Scientific Committee on

Health Environmental and Emerging Risks

SCHEER

SCIENTIFIC ADVICE ON

The state of scientific knowledge regarding a possible connection between breast implants and anaplastic large cell lymphoma

The SCHEER adopted this final Scientific Advice

by written procedure on 19 October 2017

ABSTRACT

The SCHEER was requested by the European Commission to provide an advice on the state of scientific knowledge regarding a possible association between breast implants and anaplastic large cell lymphoma (ALCL) and to determine whether sufficient scientific information was available for conducting a full risk assessment on a possible association between breast implants and ALCL.

The scientific literature search has retrieved mainly case reports and case series and, in addition, a few epidemiological studies. The available information suggests that breast implants may be associated with an increased risk for ALCL.

Although the very low incidence of ALCL and the methodological limitations of the available information/studies do not currently allow for a robust risk assessment, the SCHEER recommends that a more in-depth evaluation be conducted on the possible association of breast implants with the development of ALCL.

Keywords: breast implants, anaplastic large cell lymphoma, cancer, PIP breast implants

Scientific Advice to be cited as:

SCHEER (Scientific Committee on Health, Environmental and Emerging Risks) The state of scientific knowledge regarding a possible connection between breast implants and anaplastic large cell lymphoma, 19 October 2017

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In addition, the Commission relies upon the work of other Union bodies, such as the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHEER

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http://ec.europa.eu/health/scientific_committees/scheer/members_committee_en

This Scientific Advice has been subject to a commenting period of ten weeks after its initial publication (from 7 April until 15 June 2017). Comments received during this time were considered by the SCHEER. Most comments were already submitted during the call for information before publication of the preliminary Advice.

For this Advice, comments received resulted in the following changes:

The submitted comments did not change the Advice. However, based on the new literature published in 2017, during the commenting period, the Advice was modified and now recommends a more in depth evaluation on the possible association between breast implants and ALCL when more information becomes available.

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1 MANDATE FROM THE EU COMMISSION SERVICES

1.1 BACKGROUND

A. The safety of the PIP silicone breast implants

Over many years, the PIP manufacturer fraudulently made use of industrial silicone instead of the approved medical grade silicone in many of the breast implants produced. Investigations were triggered by an unusually high short-term breast implant rupture rate. The product was thereafter withdrawn from the EU market.

Following this fraud, SCHENIR was requested to provide two scientific Opinions on the safety of the PIP silicone breast implants. The first one, a rapid scientific Opinion, was adopted by SCENIHR on 1 February 2012[1]. This Opinion was updated by a second one, adopted on 12 May 2014[2].

Given the importance of the matter, the Commission relevant services, DG GROW and DG SANTE, are committed to monitoring the publication of new and valid scientific information and facilitating possible update of the 2014 Opinion on the PIP silicone breast implants in the light of such new scientific data.

Besides its regular consultation of the National Competent Authorities, DG GROW and DG SANTE recognise the need of a formal scientific evaluation of the current availability of the said information.

This need is also highlighted in the remarks of the European Ombudsman's Decision in case 174/2015/FOR on the Commission's alleged failure to investigate conflicts of interests relating to the adoption of a report on the safety of removing PIP breast implants: *"The Commission should continue to evaluate new scientific data relating to the safety of PIP implants."*[3]

The investigation into the availability of new scientific data that would warrant an eventual update of the May 2014 Opinion on the safety of the PIP breast implants should take into account all the necessary fields and especially those covered by the previous Opinion, such as the physiochemical properties of PIP implants, their toxicology, the clinical impact and recommendations.

B. State of scientific knowledge regarding a possible association between breast implants in general and anaplastic large cell lymphoma

Anaplastic large cell lymphoma (ALCL) is a very rare type of lymphoma. ALCL is not a cancer of the breast tissue and the prognosis of the disease is generally favourable. A possible association between breast implants and ALCL is under scrutiny in the European Union and at international level by regulators and scientists.

According to an estimation[4] of the US-Food Drug Administration, in 2011 there were between 100-250 known cases of ALCL in women with breast implants out of an estimated number of 5 to 10 million women who have received breast implants worldwide. The information to date suggests that women with breast implants may have a very low but increased risk of developing ALCL, while the rarity of the disease makes it difficult to

[1] http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_034.pdf
[2] http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_043.pdf
[3] http://www.ombudsman.europa.eu/cases/decision.faces/en/61195/html.bookmark
[4] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm

establish a definite causal relationship (Center for Devices and Radiological Health U.S. Food and Drug Administration).[5]

Given that this suspected association between breast implants and ALCL appears to be an emerging risk, the SCHEER should determine whether there is enough scientific information available to allow for a full risk assessment of the matter. The existence of information on a specific association with PIP silicone breast implants should also be investigated.

1.2 MEANS OF ACHIEVING THE GOALS

In order to collect as much relevant data as possible on the two issues described above, two types of activities are envisaged:

1) A public call for data open to all stakeholders, of a duration sufficient to ensure that any information pertaining to the two abovementioned topics may be submitted.

2) A review of the published scientific literature and of any other source of relevant data available on the two topics.

The relevant scientific information should be retained and, based on this, the SCHEER will reply to the questions described in the terms of reference. Any rejection of acquired information should be justified. The Committee will decide if both topics may be addressed by one call for data and one scientific literature review at the same time or if separate processes need to be organised.

1.3 TERMS OF REFERENCE

Following the assessment of the availability of the scientific information the SCHEER should:

1) Indicate whether there is sufficient new scientific information to warrant an update of the May 2014 SCENIHR Opinion on the safety of PIP breast implants.

2) Provide an Advice on the state of scientific knowledge regarding a possible association between breast implants and anaplastic large cell lymphoma.

[5] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239996.htm

2. CONCLUSIONS

Following the request received from the European Commission, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) performed a literature search and launched a call for information to gather new scientific information related to a possible association between breast implants and anaplastic large cell lymphoma (ALCL).

The scientific information retrieved from the literature search and the call for data shows that over the past years a body of medical literature on a possible association between breast implants and ALCL has been published. However, it consists mainly of case reports, case series and few observational epidemiologic studies.

Based on the evaluation of this scientific information, the SCHEER acknowledges that there have been new documented cases of ALCL in women with breast implants, worldwide, suggesting a breast implant – ALCL association.

The SCHEER concludes that there is currently insufficient scientific information available to establish a methodologically robust risk assessment to investigate a possible association of breast implants with ALCL development.

It is highlighted that there is an emerging need for prospective studies in order to be able to perform a more robust evaluation of the possible association between breast implants and ALCL.

Moreover, the lack of registries, throughout the world, of women with breast implants is a major challenge for providing evidence-based conclusions on the potential association between breast implants and ALCL. Such registers, and their systematic evaluations, are urgently needed.

The available information that has already been collected, together with the most recent 2017 publications, suggests that there may be such an association. Therefore, the SCHEER recommends a more in-depth evaluation on the possible association between breast implants and ALCL.

3. MINORITY OPINION

None.

4. INTRODUCTION

This document provides an inventory of the scientific information available regarding a possible association between breast implants and ALCL.

This Scientific Advice answers question two of the "Terms of Reference" of the mandate.

The evaluation of new scientific information on the safety of PIP breast implants is presented in a separate document.

4.1 Scientific background

Anaplastic Large Cell Lymphoma

Lymphoma is a type of cancer of the immune system. The two main forms of lymphoma are Hodgkin lymphoma and non-Hodgkin lymphoma. Anaplastic Large Cell Lymphoma (ALCL, ICD-10: C84.6/7) is a very rare type of non-Hodgkin lymphoma and one of the subtypes of T-cell lymphoma. According to GLOBOCAN 2012 (International Agency for Research on Cancer) the age-standardised annual incidence of non-Hodgkin lymphomas in Europe is estimated to be <6.8 cases per 100.000 individuals (Boffetta, 2011), with rates varying from 0.8 to 11.2 cases per 100.000;[6] ALCL comprises about 1% of all non-Hodgkin lymphomas and approximately 16% of all T-cell lymphomas (Clemens *et al*., 2016). However, it should be noted that ALCL in the breast is even rarer (Altekruse *et al.*, 2010).

Anaplastic Large Cell Lymphoma and breast implants

Since 1962 breast implants have been used for reconstructive and/or aesthetic reasons. Concerns about a possible association of ALCL and breast implants arose in 1995 based on a published case report about women with polyurethane silicone foam-covered, polyurethane-coated silicone and silicone implants (Duvic *et al.*, 1995).

A possible association between breast implants and ALCL is currently being investigated in the EU and at international level by several regulatory bodies and scientists, including the US Food and Drug Administration (FDA), the French National Agency for Medicines and Health Products (ANSM) and the Australian Therapeutic Goods Administration (TGA).

The World Health Organization (WHO) has recently classified the breast implant-associated ALCL as a *provisional* entity of a noninvasive disease associated with excellent outcome (Swerdlow *et al.*, 2016).

[6] http://globocan.iarc.fr/old/summary_table_site-html.asp?selection=19260&title=Non-Hodgkin+lymphoma&sex=0&type=0&window=1&europe=4&sort=4&submit=%C2%A0Execute%C2%A0

5. DATA AND METHODOLOGY

Information regarding the availability of scientific data on a possible association between breast implants and ALCL was obtained by two independent methods: (a) literature search and (b) an open call for information. All submitted information was considered but conclusions were based exclusively on peer-reviewed scientific papers.

5.1 Literature search

The literature search was conducted to retrieve scientific literature available on ALCL. The major search terms, *breast implants and ALCL*, were used in combination with the selected additional terms listed below. Searches have been carried out using PubMed and Find-eR (a tool for searching multiple library resources in one interface which includes the European Commission Library collections, plus millions of online full-text journal articles and eBooks). The publication period covered was from 1969 until August 2016. Reference lists of review papers were also retrieved and used in order to find papers that were not found through the search procedure.

The terms used for the literature search were as following:

- Breast AND implant OR implants OR implantation OR lymphoma
- Breast AND lymphoma AND implant
- Breast AND lymphoma AND prostheses
- Breast AND lymphoma AND endoprosthes
- Breast AND anaplastic large cell lymphoma AND implant
- Breast AND anaplastic large cell lymphoma AND PIP silicone breast implants

The types of documents retrieved were:

- Case reports
- Original research papers
- Letters to the Editor
- Discussions / Commentaries
- Reviews and meta-analyses
- Book chapters
- Government funded publications.

Documents retrieved were classified according to the archiving system of PubMed (i.e., original research, review, letter to the Editor, discussion paper and commentary).

Literature search using PubMed resulted in 712 entries. Table 1 illustrates the key words used and number of entries obtained.

Table 1- Results from PubMed search

Key words including MeSH terms[7]	No of entries
Breast implants: "breast implants"[MeSH Terms] OR ("breast"[All Fields] AND "implants"[All Fields]) OR "breast implants"[All Fields] Lymphoma: "lymphoma"[MeSH Terms] OR "lymphoma"[All Fields]	170
"breast"[MeSH Terms] OR "breast"[All Fields]) AND "lymphoma"[MeSH Terms] OR "lymphoma"[All Fields])) AND implant[All Fields]	140

[7] MeSH (Medical Subject Headings) is the NLM controlled vocabulary thesaurus used for indexing articles for PubMed

(("breast"[MeSH Terms] OR "breast"[All Fields]) AND ("lymphoma"[MeSH Terms] OR "lymphoma"[All Fields])) AND ("prosthesis implantation"[MeSH Terms] OR ("prosthesis"[All Fields] AND "implantation"[All Fields]) OR "prosthesis implantation"[All Fields] OR "prosthesis"[All Fields] OR "prostheses and implants"[MeSH Terms] OR ("prostheses"[All Fields] AND "implants"[All Fields]) OR "prostheses and implants"[All Fields])	155
Breast implants AND Anaplastic large cell carcinoma	52
Breast AND anaplastic large cell lymphoma AND PIP silicone breast implants	3
((breast implants) AND lymphoma) AND risk assessment	13
((systemic anaplastic large-cell lymphoma) AND PIP) AND siloxane	1
"lymphoma"[MeSH Terms] OR "lymphoma"[All Fields]) AND (large[All Fields] AND ("cells"[MeSH Terms] OR "cells"[All Fields] OR "cell"[All Fields])) AND anaplastic[All Fields]) AND ("breast"[MeSH Terms] OR "breast"[All Fields])) AND ("Phys Perspect"[Journal] OR "pip"[All Fields])	3
((CD30+[All Fields] AND ("lymphoma, large-cell, anaplastic"[MeSH Terms] OR ("lymphoma"[All Fields] AND "large-cell"[All Fields] AND "anaplastic"[All Fields]) OR "anaplastic large-cell lymphoma"[All Fields] OR ("anaplastic"[All Fields] AND "large"[All Fields] AND "cell"[All Fields] AND "lymphoma"[All Fields]) OR "anaplastic large cell lymphoma"[All Fields])) AND ("breast"[MeSH Terms] OR "breast"[All Fields])) AND implants[All Fields]	30
(("lymphoma, large-cell, anaplastic"[MeSH Terms] OR ("lymphoma"[All Fields] AND "large-cell"[All Fields] AND "anaplastic"[All Fields]) OR "anaplastic large-cell lymphoma"[All Fields] OR "ki 1 lymphoma"[All Fields]) AND ("breast"[MeSH Terms] OR "breast"[All Fields])) AND implants[All Fields]	134
((((("breast"[MeSH Terms] OR "breast"[All Fields]) AND ("Phys Perspect"[Journal] OR "pip"[All Fields])) AND implants[All Fields]) AND ("risk assessment"[MeSH Terms] OR ("risk"[All Fields] AND "assessment"[All Fields]) OR "risk assessment"[All Fields] OR ("risk"[All Fields] AND "benefit"[All Fields]) OR "risk benefit"[All Fields])) AND ("Assessment"[Journal] OR "assessment"[All Fields])	11

Literature search using FIND-eR resulted in 108 entries that included 31 additional to PubMed search entries. Table 2 shows the key words used and number of entries obtained.

Table 2 – Results from Find-eR search

Key words	No of entries
Breast Implants AND Lymphoma	63
Silicone Breast Implant AND Lymphoma	10
Breast Implants AND Anaplastic Large Cell Lymphoma	8
Implants AND Anaplastic Large Cell Lymphoma	26
Anaplastic Large Cell Lymphoma AND PIP	1

In addition to the literature review, a call for information was published by the European Commission inviting all interested parties to submit scientific information regarding a possible association between breast implants and ALCL.

The call for information was published on 14 June 2016 and closed on 4 September 2016. For on-going studies and research that was not completed by the deadline, the call

remained open until 20 November 2016. However, no contributions were received after the deadline of 4 September 2016.

5.1.1 Information retrieved from the literature review

After excluding all irrelevant papers and duplicate papers, a total of 188 papers remained from the literature search and were evaluated in this Scientific Advice (Annex 1). All scientific papers were published in peer-reviewed journals, from 1969 to 2016. The majority of the papers retrieved were case reports and case series (i.e. 82), whereas the remainder of the papers were mainly reviews, original research papers, commentaries and letters to the Editor. The original research papers (i.e., 18) referred to epidemiologic (observational) studies (7 of them were multi-centre studies), with sample sizes varying from n = 7 (i.e., Bacilious *et al.*, 2002) to n = 89,382 subjects (i.e., the National Cancer Institute's Surveillance Epidemiology and End Results program, Largent *et al.*, 2012).

In addition, 12 papers focused on PIP implants in connection with ALCL and 28 papers mentioned PIP but did not assess ALCL (e.g., they evaluated PIP rupture).

The literature review was conducted by the SCHEER members who first evaluated the papers independently and then discussed them as a group before reaching their conclusions. The papers presented in Annex 1, are listed in a table with the following information:

- Title
- Author(s)
- Journal
- Year of publication
- Peer-reviewed journal or not
- Concerning ALCL: this tag means that the paper contains information on breast implants
- Mentioning ALCL: this tag means that the paper mentions ALCL, but not breast implants
- Study design: case report, non-human experimental study, observational study, clinical trial, randomised clinical trial, other –e.g., discussion, letter to the Editor, etc.
- Sample size: number of subjects included
- Outcome: i.e., main conclusion regarding the potential breast implant and ALCL association, as reported by the authors of each study, P: a statistically significant positive association between risk of ALCL and breast implant exposure, N: a statistically significant negative association of increased risk of ALCL due to breast implant exposure, NS: a non-significant association
- Comments on the document (made by the evaluators). No quality evaluation was made in the published studies.

5.2 Information submitted during the "call for information"

Eight stakeholders submitted information regarding a possible association between breast implants and ALCL, resulting in a total of 53 submissions, which included 34 papers published in scientific journals; most of them had already been retrieved during the aforementioned literature search. The rest were various non-peer-reviewed types of information, like websites, news items and statements. Three of the papers concerned PIP breast implants.

The evaluation of the papers submitted during the call for information is presented in Annex 2. Based on the evaluation of the submitted papers, no evidence in addition to that already

obtained from the literature search was found as regards to the possible association between breast implants and ALCL.

5.2.1 Information submitted during the "commenting period"

A commenting period on the scientific advice was published on the website of the Scientific Committees from April 7th until June 15th, 2017. Two organizations participated and provided input related to the topic of the scientific advice. This contribution was carefully considered by the SCHEER. Moreover, relevant scientific papers published during this period were also retrieved from the literature, following standard procedures mentioned above, and are discussed here.

5.3 Methodology applied for the evaluation of scientific information

All information obtained via the literature search and call for information, including that from Scientific Bodies and Agencies, was examined, but conclusions were based exclusively on scientific papers published in peer-reviewed journals.

As far as possible, a preliminary evaluation of the available data was performed. However, because of lack of sufficient data to calculate robust effect size estimates, no attempt was made to meta-analyse the data and to calculate a combined effect measure of a possible association between breast implant and ALCL. Specifically, the majority of the papers retrieved through the literature search were case reports. Case reports, as well as case report series have been important components of the medical literature, highlighting possible novel cases of illness, including signs/symptoms and sometimes treatment/management; however, their value in evidence-based medicine is considered low (Nissen *et al.*, 2014; Evidence Based Medicine Working Group, 1992). This is mainly because the case or case series presented in a case report are not chosen from a random and representative sample of the referent general population (therefore an issue of selection bias is raised); therefore, they cannot be used for the calculation of effect size measures (like ratios, incidence or prevalence) since the number of persons exposed is not indicated and no evidence is provided for causal inference.

Moreover, regarding the observational studies evaluated here, it was hard to combine and compare their effects because of the different settings, and in some cases, lack of information about the lag-time from exposure (implantation) to the development of ALCL.

6. ASSESSMENT

This section presents the scientific information retrieved by the SCHEER after the evaluation of all scientific papers gathered (Annexes 1 and 2). In addition, some recent information published by scientific bodies and regulatory agencies was retrieved by the SCHEER and presented in the evaluation.

6.1 Breast Implant related ALCL epidemiology

6.1.1 Information from scientific papers

Based on case reports, De Jong *et al.*, estimated that the incidence of ALCL in the breast varies between 0.1 and 0.3 per 100,000 women with prostheses per year in the Netherlands (i.e., 5 new cases in 1.7 to 5.1 million person-years) (De Jong *et al.*, 2008).

Vase *et al.* (2013) examined lymphoma occurrence in a nationwide cohort of 19,885 Danish women who underwent breast implant surgery during 1973–2010. During the follow-up, the investigators observed 31 cases of lymphoma, but no cases of ALCL were identified.

Brody *et al.* (2015), based on an extensive review of 173 cases, throughout the world, reported that the number of cases of ALCL ranged from 1 in 500,000 to 1 in 3,000,000 women with implants.

Kuehlmann *et al.* (2016) performed retrospective evaluation of 296 breast tissues of 227 women with different breast implant types, undergoing surgical revision or explantation between January 2000 and June 2015. The mean implant residing time was 8.5±8.9 years (median: 5.8 years); the main implantation reason was for reconstruction, followed by aesthetic reasons. The main reason for explantation was capsular fibrosis. The authors reported that they could not find any pathological lymphoma cells in breast capsules, and concluded that although there are case reports about breast implants and ALCL, the number of cases is considered small and the knowledge of the pathogenesis is limited.

The case reports evaluated, described cases of women having, in majority, with anaplastic large-cell lymphoma, negative for anaplastic lymphoma kinase (ALK-negative, ICD-10, C84.7), presented as an accumulation of seroma fluid between the implant (saline or silicone filled) and the surrounding fibrous capsule. There were also few cases reported positive for anaplastic lymphoma kinase (ALK-positive, ICD-10, C84.6), or with follicular lymphoma (ICD-10, C82), lymphoplasmacytic lymphoma (ICD-10, C88), primary effusion lymphoma (ICD-10, 2B21), etc.

In May 2017, Doren et al., retrospectively evaluated the U.S. incidence and lifetime prevalence of breast implant-ALCL in women with textured[8] implants, from 1996 to 2015; the incidence and prevalence were estimated based on a literature and institutional database review of ALCL cases and textured breast implant sales from implant manufacturers' annualized data. Authors reported one hundred pathologically confirmed ALCL cases associated with breast implant, with a mean age at diagnosis of 53±12 years and mean interval from implant placement to diagnosis of 10.7±4.6 years. The authors, assuming that the breast implant-ALCL "*occurs only in textured breast implants*", calculated an incidence rate of 203 cases per 100 million person-years This rate is 67.6 times higher than that of primary ALCL of the breast in the general population (i.e., 3 per 100 million per year; $p < 0.001$). The lifetime prevalence was estimated 33 per 1.000.000 persons with textured breast implant (Doren, 2017).

Loch-Wilkinson et al., studying ALCL cases in Australia and New Zealand, as well as sales data from breast implant manufacturers, reported 55 cases of ALCL associated with breast implant, between 2007 and 2016 (mean age of 47.1 years and mean time of textured implant exposure 7.46 years). The authors also observed that the higher surface area of textured implants was positively associated with higher prevalence of ALCL (Loch-Wilkinson *et al*, 2017).

6.1.2 Information from scientific bodies and regulatory agencies

The US Food and Drug Administration (FDA) collects and evaluates medical device reports, discusses this information with other international regulators and scientific experts and reviews medical literature.

According to a 2011 estimation[9] by the FDA, there were 100-250 known cases of ALCL in women with breast implants out of an estimated number of 5 to 10 million women who have received breast implants worldwide (FDA, 2011). According to this information, the FDA cautioned patients and health care providers that women with breast implants might have a very low, but increased risk of developing ALCL. Due to the limited number of cases, it was impossible, according to the FDA, to determine which factors might increase the risk.

[8] Textured implants have rough surface in contrast with smooth implants

[9] http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm

Regarding health care providers, the FDA recommended to continue to provide patients with routine care and support and to consider the possibility of ALCL when a patient has late onset, persistent peri-implant seroma. Moreover, the FDA acknowledged that there are various limitations in the data collected due to several reasons (FDA, 2011).

In March 2017, an update was published on the FDA website, recording 359 medical device reports of ALCL associated with breast implants, including nine deaths[10]. Information on implant fill types was reported for 312 (186 filled with silicone gel and 126 filled with saline). It was highlighted that details on breast implant surface are limited, and that reports may contain incomplete, inaccurate, untimely, unverified, or biased data. It was also stated that the exact number of cases remains difficult to determine due to significant limitations in case reporting and lack of global implant sales data.

In March 2015, an expert Opinion by the French National Cancer Institute reported 18 cases of ALCL. In September 2016, 29 cases were reported[11]. With a large number of assumptions made by the investigators, the cumulative incidence of ALCL was 1 to 2 cases per 10 000 in women with a breast implants over a period of 10 years.

In December 2016 an advice was published by the Australian Therapeutics Goods Administration (TGA) with 46 cases of breast implant associated ALCL confirmed in Australia with three resulting in death.[12]

A review of 40 Government Authority Databases was published in May 2017 (Srinivasa *et al*, 2017). According to the information retrieved from 40 countries that were contacted, "*federal reporting of breast implant-associated ALCL has limitations in providing clinical history, treatment, and oncologic follow-up. Worldwide and country-specific total and textured implant sales data are needed to determine critical incidence and prevalence analysis*".

It should be noted that ALCL was diagnosed not only for silicone-filled breast implants, but also near saline-filled breast implants (De Jong *et al.*, 2008; FDA, 2016, TGA 2017). To date most ALCL tumours have been observed near textured implants (FDA 2017, TGA 2016).

In conclusion, the SCHEER notes that the estimated incidence of ALCL among women with breast implants reported by research studies and regulatory bodies varies. The information retrieved from the literature and regulatory bodies' reports, suggests that women with breast implants may have a very low, but increased risk of developing ALCL. However, the risk for women with breast implants to develop ALCL remains difficult to calculate, due to the lack of uniformity of studies' reports, the extremely low number of ALCL cases observed and the significant limitations in the estimation of the proportion of women developing ALCL out of the total population of women with a breast implants. Based on what was also discussed in 5.3, the SCHEER concludes that there is currently insufficient scientific information available to perform a methodologically robust risk assessment on a possible association of breast implant with the development of ALCL.

6.2 ALCL Diagnosis

A discussion has been noted among scientists concerning the accuracy of ALCL diagnosis. The diagnosis of ALK-positive ALCL is best made by excisional tissue biopsy, most commonly a lymph node. Thus, the diagnosis is based on the morphologic features and immune-histo-chemical patterns found on biopsy specimens in conjunction with the clinical features found on presentation.

[10] https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/ucm239995.htm
[11] http://www.e-cancer.fr/Professionnels-de-sante/Recommandations-et-outils-d-aide-a-la-pratique/Cancers-du-sein
[12] https://www.tga.gov.au/alert/breast-implants

A mammogram is in most of the cases the first imaging approach performed, whereas, ultrasound is subsequently performed and analysed in conjunction with the mammogram's findings. However, the imaging findings of ALCL are often very non-specific (Letter *et al.*, 2016).

Some investigators suggest that there is a need for standardised criteria to clinically diagnose ALCL, a need to identify risk factors and a need to update the evaluation of imaging studies, (ultrasound, computerised tomography, magnetic resonance imaging or positron emission tomography, mammography) to diagnose ALCL (Miranda, 2014; Mazzucco, 2014; Adrada *et al.*, 2014). In a review paper, Adrada *et al.,* (2014) concluded that current imaging with ultrasound, computerised tomography, magnetic resonance imaging or positron emission tomography appears suboptimal in the detection of an abnormality associated with a silicone breast implant. Therefore, it is possible that ALCL has been and continues to be under-diagnosed.

In conclusion, the evidence emphasises the need for a better understanding of the complementary role of imaging results regarding the diagnosis of ALCL.

6.3 Other cases of T cell lymphomas

During the literature review, there were reported cases of T cell lymphomas similar to ALCL that were not associated with breast implants.

Mulligan *et al.* presented a case of a woman with no history of breast implants, who developed ALCL, anaplastic lymphoma kinase-1 negative, on a background of a previous benign cyst aspiration (Mulligan *et al.*, 2014).

One case of a lymphoproliferative disorder was reported near a dental implant (Yoon et al., 2015). This was a tumour composed of CD30 positive and anaplastic lymphoma kinase (ALK) negative T-cells. Palraj et al., (2010) reported a case of a T cell lymphoma (CD30 positive and ALK negative) near a metallic implant seven years after placement of a stainless steel plate for repair of a tibia fracture.

Ozkaya et al. reported one case of ALCL without a history of an implant. The lymphoma appears to have arisen secondary to dystrophic calcifications caused by long-standing dermatomyositis (Ozkaya et al., 2016). However, similar characteristics as the aforementioned ALCL cases were noted including morphology, immunophenotyping (e.g. anaplastic lymphoma kinase (ALK)-negative, CD30 positive) and proteomic outcomes regarding matrix proteins.

In conclusion, cases of ALCL ALK-negative have been reported in the literature, also in the absence of breast implant.

6.4 Breast Implant Registries

Registries with detailed data on disease patho-biology and associated factors are powerful tools to track, study, and manage chronic diseases. The need for establishing robust registries for breast implant-associated pathologies has been suggested by several investigators (Evans *et al.*, 2011; Cooter *et al.*, 2015; Brown *et al.*, 2016).

There are some registries evaluating the clinical outcomes of silicone breast implants. For example, the International Collaboration of Breast Registry Activities (i.e., ICOBRA) involves the national plastic surgery societies of Australia, Austria, Canada, France, Germany, Ireland, Italy, the Netherlands, New Zealand, South Africa, the United Kingdom and the US, and was developed to "*establish an internationally agreed and comparable minimum data set, made up of standardised and epidemiologically sound data that reflect global best*

practice"[13]. In the US, a collaborative project has been established, with the American Society of Plastic Surgeons and the Plastic Surgery Foundation, in order to collect data through the Patient Registry and Outcomes for Breast Implants and Anaplastic Large Cell Lymphoma Etiology and Epidemiology (i.e. the PROFILE Registry). In France there is the national network of experts LYMPHOPATH, which is a government-supported network that aims to review lymphoma diagnoses or suspected lymphoma diagnoses; since 2010, 43,830 lymphomas have been registered in the database of the LYMPHOPATH network (Laurent *et al.*, 2016). In the Netherlands, the Dutch Breast Implant Associated ALCL Consortium, consisting of a multidisciplinary group of scientists, is investigating ALCL occurrences in women with breast implants[14].

In 2015, a study in 11 countries, illustrating different data collection systems and registries around the world, revealed that less than half of the participating countries had operational registries and that none of these had adequately high data capture to allow for a reliable outcome analysis. The study also revealed that the two most common problems that discouraged participation were the complexity of data sets and the opt-in consent model (Cooter *et al.*, 2015).

In a recent review of federal implantable device regulatory bodies and databases for 40 countries (Srinivasa *et al*, 2017), it was noted that "*international multi-institutional collaborations and centralized tissue consortiums working in concert with federal authorities are necessary to acquire accurate complete data on breast implant-associated ALCL*".

All of the above underline the need for registries, throughout the world, with clinical data of women with breast implants. Using the accumulated information of these registries is a major challenge for providing evidence-based conclusions in the potential association between breast implants and ALCL.

13 http://www.plasticsurgeryfoundation.org.au

14 https://www.nvpc.nl/uploads/stand/170118DOC-PL-BIA-ALCL_achtergrondinforrmatie_en_FAQ_BIA-ALCL162.pdf

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ANNEX I - Evaluation of the papers identified through literature search

In this Annex are listed the papers identified through literature search, using Pub-Med and Find-eR and the evaluation made by the SCHEER.

Annex I literature review.docx

ANNEX II - Evaluation of the papers received during the call for information

In this Annex are listed the papers received via the "call for information", which was published on June 14th, 2016 and closed on 20 November 2016 and the evaluation made by the SCHEER.

Annex II Call for information.docx