



SUMMARY OF THE 2020 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS FOR TISSUES AND CELLS

(Data collected from 01/01/2019 to 31/12/2019 and submitted to the European Commission in 2020)

EXECUTIVE SUMMARY

The human application of tissues and cells offers 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 to the recipient. These risks can be controlled and minimised by the implementation of safety and quality measures, as laid down in EU legislation. Vigilance and surveillance programmes are critical for ensuring the quality and safety of those 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 field.

In line with the obligations defined in the legislation¹, 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 legislation² (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). Following the Directive, the Commission publishes this annual summary of the reports received, making it available to the Competent Authorities, healthcare professionals, stakeholders 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. In addition, a Vigilance Expert Subgroup (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.

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

² Article 3 of Directive 2004/23/EC

This report summarises the data submitted by the Member States and EEA during 2020, collected by the reporting countries during 2019, draws general conclusions, and compares the information with data submitted in previous years.

The key findings of the 2020 reporting exercise are the following:

- The overall number of reported tissues and cells distributed in 2019 amounted to 1 360 315 units (393 625 non-reproductive, reported by 27 countries, and 966 690 reproductive tissues and cells, reported by 19 countries). Twenty-one countries for non-reproductive and 16 countries for reproductive tissues and cells reported a total of 298 897 recipients. Twenty-six countries reported the total number of tissues and cells processed, which reached 2 922 117 units (24 countries reported 503 374 tissues processed in the non-reproductive category and 21 countries reported 2 418 743 in the reproductive category).
- A total of 306 SAR were reported by 27 countries, of which 156 were related to non-reproductive and 150 to reproductive tissues and cells. Data showed that 84.6% of the SAR associated with the transplantation of non-reproductive tissues and cells were “other SAR” and 14.7% were transmitted infections. The vast majority of the reported SAR for reproductive cells were related to the transmission of genetic diseases (67.3%) and ectopic pregnancies (25.3%).
- A total of 949 SAE were reported (689 related to non-reproductive tissues and cells, reported by 17 countries, and 260 to reproductive tissues and cells, reported by 17 countries), most of which occurred during procurement, donor selection 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 2019, 903 cases of SAR in donors were reported by 17 countries. Of those, 47 were related to non-reproductive and 856 to reproductive tissues and cells.

1. DATA COLLECTION METHODOLOGY

This report provides a summary of the data reported to the Commission in 2020 by 25 Member States³, the United Kingdom⁴ and Norway pertaining to the reporting period from 1 January to 31 December 2019. 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 3.0) to be sent to a DG SANTE hosted database.
- 2) The Common Approach document (version 3.1) for the definition of reportable SAR and SAE (“Common Approach”) attached to the electronic reporting template. The aim of the

³ Belgium and Cyprus did not submit data.

⁴ The withdrawal of the United Kingdom from the European Union included a transition period which ended on 31 December 2020, so their data has been included in this report. More info:

https://ec.europa.eu/info/sites/default/files/brexit_files/info_site/substances_of_human_origin_en.pdf

document, although not legally binding, is to provide recommendations and guidance to Member States when 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.

Since 2017, written agreements have been 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 end of 2020 and the beginning of 2021, following the launch of the data collection exercise by the Commission, 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 co-operation with the Commission and Member States, and drafted this report.

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

2. MAIN FINDINGS OF THE 2019 DATA COLLECTION

2.1. Activity data (denominators)

As part of the EU SARE 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 it is also used to put into context the data on SARE. In this exercise, as stated in the Common Approach, the *number of tissues and cells distributed* and the *number 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). Hence, SAR denominators might not be complete and caution should be used when interpreting them and extracting general conclusions from this exercise.

2.1.1. Tissues and cells distributed

The overall *number of distributed tissues and cells* in 2019, as submitted by the reporting countries, amounted to 1 360 315 units. Disaggregated by category, this represents 393 625 units distributed for non-reproductive tissues and 966 690 units distributed for reproductive tissues.

2.1.1.1. Non-reproductive tissues and cells

In the case of non-reproductive tissues and cells, 27 countries reported data on *units distributed* (AT, BG, CZ, DE, DK, EE, EL, ES, FI, FR, HU, HR, IE, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SE, SK and UK).

The main types of non-reproductive tissues and cells distributed were skeletal tissues (206 207 units), haematopoietic progenitor cells (HPC; 65 637 units) and ocular tissues (42 676 units). See Figure 1 for further details.

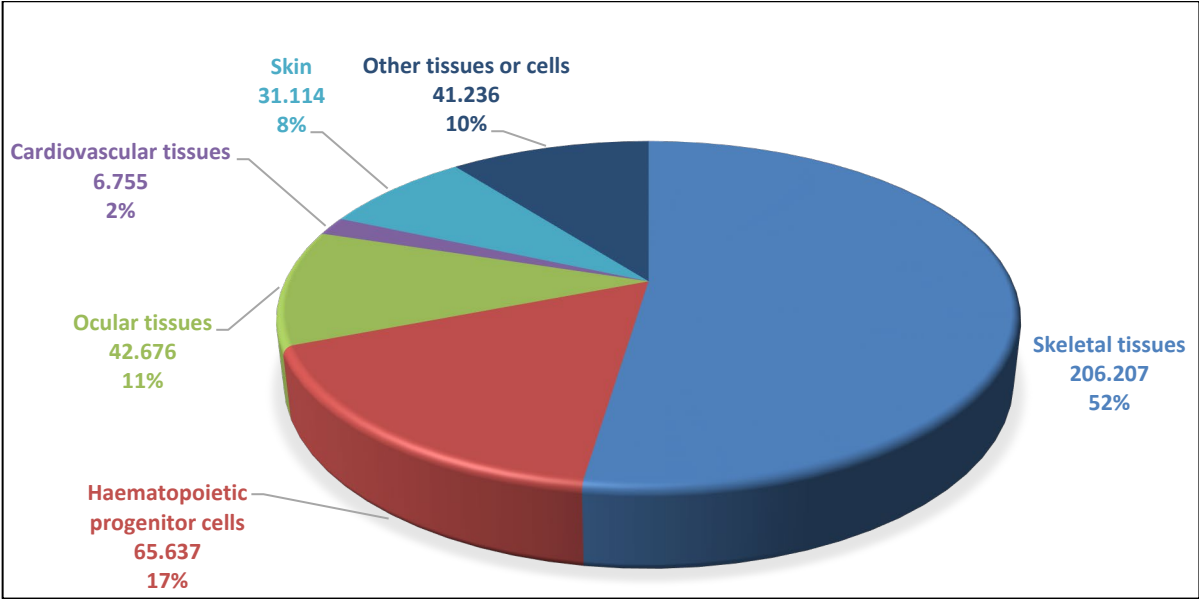


Figure 1. Total number of non-reproductive tissues and cells distributed (units); data 2019.

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 tissues and Figure 5 for cardiovascular tissues. Bone, peripheral blood stem cells, corneas and vessels were the most frequently distributed tissues in each respective category.

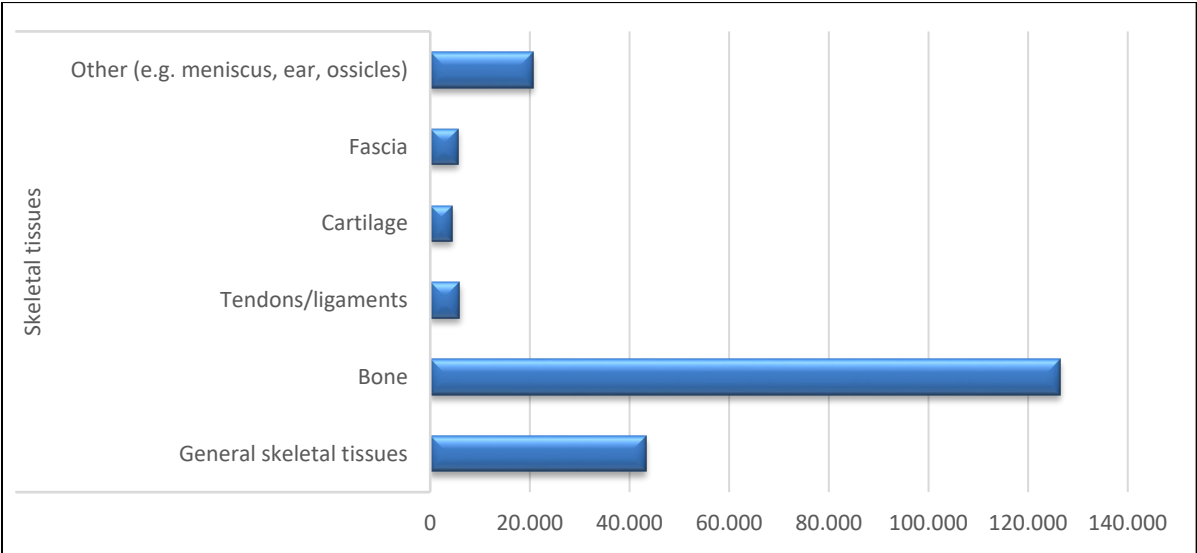


Figure 2. Number of skeletal tissues distributed per sub-category (units)⁵; data 2019.

⁵ 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).

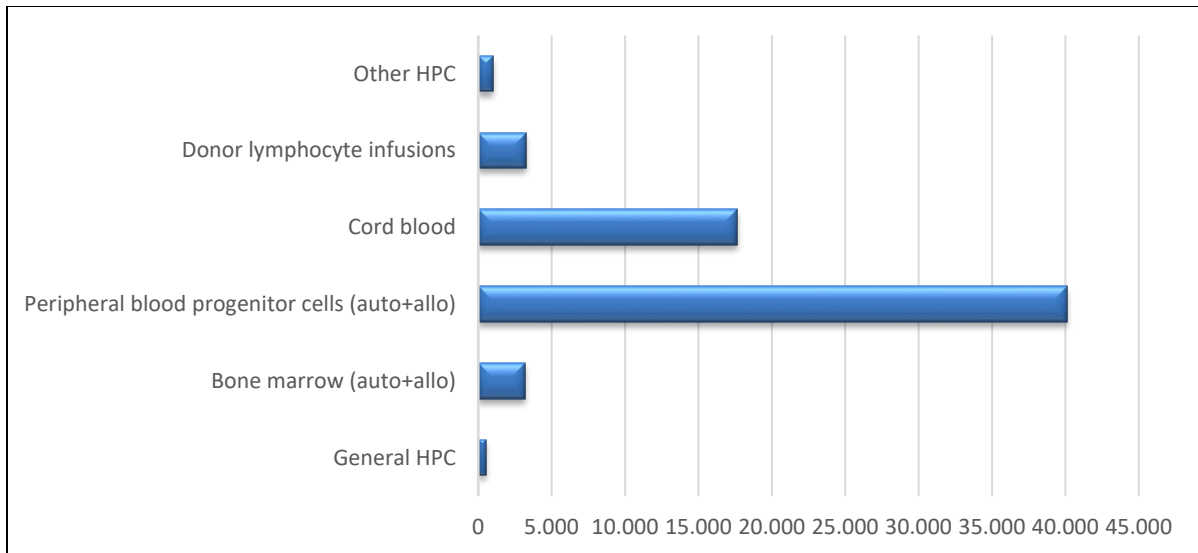


Figure 3. Number of haematopoietic progenitor cells distributed per sub-category (units)⁵; data 2019.

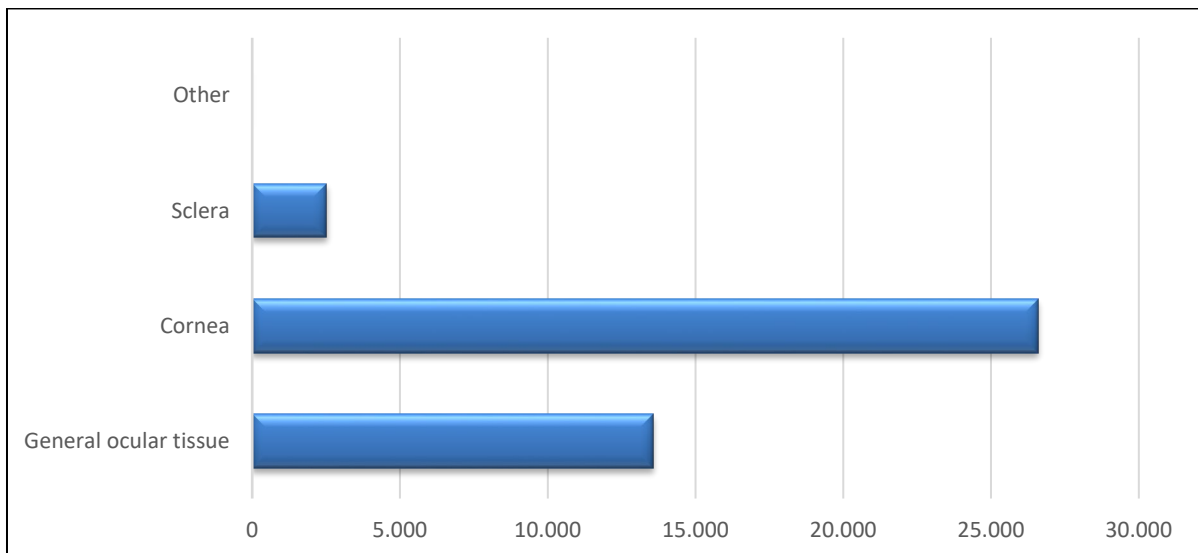


Figure 4. Number of ocular tissues distributed per sub-category (units)⁵; data 2019.

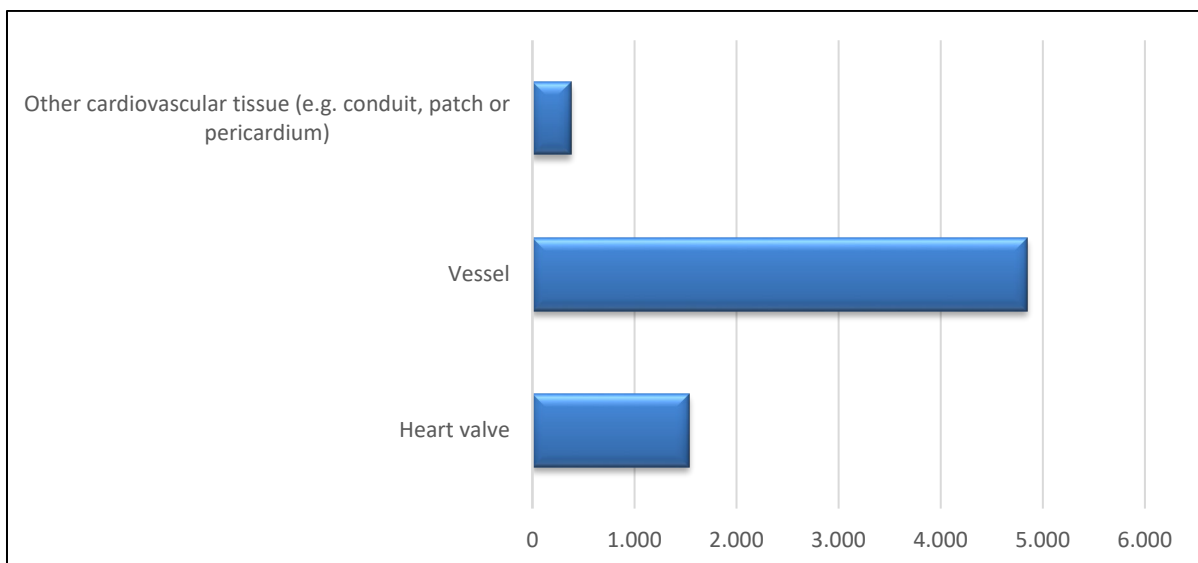


Figure 5. Number of cardiovascular tissues distributed per sub-category (units)⁵; data 2019.

2.1.1.2. Reproductive tissues and cells

For reproductive tissues and cells, 19 countries (AT, BG, CZ, DE, DK, EE, HR, HU, IE, LT, LU, LV, MT, NL, PT, RO, SI, SE and SK) reported activity data.

Of the 966 690 units of reproductive tissues distributed, 255 566 sperm units were delivered for insemination (see Figure 6), and 710 015 embryos, following partner and non-partner donation, were delivered for transfer (see Figure 7). Additionally, 91 ovarian tissues and 1 018 testicular tissues were distributed for treatments of infertility. (see Figure 8).

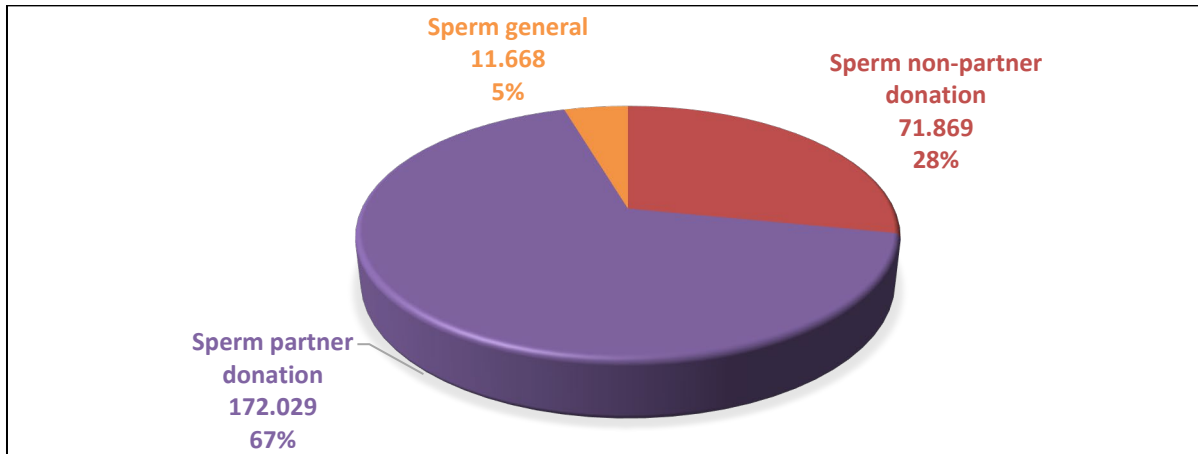


Figure 6. Number of sperm units distributed by category (absolute values and percentages); 2019 data.

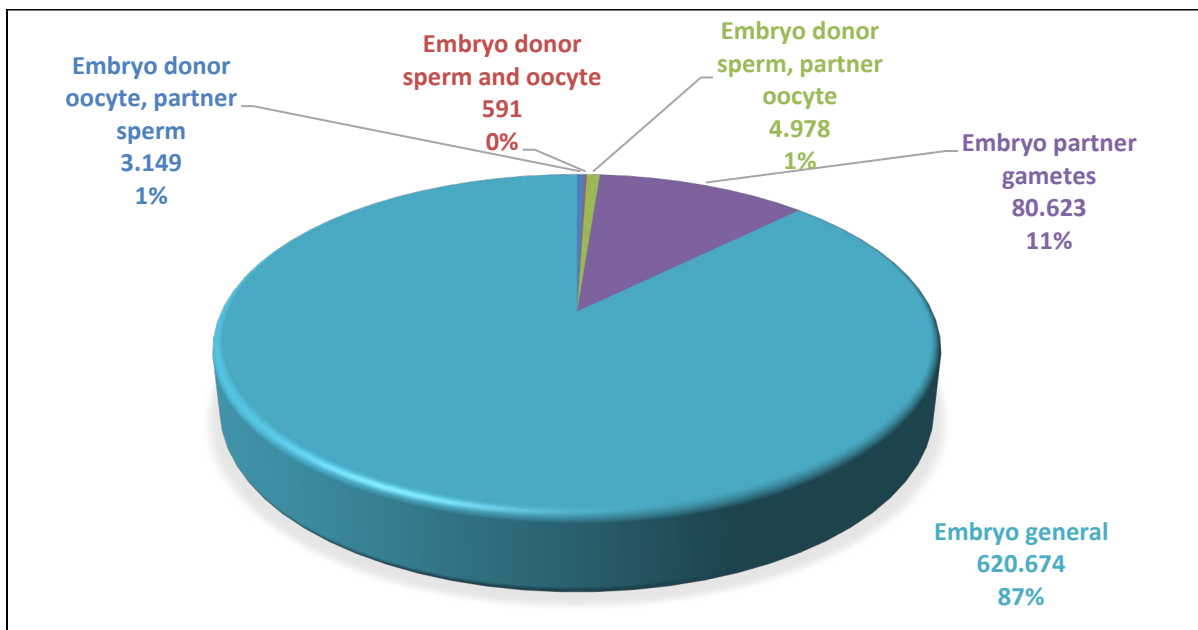


Figure 7. Number of embryos distributed by category (absolute values and percentages); 2019 data.

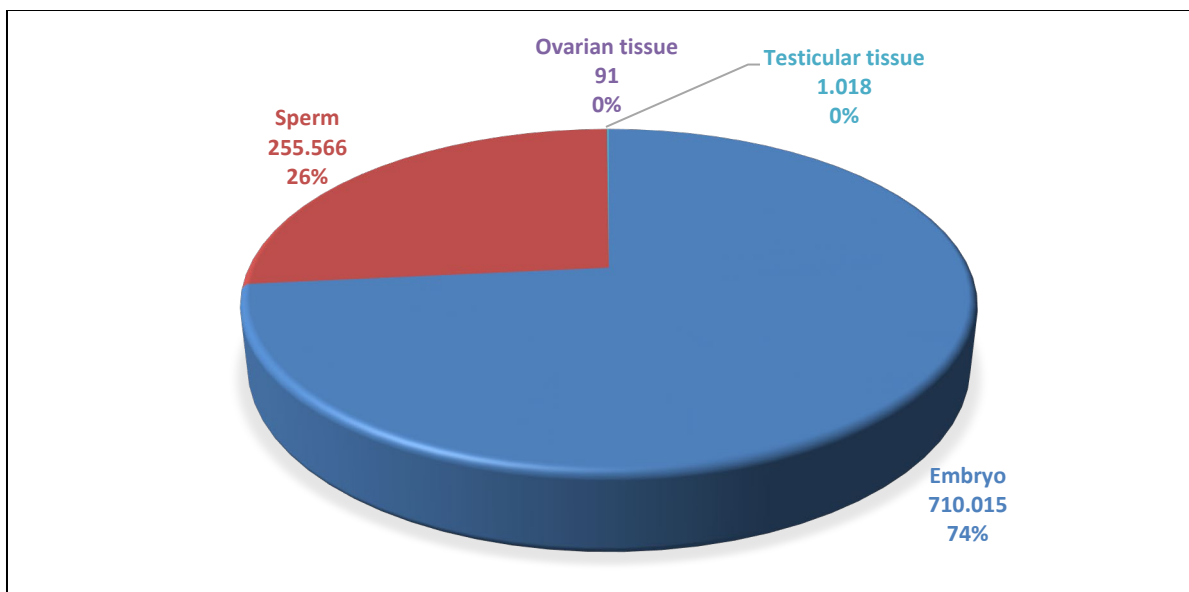


Figure 8. Total number of reproductive tissues and cells distributed (units); data 2019.

2.1.2. Number of recipients

In 2019, countries reported a total of 298 897 *recipients* (patients) having received tissues or cells. For non-reproductive tissues and cells 111 925 patients were reported as having received tissue or cells for transplantation while 186 972 patients underwent a medically assisted reproduction procedure.

2.1.2.1. Non-reproductive tissues and cells

As regards non-reproductive tissues and cells, 21 countries reported data on recipients (AT, BG, CZ, DK, EE, EL, ES, FI, FR, HR, IE, IT, LT, MT, NL, NO, PT, RO, SE, SI and SK).

Figure 9 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, followed by ocular tissue and haematopoietic stem cells.

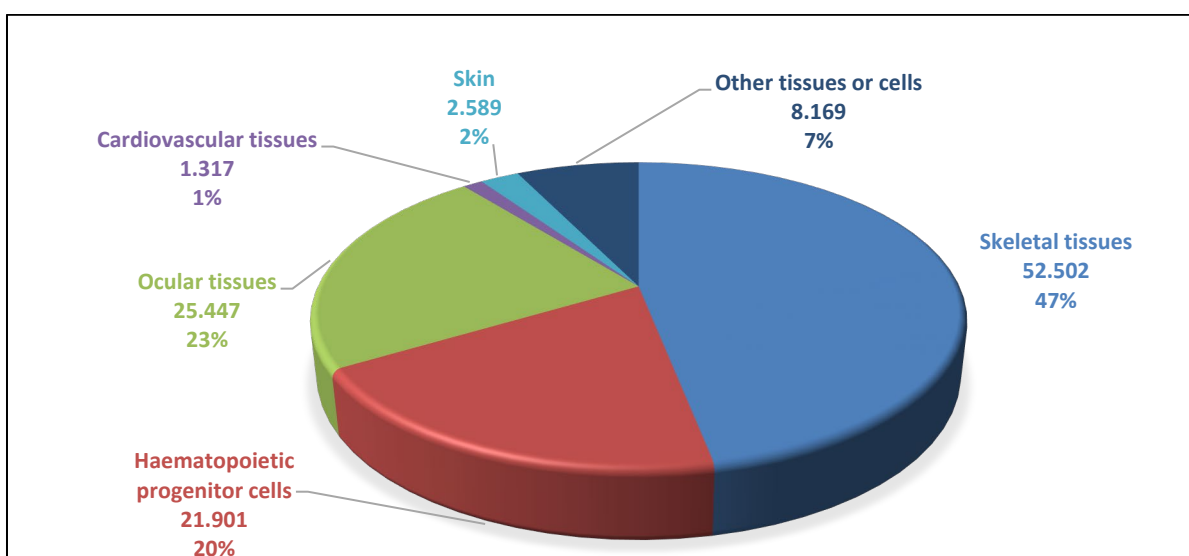


Figure 9. Total number of recipients per type of non-reproductive tissues and cells; data 2019.

2.1.2.2. Reproductive tissues and cells

Concerning reproductive cells, 16 countries (AT, BG, CZ, DK, EE, HR, IE, LU, MT, NL, NO, PT, RO, SE, SK and UK) reported 186 972 patients that underwent a medically assisted reproduction procedure. Of those, 69 110 involved partner or non-partner sperm, 117 766 involved partner or non-partner embryos, 26 involved transplantation of ovarian tissue and 70 testicular tissue (see Figure 10).

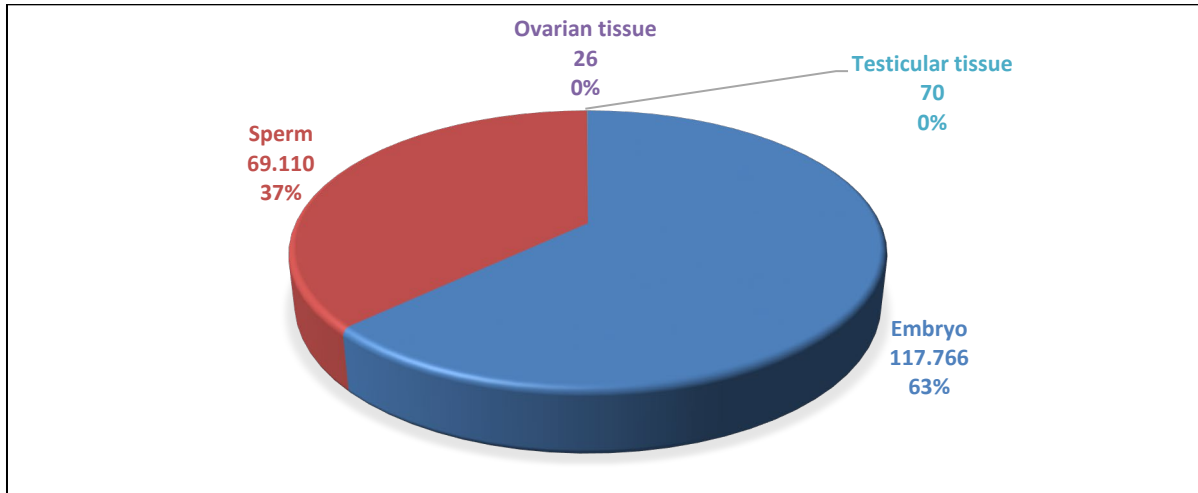


Figure 10. Total number of recipients per type of reproductive tissues and cells; data 2019.

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 2012-2020 (data pertaining to 2011-2019) for non-reproductive and reproductive tissues and cells is presented in Figures 11 and 12, respectively. It is noted that since the previous exercise, the number of tissues and cells distributed in the reproductive field has significantly increased in comparison with the previous year. The drop observed in the two previous exercises, 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 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 the required denominators.

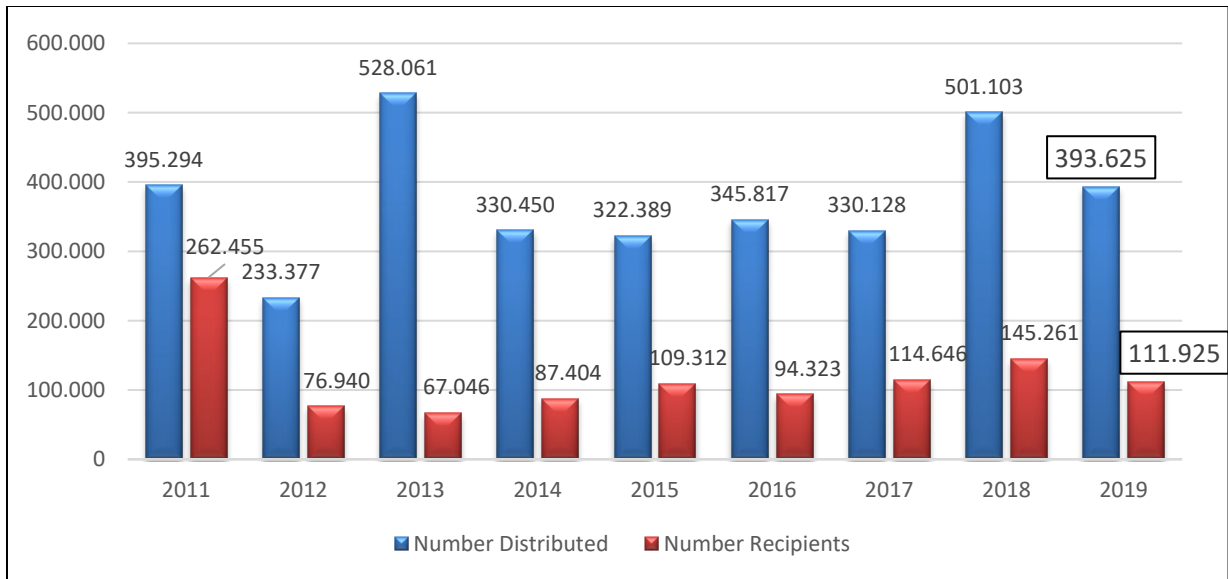


Figure 11. Total number of non-reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2019 comparative data.

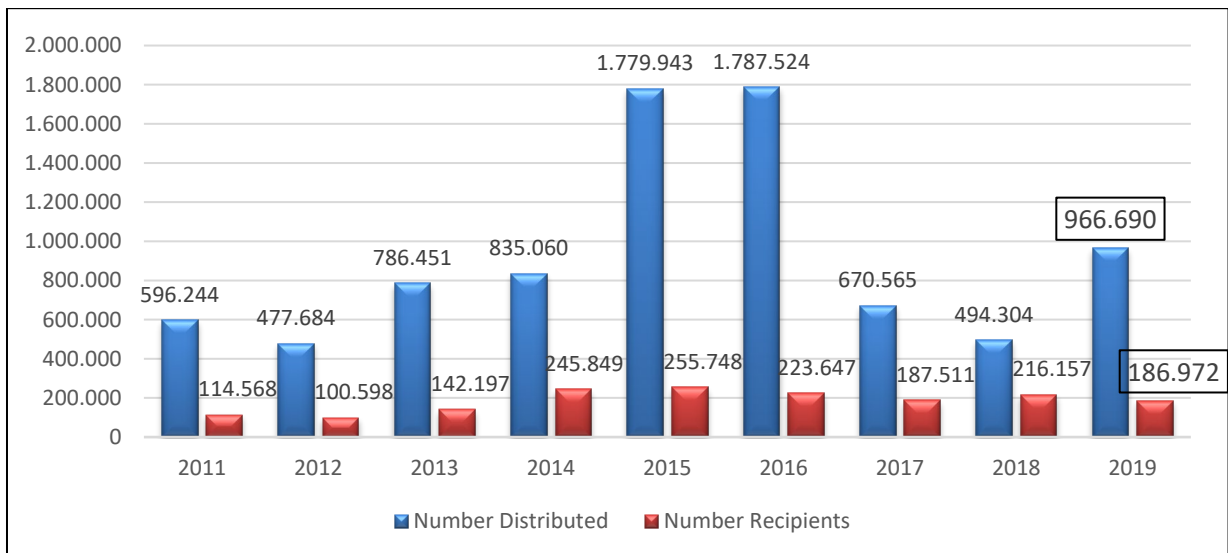


Figure 12. Total number of reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2019 comparative data.⁶

2.1.4. Number of tissues and cells processed

Twenty-four countries (AT, BG, CZ, DE, DK, EE, EL, ES, FI, HR, HU, IE, IT, LT, LV, MT, NL, NO, PL, PT, SE, SI, SK and UK) provided data regarding the *number of tissues and cells processed* for non-reproductive, and 21 countries (AT, BG, CZ, DE, DK, EE, ES, FI, HR, HU, IE, LT, LU, LV, MT, NL, NO, PT, RO, SI and SK) for reproductive tissues and cells in 2019. 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 2 922 117 tissues and cells were reported as processed in

⁶ 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.

2019. Of those, 503 374 units were for non-reproductive tissues and cells and 2 418 743 units for reproductive tissues and cells.

Comparative data from previous exercises (2010-2019 data) is presented in Figure 13.

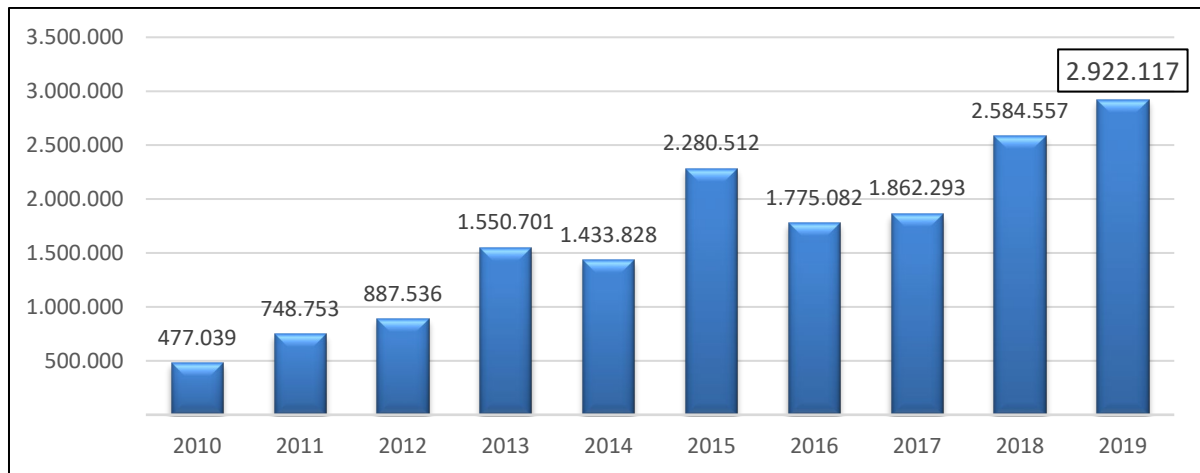


Figure 13. Total number of tissues and cells processed (units): 2010-2019 comparative data.

2.2. Serious adverse reactions

A total of 306 SAR were reported in 2019. Of these, 156 SAR were related to non-reproductive and 150 to reproductive tissues and cells. It should be noted that, none of those led to death following the clinical application of cells.⁷

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 14, showing that in the latest exercises, the figures submitted by the reporting countries have remained relatively stable.

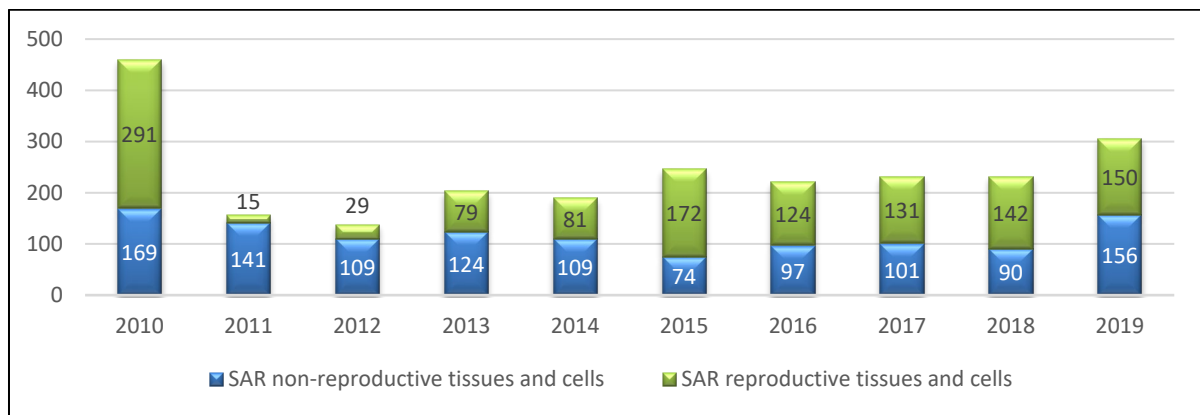


Figure 14. Total number of serious adverse reactions: 2010-2019 comparative data.⁸

⁷ 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 extremely important by all countries involved.

⁸ 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 17 Member States (AT, CZ, DE, DK, EE, EL, ES, FI, FR, HR, IE, IT, NL, PL, PT, SE and UK) and Norway reported SAR associated with the clinical application of tissues or cells. Nine Member States (BG, HU, LT, LU, LV, MT, RO, SK and SI) reported no SAR in recipients in 2019.

Regarding the transplantation of non-reproductive tissues and cells, 12 countries (AT, DE, EE, EL, ES, FI, FR, IE, IT, NL, SE and UK) reported SAR, whereas 12 Member States (CZ, DE, DK, ES, FR, HR, IT, NL, PL, PT 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 0.013–0.268% SAR/# *tissues and cells distributed* and from 0.030–0.625% SAR/# *of recipients*. For reproductive cells, this range was 0.0003–0.025% SAR/# *tissues and cells distributed* and 0.008–0.177% 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 increased 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.

2.2.2. Data by type of tissue or cell

Out of 306 SAR reported:

- 156 SAR (50.98%) were related to the transplantation of non-reproductive tissues or cells (see Figure 15). Of these:
 - 95 were related to the transplantation of HPC:
 - 2 general category⁹
 - 13 bone marrow
 - 74 peripheral blood stem cells
 - 5 cord blood and
 - 1 related to the “other general HPC” category⁹
 - 28 were related to the transplantation of ocular tissue:
 - 3 general category⁹
 - 25 corneas
 - 18 were related to the transplantation of skeletal tissues
 - 7 general category⁹
 - 10 bone
 - 1 tendons/ligaments
 - 15 were related to the transplantation of cardiovascular tissue
 - 9 heart valves

⁹ 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).

- 6 vessels
- 150 SAR (49.01%) were related to the clinical application of reproductive tissues and cells (see Figure 16). Of these:
 - 60 were related to sperm (46 following non-partner donation and 14 following partner donation) (See Figure 17)
 - 88 were related to embryos (53 reported in a general category⁹, 22 from partner gametes, 7 following sperm donation and partner oocyte, 4 following oocyte donation and partner sperm, and 2 following sperm and oocyte donation) (See Figure 18)
 - 2 were related to ovarian tissue

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

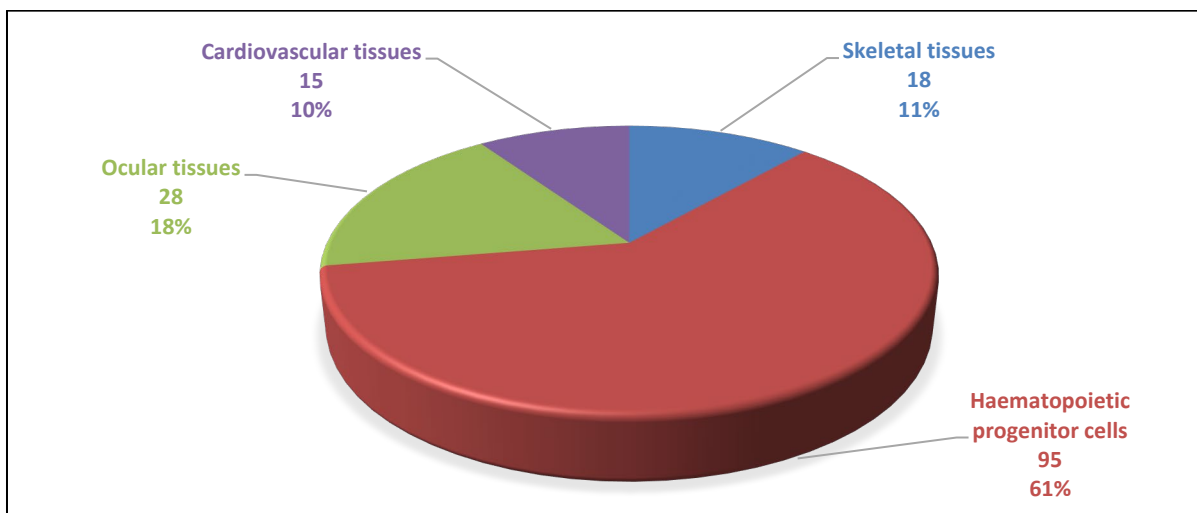


Figure 15. Number of SAR for each type of non-reproductive tissue and cells (absolute values and percentages of total recipient SAR); 2019 data.

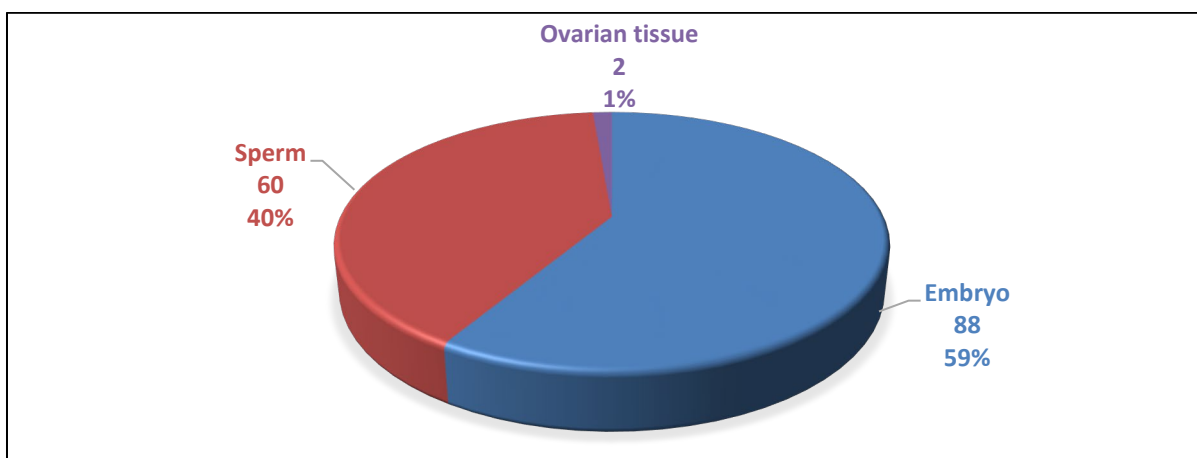


Figure 16. Number of SAR for each type of reproductive tissue and cells (absolute values and percentages of total recipient SAR); 2019 data.

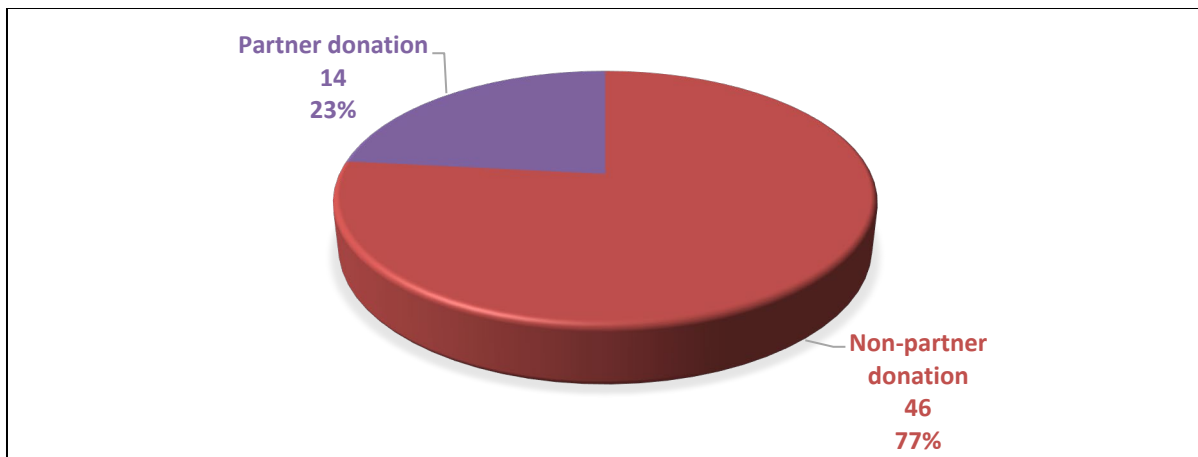


Figure 17. Number of SAR for sperm used for IUI per category (absolute values and percentages of total recipient SAR); 2019 data.

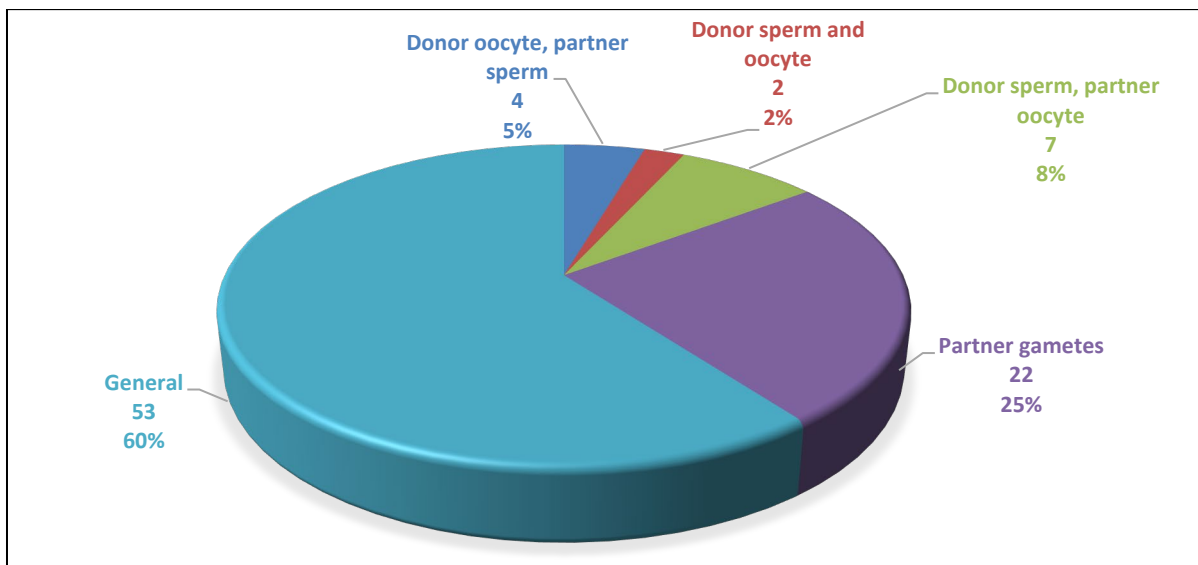


Figure 18. Number of SAR for embryos after IVF/ICSI per category (absolute values and percentages of total recipient SAR); 2019 data.

2.2.3. Data by type of serious adverse reaction

The 156 SAR related to the transplantation of *non-reproductive tissues and cells* were categorised as follows (see Figure 19):

- Transmitted infections: 23 cases (14.7% of all reported SAR for non-reproductive tissues and cells; see Figure 20), divided as follows:
 - 14 cases of bacterial infections, reported for the following transplanted tissues/cells: 8 skeletal tissues (6 general, 1 bone and 2 ligament), 3 HPC (2 peripheral blood progenitors and 1 bone marrow), 2 cardiovascular tissue (1 heart valve and 1 vessel) and 1 ocular tissue (cornea)
 - 1 case of viral HBV infection following the transplantation of HPC (peripheral blood progenitors)
 - 1 case of “other viral transmission”, reported following the transplantation of HPC (peripheral blood progenitors)

- 5 cases of fungal infections, all of them reported following the transplantation of ocular tissues (corneas)
- 2 cases of 'other transmitted infections', 1 following the transplantation of ocular tissue (general category⁸) and 1 following the transplantation of HPC (peripheral blood progenitors)

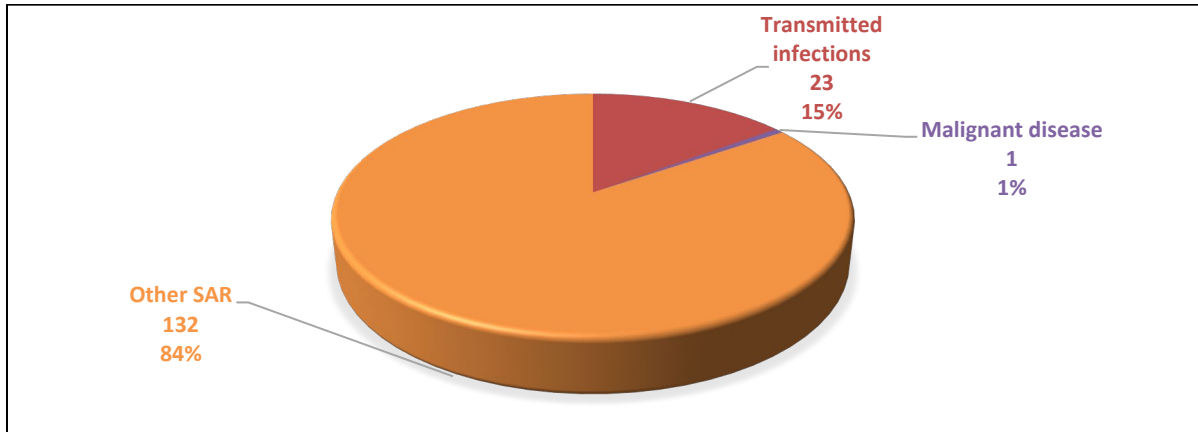


Figure 19. Number of SAR for non-reproductive tissues and cells per category (absolute values); data 2019.

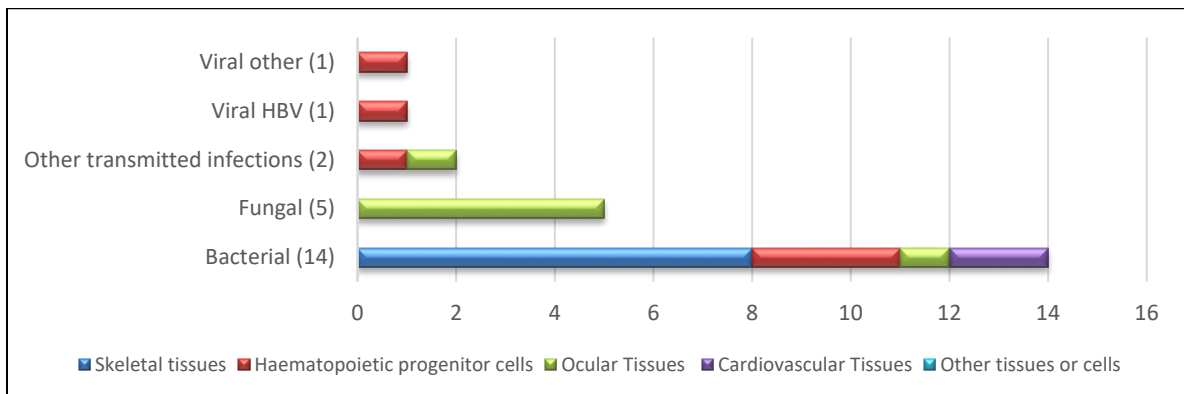


Figure 20. Number of SAR of transmitted infections for non-reproductive tissues and cells (absolute values); data 2019.

- Malignant disease: 1 case reported following peripheral blood stem cell transplantation (0.6% of all reported SAR for non-reproductive tissues and cells).
- Other SAR: 132 cases (84.6% of all reported SAR for non-reproductive tissues and cells; see Figure 21). This broad and heterogeneous category could be further divided as follows:
 - 35 cases of graft failure or delayed engraftment. Of those:
 - 16 following the transplantation of HPC (9 peripheral blood progenitors, 6 bone marrow and 1 cord blood)
 - 11 following the transplantation of ocular tissue (9 cornea and 2 general category⁹)
 - 8 following the transplantation of skeletal tissue (all bone)
 - 16 cases of cardiovascular reaction. Of those:
 - 12 following the transplantation of cardiovascular tissue (7 heart valves and 5 vessels)

- 4 following the transplantation of HPC (3 general category⁹ and 1 peripheral blood progenitors)
- 15 cases of infusion-related non-specific symptoms (including febrile reaction) for Haematopoietic progenitor cells. This was a new category introduced for the first time in this exercise. The cases were following the transplantation of HPC (11 peripheral blood progenitors and 4 bone marrow)
- 14 cases of immunological reactions following HPC transplantation (12 peripheral blood progenitors and 2 bone marrow)
- 11 pulmonary reactions following HPC transplantation (9 peripheral blood progenitors, 1 cord blood and 1 “other HPC”)
- 8 undue exposure to risk intervention (e.g. patient under anaesthesia without proper graft and surgery postponed or rescheduled. This was also a new category introduced for the first time in this exercise. Of those cases:
 - 6 following peripheral blood progenitor transplantation
 - 1 skeletal tissue (general category⁹)
 - 1 ocular tissue (cornea)
- 4 cases of toxicity following HPC transplantation (2 peripheral blood progenitors, 1 general category⁹ and 1 cord blood)
- 3 neurological reactions following HPC transplantation (2 cord blood and 1 peripheral blood progenitors)
- 26 cases of other SAR (none of the above) as follows:
 - 15 cases following the transplantation of peripheral blood progenitors
 - 9 following the transplantation of corneas
 - 1 following the transplantation of bone
 - 1 following the transplantation of a heart valve

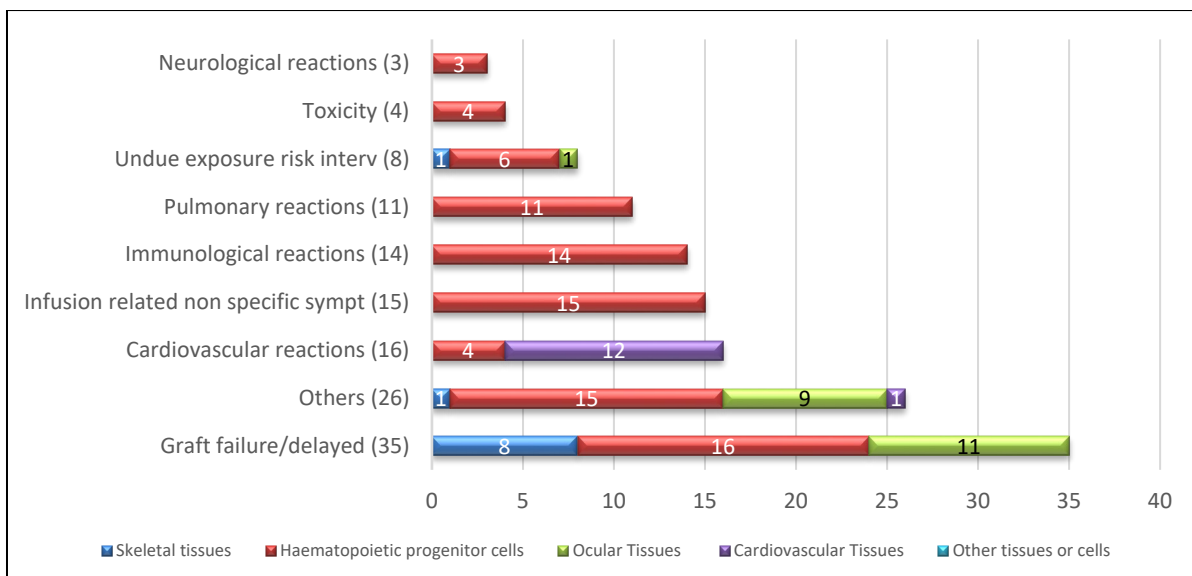


Figure 21. Number of “other SAR” for non-reproductive tissues and cells (absolute values); data 2019.

The 150 SAR associated with the application of *reproductive cells* were classified as follows (see Figures 22 and 23):

- Transmitted genetic conditions: 101 SAR (67.3% of all reported SAR for reproductive tissues and cells), divided as follows:
 - 51 cases involving embryos in the “general category”⁹
 - 3 cases involving embryos from donor oocyte and partner sperm
 - 1 case involving embryos from donated oocyte and sperm
 - 1 case involving embryos from donor sperm and partner oocyte
 - 45 cases involving non-partner sperm donation
- Bacterial infection: 4 SAR (2.6% of all reported SAR for reproductive tissues and cells) following the clinical application of sperm from partner donation (2) and embryos from partner gametes (2)
- Malignant diseases: 2 SAR (1.4% of all reported SAR for reproductive tissues and cells) following the clinical application of embryos in the “general’ category”⁹
- Ectopic pregnancy: 38 SAR (25.3% of all reported SAR for reproductive tissues and cells) divided as follows:
 - following the clinical application of embryos from partner gametes (19), embryos from donor sperm and partner oocyte (4), embryos from donor oocyte and partner sperm (1) embryos from donated sperm and oocyte (1)
 - following the clinical application of sperm from partner donation (12) and non-partner donation (1)
- Molar pregnancy: 2 SAR (1.4% of all reported SAR for reproductive tissues and cells) following the clinical application of embryos from partner gametes (1) and embryos from donor sperm and partner oocyte (1)
- Other SAR: 3 SAR (2.0% of all reported SAR for reproductive tissues and cells), divided as follows:
 - 2 following the clinical application of ovarian tissue
 - 1 following the clinical application of embryos from donor sperm and partner oocyte

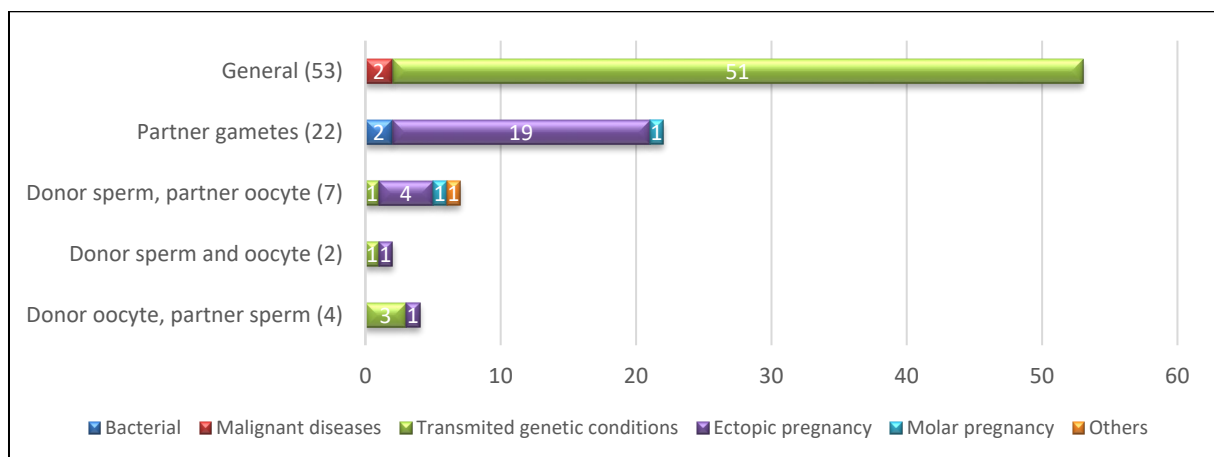


Figure 22. SAR related to the application of embryos (absolute values); 2019 data.

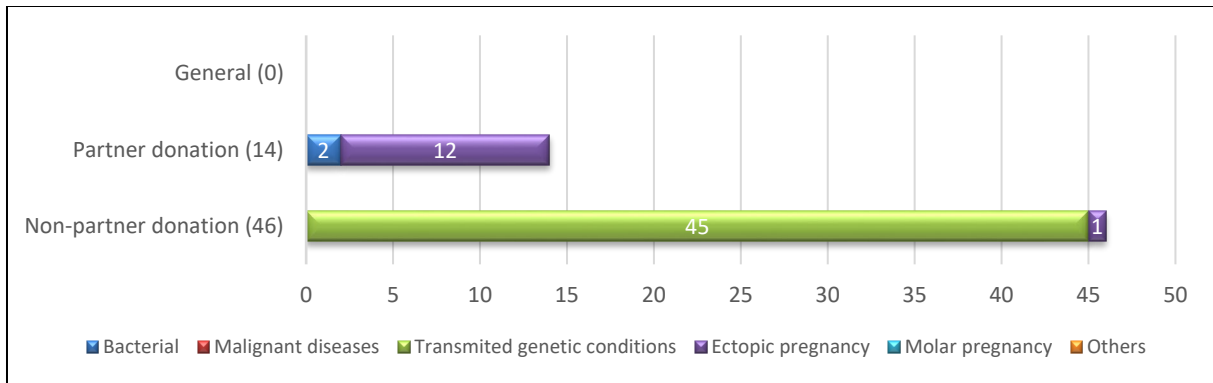


Figure 23. SAR related to the application of sperm (absolute values); 2019 data.

It is noted that of these 150 SAR associated with the application of reproductive cells, as shown in Figure 24, 59 (39.3% of all SAR reported for reproductive tissues and cells) were related to non-partner donation (46 involving non-partner sperm and 13 involving embryos [donor oocyte and partner sperm (4), donor sperm and oocyte (2) and donor sperm and partner oocyte (7)]).

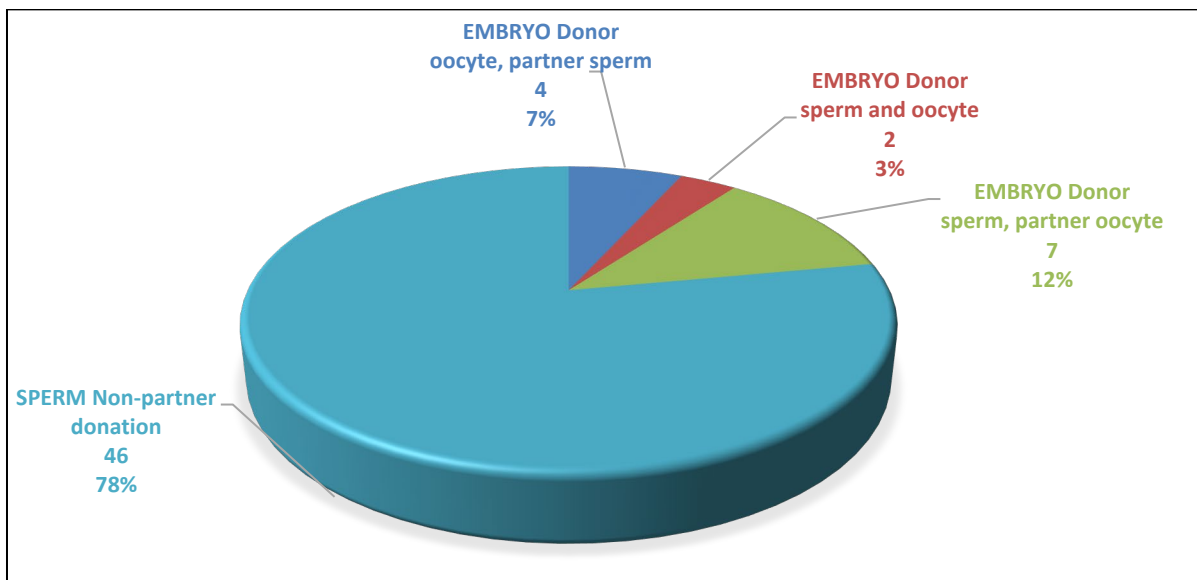


Figure 24. SAR related to the application of non-partner gametes (absolute values and percentages); 2019 data.

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.

No death in recipients were reported for this exercise.

2.3. Serious adverse events

The total number of SAE reported for 2019 was 949. Of those, 689 SAE were reported for non-reproductive tissues and cells and 260 SAE were reported for reproductive tissues and cells.

Considering the denominator for SAE: *tissues and cells processed* during this period, during 2019 in Europe, 1 SAE took place per 307 915 units of tissue processed. The disaggregated data show that, as

regards non-reproductive tissues and cells, 1 SAE occurred for every 73 059 units processed and in the case of reproductive tissues and cells, 1 SAE happened for every 903 286 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 2019 increased when compared to previous exercises, as presented in Figure 25.

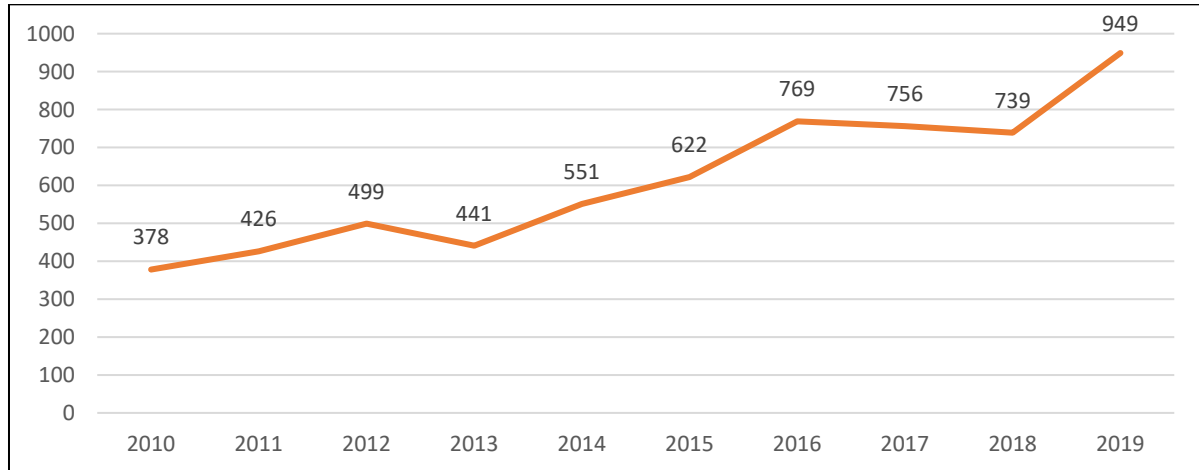


Figure 25. Total number of SAE reported: 2010-2019 comparative data.

Comparative data showing the evolution of SAE by type of event in past exercises are shown in Figure 26. Human error is the most common type of event with numbers increasing over time, although they dropped slightly in the previous exercise. Tissue/cell defects have also increased in recent years, although numbers decreased slightly in general terms in this exercise. Following this evolution, and with the aim of harmonising reporting by Member States at European level, in the previous exercise a new SAE activity step category “materials” was introduced in the reporting template; SAE in this category increased slightly this year. 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. In addition, as part of ongoing efforts to increase harmonisation, this year a new category “system failure” was introduced and was the third most reported type of SAE. This category should be understood as a failure of the quality management system due to training or education, staffing, workload or skill-mix, or inadequate processes, procedures or documentation.

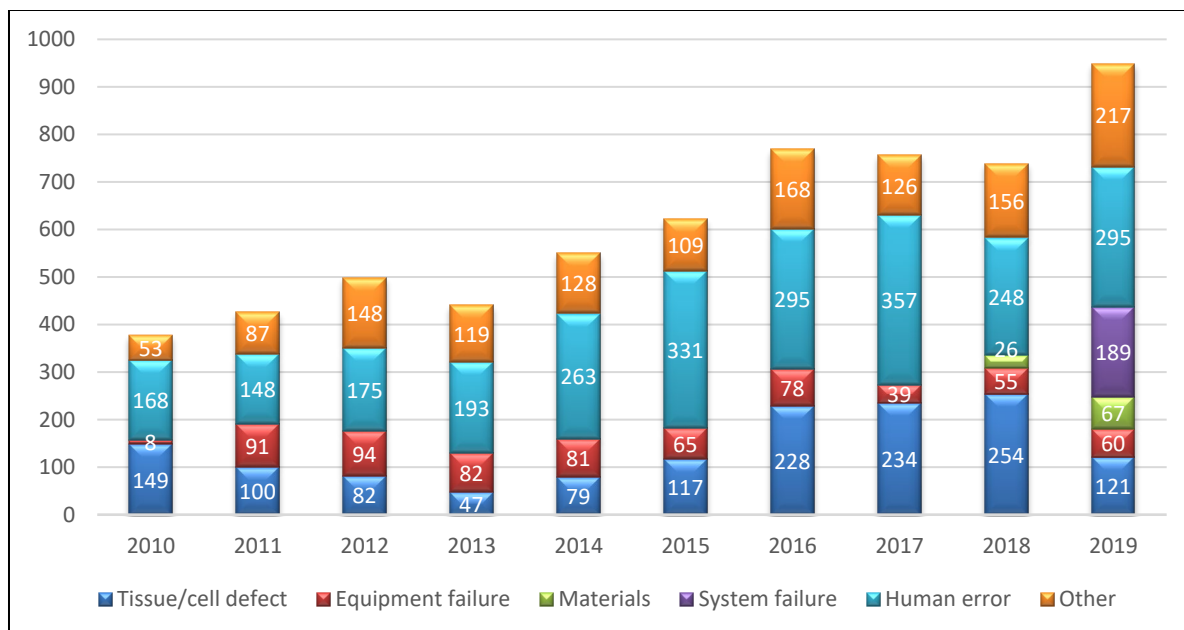


Figure 26. Total number of serious adverse events by specification: 2010-2019 comparative data.

2.3.1. Information by country

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

In 2019, following the harmonisation of practices, two new sub-categories “product selection” and “issue” were introduced in the reporting template within 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 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 for non-reproductive and reproductive tissues and cells is presented in Figures 27 and 28, respectively.

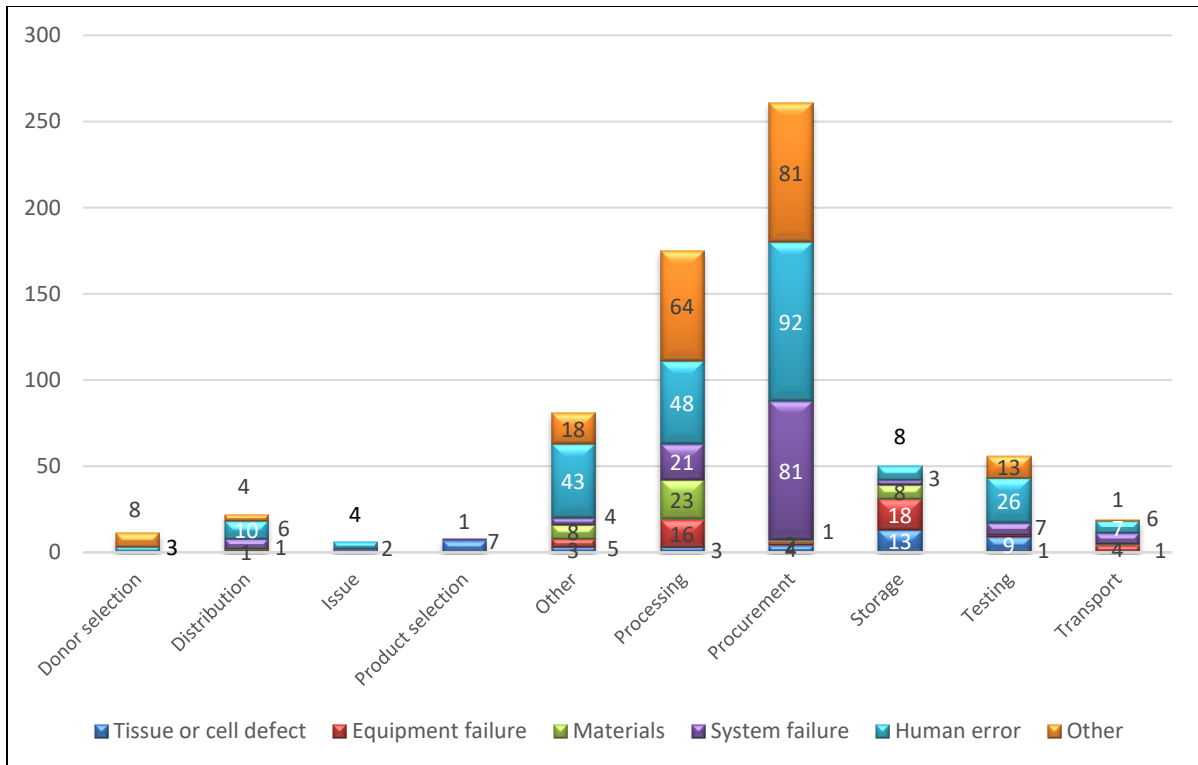


Figure 27. Total number of serious adverse events reported for non-reproductive tissues and cells, categorised by activity step; 2019 data.

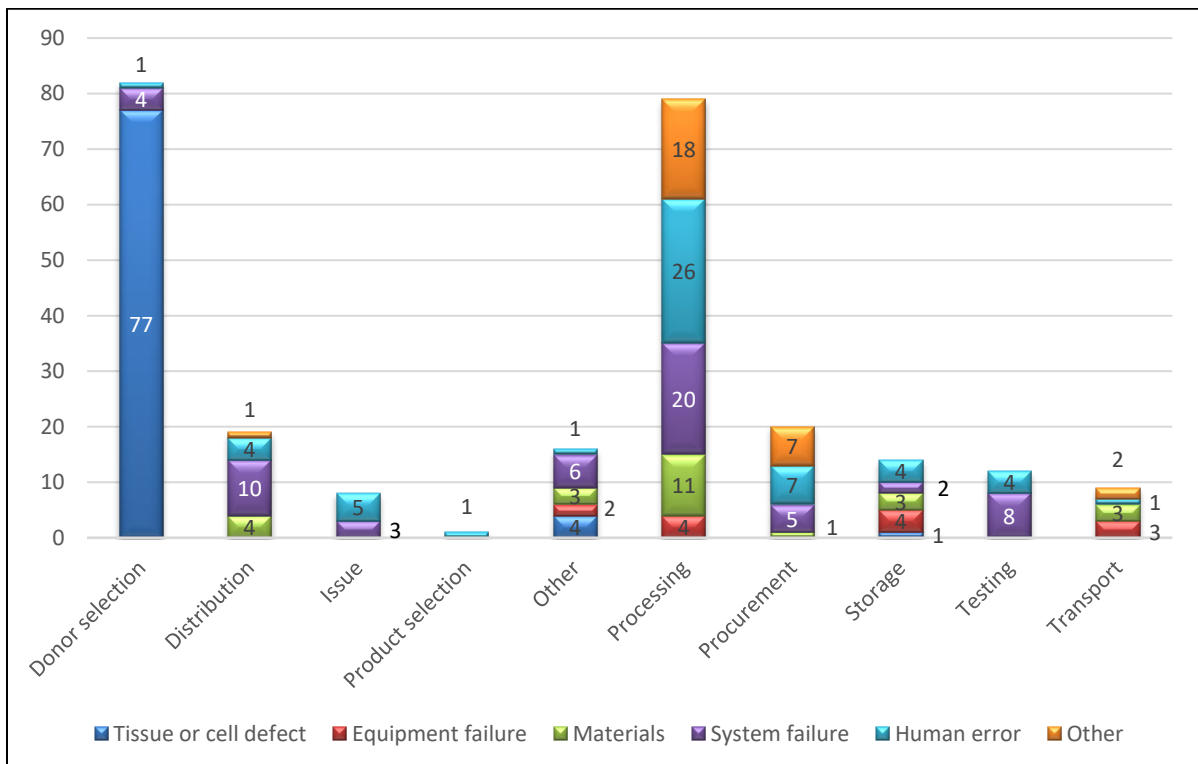


Figure 28. Total number of serious adverse events reported for reproductive tissues and cells, categorised by activity step; 2019 data.

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, followed by system failure and “other”, while for reproductive tissues and cells the largest number of reported SAE happened during donor selection due to tissue or cell defect and processing due to human error, system failure and “other”.

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 29 and 30.

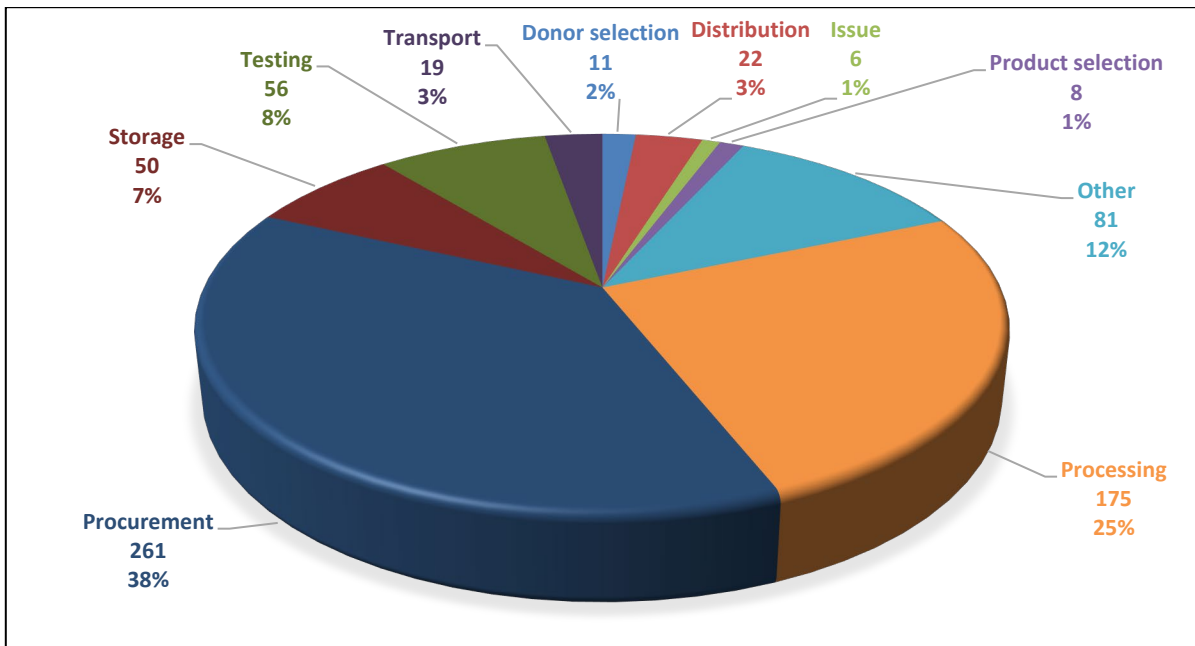


Figure 29. Number of SAE and percentage of total SAE reported for non-reproductive tissues and cells by type of activity (absolute values and percentages of total); data 2019.

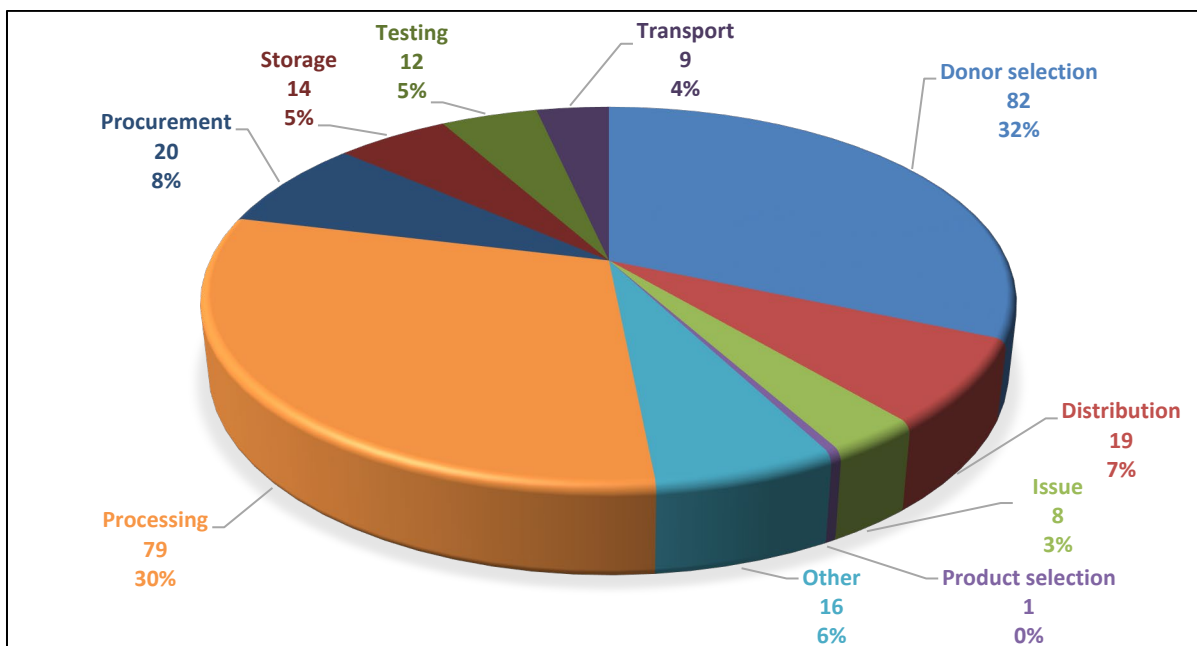


Figure 30. Number of SAE and percentage of total SAE reported for reproductive tissues and cells by type of activity (absolute values and percentages of total); data 2019.

2.3.3. Information by type of serious adverse event

The 949 SAE were classified as tissue or cell defects, human error, equipment failure, materials (a new category introduced in the previous exercise), system failure (new category in this exercise) and other types of events.

The distribution by type for non-reproductive and reproductive tissues and cells is presented in Figures 31 and 32.

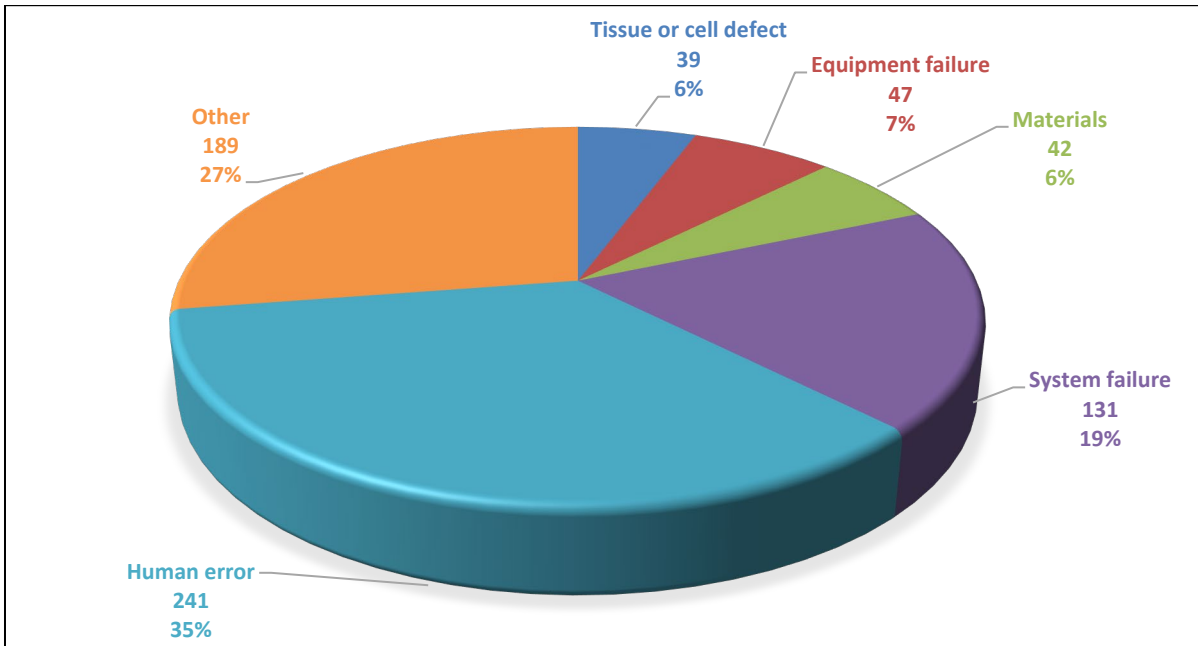


Figure 31. SAE types for non-reproductive tissues and cells (absolute values and percentages of total); 2019 data.

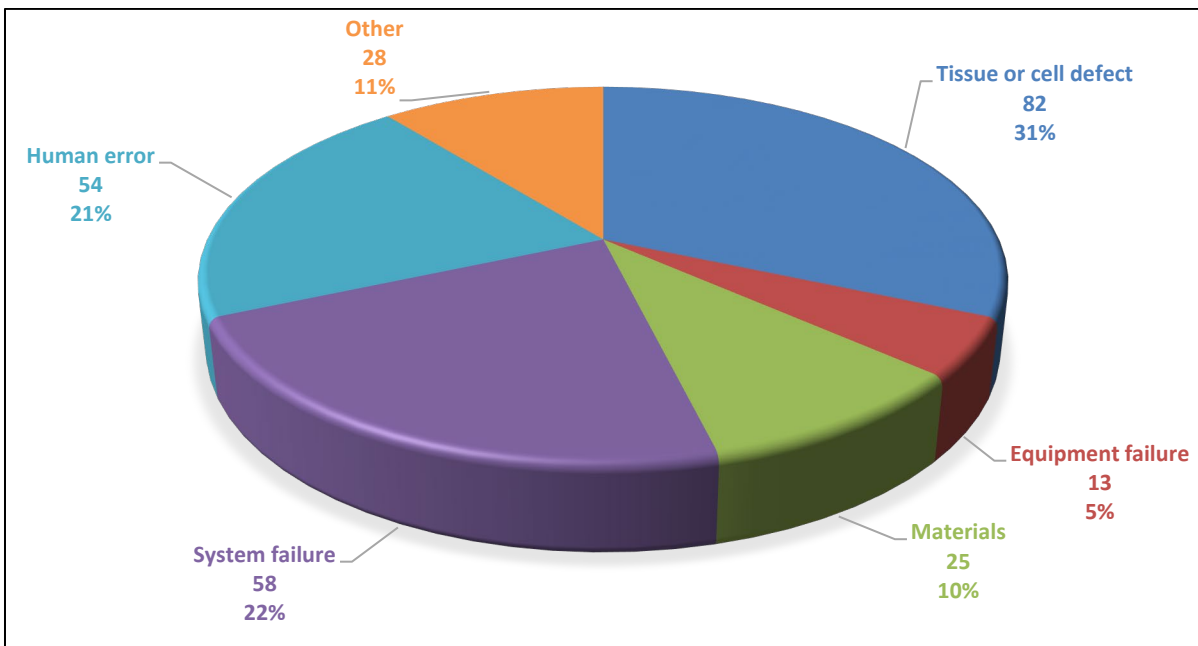


Figure 32. SAE types for reproductive tissues and cells (absolute values and percentages of total); 2019 data.

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 countries (BG, CZ, DE, EE, EL, ES, FI, FR, HR, IE, IT, NL, NO, PL, SI, SE and UK) reported a total of 903 SAR in donors in 2019. A general overview of SAR in donors during the period 2011-2020 (data pertaining to 2010-2019) is presented in Figure 33.

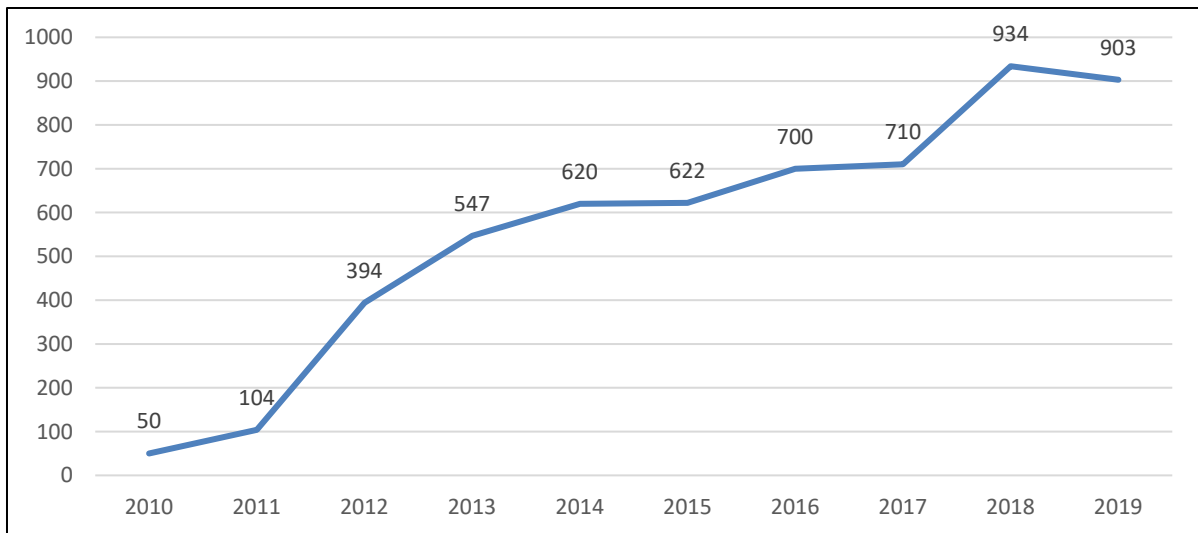


Figure 33. Number of serious adverse reactions in donors; 2010-2019 comparative data.

In this exercise, SAR in donors could be reported separately for non-reproductive and reproductive tissues. The overall sub-classification of the 903 SAR in donors reported in 2019 is shown in Figure 34.

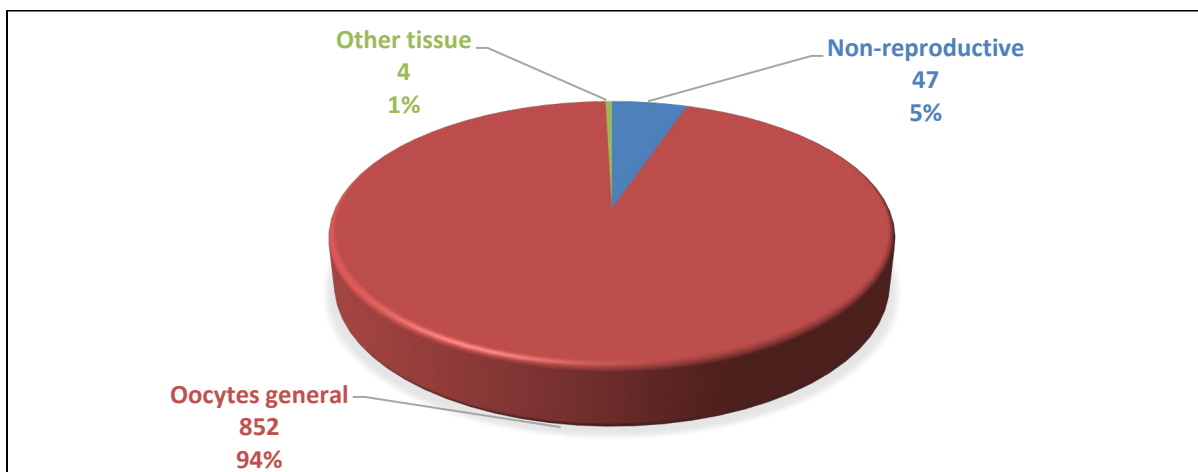


Figure 34. Number of serious adverse reactions in donors per type of donated tissue or cell (units); 2019 data.

The SAR in donors are divided as follows:

- 47 cases were related to the donation of non-reproductive tissues or cells (5.2% of all SAR in donors) and were reported by 5 countries (DE, EE, EL, FI and IT; see Figure 35 for more details).

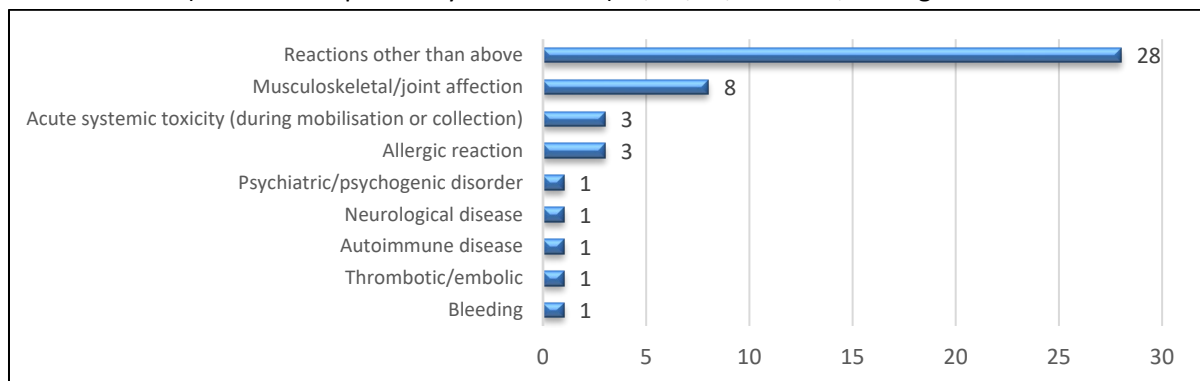


Figure 35. Number of serious adverse reactions in donors of non-reproductive tissue; 2019 data.

- 856 cases (amounting to 94.6% of all SAR in donors) were related to the donation of reproductive tissues or cells, specifically 852 with the donation of oocytes and 4 with donation of other reproductive tissues (see Figures 36 and 37). These were reported by 16 countries (BG, CZ, DE, EE, EL, ES, FR, HR, IE, IT, NL, NO, PL, SI, SE and UK).

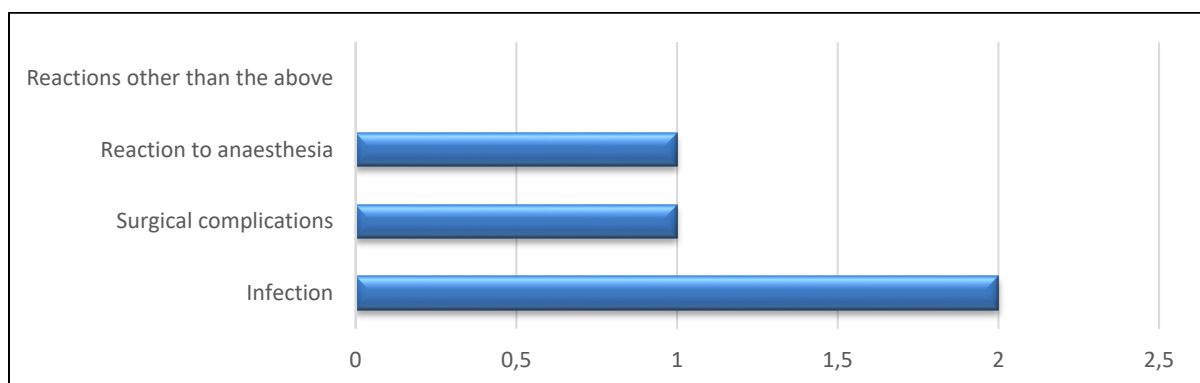


Figure 36. Serious adverse reactions in donors of other reproductive tissues (units); data 2019.

Most of the SAR in oocyte donors were critical, severe and moderate-to-severe OHSS cases (535 cases) and surgical complications (162 cases); the remaining cases included infectious complications and other types of SAR, as shown in Figure 37.

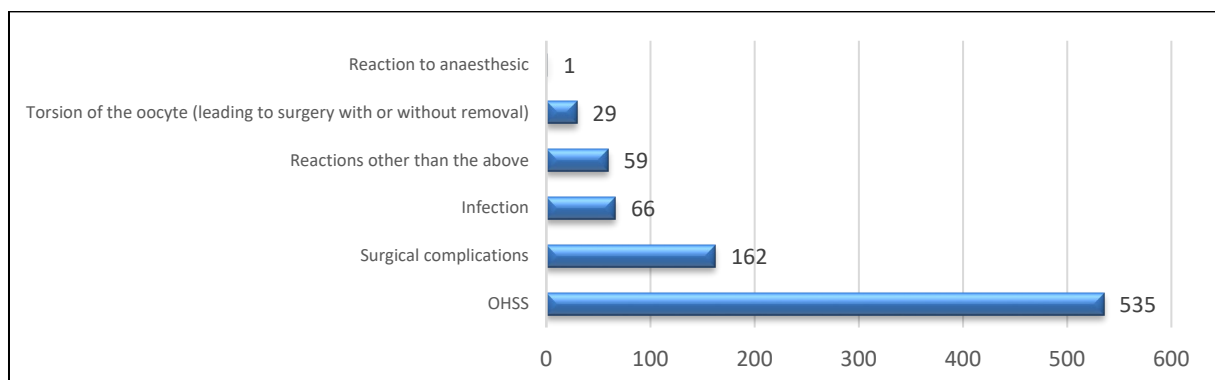


Figure 37. SAR in oocyte donors; 2019 data (absolute values and percentages of total).

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; the category of “other SAR” was the most reported, followed by musculoskeletal/joint affection.

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.

It should be noted that no deaths were reported for SAR in donors in this exercise.

3. Conclusions

Taking into account the trends of previous SARE exercises, vigilance systems and national data collection in the field of biovigilance are improving year after year. However, there are areas that still require further work and harmonisation. For example, as in previous exercises, not all reporting countries were able to provide activity data to be used as denominators for SARE. In addition, not all countries collect data using the same units of measure (e.g. units/packages of skin vs cm² vs m²; number of oocytes vs number of cycles). This lack of harmonisation creates difficulties when comparing data among Member States at European level and thus, extracting general trends and conclusions.

This situation would require additional efforts from Member States to adapt and 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. The compilation of such information would help Member States, authorities and citizens to better understand the overall activity data in Europe for the field of tissues and cells.

In order to help overcome current difficulties in collecting and reporting activity data, the EDQM, in the context of several grant agreements between them and the Commission (grant agreements 2014 54 01 and 2018 53 01), has organised a series of activities involving Member States, and relevant professional societies and established registries in the field.¹⁰ During the course of this work, it became clear, 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 third countries (outside the EU) or on a few EU countries, with the ultimate goal of achieving European self-sufficiency¹¹.

With this aim, minimum datasets¹² in the fields of replacement tissues, HPC and medically assisted reproduction that would serve the purposes of transparency for citizens and as denominators for the EU biovigilance exercises were identified. The work entailed reaching an agreement on the

¹⁰

https://www.edqm.eu/sites/default/files/medias/fichiers/Transplantation/Tissues_and_cells/tissues_and_cells_background_information_harmonising_activity_data_collection_exercises_february_2021.pdf

¹¹ https://www.edqm.eu/sites/default/files/medias/fichiers/Transplantation/to_21_07-proceedings_final_meeting_harmonisation.pdf

¹²

https://www.edqm.eu/sites/default/files/medias/fichiers/Transplantation/Tissues_and_cells/tissues_and_cells_minimum_dataset_harmonising_activity_data_collection_exercises.pdf

parameters, units and expected quality of the data to be collected, as well as making recommendations¹³ on who should be accountable for the collection and validation of this data and ensure dissemination among all relevant stakeholders. This work is of particular importance in the context of the revision of the EU legislation in the field of tissues and cells.

It is of paramount importance that tissue establishments supplying tissues and cells encourage procurement organisations and clinical users of tissues and cells to always reflect on whether adverse outcomes might have been associated with the characteristics of the donation process or caused by the tissues and cells applied. They should also report all adverse outcomes that may have taken place while processing tissues and cells registered in their quality management systems and that could be considered serious in the European context. Reporting of these cases provides 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, not only in the European context, but beyond.

For the reported SAR associated with the transplantation of non-reproductive tissues and cells, the vast majority were associated with the “other SAR” category, with graft failure or delayed engraftment the most frequently reported group, followed by the transmission of infections – mostly of bacterial and fungal origin. In the latter, the tissues with the most frequently reported SAR were ocular and skeletal tissues. In contrast, the most frequently reported SAR related to the clinical application of reproductive cells involved the transmission of genetic diseases; embryos from the general category and sperm from non-partner donation were the types of tissues with the most reported SAR in this category. This pattern has remained stable compared with previous exercises. With this in mind, and in order to better understand this phenomenon, modifications were made in the reporting template for recent exercises. However, it should be noted that the likelihood of transmitting multi-factorial genetic diseases from donor to offspring is sometimes difficult to assess and this data should be evaluated with caution.

Quality management systems are aimed at 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 may result in failures, or situations in which donors or recipients are unintentionally 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 occasions, however, a particular non-compliance incident may be of such importance that it should be considered as SAE and reported through the European vigilance system. In this exercise, “human error” was the most frequently reported category of SAE. For non-reproductive tissues and cells, procurement was the most reported step with SAE due to human error followed by system failure and “other”, whereas for reproductive tissues and cells the most reported SAE were within the donor selection and processing steps. In the former, tissue or cell defect was the most reported SAE whereas in the latter, the main causes were human error, system failure and “other”. These results suggest not only the importance of revising standard operating procedures in tissue establishments, highlighting critical

¹³

https://www.edqm.eu/sites/default/files/medias/fichiers/Transplantation/Tissues_and_cells/tissues_and_cells_conclusions_and_recommendations_harmonising_activity_data_collection_exercises.pdf

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 collected 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. The availability of this data provides an opportunity for further assessment of the underlying reasons for donor reactions and for the implementation of preventive measures to reduce them. In this exercise, the most reported SAR in donors was for the donation of reproductive tissues and cells, as in previous exercises.

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. 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. 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. Furthermore, its work also contributed to the Commission's evaluation of the legal frameworks on blood, tissues and cells, published in October 2019.¹⁴

The SARE exercise allows Member States to improve their vigilance requirements and data collection in the field while taking the opportunity to share experience and knowledge with other European countries. Member States are making efforts to improve their vigilance systems and the quality and accuracy of data submitted to this exercise. However, there is still a significant degree of under-reporting and over-reporting by some Member States, thus, general conclusions extracted from this report should be interpreted with caution. The annual reporting of SARE has been and will continue to be a learning exercise over the coming years.

¹⁴ https://ec.europa.eu/health/blood_tissues_organs/policy/evaluation_en