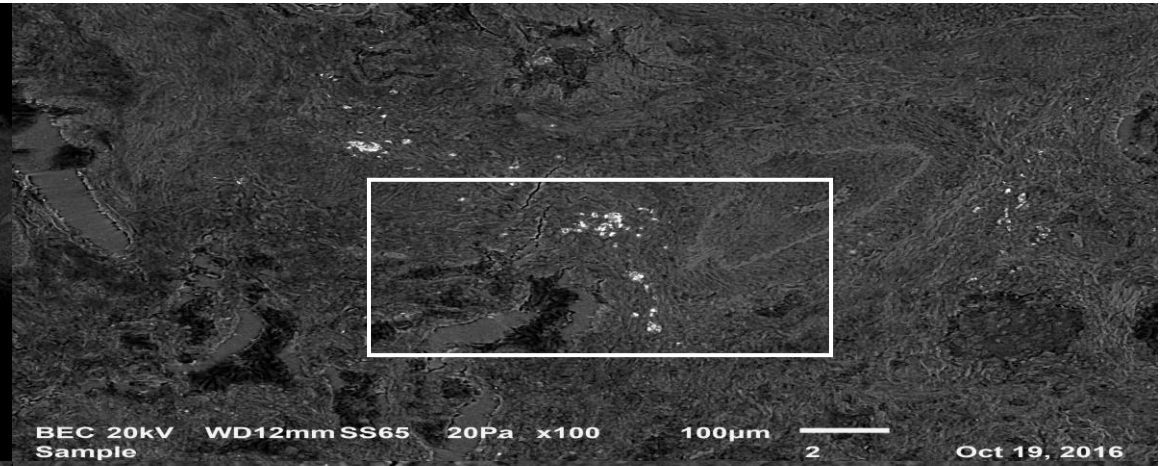
Feasability study : silicotic nodules, dental technician – outside nodule
133 Si O, 2 Si Al , 1 steel ….

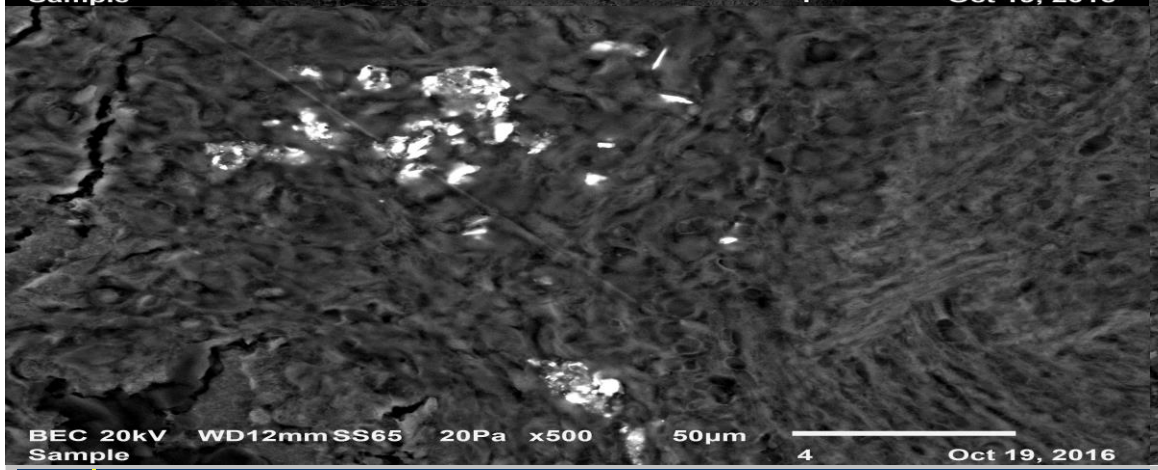


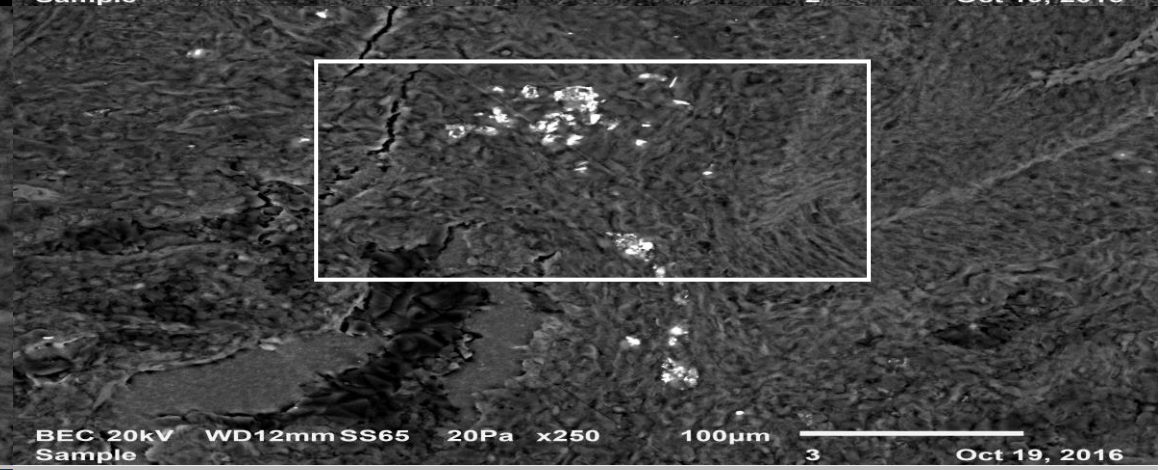




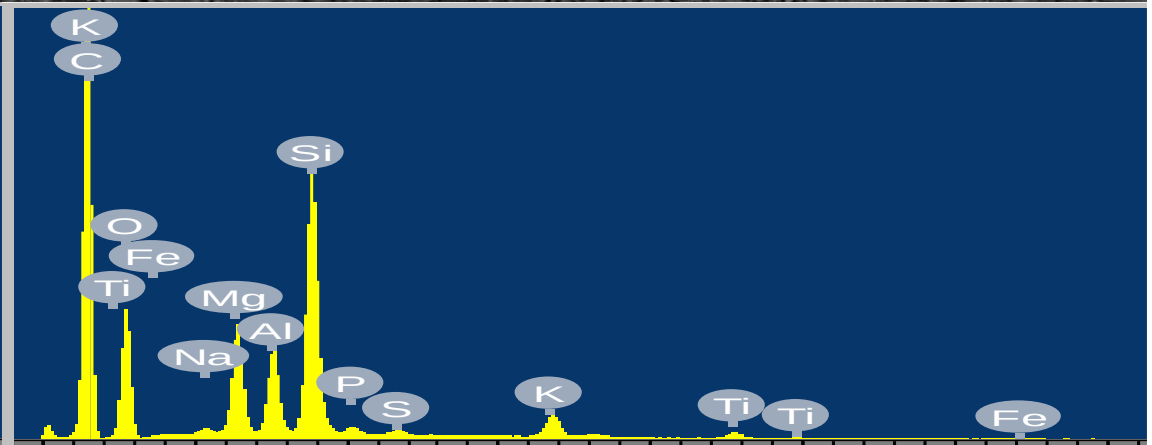

BEC 20kV WD12mm SS65 20Pa x27 500µm
Sample 1 Oct 19, 2016


BEC 20kV WD12mm SS65 20Pa x100 100µm
Sample 2 Oct 19, 2016

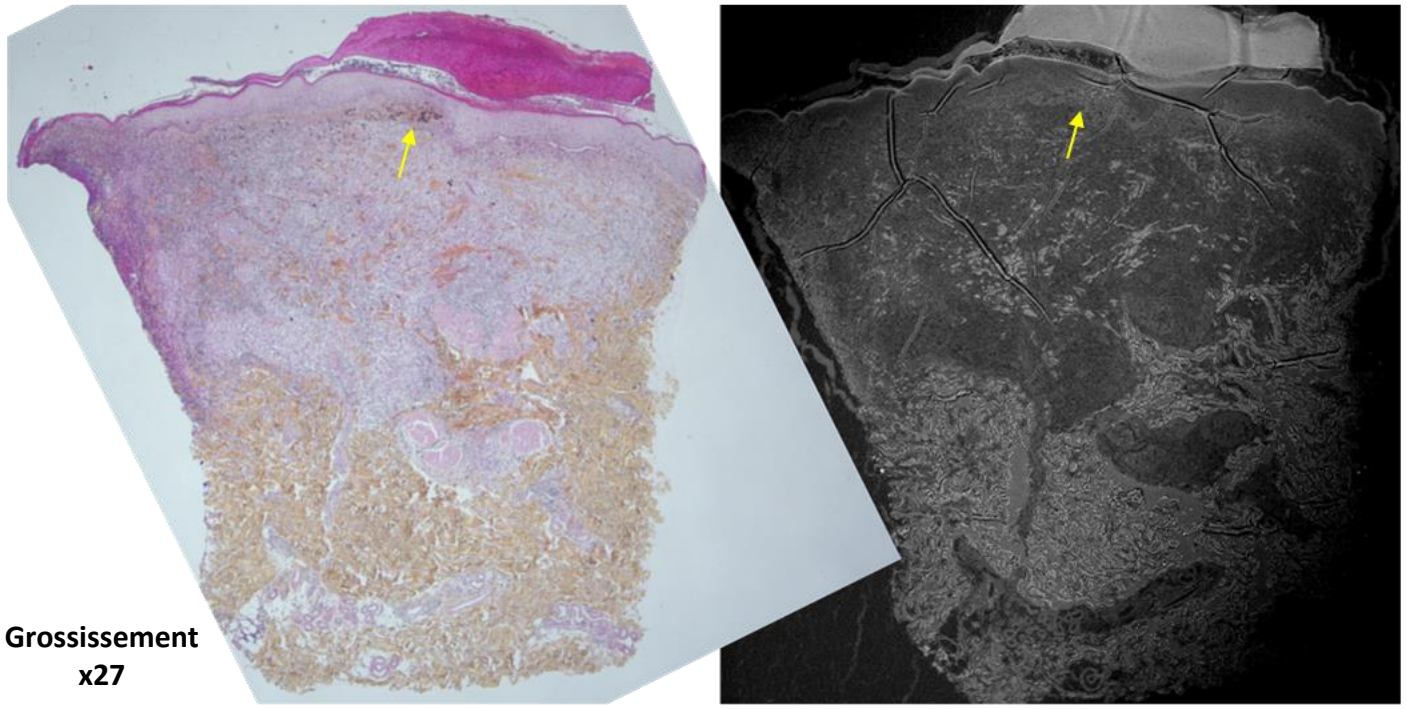

BEC 20kV WD12mm SS65 20Pa x500 50µm
Sample 4 Oct 19, 2016


BEC 20kV WD12mm SS65 20Pa x250 100µm
Sample 3 Oct 19, 2016

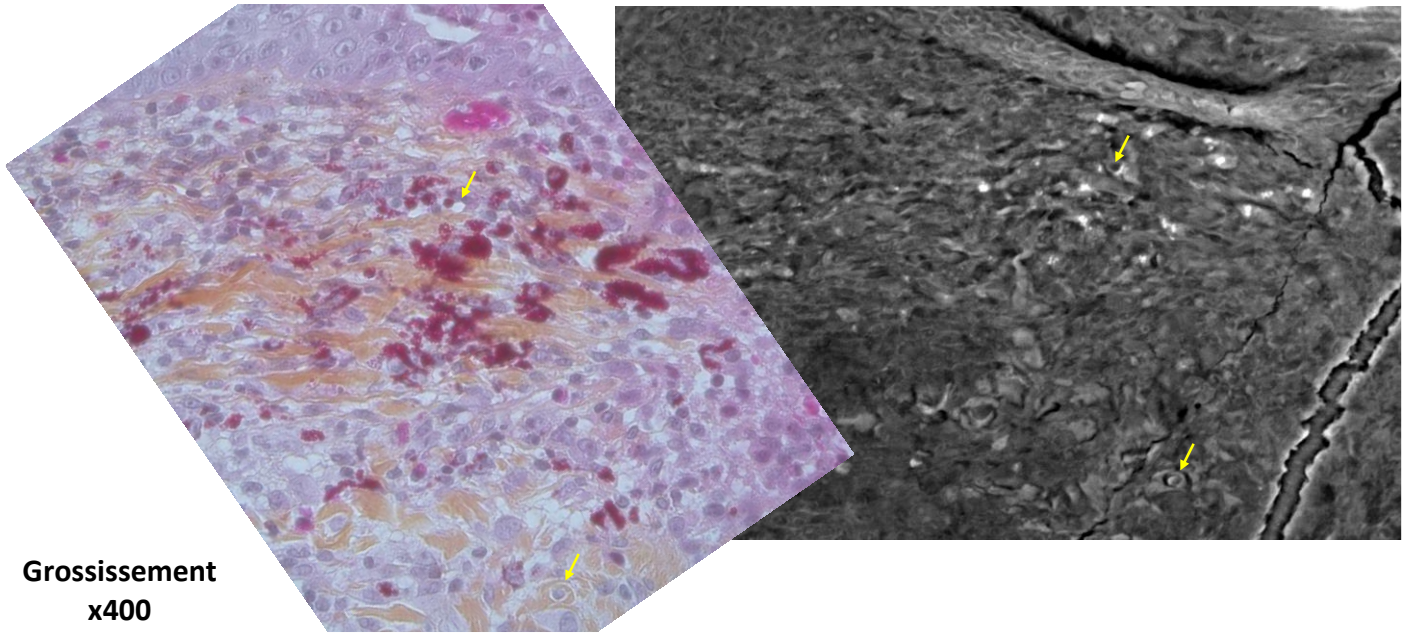

C
O
Fe
Mg
Si
Co
P
S
Fe


K
C
Si
O
Fe
Ti
Mg
Al
Na
P
S
K
Ti
Ti
Fe

Cas clinique «tatouage» biopsie cutanée (bras)



Grossissement x27



Grossissement x400

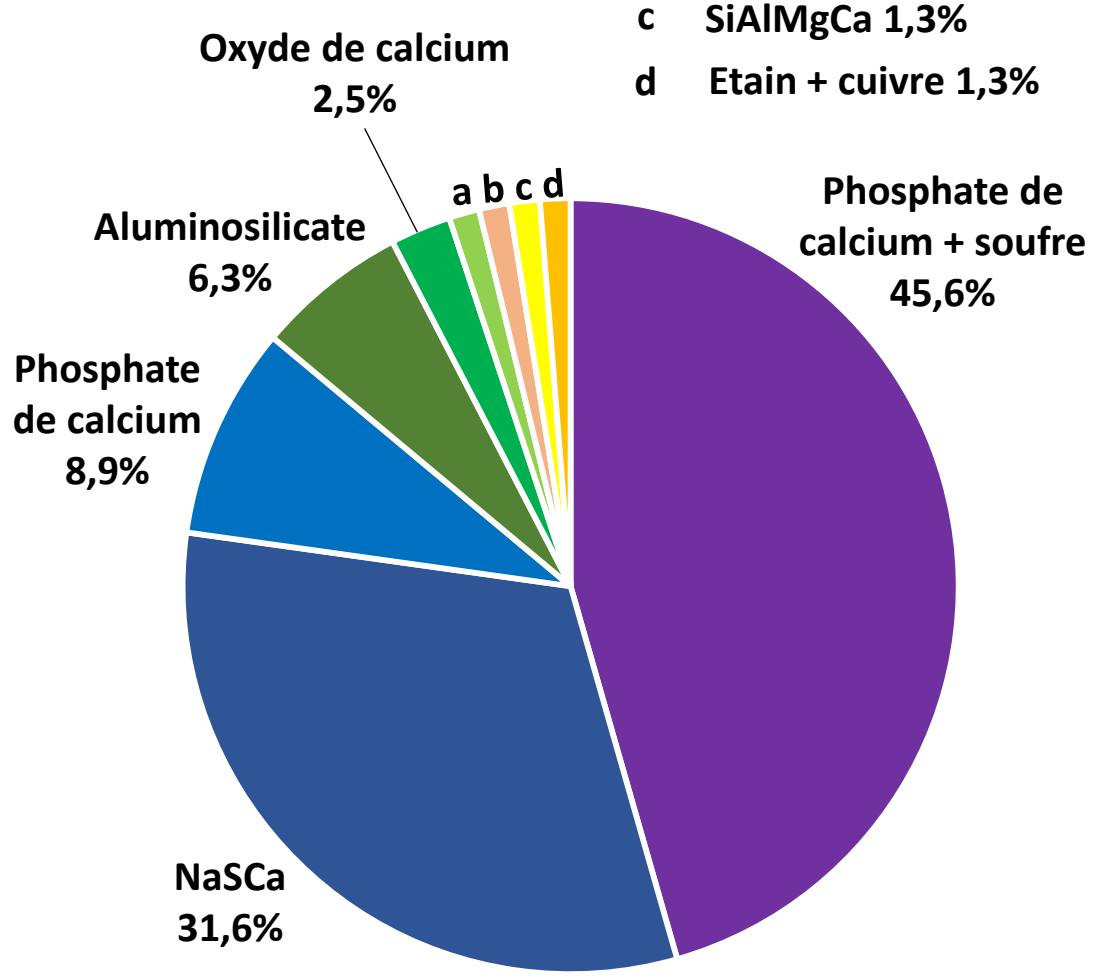
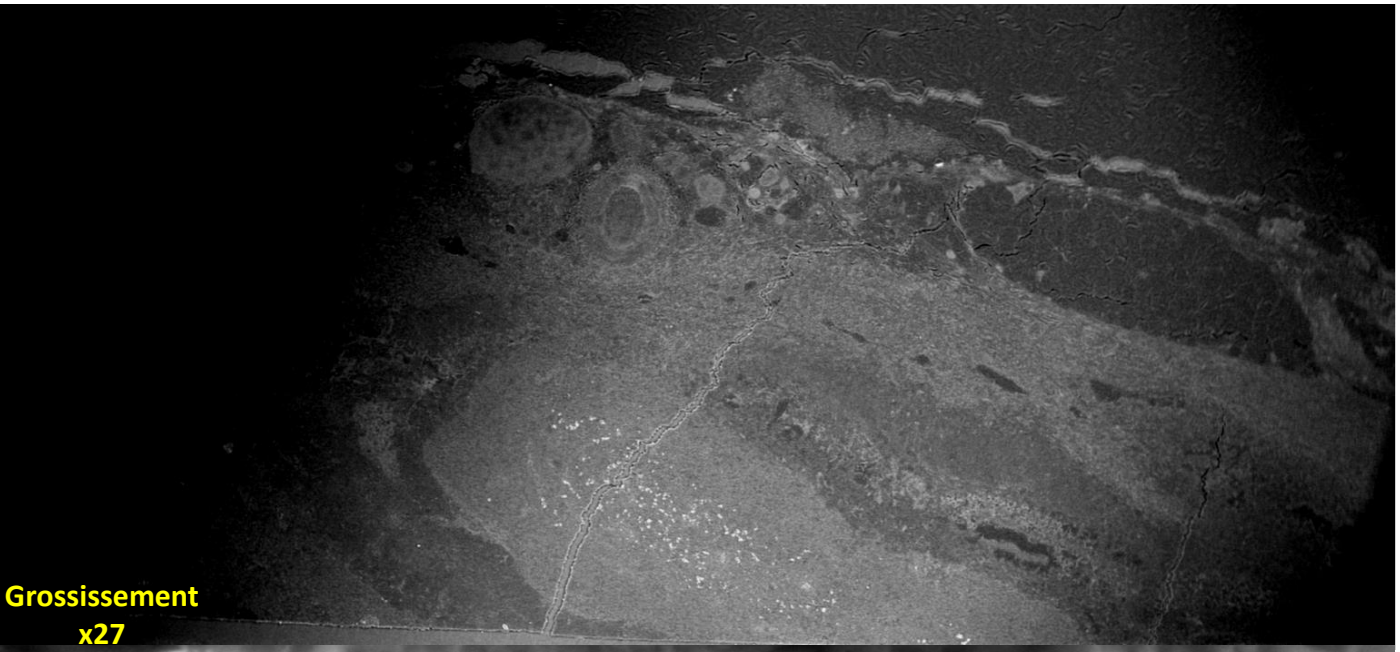
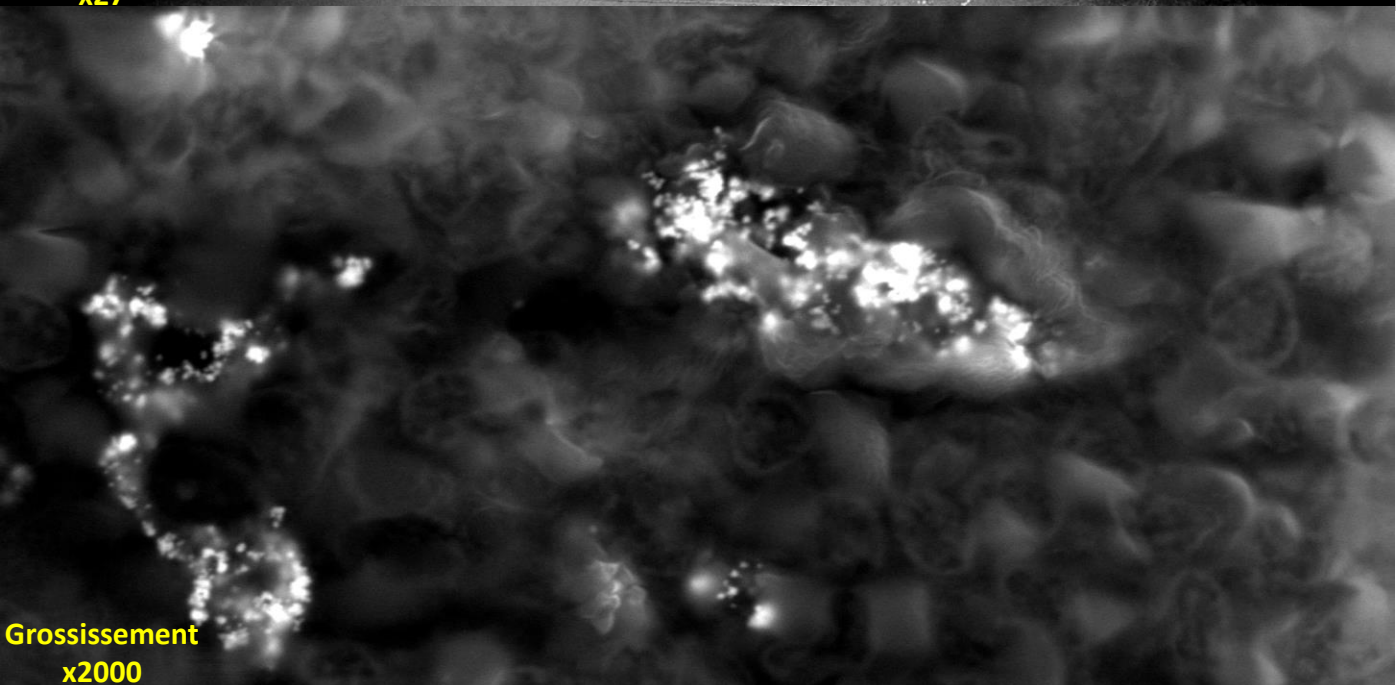


Diagramme de répartition des particules analysées par MEB (79 particules analysées)

Cas clinique «tatouage» biopsie de ganglion lymphatique





a Composé calcium 1,3%

b Phosphate de calcium + soufre 0,6%

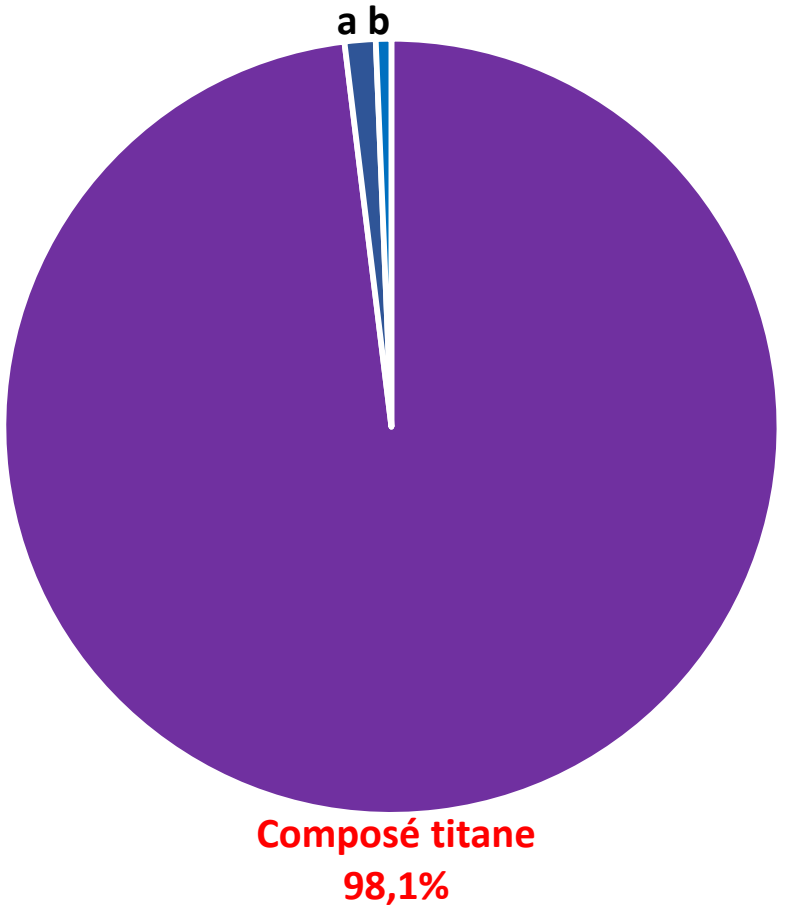
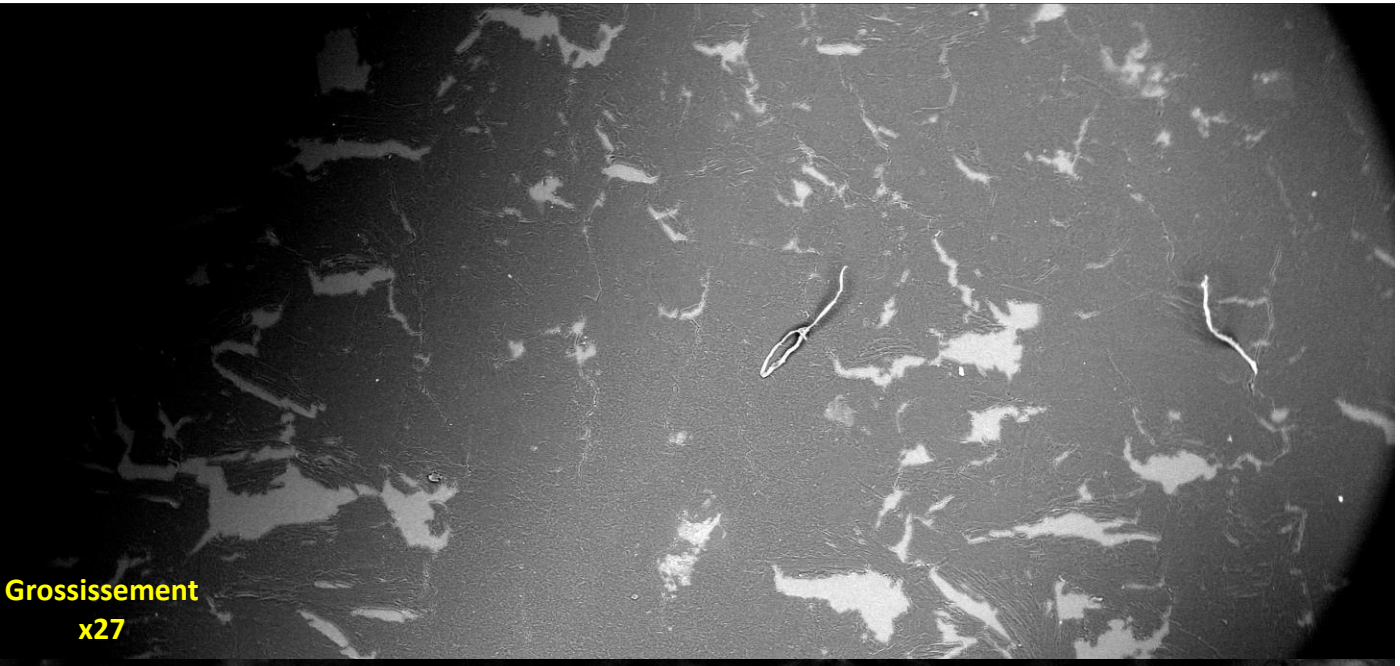
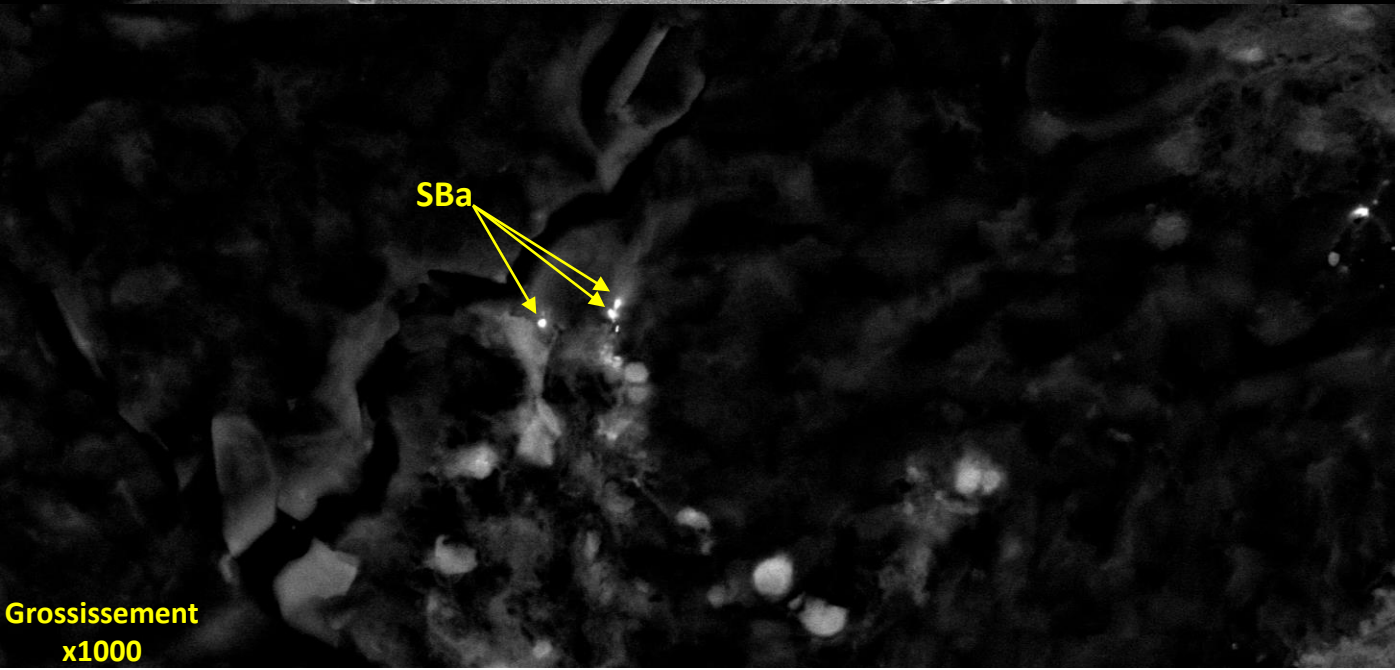


Diagramme de répartition des particules analysées par MEB (155 particules analysées)

Cas clinique «tatouage» biopsie de rein gauche





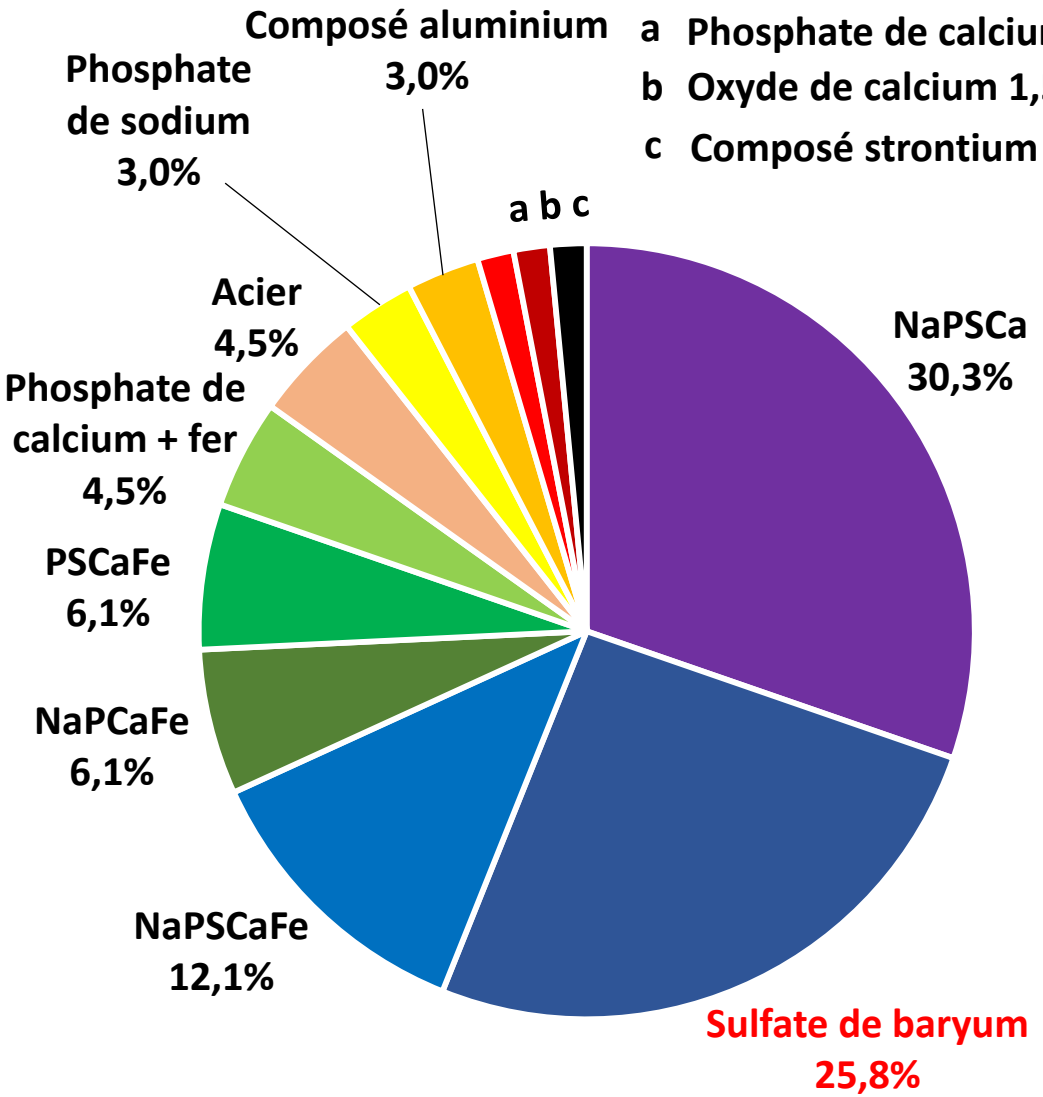
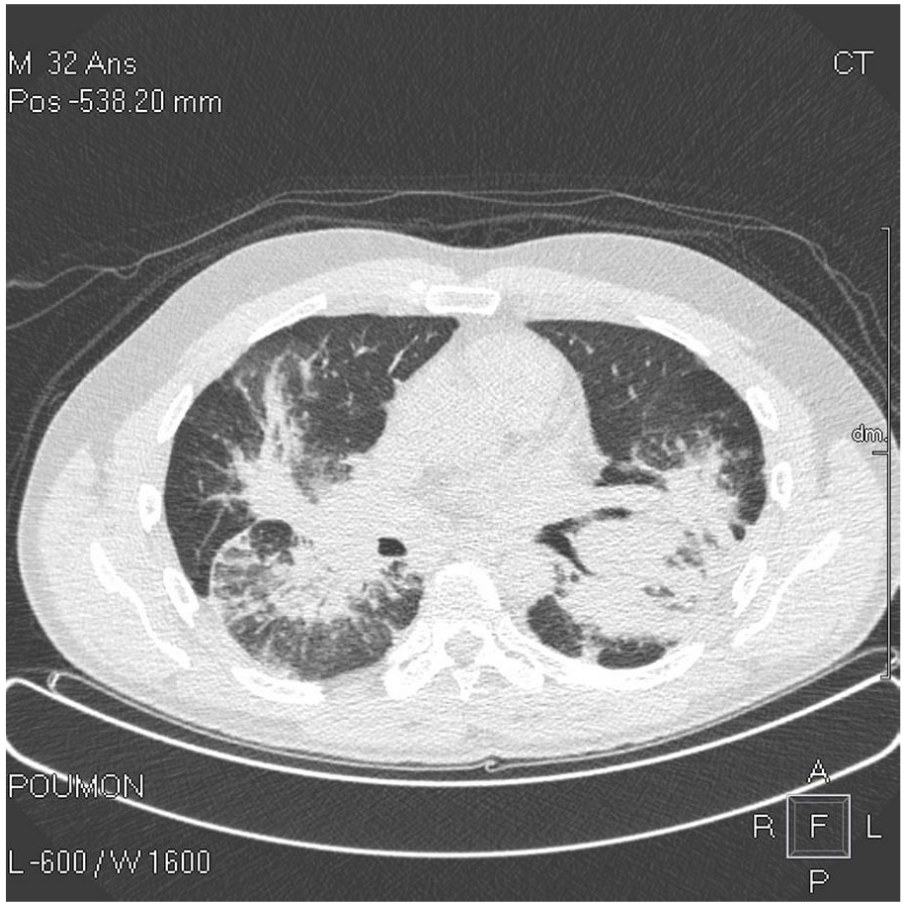
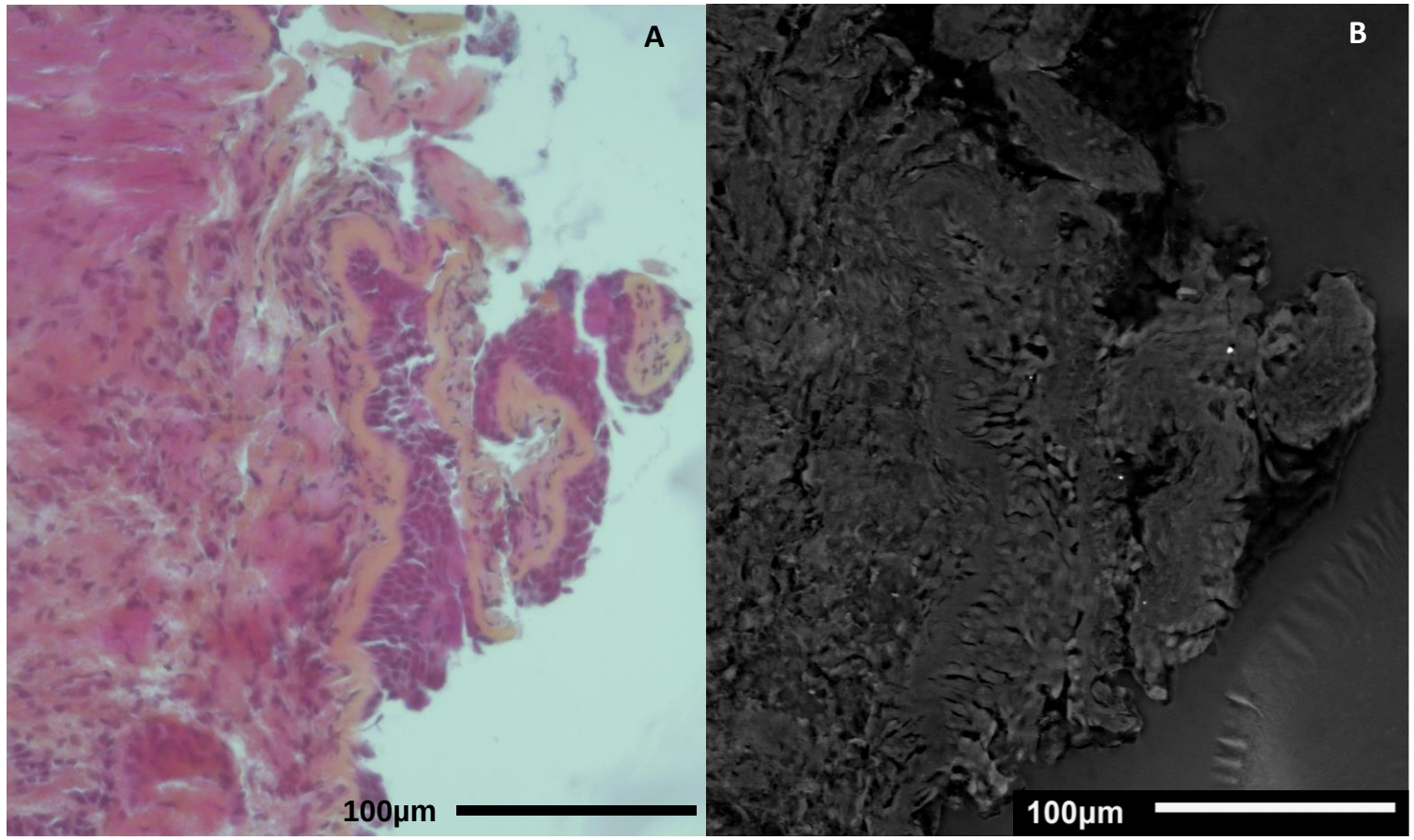


Diagramme de répartition des particules analysées par MEB (66 particules analysées)

Cas clinique «tungstène»



La tomographie axiale du thorax montre une adénomégalie hilio-médiastinale et une atteinte parenchymateuse évoquant une sarcoïdose de stade IV ou une pneumoconiose.



Observation corrélative en microscopie optique (A) et en microscopie électronique à balayage (B) d'un champ de la coupe histologique de la biopsie bronchique du patient aux grossissements originaux x200 et x250.

Cas clinique «tungstène»

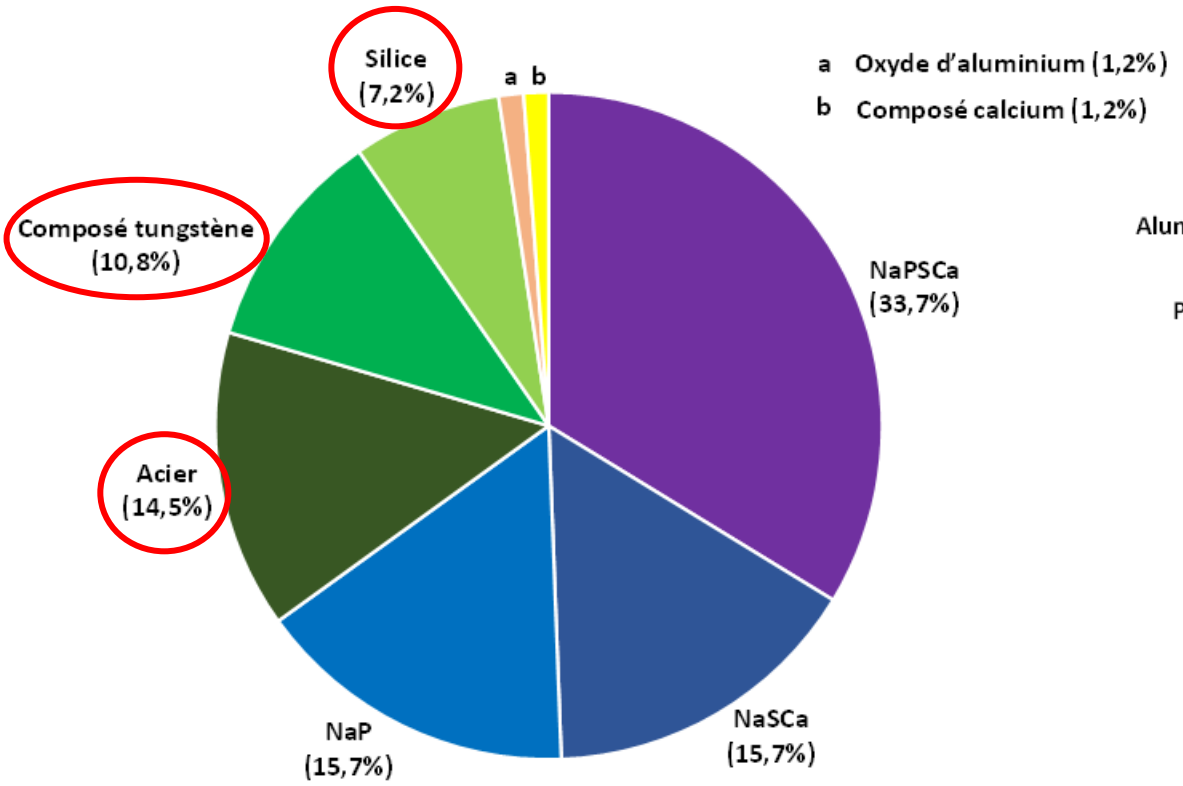


Diagramme de répartition des particules analysées par MEB (83 particules analysées)

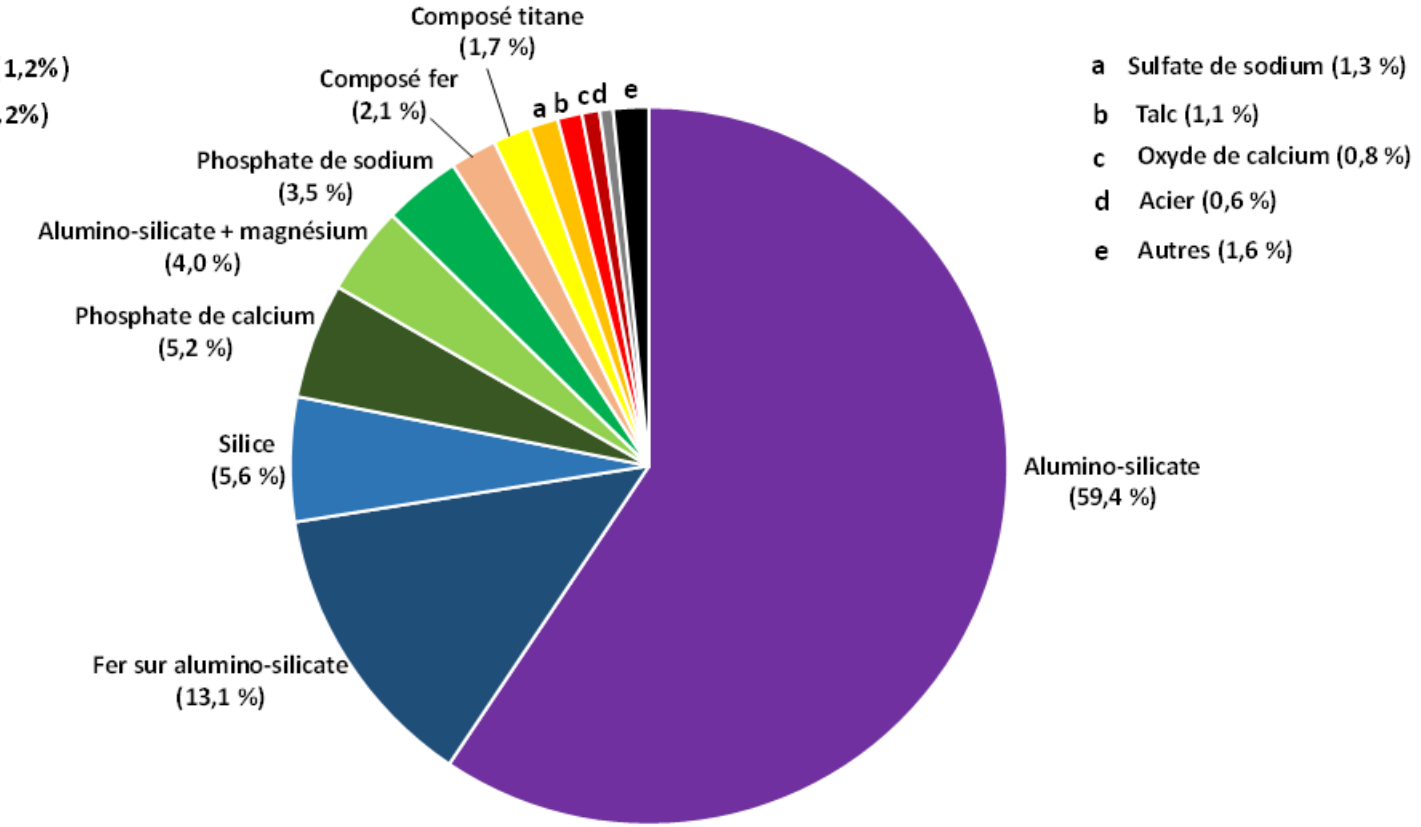
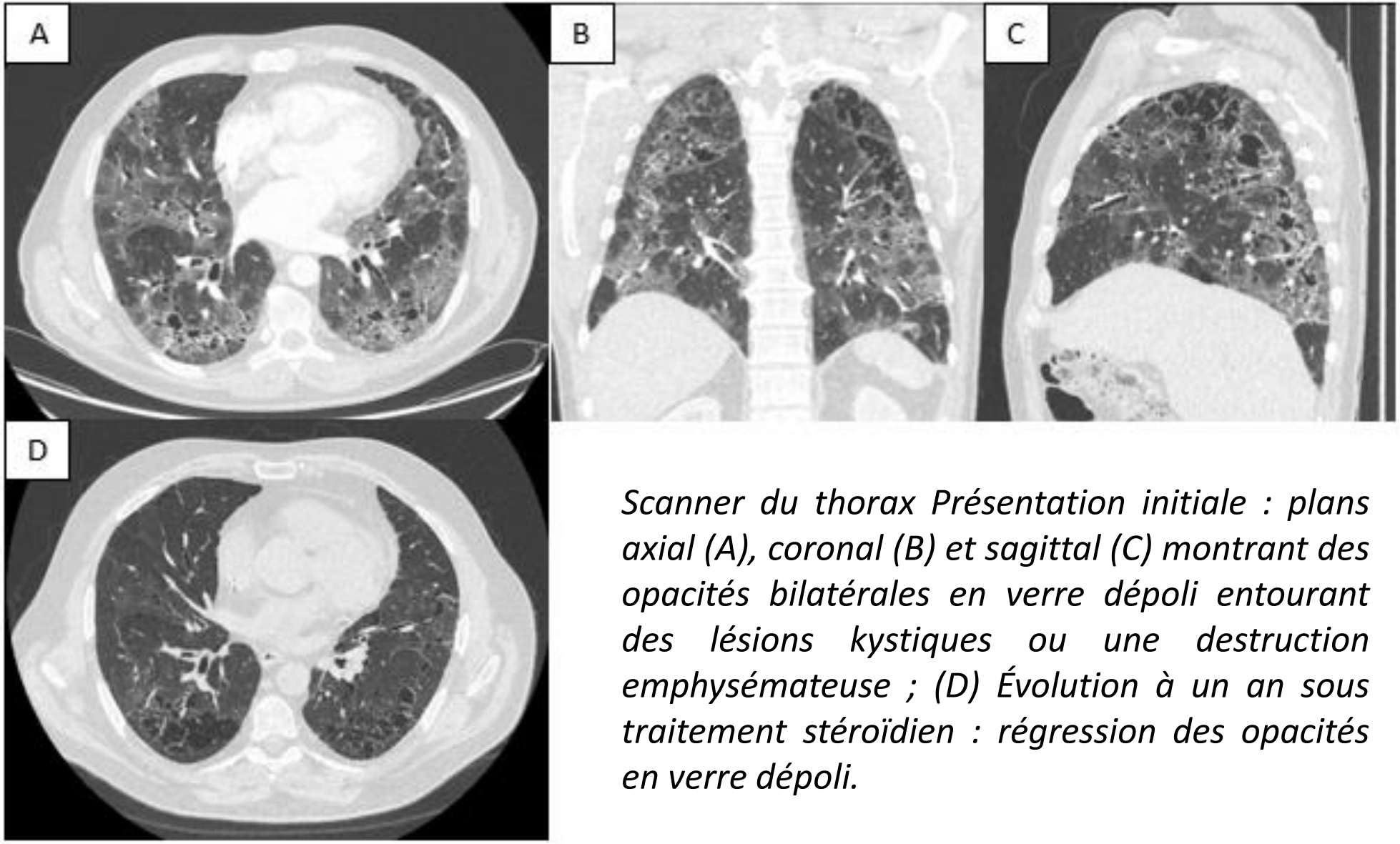


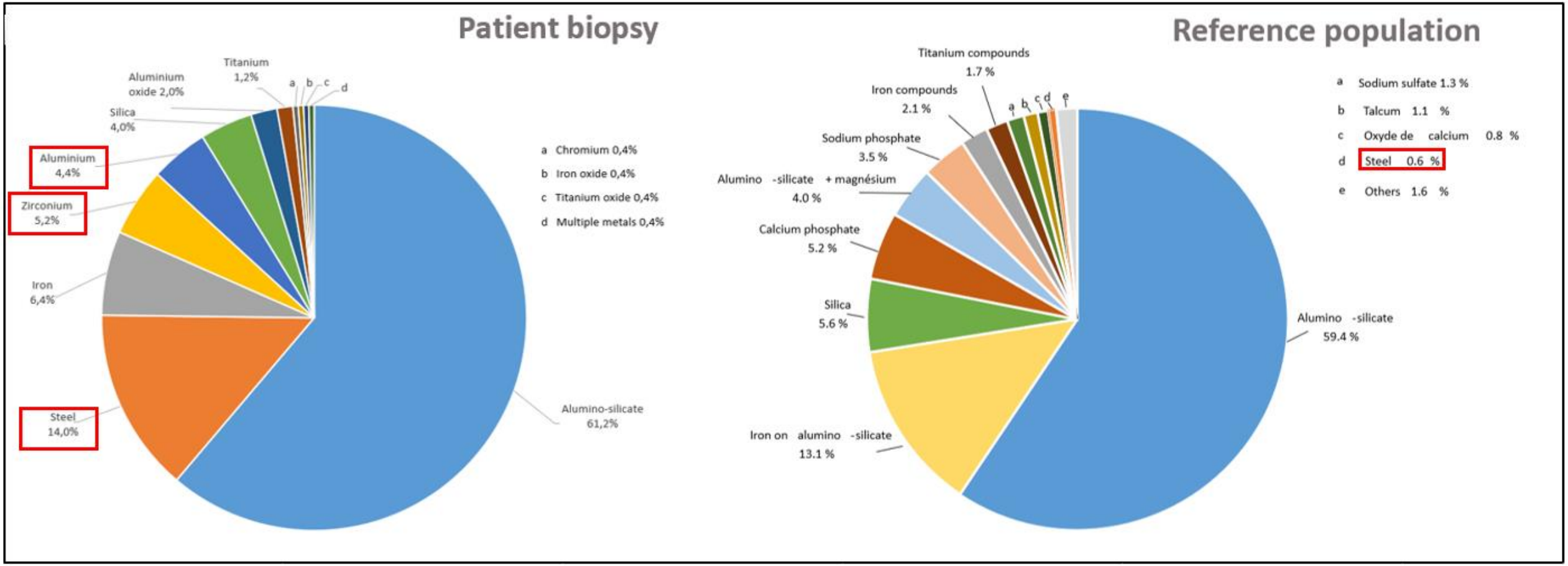
Diagramme de répartition des 4050 particules analysées par MEB sur les 53 biopsies de parenchyme pulmonaire issues de l'Institut Médicolégal de Lyon.

Cas clinique «zirconium»



Scanner du thorax Présentation initiale : plans axial (A), coronal (B) et sagittal (C) montrant des opacités bilatérales en verre dépoli entourant des lésions kystiques ou une destruction emphysémateuse ; (D) Évolution à un an sous traitement stéroïdien : régression des opacités en verre dépoli.

Cas clinique «zirconium»



Analyse minéralogique de biopsies pulmonaires. Diagramme de répartition des particules minéralogiques observées au microscope. Comparaison avec une population de référence (analyse SEM-EDX in situ de 53 blocs de parenchyme pulmonaire de l'institut médico-légal de Lyon, 4050 particules analysées).

Wire brushing wood furniture, granulomatosis and microscopic mineralogical analysis

M. Catinon, C. Chemarin, S. Assaad, S. Vuillermoz-Blas, E. Roux, A. Traverse-Glehen, C. Cavalin, P.-A. Rosental, M. Vincent

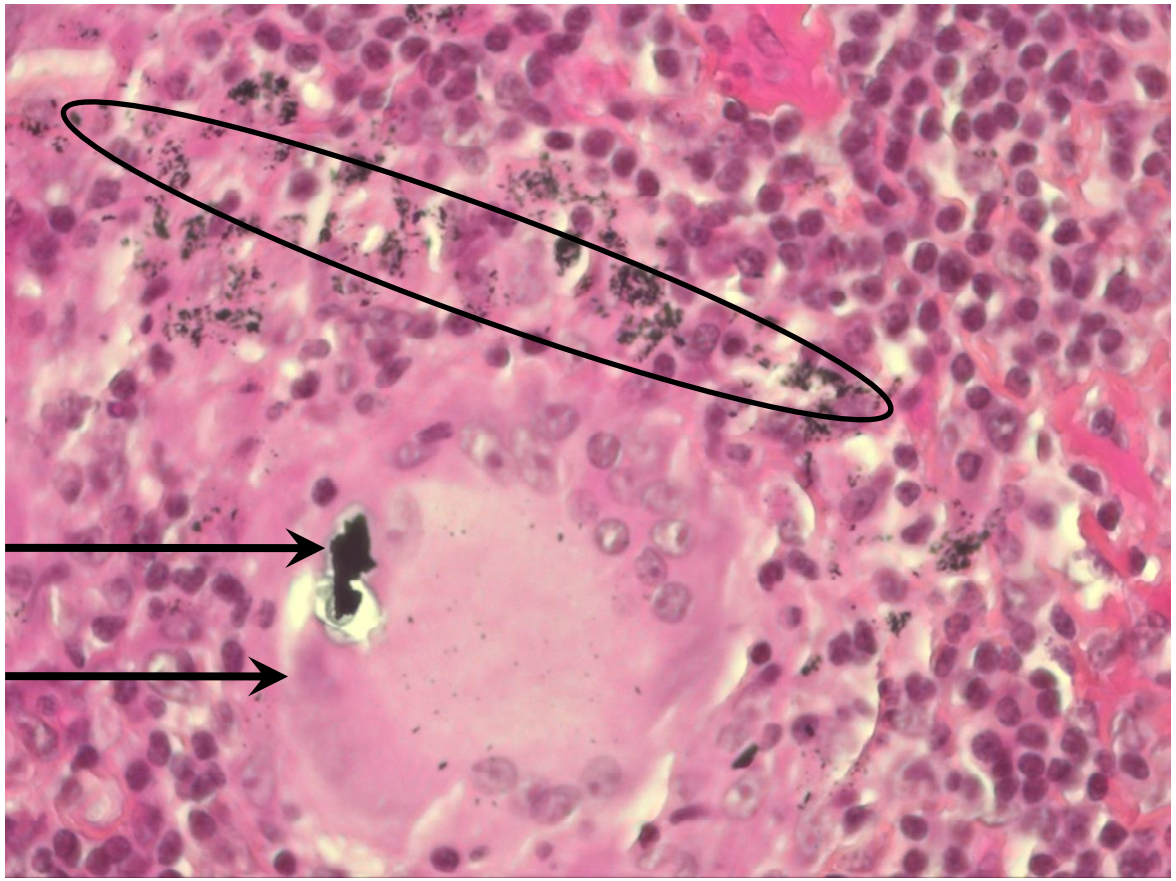
Sarcoidosis Vasculitis and Diffuse Lung Diseases 2014; 31; 262-264

Optical microscopy

Small particles

Opaque particle

Giant cell



Sub-diaphragmatic lung biopsy lymph node

Electron microscopy

Opaque particles

=

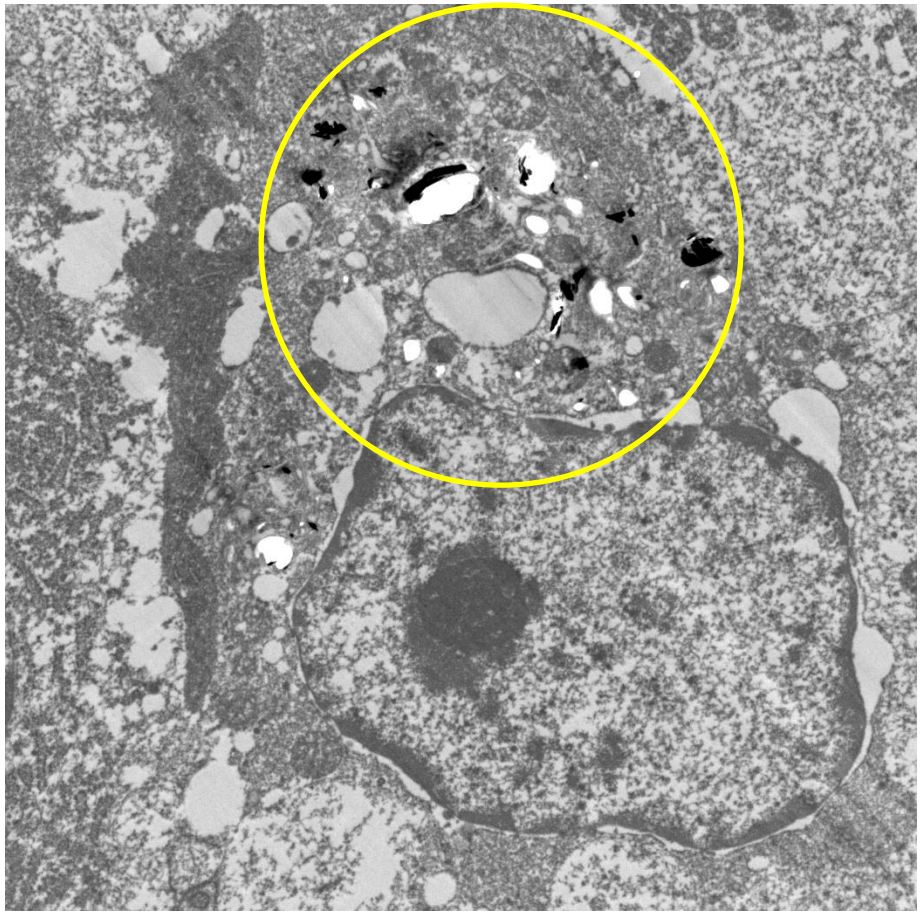
Steel particles

Composition :

Fe 64,5 ± 1,9%

Cr 20,7 ± 2,4%

Ni 15,0 ± 2,3%



Sub-diaphragmatic lung biopsy lymph node

Probable origin of the steel particles?

Using manual wire brushes

Use of motorized machinery

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 58:S6–S14 (2015

Historical Perspective

Truncating a Disease. The Reduction of Silica Hazards to Silicosis at the 1930 International Labor Office Conference on Silicosis in Johannesburg

PA Rosental[1,2,3,4]*

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 58:S31–S38 (2015)

Historical Perspective

From the Definition of Silicosis at the 1930 Johannesburg Conference to the Blurred Boundaries Between Pneumoconioses, Sarcoidosis, and Pulmonary Alveolar Proteinosis (PAP)

Michel Vincent,[1,2]* Cecile Chemarin,[1] Catherine Cavalin,[2,3,4]
Mikael Catinon,[1,2] and Paul-André Rosental[2,3,5]

Résultats Minasarc Tableau 4b sujets malades

IP	Pays d'origine	Sc E	métier en cours	BTP ancien	BTP hobby	Sc BTP	stade	AM
Bel F	Algérie	18	Chomage	non	moins d'un an	4	1	normale
Ben B	Tunisie	7	Gérant entreprise de transport	non	non	1	2	normale
Ber B	France	12	Médecin	non	non	1	2	normale
Cha L	Algerie	5	Femme au foyer	non	non	1	1	normale
Dec D	France	41	Boulanger dep 21 ans	non	moins d'un an	4	2	normale
Gui C	France	38	Salarié collectivité, communication	non	moins d'un an	4	2	suspecte (1er en CrO)
Juk J	France	118	Peintre en batiment	plus de 5 ans	plus de 5 ans	400	4	suspecte (1er FeO)
Ken J	Cameroun	48	Couturier retoucheur	non	1 à 5 ans	20	2	normale
Kes A	France	21	Agent administratif	1 à 5 ans	non	8	1	normale
laa H	Maroc	12	Salarié dans assurances	non	moins d'un an	4	2	normale
Lan C	France	73	Marchand mat de construction	1 à 5 ans	moins d'un an	80	2	suspecte (1er en Si cristalline)
Lul P	Angola	14	Chef d'équipe sécurité incendie	moins d'un an	moins d'un an	40	4	suspecte (1er en acier et TiO)
Mar P	Irak	23	Electricien du batiment	1 à 5 ans	moins d'un an	80	2	suspecte (3ème en silice et silice cristalline)
Mar J	Portugal	76	Maçon	plus de 5 ans	1 à 5 ans	320	1	normale
Mol A	France	60	Maçon	plus de 5 ans	1 à 5 ans	320	2	suspecte (2ème en silice etsilice cristalline)
Mou M	Etats-Unis	53	Chomeur	moins d'un an	1 à 5 ans	80	1	suspecte (2ème composé Chrome)
Pic M	France	32	Esthéticienne manucure	non	moins d'un an	4	1	suspecte (1er en Sulfure de Na et Ca)
Sto V	France	27	Chef de projet agence de com	non	non	1	3	normale
Xec C	Portugal	73	Décoratrice d'intérieur et restauration cadres	moins d'un an	1 à 5 ans	80	2	normale
Zac G	Etats-Unis et Italie	23	Salarié marketing communication	non	1 à 5 ans	8	3	normale

BMJ Open

Sarcoidosis and silica dust exposure among men in Sweden: a case–control study

Pål Graff ,[1] Johanna Larsson,[2] Ing-Liss Bryngelsson,[2] Pernilla Wiebert,[3] Per Vihlborg[2,4]

To cite: Graff P, Larsson J, Bryngelsson I-L, *et al*. Sarcoidosis and silica dust exposure among men in Sweden: a case–control study. *BMJ Open* 2020;**10**:e038926. doi:10.1136/bmjopen-2020-038926

ABSTRACT

Objective To determine whether occupational exposure to silica dust is associated with an increased risk of developing sarcoidosis.

Design Case–control study of all individuals between 20 and 65 years of age diagnosed with sarcoidosis (D86) in Sweden between 2007 and 2016. Controls were matched to cases (2:1) based on age, sex and county at the time of

Strengths and limitations of this study

- This case–control study includes all, in the included age groups, who were diagnosed with sarcoidosis in Sweden from 2007 to the end of 2016.
- Sweden maintains high-quality registers that cover the entire population, together with unique person-

Exposure to inorganic particles in paediatric sarcoidosis: the PEDIASARC study

Nadia Nathan ,[1] Marie-Emeline Montagne,[2] Odile Macchi,[3] Paul-André Rosental,[4] Simon Chauveau,[5] Florence Jeny,[5] Lucile Sesé,[5] Rola Abou Taam,[6] Manon Brocvielle,[7] Jacques Brouard,[8] Mickaël Catinon,[9] Catherine Chapelon-Abric,[10] Fleur Cohen-Aubart,[11] Christophe Delacourt,[6] Céline Delestrain,[12] Antoine Deschildre,[13] Antoine Dossier,[14] Ralph Epaud ,[15] Julien Haroche,[11] Véronique Houdouin,[16] Dominique Israel-Biet,[17] Karine Juvin,[17] Sylvain Le Jeune,[18] Francois Lionnet,[19] Ulrich Meinzer,[20] Marie Mittaine,[21] Hilario Nunes,[5] Sarah Mattioni,[19] Jean-Marc Naccache,[22] Marie-Hélène Odièvre,[23] Michel Vincent,[9] Annick Clement,[1] Dominique Valeyre,[5,24] Catherine Cavalin,[25,26,27] for the French Sarcoidosis Group and the Silicosis Research Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2021-217870).

For numbered affiliations see end of article.

ABSTRACT

Inorganic antigens may contribute to paediatric sarcoidosis. Thirty-six patients matched with 36 healthy controls as well as a group of 21 sickle-cell disease (SCD) controls answered an environmental questionnaire. Patients' indirect exposure to inorganic particles, through coresidents' occupations, was higher than in healthy and

lung diseases (RespiRare), without calculation of a suitable sample size. The diagnosis was confirmed by histology (91.7%) or multidisciplinary expert discussion. A control group of healthy children was matched by age ±2years and sex. In order to have a control population closer to the characteristics of the patients in terms of geographic origin, family

SHORT REPORT

Multiorgan accelerated silicosis misdiagnosed as sarcoidosis in two workers exposed to quartz conglomerate dust

Gabriella Guarnieri,[1] Rosana Bizzotto,[2] Ottorino Gottardo,[2] Emanuela Velo,[3] Mauro Cassaro,[4] Stefania Vio,[5] Maria Grazia Putzu,[6] Federica Rossi,[6] Paolo Zuliani,[6] Filippo Liviero,[1] Paola Mason,[1] Piero Maestrelli[1]

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[2]SPISAL – ULSS6 Euganea, Padova, Italy
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[5]Radiology Unit, University of Padova, Padova, Italy
[6]Department of Public Health and Pediatric Sciences, University of Turin, Turin, Italy

Correspondence to
Professor Piero Maestrelli, Department of Cardiologic,

ABSTRACT

Introduction Clusters of silicosis cases have been reported in the fabrication of quartz conglomerate, a new high-silica-content artificial stone for kitchen and bathroom benchtops (countertops).

Aim We describe two cases of accelerated-type silicosis with hepatic granulomas arising in workers exposed to artificial quartz conglomerates.

Methods A confident diagnosis of multiorgan silicosis was based on high level of respirable silica in the workplace, typical radiological alterations in chest high-resolution CT, histological findings in the lung and liver, and detection of silica crystals in both tissues by phase-contrast polarising light microscopy and scanning electron microscopy and energy dispersive spectroscopy.

Key messages

What is already known about this subject?

- Clusters of silicosis cases have been reported in the fabrication of quartz conglomerate, a new high-silica content artificial stone for kitchen and bathroom benchtops.

What are the new findings?

- We report the first cases of accelerated silicosis in workers exposed to quartz conglomerates with liver involvement.
- Compared with other studies related to quartz conglomerate exposure, we provided data on the levels of workplace respirable silica exposure and demonstrated accumulation

REVIEW

The emerging role of inorganic elements as potential antigens in sarcoidosis

Els Beijer[a] *and Marcel Veltkamp*[a,b]

Purpose of review
Previous studies mainly described a role for organic agents as possible triggers for sarcoidosis. In this review, we address recent studies suggesting a possible role for inorganic elements, such as metals or silica in sarcoidosis pathogenesis.

Recent findings
Several epidemiological papers suggest that inorganic agents, either by environmental exposures or occupational activities, could trigger sarcoidosis. Association between inorganics and sarcoidosis is also described in several recently published case reports and studies demonstrating immunological sensitization to inorganic agents in sarcoidosis patients.
Studies comparing chronic beryllium disease (CBD) and sarcoidosis suggest that although antigenic triggers may differ, underlying processes may be comparable.
Besides the fact that a growing number of studies show a possible role for inorganic triggers, it is also suggested that inorganic triggered sarcoidosis may result in a more severe phenotype, including pulmonary fibrosis.

Summary
We can use the knowledge already gained on CBD pathogenesis to conduct further research into role of inorganics, such as metals and silica as antigens in sarcoidosis. Given the importance of a lymphocyte proliferation test (LPT) in diagnosing CBD, it seems obvious to also implement this test in the diagnostic work-up of sarcoidosis to identify patients with an inorganic antigenic trigger of their disease.

Keywords
immunological sensitization, inorganic, metals, sarcoidosis, silica

CHEST

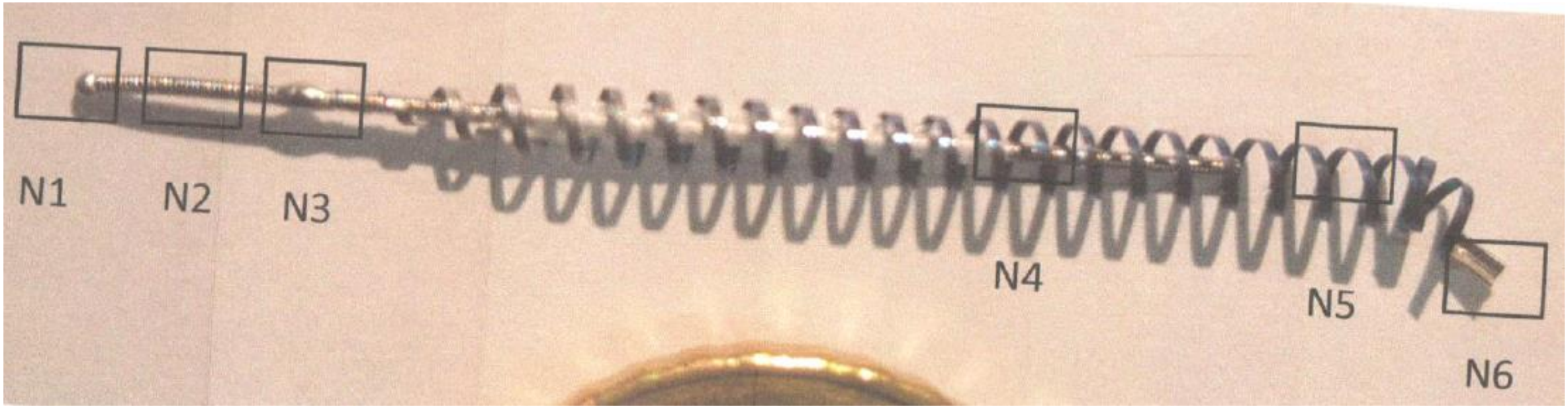
Sarcoidosis
An Occupational Disease?

L. Christine Oliver, MD; and Andrew M. Zarnke, BSc

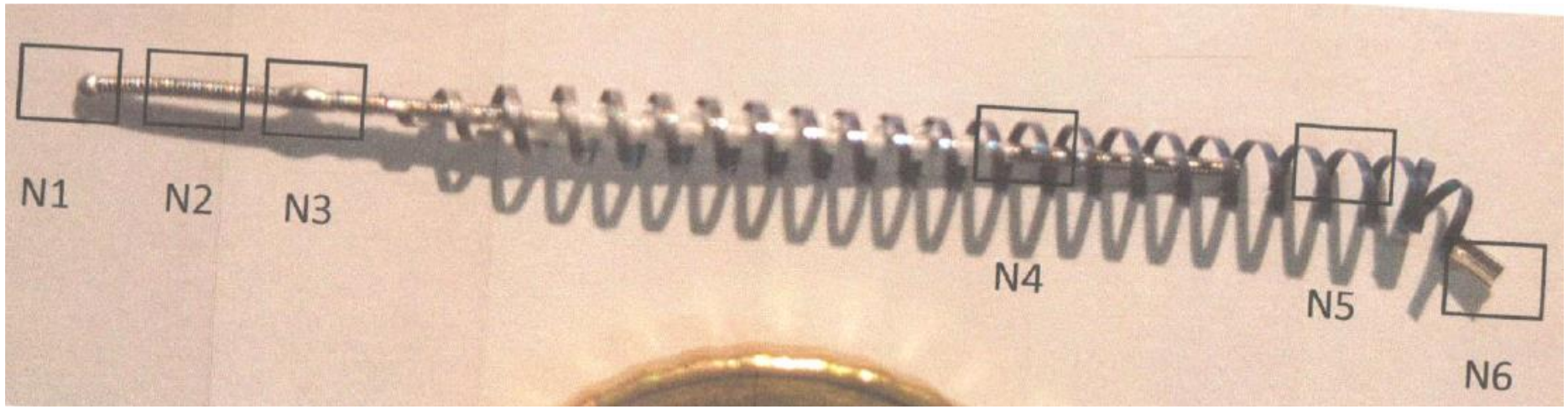
Sarcoidosis is an important member of the family of granulomatous lung diseases. Since its recognition in the late 19th century, sarcoidosis has been thought of as a disease of unknown cause. Over the past 20 years, this paradigm has been shifting, more rapidly in the past 10 years. Epidemiologic studies, bolstered by case reports, have provided evidence of causal associations between occupational exposure to specific agents and sarcoidosis. Pathogenesis has been more clearly defined, including the role of gene-exposure interactions. The use of in vitro lymphocyte proliferation testing to detect sensitization to inorganic antigens is being examined in patients with sarcoidosis. These antigens include silica and certain metals. Results of studies to date show differences in immunoreactivity of occupationally exposed sarcoidosis cases compared with control cases, suggesting that lymphocyte proliferation testing may prove useful in diagnosing work-related disease. This review discusses recently published findings regarding associations between occupational exposure to silica and silicates, World Trade Center dust, and metals and risk for sarcoidosis, as well as advances in the development of diagnostic tools. Not all cases of sarcoidosis have an identified cause, but some do. Where the cause is occupational, its recognition is critical to enable effective treatment through removal of the affected worker from exposure and to inform intervention aimed at primary prevention.

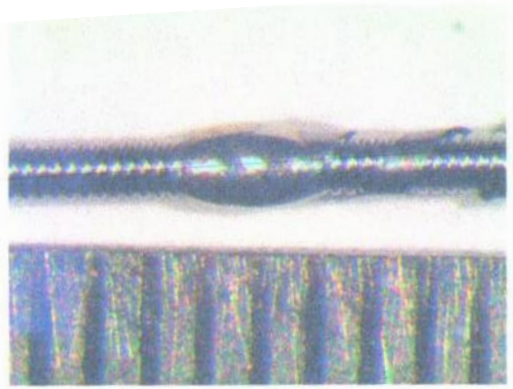
CHEST 2021; 160(4):1360-1367

Perspectives d’analyses sur Implants ESSURE (implant)



N1 = boule terminale
N2 = petit ressort
N3 = soudure
N4 = bague petit ressort
N5 = gros ressort
N6 = fin gros ressort





N3 soudure

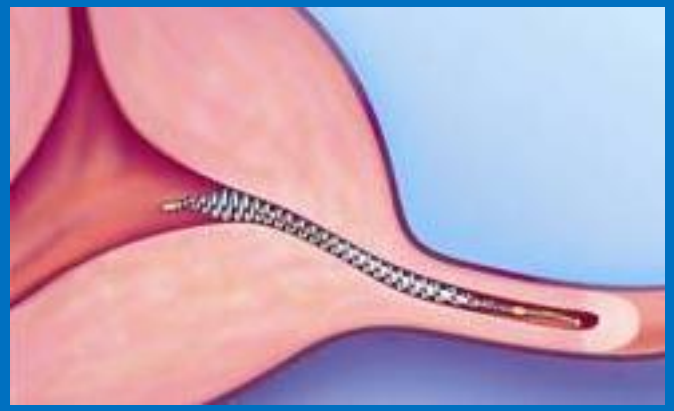
Sn 48 %
Fe 21.6 %
Ni 7.3 %
Cr 6.2 %
Ti 1.3 %
Ag 0.95 %
Mo 0.9 %
Mn 0.6 %
W 0.2 %

Traces : Cu, Co, V,
Pb, Sb, Bi, Hg, As, Mg

Total 87.1 %

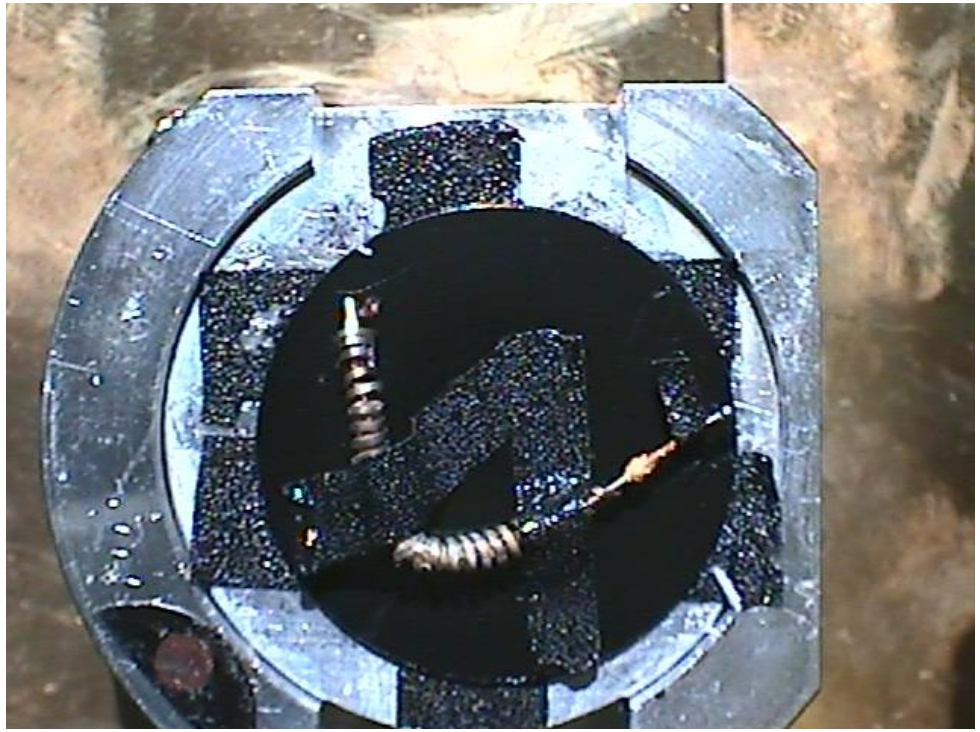
CLIPS DE HULKA
Matériel SILASTIC
Coût : 80 euros HT
TVA 20 %
TTC 96 euros
Echec : 1 / 2500
Réversibilité possible

ESSURE
Coût : 663,51 euros HT
TVA 5,5 %
TTC 700 euros
Echec DE POSE 6 à 13 %
Réversibilité impossible



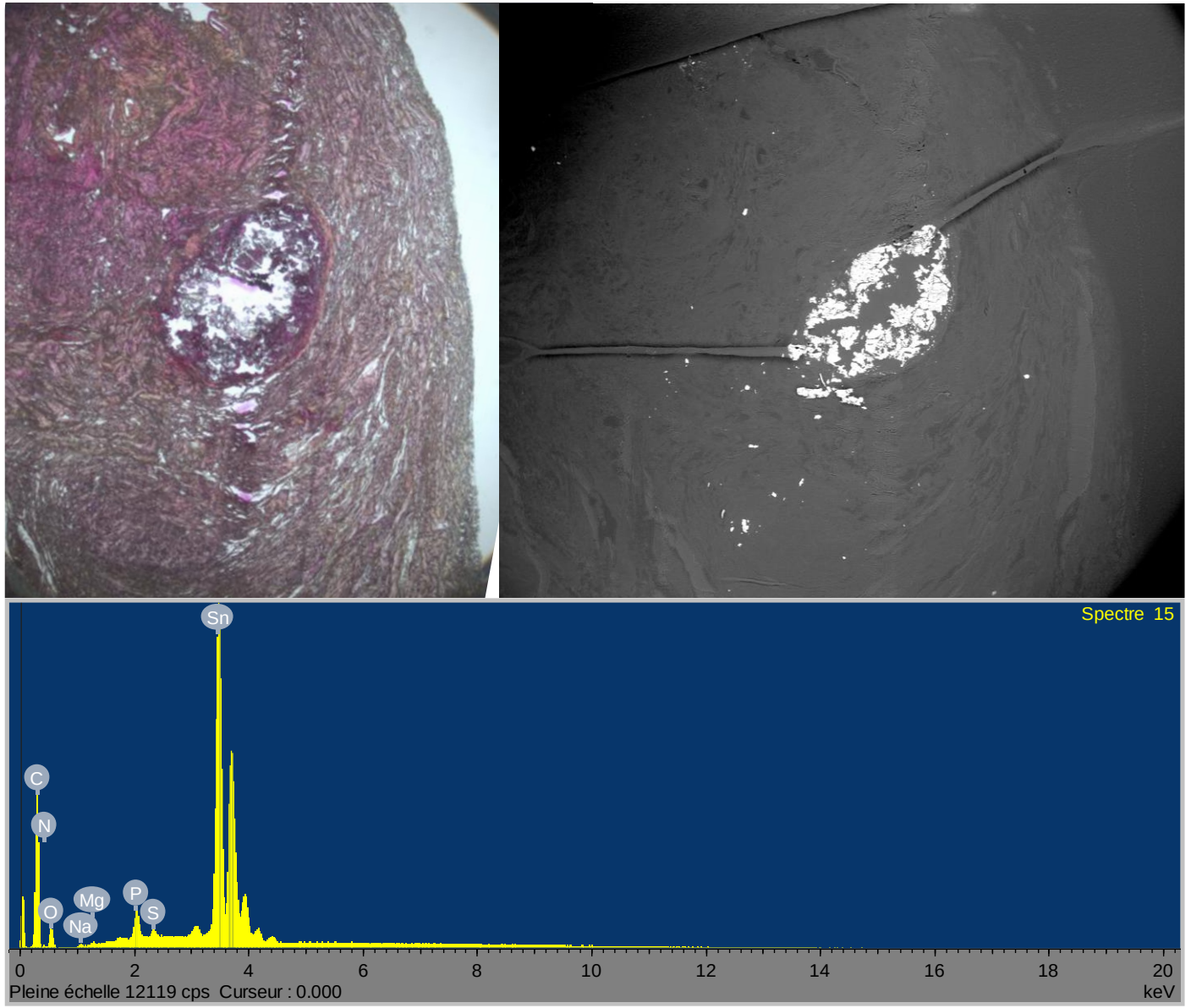
Une analyse minéralogique a été réalisée par MINAPATH sur des biopsies utérines et des implants de patientes qui ont subi une opération pour le retrait de leurs implants contraceptifs de type ESSURE.

Biopsie de trompe utérine

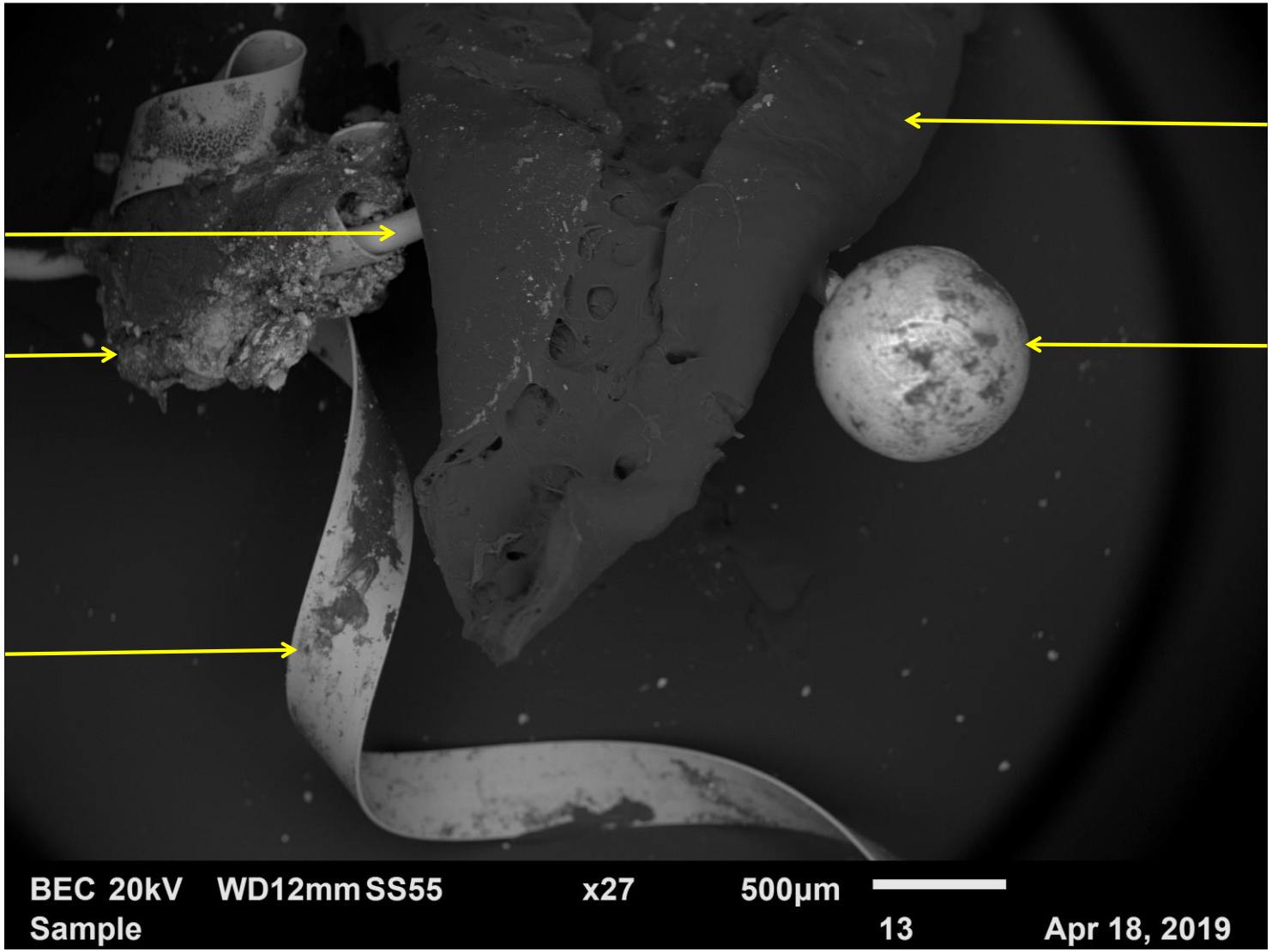


Implant ESSURE

Perspectives d’analyses sur Implants ESSURE (biopsie)

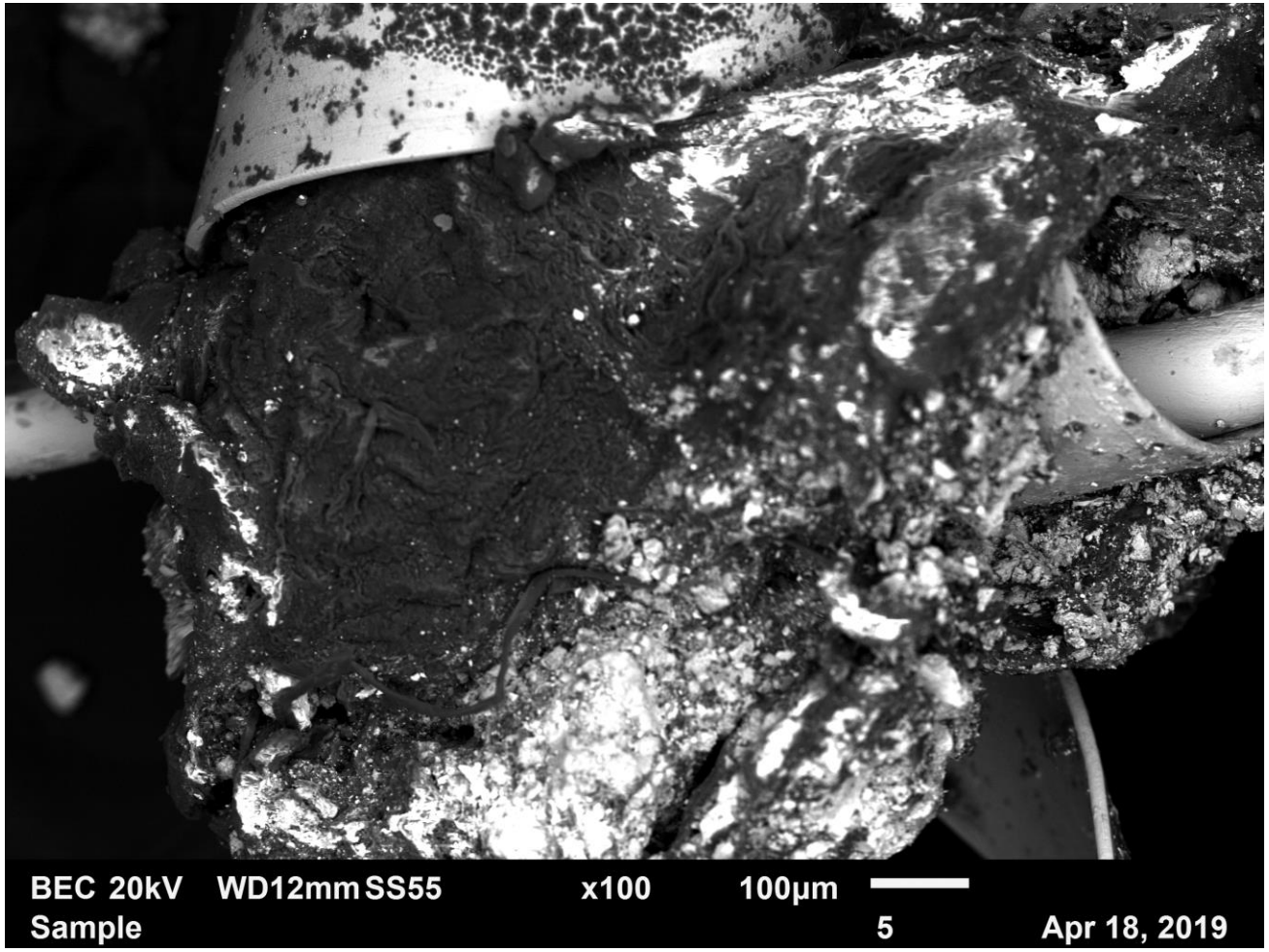


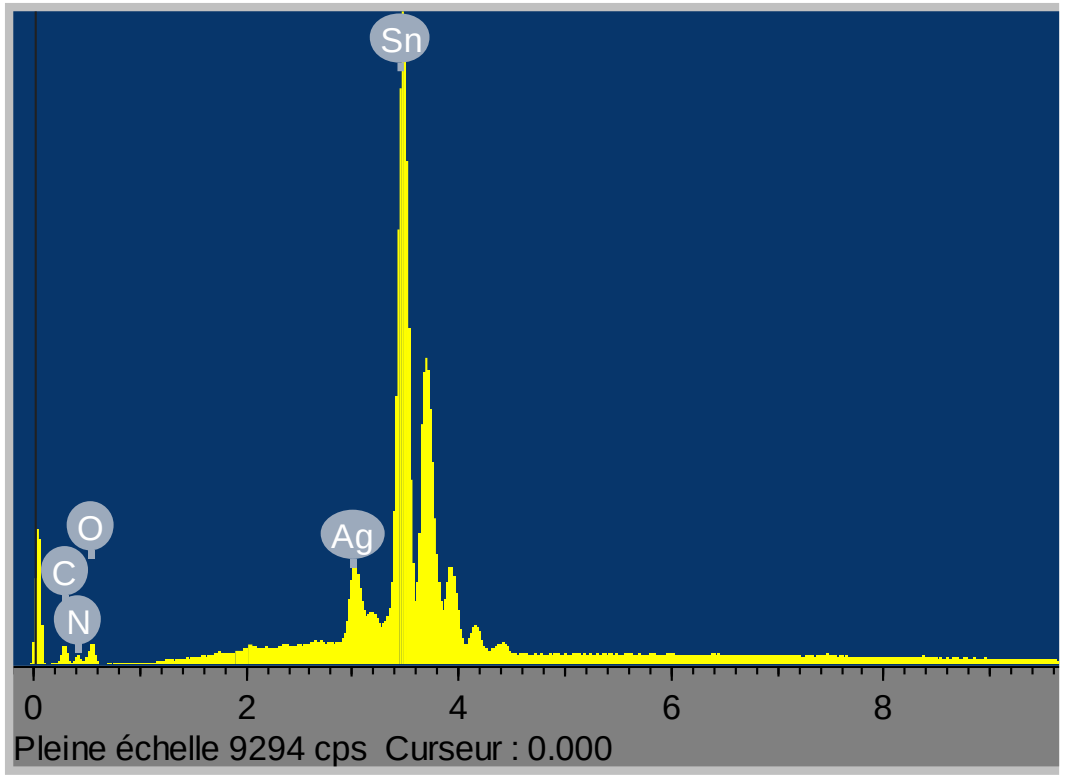
Perspectives d'analyses sur Implants ESSURE (implant)



Perspectives d’analyses sur Implants ESSURE (implant)

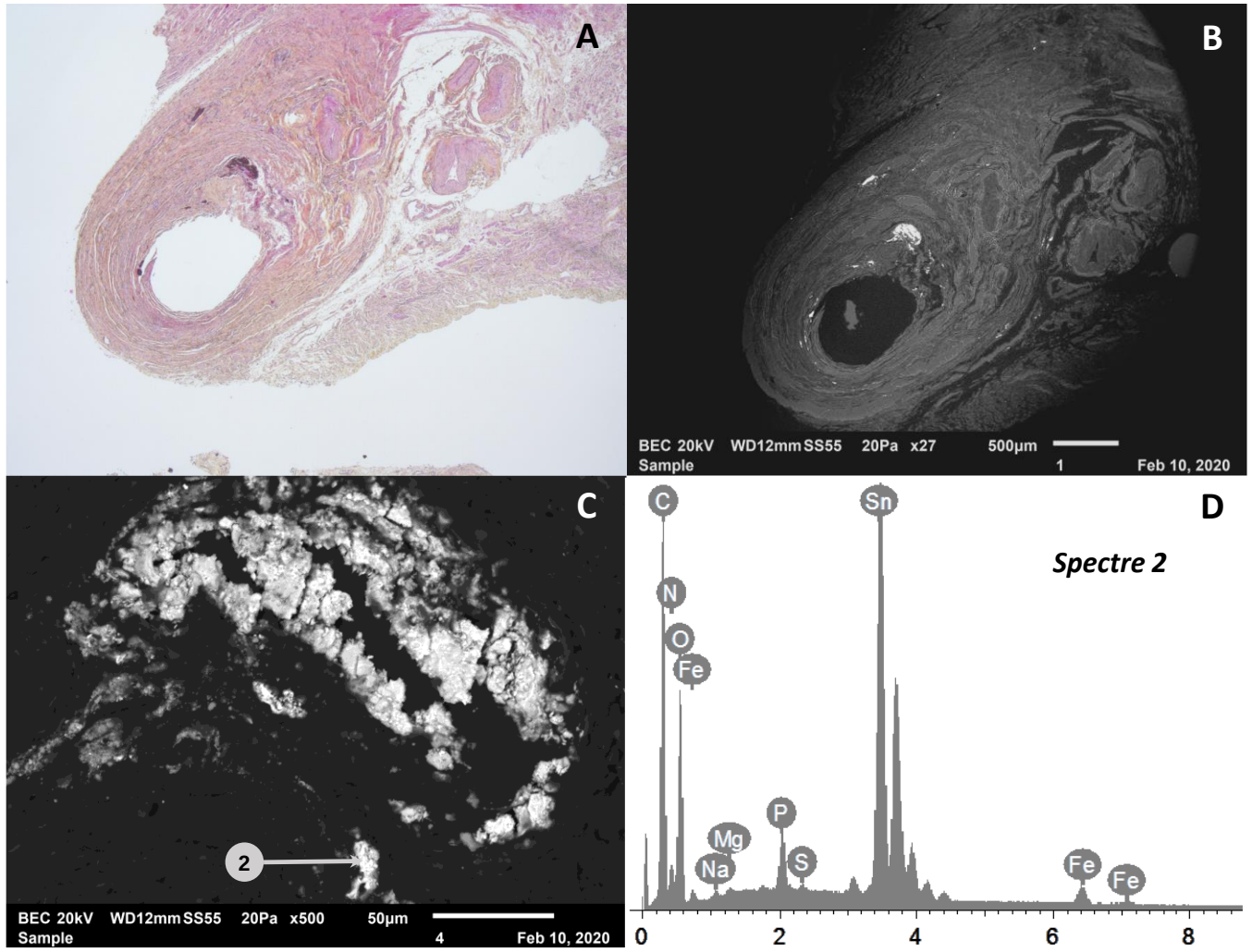
Soudure





Hypothèse organoétain

Essure et granulomatose à l'Etain : étude de 18 cas complémentaires consécutifs (Septembre 2019 à Juillet 2020) avec même protocole anatomopathologique.



Dix huit nouveaux cas consécutifs

Tableau 1 : Description des patientes, des différentes biopsies analysées et détails de l'étude anatomopathologique. tf: trompe de Fallope ; cu: corne utérine.

N° patient	Âge	Biopsie	Temps avant retrait (mois)	Granulome	Fibrose	Inflammation non-spécifique	Corps étrangers	Adénomyose	Autres
1	49	tf + cu	127	X				X	Dystrophie épidermique cervicale
2	52	cu	90	X		X	X	X	
3	49	cu	73	X				X	Endomètre dystrophique
4	56	tf	114	X				X	Myomes
5	52	tf	66	X		X	X	X	Calcifications
6	43	tf	80	X				X	Cystostéanonécrose
7	46	tf	60	X		X		X	Kystes paratubaires
8	48	tf	103	X				X	Myomes
9	36	tf	44	X		X	X		
10	54	cu	178	X		X	X	X	Kystes ovariens et paratubaires
11	38	tf + cu	55	X		X		X	Kystes paratubaires
12	51	tf	80	X					Myomes
13	45	tf	61		X				Kystes paratubaires
14	56	cu	121	X				X	Myomes
15	49	cu	107	X		X	X	X	
16	50	cu	91	X		X	X	X	Kystes paratubaires
17	56	tf	162	X		X			Myomes
18	55	tf + cu	89	X		X	X	X	

Dix huit nouveaux cas consécutifs

Tableau 2 : les résultats de l'analyse minéralogique des biopsies. ++++: 75 à 100%; +++: 50 à 75%; ++: 25 à 50%; +: 0 à 25%. tf: trompe de Fallope ; cu: corne utérine. La patiente N°12 n'a pas répondu au questionnaire.

N° patient	Biopsie	Composé Sn	Composé Ca	Silicate	Acier	Composé Fe	Composé Ti	Composé Pt	AgO	Nombre de particules analysées
1	tf + cu	++++							+	96
2	cu	++++	+		+					133
3	cu	++++	+							30
4	tf	++++								59
5	tf	++++								40
6	tf	++++								45
7	tf	+++					+	+		40
8	tf	++++	+				+			50
9	tf	++++			+					30
10	cu	++++								30
11	tf + cu	++++								45
12	tf	++				+++				70
13	tf	++++	+		+					32
14	cu	++++								30
15	cu	+++	++	+						47
16	cu	++++								30
17	tf	++	++	+	+		+	+		42
18	tf + cu	++++								45

MINAPATH
Mineral exposome

Evolution signes locaux après explantations

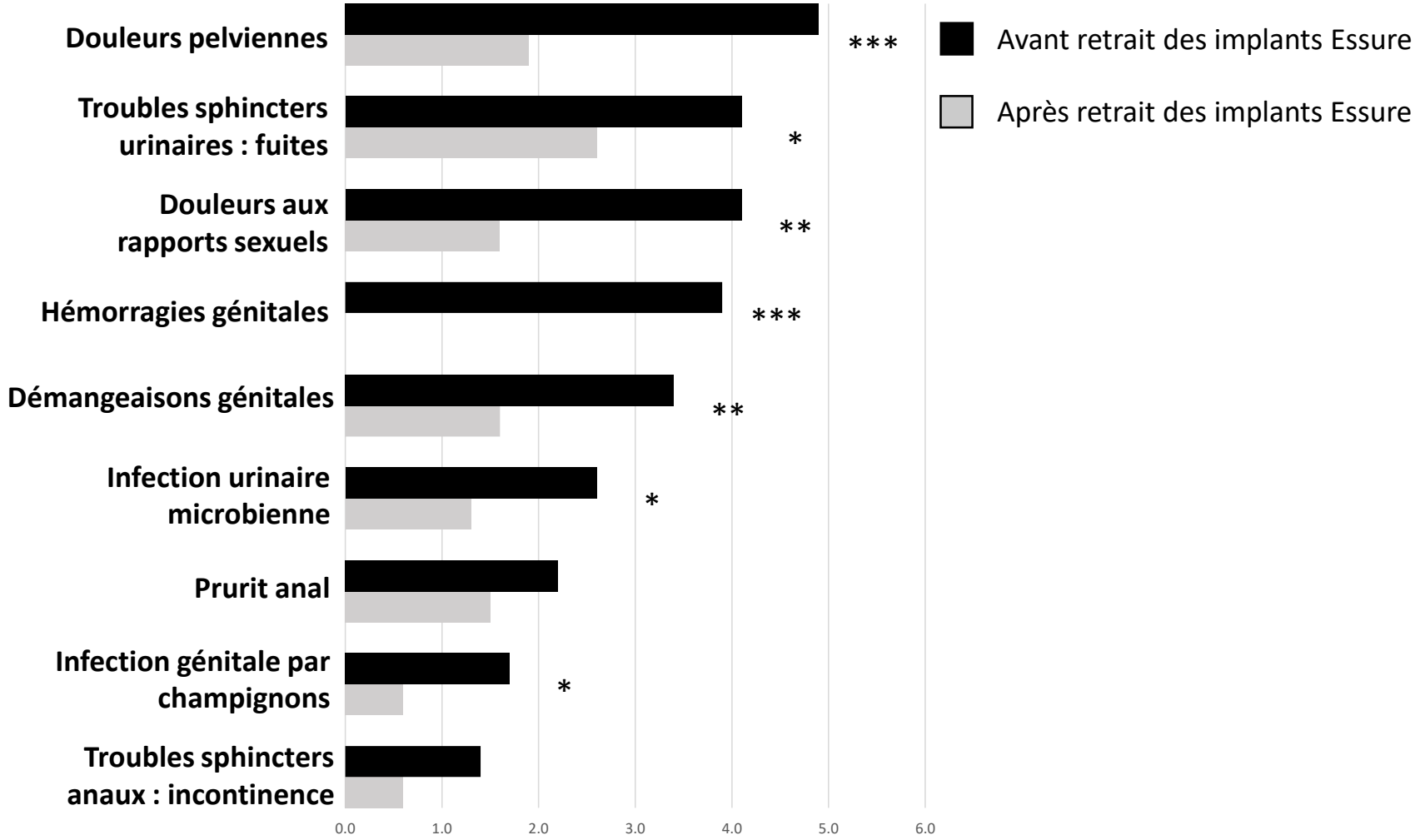


Figure 2 : Histogramme représentant le score pour chaque symptôme local avant (histogrammes noirs) et après le retrait des implants (histogrammes gris). Les résultats sont exprimés sous forme de moyennes. Un test des rangs signés de Wilcoxon pour échantillons appariés a été effectué pour chaque symptôme. $0,05<p<0,1$ (*) ; $0,01<p<0,05$ (**) ; $p\leq0.01$ (***).

Evolution signes systémiques après explantation

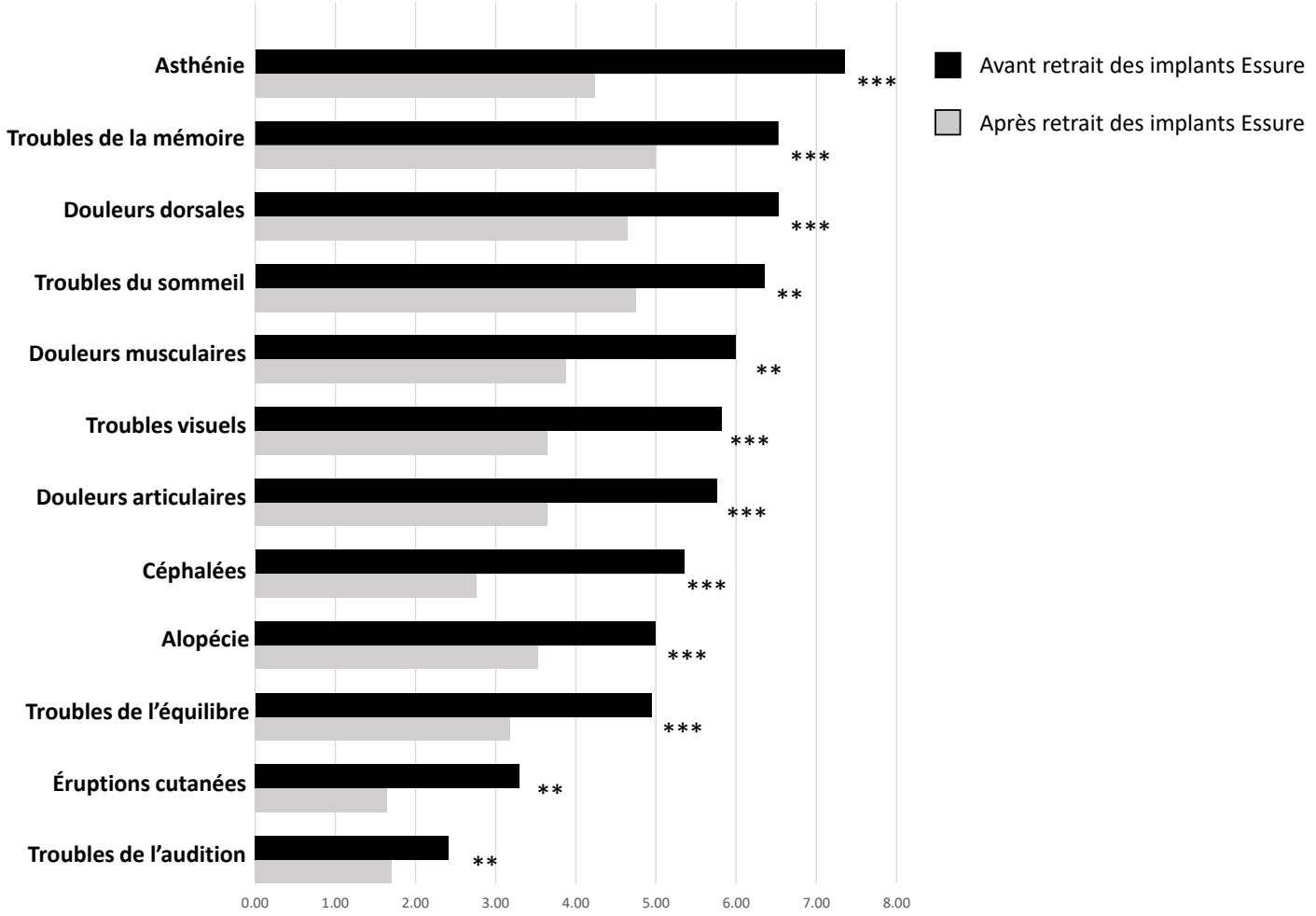


Figure 3 : Histogramme représentant le score pour chaque symptôme systémique avant (histogrammes noirs) et après le retrait des implants (histogrammes gris). Les résultats sont exprimés sous forme de moyennes. Un test des rangs signés de Wilcoxon pour échantillons appariés a été effectué pour chaque symptôme. 0,01<p<0,05 (**) ; p≤0.01 (***).

1/Erreur d'appréciation dans les études précliniques de relargage d'étain par la soudure.

- Confusion entre dose quotidienne et dose maximum tolérée.
- Pas de prise en compte de la faible absorption digestive et de la durée exposition
- Pas d'études MEB-EDX chez l'animal mais aussi dans l'étude préclinique avant obtention de l'AMM: Ces études auraient pu montrer la dissémination de l'étain.
- Objectif principal : l'obtention d'une fibrose de la trompe sans souci de la persistance possible d'une majoration de la corrosion les années qui suivent.

Tests de corrosion Conceptus 2004

8.0 ACCEPTANCE CRITERIA

8.1 Leaching Rate of Nickel

The leaching rate of nickel ions from the samples must be lower than the average levels of human intake of nickel from diet and the environment.

8.2 Mechanical Integrity

The Micro-inserts must maintain mechanical integrity for at least three months. That is, each Micro-insert must still be in one piece after exposure to a corrosive saline environment for three months. In particular, the fibered inner coil must remain attached to the outer coil.

9.0 RESULTS AND DISCUSSION

The test passed both acceptance criteria. The leaching rate of nickel and tin ions released due to corrosion were at least 2000 times lower than the daily human intake of these metal ions from the diet and environment. The leaching rate of chromium was below the detection limit. All of the samples tested maintained mechanical integrity, not just for three months, but for all six months of the study.

Expertise conceptus 2004 remise à HAS et ANSM

measured leaching rates for the three metals monitored are as follows:

Table 2: Highest Metal Leaching Rates Compared to Normal Human Intake

Metal	Normal Human Daily Intake[3]	Highest Measured Leaching Rates
Nickel	300 µg/day	0.14 µg/day
Tin	100,000 µg/day	27 µg/day
Chromium	no published data is available	less than 0.03 µg/day (below detection limit)

9.1.1 Metal Ion Leaching Analysis Cumulative Data

Figure 2 and **Figure 3** show the leaching rate of nickel and tin as analyzed in the cumulative test (A samples). The leaching rate of

Rapport Conceptus 2004

9.2 Mechanical Integrity

The samples passed the acceptance criteria for mechanical integrity. All of the samples tested maintained mechanical integrity, not just for three months, but for all six months of the study.

After the Micro-insert samples were removed from the vials of solution, they were cleaned in an ultrasonic bath, dried, and examined using scanning electron microscopy (SEM). No Micro-inserts showed loss of mechanical integrity. In all cases, the outer coil remained attached to the fibered inner coil.

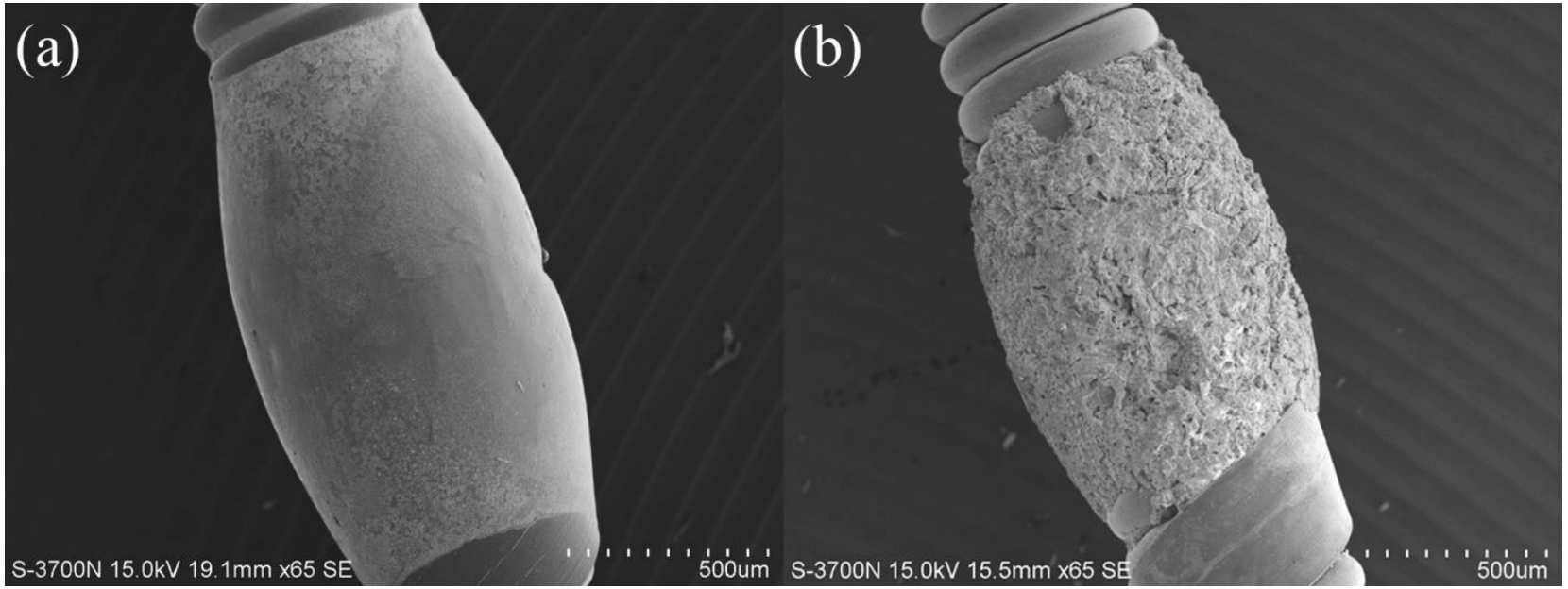
Rapport Conceptus 2004

At the six-month time point, the ball tips of some of the samples were almost completely corroded, but all of the solder bonds continued to hold together. In all cases, the outer coil remained attached to the fibered inner coil. This is an acceptable level of solder corrosion, because it did not result in the loss of mechanical integrity. No other components showed signs of corrosion.

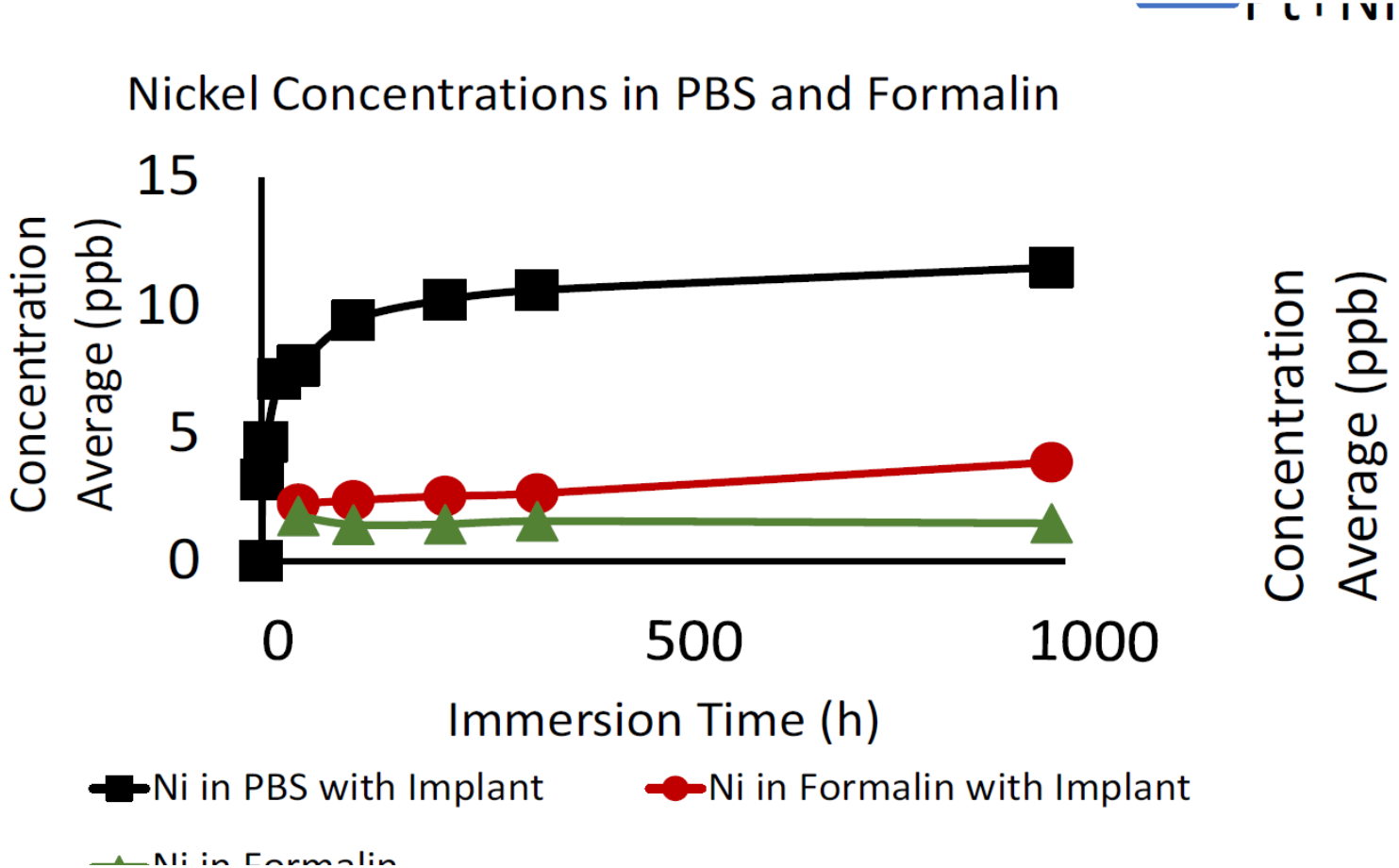
0.0 DEVIATIONS

10.1 In the Scope section of the protocol, one goal of the study was described as "determine minimum time needed for structural disintegration /detachment in a simulated body environment." This goal was not achieved, since none

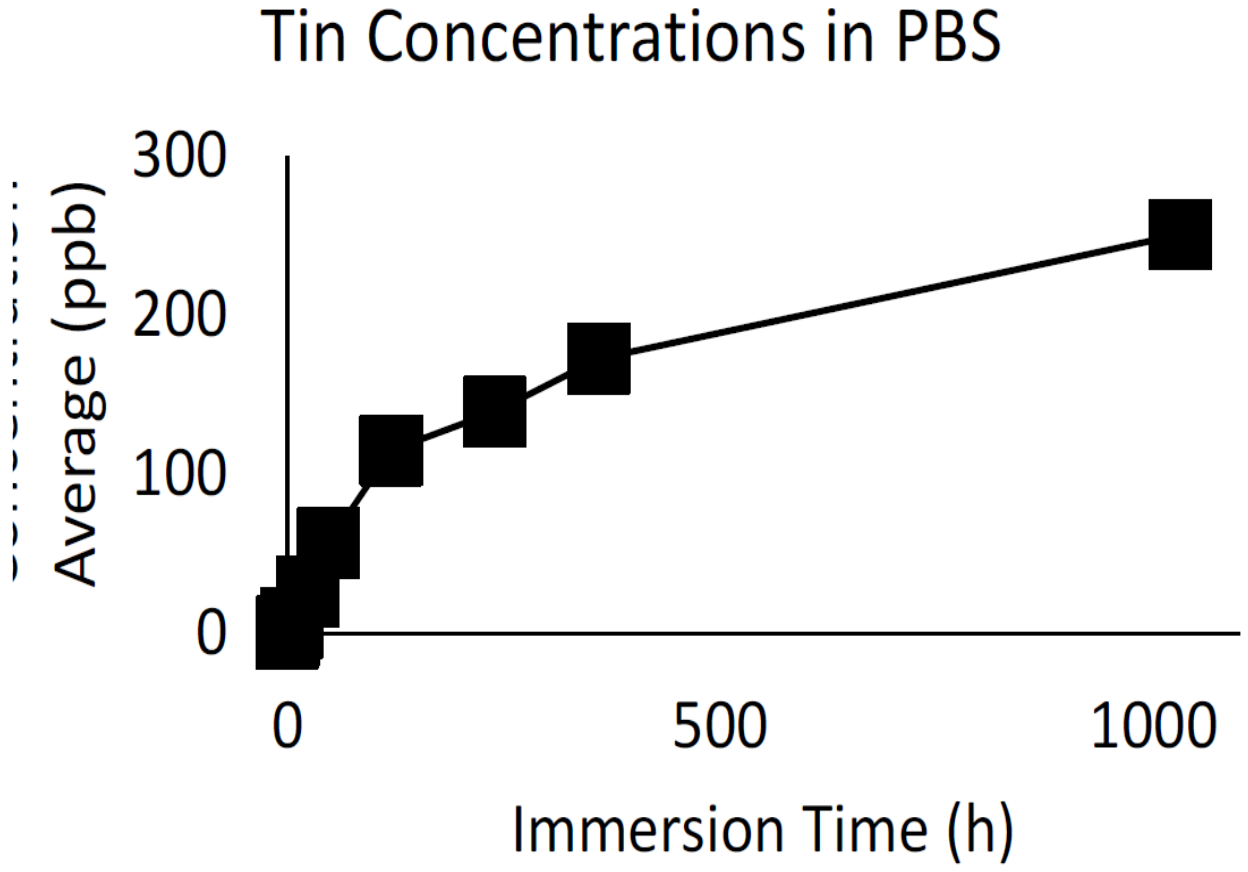
2019 Travail du Pr Gilbert Charleston Etude relarguage d'ions avant et après 12 jours d'immersion dans solution PBS



Etude relargage ions par Gilbert Charleston 2019



Travail Gilbert 2019



1/Erreur d’appréciation dans les études précliniques de relarguage d’étain par la soudure

- Confusion entre dose quotidienne et dose maximum tolérée
- Pas de prise en compte de la faible absorption digestive
- Pas d’étude MEB-EDX chez l’animal mais aussi l’étude préclinique avant obtention de l’AMM: Ces études auraient pu montrer la la dissémination de l’étain
- Objectif principal : l’obtention d’une fibrose de la trompe sans souci de la persistance possible d’une majoration de la corrosion les années qui suivent

2/ La possibilité d'une transformation de l'étain inorganique en organoétain

- Les travaux d'Agnatopulos en 1993
- Le rôle du biotope infectieux dans les ecosystèmes (travaux de David Amouroux)
- Le rôle possible d'un mécanisme de nanotoxicité

Article Anagnostopoulos

Toxicological and Environmental Chemistry, Vol. 39, pp. 207–215
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METHYLATION OF Sn°, Pb° AND Sn(II), Pb(II) INORGANIC SALTS BY CARBONIUM ION DONORS

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(Received in final form 2 July 1993)

Methylation experiments of Sn°, Pb° and inorganic salts of Sn(II), Pb(II) by carbonium ion (CH_3^+) donors have

Article Agnastopulos

Table 3 Products $(CH_3)_nM^{(4-n)+}$ (n = 2, 3) and (M = Sn, Pb) using as methyldonor NTMG in reactions with Sn and Pb sources[a]

Metal Source (4 mmole)	*$(CH_3)_3M^+$ µg*	*$(CH_3)_2M^{2+}$ µg*	*% Total yield of methylproducts*
1. Sn°	15	40	$4.0 * 10^{-9}$
2. $SnCl_2$	–[b]	–	–
3. $Sn(COO)_2$	1.4	0.6	$1.6 * 10^{-4}$
4. $SnCl_4.5H_2O$	–[b]	–	–
5. Na_2SnO_3	–[b]	–	–

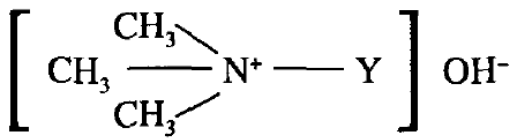
[a] 16 mmoles (=1.872 g) of NTMG were used in every case.
[b] Not detectable (also for all Pb sources).

Table 4 Products $(CH_3)_nM^{(4-n)+}$ (n = 2, 3) and (M = Sn, Pb) using as methyldonor Choline (Ch) in reactions with Sh and Pb sources[a]

Metal Source (4 mmole)	*$(CH_3)_3M^+$ µg*	*$(CH_3)_2M^{2+}$ µg*	*% Total yield of methylproducts*
1. Sn°	27	78	$8.00 * 10^{-3}$
2. $SnCl_2$	–[b]	–	–
3. $Sn(COO)_2$	3.2	1.5	$3.75 * 10^{-4}$
4. $SnCl_4.5H_2O$	–[b]	–	–

Article Agnastopulos

The methyldonors NTMG, Ch and ACh reveal structural resemblance, because all of them posses the betaine structure:



Where:

for Y = —CH_2COOH (N-trimethyl-glycine, NTMG)
Y = —CH_2CH_2OH (Choline, Ch)
Y = —$CH_2CH_2OCOCH_3$ (Acetylcholine, ACh)

For all the above CH_3^+ -donors, the methylation mechanism should be the same, because NTMG is known that is a CH_3^+ source in oxidative addition reactions[7-9].

Substrates for successful methylation by betaines were Sn° and $Sn(COO)_2$ eventually (Tables 2, 3 and 4), according to the following mechanism:

Article Agnastopoulos

CONCLUSIONS

In the methylation experiments of Sn and Pb (in 0 and +2 oxidation states) by naturally occurring CH_3^+ donors it was confirmed that tin was methylated to a much greater extent than lead.

The reason for that is, as mentioned above, the extremely low stability of monomethyl-lead derivatives in aqueous solution, the existence of which is an essential prerequisite for redistribution reactions (Dp) to occur. In the first phase we have oxidative addition of CH_3^+, in the corresponding substrate and then, a disproportionation reaction, during which, more methylated species are formed.

It was also concluded that the molar ratio: methyl-donor/metal is a factor of crucial importance, for the methylation yield, at least for tin (optimum value: 4/1). For elucidation of the role played by this factor, further work is necessary.

It is important to point out here the environmental significance of theses results. Although the yields of methyl-products are generally low, one should consider, that environmental methylation is a continuous process, hence yields of methyl-products may be higher, if favourable conditions for that are prevailing for a long time in a given ecosystem containing metal species and methyl-donors.

The betaine like structure of Choline and Acetylcholine render them proximate methyldonors to metal species occurring in several parts of CNS.

De l’étain inorganique à l’organoétain

Chemosphere 208 (2018) 871–879

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Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

Methylation and dealkykation of tin compounds by sulfate- and nitrate-reducing bacteria

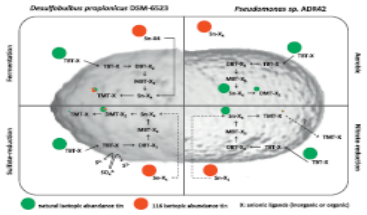
Romain Bridou, Pablo Rodriguez-Gonzalez [1], Teodor Stoichev [2], David Amouroux*, Mathilde Monperrus, Patricia Navarro [3], Emmanuel Tessier, Rémy Guyoneaud**

CNRS / Univ. Pau & Pays Adour, Institut des Sciences Analytiques et de Physico-chimie pour L'Environnement et les Matériaux, UMR5254, 64000, Pau, France

HIGHLIGHTS

- Microbial transformations of tin compounds under anoxic/oxic conditions were evaluated.
- *Pseudomonas* degrades TBT at higher rates under oxic than anoxic conditions.
- *Desulfobulbus* degrades TBT more under fermentative than sulfate-reducing conditions.
- Methylation of Sn species and degradation of TBT depend on availability and reactivity.

GRAPHICAL ABSTRACT



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ABSTRACT

In this study, axenic cultures of sulfate-reducing (SRB) and nitrate-reducing (NRB) bacteria were examined for their ability to methylate inorganic tin and to methylate or dealkylate butyltin compounds. Environmentally relevant concentrations of natural abundance tributyltin (TBT) and ^{116}Sn-enriched inorganic tin were added to bacterial cultures to identify bacterial-mediated methylation and dealkylation reactions. The results show that none of the *Desulfovibrio* strains tested was able to induce any

L'affaire du Stalinon

L'affaire du Stalinon et ses conséquences réglementaires, 1954-1959

« Sécurité sanitaire » et innovation thérapeutique en France il y a 50 ans

Le Stalinon, médicament à base d'étain contre la furonculose, ayant obtenu son visa en 1953 *pour être commercialisé, provoqua l'année suivante une catastrophe sanitaire.* Le scandale fut à l'origine de la modification des règles d'autorisation et de contrôle des médicaments par l'ordonnance du 4 février 1959, établissant le « visa nouvelle législation », une étape significative dans l'histoire de la législation pharmaceutique en France.

par **Christian Bonah** ✔

Figure 1: Stalinon tablets. The nominal active ingredients were diiododiethyltin and Vitamin F (essential fatty acids), but it was the triethyltin contaminant that proved lethal.

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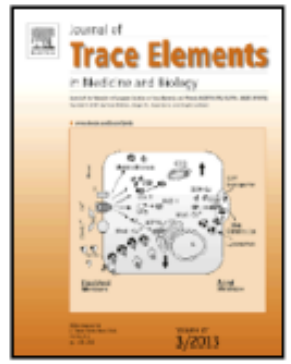
Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb



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 [a], E. Roux [a], A. Auroux [b], A.M. Trunfio-Sfarghiu [c], C. Lauro-Colleaux [d], E. Watkin [e], G. Sournies [f], M. Vincent [a, *]

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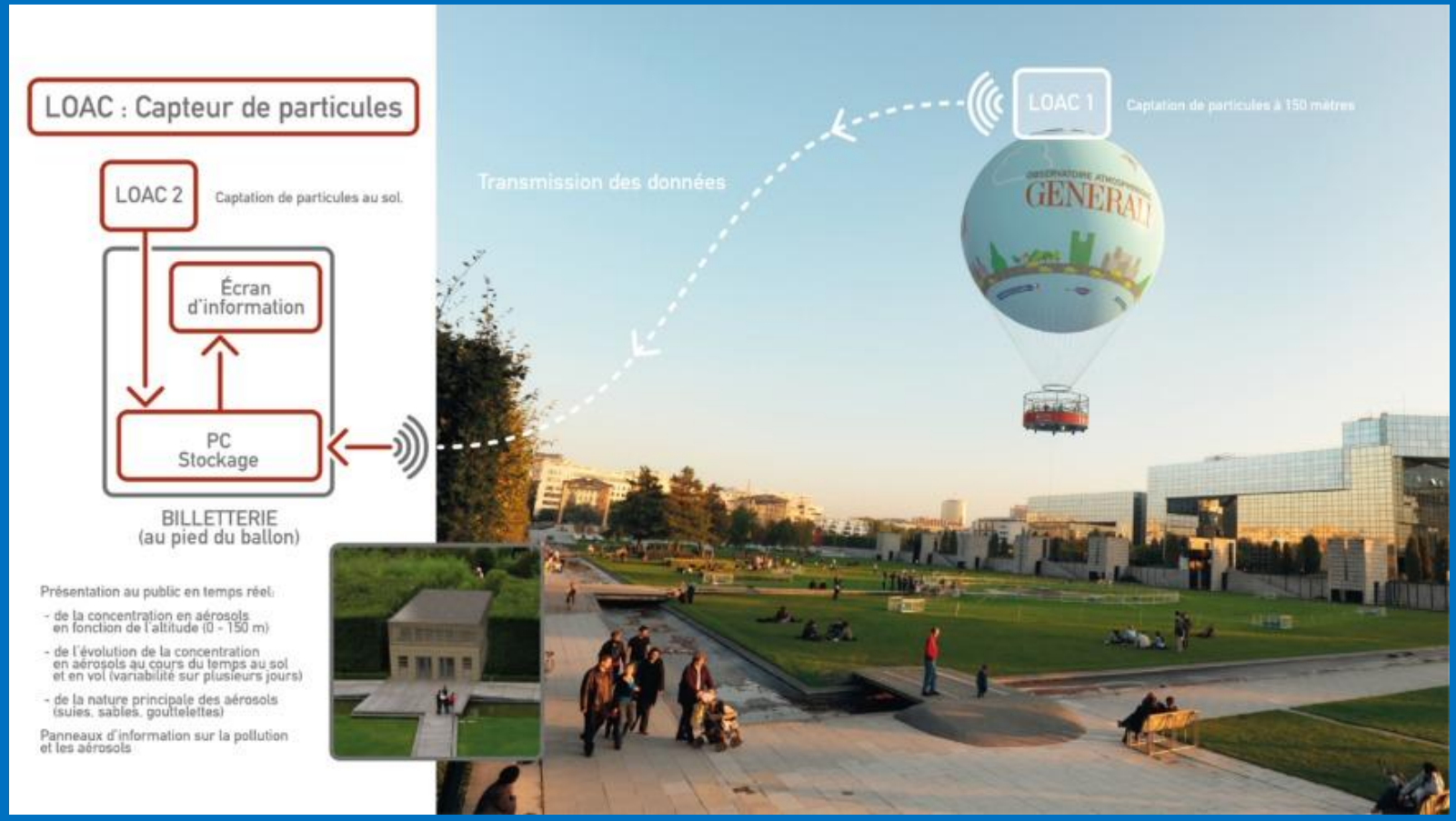
[f] *Natecia Service de gynécologie, 28 Avenue Rockfeller, 69008, Lyon, France*

Pollution minérale et mortalité dans les villes

- Impact à court terme des PM10 sur la mortalité dans 17 villes Françaises (BEH Janvier 2015 : 14-20) : PSAS, données CépiDc-Inserm, données AASQA
- Excès de mortalité non accidentelle et cardiovasculaire pour une augmentation de 10 µg/m3 des PM10 le jour même et jusqu'à 5 jours précédents.
- Excès risque relatif: 0, 51% (IC 95% :0,08-0,94) pour la mortalité non accidentelle.
- Mortalité en moyenne journalière :
  - Lyon (1031 266 habitants de la métropole): 18,1 dont 67% de plus de 74 ans en mortalité non accidentelle Soit 1 décès supplémentaire sur environ 11j jours de pollution de plus de 10 microgramme /m3: 1 décès prématuré sur 200 décès
  - Paris (6630370) : 103,6 dont 63% de plus de 74 ans

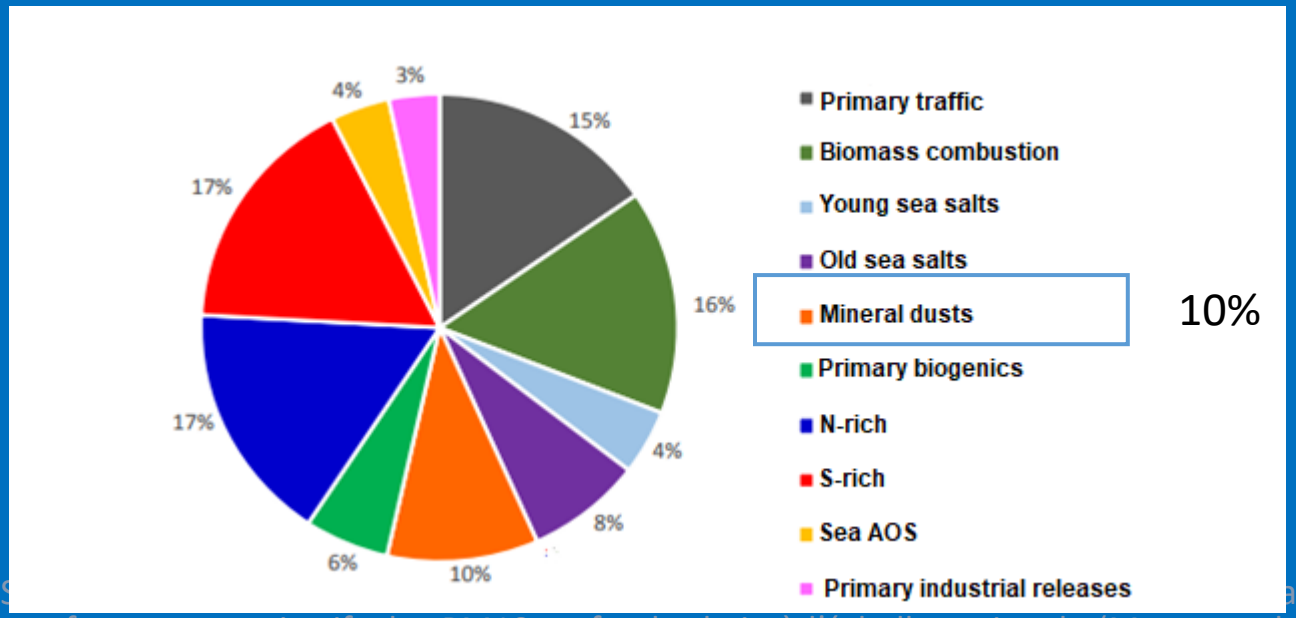
Capteurs massiques de particules

Capteurs laser : nombre et taille LIDAR et analyseur d'Ozone



French Central Laboratory for air quality monitoring data: only 10% of mineral particles ?

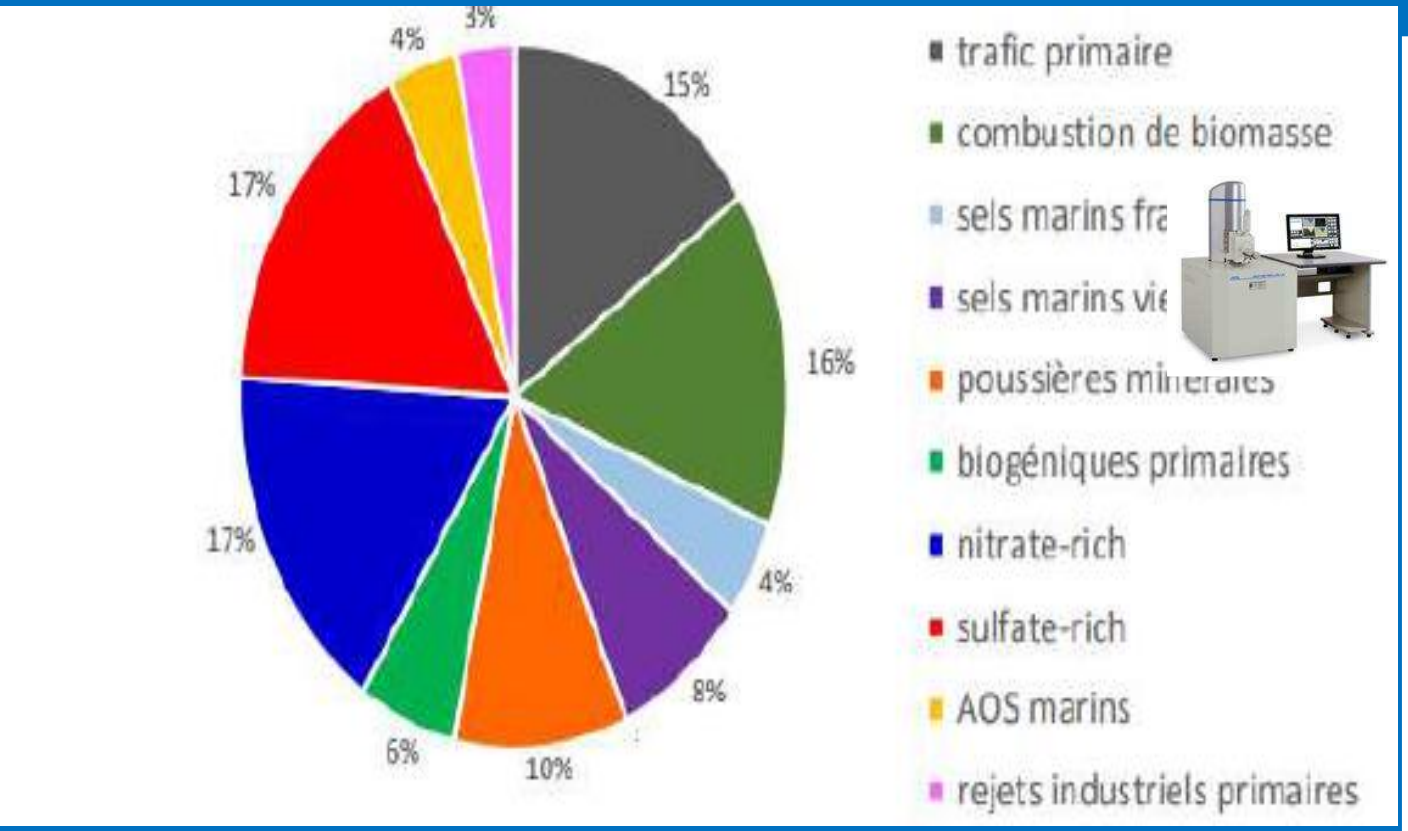
Ammoniac, ammonium, sulfate, nitrate, chlore, organic matter,elementary carbon, organic carbon, black carbon ….

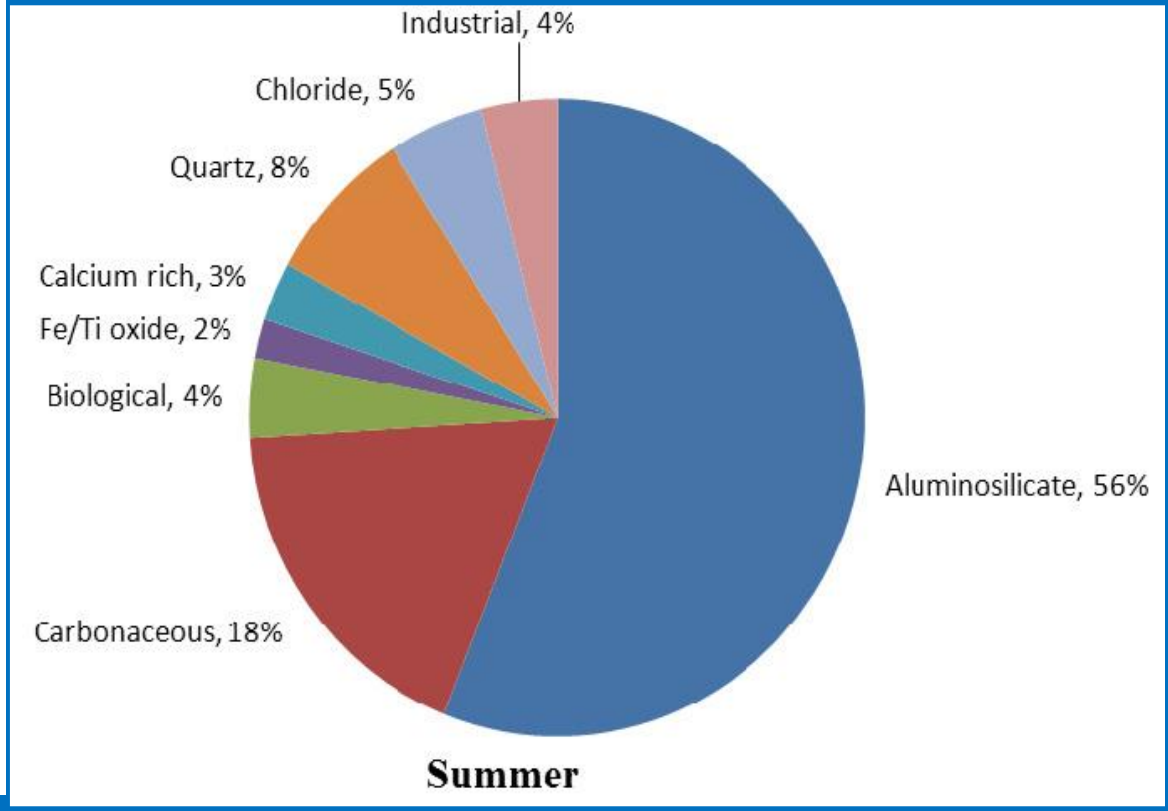


Source : LCS … annuelles moyennes des principaux facteurs constitutifs des PM10 en fond urbain à l'échelle nationale (Moyenne des résultats obtenus par analyse PMF harmonisée sur 10 sites de fond urbain du projet SOURCES).

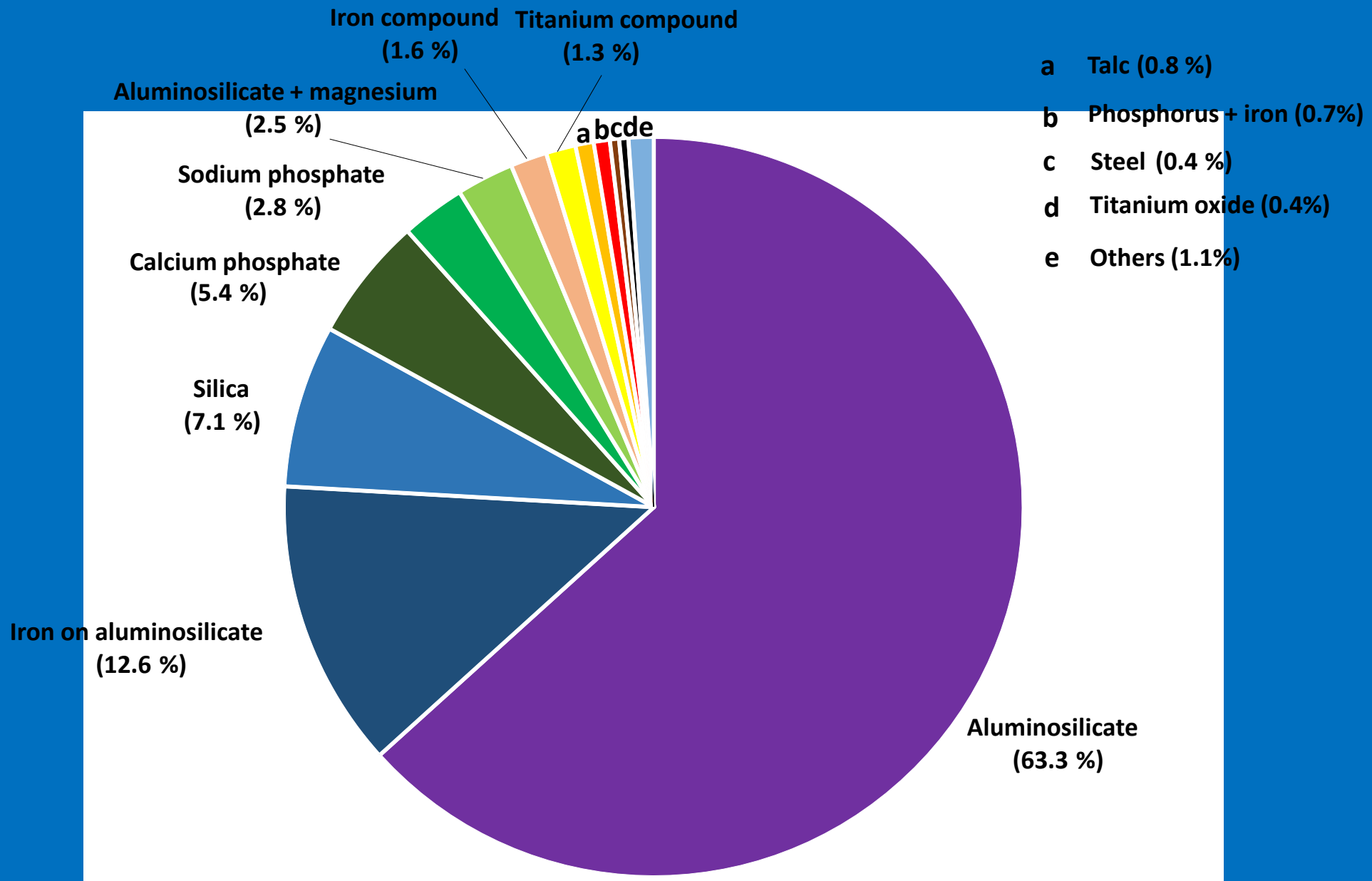
Intérêt de la Microscopie électronique à balayage avec EDX

Comparaison données air atmo (LCSQA et INERIS 2016 et résultats analyses MEB (Agra India)



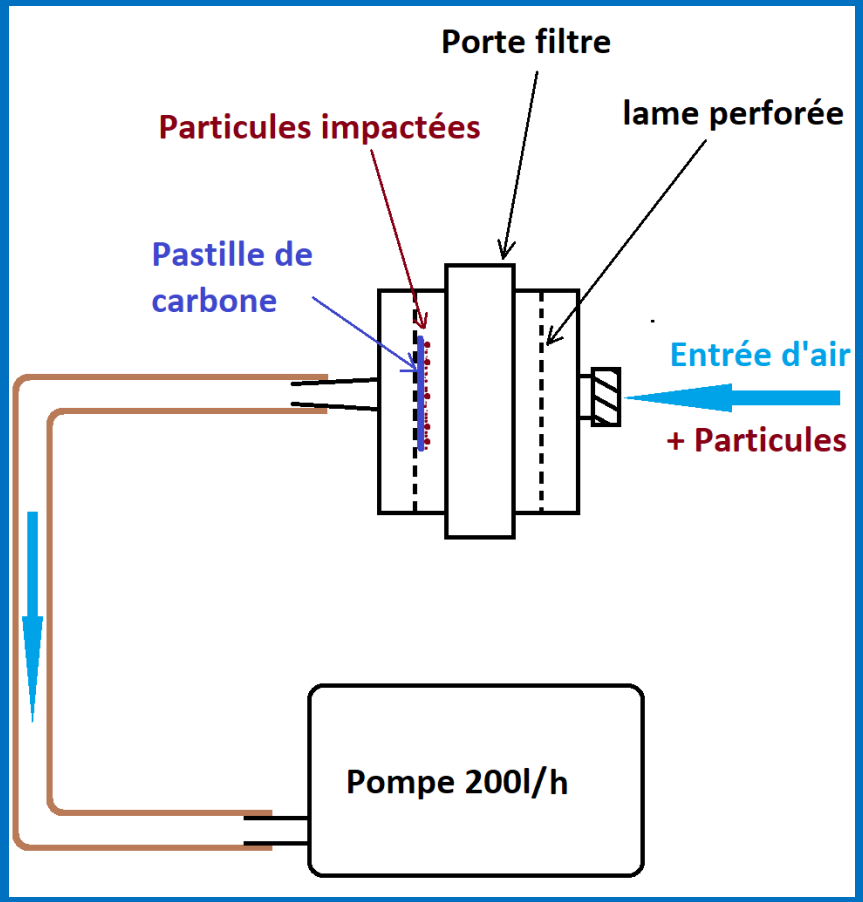


In situ SEM of 40 blocks of IML pulmonary parenchyma (2754 particles analyzed)



Authors	Date	Location	Methods	Results	Other
Bernabé *et al.* *Atmosphere Environement*	2005	Huelva, Spain	Polarized microscopy, SEM-EDS on graphite and glass stub, X-ray diffraction. Passive recolting technique, 1 week	Quartz (25-120µm) is the major mineral phase Metalic particles not registred Lot of silicates with metalic components	Interested only on mineral particles, not other non-biological particles
Campos *et al.* *Microscopy Sciences Technol*	2010	Colina, Mexico	SEM-EDX on glass fiber filter Sampling the closer possible to the emission sources, PM10 only	Carbon-rich (29%), metalic oxids (27%), silicates (20%) Rocky origin particules >10µm excluded	Glass-fiber filter, then no quartz is found
Yue *et al.* *J Environ Sci*	2006	Shanghai, China	SEM-EDX on polycarbonate filter SXRF on nitrocellulose filter Samples : central city, industrial area and clean air suburban	Most of the particles between 0,2-0,6µm Most of them are ashes with Fe, Mn, Si or Al Mineral are from natural sources (dust, construction) with a lot of quartz	
Lu *et al.* *J environ Sci*	2006	Beijing, China	SEM-EDX on polycarbonate filters, PM10 only	Clay (30,1%) > Silica (13,5%) > Compounds (11,9%) > Cabon particles (11,3%) > Calcite (10,9%) > Calcite/GypseFeldspar/dolomite 10,9/9,27,5/3,8%)	
Conner *et al.* *Atmosph Envrion*	2001	Baltimore, USA	24h indoor and outdoor samples in an retirement center SEM-EDX on polycarbonate filter	Little in mass for indoor samples, Al-Zr-Cl from personnal spray. Anywhere : Al-, Cr-, Ni- and V-rich from industry Outdoor : most ofparticles are Ca-rich	Don't look for SiO
Genga *et al.* *Chemister Centr Journal*	2012	Central Italy	3 samples : thermic station + construction, city parc, rural area. PM10 only.	There is a lot of aluminosilicates (45,1%), calcium-rich particles (21,7%), metal (7,5%), soot (7,2%) and biological carbon (4,8%).	Risk for Health from size and form, not from composition
Margiotta *et al.* *Nat Hazards Earth Syst Sci*	2015	Basilicata, Italy	Sampling on polycarbonate filter by low-volume gravimetric sampler. Analyze by SEM-EDX. PM1 only.	Soot > aluminosilicates > silica > S- rich > biogenic > carbonates > metal particles. SiAl/SiO is between 1/9 and 1/3	Soot is the main anthropogenic component. SiO and SiAl- are provided by saharan winds.
Pachauri *et al.* *Aerosol and air quality research*	2013	Agra, India	Sampling during 24h at 1,2m^3/min on quartz fiber filters.	Average mass : 306µg/m^3 Aluminosilicates (46-56%) > Carbonaceous (18-33%) > Quartz (7-8%) > Industrial (4%) > Biological (3-4%)	High level of mass in winter due to different souces of emission and to meteorological conditions

Le projet Minapath: apport du MEB et prélèvement sur disque carbone



Conclusions

- Pour comprendre les relations santé et pollution il faut mieux connaitre la taille et la nature chimique des particules auxquelles nous sommes exposés
- Complémentarité de l'approche épidémiologique (Top Down) et anatomoclinique (Bottom Up)
- Sujet sensible et potentiellement politiquement incorrect
- Intérêt Questionnaire et MEB-EDX dans une nouvelle approche disruptive des pathologies chroniques non infectieuses inflammatoires , fibrosantes et cancéreuse