Preliminary Opinion on the safety of breast implants in relation to anaplastic large cell lymphoma
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Scientific Committee on Health, Environment and Emerging Risks
(SCHEER)
DG Health and Food Safety
European Commission

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(SCHEER)

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Mandate
Safety of breast implants in relation to BIA-ALCL

1. To describe specific clinical indications and uses of (S)BI
2. To describe what is BIA-ALCL (diagnostic criteria, treatment, prognosis)
3. What is the knowledge on incidence/occurrence
4. What is the state on characterisation and classification of breast implants shells
5. Evaluate if there is a causal relationship between (S)BI and BIA-ALCL including what are the pathogenic mechanisms
6. What factors determine risk for BIA-ALCL
7. What are alternatives for breast implants
8. What are the needs for further research and best ways for collecting missing data on SBI and ALCL

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Methodology

- Weight of Evidence according to Scientific Committee rules
- Literature searches September 1st 2016 – August 31st 2019, and September 1st 2019 – April 30th 2020.
- Literature provided by WG members

- Breast AND implant OR implants OR implantation OR lymphoma
- Breast AND lymphoma AND implant
- Breast AND lymphoma AND prostheses
- Breast AND lymphoma AND endoprostheses
- Breast AND anaplastic large cell lymphoma AND implant
- Breast AND anaplastic large cell lymphoma AND PIP silicone breast implants
- Breast AND ALCL AND implant
- Breast AND BIA-ALCL AND implant
- Breast AND textured implant
- Breast AND smooth implant

In total 1298 hits were found in the literature search.
After excluding irrelevant papers and duplicates a total of 605 papers remained for evaluation in the Opinion.

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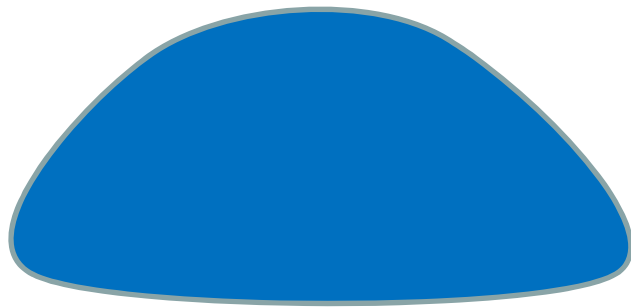
Introduction
Use of breast implants

- Reconstructive (ca. 25%)
  - Mastectomy (amputation), after breast cancer, preventive in BRCA gene mutations.
  - Breast anomalies (asymmetric, undeveloped breasts)
  - Accidental or iatrogenic trauma after peadiatric surgery or radiotherapy
- Aesthetic (ca. 75%)
  - Change in body image by increasing breast volume or improving shape
- Tissue expanders
  - Temporary implants before breast implant or autologous tissue transplant

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Introduction
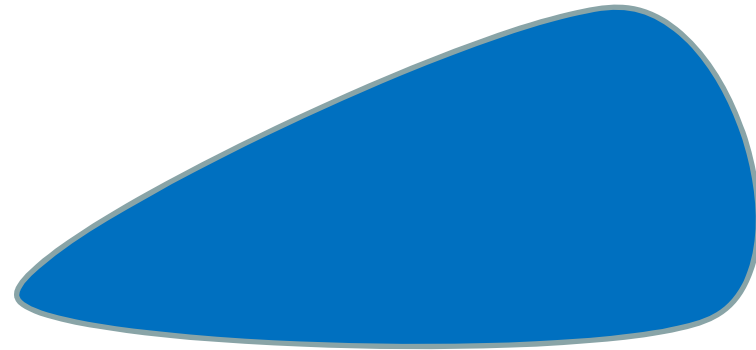## Characteristics of breast implants

- Fill
  - Mainly silicones and/or saline, (less common methylcellulose, polyvinylpyrrolidone (PVP), soybean oil (discarded), or a combination of these)

- Shell surface
  - Envelope, 3-5 layers of silicone shell
  - Surface texture or non (smooth) textured

- 3-Dimensional shape
  - Round (lenticular shape) or anatomical (teardrop shape)

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Breast implant shapes

Round (lenticular) shape

Anatomical (teardrop) shape

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Introduction
Alternatives to breast implants

For reconstructive use of breast implants

– Breast conserving surgery

– Autologous tissue

- Flap operation (whole tissue with or without blood vessels, depending on site availability and surgeon experience)
- Autologous fat transplantation (may need multiple procedures, outcome less certain in view of breast size and shape)

– Combination of implant and autologous tissue

For aesthetic use of breast implants

- Autologous fat transplantation

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Introduction
ALCL

- ALCL (anaplastic large cell lymphoma)
  - Non-Hodgkin lymphoma
    - Incidence Europe estimated at 0.8 – 11.2 cases per 100,000
  - T cell origin
  - ALCL very rare class non-Hodgkin lymphoma
    - Approximately 10 – 15% of the NHL
    - Anaplastic Lymphoma Kinase (ALK) pos or neg
    - Cutaneous or in breast (BIA-ALCL) always ALK-negative

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Introduction
BIA-ALCL

- Uncommon occurrence adjacent to breast implant
- Recognised as provisional entity by WHO (2016)
- Characterized by primary capsular fluid accumulation (seroma) and/or solid mass or combination thereof
- Median time of occurrence 10 years after implantation (but also seen a few to >20 years)
- Excellent prognosis (when early diagnosed and treated)
- Diagnosis by cytopathology in aspirate of 10-50 mL (+ immunocytochemistry, and if possible flow cytometry, molecular analyses). CD30 presence important.
- Histopathology for solid tumor mass

Introduction
Treatment and prognosis

- Complete surgical resection
  - Removal implant with total capsulectomy and any mass with negative margins of healthy tissue
  - No need for further therapy
- Lymph node resection when enlarged
- Additional therapy when needed
  - Chemotherapy (CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone ± etoposide)
  - Immunotherapy with brentuximab vedotin (anti CD30 antibody drug conjugate)
  - Radiotherapy
- Prognosis favourable but deaths have occurred

Assessment Epidemiology

- Increase in numbers reported worldwide
  - Raised awareness
  - Specific diagnostic criteria (cyto/histopathology)
  - Improved diagnostic tools

- Major problems
  - Denominator not known
  - Estimation >35 million women with BI
  - 2016 ca. 1.5 million implantations
  - 2018 ca. 1.8 million implantations
  - Knowledge on subtype of implant used lacking

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Assessment Epidemiology

Ref	ALCL cases	BI	Controls	BI	Odds Ratio	Number at risk
De Jong 2008	11	5	35	1	18.2	1- 3 per 100.000
Vase 2013	0	19885	-	-	-	
Brody 2015	173					
Doren 2017	100					1/30000
McGuire 2017 (2019)	4 (8)	31985				1/2207
De Boer 2018	43	32	146	1	421.8	1/6920
Cordeiro 2020	10	3546				1/355
Loch-Wilkinson 2020	104	4 brands				1/2596 1/3194 1/6024 1/36730
NL						1/2969
Australia						1/2976

Estimation for lifetime incidence varies from 1.65 cases to 35 cases per 100,000 women with breast implants.

BIA-ALCL Cases worldwide

	BIA-ALCL Cases	Filler[a]		Surface[b]	
		Silicone	Saline	Textured	Smooth
EU Member and assiociated States (July 2020) CH, FR, BE, DK, IT, DE, NL, SE, FI, AT, PT, ES, IE, UK					
TOTAL	**345**	**288**	**4**	**279**	
Rest of the world (November 2018) Argentina, Brazil, Canada, Chili, China, Colombia, Egypt, Japan, Mexico, New Zealand, Russia, Singapore, South Africa, South Korea, Thailand					
TOTAL	**68**				
FDA (worldwide reported, January 2020)	**733**			**496**	**1**
FDA US (January 2020)	**384**				
TGA (July 2020)	**107**			**63+22**	
Health Canada (December 2019)	**106**				
Reported to scientific societies					
TOTAL	**433**				

When we look at number of identified surfaces in BIA-ALCL cases, 860 were identified as being textured, and only 1 case of BIA-ALCL could be identified for a smooth breast implant.

More patients with smooth implants were identified but these had either a history of textured implants or the history could not be confirmed.

Breast implant surface textures
(Based on Jones et al., 2018)
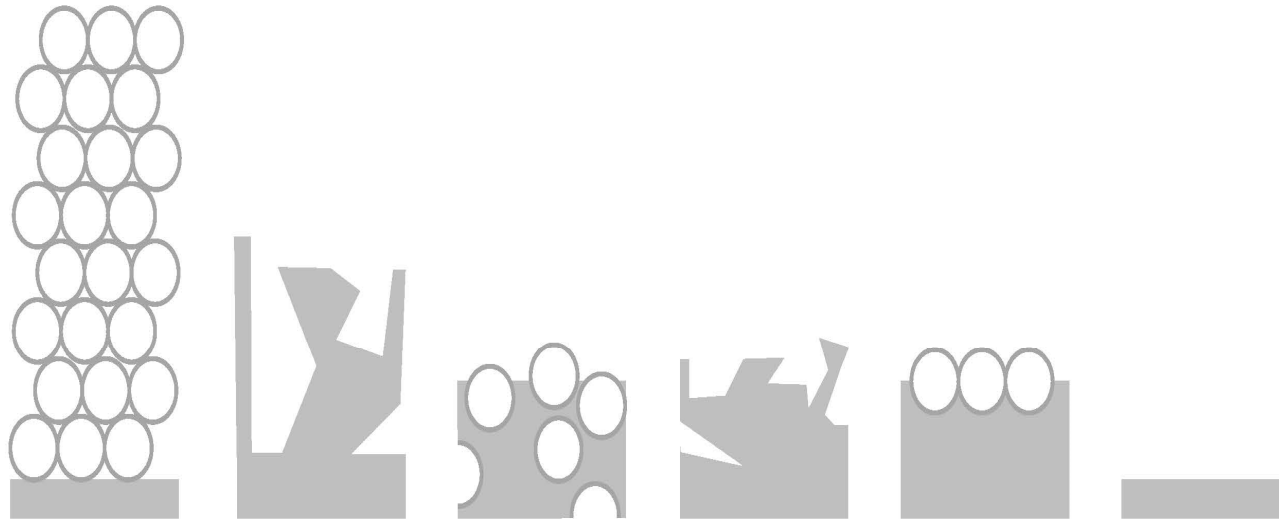
Manufacturing Process	Polyurethane foam	Salt loss	Vulcanisation	Salt loss	Imprinting	Smooth/Nano
Surface Area	High	Intermediate	Intermediate	Low	Low	Minimal
Roughness	High	Intermediate	Low	Low	Low	Minimal

For characterisation the *ISO 14607:2018* standard is the most widely accepted method and divides breast implants into Smooth (<10µm), Micro (10 - 50µm) or Macro (>50µm) textured surfaces based on the implant's average surface roughness**.**

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Moderating factors

1. Genetic alterations
2. Bacterial contamination/chronic inflammation
3. Shell shedding microparticles
4. Shell surface characteristics
5. Implant associated reactive compounds

Major issue seems to be induction of chronic inflammation by T cells that obtain lymphoproliferative properties resulting in ALCL.

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Answers to Mandate

1. Specific clinical use implants: reconstructive or aesthetic
2. BIA-ALCL: T cell lymphoma near BI as seroma and/or solid mass
3. Incidence BIA-ALCL: low but at risk ca 1/3000
4. Shell: characterisation according to ISO 14607:2018
5. Causal relationship: moderate evidence with textured implant (lack of knowledge on pathogenesis)
6. Factors: Genetic alterations, Bacterial contamination / chronic inflammation, Shell shedding microparticles, Shell surface characteristics, Implant associated reactive compounds
7. Alternatives: autologous tissue or fat transfer
8. Research needs/recommendations

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Recommendations 1

- ## REGISTRIES:
  - Breast implant registries should be established and be mandatory, and include a minimum harmonised dataset of device characteristics, which is globally uniform, in order to optimise global post-market surveillance of breast implants. This should include the UDI (Unique Device Identification) or reference/serial number to provide structured denominator data for risk calculations.
  - Funding of such registries should be independent from industry, and it is recommended that General Data Protection Regulation should provide a means to allow data connection between data sources.
  - NOTE: A number of registries has been established already (ICOBRA= International Collaboration of Breast Registry Activities)

- ## EPIDEMIOLOGY:
  - The incidence of BIA-ALCL should be monitored with systematic data collection in registries (e.g. for breast surgery or pathology diagnosis) in preference to ad hoc case reporting and case findings.

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Recommendations 2

- IMPLANT SURFACE:
  - A universal grading system for implant surfaces and surface characterisation should be further explored. Research should be conducted to identify surface roughness characteristics, which contribute to BIA-ALCL development. This should include research on the role of surface roughness in relation to particle shedding and surface characterisation related to chemical moieties for their carcinogenic potential. Especially implants exposed to an in vivo environment (i.e. explants) should be evaluated for surface characteristics.
  - The role of the aforementioned implant qualities in inducing chronic inflammation should be investigated including possible roles of particle shedding, bacterial contamination, and chemical moieties on the surface of breast implants.

- BIA-ALCL:
  - Further research should be conducted into the aetiology of BIA-ALCL regarding the potential contribution of genetic predisposition.

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Acknowledgement WG members

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Public Consultation

Six weeks consultation period

October 26th – December 7th

https://ec.europa.eu/health/scientific_committees/open_con
sultation_en

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