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 2022 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS FOR TISSUES AND CELLS

(DATA COLLECTED FROM 01/01/2021 TO 31/12/2021 AND SUBMITTED TO THE EUROPEAN COMMISSION IN 2022)

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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. Therefore, vigilance and surveillance systems are critical for ensuring adequate quality and safety of tissues and cells donated for human application. Such systems should allow the timely detection of any potential adverse incidents that can pose a risk to the quality and safety of tissues and cells, as well as the investigation of root cause(s) and implementation of effective corrective and preventive measures, making them an indispensable element of any quality system.

In line with the obligations defined in the legislation,[1] EU member states (MS) submit an annual report to the European Commission (hereinafter referred to as "the Commission") on Serious Adverse Reactions (SAR) and Serious Adverse Events (SAE) – collectively referred to as SARE – from the previous year, compiled at national level by each National Competent Authority (NCA).

The consistency and completeness of the data submitted by MS have gradually improved over the years in parallel with the development of national vigilance systems supported by the Vigilance Expert Subgroup (VES). In addition, tissues and cells have been categorised into three groups (replacement, haematopoietic stem cells (HSC) and reproductive) with the aim of improving reporting and in line with the recommendations of the EU co-funded project *Harmonising Activity Data Collection Exercises in the Field of Tissues and Cells in Europe*, 2018.[2]

This report is the result of the joint efforts of and collaboration between healthcare professionals, NCAs, the VES, the EDQM and the Commission. It summarises SARE data for 2021 submitted by **26 MS** plus Iceland, Liechtenstein, Norway and the United Kingdom (Northern Ireland). The report highlights the main findings, conclusions and trends in the use of tissues and cells in humans across Europe in terms of SARE occurrence and distribution (by category and type).

2 EXECUTIVE SUMMARY

The key findings of the 2021 reporting exercise are listed below:

- More than **3 million units of tissues and cells were processed** by 25 countries (3 159 362), of which **373 486** were **replacement tissues and cells** (reported by 22 countries), **57 941** were **HSC** (reported by 18 countries) and **2 727 935** were **reproductive tissues and cells** (reported by 18 countries). This is a 19.39% percent increase compared to 2020.

- More than **1 million units of tissues and cells were distributed**[3] (1 192 203) for application, representing a 6.7% increase compared to 2020, of which **761 919** were **reproductive tissues and cells** (reported by 21 countries), **391 687**[3] were **replacement tissues and cells** (reported by 27 countries) and **38 597** were **HSC** (reported by 21 countries).

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

[2] https://www.edqm.eu/documents/52006/162284/tissues-and-cells-conclusions-and-recommendations-harmonising-activity- data-collection-exercises.pdf/b53fa49e-180e-c4ec-daaf-648f087da606?t=1629883980927

[3] Note that the total number of tissues and cells distributed and the total number of replacement tissues and cells distributed include 46 327 units of replacement tissues and cells, mainly bone and skin (reported by the Netherlands) that are not in the scope of SARE exercises (distributed internationally). Those data give a wrong reflection of the situation and is therefore deleted OR should not be taken into account. It was not possible to correct this error in time for the analysis performed for this report.

- **318 467 recipients** underwent transplant/infusion, which represents a 30% increase compared to 2020.

- Nineteen countries reported a total of **326 SAR in recipients**, of which 55% were related to reproductive tissues and cells, 27% to HSC and 18% to replacement tissues and cells:
    - 70% of the SAR associated with **reproductive tissues and cells** were due to the **transmission of genetic conditions**
    - 40% of the 87 SAR associated with **HSC** resulted in **graft failure or delayed function** and 19% were classified as **immunological reactions**
    - 81% of the SAR associated with **replacement tissues and cells** were **unclassified** (Other), while **transmitted infections** accounted for 19%

- An **imputability level was not assigned for 65%** of the reported SAR in 2021. In most cases, conclusive evidence for attributing the adverse reactions to the quality/safety of tissues and cells was not available and, as a result, imputability level 1 was assigned. This was also the case for several fatalities following infusion of HSC; the clinical condition of patients was assessed as playing the predominant role in the outcome.

- In 2021, **20 deaths** of recipients were reported (significantly more than the 14 reported in 2020), of which 16 were potentially attributed to HSC and four to reproductive tissues and cells.

- A total of **694 SAE** were reported in 2021 (compared to 910 in 2020). This decrease is due to the UK, a significant contributor throughout the years, no longer participating in SARE reporting as a whole in 2021 subsequent to its withdrawal from the EU. As a result, Northern Ireland was the only part of the UK to contribute to the exercise. Out of the 694 SAE, 170 were related to replacement tissues and cells (reported by 11 countries), 291 to HSC (18 countries) and 233 to reproductive tissues and cells (16 countries).
    - In terms of the type of SAE, **tissues or cells defect** was the most commonly reported event (40%), followed by **system failure** (21%) and **human error** (17%); the number of events attributable to **human error** or **Other** events reported was lower than in 2020. **Tissues or cells defect** was the most frequent type of SAE associated with replacement tissues and cells and HSC, while **human error** was the most frequent type of SAE associated with reproductive tissues and cells.
    - In terms of **activity steps**, SAEs for replacement tissues and cells most frequently occurred or were identified during **Other** activity steps, followed by **testing** and **processing**; events that involved HSC occurred or were identified during **procurement, processing** and **testing**, while the most reported SAE for reproductive tissues and cells were attributed to **processing** and **donor selection**, similar to the previous year.

- **795 SAR in donors** were reported on a voluntary basis by 17 countries, the vast majority (90%) of which related to the donation of reproductive tissues and cells, all following **donation of oocytes**. The most frequent types of SAR in oocyte donors were ovarian hyperstimulation syndrome (OHSS) and surgical complications, while the remaining cases included transmitted infections, ovarian torsion, and other. No instances of death in living donors of tissues and cells were reported.

3 DATA COLLECTION AND ANALYSIS

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

- ***A new electronic reporting form (online form, 2022 version)***
  It should be noted that this new form categorises tissues and cells into three groups (replacement, HSC and reproductive), as opposed to just two in the past. The online form is stored in the DG SANTE Data Collection Platform, with access to authorised users only.
- ***The Common Approach document (2022 version)***, which complements the electronic reporting form and provides updated user instructions for data compilation.

The VES subgroup for SARE reporting improvement provided technical assistance with reporting for the 2022 SARE exercise and helped the Commission to test the online forms. Overall, the 2022 SARE exercise ran smoothly with only minor issues to be considered for the 2023 exercise.

For the purpose of this year's report, data analysis was performed for the three categories of tissues and cells as set out in the new online form and the report structure was updated accordingly.

Both the reporting countries and the Commission verified the accuracy of the EDQM's analysis and interpretation of SARE data for 2021.

4 MAJOR FINDINGS

4.1 Activity data (denominators)

As part of the EU SARE exercise, MS are requested to provide data on not only SAR and SAE, but also national tissue and cell activity. Although not legally binding, having access to data on the **number of tissues distributed**, the **number of recipients** and the **number of tissues processed** at national level helps to provide a better overview and understanding of the different activities within MS, with the data also being used to give context to the SARE data.

In this exercise, as stated in the *Common Approach*, the **number of tissues and cells distributed** and the **number of recipients** were used as denominators in the analysis of the SAR, while the **number of tissues processed** was used as a denominator in the analysis of the SAE.

As in previous exercises, some countries had difficulty collecting complete and accurate activity data for certain types of tissues and cells or certain activities, while 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 numbers of cycles). Hence, SAR denominators might not be complete, and caution should be used when interpreting them and deriving conclusions from this exercise.

4.1.1 Tissues and cells distributed

The total number of **tissues and cells distributed** in 2021 as submitted by the reporting countries was 1 192 203 units[4], comprising 391 687[4] units of replacement tissues and cells, 38 597 units of HSC and 761 919 units of reproductive tissues and cells.

[4] Note that the total number of tissues and cells distributed and the total number of replacement tissues and cells distributed include 46 327 units of replacement tissues and cells, mainly bone and skin (reported by the Netherlands) that are not in the scope of SARE exercises (distributed internationally). Those data give a wrong reflection of the situation and is therefore deleted OR should not be taken into account. It was not possible to correct this error in time for the analysis performed for this report.

4.1.1.1 Replacement tissues and cells

In the case of replacement tissues and cells, 24 countries reported data on **units distributed** (AT, BE, BG, HR, CZ, DK, EE, FI, FR, DE, EL, HU, IE, IT, LT, LU, NL, NO, PL, PT, SI, ES, SE and UK). The main types of replacement tissues and cells distributed were skeletal tissues (311 673 units) and ocular tissues (30 858 units). See *Figure 1* for more details.

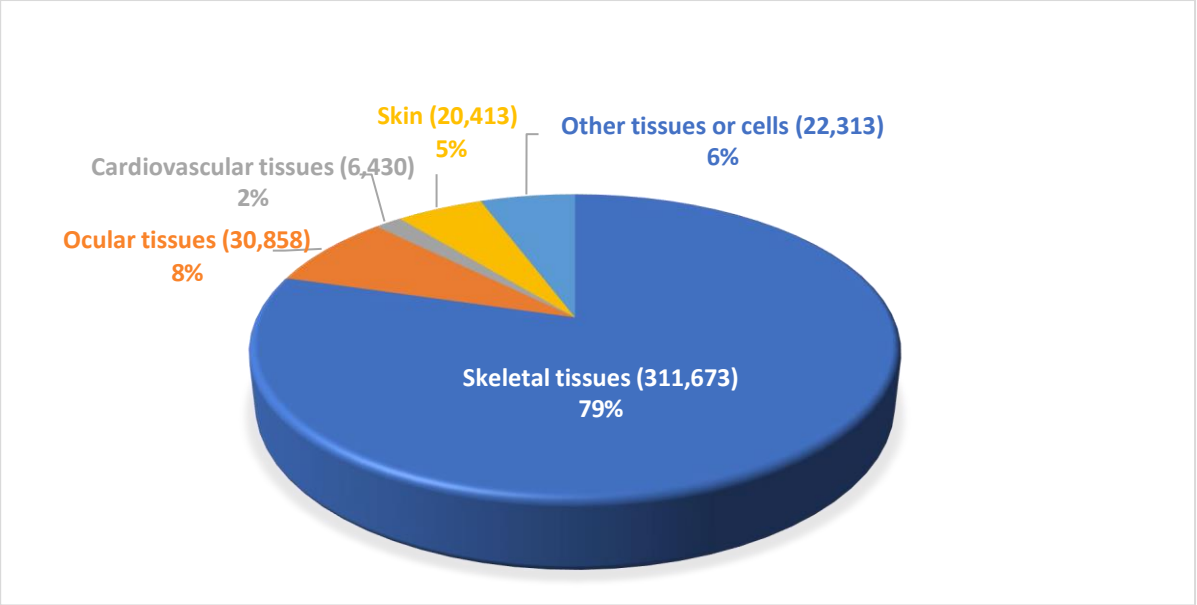

Figure 1. Total number of replacement tissues and cells distributed (units); data 2021

The sub-classification of the activity data by type of tissue for the main categories is shown in *Figure 2* for skeletal tissues, *Figure 3* for ocular tissues, *Figure 4* for cardiovascular tissues and *Figure 5 for* other replacement tissues. Bones, corneas and blood vessels were the most frequently distributed tissues in each respective category.

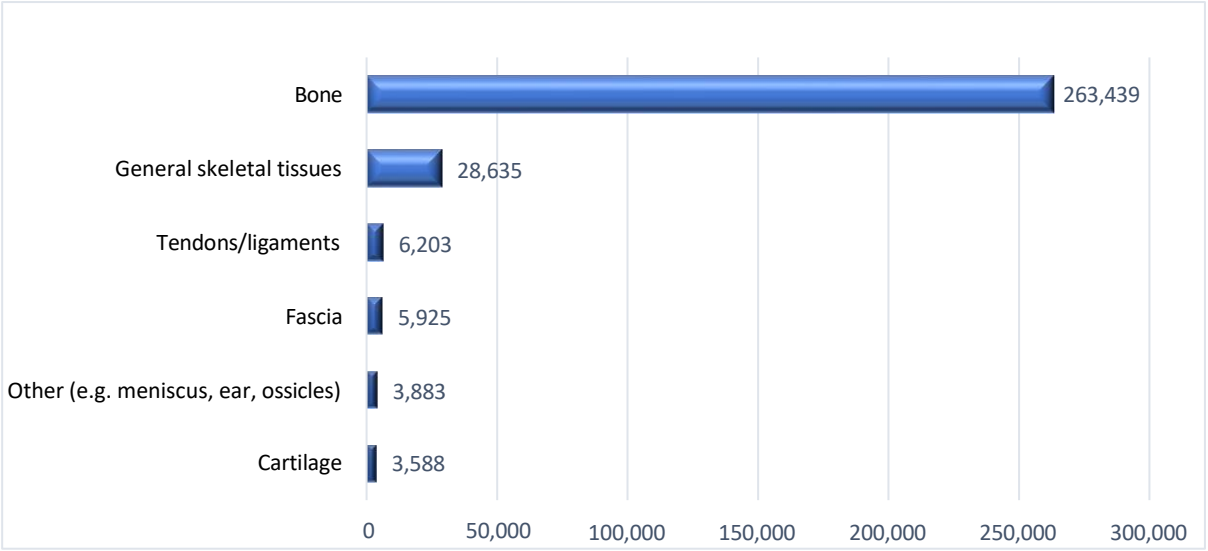

Figure 2. Number of skeletal tissues distributed per subcategory (units); [5] *data 2021*

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

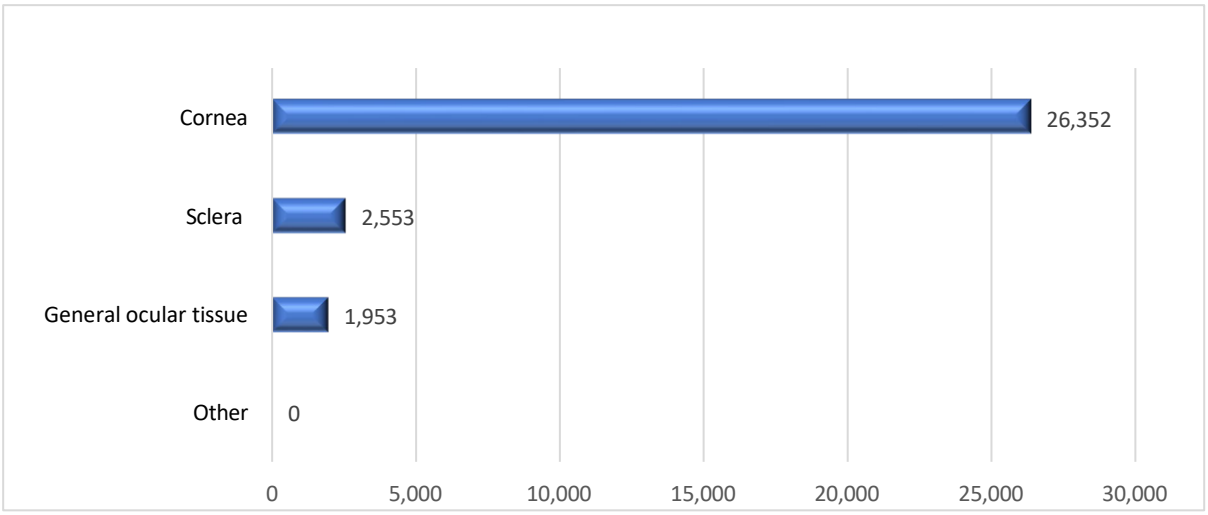

Figure 3. Number of ocular tissues distributed per subcategory (units); data 2021

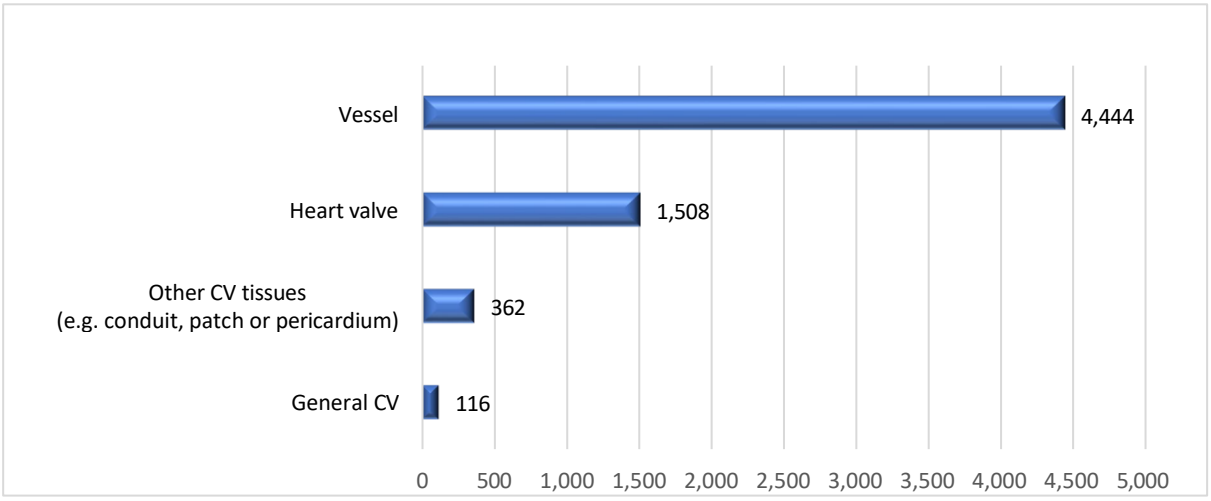

Figure 4. Number of cardiovascular tissues distributed per subcategory (units); data 2021

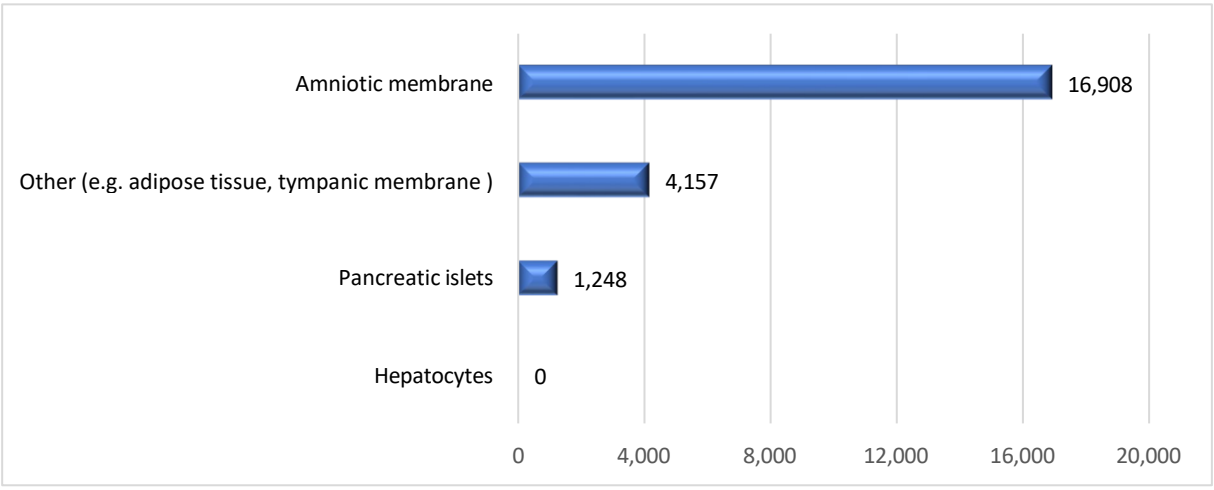

Figure 5: Other replacement tissues distributed per subcategory (units); data 2021

4.1.1.2 Haematopoietic stem cells

Seventeen countries reported data on distributed HSC (AT, BE, BG, DK, HR, CZ, EE, FI, EL, IE, IT, NL, PL, PT, RO, SI and SE). Out of 38 597 units HSC reported as distributed, the majority (27 374 units) were represented by peripheral blood stem cells (PBST), followed by general haematopoietic progenitor cells (HPC, 4 347 units) and cord blood (2 604 units). See *Figure 6* for more details.

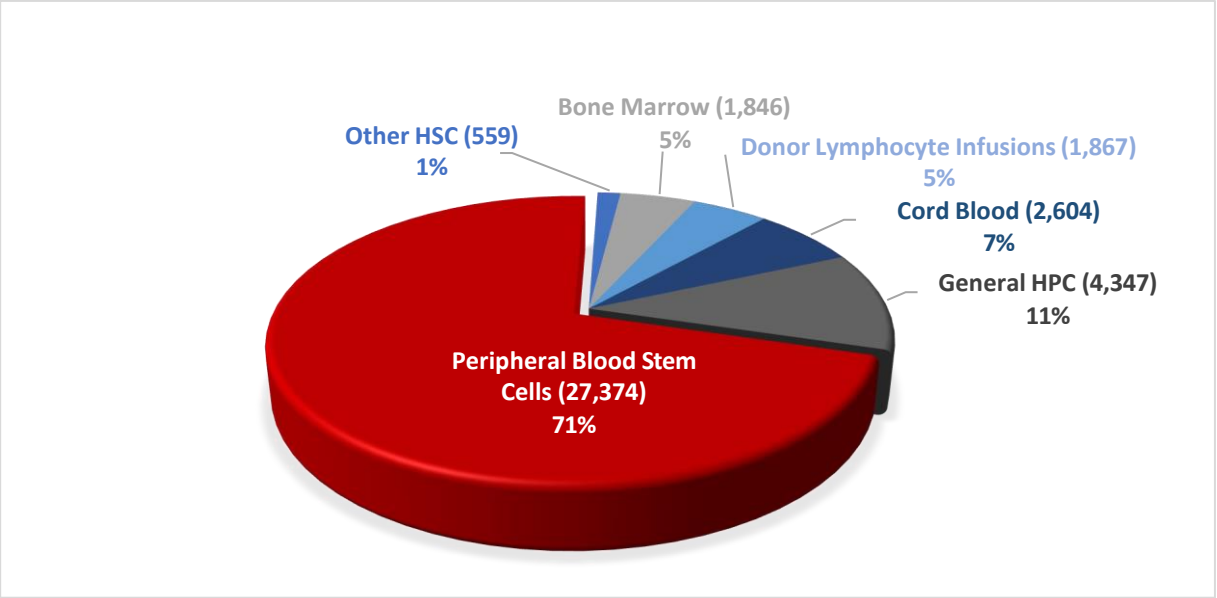

Figure 6. Total number of hematopoietic stem cell units distributed (absolute values and percentage); data 2021

Data on subcategories of HSC is presented in *Figures 7-11* below.

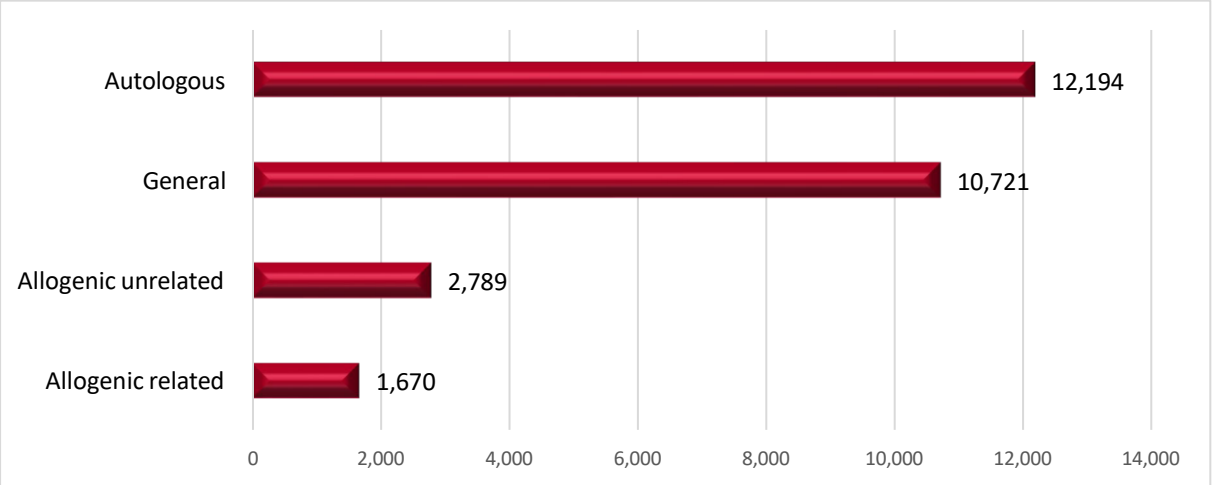

Figure 7. Number of peripheral stem cell units distributed by type; data 2021

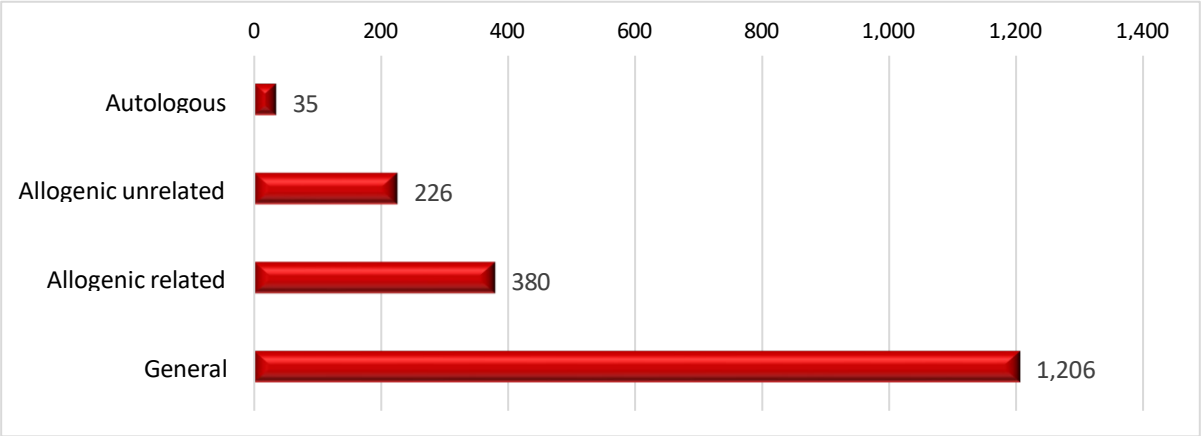

Figure 8. Number of bone marrow units distributed by type; data 2021

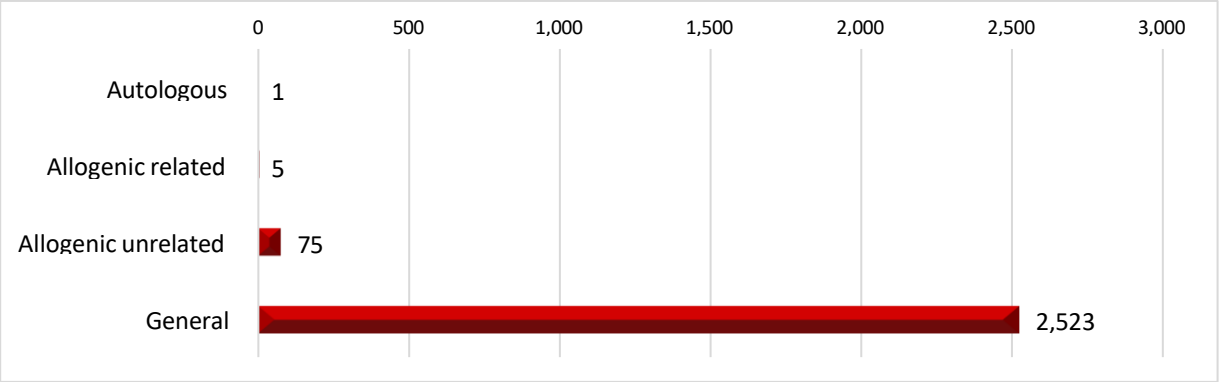

Figure 9. Number of cord blood units distributed by type; data 2021

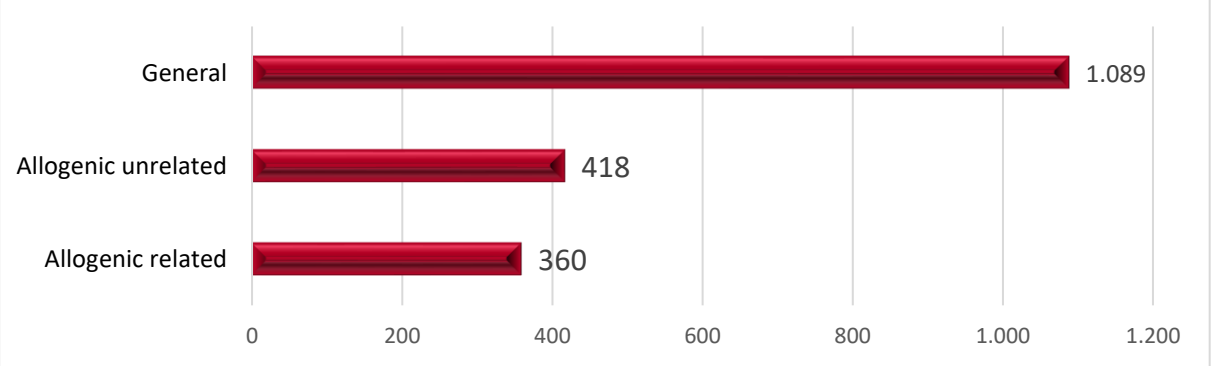

Figure 10. Number of donor lymphocyte infusion units distributed by type; data 2021

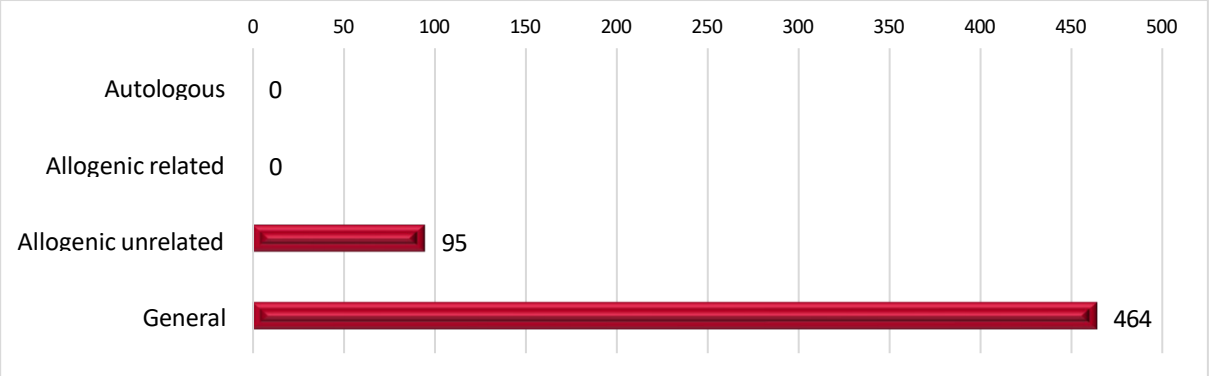

Figure 11. Number of other HSC unit distributed by type; data 2021

4.1.1.3 Reproductive tissues and cells

Twenty-one countries (AT, BE, BG, HR, CZ, DE, DK, FI, HU, IE, LI, LT, LU, LV, MT, NL, NO, PT, RO, SI and SE) reported activity data for reproductive tissues and cells.

Of the 761 919 units of reproductive tissues distributed, 234 661 sperm units were delivered for insemination (*Figure 12*) and 524 610 embryos were delivered for transfer following partner and non-partner donation (*Figure 13*). In addition, 183 ovarian tissues and 2 465 testicular tissues were distributed for the treatment of infertility (*Figure 14*).

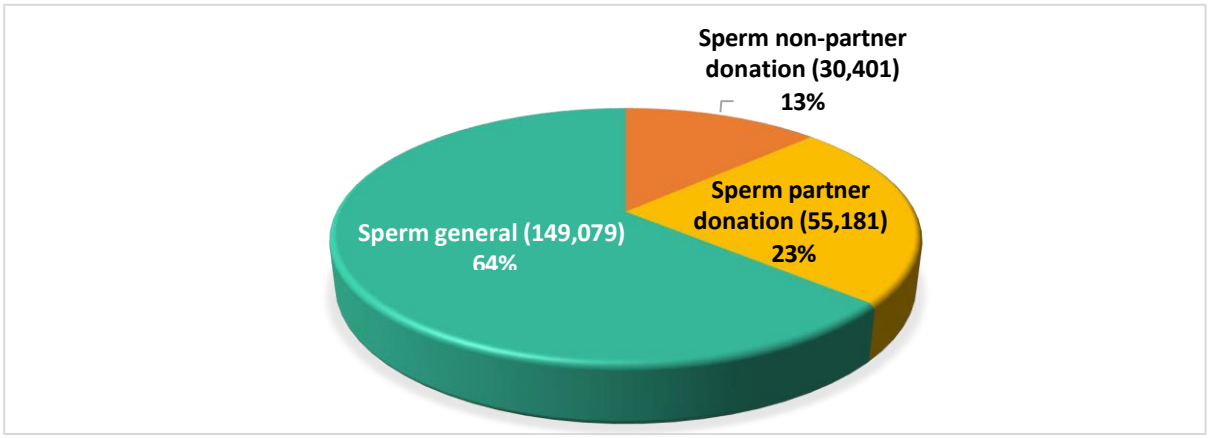

Figure 12. Number of sperm units distributed by category (absolute values and percentage); data 2021

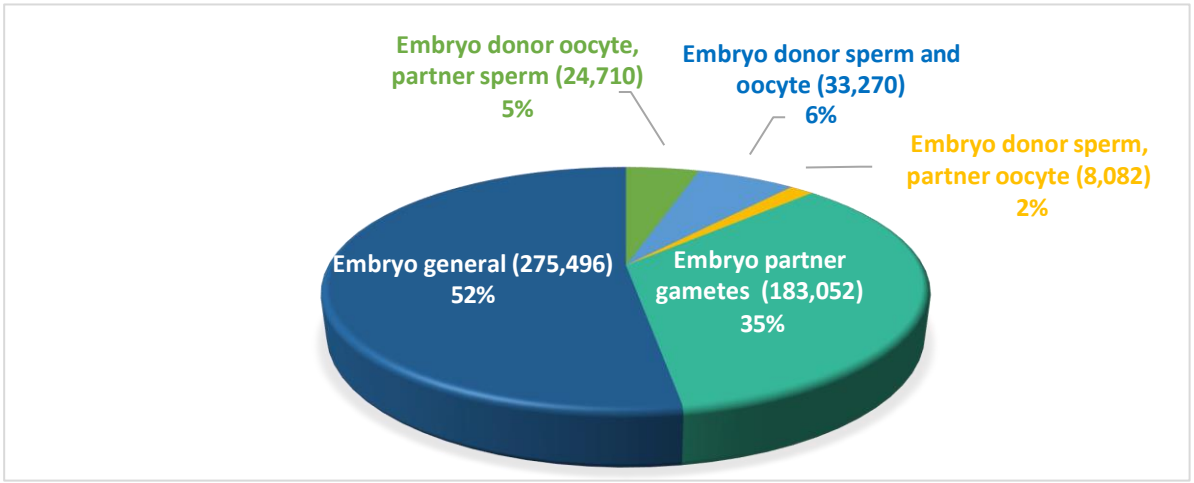

Figure 13. Number of embryos distributed by category (absolute values and percentage); data 2021

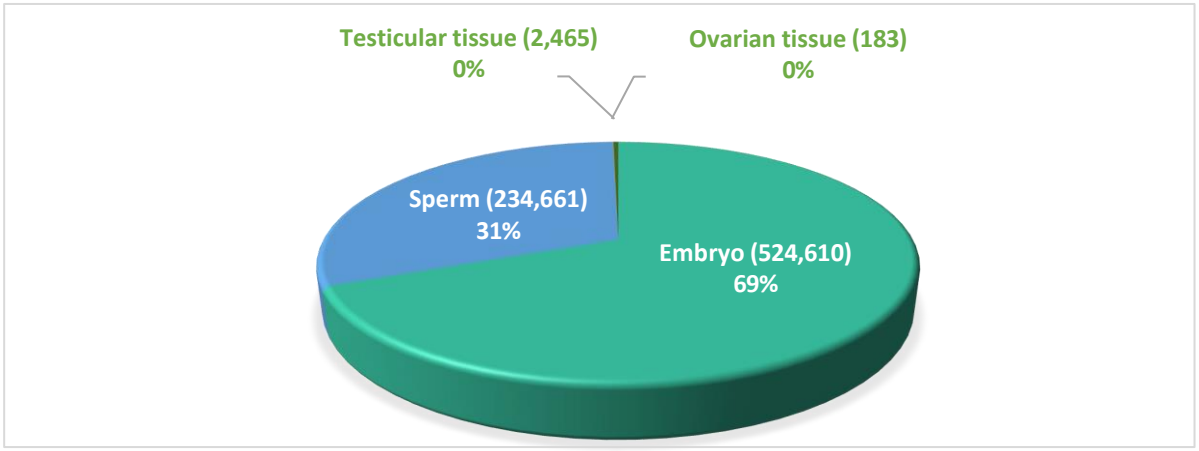

Figure 14. Total number of reproductive tissues distributed (units); data 2021

4.1.1.4 Incidence of replacement tissues and cells (per million population)

Taking into account the demographic data of the reporting countries on 1 January 2021,[6] the incidence of replacement tissues and cells, HSC and reproductive tissues and cells, presented comparatively by distributed units and number of recipients (per million population), is shown in *Figures 15*, *16* and *17*. It should be noted that incidence was calculated only for those countries that reported distribution data and/or number of recipients.

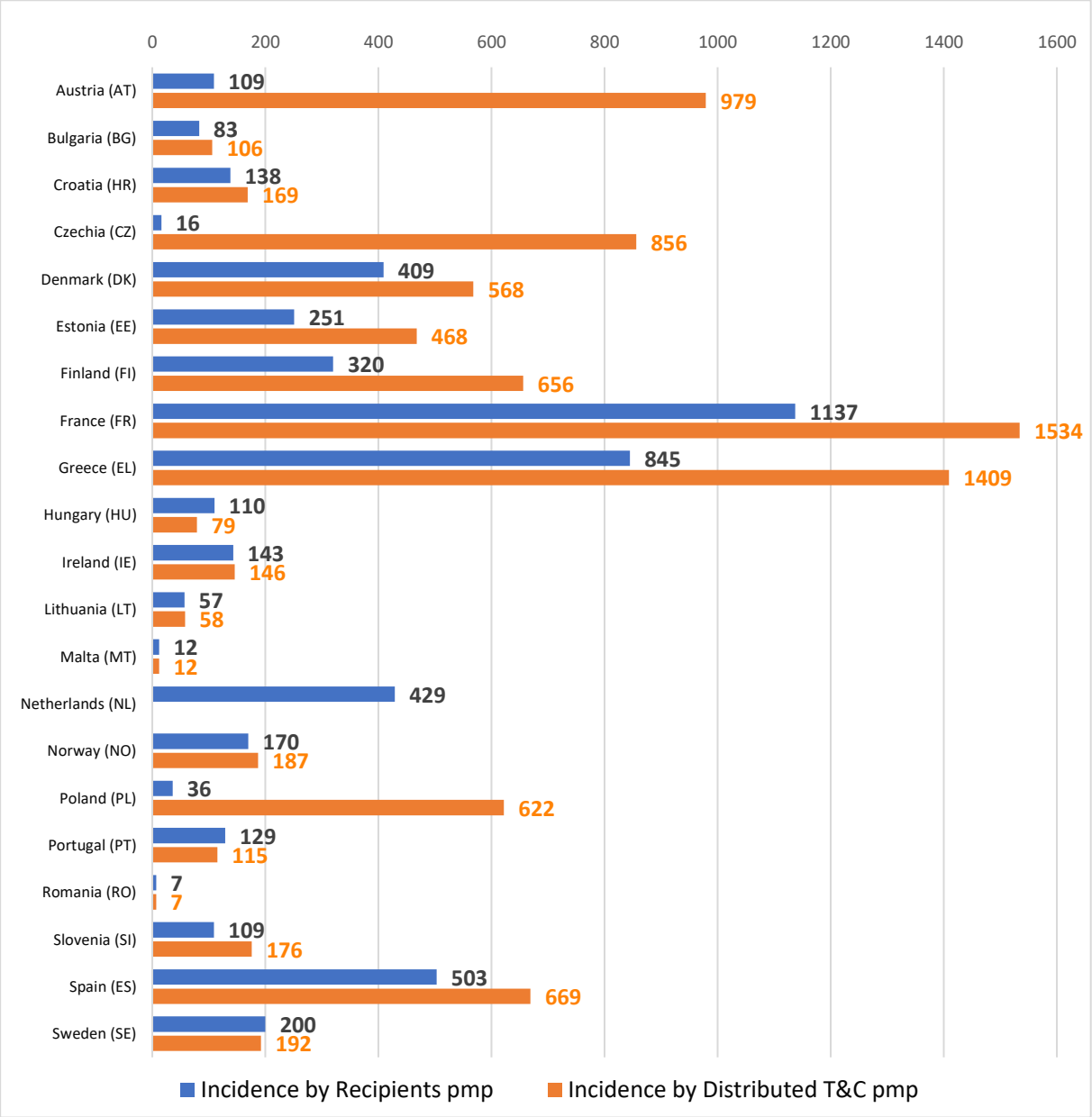

Figure 15. Incidence of replacement tissue and cell units (number of units distributed and number of recipients per million population); data 2021

* https://www.nisra.gov.uk/publications/census-2021-table-lookups

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

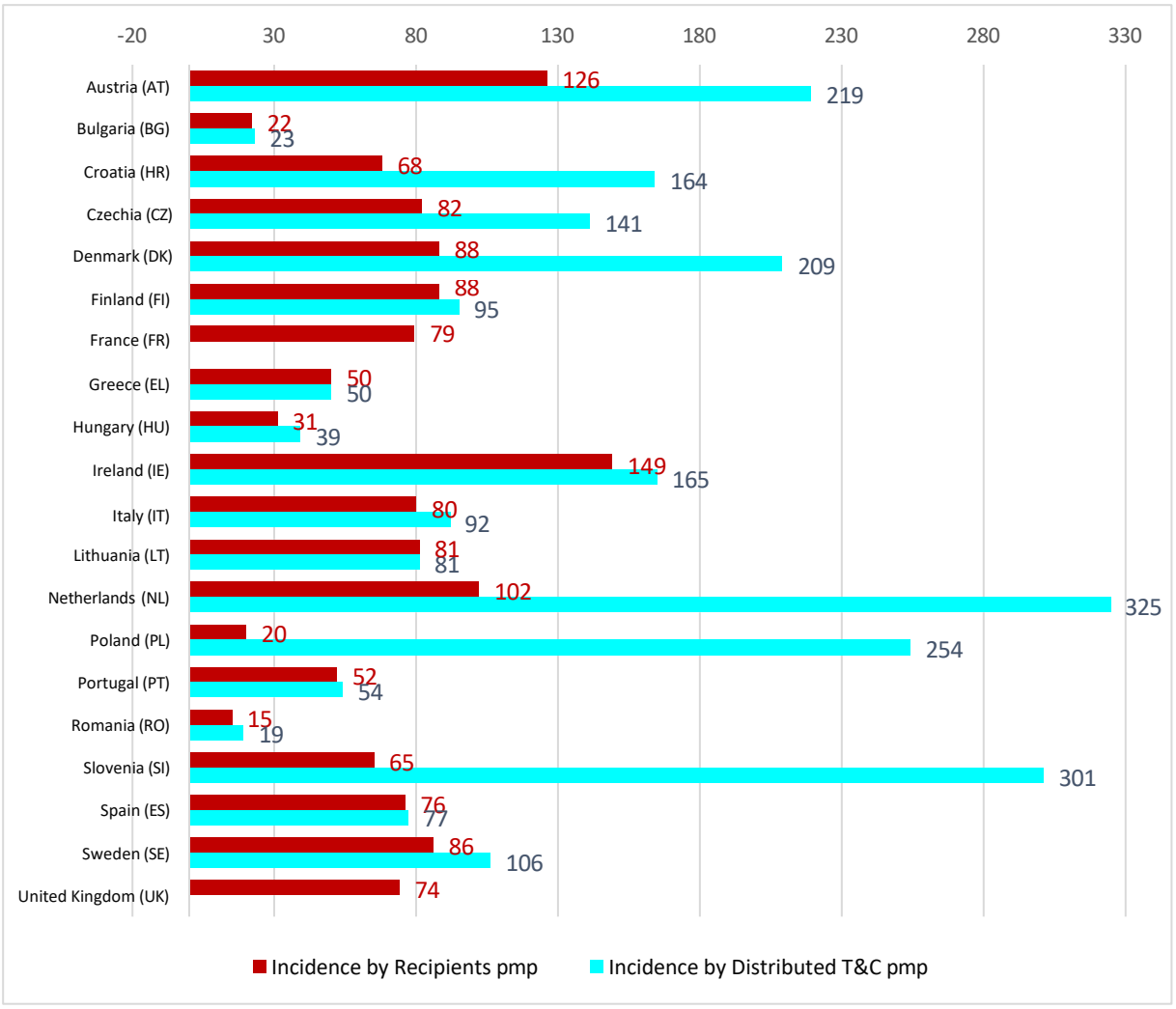

Figure 16. Incidence of haematopoietic stem cells (number of units distributed and number of recipients per million population); data 2021

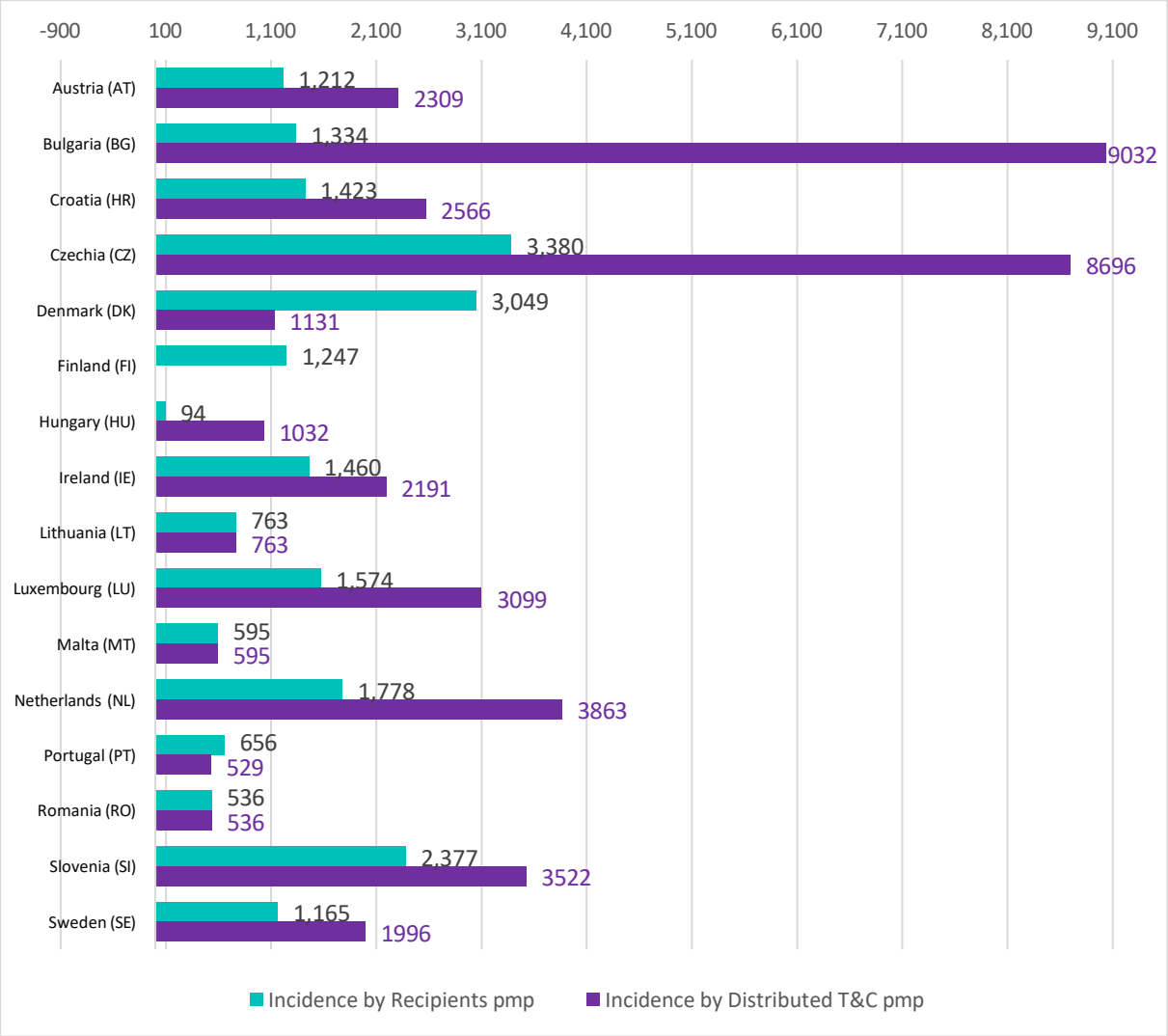

Figure 17. Incidence of reproductive cells (number of units distributed and number of recipients per million population); data 2021

4.1.2 Number of transplant recipients

In 2021, 24 countries reported a total of **318 467 recipients** having undergone a transplant of tissues or cells (132 176 recipients of replacement tissue and cells, 23 423 recipients of HSC and 162 868 recipients were subjected to a MAR procedure).

4.1.2.1 Non-reproductive tissues and cells

As regards non-reproductive tissues and cells, 22 countries reported data on recipients (AT, BG, HR, CZ, DK, EE, FI, FR, EL, IE, IT, LT, MT, NL, NO, PL, PT, RO, SI, ES, SE and UK).

Figures 18 and *19* show the total number of patients reported as having received each type of non-reproductive tissue or cells: the most frequently transplanted were skeletal tissue, peripheral blood stem cells and ocular tissues.

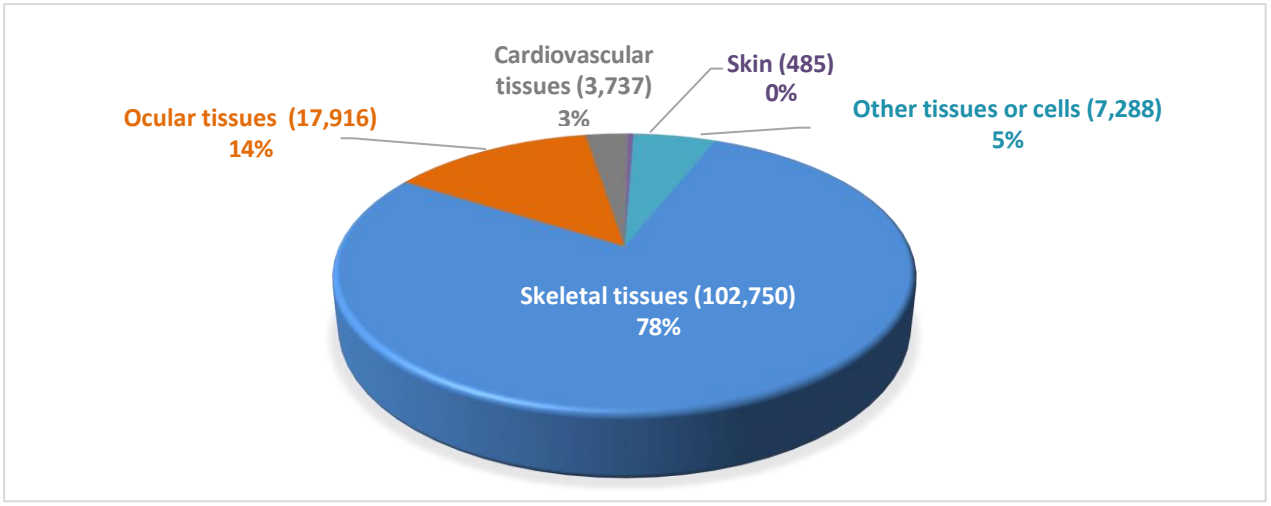

Figure 18. Total number of recipients per type of replacement tissue and cells; data 2021

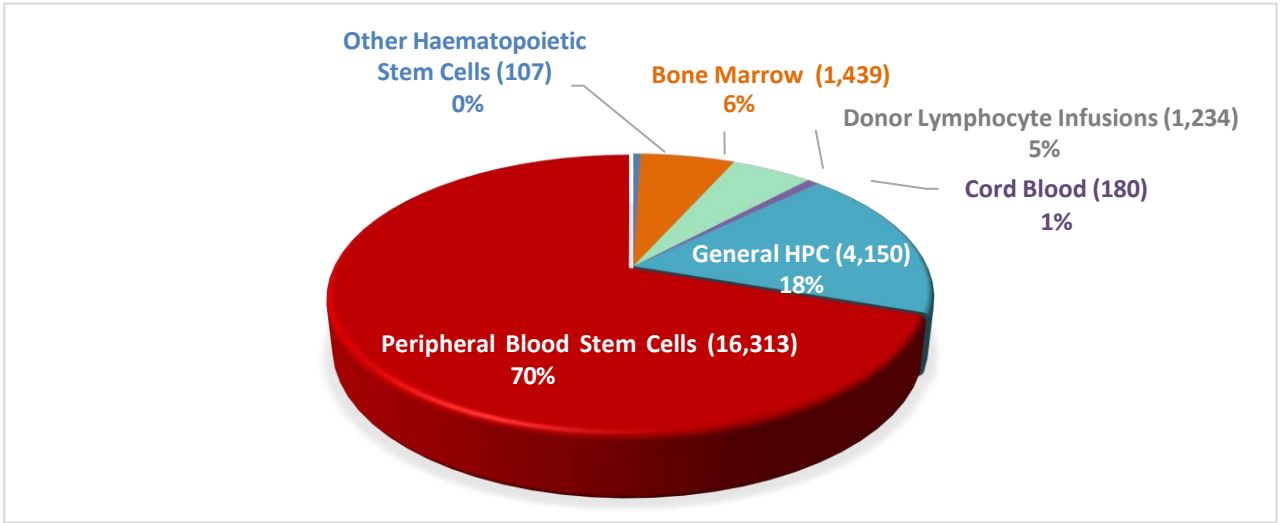

Figure 19. Total number of recipients per type of hematopoietic stem cells; data 2021

4.1.1.2 Reproductive tissues and cells

Concerning reproductive cells, only 16 countries (AT, BG, HR, CZ, DK, HU, FI, IE, LT, LU, MT, NL, PT, RO, SI and SE) reported data indicating that 162 868 patients underwent a MAR procedure. Of those, 111 364 involved partner or non-partner embryos (68%), 51 163 involved partner or non-partner sperm (32%), and less than 1% involved transplantation of testicular tissue (318 patients) or ovarian tissue (23 patients) (*Figure 20*).

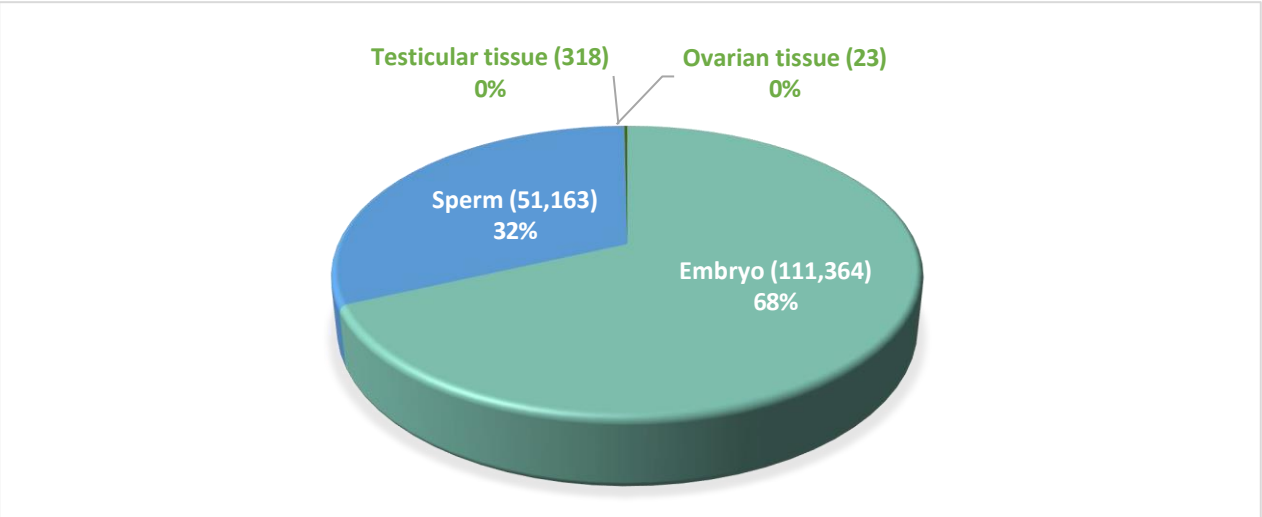

Figure 20. Total number of recipients per type of reproductive tissue and cells; data 2021

4.1.3 Trends in the distribution and application of tissues and cells

An overview of the data for the SAR denominators (number of tissues and cells distributed and number of recipients) provided by the reporting countries for non-reproductive and reproductive tissues and cells in the period 2012-2021 (data pertaining to 2011-2021) is presented in *Figures 21 and 22*, respectively.

It should be noted that the total number of tissues and cells distributed[7] (non-reproductive and reproductive) in 2021 increased compared to the previous year. This is due to the increased contribution from Germany and France, which compensated for the UK ceasing reporting as a whole and for very low reporting by Italy. This situation is different for transplant recipients: countries that reported data on distribution did not necessarily report, or only partially reported, on transplantation (e.g. Belgium, France, Germany, Italy, Poland); this was because the data were not collected in their country, the data were not available at the time of reporting or for a different reason (e.g. more than one organisation was responsible for a given country and only their data were reported). We acknowledge not only the continued contribution, but also improvement in the reporting of the number of transplant recipients by Spain, France, Greece, Norway and Poland. Finally, it can be assumed that the impact of the COVID-19 pandemic on healthcare systems was less in 2021 compared to the previous two years.

For reproductive tissues and cells, the slight increase in both the number of units distributed (about 10%) and number of recipients (about 15%) of MAR procedures compared to 2020 is due to a significant increase in reporting by several countries (Bulgaria, Norway, Germany, Belgium and the Netherlands).

[7] Note that the total number of tissues and cells distributed and the total number of replacement tissues and cells distributed include 46 327 units of replacement tissues and cells, mainly bone and skin (reported by the Netherlands) that are not in the scope of SARE exercises (distributed internationally). Those data give a wrong reflection of the situation and is therefore deleted OR should not be taken into account. It was not possible to correct this error in time for the analysis performed for this report.

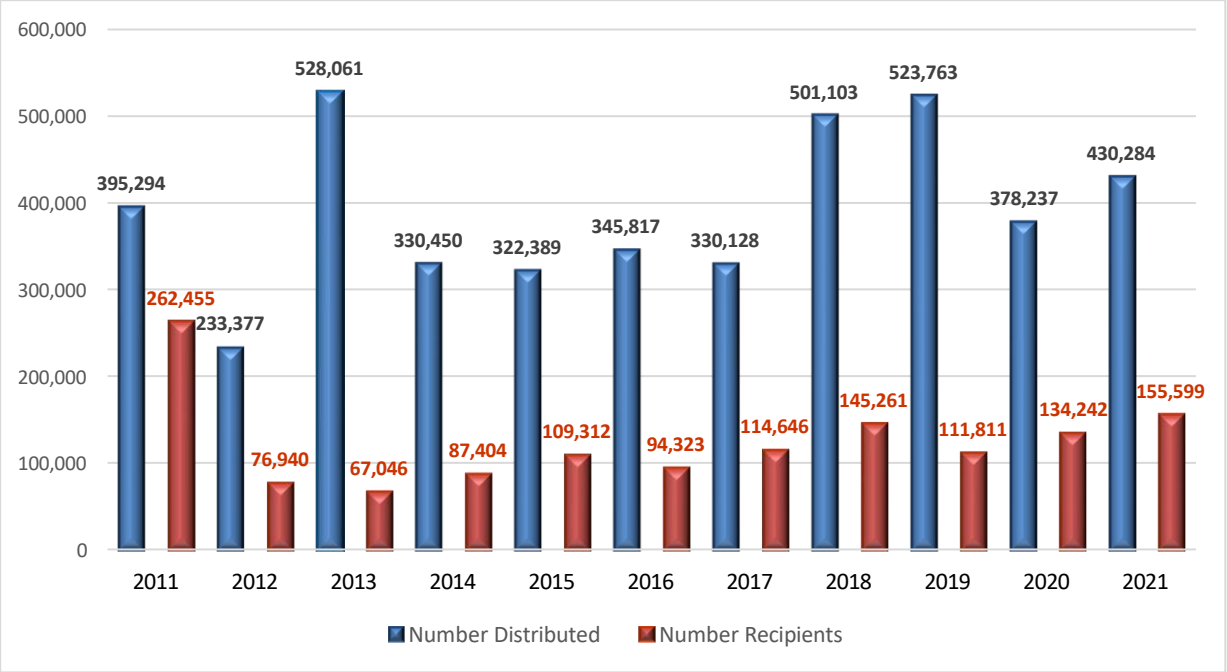

Figure 21. Total number of non-reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2021 comparative data

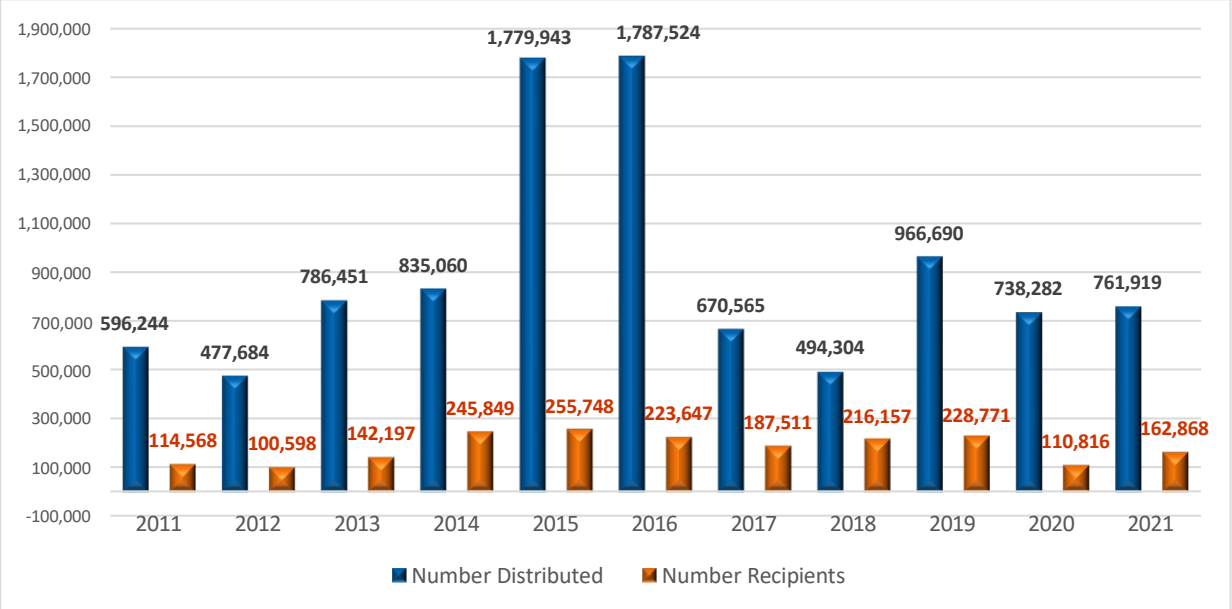

Figure 22. Total number of reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2021 comparative data[8]

4.1.4 Number of tissues and cells processed

Twenty-five countries (AT, BE, BG, HR, CZ, DK, EE, FI, DE, EL, HU, IE, IT, LU, LV, , MT, NL, NO, PL, PT, RO, SI, ES, SE and UK) provided the number of **non-reproductive tissues and cells processed**, and 18 countries (AT, BG, BE, HR, CZ, DK, DE, HU, IE, LI, LV, LU, MT, NL, PT, RO, SI and SE) provided the number of **reproductive tissues and cells processed** in 2021.

[8] 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.

As per the *Common Approach*, the term **tissues and cells processed** refers to tissues and cells processed in tissue establishments (TEs), but not necessarily distributed to end users. A total of 3 159 362 tissues and cells were reported as processed in 2021, 29% more than in 2020 (2 647 079). Of those, 373 486 units (12%) were replacement tissues and cells, 57 941 units (2%) were HSC and 2 727 935 units (86%) were reproductive tissues and cells. Comparative data from previous exercises (2011-2021 data) is presented in *Figure 23*.

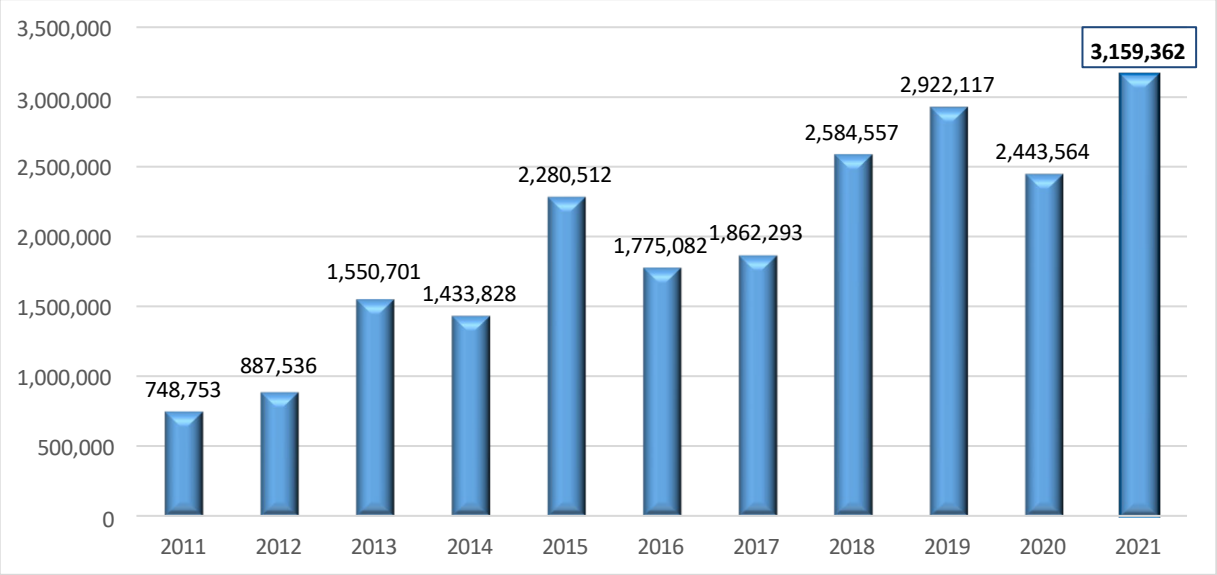

Figure 23. Total number of tissues and cells processed (units): 2011-2021 comparative data

4.2 Serious adverse reactions in recipients

A total of 326 SAR were reported in 2021, a 7% decrease compared to 2020 (350). Of these, 58 (18%) were related to replacement tissues and cells, 87 (27%) to HSC and 181 (55%) to reproductive tissues and cells.

In 2021, 19 SAR related to the transplantation of HSC (15) and reproductive cells (4) were associated with fatalities. In all but one case, the imputability level assigned was possible (level 1) or likely/probable (level 2). While imputability due to graft failure cannot be excluded, the patient's underlying condition was a major factor in the outcome of these cases.

A comparison of the number of SAR reported by countries between 2011-2021 for both categories (non-reproductive and reproductive tissues and cells) is presented in *Figure 24*. In general, there has been an increasing trend in SAR reported for reproductive tissues and cells, while the number of SAR reported for non-reproductive tissues and cells has remained relatively constant.

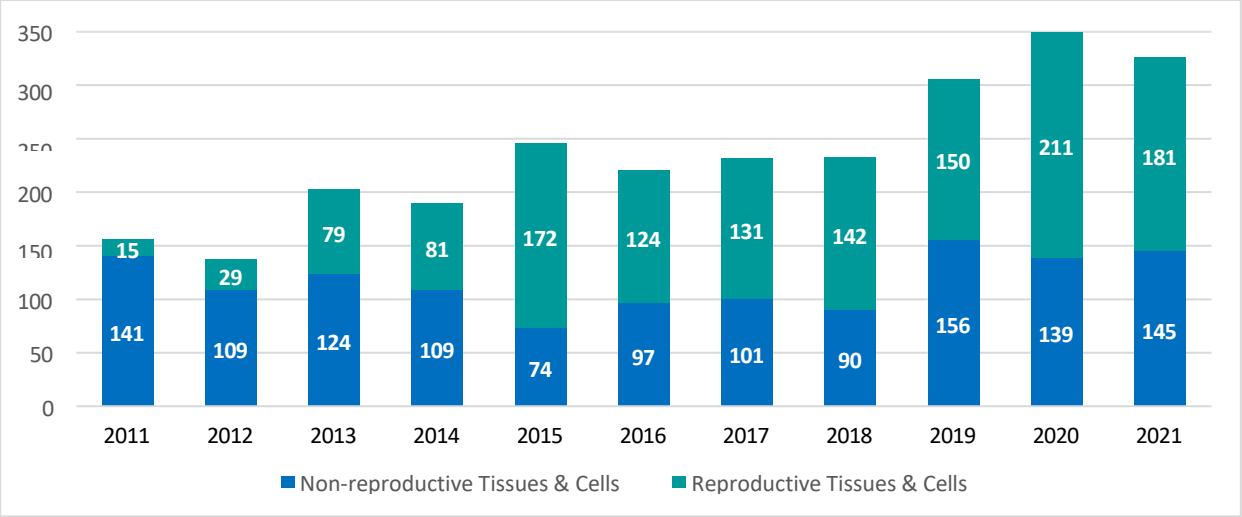

Figure 24. Non-reproductive versus reproductive tissues and cells SAR: 2011-2021 comparative data

4.2.1 General information

Of the 29 reporting countries, 19 (AT, BE, CZ, DK, EE, FI, FR, DE, EL, IE, IT, HR, NL, PT, PL, ES, SE, NO and UK) reported SAR associated with the clinical application of tissues or cells. Nine EU MS (BG, HU, LU, LV, LT, MT, RO, SK and SI) reported no SAR in recipients in 2021. A graphical representation of the number of SAR in transplant recipients by country in 2021 is available in *Figure 25*.

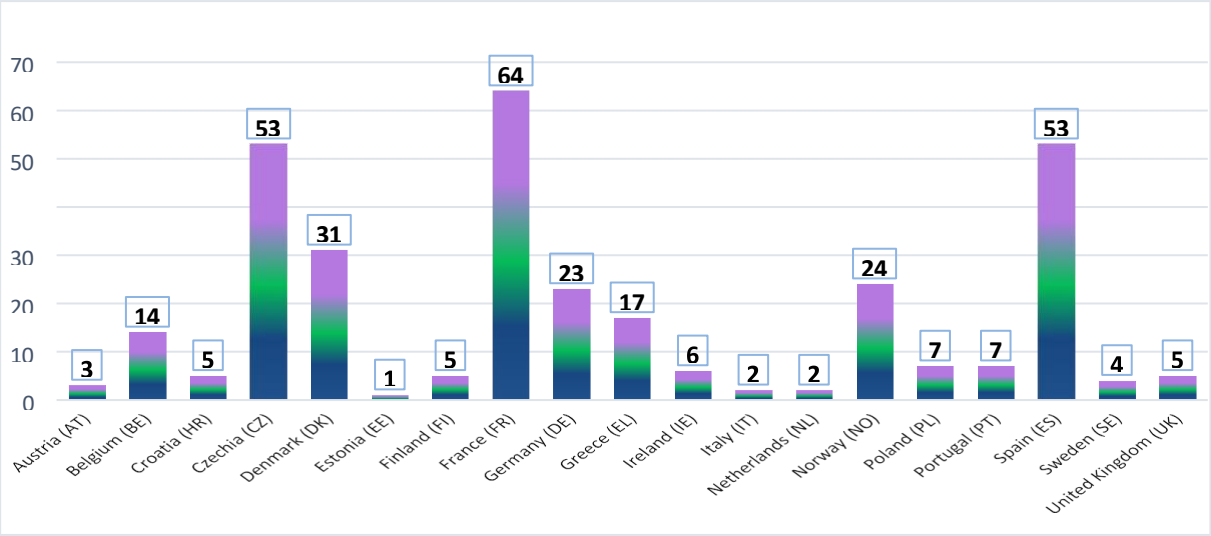

Figure 25. Total number of SAR by country in transplant recipients; data 2021

Ten countries (BE, DK, FR, DE, EL, IE, IT, NL, PT and ES) reported SAR associated with the transplantation of **replacement tissues and cells**, nine (AT, BE, FR, DE, EL, IE, NL, PL and ES) reported SAR associated with the transplantation of **HSC**, and 13 (BE, HR, CZ, DK, EE, FI, IE, IT, NO, PT, ES, SE and UK) reported SAR following the clinical application of **reproductive tissues or cells**.

The frequency of SAR was assessed by calculating the incidence in relation to the number of tissues and cells transplant/application procedures. SAR from countries that did not report the number of recipients were not considered.

SAR incidence was calculated per 10 000 transplant recipients (based on data provided by seven countries for replacement tissues and cells, seven countries for HSC and five countries for reproductive tissues and cells). It varies largely from country to country and is significantly higher for HSC (*Tables 1-3*).

Country	Number of recipients	Number of SAR	Incidence of SAR / 10 000 recipients
Denmark (DK)	685	2	29
France (FR)	10 738	18	17
Greece (EL)	328	3	91
Ireland (IE)	46	1	217
Netherlands (NL)	1 591	1	6
Portugal (PT)	931	1	11
Spain (ES)	23 753	11	5

Table 1. Number of SAR per 10 000 recipients of replacement tissues and cells; data 2021

Country	Number of recipients	Number of SAR	Incidence of SAR / 10 000 recipients
Austria (AT)	329	3	91
France (FR)	4 971	46	92
Greece (EL)	358	14	391
Ireland (IE)	676	2	29
Netherlands (NL)	30	1	333
Poland (PL)	747	7	94
Spain (ES)	3 620	4	11

Table 2. Number of SAR per 10 000 recipients of haematopoietic stem cells; data 2021

Country	Number of recipients	Number of SAR	Incidence of SAR / 10 000 recipients
Croatia (HR)	5 744	5	9
Czechia (CZ)	29 064	14	5
Denmark (DK)	4 511	29	64
Ireland (IE)	321	3	93
Portugal (PT)	3205	6	19

Table 3. Number of SAR per 10 000 recipients of reproductive cells; data 2021

These data should be interpreted with caution, as they may not reflect the improvement/deterioration of quality and safety measures but rather the increased effectiveness and completeness of the national vigilance and reporting systems – higher incidence may be an indication of more effective detection and reporting systems rather than an actual increase in the number of SAR.

4.2.2 SAR by category of tissues and cells

In total, 55% of the 326 SAR in recipients reported were associated with the application of reproductive tissues and cells, compared to 27% associated with the transplantation of HSC and 18% for replacement tissues and cells (*Figure 26*).

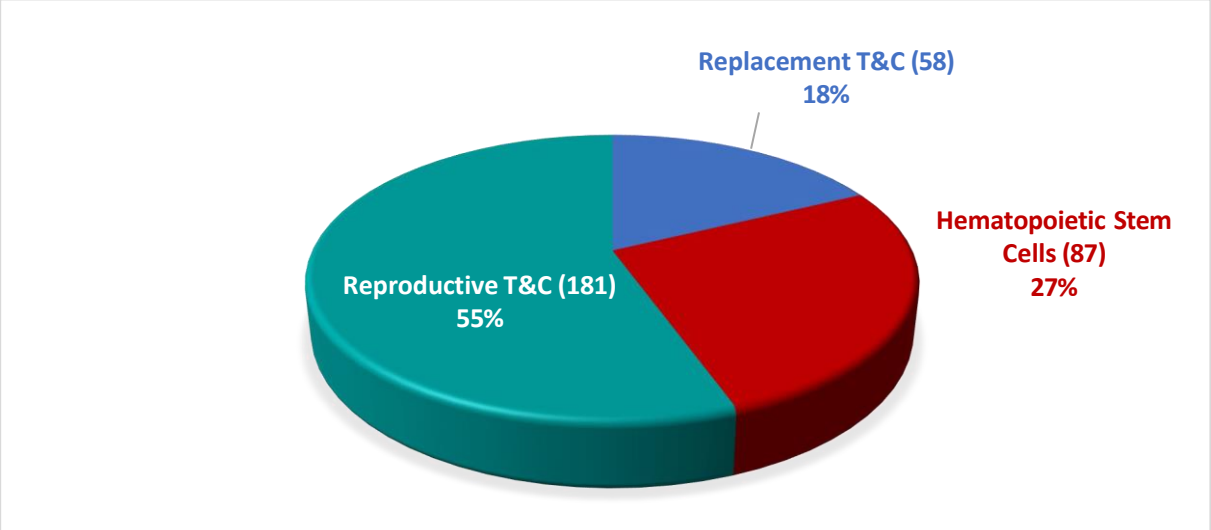

Figure 26. Number of SAR by category of tissue and cells; data 2021

The distribution of SAR per reporting country and category of tissue and cells is presented in *Figure 27*.

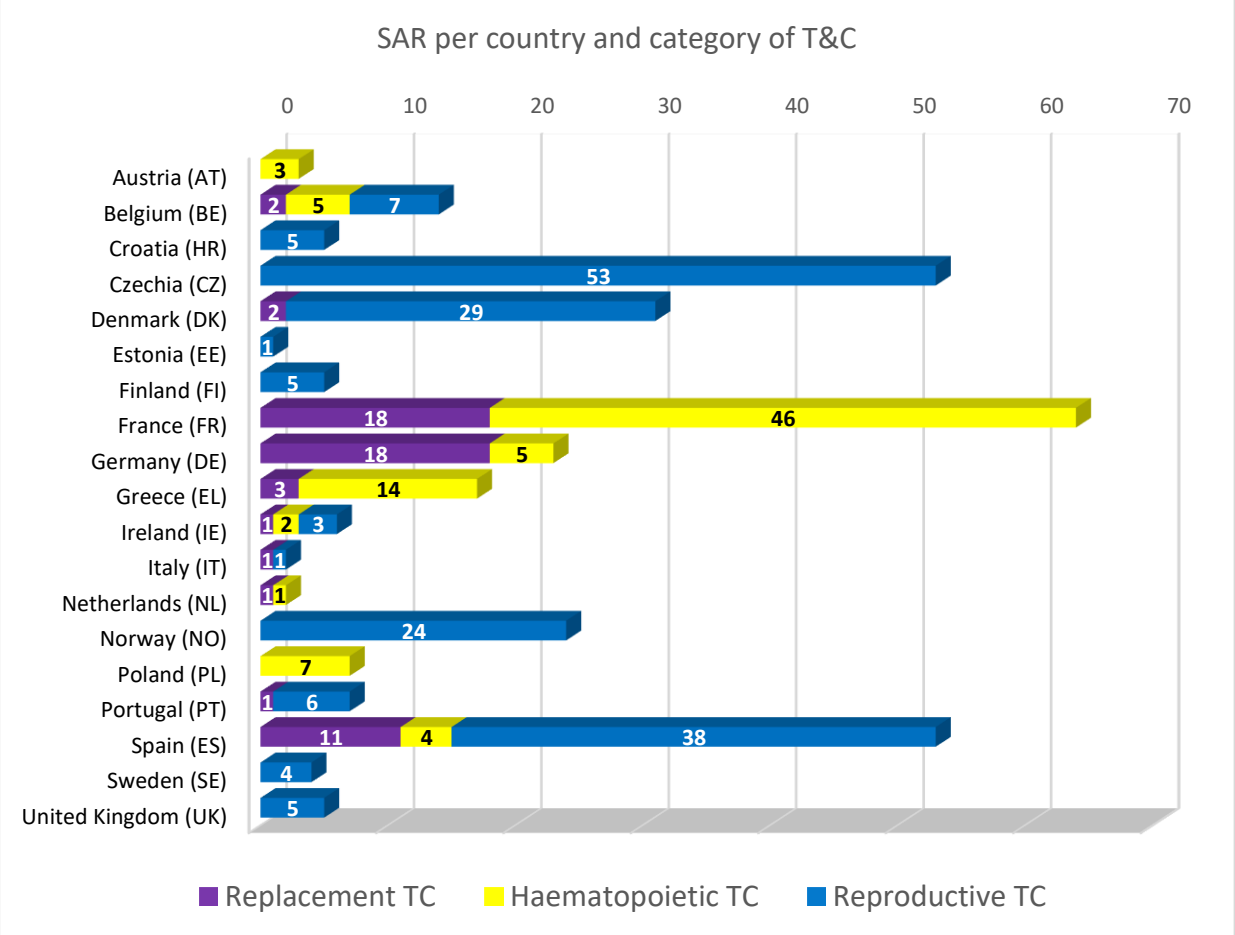

Figure 27. Number of SAR per country and category of tissues and cells; data 2021

A breakdown of SAR by subcategory of tissues and cells is presented in *Figures 28-30*.

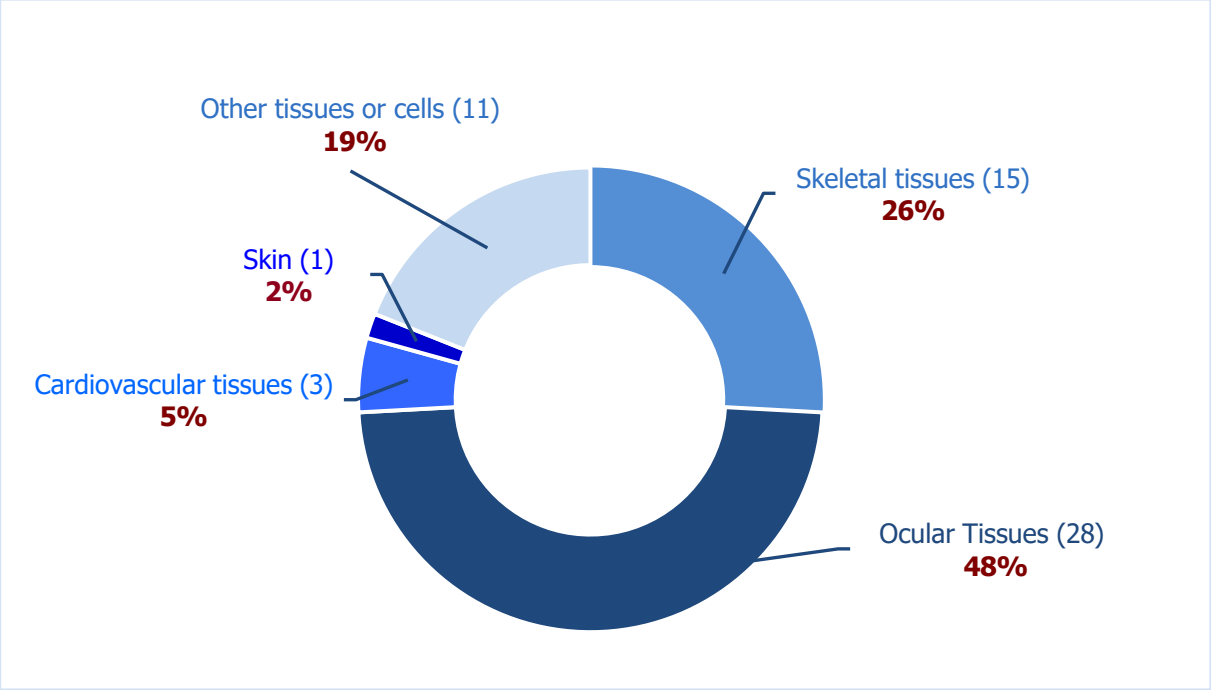

Figure 28. Number of SAR per subcategory of replacement tissues and cells (absolute values and percentages of total SAR in recipients); data 2021

Out of the 58 SAR associated with transplant of replacement tissues and cells, the most frequent were for ocular tissues (48%), specifically corneal tissue. As regards skeletal tissues, the largest number of reactions was associated with bones (10), with two cases each for cartilage and tendons and ligaments. The number of SAR for each subtype of replacement tissues and cells is presented in *Table 4.*

Replacement tissues and cells	Tissues and cells subtype	Number of SAR
Skeletal tissues	Bone	**10**
	Tendons/ligaments	2
	Cartilage	2
	General skeletal tissues	1
Ocular tissues	Cornea	**28**
Cardiovascular tissues	Heart valve	1
	Vessel	2
Skin	Skin	1
Other tissues or cells	Amniotic membrane	**11**

Table 4. Number of SAR by subtype of replacement tissues and cells; data 2021

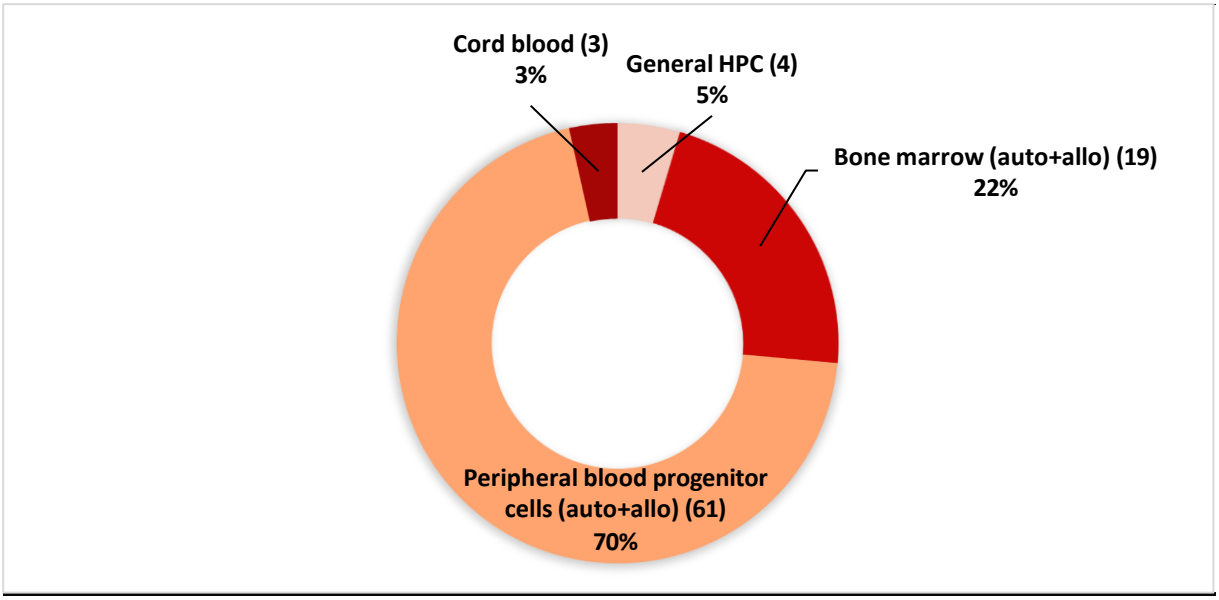

Figure 29. Number of SAR per subcategory of haematopoietic stem cells (absolute values and percentage of total SAR in recipients); data 2021

The HSC subcategory most frequently associated with severe adverse reactions was the transplant of allogenic related peripheral blood progenitor cells. Details for all types and subtypes of HSC are presented in *Table 5*.

HSC	HSC subtype	Number of SAR
Bone marrow	Allogenic related	8
	Allogenic unrelated	5
	General	6
Cord blood	Allogenic related	3
Peripheral blood progenitor cells	Allogenic related	10
	Allogenic unrelated	31
	Autologous	7
	General	13
General HPC		4

Table 5. Number of SAR by subtype of haematopoietic stem cells; data 2021

MAR procedures involving embryos were responsible for 66% of SAR in 2021, followed by sperm insemination as shown in *Figure 30*.

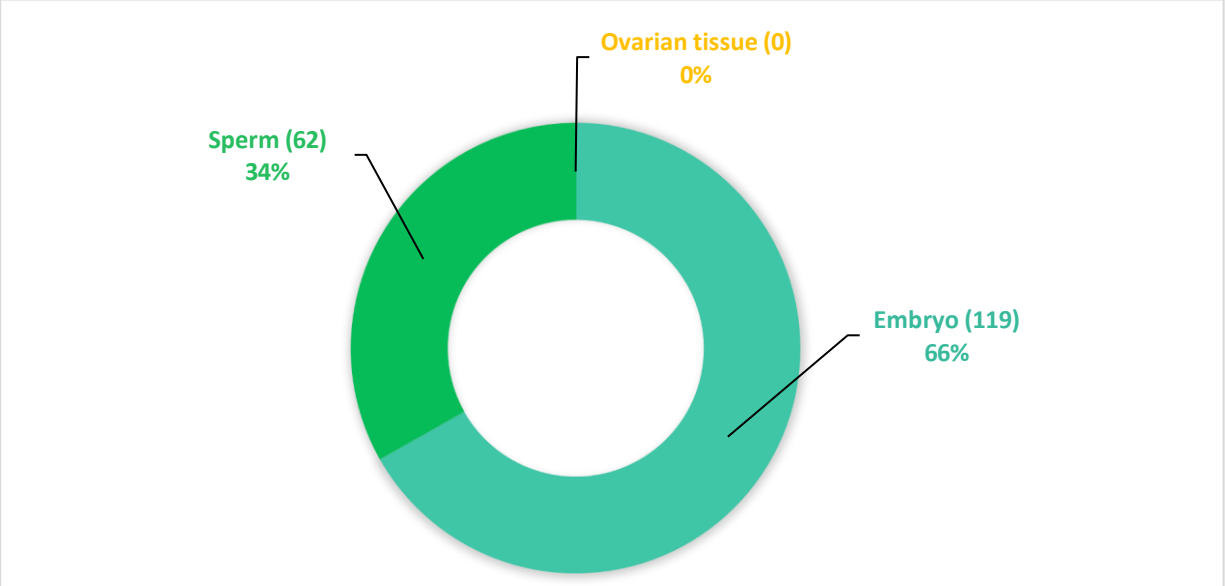

Figure 30. Number of SAR per subcategory of reproductive cells (absolute values and percentages of total SAR in recipients); data 2021

SAR for sperm used in both IUI procedures and embryos after IVF/ICSI were reported; the number for each subtype of tissues and cells involved is presented in *Table 6*.

Reproductive tissues and cells	Tissues and cells subtype	Number of SAR
EMBRYO	Donor oocyte, partner sperm	**50**
	Donor sperm and oocyte	15
	Donor sperm, partner oocyte	17
	Partner gametes	**29**
	General	8
SPERM	Non-partner donation	**56**
	Partner donation	6

Table 6. Number of SAR by subtype of reproductive tissues and cells; data 2021

4.2.3 SAR by type of reaction

Major categories of reactions following application of **replacement tissues and cells** and **HSC** 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, immunological reactions, graft failure/delayed engraftment, etc.).

4.2.3.1 SAR – replacement tissues and cells

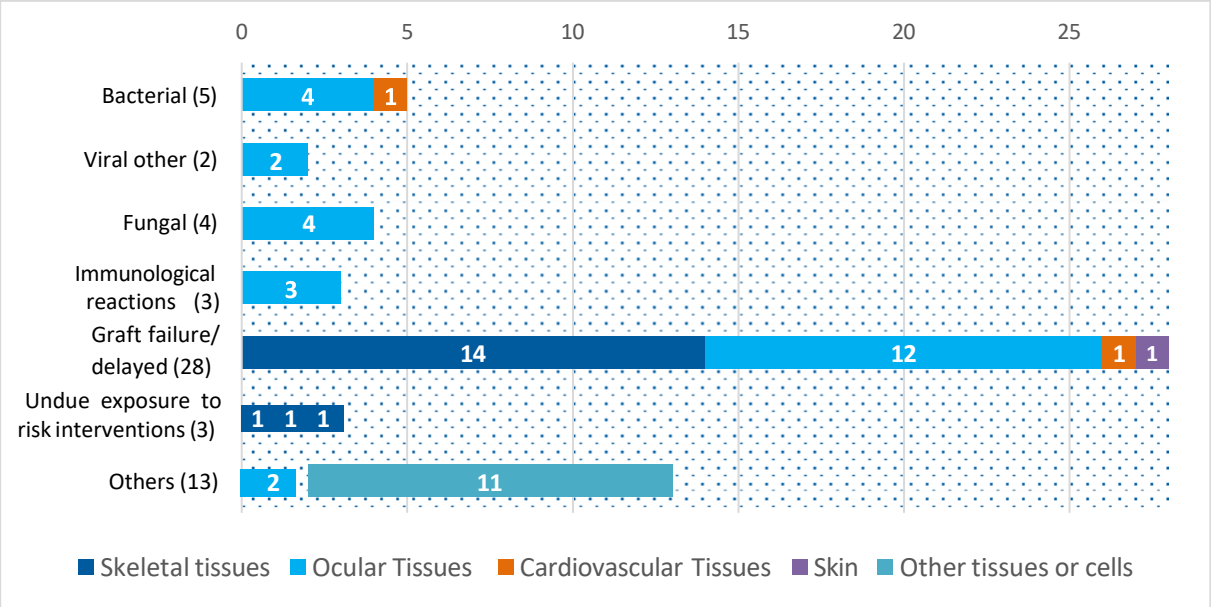

Figure 31. Distribution of SAR for replacement tissues and cells per type of reaction; data 2021

Details on the breakdown of SAR by type of reaction for replacement tissues and cells are provided below:

1. **Transmitted infections** were reported in 11 patients, representing 19% of all reported SAR for replacement tissues and cells. Ten cases of bacterial (*Enterococcus faecium*, sclerokeratitis), viral (herpes infection, herpetic uveitis) and fungal infections (*Candida albicans*, *Candida glabrata*) were associated with the corneal transplants and one reaction was reported in connection with a cryopreserved vascular graft.

2. **Other SAR**: of the 47 SAR reported (representing 81% of all reported SAR for replacement tissues and cells), the largest specified subcategory was related to graft function failure, followed by undue exposure to risk intervention; the number of reactions not classified decreased from 48 in 2020 to 13 in 2021.

    - 28 cases of **graft failure or delayed engraftment**, as follows:
        - 14 following the transplantation of skeletal tissue (10 related to bones, two to cartilage and two to tendons and ligaments)
        - one following the transplantation of cardiovascular tissue (vessel)
        - 12 following the transplantation of ocular tissue (all corneas)
        - one following transplantation of skin

    - Three cases of **undue exposure to risk interventions** (e.g. patient under anaesthesia without a suitable graft available and surgery postponed or rescheduled, incorrect graft size):
        - one following cardiovascular tissue transplantation (heart valve)
        - one ocular tissues (cornea)
        - one general skeletal tissue

    - Three cases of **immunological reactions** (graft failure) following transplantation of ocular tissues (corneas)

- 13 SAR were classified as **Other**, including 11 cases of corneal pannus related to the application of amniotic membrane and two SAR that occurred following the transplantation of ocular tissue (post-graft corneal striae and corneal oedema).

4.2.3.2 SAR – haematopoietic stem cells

The second most prevalent of all SAR reported in 2021 were those associated with transplant of HSC (87). Apart from one case of fungal infection and one of other disease transmission (immunological disease), the remaining 85 SAR were reported as **Other SAR**. No instances of malignant disease were reported. The types of reaction encountered in 2021 are presented in *Figure 32*.

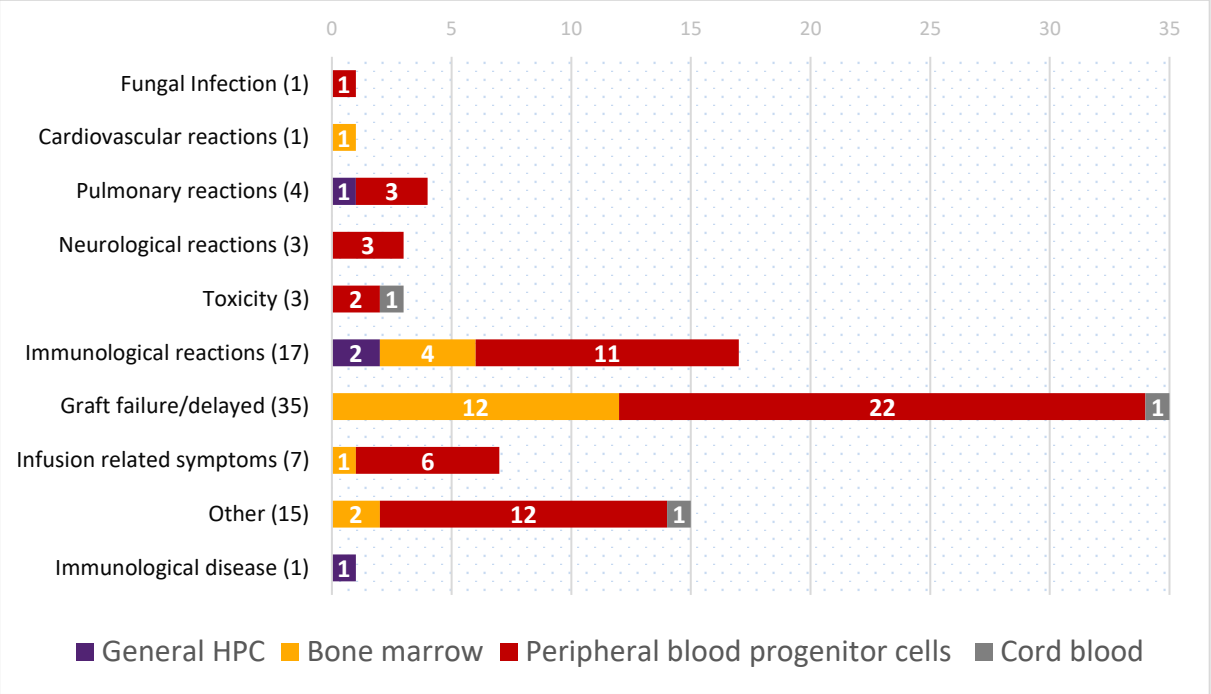

Figure 32. Distribution of SAR for haematopoietic stem cells by type of reaction; data 2021

The breakdown of SAR by type of reaction for replacement tissues and cells is provided in *Table 7* below:

1. **Transmitted infections**: One instance of fungal infection caused by *Candida glabrata* in a patient that had undergone a transplant of peripheral blood stem cells (PBSC).

2. **Other SAR**:
   - 35 cases of **graft failure or delayed engraftment** following transplantation of bone marrow (three allogenic related, three allogenic unrelated and three general), cord blood (1 allogenic unrelated) and PBSC (four allogenic related, 11 allogenic unrelated, one autologous and three general)
   - 17 cases of **immunological reactions** following transplantation of bone marrow (two allogenic related, one allogenic unrelated and one general), HSC (two general), and PBSC (four allogenic related, six allogenic unrelated, and one autologous)
   - seven cases of **infusion related non-specific symptoms** following transplantation of bone marrow (one general), and PBSC (one allogenic unrelated, two autologous and three general)
   - 15 SAR were classified as **Others** and occurred following transplantation of bone marrow (one autologous unrelated and one general), cord blood (one autologous unrelated), HSC (one general), and PBSC (one allogenic related, three allogenic unrelated, one autologous and six general)

- four cases of **pulmonary reactions** following transplantation of PBSC (three allogenic unrelated and one autologous)
- three cases of **neurological reactions** following transplantation of PBSC (one allogenic related and two allogenic unrelated)
- one case of **cardiovascular reaction** following transplantation of bone marrow (allogenic related)
- three cases of **toxicity** following transplantation of cord blood (one allogenic unrelated) and PBSC (one allogenic unrelated and one general)

3. **Other disease transmission**: one case of immunological reaction (anaphylactic shock) following transplantation of allogenic unrelated PBSC.

SAR type	SAR subtype	HSC type	HSC subtype			
			Allogenic related	Allogenic unrelated	Autologous	General
Transmitted infections (1)	**Fungal infection** (*Candida glabrata*) (1)	PBSC (1)			1	
Other disease transmission (1)	**Immunological reaction** (anaphylactic shock) (1)	PBSC (1)		1		
Other SAR (85)	**Graft failure/delayed engraftment** (35)	Bone marrow (12)	6	3		3
		Cord blood (1)		1		
		PBSC (23)	4	14	1	3
	Immunological reactions (17)	Bone marrow (4)	2	1		1
		General HSC (1)				
		PBSC (11)	4	6	1	
	Infusion related non-specific symptoms (7)	Bone marrow (1)				1
		PBSC (6)		1	2	3
	Pulmonary reactions (4)	General HSC (1)				
		PBSC (3)		3		
	Neurological reactions (3)	PBSC (3)	1	2		
	Cardiovascular reaction (1)	Bone marrow (1)	1			
	Toxicity (3)	Cord blood (1)		1		
		PBSC (2)		1		1
	Others (15)	Bone marrow (2)	1			1
		Cord blood (1)	1			
		General HSC (1)				
		PBSC (11)	1	3	1	6

Table 7. Breakdown of SAR in HSC by type and by reaction and HSC subtype; data 2021

4.2.3.3 SAR – reproductive tissues and cells

Major categories of SAR associated with the application of **reproductive tissues and cells** listed in the *Common Approach* include **transmitted infections** (bacterial, viral, parasitical, fungal, prion disease, other transmitted infections), **transmitted malignant diseases**, **transmitted genetic conditions** and **Other SAR** (cardiovascular reaction, pulmonary reaction, anaphylactic reaction, ectopic or molar pregnancy, etc.).

Among the 181 SAR associated with the application of reproductive tissues and cells, 59% (107) were classified as **transmitted genetic conditions**, and the rest were reported as **Other SAR** (61) and **other disease transmissions** (13). The types of SAR per type of gametes (partner/non-partner), embryo application and sperm application are presented in *Figures 33* and *34* respectively.

1. **Transmitted infection**: no cases reported.
2. **Transmitted malignant disease** no cases reported.
3. **Transmitted genetic conditions**: 107 SAR were reported in this category and represent the most common type related to reproductive tissues and cells (59%). These comprised:
    - 46 cases involving embryos from donor oocytes and partner sperm, 14 cases of embryos from donor sperm and oocytes,
    - 14 cases of embryos from donor sperm and partner oocytes
    - 24 cases of sperm from non-partner donation
    - five cases related to embryos from partner gametes
    - four cases concerning sperm in the **general** category
4. **Other SAR**: ectopic pregnancy was the most common of the 61 SAR categorised as **Other**, representing 20% of all reported SAR for reproductive tissues and cells. Nine cases of donors with germline mutations, one case of RASopathy and seven cases of anaphylactic reaction were also included in this category. Of the SAR reported as **Other**:
    - 24 cases occurred following clinical application of embryos from partner gametes
    - four cases involved general embryos
    - four cases involved embryos from donor oocytes and partner sperm
    - three cases involved embryos from donor sperm and partner oocytes
    - one case involved embryos from donor sperm and oocytes, 20 cases involved sperm from non-partner donation
    - six cases involved partner sperm
5. **Other disease transmissions:** the cases reported in this category include eight instances of germline mutation, three cases of genetic diseases and one case of spina bifida.

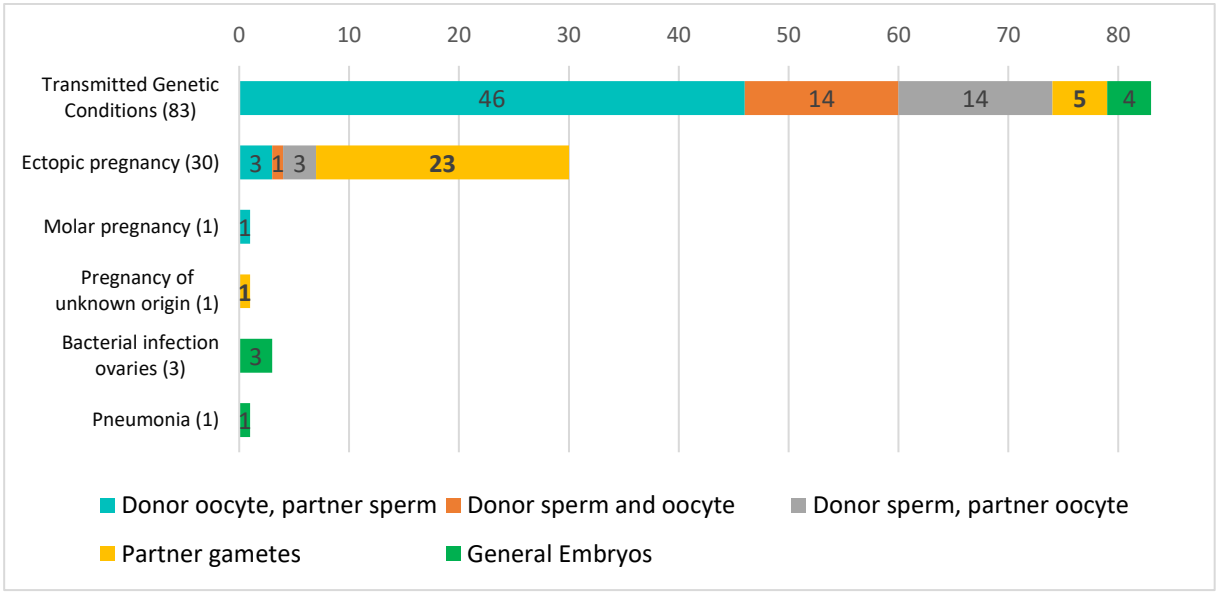

Figure 33. Distribution of SAR per type of gametes (partner/non-partner), embryo application; data 2021

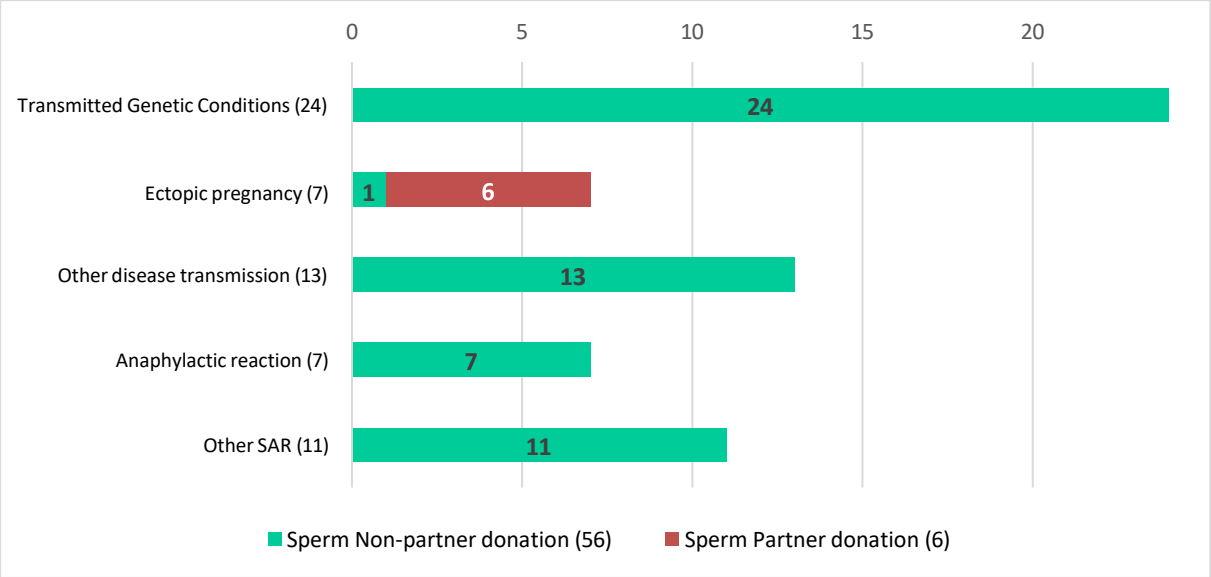

Figure 34. Distribution of SAR per type of gametes (partner/non-partner), sperm application; data 2021

It should be noted that of the 181 SAR associated with the application of reproductive cells, 76% were related to non-partner donation – 56 involved non-partner sperm, 50 involved embryos from donated oocytes, 15 embryos from donated sperm and oocytes and 17 embryos from donated sperm (*Table 8*).

Reproductive tissues and cells	Tissues and cells subtype	Number of SAR	SAR %
EMBRYO	Donor oocyte, partner sperm	50	28
	Donor sperm and oocyte	15	8
	Donor sperm, partner oocyte	17	9
	Partner gametes	29	16
	General	8	4
SPERM	Non-partner donation	56	31
	Partner donation	6	3

Table 8. SAR related to the application of non-partner gametes (absolute values and percentage); data 2021

4.2.3.4 SAR Imputability

The *Common Approach* (2022 version) requires that the imputability assessment tool provided be used to determine which reactions must be reported for the purpose of this exercise. In 2021, an imputability level was assigned to only 35% of the SAR reported (115 out of 326). As shown in *Table 9* below, for most events, conclusive evidence for attributing the reaction to the quality or safety of the tissue or cells (for recipients) or to the donation process (for donors) was not present. In most cases of SAR in recipients of HSC infusions associated with fatalities, imputability was assessed as level 1 (possible) or level 2 (likely, probable) and the evidence supported the hypothesis of death due to the clinical condition of the patients rather than a relationship to the tissue or cells.

The types of SAR to which imputability level 3 (definite/certain) was assigned included immunological reactions (6), graft failure/delayed engraftment (3), transmitted fungal and bacterial infections (2 and 1, respectively), undue exposure to risk interventions (2), pulmonary reaction (1), immunological disease (1) and transmitted genetic conditions in conjunction with MAR procedures (2).

Tissues and cells category	Total number of SAR in 2021	Imputability reported		Imputability level		
		Number	**%**	**IL1**	**IL2**	**IL3**
Replacement tissues and cells	58	41	e12	27	7	7
HSC	87	65	20	41	14	10
Reproductive tissues and cells	181	9	3	7	-	2
Total	326	115	35	75	21	19

Table 9. SAR with imputability level reported per category of tissues and cells; data 2021

4.2.4 Deaths of recipients of tissues and cells

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

Twenty deaths in recipients were reported in 2021: 16 were potentially attributable to HSC application and four to reproductive tissue and cell application; 14 fatalities among recipients potentially attributable to tissue and cell application were reported the previous year.

4.2.4.1 Deaths following the application of HSC

Detailed information on the **eight reported deaths** potentially attributable to **HSC** is provided below:

- **one death after a second autologous peripheral blood stem cell transplant (PBSCT)** due to septic shock by bacterial translocation and significant immunosuppression (acute digestive graft-versus-host disease and post-transplant infections); imputability to graft quality could not be completely ruled out (previous clinical status of the patient was IgA lambda multiple myeloma)
- **one death after allogenic related bone marrow transplant** due to cardiogenic shock following myopericarditis
- **one death after autologous PBSCT** with unidentified cause
- **one death after PBSC** graft failure and thrombocytopenia complicated by cerebral haemorrhage, possibly attributable to graft quality (low viability of cryopreserved CD34+ after thawing)
- **one death allogenic PBSCT** due to multiple organ failure; imputability to graft quality could not be completely ruled out (previous clinical status of the patient was severe aplastic anaemia and treatment with ATGAM/CsA/steroids; haemoculture result was negative and donor and recipients were serologically compatible)
- **three deaths after PBSCT** or during the first hospitalisation associated with the transplant

4.2.4.2 Deaths following the application of reproductive tissues and cells

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

- **three deaths related to IVF (death of offspring)**
- **one death related to partner sperm donation**: oocyte donor detected as heterozygote carrier (induced abortion due to diagnosis of spina bifida).

4.3 Serious adverse events

4.3.1 General information

The reported number of tissues processed was 16% higher in 2021 compared to 2020 (*Figure 35*); this was due to the significant contribution of one country that did not report in previous years and a few other countries whose reporting increased in 2021, thus compensating for the reduced reporting by other countries. The total number of SAE reported was down 24% compared to the previous exercise and 27% compared to 2019 (*Figure 36*). This does not necessarily signify a reduction in SAE reporting; this could be a sign of mature quality systems and better understanding of SAE reporting.

Eleven countries reported SAE for replacement tissues and cells (AT, BE, FR, DE, HU, IT, MT, NL, PL, ES and SE), 18 for HSC (AT, BE, BG, HR, CZ, FI, FR, DE, EL, IE, IT, NL, NO, PL, PT, ES, SE and UK) and 16 for reproductive tissues and cells (BE, BG,HR, CZ, DK, EE, FI, FR, DE, IE, IT, LV, NL, PT, ES and SE). Fewer countries reported SAE in 2021 than in 2020.

Of the 694 SAE reported for 2021, 42% were related to HSC, 34% to reproductive cells and tissues and 24% to replacement tissues and cells. The proportion is similar to the previous year (72% non-reproductive tissue and cells and 28% reproductive tissues and cells).

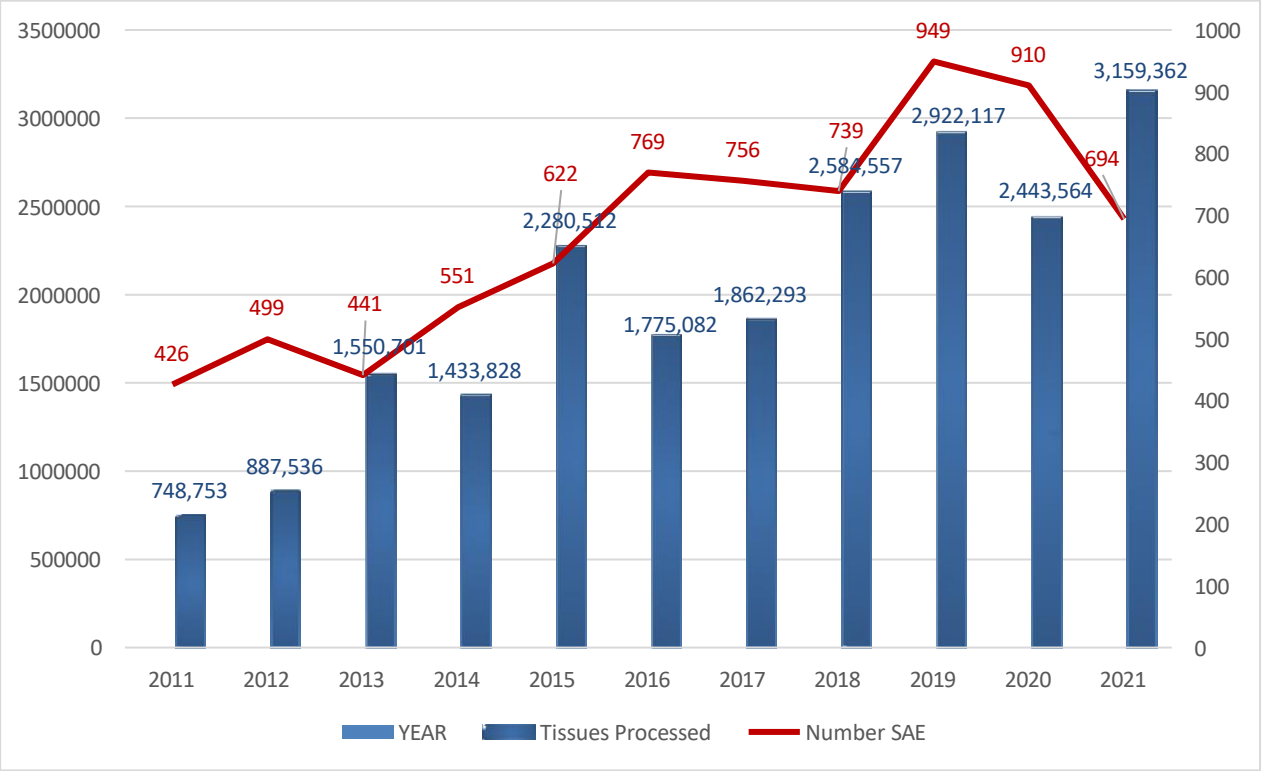

Figure 35. Number of tissues processed and number of SAE reported; 2011-2021 comparative data

The frequency of SAE was assessed by calculating its incidence in relation to the number of tissues and cells processed. SAE from countries that did not report the number of processed tissues and cells were not considered.

The incidence of SAE was calculated per 10 000 tissues and cells processed (based on data provided by 10 countries for replacement tissues and cells, 13 countries for HSC and 11 countries for reproductive tissues and cells). Similar to SAR, the incidence of SAE varies largely from country to country and is significantly higher for HSC (*Tables 10-12).*

Country	Number of tissues and cells processed	Number of SAE	Incidence of SAE / 10 000 tissues and cells processed
Austria (AT)	66 786	5	0.75
Belgium (BE)	22 529	32	14.2
France (FR)	103 773	17	1.6
Germany (DE)	159 566	9	0.56
Hungary (HU)	1 226	55	9
Italy (IT)	8 996	10	11
Netherlands (NL)	12 670	6	5
Poland (PL)	46 367	1	0.2
Spain (ES)	29 251	27	9
Sweden (SE)	3 459	7	20

Table 10. Number of SAE per 10 000 replacement tissues and cells processed; data 2021

Country	Number of HSC processed	Number of SAE	Incidence of SAE / 10 000 tissues and cells processed
Austria (AT)	2 856	3	10
Belgium (BE)	3 134	17	54
Bulgaria (BG)	774	3	39
Croatia (HR)	1 602	3	19
Czechia (CZ)	2 209	2	9
Finland (FI)	1 018	5	49
Ireland (IE)	434	8	184
Italy (IT)	6 023	11	18
Netherlands (NL)	3 105	3	10
Poland (PL)	31 040	5	2
Portugal (PT)	711	34	478
Sweden (SE)	1 795	7	39
United Kingdom (UK)	131	1	76

Table 11. Number of SAE per 10 000 haematopoietic stem cells processed; data 2021

Country	Number of tissues and cells processed	Number of SAE	Incidence of SAE / 10 000 tissues and cells processed
Belgium (BE)	462 323	33	0.7
Bulgaria (BG)	128 270	1	0
Croatia (HR)	51 507	2	0.4
Czechia (CZ)	377 585	6	0.2
Denmark (DK)	49 627	24	5
Germany (DE)	870 300	5	0
Ireland (IE)	102 932	3	0.3
Latvia (LV)	31 780	1	0.3
Netherlands (NL)	245 607	4	0.2
Portugal (PT)	10 686	8	7
Sweden (SE)	190 052	11	0.6

Table 12. Number of SAE per 10 000 reproductive tissues and cells processed; data 2021

4.3.2 SAE by type of event

The *Common Approach* includes six categories of SAE: **tissues and cells defect**, **system failure**, **equipment failure**, **materials**, **human error** and **Other**.

Tissues and cells defect remained the leading category of events with 40% out of the total 694 SAE that occurred in 2021, followed by **system failure** (21%). *Figure 36* shows the positive evolution of events reported as being related to **human error** (a decrease from 31% in 2019 to 20.8% in 2020 and 17% in 2021) and of those classified as **Other** (from 23% in 2019 to 23.4% in 2020 and 10% in 2021).

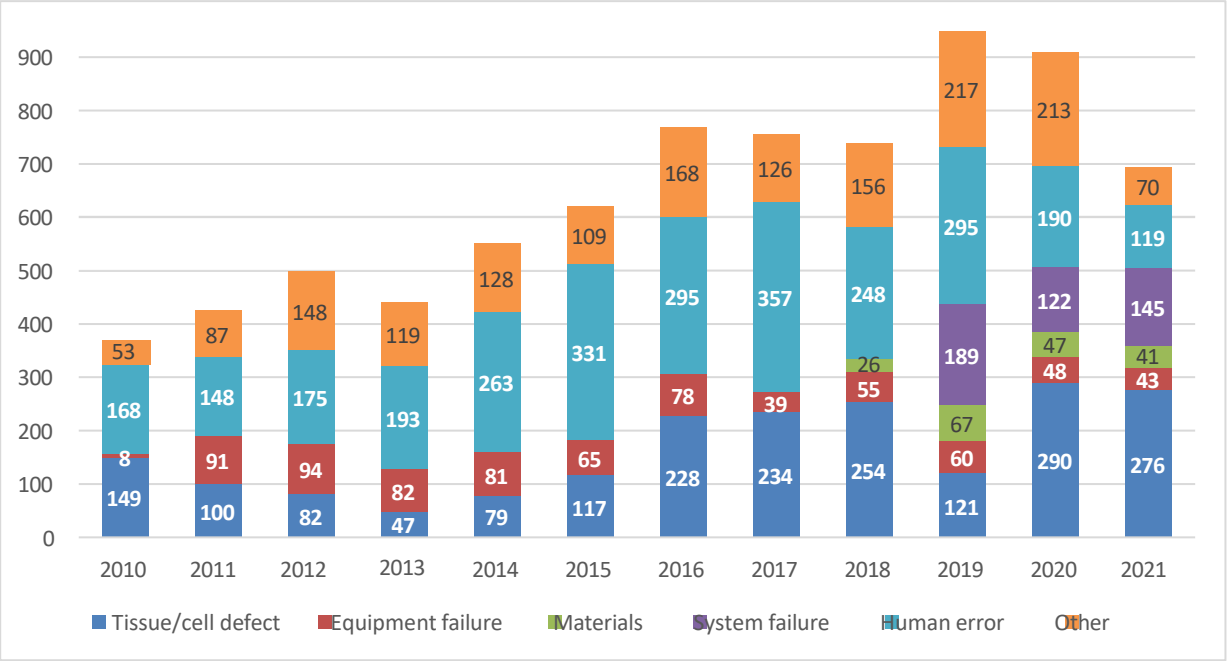

Figure 36. Distribution of SAE by type/specification; 2010-2021 data

The distribution of SAE by type/specification for each of the three categories of tissues and cells is presented in *Figures 37-39*.

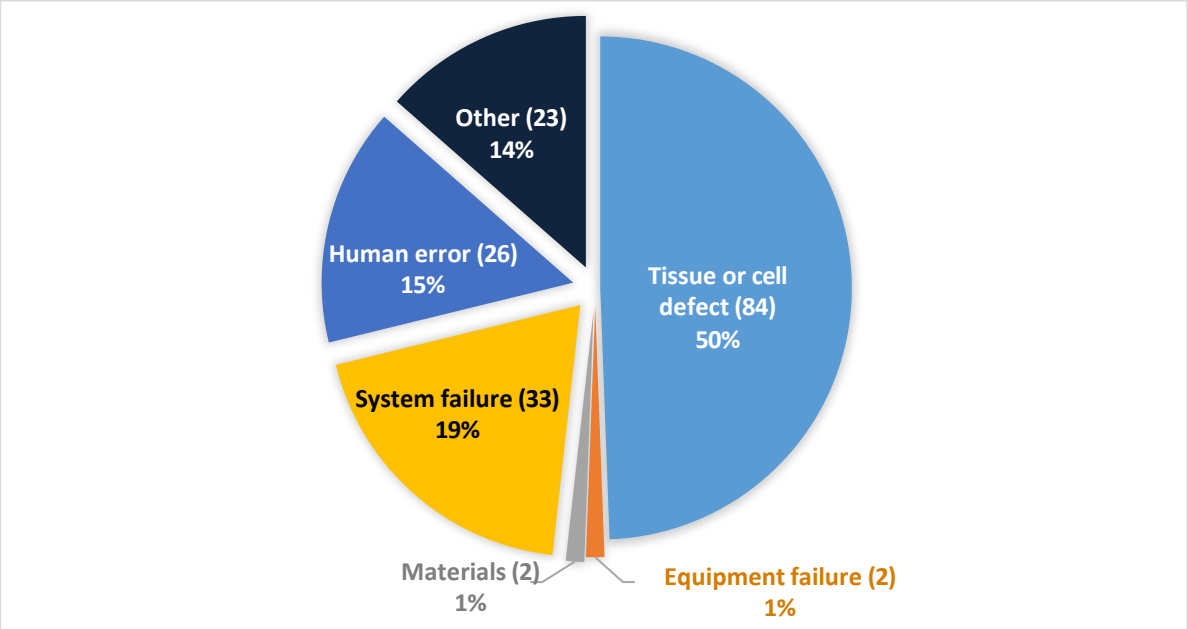

Figure 37. SAE types for replacement tissues and cells (absolute values and percentages); data 2021

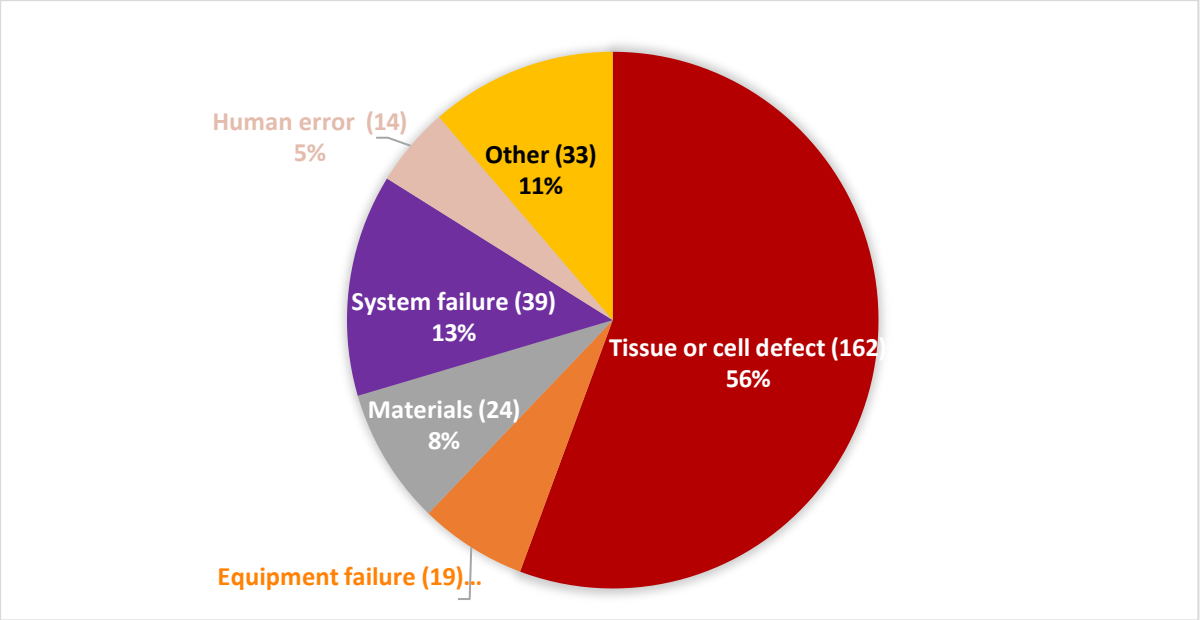

Figure 38. SAE types for haematopoietic tissues and cells (absolute values and percentage); data 2021

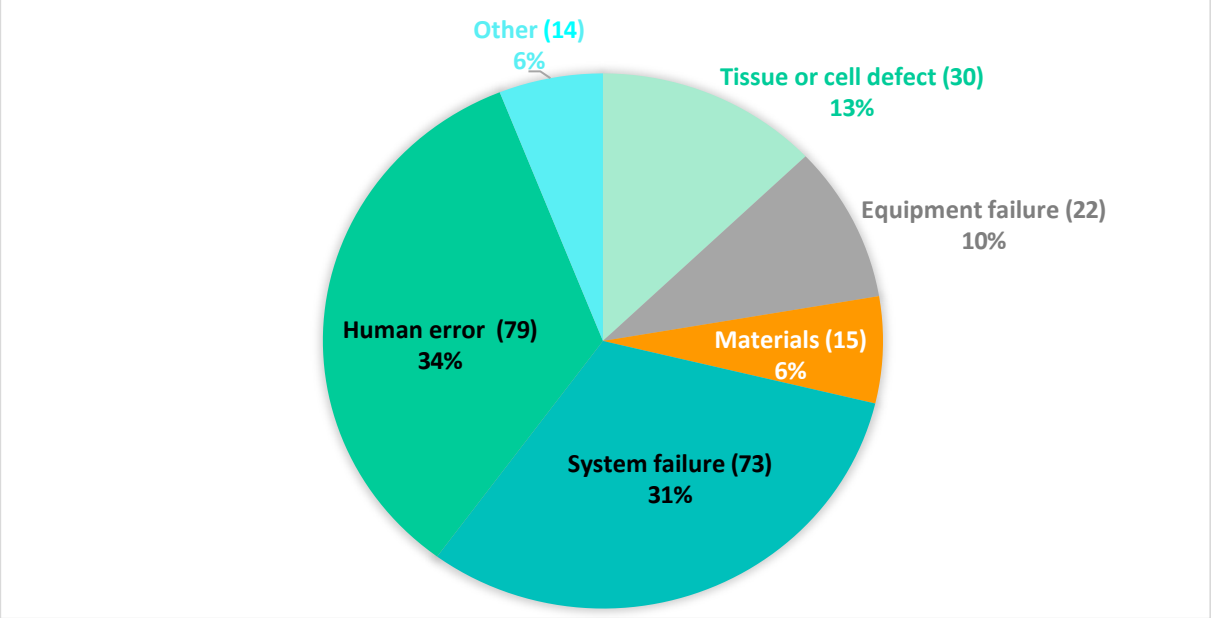

Figure 39. SAE types for reproductive tissues and cells (absolute values and percentage); data 2021

4.3.3 SAE by activity step

Following the harmonisation of practices, two new activity steps – **product selection** and **issue** – were added to the reporting template for 2019.
An overview of the SAE reported for each of the three categories of tissues and cells by activity step is presented in *Figures 40-42*.

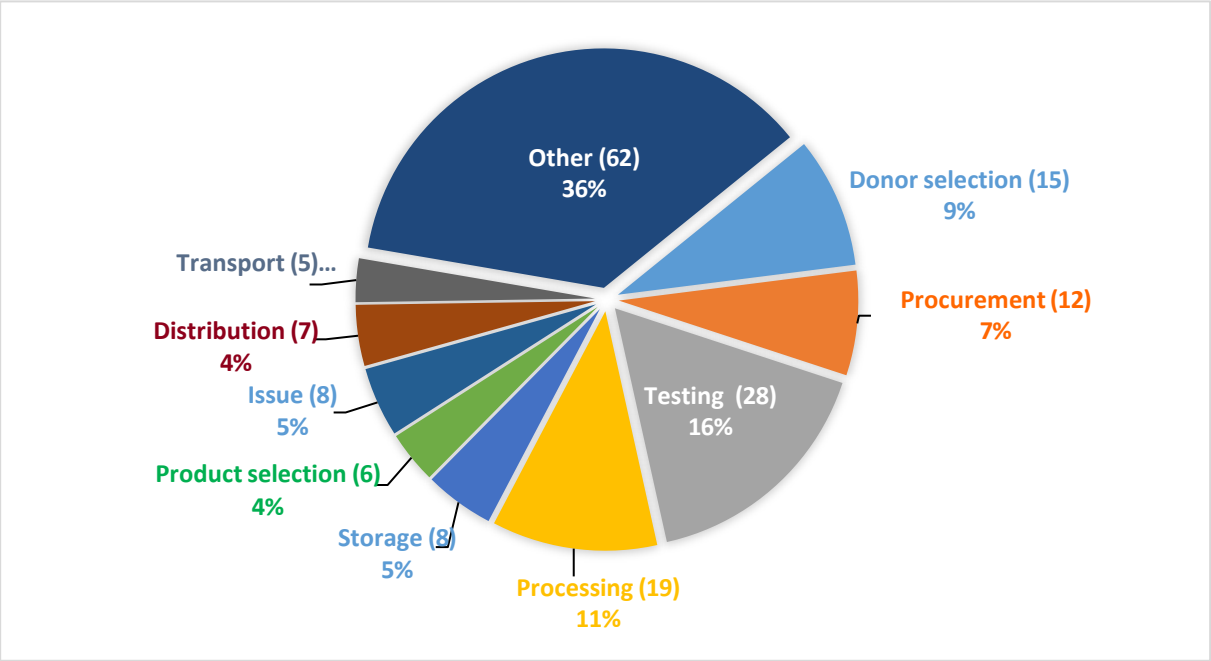

Figure 40. Distribution of SAE for replacement tissues and cells by activity step; data 2021

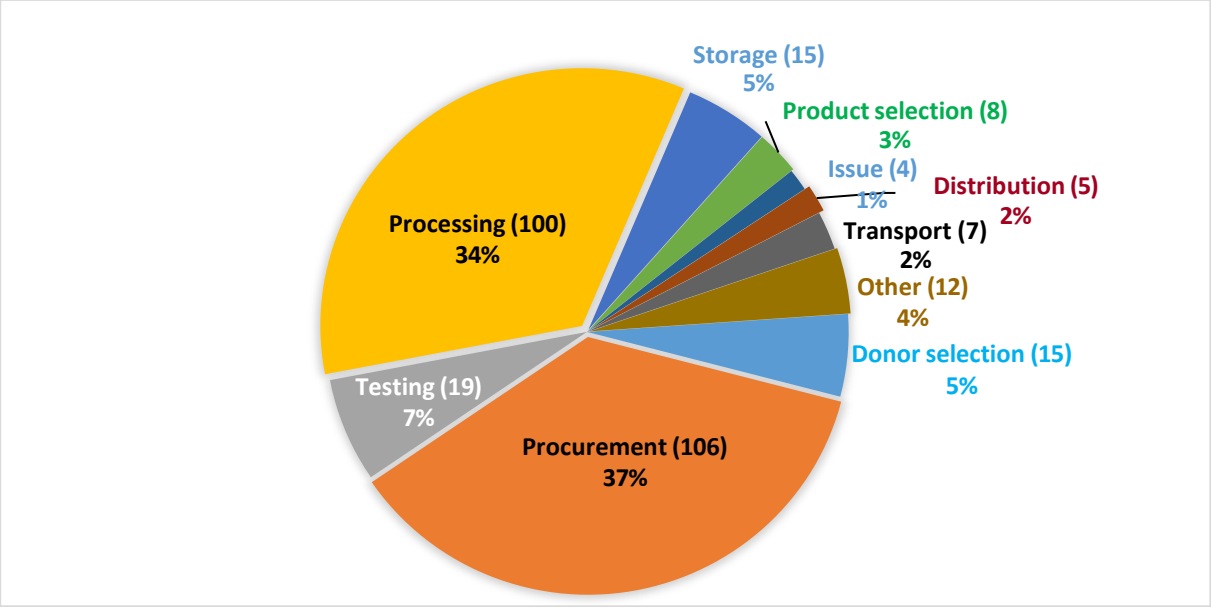

Figure 41. Distribution of SAE for haematopoietic stem cells by activity step; data 2021

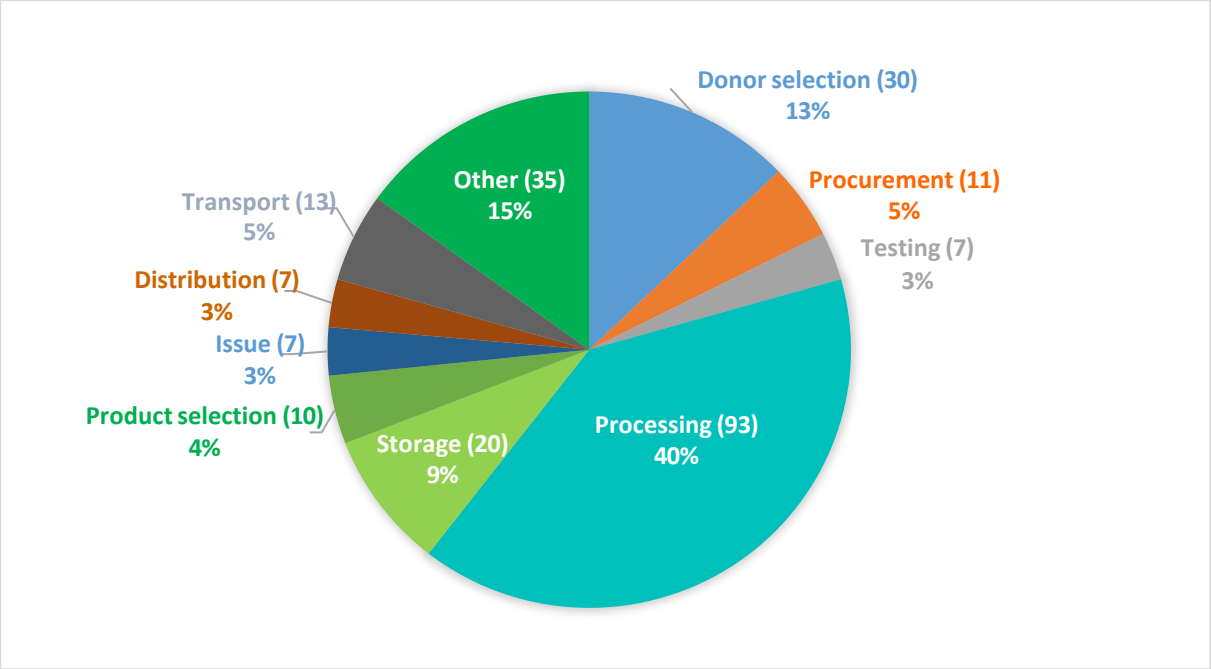

Figure 42. Distribution of SAE for reproductive tissues and cells by activity step; data 2021

The distribution of SAE by activity step differs among the three categories of tissues and cells. However, SAE reported as occurring or being discovered during **processing, procurement, donor selection** and **testing** are the most frequent for all categories of cells, and account for 59% of all SAE in 2021. An overview of the SAE reported for each of the three categories of tissues and cells by activity step is presented in *Figures 43-45.*

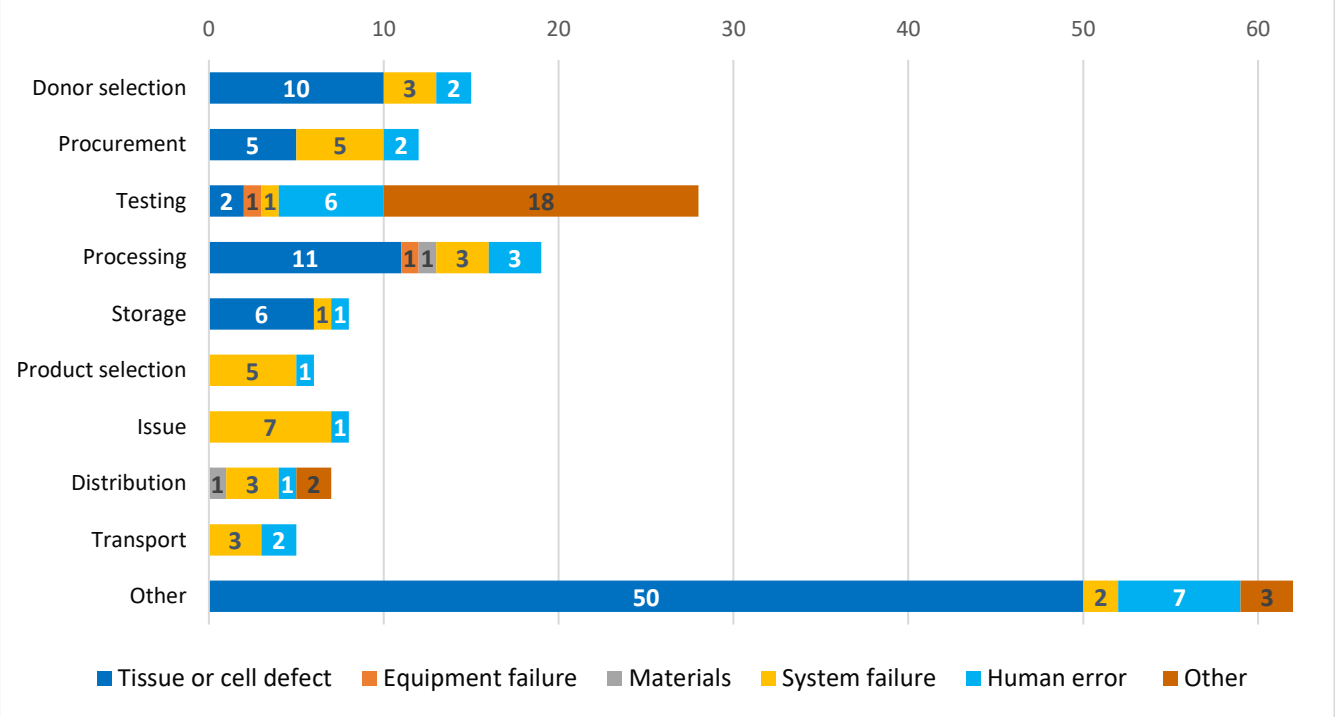

Figure 43. Distribution of SAE for replacement tissues and cells by activity step and SAE type (absolute values and percentages); data 2021

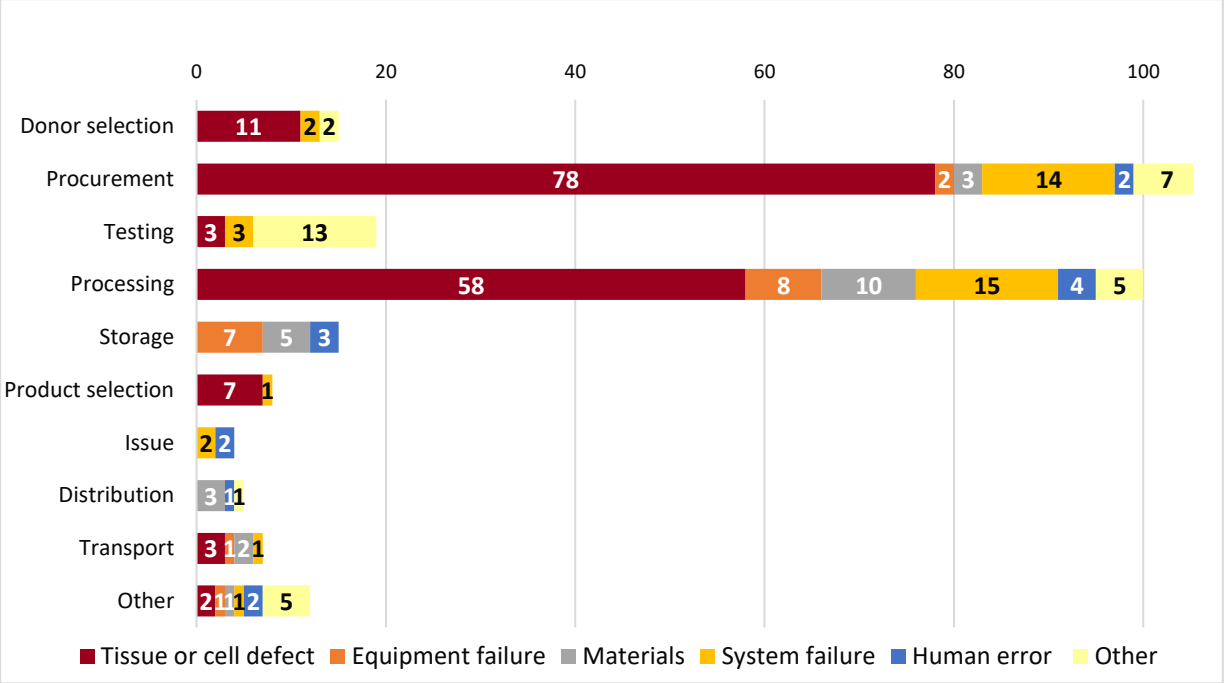

Figure 44. Distribution of SAE for haematopoietic stem cells by activity step and SAE type (absolute values and percentages); data 2021

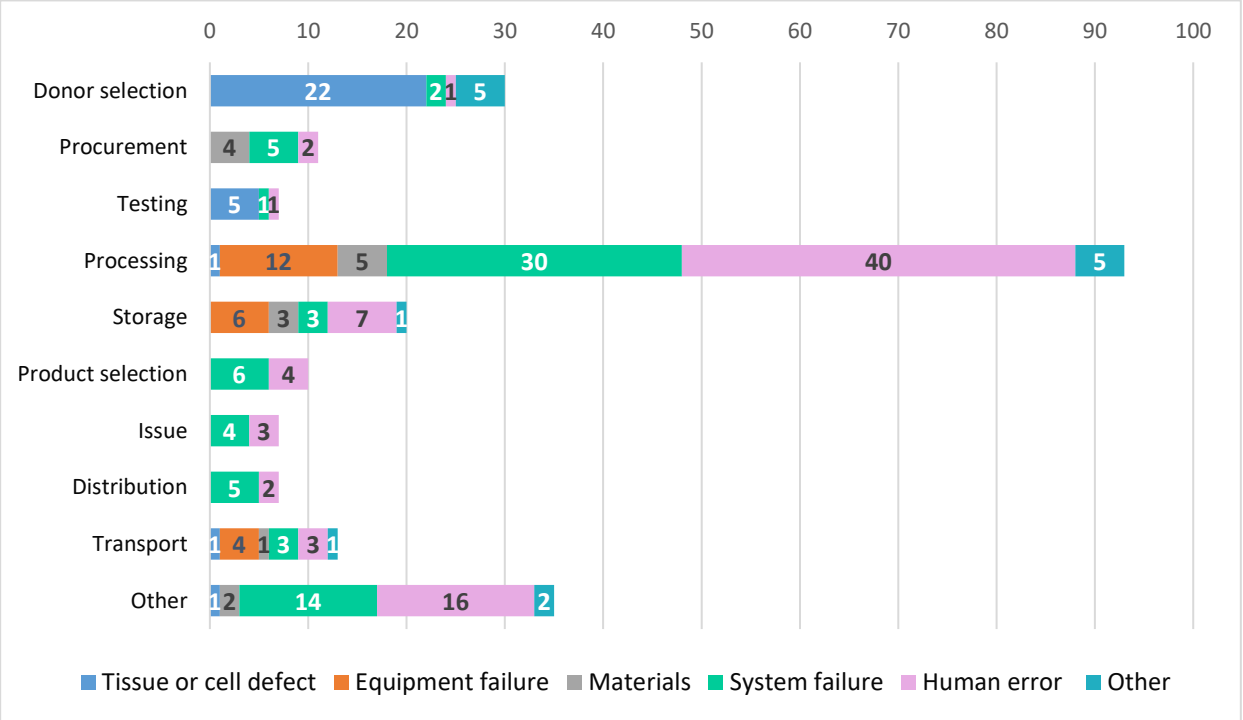

Figure 45. Distribution of SAE for reproductive tissues and cells by activity step and SAE type (absolute values and percentages); data 2021

For **replacement tissues and cells**, the largest number of reported SAE, after **Other** (62 / 36%), were SAE that occurred during **testing** (28 / 16%), **processing** (19 / 11%) **and donor selection** (15 / 9%). 50 out of the 62 SAE reported as **Other** were identified as **tissues and cells defects**, two were **system failures**, seven **human errors** and three unclassified (**Other**). Among the seven SAE in the **human error** group, three were identified as **human error - incorrect decision or omission following the correct procedure**, and four as **Other**: transplant of tissue after expiry date (2), splitting of tissue with risk of losing traceability (1) and missing tissue with loss of traceability (1).

The three SAE reported as **Other** included positive microbiological test result of tissues culture prior to implantation (bacterial contamination of skeletal tissue (1) and contamination of ocular tissue with fungi (2)).
Out of the 28 SAE in relation to testing, 18 were reported as **Other** and included bacterial and fungal contamination of pre-implant culture or transport medium of ocular tissue (cornea, scleral ring), along with identification of gram-positive bacteria in exudate post-skeletal tissue (bone) implant. The six SAE reported as **human error – incorrect decision or omission following the correct procedure** were due to a failure to perform SARS COV-2 testing timely, resulting in the loss of ocular tissue.

In the **HSC** category, the top three activities in the transfusion cycle where SAE occurred or were identified, were **procurement** (106 / 37%), **processing** (100 / 34%) and **testing** (19 / 7%). The most prevalent events encountered throughout the transfusion cycle for HSC were represented by **tissues and cells defect**, and within this type, by bacterial contamination. In the subgroup procurement, over 70% of SAE were cases of **tissues and cells defect**, followed by **system failure** (13) and **Other** (7); the most frequent type of defect reported was bacterial contamination of HSC (57 SAE); eight of the system failure SAE were positive test results for bacteria, and in the non-classified group of SAE, bacterial contamination was the issue. The SAE related to processing were predominantly cases of **tissues and cells defect** (58 cases), specifically insufficient cell count/low cell viability after thawing and bacterial contamination of HSC. Materials and system failure contributed 10 SAE each to sub-groups of events related to processing.

The SAE reported in relation to **MAR procedures** were of a different nature to those for the other two categories of cells. Most events occurred or were identified during **processing** (93 / 40%), **donor selection** (30 / 13%), while 35 SAE (15%) were unclassified (**Other**). Two-thirds of SAE during processing were attributed to **human error** (40 out of 93) and **system failure** (30 out of 93), followed by **equipment failure** (12 / 13%). In the donor selection group of SAE, **tissues and cells defects** were the most frequent. Out of 35 unclassified SAE, 11 were attributed to **system failure** and 16 to **other human error**.

Examples of SAE and the assigned specification for the three categories of tissue and cells are provided in Annex 1. Note that the intent was to provide an illustration of SAE reported for the chosen activities, not an exhaustive list. The concern is that the SAE specification was not always adequately assigned. In addition, the description provided was not always clear, preventing understanding of the events reported.

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. OHSS following oocyte donation and reactions subsequent to the administration of granulocyte colony-stimulating factor for the collection of PBSC), the Commission continues to collect such data on a voluntary basis, in agreement with the NCAs.

Seventeen countries (BE, BG, HR, CZ, EE, FI, FR, DE, EL, IE, IT, NL, PL, PT, SI, ES and SE) reported a total of 795 SAR in donors in 2021. An overview of SAR in donors during the period 2012-2022 (data pertaining to 2011-2021) is presented in *Figure 46*.

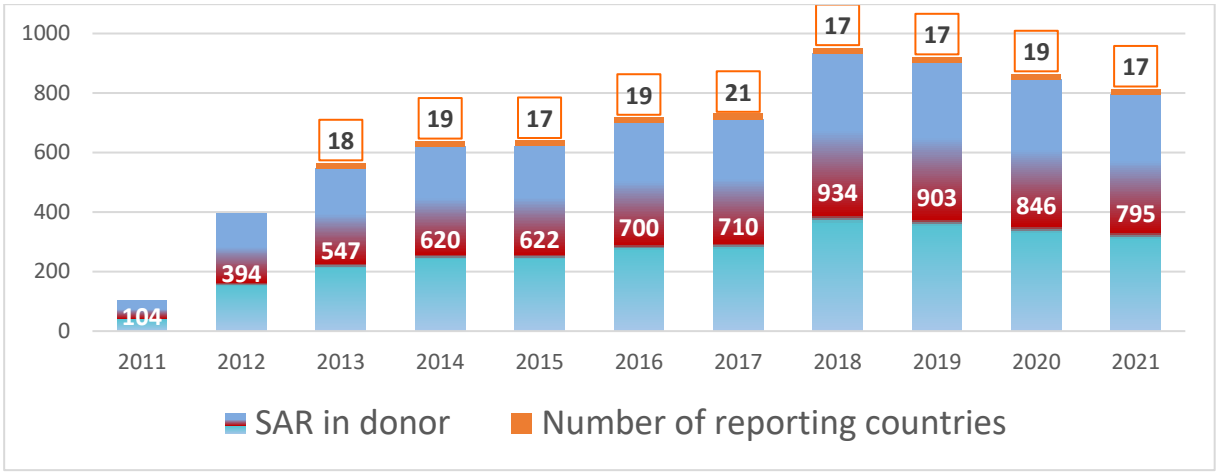

Figure 46. Number of SAR in donors by reporting countries and year; 2011-2021 comparative data

The distribution of the 795 SAR in donors reported in 2021 for the three categories of tissues and cells is presented in *Figure 47.*

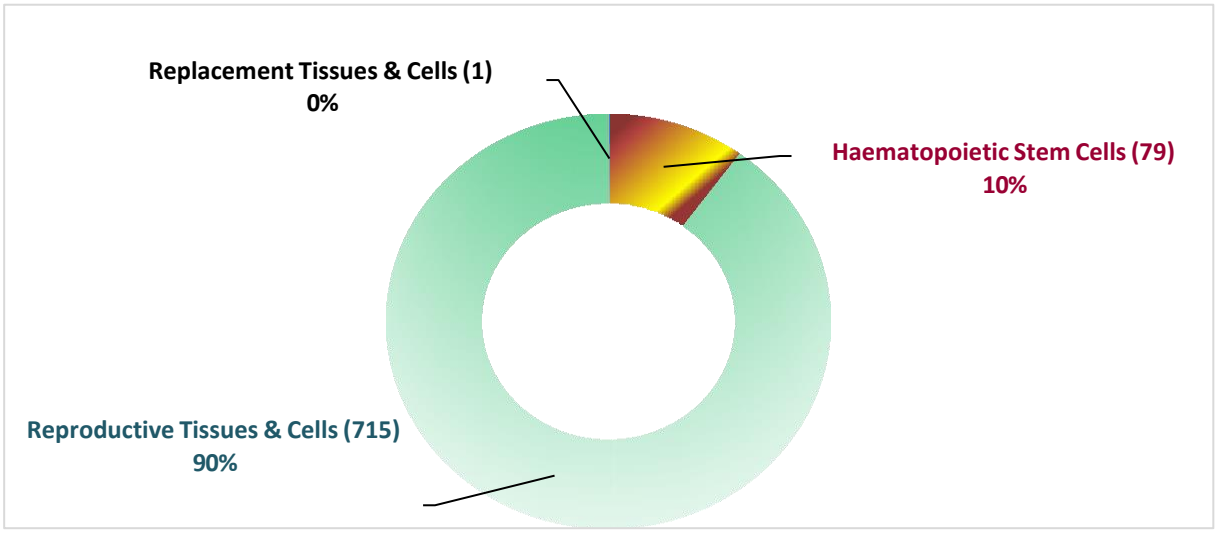

Figure 47. SAR in donors per category of donated tissue or cells (units); data 2021

The number of SAR per category of tissues and cells for the 17 countries that reported SAR in donors in 2021 is represented in *Figure 48*.

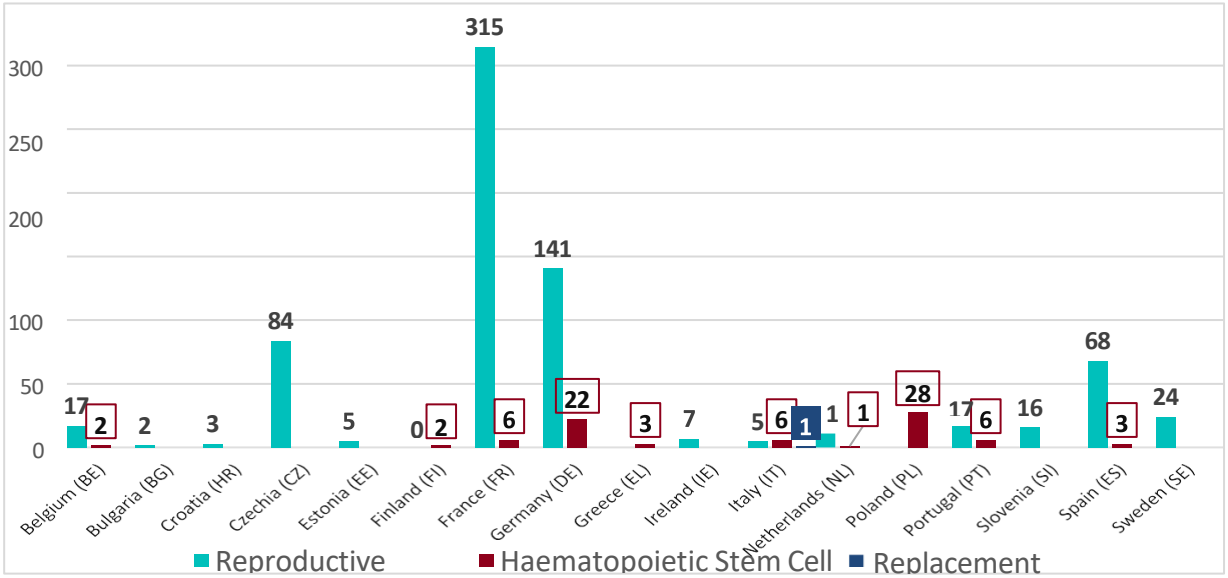

Figure 48. Number of SAR per category of tissue and cells and per country; data 2021

SAR in donors are distributed among the three categories of tissues and cells as follows:

- one case reported by Italy was associated with the donation of replacement tissues or cells (0% of all SAR in donors).
- 79 cases (10%) of SAR in donors associated with HSC were reported by ten countries (BE, FI, FR, DE, EL, IT, NL, PT, ES and SE). **Thrombotic / embolic reactions** and **Other** account for 49% of SAR in donors of HSC, followed by **autoimmune disease** (11%), **mechanical damage** (11%), **infections** (10%) and **acute systemic toxicity during mobilization or collection** (10%). Refer to *Figure 49* for all categories of reactions.

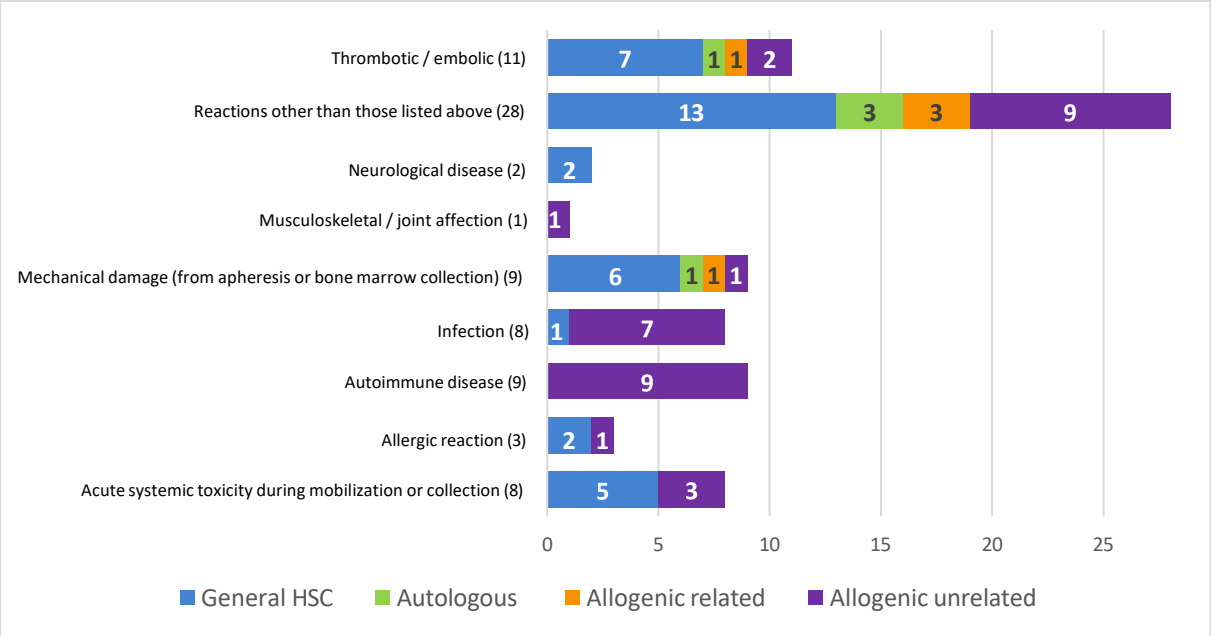

Figure 49. SAR in donors by type of haematopoietic stem cells and type of reaction; data 2021

Reaction types for the most frequent categories of reactions are presented in *Table 13* below.

Reaction category	Reaction type
Reactions other than those listed above	Hypocalcaemia, anaemia, chest pain not of cardiac or pulmonary aetiology Vasovagal reaction with syncope; seminoma; chest pain; upper abdominal pain, vomiting, increased liver enzymes No mobilization Lipothymic episode with loss of consciousness during mobilization Procedure suspended and target not reached Neoplasm, high haematocrit, product destroyed during transport, donor not starting G-CSF as scheduled STEMI following donation; patient with cardiovascular history Positive test to COVID-19 in asymptomatic and immunized patient Positive serology test for Hepatitis E in donor before apheresis
Acute systemic toxicity during mobilization or collection	Ventricular tachycardia during anaesthesia induction
Mechanical damage (from apheresis or bone marrow collection)	Catheter site pain, haematoma Spleen rupture Inadequate collection Tissue compromised due to improper bag sealing
Thrombotic / embolic	Increase in myocardial necrosis enzymes, hypokinesia of the septal and inferior apex and severe anterior descending artery stenosis Deep vein thrombosis

Table 13. SAR in donors of haematopoietic stem cells; data 2021

715 cases of SAR in donors (90%) were related to the donation of reproductive tissues or cells, of which 712 occurred following donation of oocytes, as shown in *Table 13.* Fourteen countries (BE, BG, HR, CZ, EE, FR, DE, IE, IT, NL, PT, SI, ES and SE) reported. Most of the SAR in oocyte donors were **OHSS** (394 cases) and **surgical complications** (186 cases); the remaining cases included **infectious complications**, **ovarian torsion** and **Other** types of SAR, as shown in *Table 14* and *Figure 50*. Surgical complications varied in severity, spanning from bleeding following oocyte aspiration, bladder injury/perforation with urinary retention, intestinal obstruction and pelvic haemorrhage or peritonitis, to life threatening complications. The SAR reported as **Other** include abdominal pain of various degrees of severity, bleeding, haemoperitoneum, allergy to medicines, tubal/ectopic/multiple pregnancy, OHSS post embryo transfer, etc.

Tissue category	Reaction type	Number of SAR	SAR %
Oocytes	• OHSS	394	55
	• Surgical complications	186	26
	• Other reactions	55	8
	• Infection	51	7
	• Ovarian torsion	29	4
Sperm	• Surgical complications	2	0
Other reproductive tissues	• Male genital organ cellulitis	1	0-

Table 14. Type of SAR in donors per subcategory of reproductive tissues and cells; data 2021

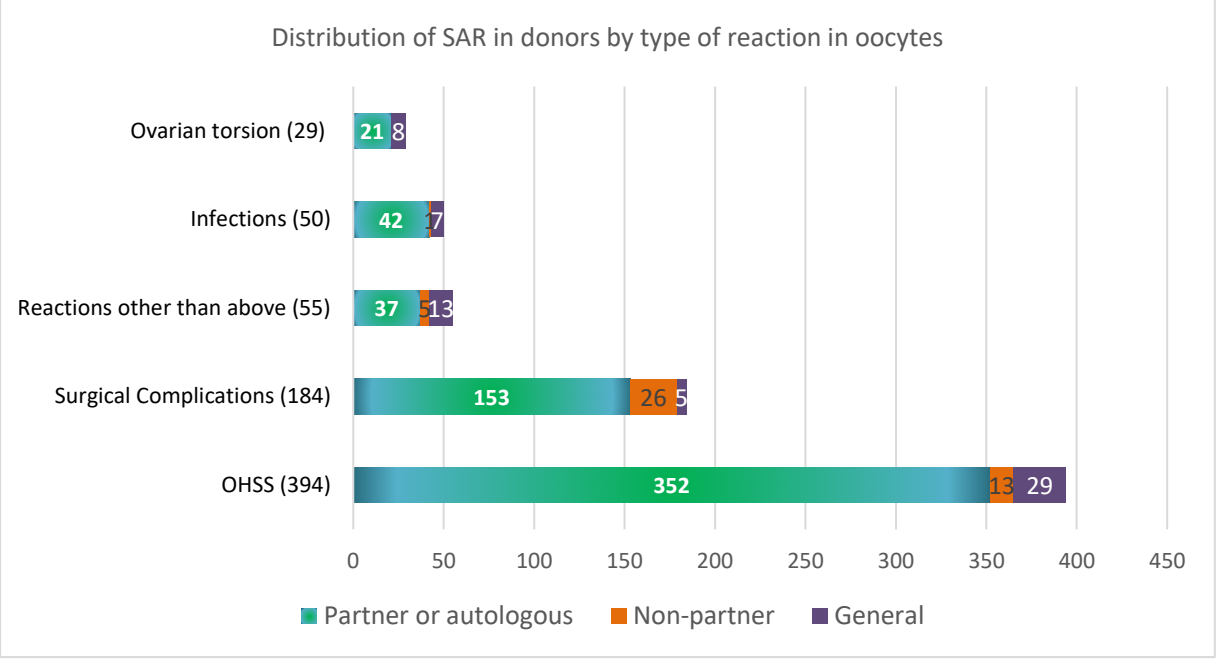

Figure 50. Distribution of SAR in donors by type of reaction in oocytes; data 2021

5 CONCLUSIONS

EU member and non-member states continued to support this initiative in 2021. Overall, the number of reporting countries remained the same, with exception that the UK only provided data for Northern Ireland following its withdrawal from the EU.

In general, the number of SAR reported since the initiative was launched in 2010 has trended upwards, thanks to the commitment of countries to the vigilance program. In terms of **non-reproductive** tissues, most of the SAR (81%) were classified as **Other SAR** (similar to previous years) indicating a need for more precise classification of types or SAR related to non-reproductive tissues and cells. The same is true for HSC and reproductive tissues and cells, where many SAR were reported as **Other SAR** due to the limited number of listed categories available, indicating a need to expand the list of types of SAR for each specific category of tissues and cells. The pattern for **reproductive** cells remained unchanged from previous years: **transmission of genetic diseases** was once again the most frequently reported SAR affecting offspring. It should be noted that the likelihood of transmitting multifactorial genetic diseases from donor to offspring is sometimes difficult to assess, and these data should be evaluated with caution.

The SAE analysis revealed specific areas of concern for each of the three categories of tissues and cells. The high percentage of **Other SAE** related to replacement tissues and cells indicates that a more concerted effort is required to improve the classification of SAE, which, in turn, would translate into more accurate determination of causes and corrective/preventive actions. **Microbial contamination** was mostly associated with HSC, while **human error** and **system failure** SAE were most commonly associated with MAR procedures.

Despite the significant improvement in data completeness and accuracy over previous years, there are still many inconsistencies among reporting countries in terms of data completeness and classification/interpretation that makes it difficult to conduct more comprehensive data analysis and draw reliable conclusions about safety and quality risks (trends) of tissues and cells. This implies the need for additional concerted efforts to strengthen national vigilance systems and encourage the implementation of a harmonised reporting dataset at the European level to enable the identification of trends and risks associated with tissue and cell treatments.

Any interpretation of the analysis and results provided in this report should take into account the limitations of the reporting exercise, notably the completeness and quality of the data reported.

Annex 1: Examples of SAE and assigned specification for replacement, HSC and reproductive tissues and cells

Replacement tissues and cells			
Activity	**SAE specification**	**Number of SAE**	**Examples**
Donor selection (15 / 9%)	Human error - Incorrect decision or omission following the correct procedure	1	Tissue rejected in time to avoid implantation of unsuitable product Retrieval of tissue from donor with exclusion criteria
	Human error - Other	1	Positive blood culture in donor
	System failure - Inadequate process, procedure or documentation	3	Electronic form not requiring critical health information resulting on release of tissue from donor with malignancy Late receipt by TE of information from foreign procurement facility concerning infection in donor
	Tissue or cell defect	10	Positive post-mortem COVID-19 test results; tissues rejected (pre-mortem test result negative) Cells not meeting specification deemed unsuitable Retrospective contraindication Malignant disease transmission in recipient from tissue donor Contraindication for donation identified post-transplantation
Testing (28 / 16%)	Equipment failure	1	Malfunctioning testing instrument, delaying release of tissues
	System failure - Inadequate process, procedure or documentation	1	Invalid test performed with loss of one tissue
	Tissue or cell defect	2	Donor test positive result for sexually transmitted disease (STD) pathogen
	Human error - Incorrect decision or omission following the correct procedure	6	Failure to perform SARS COV-2 testing timely with loss of ocular tissue
	Other	18	Bacterial and fungal contamination of pre-implant culture or transport medium of ocular tissue (cornea, scleral ring) Identification of gram-positive bacteria in exudate post-skeletal tissue (bone) implant
Processing (19 / 11%)	Equipment failure	1	Malfunctioning of HVAC system in clean room designated for processing requiring cease of activity
	Human error – Following the wrong procedure	1	Processing of tissue not as per specification resulting in delay of treatment
	Human error - Incorrect decision or omission following the correct procedure	1	Packaging of tissue not as per specification
	Human error - Other	1	Loss of tissue (fell on the ground)
	Materials	1	Improper sealing of packaging impacting sterility of internal package

Replacement tissues and cells			
Activity	**SAE specification**	**Number of SAE**	**Examples**
	System failure - Inadequate process, procedure or documentation	2	Secondary packaging omitted (multiple tissues affected) Contamination of tissue with gram-positive bacteria (multiple tissues affected)
	System failure - Other failure of the quality management system	1	Mechanical impurities detected in tissues
	Tissue or cell defect	11	Bacterial contamination of tissue after aseptic processing Loss of tissue during processing through rupture Tissue not meeting the specification resulting in cancellation of transplant Graft failure due to tissue not having the required characteristic Bacterial contamination of tissue
Other (62 / 36%)	Human error - Incorrect decision or omission following the correct procedure	3	Loss of tissue (fell on the ground) Tissue culture not performed prior to transplantation Tissue from donor with malignancy implanted
	Human error - Other, or no information to assign the above options	4	Tissue transplanted after expiry date Tissue splitting with risk of losing traceability Missing tissue with loss of traceability
	System failure - Inadequate process, procedure or documentation	1	Contamination of tissue during manipulation in the operating theatre
	System failure - Staffing, workload or skill-mix	1	Lack of communication resulting in operating theatre being unavailable for scheduled transplant; transplant cancellation
	Tissue or cell defect	50	Bacterial contamination of tissue Malignant disease transmission in recipient from tissue donor (discovered months after transplant) Post donation information about malignancy in donor Positive microbiological test results (multiple tissues)
	Other	3	Fungal contamination of tissue identified post-transplantation Bacterial and fungal contamination of pre-implant culture

Haematopoietic stem cells			
Activity	**SAE specification**	**Number of SAE**	**Examples**
Procurement (106 / 37%)	Equipment failure	2	Out-of-specification test result Malfunction of collection set
	Human error - Incorrect decision or omission following the correct procedure	2	Microbial contamination of HSC Non-conforming apheresis product
	Materials	3	Difficulties during collection due to malfunctioning equipment
	System failure - Inadequate process, procedure or documentation	13	Inadequate assessment of patient's peripheral veins prevented collection of autologous HSC Improper sampling for quality control resulting in an overestimate of cell amount Incomplete information and documentation provided by international donor centre Insufficient cell count Positive test result for bacteria (8 SAE) Non-conforming HSC distributed due to lack of procedure
	System failure - Staffing, workload or skill-mix	1	Processing and procurement temporarily paused
	Tissue or cell defect	78	Non-conforming imported bone marrow; processing did not render it suitable for use Bacterial contamination of HSC (57 SAE) HSC not meeting the specification (low cell count, low cell viability after thawing) HSC not meeting the specification (Low cell count and viability of collected cells) Non-conforming HSC (presence of clots of unknown cause); alternate type of HSC administered subsequently Bacterial contamination of apheresis product requiring new apheresis procedure
	Other	7	Bacterial contamination (6 SAE) Contaminated HSC were released for distribution and were transplanted before test results were available
Processing (100 / 34%)	Equipment failure	8	Power outage (freezer impacted) Plant utility system malfunction resulted in a significant increase in the cell therapy unit temperature Stem cell container deterioration ("bag rupture") during thawing Defective freezer bag resulting in loss of cells Centrifuge malfunction

Haematopoietic stem cells			
Activity	**SAE specification**	**Number of SAE**	**Examples**
	Human error - Incorrect decision or omission following the correct procedure	3	Incorrect operating parameters set-up resulting in low yield of cells Inadvertently leaving a pocket in freezer “presence of gram germ in lymphoapheresis product infused to the patient” (ES) contaminated HSC infused?
	Human error – Other	1	Sterility of HSC potentially compromised due to container integrity issue; cells discarded with no consequence
	Materials	10	“product error in stem cells freezing bag” Failure of process step with loss of autologous HSC “failure of red blood cell depletion before pre-freezing” Bacterial contamination of HSC Circuit break or container (pocket) leak Non-conforming product (low cell viability after thawing) “CBU pocket freezing program error”
	Other	5	HSC destroyed based on positive control of operator’s fingers Contamination False positive result of first quality control Processing delayed due to late delivery of materials as a consequence of a strike in another country
	System failure - Inadequate process, procedure or documentation	10	“Anomaly during the identification process” Improper selection of container for cell collection Use of expired critical chemical (DMSO) “Concentration error of DLI graft delivered and prepared from cryopreserved HSC” FR “Set error for dilutions of a mononuclear cell graft” “Positive test for Cutibacterium acnes” DE
	System failure - Other failure of the quality management system	1	Bacterial contamination of HSC
	System failure - Training or education	4	Inadvertent destruction of HSC by operator due to lack of knowledge HSC destroyed based on positive control of operator’s fingers DMSO omitted (cryopreservation)

Haematopoietic stem cells			
Activity	**SAE specification**	**Number of SAE**	**Examples**
	Tissue or cell defect	58	Bacterial contamination of HSC (multiple) Exceptional release of autologous unit of HSC with bacterial contamination; no infection in recipient Cell viability affected by a combination of factors, transport included Non-conforming product (insufficient cell quantity; low cell viability after thawing – 35 SAE) Non-conforming product following thawing (bone marrow aggregates) Aggregates formation during cryopreservation Clots and aggregated formed during deplasmation required manual filtration that ended on significant loss of cells Non-conforming product (insufficient cells collected)
Testing (19 / 7%)	System failure - Inadequate process, procedure or documentation	3	Omission to confirm virological testing
	Tissue or cell defect	3	Positive test result (marker of transmissible infection present)
	Other	13	Positive test results

Reproductive tissues and cells			
Activity	**SAE specification**	**Number of SAE**	**Examples**
Processing (93 / 40%)	Equipment failure	12	Loss of cells during transport from one TE to another Incubator power outage; cells not impacted Loss of oocytes Sensor failure during cell freezing Incubator incident (increase in O_2 level; drop in temperature) Incorrect distribution of gas in incubators Cryotube deterioration; loss of cell sample Power outage in microinjection microscope preventing assessment of cells
	Human error - Incorrect decision or omission following the correct procedure	14	Failure to perform task without complete loss of cycle for recipient Inadvertent destruction of cells due to incorrect entry made in the patient's electronic file Incorrect assumption about the status of cells and omission of banking of straws; cells loss Identification error (label) Partial processing of cells (some cells forgotten) Failure to follow instructions (embryo not frozen; transfer of incorrect type of cell) Degeneration of oocytes due to insufficient oil drops to cover the culture medium; patient cycle affected
	Human error – Other	21	Operator manipulation error resulting in loss of cells Only embryo lost during processing (plate falling to the ground) Mix-up of gametes with loss of traceability Quarantined gametes used) no information on partner or donor oocyte) Mix-up of sperm from two different donors; loss of gametes Handling incidents (excluding falls) Loss of traceability of two embryos Embryo compromised irreversibly due to lack of oil
	Human error - Following the wrong procedure	5	Handling incidents (excluding falls) Non-compliance with prescription instructions (incorrect embryo transferred) Inadvertent discarding of cell by placing it in the incorrect disc (only available oocyte)
	Materials	5	Incorrect labelling of culture dishes ending up in loss of the cycle by multiple patients Material fall Handling incidents (excluding falls)

Reproductive tissues and cells			
Activity	**SAE specification**	**Number of SAE**	**Examples**
	Other	5	Only available embryo lost during thawing procedure (blastocyst remaining attached to the pipette) Only available embryo lost during transfer (degraded blastocyst while trying to detach it from the pipette) Material fall Culture contamination Bacterial growth during incubation; bacteria from donor
	System failure - Inadequate process, procedure or documentation	14	Identification error (vial label) Not following prescription instruction (request for straw instead of donor insemination) Identification error (culture dish label); mix-up of gametes Non-compliance with prescription instruction; erroneous freezing of cells Defects in the management of thawing planning Transcription error on the transfer sheet Handling incidents (excluding falls) Non-compliance with prescription instructions (incorrect embryo transferred) Inappropriate use of a product during vitrification Accidentally discarded cells (oocytes) Contamination of dish with cells of a different type
	System failure - Other failure of the quality management system	13	Mix-up of cells identified (cells from two donors collected in the same tube) at receipt on tissue bank; one patient was affected by the need to destroy cells intended for treatment Misplacement of one patient's cells (embryos) in an incubator container destined for another patient; no new box possible for affected patient due to lack of balance medium Inadvertently discarded cell (embryo) during transfer to new culture medium Cells development impaired (mitotic arrest due to hyperosmotic medium; insufficient oil droplets to cover culture medium) Culture contamination Storage tank overloaded; while retrieving a vial for thawing, vials with another patient's material fell
	System failure - Training or education	1	Cells incubated in out of order equipment CO_2 and O_2 turned off); treatment cycle lost
	System failure - Staffing, workload or skill-mix	2	Failed vitrification of embryo; omission following the correct procedure

Reproductive tissues and cells			
Activity	**SAE specification**	**Number of SAE**	**Examples**
	Tissue or cell defect	1	Contamination of culture medium
Donor selection (30/ 13%)	Human error - Incorrect decision or omission following the correct procedure	1	Omission of partner testing prior to IUI procedure; no consequence; post treatment testing results were negative
	System failure - Inadequate process, procedure or documentation	2	Positive test result for STD pathogen on a single sample from a given donor; no positive test results on samples from other donations; all straws from current donation destroyed Omission of biological tests prior to IUI
	Tissue or cell defect	22	Offspring of oocyte donor with psychiatric syndrome Unknown genetic factor (non-partner donation) Donor not disclosing previous donations and being permanently blocked by another bank Genetic mutation not initially detected during screening testing Donor diagnosed later with a multifactorial or possibly hereditary condition Unknown at the time of donation that the donor was a carrier of a genetic condition; donor blocked afterwards Donor with congenital retinal dystrophy; embryos lost Donor of oocyte carrier of genetic mutation
	Other	5	Donor found to have donated in another sperm bank Positive Zika serology test after biopsy