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 2021 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS FOR TISSUES AND CELLS

(DATA COLLECTED FROM 01/01/2020 TO 31/12/2020 AND SUBMITTED TO THE EUROPEAN COMMISSION IN 2021)

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1. INTRODUCTION

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 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). 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 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 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.

This report summarises the data submitted by the Member States, Norway and the United Kingdom during 2021, collected by the reporting countries during 2020, highlights major findings, draws general conclusions, and interprets trends by comparing the information with data submitted in previous years.

2. EXECUTIVE SUMMARY

The key findings of the 2021 reporting exercise are the following:

- The overall number of reported tissues and cells distributed in 2020 amounted to 1 116 519 units (378 237 non-reproductive, reported by 26 countries, and 738 282 reproductive tissues and cells, reported by 22 countries). Nineteen countries for non-reproductive and 15 countries

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

for reproductive tissues and cells reported a total of 245 058 recipients. Twenty-four countries reported the total number of tissues and cells processed, which reached 2 443 564 units (23 countries reported 396 639 tissues processed in the non-reproductive category and 19 countries reported 2 046 925 in the reproductive category).

- A total of **350 SAR were reported** by 18 countries, of which 139 were related to non-reproductive and 211 to reproductive tissues and cells. Data showed that 95% of the SAR associated with the transplantation of non-reproductive tissues and cells were classified as "other SAR", 4.3% were transmitted infections and 0.7% were transmitted malignant disease. The majority of the reported SAR for reproductive cells were related to the transmission of genetic diseases (51%).

- In 2020, **14 deaths of recipients** were reported (8 deaths potentially attributed to non-reproductive tissue and cell application, and 6 deaths potentially attributed to reproductive tissue and cell application).

- A total of **910 SAE** were reported (660 related to non-reproductive tissues and cells, reported by 19 countries, and 250 to reproductive tissues and cells, reported by 20 countries), most of which occurred during procurement and processing stages. These were mainly attributed to human error, "other" not classified failures, and suboptimal quality (tissue/cell defects).

- Recognising the importance of protecting donors, the Commission continues to collect details of donor adverse reactions on a voluntary basis. In 2020, 846 cases of SAR in donors were reported by 19 countries. The majority (751) were related to reproductive tissues and cells. For the first time **deaths of 2 donors** of tissues and cells were reported.

3. DATA COLLECTION AND ANALYSIS

This report provides a summary of the data reported to the Commission in 2021 by 26 EU Member States[3], Norway and the United Kingdom. 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 3.2),
2) The **Common Approach document** (version 2021) with definitions of reportable SAR and SAE ("Common Approach") complementing the electronic reporting template. The aim of the Common Approach is to provide recommendations and guidance to Member States when reporting.

[3] Cyprus did not submit data.

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.

Following the launch of the data collection exercise by the Commission, the EDQM approached 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.

4. MAJOR FINDINGS

4.1. 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 national tissue and cell 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, while 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 (MAR), 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.

4.1.1. Tissues and cells distributed

The overall *number of tissues and cells distributed* in 2020, as submitted by the reporting countries, amounted to 1 116 519 units. Disaggregated by category, this represents 378 237 units distributed for non-reproductive tissues and 738 282 units distributed for reproductive tissues.

4.1.1.1. Non-reproductive tissues and cells

In the case of non-reproductive tissues and cells, 26 countries reported data on *units distributed* (AT, BE, BG, HR, CZ, DE, DK, EE, FI, FR, EL, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, ES, SE and UK). The

main types of non-reproductive tissues and cells distributed were skeletal tissues (255 021 units), haematopoietic progenitor cells (HPC; 45 915 units) and ocular tissues (30 388 units). See *Figure 1* for further details.

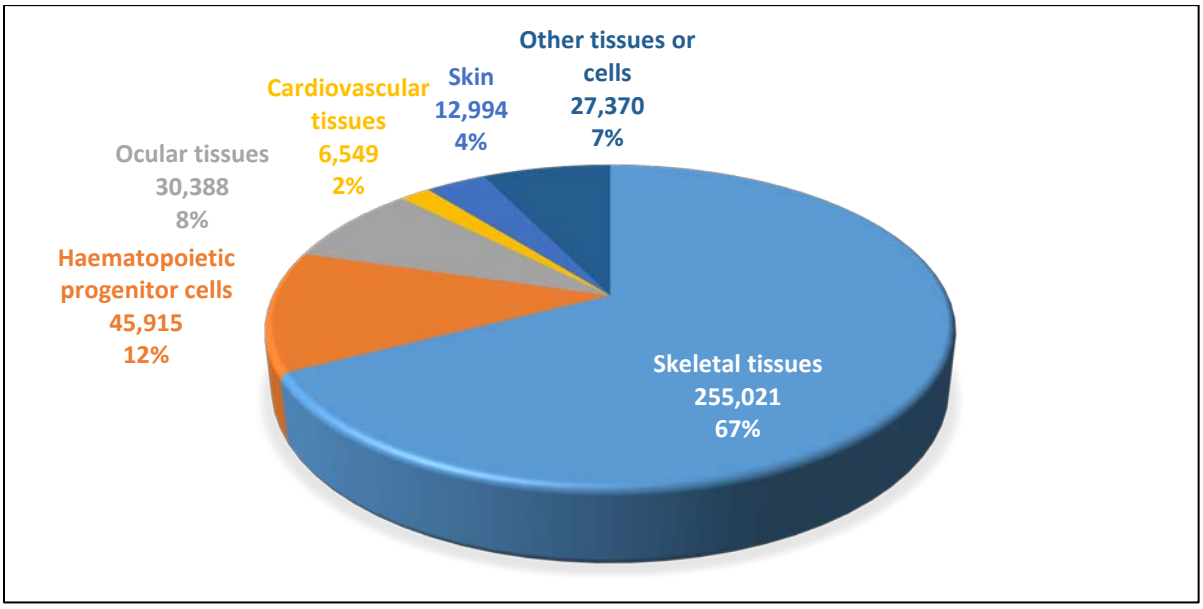

Figure 1. Total number of non-reproductive tissues and cells distributed (units); data 2020.

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. Bones, peripheral blood stem cells, corneas and vessels were the most frequently distributed tissues in each respective category.

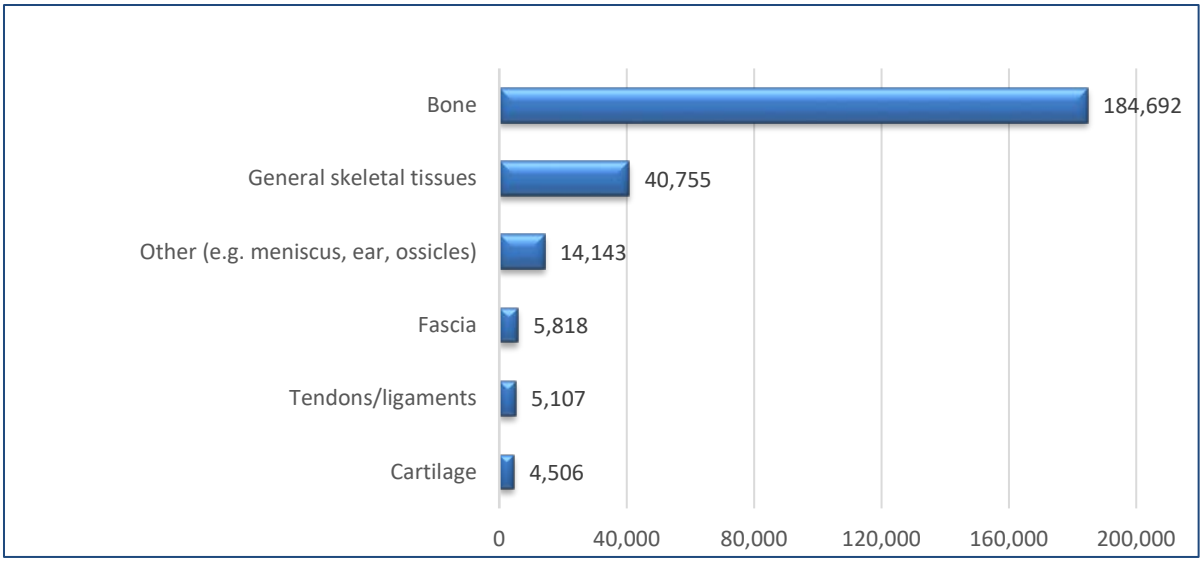

Figure 2. Number of skeletal tissues distributed per sub-category (units)[4]; data 2020.

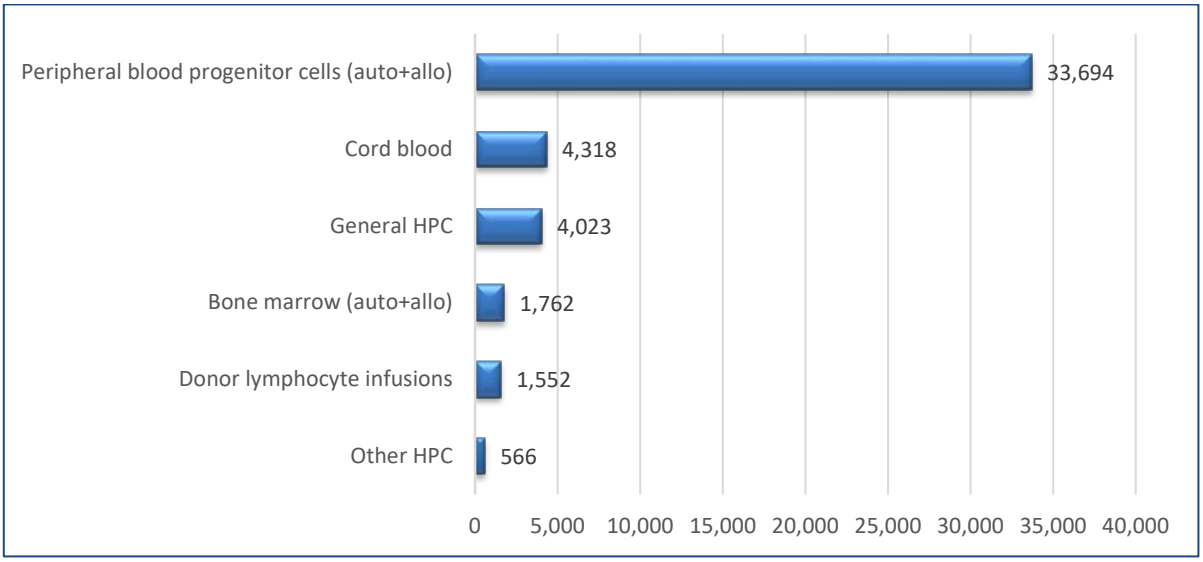

Figure 3. Number of HPC distributed per sub-category (units)[4]; data 2020.

[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).

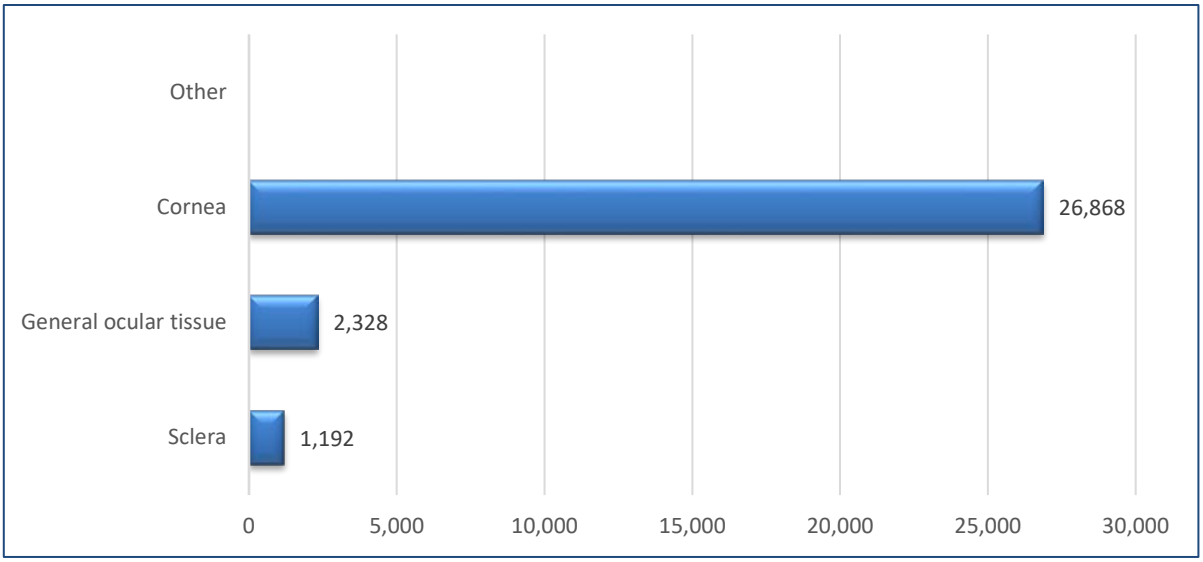

Figure 4. Number of ocular tissues distributed per sub-category (units)[4]; data 2020.

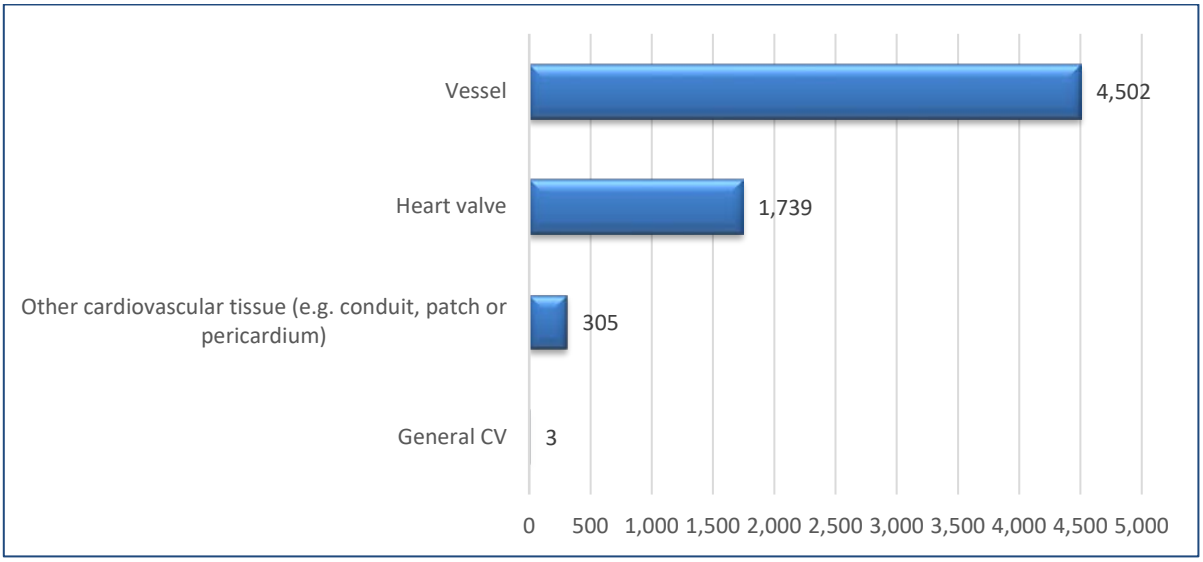

Figure 5. Number of cardiovascular tissues distributed per sub-category (units)[4]; data 2020.

4.1.1.2. Reproductive tissues and cells

For reproductive tissues and cells, 22 countries (AT, BE, BG, HR, CZ, DK, EE, FI, DE, HU, IE, LV, LT, LU, MT, NL, NO, PT, RO, SI, SE and UK) reported activity data.

Of the 738 282 units of reproductive tissues distributed, 284 971 sperm units were delivered for insemination (see *Figure 6*), and 452 212 embryos, following partner and non-partner donation, were delivered for transfer (see *Figure 7*). Additionally, 107 ovarian tissues and 992 testicular tissues were distributed for the treatment of infertility (see *Figure 8*).

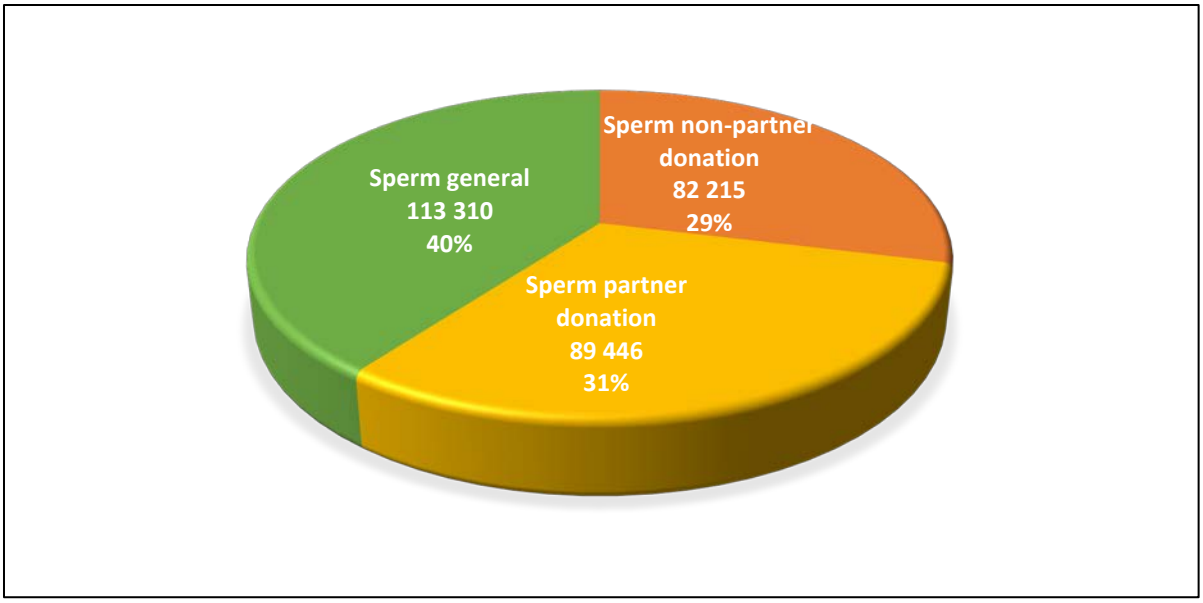

Figure 6. Number of sperm units distributed by category (absolute values and percentages); 2020 data.

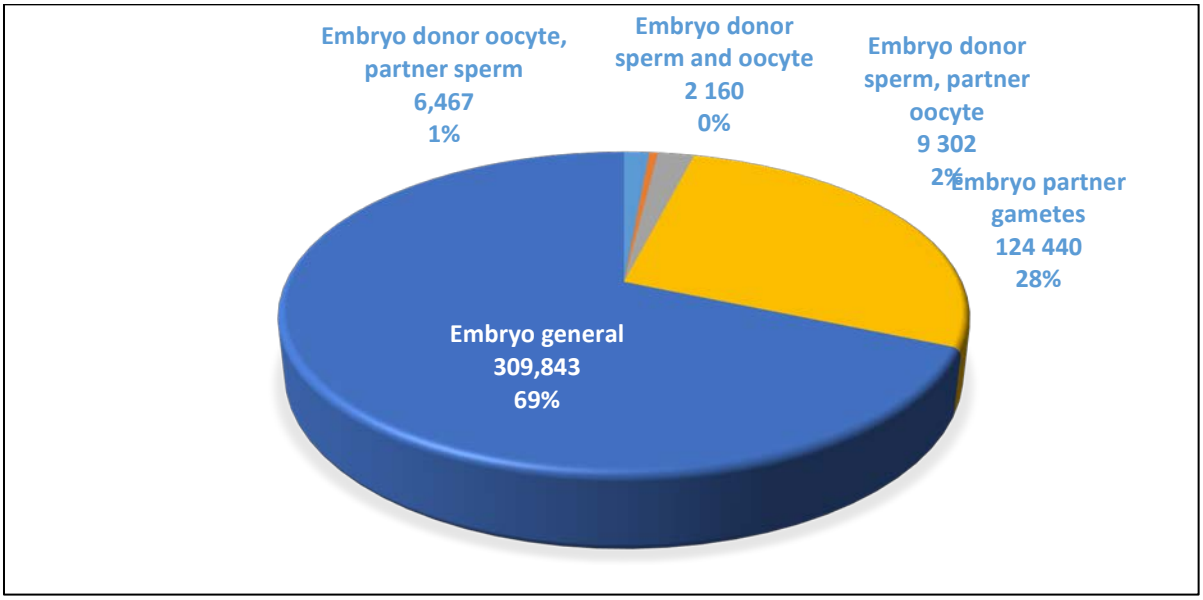

Figure 7. Number of embryos distributed by category (absolute values and percentages); 2020 data.

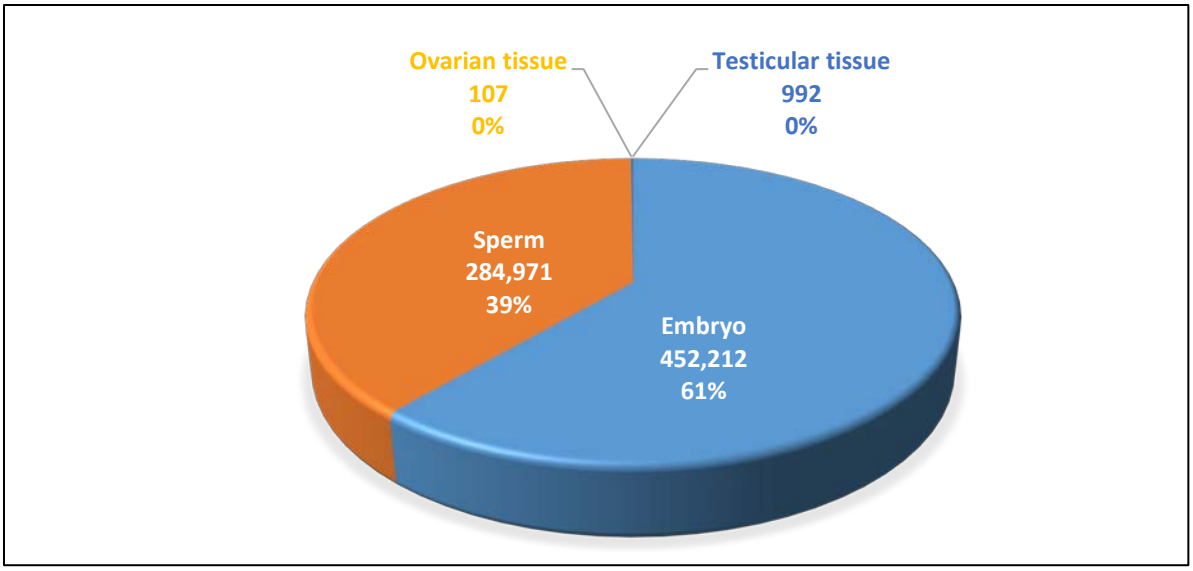

Figure 8. Total number of reproductive tissues distributed (units); 2020 data.

4.1.1.3. Distribution of reproductive tissues and cells (per million population)

Taking into account the demographic data of the reporting countries on 1 January 2020[5], the incidence of distributed non-reproductive and reproductive tissues and cells (per million population) is shown in *Figures 9*, *10* and *11*. It should be noted that for some countries (NO, ES, FR) the full data set was not available at the time of reporting.

[5] https://ec.europa.eu/eurostat/web/population-demography/demography-population-stock-balance/database

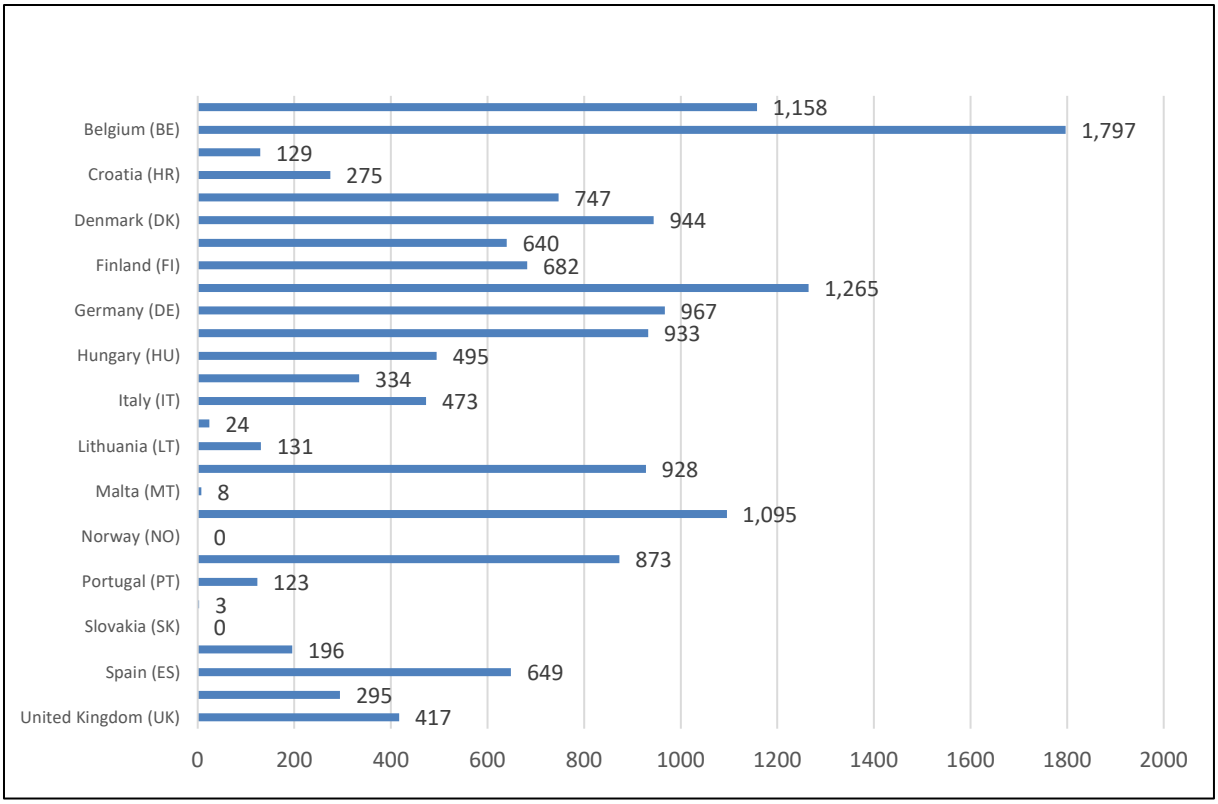

Figure 9. Number of non-reproductive tissue and cell units distributed per million population; data 2020.

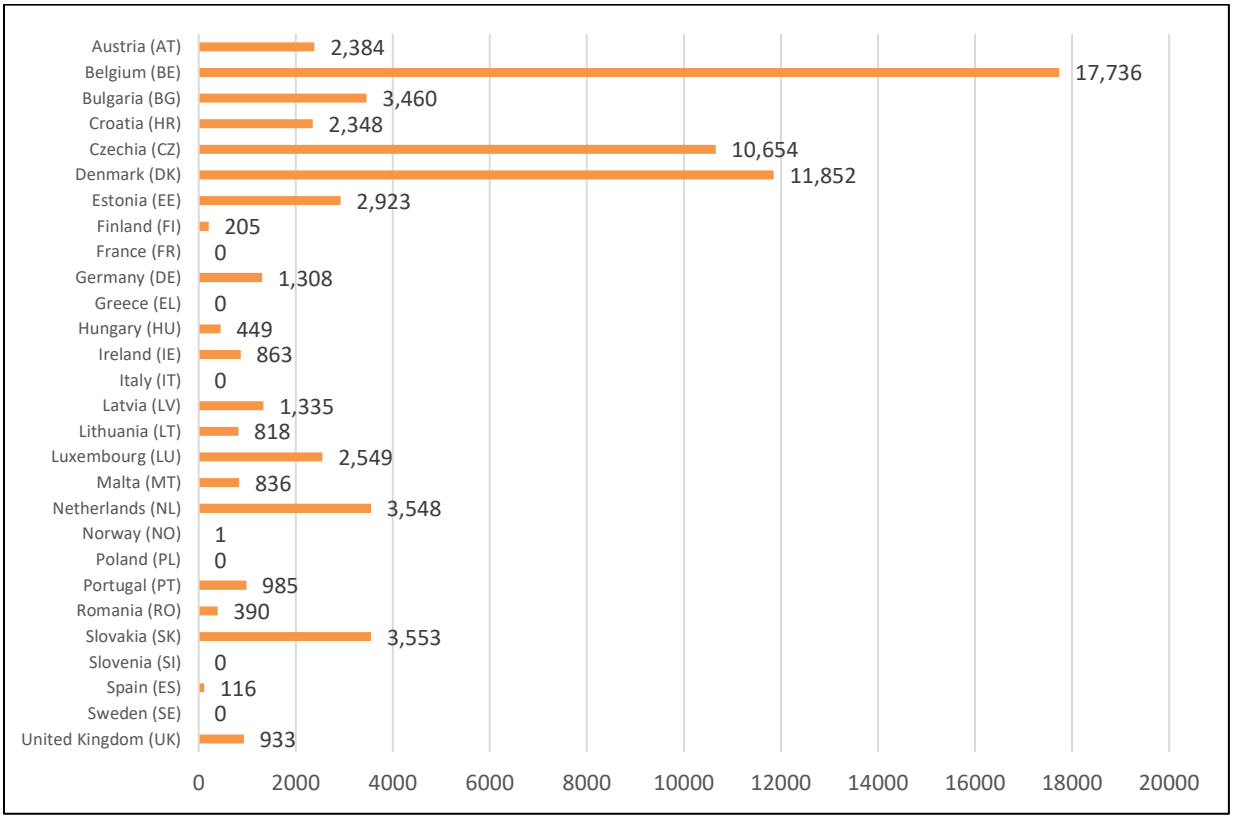

Figure 10. Number of reproductive tissue and cell units distributed per million population; data 2020.

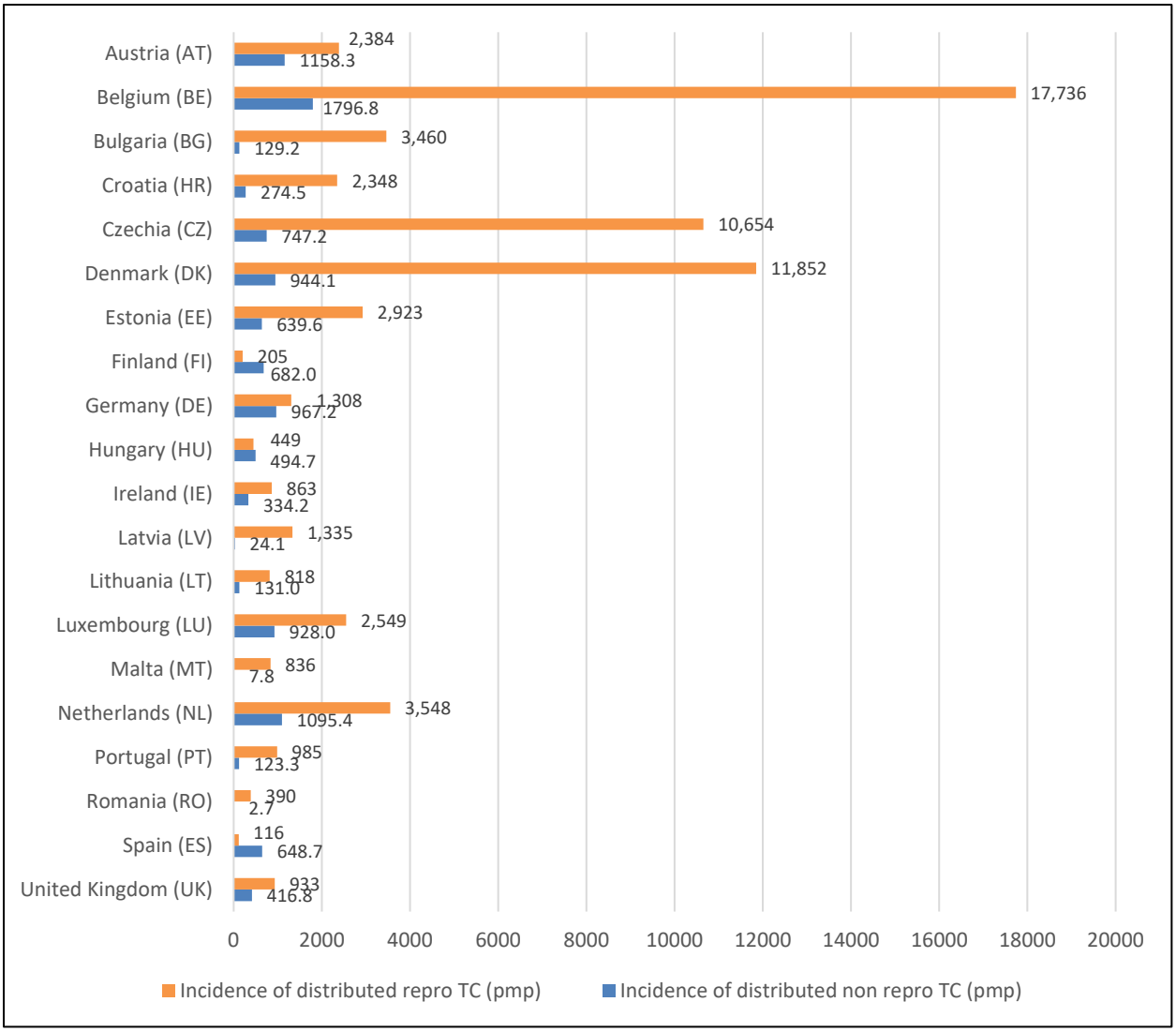

Figure 11. Number of non-reproductive and reproductive tissue and cell units distributed per million population; data 2020 (countries that did not provide data for both non-reproductive and reproductive distributed tissues and cells have not been included in this comparative graph).

4.1.2. Number of transplanted recipients

In 2020, 21 countries reported a total of 245 058 *recipients* (patients) having received tissues or cells. For non-reproductive tissues and cells, 134 242 patients were reported as having received tissue or cells for transplantation while 110 816 patients underwent a MAR procedure.

4.1.2.1. Non-reproductive tissues and cells

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

Figure 12 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 (61%), followed by haematopoietic stem cells (16%) and ocular tissues (13%).

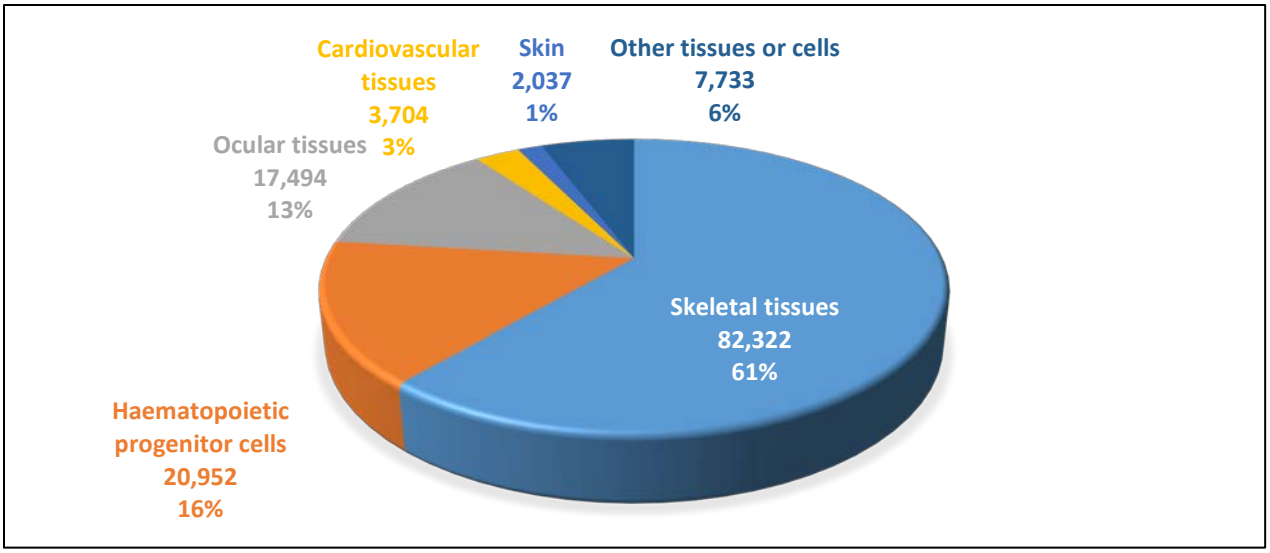

Figure 12. Total number of recipients per type of non-reproductive tissue and cells; data 2020.

4.1.2.2. Reproductive tissues and cells

Concerning reproductive cells, only 15 countries (AT, BG, HR, DK, EE, FI, IE, LU, MT, NL, NO, PT, RO, SI and SE) reported data indicating that 110 816 patients underwent a MAR procedure. Of those, 69 217 involved partner or non-partner embryos (63%), 41 449 involved partner or non-partner sperm (37%), and less than 1% involved transplantation of testicular tissue (120 patients) or ovarian tissue (30 patients) (see *Figure 13*).

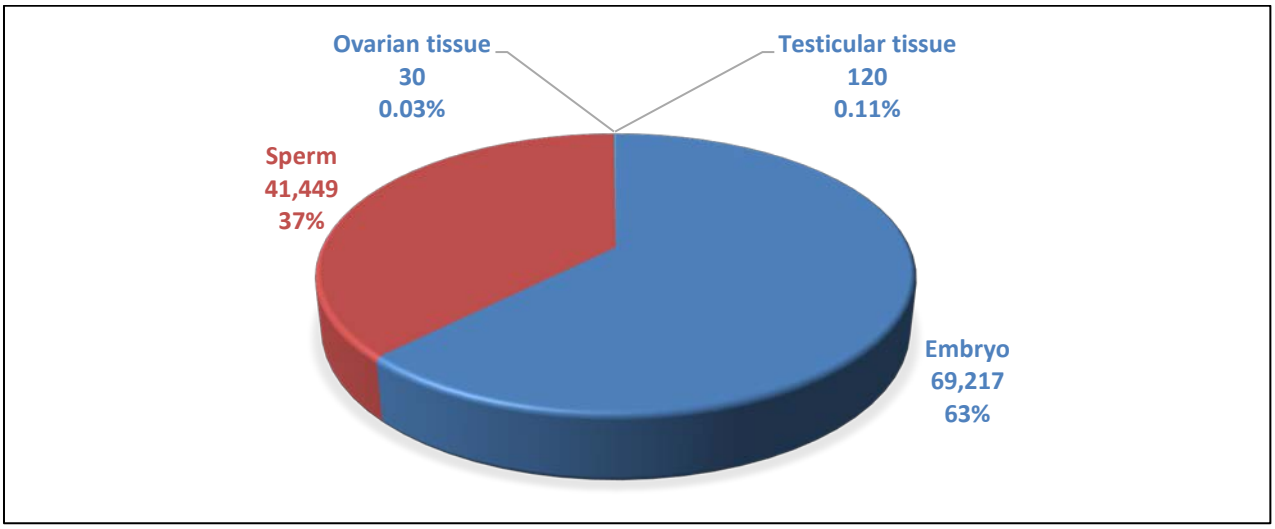

Figure 13. Total number of recipients per type of reproductive tissue and cells; data 2020.

4.1.3. Trends in the distribution and application of tissues and cells

A general overview of the data for the SAR denominators (number of tissues and cells distributed, and number of recipients) provided by the reporting countries in the period between

2012-2021 (data pertaining to 2011-2020) for non-reproductive and reproductive tissues and cells is presented in *Figures 14 and 15*, respectively.

It is noted that the total number of tissues and cells distributed (non-reproductive and reproductive) in 2020 decreased by up to 28% in comparison with the previous year. This can be partially explained by the fact that in this reporting exercise, a few countries with high activity in these fields were not able to provide all the required data (denominators) at the time of reporting (such as Norway, France, Italy and Spain). In addition, the COVID-19 pandemic has impacted healthcare systems, including the tissue and cell field, which may result in fewer tissues and cells being distributed.

For reproductive tissues and cells, the decreased number of units distributed (in comparison with 2019) can be explained by the fact that the full data set was not available for all countries at the time of reporting for this exercise. This was because a new classification of the reproductive tissues and cells category was included in the reporting template to facilitate the description of practices in the MAR field.

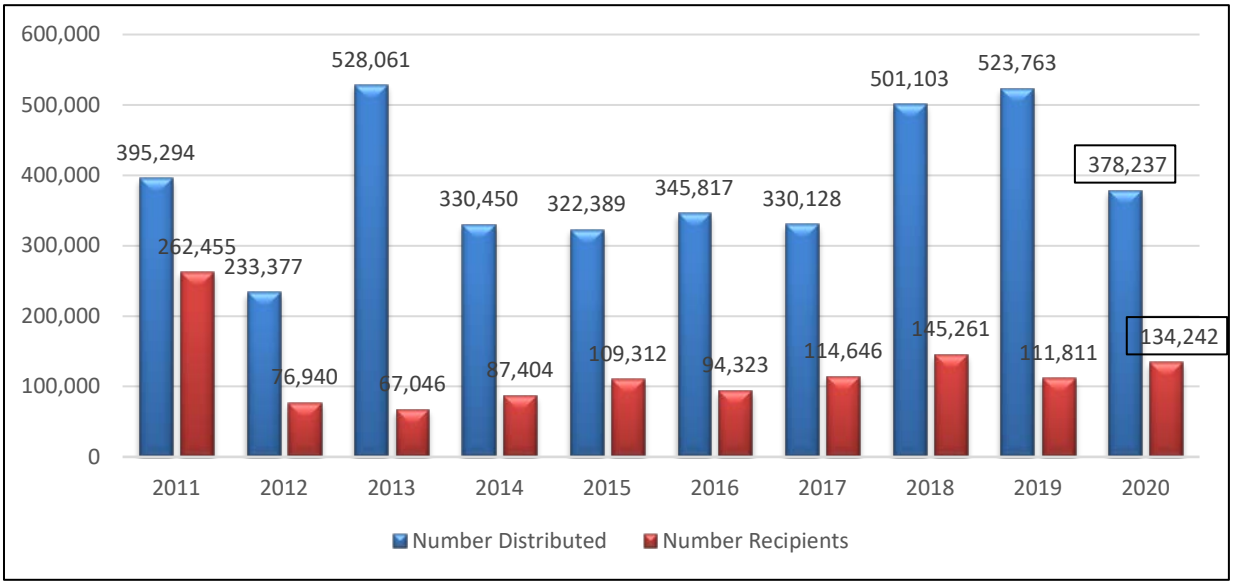

Figure 14. Total number of non-reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2020 comparative data.

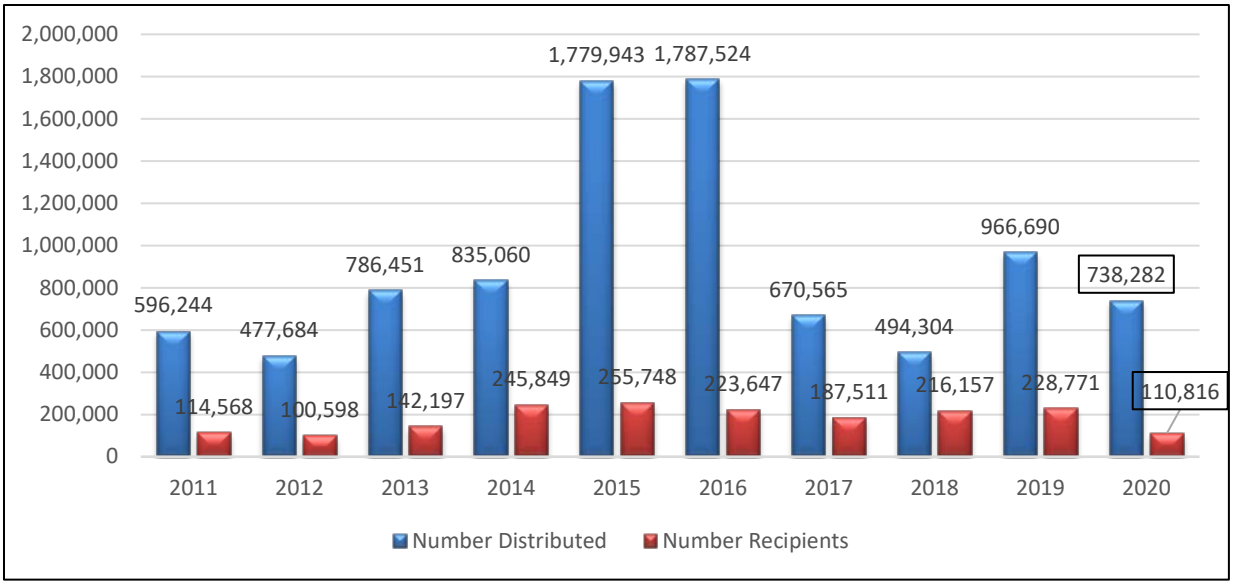

Figure 15. Total number of reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2020 comparative data. [6]

4.1.4. Number of tissues and cells processed

Twenty-three countries (AT, BG, HR, CZ, DK, EE, FI, DE, EL, HU, IE, IT, LV, LT, MT, NL, PL, PT, RO, SI, ES, SE and UK) provided the number of *non-reproductive tissues and cells processed*, and 19 countries (AT, BG, HR, CZ, DK, EE, DE, HU, IE, LV, LT, LU, MT, NL, PT, RO, SI, SE and UK) the number of *reproductive tissues and cells processed* in 2020.

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 2 443 564 tissues and cells were reported as processed in 2020, 16% less than in 2019. Of those, 396 639 units (16%) were for non-reproductive tissues and cells and 2 046 925 units (84%) for reproductive tissues and cells. Comparative data from previous exercises (2011-2020 data) are presented in *Figure 16*.

[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.

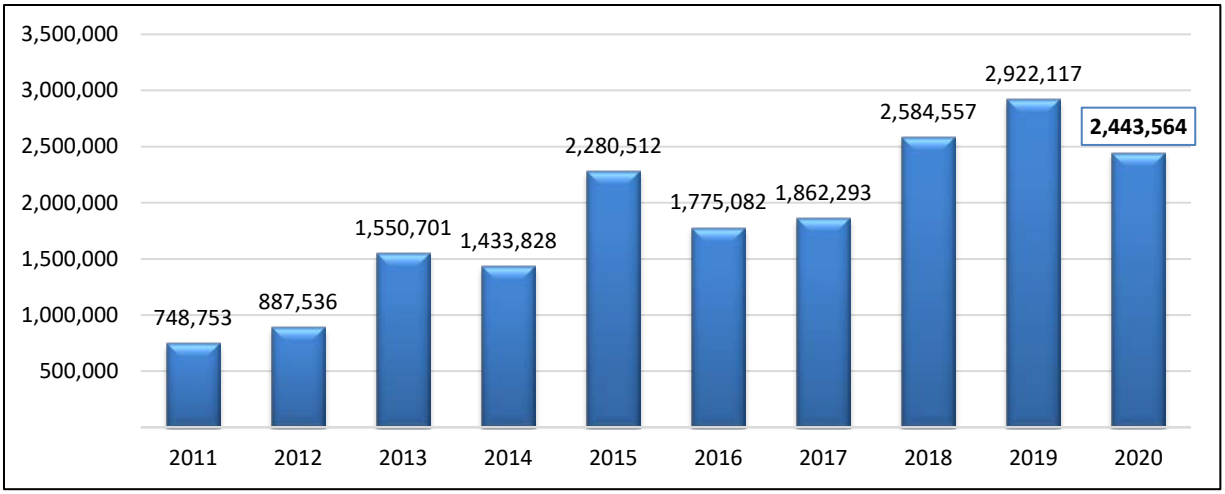

Figure 16. Total number of tissues and cells processed (units): 2011-2020 comparative data.

4.2. Serious adverse reactions in recipients

A total of 350 SAR were reported in 2020, which represents an increase of 14% compared to 2019 (306). Of these, 139 SAR (40%) were related to non-reproductive and 211 (60%) to reproductive tissues and cells.

In 2020, 14 SAR led to death following the clinical application of cells (4%), in contrast to the previous exercise where, according to the reported data, no SAR associated with the clinical application of cells resulted in the death of recipients.

A 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 17*. In general, there has been an increasing trend in SAR reported for reproductive tissues and cells, while the numbers of SAR reported for non-reproductive tissues and cells remain stable.

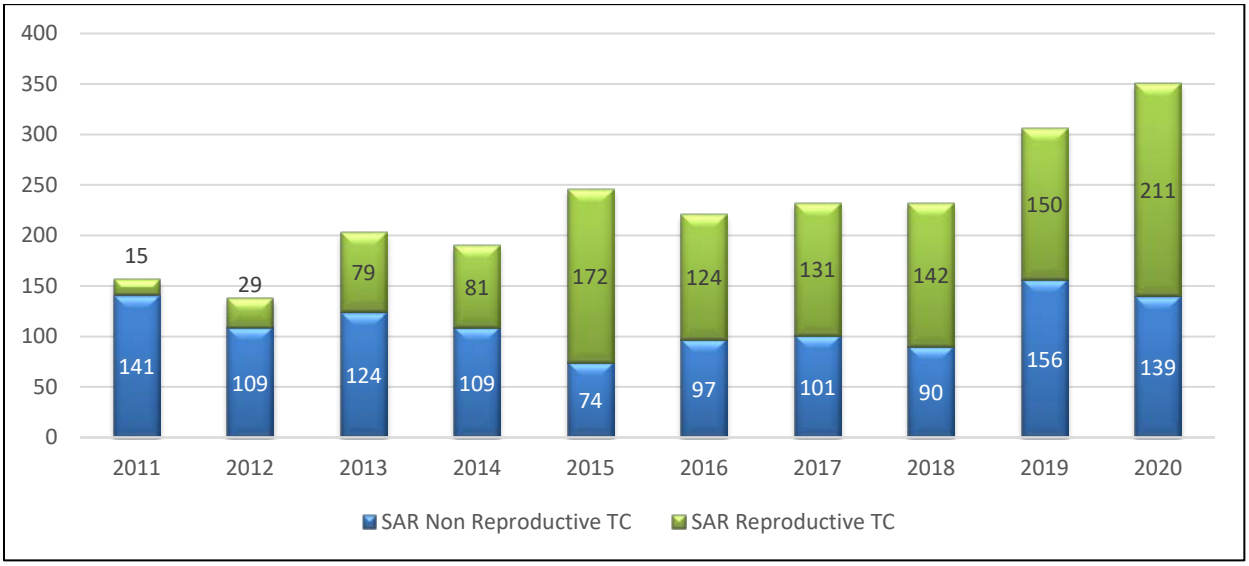

Figure 17. Total number of SAR: 2011-2020 comparative data

4.2.1. General information

Of the 28 reporting countries, only 18 (BE, CZ, DK, EE, FI, FR, DE, EL, IE, IT, HR, LU, NL, PT, ES, SE and Norway and United Kingdom) reported SAR associated with the clinical application of tissues or cells. Ten EU Member States (AT, BG, HU, LV, LT, MT, PL, RO, SK and SI) reported no SAR in recipients in 2020.

Regarding the transplantation of **non-reproductive tissues and cells**, 15 countries (BE, HR, DK, FI, FR, DE, EL, IE, IT, NL, NO, PT, ES, SE and UK) reported SAR, whereas 17 countries (BG, HR, CZ, DK, EE, FI, FR, DE, IE, IT, LU, NL, NO, PT, ES, SE and UK) reported SAR following the clinical application of **reproductive tissues or cells**.

The frequency of SAR should be assessed by calculating its incidence in relation to the number of tissues and cells transplant/application procedures, however these data are currently not collected within SARE exercise. Therefore, in this exercise, the incidence of SAR is calculated using number of tissues and cells distributed as denominator. This should be interpreted with caution as the distribution in the current reporting system is not representative of the distribution for final users, neither of the number of transplant/application procedures.

The incidence of SAR is calculated per 10 000 tissues and cells distributed (based on data provided by 26 countries for non-reproductive tissues and cells, and 22 countries for reproductive tissues and cells). The incidence of SAR for all tissues and cells is 2.7 per 10 000 tissues and cells distributed, and it is slightly higher for non-reproductive tissues and cells (3.6) than for reproductive tissues and cells (2.2), as shown in the *Table 1*.

2021 Exercise (data 2020)	Number of TC distributed	Number of SAR*	Incidence of SAR/10 000 TC distributed
All TC	1 116 519	303*	**2.7**
Non-reproductive TC	378 237	138*	**3.6**
Reproductive TC	738 282	165*	**2.2**

Table 1. Number of SAR per 10 000 tissues and cells (TC) distributed; data 2020

*(*SAR data from countries that did not report the number of tissues distributed have not been included in this table.)*

These data should be interpreted with caution, as they may not reflect 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 incidence may indicate more effective detection and reporting systems rather than an actual increase in the number of SAR.

4.2.2. SAR by type of tissue or cell

In total, 60% of the 350 SAR in recipients reported were associated with the application of reproductive tissues and cells, compared to 40% associated with the transplantation of non-reproductive tissues or cells, as shown in *Figure 18.* Most of the 139 SAR following application of **non-reproductive** tissues and cells were related to transplantation of HPC (78%), followed by transplantation of skeletal tissues (9%) and transplantation of ocular tissues (8%), as shown in *Figure 19*.

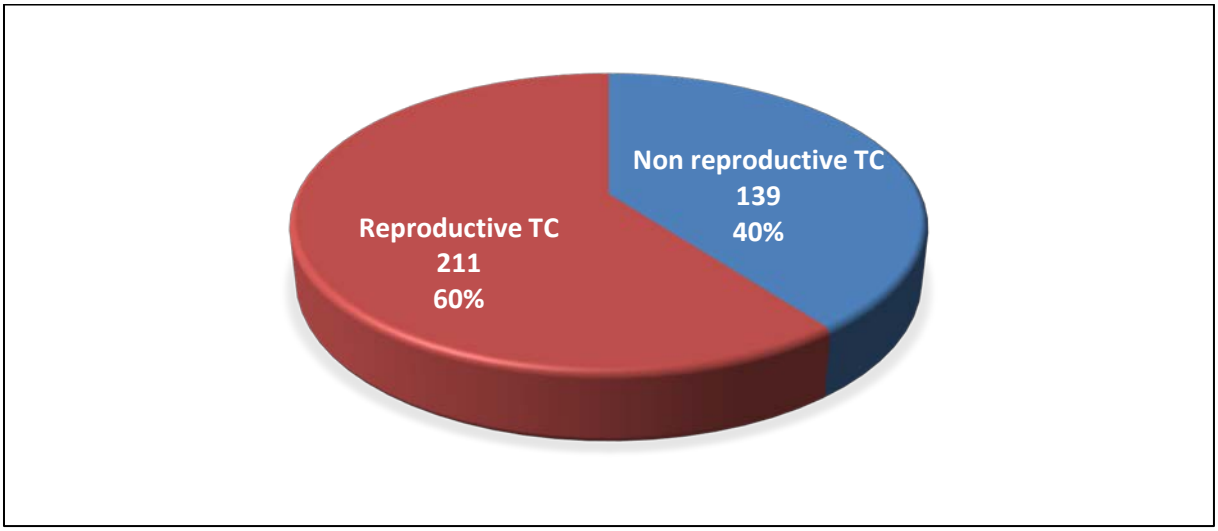

Figure 18. Number of SAR per type of tissues and cells; data 2020

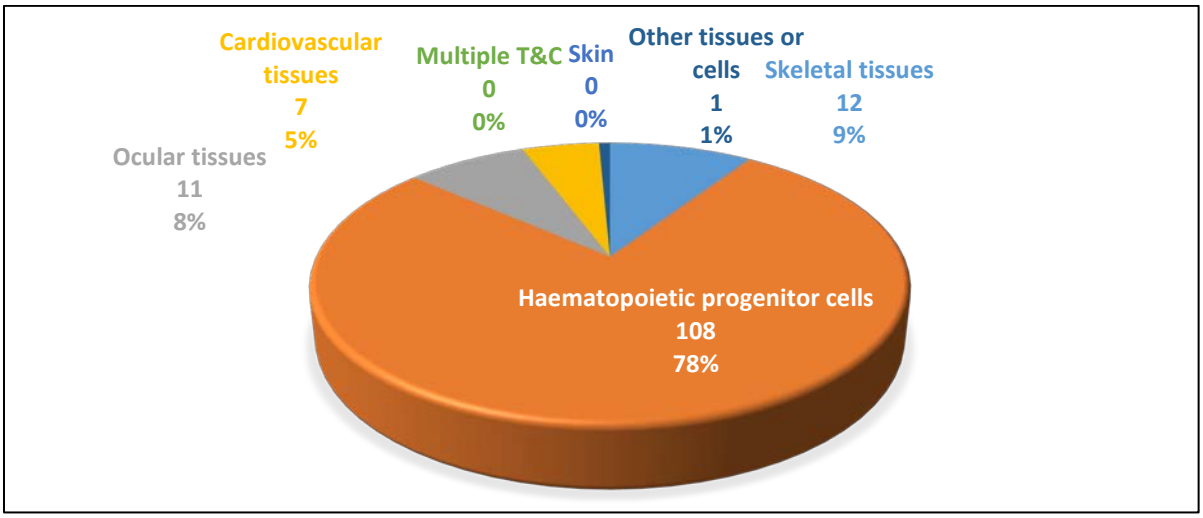

Figure 19. Number of SAR for each type of non-reproductive tissue and cells (absolute values and percentages of total SAR in recipients); 2020 data.

More detailed information on the breakdown of SAR by type of non-reproductive tissue and cells is given below:

- 108 SAR related to the transplantation of HPC:
  - 78 peripheral blood stem cells

- 15 general category[7]
- 11 bone marrow
- 2 cord blood
- 2 related to the "other HPC" category

- 12 SAR related to the transplantation of skeletal tissues:
  - 8 bone
  - 4 cartilage

- 11 SAR related to the transplantation of ocular tissue:
  - 11 corneas

- 7 SAR related to the transplantation of cardiovascular tissue:
  - 6 heart valves
  - 1 vessel

- 1 SAR related to the transplantation of other tissues and cells:
  - 1 pancreatic islet

Most of the 211 SAR following clinical application of **reproductive** tissues and cells were associated with clinical application of embryos (67%), followed by sperm insemination (33%), as shown in *Figure 20*.

More detailed information on the breakdown of SAR by type of reproductive tissue and cells is given below:

- **70 SAR associated with sperm insemination** (see *Figure 21*)
  - 59 following non-partner donation
  - 5 reported in a general category[7]
  - 6 following partner donation

- **141 SAR associated with clinical application of embryos** (see *Figure 22*)
  - 87 reported in a general category[7]
  - 22 from partner gametes
  - 19 following oocyte donation and partner sperm
  - 5 following sperm donation and partner oocyte
  - 8 following sperm and oocyte donation

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

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

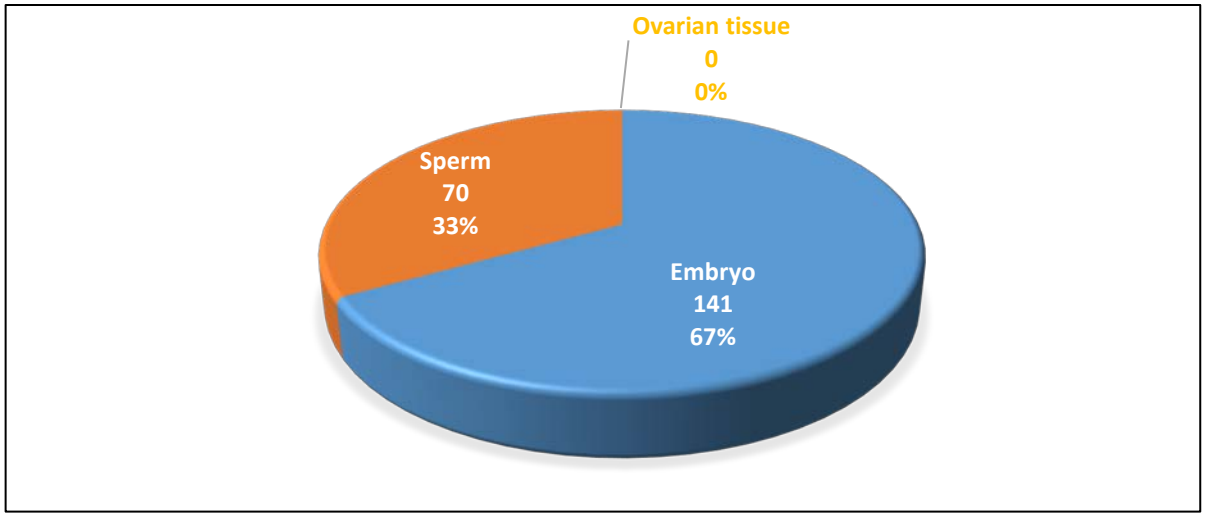

Figure 20. Number of SAR for each type of reproductive tissue and cells (absolute values and percentages of total SAR in recipients); 2020 data.

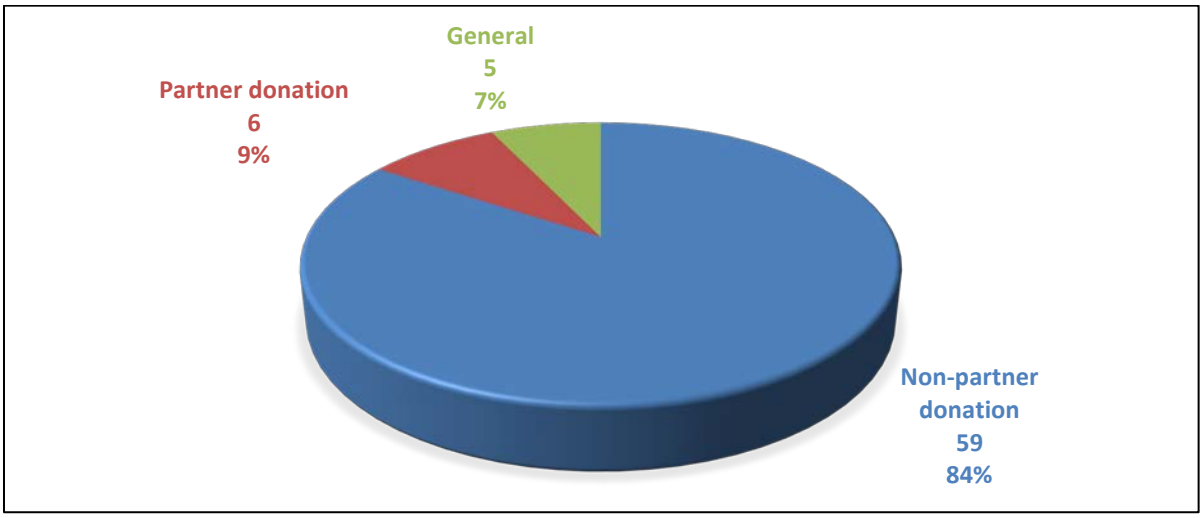

Figure 21. Number of SAR for sperm used for IUI per category (absolute values and percentages of total SAR in recipients); 2020 data.

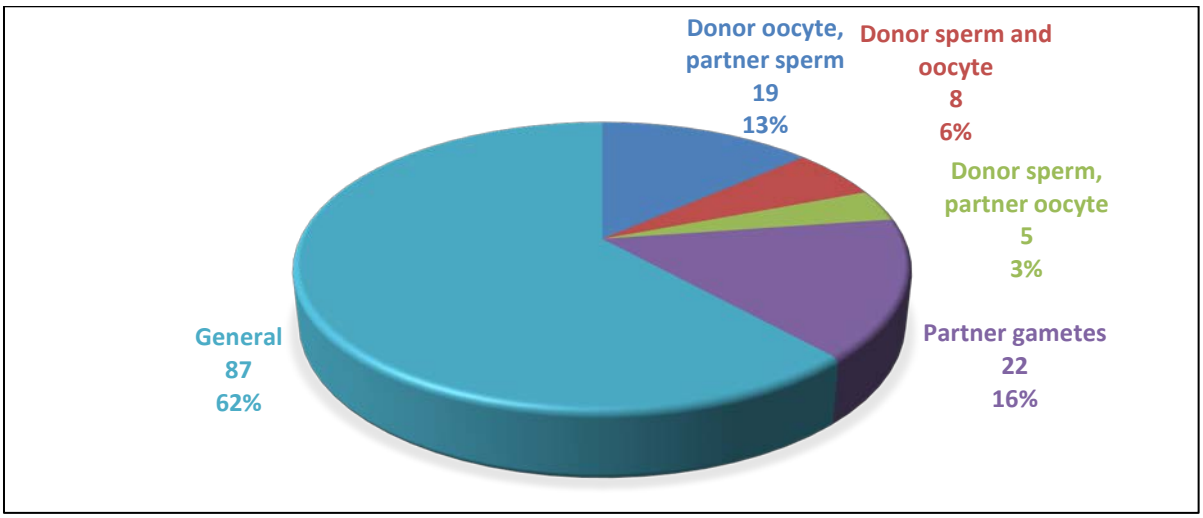

Figure 22. Number of SAR for embryos after IVF/ICSI per category (absolute values and percentages of total SAR in recipients); 2020 data.

4.2.3. SAR by type of reaction

Major categories of reactions following application of **non-reproductive tissues and cells** listed in the Common Approach include *transmitted infections* (bacterial, viral, parasitical, fungal, prion disease, other transmitted infections), *transmitted malignant diseases*, *other disease transmission* (immunological, genetic, other donor derived disease), and *other SAR* (cardiovascular reaction, pulmonary reaction, neurological reaction, toxicity, etc.).

Among 139 SAR reported for non-reproductive tissues and cells, 95% (132) were classified as *other,* followed by 4% transmitted infections (6), and 1% transmitted malignant disease (1), as shown in *Figure 23*.

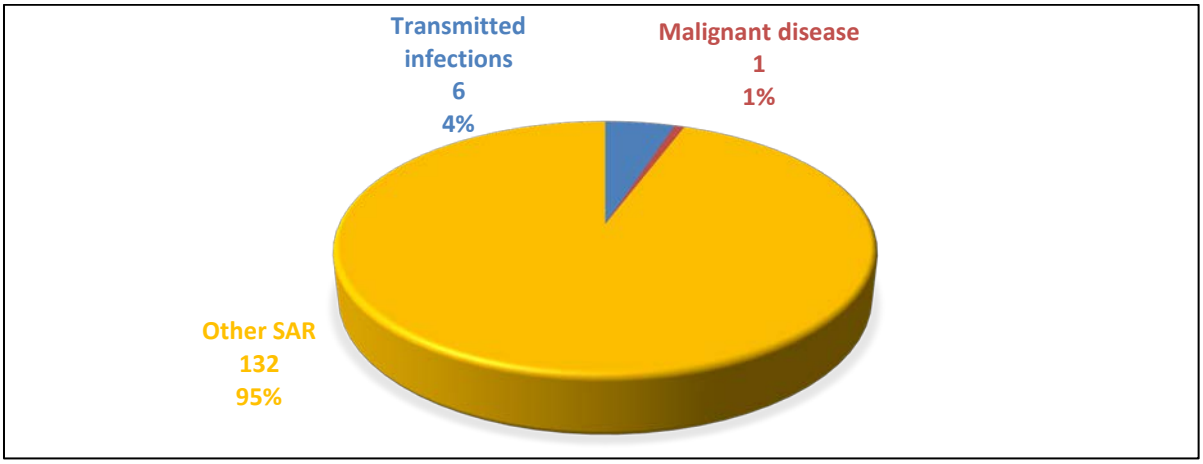

Figure 23. Number of SAR for non-reproductive tissues and cells per category (absolute values and percentages); data 2020.

More detailed information on the breakdown of SAR by type of reaction for non-reproductive tissues and cells is given below:

1. **Transmitted infections** were reported in 6 patients, representing 4% of all reported SAR for non-reproductive tissues and cells, as shown in *Figure 24*:
    - 1 bacterial infection (*Streptococcus viridans)* transmitted by imported **bone marrow**
    - 1 bacterial infection (*Staphylococcus epidermis)* transmitted via **heart valve**
    - 4 *non-specified* infections after **corneal** transplants reported as endophthalmities

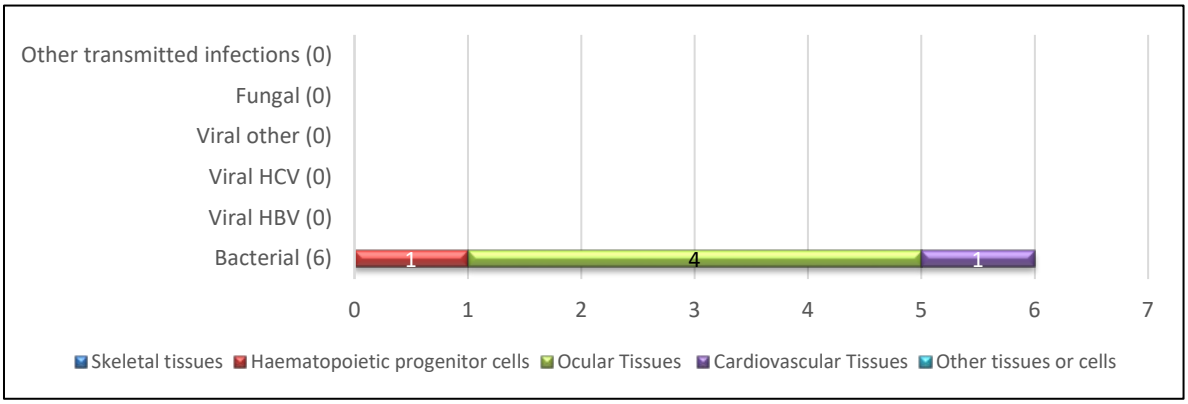

Figure 24. Number of SAR of transmitted infections for non-reproductive tissues and cells (absolute values); data 2020.

2. **Transmitted malignant disease**: 1 case of malignant disease transmission was reported following pancreatic islet transplantation, but the type of malignancy was not specified (representing 0.7% of all reported SAR for non-reproductive tissues and cells).

3. **Other SAR**: among 132 SAR reported (representing 95% of all reported SAR for non-reproductive tissues and cells), the largest specified category was related to graft function failure, followed by infusion-related non-specific symptoms, and undue exposure to risk intervention (logistical issue), then immunological, cardiovascular or neurological reactions, and toxicity; 48 reactions were not classified at all, as shown in *Figure 25.*

    - 31 cases of **graft failure or delayed engraftment**, among those:
        - 18 following the transplantation of HPC (12 peripheral blood progenitors, 3 bone marrow, 2 general category and 1 cord blood)
        - 7 following the transplantation of skeletal tissue (all bones)
        - 4 following the transplantation of cardiovascular tissue (all heart valves)
        - 2 following the transplantation of ocular tissue (all corneas)

    - 15 cases of **infusion-related non-specific** symptoms following the transplantation of HPC (8 peripheral blood progenitors, 4 general category, 2 bone marrow and 1 other HPC)

    - 11 cases of undue **exposure to risk** intervention (e.g. patient under anaesthesia without proper graft and surgery postponed or rescheduled):
        - 4 following skeletal tissue transplantation (cartilage)
        - 3 following HPC transplantation (1 general category, 1 peripheral blood progenitor cells and 1 cord blood)
        - 4 ocular tissues (corneas)

    - 11 cases of **immunological reactions** following HPC transplantation (9 peripheral blood progenitors, 1 bone marrow and 1 other HPC)

    - 6 cases of **cardiovascular reaction** following HPC transplantation (3 peripheral blood progenitors, 2 general category and 1 bone marrow)

    - 5 cases of **neurological reactions** following HPC transplantation (4 peripheral blood progenitor cells, 1 bone marrow)

    - 5 cases of **toxicity** following HPC transplantation (3 peripheral blood progenitor cells and 2 bone marrow)

    - 48 SAR were classified as **other** (none of the above), of which the vast majority (44) were related to the application of HPC (peripheral and general HPC), as listed below:
        - 38 cases following the transplantation of peripheral blood progenitor cells
        - 6 in the HPC general category[7]
        - 1 following the transplantation of bone

- 1 following the transplantation of a cornea
- 1 following the transplantation of a heart valve
- 1 following the transplantation of a vessel

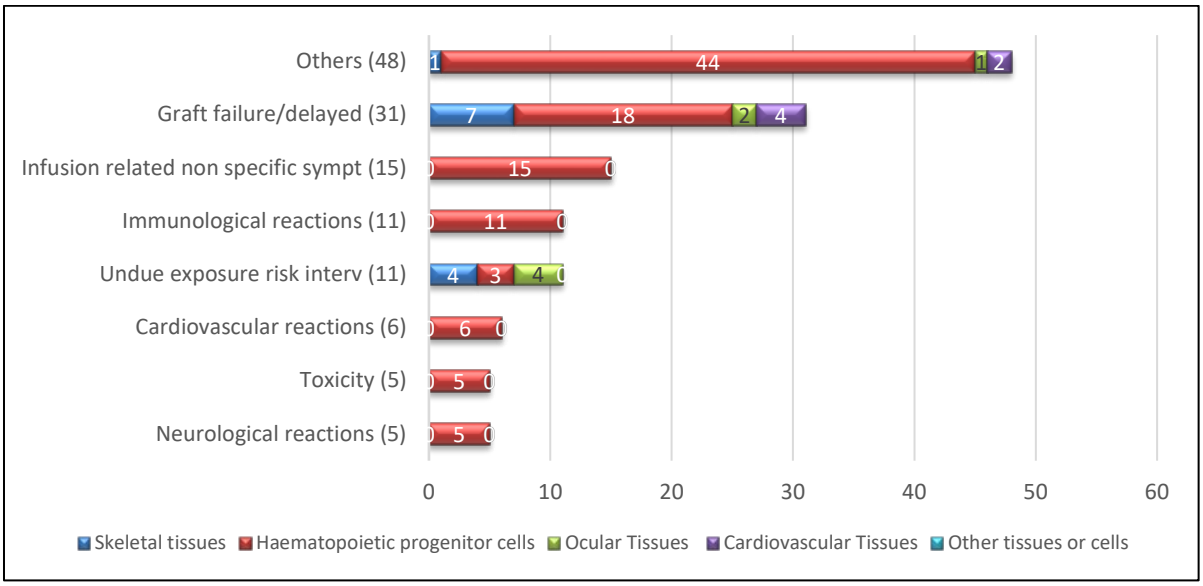

Figure 25. Number of "other SAR" for non-reproductive tissues and cells (absolute values); data 2020.

Major categories of SAR associated with the application of **reproductive tissues and cells,** as listed in the Common Approach, include *transmitted infections* (bacterial, viral, parasitical, fungal, prion disease, other transmitted infections), *transmitted malignant diseases*, *other disease transmission* (immunological, genetic, other donor-derived disease) and *other SAR* (anaphylactic reaction, ectopic pregnancy, etc.)

Among the 211 SAR associated with the application of reproductive tissues and cells, 52% were classified as *other disease transmission*, followed by *other SAR* (47%) and *transmitted infection* (1%), as shown in *Figure 26*.

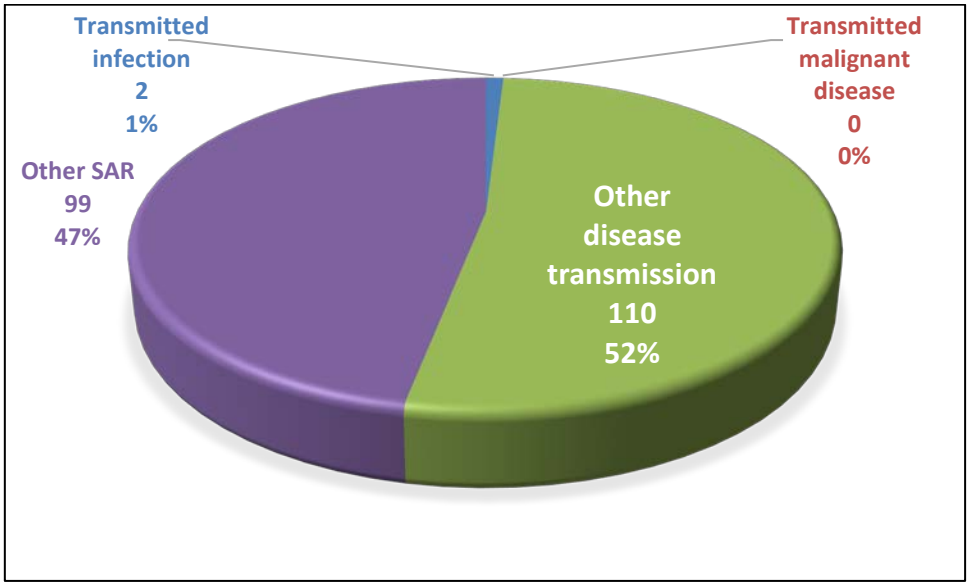

Figure 26. Distribution of SAR per type of reaction for reproductive tissues and cells; data 2020.

More detailed information on the breakdown of SAR by type of reaction for **reproductive tissues and cells** is given below, and shown in *Figures 27 and 28*:

- **Transmitted infection** (2): Bacterial infections:
  - 1 pelvic inflammatory disease caused by *Mycoplasma genitalium* transmitted via clinical application of sperm from partner donation
  - 1 pelvic inflammatory disease requiring hospitalisation, following non-partner sperm donation (type of bacteria not specified)
- **Transmitted malignant disease** No transmission of malignant diseases was reported.
- **Other disease transmission**: In this category, **transmitted genetic conditions** were reported in 110 cases of SAR and represent the most common type of SAR related to reproductive tissues and cells (52.1% of all reported SAR for reproductive tissues and cells).

Notably the largest category for transmitted genetic conditions is associated with **non-partner** (donated) reproductive cells, whereas only 1 case of transmitted genetic condition was reported for partner reproductive cells, as specified below:

→ 52 cases involving non-partner sperm donation
→ 36 cases involving embryos in the "general" category
→ 11 cases involving embryos from donor oocyte and partner sperm
→ 4 cases involving embryos from donated oocyte and sperm
→ 4 cases involving embryos from donor sperm and partner oocyte
→ 1 case involving sperm in the "general" category
→ 1 case involving embryo from partner gametes

- **Other SAR**: among reported SAR categorised as ***other,*** ectopic pregnancy (EP) was the most common, representing 22% of all reported SAR for reproductive tissues and cells: EP was underlying in 47 reported SAR, as specified below:
  → 20 EP following the clinical application of embryos from partner gametes
  → 7 EP embryos from donor oocyte and partner sperm
  → 4 EP embryos from donor sperm and oocyte
  → 4 EP embryos from "general" category
  → 1 EP embryo from donor sperm and partner oocyte
  → 5 EP following the clinical application of sperm from partner donation
  → 4 EP following non-partner sperm donation
  → 2 EP not classified by type of MAR (sperm from "general" category)

The other 52 **non-classified** SAR, representing 24.7% of all reported SAR for reproductive tissues and cells, were defined as follows:

→ 47 SAR following the clinical application of embryos from "general" category
→ 2 SAR following the clinical application of sperm from non-partner donation
→ 1 SAR following the clinical application of sperm from "general" category
→ 1 SAR following the clinical application of embryo from donor oocyte and partner sperm
→ 1 SAR following the clinical application of embryo from partner gametes

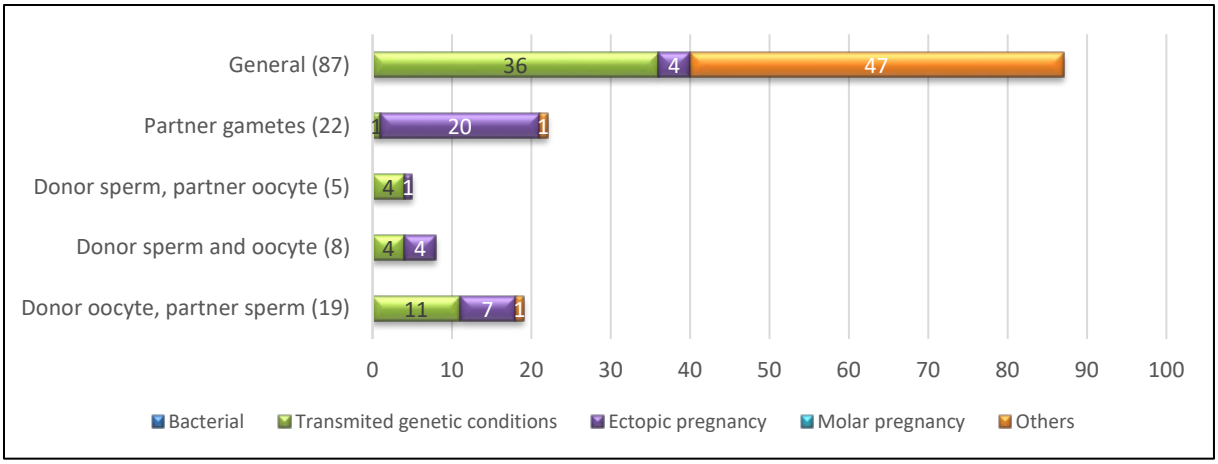

Figure 27. Number of SAR per type of gametes (partner/non-partner), embryo application; 2020 data.

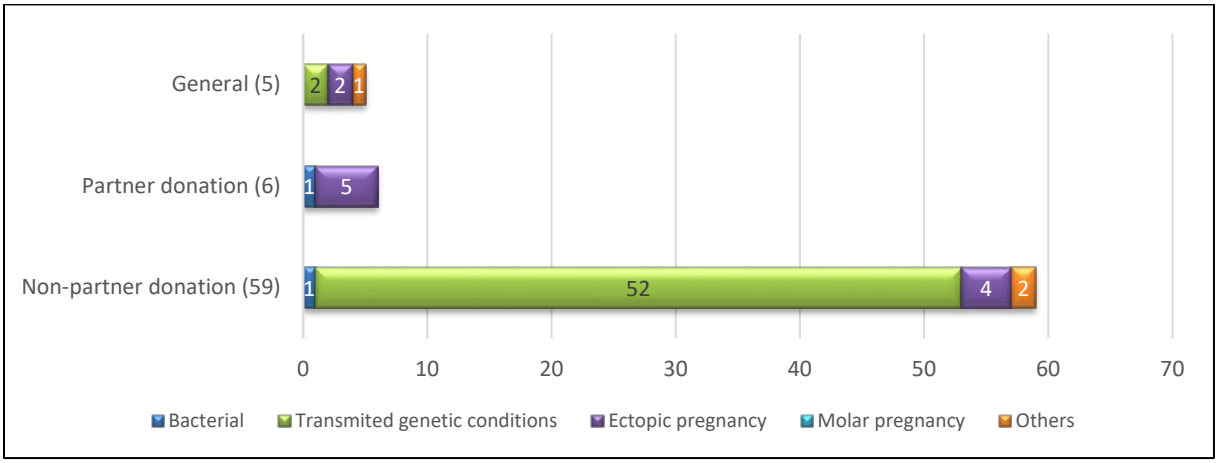

Figure 28. Number of SAR per type of gametes (partner/non-partner), sperm application; 2020 data.

It is notable that of the 211 SAR associated with the application of reproductive cells, 43.1% were related to non-partner donation (59 involving non-partner sperm and 32 involving embryos from donated oocyte (19), or donated sperm and oocyte (8), or donated sperm (5)), see *Figure 29*.

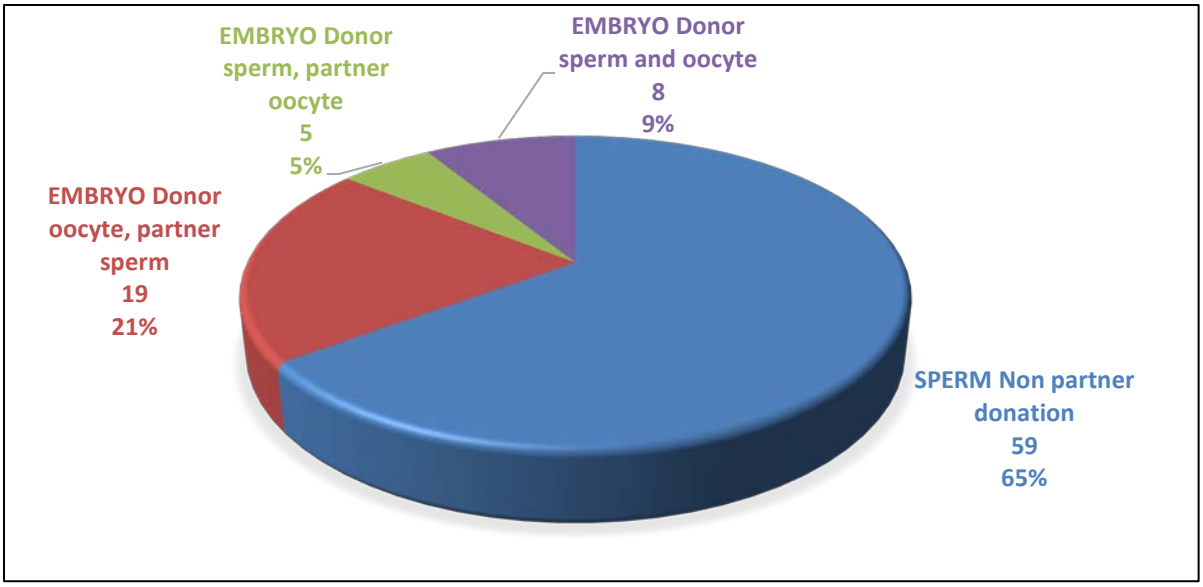

Figure 29. SAR related to the application of non-partner gametes (absolute values and percentages); 2020 data.

4.2.4. Death of recipients of tissues and cells

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 on reported deaths.

In this exercise **14 deaths in recipients** were reported (8 deaths potentially attributed to non-reproductive tissue and cell application, and 6 deaths potentially attributed to reproductive tissue and cell application). It should be noted that no deaths of recipients attributable to tissue and cell application were reported in the previous year.

4.2.4.1. Deaths following the application of non-reproductive tissues and cells

Detailed information on the **8 reported deaths** potentially attributable to **non-reproductive** tissue and cell application is given below:

- **1 death associated with peripheral blood stem cells** (graft failure), possibly attributed to the quality of the graft (low viability of cryopreserved CD34+ after thawing)
- **2 deaths after cell infusion**, imputability to graft quality cannot be fully excluded (previous clinical status of the patient: immune haemolytic anaemia/COVID-19)
- **1 death after rupture of arterial graft** during surgery (abdominal aorta aneurysm), imputability to graft quality cannot be fully excluded
- **1 death related to a HPC sample crossover in HLA laboratory**
- **1 death after peripheral blood cell infusion** (human error in calculation of CD34, grade IV hyperacute GVHD)
- **1 death related to bone marrow unrelated infusion** (haemolytic crisis)
- **1 death related to stem cell transplant** (cerebral oedema, autopsy not approved, so investigation not fully performed)

It should be noted that all reported deaths were related to haematopoietic stem cells, except 1 related to arterial graft.

4.2.4.2. Deaths following the application of reproductive tissues and cells

Details of the **6 reported MAR-related deaths** (i.e. reproductive tissues and cells), which include offspring and foetal deaths (at various stages of pregnancy), are listed below;

- **3 deaths of offspring** (IVF) with no specified cause
- **3 terminations of pregnancy** associated with suspected **congenital abnormality** from non-partner sperm donation (including 1 death of foetus by induced abortion due to diagnosis of prosencephaly[8]).

4.3. Serious adverse events

4.3.1. General information

The total number of SAE reported in 2020 slightly decreased (4%) when compared to the previous exercise, as presented in *Figure 31*. This can be partially explained by the decrease in the total number of tissues processed in 2020 (see *Figure 30*).

Nineteen countries reported SAE for non-reproductive tissues and cells (AT, BE, HR, CZ, DK, FI, FR, DE, GR, HU, IE, IT, NL, NO, PL, PT, ES, SE and UK) and 20 countries for reproductive tissues and cells (AT, BE, BG, CZ, DK, EE, FI, FR, DE, HU, IE, IT, LV, NL, NO, PL, PT, ES, SE and UK).

Of the SAE reported for 2020, **72%** were related to **non-reproductive tissues and cells**, and less than 30% to reproductive tissues and cells.

[8] An etiology of prosencephaly is in most of cases due to congenital abnormality but can also be linked to other factors.

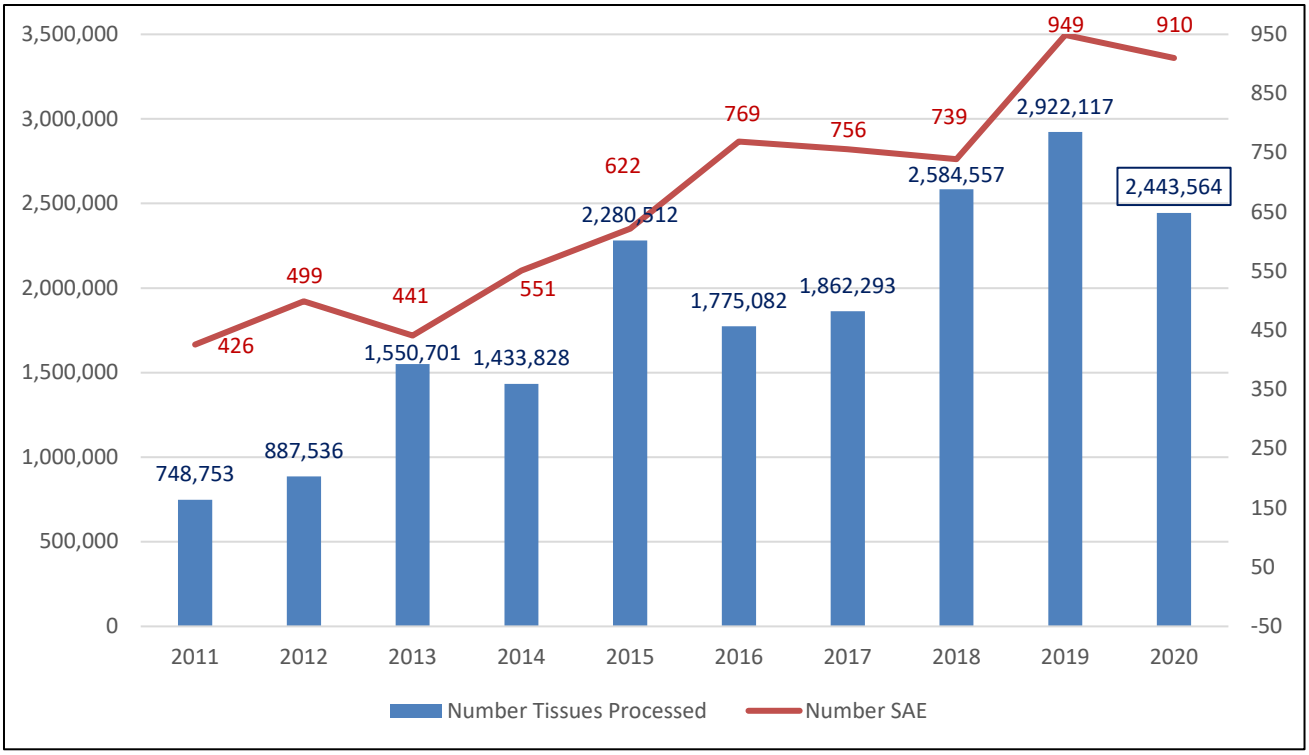

Figure 30. Number of tissues processed and number of SAE reported, 2011-2020 comparative data.

4.3.2. SAE by type of event

SAE are divided into several categories addressing *tissue/cell defects*, *human error*, *equipment failure*, as well as the recently introduced *materials* and *system failure* (reporting templates 2019 and 2020, respectively):

- *materials* - refers to suboptimal quality and safety of the tissues or cells due to defective materials (used during procurement, processing, storage or distribution)
- *system failure* - refers to the failure of the quality management system (due to training or education, staffing, workload or skill-mix, or inadequate processes, procedures or documentation)

In 2020 the reported SAE were most commonly attributable to **defects of tissues and cells (31%),** while **25% of SAE remained unclassified,** as shown in *Figure 31*. The rate of human error decreased from 31% in 2019 to 21%.

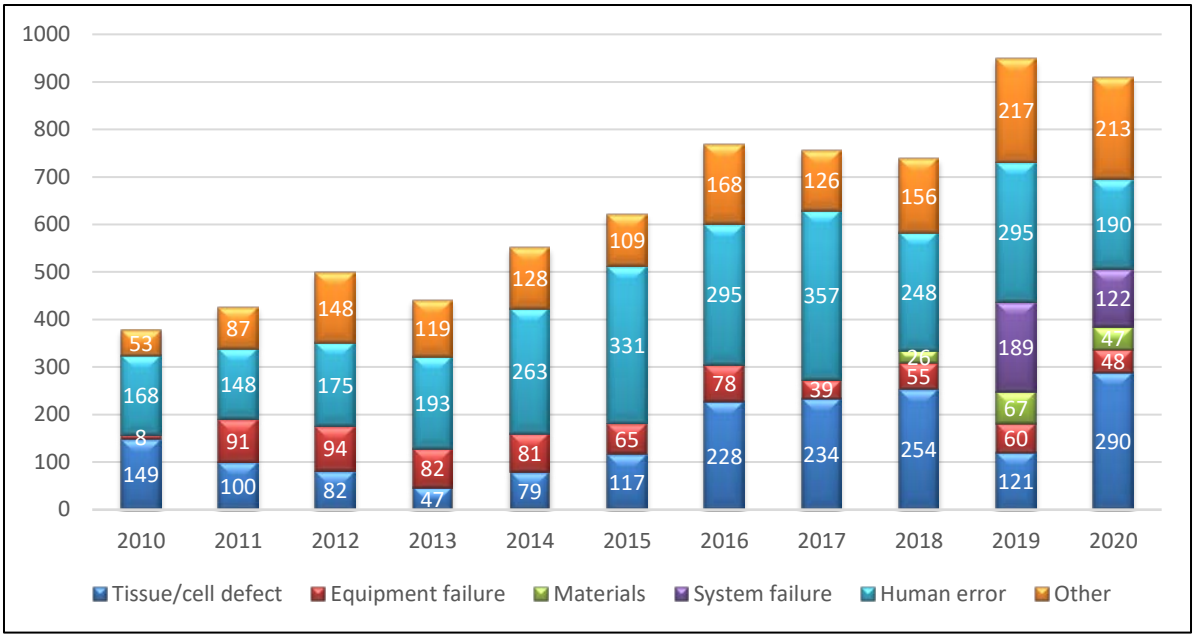

Figure 31. Number of SAE by type: 2010-2020 data.

The distribution by type for non-reproductive and reproductive tissues and cells is presented in *Figures 32 and 33* (respectively).

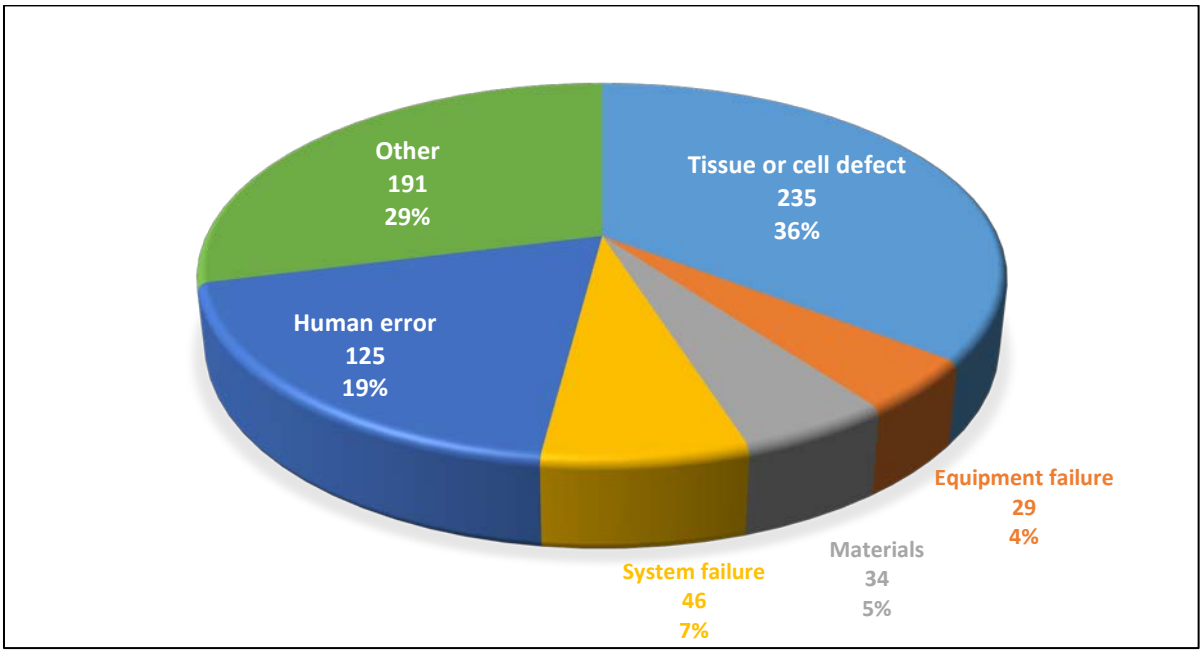

Figure 32. SAE types for non-reproductive tissues and cells (absolute values and percentages of total); 2020 data.

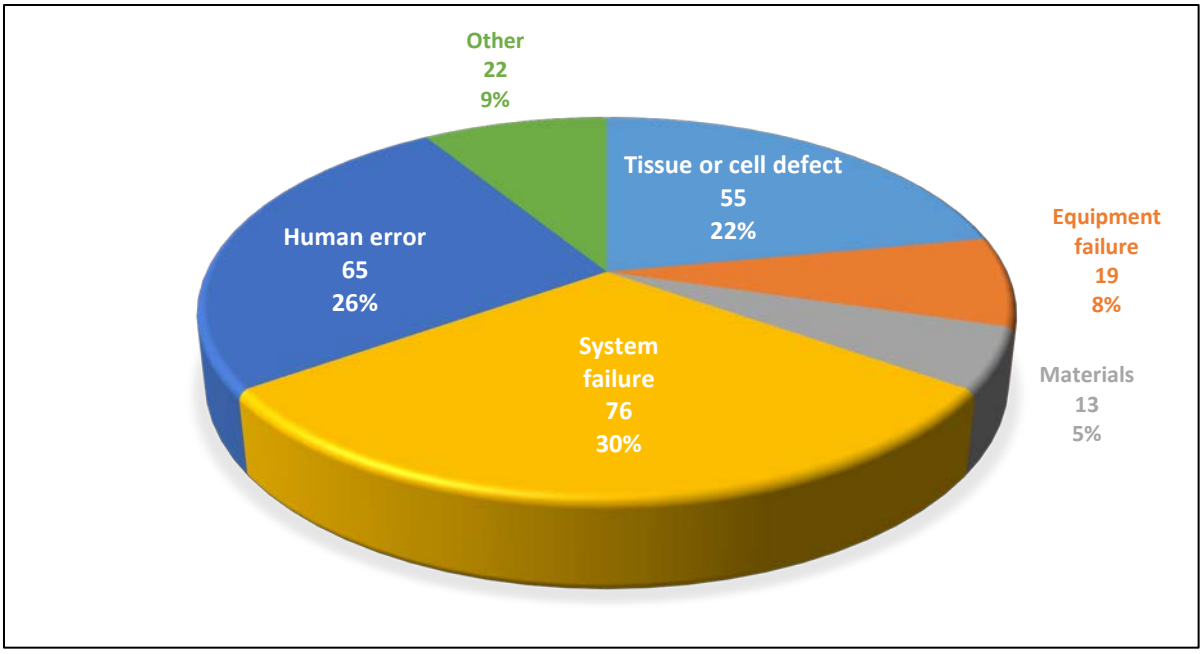

Figure 33. SAE types for reproductive tissues and cells (absolute values and percentages of total); 2020 data.

4.3.3. SAE by activity step

Following the harmonisation of practices, two new activity steps on "*product selection*" and "issue" were introduced in the reporting template for the year 2019. According to the Common Approach "product selection" refers to the selection of the appropriate tissues and cells for human application, on the basis of biological as well as clinical criteria, including administrative handling.

"Issue" refers to the activity step for 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 reported for different activity steps is presented in *Figures 34* and *35* (non-reproductive and reproductive tissues and cells, respectively).

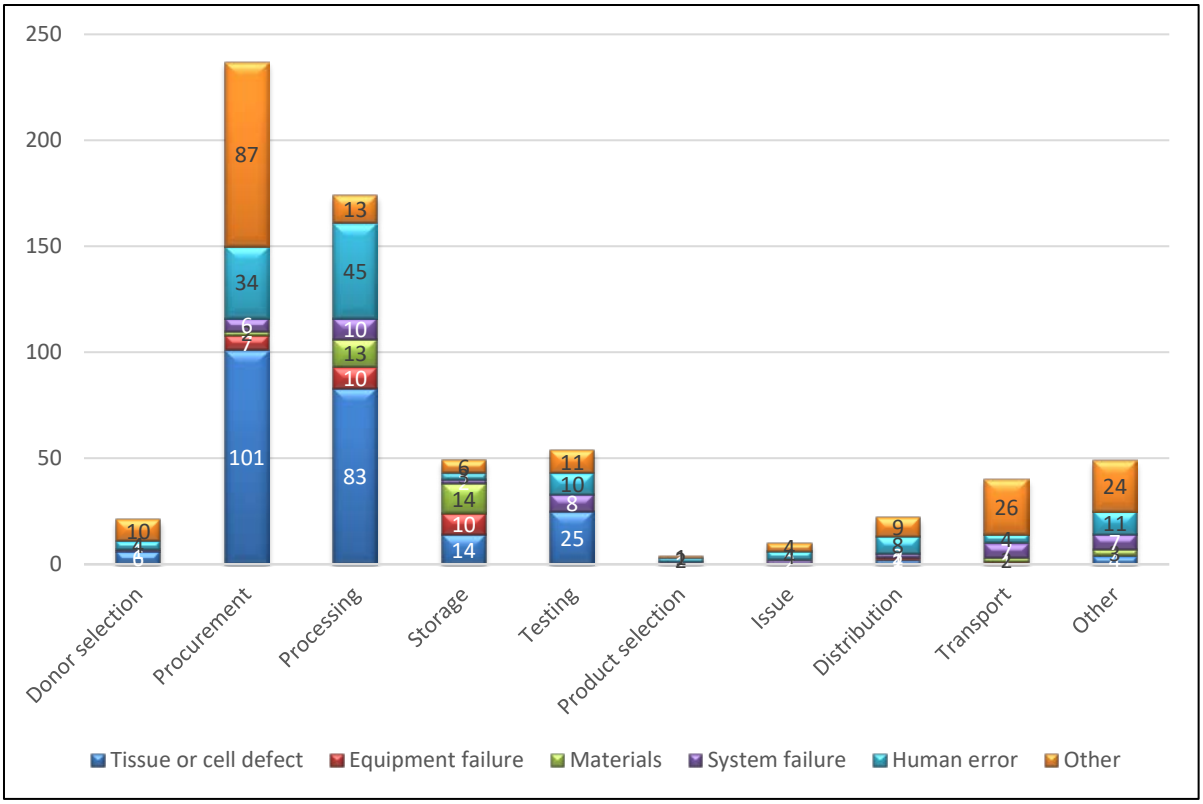

Figure 34. Number of SAE for non-reproductive tissues and cells, per activity step; 2020 data.

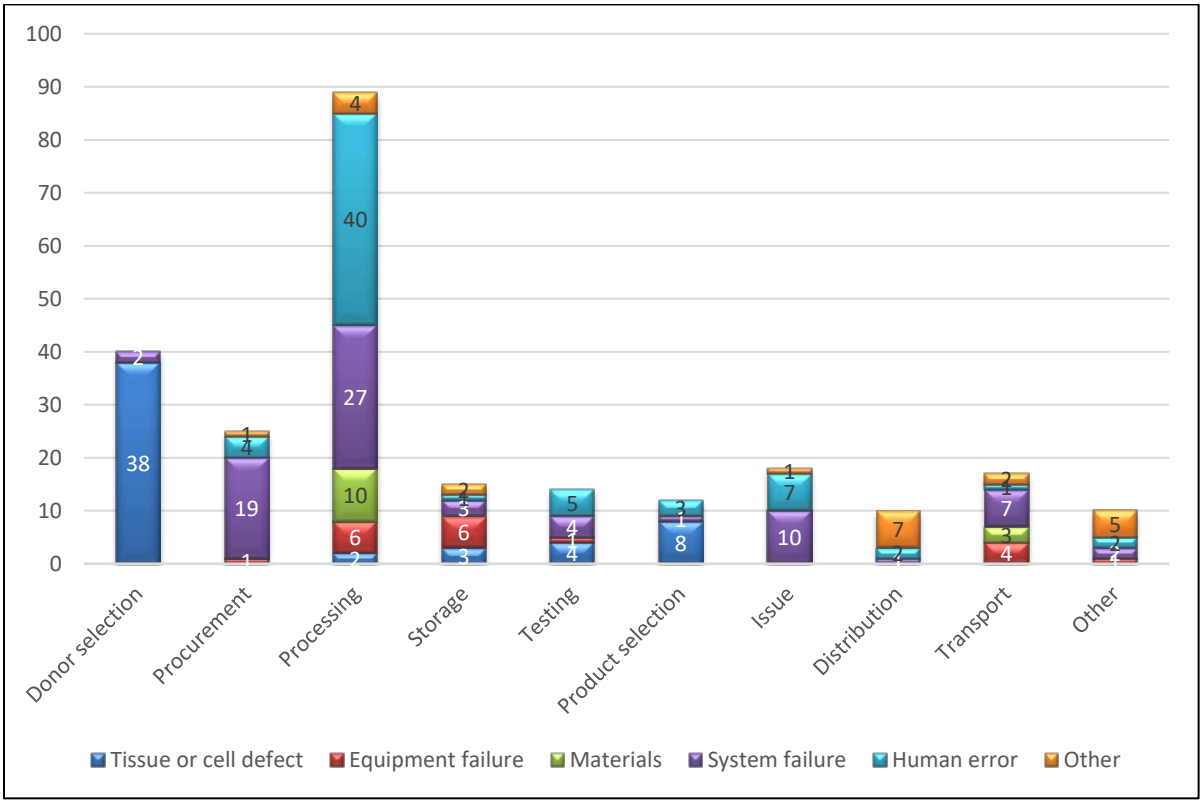

Figure 35. Number of SAE for reproductive tissues and cells, per activity step; 2020 data.

The distribution of SAE per activity step differs slightly for non-reproductive compared to reproductive tissues and cells. For the former, the category with the largest number of reported SAE was **procurement** (tissue or cell defect being the main origin), while for reproductive tissues and cells it was the **processing** step (human error being the main origin).

An overview of the SAE reported for non-reproductive and reproductive tissues and cells, by type of activity step, is presented in *Figures 36* and *37*.

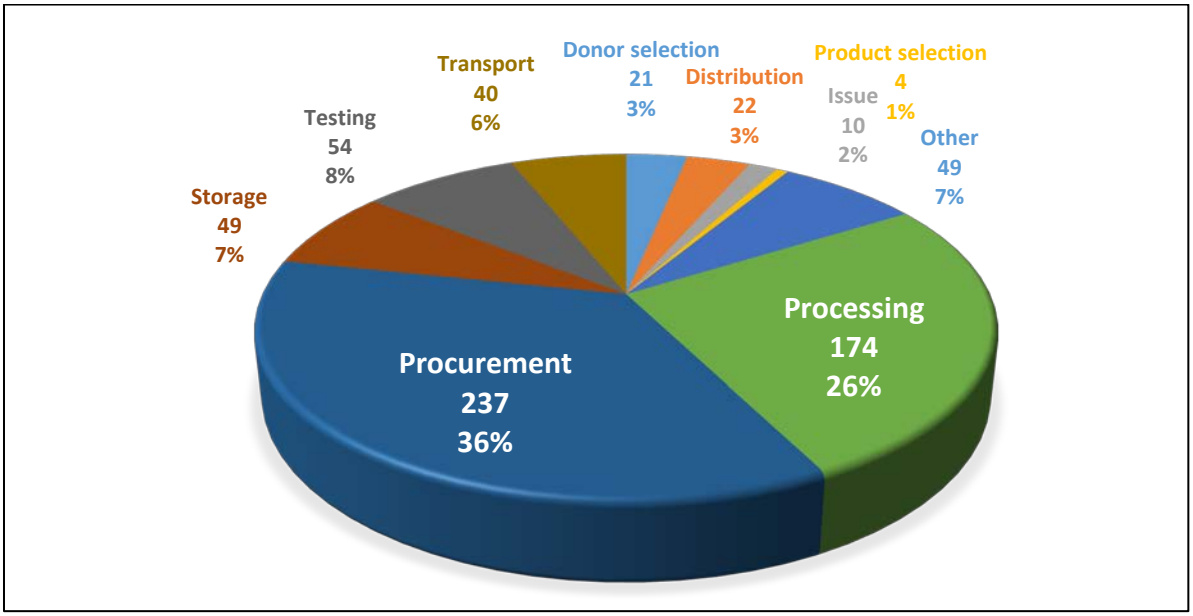

Figure 36. Number of SAE and percentage of total SAE reported for non-reproductive tissues and cells by type of activity (absolute values and percentages of total); data 2020.

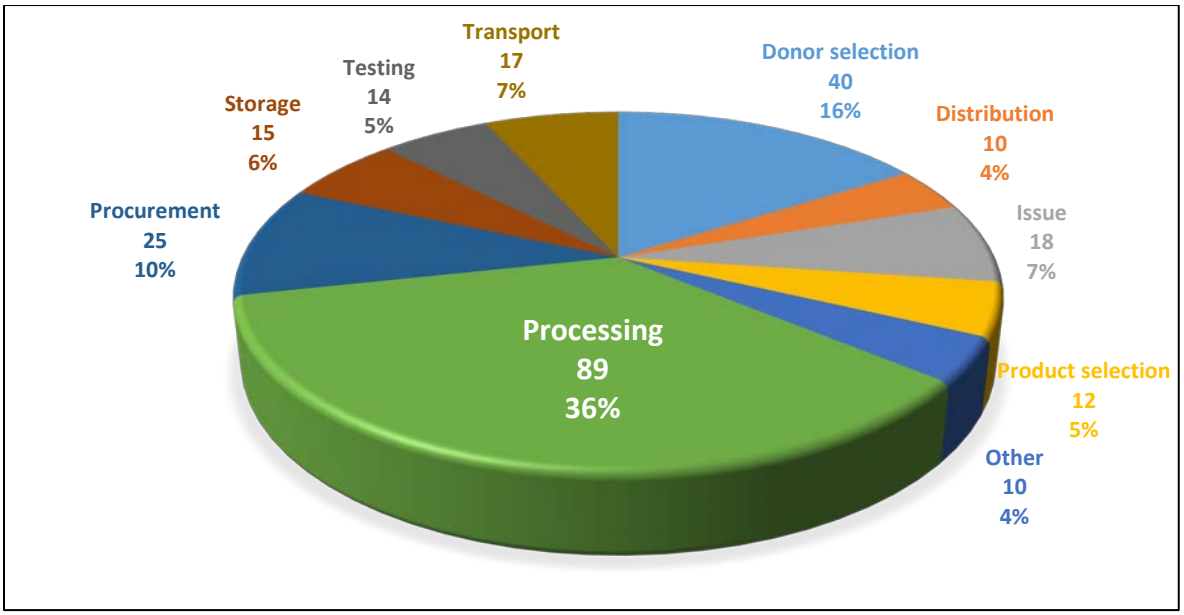

Figure 37. Number of SAE and percentage of total SAE reported for reproductive tissues and cells by type of activity (absolute values and percentages of total); data 2020.

4.4. 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 Hyperstimulation 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.

Nineteen countries (AT, BE, HR, CZ, EE, FI, FR, DE, GR, IE, IT, LU, NL, PL, PT, SI, ES, SE and UK) reported a total of 846 *SAR in donors* in 2020. A general overview of SAR in donors during the period 2012-2021 (data pertaining to 2011-2020) is presented in *Figure 38*.

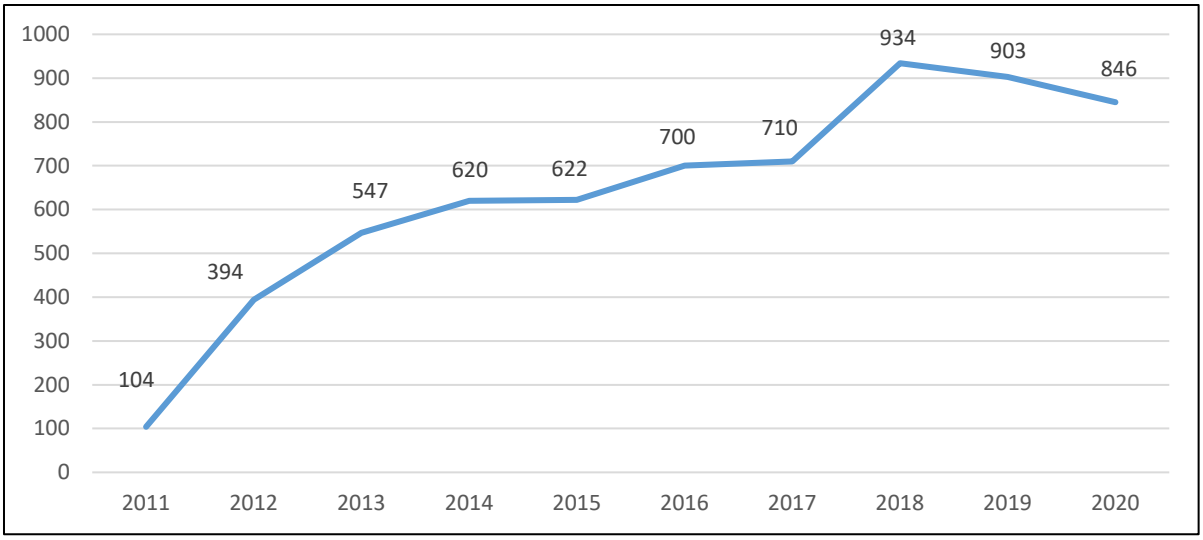

Figure 38. Number of SAR in donors; 2011-2020 comparative data.

In this exercise, SAR in donors could be reported separately for non-reproductive and reproductive tissues. The overall sub-classification of the 846 SAR in donors reported in 2020 is shown in *Figure 39*.

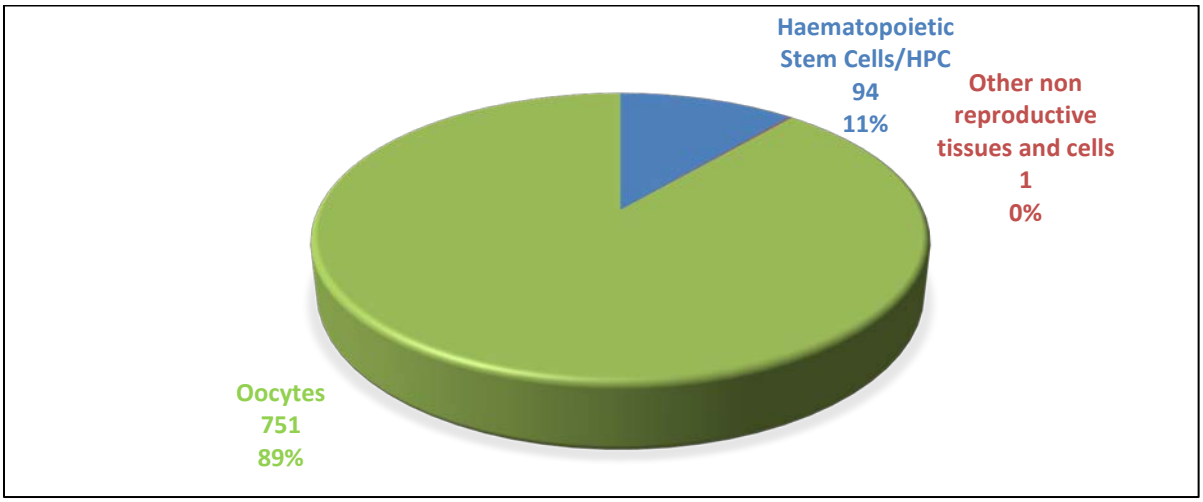

Figure 39. Number of SAR in donors per type of donated tissue or cells (units); 2020 data.

The SAR in donors are divided as follows:

- 95 cases were related to the donation of non-reproductive tissues or cells (11.2% of all SAR in donors) and were reported by 10 countries (AT, FI, FR, DE, GR, IE, IT, PL, SI and ES); see *Figure 40* for more details.

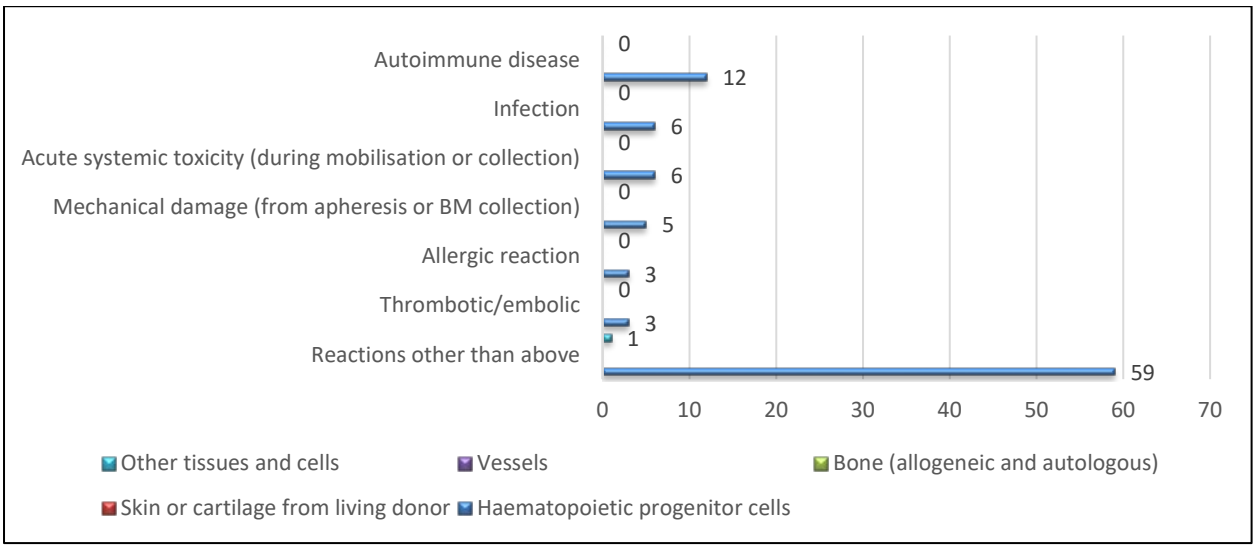

Figure 40. Number of SAR in donors of non-reproductive tissue; 2020 data.

- 751 cases (amounting to 88.8% of all SAR in donors) were related to the donation of reproductive tissues or cells, all of them following donation of oocytes. These were reported by 17 countries (AT, BE, HR, CZ, EE, FR, DE, IE, IT, LU, NL, PL, PT, SI, ES, SE and UK). Most of the SAR in oocyte donors were OHSS (471 cases) and surgical complications (159 cases); the remaining cases included infectious complications, torsion of ovary, reaction to anaesthetic and other types of SAR, as shown in *Figure 41*.

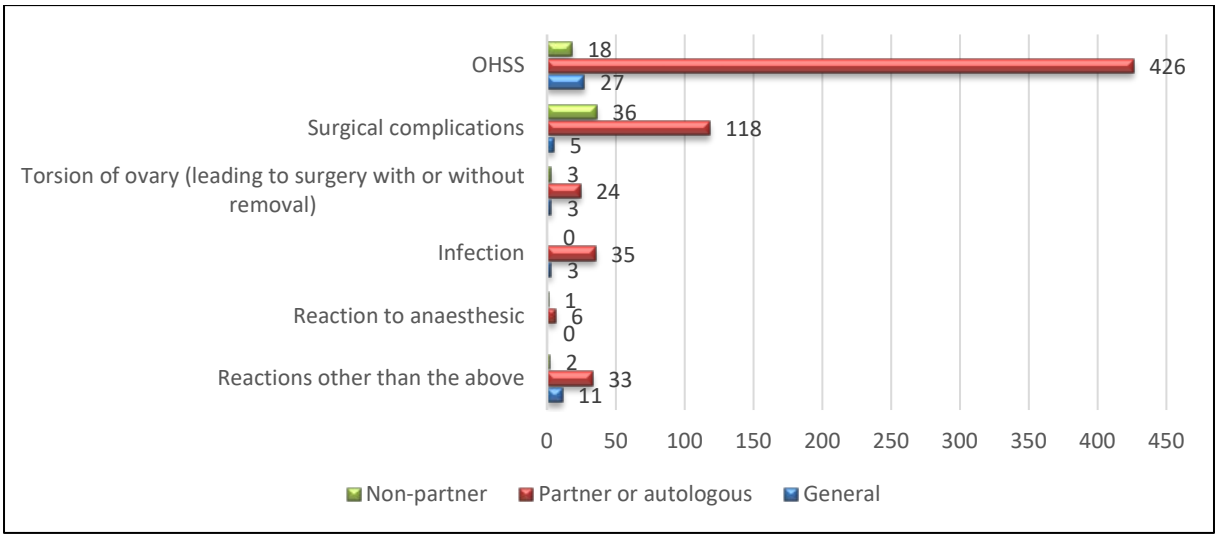

Figure 41. SAR in donors of reproductive tissues (units); data 2020.

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

frequently reported, followed by autoimmune disease. In the case of reproductive tissues or cells, the SAR in donors were frequently reported in the same categories (OHSS, followed by surgical complications).

~~4.4.1. Deaths associated with donation of tissues/cells~~

It should be noted that 2 deaths associated with cell collection/donation were reported in 2020:

- **1 death** related to allergic reaction during **autologous collection of HPC** (anaphylactic shock after Mozobil injection, no previous history of allergy).
- **1 death** related to reaction to anaesthetics during **oocyte retrieval** (bacterially contaminated anaesthetic)

5. CONCLUSIONS

5.1. SARE Trends in 2020

In 2020, there was a 14% increase in reported SAR compared to 2019. In general, over the years there has been an increasing trend of SAR reported for reproductive tissues and cells while the numbers of SAR reported for non-reproductive tissues and cells remain stable.

The most reported type of SAR, in terms of **non-reproductive** tissues and cells, were classified as "**other SAR**" which includes a wide range of different reactions (from delayed/failed graft function to non-specific symptoms associated with haematopoietic stem cell infusion). This implies that the current SAR classification should be further extended to enable more specific SAR data analysis and interpretation.

The pattern for **reproductive** cells has remained unchanged compared to the previous exercises, so the most frequently reported SAR related to reproductive cells was the **transmission of genetic diseases**, as in previous years. It should be noted that the likelihood of transmitting multi-factorial genetic diseases from donor to offspring is sometimes difficult to assess, and these data should be evaluated with caution.

Unlike in the previous exercise where no deaths of recipients of tissues or cells were reported, in 2020 there were **14 deaths** reported as potentially attributable to the clinical application of cells (tissues).

In terms of **SAE,** in 2020 the most commonly reported were tissue or cell **defects**, followed by "human error" and "system failures". Specified by type of tissue/cells, human error was most frequently reported in non-reproductive tissues and cells, while SAE related to tissue or cell defects were most frequently reported for reproductive tissues and cells.

As expected, regarding steps in the tissue and cell preparation process, "defects of non-reproductive tissues or cells" could most often be attributed to the **procurement** step, while the most commonly reported SAE for reproductive tissues and cells were attributed to **processing**, and **donor selection**.

These results suggest not only the importance of revising standard operating procedures and risk assessment 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.

Ultimately, these results highlight the importance of the quality management system in preventing errors and maintaining a consistent standard of agreed specification for tissues and cells for clinical application. Residual risks or procedural errors may occasionally 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 management.

Therefore, in addition to the internal quality management system, any major incidence of non-compliance considered an SAE should be reported through a national Competent Authority to the European surveillance system, especially in light of international tissue and cell exchange and import/export activities.

5.2. Donor safety

Data on donor SAR are submitted on a voluntary basis by an increasing number of countries. This indicates that the majority of Competent Authorities support the existence of appropriate mechanisms for monitoring donor protection and reporting on donor SAR. As in previous years, the majority (88.8%) of all reported SAR in donors in 2020 were related to the donation of reproductive tissues and cells, all of them following **donation of oocytes**. The most frequent SAR in oocyte donors were OHSS and surgical complications, while the remaining cases included infectious complications, torsion of ovary, reaction to anaesthetic and other types of SAR.

Two deaths were reported (1 related to the autologous collection of HPC and the other related to the retrieval of oocytes).

5.3. Strengthening biovigilance capacities

Reporting of these cases provides important learning opportunities that can help all procurement organisations, tissue establishments, cell therapy and MAR facilities and clinical users to improve their processes and to achieve higher standards of safety and quality at all levels for donors and recipients, in Europe and beyond.

In recent years, the SARE exercise and national vigilance data submission have significantly improved in terms of data completeness and accuracy.

However, the lack of a complete and fully harmonised set of data from all participating countries prevents the correct analysis and comparison of data, which makes it difficult to draw reliable conclusions about general/European or national trends with regard to the level of risk and the safety of the application of tissues and cells, and ultimately the development of more effective protection strategies for donors and recipients.

This implies that additional concerted efforts are needed to further strengthen national vigilance systems and encourage the implementation of a fully harmonised reporting dataset at European level to enable a more sophisticated insight into trends and risks associated with tissue and cell treatments.

Under the umbrella of grant agreements with the Commission (grant agreements 2014 54 01 and 2018 53 01), the EDQM has provided a series of biovigilance-related activities to assist Member States with

data collection and reporting. One of the major findings of a set of recommendations was that realistic assessment of the tissue and cell supply and patients' needs is paramount for governments to ensure an optimal distribution of tissues and cells. Such an assessment requires an overview of accurate and valid national data. To this end, three different minimum datasets (relating to the three main categories of tissues and cells: tissue replacement, HPC and MAR) were identified by experts to serve as denominators for the EU SARE exercise. Consensus was achieved on the minimum data set, in terms of data parameters, standard units and expected quality of collected data, as well as the responsibilities and roles of stakeholders for data management. It laid solid foundations for a more harmonised European approach to data collection, which is a basic prerequisite for the statistical processing of the data, as well as assessment and understanding of dynamics, trends, incidence, type and level of security risk for the recipients and providers of tissues and cells.

This would ultimately enable the practical application of the collected data by identifying more effective strategies to prevent and reduce the perceived risks to recipients and donors of tissues and cells.

General conclusions extracted from this report should be interpreted with caution.