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 2019 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS FOR TISSUES AND CELLS

(Data collected from 01/01/2018 to 31/12/2018 and submitted to the European Commission in 2019)

EXECUTIVE SUMMARY

The human application of tissues and cells provides 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 or other potential adverse effects in the recipient. As laid down in EU legislation, these risks can be monitored and reduced by the implementation of safety and quality measures. Vigilance and surveillance programmes are essential for ensuring the quality and safety of tissues and cells for human application. Those systems 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[1], 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 at national level by each Competent Authority. For this purpose, definitions of SAR and SAE are provided in the EU legislation[2] (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 at European level. 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 Subgroup (VES, a subgroup to the Competent Authorities on

[1] Article 7 and Annexes III, IV and V of Directive 2006/86/EC
[2] Article 3 of Directive 2004/23/EC

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.

This report summarises the data submitted by the Member States and EEA during 2019, collected by the reporting countries during 2018, and draws general conclusions, comparing the information with data submitted in previous years. The key findings of the 2019 reporting exercise are the following:

- The overall number of reported tissues and cells distributed in 2018 amounted to 995 407 units (501 103 non-reproductive, reported by 25 countries, and 494 304 reproductive tissues and cells, reported by 18 countries). Nineteen countries for non-reproductive and 12 countries for reproductive tissues and cells reported a total of 361 418 recipient patients. Twenty-four countries reported the total number of tissues and cells processed, which reached 2 715 953 units (22 countries reported 347 266 tissues processed in the non-reproductive category and 19 countries reported 2 368 687 in the reproductive category).
- A total of 232 SAR were reported by 27 countries, of which 90 were related to non-reproductive and 142 to reproductive tissues and cells. Data showed that 22.2% of the SAR associated with the transplantation of non-reproductive tissues and cells were immunological reactions (mainly due to the transplantation of haematological stem cells). The vast majority of the reported SAR for reproductive cells (97%) were related to the transmission of genetic diseases and "other SAR".
- A total of 739 SAE were reported (531 related to non-reproductive tissues and cells, reported by 16 countries, and 208 to reproductive tissues and cells, reported by 16 countries), most of which occurred during procurement and processing 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 2018, 934 cases of SAR in donors were reported by 17 countries. Of those, 30 were related to non-reproductive and 904 to reproductive tissues and cells.

1. DATA COLLECTION METHODOLOGY

This report provides a summary of the data reported to the Commission in 2019 by 26 Member States and Norway[3] pertaining to the reporting period from 1 January to 31 December 2018. 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 2.8.2) to be sent to a DG SANTE hosted database.
2) The Common Approach document (version 2.8) 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

[3] Cyprus submitted a blank template. Belgium never submitted data. Greece submitted their data after the deadline, and consequently have not been included in this analysis.

reporting. The Common Approach has been regularly updated to improve the data reporting methodology and clarify points of ambiguity. This has resulted in a gradual increase in the quality and accuracy of the data collected from the Member States.

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 and analysis of the SARE data reported by Member States and the drafting of the summary report of the SARE exercise.

At the beginning of 2020, the EDQM started contacting reporting countries, when needed, in order to clarify and verify the accuracy of the reported data. Subsequently, the EDQM performed a detailed analysis of the verified information in close cooperation with the Commission and Member States, and drafted this report.

Before publishing this summary report, the data and analysis were revised by Competent Authorities for Tissue and Cells.

2. MAIN FINDINGS OF THE 2018 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, provision of the 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 exercises, some countries had difficulty in collecting accurate activity data for certain types of tissues and cells or certain activities. Some others could not provide data as the measurement units used at national level were not the same as those requested in the EU exercise (e.g. in the field of medically assisted reproduction, some countries collected data as number of cycles).

Thus, SAR denominators are not complete and caution should be used when interpreting them.

2.1.1. Tissues and cells distributed

The overall *number of distributed tissues and cells* in 2018, as submitted by the reporting countries, amounted to 995 407 units. As regards non-reproductive tissues, 501 103 units were distributed, whereas 494 304 units were distributed for reproductive tissues

2.1.1.1. Non-reproductive tissues and cells

In the case of non-reproductive tissues and cells, 25 countries reported data on *units distributed* (AT, BG, CZ, DE, DK, EE, ES, FI, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, SE and UK). The main types of non-reproductive tissues and cells distributed were skeletal tissues (347 241 units), haematopoietic progenitor cells (HPC; 56 604 units) and ocular tissues (40 310 units). See Figure 1 for further details.

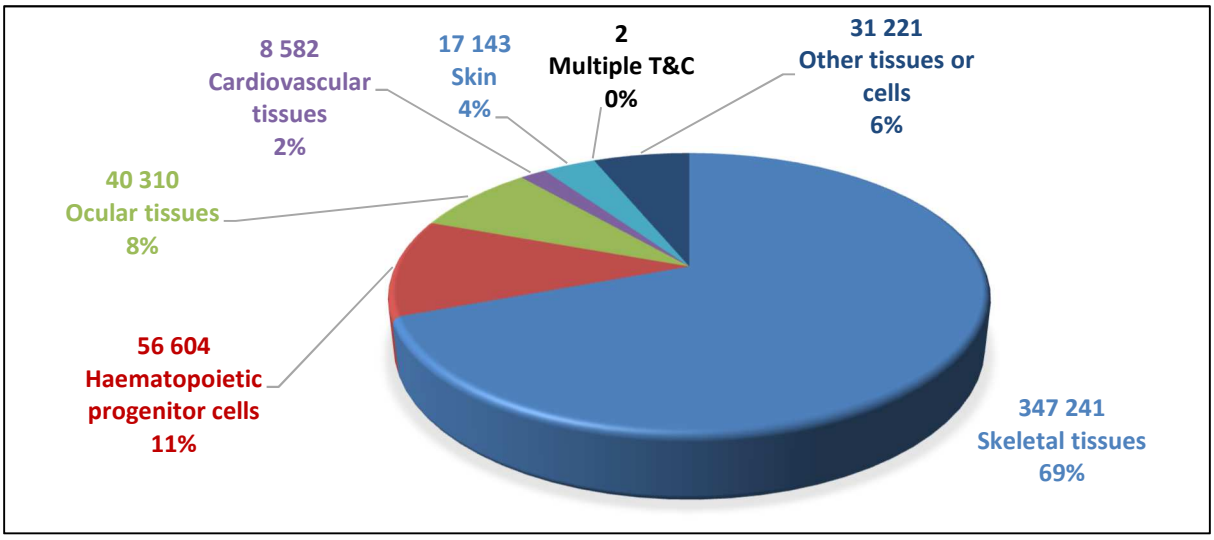

Figure 1. Total number of non-reproductive tissues and cells distributed (units); data 2018.

The sub-classification of the activity data per type of tissue for the main categories is shown in Figure 2 for skeletal tissues, Figure 3 for HPC, Figure 4 for ocular tissue and Figure 5 for cardiovascular tissue. Bone, peripheral blood stem cells, corneas and vessels were the most frequently distributed tissues in each category.

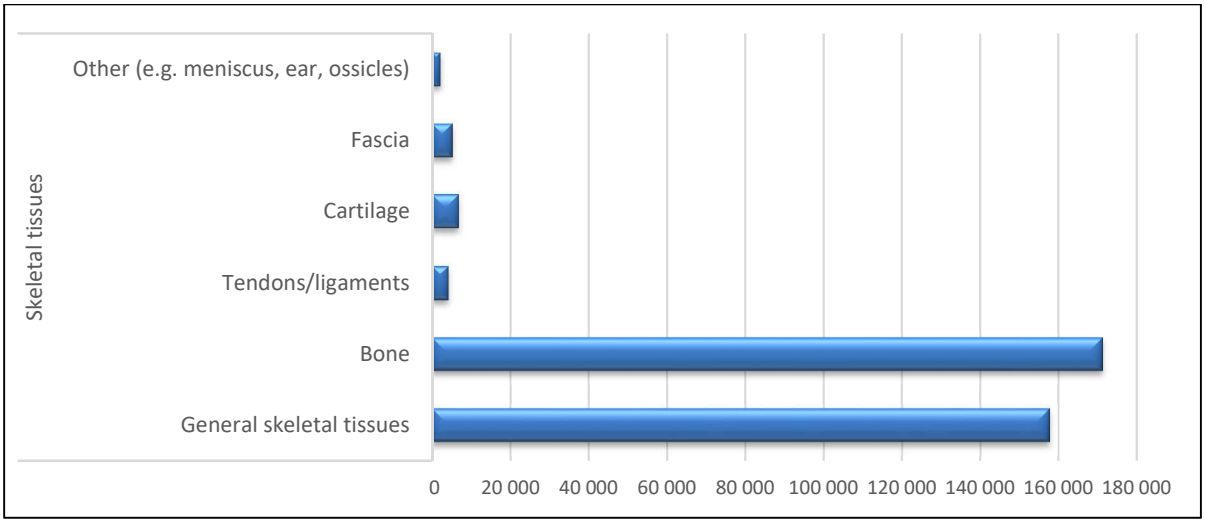

Figure 2. Number of skeletal tissues distributed per sub-category (units)[4]; data 2018.

[4] 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).

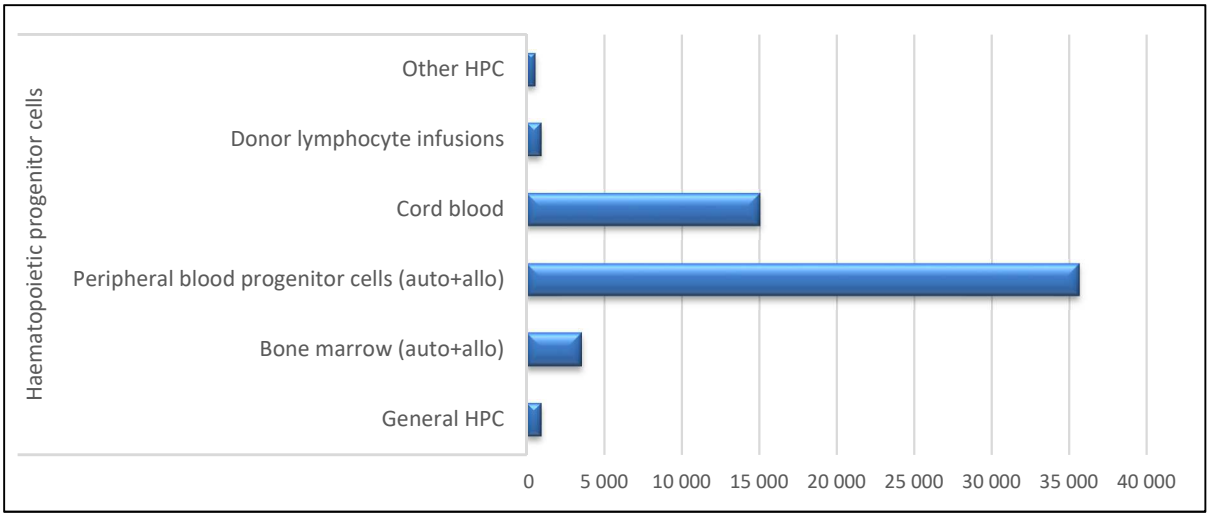

Figure 3. Number of haematopoietic progenitor cells distributed per sub-category (units)[4]; data 2018.

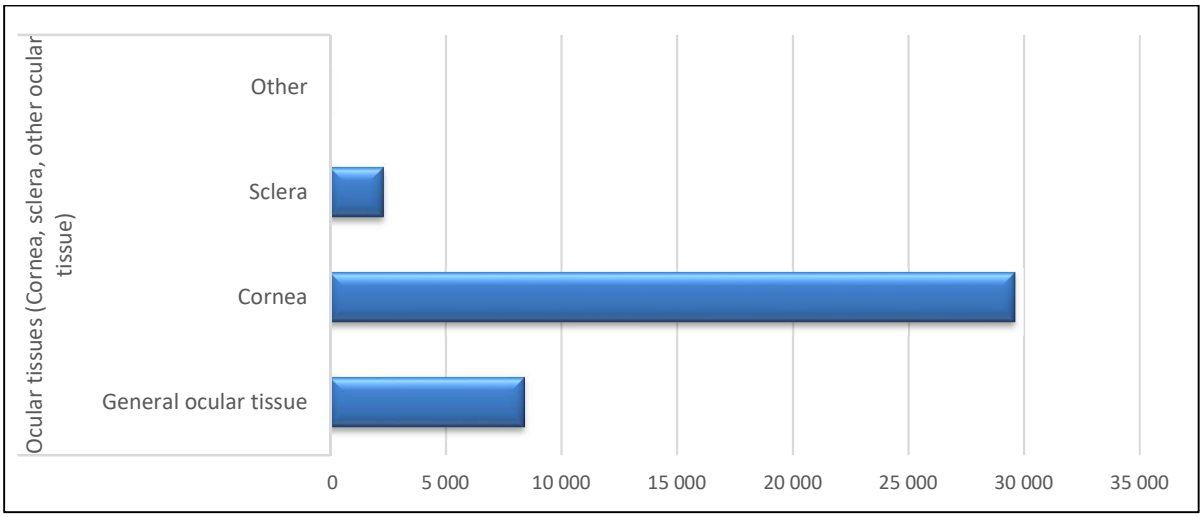

Figure 4. Number of ocular tissues distributed per sub-category (units)[4]; data 2018.

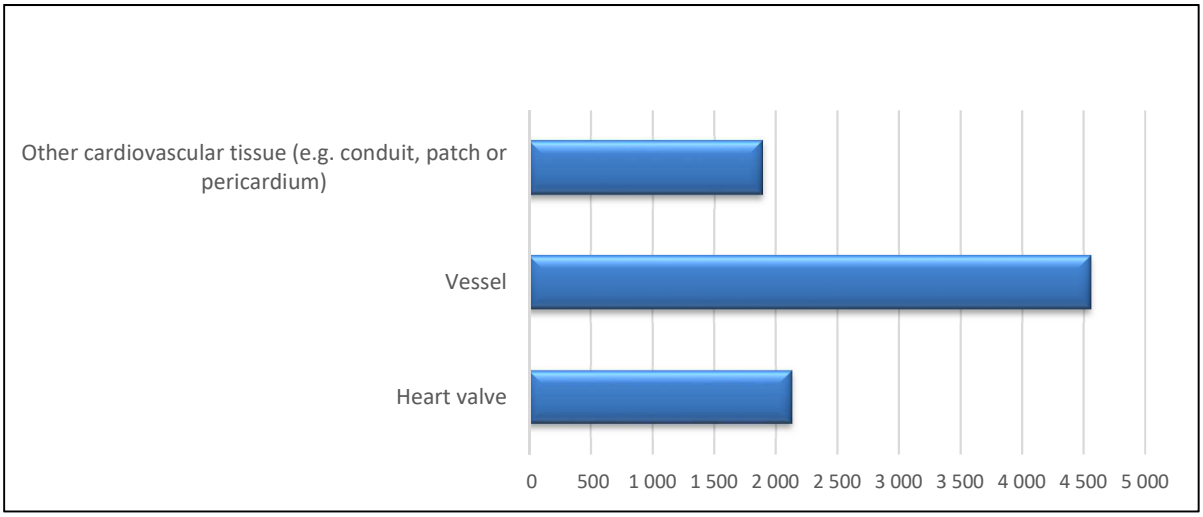

Figure 5. Number of cardiovascular tissues distributed per sub-category (units)[4]; data 2018.

2.1.1.2. Reproductive tissues and cells

For reproductive tissues and cells, 18 countries (AT, BG, CZ, DE, DK, EE, HR, HU, IE, LT, LU, LV, MT, NL, RO, SI, SK and SE) reported activity data.

Of the 494 304 units of reproductive tissues distributed, 249 353 sperm units were delivered for insemination and 244 357 embryos, following partner and non-partner donation, were delivered for transfer. Additionally, 30 ovarian tissues and 564 testicular tissues were distributed for the preservation of fertility, see Figure 6.

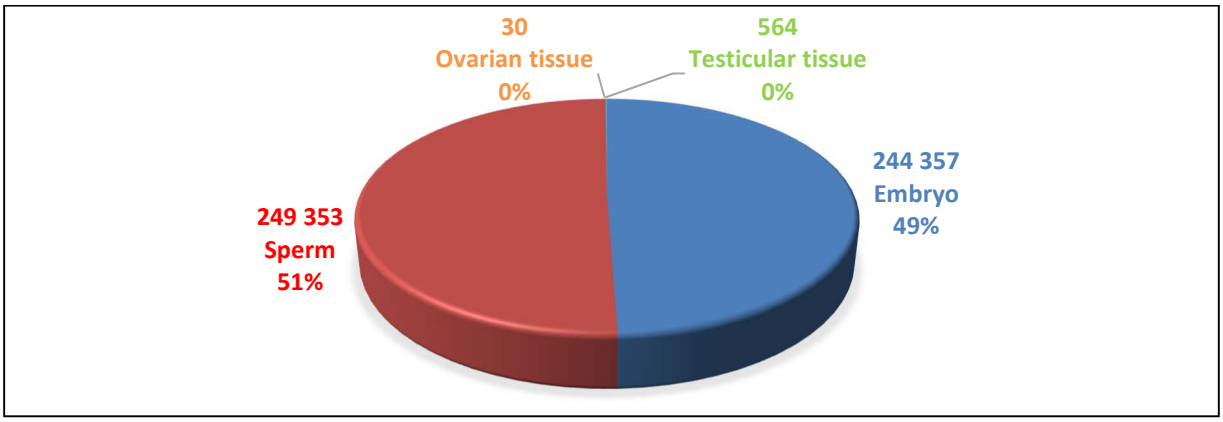

Figure 6. Total number of reproductive tissues and cells distributed (units); data 2018.

2.1.2. Number of recipients

In 2018, 19 countries reported a total of 361 418 *recipients* (patients) having received tissues or cells. For non-reproductive tissues and cells 145 261 patients were reported as having received tissue or cells for transplantation while 216 157 patients underwent a medically assisted reproduction procedure.

2.1.2.1. Non-reproductive tissues and cells

As regards non-reproductive tissues and cells, 19 countries reported data on recipients (AT, BG, CZ, DK, EE, ES, FI, FR, HR, IE, IT, LT, MT, NL, PT, RO, SI, SK and SE).

Figure 7 shows the total number of patients reported as having received each type of non-reproductive tissue or cells: skeletal tissue was the most frequently transplanted tissue followed by haematopoietic stem cells and ocular tissue.

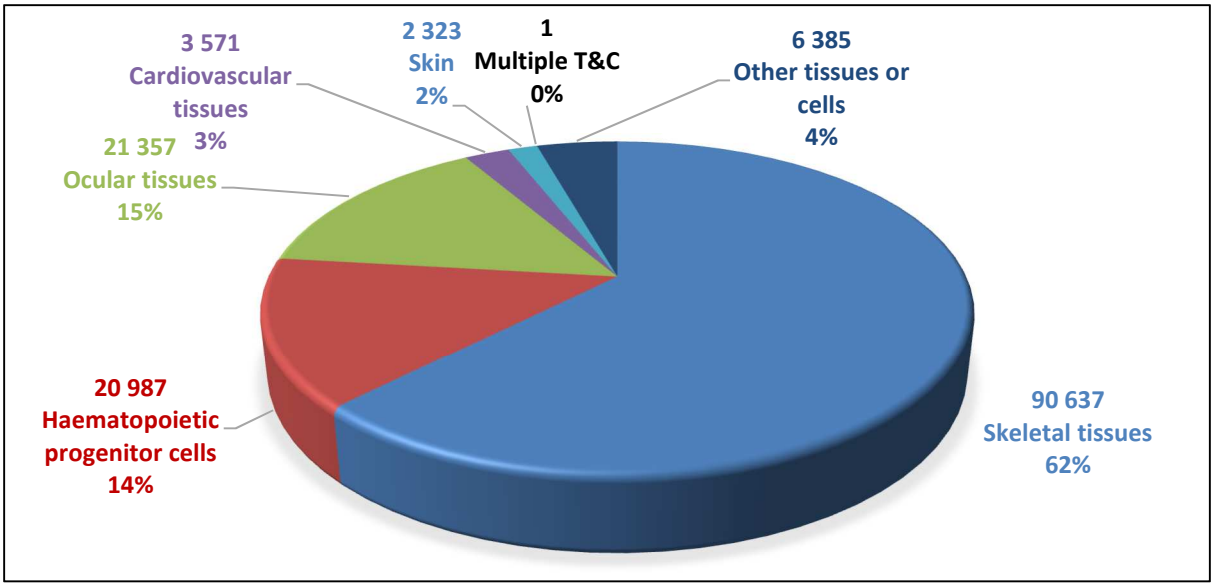

Figure 7. Total number of recipients per type of non-reproductive tissues and cells; data 2018.

2.1.2.2. Reproductive tissues and cells

Concerning reproductive cells, 12 countries (AT, BG, CZ, DK, HR, IE, LT, MT, NL, SK, SE and UK) reported 216 157 patients that underwent a medically assisted reproduction procedure. Of those, 64 768 involved partner or non-partner sperm, 151 367 involved partner or non-partner embryos, and 22 involved transplantation of ovarian tissue, see Figure 8.

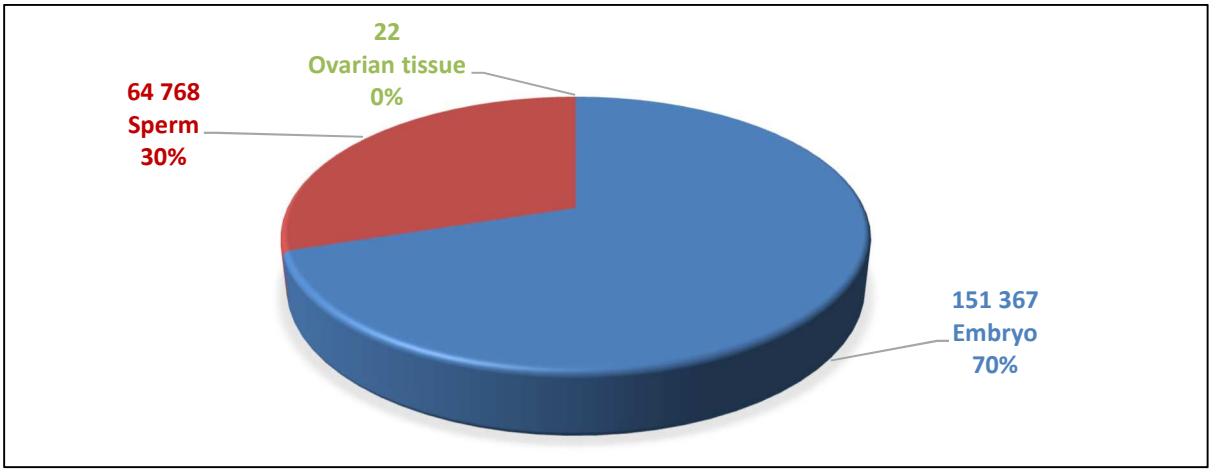

Figure 8. Total number of recipients per type of reproductive tissues and cells; data 2018.

2.1.3. Trends in the reported number of tissues and cells distributed and recipients.

A general overview of the data for the SAR denominators provided by the reporting countries in the period between 2012-2019 (data pertaining to 2011-2018) for non-reproductive and reproductive tissues and cells is presented in Figures 9 and 10, respectively. It is noted that since the previous exercise, the number of tissues and cells distributed in the reproductive field has significantly decreased in comparison with previous years. This drop can be partially explained by the fact that following the exercise to harmonise reporting practices, the category for reporting data for reproductive tissues and cells data was revised and modified, and a new classification of the reproductive tissues and cells category was included in the reporting template. This change is aimed

at facilitating the description of practices in the medically assisted reproduction field. In addition to this, in this reporting exercise, a few countries with high activity in this field were not able to provide denominators.

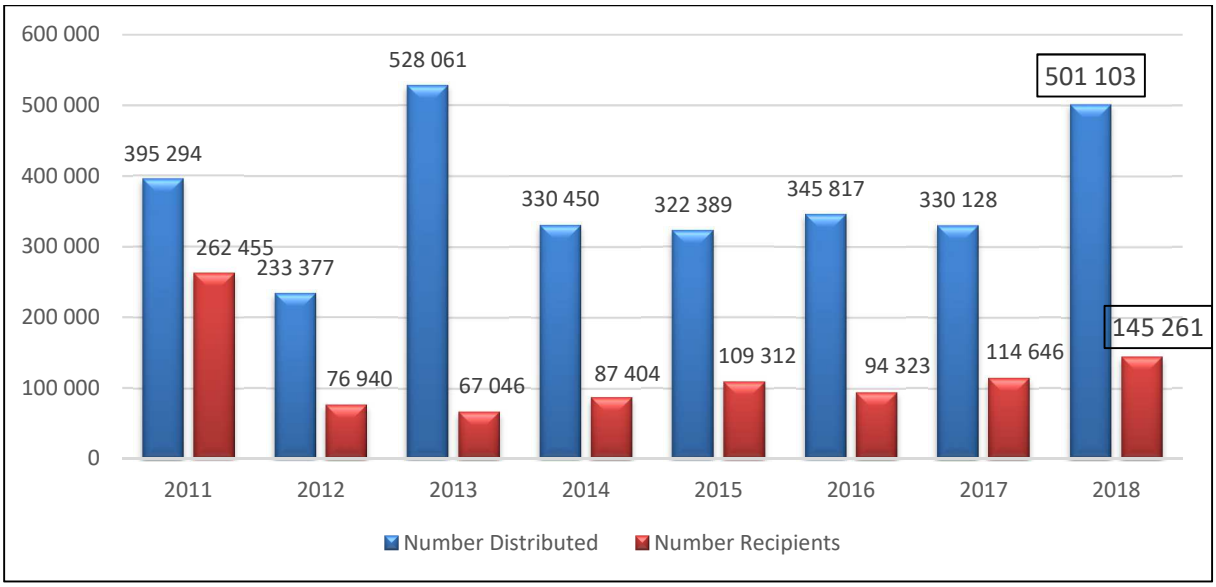

Figure 9. Total number of non-reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2018 comparative data.

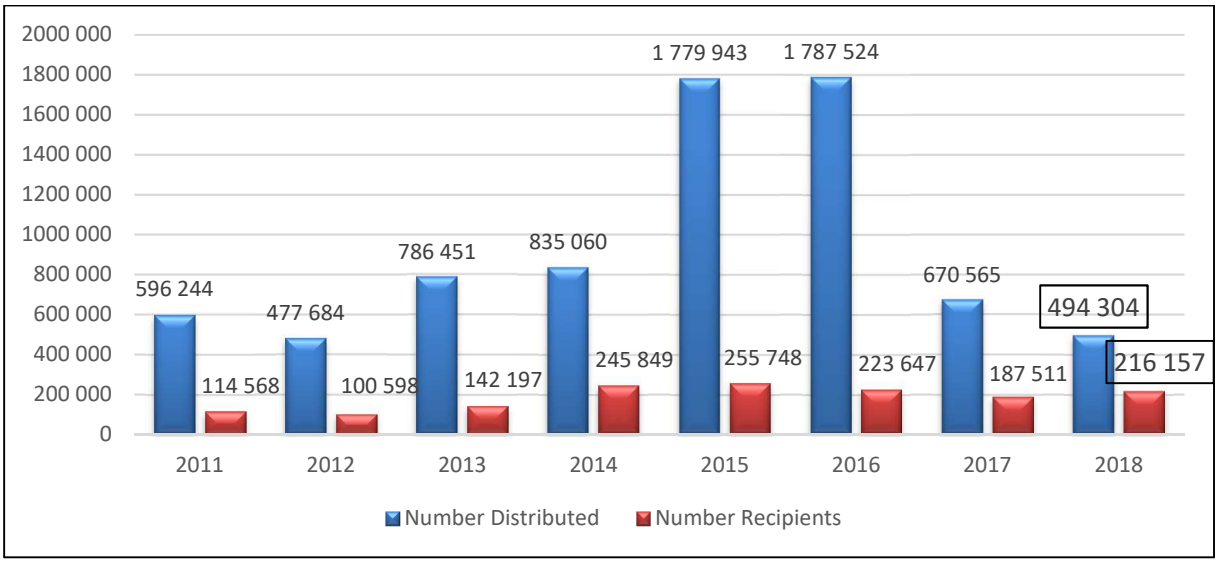

Figure 10. Total number of reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2018 comparative data.[5]

2.1.4. Number of tissues and cells processed

Twenty-four countries (AT, BG, CZ, DE, DK, EE, ES, FI, HU, HR, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SE, SI, SK and UK) provided data regarding the *number of tissues and cells processed* in 2018. Following the Common Approach, the term *"tissues and cells processed"* refers to tissues and cells processed in

[5] 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.

tissue establishments, but not necessarily distributed to end users. Overall, a total of 2 715 953 tissues and cells were reported as processed in 2018, 347 266 units for non-reproductive tissues and cells and 2 368 687 units for reproductive tissues and cells.

Comparative data from previous exercises (2010-2018 data) is presented in Figure 11.

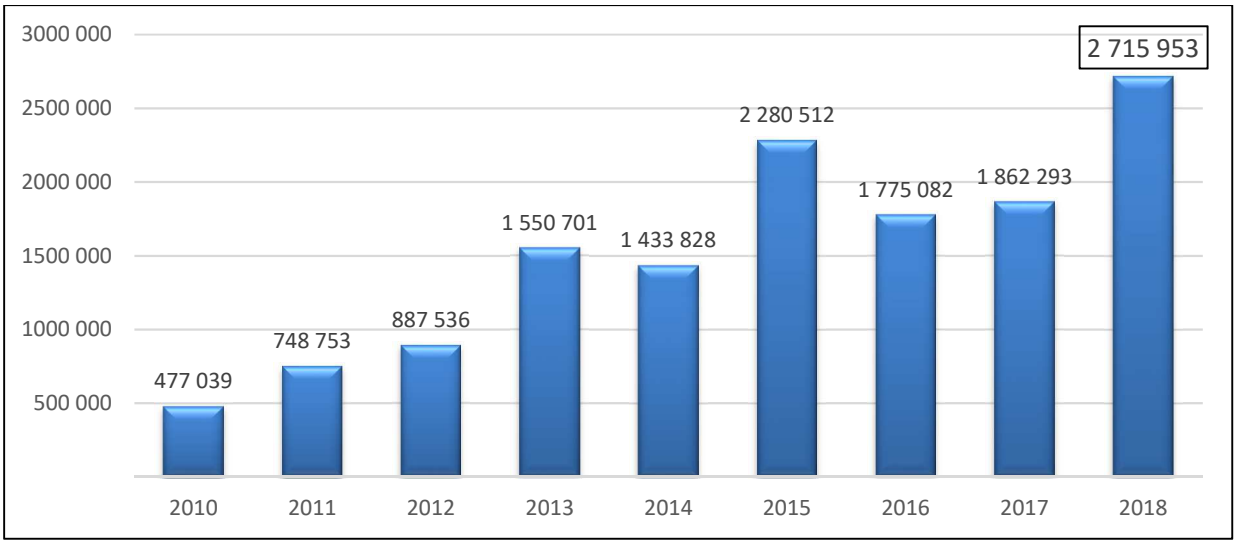

Figure 11. Total number of tissues and cells processed (units): 2010-2018 comparative data.

2.2. Serious adverse reactions

A total of 232 SAR were reported in 2018. Of these, 90 SAR were related to non-reproductive and 142 to reproductive tissues and cells. Of those, 1 case led to death following the clinical application of cells.[6] This information is further developed in section 2.2.4 of this report.

The comparison of number of SAR reported by countries over the years for both categories (non-reproductive and reproductive tissues and cells) is presented in Figure 12, showing that in the latest exercises, the figures submitted by the reporting countries have remained stable.

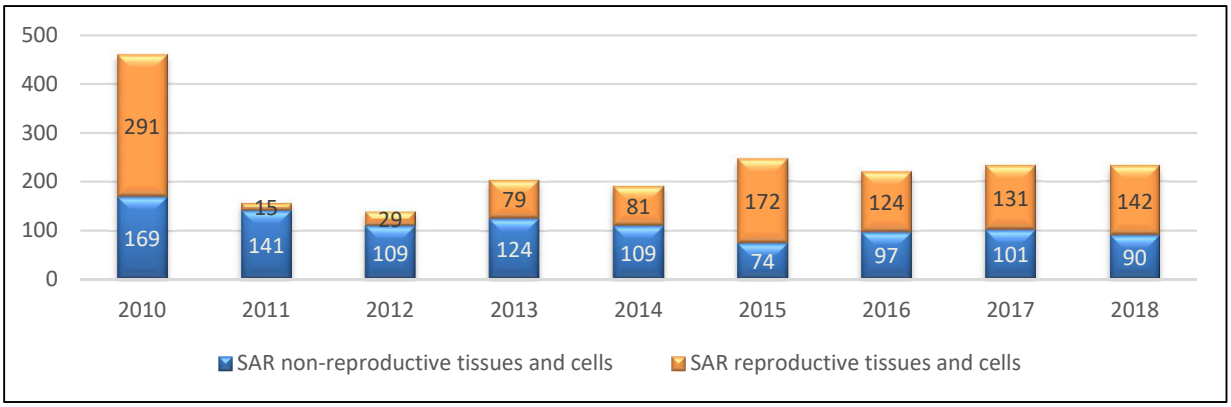

Figure 12. Total number of serious adverse reactions: 2010-2018 comparative data.[7]

[6] 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.

[7] 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 13 Member States (AT, CZ, DE, DK, ES, FI, FR, IE, IT, MT, NL, SE, UK) and Norway reported SAR associated with the clinical application of tissues or cells. Twelve Member States (BG, EE, HU, HR, LT, LU, LV, PL, PT, RO, SK and SI) reported no SAR in recipients in 2018.

Regarding the transplantation of non-reproductive tissues and cells, 11 countries (AT, CZ, DE, ES, FI, FR, IE, IT, NL, SE and UK) reported SAR, and 11 Member States (CZ, DE, DK, ES, FI, IE, IT, MT, NL, SE and 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, following the analysis of those countries who were able to provide the denominators and the SAR, the percentage of SAR related to the use of non-reproductive tissues and cells among reporting countries ranged from 0.008-0.114% SAR/# *tissues and cells distributed* and from 0.010-0.198% SAR/# of *recipients*. For reproductive cells, this range was 0.002-0.215% SAR/# *tissues and cells distributed*, and 0.013-0.363% 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, 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 232 SAR reported:

- 90 SAR (38.7%) were related to the transplantation of non-reproductive tissues or cells (see Figure 13). Of these:
    - 59 were related to the transplantation of HPC:
        - 1 general category[8]
        - 7 bone marrow
        - 45 peripheral blood stem cells
        - 5 cord blood and
        - 1 related to the 'other general HPC' category[8]
    - 31 were related to the transplantation of replacement tissues:
        - 8 skeletal tissue (all bone)
        - 18 ocular tissue (6 general,[8] 12 cornea)
        - 3 cardiovascular tissue (all heart valve) and
        - 2 skin

[8] 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).

- 142 SAR (61.3%) were related to the clinical application of reproductive tissues and cells (see Figure 14). Of these:
    - 42 were sperm (35 following non-partner donation, 2 following partner donation and 5 in the general category[8]). (See Figure 15)
    - 99 were embryos (1 from partner gametes, 68 reported in a general category[8], 19 following oocyte donation and partner sperm, 4 following sperm and oocyte donation and 7 following sperm donation and partner oocyte). (See Figure 16) and
    - 1 was 'other reproductive tissues'.

No SAR were reported in this exercise for the categories of general skeletal tissues, tendons/ligaments, cartilage, fascia, other skeletal tissues (meniscus and/or ear ossicles), sclera, other ocular tissues, donor lymphocyte infusions, general cardiovascular, vessel, other cardiovascular tissues (e.g. conduit or patch or pericardium), multiple tissues and cells, pancreatic islets, hepatocytes, amniotic membrane, adipose tissue, tympanic membrane or ovarian and testicular tissues.

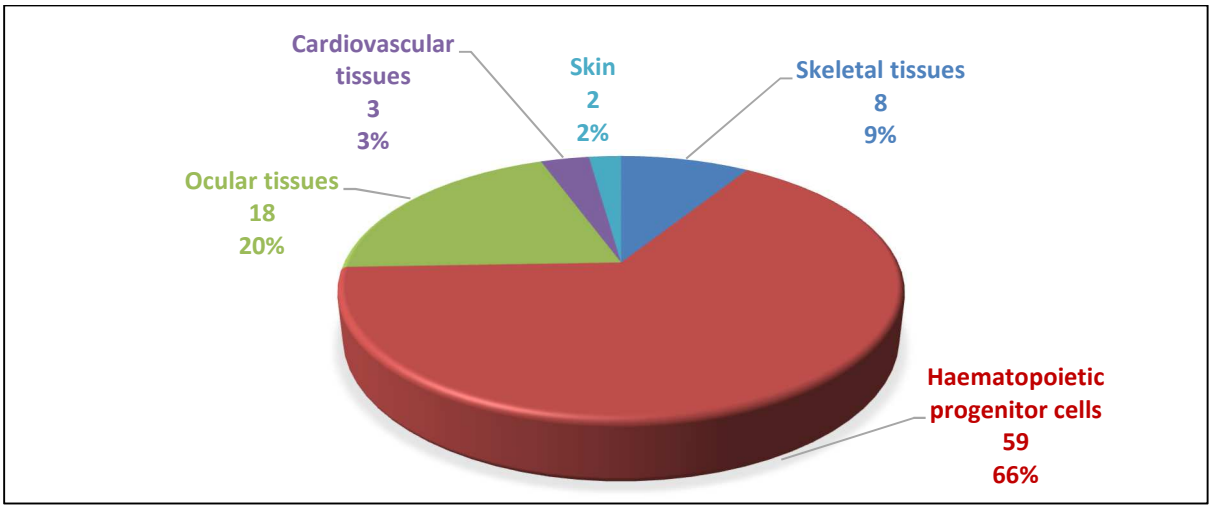

Figure 13. Number of SAR for each type of non-reproductive tissues and cells (absolute values and percentages of total recipient SAR); 2018 data.

[8] 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).

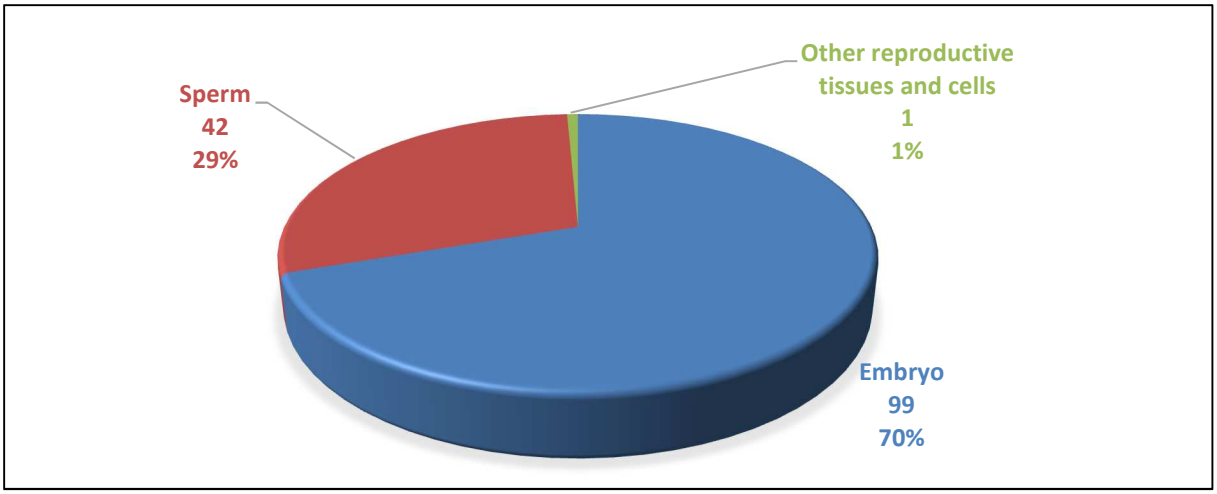

Figure 14. Number of SAR for each type of reproductive cell (absolute values and percentages of total recipient SAR); 2018 data.

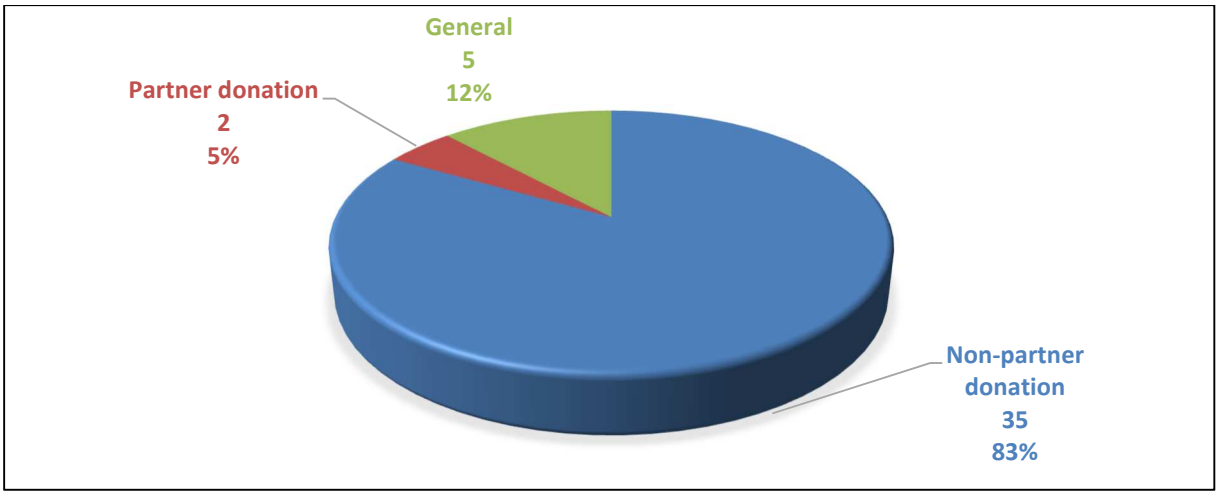

Figure 15. Number of SAR for sperm used for IUI per category (absolute values and percentages of total recipient SAR); 2018 data

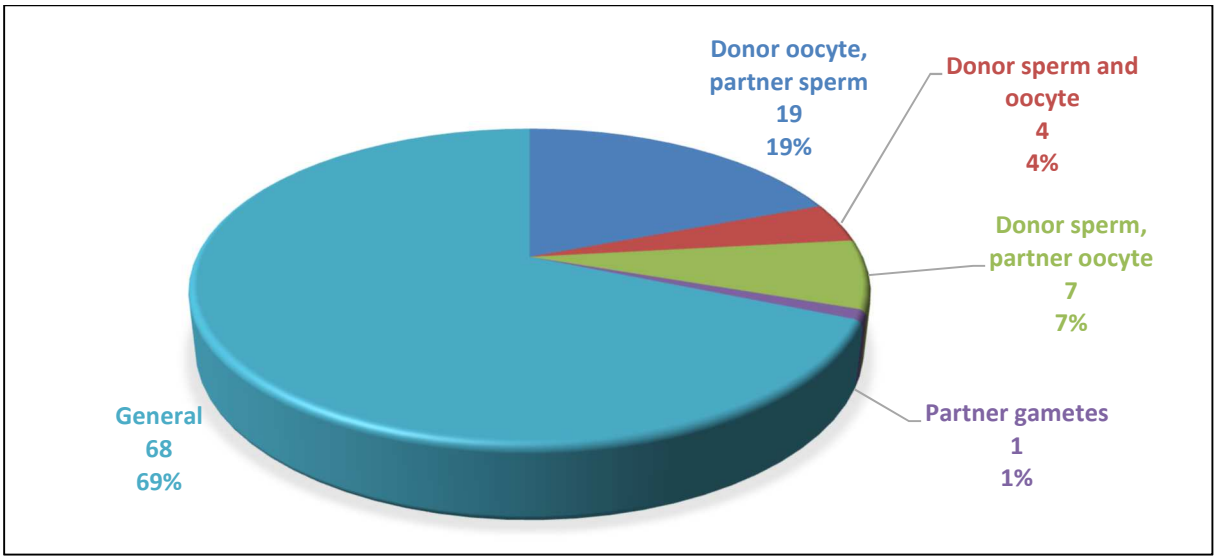

Figure 16. Number of SAR for embryos after IVF/ICSI per category (absolute values and percentages of total recipient SAR); 2018 data.

2.2.3. Data by type of serious adverse reaction

The 90 SAR related to the transplantation of *non-reproductive tissues and cells* were categorised as follows (see Figure 17):

- Transmitted infections: 16 cases (17.8% of all reported SAR for non-reproductive tissues and cells; see Figure 18), divided as follows:
  - 6 cases of bacterial infections, reported for the following transplanted tissues/cells: 4 ocular tissues and 2 HPC
  - 5 cases of fungal infections, all of them reported following the transplantation of ocular tissues
  - 2 cases of "other viral transmission", both reported following the transplantation of ocular tissues
  - 3 cases of 'other transmitted infections', also following the transplantation of ocular tissue

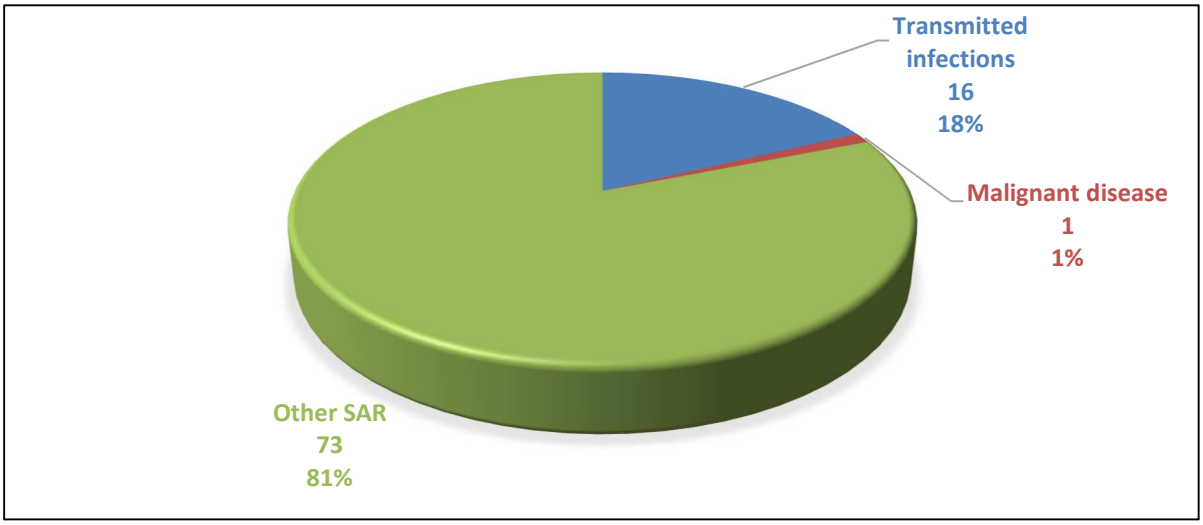

Figure 17. Number of SAR for non-reproductive tissues and cells per category (absolute values); data 2018.

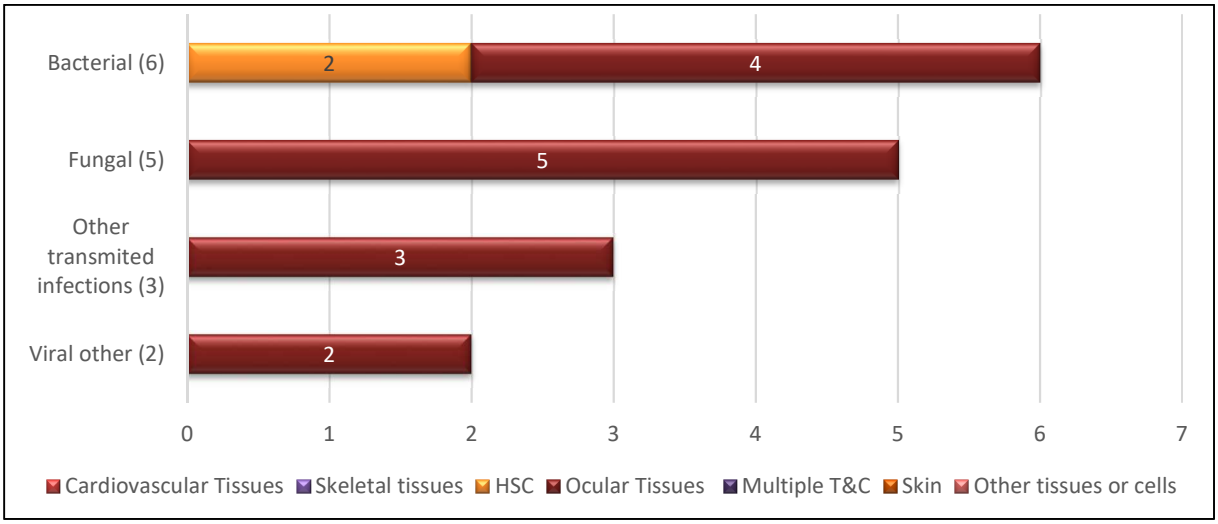

Figure 18. Number of SAR of transmitted infections for non-reproductive tissues and cells (absolute values); data 2018.

- Malignant disease: 1 case reported following peripheral blood stem cell transplantation (1.1% of all reported SAR for non-reproductive tissues and cells).
- Other SAR: 73 cases (81.1% of all reported SAR for non-reproductive tissues and cells; see Figure 19). This broad and heterogeneous category could be further divided as follows:
    - 20 cases of immunological reactions following the HPC transplantation (17; of those 15 following peripheral blood stem cell transplantation and 2 following bone marrow transplantation), skin transplantation (2) and bone transplantation (1)
    - 18 cases of graft failure or delayed engraftment. Of those:
        - 9 cases following the transplantation of HPC (4 following peripheral blood stem cell transplantation, 3 following cord blood transplantation and 2 following bone marrow transplantation)
        - 6 cases following the transplantation of skeletal tissues, in all of which the tissue transplanted was bone
        - 2 cases following the transplantation of ocular tissue; in all cases the tissue transplanted was cornea
        - 1 case following the transplantation of a heart valve
    - 7 cases of toxicity following HPC transplantation (5 following the transfusion of peripheral blood stem cells, 1 following bone marrow transplantation and 1 following transplantation of the general category of HPC[8])
    - 4 cases of cardiovascular complications following the transplantation of peripheral blood stem cells (HPC)
    - 2 cases of neurological complications following the transplantation of peripheral blood stem cells (HPC)
    - 2 cases of pulmonary complications following HPC transplantation (1 following transfusion of peripheral blood stem cells and 1 following transfusion of cord blood)
    - 2 cases of renal complications following HPC transplantation (1 following the transplantation of bone marrow and 1 following the transfusion of peripheral blood stem cells)
    - 18 cases of other SAR (none of the above) following the transplantation of bone (1), HPC (13; 12 following peripheral blood stem cell transfusion and 1 following cord blood transfusion), cornea (2), and heart valve (2)

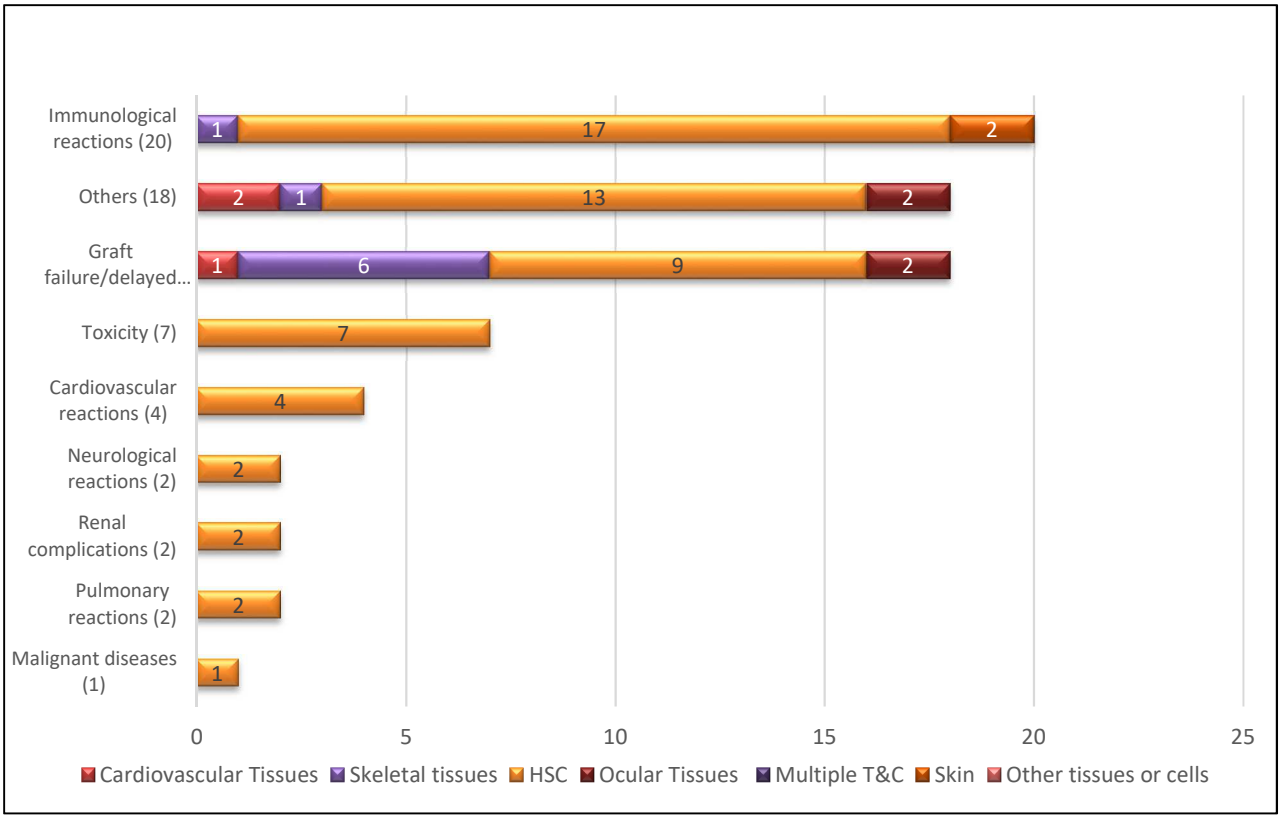

Figure 19. Number of "other SAR" for non-reproductive tissues and cells (absolute values); data 2018.

The 142 SAR associated with the application of *reproductive cells* were classified as follows (see Figures 20 and 21):

- Transmitted genetic conditions: 68 SAR (48% of all reported SAR for reproductive tissues and cells), divided as follows:
    - 33 cases involving non-partner sperm donation
    - 14 cases involving embryos from donor oocyte and partner sperm
    - 9 cases involving embryos in the 'general' category[8]
    - 6 cases involving embryos from donor sperm and partner oocyte
    - 3 cases involving embryos from donor sperm and oocyte and
    - 3 cases involving sperm in the 'general' category[8]

- Bacterial infection: 1 SAR (0.7% of all reported SAR for reproductive tissues and cells) following the clinical application of sperm from partner donation).
- Other SAR: 73 SAR (51.4% of all reported SAR for reproductive tissues and cells), divided as follows:
    - 59 cases involving embryos in the 'general' category[8]
    - 5 cases involving embryos from donor oocyte and partner sperm
    - 1 cases involving embryos from donor sperm and oocyte
    - 1 cases involving embryos from donor sperm and partner oocyte
    - 1 case involving embryos from partner gametes
    - 2 cases involving sperm from 'general' category[8]
    - 2 cases involving sperm from non-partner donation
    - 1 case involving sperm from partner donation and

- 1 case involving 'other reproductive tissues and cells'.

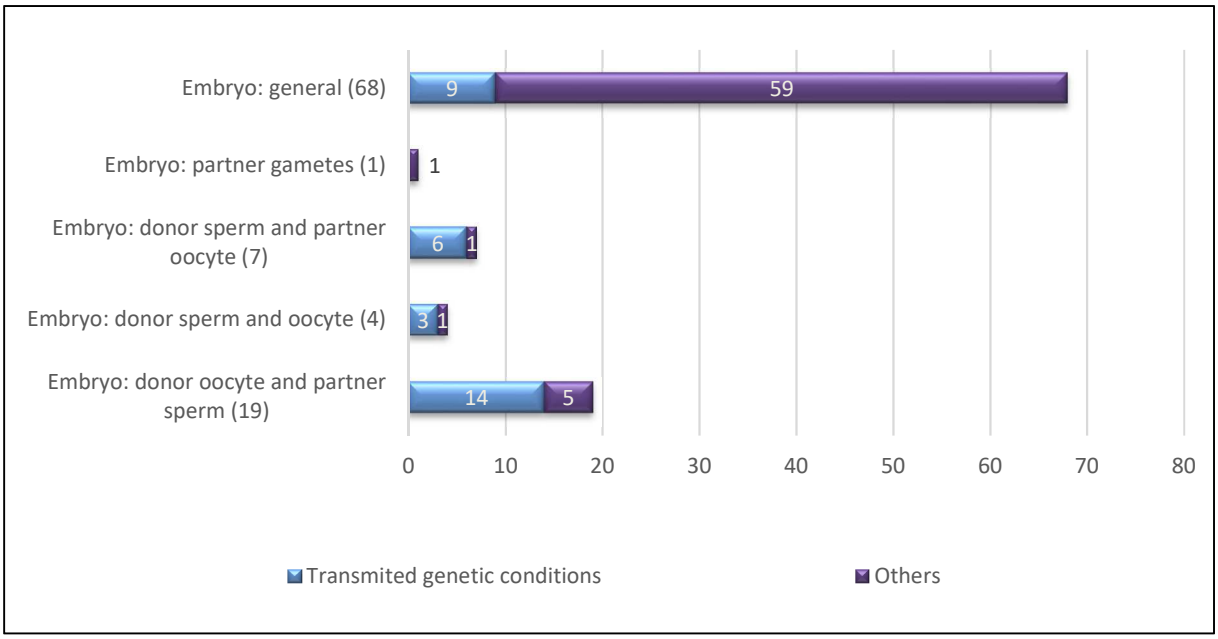

Figure 20. SAR related to the application of embryos (absolute values); 2018 data.

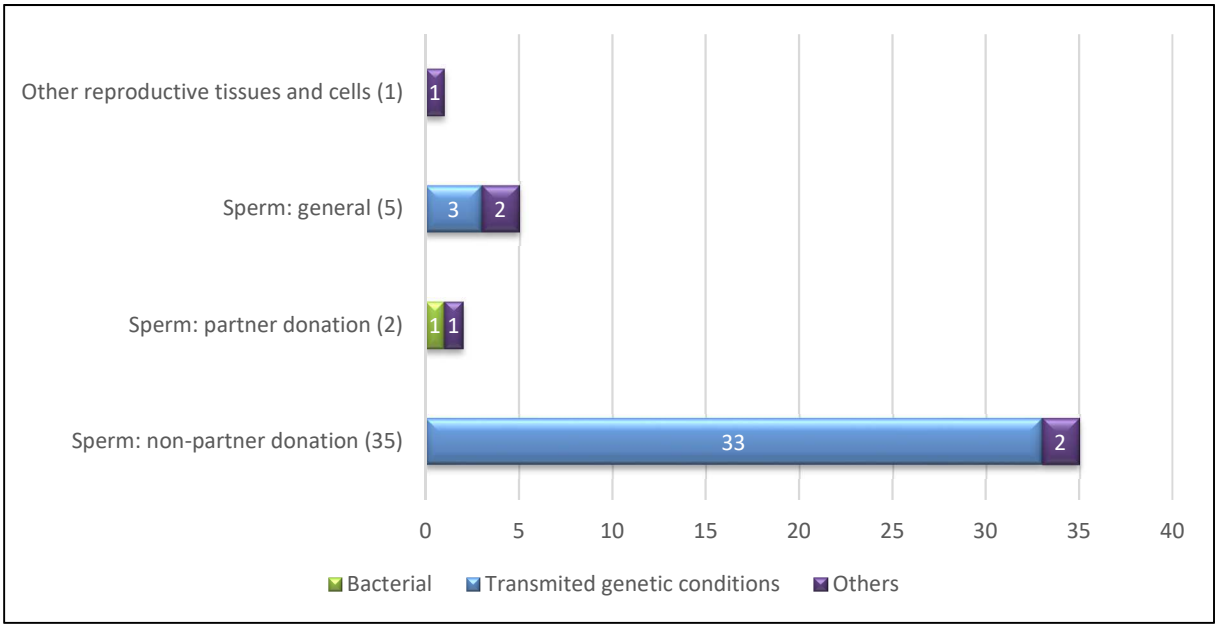

Figure 21. SAR related to the application of sperm and other reproductive tissues and cells (absolute values); 2018 data.

It is noted that of these 142 SAR associated with the application of reproductive cells, as shown in Figure 22, 65 (46% of all SAR reported for reproductive tissues and cells) were related to non-partner donation (35 involving non-partner sperm and 30 involving embryos [donor oocyte and partner sperm (19), donor sperm and oocyte (4) and donor sperm and partner oocyte (7)].

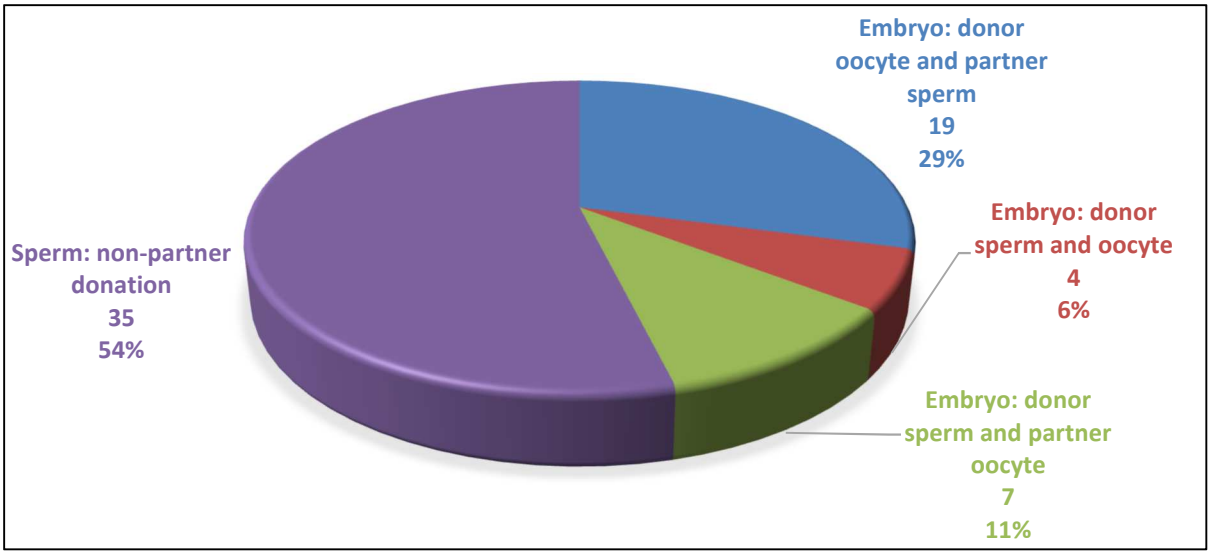

Figure 22. SAR related to the application of non-partner gametes (absolute values and percentages); 2018 data.

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, on a voluntary basis, information for reported deaths.

One death was reported in 2018 following the application of reproductive cells. The death was as a result of an elective abortion after concluding that following non-partner gamete donation, a serious genetic condition was transmitted to the foetus.

2.3. Serious adverse events

The total number of SAE reported for 2018 was 739. Of those, 531 SAE were reported for non-reproductive tissues and cells and 208 SAE were reported for reproductive tissues and cells.

Considering the denominator for SAE: *tissues and cells processed* during this period, during 2018 in Europe, 1 SAE took place per 367 517 units of tissue processed. The disaggregated data show that, as regards non-reproductive tissues and cells, 1 SAE occurred for every 65 398 units processed and in the case of reproductive tissues and cells, 1 SAE happened for every 1 138 791 units processed. However, this calculation should be interpreted with caution, as not all countries are able to report these data.

The total number of SAE reported in 2018 remained stable when compared to previous exercises, as presented in Figure 23.

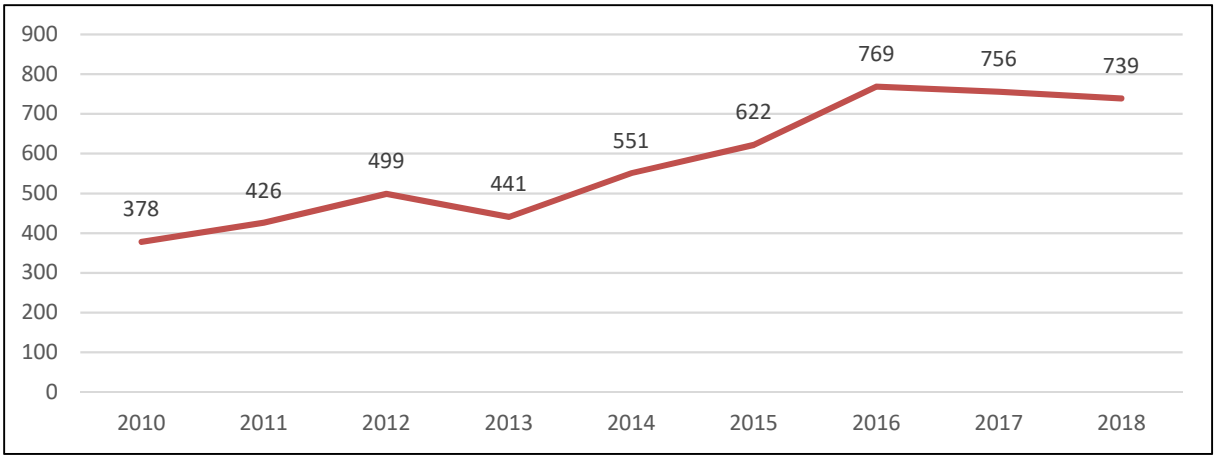

Figure 23. Total number of SAE reported: 2010-2018 comparative data.

Comparative data showing the evolution of SAE by type of event in the past exercises are shown in Figure 24. Human error is the most common type of event with numbers increasing over time, although they dropped slightly in the latest exercise. Tissue/cell defects have also increased in recent years, whereas numbers of other types of events remain stable. Following this evolution, and with the aim of harmonising reporting by Member States at European level, this year for the first time a new category for specification of SAE: "materials" has been introduced in the reporting template. As stated in the Common Approach, this should be understood as a defect in the quality and safety of the tissues or cells due to defective materials used during procurement, processing, storage or distribution.

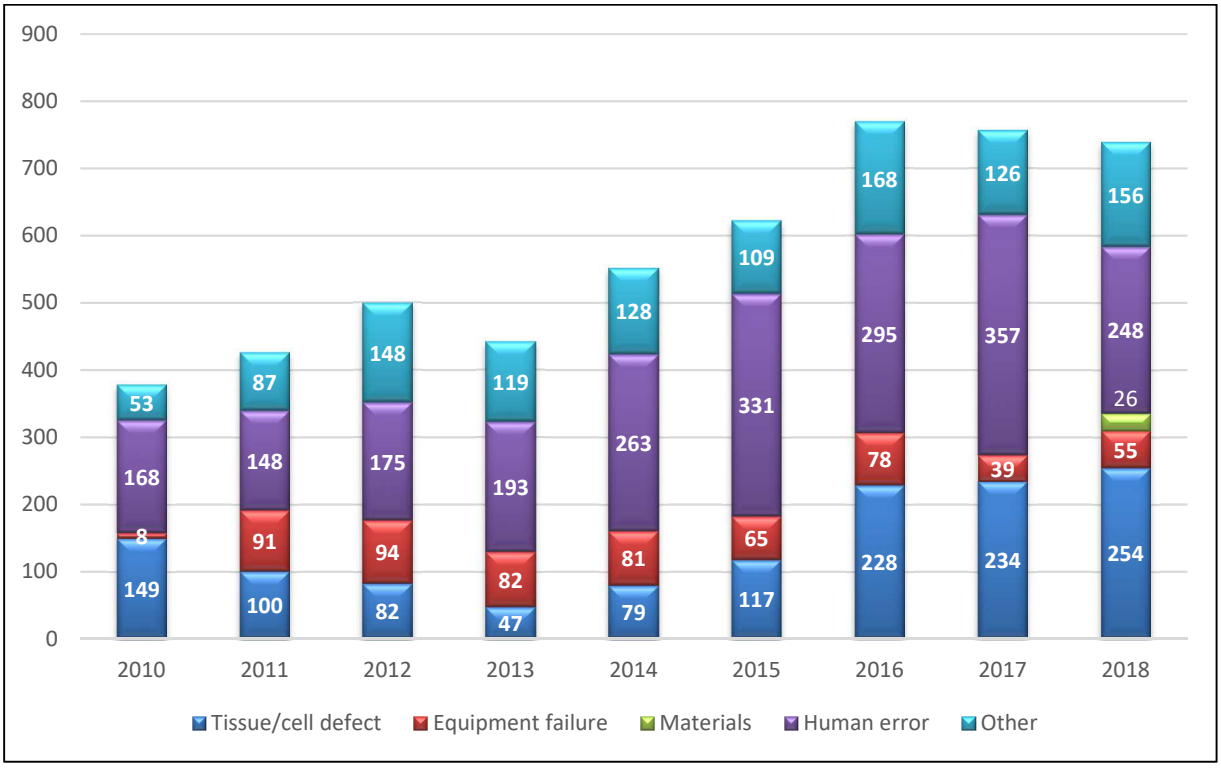

Figure 24. Total number of serious adverse events by specification: 2010-2018 comparative data.

2.3.1. Information by country

Sixteen countries reported SAE for non-reproductive tissues and cells (AT, DE, ES, FI, FR, HR, HU, IE, IT, NL, PL, PT, SE, SI, UK and NO) and 16 countries for reproductive cells (AT, CZ, DK, DE, ES, FI, FR, HR, IE, IT, LV, NL, PT, SE, UK and NO).

In this reporting exercise, following the harmonisation of practices, 2 new sub-categories "product selection" and "issue" had been introduced in the reporting template under activity steps. In this regard, the Common Approach refers to "product selection" as the selection of the appropriate tissues and cells for human application, on the basis of biological as well as clinical criteria, including the administrative handling. In the case of "issue", it refers to the activity step of the provision of tissues or cells for transplantation, infusion, insemination or transfer. It should be noted that this category does not include transportation and delivery, which should be reported in the relevant activity step.

An overview of the SAE types reported per non-reproductive and reproductive tissues and cells is presented in Figures 25 and 26, respectively.

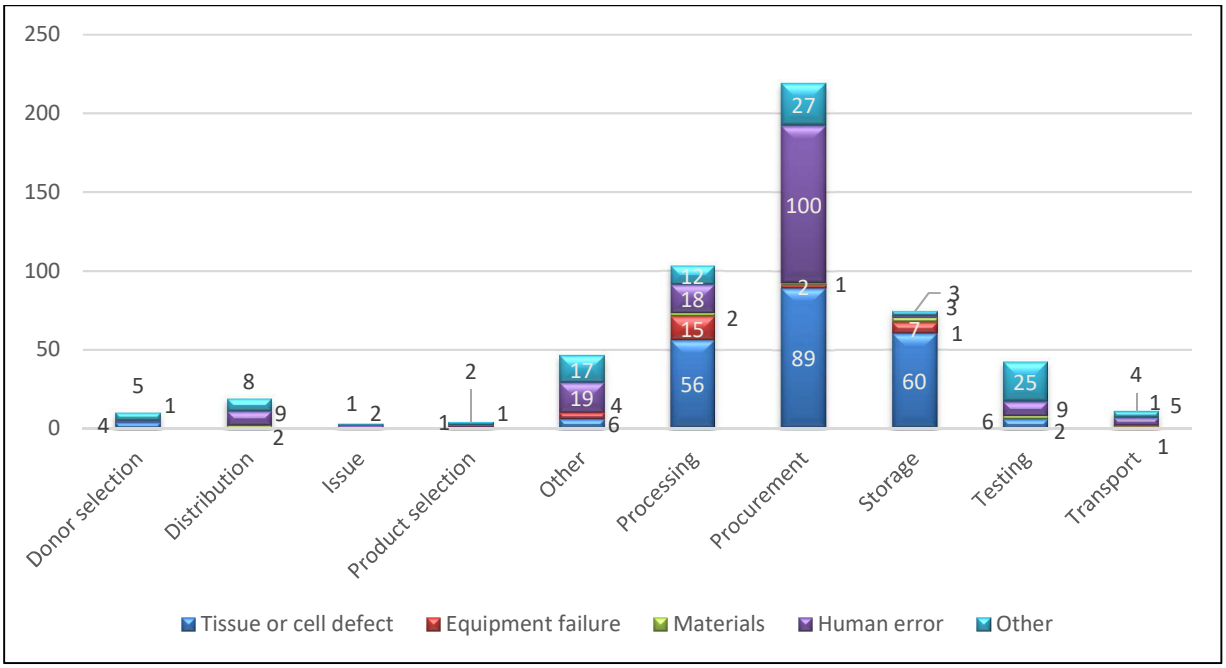

Figure 25. Total number of serious adverse events reported for non-reproductive tissues and cells, categorised by activity step; 2018 data.

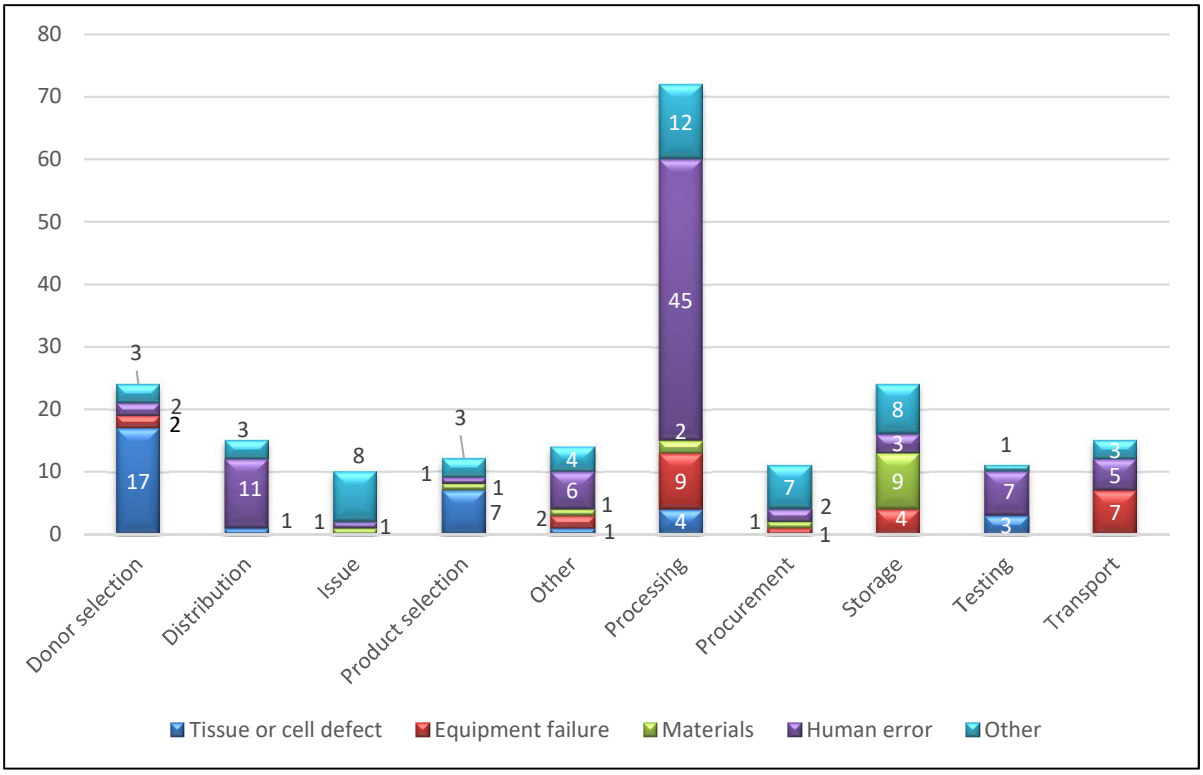

Figure 26. Total number of serious adverse events reported for reproductive tissues and cells, categorised by activity step; 2018 data.

The classification of SAE per activity step differs slightly when comparing non-reproductive and reproductive tissues and cells. For the former, the largest number of reported SAE occurred during procurement with human error being the main origin, while for reproductive tissues and cells the largest number of reported SAE happened during processing but also due to human error.

2.3.2. Information by activity

An overview of the SAE reported for non-reproductive and reproductive tissues and cells, by type of activity step, is presented in Figures 27 and 28.

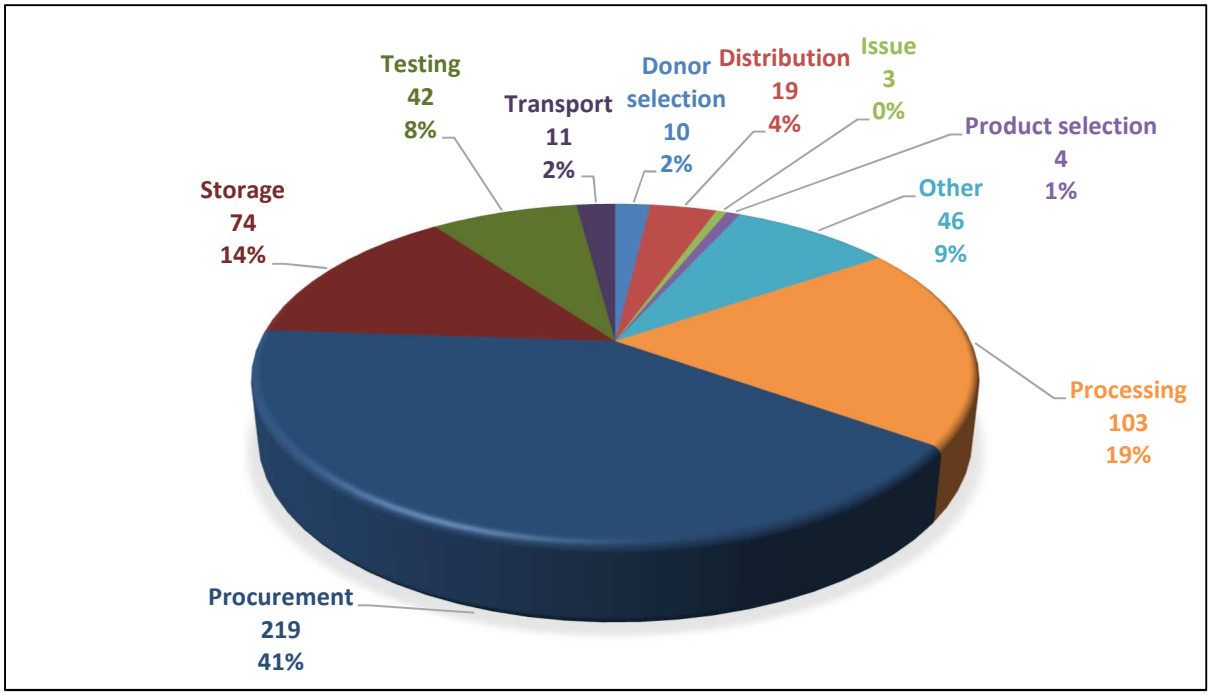

Figure 27. Number of SAE and percentage of total SAE reported for non-reproductive tissues and cells by type of activity (absolute values and percentages of total); data 2018.

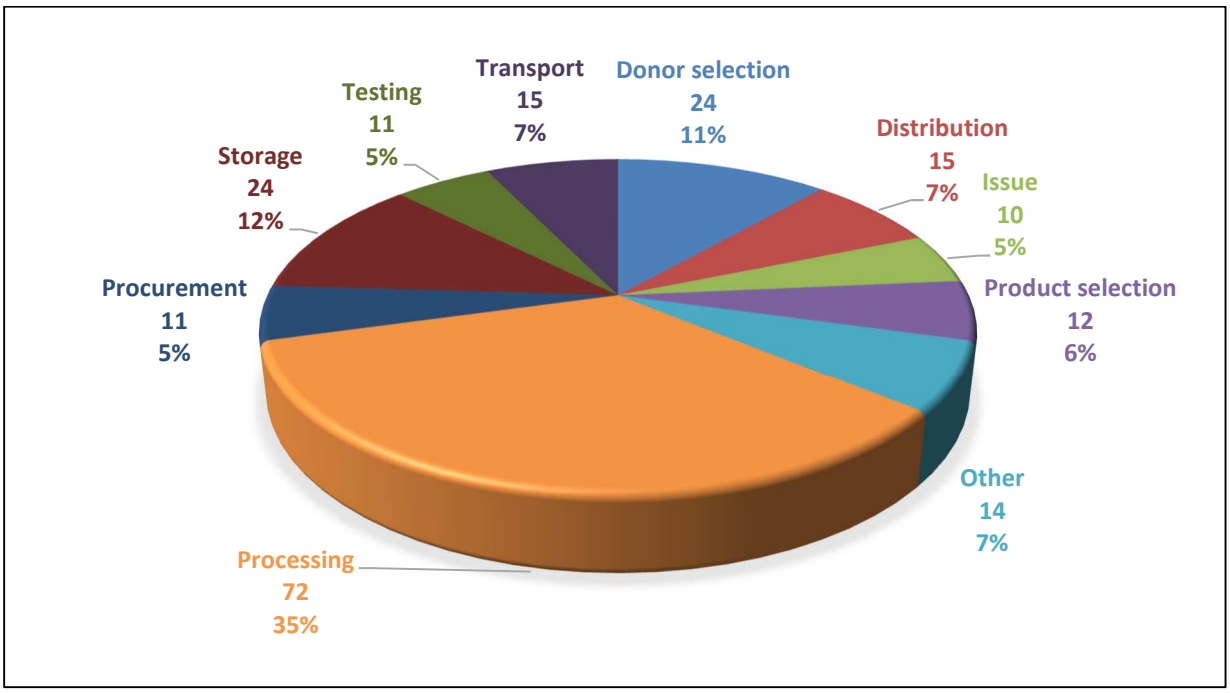

Figure 28. Number of SAE and percentage of total SAE reported for reproductive tissues and cells by type of activity (absolute values and percentages of total); data 2018.

2.3.3. Information by type of serious adverse event

The 739 SAE were classified as tissue or cell defects, human error, equipment failure, materials (a new category in this reporting exercise) and other types of events.

The distribution by type for non-reproductive and reproductive tissues and cells is presented in Figures 29 and 30.

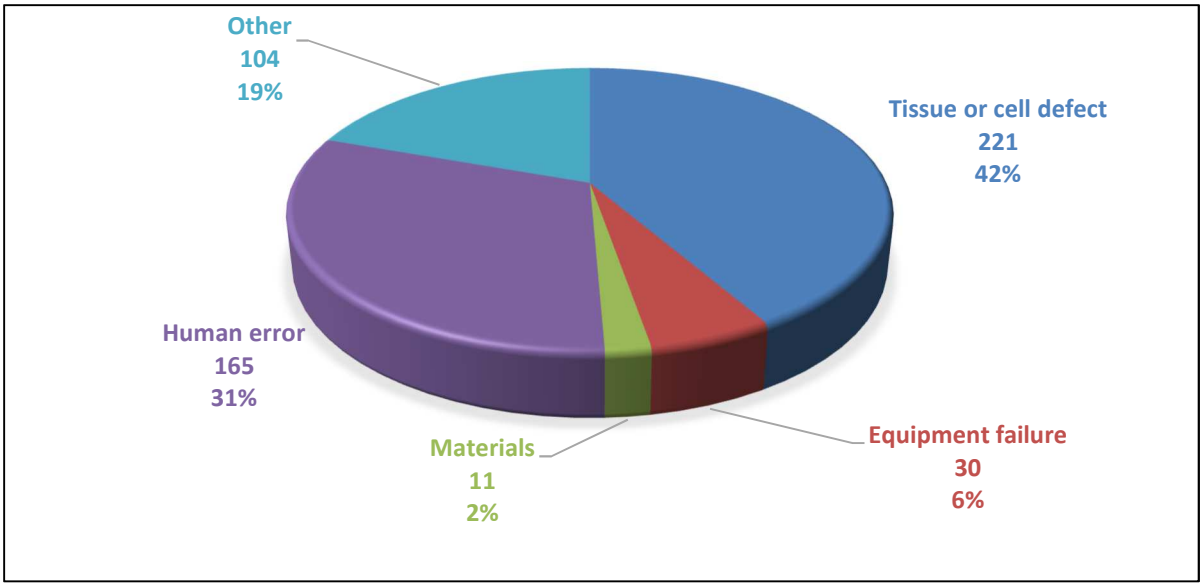

Figure 29. SAE types for non-reproductive tissues and cells (absolute values and percentages of total); 2018 data.

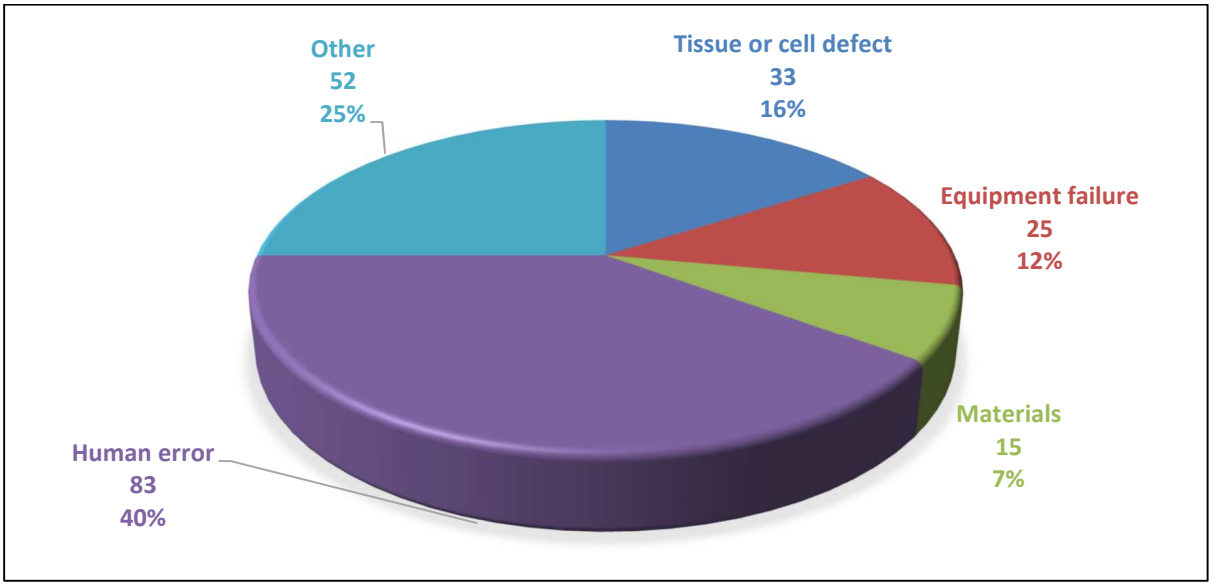

Figure 30. SAE types for reproductive tissues and cells (absolute values and percentages of total); 2018 data.

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 [GCSF] for collection of peripheral blood stem cells), the Commission continues to collect such data on a voluntary basis, in agreement with Competent Authorities.

Seventeen Member States (AT, BG, CZ, DE, EE, ES, FI, FR, HR, IE, IT, NL, PL, PT, SI, SE, and UK) reported a total of 934 *SAR in donors* in 2018. A general overview of SAR in donors during the period 2011-2019 (data pertaining to 2010-2018) is presented in Figure 31.

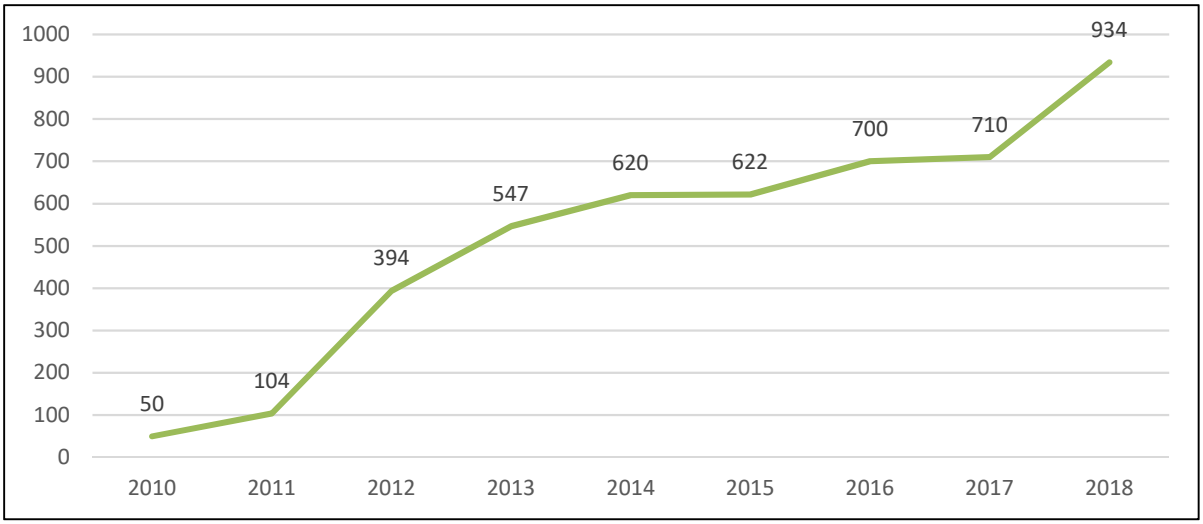

Figure 31. Number of serious adverse reactions in donors; 2010-2018 comparative data.

Of the 934 SAR in donors reported in 2018:

- 30 cases were related to the donation of non-reproductive tissues or cells (3.2% of all SAR in donors) and were reported by 6 countries (DE, FI, FR, IT, NL, PL); 29 cases reported were associated with donation of HPC and 1 with other tissues and cells.
- 904 cases (amounting to 96.8% of all SAR in donors) were related to the donation of reproductive tissues or cells, specifically 902 with the donation of oocytes, 1 with donation of sperm and 1 with other reproductive tissues (see Figure 32). These were reported by 15 Member States (AT, BG, CZ, DE, EE, ES, FR, HR, IE, IT, NL, PT, SI, SE and UK). SAR in donors of reproductive tissues or cells were reported under the following categories: oocytes 'general' (181), oocytes for non-partner donation (44), oocytes for partner donation (678), and sperm for partner donation (1).

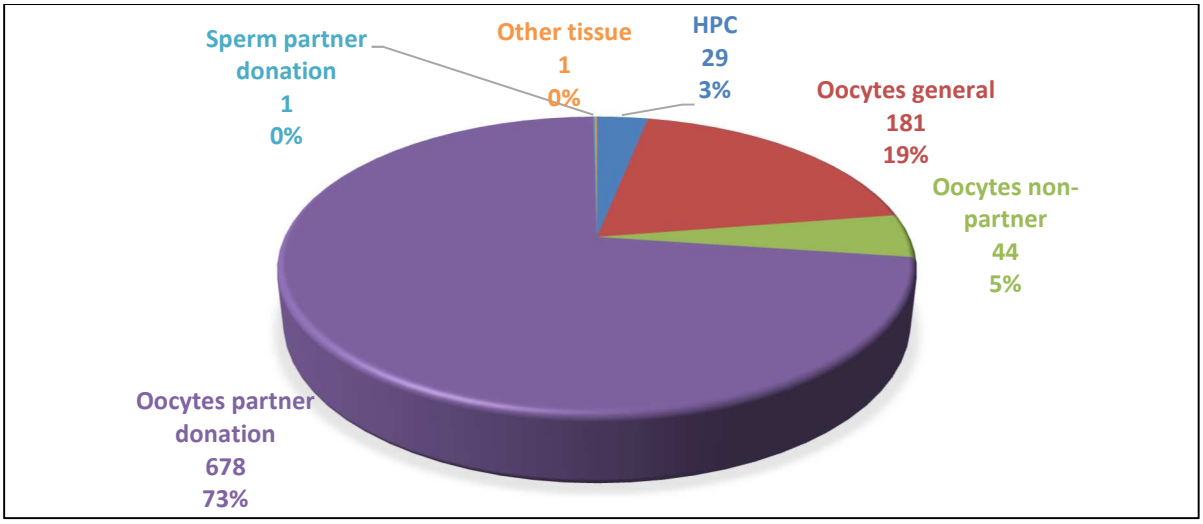

Figure 32. Serious adverse reactions in donors per type of donated tissue or cell (units); data 2018.

In the case of non-partner donation, the main SAR reported were severe OHSS (18), haemoperitoneum (18), hospitalisation (2), complications resulting in ovariectomy or partial ovarian resection (2), infection (1) and other (3), as shown in Figure 33.

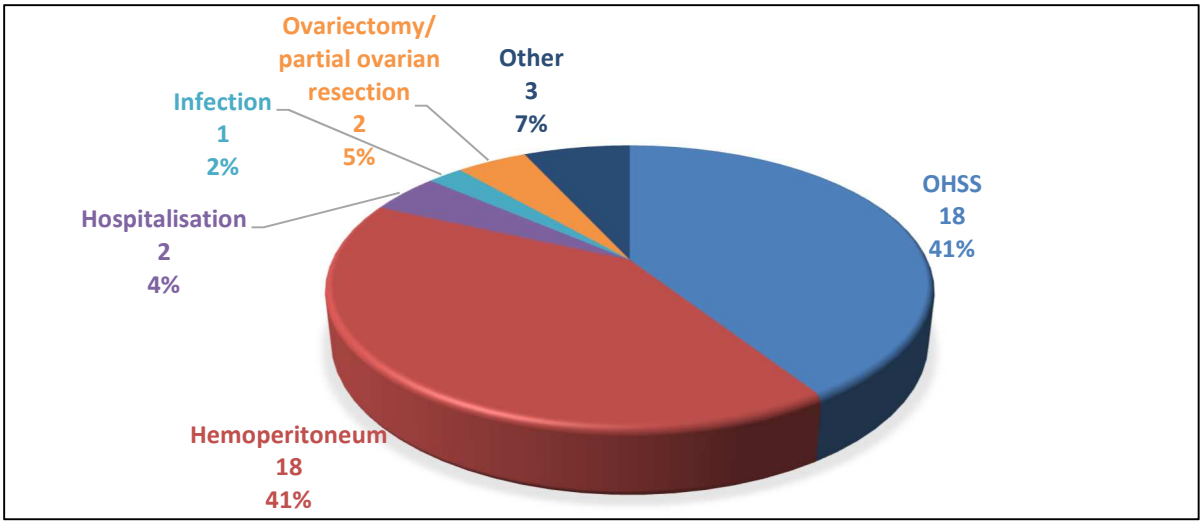

Figure 33. Classification of SAR in donors for non-partner oocyte donors.

Most of the SAR in oocyte donors were critical, severe and moderate-to-severe OHSS cases (651 cases) and haemoperitoneum (113 cases), the remaining cases included infectious complications and other types of SAR, as shown in Figure 34.

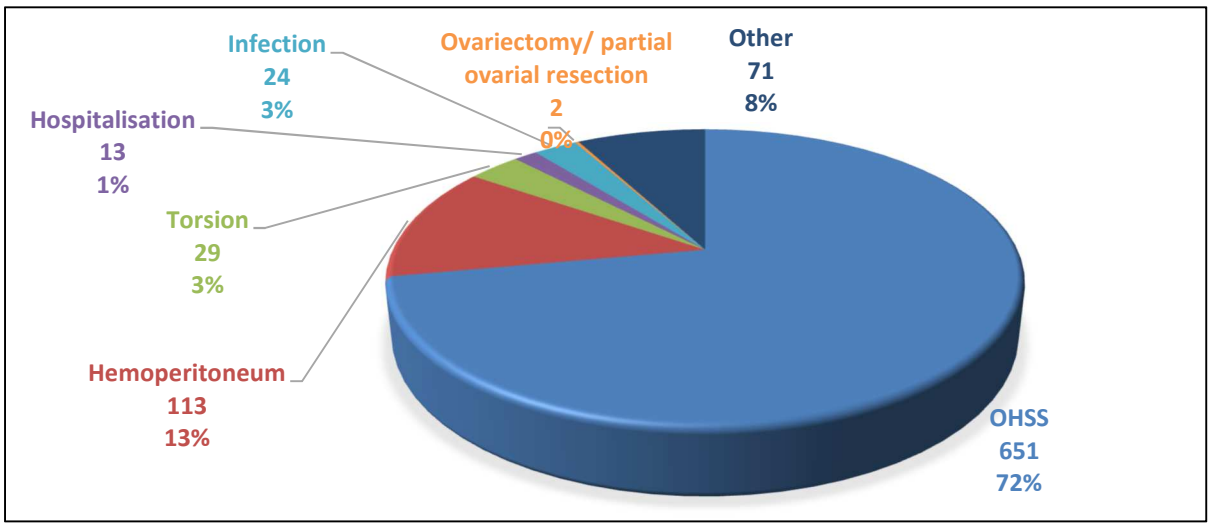

Figure 34. SAR in oocyte donors; 2018 data (absolute values and percentages of total).

The vast majority of the 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. However, it should be noted that 4 of the SAR in donors reported in 2018 resulted in the death of the donor, in all cases following partner donation. The reported cases have different aetiology: 1 death resulted during the retrieval of the oocytes, probably due to an undiagnosed underlying pathology in the donor at the time of collection; 2 cases were reported during the embryo transfer: both donors died after suffering complications (one after cardiac arrest during the procedure and the other presented with pulmonary embolism the day after the transfer); and lastly, a donor died due to a pulmonary embolism during the first quarter of

pregnancy. It should be noted that the investigations performed did not conclude that those reactions were directly linked to the quality of the cells. However, this voluntary reporting of deaths in donors highlights the need for Competent Authorities, and the EU Commission, to ensure appropriate follow-up and protection mechanisms for living donors of tissues and cells.

3. Conclusions

From the results of this report and the trends of previous SARE exercises, vigilance systems and national data collection in the field of biovigilance are improving year after year. Nevertheless, there are areas that still require further work. For example, not all reporting countries are able to provide activity data to be used as denominators for SARE. This situation would require additional efforts from Member States to obtain more accurate and complete activity data from tissue establishments, cell therapy and medically assisted reproduction facilities and organisations responsible for human application, who are ultimately responsible for applying those tissues and cells to patients.

In addition, not all countries collect data using the same units of measure (e.g. units/packages of skin vs cm^2 vs m^2; number of oocytes vs number of cycles). This lack of harmonisation in collecting data creates difficulties when comparing data among Member States at European level and thus, extracting general trends and conclusions.

The current difficulties in collecting and reporting activity data were 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 within 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. A realistic assessment of how many tissues and cells are available and how many are required are fundamental for governments to ensure a rational, fair, and effective distribution of tissues and cells and to avoid overreliance on 3rd countries (outside the EU) or on a few EU countries with the final goal of achieving European self-sufficiency. The participants agreed that further meetings should be organised to continue the discussions and ensure an appropriate and non-redundant collection of activity data in the future. As a result, within the framework of a new grant agreement between the Commission and the EDQM (2018 53 01), several activities aimed at improving vigilance systems and training professionals, harmonising activity data reporting and reducing the burden on reporting tissue establishments, cell therapy and medically assisted reproduction facilities and Competent Authorities, as well as enhancing co-operation with professional societies carrying out similar work, are currently being implemented. The resulting outcomes will serve to improve this lack of harmonisation in the future.

Tissue establishments that supply tissues and cells should encourage procurement organisations and clinical users of tissues and cells to always consider whether adverse outcomes might have been associated with the donation process or caused by the tissues and cells applied. Reporting those cases presents important learning opportunities that can help all procurement organisations, tissue establishments, cell therapy and medically assisted reproduction facilities and clinical users to improve their processes and to achieve higher standards of safety and quality at all levels: from tissue establishments to donors and recipients.

For the reported SAR related to the transplantation of non-reproductive tissues and cells, most were associated with "other SAR" and infection – mostly of bacterial and fungal origin. 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 should be noted that the likelihood of transmitting multi-factorial genetic diseases from donor to offspring is sometimes difficult to assess.

Quality systems focus on preventing errors and maintaining a consistent standard of agreed specification for tissues and cells released for clinical application. However, occasionally, residual risks or procedural errors result in failures, or situations in which donors or recipients are exposed to risk. Instances of non-compliance with the quality system should be documented and investigated as part of the internal quality system management. On occasion, however, a particular non-compliance incident may be of such importance that it should be considered as SAE and reported through the vigilance system. The majority of SAE were reported under the category of "human error", mostly during procurement for non-reproductive tissues and cells and during processing steps for reproductive tissues and cells. These findings suggest not only the importance of revising standard operating procedures in tissue establishments, highlighting critical steps and providing continuous training to personnel, but also the importance of effective detection of adverse events by all relevant stakeholders who must be aware of their responsibility to identify errors or unexpected results

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. Thus, the Commission and Member States have deemed appropriate to include a specific field to categorise the reported SAR in donors in future exercises contributing to the harmonised reporting practices at European level. The availability of this data gives an opportunity for further assessment of the underlying reasons for donor reactions and for the implementation of preventive measures to reduce them.

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 Subgroup (a subgroup to the Competent Authorities on Substances of Human Origin Expert Group) was established by the EU Commission, in agreement with the Member States. The objective of this subgroup 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.[9]

[9] https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en

At European level, the exercise has allowed Member States to improve the implementation of their vigilance requirements and data collection in the field. Member States are making efforts to improve their vigilance systems and the quality and accuracy of data submitted to this exercise, while taking the opportunity to share experience and knowledge in a European forum. However, there is still a significant degree of under-reporting by some Member States; thus, general conclusions extracted from this report should be interpreted with caution.