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HEALTH AND FOOD DIRECTORATE GENERAL

Health Systems and Products Directorate
Substances of Human Origin and Tobacco Control

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**SUMMARY OF THE 2013 ANNUAL REPORTING OF SERIOUS ADVERSE EVENTS AND
REACTIONS FOR TISSUES AND CELLS
(DATA COLLECTED FROM 01/01/2012 TO 31/12/2012)**

Article 7 of Directive 2006/86/EC¹ 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.

This document intends to provide a report of the data collected by the Member States for the year 2012 (from 1st January to 31st of December). The first and second report regarding SARE recorded by the Member States (2010 and 2011 data, submitted to the Commission in 2011 and 2012) were published in 2013² and 2014³, respectively.

1. DATA COLLECTION METHODOLOGY

For 2013, the tools used for the SAR and SAE reporting to the European Commission were:

1) The electronic reporting template adjusted in 2012 in collaboration with a group of Tissues and Cells Competent Authorities participating in the EU-funded project SOHO Vigilance & Surveillance⁴. Definitions or clarifications for the requested data are available as mouse-overs. The classification for "Other serious reactions" (for which further details were not provided in Annex V of the Directive 2006/86/EC) proposed in 2012 was not modified. Additionally, following a suggestion from the ART sector, the template was improved by allowing reporting of SAR in donors separately for non-reproductive and reproductive cells. The template used in 2013 (for 2012 data) was version 2.2.

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 2013, the document was updated to accommodate the changes in the electronic template; the version of the Common Approach document used in 2013 (for 2012 data) was 2.2.

¹ <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF>

² http://ec.europa.eu/health/blood_tissues_organ/docs/tissues_cells_adverse_events_2011_en.pdf

³ http://ec.europa.eu/health/blood_tissues_organ/docs/ratc_report_2012_en.pdf

⁴ <http://ec.europa.eu/chafea/projects/database.html?prjno=20091110>

2. MAIN FINDINGS OF THE 2013 ANNUAL REPORT – DATA COLLECTED DURING 2012

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, except Greece, submitted their SARE reports.

2013 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 two years, many Member States acknowledged that accurate activity data for certain types of tissues/cells were difficult to collect and provided incomplete/approximate numbers. This may explain why estimates for the denominators *i.e.* the numbers for the tissues and cells distributed and the number of recipients of tissue/cell therapies were lower than those reported in 2011. An overview of the data for the denominators for tissues and cells as provided by the Member States in 2011-2013 (data recorded for 2010-2012) is presented in figure 1.

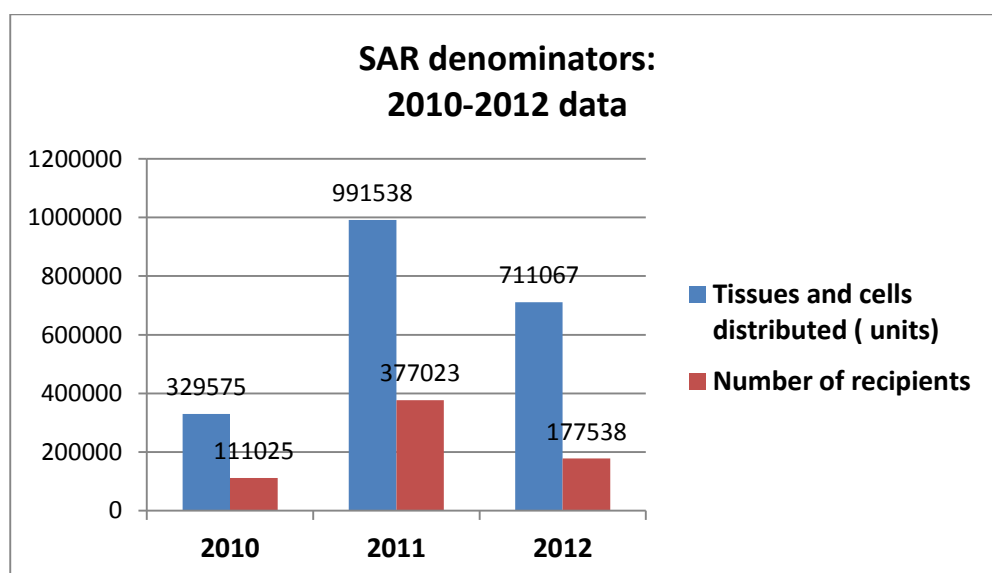


Fig. 1. SAR: 2010-2012 comparative data: Total number of tissues and cells distributed and number of recipients of human tissues and cells

A total number of 138 SAR were reported by 16 Member States for 2012. Overall this number is slightly lower than 2011. The figure is considerably lower than in 2010 (when OHSS⁵ cases following hormonal therapy in donors/patients undergoing ART procedures were included; now such cases are reported as SAR in donors, see section 2.4). A comparison with the number of SAR reported by the Member States in the previous two years for the two main categories of tissues and cells is presented in figure 2.

⁵ OHSS = Ovarian hyper-stimulation syndrome

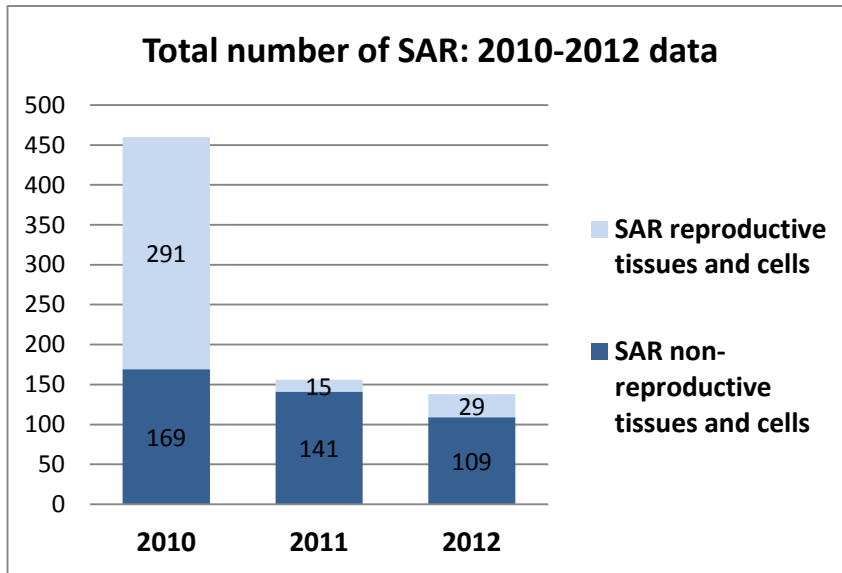


Fig. 2. Total number of SAR: 2010-2012 comparative data (2010 SAR data also include 209 cases of OHSS reported under SAR, which should have been reported under SAR in donors)

As regards reporting of SAE, the total number of tissues and cells processed (used as denominator for SAE evaluation) increased, reaching 887 536 units in 2012 (figure 3). The increase was probably due to improvements made in collecting data from establishments. The number of SAE reported in 2012 is also slightly higher than those reported in the previous two years (499, compared to 426 and 378, respectively), with a significant rise in the category “Other SAE” (figure 4).

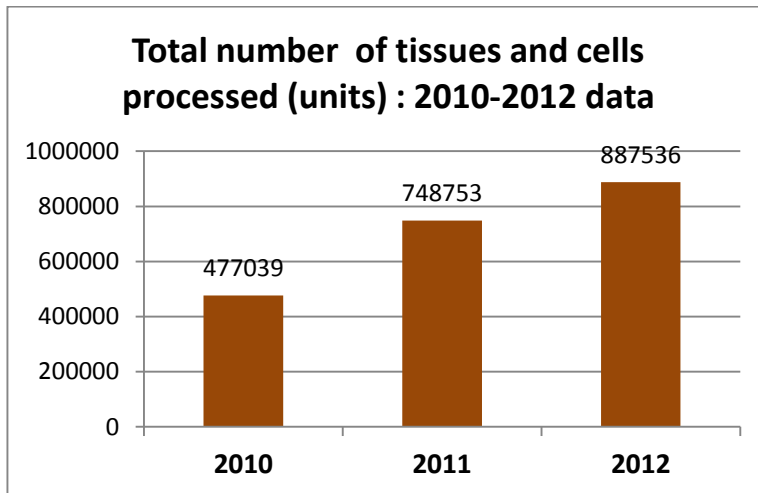


Fig. 3. Total number of tissues and cells processed: 2010-2012 comparative data

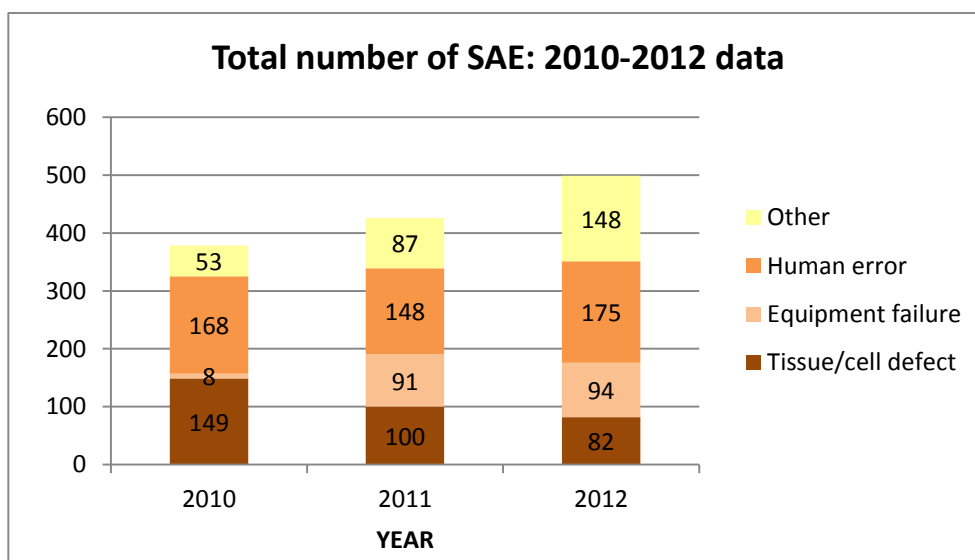


Fig. 4. Total number of serious adverse events (SAE): 2010-2012 comparative data

2.2. Serious Adverse Reactions (SAR)

2.2.1. Information by country

Twenty-seven Member States, as well as Liechtenstein, Norway and Croatia 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 distributed⁶ and number of recipients⁷. 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). An overview of the reports by the Member States of the SAR denominators for both non-reproductive and reproductive tissues and cells is presented in Fig. 5 and 6.

A total number of 711 067 units of tissues and cells were reported as having been distributed by tissue establishments in EU and EEA countries (233 377 units of non-reproductive tissues and cells and 477 690 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).

⁶ "the total number transported or delivered to a clinical unit, even if the clinical unit is in the same building or the same floor"

⁷ "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"

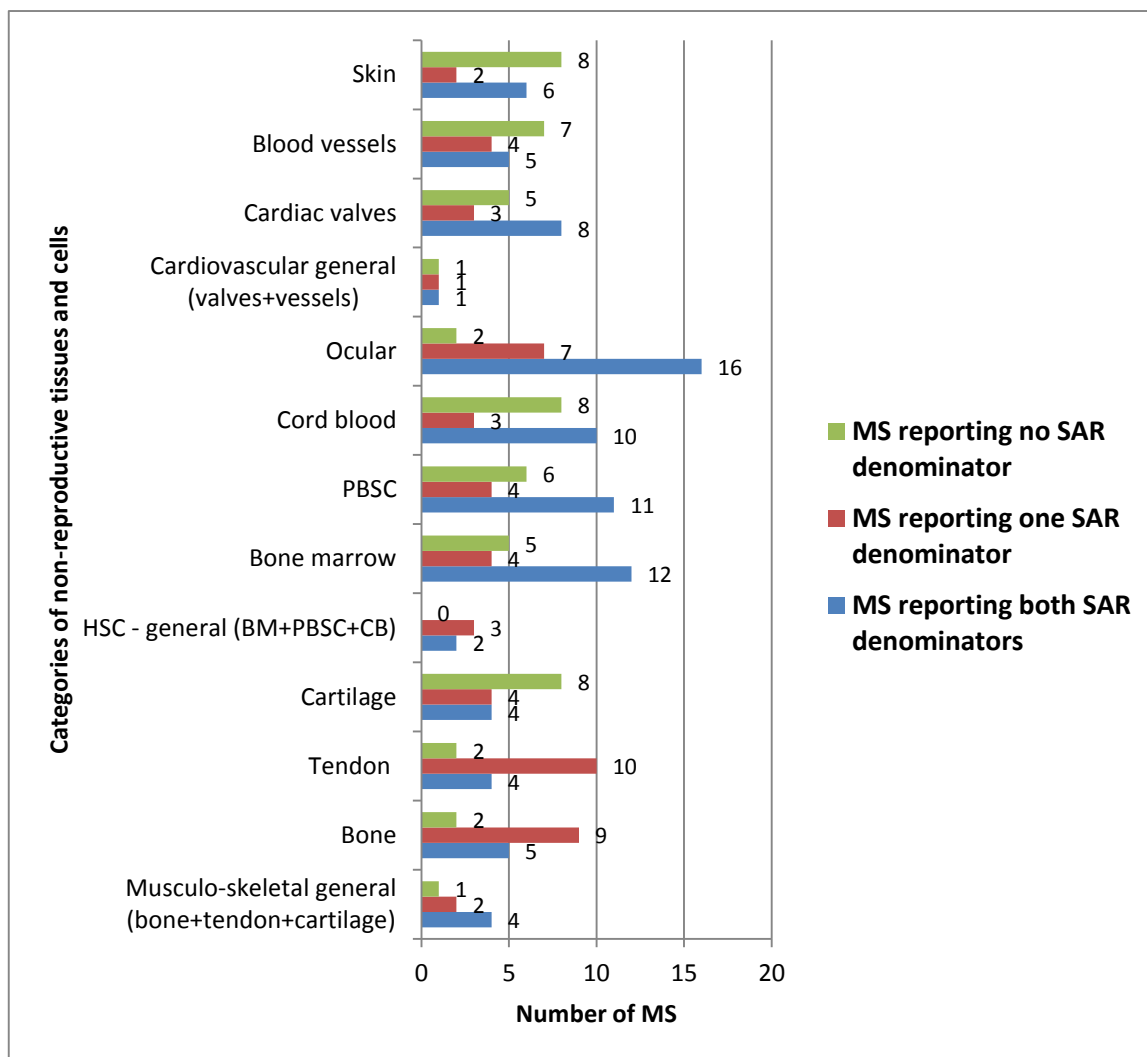


Fig. 5. Reporting of the SAR denominators for non-reproductive tissues and cells (number of tissues and cells distributed and number of recipients) by the Member States (2012 data)⁸

In 2012, 177 538 recipients (patients) were reported as having been treated with tissues or cells (76 940 recipients of a tissue or cell transplantation and 100 598 patients who underwent an ART procedure with sperm, oocytes or embryos).

A total of 138 SAR were reported, of which 109 were related to non-reproductive tissues and cells, and 29 to reproductive cells. Thirteen Member States (AT, DE, ES, FI, FR, HU, IE, IT, NL, PT, SI, SE, UK) reported SAR related to the transplantation of non-reproductive tissues and cells and eight Member States (BE, DE, DK, FI, HR, NL, SE, UK) reported SAR following the application of reproductive cells. Therefore, for non-reproductive tissues and cells, there were 0,05% SAR/tissues and cells distributed and 0,15% SAR/number of recipients. For reproductive tissues and cells, there were 0,01% SAR/tissues and cells distributed and 0,06% 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.

⁸ Activities with certain categories of tissues and cells are not organised in all Member States.

Eleven countries (BG, CY, CZ, EE, LT, LV, MT, PL, RO, SK and LI) reported that in 2012 there were no occurrences of SAR related to the human application of tissues and cells. Seven of the above mentioned countries (CY, CZ, LT, LV, MT, RO and LI) reported no SAR for 2011. As already highlighted in the previous report, for smaller countries where these medical services are on a smaller scale, these data seem plausible. In the case of larger countries, however, this may indicate that SARE reporting procedures had not been sufficiently embedded at a national level to ensure reporting by professionals in the field and/or tissue establishment staff.

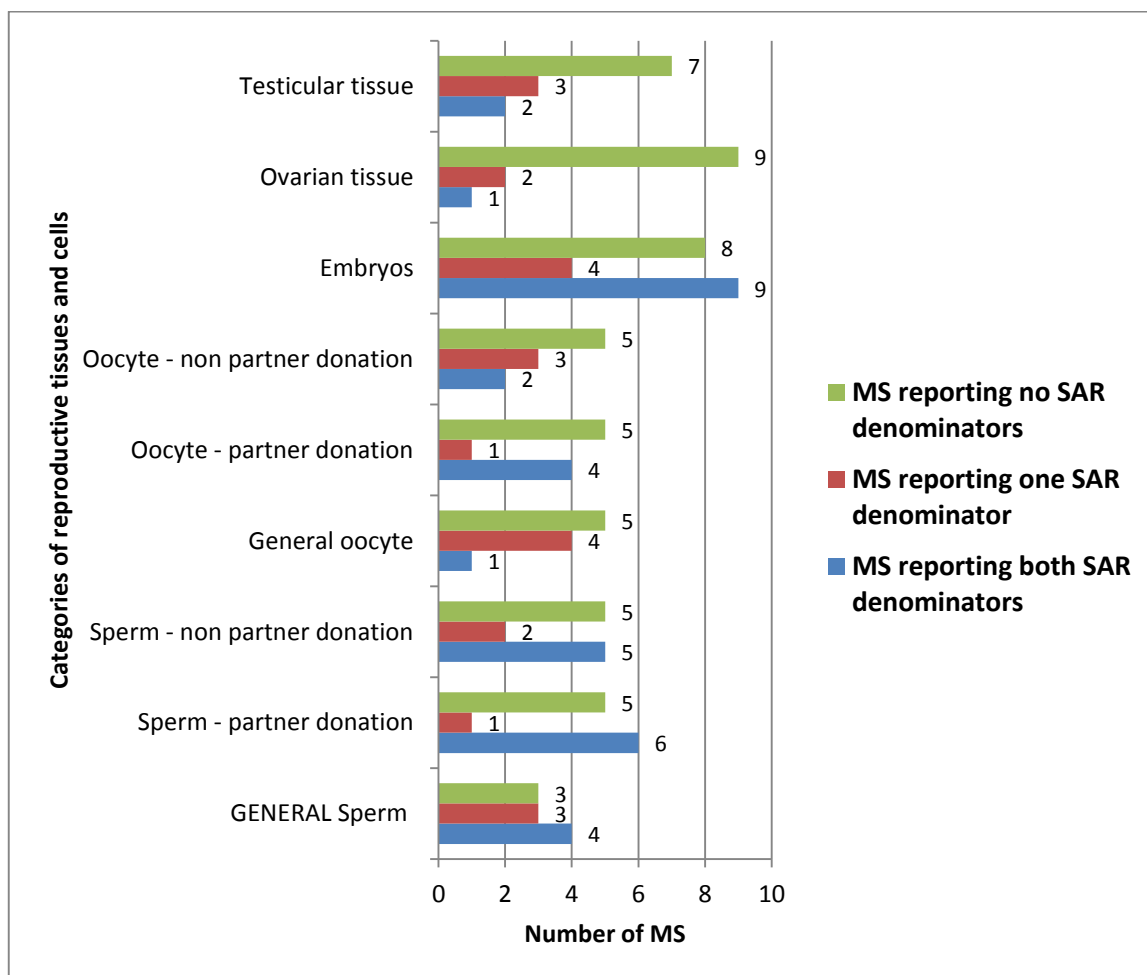


Fig. 6. Reporting of the SAR denominators for reproductive tissues and cells (number of tissues and cells distributed and number of recipients) by the Member States (2012 data)⁹

2.2.2. Information by type of tissue/cell

Of the 138 SAR reported:

- 109 SAR (92%) were related to the transplantation of non-reproductive tissues or cells (Fig. 7):

⁹ Activities with certain categories of tissues and cells are not allowed and/or not organised in all Member States.

- 74 SAR were related to haematopoietic stem cell transplants (including bone marrow 34, blood peripheral stem cells 30, and cord blood 10);
- 35 SAR were related to transplantation of replacement tissues (bone 5, tendons/ligaments 2, other musculo-skeletal tissue 1, ocular tissues 22, blood vessels 2, skin 1, amniotic membrane 1, other tissues 1).
- 29 SAR (8%) were related to the human application of reproductive cells and tissues (sperm, oocytes) (Fig. 8);

No SAR were reported for the following categories of tissues and cells: cartilage, cardiac valves and other cardiovascular tissues, hepatocytes, pancreatic islets, donor lymphocyte infusions (DLI), other haematopoietic progenitor cells (HPC), other tissues and reproductive tissues (ovarian and testicular tissue).

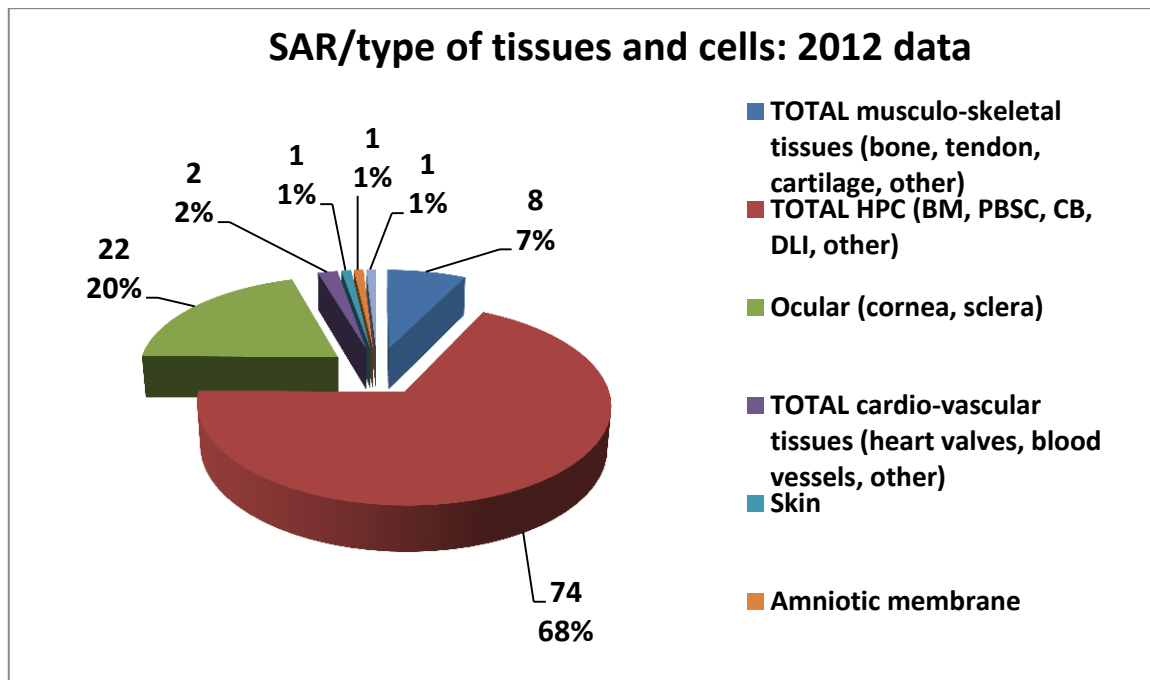


Fig.7. Number of SAR for each type of non-reproductive tissues and cells (absolute values and percentage from total SAR), 2012 data

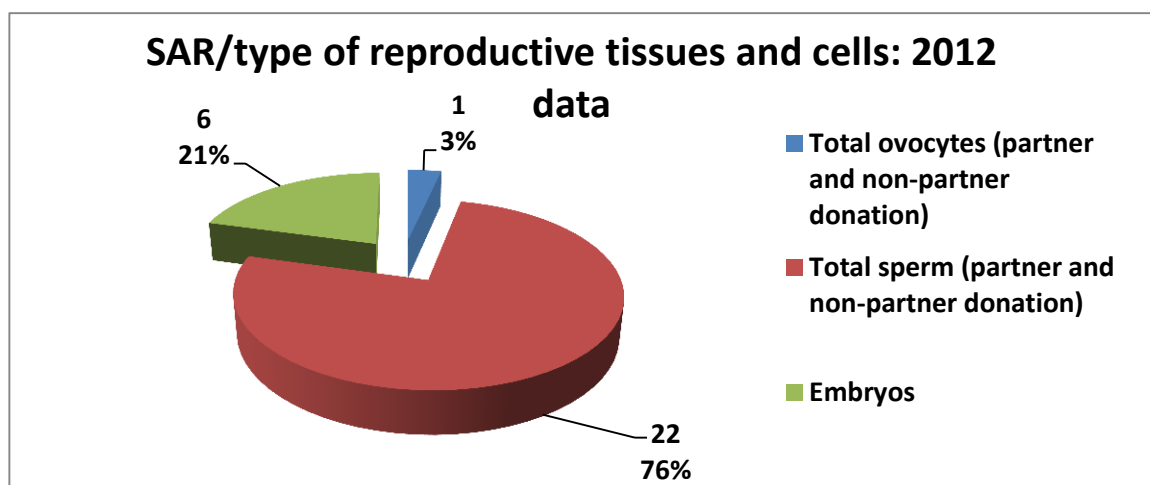


Fig.8. Number of SAR for each type of reproductive cells (absolute values and percentage from total SAR), 2012 data

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: 22 cases (20% of all reported SAR for non-reproductive tissues and cells) as following:

- 15 cases of bacterial infections, reported for the following transplanted tissues/cells: HPC 5, musculo-skeletal 5, ocular tissues 5;
- 3 cases of viral infections (1 viral encephalitis in the context of an EBV lympho-proliferative syndrome following bone marrow transplantation, 1 graft failure following transmission of HHV-6 subsequent to cord blood transplantation, 1 case of EBV transmission following composite tissue transplantation¹⁰);
- 4 cases of other transmitted infections (1 case of pneumonia after PBSC transplantation, 3 fungal infections following cornea transplantation).

- Transmitted malignant diseases: 1 case reported subsequent to PBSC transplantation (1% of all reported SAR for non-reproductive tissues and cells).

- Other SAR: 86 cases (79% of reported SAR for non-reproductive tissues and cells). In this broad and heterogeneous category:

- 65 SAR concerned haematopoietic stem cells transplantation procedures, and
- 21 SAR concerned transplantation procedures with other tissues (ocular tissues 14, musculo-skeletal tissues 3, cardio-vascular tissues 2, skin 1, amniotic membrane 1).

More details concerning the SAR reported for different types of non-reproductive tissues and cells are presented in figures 9, 10 and 11.

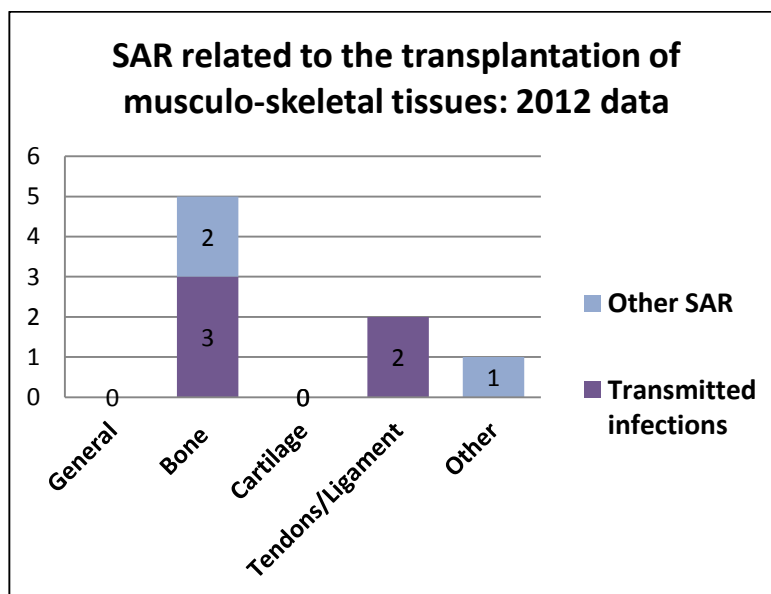


Fig. 9. SAR following transplantation of musculo-skeletal tissues – 2012 data (Total 8 SAR; 0,006% SAR/total distributed musculoskeletal tissues)

¹⁰ Competent Authorities for tissues and cells and for organ transplantation agreed that vascularised composite tissues should be covered by the organ transplantation Directives (http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_mi_20121203_en.pdf), therefore in the future such cases should not be reported under tissues and cells SARE.

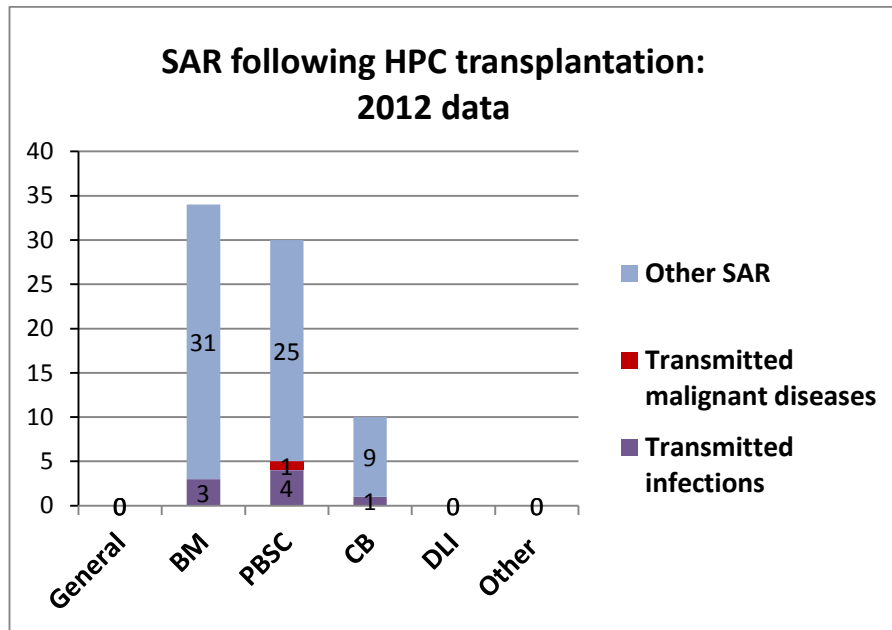


Fig. 10. SAR subsequent to HPC¹¹ transplantation – 2012 data (Total 74 SAR; 0,15% SAR/total distributed HPC)

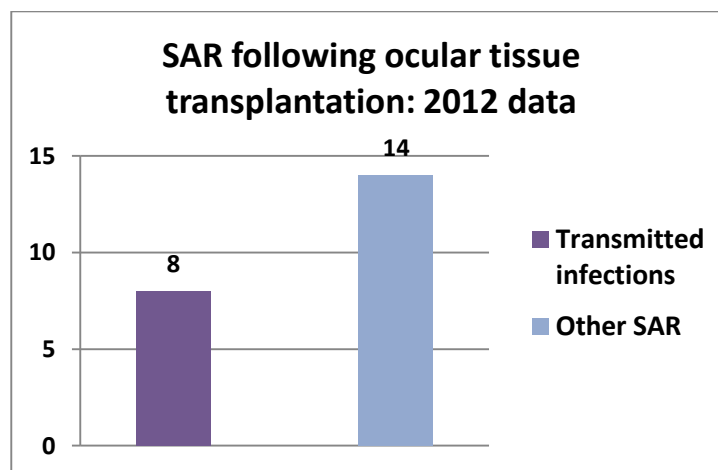


Fig. 11. SAR following ocular tissue (cornea) transplantation - 2012 data¹² (Total 22 SAR; 0,08% SAR/total distributed ocular tissues)

The 29 SAR associated with the application of reproductive cells were classified as following:

- Transmitted infections: 1 bacterial infection reported following sperm application (4% of reported SAR for this category of cells)
- Transmitted malignant diseases: 0

¹¹ HPC = human progenitor cells; BM = bone marrow; PBSC = peripheral blood stem cells; CB = cord blood; DLI = donor lymphocyte infusion

¹² Only unexpected graft rejection and graft failure due to quality of the graft are reported under SAR.

- Other disease transmissions (e.g. genetic diseases): 21 cases (72%) subsequent to ART procedures with oocytes (1 case) and sperm (20 cases).
 - Other SAR: 7 cases (24% of reported SAR), 3 occurred after embryo implantation, and 4 following ART fertility treatment with oocytes (3) and sperm (1).
- Of the total 29 SAR, 28 were reported for non-partner donation cases and only one SAR was reported for partner donation.

2.3. Serious Adverse Events (SAE)

2.3.1. Information by country

A total of 28 countries (26 Member States, Liechtenstein and Croatia) submitted the annual report template and therefore complied with the annual report submission established by Article 7.

Eighteen countries (AT, BG, CY, EE, ES, FI, HR, HU, IE, IT, LT, NL, PL, PT, SK, SE, SI, UK) provided data regarding the number of tissues and cells processed in 2012. 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 887 536 units of tissues and cells were reported as processed in 2012.

SAE were reported by 17 Member States (AT, BE, DE, DK, ES, FI, FR, HU, HR, IE, IT, NL, PL, PT, SE, SI, UK). The total number of SAE reported for 2012 was 499, showing that such events occurred for 0,056% 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 a national level.

2.3.2. Information by activity

A total of 499 SAE were reported by 17 Member States. An overview of the SAE reported by type of activity is presented in Fig. 12.

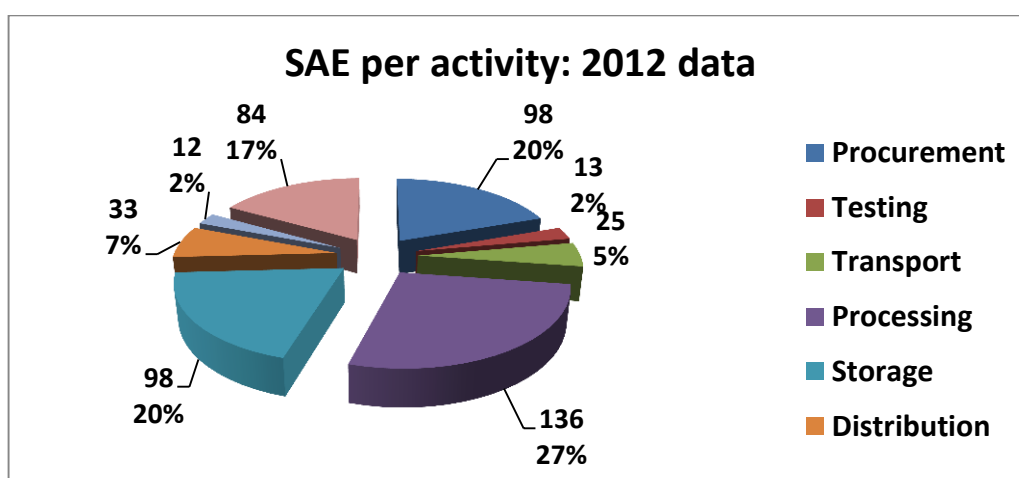


Fig. 12. Number of serious adverse events and percentage of total SAE reported per type of activity

Examples of SAE reported in 2012 are included in Annex I of this report.

2.3.3. Information by type of SAE

The 499 SAE were attributed to one of the four types of SAE, tissues and cells defects, human error, equipment failure, and other (Fig. 13).

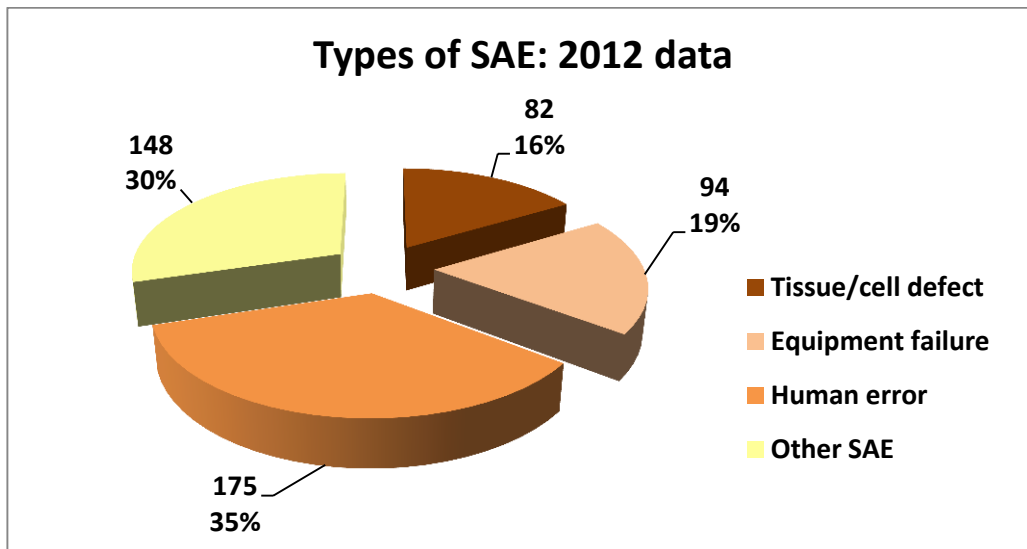


Fig. 13. Serious adverse events relating to each type of SAE

2.3.1. Information by type of SAE and activities

An overall analysis of SAE reported in 2012, taking into account both the donation-distribution chain activities and the specification, is shown in Fig. 14.

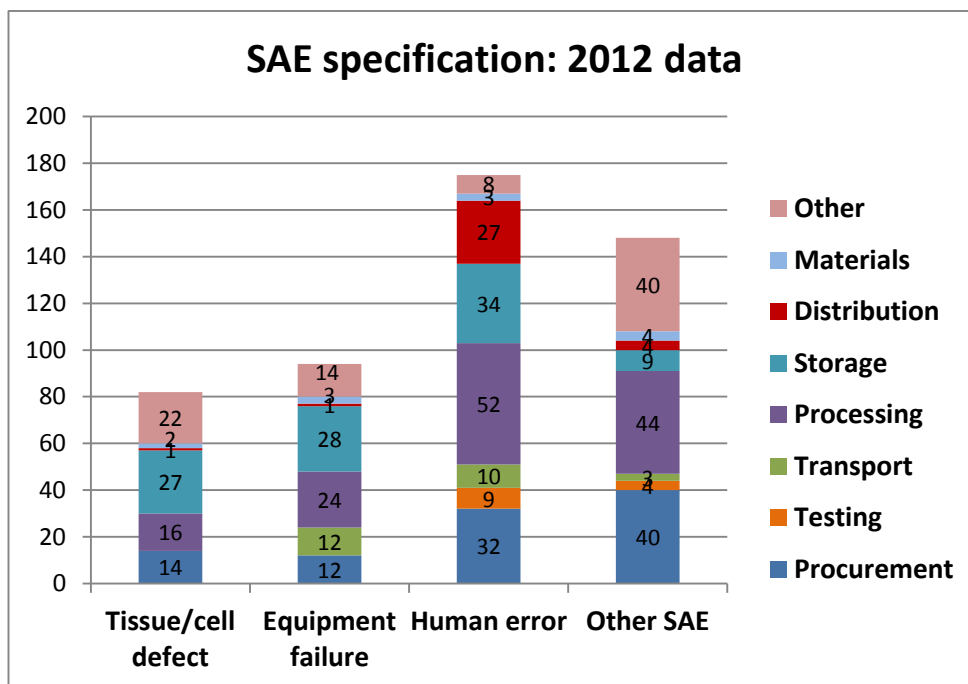


Fig. 14. Types of Serious adverse events per type and activities within each type, 2012 data

The graph shows that SAE occur mostly during the procurement, processing and storage steps. 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.

Fifteen Member States reported 294 SAR occurring in donors in 2012.

Ten Member States provided data related to SAR in donors of non-reproductive tissues and cells (BE, DE, DK, FR, IT, NL, PL, PT, SE, UK), as follows:

- 20 were associated with haematopoietic stem cells collection procedures (Fig. 15), and
- 3 were associated with procedures involving procurement of other tissue types (bone, cartilage, chondrocytes).

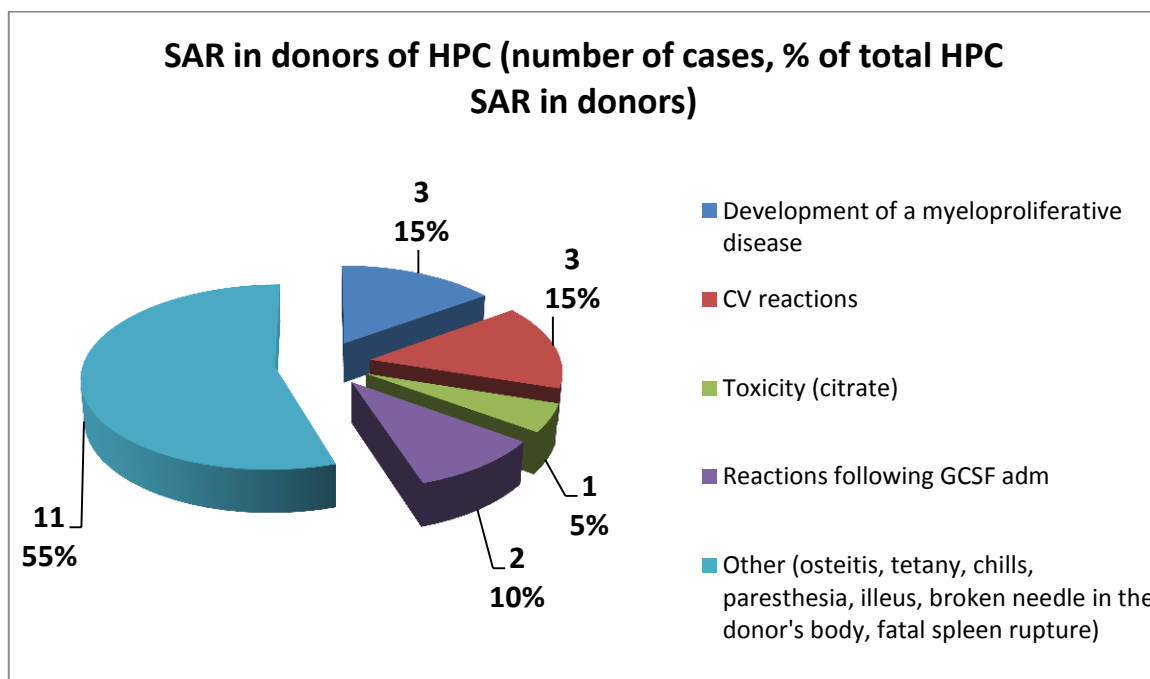


Fig. 15. SAR in HPC donors – 2012 data (Total number 20, amounting to 6,8% of all reported SAR in donors)

Eight Member States (AT, BG, EE, DE, IE, SI, SE, UK, FR) reported 271 cases of SAR in oocyte donors. Most of the SAR reported in oocyte donors were critical, severe and moderate to severe OHSS cases (118). Surgery and anaesthesia complications, infectious complications, arterial and venous thrombosis, and other type of SAR were also reported (Fig. 16).

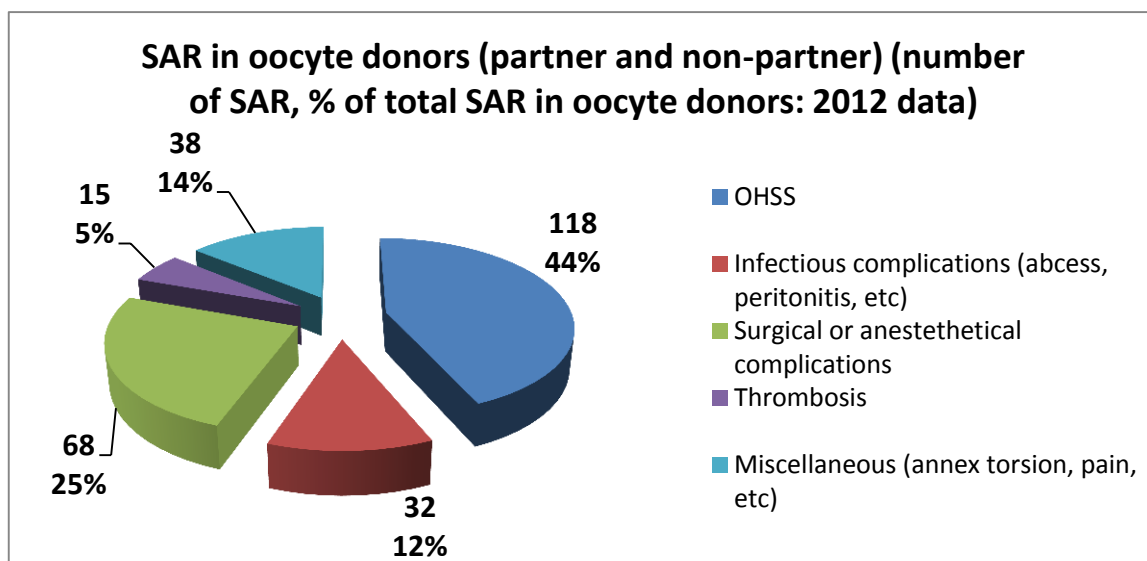


Fig.16. SAR in oocyte donors – 2012 data (Total 271; 92,2% of total SAR in donors)

The 2013 reporting template enabled, for the first, time separate data collection for partner and non-partner oocyte donors. According to data reported by the Member States, 180 SAR were recorded for partner-donation (AT, FR, IE, UK), two for non-partner donation (FR), and for 91 cases the origin of the donation (partner or non-partner) was not specified (BG, DE, EE, SE, SI).

Conclusions

As in previous years, the number of SAR and SAE reported for 2012 is very low (138 and 499 respectively), especially when compared to the number of tissues and cells distributed and processed at EU level (0,02% and 0,06% 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 organisations responsible for human application (e.g. hospitals, clinics) should be made aware that provision of data on the number of recipients as well as full traceability of tissues and cells constitute essential components of 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 cm^2 vs or m^2 ; oocytes in units/cycles) may explain why some Member States choose not to report SAR denominator data for these tissues and cells.

As in the past two years, most of the SAR have been related to HPC transplantation, cornea transplantation and to the use of musculo-skeletal tissues, which may indicate that

more attention needs to be focused on these sectors. However the high number of SAR may be also explained by the fact that these are the most common type of transplantations performed across EU.

As regards the type of SAR, the data reported in 2010-2012 show that approximately 20% are infections, mostly of bacterial and fungal origin. Since 2009 (when Member States reported SAR data for the first time), a very low number of viral infections were registered (8), mostly for viruses for which screening is not mandatory (e.g. EBV, HHV, CMV); up to this date only one case of HCV transmission was reported (in 2011), confirming the value of the EU safety and quality requirements. Almost 80% of the recorded SAR were included in the broad category of “Other SAR”, which requires more in depth analysis at EU level.

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.

With regard to SAE, the high proportion of incidents under the human error category, especially in the procurement, processing and storage phases, may suggest a need to improve both SOPs and training of personnel, competency assessments as well as staffing needs in EU tissue banks.

The 2013 reporting exercise also showed an increase in the number of Member States voluntarily reporting SAR in donors, suggesting that in general competent authorities are becoming more interested in collecting such data and putting in place appropriate follow-up mechanisms of tissue and cell donors.

Overall, the implementation of vigilance requirements in the tissue and cell sector seems 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. There is a need to identify the reasons for under reporting and address the concerns which may include insufficient training of personnel (in tissue establishments and organisations responsible for human application), the risk of negative publicity and/or the fear of adverse regulatory consequences for reporting institutions/professionals. DG SANTE will continue to support the sector with these efforts.

ANNEX I. Examples of SAE reported in 2013 (recorded between 01/01/2012 and 31/12/2012)

Activity	Type	Examples of SAE
Procurement	Human error	Incorrect retrieval of tissue Failure to label the tissue No evaluation of a donor before procurement (with testing results negative)
	Equipment failure	Leaks in collection bags
Testing	Human error	Incorrect interpretation of test results
Processing	Tissue or cell defect	Contamination of the tissue
	Human error	Mix-up of cells during processing Inappropriate processing of cornea (discarded) Accidental heating of cord blood stem cells
	Equipment failure	Incubator set at inappropriate temperature (accidental heating) Defect in bag containing cord blood
Storage	Tissue or cell defect	Bacterial contamination;
	Human error	Staff from company supplying liquid nitrogen did not close the lid completely after filling the tank. Accidental thawing of several stem cell bags; problems with liquid nitrogen tanks (e.g. low level of liquid nitrogen) Inappropriate release of tissues stored in quarantine.
	Equipment failure	Failure of the refrigeration system. Defect in cryopreservation and alarm system.
Distribution	Human error	Error in identification of the recipients resulted in distribution of tissue to the wrong clinics Straws dropped in the liquid nitrogen tank Wrong labelling (incorrect label applied on the bag) Incorrect documentation sent along with the tissue graft Non-compliant labelling Incorrect tissue release procedure
	Equipment failure	Cord blood bag broke during distribution;
Transport	Human error	Tissues irradiated in the airport despite appropriate labelling on the transport container (material discarded);
	Equipment failure	Temperature outside acceptable range during transport of tissues
Materials	Human error	Wrong labelling of corneas (discarded)
	Equipment failure	Incubator malfunction overnight following electric breakdown Defective tissue container
Other	Tissue or cell defect	Presence of clots in stem cell bag Rejection of stem cell bag by the transplantation centre because it was not within acceptable range
	Human error	Mix-up of stem cell donors Incorrect donor selection
	Other	Unauthorised importation (material recalled);