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SUMMARY OF THE 2015 ANNUAL REPORTING OF SERIOUS ADVERSE EVENTS AND REACTIONS FOR TISSUES AND CELLS (DATA COLLECTED FROM 01/01/2014 TO 31/12/2014)

EXECUTIVE SUMMARY

Transplantation and application of human tissues and cells is a life-saving, -enhancing or -generating therapy for hundreds of thousands of EU citizens every year. However, the use of substances of human origin always carries some risks, such as the possible transmission of infectious diseases in the donor.

These risks can be controlled and minimised by the application of a comprehensive safety and quality system, as laid down in EU legislation. Vigilance and surveillance is one of the pillars of such a system, allowing the identification and reporting these risks early on and ensuring that appropriate corrective and preventive actions are taken.

Since 2008, the reporting countries (i.e. EU Member States and Liechtenstein and Norway) have submitted to the Commission annual vigilance reports on the notification of serious adverse reactions (SAR) that occur in recipients of tissues and cells and serious adverse events (SAE) that occur during the transplantation chain, posing potential risk, in line with obligations defined in the legislation.[1]

The Commission has been working with the Tissues and Cells Competent Authorities for several years to improve the data collection procedure and to strengthen the reliability and comparability of the submitted information. The consistency and completeness of data collection and submission to the Commission in the tissues and cells sector has improved over time. The expert discussions show that the SARE reporting exercise is functional and assists countries in pinpointing and improving safety and quality issues in this sector and across the EU.

This report summarises the data collected by the reporting countries for the year 2014 and assesses them in the light of the information submitted in the previous years. Some key results of the reporting exercise were the following:

[1] Article 7 of Directive 2006/86/EC provides that Member States shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions (SAR) and serious adverse events (SAE) received by the competent authority using the formats in Part A and B of Annex V. See http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF
The summary reports published by the Commission:
http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_cells_adverse_events_2011_en.pdf
http://ec.europa.eu/health/blood_tissues_organs/docs/ratc_report_2012_en.pdf
http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_cells_adverse_events_2013_en.pdf

The overall number of distributed tissues and cells in 2014 amounted to 1,165,510 units, as reported by the countries. The total number of tissues and cells processed reached 1,433,828 units and the number of recipients - to 333,253.

A total of 190 SAR were reported, of which 109 were related to non-reproductive and 81 to reproductive tissues and cells. The data show that 19% of the SAR associated with the transplantation of non-reproductive tissues and cells are infections, mostly of bacterial or fungal origin. Due to the significant number of transmissions of infections revealed in the previous years' reports[2], the Commission has requested ECDC to prepare risk assessments for the benefit of the professionals involved in these sectors. Most of the reported SAR for reproductive cells relate to genetic diseases for which the transmission from the gamete donors was considered at least "possible".

551 serious adverse events were reported, most of which occurred during the processing, procurement and storage stages and were attributed mainly to human error.

The reports submitted by the countries included information not only on recipients but also donors. The reporting showed that there were 620 SAR cases in donors. Recognising the importance of these donor adverse reactions, the Commission continues to collect such data on a voluntary basis in agreement with the Tissues and Cells Competent Authorities, who are interested in putting in place appropriate follow-up and protection mechanisms for tissue and cell donors. It is important to assess and understand the underlying reasons beyond these SAR in donors, in order to better protect those persons who make transplantation medicine in tissues and cells sector possible.

Before publishing the summary report, the Commission presented the data contained in this report at the meetings of Tissues and Cells Competent Authorities in 2015 and 2016 and allowed the reporting countries to interact and share experience and knowledge.

1. DATA COLLECTION METHODOLOGY

This document provides a summary report of the data collected during 2014 (from 1st January to 31st of December) by Liechtenstein, Norway and all Member States except Cyprus and submitted to the Commission in 2015. It also includes a comparison with the data from the previous years and draws general conclusions. The Commission provided the following tools to the participating authorities to promote a standardised approach to data reporting:

1) An electronic reporting template to be sent to a DG SANTE hosted database. The electronic reporting template used in 2015 (for 2014 data) was version 2.4.1.

2) A 'common approach' document attached to the electronic reporting template, thus making it easily accessible to the user. The document, although not legally binding, provides guidance to the reporting countries when filling out the electronic reporting template as required by Directive 2006/86/EC. In 2015, version 2.4 of the Common Approach document was available to those reporting SARE 2014 data.[3]

[2] Cf. the summary of the 2014 annual reporting of SARE for tissues and cells.

[3] Over the years, the Common Approach document has been regularly updated to clarify points of ambiguity and inconsistency. This has in turn resulted in a gradual increase of the quality of the data collected from the Member States.

2. MAIN FINDINGS OF THE 2014 DATA COLLECTION

2.1. General comments

The reporting template was sent to the EU 28 Member States as well as to Liechtenstein, and Norway. All reporting countries except Cyprus complied with the requirement of Article 7 of Directive 2006/86/EC to submit information by completing the annual report template.

As in the previous years, many Member States acknowledged that accurate activity data for certain types of tissues/cells were difficult to collect and some of them provided incomplete numbers for SAR denominators (i.e. number of tissues and cells distributed and number of recipients). In particular, there were 24 and 15 countries that reported data for distributed non-reproductive and reproductive tissues and cells, respectively. Concerning the recipients, there were 15 and 11 countries reporting number of recipients of non-reproductive and reproductive tissues and cells, respectively. Similarly, there were 12 and 10 countries that reported SAR for non-reproductive and reproductive tissues and cells, respectively. The conclusions should therefore be drawn with caution.

The overall number of distributed tissues and cells in 2014, as submitted by the reporting countries, amounted to 1,165,510 units. The number is lower compared to the previous year 2013 but higher than in 2010 - 2012. The number of recipients amounted to 333,253. This number increased compared to the previous years. An overview of the data for the denominators for tissues and cells as provided by the countries in 2011-2015 (data recorded for 2010-2014) is presented in figure 1.

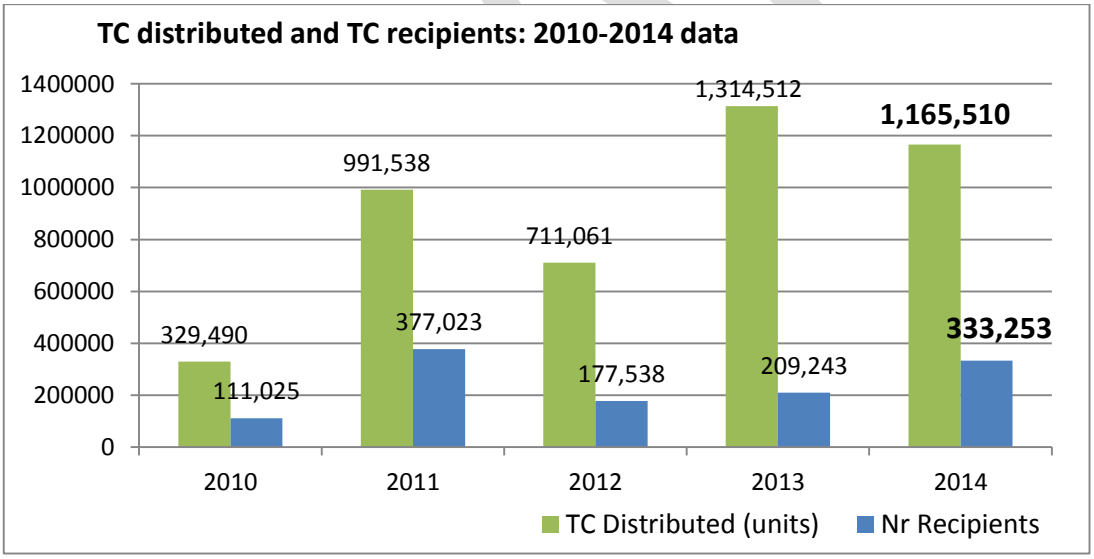

Figure 1. Total number of tissues and cells distributed (units) and number of recipients of human tissues and cells: 2010-2014 comparative data.

A total number of 190 SAR were reported for 2014. There were 12 and 10 countries that reported SAR for non-reproductive and reproductive tissues and cells, respectively. Overall this number is slightly lower than the one reported in the previous year but higher

compared to the two other years (cf. 190 SAR in 2014 compared to 203 SAR in 2013, 138 SAR in 2012, 156 SAR in 2011 and 460 SAR in 2010[4]).

A comparison of SAR reported by the Member States in the previous years for both categories non-reproductive and reproductive tissues and cells is presented in figure 2.

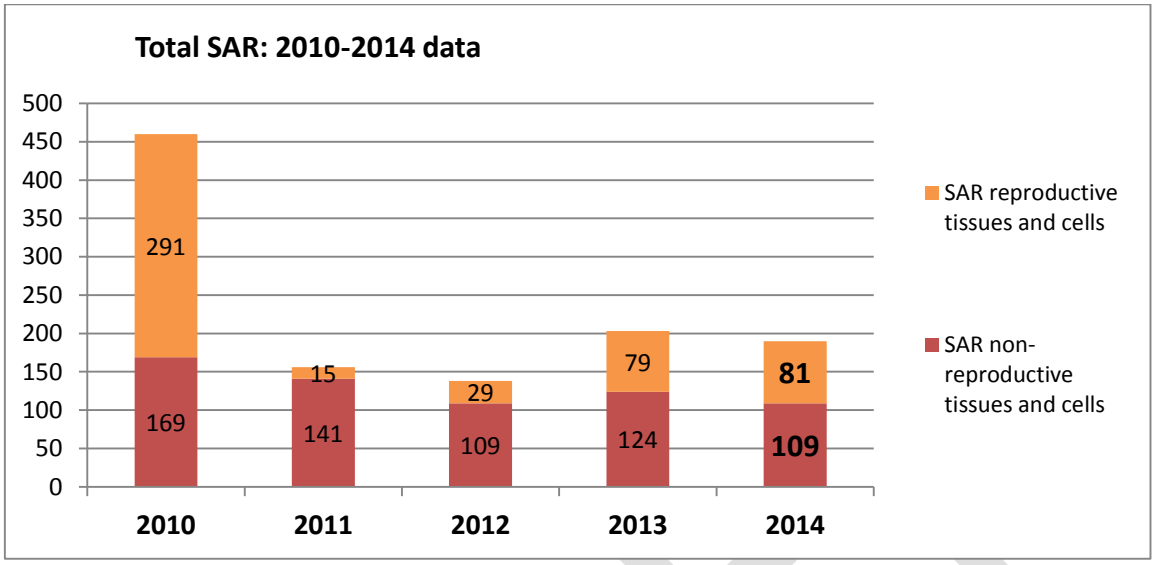

Figure 2. Total number of serious adverse reactions (SAR): 2010-2014 comparative data.

The total number of tissues and cells processed, as reported by the countries, reached 1,433,828 units. A slight decrease is observed compared to the previous year as presented in figure 3. This decrease is partially due to a lower number of countries reporting this denominator but also due to a significant reduction in the number of distributed non-reproductive tissues and cells in one Member State.

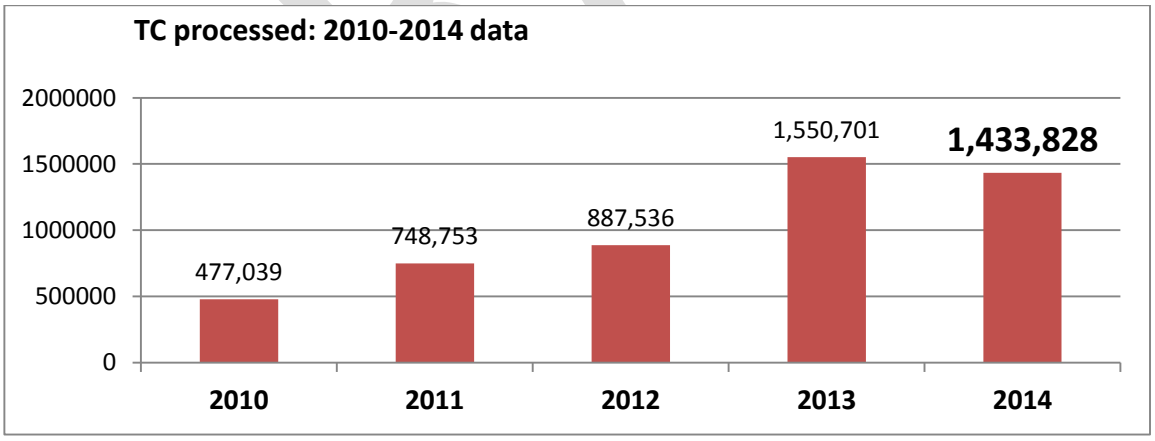

Figure 3. Total number of tissues and cells processed (units): 2010-2014 comparative data.

The number of SAE reported in 2014 increased compared to the previous years as presented in figure 4 (cf. 551 SAE in 2014 compared to 441 SAE in 2013, 499 SAE in 2012, 426 SAE in 2011 and 378 SAE in 2010).

[4] 2010 SAR data also include 209 cases of OHSS reported under SAR, which should have been reported under SAR in donors.

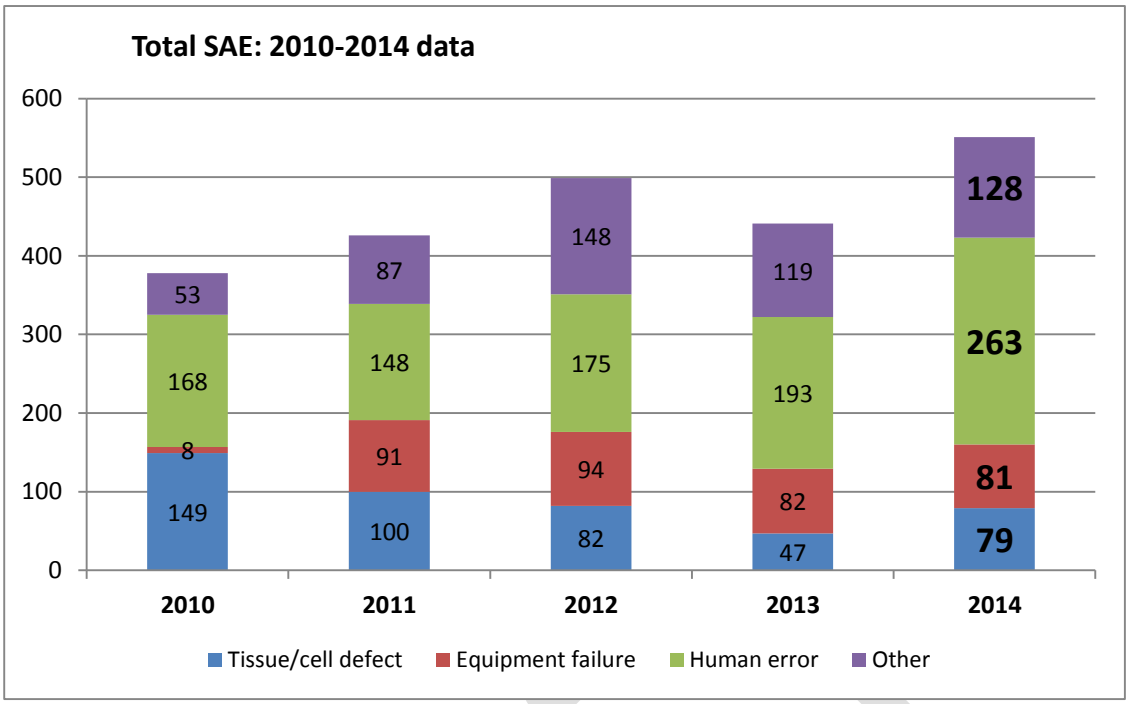

Figure 4. Total number of serious adverse events (SAE): 2010-2014 comparative data.

2.2. Serious Adverse Reactions (SAR)

2.2.1. Information by country

Two denominators are requested to analyse SAR - number of tissues and cells distributed[5] and number of recipients[6]. Only a small number of Member States reported both denominators, most provided data only for the number of tissues and cells distributed to transplantation centres (probably easier to collect by the tissue establishments than the number of recipients).

A total number of 1,165,510 units of tissues and cells were reported as having been distributed by tissue establishments in EU and EEA countries (330,450 units of non-reproductive tissues and cells and 835,060 units of reproductive tissues and cells). It has to be underlined that as in the previous years, for some groups of tissues and cells, several Member States preferred to report "no available data" for this denominator than providing approximate, imprecise numbers and in some cases (e.g. for distribution of oocytes), data were not provided because of measurement units used at national level not being standardised (e.g. national use of number of cycles of artificial insemination rather than units of oocytes distributed as requested in the reporting template).

In 2014, 333,253 recipients (patients) were reported as having been treated with tissues or cells (87,404 recipients of a tissue or cell transplantation and 245,849 patients who underwent an ART procedure with sperm, oocytes or embryos).

A total of 190 SAR were reported, of which 109 were related to non-reproductive tissues and cells, and 81 to reproductive cells. Eleven Member States (BE, DE, ES, FI, FR, IE,

[5] "total number of tissues and cells distributed (including type of tissue and cell for which no serious adverse reaction s were reported)" – Directive 2004/23/EC
[6] "number of recipients affected (total number of recipients)" – Directive 2004/23/EC

IT, NL, PT, SE, UK) and Norway reported SAR related to the transplantation of non-reproductive tissues and cells and nine Member States (BE, CZ, DK, ES, FI, IE, NL, SE, UK) and Norway reported SAR following the transplantation of reproductive cells. Therefore, for non-reproductive tissues and cells, there were 0.03% SAR/tissues and cells distributed and 0.13% SAR/number of recipients. For reproductive tissues and cells, there were 0.01% SAR/tissues and cells distributed and 0.03% SAR/number of recipients.

However, the data should be interpreted with caution because many countries indicated not having accurate denominator data for this year's report. Fifteen countries (AT, BG, EE, EL, HR, HU, LI, LT, LU, LV, MT, PL, RO, SI and SK) reported that in 2014 there were no occurrences of SAR related to the human application of tissues and cells. As already highlighted in the previous reports, this may suggest that SARE reporting procedures need to be improved at national level to ensure reporting by professionals in the field and/or tissue establishment staff.

2.2.2. Information by type of tissue/cell

Of the 190 SAR reported:

- 109 SAR (57% of all reported SAR) were related to the transplantation of non-reproductive tissues or cells (Figure 5):
    - 42 SAR were related to haematopoietic progenitor cell (HPC) transplants (including bone marrow 8, blood peripheral stem cells 30, and cord blood 4);
    - 67 SAR were related to transplantation of replacement tissues (general[7] musculo-skeletal tissue 1, bone 8, cartilage 4, ocular tissues 49, amniotic membranes 1, heart valves 2, other cardiovascular tissues 1 and other tissues 2).
- 81 SAR (43% of all reported SAR) were related to the human application of reproductive cells and tissues (sperm, oocytes, embryos) (Figure 6);

No SAR were reported for few types of tissues and cells including skin, hepatocytes, pancreatic islets and reproductive tissues (e.g. testicular tissue, and other reproductive tissues).

[7] "General" category should be used only by Member States who do not collect data separately for each type of tissues/cells in some categories (i.e. musculo-skeletal tissues vs, bone, cartilage, tendons, ligaments and other musculo-skeletal tissues).

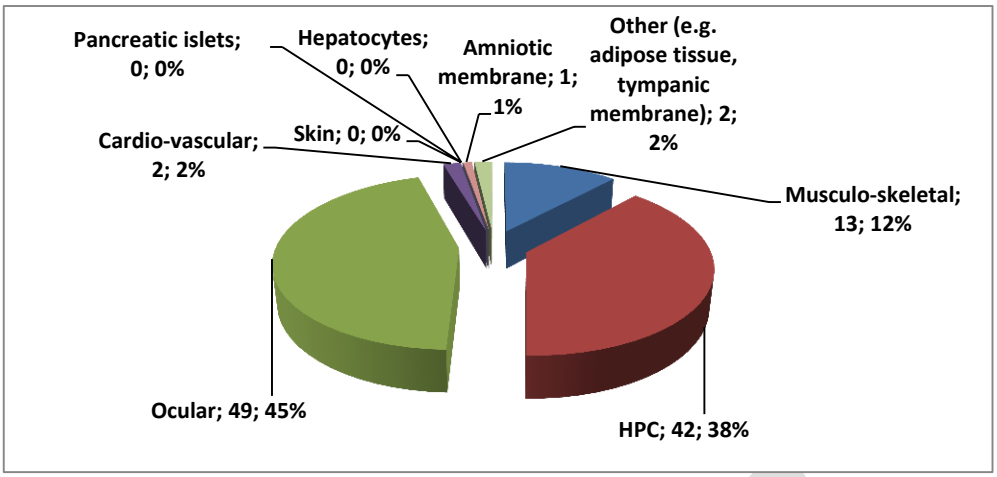

Figure 5. Number of SAR for each type of non-reproductive tissues and cells (absolute values and percentage from total SAR), 2014 data.

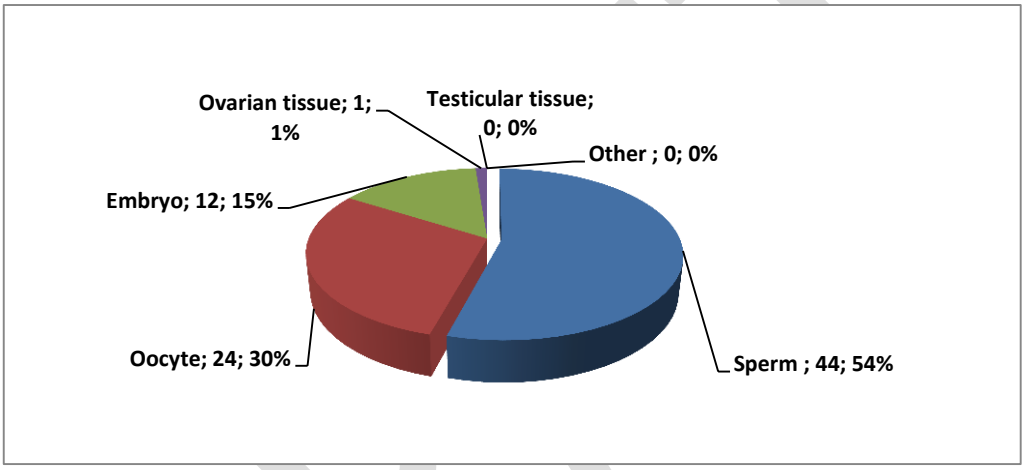

Figure 6. Number of SAR for each type of reproductive cells (absolute values and percentage from total SAR), 2014 data.

2.2.3. Information by category of SAR

The 109 SAR associated with tissue and cell transplantation of **non-reproductive** tissues and cells were categorised as following:

- Transmitted infections: 21 cases (19% of all reported SAR for non-reproductive tissues and cells) as following:

- 16 cases of bacterial infections, reported for the following transplanted tissues/cells: haematopoietic progenitor cell (HPC) 4, musculo-skeletal 7, ocular tissues 4, amniotic membrane 1;
- 1 case of viral infections: haematopoietic progenitor cell (HPC 1);
- 4 cases of other transmitted infections (ocular tissues 4: 1 case of primary graft failure due to an infection, 1 recipient developed endopthalmitis following corneal transplant, 2 cases of mycotic infections).

- Other SAR: 88 cases (81% of reported SAR for non-reproductive tissues and cells). In this broad and heterogeneous category:

- 37 SAR concerned haematopoietic stem cells transplantation procedures, and

- 51 SAR concerned transplantation procedures with other tissues (ocular tissues 41, musculo-skeletal tissues 6, cardio-vascular tissues 2, other 2).

More details concerning the SAR reported for different types of non-reproductive tissues and cells are presented in figures 7, 8 and 9.

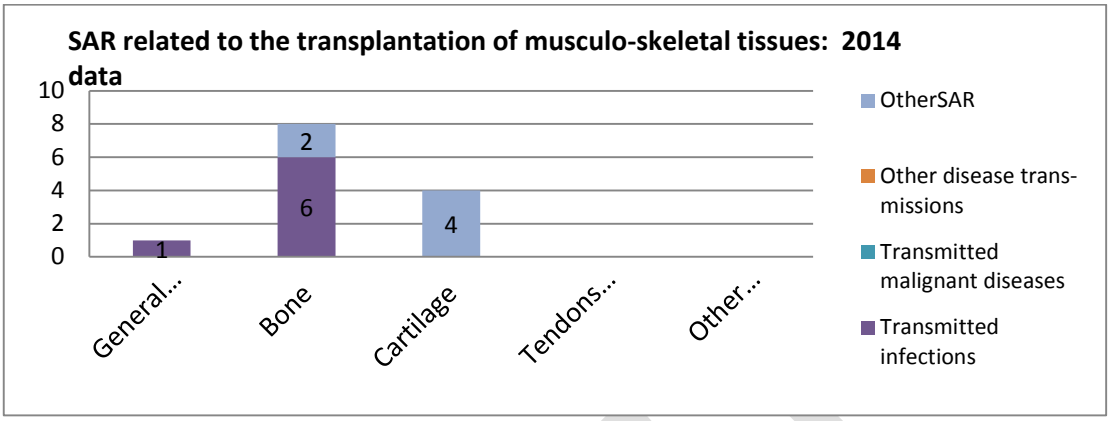

Figure 7. SAR following transplantation of musculo-skeletal tissues – 2014 data (Total 13 SAR; 0,006% SAR/total distributed musculoskeletal tissues)

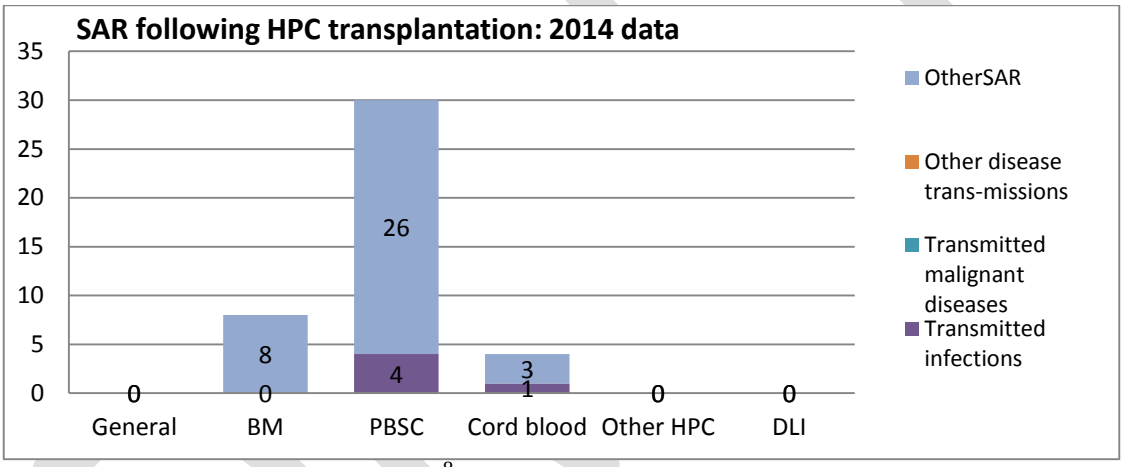

Figure 8. SAR subsequent to HPC[8] transplantation – 2014 data (Total 42 SAR; 0,060% SAR/total distributed HPC).

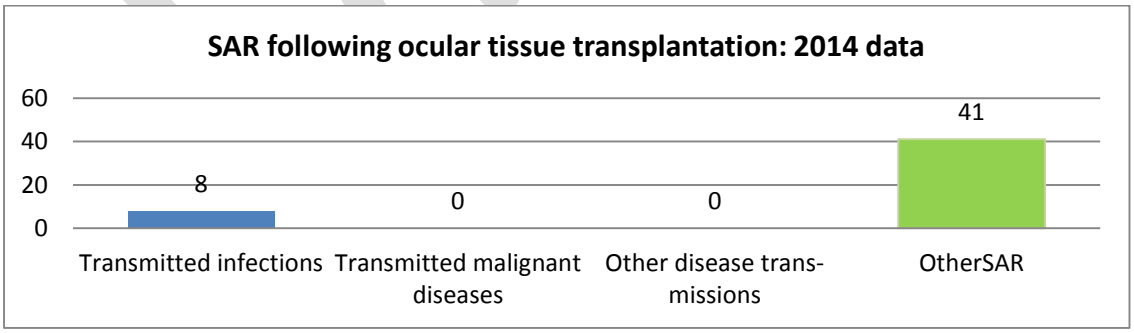

Figure 9. SAR following ocular tissue (cornea) transplantation - 2014 data[9]

[8] HPC = human progenitor cells; BM = bone marrow; PBSC = peripheral blood stem cells; CB = cord blood; DLI = donor lymphocyte infusion

[9] Only unexpected graft rejection and graft failure due to quality of the graft are reported under SAR.

(Total 49 SAR; 0,122% SAR/total distributed ocular tissues).

8 SAR related to 'transmitted infections' include 4 bacterial and 4 other transmitted infections (for more details see the sub-section 2.2.3 of this document). 41 SAR related to 'other SAR' include 1 leucoma, 3 graft failure and 37 graft rejection.

The 81 SAR associated with the application of **reproductive cells** were classified as following:

- Transmitted infections: 4 SAR related to the application of sperm (1) and embryos (3).
- Other disease transmissions (e.g. genetic diseases): 49 cases subsequent to ART procedures with oocytes (14), sperm (32) and embryos (3).
- Other SAR: 28 cases as following: 6 occurred after embryo implantation, and 21 subsequent to ART fertility treatment with oocytes (10) and sperm (11) and 1 related to ovarian tissue.

Of the total 81 SAR, 63 were reported for non-partner donation cases (42 cases following application of donated sperm and 21 cases subsequent to the use of donated oocytes).

2.3. Serious Adverse Events (SAE)

2.3.1. Information by country

A total of 29 countries (27 Member States, Liechtenstein and Norway) submitted the annual report template and therefore complied with the annual report submission established by Article 7.

16 countries (AT, DE, HU, IE, IT, LV, LU, LT, MT, NL, PL, PT, SI, ES, SE, UK) provided data regarding the number of tissues and cells processed in 2014. For the purpose of this reporting exercise, the term "tissues and cells processed" refers to tissues and cells processed in the tissue establishments, but not necessarily distributed to the end-users. Overall, a total number of 1,433,828 units of tissues and cells were reported as processed in 2014.

SAE were reported by 19 countries (AT, BE, HR, CZ, DK, EE, FI, FR, DE, IE, IT, NL, NO, PL, PT, SI, ES, SE, GB). The total number of SAE reported for 2014 was 551, showing that such events occurred for 0,038% of the tissues and cells processed during the same period. As in the case for SAR, where complete denominator data for the number of recipients and tissues and cells distributed was not available, the percentage of SAE in relation to the total number of tissues and cells processed should be interpreted with caution. Many countries reporting SAE could not provide, or could only approximate, the number of tissues and cells processed at national level.

2.3.2. Information by activity

A total of 551 SAE were reported by 19 countries. An overview of the SAE reported by type of activity is presented in Figure 10.

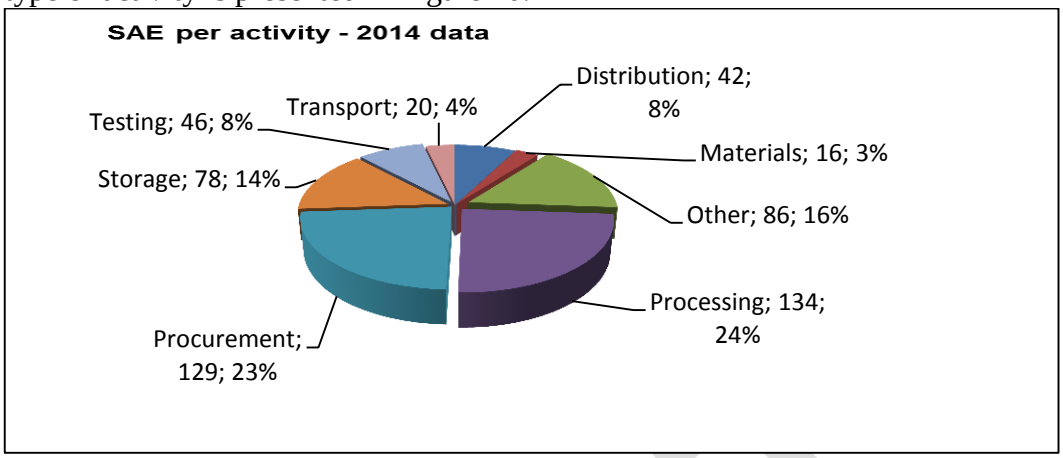

Figure 10. Number of SAE and percentage of total SAE reported per type of activity - 2014 data

2.3.3. Information by type of SAE

The 551 SAE were attributed to one of the four types of SAE, tissues and cells defects, human error, equipment failure, and other (Figure 11).

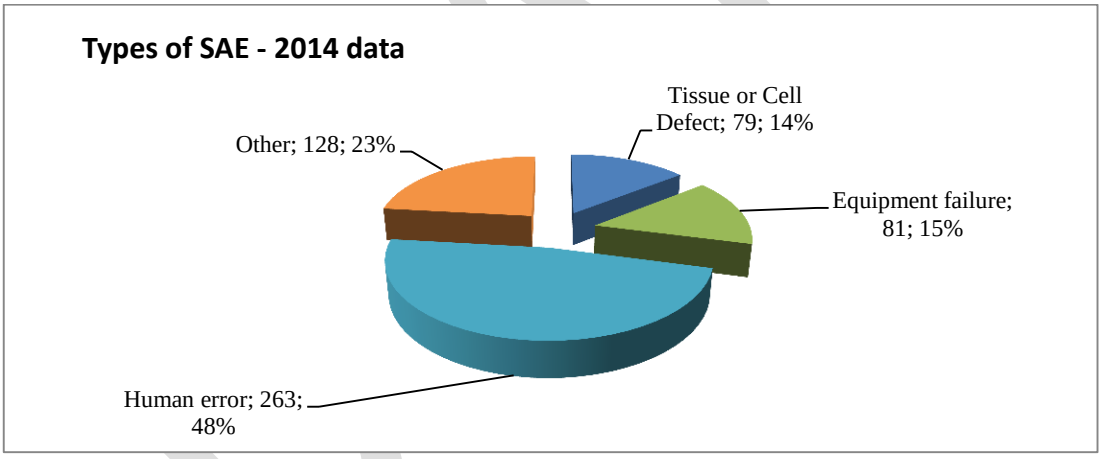

Figure 11. SAE relating to each type of SAE - 2014 data.

2.3.1. Information by type of SAE and activities

An overall analysis of SAE reported for 2014, taking into account both the donation-distribution chain activities and the specification, is shown in Figure 12.

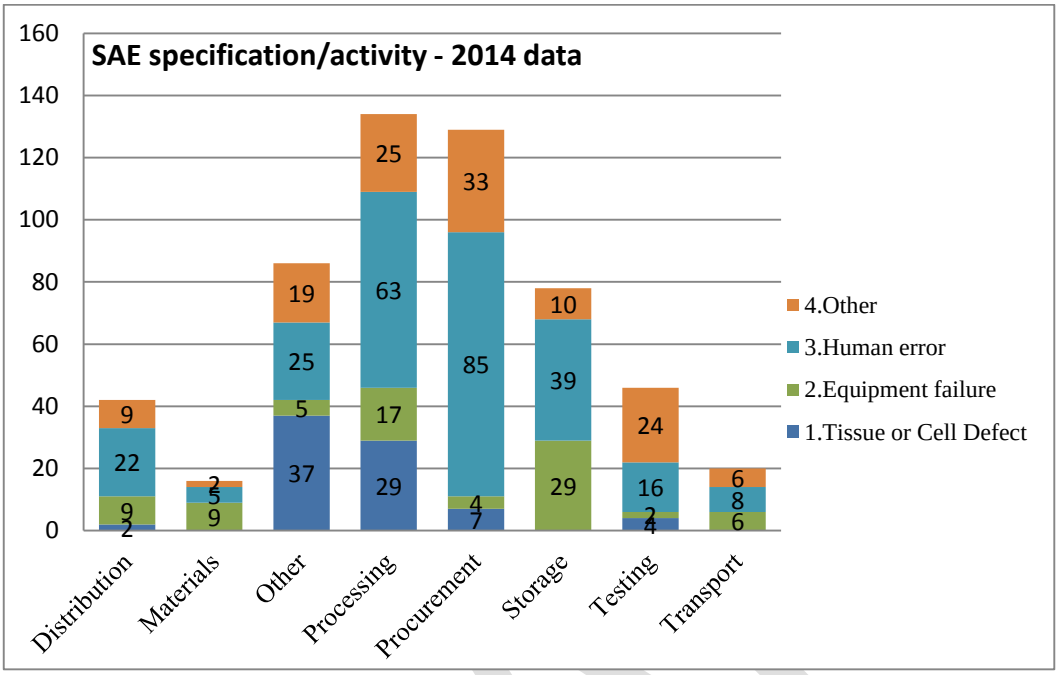

Figure 12. SAE per type and activities - 2014 data.

The graph shows that SAE occur mostly during the processing and procurement steps, with a significant number reported also under the "Other" category. Tissue establishment personnel should be encouraged to submit detailed reports of SAE, including an appropriate root cause analysis, and, if possible, provide preventive and corrective actions so that lessons can be shared with other establishments.

2.4. Serious Adverse Reactions (SAR) in donors

As in previous years, serious adverse reactions in donors were also included in the annual report. Recognising the importance of all donor adverse reactions, including those not influencing the quality and safety of tissues and cells which are reportable under the pharmacovigilance systems (e.g. OHSS following oocyte donation, reactions subsequent to the administration of GCSF for collection of peripheral blood stem cells, etc.), the Commission continues to collect such data on a voluntary basis in agreement with the Tissues and Cells Competent Authorities. These figures were, however, calculated separately, and are not included under the total number of SAR.

19 countries reported 620 SAR occurring in donors in 2014.

12 countries provided data related to SAR in donors of non-reproductive tissues and cells (BE, CZ, FI, FR, DE, IE, IT, NL, PL, PT, ES and UK). The 55 cases were associated with haematopoietic stem cells collection procedures (53) and cartilage (2) (Figure 13).

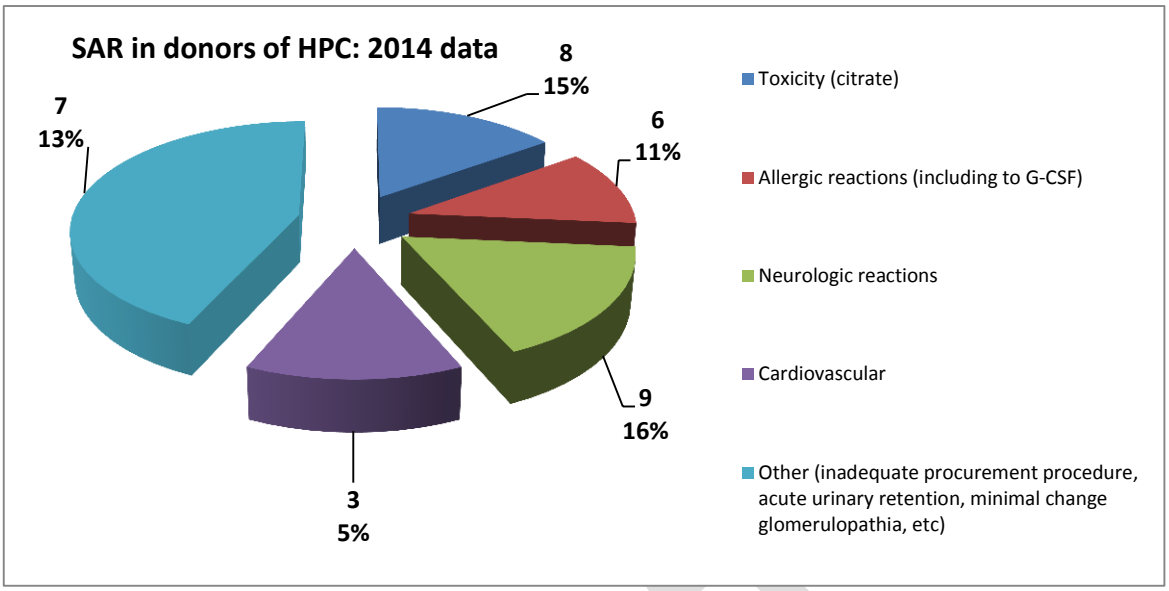

Figure 13. SAR in HPC donors: total number 53, amounting to 8.5% of all reported SAR in donors – 2014 data

15 countries (AT, BE, BG, HR, CZ, EE, FR, DE, IE, IT, NO, SI, ES, SE and UK reported 565 cases of SAR in oocyte donors. Most of the reported SAR reported in oocyte donors were critical, severe and moderate to severe OHSS cases (384). Surgery and complications, infectious complications, and other type of SAR were also reported (Figure 14).

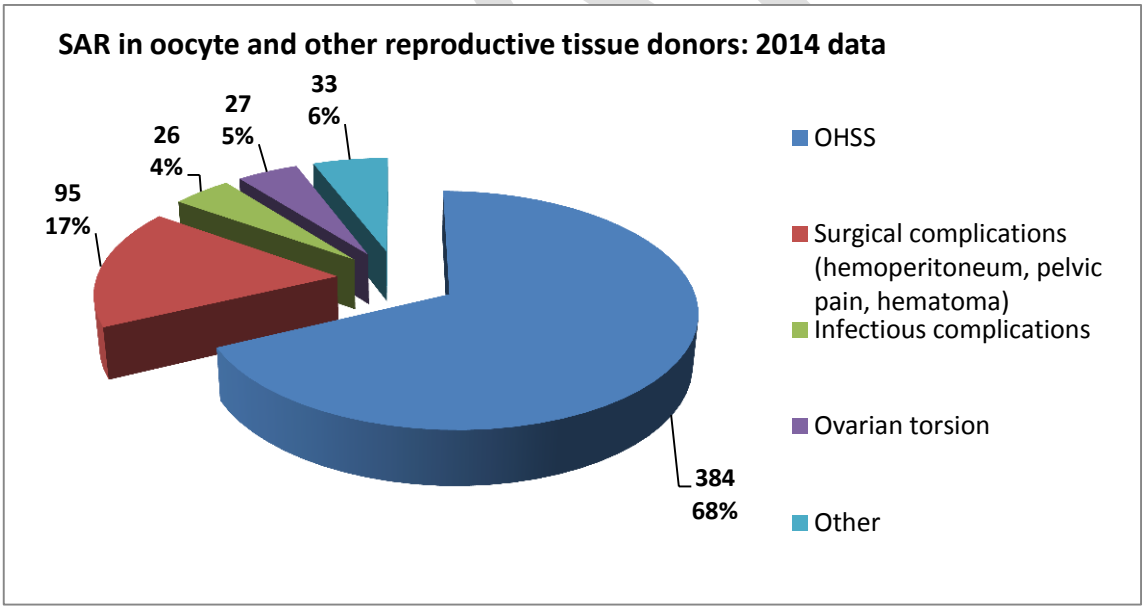

Figure 14. SAR in oocyte donors: total 565; 91% of total SAR in donors – 2014 data

This was the third year when countries reported separately the SAR recorded in partner and non-partner oocyte donors. According to data reported by the Member States, most SAR were recorded for partner-donation (480), 7 for non-partner donation, and for 76 cases the origin of the donation (partner or non-partner) was not specified.

Conclusions

Overall, the implementation of vigilance requirements and data collection in the tissue and cell sector seems to have improved over time. In the SARE 2015 annual reporting exercise, all countries except Cyprus submitted reports which include data on SARE and corresponding denominators.

The aggregated results show that the number of SAR and SAE reported for 2014 accounts to 190 and 551, respectively. As in previous years, the numbers remains relatively low when compared to the numbers of tissues and cells distributed and processed at EU level (0.016% and 0.038% respectively).

As regards the type of SAR, the data show that out of 190 SAR cases, 57% were related to the transplantation of non-reproductive and 43% - to reproductive tissues and cells (109 and 81 cases, respectively).

20% of the SAR associated with the transplantation of non-reproductive tissues and cells are infections, mostly of bacterial origin. Due to the high number of transmissions of bacterial infections, the Commission requested to ECDC to analyse the most relevant bacteria which can be transmitted through transplantation and transfusion and prepare risk assessments that should be made publicly available for the benefit of all professionals involved in these sectors.

For the clinical application of reproductive cells, most of the reported SAR were genetic diseases for which the transmission from the gamete donors was considered at least "possible". However the likelihood of transmitting a multi-factorial genetic disease from the donor to the offspring is sometimes difficult to assess.

As in the previous years, the high proportion of SAE reported under the human error category, especially in the processing, procurement and storage phases, may suggest the need to further clarify what are the most critical aspects that need to be addressed when revising SOPs and assessing the training needs and competencies of the personnel in EU tissue establishments.

The reporting exercise also revealed an increase in the number of SAR in donors (cf. 620 in year 2014, 547 in year 2013, and 294 in year 2012). The competent authorities are interested in collecting such data and putting in place appropriate follow-up mechanisms of tissue and cell donors.

The data should be interpreted with caution because few countries could not provide data for SARE and/or their denominators. It has to be highlighted that the lack of consensus on the most appropriate units for the collection of data for certain tissue and cell types (e.g. units of skin vs cm^2 vs or m^2; oocytes in units/cycles) may explain why some Member States choose not to report data. The Commission together with the Member States will reflect on the most appropriate solution for this issue. This and other issues will be addressed by the Joint Action VISTART[10] which includes a work-package dedicated to vigilance reporting for blood, tissues and cells. In collaboration with the Member States competent authorities DG SANTE will continue to support the sector with these efforts.

[10] "Vigilance and Inspection for the Safety of Transfusion, Assisted Reproduction and Transplantation" is a Joint Action co-funded by the European Union. The duration of the action will be 36 months as of 10 October 2015.