



**EUROPEAN COMMISSION**  
DIRECTORATE GENERAL FOR HEALTH AND FOOD SAFETY

**Directorate B - Health systems, medical products and innovation**  
**B4 – Medical products: quality, safety, innovation**

## **SUMMARY OF THE 2018 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS FOR TISSUES AND CELLS**

(Data collected from 01/01/2017 to 31/12/2017 and submitted to the European Commission in 2018)

### **EXECUTIVE SUMMARY**

Human tissues and cells for human application provide important benefits to the lives of thousands of EU citizens every year. However, the use of any substance of human origin carries some risk, notably the potential for transmission of disease from the donor. These risks can be minimised by the application of safety and quality measures as laid down in EU legislation. Vigilance and surveillance programmes allow the detection and investigation of adverse incidents and the application of corrective and preventive measures, making them indispensable for improving safety and quality in the fields of donation, transplantation and medically assisted reproduction.

In line with the obligations defined in the legislation<sup>1</sup>, EU Member States submit to the European Commission (henceforth referred to as 'the Commission') an annual report on the notifications of Serious Adverse Reactions (SAR) and Serious Adverse Events (SAE) compiled by each Competent Authority. For this purpose, definitions of SAR and SAE are provided in the EU legislation<sup>2</sup> (SAR are incidents where actual harm to a donor or patient has occurred; SAE are incidents where no harm has occurred but a risk of harm was detected). The Commission, in turn, publishes this annual summary of the reports received, making it available to the Competent Authorities, healthcare professionals and the general public.

Since 2008, the reporting countries (EU Member States, Liechtenstein and Norway) have submitted to the Commission annual vigilance reports on the notification of SAR occurring in recipients of tissues and cells, and SAE which can occur at all of the different stages from donation to the clinical application of those tissues or cells.

The Commission works with the relevant Competent Authorities to standardise data collection procedures and to improve both the accuracy and the comparability of the information submitted. The consistency and completeness of the data collection and submission to the Commission have improved over time. The SAR/SAE (henceforth referred to as 'SARE') exercise has also facilitated the development and consolidation of the Member States' national vigilance programmes. A Vigilance Expert Sub-Group (VES, a subgroup to the Competent Authorities on Substances of Human Origin Expert Group) was established by the Commission in 2017, with the aim of supporting the development and improvement of the SARE reporting system.

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<sup>1</sup> Article 7 and Annexes III, IV and V of Directive 2006/86/EC

<sup>2</sup> Article 3 of Directive 2004/23/EC

This report summarises the data submitted by the Member States during 2018, collected by the reporting countries during 2017, and draws general conclusions, comparing the information with data submitted in previous years. The key findings of the 2018 reporting exercise are the following:

- The overall number of reported tissues and cells distributed in 2017 amounted to 1,000,693 units (330,128 non-reproductive, reported by 25 countries, and 670,565 reproductive tissues and cells, reported by 14 countries). Nineteen countries reported a total of 302,157 recipient patients. Twenty-two countries reported the total number of tissues and cells processed, which reached 1,862,293 units (20 countries reported 264,637 tissues processed in the non-reproductive category and 14 countries reported 1,597,656 in the reproductive category).
- A total of 231 SAR were reported by 27 countries, of which 101 were related to non-reproductive and 130 to reproductive tissues and cells. Data showed that 14% of the SAR associated with the transplantation of non-reproductive tissues and cells were infections, mostly of bacterial or fungal origin. The vast majority of the reported SAR for reproductive cells (96%) were related to the transmission of genetic diseases.
- A total of 756 SAE were reported (611 related to non-reproductive tissues and cells, reported by 18 countries, and 145 to reproductive tissues and cells, reported by 17 countries), most of which occurred during procurement, processing or testing stages. These were mainly attributed to human error or tissue or cell defects.
- Recognising the importance of protecting donors, the Commission continues to collect details of donor adverse reactions on a voluntary basis. In 2017, 710 cases of SAR in donors were reported by 21 countries. Of those, 34 were related to non-reproductive and 676 to reproductive tissues and cells.

Before publication, the data in this report was presented at the Tissues and Cells Competent Authority meetings in May and October 2019. The participating countries had the opportunity to verify their national data and to discuss and share experience and knowledge on the field.

## **1. DATA COLLECTION METHODOLOGY**

This report provides a summary of the data reported to the Commission in 2018 by 26 Member States and Liechtenstein and Norway (Cyprus and Slovakia did not provide data) pertaining to the reporting period from 1 January to 31 December 2017. It also includes comparisons with the data from previous years and provides general conclusions determined from the analysis performed.

The Commission provided the following tools to the participating authorities to promote a standardised approach to data reporting:

- 1) An electronic reporting template (template version 2.7) to be sent to a DG SANTE hosted database.
- 2) The Common Approach document for the definition of reportable SAR and SAE (“Common Approach”) attached to the electronic reporting template. The aim of the document, although not legally binding, is to provide guidance to Member States when reporting. The Common Approach has been regularly updated to clarify points of ambiguity and inconsistency. This has in turn resulted in a gradual increase in the quality and accuracy of the data collected from the Member States. In 2018, version 2.7 of the Common Approach document was available to those countries reporting 2017 SARE data.

In December 2018, a grant agreement was signed between the Commission and the European Directorate for the Quality of Medicines & HealthCare (EDQM), Council of Europe, to carry out the verification, analysis and drafting of the summary report of the SARE exercise. Therefore, at the beginning of 2019, the EDQM started contacting reporting countries, when needed, in order to clarify and verify the accuracy of the reported data. Subsequently, the EDQM performed the detailed analysis of the information presented in this report.

## 2. MAIN FINDINGS OF THE 2017 DATA COLLECTION

### 2.1. Activity data (denominators)

As part of the reporting exercise, Member States are requested to provide data not only on SAR and SAE but also concerning their national activity. Although not legally binding, providing data on the *number of tissues distributed*, the *number of recipients* and the *number of tissues processed* at national level facilitates a better overview and understanding of the different activities in the Member States and helps to put the data on SARE into context. In this exercise, as stated in the Common Approach, the *number of tissues and cells distributed* and the *numbers of recipients* are used as denominators in the analysis of the SAR and the *number of tissues processed* is used as a denominator in the analysis of the SAE.

As in previous years, many countries acknowledged that accurate activity data for certain types of tissues and cells were difficult to collect and some provided incomplete numbers for the SAR denominators. A few countries could not provide data as the measurement units used at national level were not harmonised with those requested in the EU exercise (e.g. in the field of medically assisted reproduction, some countries collected data as number of cycles).

In the case of non-reproductive tissues and cells, 25 countries reported data on *units distributed* (AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, HU, IE, IT, LT, LV, MT, NL, PL, PT, RO, SI, SE and UK) and 18 (AT, BG, CZ, DK, EE, EL, FI, FR, HR, HU, IE, IT, LT, MT, NL, PT, RO and SE) on *recipients*. For reproductive tissues and cells, 14 countries (AT, BE, BG, CZ, DK, EE, HR, HU, IE, LV, MT, NL, SI and SE) and 12 countries (AT, BG, CZ, DK, EE, HR, IE, LT, MT, NL, SE and UK) reported data on *units distributed* and *number of recipients*, respectively.

The overall *number of distributed tissues* and cells in 2017, as submitted by the reporting countries, amounted to 1,000,693 units. For non-reproductive tissues, 330,128 units were distributed, whereas 670,565 units were distributed for reproductive tissues. Of those, 276,702 sperm units were delivered for insemination and 392,623 embryos, following partner and non-partner donation, were delivered for transfer. Additionally, 122 ovarian tissues and 1,118 testicular tissues were distributed for the preservation of fertility.

The main types of non-reproductive tissues and cells distributed were skeletal tissues<sup>3</sup> (209,102 units), haematopoietic stem cells (HSC; 51,163 units) and ocular tissues (37,542 units). See Figure 1 for further details.

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<sup>3</sup> The “general” category is used by Member States that do not collect data separately for each type of tissue or cell in some categories (i.e. musculoskeletal tissues vs bone, cartilage, tendons/ligaments and other musculoskeletal tissues such as meniscus or ear ossicles).

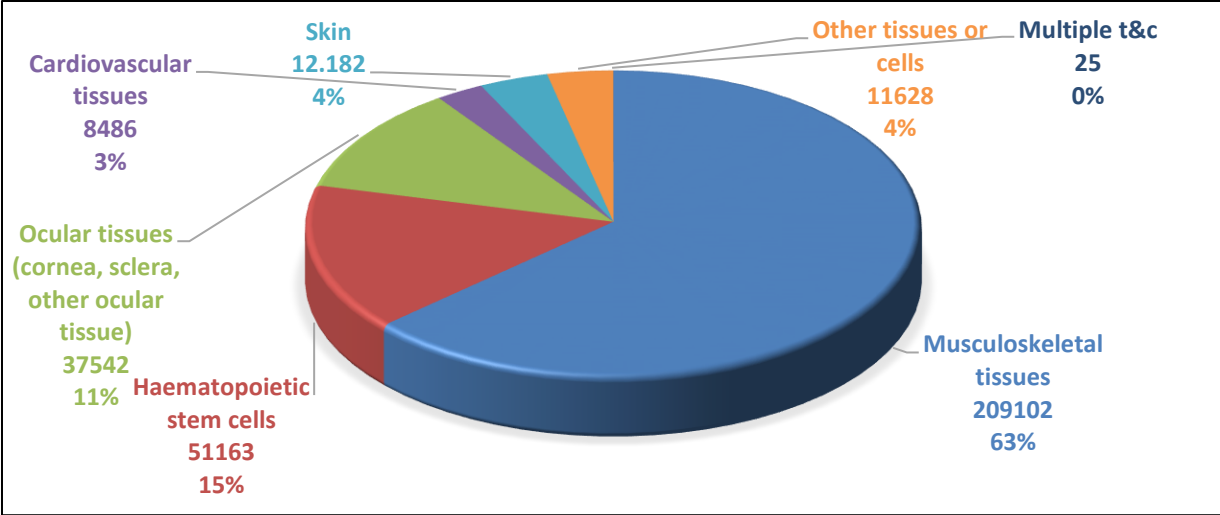


Figure 1. Total number of non-reproductive tissues and cells distributed (units); data 2017.

In 2017, 19 countries reported a total of 302,157 recipients (patients) having received tissues or cells. Of these, 114,646 were recipients of non-reproductive tissues or cells. Figure 2 shows the total number of patients reported as having received each type of non-reproductive tissue or cell.

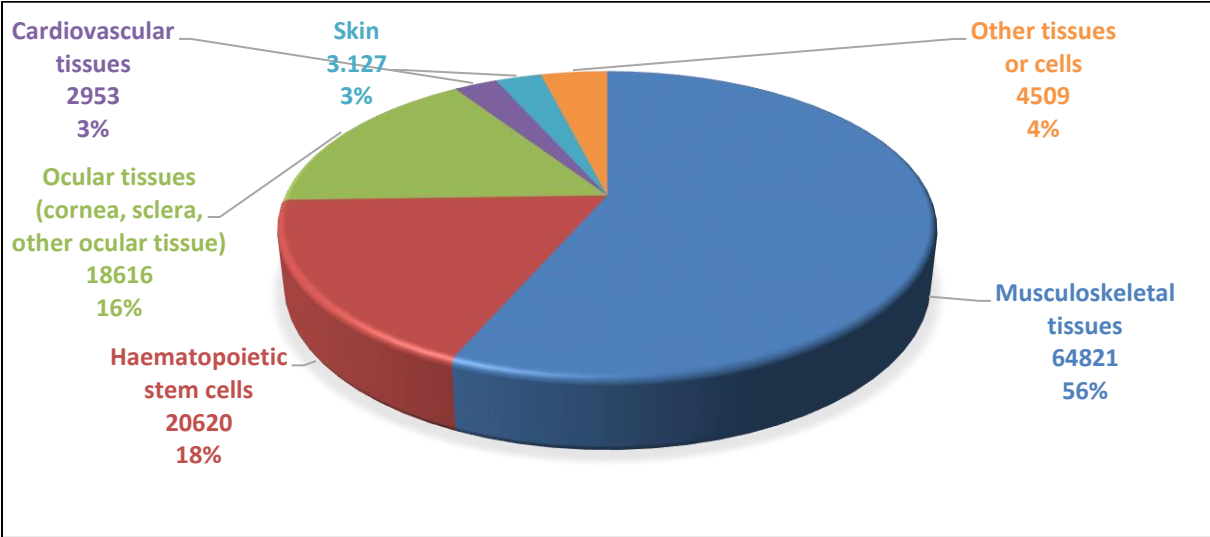


Figure 2. Total number of recipients per type of non-reproductive tissues and cells; data 2017.

For reproductive cells, 187,511 patients underwent a medically assisted reproduction procedure. Of those, 40,509 involved partner or non-partner sperm, 146,869 involved partner or non-partner embryos, 28 involved transplantation of ovarian tissue and 105 of testicular tissue.

A general overview of the data for the SAR denominators for non-reproductive and reproductive tissues and cells provided by the reporting countries in the period between 2012-2018 (data pertaining to 2011-2017) is presented in Figures 3 and 4, respectively. It is noted that in this exercise, the number of tissues and cells distributed in the reproductive field has significantly decreased in comparison with previous exercises. This can be partially explained by the fact that in this exercise, for the first time, the category of reporting data for reproductive tissues and cells data has been modified and a revised classification of the reproductive tissues and cells category has been included in the reporting template. This change is aimed at facilitating the description of practices in the medically assisted

reproduction field (i.e. sperm for insemination and embryos). In addition to this, some countries with high levels of activity in this field were not able to provide denominators in this reporting exercise.

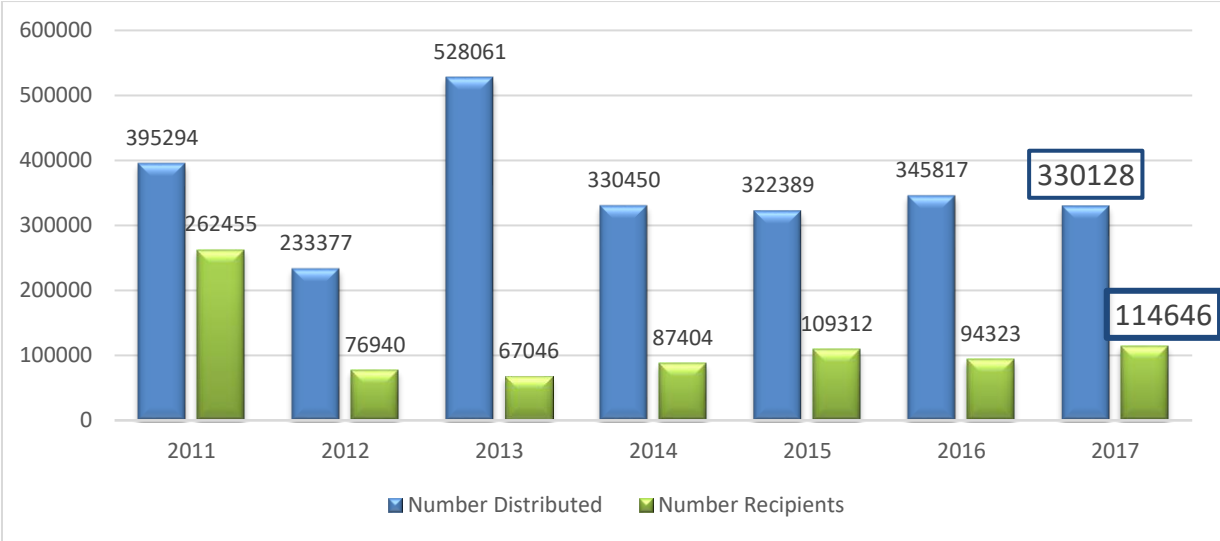


Figure 3. Total number of non-reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2017 comparative data.

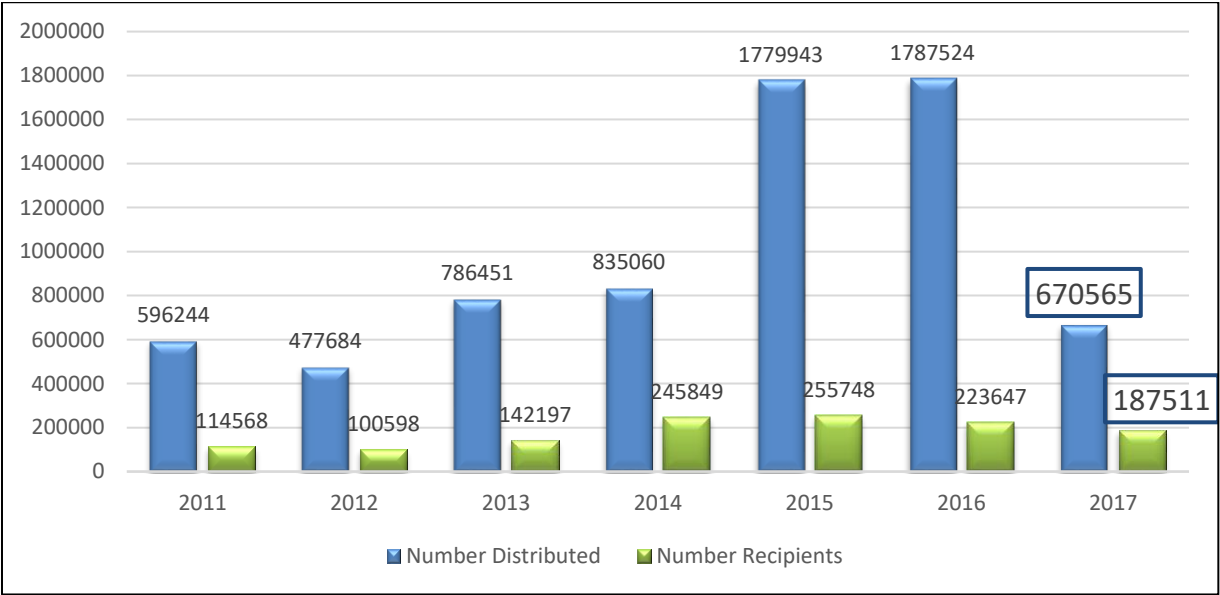


Figure 4. Total number of reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2017 comparative data.<sup>4</sup>

Twenty-two countries (AT, BG, DE, DK, EE, EL, ES, FI, HU, HR, IE, IT, LI, LT, LV, MT, NL, PL, PT, SI, SE and UK) provided data regarding the *number of tissues and cells processed* in 2017. Following the Common Approach, the term “*tissues and cells processed*” refers to tissues and cells processed in tissue establishments, but not necessarily distributed to end users. Overall, a total of 1,862,293 tissues and cells were reported as processed in 2017.

<sup>4</sup> As stated in the Common Approach this data includes the number of sperm delivered to a clinic for insemination or to a laboratory for IVF, the number of oocytes delivered to a laboratory for IVF and the number of embryos delivered to a clinic for transfer to patients.

Comparative data from previous exercises (2010-2017 data) is presented in Figure 5.

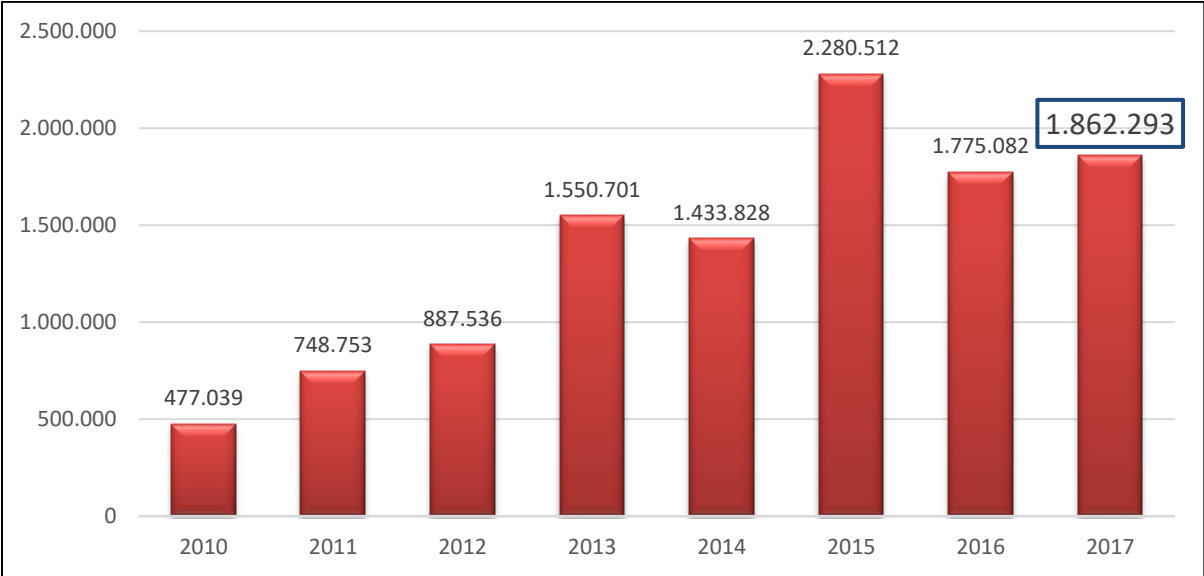


Figure 5. Total number of tissues and cells processed (units): 2010-2017 comparative data.

**2.2. Serious adverse reactions**

A total of 231 SAR were reported in 2017. Of these, 101 SAR were related to non-reproductive and 130 to reproductive tissues and cells. There were 13 cases where the recipient died following the transplant of tissues or cells<sup>5</sup>. This information is further developed in section 2.2.4 of this report.

The number of SAR reported by countries over the years for both categories (non-reproductive and reproductive tissues and cells) is presented in Figure 6. In the latest exercises, the figures submitted by the reporting countries have remained stable.

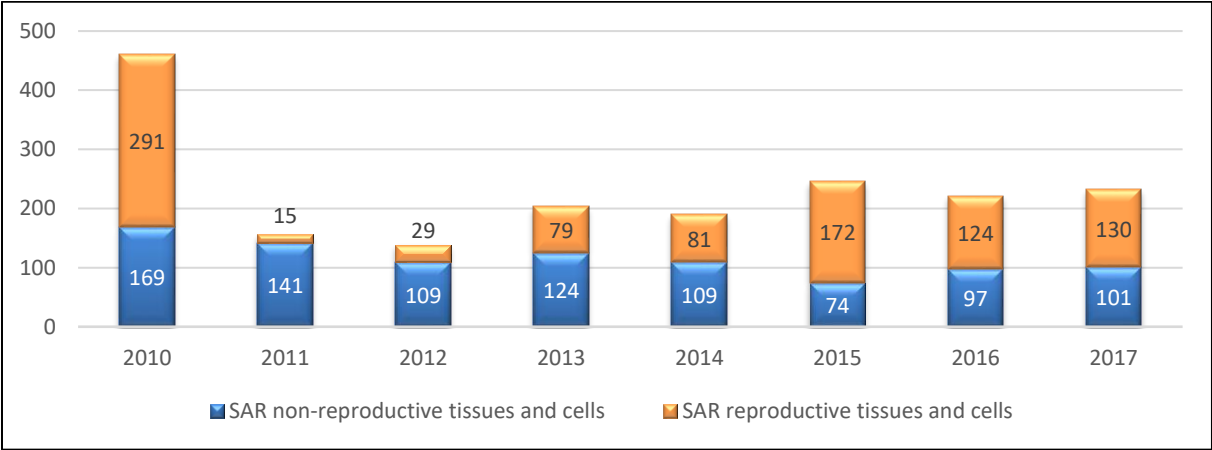


Figure 6. Total number of serious adverse reactions: 2010-2017 comparative data<sup>6</sup>.

<sup>5</sup> The Commission has included this specific, non-mandatory section for the reporting of deaths. This is a result of the experience gained in previous blood SARE exercises, where this information was considered essential by all countries involved.

<sup>6</sup> 2010 SAR data also include 209 cases of ovarian hyperstimulation syndrome (OHSS) reported under SAR, which should have been reported as SAR in donors.

### 2.2.1. Information by country

Among all reporting countries, only 14 Member States (BE, CZ, DE, DK, EL, ES, FI, FR, IE, IT, NL, PT, SE, UK) and Norway reported SAR associated with the clinical application of tissues or cells. Eleven Member States (AT, BG, EE, HU, HR, LT, LV, MT, PL, RO, and SI) and Liechtenstein reported no SAR in recipients in 2017.

Regarding the transplantation of non-reproductive tissues and cells, 11 countries (BE, DE, EL, ES, FR, IE, IT, NL, PT, SE and UK) reported SAR, and 11 Member States (BE, CZ, DK, ES, FI, FR, IT, NL, PT, SE, UK) and Norway reported SAR following the clinical application of reproductive tissues or cells.

The frequency of SAR can be put into context by calculating percentages in relation to national activity data submitted by the reporting countries. In this exercise, the percentage of SAR related to the use of non-reproductive tissues and cells among reporting countries ranged from 0.007-0.489% SAR/# *tissues and cells distributed* and from 0.029-0.863% SAR/# of *recipients*. For reproductive cells, this range was 0.0004-0.265% SAR/# *tissues and cells distributed*, and 0.001-0.267% SAR/# of *recipients*.

These percentages should be interpreted with caution, as they may not reflect the incidence of SAR and the improvement/worsening of quality and safety measures but rather the effectiveness and completeness of the national vigilance and reporting systems, i.e. higher percentages may indicate more effective detection and reporting systems rather than an actual increase in the number of SAR. Percentages calculated individually for each country having reported denominators and SAR have been made available to Member States during meetings of the Competent Authorities, allowing them to benchmark their results against their own previous national exercises and against other Member States.

### 2.2.2. Data by type of tissue or cell

Out of 231 SAR reported:

- 101 SAR (43.7%) were related to the transplantation of non-reproductive tissues or cells (see Figure 7). Of these:
  - 64 were related to the transplantation of HSC:
    - 9 bone marrow
    - 51 peripheral blood stem cells
    - 2 cord blood
    - 1 donor lymphocyte infusion and
    - 1 related to the 'other general HPC' category<sup>8</sup>.
  - 37 were related to the transplantation of replacement tissues:
    - 8 bone
    - 17 ocular tissue (7 general<sup>8</sup>, 10 cornea)
    - 9 cardiovascular tissue (5 heart valve and 4 vessel)
    - 2 skin and
    - 1 'other tissues' (amniotic membrane).
- 130 SAR (56.3%) were related to the clinical application of reproductive tissues and cells, see Figure 8). Of these:
  - 36 sperm (32 following non-partner donation and 4 in the general category<sup>8</sup>)

- 90 embryos (53 from partner gametes, 17 reported in a general category<sup>7</sup>, 11 following oocyte donation and partner sperm, 7 following sperm and oocyte donation, and 2 following sperm donation and partner oocyte). (See Figure 9) and
- 4 ‘other reproductive tissues’.

No SAR were reported for tendons/ligaments, cartilage, fascia, other skeletal tissues (meniscus and/or ear ossicles), sclera, other HSC, other cardiovascular tissues (e.g. conduit or patch or pericardium), pancreatic islets, hepatocytes, adipose tissue, tympanic membrane or ovarian and testicular tissues.

In 2017, for first time, the Commission decided implemented new subcategories for each type of tissue or cell when reporting SAR. For example, fascia has been added to the skeletal tissue category and the ocular tissue category has been divided into general cornea, sclera and other. These modifications contribute to the refinement of the reported data.

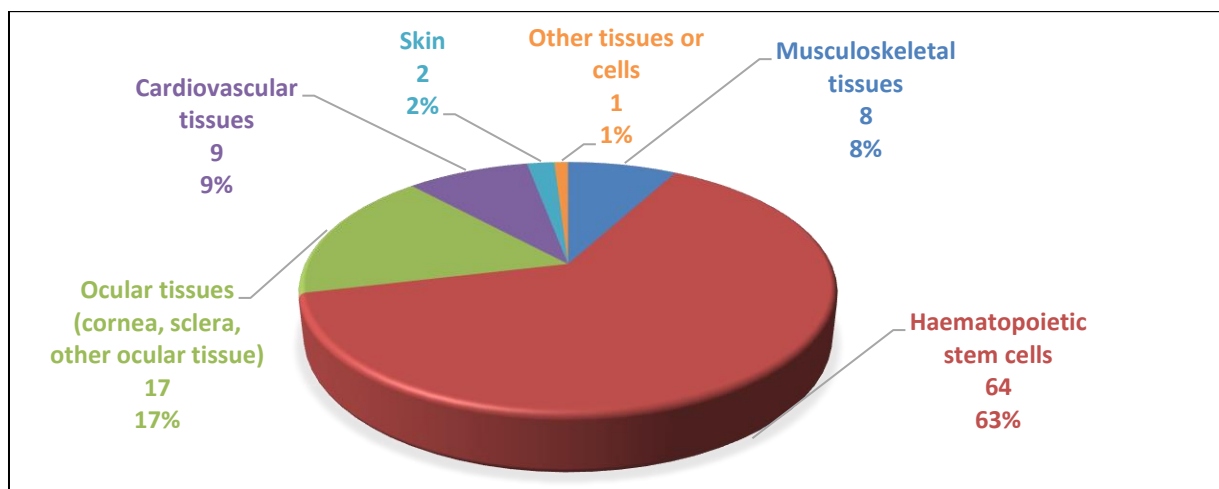


Figure 7. Number of SAR for each type of non-reproductive tissues and cells (absolute values and percentages of total recipient SAR); 2017 data.

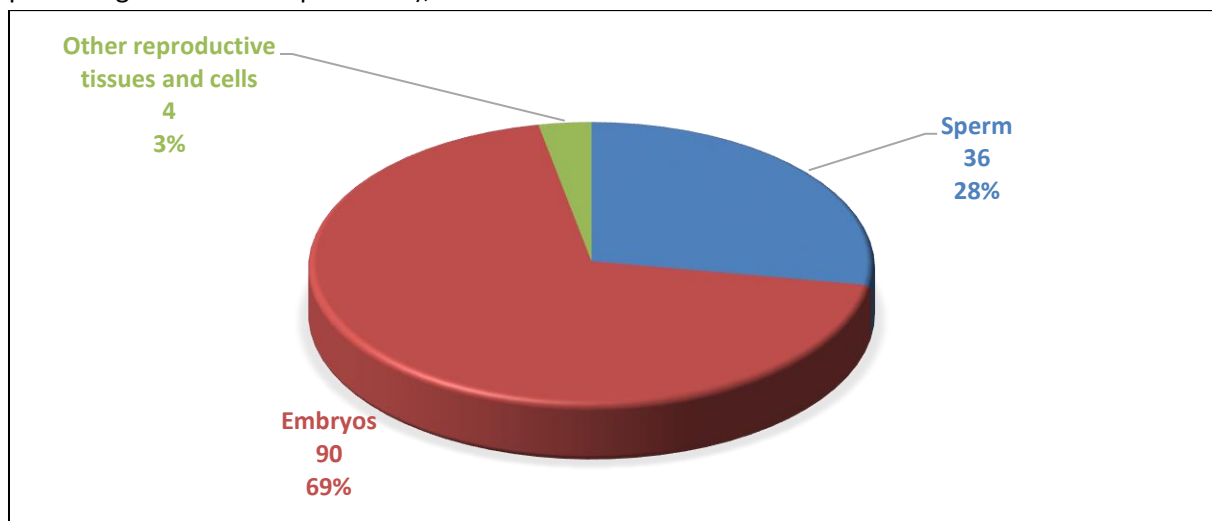


Figure 8. Number of SAR for each type of reproductive cells (absolute values and percentages of total recipient SAR); 2017 data.

<sup>7</sup> The “general” category is used by Member States that do not collect data separately for each type of tissue or cell in some categories (i.e. musculoskeletal tissues vs bone, cartilage, tendons/ligaments and other musculoskeletal tissues such as meniscus or ear ossicles).



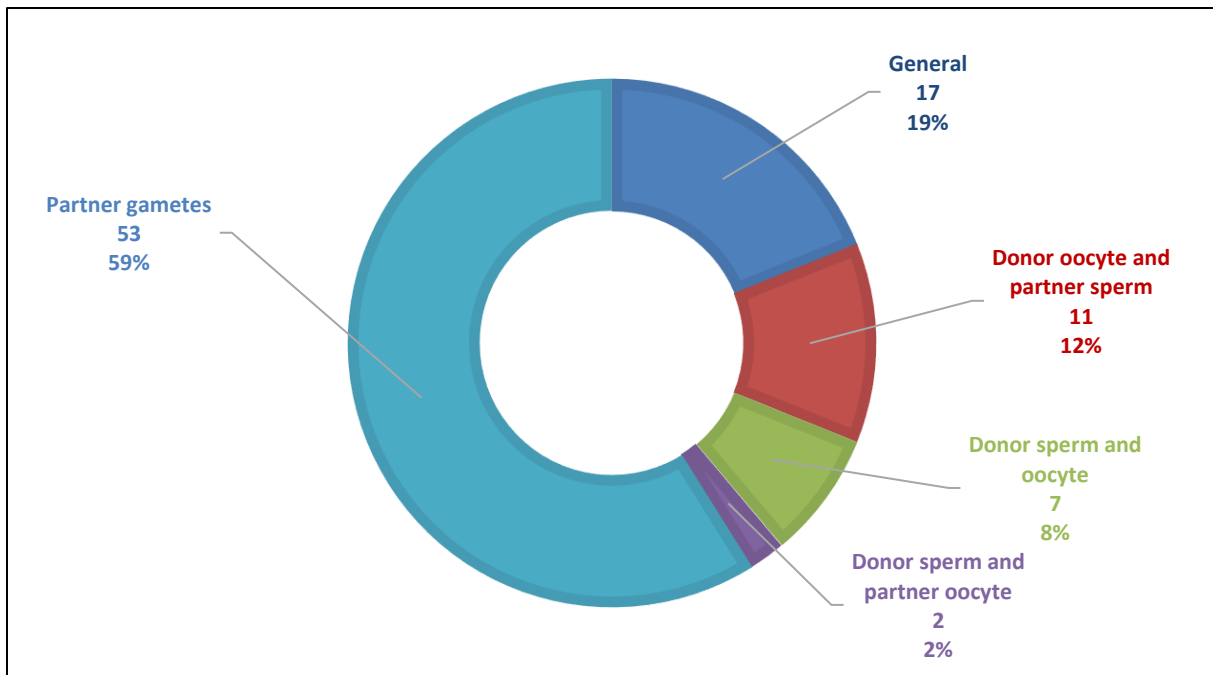


Figure 9. Number of SAR for embryo per category (absolute values and percentages of total recipient SAR); 2017 data.

### 2.2.3. Data by type of serious adverse reaction

The 101 SAR related to the transplantation of non-reproductive tissues and cells were categorised as follows (see Figure 10):

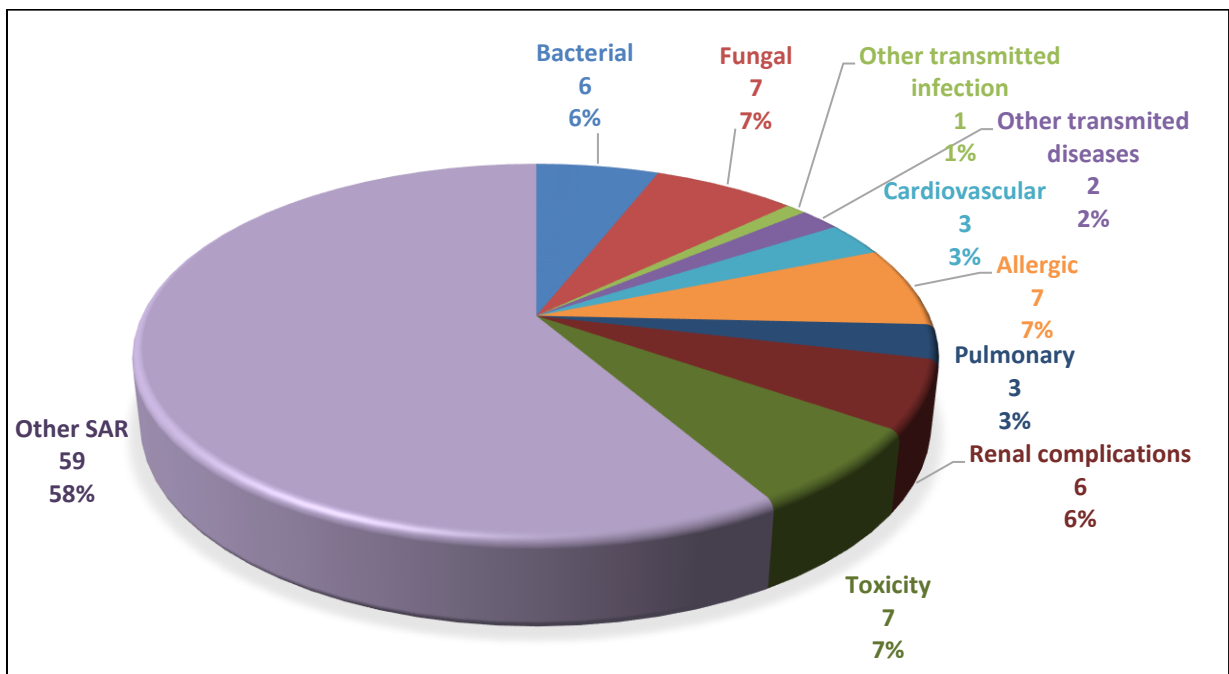


Figure 10. Number of SAR for non-reproductive tissues and cells per category (absolute values and percentages); data 2017.

- Transmitted infections: 14 cases (13.8% of all reported SAR for non-reproductive tissues and cells; see Figures 11 and 12), divided as follows:

- 6 cases of bacterial infections, reported for the following transplanted tissues/cells: 3 ocular tissues and 3 HSC
- 7 cases of fungal infections, all of them reported following the transplantation of ocular tissues. Fungal infections were frequently reported in previous exercises but had no specific category in the reporting template; the Commission included it as a new category in this reporting exercise
- 1 case of 'other transmitted infections', also following the transplantation of ocular tissue.

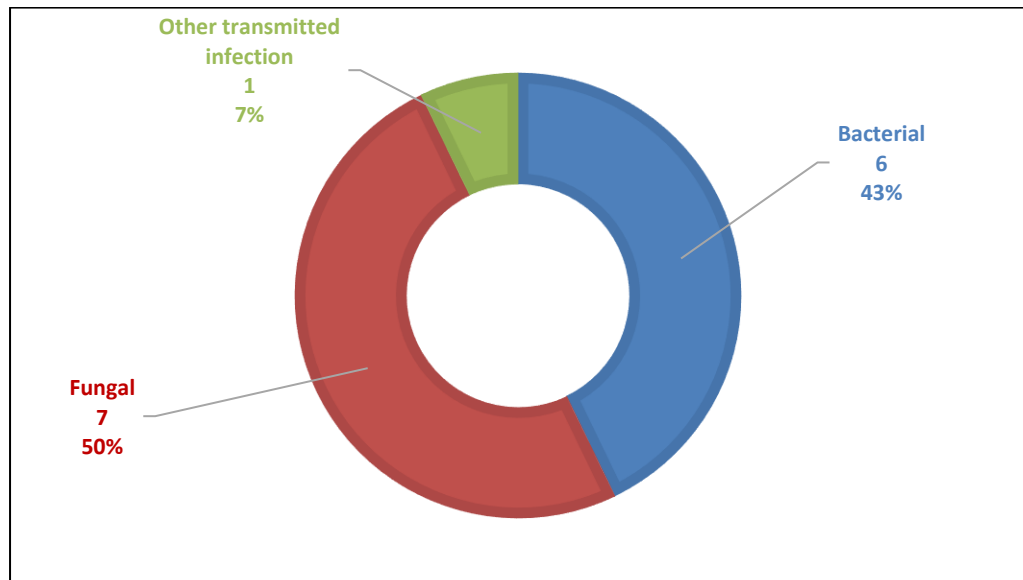


Figure 11. Transmitted infections in non-reproductive tissues and cells; data 2017.

- Other transmitted disease: 2 cases reported following peripheral blood stem cell transplantation (2% of all reported SAR for non-reproductive tissues and cells).
- Other SAR: 85 cases (84.2% of all reported SAR for non-reproductive tissues and cells; see Figure 13). This broad and heterogeneous category could be further divided as follows:
  - 3 cases of cardiovascular complications following the transplantation of HSC (2) and cardiovascular tissue (1)
  - 7 cases of allergic complications following HSC transplantation
  - 3 cases of pulmonary complications following HSC transplantation
  - 6 cases of renal complications following HSC transplantation
  - 7 cases of toxicity following HSC transplantation
  - 59 cases of other SAR (none of the above) following the transplantation of musculoskeletal tissues (8), HSC (34), ocular tissues (6), cardiovascular tissues (8), skin (2) and other tissues or cells (1).

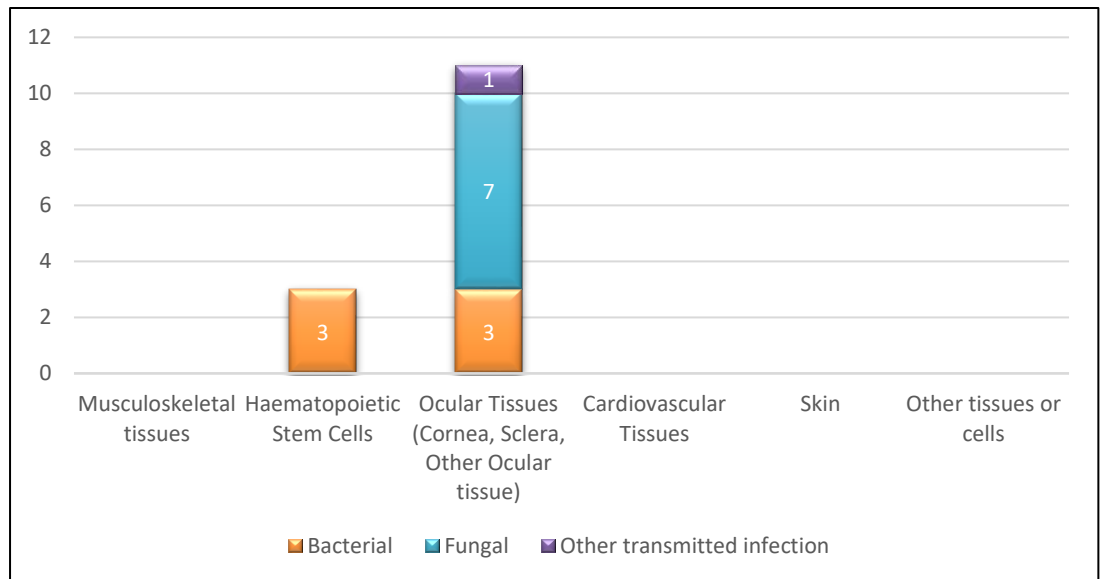


Figure 12. Transmitted infections per type of non-reproductive tissues and cells; data 2017

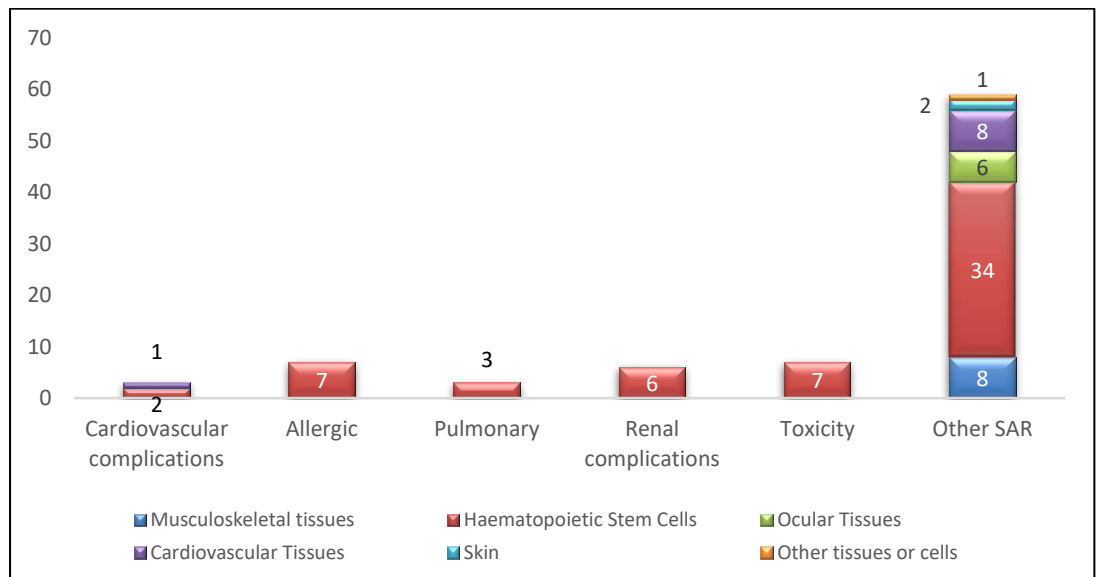


Figure 13. SAR in "Other category" in non-reproductive tissues and cells; data 2017 (absolute values and percentages of total).

The 130 SAR associated with the application of reproductive cells were classified as follows (see Figure 14):

- Transmitted genetic conditions: 125 SAR (96.3% of all reported SAR for reproductive tissues and cells), divided as follows:
  - 2 cases involving sperm in the 'general' category<sup>4</sup>
  - 32 cases involving non-partner sperm donation
  - 16 cases involving embryos in the 'general' category<sup>4</sup>
  - 11 cases involving donor oocytes and partner sperm
  - 6 cases involving donor sperm and donor oocytes
  - 2 cases involving donor sperm and partner oocytes

- 53 cases involving partner gametes, and
- 3 cases involving other reproductive tissues and cells.
- Other transmitted infections: 1 SAR (0.7% of all reported SAR for reproductive tissues and cells) following the clinical application of embryos ('general' category<sup>4</sup>).
- Other SAR: 4 SAR (3% of all reported SAR for reproductive tissues and cells), divided as follows:
  - 1 case involving embryos (donor sperm and oocyte)
  - 2 cases involving sperm ('general' category<sup>4</sup>), and
  - 1 case involving 'other reproductive tissues and cells'.

It is noted that of these 130 SAR associated with the application of reproductive cells, 52 (40% of all SAR reported for reproductive tissues and cells) were related to non-partner donation (32 involving non-partner sperm and 20 involving embryos [donor oocyte and partner sperm (11), donor sperm and oocyte (7) and donor sperm and partner oocyte (2)]).

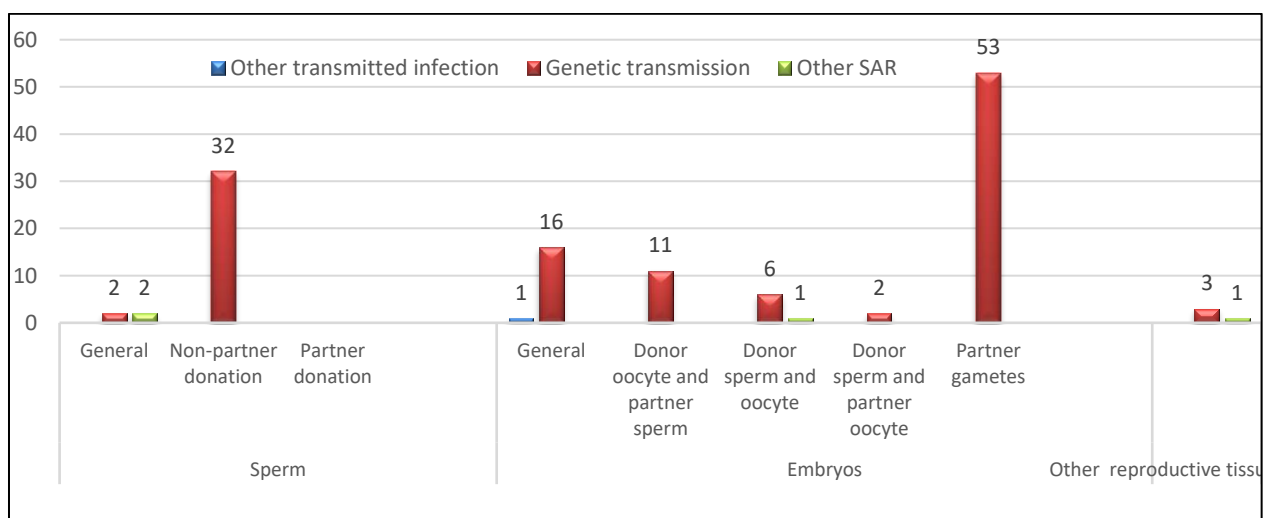


Figure 14. SAR related to the application of gametes and embryos; 2017 data.

#### 2.2.4. Serious adverse reactions that resulted in recipient death

As vigilance systems are in place to protect donors and recipients, the Commission and Member States deemed it appropriate to regularly collect information for reported deaths on a voluntary basis.

Fifteen recipient deaths were reported in 2017. Of those, 13 were reported in the non-reproductive category. These followed the transplantation of the following tissues or cells:

- 10 related to HSC transplant
- 1 to peripheral blood stem cells
- 1 to bone marrow
- 1 to heart valve transplant.

It is noted that none of these deaths were directly attributable to the quality and safety of the tissues or cells transplanted but rather to unforeseeable clinical complications connected with the underlying conditions of the recipients.

In the reproductive category, 2 deaths were reported following the transmission of a genetic disease. The subsequent investigations concluded these deaths were linked to non-partner gametes and resulted in the donors being permanently blocked.

**2.3. Serious adverse events**

The total number of SAE reported for 2017 was 756, showing that such events occurred for 0.04% of *tissues and cells processed* during this period. The percentage of SAE in relation to the total number of *tissues and cells processed* (denominator for SAE) should be interpreted with caution as not all countries are able to report these data.

The total number of SAE reported in 2017 remained stable when compared to previous exercise, as presented in Figure 15.

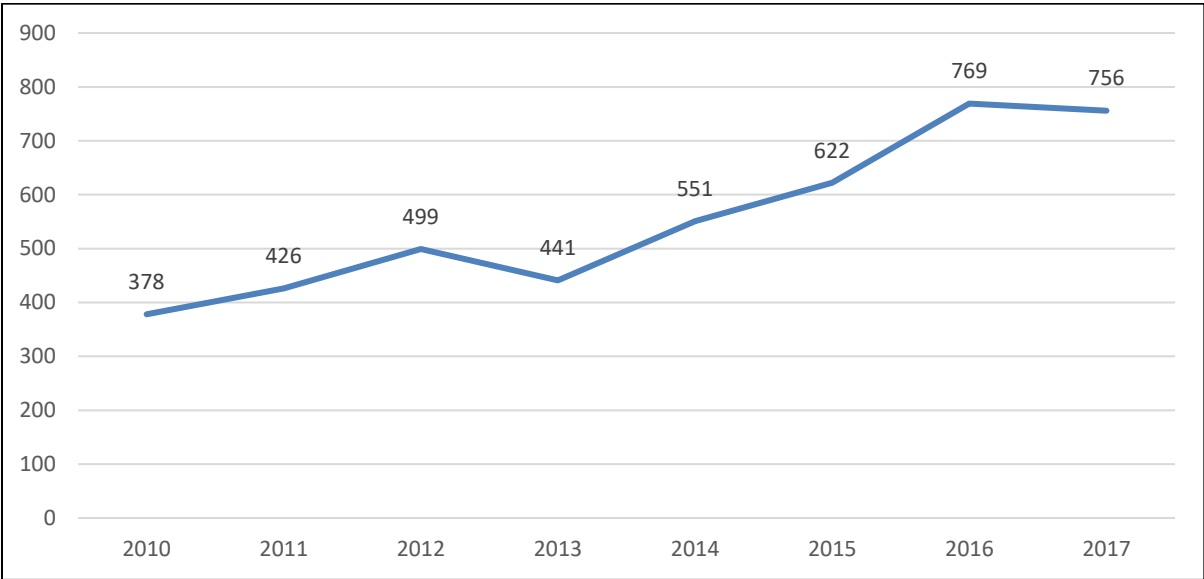


Figure 15. Total number of SAE reported: 2010-2017 comparative data.

Comparative data showing the evolution of SAE by type of event are shown in Figure 16. Human error is the most common type of event with numbers increasing over time. Tissue/cell defects have also increased in recent years, whereas numbers of other types of events remain stable.

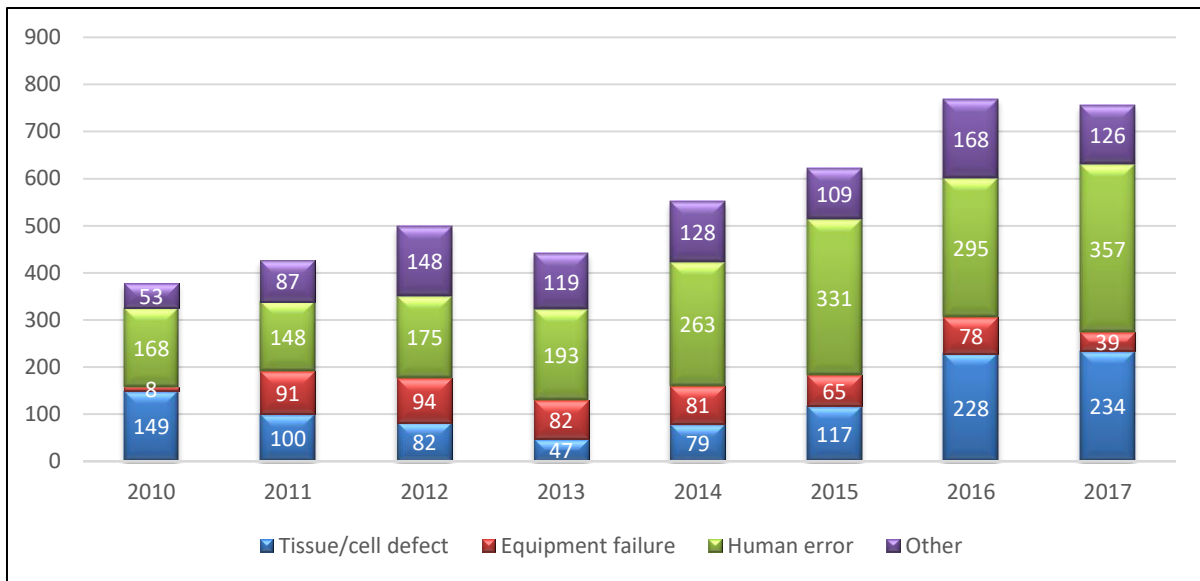


Figure 16. Total number of serious adverse events by specification: 2010-2017 comparative data.

It is noted that for this exercise the Commission further subdivided the specification “human error” to better understand in which part of the process the SAE took place. The largest specification of SAE “human error” occurred during the testing, processing and procurement stages. An overview of SAE types reported is presented in Figure 17.

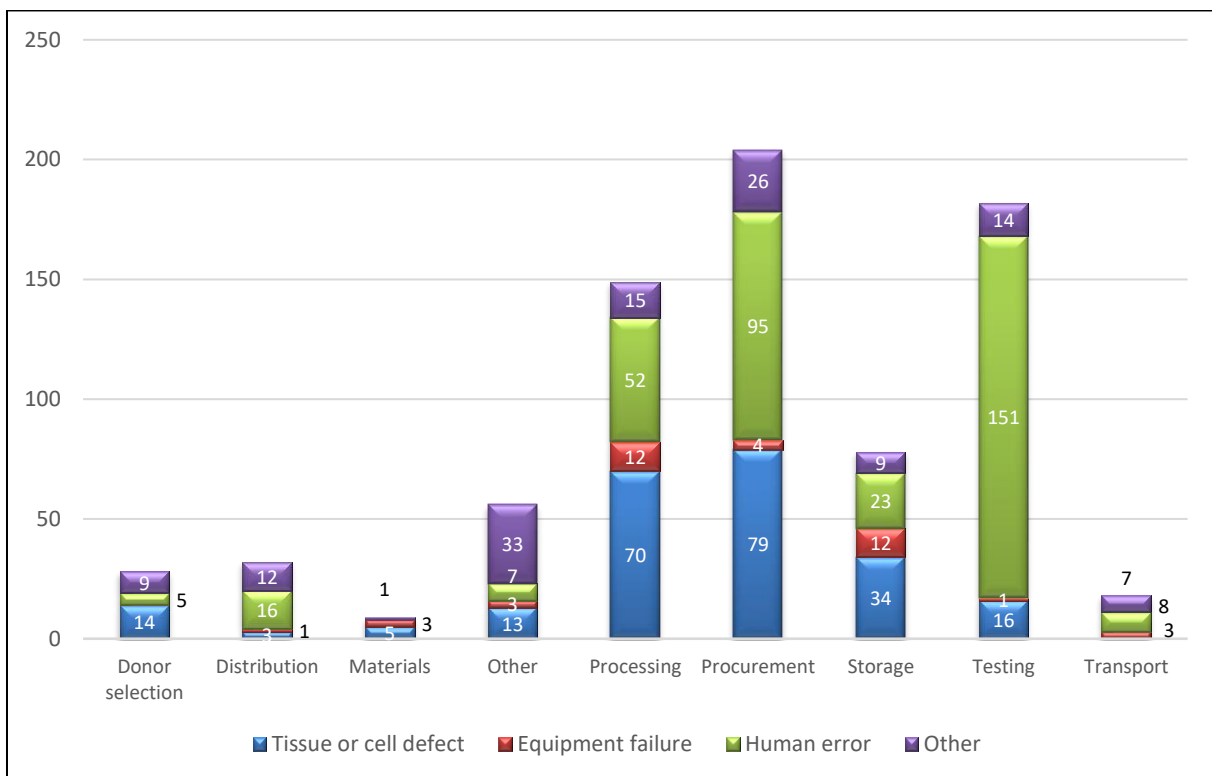


Figure 17. Total number of serious adverse events reported, categorised by activity step; 2017 data.

### 2.3.1. Information by country

Eighteen countries reported SAE for non-reproductive tissues and cells (AT, BE, DE, DK, ES, EL, FI, FR, HU, IE, IT, LT, NL, PL, PT, SE, UK and NO) and 17 countries for reproductive cells (AT, BE, CZ, DE, EE, ES, FI, FR, IE, IT, MT, NL, PT, SI, SE, UK and NO).

### 2.3.2. Information by activity

An overview of the SAE reported by type of activity is presented in Figure 18.

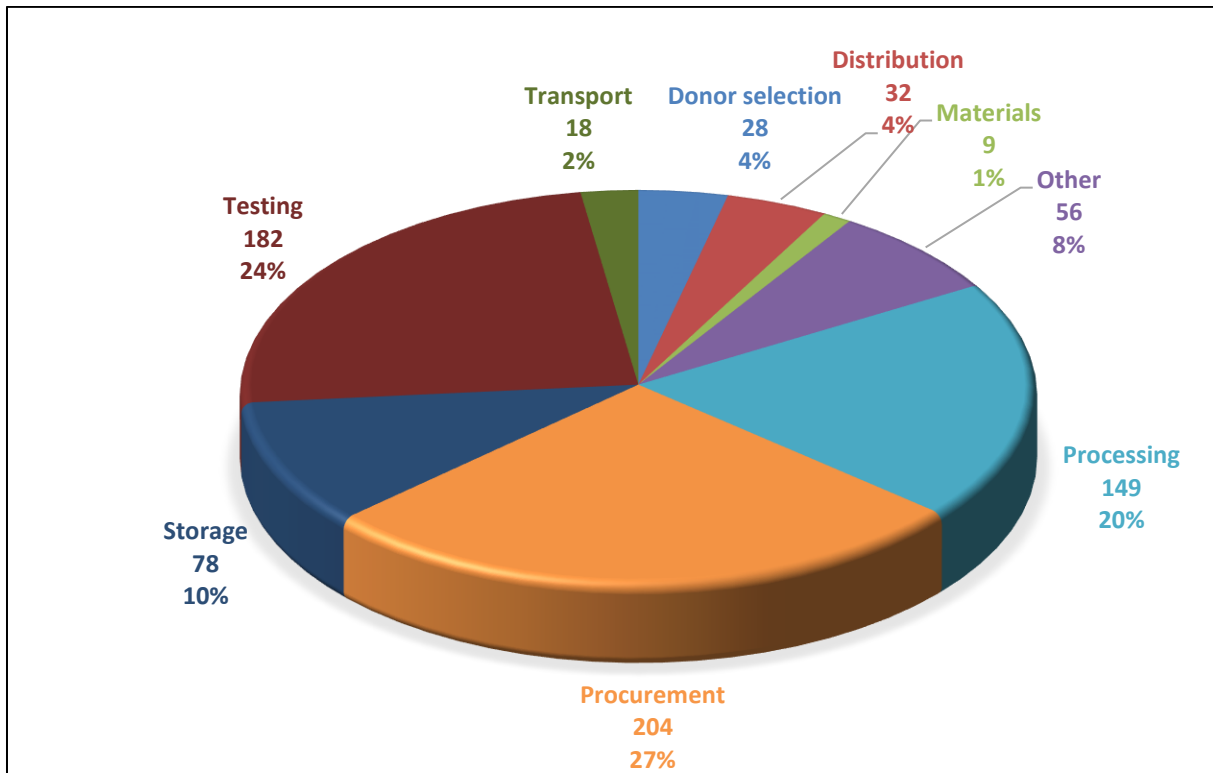


Figure 18. Number of SAE and percentage of total SAE reported by type of activity (absolute values and percentages of total); data 2017.

### 2.3.3. Information by type of serious adverse event

The 756 SAE were classified as tissue or cell defects, human error, equipment failure and other types of events. The distribution by type is presented in Figure 19.

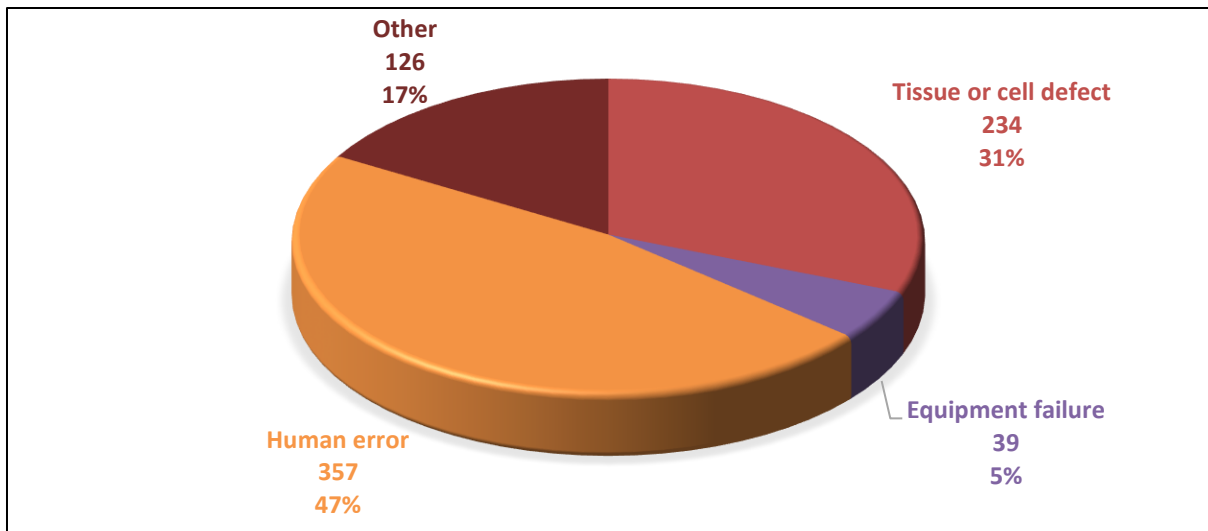


Figure 19. SAE types (absolute values and percentages of total); 2017 data.

Taking into account the type of SAE and the stage at which they occurred during the donation-distribution chain, SAE were categorised as shown in Figures 20 and 21, divided into non-reproductive and reproductive categories, respectively.

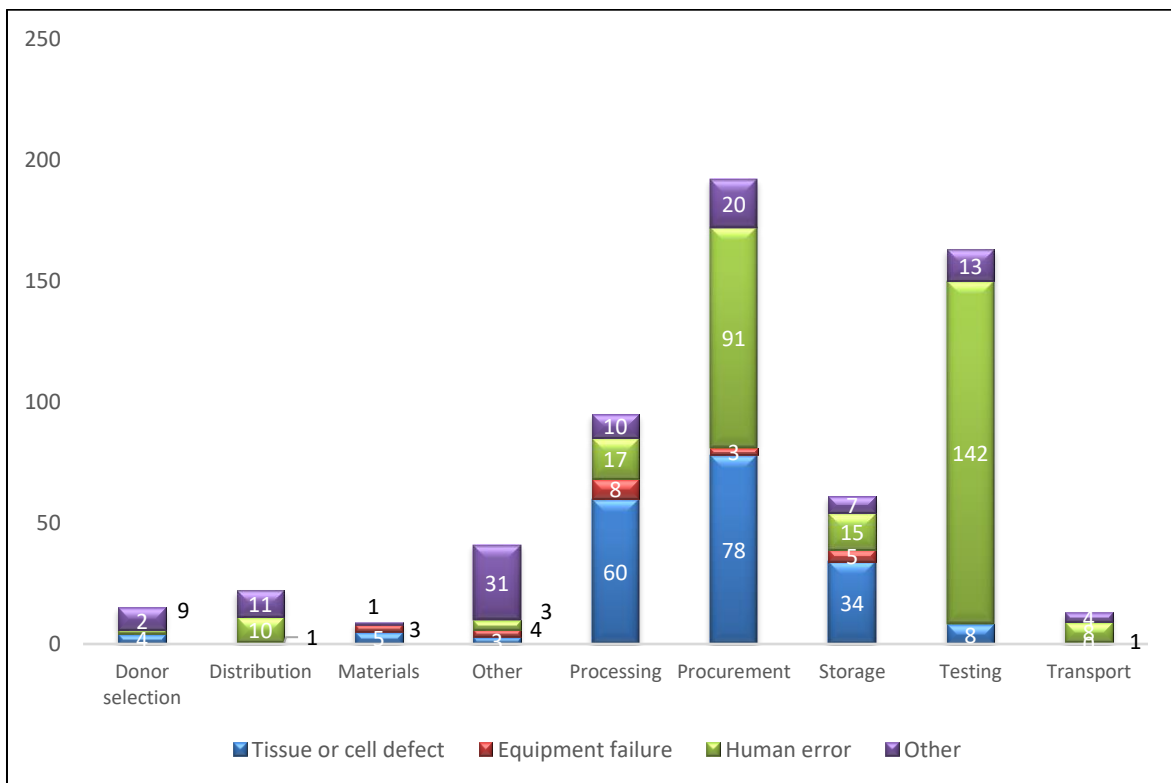


Figure 20. SAE in the non-reproductive category per type and stage at which they occurred during the donation-distribution chain; data 2017.



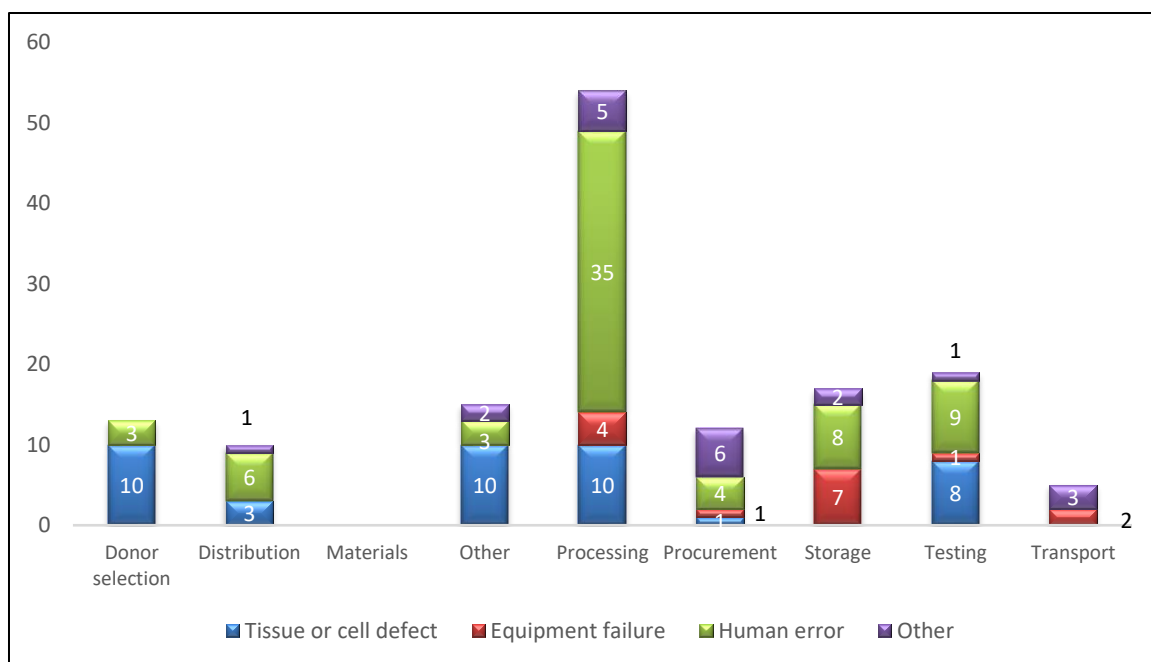


Figure 21. SAE in the reproductive category per type and stage at which they occurred during the donation-distribution chain; data 2017.

The non-reproductive SAE (611 cases) occurred mostly during the procurement and testing stages, mainly due to human error and tissue or cell defects, whereas the reproductive SAE (145 cases) occurred primarily during processing and testing, followed by storage; these were mainly due to human error and tissue or cell defects.

#### 2.4. Serious adverse reactions in donors

Recognising the importance of all donor adverse reactions, including those not directly impacting the quality and safety of tissues and cells and reported through pharmacovigilance systems (e.g. ovarian hyper-stimulation syndrome [OHSS] following oocyte donation, reactions subsequent to the administration of granulocyte colony-stimulating factor [G-CSF] for collection of peripheral blood stem cells), the Commission continues to collect such data on a voluntary basis, in agreement with Competent Authorities.

Twenty Member States (AT, BE, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HR, IE, IT, NL, PL, PT, SI, SE, UK) and Norway reported a total of 710 SAR *in donors* in 2017. A general overview of SAR in donors during the period 2011-2018 (data pertaining to 2010-2017) is presented in Figure 22. The steady increase shown reflects the gradual introduction of this reporting parameter, rather than an increase in donor reactions.

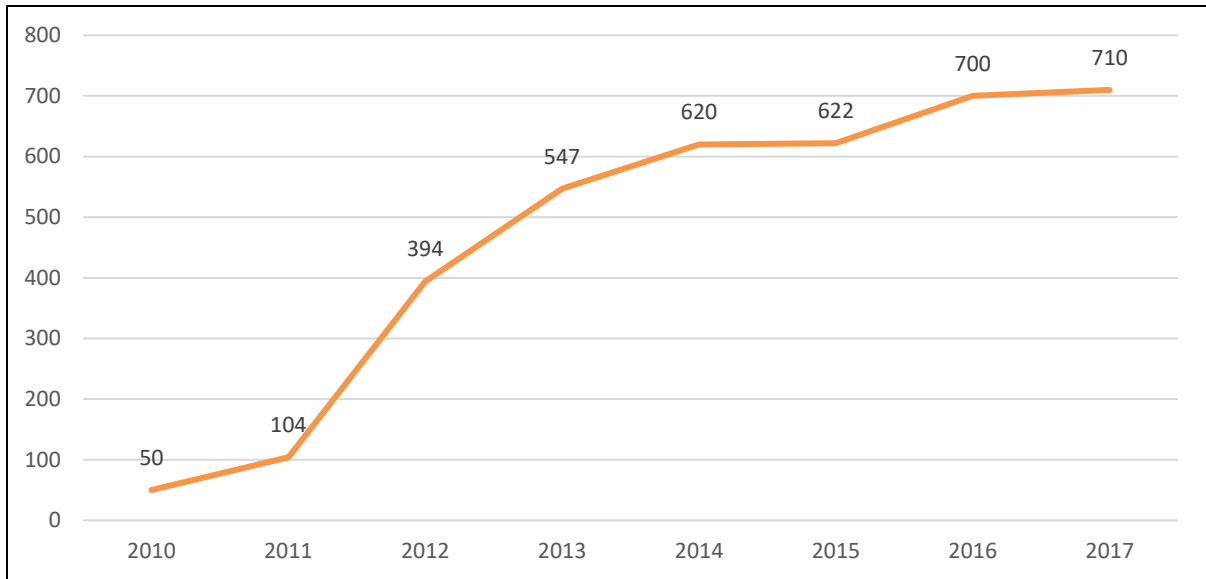


Figure 22. Number of serious adverse reactions in donors (units): 2010-2017 comparative data.

Of the 710 SAR in donors reported in 2017 (see Figure 23):

- 34 cases were related to the donation of non-reproductive tissues or cells (4.8 % of all SAR in donors) and were reported by 10 countries (DE, DK, EL, FI, FR, IE, IT, NL, PT) and Norway. All cases reported were associated with donation of HSC
- 675 cases (amounting to 95.2% of all SAR in donors) were related to the donation of reproductive tissues or cells, specifically the donation of oocytes and 1 with other reproductive tissues. These were reported by 17 Member States (AT, BE, BG, CZ, DK, DE, EE, ES, FR, HR, IE, IT, PL, PT, SI, SE and UK). SAR in donors of reproductive tissues or cells were reported under the following categories: oocytes 'general' (133), oocytes for non-partner donation (28), oocytes for partner donation (514) and other reproductive tissue (1).

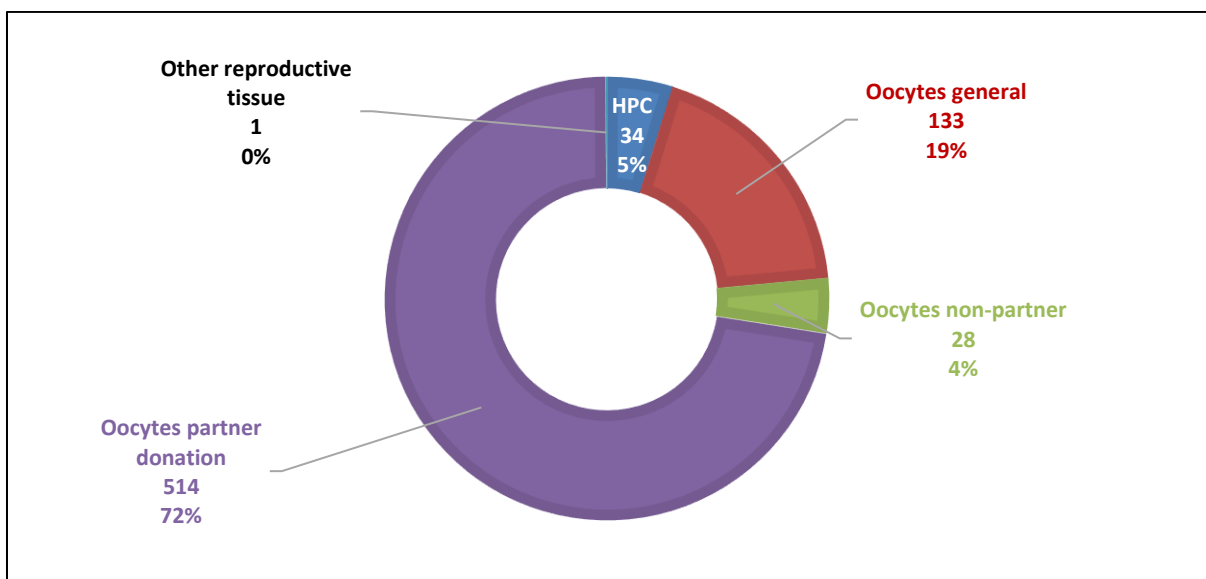


Figure 23. Serious adverse reactions in donors per type of donated tissue or cell (units); data 2017.

In the case of non-partner donation, the main SAR reported were severe OHSS (19), haemoperitoneum (6), complications resulting in ovariectomy (1), haematuria (1), and respiratory arrest and asystole (1), as shown in Figure 24.

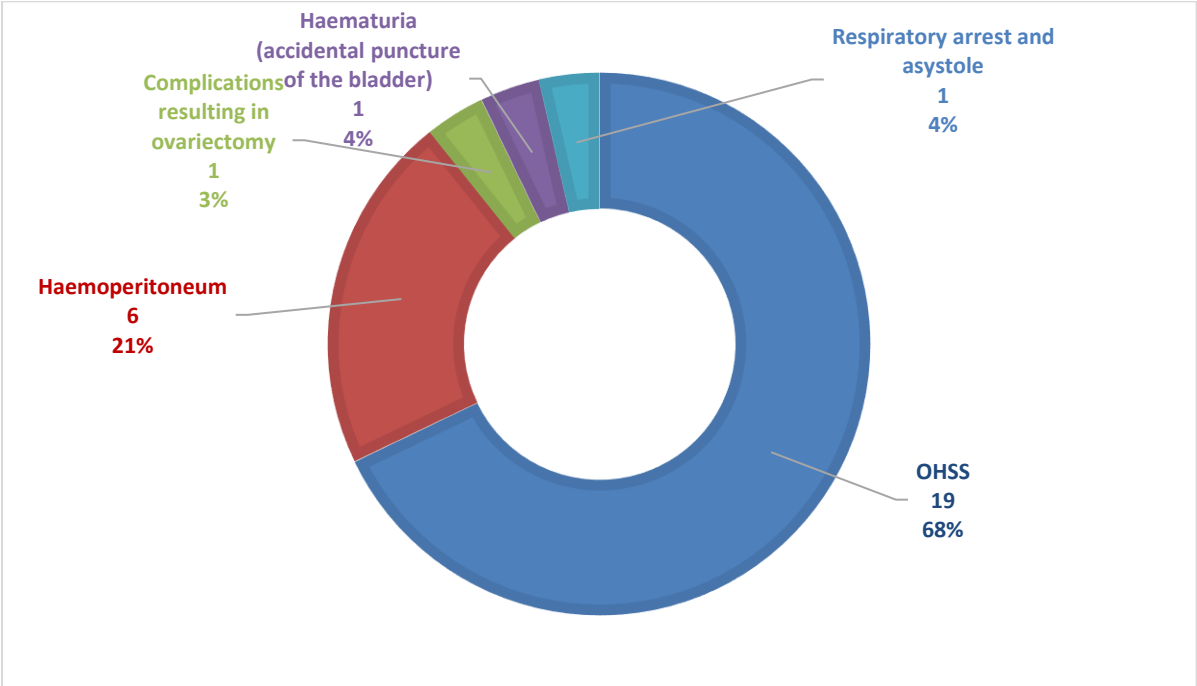


Figure 24. Classification of SAR in donors for non-partner oocyte donors.

Most of the SAR in oocyte donors were critical, severe and moderate-to-severe OHSS cases (426 cases) and haemoperitoneum (100 cases), the remaining cases included infectious complications and other types of SAR, as shown in Figure 25.

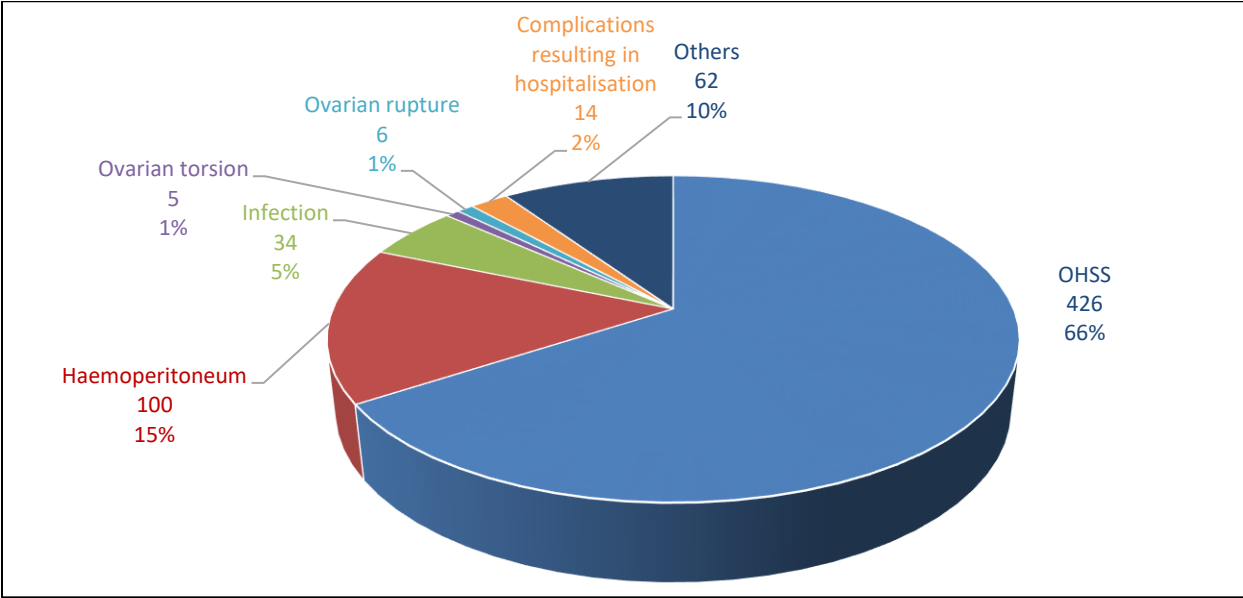


Figure 25. SAR in oocyte donors; 2017 data (absolute values and percentages of total).

It is noted that all reported cases of SAR in donors of non-reproductive tissues or cells were linked to clinical complications with different aetiologies following the administration of granulocyte colony-

stimulating factor for collection of peripheral blood stem cells. In the case of reproductive tissues or cells, the SAR in donors were frequently reported in the same categories, allowing a comprehensive classification of such reactions. None of the SAR in donors reported in 2017 resulted in the death of the donor. However, the data submitted highlights the need for Competent Authorities to ensure appropriate follow-up and protection mechanisms for living donors of tissues and cells.

### **3. Conclusions**

This report reflects that vigilance systems and national data collection in this field are improving year after year. Nevertheless, there are areas that still require further improvement. For example, even now, not all reporting countries are able to provide activity data to be used as denominators for SARE. This would require additional efforts from Member States to obtain more accurate and complete activity data, both from tissue establishments and organisations responsible for human application, who are ultimately responsible for applying those tissues and cells to patients.

All health professionals involved in the clinical application of tissues and cells and tissue establishments should be encouraged to submit case reports to their authorities in order to contribute to a more accurate understanding of the current situation. This will help to facilitate learning from past mistakes, identify preventive and corrective measures to be taken, and contribute to the exchange of knowledge, ultimately leading to the improvement of the vigilance systems.

In addition, not all countries collect data using the same units of measure (e.g. units/packages of skin vs cm<sup>2</sup> vs m<sup>2</sup>; number of oocytes vs number of cycles). This lack of harmonisation in collecting data creates difficulties when comparing data among Member States and extracting general conclusions. This situation was discussed during a technical meeting on national and EU-level tissue and cell activity data collection and reporting, which was organised by the EDQM in March 2018 in Strasbourg in the framework of grant agreement 2014 54 01 with the EC. The main conclusions from the meeting were the importance of the general collection of a minimum set of data that could be common to health authorities and professional societies. The participants agreed that further meetings should be organised to continue with the discussions and ensure the appropriate implementation of these recommendations. Subsequently, in the framework of a new grant agreement between the Commission and the EDQM (2018 53 01), several activities to improve vigilance systems and train professionals, to harmonise activity data reporting and reduce the burden on reporting tissue establishments and Competent Authorities, as well as to enhance cooperation with professional societies carrying out similar work, will be carried out.

Of the SAR related to the transplantation of non-reproductive tissues and cells not categorised as “other”, most were associated with infection – mostly of bacterial and fungal origin. A significant number (58%) continue to be classified as ‘other’. This merits further work by the VES to categorise these SAR in a more informative way in the future. In contrast, the most frequently reported SAR related to the clinical application of reproductive cells involved the transmission of genetic diseases. This pattern has remained stable throughout the years. However, it is noted that the likelihood of transmitting multi-factorial genetic diseases from donor to offspring is sometimes difficult to assess.

The majority of SAE were reported under the category of “human error”, mostly during the procurement, testing and processing steps. These findings suggest the importance of revising standard

operating procedures in tissue establishments, highlighting critical steps and providing continuous training to personnel.

The exercise also reported information on SAR in donors, which is submitted on a voluntary basis by the reporting countries, demonstrating that Competent Authorities support reporting of these types of SAR and drawing attention to the importance of ensuring that appropriate follow-up mechanisms for tissue and cell donors are in place.

Since 2017, through contractual arrangements signed with the Commission, the EDQM has been responsible for carrying out the verification and analysis of the blood and tissues and cells SARE exercises and drafting the final summary reports. Due to the expertise of the EDQM in the field of biovigilance and with international data collection activities, this collaboration has greatly contributed to improving the quality of the EU SARE exercise and has led to the refinement of the common approach document and the reporting template forms. Moreover, an additional data verification step and in-depth analysis of data and trends has resulted in better quality data and improved subsequent conclusions.

In addition, in January 2017, a Vigilance Expert Sub-group (a sub-group to the Competent Authorities on Substances of Human Origin Expert Group) was established by the Commission, in agreement with the Member States. The objective of this sub-group is to support the development and improvement of the SARE reporting system both at national and European Commission level. In addition, its work had also contributed to the Commission's evaluation of the legal frameworks on blood, tissues and cells, published in October 2019<sup>8</sup>.

Overall, the implementation of vigilance requirements and data collection in the field is improving over time, as Member States make efforts to improve their vigilance systems and the quality and accuracy of data submitted. However, there is still a significant degree of under-reporting by some Member States; thus data should be interpreted with caution.

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<sup>8</sup> [https://ec.europa.eu/health/blood\\_tissues\\_organ/policy/evaluation\\_en](https://ec.europa.eu/health/blood_tissues_organ/policy/evaluation_en)