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Substances of Human Origin and Tobacco Control

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SUMMARY OF THE 2012 ANNUAL REPORTING OF SERIOUS ADVERSE EVENTS AND REACTIONS FOR TISSUES AND CELLS (DATA COLLECTED FROM 01/01/2011 TO 31/12/2011)

Article 7 of Directive 2006/86/EC[1] provides that Member States shall submit to the Commission an annual report, by 30 June of the following year, on the notification of serious adverse reactions and events (SARE) received by the competent authority(ies) using the formats in Part A and B of Annex V.

This document intends to provide a brief report of the data collected by the Member States during 2011 (from 1st January to 31st of December). The first report regarding SARE recorded by the Member States (2010 data, reported to the Commission in 2011) was published in 2013[2].

1. DATA COLLECTION METHODOLOGY

Early in 2012, the European Commission in collaboration with a group of tissues and cells competent authorities participating in the EU-funded project SOHO Vigilance & Surveillance[3] revised the tools for the SARE reporting to the European Commission.

The following amendments were operated:

1) The electronic reporting template was adjusted in order to providing a clear, well-structured layout to make it easier for the user to fill out and revise the information in each field. Definitions or clarifications for the requested data were also added as mouse-overs. A classification for "Other serious reactions" (for which further details were not provided in Annex V of the Directive 2006/86/EC) was also proposed to allow an appropriate classification of the data reported under this broad category. The template used in 2012 (for 2011 data) was version 2.1.

2) An updated version of the Common Approach document was attached to the electronic reporting template, thus making it easily accessible to the user. In 2012, the document was updated to accommodate the changes in the electronic template; the version of the Common Approach document used in 2012 (for 2011 data) was 2.1.

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF
[2] http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_cells_adverse_events_2011_en.pdf
[3] http://www.sohovs.org/soho/

2. MAIN FINDINGS OF THE 2012 ANNUAL REPORT – DATA COLLECTED DURING 2011

2.1. General comments

The reporting template was sent to the EU27 Member States as well as to Liechtenstein, Norway and Croatia. All the above mentioned countries, except Greece, sent back their SARE reports.

Following the last revision of the Common Approach document, an acceptable level of standardisation of the information was reached, showing that clear and explicit instructions are needed to ensure that the information contained in annual reports from different competent authorities could be compared.

2012 was the second year when Member States were asked to discriminate between missing/non-available data (NA in the template) and no reactions/no events/no tissues/cells distributed or processed (0 in the template). In this respect, many Member States acknowledged that accurate data for certain types of tissues/cells was not available and did not provide incomplete/approximate numbers. Despite this, the numbers reported for tissues and cells distributed/processed and the number of recipients of a tissue/cell therapy were three times higher than those reported in 2011[4].

Nineteen countries (16 MS, HR, LI and NO) reported that there were no occurrences of SAR related to the human application of human tissues and cells during 2011. Moreover, 10 countries (CY, CZ, LI, LT, LV, LU, MT, RO, LI, HR and NO) reported that no SAR and no SAE occurred at national level. For smaller countries where these medical services are on a smaller scale these data seem plausible, but in case of larger countries this may indicate that SARE reporting procedures had not been sufficiently embedded at a national level to ensure reporting by professionals in the transplantation field and/or tissue establishment staff.

2.2. Serious Adverse Reactions (SAR)

2.2.1. Information by country

Twenty-six MS, as well as Liechtenstein, Norway and Croatia complied with the requirement of Article 7 to submit information on SARs by completing the annual report template.

A total number of 991,538 units of tissues and cells were distributed by tissue establishments in EU and EEA countries (395,294 were units of non-reproductive tissues and cells and 596,244 were units of reproductive tissues and cells). It has to be underlined that as in the previous years, for some groups of tissues/cells, several Member States preferred to report "no available data" for this denominator rather than providing approximate, imprecise numbers. In some cases (e.g. for distribution of oocytes), data were not provided because of atypical measurement units used at national level (e.g. cycles of artificial insemination instead of units of oocytes distributed).

[4] http://ec.europa.eu/health/blood_tissues_organs/docs/tissues_cells_adverse_events_2011_en.pdf

377,023 recipients (patients) were reported as having received some kind of tissue/cell (262,455 recipients of a tissue or cell transplantation and 114,568 patients who underwent an ART procedure with sperm, oocytes or embryos). This data is incomplete because for various groups of tissues or cells, several Member States acknowledged that accurate data was not available.

A total of 156 SAR were reported, of which 141 were related to non-reproductive tissues and cells (90.4%), and only 15 to reproductive tissues and cells (9.6%). 11 MS reported SAR related to the transplantation of non-reproductive tissues and cells (BE, DE, ES, FR, IE, IT, NL, PT, SE, SI, UK) and only 4 MS reported SAR following the application of reproductive cells (BE, BG, IE, UK). Therefore, for non-reproductive tissues and cells, there were 0.036% SAR/tissues and cells distributed and 0.054% SAR/number of recipients. For reproductive tissues and cells, there were 0.0025% SAR/tissues and cells distributed and 0.013% SAR/number of recipients. However, the data requires careful interpretation because even though the total number of SARs reported in 2012 was three times higher than the number of SARs reported during 2011, many countries did not report any SAR.

Nineteen countries (16 MS, HR, LI and NO) reported that no SAR related to the human application of human tissues and cells occurred in their countries in 2011. It should be noted that for 2010, 13 out of the 16 MS mentioned above, as well as LI and NO reported no SAR related to the medical application of human tissues and cells.

2.2.2. Information by type of tissue/cell

Out of the 156 SAR reported:

- 15 SAR were related to the human application of reproductive cells and tissues (sperm, oocytes);
- 141 SAR were related to the transplantation of non-reproductive tissues or cells (Fig.1):
    - 86 SAR were related to haematopoietic stem cell (HSC) transplants (including bone marrow, blood peripheral stem cells, cord blood, donor lymphocyte infusion and other stem cells);
    - 55 SAR were related to transplantation of replacement tissues (bone, cartilage, tendons and ligaments, other skeletal tissues, ocular tissues, heart valves, amniotic membrane, hepatocytes).

No SAR were reported for the following categories of tissues and cells: skin, blood vessels and other cardiovascular tissues, pancreatic islets, other tissues (e.g. fat tissues, tympanic membrane), embryos and other reproductive tissues (e.g. ovarian and testicular tissue).

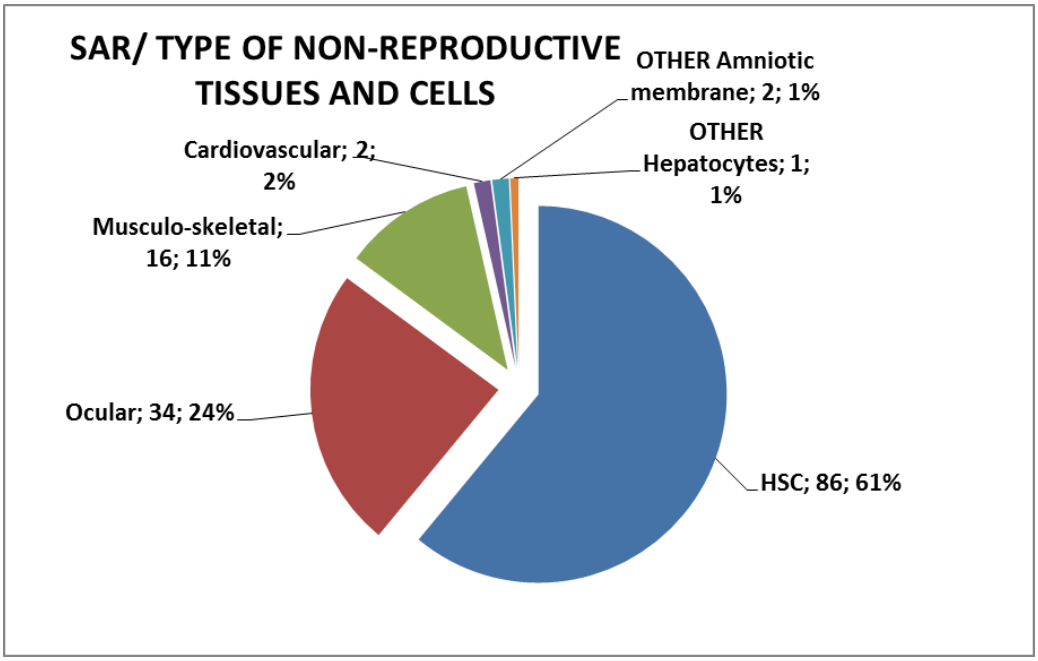

Fig.1. Number of SARs and percentage of total reported SARs for each type of non-reproductive tissues and cells.

2.2.3. Information by category of SAR

The 156 SAR reported were classified as following:

- Transmitted infections: 27 cases (17.3% of reported SARs) as following:
  - 22 cases of bacterial infections (reported for the following transplanted tissues/cells: HSC 10, musculo-skeletal 8, ocular tissues 3, amniotic membrane 1)
  - 2 cases of viral infections (1 HEV infection following DLI administration; 1 HHV6 infection following transplantation of PBSC);
  - 3 cases of other transmitted infections (1 case of endophthalmitis after cornea transplantation, 1 case of fungal infection following HSC transplantation and 1 case of Candida infection subsequent to heart valve transplantation);
- Transmitted malignant diseases: 0 cases.
- Other disease transmissions: 13 cases (8.3% of reported SAR) were reported as following:
  - bone transplantation (1 broncho-pneumonia),
  - cornea transplantation (1 meningo-encephalitis, 1 fungal infection),
  - ART procedures involving application sperm and oocytes (10 genetic diseases).
- Other SAR: 116 cases (74.4% of reported SAR). In this broad and heterogeneous category:
  - 5 SARs were associated to ART procedures (1 extra-uterine pregnancy, 2 ovary torsion, 1 achondroplasya, 1 haemoperitoneum),
  - 73 SARs concerned haematopoietic stem cells transplantation procedures, and
  - 38 SARs concerned transplantation procedures with replacement tissues (ocular tissues 28, musculo-skeletal tissues 7, cardio-vascular tissues 1, amniotic membrane 1 and hepatocytes 1).

More details concerning the SARs reported under the "Other SAR" category for the different types of non-reproductive tissues and cells are presented in figures 2, 3 and 4.

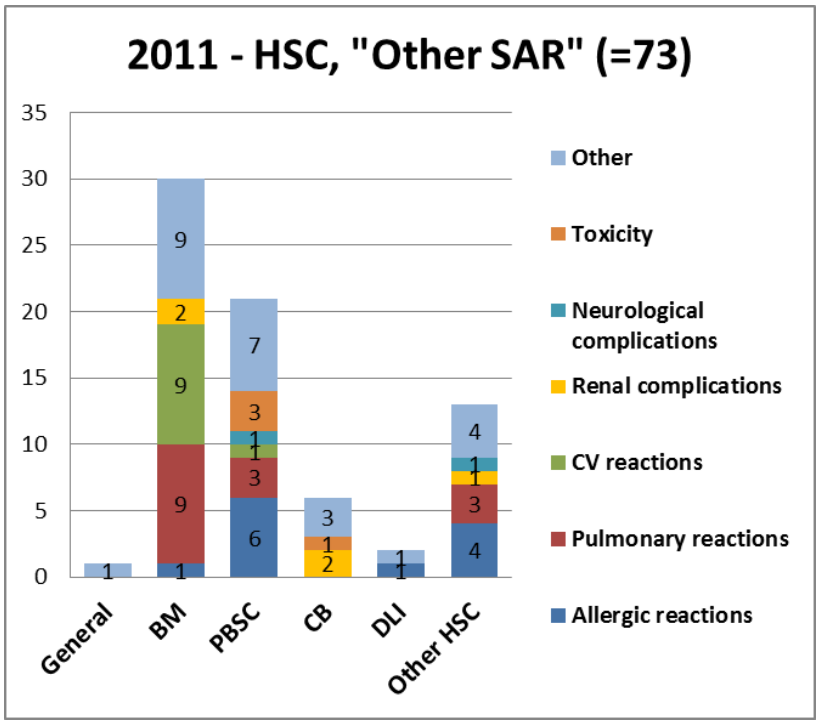

Fig. 2. Number of SAR in the "Other category" subsequent to HSC transplantation (Legend: BM = bone marrow, PBSC = peripheral blood stem cells, CB = cord blood, DLI = donor lymphocyte infusion)

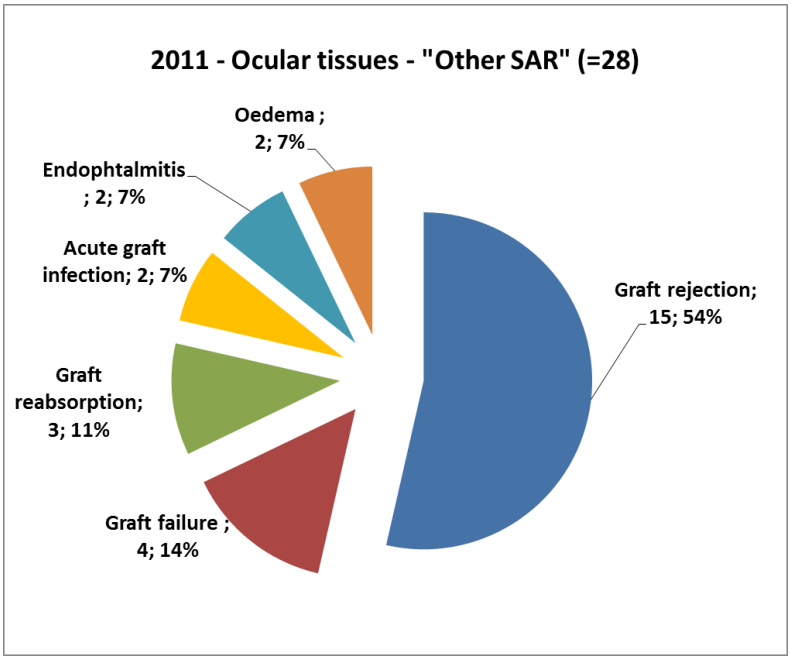

Fig. 3. Number of SAR in the "Other category" following cornea transplantation[5]

[5] Only unexpected graft rejection and graft failure due to quality of the graft are reported under SARs.

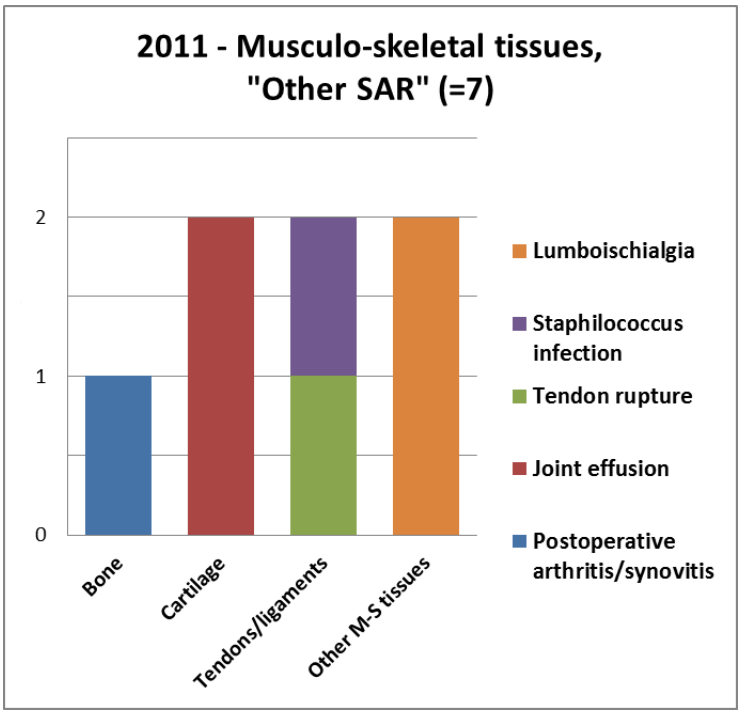

Fig. 4. Number of SAR in the "Other category" following transplantation of musculo-skeletal tissues

2.3. Serious Adverse Events (SAE)

2.3.1. Information by country

A total of 29 countries (26 MS, Lichtenstein, Norway and Croatia) submitted the annual report template and therefore complied with the annual report submission established by Article 7. However, only thirteen countries (AT, EE, ES, HU, IE, LT, MT, NL, PL, PT, SE, SI and UK) provided data regarding the number of tissues and cells processed in 2011. For the purpose of this reporting exercise, the term "tissues and cells processed" refers to tissues and cells processed in the tissue establishments, but not necessarily distributed to the end-users. Overall, a total number of 748,753 units of tissues and cells were processed in 2011.

SAE were reported by 17 MS (AT, BE, DE, DK, EE, ES, FI, FR, HU, IE, IT, NL, PL, PT, SE, SI, UK). The total number of SAE reported for 2011 was 426, representing 0.057% of the tissues and cells processed in the same time period. As in case of SAR, the percentage of SAE in relation to the total number of tissues and cells processed should be interpreted with prudence because many countries reporting SAE did not provide or provided only an approximate number of the tissues and cells processed at national level.

2.3.2. Information by type of SAE

Out of the 426 reported SAE:

- 115 SAEs (27.0%) were linked to "Procurement",
- 50 SAEs (11.7%) were linked to "Testing",

– 18 SAEs (4.2%) were linked to "Transport,
– 112 SAEs (26.3%) were related to "Processing",
– 39 SAEs (9.2%) were linked to "Storage",
– 25 SAEs (5.9%) were linked to "Distribution",
– 17 SAEs (4.0%) were linked to "Materials",
– 50 SAEs (11.7%) were included in the category "Other SAE".

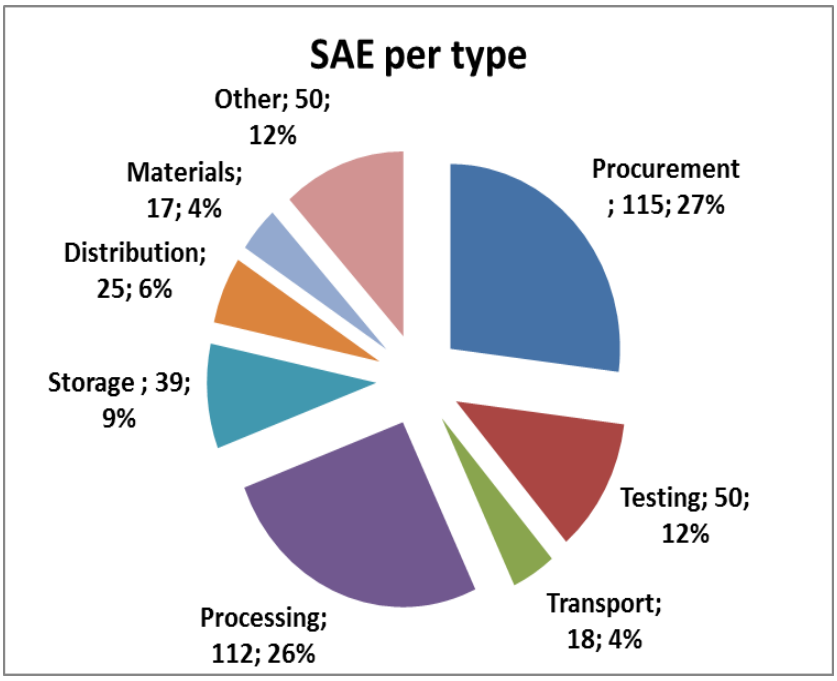

Fig. 5. Number of serious adverse events and percentage of total SAEs reported per type

2.3.3. Information by Specification of SAE

The 426 SAE were attributed to one of the 4 specifications:

- Tissues and cells defects: 100 SAEs (23.5%)
- Human Error: 148 SAEs (34.7%)
- Equipment failure: 91 SAEs (21.4%)
- Other: 87 SAEs (20.4%).

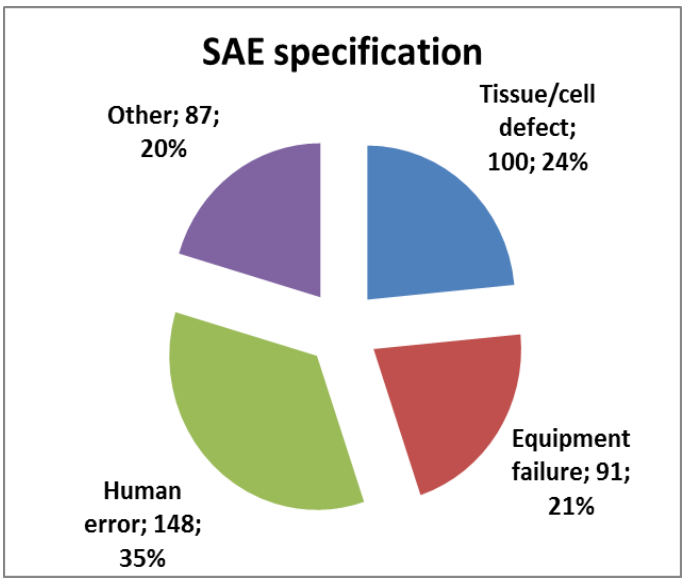

Fig. 6. Number of serious adverse events and percentages per specification

2.3.1. Information by type of activity and specification of SAE

An overall analysis of SAE reported in 2011, taking into account both the donation-distribution chain' activities and the specification, is shown in figure 7.

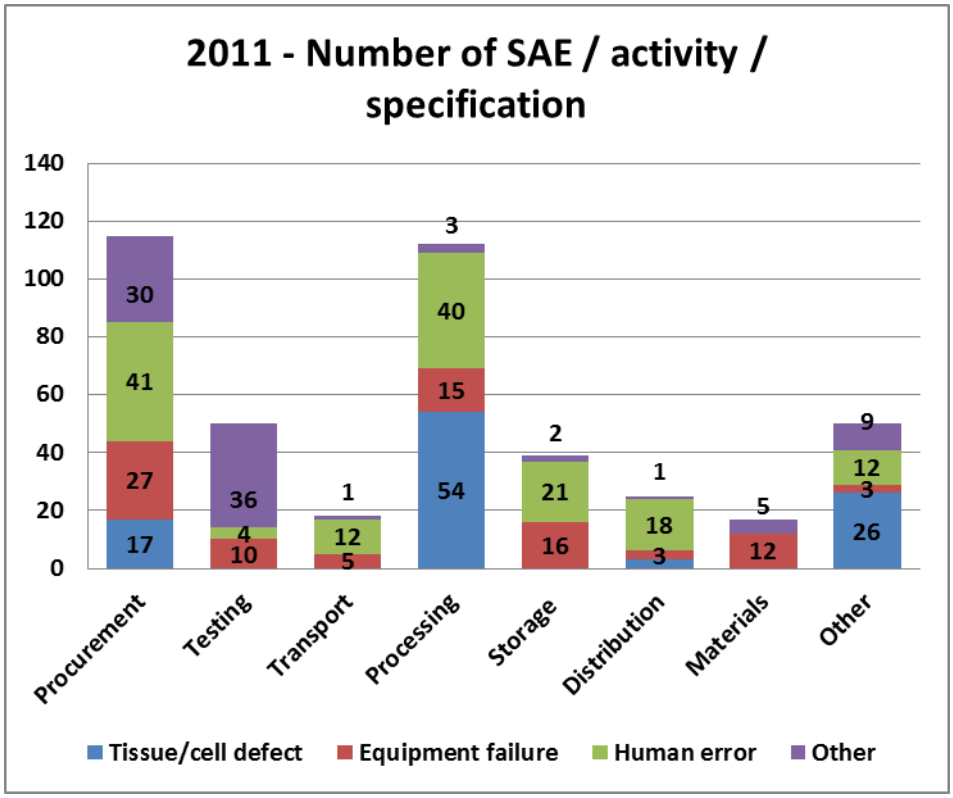

Fig. 7. Serious adverse events per activity and specification

2.4. Serious Adverse Reactions (SAR) in donors

As in previous years, serious adverse reactions in donors were also included in the annual report because the definition of SAR in Directive 2004/23/EC also refers to adverse reactions in donors. Recognising the value of all donor adverse reactions, including those not influencing the quality and safety of tissues and cells (e.g. OHSS following oocyte donation, reactions subsequent to the administration of GCSF for collection of peripheral blood stem cells, etc.) which are reportable under the pharmacovigilance systems, the Commission continues to collect such data on a voluntary basis in agreement with the tissues and cells competent authorities. These figures were calculated separately, and are not included under the total number of SAR.

For 2011, 104 SAR in donors were reported. Nine MS provided data related to SAR in donors (BE, DK, ES, FR, IE, PT, SE, SI, UK), as following:

- 81 were related to activities in the field of ART (e.g. OHSS, bleeding in urinary bladder, pleurisy, thrombosis),
- 19 were connected to the haematopoietic stem cells transplantation procedures (e.g. complications post-GCSF treatment, septic shock, anemia, etc.), and
- 4 were associated to procedures involving other tissue types (ocular, musculo-skeletal and other tissues).

3. CONCLUSION

Based on the reported data, the number of SAR and SAE reported for 2011 is very low (156 and 426 respectively), especially when compared to the number of tissues and cells distributed and processed at EU level (0.016% and 0.057% respectively).

The updated template and Common Approach document, used to collect SAREs reported in 2011, helped to ensure better collection of data particularly when compared with data received during previous years. This was especially true for the denominators "tissues and cells distributed" and "number of recipients", for which the numbers reported were three times higher than in the previous year. Nevertheless, both the Commission and national competent authorities for tissues and cells acknowledge that there is still a high degree of under-reporting, requiring careful consideration when analysing these data.

It should be emphasised that reporting of errors that have resulted in patient harm, as well as near misses, can potentially help to strengthen working practices in the transplantation chain and ultimately improve the safety and quality of tissue transplantation. However, because many errors are not always reported voluntarily or are discovered at a later stage (through other mechanisms like inspections), these improvements may not be made in a timely manner.

Both the Commission and the tissues and cells competent authorities agree that once errors are detected and the underlying “root causes” are identified, appropriate dissemination of such errors (including the combination of causal/contributory factors, evaluation of their frequency and chances to happen again) may reduce the occurrence of similar errors and improve patient safety.

Therefore, the focus for the next reporting period is to continue addressing under-reporting and failure to report errors/near misses. In order to support Member States, the European

Commission has funded the SOHO V&S project[3], which issues several guidance documents. One document aimed at competent authorities provides guidance on communication and investigation of serious adverse reactions associated with human tissues and cells. Two additional documents "Guidelines for Healthcare Professionals on Vigilance and Surveillance of Human Tissues and Cells" provide guidance to professionals who use tissues and haematopoietic stem cells. It is hoped that these guidance documents will help Member States in their efforts to develop policies that support the routine and voluntary reporting of errors by helping to remove the perception of a punitive regulatory environment and rather build a culture of safety.