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**SUMMARY OF THE 2014 ANNUAL REPORTING OF SERIOUS ADVERSE EVENTS AND
REACTIONS FOR TISSUES AND CELLS
(DATA COLLECTED FROM 01/01/2013 TO 31/12/2013)**

EXECUTIVE SUMMARY

Tissues and cells are applied in transplantation and assisted reproduction programmes across the European Union (EU) with important healthcare benefits for hundreds of thousands of citizens. However, the use of any substance of human origin carries some risk, notably the possible transmission of infectious diseases from the donor. These risks can be controlled and minimised by the application of comprehensive safety and quality measures as laid down in EU legislation. Despite these measures, rare adverse outcomes are detected and, in line with the legislation, must be reported and monitored at the national and EU level through vigilance and surveillance programmes.

Since 2008, the EU Member States have submitted to the Commission annual vigilance reports on the notification of serious adverse reactions which occur in recipients of tissues and cells (SAR), and serious adverse events (SAE) which occur in the chain from donation to clinical application.¹

The Commission works with competent authority experts to verify the consistency and clarity of the submitted information on serious adverse reactions and events (SARE) and to improve the data collection procedure. The completeness and comparability of the data collected in the tissue and cell sector has improved over time. The exercise has also facilitated the development of the Member State national vigilance programmes.

This report summarises the data submitted by the Member States for the year 2013 and assesses it in the light of the information submitted in the previous years.

Overall, a total of 203 SAR were reported, of which 124 were related to non-reproductive and 79 to reproductive tissues and cells. The data show that 33% of the SAR associated with the transplantation of non-reproductive tissues and cells are infections, mostly of bacterial and fungal origin. In response to this number of infectious transmissions, the Commission asked ECDC to prepare publicly available risk assessments for the benefit

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>

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 to be at least “possible”.

In 2013, 441 serious adverse events were reported, most of which occurred during the procurement, processing and storage stages and were attributed mainly to human error. This underlines the importance of adequate training and good working conditions for staff undertaking these activities in or for tissue establishments.

The 2014 reporting showed a significant increase in the voluntary reporting of SAR in donors. Recognising the importance of 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 these donors, on whom the success of the services rely.

1. DATA COLLECTION METHODOLOGY

As with previous reports regarding SARE submitted to the Commission by the Member States (2010, 2011, and 2012 data, submitted to the Commission in 2011, 2012 and 2013, respectively) and published (in 2013, 2014 and 2015, respectively²), the data in this report were presented at the meetings of Tissues and Cells Competent Authorities and verified through direct communication with individual Member States following the meetings.

For 2014, the tools used for the SAR and SAE reporting to the European Commission were:

- 1) The electronic reporting template used in 2014 (for 2013 data) was version 2.3.
- 2) An updated version of the Common Approach document was attached to the electronic reporting template, thus making it easily accessible to the user. In 2014, the document was updated by including a clarification on the reporting of OHSS³ cases under "SAR in donors" (voluntary reporting). Most of the OHSS cases reported under pharmacovigilance fall also in the scope of ART vigilance system and their reporting under SAR in donors is encouraged. It was clarified that only severe/critical OHSS cases should be reported, also specifying whether they occurred in oocyte non-partner donors, or in women having IVF themselves. For the classification of OHSS, the references indicated by the SOHO V&S project in the deliverable “Guidance on Vigilance & Surveillance in Assisted Reproductive Technologies in the EU”⁴ were recommended; the version of the Common Approach document used in 2014 (for 2013 data) was 2.3.

² 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

³ OHSS = Ovarian hyper-stimulation syndrome

⁴ http://www.sohovs.org/soho/file.php/1/Deliverable_5_WP5_ART_Vigilance.pdf

2. MAIN FINDINGS OF THE 2014 ANNUAL REPORT – DATA COLLECTED DURING 2013

2.1. General comments

The reporting template was sent to the EU28 Member States as well as to Liechtenstein, and Norway. All the above mentioned countries submitted their SARE reports.

2014 was the third year when Member States were asked to distinguish between missing/non-available data (NA in the template) and no reactions/no events/no tissues/cells distributed or processed (0 in the 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 provided incomplete/approximate numbers. However, the overall numbers for both SAR denominators (i.e. number of tissues and cells distributed and number of recipients) were significantly higher than in the previous years, which may suggest an improvement in data collection. An overview of the data for the denominators for tissues and cells as provided by the Member States in 2011-2014 (data recorded for 2010-2013) is presented in figure 1.

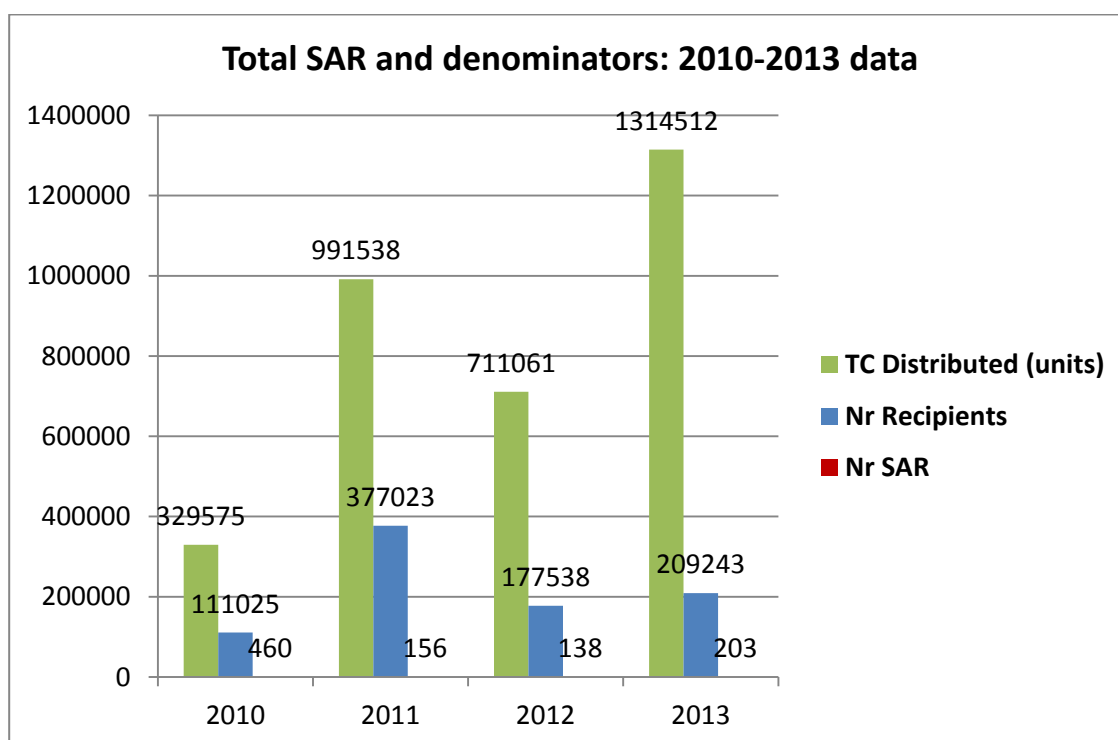


Fig. 1. SAR: 2010-2013 comparative data: Total number of tissues and cells distributed and number of recipients of human tissues and cells

A total number of 203 SAR were reported by 16 Member States for 2013. Overall this number is slightly higher than those reported in the previous years. A comparison with the number of SAR reported by the Member States in the previous three years for the two main categories of tissues and cells is presented in figure 2.

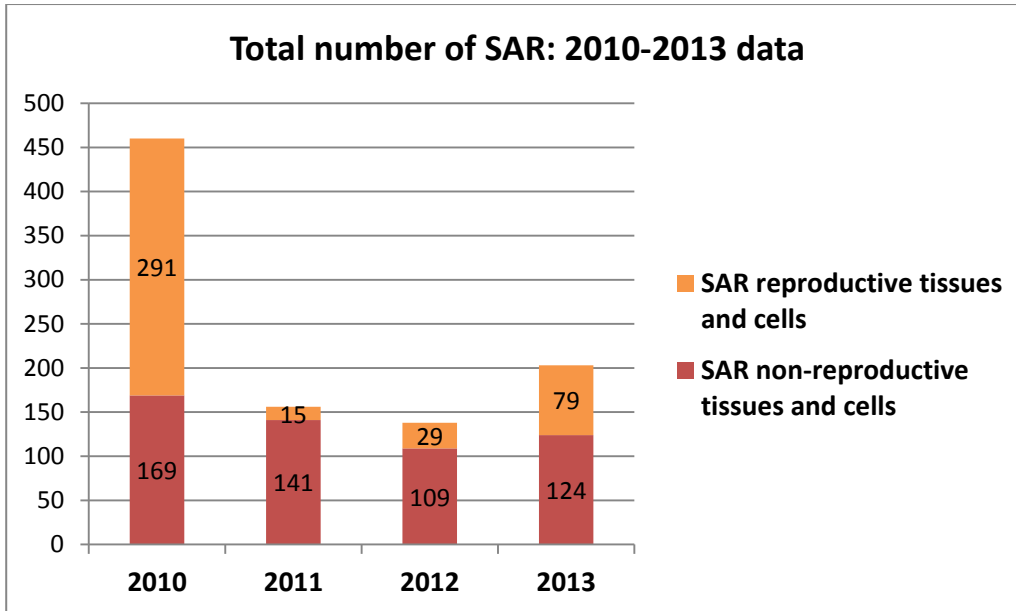


Fig. 2. Total number of SAR: 2010-2013 comparative data (2010 SAR data also include 209 cases of OHSS reported under SAR, which should have been reported under SAR in donors)

As regards reporting of SAE, the total number of tissues and cells processed (used as denominator for SAE evaluation) increased, reaching 1 550 701 units in 2013 (figure 3). The increase may be partially explained by progresses made in collecting data from tissue establishments. The number of SAE reported in 2013 is slightly lower than the one reported in 2012 (441, compared to 499), but higher than in 2010 or 2011. (figure 4).

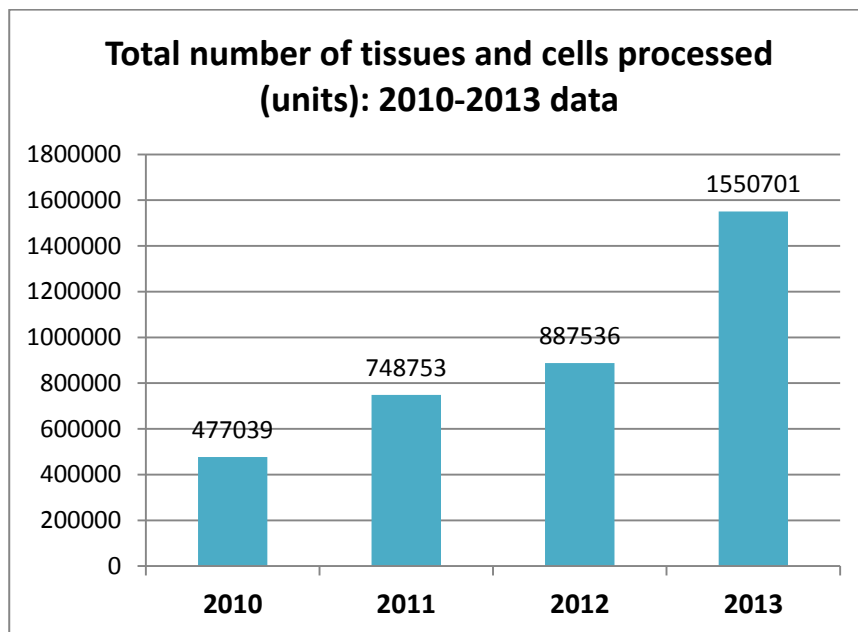


Fig. 3. Total number of tissues and cells processed: 2010-2013 comparative data

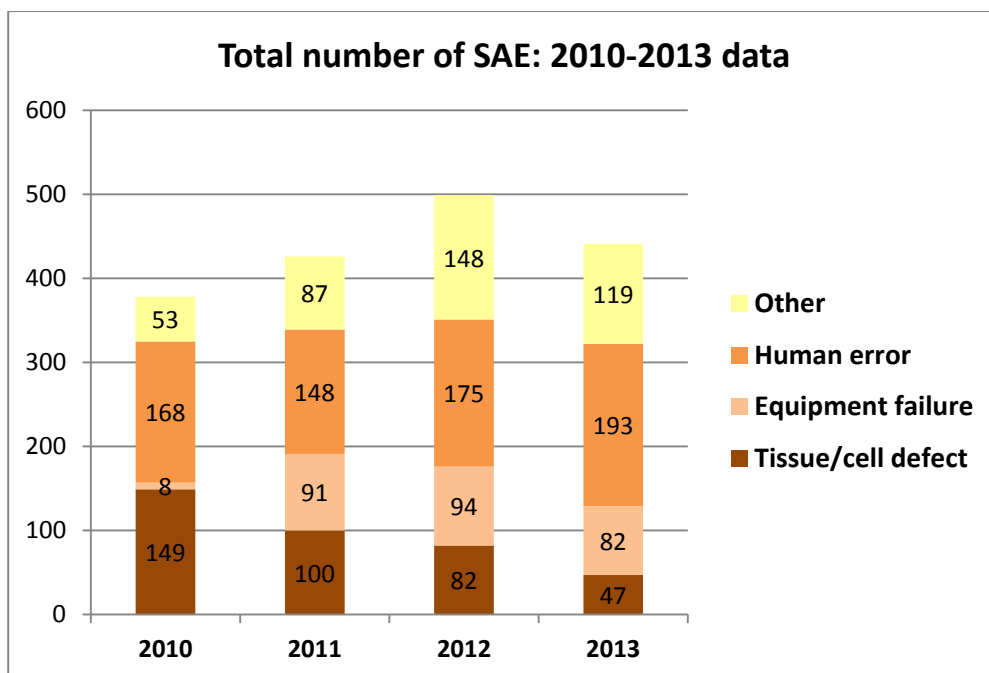


Fig. 4. Total number of serious adverse events (SAE): 2010-2013 comparative data

2.2. Serious Adverse Reactions (SAR)

2.2.1. Information by country

All Member States, as well as Liechtenstein and Norway complied with the requirement of Article 7 to submit information on SAR and denominators by completing the annual report template.

Two denominators are required to analyse SAR - number of tissues and cells distributed⁵ and number of recipients⁶. Only a small number of Member States reported both denominators, most Member States provided data for one denominator which for most of them was 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 1 314 512 units of tissues and cells were reported as having been distributed by tissue establishments in EU and EEA countries (528 061 units of non-reproductive tissues and cells and 786 451 units of reproductive tissues and cells). It has to be underlined that as in the previous years, for some groups of tissues/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 instead of units of oocytes distributed as requested in the reporting template).

⁵ "the total number transported or delivered to a clinical unit, even if the clinical unit is in the same building or the same floor"

⁶ "total number of patients who had at least one unit of tissues or cells applied during the year concerned in a given country, regardless of whether they had a reaction or not"

In 2013, 209 243 recipients (patients) were reported as having been treated with tissues or cells (67 046 recipients of a tissue or cell transplantation and 142 197 patients who underwent an ART procedure with sperm, oocytes or embryos).

A total of 203 SAR were reported, of which 124 were related to non-reproductive tissues and cells, and 79 to reproductive cells. Thirteen Member States (AT, BE, DE, DK, ES, FR, IE, IT, NL, PT, SE, SI, UK) and Norway reported SAR related to the transplantation of non-reproductive tissues and cells and eight Member States (BE, CZ, DK, ES, HR, IE, SE, UK) reported SAR following the application of reproductive cells. Therefore, for non-reproductive tissues and cells, there were 0,03% SAR/tissues and cells distributed and 0,23% SAR/number of recipients. For reproductive tissues and cells, there were 0,01% SAR/tissues and cells distributed and 0,55% 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.

Fourteen countries (BG, CY, EE, EL, FI, HU, LT, LU, LV, MT, PL, RO, SK and LI) reported that in 2013 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/perfected 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 203 SAR reported:

- 124 SAR (61%) were related to the transplantation of non-reproductive tissues or cells (Fig. 5):
 - 68 SAR were related to haematopoietic progenitor cell (HPC) transplants (including bone marrow 13, blood peripheral stem cells 43, and cord blood 12);
 - 56 SAR were related to transplantation of replacement tissues (general⁷ musculo-skeletal tissue 18, bone 4, tendons/ligaments 2, ocular tissues 25, heart valves 2, blood vessels 2, skin 3).
- 79 SAR (39%) were related to the human application of reproductive cells and tissues (sperm, oocytes, embryos) (Fig. 6);

No SAR were reported for the following categories of tissues and cells: cartilage, other musculo-skeletal tissues, other cardiovascular tissues, hepatocytes, pancreatic islets, donor lymphocyte infusions (DLI), other haematopoietic progenitor cells (HPC), other tissues (e.g. amniotic membrane) and reproductive tissues (ovarian and testicular tissue).

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).

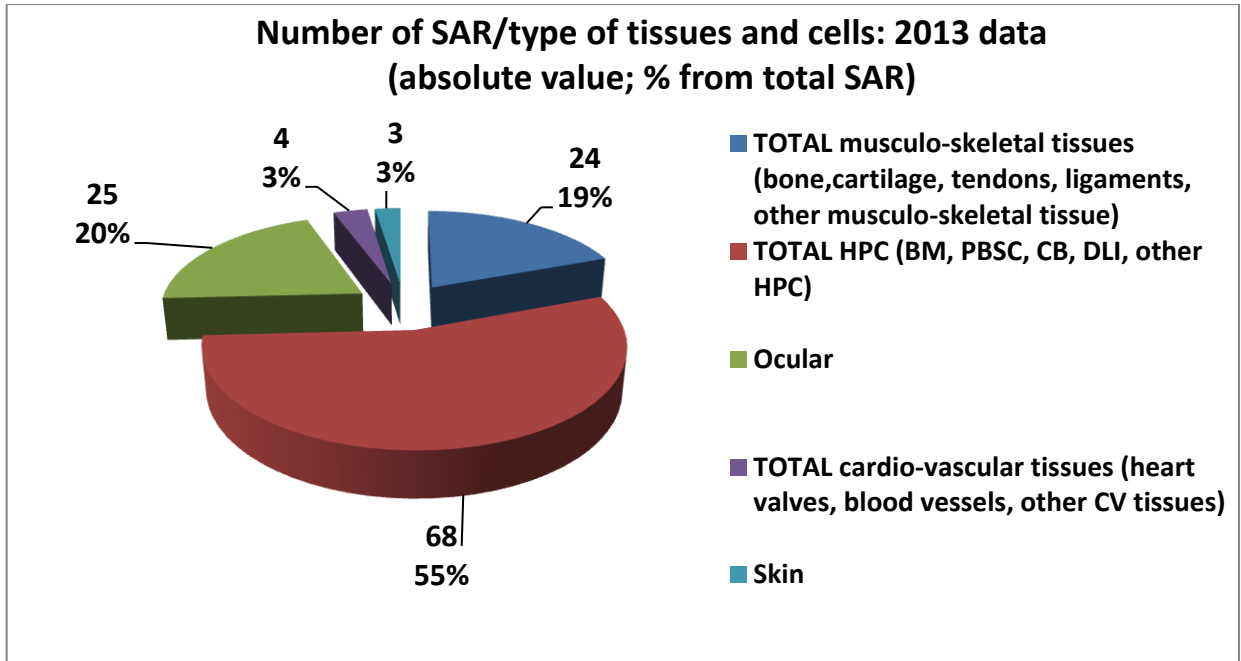


Fig.5. Number of SAR for each type of non-reproductive tissues and cells (absolute values and percentage from total SAR), 2013 data

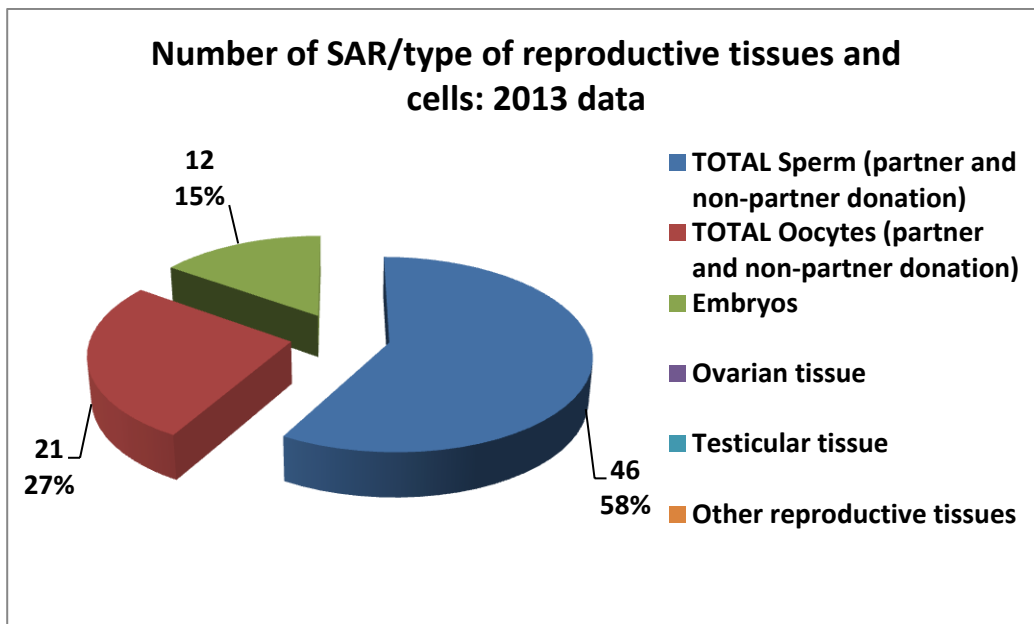


Fig.6. Number of SAR for each type of reproductive cells (absolute values and percentage from total SAR), 2013 data

2.2.3. Information by category of SAR

The 124 SAR associated with tissue and cell transplantation of non-reproductive tissues and cells were categorised as following:

- Transmitted infections: 33 cases (27% of all reported SAR for non-reproductive tissues and cells) as following:

- 27 cases of bacterial infections, reported for the following transplanted tissues/cells: HPC 9, musculo-skeletal 13, ocular tissues 3, skin 2;
- 1 case of viral infections (1 case of herpes simplex associated to PBSC transplantation);

- 5 cases of other transmitted infections (2 cases of fungal infections (Aspergillus) following PBSC transplantation, 3 cases of fungal infections (Candida) following cornea transplantation).
- Transmitted malignant diseases: 1 case of myelodysplastic syndrome with excess of blasts (REAB) with trisomy 8 of donor origin developed 2,5 years after PBSC transplantation (1% of all reported SAR for non-reproductive tissues and cells).
- Other SAR: 90 cases (72% of reported SAR for non-reproductive tissues and cells). In this broad and heterogeneous category:
- 55 SAR concerned haematopoietic stem cells transplantation procedures, and
 - 35 SAR concerned transplantation procedures with other tissues (ocular tissues 19, musculo-skeletal tissues 11, cardio-vascular tissues 4, skin 1).

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

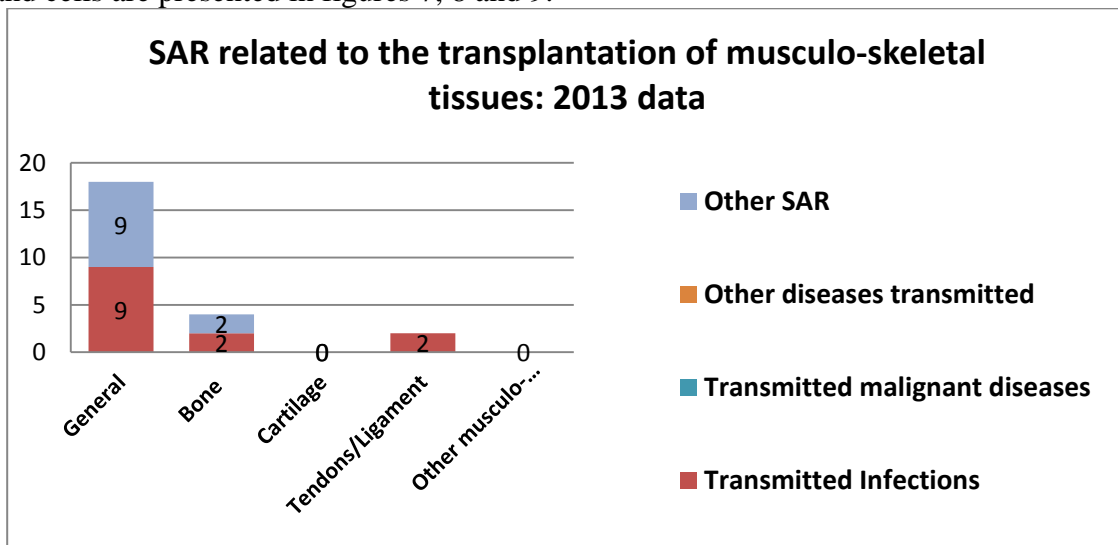


Fig. 7. SAR following transplantation of musculo-skeletal tissues – 2013 data (Total 24 SAR; 0,014% SAR/total distributed musculoskeletal tissues)

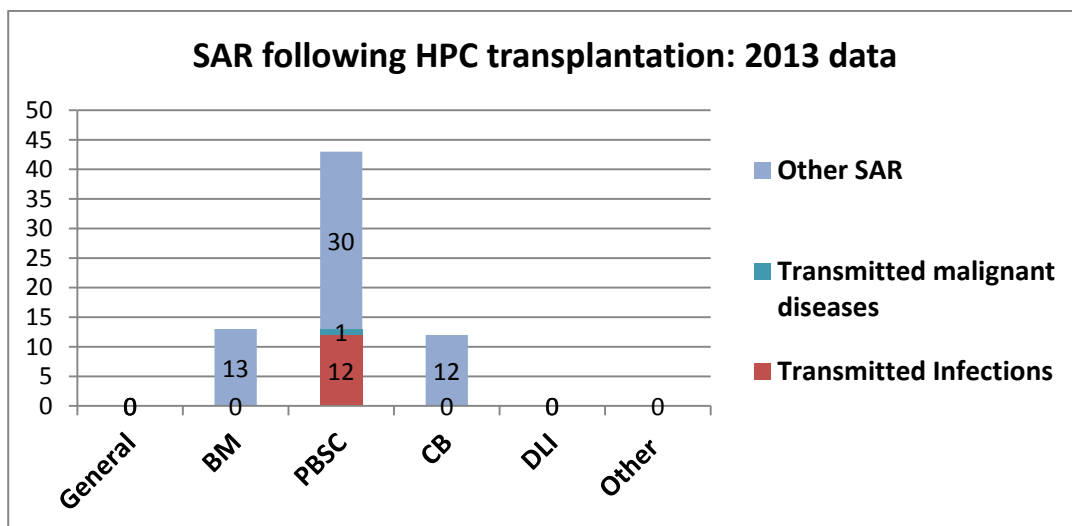


Fig. 8. SAR subsequent to HPC⁸ transplantation – 2013 data (Total 68 SAR; 0,065% SAR/total distributed HPC)

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

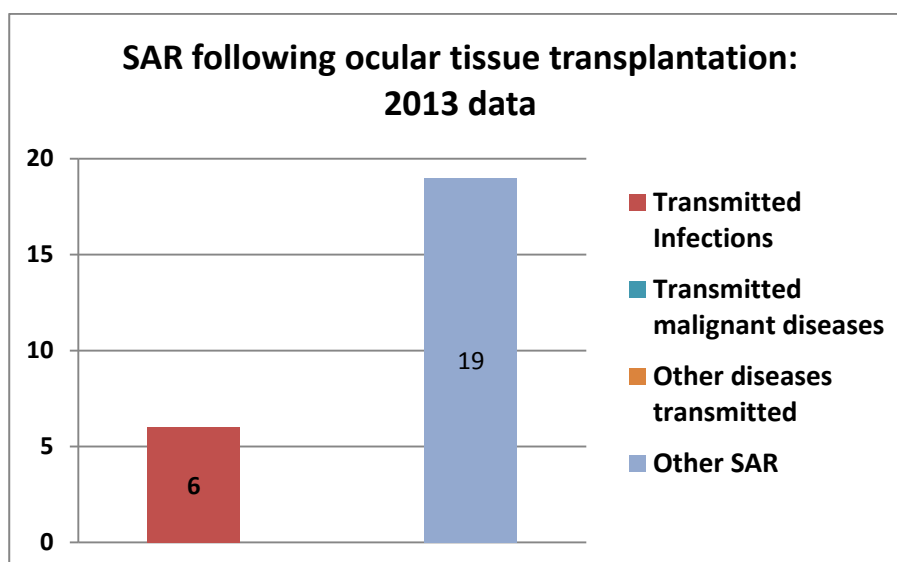


Fig. 9. SAR following ocular tissue (cornea) transplantation - 2013 data⁹ (Total 25 SAR; 0,075% SAR/total distributed ocular tissues)

The 79 SAR associated with the application of reproductive cells were classified as following:

- Transmitted infections: 0
- Transmitted malignant diseases: 0
- Other disease transmissions (e.g. genetic diseases): 51 cases (65%) subsequent to ART procedures with oocytes (40), sperm (8) and embryos (3).
- Other SAR: 28 cases (35% of reported SAR) as following: 9 occurred after embryo implantation, and 19 subsequent to ART fertility treatment with oocytes (6) and sperm (13).

Of the total 79 SAR, 66 were reported for non-partner donation cases (46 cases following application of donated sperm and 20 cases subsequent to the use of donated oocytes).

2.3. Serious Adverse Events (SAE)

2.3.1. Information by country

A total of 30 countries (28 Member States, Liechtenstein and Norway) submitted the annual report template and therefore complied with the annual report submission established by Article 7.

Eighteen countries (AT, CY, DE, EE, HU, IE, IT, LV, LT, MT, NL, PL, PT, SK, SE, SI, UK and LI) provided data regarding the number of tissues and cells processed in 2013. 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 1 550 701 units of tissues and cells were reported as processed in 2013.

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

SAE were reported by 17 Member States (AT, BE, DE, DK, EE, ES, FI, FR, HR, IE, IT, NL, PL, PT, SE, SI, UK) and Norway. The total number of SAE reported for 2013 was 441, showing that such events occurred for 0,028% 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 prudence. 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 441 SAE were reported by 18 Member States. An overview of the SAE reported by type of activity is presented in Fig. 10.

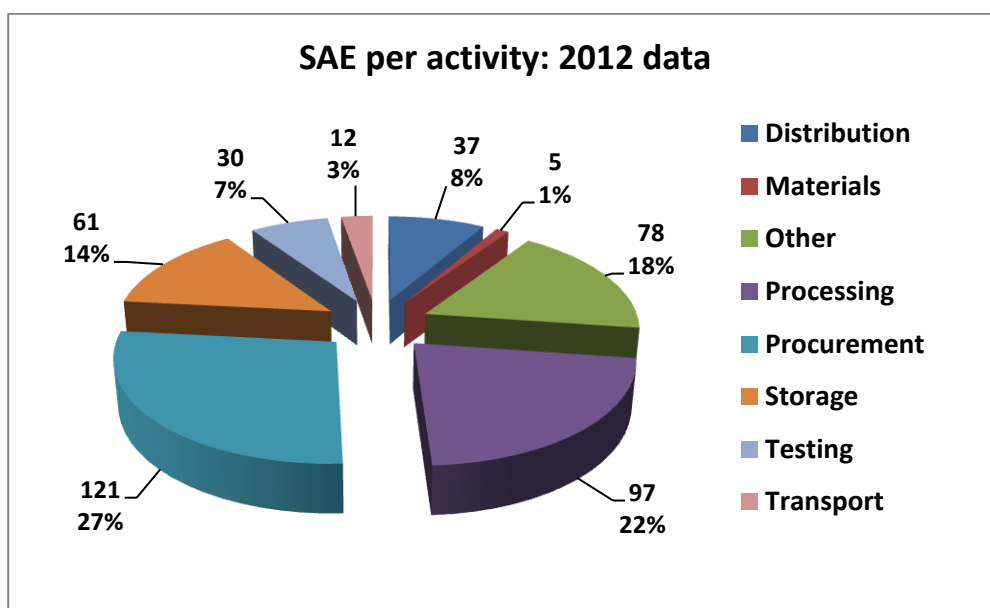


Fig. 10. Number of serious adverse events and percentage of total SAE reported per type of activity

2.3.3. Information by type of SAE

The 441 SAE were attributed to one of the four types of SAE, tissues and cells defects, human error, equipment failure, and other (Fig. 11).

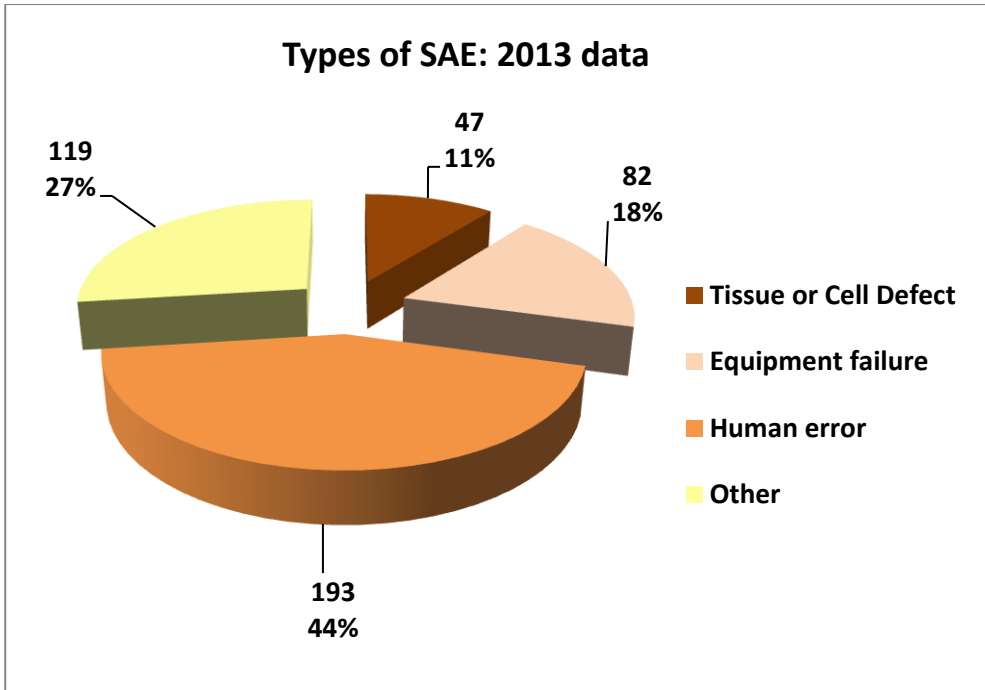


Fig. 11. Serious adverse events relating to each type of SAE

2.3.1. Information by type of SAE and activities

An overall analysis of SAE reported in 2013, taking into account both the donation-distribution chain activities and the specification, is shown in Fig. 12.

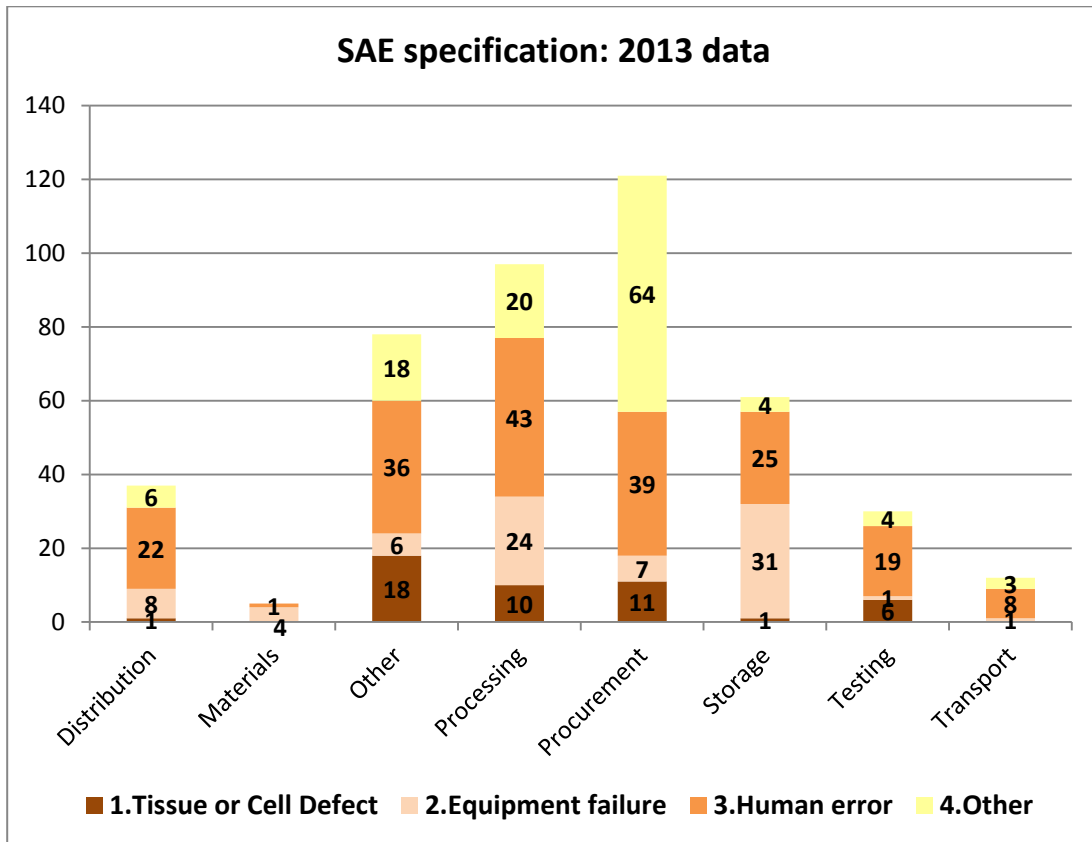


Fig. 12. SAE per type and activities, 2013 data

The graph shows that SAE occur mostly during the procurement and processing 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 G-CSF 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.

Eighteen Member States reported 547 SAR occurring in donors in 2013.

Ten Member States provided data related to SAR in donors of non-reproductive tissues and cells (DE, EL, ES, FI, FR, IE, IT, NL, PT, UK). All 45 cases were associated with haematopoietic stem cells collection procedures (Fig. 13).

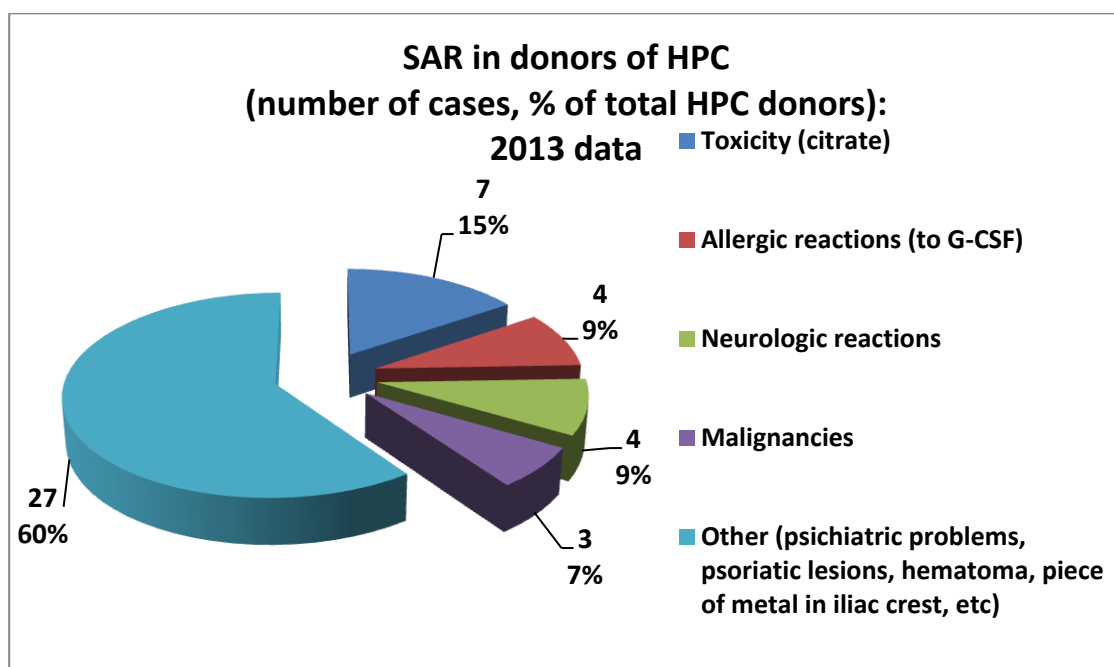


Fig. 13. SAR in HPC donors – 2013 data (Total number 45, amounting to 8% of all reported SAR in donors)

Thirteen Member States (AT, BE, BG, DE, EE, FR, HR, IE, IT, PT, SI, SE, UK) and Norway reported 502 cases of SAR in oocyte donors. Most of the reported SAR reported in oocyte donors were critical, severe and moderate to severe OHSS cases (376). Surgery and anaesthesia complications, infectious complications, and other type of SAR were also reported (Fig. 14).

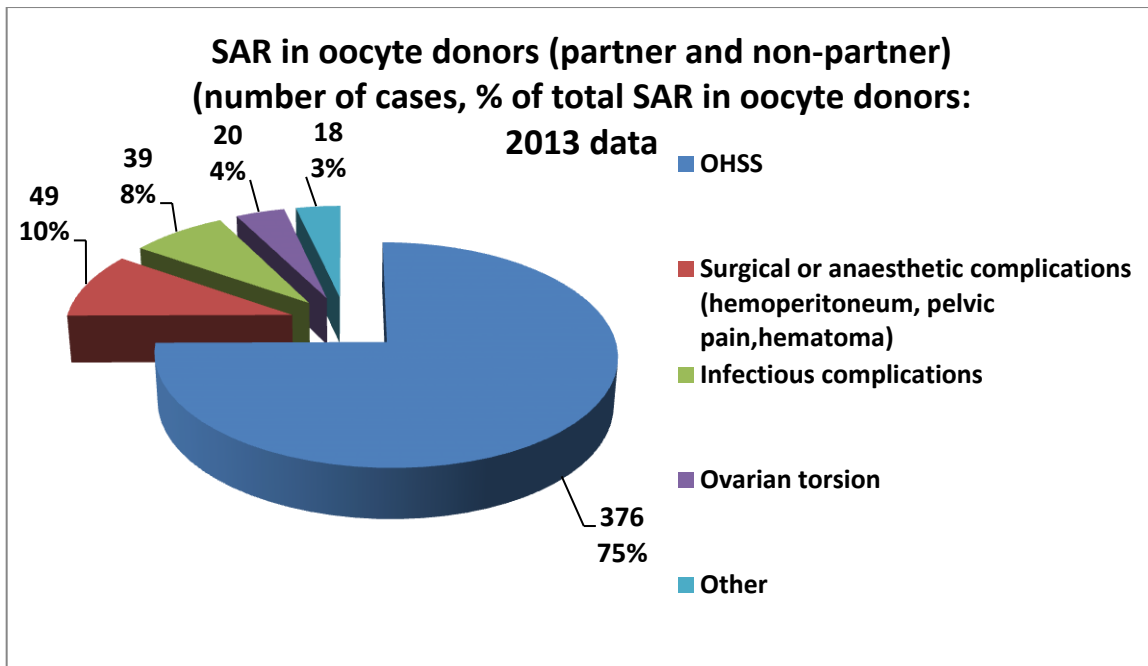


Fig.14. SAR in oocyte donors – 2013 data (Total 502; 92% of total SAR in donors)

This was the second year when Member States reported separately the SAE recorded in partner and non-partner oocyte donors. According to data reported by the Member States, most SAR were recorded for partner-donation (396), 6 for non-partner donation, and for 100 cases the origin of the donation (partner or non-partner) was not specified.

Conclusions

As in previous years, the number of SAR and SAE reported for 2013 is very low (203 and 441 respectively), especially when compared to the number of tissues and cells distributed and processed at EU level (0,015% and 0,028% respectively).

The fact that most Member States find it easier to report data on the amount of tissues and cells distributed, than the number of recipients suggests that more work is needed at the level of organisations responsible for human application (e.g. hospitals, clinics), who are key actors for ensuring not only traceability of tissues and cells, but also an effective tissue vigilance systems. Health professionals involved in transplanting/applying human tissues and cells should be encouraged to submit SAR reports in order to contribute to their understanding and identify possible ways of avoiding SAR.

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 cm² vs or m²; oocytes in units/cycles) may explain why some Member States choose not to report SAR denominator data for these tissues and cells. The Commission together with the Member States will reflect on the most appropriate solution for this issue.

As regards the type of SAR, the data reported in 2010-2013 show that 33% of the SAR associated to the transplantation of non-reproductive tissues and cells are infections, mostly of bacterial and fungal 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 procurement, processing and storage phases, may suggest the need to further clarify what are the most critical aspects need be addressed when revising SOPs and assessing the training needs and competencies of the personnel in EU tissue banks.

The 2014 reporting exercise also showed a significant increase in the number of SAR in donors, suggesting that more and more competent authorities are becoming interested in collecting such data and putting in place appropriate follow-up mechanisms of tissue and cell donors.

Overall, the implementation of vigilance requirements and data collection in the tissue and cell sector seem to have improved over time, as evidenced by the increased number of Member States reporting not only SAR and SAE, but also corresponding denominators. However, as in the previous years, there is still a significant degree of underreporting by some Member States. This issue should be addressed by the new Joint Action VISTART¹⁰ 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.