EUROPEAN COMMISSION
DIRECTORATE GENERAL FOR HEALTH AND FOOD SAFETY

Medical Products and Innovation
Medical Products: Quality, Safety, Innovation

SUMMARY OF THE 2023 ANNUAL REPORTING OF SERIOUS ADVERSE REACTIONS AND EVENTS FOR TISSUES AND CELLS

(DATA COLLECTED FROM 01/01/2022 TO 31/12/2022 AND SUBMITTED TO THE EUROPEAN COMMISSION IN 2023)

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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).

For the purposes of this report, tissues and cells have been categorised into three groups (replacement, haematopoietic stem cells (HSC) and reproductive) 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 2022 submitted by **26 MS** plus Iceland, Liechtenstein, Norway and the United Kingdom (Northern Ireland). The report highlights the main findings and trends in the application of human tissues and cells across Europe, in terms of SARE occurrence and distribution (by category and type).

[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

2 EXECUTIVE SUMMARY

Parameter	2020 (Data 2019)	2021 (Data 2020)	2022 (Data 2021)	2023 (Data 2022)
Reporting Countries	27 25 EU MS plus Norway and the UK	28 26 EU MS plus Norway and the UK	29 25 EU MS plus Iceland, Liechtenstein, Norway and the UK (Northern Ireland)	30 26 EU MS plus Iceland, Liechtenstein, Norway and the UK (Northern Ireland)
Units processed	**2 922 117** (26 countries)	**2 646 079** (24 countries)	**3 159 362** (25 countries)	**2 892 459** (27 countries)
Units distributed	**1 360 315** (27 countries)	**1 116 519** (26 countries)	**1 192 203*** (28 countries)	**957 775**** (29 countries)
Transplant recipients**	**298 897** (22 countries)	**245 058** (19 countries)	**318 467** (24 countries)	**327 961** (26 countries)
SAR	**306** (18 countries)	**350** (18 countries)	**326** (19 countries)	**347** (17 countries)
Fatalities in recipients	-	16 (7 countries)	**20** (6 countries)	**12** (3 countries)
SAE	**949** (20 countries)	**910** (22 countries)	**694** (23 countries)	**1 133** (22 countries)
SAR in donors	**903** (17 countries)	**846** (19 countries)	**795** (17 countries)	**777** (19 countries)
Fatalities in donors	**-**	**-**	**-**	**4** (2 countries)

NOTE: FI and AT identified very minor discrepancies in the data regarding skeletal tissues and other tissues (amniotic membrane), and HSC, respectively, mainly for distributed units. Due to the negligible impact on the SARE analysis and the late communication, the initially reported data were used in the analysis.

**The number of distributed T&C in 2021 was 1 145 876 (the total in the 2021 annual report includes 46 000 replacement T&C distributed internationally by NL that are not in the scope of the SARE exercise).*

***The 957 775 units distributed in 2022 include 15 168 units of autologous cord blood (PL) (1.6% of the total distributed) that were not reportable. Due to late clarification, these data were included in the analysis, and this should be considered in the interpretation of the SARE report results.*

****Due to the minor impact on the SARE analysis and late communication, data from DE (number of HSC transplant recipients) are not included in the analysis.*

The key findings of the 2022 reporting exercise are listed below:

- Almost **3 million units of tissues and cells were processed** by 27 countries (2 892 459), of which **456 953** were **replacement tissues and cells** (reported by 23 countries), **76 236** were **HSC** (reported by 20 countries) and **2 359 270** were **reproductive tissues and cells** (reported by 18 countries). This is an 8.44% percent decrease compared to 2021.

- Almost **1 million units of tissues and cells were distributed** (957 775) for application, representing a 16.41% decrease compared to 2021, of which **506 429** were **reproductive tissues and cells** (reported by 22 countries), **405 055** were **replacement tissues and cells** (reported by 28 countries) and **46 291** were **HSC** (reported by 23 countries).

- **327 961 recipients** underwent transplant/infusion, which represents a 3% increase compared to 2021.
- Seventeen countries reported a total of **347 SAR in recipients**, of which 73% were related to reproductive tissues and cells, 17% to HSC and 10% to replacement tissues and cells:
    - 68% of the SAR associated with **replacement tissues and cells** (23 SAR) were **graft failure or delayed function**, while **transmitted infections** accounted for 18% (6 SAR)
    - 25% of the 60 SAR associated with **HSC** resulted in **graft failure or delayed function**, 12% were classified as **immunological reactions** and **23% were unclassified (other)**
    - 49% of the SAR associated with **reproductive tissues and cells** were due to the transmission of genetic conditions

- An **imputability level was not assigned for 62%** of the reported SAR in 2022, a slight improvement compared to the previous year (65%). In 53% of cases for which imputability was reported, 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 and medically assisted reproduction (MAR) procedures.

- In 2022, **12 fatalities in** recipients and offspring were reported (lower than the 20 reported in 2021, but comparable to 2020), of which five were potentially attributed to HSC and six to reproductive tissues and cells; the only fatality associated with replacement tissues and cells occurred years after a heart valve transplant (imputability level 1).

- A total of **1 133 SAE** were reported in 2022 (compared to 694 in 2021 and 910 in 2020). Out of the 1 133 SAE, 209 were related to replacement tissues and cells (reported by 14 countries), 689 to HSC (17 countries) and 235 to reproductive tissues and cells (17 countries).
    - In terms of the type of SAE, **other** was the most commonly reported category of events (35%), followed by **system failure** (27%), **tissues and cells defect** (16%) and **human error** (13%); the number of events attributable to **human error** was lower compared to the previous two years, but the number of **unclassified events (other)** reported increased. **System failure** and **other** were the most frequent types of SAE associated with replacement tissues and cells and HSC, while **human error** and **system failure** were the most frequent types of SAE associated with reproductive tissues and cells.
    - In terms of **activity steps**, SAE for replacement tissues and cells most frequently occurred or were identified during **processing**, followed by **testing** and **other**; events that involved HSC occurred or were identified during **processing**, **testing** and **procurement**, while the most reported SAE for reproductive tissues and cells were attributed to **processing** and **donor selection**, similar to the previous years.

- **777 SAR in donors** were reported on a voluntary basis by 19 countries, the vast majority (90%) of which were 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.

- **Four fatalities in living donors** of tissues and cells were reported for the first time: two related to autologous donation of HSC and two related to MAR procedures (oocyte retrieval and fertility preservation procedures). Reporting of imputability is not required for fatalities in donors. In one case, the imputability was assessed as unlikely.

3 DATA COLLECTION AND ANALYSIS

To ensure a harmonised approach to data collection, the Commission provided participating NCAs with access to the following standardised reporting tools:

α. ***An electronic reporting form (2023 version)***

β. ***The Common Approach document (2023 version)***, which complements the electronic reporting form and provides updated user instructions for data compilation.

Both the reporting countries and the Commission verified the accuracy of the EDQM's analysis and interpretation of SARE data for 2022.

4 MAJOR FINDINGS

4.1 Activity data (denominators)

As part of the EU SARE exercise, MS provide data on the TC activities (**number of tissues distributed**, the **number of recipients** and the **number of tissues processed) that serve as denominators for analysis of SARE occurrences.** Accordingly, 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 still faced challenges in providing complete data, especially for certain types of tissues and cells, certain activities or certain measurement units. Therefore, caution should be used when interpreting results and deriving conclusions from this exercise.

4.1.1 Tissues and cells distributed

The total number of **tissues and cells distributed** in 2022 reported by countries was 16.41% lower than in the previous year, totalling 957 775 units, of which 405 055 units were replacement tissues and cells, 46 291 units were HSC and 506 429 units were reproductive tissues and cells.

4.1.1.1 Replacement tissues and cells

In the case of replacement tissues and cells, 28 countries reported data on **units distributed** (AT, BE, BG, HR, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LV, LT, LU, MT, NL, NO, PL, PT, RO, SI, SE and UK (NI)). There was a 3% increase in the number of units distributed, from 391 687 in 2021 to 405 055 in 2022. In addition to skeletal tissues (302 904 units) and ocular tissues (40 327 units) – the main types of replacement tissues and cells distributed – a large number of other tissues or cells was reported in 2022 (40 643 units, an 82% increase from 2021). See *Figure 1* for more details.

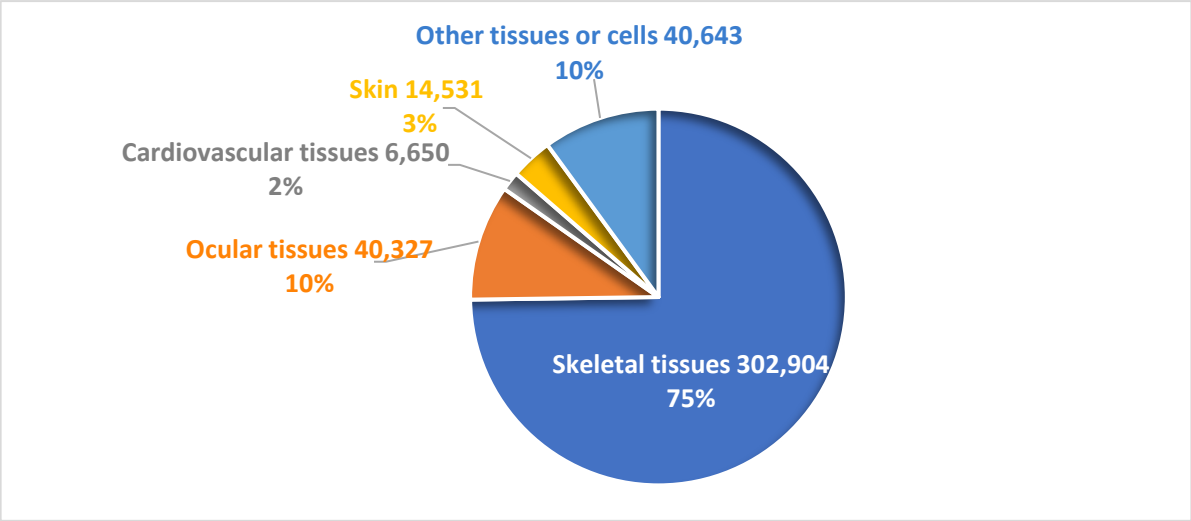

Figure 1. Total number of replacement tissues and cells distributed (units); data 2022

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. Although bone, corneas and blood vessels remained the most frequently distributed tissues in each respective category, the reporting on general skeletal tissues, general ocular tissues and other replacement tissues and cells increased substantially in 2022 compared to 2021 (+62%, +625% and +287%), while the number of units of bone and cornea distributed decreased by 10% and 29%, respectively.

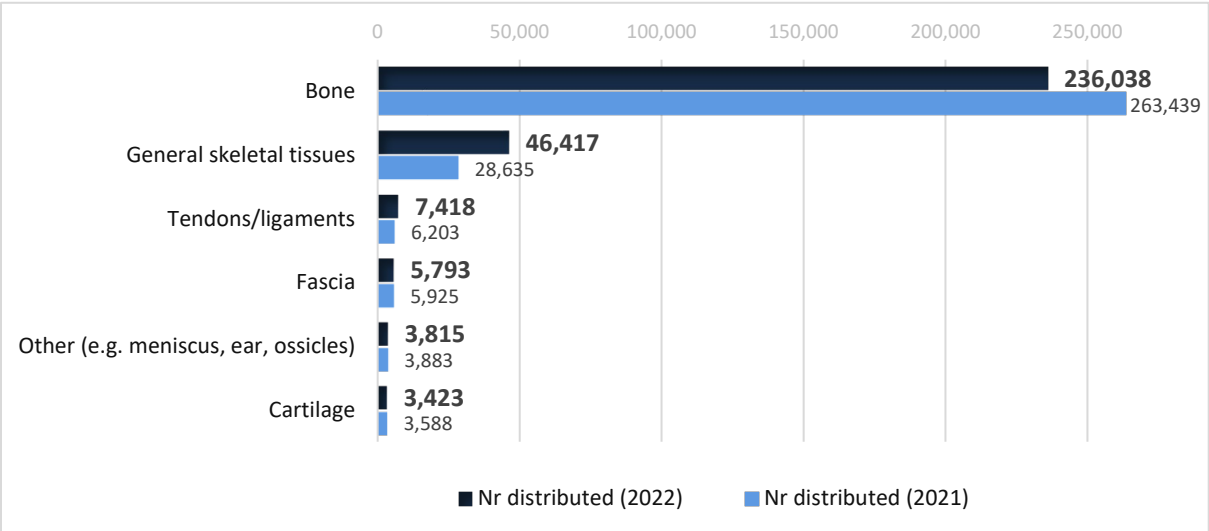

Figure 2. Number of skeletal tissues distributed per subcategory (units);[3] comparative data (2021 and 2022)

[3] 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).

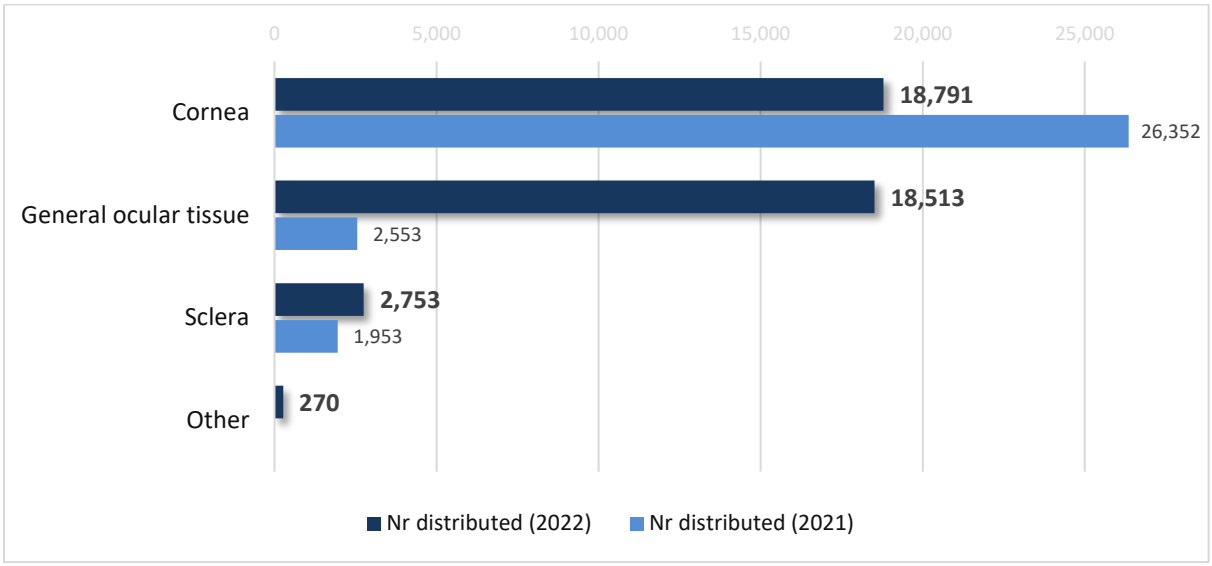

Figure 3. Number of ocular tissues distributed per subcategory (units); comparative data (2021 and 2022)

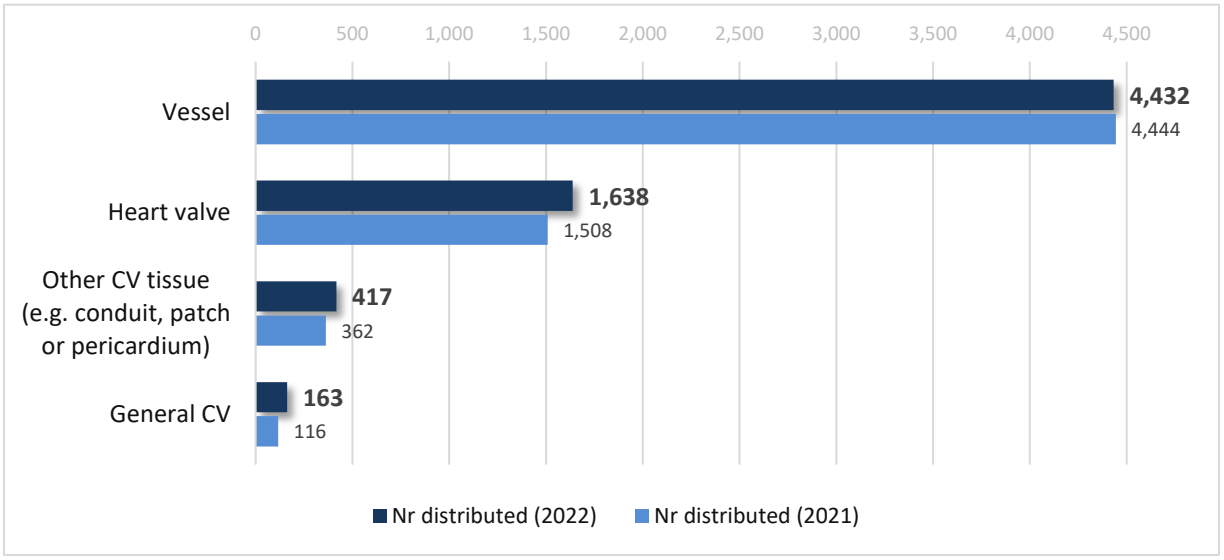

Figure 4. Number of cardiovascular tissues distributed per subcategory (units); comparative data (2021 and 2022)

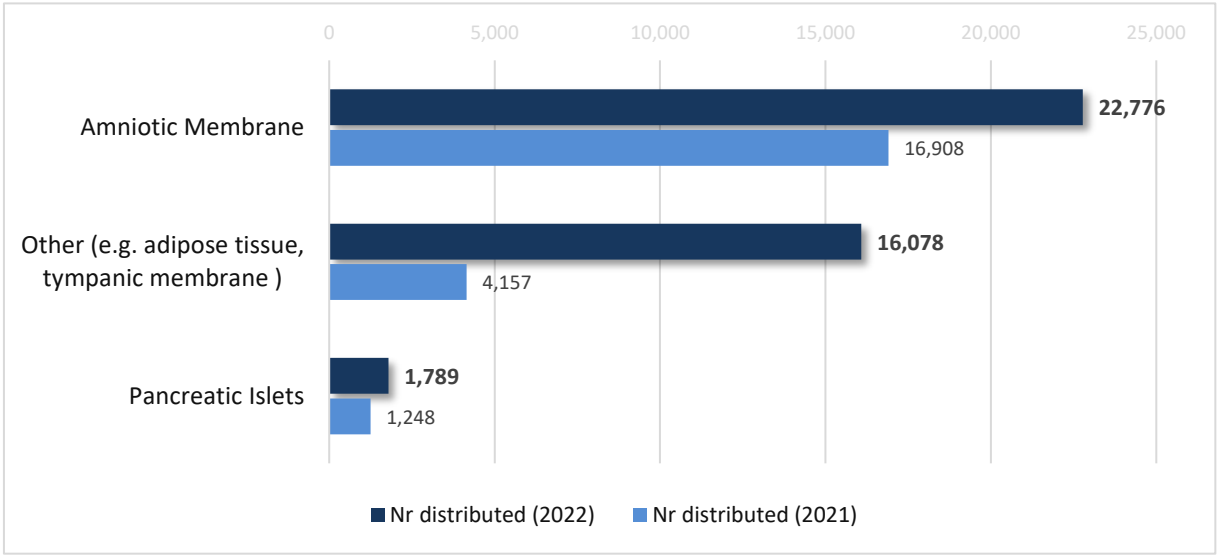

Figure 5. Other replacement tissues distributed per subcategory (units); comparative data (2021 and 2022)

A total of 14 531 units of skin were distributed in 2022. Note that skin units reported in square centimetres (cm^2) were not included in the total above. Refer to the table below for details.

Country	Processed (cm^2)		Distributed (cm^2)	
	2022	2021	2022	2021
Belgium	N/A	-	209 197	209 557
France	600 000	N/A	420 000	380 000
Germany	113 174	126 748	202 646	150 067
Spain	-	860 364	341 778	419 294

4.1.1.2 Haematopoietic stem cells

Twenty-three countries reported data on distributed HSC (AT, BE, BG, CY, CZ, DK, EE, FI, EL, HR, HU, IE, IS, IT, LT, NL, NO, PL, PT, RO, SI, SE and UK(NI)). Out of 46 291 HSC units reported as distributed, the majority (26 233 units) were peripheral blood stem cells (PBST), followed by cord blood (15 494 units) and bone marrow (1 904 units).

Note: *The increase in the total number of HSC distributed in 2022 is explained by the reporting of 15 168 units of autologous cord blood by PL. The cord blood units were not reportable, but due to late clarification, data were included in the analysis, and this should be considered in the interpretation of the results of this report.*

See *Figure 6* for more details.

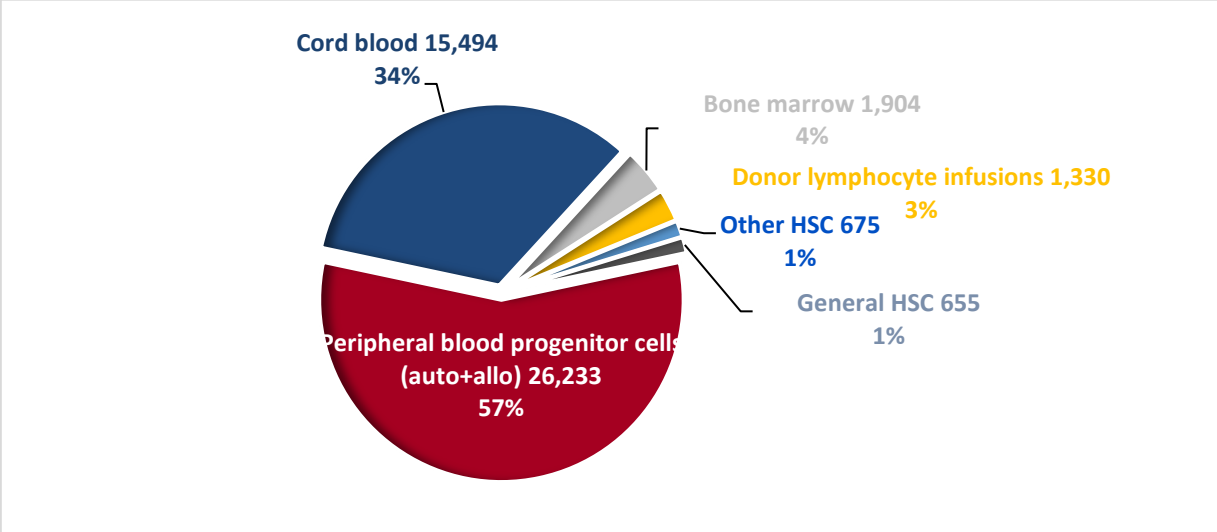

Figure 6. Total number of haematopoietic stem cell units distributed (absolute values and percentage); data 2022

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

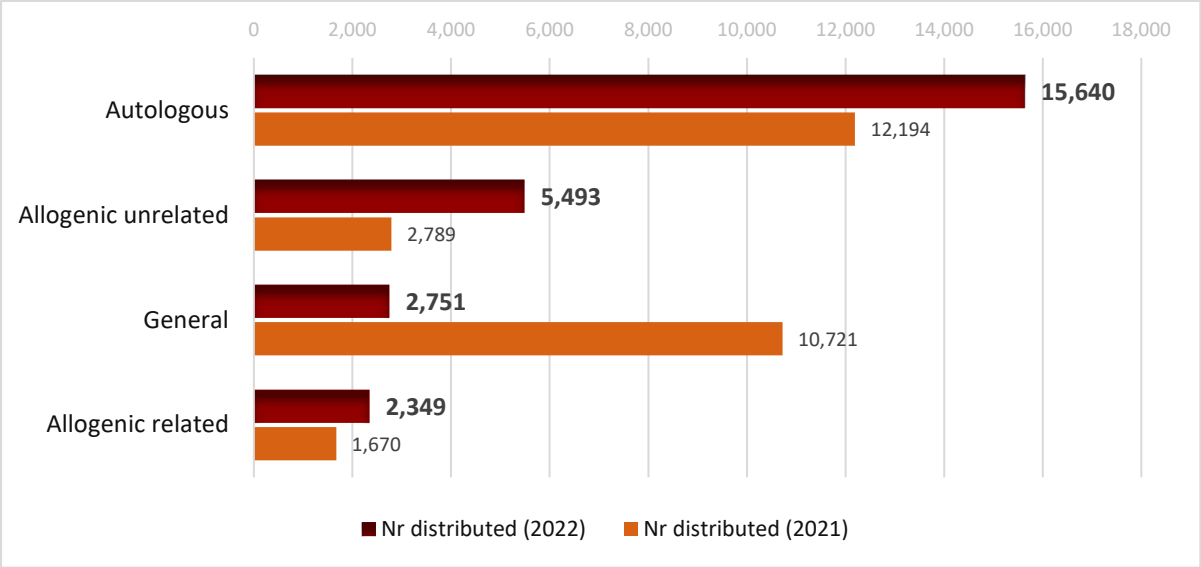

Figure 7. Number of peripheral stem cell units distributed by type; comparative data (2021 and 2022)

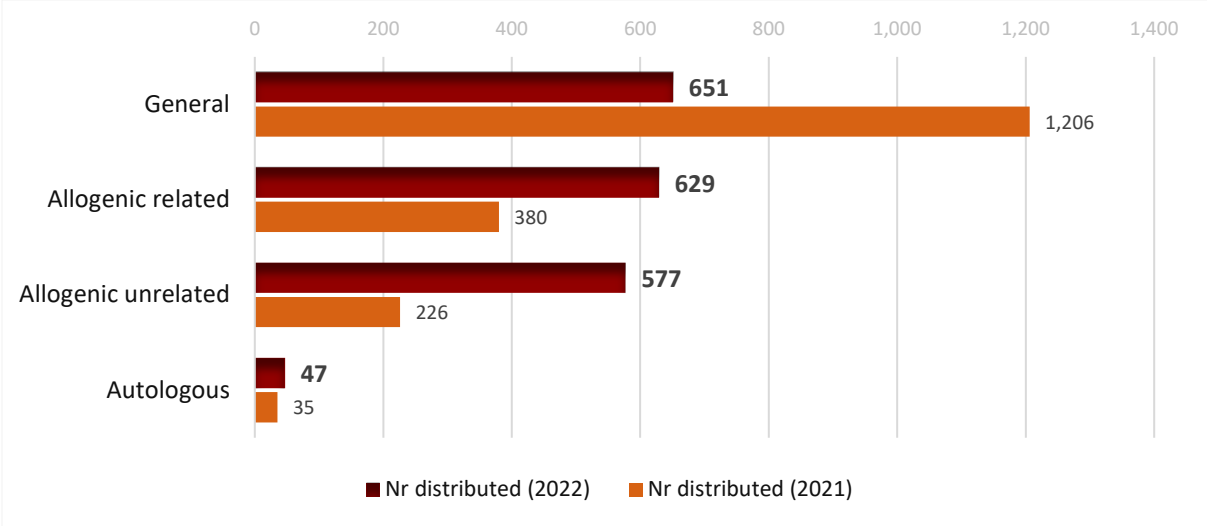

Figure 8 Number of bone marrow units distributed by type; comparative data (2021 and 2022)

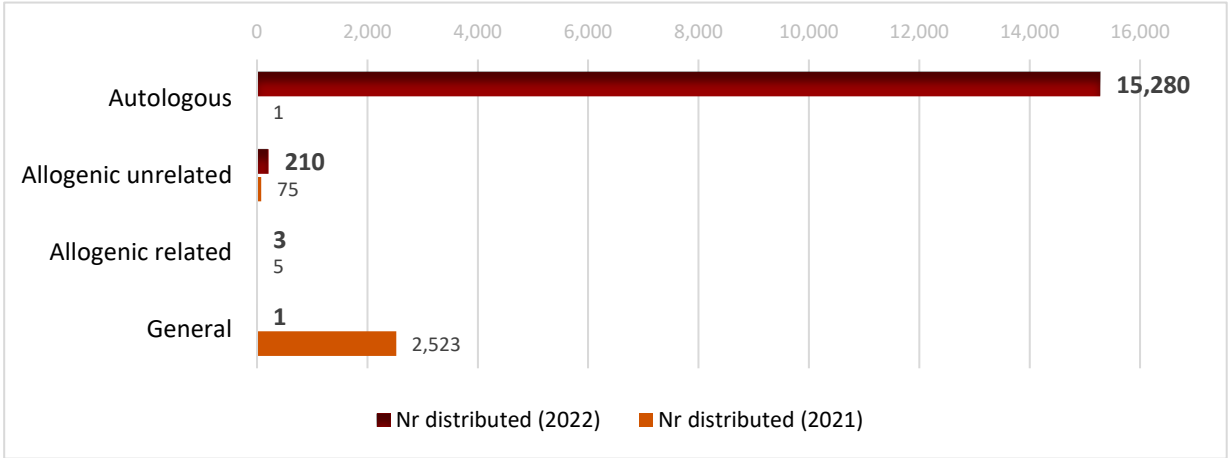

Figure 9. Number of cord blood units distributed by type; comparative data (2021 and 2022)

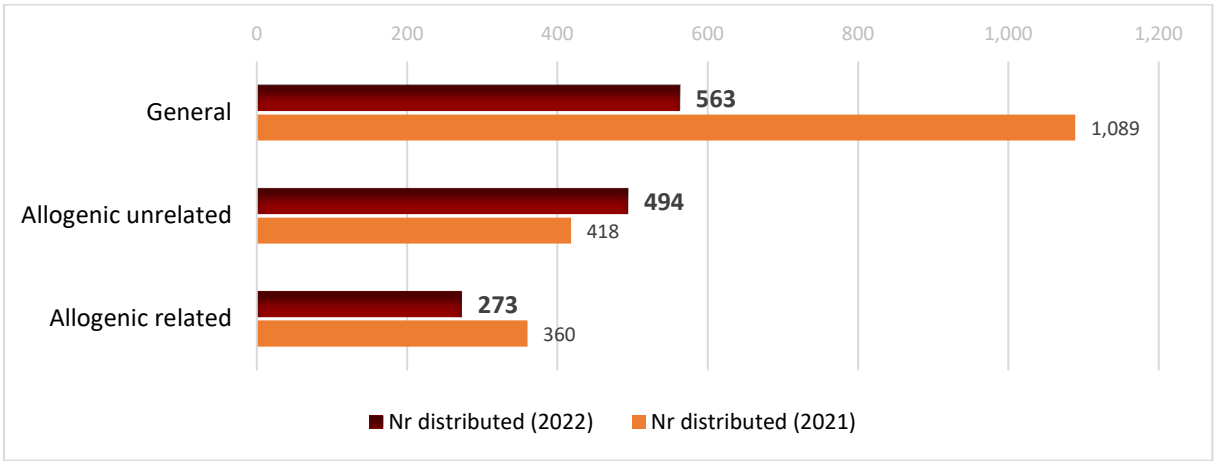

Figure 10. Number of donor lymphocyte infusion units distributed by type; comparative data (2021 and 2022)

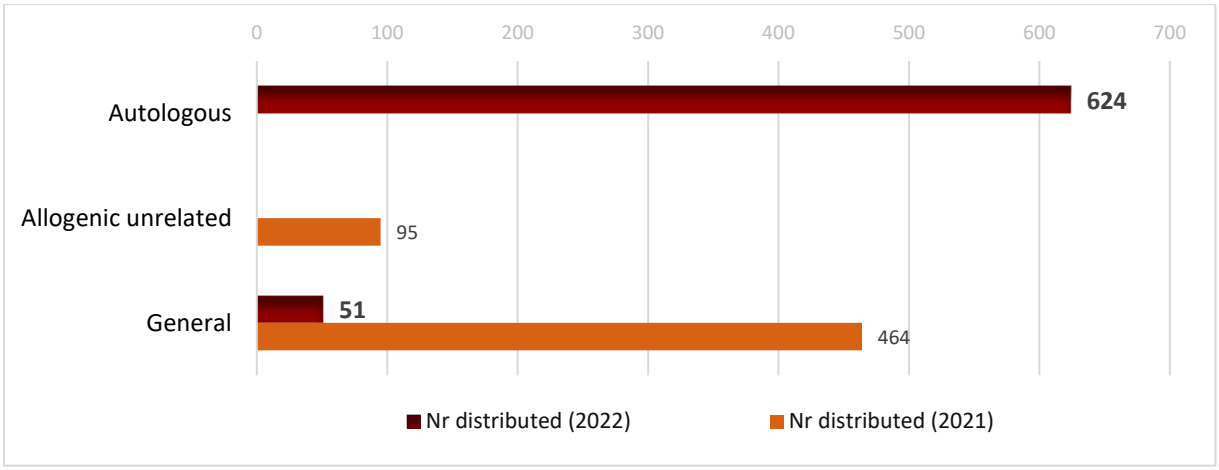

Figure 11. Number of other HSC units distributed by type; comparative data (2021 and 2022)

4.1.1.3 Reproductive tissues and cells

Twenty-two countries (AT, BE, BG, CY, CZ, DE, DK, EE, FI, HR, HU, IS, IE, LT, LU, LV, MT, NL, NO, RO, SI and SE) reported activity data for reproductive tissues and cells. Of the 506 429 units of reproductive tissues distributed, 242 409 sperm units were delivered for insemination (*Figure 12*) and 246 743 embryos were delivered for transfer following partner or non-partner donation (*Figure 13*). In addition, 14 376 ovarian tissues and 2901 testicular tissues were distributed for the treatment of infertility (*Figure 14*). The reduction in the number of units distributed in 2022 compared with previous years does not reflect a real decrease in activity or reporting (957 775 units distributed in 2022, 1 145 876 in 2021 and 1 116 519 in 2020). Unlike in previous years, BE did not report 196 000 units of sperm and oocyte units for IVF/ICSI procedures, as these categories are not included in the *Common Approach.*

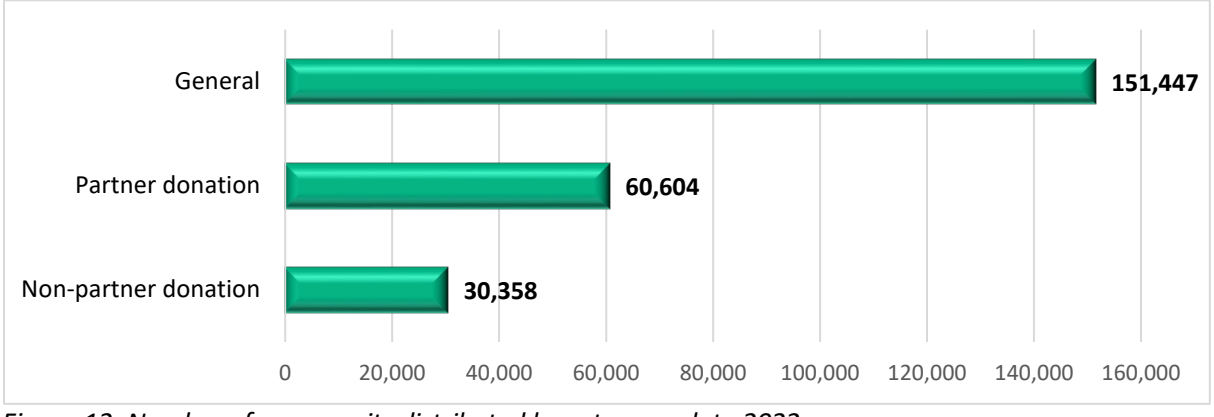

Figure 12. Number of sperm units distributed by category; data 2022

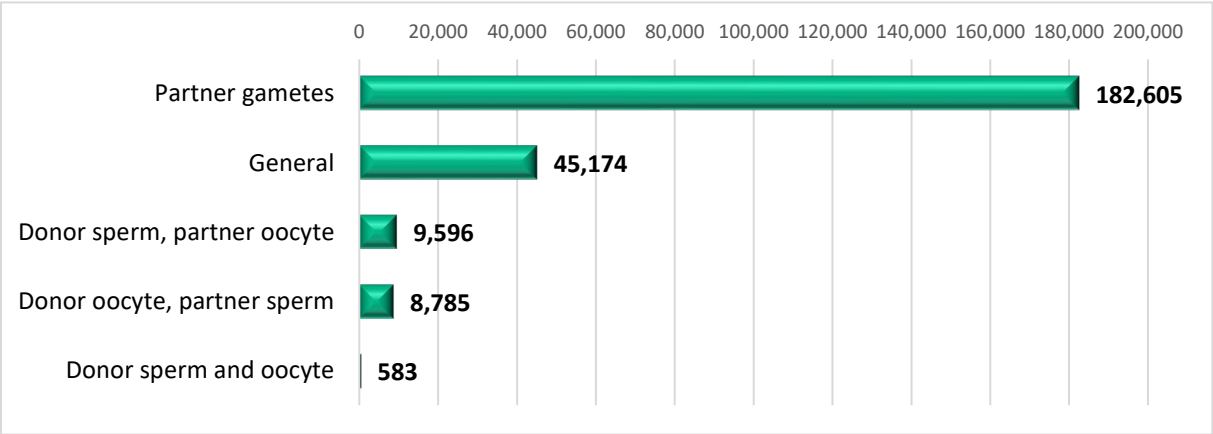

Figure 13. Number of embryos distributed by category; data 2022

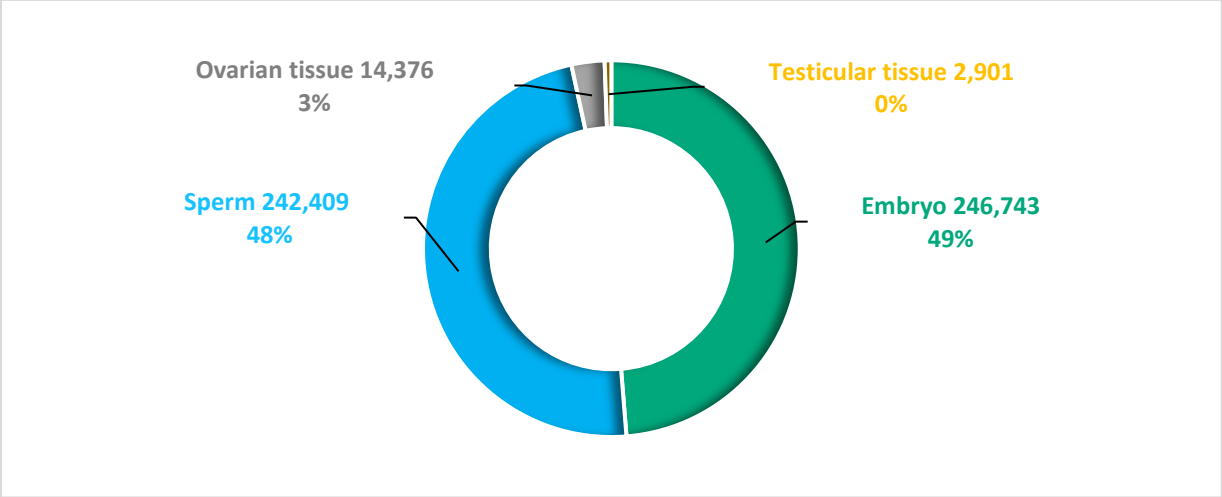

Figure 14. Total number of reproductive tissues distributed (units); data 2022

4.1.1.4 Incidence of distributed tissues and cells and recipients (per million population)

Taking into account the demographic data of the reporting countries on 1 January 2022,[4] 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.

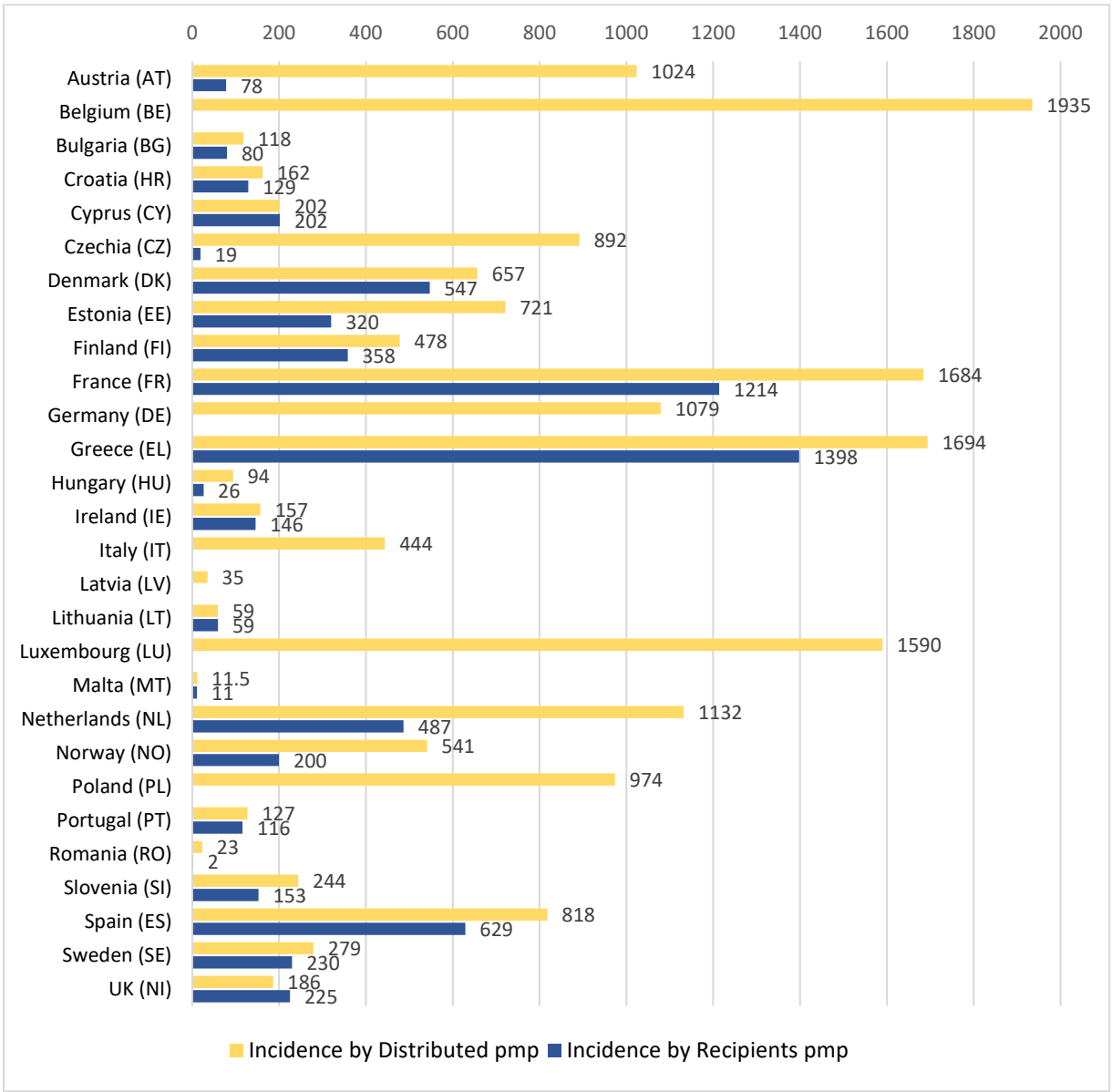

Figure 15. Incidence of replacement tissue and cell units (number of units distributed and number of recipients per million population); data 2022

[4] https://ec.europa.eu/eurostat/web/population-demography/demography-population-stock-balance/database; https://www.nisra.gov.uk/publications/2022-mid-year-population-estimates-northern-ireland

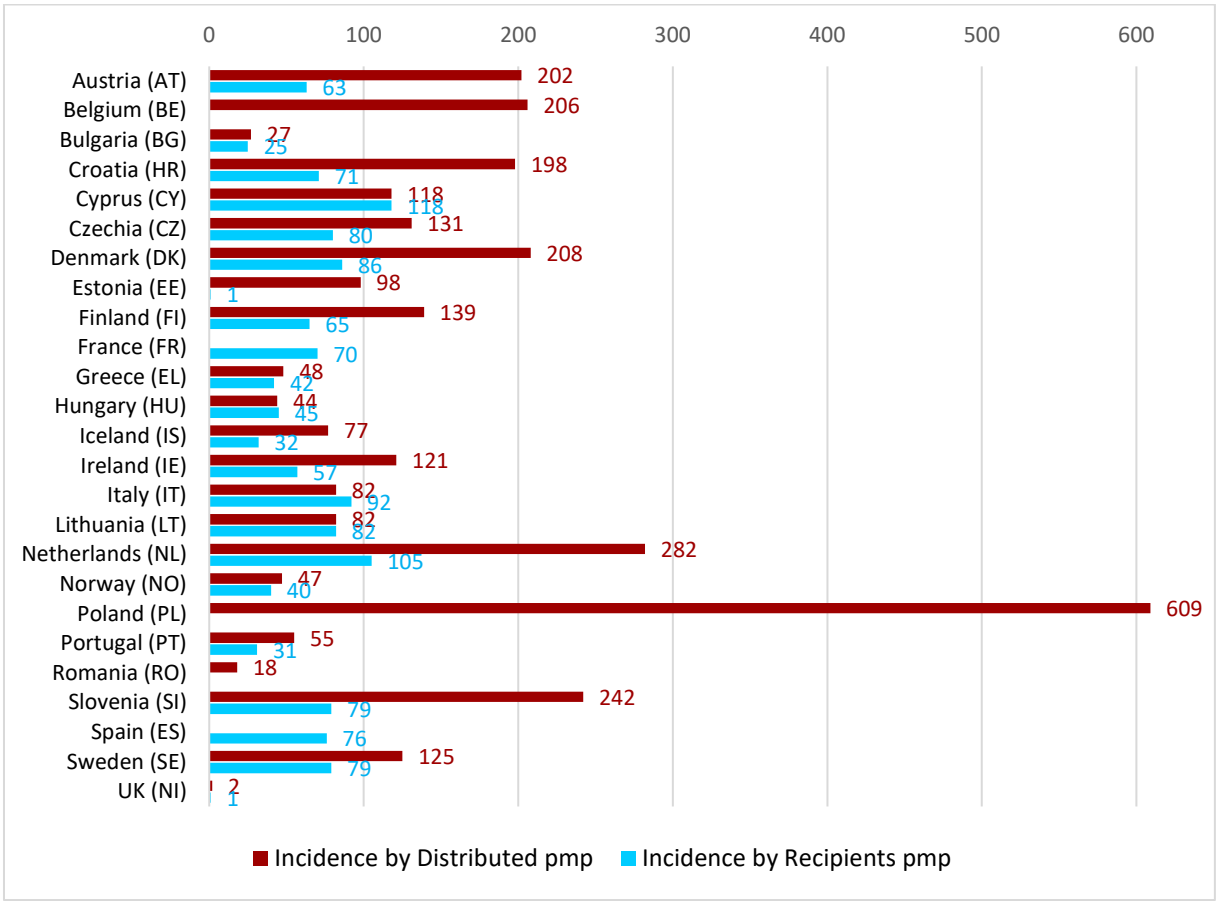

Figure 16. Incidence of haematopoietic stem cells (number of units distributed and number of recipients per million population); data 2022

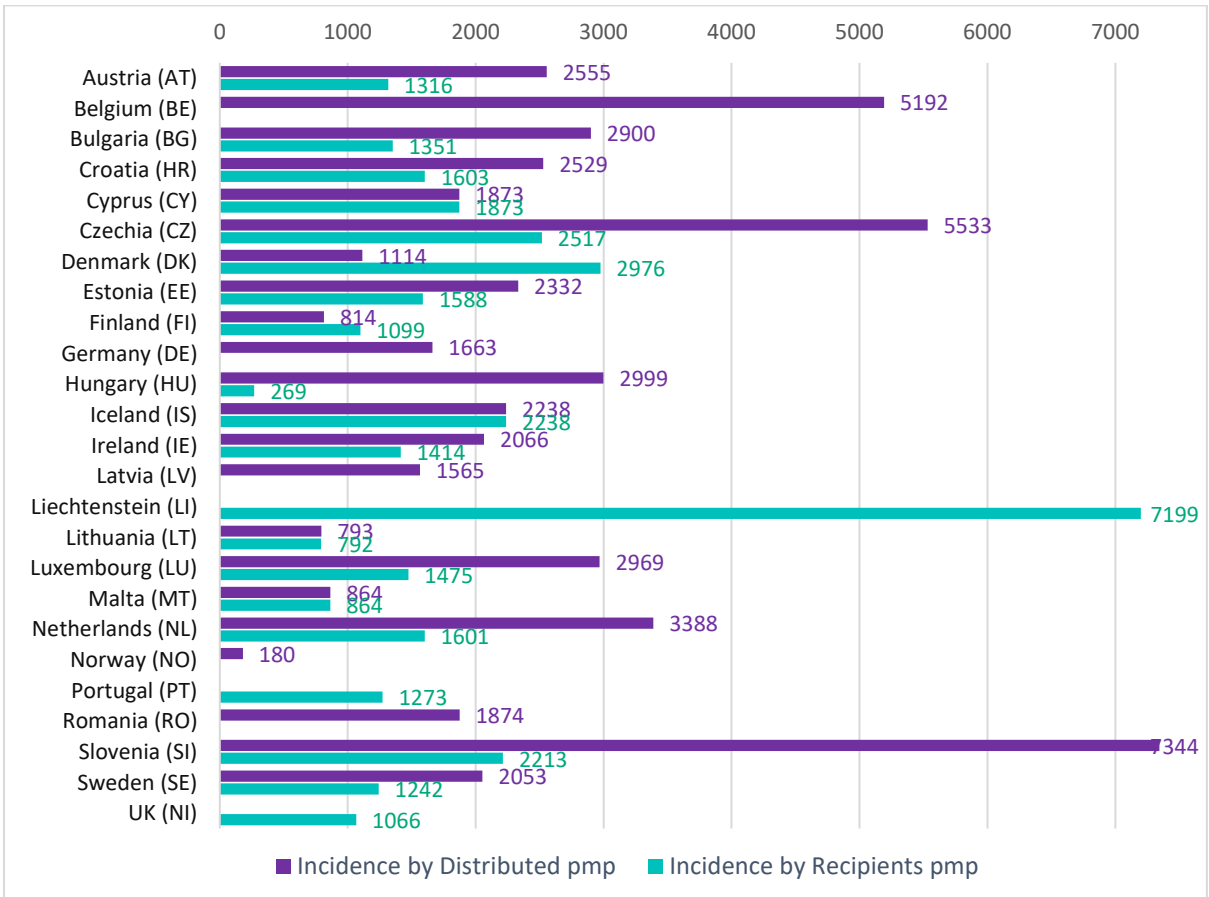

Figure 17. Incidence of reproductive cells (number of units distributed and number of recipients per million population); data 2022

4.1.2 Number of transplant recipients

In 2022, 26 countries reported a total of **327 961 recipients** having undergone a transplant of tissues or cells (149 823 recipients of replacement tissues and cells, 21 487 recipients of HSC and 156 651 recipients who underwent a MAR procedure).

Note: Due to the minor impact on the SARE analysis and late communication, the number of HSC transplant recipients reported by DE is not included in the analysis.

4.1.2.1 Non-reproductive tissues and cells

As regards non-reproductive tissues and cells, 23 countries reported data on recipients (AT, BG, HR, CY, CZ, DK, EE, FI, FR, EL, HU, IE, IT, LT, MT, NL, NO, 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 tissues or cells; similar to previous years, the most frequently transplanted were skeletal tissues, peripheral blood stem cells and ocular tissues.

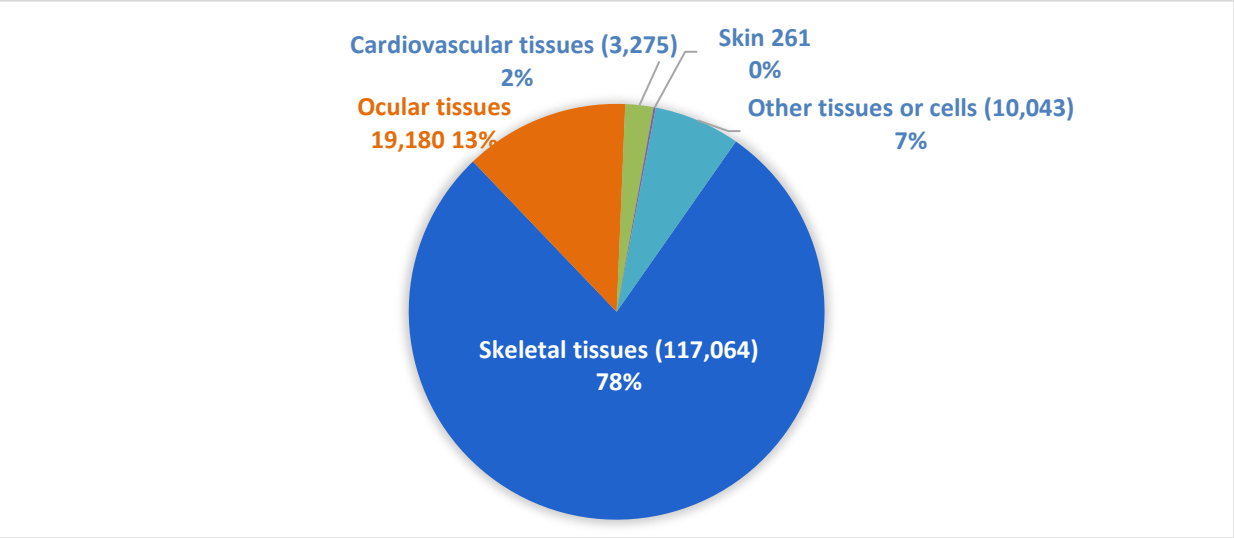

Figure 18. Total number of recipients per type of replacement tissue and cells; data 2022

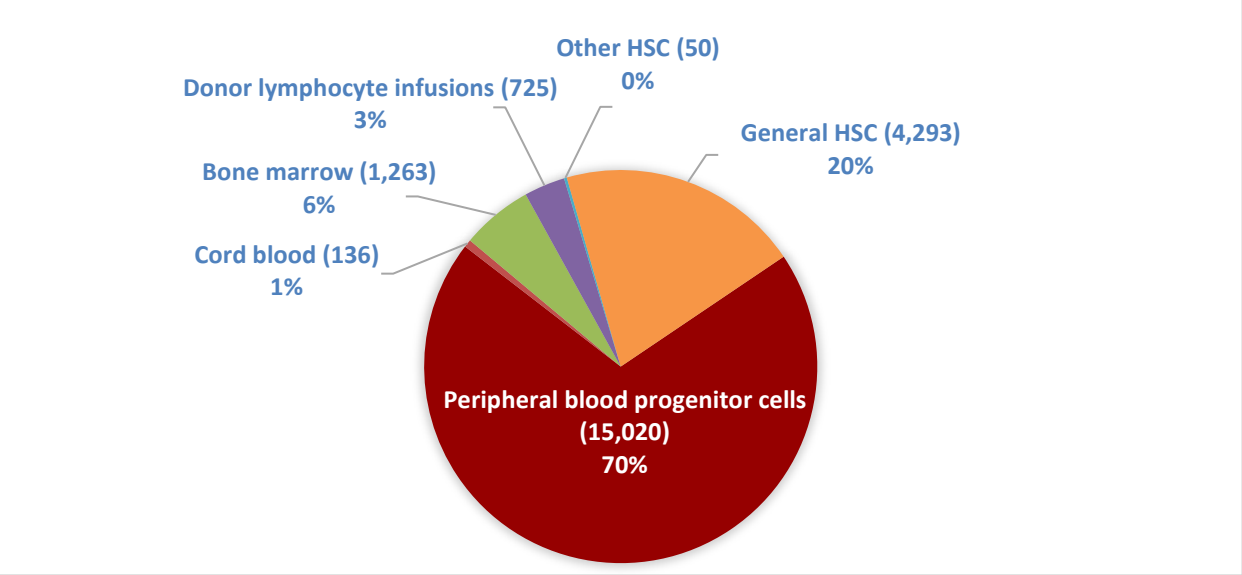

Figure 19. Total number of recipients per type of haematopoietic stem cells; data 2022

4.1.2.2 Reproductive tissues and cells

Concerning reproductive cells, 20 countries (AT, BG, HR, CY, CZ, DK, EE, FI, HU, IE, IS, LI, LT, LU, MT, NL, PT, SI, SE and UK(NI)) reported data indicating that 156 651 patients underwent a MAR procedure. Of those, 111 479 involved partner or non-partner embryos (71%), 44 438 involved partner or non-partner sperm (29%) and less than 1% involved transplantation of testicular tissue (450 patients), ovarian tissue (20 patients) and other reproductive tissues and cells (264 patients) (*Figure 20*).

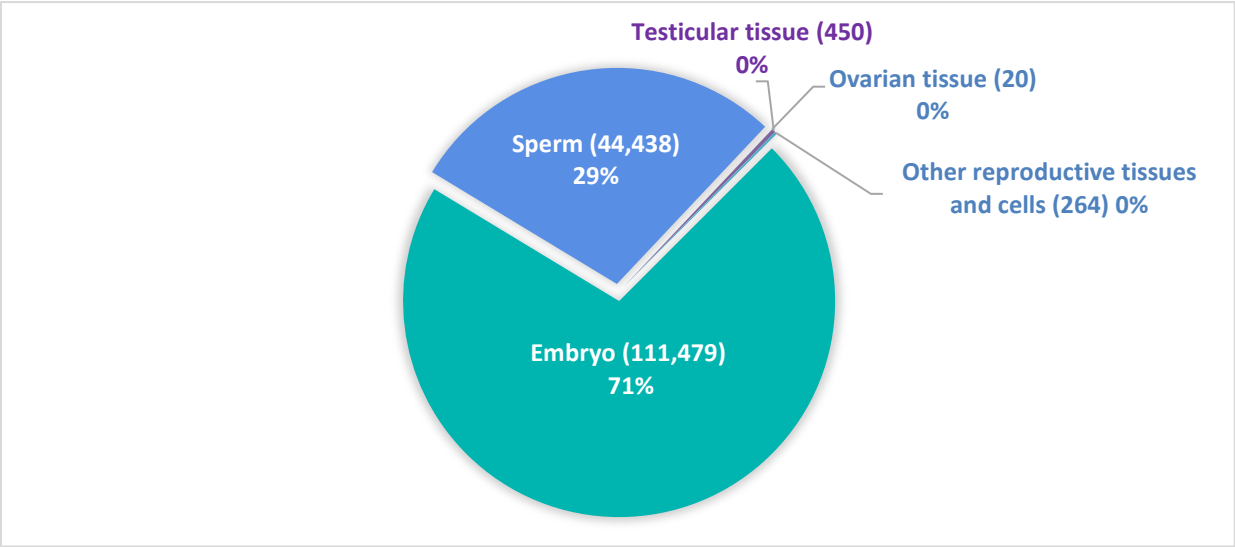

Figure 20. Total number of recipients per type of reproductive tissue and cells; data 2022

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 2012-2023 (data pertaining to 2011-2022) is presented in *Figures 21 and 22*, respectively.

As explained in section 4.1.1.3, the reduction in the number of units distributed in 2022 compared with previous years does not reflect a real decrease in activity or reporting (957 775 units distributed in 2022, 1 145 876 in 2021 and 1 116 519 in 2020). BG and CZ reported significantly fewer units distributed than in 2021, but that was compensated by higher numbers reported by other countries (FR, HU, IE, PL, RO and SI). The number of transplant recipients increased slightly (327 961 recipients reported in 2022 by 26 countries vs 318 467 recipients in 2021 from 24 countries); partial data regarding number of recipients was provided by BE, FR, DE, IT, PL and RO. Finally, the level of reporting in terms of number of participating countries and activity reported is at pre-pandemic levels or higher.

In terms of recipients, the number reported was comparable to 2021 for reproductive tissues and cells (156 651 vs 162 868) and HSC (21 487 vs 23 423), and 13% higher for replacement tissues and cells (149 823 vs 132 176), mainly due to a higher number of recipients of skeletal tissues.

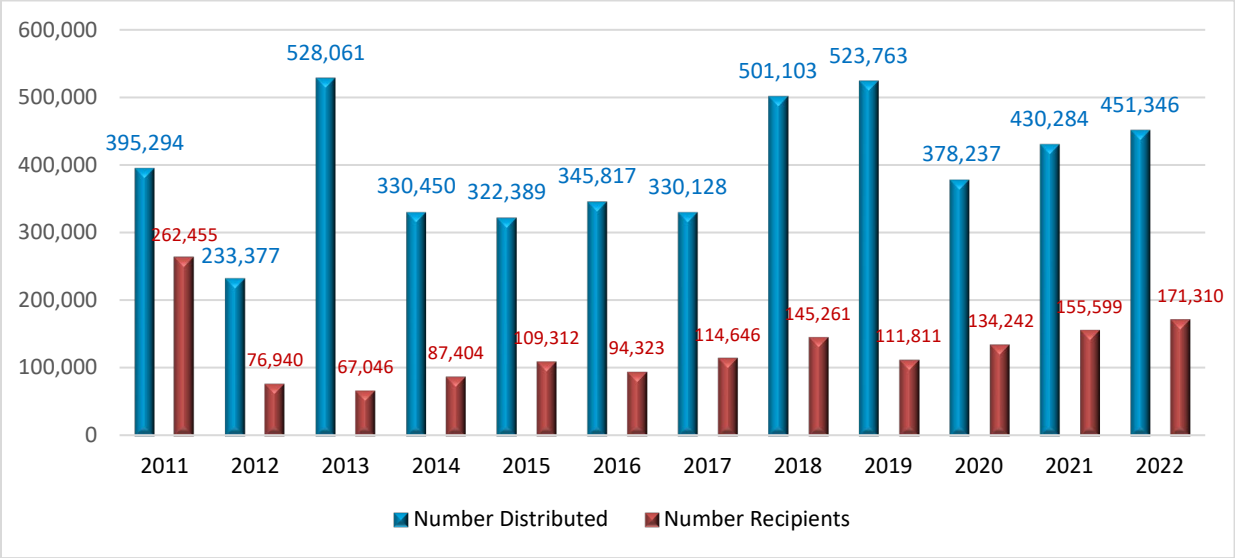

Figure 21. Total number of non-reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2022 comparative data

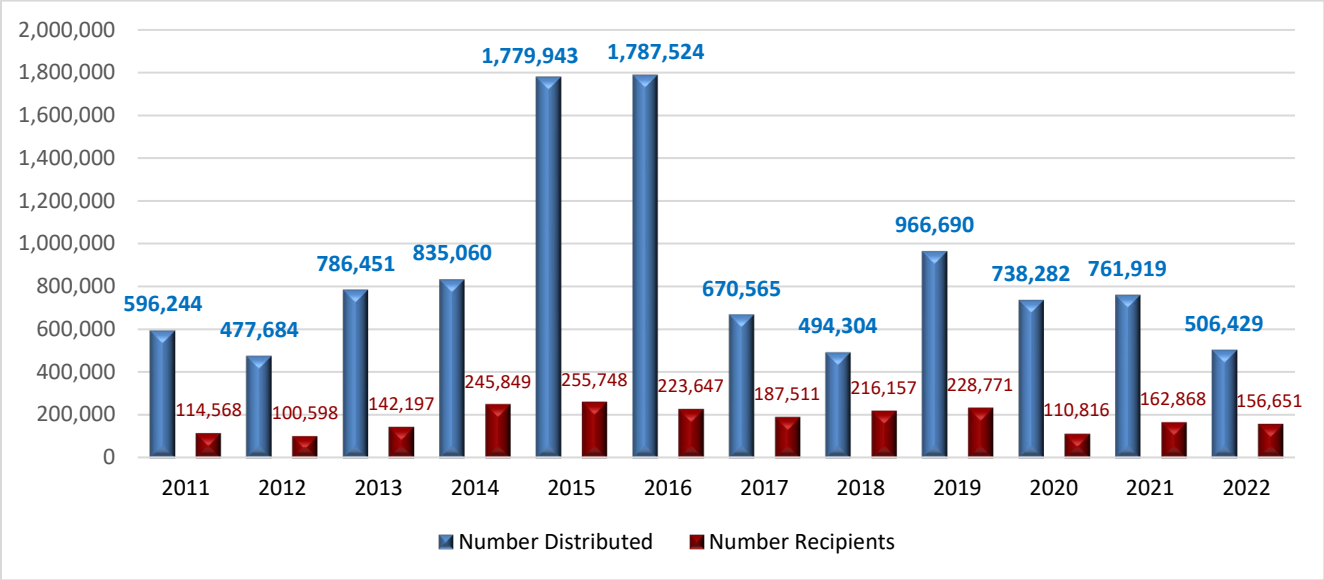

Figure 22. Total number of reproductive tissues and cells distributed (units) and number of recipients of human tissues and cells: 2011-2022 comparative data[5]

4.1.4 Number of tissues and cells processed

Similar to 2021, 25 countries (AT, BG, CY, CZ, DE, EE, FI, FR, DE, EL, HR, HU, IS, IE, IT, LV, MT, NL, PL, PT, RO, SI, ES, SE and UK(NI)) provided the number of **non-reproductive tissues and cells processed**, and 18 countries (AT, BG, HR, CY, CZ, DE, DK, FI, HU, IS, IE, LI, LV, LU, MT, NL, SI and SE) provided the number of **reproductive tissues and cells processed** in 2022.

Note that data reported by DE as 'transplantation units' (the number of units needed for one patient) were not included in the analysis.

[5] As stated in the Common Approach these data include 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 2 892 459 tissues and cells were reported as processed in 2022, 8.4% fewer than in 2021 (3 159 362). Of those, 456 953 units (16%) were replacement tissues and cells, 76 236 units (3%) were HSC and 2 359 270 units (81%) were reproductive tissues and cells. Comparative data from previous exercises (2011-2022 data) are presented in *Figure 23*.

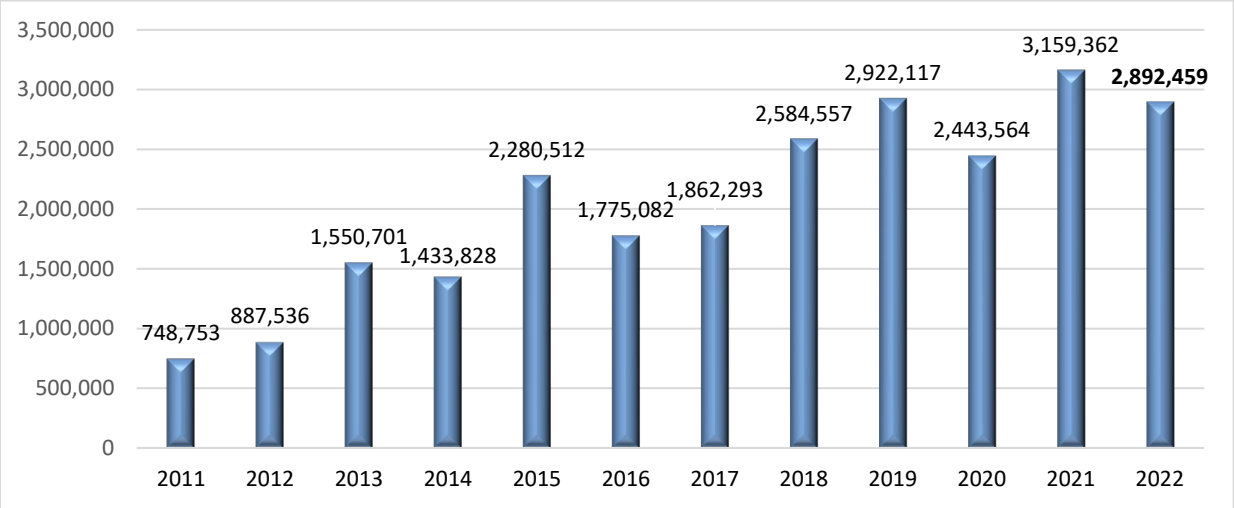

Figure 23. Total number of tissues and cells processed (units): 2011-2022 comparative data

4.2 Serious adverse reactions in recipients

Seventeen countries reported a total of 347 SAR in 2022, a 6% increase compared to 2021 (326) and the same as in 2020 (350). Of these, 34 (10%) were related to replacement tissues and cells, 60 (17%) to HSC and 253 (73%) to reproductive tissues and cells.

4.2.1 General information

Of the 30 reporting countries, 17 (BE, BG, CZ, DE, DK, EE, ES, FI, FR, EL, IT, LU, NL, NO, PL, PT and SE) reported SAR associated with the clinical application of tissues or cells. Thirteen countries (AU, BG, HR, HU, IE, LU, LV, LT, MT, RO, SK, SI and UK) reported no SAR in recipients in 2022. Four countries have not reported any SAR in the last four years (CY, LI, LT and RO). A graphical representation of the number of SAR in transplant recipients by country in 2022 is available in *Figure 24*.

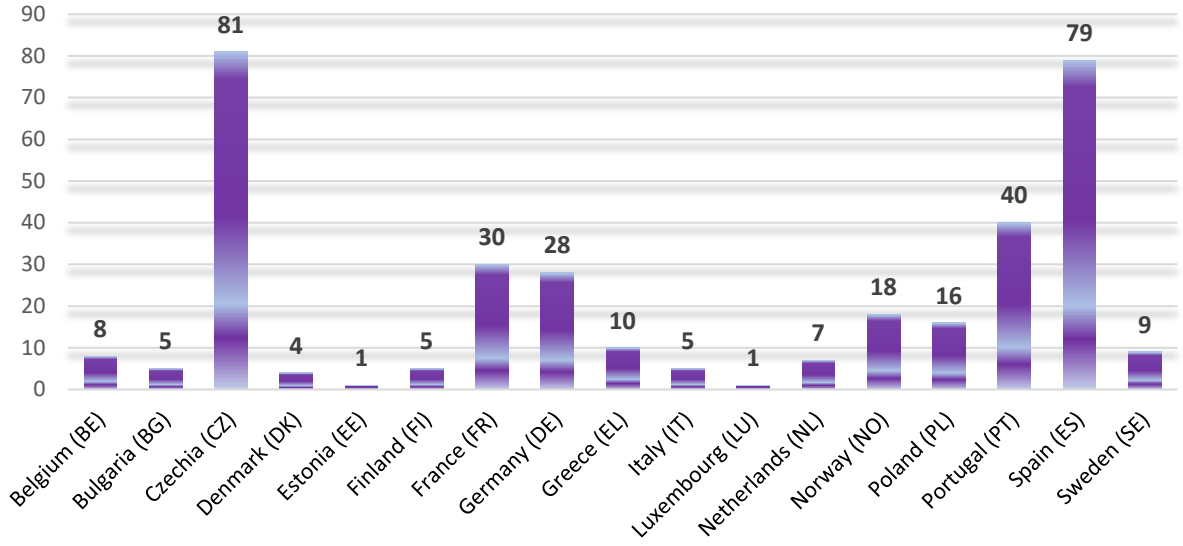

Figure 24. Total number of SAR by country in transplant recipients; data 2022

Seven countries (BE, DE, DK, EL, ES, FR and IT,) reported SAR associated with the transplantation of **replacement tissues and cells**, ten (BE, BG, DE, EL, ES, FR, IT, NL, PT and SE) reported SAR associated with the transplantation of **HSC** and 14 (BE, CZ, DE, DK, EE, ES, FI, IT, LU, NL, NO, PL, PT and SE) reported SAR following the clinical application of **reproductive tissues or cells**.

4.2.2 SAR by category of tissues and cells

In total, 73% of the 347 SAR in recipients reported were associated with the application of reproductive tissues and cells (vs 55% in 2021), compared to 17% associated with the transplantation of HSC (vs 27% in 2021) and 10% for replacement tissues and cells (vs 18% in 2021) (*Figure 25*).

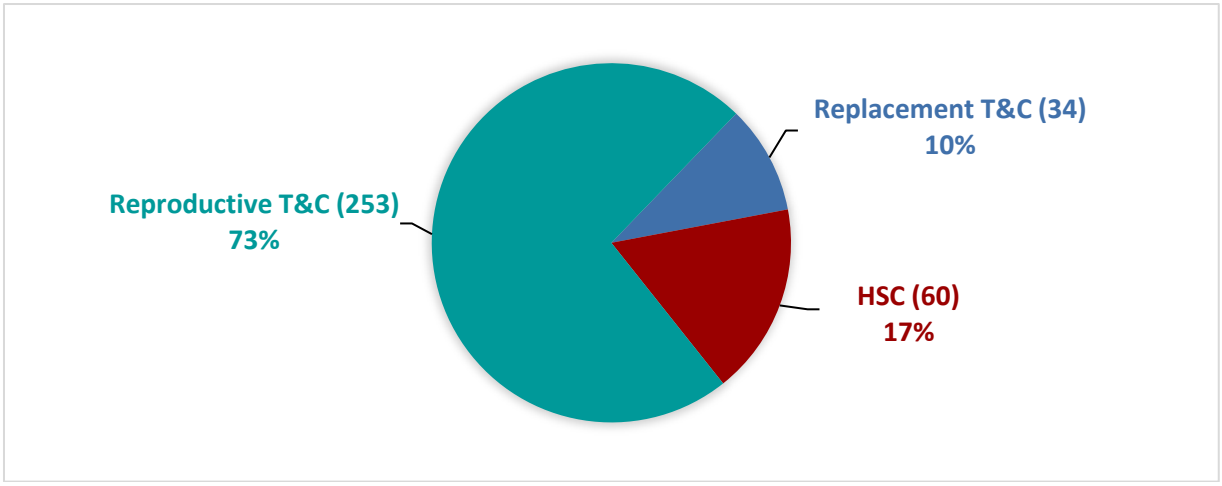

Figure 25. Number of SAR by category of tissue and cells; data 2022

The distribution of SAR by reporting country and category of tissue and cells is presented in *Figure 26*.

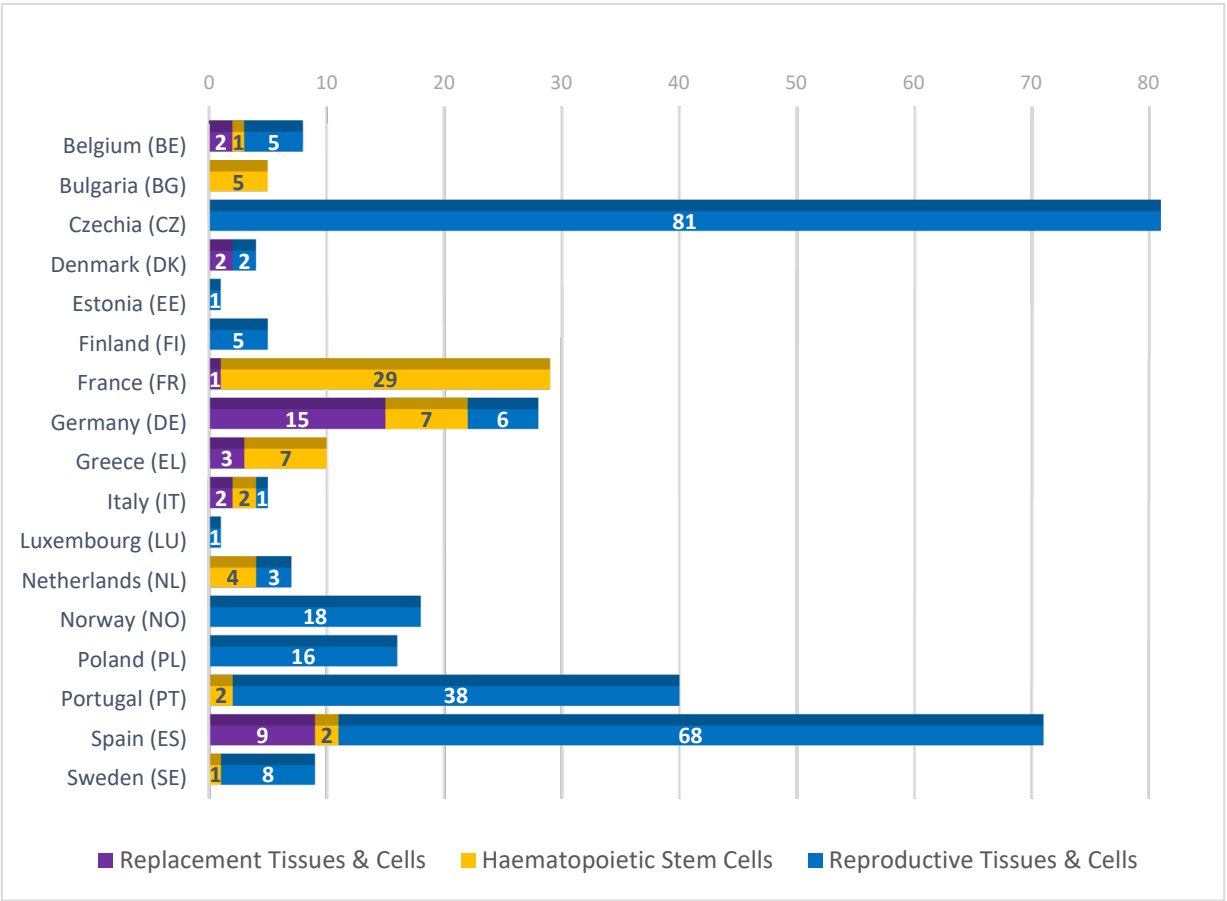

Figure 26. Number of SAR per country and category of tissues and cells; data 2022

A breakdown of SAR by subcategory of tissues and cells is presented in *Figures 27-29*.

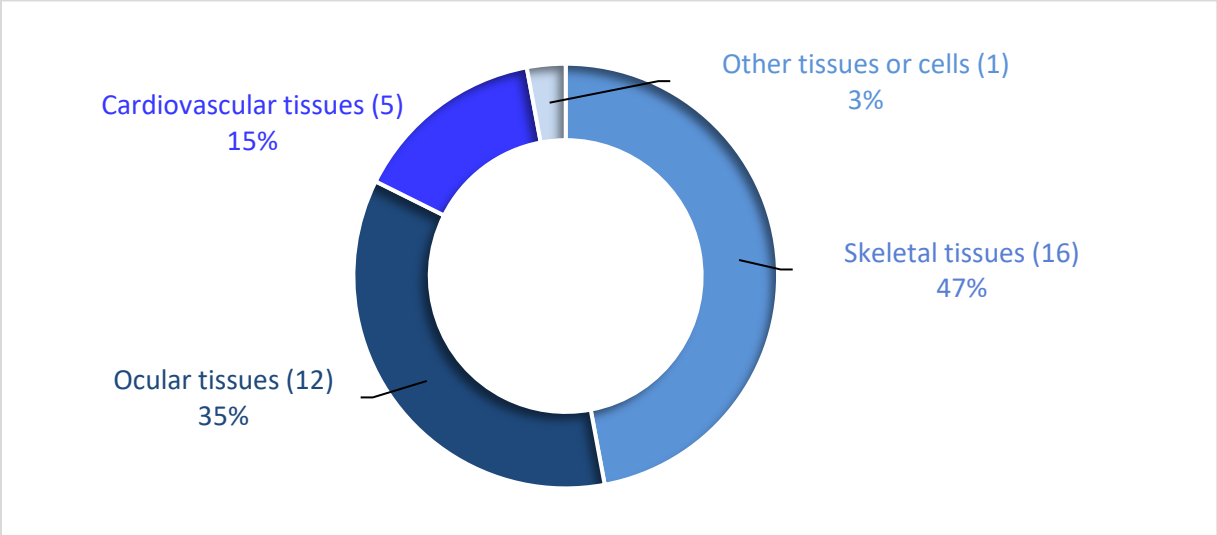

Figure 27. Number of SAR per subcategory of replacement tissues and cells (absolute values and percentages of total SAR in recipients); data 2022

Unlike 2021, when the most frequent SAR associated with transplant of replacement tissues and cells were for ocular tissues (28/48%), in 2022, out of the 34 SAR, the largest number of reactions was related to bone (11/32%), followed by general ocular tissue (7/20%) and heart valves (5/15%). The number of SAR for each subtype of replacement tissues and cells is presented in *Table 1.*

Replacement Tissues & Cells	T&C Subtype	SAR 2022	SAR 2021
Skeletal tissues	**Bone**	**11**	10
	Tendons/ligaments	1	2
	Cartilage	-	2
	General skeletal tissues	3	1
	Other (e.g., meniscus, ear, ossicles)	1	-
Ocular tissues	Cornea	2	28
	General ocular tissue	**7**	-
	Other	3	-
Cardiovascular tissues	**Heart valve**	**5**	1
	Vessel	-	2
Skin	Skin	-	1
Other tissues or cells	Amniotic membrane	-	11
	Other (adipose, tympanic membrane)	1	-
	Total SAR	**34**	**58**

Table 1. Number of SAR by subtype of replacement tissues and cells; data 2022

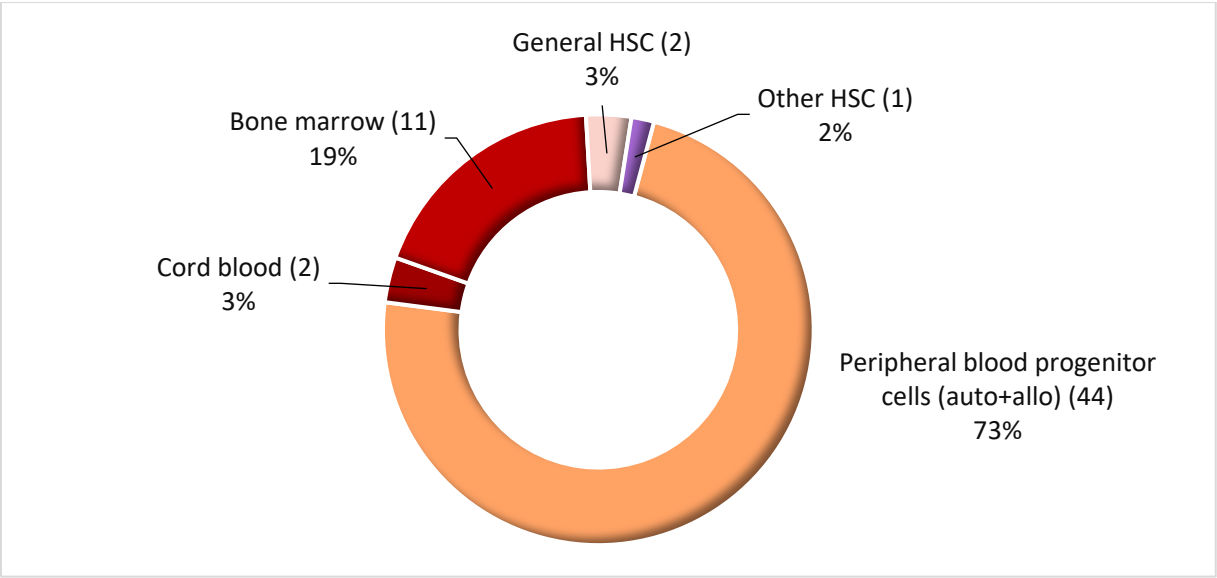

Figure 28. Number of SAR per subcategory of haematopoietic stem cells (absolute values and percentage of total SAR in recipients); data 2022

The HSC subcategory most frequently associated with SAR was the transplant of allogenic unrelated peripheral blood progenitor cells. Details for all types and subtypes of HSC are presented in *Table 2*.

HSC Category	HSC Type	SAR 2022	SAR 2021
Bone marrow	Allogenic related	4	8
	Allogenic unrelated	6	5
	General	1	6
Cord blood	Allogenic related	-	3
	Allogenic unrelated	2	-
Peripheral blood progenitor cells	**Allogenic related**	9	10
	Allogenic unrelated	19	31
	Autologous	10	7
	General	6	13
General HSC	-	2	4
Other HSC	Autologous	1	-
	Total SAR	**60**	**87**

Table 2. Number of SAR by subtype of haematopoietic stem cells; data 2022

MAR procedures involving embryos were responsible for 77% of SAR in 2022 followed by sperm insemination as shown in *Figure 29*.

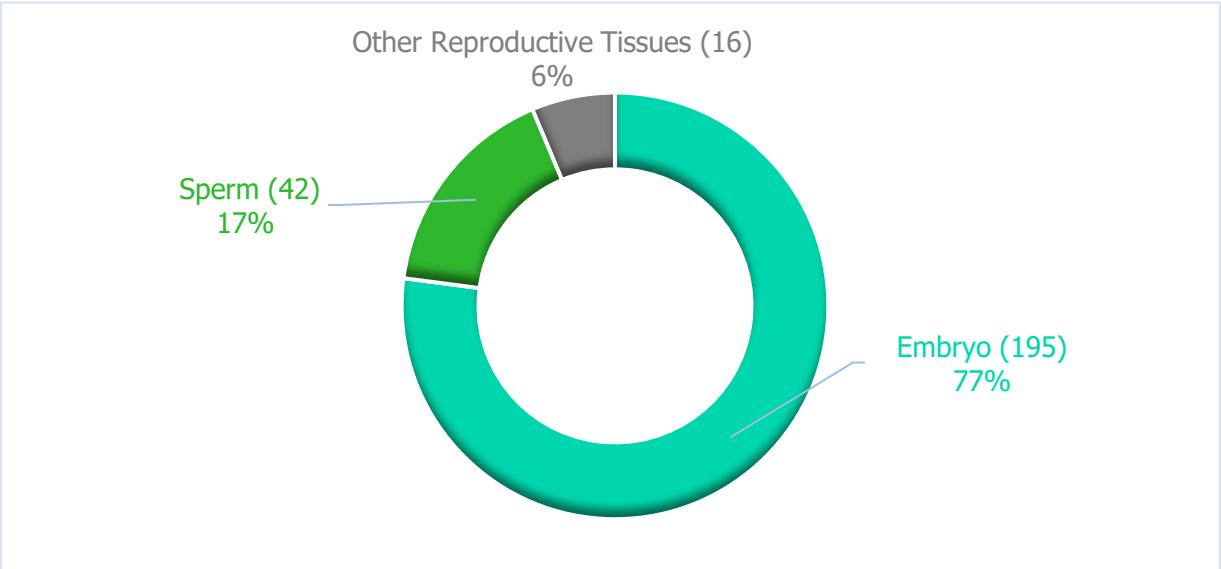

Figure 29. Number of SAR per subcategory of reproductive cells (absolute values and percentages of total SAR in recipients); data 2022

SAR for both sperm used in IUI procedures and embryos after IVF/ICSI were reported; the number for each subtype of tissues and cells involved is presented in *Table 3*.

Reproductive Tissues & Cells	T&C Subtype	SAR 2022	SAR 2021
Embryo	**Donor oocyte, partner sperm**	**83**	50
	Donor sperm and oocyte	**21**	15
	Donor sperm, partner oocyte	**19**	17
	Partner gametes	**55**	29
	General	17	8
Sperm	**Non-partner donation**	**31**	56
	Partner donation	7	6
	General	4	-
Other Reproductive T&C	Other	16	-
	Total	**253**	181

Table 3. Number of SAR by subtype of reproductive tissues and cells; data 2022

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

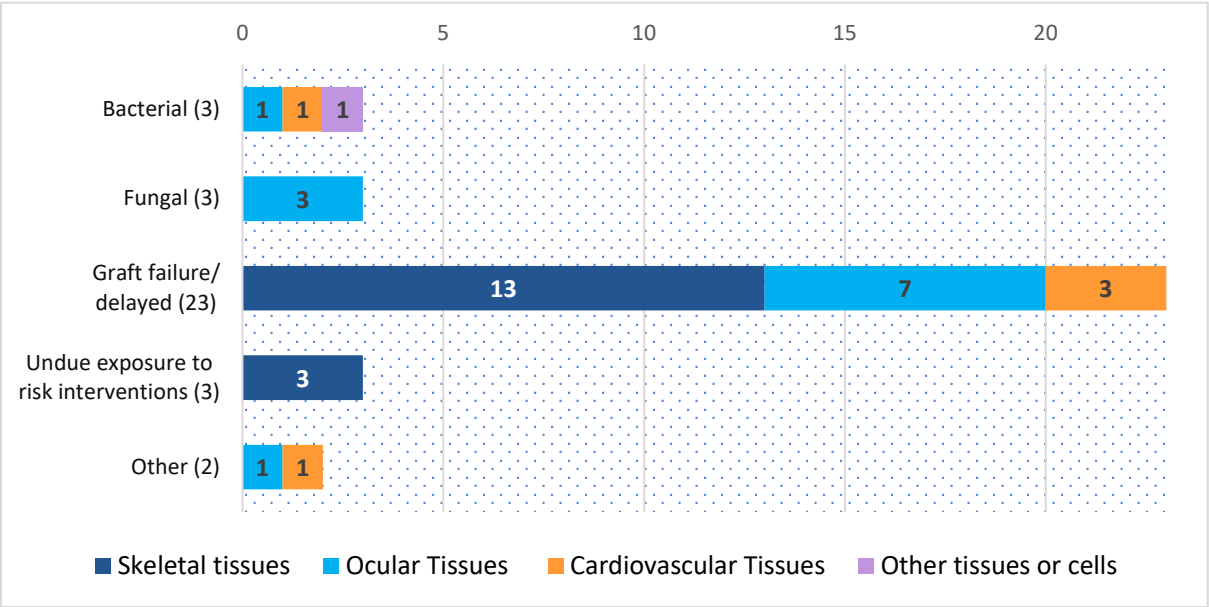

Figure 30. Distribution of SAR for replacement tissues and cells per type of reaction; data 2022

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

1. **Transmitted infections** were reported in six patients, representing 18% of the 34 SAR for replacement tissues and cells. The three cases of bacterial infections included one instance of heart valve contaminated with *Staphylococcus epidermidis*, one patient experiencing ocular infection with *Corynebacterium striatum* and one infection in a recipient with *Proteus mirabilis* following transplant of contaminated decellularised dermal matrix. The fungal infections reported in 2022 were two cases of contamination of storage media leading to infection in cornea and one case of endophthalmitis caused by *Candida albicans*.

2. **Other SAR**: of the remaining 28 SAR reported (representing 82% 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 and two in 2022.

    - 23 cases of **graft failure or delayed engraftment**, as follows:
        - 13 following the transplantation of skeletal tissue (11 related to bone, one to cartilage and one to a tendon)
        - three following the transplantation of cardiovascular tissue (heart valve)
        - seven following the transplantation of ocular tissue

    - Three cases of **undue exposure to risk interventions** (two cases of patients under anaesthesia without suitable grafts available and one instance of tendon deemed of inadequate quality during surgery)

    - Two SAR were classified as **other**:
        - tissue contamination that required a second corneal transplant
        - fatal acute aortic insufficiency due to endocarditis (imputability level 1)

4.2.3.2 SAR – haematopoietic stem cells

The second most prevalent of all SAR reported in 2022 were those associated with transplant of HSC (60). There were three cases of infection and the remaining 57 SAR were reported as **Other SAR**. No instances of malignant disease were reported. The types of reaction encountered in 2022 are presented in *Figure 31*.

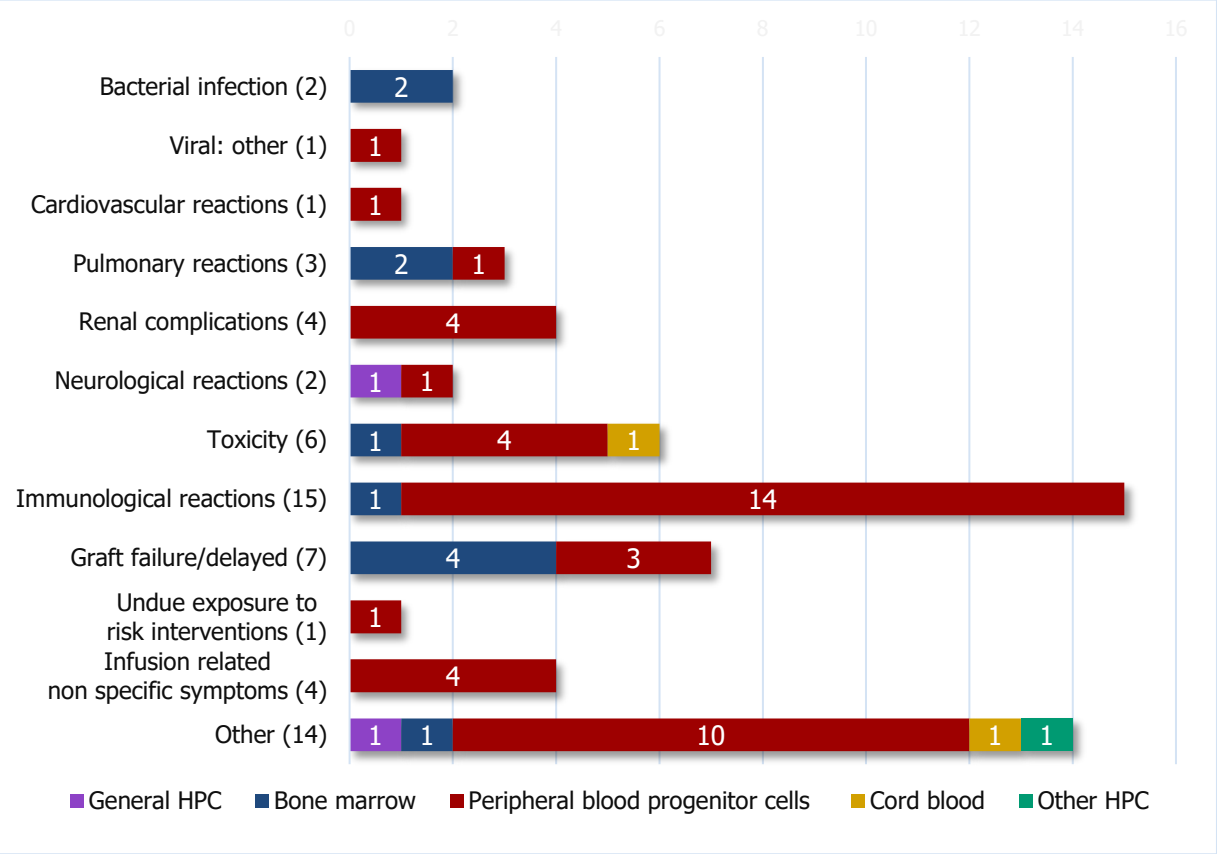

Figure 31. Distribution of SAR for haematopoietic stem cells by type of reaction; data 2022

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

1. **Transmitted infections**:
    - two cases of bacterial infection caused by *Staphylococcus saccharolyticus* and *Cutibacterium acnes* following infusion of allogenic related bone marrow; both responded to treatment with antibiotics.
    - one instance of other viral infection (pathogen not specified) in a patient that had undergone an infusion of allogenic related PBSC
2. **Other SAR**:
    - seven cases of **graft failure or delayed engraftment** following transplantation of bone marrow (one allogenic related, three allogenic unrelated) and PBSC (one allogenic related, one allogenic unrelated and one autologous)
    - 15 cases of **immunological reactions** following transplantation of bone marrow (one allogenic unrelated) and PBSC (four allogenic related, four allogenic unrelated, four autologous and two general)
    - four cases of **infusion-related non-specific symptoms** following transplantation of PBSC (three allogenic unrelated and one general)
    - 14 SAR were classified as **other** and occurred following transplantation of bone marrow (one allogenic unrelated), cord blood (one allogenic unrelated), HSC (one general), PBSC (one allogenic related, five allogenic unrelated, three autologous and one general), and other HSC (one autologous)

- four cases of **renal complications** following transplantation of PBSC (one allogenic related and three allogenic unrelated)
- three cases of **pulmonary reactions** following transplantation of bone marrow (one allogenic related and one allogenic unrelated) and PBSC (one allogenic related)
- two cases of **neurological reactions** following transplantation of PBSC (one allogenic unrelated) and one general HSC
- one case of **cardiovascular reaction** following transplantation of PBSC (autologous)
- six cases of **toxicity** following transplantation of cord blood (one allogenic unrelated), PBSC (one allogenic unrelated, one autologous and two general) and one general HSC
- one case of undue exposure to risk interventions following transplantation of PBSC (allogenic unrelated)

Type of SAR	Subtype of SAR	HSC Type	HSC Subtype			
			Allogenic Related	Allogenic Unrelated	Autologous	General
Transmitted infections (3)	**Bacterial infection (2)**	Bone marrow (2)	2			
	Viral: other (1)	PBSC (1)	1			
Other SAR (57)	**Graft failure/delayed engraftment (7)**	Bone marrow (4)	1	3		
		PBSC (3)	1	1	1	
	Immunological reactions (15)	Bone marrow (1)		1		
		PBSC (14)	4	4	4	2
	Infusion-related non-specific symptoms (4)	PBSC (4)		3		1
	Renal complications (4)	PBSC (4)	1	3		
	Pulmonary reactions (3)	Bone marrow (2)	1	1		
		PBSC (1)	1			
	Neurological reactions (2)	General HSC (1)				
		PBSC (1)		1		
	Cardiovascular reaction (1)	PBSC (1)			1	
	Toxicity (6)	General HSC (1)				
		Cord blood (1)		1		
		PBSC (4)		1	1	2
	Undue exposure to risk interventions (1)	PBSC (1)		1		
	Others (14)	Bone marrow (1)		1		
		Cord blood (1)		1		
		General HSC (1)				
		PBSC (10)	1	5	3	1
		Other HSC (1)			1	

Table 4. Breakdown of SAR in HSC by type and by reaction and HSC subtype; data 2022

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 253 SAR associated with the application of reproductive tissues and cells, 43% (108) were classified as **transmitted genetic conditions** and the rest were reported as **Other SAR** (125) and **other disease transmission** (15). A 100% increase in the number of ectopic pregnancies was observed in 2022 compared to 2021 (from 37 to 72). The types of SAR by type of gametes (partner/non-partner), embryo application and sperm application are presented in *Figures 32* and *33*, respectively.

1. **Transmitted infections**: five cases reported, four of bacterial infection after IVF embryo transfer and one other transmitted infection following an IUI procedure involving sperm non-partner donation.

2. **Transmitted malignant disease** no cases reported.

3. **Transmitted genetic conditions**: 108 SAR were reported in this category and represent the most common type related to reproductive tissues and cells (43%). These comprised:
    - 63 cases involving embryos from donor oocytes and partner sperm
    - 16 cases of embryos from donor sperm and oocytes
    - 15 cases of embryos from donor sperm and partner oocytes
    - 13 cases related to embryos from partner gametes
    - one case concerning sperm in the general category

4. **Other SAR**: the 62 cases of ectopic pregnancy were the most common of the 125 SAR categorised as **other**, representing 28% of all reported SAR for reproductive tissues and cells. Twenty cases of OHSS, three molar pregnancies, pelvic inflammatory disease, ovarian torsion after embryo transfer, newborn with cleft palate, epilepsy, mix-up of embryo during transfer and cervical stenosis were also included in this category. Of the SAR reported as **other**:
    - 42 cases occurred following clinical application of embryos from partner gametes
    - 20 cases involved embryos from donor oocytes and partner sperm
    - 12 cases involved general embryos
    - five cases involved embryos from donor sperm and oocytes
    - four cases involved embryos from donor sperm and partner oocytes
    - 15 cases involved sperm from non-partner donation
    - seven cases involved partner sperm
    - four cases involved sperm, general
    - 16 cases involved other reproductive tissues and cells

5. **Other disease transmissions:** the 15 cases reported in this category include various suspected or confirmed genetic diseases.

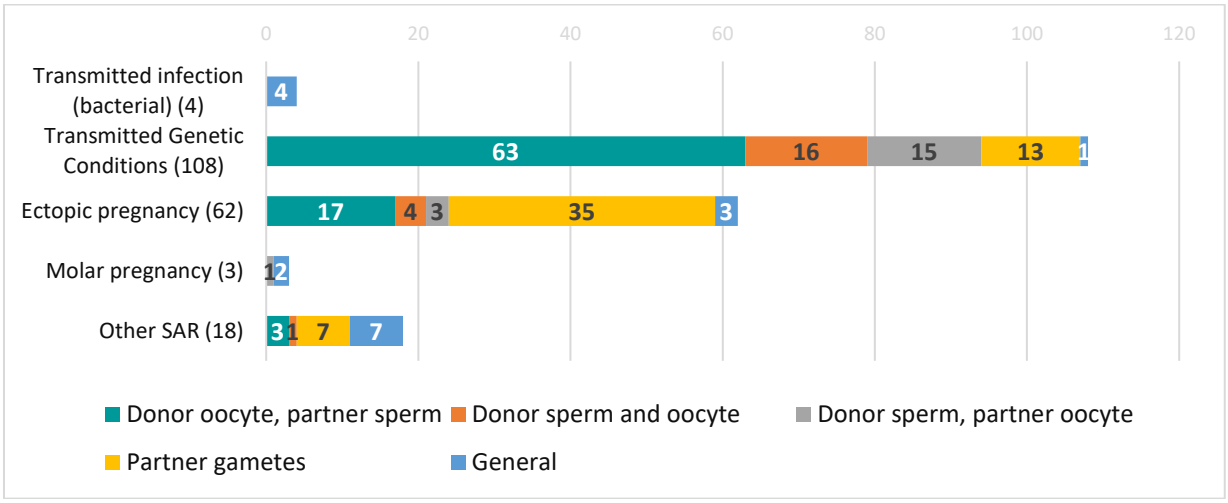

Figure 32. Distribution of SAR per type of gametes (partner/non-partner), embryo application; data 2022

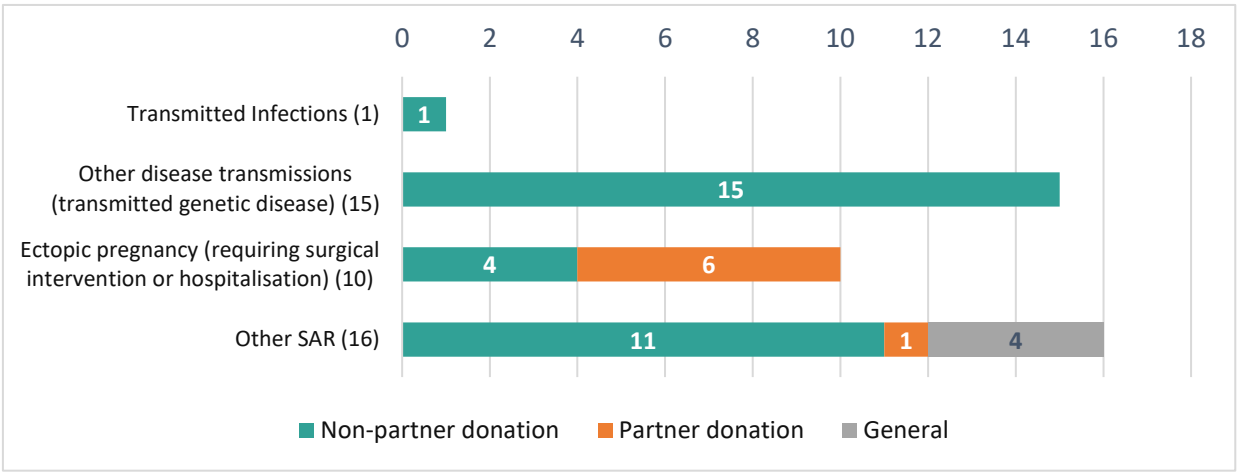

Figure 33. Distribution of SAR per type of gametes (partner/non-partner), sperm application; data 2022

4.2.3.4 SAR Imputability

The *Common Approach* (2023 version), section 5.6 *Imputability Assessment* requires that the imputability assessment tool provided be used to determine which reactions must be reported for the purpose of this exercise, specifically "only reactions that are reasonably considered to have been caused by the tissues or cells applied and linked to the quality and safety of the tissues and cells, or the procurement process in the case of a donor". Although slightly improved in 2022, an imputability level was assigned to only 38% of the SAR reported (133 out of 347). As shown in *Table 5* below, for most reactions, conclusive evidence for attributing the reaction to the quality or safety of the tissues 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 (1), graft failure/delayed engraftment (3), transmitted fungal and bacterial infections (3 and 1, respectively), undue exposure to risk interventions (4), pulmonary reaction (1), immunological disease (1), transmitted genetic diseases (8) and conditions (9) in conjunction with MAR procedures and reactions other than the above (4).

T&C Category	Total number of SAR		SAR with imputability reported		Imputability Level					
					2022			2021		
	2022	2021	**2022**	2021	**IL1**	**IL2**	**IL3**	IL1	IL2	IL3
Replacement T&C	**34**	58	**29 (85%)**	41 (71%)	**18**	**2**	**9**	27	7	7
HSC	**60**	87	**45 (75%)**	65 (75%)	**23**	**16**	**6**	41	14	10
Reproductive T&C	**253**	181	**59 (23%)**	9 (5%)	**29**	**10**	**20**	7	-	2
Total	**347**	326	**133 (38%)**	115 (35%)	**70**	**28**	**35**	75	21	19

Table 5. SAR with imputability level reported per category of tissues and cells; comparative data 2021 - 2022

4.2.4 Fatalities in donors, recipients and offspring

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

Twelve fatalities in recipients and offspring were reported in 2022: one was potentially attributable to replacement tissues and cells, five to HSC application and six to reproductive tissue and cell application; 20 fatalities among recipients potentially attributable to tissue and cell application were reported in 2021 and 14 in 2020.

4.2.4.1 Fatalities in donors

- **one death within days of autologous mononuclear cells collection;** atrial fibrillation during cataphoresis evolved into death
- **one death within days after autologous donation of HSC (apheresis);** cause of death unknown
- **one death during anaesthetic induction (anaphylactic shock) for oocyte retrieval for ART (partner donor)**
- **one death after puncture for fertility preservation** in a patient diagnosed with aplasia medulla; severe hemoperitoneum, leukopenia leading to sepsis which ended in death

4.2.4.2 Fatality following the application of replacement tissues and cells 6 years after heart valve transplant in a patient with congenital aortic stenosis. The cause of death established through autopsy was acute cardiac circulatory failure; imputability to graft quality could not be completely ruled out (imputability level 1).

4.2.4.3 Fatalities following the application of HSC

Information on the **five reported fatalities** potentially attributable to **HSC** is provided below:

- **one death after autologous peripheral blood stem cell transplant (PBSCT)** due to neutropenic colitis developed within days after transplant, recommended in response to relapse of an IgA kappa mixed myeloma at stage III; imputability to graft quality could not be completely ruled out
- **one death months after PBSCT** due to aggravation of thrombotic microangiopathy syndrome; PBSC were administered as treatment for immature acute myeloblastic leukaemia with abnormal karyotype (imputability level 2)
- **one death two months after allogenic related PBSCT** due to an acute cutaneous, digestive, oral and hepatic graft-versus-host disease and multiple infections; infusion of PBSC was prescribed for refractory acute myeloid leukaemia; imputability to graft quality could not be completely ruled out
- **one death after PBSCT** due to massive cerebral haemorrhage; PBSCT was recommended as treatment for myelofibrosis; imputability to graft quality could not be completely ruled out
- **one death after PBSCT** due to leukaemia relapse

4.2.4.4 Fatalities following the application of reproductive tissues and cells

Information on the **six reported MAR-related deaths** (i.e. reproductive tissues and cells), which include offspring and foetal deaths (at various stages of pregnancy), is provided below:

- two deaths related to IVF (death of offspring)
- four cases of voluntary termination of pregnancy due to foetal malformations

4.3 Serious adverse events

4.3.1 General information

The reported number of tissues processed was 8.4% lower in 2022 compared to 2021 (*Figure 34*). The substantial increase in the reported number of units processed by some countries (CZ, DK, FI, FR and SE) could not compensate for the very high number of units reported by BE and BG in 2021 but no longer reported in 2022. The total number of SAE reported was 63% higher compared to the previous exercise and 24% higher compared to 2019 (*Figure 35*). The difference is due to a large number of events related to cord blood that are potentially non-reportable.

Fourteen countries reported SAE for replacement tissues and cells (BE, CZ, ES, FI, DE, EL, FR, HU, IT, MT, NL, PT, SI and SE), 17 for HSC (AT, BE, BG, CZ, DE, ES, FR, EL, HU, IE, IT, NL, NO, PL, PT, SE and SI) and 17 for reproductive tissues and cells (AT, BE, CZ, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, NL, PL, PT and SE). The number of countries that reported SAE in 2022 is comparable to 2021.

Of the 1 133 SAE reported for 2022, 61% were related to HSC, 21% to reproductive tissues and cells and 18% to replacement tissues and cells. The proportion remained constant (76% non-reproductive tissues and cells and 24% reproductive tissues and cells).

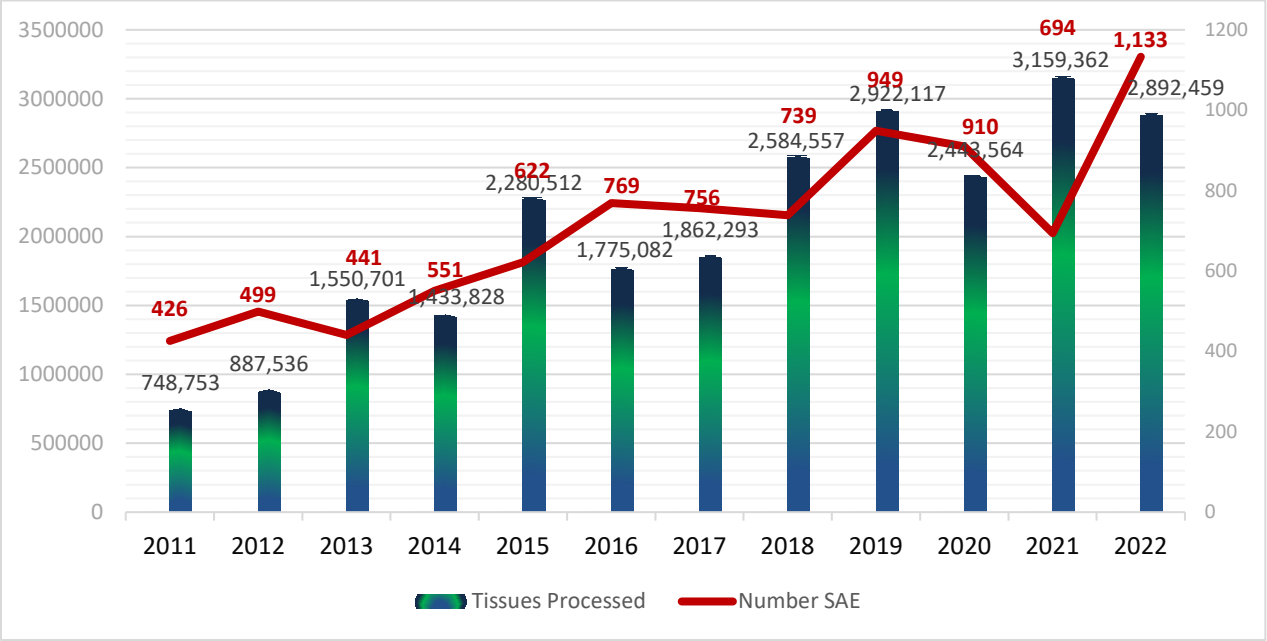

Figure 34. Number of tissues processed and number of SAE reported; comparative data (2011-2022)

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**.

Unlike the previous two years, **tissues and cells defect** was no longer the leading category of events; in 2022, the most frequent were events in the category **other (**399 SAE accounting for 35% out of the 1 133 SAE reported), followed by **tissues and cells defect** (188 SAE representing 16%) and **human error** (149/13%). *Figure 35* shows the positive evolution of events reported as being related to **human error** (a decrease from 31% in 2019 to 20.8% in 2020, 17% in 2021 and 13% in 2022); the significant increase in the number of SAE classified as **other** (35% in 2022 vs 23% in 2019, 23.4% in 2020 and 10% in 2021) is due to the reporting of a large number of SAE in relation to cord blood (positive microbiology results before and after transplant and low cell count) that may not be reportable.

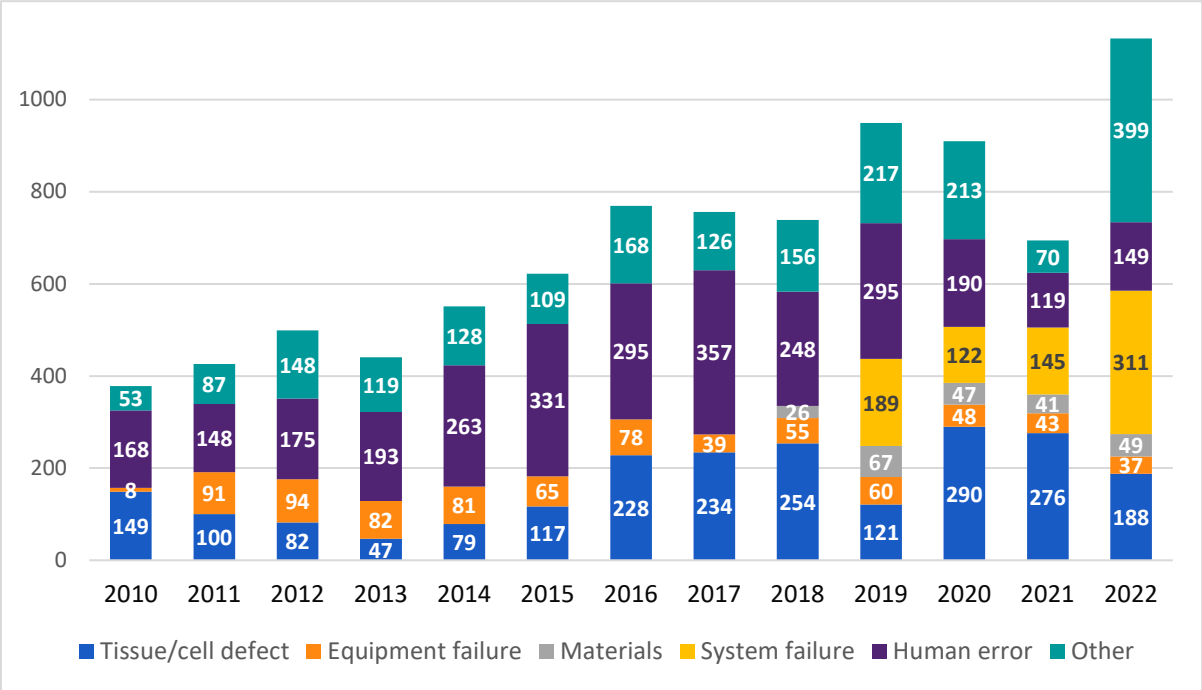

Figure 35. Distribution of SAE by type/specification; 2010-2022 data

The distribution of SAE by type/specification for each of the three categories of tissues and cells is presented in *Figures 36-38*.

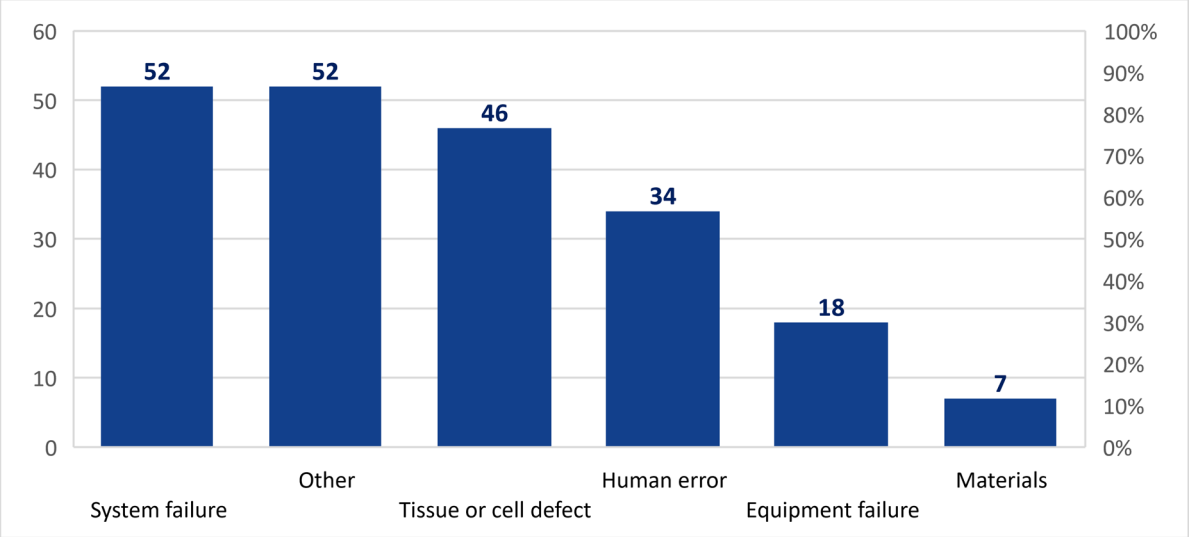

Figure 36. SAE types for replacement tissues and cells (absolute values and percentages); data 2022

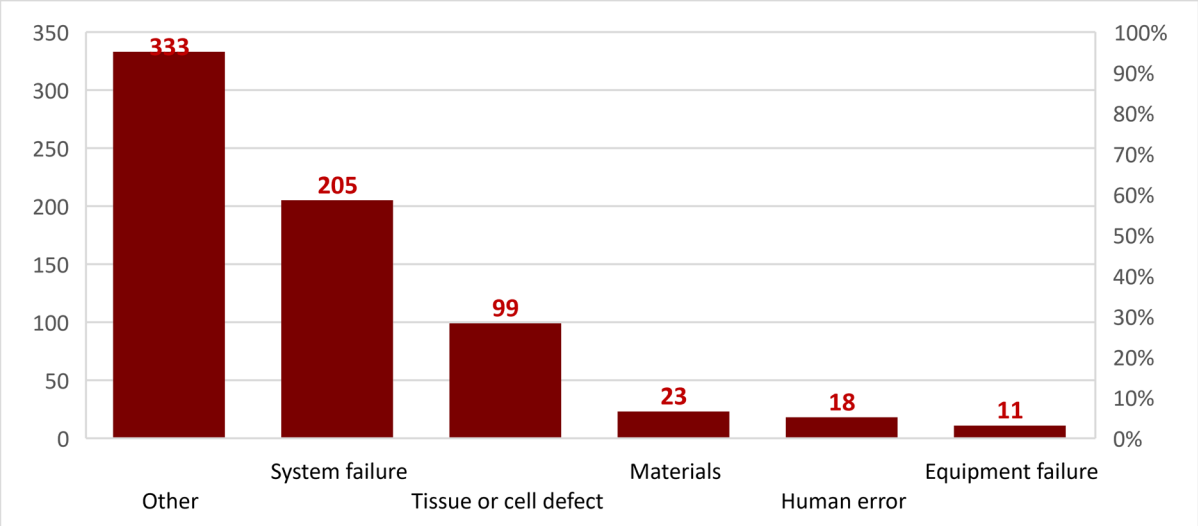

Figure 37. SAE types for haematopoietic tissues and cells (absolute values and percentage); data 2022

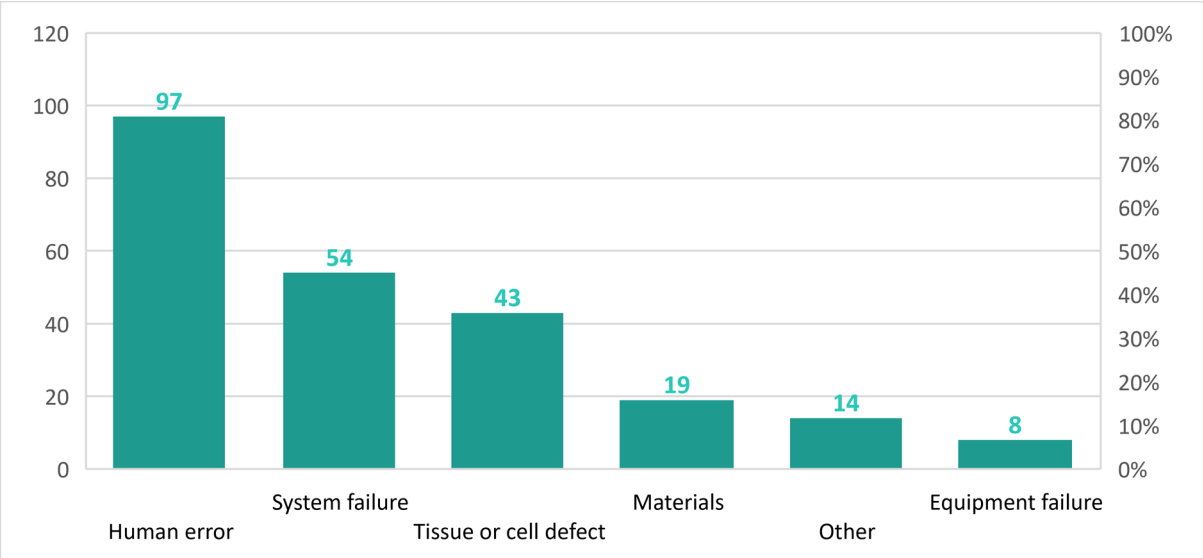

Figure 38. SAE types for reproductive tissues and cells (absolute values and percentage); data 2022

4.3.3 SAE by activity step

An overview of the SAE reported for each of the three categories of tissues and cells by activity step is presented in *Figures 39-41*.

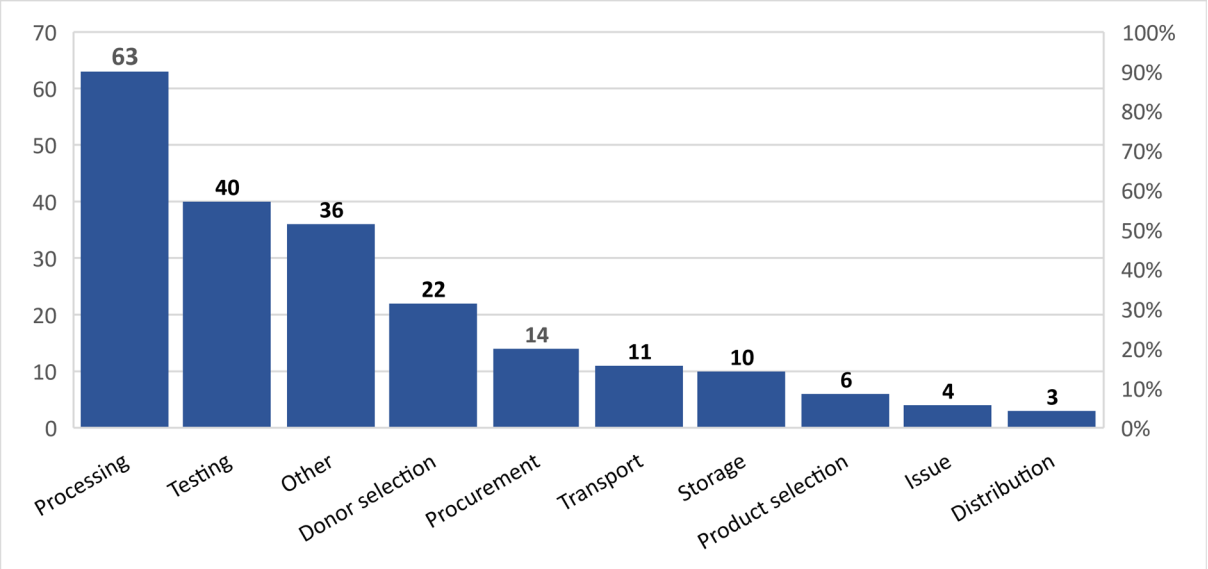

Figure 39. Distribution of SAE for replacement tissues and cells by activity step; data 2022

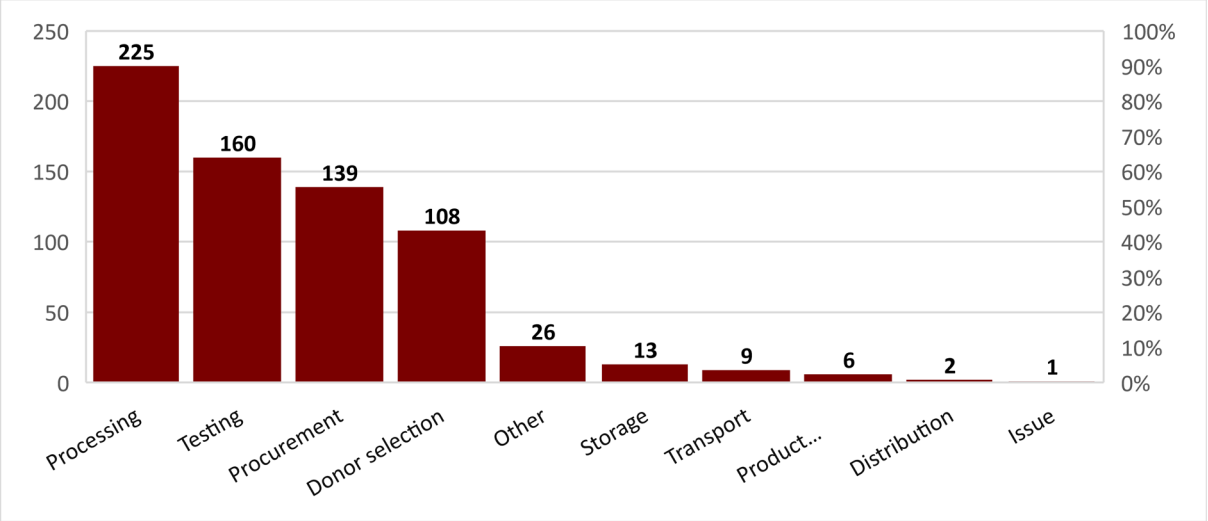

Figure 40. Distribution of SAE for haematopoietic stem cells by activity step; data 2022

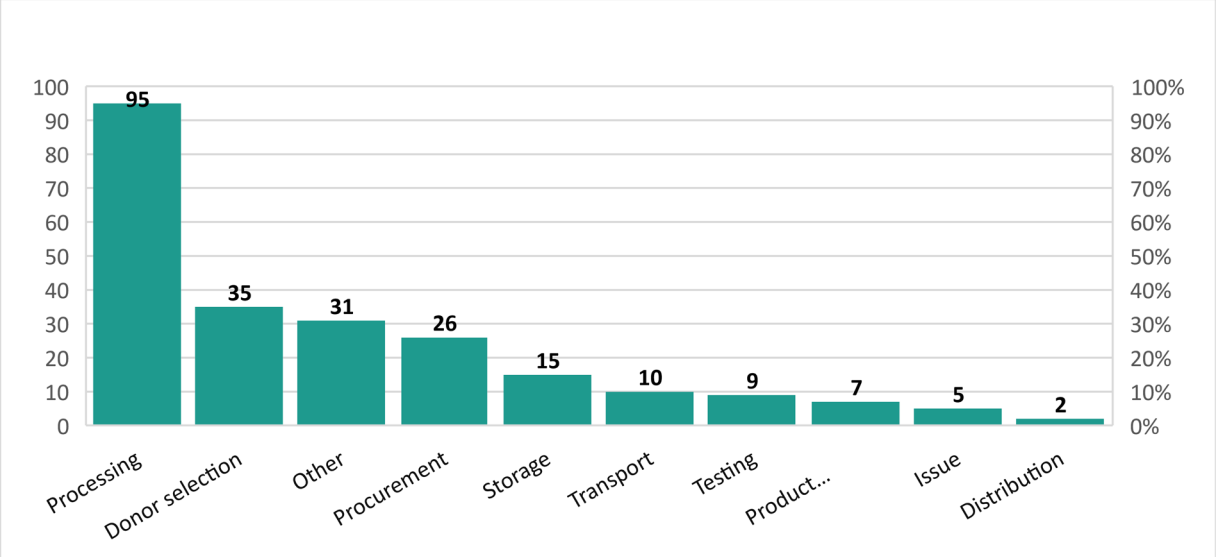

Figure 41. Distribution of SAE for reproductive tissues and cells by activity step; data 2022

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, testing** and **other** are the most frequent for all categories of cells. An overview of the SAE reported for each of the three categories of tissues and cells by activity step is presented in *Figures 42-44.*

For **replacement tissues and cells**, **system failure** and **other** were the most frequent types of SAE (52 SAE each accounting for 25% out of the total 209 SAE), followed by **tissues and cells defect** (46/22%), human error (34/16%), equipment failure (18/9%) and materials (7/3%).

Out of the 63 SAE related to processing (30% of 209 SAE):

- 24 were reported as tissues and cells defect; most concerned ocular tissues (cornea) and were defined as anatomical change of tissue pending implantation
- 12 other; eight were unforeseen events during cornea preparation
- Ten equipment failure; eight were failures of freezing equipment
- Eight human error, of which two were human error following the wrong procedure, two cases of human error/incorrect decision following the correct procedure and the remaining four were not classified (bacterial contamination of cornea, sampling procedure not respected, a case of a vial from which the corneal graft was missing and the discovery of hair while processing an amniotic membrane)
- Six system failure (bacterial contamination of graft and loss of graft)
- Three related to materials (bacterial contamination of graft and issue related to use of equipment)

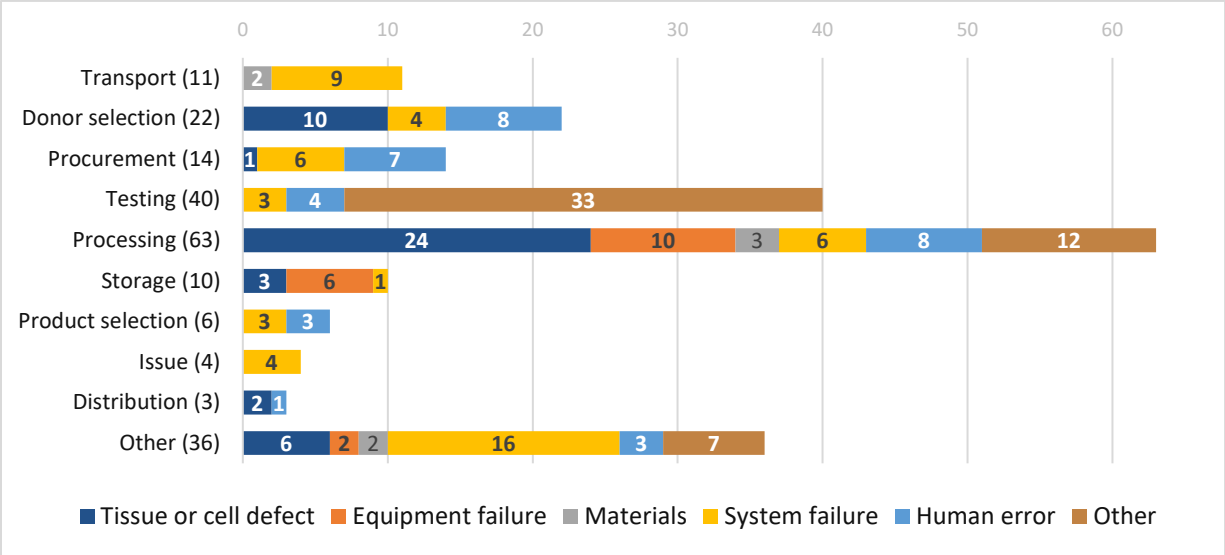

Figure 42. Distribution of SAE for replacement tissues and cells by activity step and SAE type; data 2022

In the **HSC** category, the top three activities in the transfusion cycle where SAE occurred or were identified were **processing** (225/33%), **testing** (160/23%) and **procurement** (139/20%), a change from the previous year when procurement was the activity associated with the highest number of SAE. The most prevalent classified events encountered during processing were tissues and cells defect (40, mainly poor recovery of cryopreserved CD34+ cells after thawing) and system failure (18), while the majority were not classified (147 other; low cell count of cord blood).

The events that occurred or were identified during testing were mainly positive microbiological results prior to and after transplant identified primarily during the testing of cord blood, but also bone marrow and PBSC (148 SAE/21 %). These events were unclassified (other).

In the subgroup procurement, 59% of SAE were classified as **system failure** (82 SAE: bacterial contamination of bone marrow and PBSC and poor recovery of cryopreserved CD34+ cells after thawing) and **tissues and cells defect** (37 SAE; insufficient cell quantity and quantitative error).

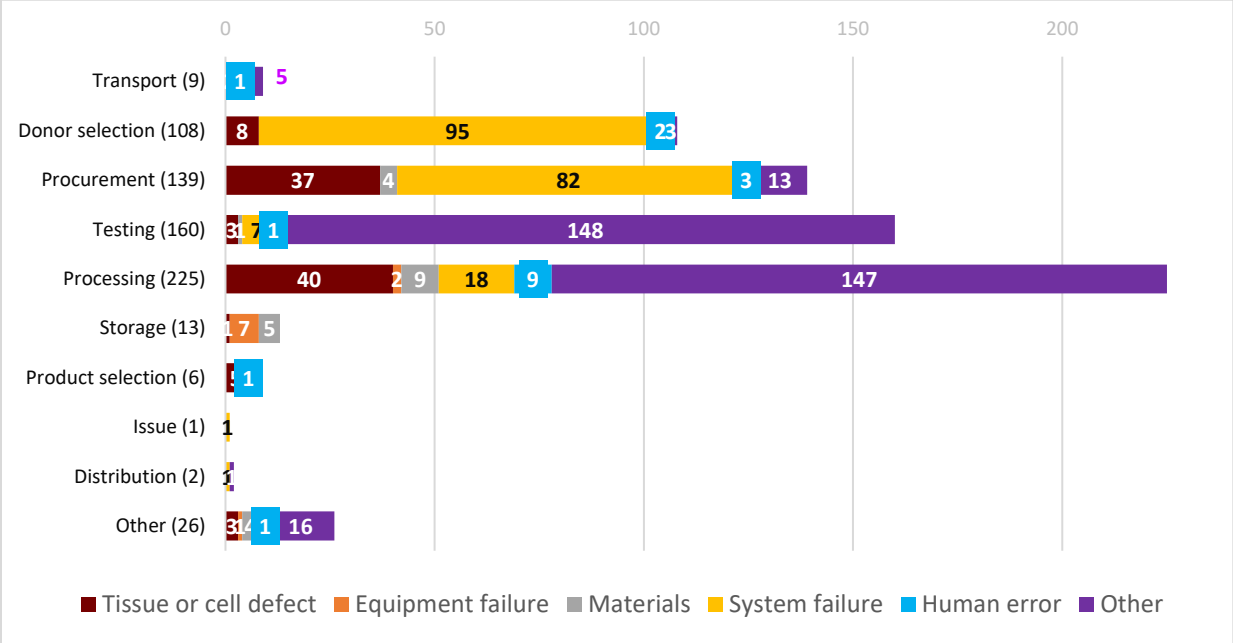

Figure 43. Distribution of SAE for haematopoietic stem cells by activity step and SAE type; data 2022

Similar to the previous year, most of the SAE reported in relation to **MAR procedures** occurred or were identified during **processing** (95/40%) and **donor selection** (35/15%), while 31 SAE (13%) were unclassified (**other**). Two-thirds of SAE during processing were attributed to **human error** (54 out of 95; other, incorrect decision and following the wrong procedure) and **system failure** (18 out of 95; culture contamination, handling incidents, non-compliance with prescription instructions), followed by **materials** (10/10%). In the donor selection group of SAE, **tissues and cells defect** was the most frequent. Out of 31 SAE from **other** steps, 14 were classified as **system failure** and 12 were attributed to **human error**.

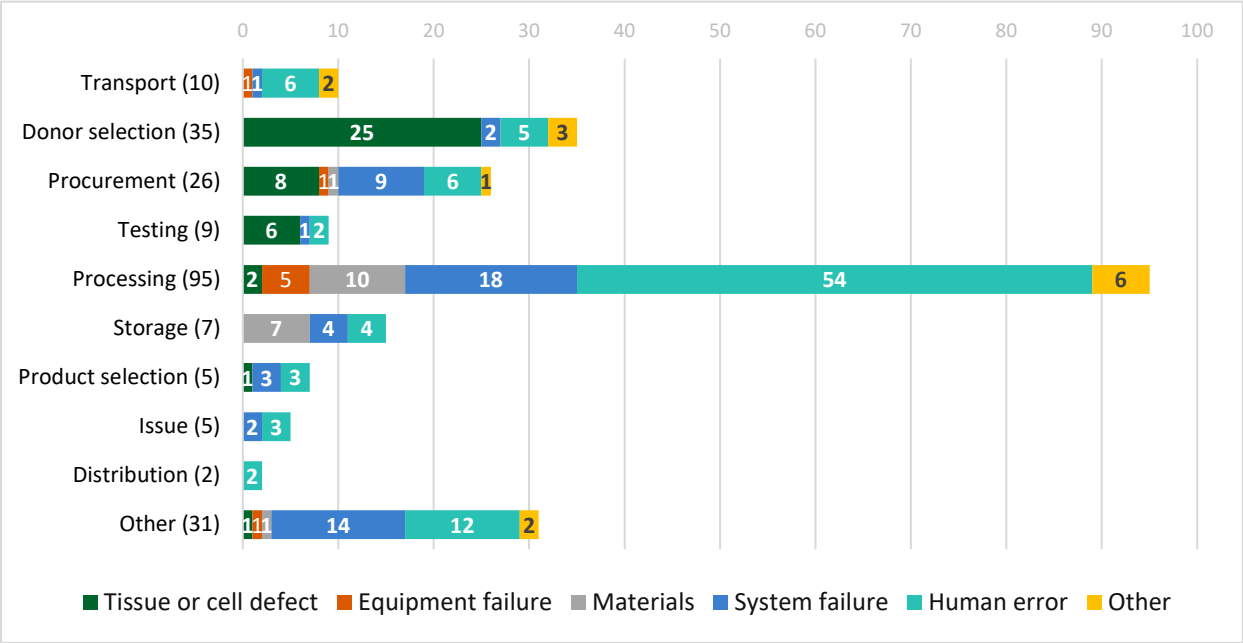

Figure 44. Distribution of SAE for reproductive tissues and cells by activity step and SAE type; data 2022

Examples of SAE and the assigned specification for the three categories of tissue and cells are provided in Annex 1. Note that this is intended an illustration of SAE reported for the chosen activities, not an exhaustive list. There is a concern that the SAE specification was not always adequately assigned, and some were potentially not reportable. In addition, the description provided was not always clear and the information provided was sometimes insufficient.

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 (G-CSF) for the collection of PBSC), the Commission continues to collect such data on a voluntary basis, in agreement with the NCAs.

Nineteen countries (AT, BE, CZ, DE, EE, EL, ES, FI, FR, HR, IE, IT, LU, NL, NO, PL, PT, SE and SI) reported a total of 777 SAR in donors in 2022. An overview of SAR in donors during the period 2012-2023 (data pertaining to 2011-2022) is presented in *Figure 45*.

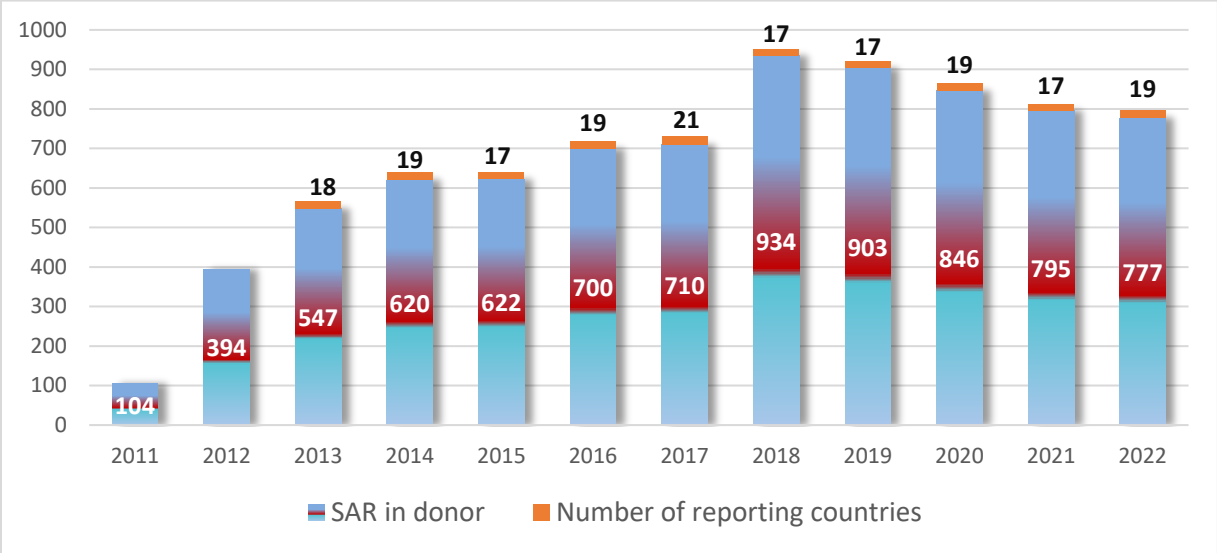

Figure 45. Number of SAR in donors by number of reporting countries and year; 2011-2022 comparative data

The distribution of the 777 SAR in donors reported in 2022 for the three categories of tissues and cells is presented in *Figure 46.*

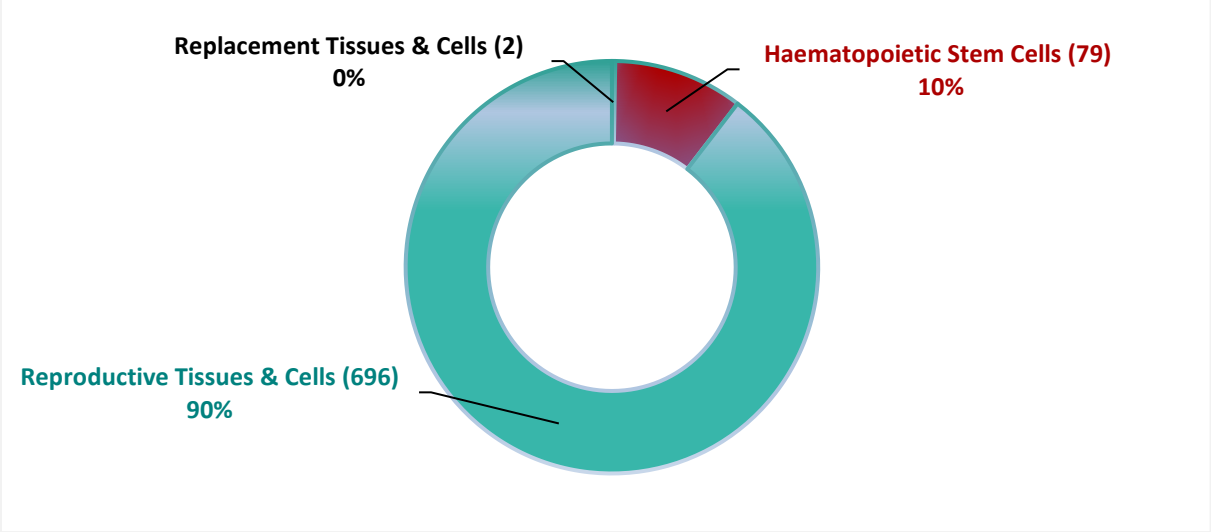

Figure 46. SAR in donors per category of donated tissue or cells (units); data 2022

The number of SAR per category of tissues and cells for the 19 countries that reported SAR in donors in 2022 is shown in *Figure 47.*

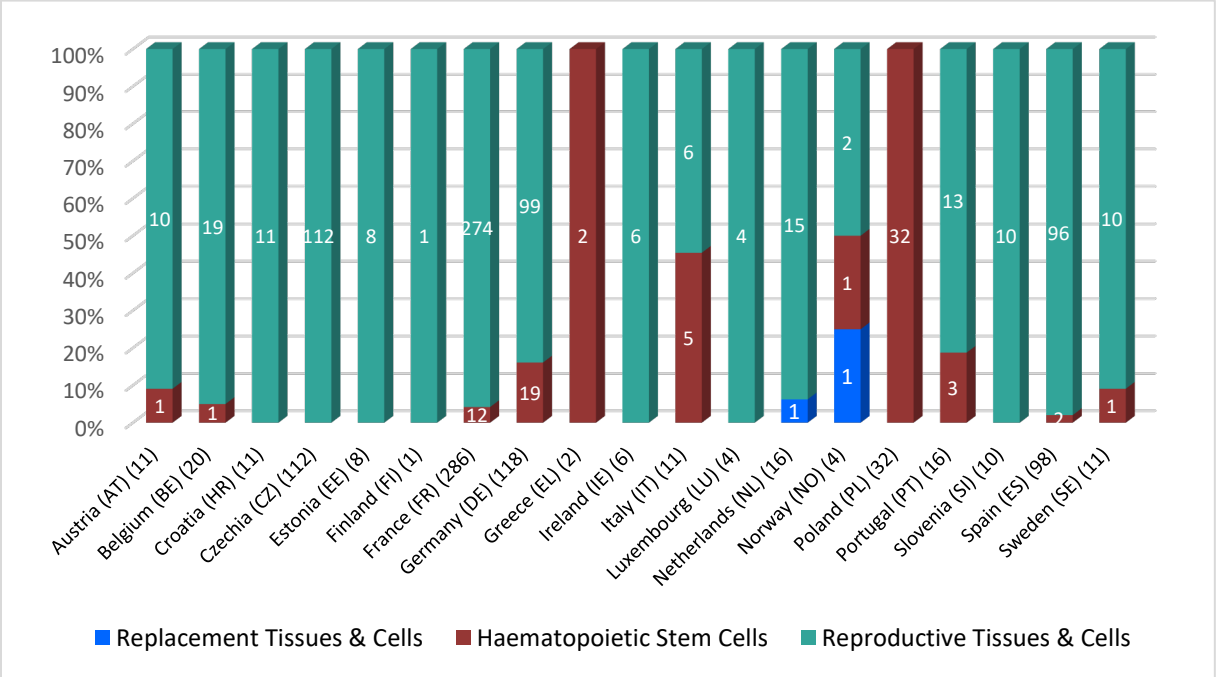

Figure 47. Number of SAR per category of tissue and cells and per country; data 2022

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

- Two cases reported by the NL and NO associated with the donation of replacement tissues or cells (one infection - septic arthritis of knee after procurement of cartilage and one pain) (<1% of all SAR in donors).
- 79 cases (10%) of SAR in donors associated with HSC were reported by 11 countries (AT, BE, ES, FR, DE, EL, IT, NO, PL, PT and SE). The category **other** accounts for 48% of SAR in donors of HSC, followed by **acute systemic toxicity during mobilisation or collection** (15%) **autoimmune disease** and **infection** (each 9%), **mechanical damage** (6%) and **thrombotic/embolic reactions** (5%).

Refer to *Figure 48* for all categories of reactions.

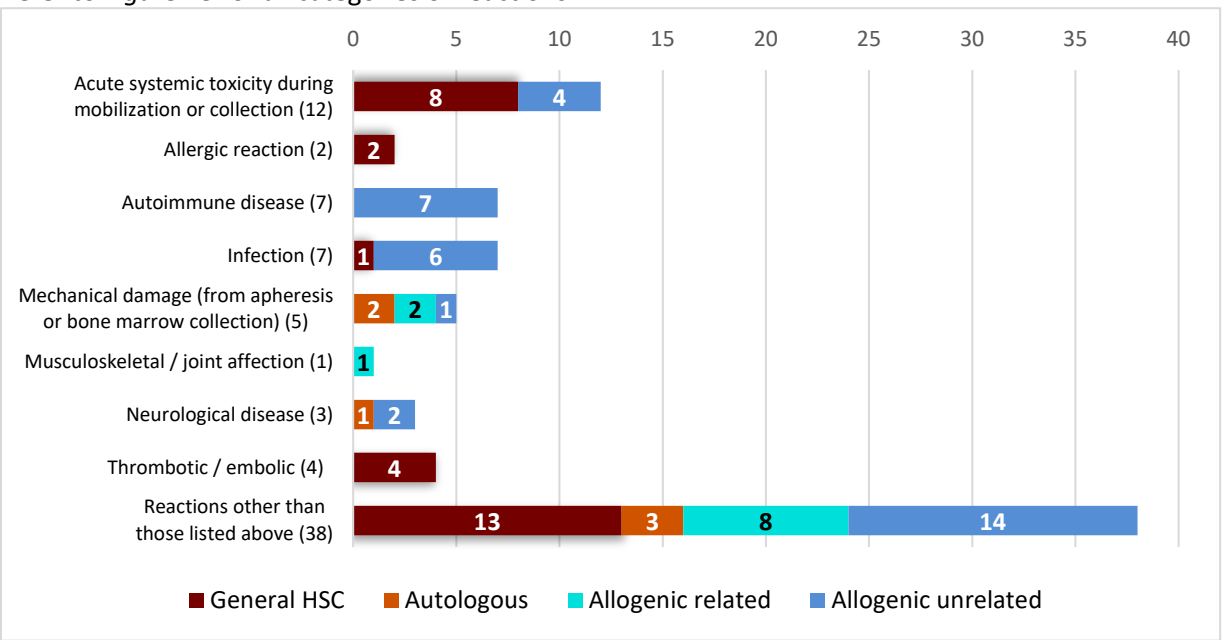

Figure 48. SAR in donors by type of haematopoietic stem cells and type of reaction; data 2022

Reaction types for the most frequent categories of reactions are presented in *Table 6* below. Note that a description was not provided for all reactions.

Reactions other than those listed above (38)	Fatality: syncope 10 days after donation. Cause of death unknown Fatality 2 days post-procurement Multiple cases of neoplasm >6 months after donation (11 SAR) Reaction to citrate (severe hypocalcaemia) (5 SAR) Splenic rupture (2 SAR) Atrial fibrillation during cytapheresis (harvesting of CAR T cells) Acute coronary syndrome Sinus tachycardia Anaemia Vomiting (2 SAR) Hypertension, dyspnoea, chest pain, arm pain Palpitations, hot flush, hypokalaemia Presyncope Partial hearing loss, tinnitus Donor withdrawal during mobilisation step Unexpected effects (rare or not described in the literature) that may be connected to the donation process Reaction to inadequate harvesting New mobilisation required (2 SAR) Lipothymia corrected with medication and donation resumed
Acute systemic toxicity during mobilisation or collection (12)	Citrate cytotoxicity
Mechanical damage (from apheresis or bone marrow collection) (5)	Haematoma at application and catheter site (3 SAR) Bleeding at puncture site of groin catheter after catheter removal
Infection (7), Autoimmune disease (7), Thrombotic/embolic (4)	No description provided.

Table 6. SAR in donors of haematopoietic stem cells; data 2022

A total of 696 cases of SAR in donors (89%) were related to the donation of reproductive tissues or cells, of which 645 occurred following donation of oocytes, as shown in *Table 7.* Seventeen countries (AT, BE, DE, CZ, EE, ES, FI, FR, HR, IE, IT, LU, NL, NO, PT, SI and SE) reported. Most of the SAR in oocyte donors were **OHSS** (355 cases/51%) and **surgical complications** (181 cases/26%); the remaining cases included **infectious complications**, **ovarian torsion** and **other** types of SAR, as shown in *Table 7* and *Figure 49*.

Tissue Subtype	Reaction Type	SAR #/ % 2022	SAR #/ % 2021
Oocytes	OHSS	355/51%	394/55%
	Surgical complications	181/26%	186/26%
	Infection	44/6%	51/7%
	Ovarian torsion	24/3%	29/4%
	Reactions other than above	40/6%	55/8%
Sperm	Reaction to anaesthetic	1/0%	-
	Reactions other than above	2/0%	-
	Surgical complications	-	2/0%
Other Reproductive tissues	Infection	4/0.6%	-
	Surgical complications	28/4%	-
	Reactions other than above	15/2%	1/0%

Table 7. Type of SAR in donors per subcategory of reproductive tissues and cells; 2021-2022 comparative data 2022

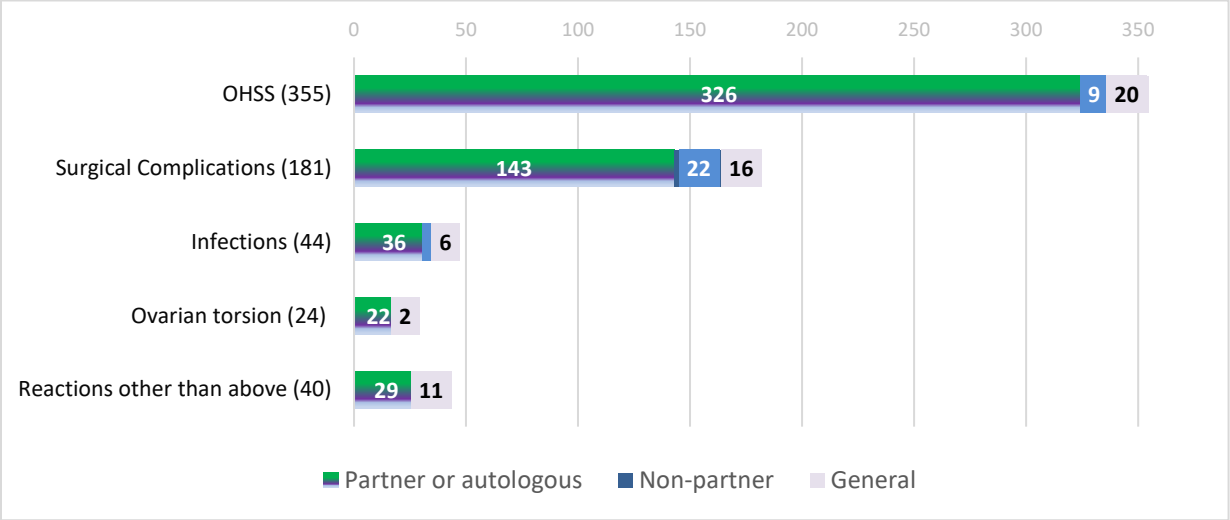

Figure 49. Distribution of SAR in donors by type of reaction in oocytes; data 2022

Examples of SAR in donors of reproductive cells are presented in *Table 8* below.

Reaction Type	Examples
Surgical complications (181)	• Hemoperitoneum (124/68.5%) • Difficult urination and haematuria following follicle puncture of oocytes; surgery: bladder coagulation and bladder irrigation • Bladder puncture during oocyte pick up (OPU) • Intra-abdominal haemorrhage 2 days after oocyte aspiration • Suspected pulmonary embolism • Bladder injury, ovarian haematoma • Bleeding; ovarian abscess requiring salpingectomy • Suspected ovarian haematoma • Bladder puncture that required surgery or hospitalisation
Infection (44)	• Suspicion of pelvic infection: abdominal pain, sub-febrile state • Suspicion of pelvic infection: abdominal pain, sub-febrile state, nausea, diarrhoea • Purulent inflammation of the right ovary after oocyte retrieval. Patient recovered completely. • Abscess following oocyte harvesting • Ovarian abscess, acute pyelonephritis, pelvic abscess, pelvic infection, pelvic peritonitis, pyosalpinx, salpingitis, tubo-ovarian abscess • Infection post egg collection with hospitalisation • Pelvic infection • Bacterial infection
Other reactions (40)	• Abdominal pain and swelling that required surgery or hospitalisation • Various reactions after oocyte aspiration: ovarian abscess; bleeding; pain, vagal reaction and nausea • Thrombosis • Haematuria • Renal insufficiency • Pulmonary embolism • Anaphylactic shock • Jugular vein thrombosis • Pelvic pain • SV tachycardia • Reaction to opioid analgesia (repeated fainting requiring hospitalisation) • Venous bleeding

Table 8. Examples of SAR in donors of reproductive cells; data 2022

5 CONCLUSIONS

EU member and non-member states continued to support this initiative in 2022. Overall, the number of reporting countries increased slightly in the last four years (from 27 in 2019 to 30 in 2022).

In general, reporting of SAR has improved since the initiative was launched in 2010, both qualitatively and quantitatively, thanks to the commitment of countries to the vigilance programme. However, there are persistent issues that require diligence:

- High variability among countries in terms of SAR/SAE reporting style persists. Improvement is required in terms of data completeness. Reporting of transmitted infections and fatalities in general, but especially infections associated with MAR procedures, requires improvement; no relevant information was provided in 2022 for the infections following MAR treatment.
- Eight countries report sparingly or never report any SAR or SAE. As in previous years, 17 out of the 30 countries participating reported SAR and 22 countries reported SAE in 2022.
- Requirements for reporting fatalities in recipients as stated in the *Common Approach* are largely not met, especially for SAR with imputability level 3 (certain) for which an investigation should be conducted, and the results and actions implemented and reported.
- Determination of imputability poses difficulties, especially for SAR in recipients of MAR procedures.

Similar to SAR, the SAE analysis revealed several areas that have not improved:

- The proportion of SAE in categories *Human error* and *Other* remains very high, especially for SAE related to reproductive cells. In 2022, 41% (97 out of 235) SAE related to reproductive cells were reported as human error: *Human error - Incorrect decision following the right procedure (42), Human error - Following the wrong procedure (5) and Human error - Other (50).* The group *Other* is problematic as it includes events that are potentially not managed adequately. Each of the 50 unclassified events (*Other)* could be attributed to one of the other five current categories (system failure, equipment failure, materials, tissues and cells defect and human error).
- Similar to SAR, the information provided regarding the events and course of action is insufficient, preventing a determination of the effectiveness of the management of events at individual country level and EU level. The SAE specification assigned is not always accurate.
- Some of the events reported are potentially not reportable as SAE; this explains the high number of SAE in 2022 compared to previous years.

The distribution of SAR in donors among the three categories of T&C remained unchanged in 2022. Four fatalities in donors were reported this year; imputability of one was assessed as unlikely.
Despite the improvement in data completeness and accuracy throughout the years, there are still many inconsistencies among reporting countries in terms of data completeness and classification/interpretation that make 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. An example of this is the Belgian *Symposium sur la vigilance dans le domaine des cellules et tissus le 5 février 2024*[6] that brought together the NCA and stakeholders in the field of tissue and cell transplantation. It was a successful forum where the requirements for vigilance as currently defined in the EU Directives and in the BTC Regulations were presented, along with a ready-to-use vigilance model; there was also an interactive session and an open dialogue on practical aspects and challenges, current and future.

[6] https://www.afmps.be/fr/presentations

Communication at national level is instrumental for advancement of individual countries' vigilance programmes and needs to be complemented by communication and collaborative work between competent authorities to share best practices and discuss improvements in vigilance at European level. This would benefit both countries with well-established vigilance programmes and those with less developed programmes. The implementation of a harmonised reporting dataset at the European level would 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	
SAE Specification	**Examples**
System failure 25% (52 out of 209)	• Identification errors of cardiovascular tissue discovered during interbank transfer • Corneas implanted with subsequent receipt of various positive culture results at different phases of the process • Inadequate transport conditions of heart from procurement centre to the TE • Incomplete registry • Loss of graft • Mix-up of serological tests during transport, procured tissues lost • Non-compliance with the procurement procedure (cut in the commissure of the pulmonary valve during heart removal, incision of the pulmonary and aortic valves). Loss of tissue • Non-conforming cardiovascular tissue shipped inadvertently (positive bacteriological result not in the system). Tissue returned and rejected • Positive test for *Cutibacterium acnes* in smear of pulmonary heart valve during implantation • Positive test in smear of pulmonary heart valve during implantation: *Staphylococcus lugdunensis* • Post-donation information • Recipient ocular infection prior to transplant • Retrieval of ocular tissues without prior consent on the basis that, by law, everyone is a donor unless they declared otherwise during their lifetime • Temperature probe for traceability not included in the transport boxes • Transport box of the graft brought by the carrier not adapted • Traceability loss due to failure of repositories to provide tissue bank with documentation • Traceability to transplanted bone lost due to missing user report
Other 25% (52 out of 209)	• Positive microbiology results found before transplant (19) • Positive microbiology results found after transplant (11) • Unforeseen events during tissue preparation (8) • Contamination • Anaerobic culture bottle post cornea transplantation positive for *Cutibacterium acnes*. No patient reactions/issues • Post-donation information • Preparation error • Storage time expired • Different serological test detection threshold at tissue bank and receiving blood vessel bank. Patient died days later. Remaining tissue rejected. Tissue bank released femoral veins to blood vessel bank. One vein had been transplanted when the tissue bank notified the blood vessel bank about a slight positive NAT result for HCV. NAT test performed by receiving bank; negative result.

Replacement tissues and cells	
SAE Specification	**Examples**
Tissues and cells defect 22% (46 out of 209)	• Anatomical change of the tissue impeding transplantation (19 SAE) • Neuroendocrine tumour in recipient of liver transplant related to donor who donated organs and tissues (bone) 4 years before; no evidence for NET in other organ recipients • Tissue contamination (corneas) identified before tissue use • Tissue contamination detected after transplant • Positive microbiological test (skeletal tissues) • Positive serological and PCR tests one week after collection. Tissue (skin) destroyed • Blood culture of ocular tissue donor positive for *Finegoldia magna* • Valve graft failure due to friable frill • Cutting of the cornea not feasible perioperatively, making transplantation impossible • Multi-organ/tissue donation: recipient of kidney experienced oncocytoma (non-malignant) in donated kidney. The donor of the kidney also donated a pulmonary valve • Expired storage, imperfect quality • Failure of trepanation • Diagnosis of Alzheimer's disease (brain autopsy) • Microscopic pathology reports possible contra-indications for donation (neurodegenerative disease, haematologic malignancy), corneas already transplanted • Rupture in a homograft (aorta/aortic valve) detected in connection with transplantation. Graft discarded and another graft used. No certain underlying factor identified; graft rupture can, in rare cases, occur in connection with freezing
Human error - Other, or no information to assign 6% (13 out of 209)	• Donor accepted in the absence of test result for sexually transmitted disease pathogen • Positive microbiological test result after cornea was distributed; secondary contamination suspected • Bacterial contamination of graft • Contamination • Sampling procedures not respected • Missing corneal graft found upon opening of container • Hair observed while preparing the graft • Loss of bulbi, box dropped • Failure of transport service to deliver samples for standard serological and bacteriological tests (skeletal tissue; live donor); graft destroyed as resampling is not possible

Haematopoietic stem cells	
SAE Specification	**Examples**
Other 48% (333 out of 689)	• Low cell count (under minimum required) (cord blood) (147 SAE) • Positive microbiology results found before transplant (cord blood) (137 SAE) • Positive microbiology results found after transplant (cord blood) (11 SAE) • Bacterial contamination • Bacterial contamination. Product infused. • Bacterial contamination. Required extra days harvest. Implicated product was not used. • Contamination • Bursting of cryobag containing stem cells • Delayed delivery of samples for testing • Donor with donation contraindication (travel less than 6 months earlier in Zika and malaria risk zone). NAT test performed in a non-EU-recognised lab (US) was accepted as samples requested did not arrive in time • Microbial contamination due to skin infection of patient • Microbiological contamination of procured biological material • Number of cells in material released for transplantation lower than the value in the Formal Request (donor centre refused to perform another HSC separation) • Post-donation information: mutation not previously known in a recipient, discovered post-allograft and post-DLI; donor positive for COVID-19 (positive COVID antigen test); positive Sars CoV-2 PCR performed on donor blood sample on the day of donation. • Related donor with donation contraindication (recent piercing, tattoo) selected to donate PBSC (exceptional release). Tests for infectious disease markers to be performed on donor. • Time or temperature exceeded • Without specification • Wrong or absent labelling • Not specified • Other
System failure 30% (205 out of 689)	• Incomplete registry (95 SAE) • Detection of *Cutibacterium acnes*, *Escherichia coli*, *Staphylococcus* sp., *Bacillus cereus*, aerobic spore formers (22 SAE) • Anaerobic culture positive for *Cutibacterium acnes*. Result available after infusion of allogenic PBSC. All other results negative, including sterility test for the 2nd unit collected at the same time. • Anomaly during the identification process • Bacterial contamination of graft • Bacteriological test result of cells (PBSC) positive for *Staphylococcus capitis*. Prophylactic antibiotics; negative test results for additional blood cultures from used units • Inadequate incubation time of blood culture • Cancellation of ongoing DLI thaw, loss of mononuclear cells • Inadvertent discarding of culture flasks • Delayed delivery of lymphocyte infusions and incomplete documentation (serology testing results not provided) • Incomplete and inaccurate documentation provided along with cellular product

Haematopoietic stem cells	
SAE Specification	**Examples**
System failure 30% (205 out of 689)	• Insufficient cell quantity; venous access problem • Mislabelling (incorrect warning information) • Failure to perform microbiological testing in anaerobic conditions discovered after bone marrow infusion. No consequence for the allograft recipient. Other results negative. Physician notified. Patient under observation. • Organisational failure of the graft, lack of co-ordination between the various teams involved in the care of a patient, destruction of a labile blood product • Poor recovery of CD34+ cells after de erythrocytosis • Poor recovery of cryopreserved lymphocyte after thawing • Suspected mix-up of cryopreserved stem cells
Tissues and cells defect 14% (99 out of 689)	• Poor recovery of cryopreserved CD34+ cells after thawing (42 SAE) • Quantitative error (10) • Positive markers for a transmissible infection or a positive microbiological test (3 SAE) • Contamination of bone marrow suspected to have occurred during harvesting. Prophylactic antibiotics administered • Ten-year-old autologous PBSC units deemed non-conforming after thawing (autolysis) • PBSC autolysis; no explanation • Donor not meeting selection criterion (COVID-19 test positive) selected to donate PBSC; unique source for a patient already conditioned. No infection in recipient. • Insufficient viability and autolysis (PBSC) after thawing; no deviation during collection and treatment; new apheresis planned • Autologous PBSC unit contaminated with *Escherichia coli* potentially from donor diagnosed with urinary infection. Unit infused (exceptional release). Post-infusion haemocultures negative. • PBSC with lower than recommended viability were infused with no adverse reactions in patient. • Incomplete and inaccurate documentation provided along with cellular product • Insufficient cell quantity • Unsatisfactory recovery of CD34+ cells after buffy-coat • Graft loss, coagulated harvested graft • Low cell viability after thawing of PB unrelated HPC sample during quality control before conditioning regimen. Cells not used for transplant • Bacterial contamination of tumour tissue procured for production of TILs; surgical procurement repeated • Detection of initial positive COVID-19 test on day 4 of mobilisation with G-CSF

Reproductive tissues and cells	
SAE Specification	**Examples**
Human error - Other, or no information to assign 21% (50 out of 235)	• Treatment cycle missed due to failure to assign donor oocytes; only a straw of the couple's semen was thawed • Loss of embryos during observation due to accidental overturning of culture plate • Loss of half of oocytes due to misplacement of devitrified oocyte plate label • Loss of chance of pregnancy for the cycle due to accidental discarding of dish • Loss of pregnancy for one cycle due to accidental loss of oocytes following the drop of a microinjection plate • Accidental loss of all oocytes collected • Accidental loss of multiple embryos • Breaking of the cold chain in an oocyte support during handling for storage • Cancellation of embryo transfer by thawing due to error of euploid embryo instead of aneuploid during thawing of non-viable (aneuploid) embryos • Culture contamination • Defect during the identification process • Power outage affected two incubators containing embryos; embryos discarded. • Loss of unique viable embryo during transfer (excessive manipulation of the transfer catheter, as cannulation of cervix was not possible on the first attempt)
Human error - Incorrect decision following the right procedure 18% (42 out of 235)	• Failure to add oil to culture dishes resulting in degeneration of inseminated oocytes due to desiccation of culture drops • Inadvertent discarding of culture dish containing both good quality and non-conforming embryos on D3 instead of transferring the conforming embryos to fresh medium • Loss of oocytes by inadvertent discarding of culture dish containing the oocytes during the treatment of the patient's material; patient was notified and treatment stopped • Loss of all oocytes following dropping of Petri dish • Failure to freeze embryos • Incorrect labelling of embryo in storage • Failure to move one of three frozen straws to permanent storage • Use of donor sperm under quarantine for treatment in a fertility clinic • Use of known sperm donor’s gametes without performing donor evaluation • Distribution of sperm straws from a donor other than the donor selected by the recipient • Donors with negative NAT tests but missed antibody tests invited back for serology testing; serology tests negative • Deficient withdrawal of embryos when the donor was blocked • Non-compliance with prescription instruction • Error in counting follicles during radiology • Wrong sperm used for IVF • Hep B core antigen-positive embryos not stored in a quarantine tank • Incorrect partner added to patient record on electronic witnessing system. Picked up at IVF insemination. No cells used incorrectly. • Donor's suitability results not verified prior to distribution. All centres contacted, five samples blocked and recovered before use. However, three samples were used. In two out of three cases there was no pregnancy and in the third, the embryos were analysed for the CFTR gene with negative results.

• Reproductive tissues and cells	
SAE Specification	**• Examples**
System failure 23% (54 out of 235)	• Culture contamination (11 SAR) • Contamination with *Candida* detected after thawing • Defect during the identification process • Non-compliance with prescription instruction • Error in counting follicles during radiology • Error in anticoagulant treatment • Error during treatment administration • Error(s) in hormone treatment - prescription/administration • Failure to prescribe anticoagulant to an oocyte donor presenting high risks • Organisational failures of the MAR procedure • Valid embryos discarded along with embryos that reached the end of retention period • Inadvertent discarding of all embryos of a couple in spite of renewed contract for storage • A posteriori discovery of abnormal biological tests • Release of couple's embryo transfers with invalid serology for male partner. Appropriate contracts and other release criteria met • Handling incidents (excluding falls) • Thawing of sperm straws due to lack of nitrogen • Misidentification of donor to be blocked (two donors with similar names) • Loss of donor oocytes: delayed delivery due to logistical issues at shipping supplier resulted in loss of cold chain (oocytes received at 20°C) • Loss of oocyte viability due to loss of cryogenic temperature during distribution, affecting multiple partner oocytes.
Tissues and cells defect 18% (43 out of 235)	• Unknown genetic factor (6 SAE) • Sudden death of a gestated child after artificial insemination with donor semen from a donor carrying a variant of the SCN5A gene associated with severe heart rhythm disturbances • Donor carrier of a probably pathogenic variant in the MIECP2 gene, linked to the X chromosome; donor blocked and embryos discarded • Two couples treated with cells from anonymous donor carrier of a mutation in the MSH6 gene (Lynch syndrome); remaining samples quarantined and destroyed at the fertility clinic. No child born with the anomaly to date, but the couples treated with cells from this donor will be invited to the human heredity centre for advice concerning genetics and Lynch syndrome, heredity, the possible risks for their children and the possibility of having their children tested for a mutation of the MSH6 gene at the age of 18. Psychological support will also be available, if necessary. • Donor with congenital adrenal syndrome • Donor later diagnosed with Brugada syndrome, idiopathic generalised epilepsy, sclerosis; bipolar disorder type II; rheumatoid arthritis • Bacterial contamination ascribed to procurement of gametes detected during embryo culture (3 SAE) • Contamination of embryo culture medium with *Enterococcus faecalis*. The operator observed aseptic technique while preparing the culture dish. The semen subjected to IVF insemination is considered the probable cause of contamination; semen no longer available for a microbiological test. • Contamination of IVF culture drops manifest on day 3 but observed on day 4. The processed semen sample was also contaminated, confirming the semen as the source of the event. • Embryo degeneration on day 2 of embryo development due to an infection with *Escherichia coli* in a patient couple. *E. coli* is found in all samples (female, male). Both partners begin a course of antibiotics. For a subsequent OPU, a vaginal swab and a semen culture are planned. • Degeneration of all zygotes due to *E. coli* contamination of semen • Bacterial infection of semen contaminating multiple embryos