TRIP REPORT 2015

Biovigilance

Extended version

TRIP
Hemo-en biovigilantie

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Biovigilance

Extended version

The TRIP report 2015 regarding biovigilance in
The Netherlands is published under responsibility of the TRIP
(Transfusion & Transplantation Reactions In Patients) Foundation

TRIP
Hemo- en biovigilantie

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Table of content

Introduction

The TRIP 2015 Biovigilance report is the 9th consecutive annual report describing adverse reactions and events related to processing and use of human tissues and cells. The reports are registered by TRIP in cooperation with all stakeholders in the field of human tissues and cells in order to make recommendations for improving quality and safety.

In 2015 a total of 115 reports were submitted by 35 institutions, which constituted a small rise compared to precious years. The reports are analysed and commented on in the chapters of this annual report. All tissue establishments and institutions that apply human tissues and cells in patients are annually surveyed for the numbers of products of human origin. The participation of both tissue establishments and hospitals and clinics that apply human tissues and cells is stable and almost complete. The participation of oral implantology practices is steadily increasing.

There are two noteworthy clusters of reports relating to assisted reproductive techniques. The first cluster concerns reports of egg cells (oocytes) and embryos that stuck in pipettes during transfer in the laboratory and were consequently lost. The other cluster regards reports of donation complications before or at the time of harvesting egg cells. In Chapter 2 these clusters are commented on. The reporting of adverse reactions in donors is relevant and is also encouraged by the European Commission, although these adverse reaction do not generally influence quality or safety of tissues and cells.

The 2013 recommendation regarding the timely reporting of adverse events and reactions was followed and there were no late reports regarding 2014. At the time of writing only two late reports from 2015 had been submitted after the closing date for this report.

Chapter 3 of this report presents an overview of the largest category of reports that have been registered by TRIP in the past nine years: loss of gametes and embryos. The majority of these reports were related to the processing phase in the laboratory. Omission of a processing step, accidental knocking of a pipette, accidentally dropping or erroneously discarding gametes or embryos were the most frequently reported errors in the processing phase. These errors might (in part) be preventable by redesign of working processes with renewed protocols and introduction of extra checks to limit avoidable loss.

In November 2015 the Healthcare Inspectorate sent a letter to all tissue establishments and healthcare institutions that apply substances of human origin clarifying the mandatory reporting to the competent authority alongside reporting to TRIP. These reporting routes are also described in the annual TRIP Biovigilance reports.

TRIP Foundation wishes to acknowledge the indispensable part played by all the professionals who have contributed to the information in this report and hopes it will play a part in further increasing safety and quality of the chain of human tissues and cells.

Findings and recommendations

2015 findings

1 Participation of hospitals and clinics rose to 100% for the first time since the start of the biovigilance system in 2006. Out of 112 organisations, seven reported they could only provide incomplete data on application or transplantation.

2 The number of oral implantology practices registered in the TRIP database increased in 2015, in part because a distributing tissue establishment alerted practices that they should to provide application data to TRIP.

3 In 2015 63% (72/115) of the total number of reports concerned assisted reproductive techniques (ART). Among these reports there were 11 reports regarding donation complications in ART. Seven out of these 11 were cases of ovarian hyperstimulation syndrome.

4 Concerning hematopoietic stem cells, six reports of donation complications were reported with probable or certain imputability.

5 In 2015 the number of reports concerning reproductive cells in the category loss of tissues or cells was the highest it has been since 2007. The majority of adverse events leading to loss of gametes or embryos occurred in the laboratory processing phase.

6 Compared to previous years a larger number of reports concerned embryos and oocytes that remained stuck in pipettes during IVF or ICSI treatment, leading to loss.

7 One report concerned a sperm donor brought by the patient for an IVF procedure who was not fully tested according to the IVF laboratory screening protocol. The transport clinic had a less comprehensive screening protocol not testing for chlamydia. Screening for chlamydia was positive, the IVF procedure had to be discontinued and embryos destroyed.

2015 recommendations

1 In accordance with EU recommendations tissue establishments are requested to report to TRIP serious adverse reactions following pharmaceutical stimulation of stem cells or egg cells for donation. TRIP will include this information in its annual review of relevant data with Lareb, the Dutch pharmacovigilance agency.

2 As there has been an increase in reports concerning loss of oocytes or embryos that remained stuck in pipettes, a risk analysis of these adverse events including type and make of pipettes used may identify possible causes.

3 Transport clinics that transport gametes to another institution for the laboratory phase of IVF should ensure that their screening for transmissible infectious diseases matches that of the IVF laboratory, which may use a more comprehensive screening protocol.

4 Processing errors in ART, like omitting a processing step leading to loss or erroneous discarding of gametes or embryos could (in part) be avoided by redesigning working procedures and introducing extra checks to limit avoidable loss. TRIP recommends that all fertility laboratories evaluate their working procedures and always perform a double check before discarding gametes or embryos.

Actions and developments following recommendations in the 2014 TRIP report

In the TRIP 2014 Biovigilance report six recommendations were made. Recommendations followed by relevant developments are mentioned here.

1 Tissue establishments that use donor semen should verify that their procedures adequately monitor the recommended maximum of 25 children per donor.

Development: This recommendation was discussed during a national meeting of donor sperm banks. Verification of procedures and compliance with the norm are not yet standard practice.

6 In case of revision surgery explanted tissue should always be returned to the distributing tissue establishment to enable it to initiate further investigations for improvement of safety.

Development: In 2015 there was one reported case of revision surgery for suspected corneal transplant fungal infection. The explanted cornea was returned to the tissue establishment.

CHAPTER 1

Reports to TRIP

1.1 Reports in 2015

Regarding reporting year 2015 there were 115 reports of adverse reactions and events related to human tissues and cells. There were 88 adverse events (77%) and 27 (23%) adverse reactions, including 17 donation complications. The closing date for inclusion in the annual Biovigilance report 2015 and EU overview was 1 March 2016. Out of the total 40 reports (35%) were assessed as serious and included in the overview for the European Commission (Annex 4). Figure 1 shows the number of registered reports over the years, subdivided in serious and non-serious reports. In Figure 2 the reports are broken down according to tissue and cell type.

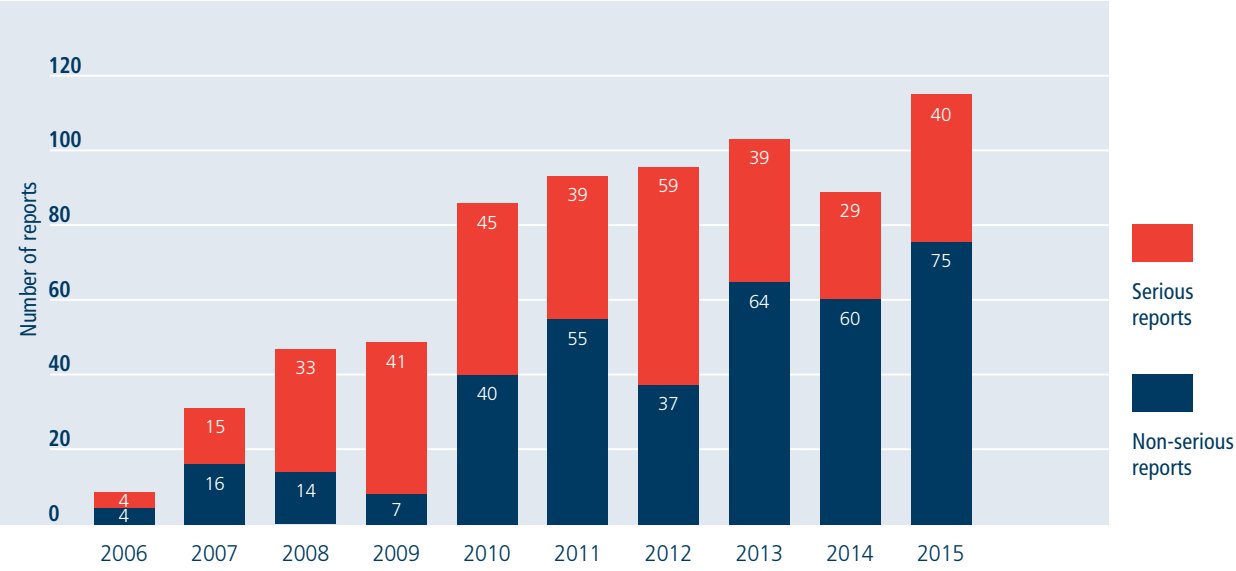


Figure 1. Reports to TRIP, 2006-2015

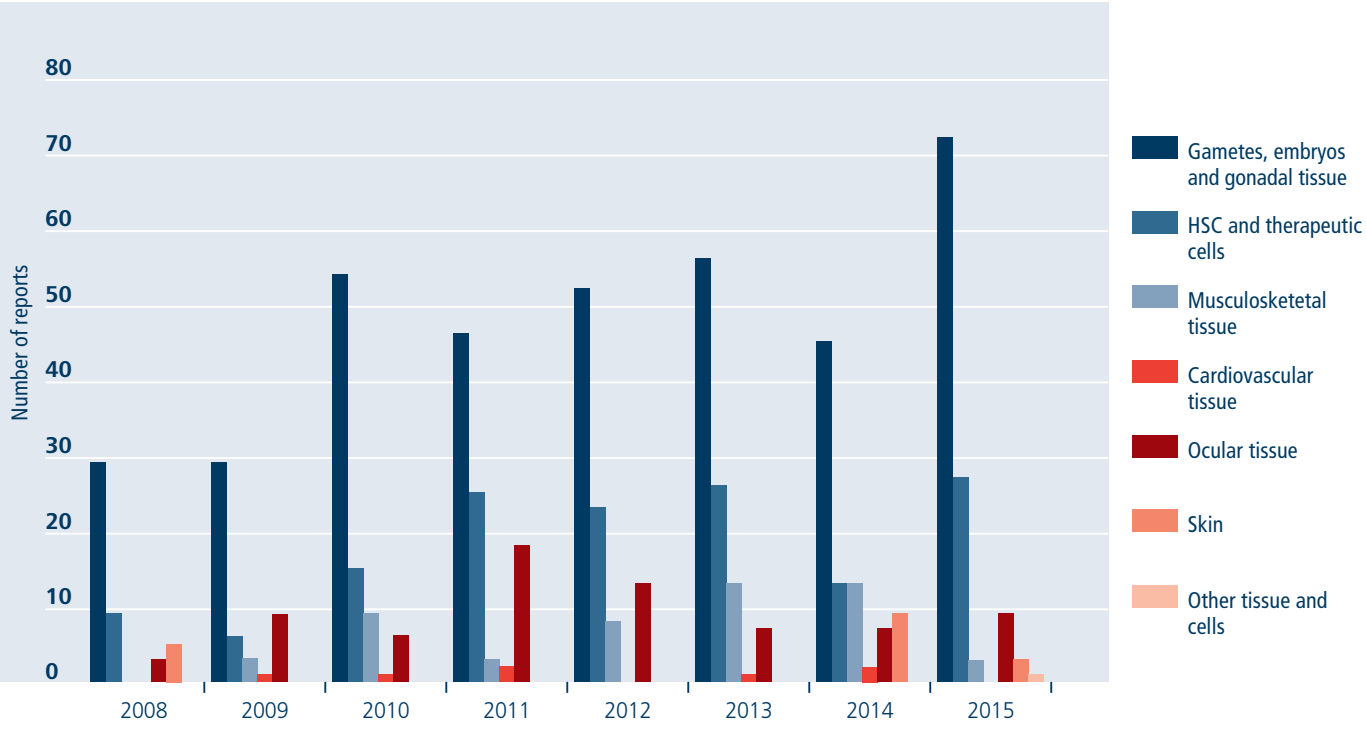


Figure 2. Reports per tissue or cell type, 2006-2015

Table 1 gives an overview of the number of serious and non-serious 2015 reports per tissue or cell type.

Table 1. Serious and non-serious reports per type tissues and cells in 2015

	Total	Non-serious	Serious
Gametes, embryos and gonadal tissue	72	43	29
Hematopoietic stem cells and therapeutic cells	27	18	9
Bone and other musculoskeletal tissue	3	3	0
Skin	3	3	0
Ocular tissue	9	7	2
Cardiovascular tissue	0	0	0
Other tissue and cells	1	1	0
Total	**115**	**75**	**40**

The percentage of reports relating to gametes, embryos and gonadal tissue is 63% (72 out of 115). In recent years this percentage has varied between 48 and 64%.

1.2 Late 2014 reports

After the closing date for the 2014 Biovigilance report there were no late reports. The 2013 recommendation regarding timely reporting was successful, partly because reporters were also personally contacted about timely reporting. Figure 3 shows the number of late reports per reporting year in the past nine years.

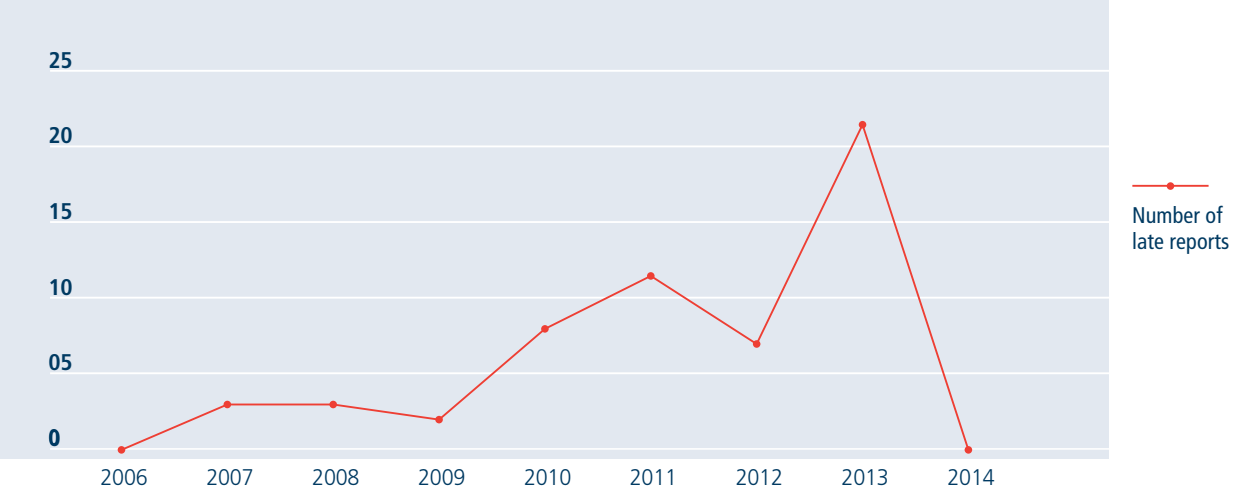


Figure 3. Number of late reports, 2006-2014

CHAPTER 2

Tissues and cells

In this chapter the processing/distribution and application data are presented for each type of human tissue and cells. The reports for each type are briefly described and analysed. Several reports concerning assisted reproductive technologies (ART) are highlighted as case descriptions.

2.1 Gametes, embryos and gonadal tissue

Sometimes assisted reproductive technologies are needed to enable a couple to conceive. The three best-known techniques are: intra-uterine insemination (IUI), in vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI). These assisted reproductive technologies all increase the chance of fertilisation of an ovum by a sperm cell. They all involve a laboratory phase in which gametes are processed. In IVF and ICSI this is followed by an incubation phase for the development of embryos and subsequent selection of embryos for transfer or cryopreservation.

In 2015 in The Netherlands 13 laboratories (tissue establishments) provide IVF and ICSI treatment. They may also process gametes from patients treated in other clinics (so-called transport clinics). There are 60 licensed tissue establishments, mostly hospital biomedical laboratories, that process semen (sperm) for IUI. Only semen laboratories which are licensed as organ banks may process and store donor sperm. One clinic is licensed for the processing of semen as well as oocytes but does not actually carry out IVF or ICSI treatment.

Processing, distribution and application

Tables 2 and 3 present the numbers processed, distributed and applied. Some cryopreserved embryos are found not to be viable after thawing, which explains the difference between the numbers of distributed and applied cryopreserved embryos. The discrepancy in semen distributed and applied is an artefact caused by the distribution figures: some tissue establishments have included semen used in IVF treatment in their distribution figures.

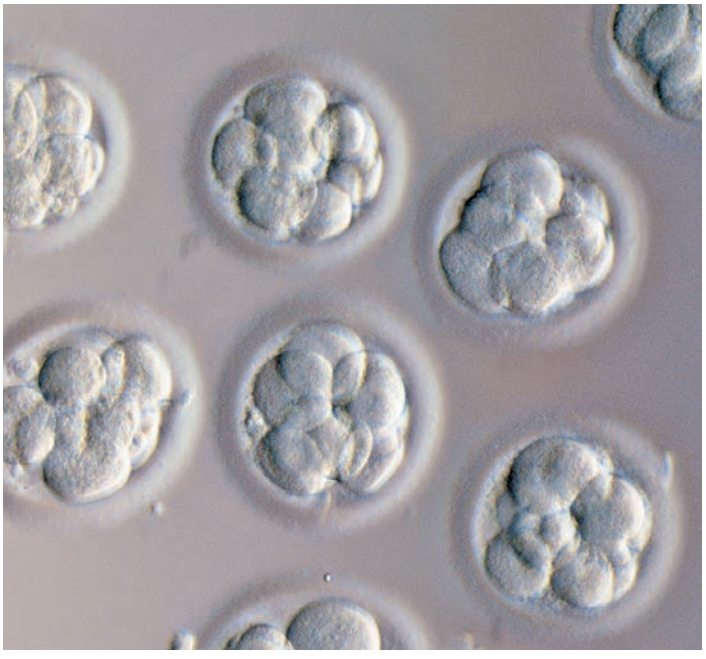


Table 2. Processing and distribution of gametes, embryos and gonadal tissue in 2015

Cell/tissue type	No. of tissue establish-ments	Processed	Distributed in					
			Unit	NL on-site clinic	NL Transport clinic	EU	Non EU	Total
Partner semen, fresh	73	35665	Donation	330505	0	91	0	33596
Partner semen, cryo	20	2314	Straw	1234	540	535	0	2309
Donor semen, fresh	6	89	Donation	75	0	0	0	75
Donor semen, cryo	16	7625	Straw	14626	673	201	0	15500
Partner semen MESA/ PESA/ TESE, fresh	8	303	Aspiration or biopsy	60	0	0	0	60
Partner semen MESA/ PESA/ TESE, cryo	10	641	Aspiration or biopsy	588	44	80	0	712
Donor semen MESA/ PESA/ TESE, cryo	0	0	Aspiration or biopsy	0	0	0	0	0
Oocytes, fresh	14	115925	Oocyte	103906	0	3495 *	0	107401
Oocytes, cryo	12	3622	Oocyte	595	17	20	0	632
Oocytes for donation, fresh	12	2345	Oocyte	709	0	1169 *	0	1878
Oocytes for donation, cryo	3	423	Oocyte	31	0	0	0	31
Embryos, fresh	14	45289	Embryo	18939	0	0	0	18939
Embryos, cryo	14	26499	Embryo	14181	26	14	0	14221
Embryos for donation, fresh	1	270	Embryo	36	0	0	0	270
Embryos for donation, cryo	2	234	Embryo	18	0	0	0	234
Ovarian tissue	3	404	Graft	10	0	0	0	404
Testicular tissue	3	30	Graft	4	0	0	0	4

** Oocytes distributed to an IVF tissue establishment in another EU member state*
Abbreviation: cryo = cryopreserved

Table 3. Application of gametes, embryos and gonadal tissue in 2015

Cell/tissue type	Hospitals/ clinics	Recipients	Applications					
			Unit	On-site lab	NL	EU	Non EU	Total
Partner semen, fresh	72	11940	Donation	23452	50	0	0	23502
Partner semen, cryo	21	166	Straw	509	10	0	0	519
Donor semen, fresh	6	32	Donation	67	0	0	0	67
Donor semen, cryo	16	2698	Straw	10555	1157	1965	46	13723
Embryos, fresh	14	9016	Embryo	13447	0	0	0	13447
Embryos, cryo	14	5846	Embryo	12426	0	4	0	12430
Embryos for donation, fresh	1	33	Embryo	36	0	0	0	36
Embryos for donation, cryo	2	5	Embryo	7	0	0	0	7
Ovarian tissue	1	1	Graft	10	0	0	0	10
Testicular tissue	1	3	Graft	4	0	0	0	4

Abbreviation: cryo = cryopreserved

The total number of inseminations with fresh partner semen in 2015 stabilised after a declining trend in the past years. There was a small increase in the number of inseminations using cryopreserved donor semen. The number of fresh embryo transfers has decreased and cryopreserved embryo transfers have risen from 2013 onward. In contrast to previous years the number of transfers of donated fresh embryos was larger than transfers of donated cryopreserved embryos

Reports

In 2015 TRIP received 72 reports relating to procedures or application of gametes, embryos and/or gonadal tissue in assisted reproductive technologies. These represent 63% of all reports to TRIP. There were 61 adverse events, out of which 18 were assessed as serious, and eleven adverse reactions, all serious donation complications. There is an increase in the number of reports compared to the mean of 51 reports in the previous five years. This can be explained by the fact that there were a number of reports of donation complications – this was not the case in previous years.

Table 4. Overview of 2015 reports per type of fertility tissue establishment

Fertility tissue establishment	Number in NL	Reports submitted by	Number of 2015 reports
13 IVF laboratories and 1 IVF preparatory laboratory	14	12 (86%)	60
Semen laboratory	60	6 (10%)	12
Total	**74**	**18 (24%)**	**72**

** 2 IVF laboratories stated they had no (serious) adverse events or reactions to report in 2015*

Adverse reactions

Adverse reactions in Assisted Reproductive Techniques (ART) are seldom reported. In the previous eight years a total of three adverse reactions were submitted: two cases of ovarian and/or Fallopian tube infection following IUI and one allergic reaction following IUI. In 2015 there were 11 adverse reactions which were all classified as donation complications. There were seven reports of ovarian hyperstimulation syndrome (OHSS) after drug-induced stimulation of oocytes for OPU (Ovum Pick-UP) in infertility treatment. This type of adverse reaction has not previously been reported to TRIP.

Ovarian hyperstimulation syndrome

Ovarian hyperstimulation syndrome (OHSS) is a potentially life-threatening complication following treatment of anovulation by drug induced ovulation or during controlled ovarian hyperstimulation in assisted reproductive techniques for infertility treatment. In 0.1-2% of treated patients severe OHSS can occur. OHSS arises during the luteal phase of the menstrual cycle following stimulation with gonadotrophic hormones, particularly when these are combined with GnRH-agonist. The syndrome is mostly limited to the use of hCG (that may also be produced during pregnancy). OHSS is characterised by abdominal pain, swollen abdomen, dyspnoea and general malaise due to enlarged ovaries, ascites and diminished organ perfusion. As the pathophysiologic mechanism is unknown no causal therapy is available. Prevention is therefore important. Preventive measures may be taken both before and during ovulation induction and controlled ovarian hyperstimulation. Even with the best care OHSS is not always preventable. Treatment is symptomatic. Serious complications of OHSS are mainly thrombo-embolic sequelae. OHSS may be subdivided in three clinical stages: mild to moderate, serious and life-threatening. For serious OHSS hospital admission is indicated.

(Source: Dutch Society for Obstetrics and Gynaecology Guideline Ovarian hyperstimulation syndrome Version 2.0)

Essentially OHSS is an adverse drug reaction and is therefore covered by pharmacovigilance, for which Lareb, the Netherlands Pharmacovigilance Centre is responsible. However, the Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC, version 2.3 (2014) states the following:

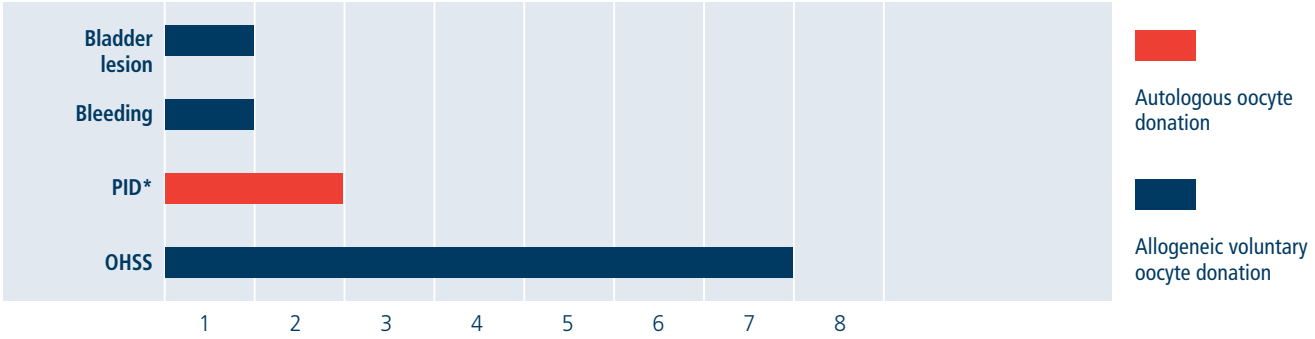
It is noted that many EU Member State competent authorities collate information on donor adverse reactions not influencing the quality and safety of tissues and cells. Reactions which fall outside the scope of the tissues and cells Directives and should be reported elsewhere as appropriate (e.g. to pharmacovigilance systems) include:

- Ovarian Hyper-Stimulation Syndrome (OHSS) as an exaggerated response to the use of ovulation induction medications
- Reactions to Granulocyte Colony-Stimulating Factor (GCSF) following peripheral blood stem cell collection
- Reactions which result in harm to the donor (i.e. cardiac or neurological episodes).

Nevertheless, the EU Commission recognizes the value of these data in the context of tissue and cells regulation, and invites Member States to submit an annual report concerning donor reactions reported to the CA on a voluntary basis. An additional non-mandatory category on donor reactions not influencing the quality and safety of tissues and cells has been inserted in the electronic report template. The declared data will not be calculated as part of the total number of SARs.

TRIP will respond to the European Commission's request to submit these reports on a voluntary basis and recommends that involved medical professionals report these donor adverse reactions to TRIP. TRIP will consult with Lareb Netherlands Pharmacovigilance Centre and the professionals regarding the reporting of these donation complications.

The remaining four reports concerned other donation complications at or caused by OPU and meet the EU criterion: adverse reactions that result in harm to the donor. Figure 4 presents an overview of donation complications at oocyte retrieval. In two cases the donor was a voluntary oocyte donor.



** Pelvic inflammatory disease*

Figure 4. Overview of donation complication reports at oocyte retrieval

All eleven cases of donation complications led to hospital admission but the patients made a full recovery. Imputability was certain for all OHSS cases, bleeding and the bladder lesion. Imputability in the two cases of pelvic inflammatory disease after oocyte donation was assessed as probable.

Adverse events

In 2015 there were 61 adverse event reports concerning gametes and embryos, out of which 18 were assessed to be serious.

In 2012 the "Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC" was updated following the EU project SOHO V&S. Regarding assisted reproductive technologies, specific criteria were set for the assessment of severity of adverse reactions and events. Events which are classified as serious and reportable are those which events leading to the loss of a complete fertility cycle or to transmission of a genetic disorder by donated gametes or embryos (see Tables 56 and 57 in Annex 3). Up to 2012, the Dutch Association of Clinical Embryologists' (KLEM) guideline was followed for assessing the severity of an adverse event. The loss of reproductive tissues or cells used to be classified as serious if there was a considerable reduction of the likelihood of pregnancy in that cycle (loss of ≥ 50% of tissues/cells). This change regarding reproductive tissues and cells resulted in a drop in serious adverse events compared to previous years.

Table 5 shows the total number of reports alongside the numbers assessed as serious according to the clinical embryologists' guideline and the new EU guidance, respectively. A revision of the clinical embryologists' guideline in line with the EU criteria is under preparation.

Table 5. Overview of adverse events concerning gametes, embryos and gonadal tissue in 2015

Tissue/cell type	Category of event	Total	Serious according to KLEM*	Serious according to EU**
Semen	Loss of tissues or cells	5	3	3
	Other incident	6	0	0
	Viral contamination of product	1	1	1
	Near miss	3	0	0
Oocytes	Loss of tissues or cells	13	5	4
	Other incident	1	0	0
Semen and oocytes	Loss of tissues or cells	1	1	1
	Bacterial contamination of product	1	1	1
Embryos	Loss of tissues or cells	23	13	6
	Incorrect product transplanted	1	1	1
	Other incident	4	0	0
	Bacterial contamination of product	1	1	1
	Near miss	1	0	0
Total		**61**	**26**	**18**

* *Serious according to the Dutch Association of Clinical Embryologists' guideline (KLEM): significantly reduced chance of a pregnancy due to loss of oocytes, embryos or irreplaceable semen*

***Serious according to EU criteria: loss of a complete fertility cycle*

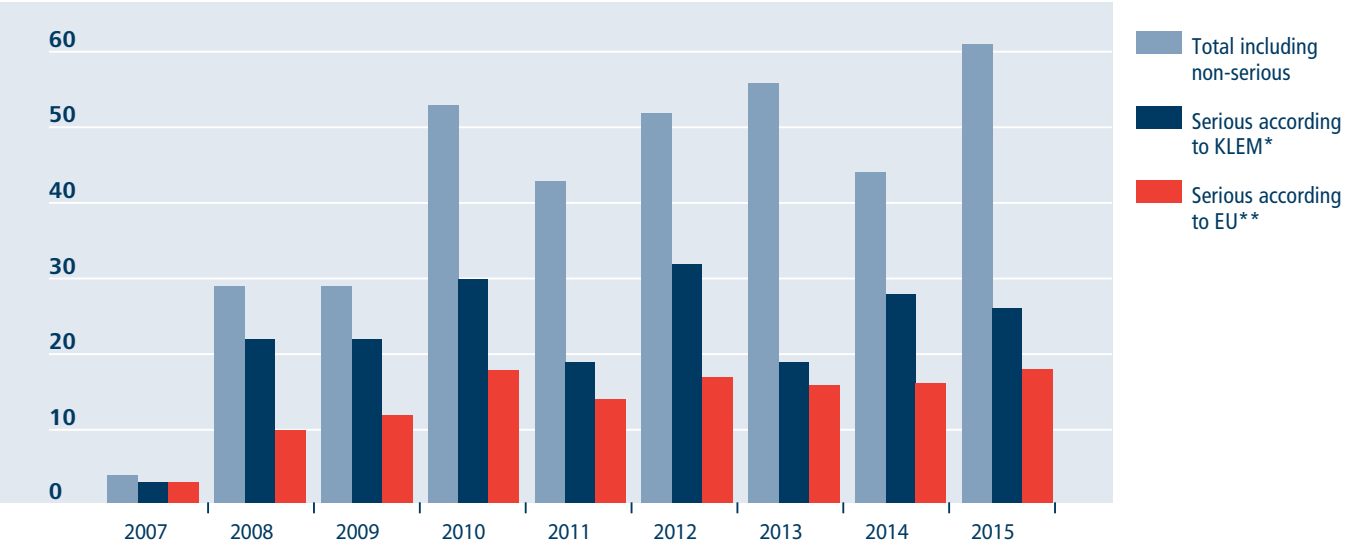


Figure 5. Number of reports of adverse events concerning gametes, embryos and gonadal tissue, 2007-2015

** Serious according to the Dutch Association of Clinical Embryologists' guideline (KLEM): significantly reduced chance of a pregnancy due to loss of oocytes, embryos or irreplaceable semen*
***Serious according to EU criteria: loss of a complete fertility cycle*

Figure 6 presents an overview of numbers and types of adverse event per cell or tissue type in 2015. As in previous years the category loss of tissues or cells represents the largest number of reported adverse events.

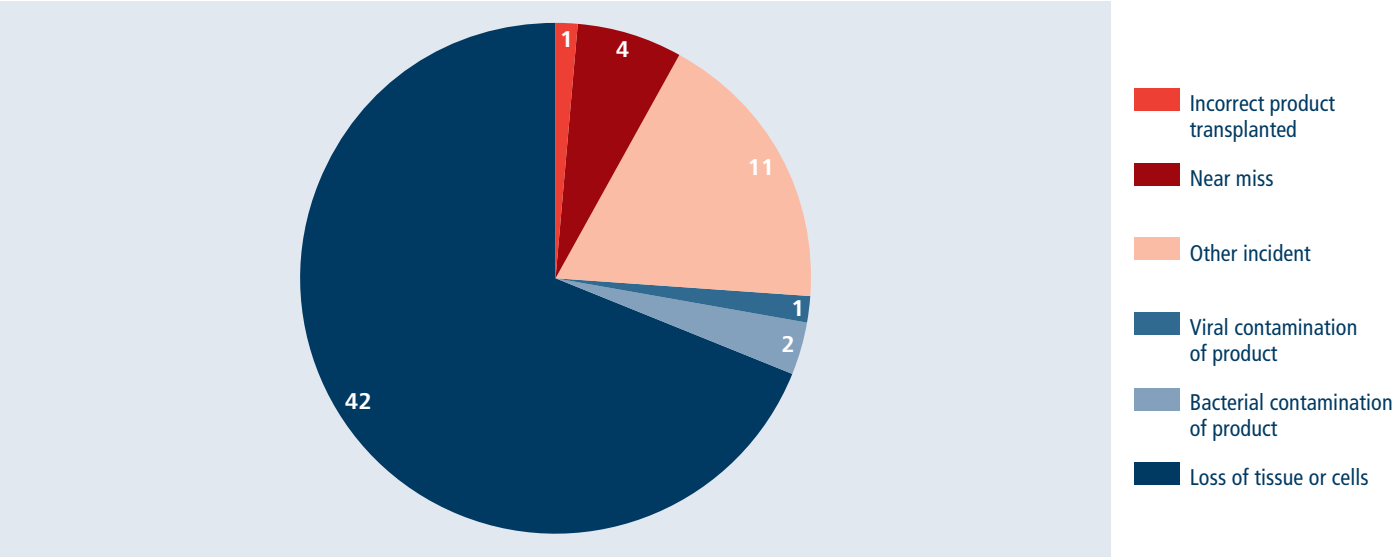


Figure 6. Reports concerning gametes, embryos and gonadal tissue per category of event in 2015

Loss of tissues or cells

In 2015 there were 42 reports in the category loss of tissues or cells. The percentage of events in this category varied in previous years between 54 and 81% (2015: 58%). The category loss of tissues or cells has been the largest category over the years. This was also the case in 2015 as shown in Figure 6. Loss of tissues or cells has serious consequences when it leads to loss of a complete fertility cycle or when it concerns reproductive tissues for fertility preservation that cannot be processed or cryopreserved.

In Chapter 3 reports of loss of tissues or cells in the period 2007-2015 will be analysed in detail. Figure 7 presents an overview of the numbers of reports of loss of tissues or cells from 2007 up to and including 2015. Figure 8 shows the reports of loss of tissue or cells in 2015, broken down according to the type of cells or tissue, step in the procedure and type of error.

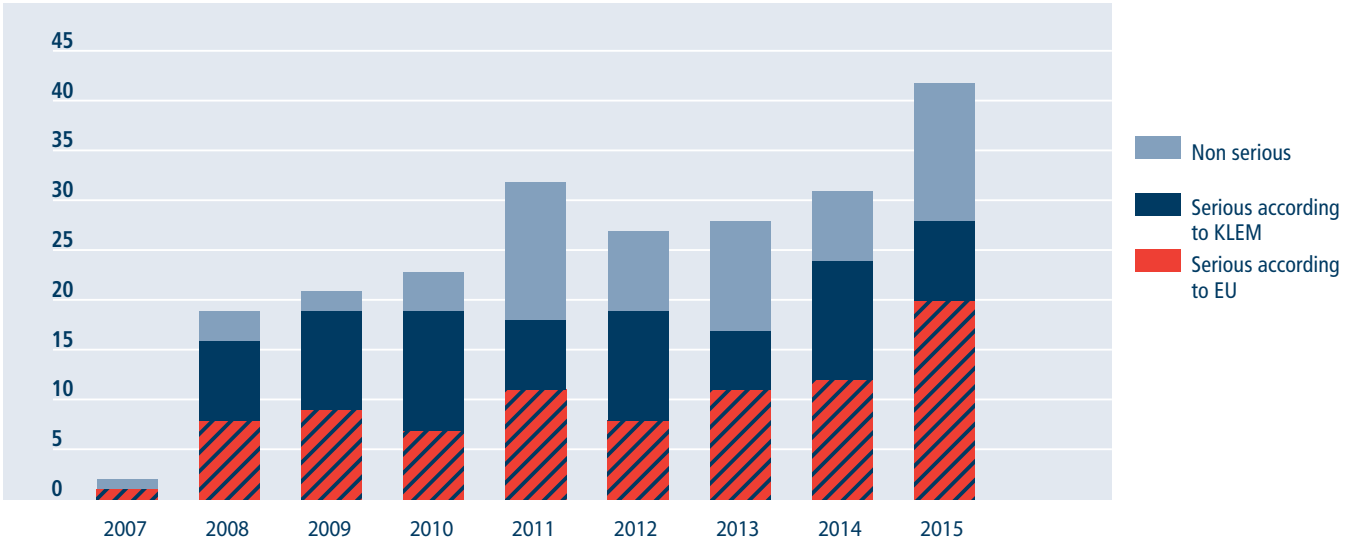


Figure 7. Reports of loss of tissues or cells concerning gametes, embryos and gonadal tissue, 2007-2015

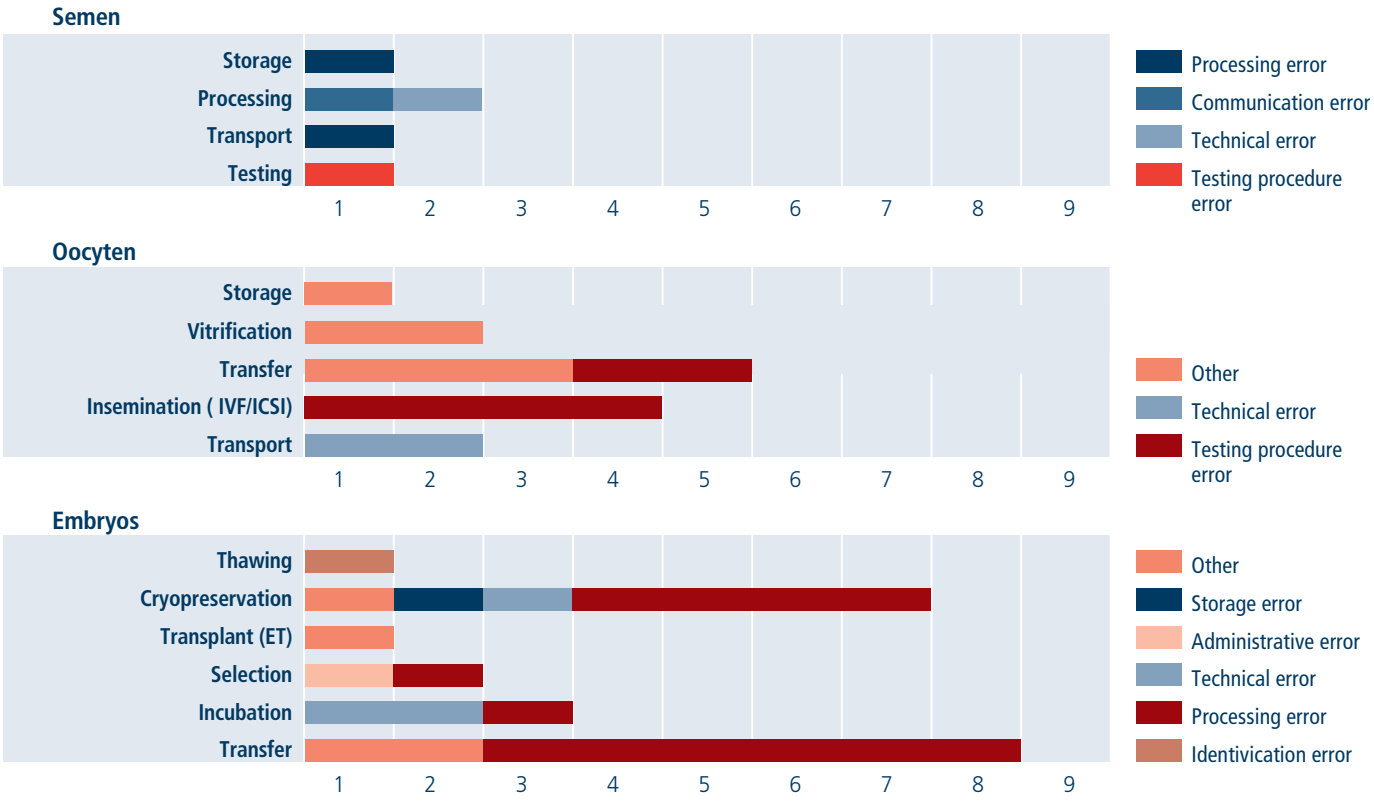


Figure 8. Reports of loss of tissues or cells broken down according to step in procedure and type of error in 2015

The highest number of adverse events (13) occurred during transfer of oocytes and embryos. In 11 of these cases embryos or oocytes remained stuck in pipettes or catheters during transfer or vitrification and consequently were lost. In four reports it was unclear whether the cells did stick, but it is very likely. This type of report was submitted by three fertility laboratories. In the past five years there was a total of five similar reports. As there is a sudden rise in this type of report it is important to observe the trend and consider investigating the types of pipettes and catheters involved with regard to risk of cells remaining stuck. Case 1 illustrates one of these cases.

Case 1. Stuck in pipette

During preparation for ICSI three out of five oocytes remained stuck in the pipette. One oocyte was recovered, but two oocytes were lost. Consequently the patient's chance of pregnancy in this fertility cycle may have been reduced.

Another noteworthy case of loss of tissues or cells concerned infectious disease screening of a sperm donor for IVF who was selected by the patient from her social circle (Case 2 below).

Casus 2. Screening semen van eigen donor

The donor donated fresh semen for IUI and was screened according to hospital protocol for this particular purpose. As IUI did not lead to pregnancy the donor agreed to donate semen for IVF. The IVF laboratory phase was to be carried out in a different institution. When semen and oocytes were brought there it was noted that infectious disease screening was incomplete according to this institution's protocol. The IVF procedure was carried out while additional screening was done. The donor proved to be chlamydia positive and IVF treatment was stopped. The embryos were neither transferred nor cryopreserved but were discarded

EU directive 2006/17/EC states that gamete donors should at least be tested for HIV 1/2, HBV, HCV, chlamydia and syphilis. The Dutch "Position on Assisted Reproductive Techniques and Infections" states that the EU directive does not specifically define gamete donors that are selected by the patient from their social circle. In these cases, in consultation with the patient a decision is taken whether to use cryopreserved or fresh gametes. If for reasons of reduction of the risk of transmitted infections, it is decided to use cryopreserved gametes, these will be screened and stored in quarantine according to the procedure for regular voluntary donors. When fresh semen is to be used infectious diseases screening should at least be equal to partner screening. This case illustrates that the involved medical professionals have decided to accept a calculated risk by not following the EU directive completely. Transport clinics that send gametes to a different institution for the laboratory phase of IVF are advised to check their protocols for infectious disease screening against those of the other institution which may require more comprehensive screening.

Other incident

The category 'other incident' comprised mainly adverse events that led to loss of volume or possible loss of quality of reproductive tissues or cells. The annual percentage of adverse events in this category varied from 8 to 27%.

Figure 9 provides an overview of the number of reports of other incidents in the period 2008-2015.

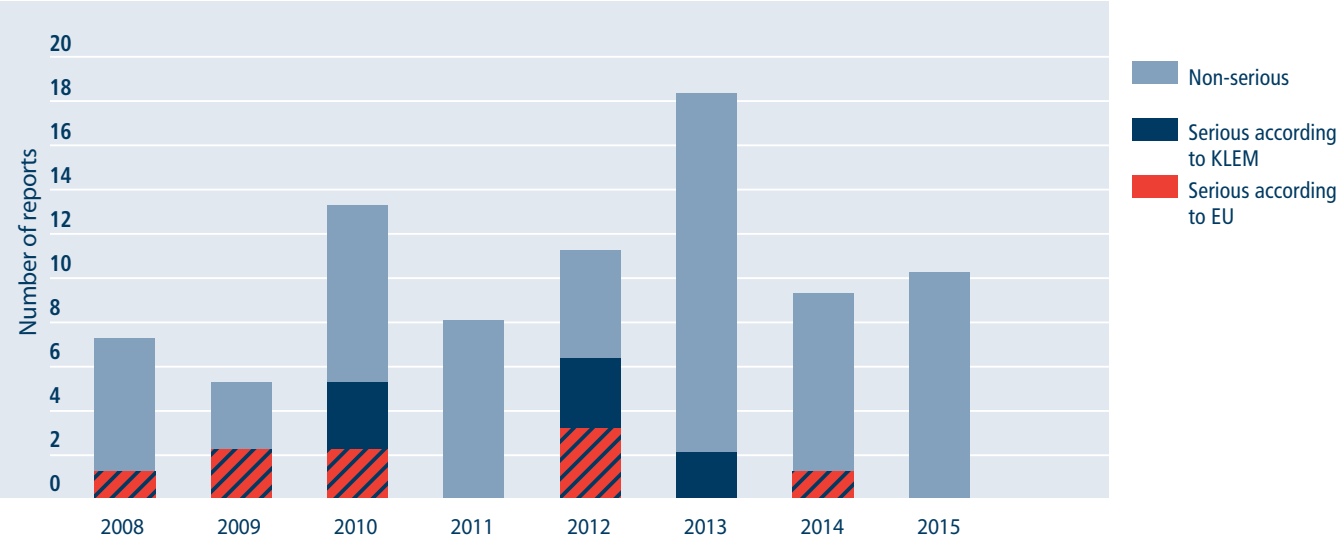
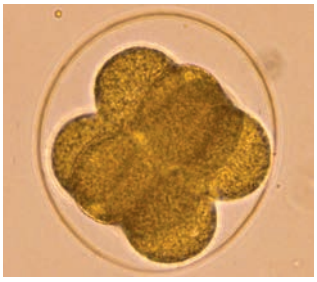


Figure 9. Reports of other incident concerning gametes, embryos and gonadal tissue, 2008-2015

In 2015 ten reports were registered in the category other incident. Table 6 offers short descriptions of these "other incident" reports.

Table 6. Reports of other incidents concerning gametes, embryos and gonadal tissue in 2015

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Storage error	3	Donation	Partner semen	1x inappropriate container for semen provided
		Collection	Partner semen	2x semen supplied in inappropriate container
Processing error	3	Cryopreservation	Embryos	2x temperature fluctuation during cryopreservation run
		Retrieval	Oocytes	Follicular fluid spilled
Identification error	2	Thawing	Embryo	Incorrect embryo thawed and refrozen
		Storage	Donor semen	Incorrect code used for storage in liquid nitrogen container.
Administrative error	1	Storage	Donor semen	Storage location in cryopreservation container incorrectly listed
Other	1	Incubation	Embryo	Monochorionic tri-amniotic triplets after assisted hatching



Case 3 offers a more detailed description of one other incident.

Case 3. Mono-chorionic, tri-amniotic triplets

Assisted hatching was performed on day 3 for laser thinning of the zona pellucida in order to improve nidation of the embryo after transfer. The embryo was transferred on day 5. On ultrasound examination monochorionic tri-amniotic triplets were demonstrated. It is well known that chance of monochorionic twins is increased in assisted hatching procedures. Triplets are however extremely rare[1].

Near miss

In 2015 there were four reports of near miss. The near miss reports in 2008-2015 are shown in Figure 10. In the near miss category TRIP registers reports of switch or misidentification errors that, if undetected, could have led to transfer of incorrect embryos or insemination of an incorrect recipient.

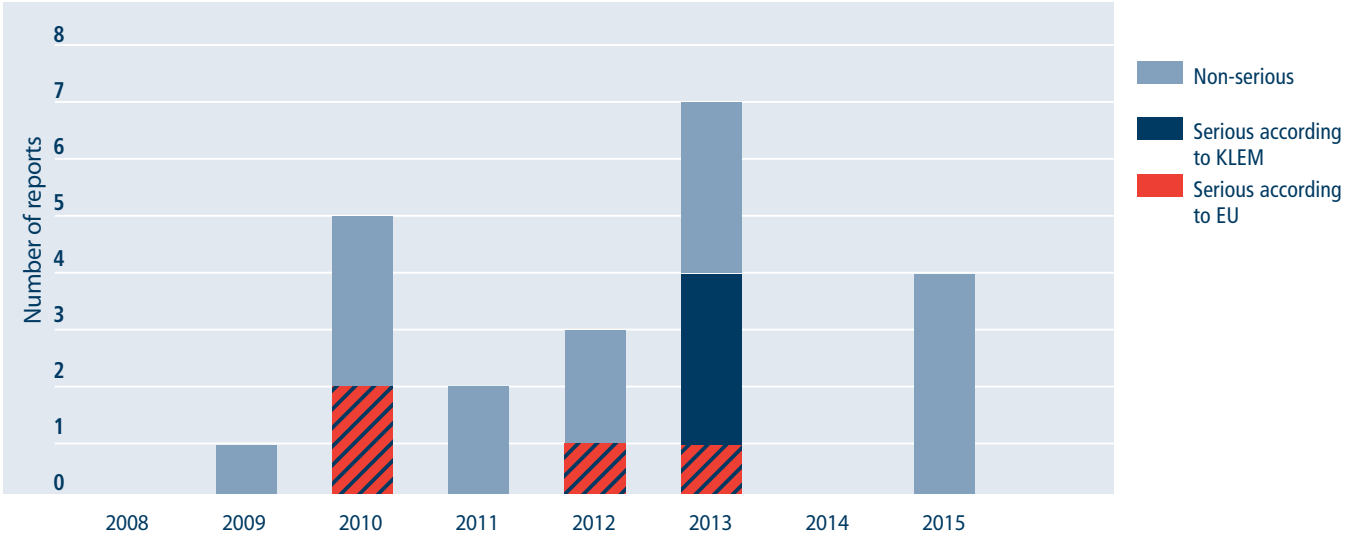


Figure 10. Reports of near misses concerning gametes, embryos and gonadal tissue, 2008-2015

The four reports from 2015 all regarded identification errors. Table 7 offers short descriptions.

Table 7. Reports of near misses concerning gametes, embryos and gonadal tissue in 2015

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Identification error	4	Donation	Partner semen	2 semen samples had identical label and 1 sample had 2 labels
		Thawing	Donor semen	Identification label of incorrect recipient on donor insemination form
		Cryopreservation	Embryo	Incorrect recipient label put ready for labelling of embryo transfer catheter
		Distribution	Donor semen	Semen of 2 donors stored for one recipient. Patient had one child by one donor and wanted a second child from the same donor. Semen of incorrect donor thawed for insemination

[1] Schieve L.A. et al. Does assisted hatching pose a risk for monozygotic twinning in pregnancies conceived through in vitro fertilization? Fertility and sterility August 2000 Vol.74 No.2; 288-94

Bacterial contamination

Two reports of bacterial contamination of product were submitted in 2015. Both were serious as the fertility cycles were completely lost. The reports are summarised in Table 8.

Table 8. Reports of bacterial contamination concerning gametes, embryos and gonadal tissue in 2015

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Other error	2	Incubation	Embryos	Bacterial contamination by E. coli. Origin unknown Bacterial contamination by Proteus Mirabilis originating in partner semen

The numbers of reports of bacterial contamination of product in the period 2008-2015 are shown in Figure 11.

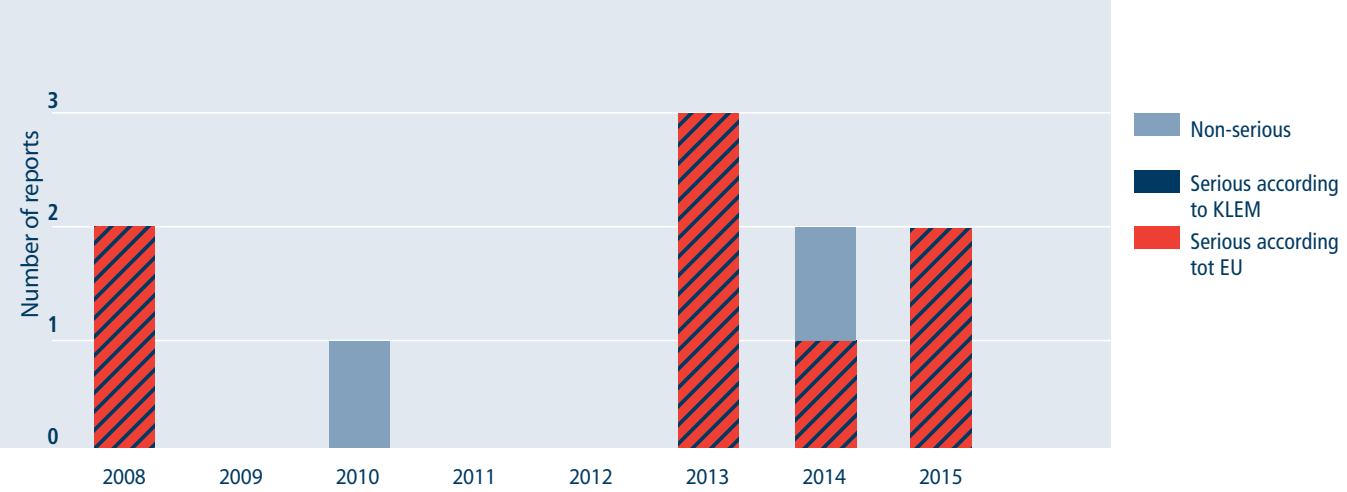


Figure 11. Reports of bacterial contamination concerning gametes, embryos and gonadal tissue, 2008-2015

Viral contamination

One report of viral contamination of product was submitted. The case is summarised in Table 9. The only previous report of viral contamination was reported in 2008.

Table 9. Report of viral contamination of product concerning gametes, embryos and gonadal tissue in 2015

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Assessment	1	Testing	Partner semen	Partner is HBsAg positive. Failure to determine viral load prior to ICSI treatment. Viral load turned out to be high and procedure had to be stopped, embryos were discarded

Incorrect product transplanted

In 2015 one report of incorrect product transplanted was submitted, described in Case 4. Reports in this category are always classified as serious. Figure 12 gives an overview of reports of incorrect product transplanted in assisted reproductive techniques 2008-2015.

Case 4. Incorrect product transplanted

An embryo consisting of 4 pronuclei was cryopreserved and transferred after thawing. During authorisation of the cryopreservation cycle it was noted that this embryo should not have been preserved due to abnormal fertilisation. However this was not properly recorded on the form for embryo assessment. Embryo transfer did not result in ongoing pregnancy.

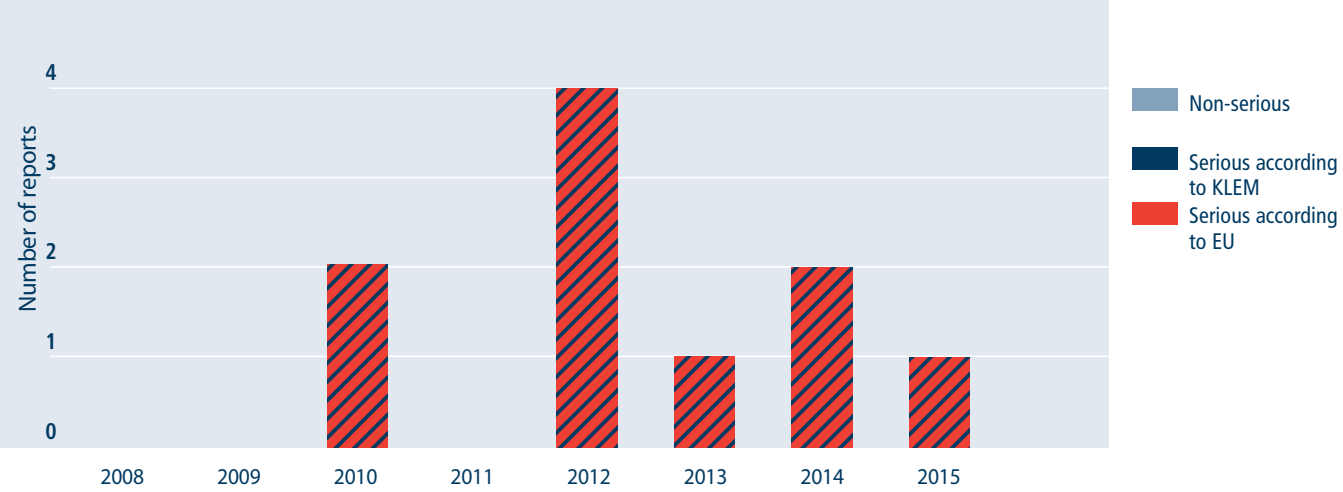


Figure 12. Reports of incorrect product transplanted involving gametes, embryos and gonadal tissue, 2008-2015

Congenital malformation

In reporting year 2015 there were no reports in the category of congenital malformation. A pregnancy involving donated gametes or embryos (i.e. not from the partner) leading to birth of a child or termination of pregnancy with a congenital malformation is considered to be a serious adverse event. This is also the case if a genetic abnormality is found in a donor (non partner) after donation of gametes or embryos.

2.2 Hematopoietic stem cells and therapeutic cells

Hematopoietic stem cells (HSC) can be transplanted into patients whose own blood production system needs replacing. The HSC transplant may be derived from the patient (autologous), from an allogeneic donor compatible for Human Leukocyte Antigen (HLA) tissue markers (a family member or an unrelated donor) or from HLA compatible cord blood.

Autologous or allogeneic HSC are collected by bone marrow aspiration under anaesthesia or from the peripheral circulation (peripheral blood stem cells, PBSC) by apheresis after pre-treatment with the growth factor granulocyte colony stimulating factor (G-CSF). In recent years PBSC collection by apheresis has become the procedure of choice for adults as potentially greater numbers of stem cells can be harvested and this procedure does not involve anaesthesia. Therapeutic cells, e.g. mesenchymal stem cells and donor lymphocyte infusion (DLI) are often applied as an adjuvant treatment in haematopoietic stem cell transplantation.

In The Netherlands thirteen stem cell laboratories are licensed for the collection, processing, preservation, storage and distribution of HSC from autologous and related donors. Stem cell products from unrelated donors (including cord blood) are distributed by Matchis (formerly Europdonor Foundation) to the eight academic transplant centres for specific recipients, usually via the stem cell laboratory. Unrelated stem cell transplants for Dutch patients most commonly come from foreign volunteer donors (95 % in 2015, see Table 12). In collaboration with Sanquin, Matchis arranges collection of bone marrow and peripheral stem cells from Dutch volunteer donors in two university hospitals. A minority of these donations is applied in Dutch patients; the majority of donations is distributed via Matchis to foreign transplantation centres.

In The Netherlands there is one cord blood bank (Sanquin) that processes and stores cord blood transplants, making them available for unrelated patients Two private cord blood banks store cord blood for potential future autologous application.

Processing, distribution and application

In Tables 10, 11 and 12 the figures for processing, distribution and transplantation of hematopoietic stem cells (HSC) and therapeutic cells are presented with the number of institutions performing each activity.

Table 10. Processing of hematopoietic stem cells and therapeutic cells in 2015

Type of cells	No. of tissue establishments	Transplants processed*			
		From NL	From EU	From non-EU	Total
HSC unrelated					
Bone marrow	4	8	23	2	33
PBSC	6	34	227	20	281
Cord blood	7	1625	73	15	1713
HSC related					
Bone marrow	5	14	0	0	14
PBSC	6	123	0	0	123
Cord blood	2	6	0	0	6
HSC autologous					
Bone marrow	3	8	0	0	8
PBSC	10	3181	0	0	3181
Cord blood	2	733	6438	2204	9375
Therapeutic cells					
Mesenchymal stem cells unrelated	4	24	2	0	26
Mesenchymal stem cells autologous	1	10	0	0	10
Lymphocytes (DLI) unrelated	6	78	146	9	233
Lymphocytes (DLI) related	6	152	0	0	152
Dendritic cells unrelated	1	9	0	0	9
Dendritic cells related	2	5	0	0	5
Dendritic cells autologous	1	18	0	0	18
Natural Killer cells unrelated	1	5	0	0	5
Granulocytes related	1	6	0	0	6
TC-Til cells autologous	0	0	0	0	0

** If a transplant unit is reprocessed in the receiving stem cell laboratory it is counted a second time*

Table 11. Distribution of hematopoietic stem cells and therapeutic cells in 2015

Type of cells	No. of tissue establishments	Distributed units			
		In NL	In EU	Outside EU	Total
HSC unrelated					
Bone marrow	6	30	1	4	35
PBSC	7	307	11	11	329
Cord blood	7	111	1	1	113
HSC related					
Bone marrow	5	15	0	0	15
PBSC	7	139	0	0	139
Cord blood	2	3	0	0	3
HSC autologous					
Bone marrow	2	7	0	0	7
PBSC	10	2945	0	0	2945
Cord blood	1	0	1	0	1
Therapeutic cells					
Mesenchymal stem cells unrelated	5	125	0	0	125
Mesenchymal stem cells autologous	1	10	0	0	10
Lymphocytes (DLI) unrelated	5	125	4	1	130
Lymphocytes (DLI) related	6	87	0	0	87
Dendritic cells unrelated	1	9	0	0	9
Dendritic cells related	2	9	0	0	9
Dendritic cells autologous	0	0	0	0	0
Natural Killer cells unrelated	1	3	0	0	3
Granulocytes related	1	6	0	0	6
TC-Til cells autologous	1	8	0	0	8

Table 12. Transplantation of hematopoietic stem cells and therapeutic cells in 2015

Type of cells	Transplant centres	Recipients	Transplanted units			
			From NL	From EU	From non EU	Total
HSC unrelated						
Bone marrow	6	33	3	28	4	35
PBSC	8	312	12	263	32	307
Cord blood	7	55	3	80	16	99
HSC related						
Bone marrow	6	15	15	0	0	15
PBSC	7	115	139	0	0	139
Cord blood	2	2	3	0	0	3
HSC autologous						
Bone marrow	2	5	6	0	0	6
PBSC	11	807	2852	1	0	2853
Cord blood	0	0	0	0	0	0
Therapeutic cells						
Mesenchymal stem cells unrelated	5	41	123	2	0	125
Mesenchymal stem cells autologous	1	5	10	0	0	10
Lymphocytes (DLI) unrelated	4	74	80	13	0	93
Lymphocytes (DLI) related	6	62	87	0	0	87
Dendritic cells unrelated	2	3	9	0	0	9
Dendritic cells related	2	2	6	0	0	6
Dendritic cells autologous	0	0	0	0	0	0
Natural Killer cells unrelated	1	3	3	0	0	3
Granulocytes related	1	1	6	0	0	6
TC-Til cells autologous	1	8	8	0	0	8

There is a remarkable rise in the number of processed allogeneic cord blood units from 284 in 2014 to 1713 in 2015; inquiries at the cord blood bank revealed that previously they only submitted numbers of processed units that were suitable for transplant. The number of cryopreserved units for autologous use decreased by 23% compared to 2014. As in 2014, one autologous cord blood unit was distributed outside The Netherlands. With regard to therapeutic cells there is a 30% rise in numbers of recipients of related and unrelated DLIs. In Figure 13a-b the numbers of recipients of various types of stem cells is presented. The decreasing trend in the number of autologous bone marrow transplants continues: in 2015 there were five recipients. There is an increasing preference for harvesting autologous stem cells by an apheresis procedure. The total number of autologous stem cell transplants increased slightly by 14% compared to 2014.

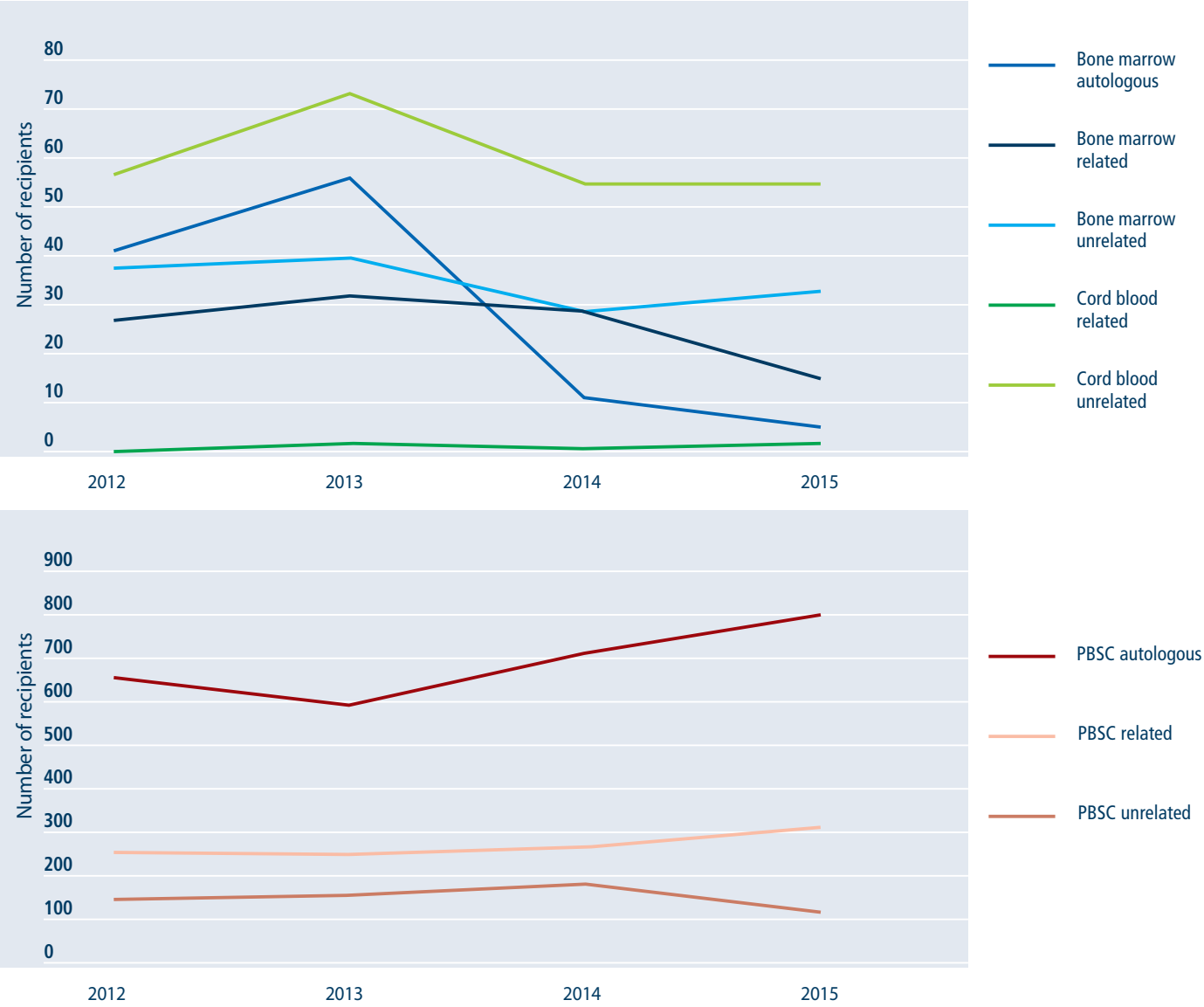


Figure 13 a-b. Numbers of recipients broken down according to HSC source, 2012-2015

Reports

In 2015 there were 27 reports of adverse events and reactions concerning hematopoietic stem cells and therapeutic cells. Figure 14 gives an overview of the number of reports from 2007 up to and including 2015. In 2014 there were fewer reports, but in 2015 numbers are again at the 2013 level. In 2015 as in 2014 there were no serious adverse events. Prior to 2014 leaking units were classified as serious based on the potential risk instead of the actual serious risk for the patient. These potentially serious reports do not qualify for reporting to the Healthcare Inspectorate.

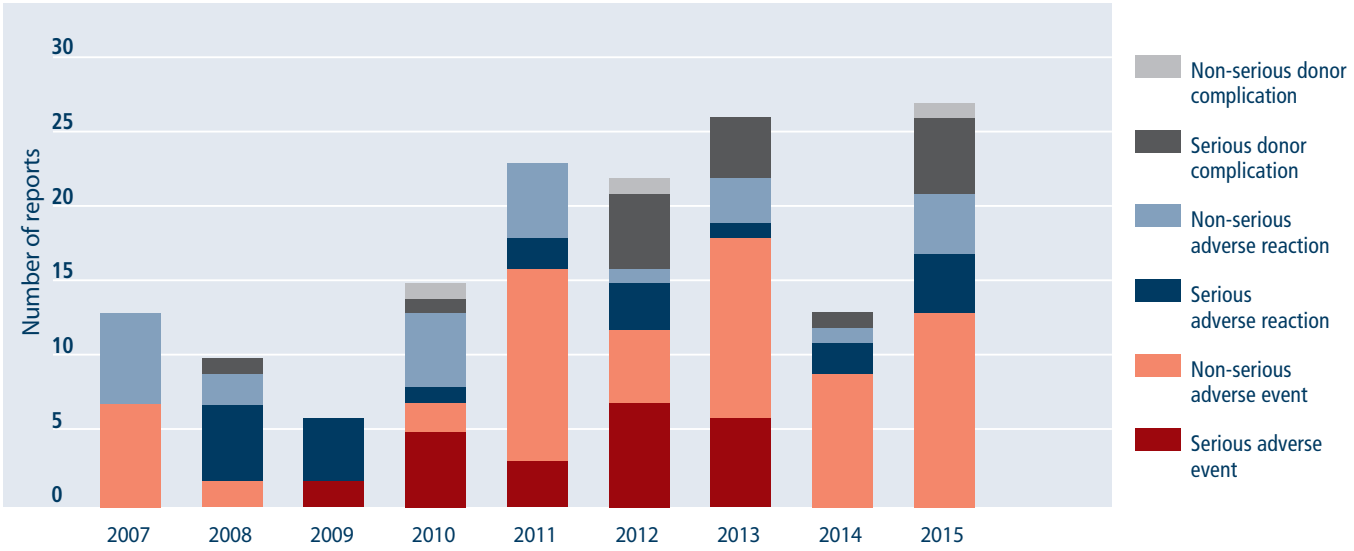
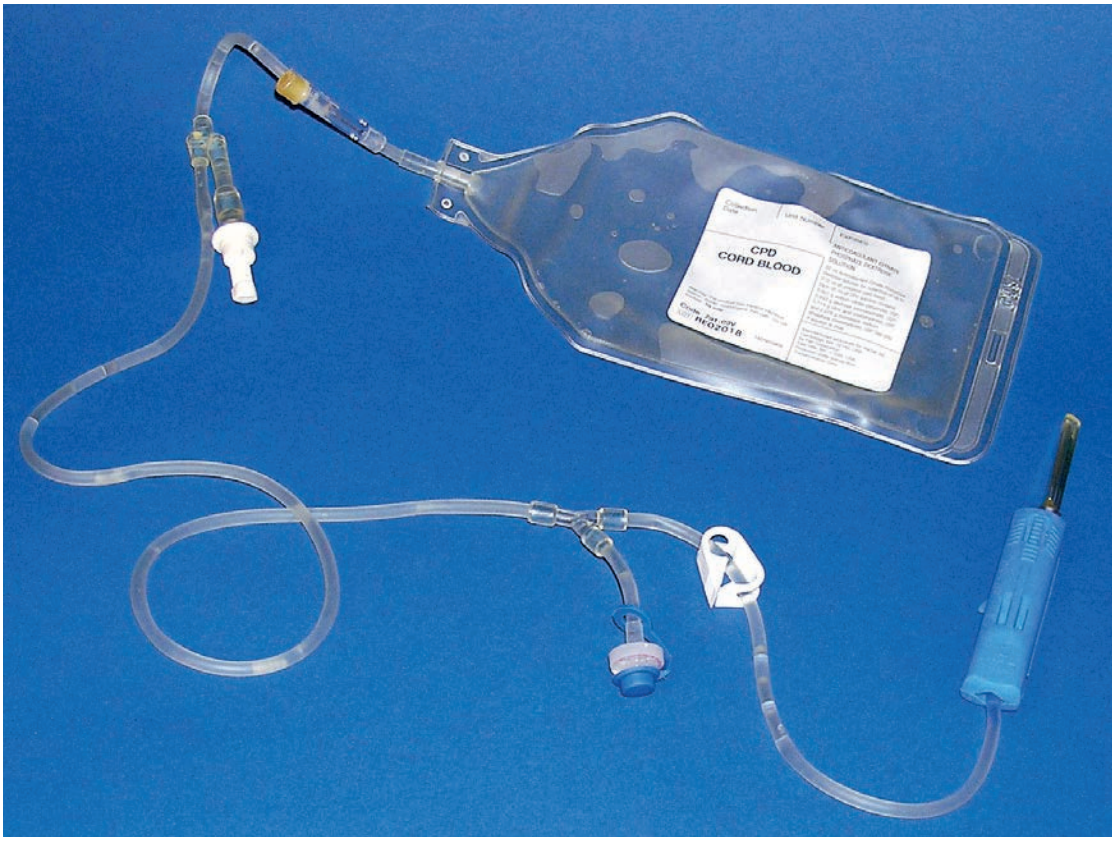


Figure 14. Reports concerning HSC and therapeutic cells, 2007-2015



The 2015 reports concerned 13 non-serious adverse events, eight adverse reactions among which there four were serious and six donation complications. The adverse events are broken down according to HSC type and summarised in Table 13.

Table 13. Overview of adverse event per type HSC or therapeutic cells in 2015

HSC type	Adverse event category and description	Number
Peripheral blood stem cells, (PBSC) autologous	Loss of tissues or cells • PICC line did not run properly leading to clot formation in unit. Half of unit had to be discarded. No adverse consequences for the patient	1
	Other incident • Technical issue of apheresis device leading to a longer apheresis procedure • Tear in cryopreserved unit	2
	Bacterial contamination of product • Staphylococcus epidermidis, no sequelae for the patient • Staphylococcus epidermidis in product collected by inguinal catheter; infused under antibiotic prophylaxis	2
PBSC related	Loss of tissues or cells • Administration error during donor lymphocyte infusion leading to loss of 10 ml	1
PBSC, allogeneic unrelated	Bacterial contamination of product • Staphylococcus epidermidis, no adverse consequences for the patient	1
Bone marrow, autologous	Bacterial contamination of product • Paenibacillus, no adverse consequences for the patient	1
	Other incident • Paenibacillus in culture medium, no adverse consequences for the patient	1
Bone marrow, allogeneic related	Bacterial contamination product • Propionibacterium, no adverse consequences for the patient • Staphylococcus epidermidis, no adverse consequences for the patient	2
	Loss of tissues or cells • Staphylococcus saccharolyticus found in surplus bone marrow intended for ATMP (mesenchymal stromal cells) production. No adverse consequences for the patient	1
Cord blood, allogeneic related	Loss of tissues or cells • 20% of volume lost due to leakage of cryopreserved unit, no adverse consequences for the patient	1
Total		**13**

Abbreviations: PICC= peripherally inserted central catheter, DLI=Donor Lymphocyte Infusion

Among the 2015 reports there were two adverse events concerning leakage or rupture of a stem cell unit. Figure 15 gives an overview of the reports of leaking units and collection sets for stem cells in the period 2007-2015.

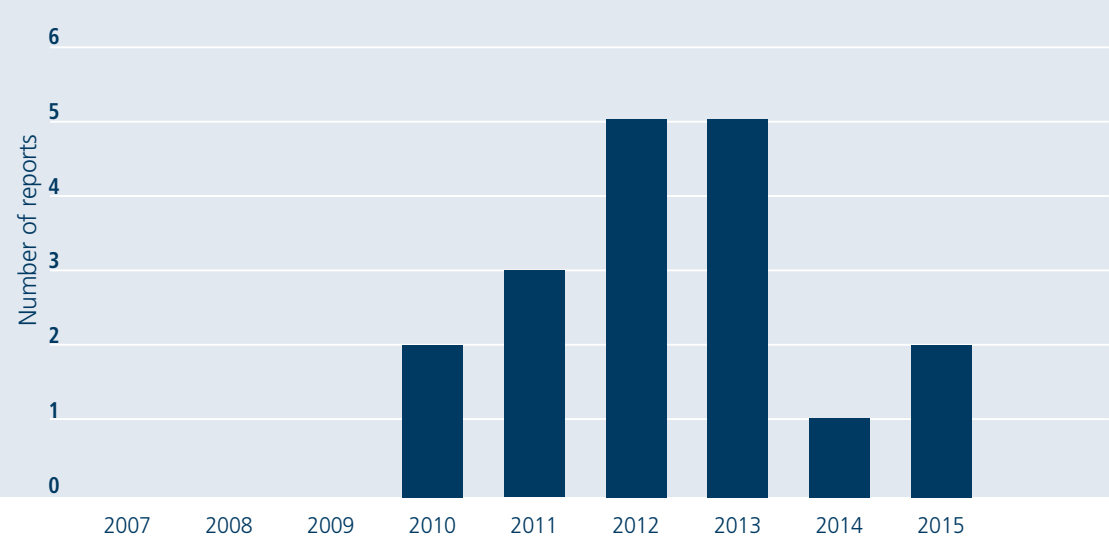


Figure 15. Reports of leaking or ruptured HSC collection and storage bags, 2007-2015

In Tables 14 and 15 the 2015 reports of adverse reactions and donation complications are summarised.

Table 14. Overview of adverse reactions per type HSC or therapeutic cells in 2015

HSC type	Adverse reactions (category and description)	Number
Patient: PBSC autologous	Other reaction • Epileptic seizure during infusion, assumed to be caused by encephalopathy due to DMSO* • Dyspnea and drop in O2 saturation shortly after administration. CT scan shows pulmonary emboli associated with DVT* • Hypotension, bradycardia, temporary neurological deficit*	3
Patient: PBSC, allogeneic related	Anaphylactic reaction • Tensiedaling, flushing, misselijk en buikpijn	1
Patient: PBSC allogeneic unrelated	Anaphylactic reaction • BP drop and dizziness, quickly reversed by clemastine administration Other reaction • During infusion of major and minor ABO incompatible stem cell transplant the patient became unwell with rigors, tachycardia, chest pain, nausea and vomiting. Recovery after slowing infusion* Post-transplantation febrile reaction • Not related to quality or safety of product	1 1 2
Total		**8**

* *Serious*

Abbreviations: GCSF=granulocyte colony stimulating factor (growth factor administered for +/- five days prior to harvesting of peripheral blood stem cells), BP=blood pressure

Table 15. Overview of donation complications associated with HSC and therapeutic cells in 2015

HSC type	Donation complication	Number
Donor: PBSC related	• Deep venous thrombosis complicated by pulmonary embolism after insertion of inguinal catheter* • Inflammatory bowel disease diagnosed several weeks after stem cell donation*	2
Donor: PBSC unrelated	• Severe tetany and laryngeal spasm due to hypocalcaemia. Second apheresis procedure had to be abandoned due to signs of hypocalcaemia despite prophylactic calcium administration Insufficient HSC collected* • Hematuria during GCSF mobilisation phase that was found to be caused by exacerbation of subclinical IgA nephropathy*	2
PBSC autologous	• Splenic rupture caused by GCSF stimulation 2 days after stem cell collection. Splenectomy had be performed*	1
Donor: therapeutic cells	• Vitiligo after GCSF and dexamethason stimulation for granulocytapheresis	1
Total		**6**

** Serious*
Abbreviation: GCSF=granulocyte colony stimulating factor (growth factor, that is administered during +/- five days prior to harvesting of peripheral blood stem cells)

With respect to reporting year 2015 the high number of donation complications (6) is noteworthy, particularly as they are all, in contrast to previous years, of high imputability. These donation complications are partly rare but well-known side effects of GCSF (splenic rupture, IgA nephropathy) and partly part complications (vitiligo, inflammatory bowel disease) in which GCSF could play a role. In addition there were two serious reports of complications during the stem cell apheresis procedure: severe tetany and laryngeal spasm due to hypocalcaemia and deep venous thrombosis followed by pulmonary embolism in a healthy donor after insertion of an inguinal catheter for stem cell collection.

Table 16 gives an overview of donation complications reported to TRIP from 2007 up to and including 2015.

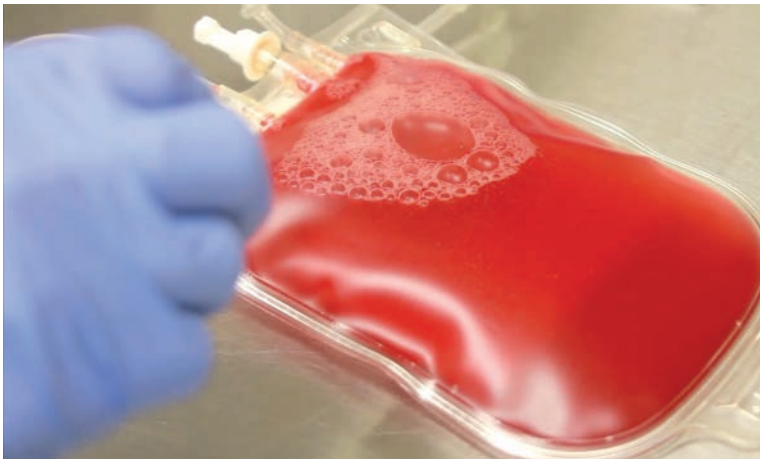


Table 16. Overview of donation complications associated with HSC, 2007-2015

HSC type	Number	Donor complication	Interval after donation	Imputability
PBSC related	8	• Shoulder abscess (S. aureus) • AML • MDS-RAEB • Transient rise of creatinine level • Benign paroxysmal positional vertigo • Exacerbation of asthma and back pain • Inflammatory bowel disease • Deep venous thrombosis followed by pulmonary embolism	12 days 7 years 5 years During apheresis procedure Immediate 7 days 6 months During apheresis procedure	possible possible possible probable probable probable possible certain
PBSC unrelated	7	• Breast cancer • Phlebitis • Stroke • Rheumatoid arthritis • Polyarthritis rheumatica • Tetany and laryngospasm due to hypocalcaemia • IgA nephropathy	2 years ? 2 months 6 years 4 years During apheresis procedure During GCSF stimulation	unlikely probable unlikely unlikely unlikely certain probable
Bone marrow unrelated	2	• Breast cancer • TIA	2 years 8 months	unlikely unlikely
PBSC autologous	2	• Thrombocytopenia • Splenic rupture	During apheresis procedure 2 days	certain certain
Therapeutic cells, related	1	• Vitiligo	6 months	certain
Total	**20**			

The follow-up and complication registration for related donors is not yet well established, in contrast to that for unrelated donors. As part of the protection of donor health these complications are registered at international level by the World Marrow Donor Association (WMDA). TRIP therefore considers it worthwhile to register these complications as well.

2.3 Bone and other musculoskeletal tissues

In healthcare bone and other musculoskeletal tissues are used in the reconstruction of the bony skeleton, in joint injuries, for reconstruction of other parts of the human body, for filling bony defects but also as osteo-inductive material to promote healing. Bone is procured both from post-mortem donors and from living donors, who may donate a femoral head at hip replacement surgery. The femoral head can be processed, for instance into bone chips. In The Netherlands ten bone banks are located in hospitals and specialised orthopaedic clinics. Two independent bone banks are licensed as organ banks. Another eight tissue establishments import musculoskeletal tissues, mainly from the USA, and are licensed to distribute them in Europe. One tissue establishment cultures chondrocytes for autologous transplantation.

Bone

Processing, distribution and transplantation

In Table 17 the numbers of processed and distributed units of bone are presented. Table 18 shows the numbers of transplanted bone units with the numbers of recipients. The data were provided by 20 bone banks, 66 hospitals, three clinics and 32 oral implantology practices.

Table 17. Processing and distribution of bone tissue in 2015

Type	Tissue establishments*	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Bone, whole	1	187	Bone	85	5	0	90
Bone filler, mineralised: chips, blocks and wedges	11	2544	Pack	4199	5159	3678	13036
Bone filler, mineralized: whole and half femoral heads	12	2989	Bone (piece)	2437	419	0	2856
Bone filler, demineralised	6	6121	Pack	1672	20157	21445	43274
Auditory ossicles	1	0	Graft	33	0	0	33
Cranial bone (autologous)	5	208	Graft	119	0	0	
Other	0	0	Graft	0	0	0	0

* *Including hospital bone banks (also cranial bone banks) and tissue establishments which only distribute bone tissue*

Table 18. Application of bone tissue in 2015

Type	Hospitals/ clinics/ practices	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Totaal
Bone, whole	13	84	Bone	89	2	0	91
Bone filler, mineralised: chips, blocks and wedges	73	2582	Pack	2184	403	139	2726
Bone filler, mineralized: whole and half femoral heads	56	1371	Bone (piece)	1502	0	0	1502
Bone filler, demineralised	17	225	Pack	186	0	46	232
Auditory ossicles	2	15	Graft	0	15	0	15
Cranial bone (autologous)	7	105	Graft	104	0	1	105
Other	0	0	Graft	0	0	0	0

The numbers of processed and distributed units of demineralised bone filler tripled compared to 2014. These products are mainly distributed outside the European Union. The numbers of recipients of different bone products did not show significant changes except for mineralised bone filler. There was a 40% increase in the total number of recipients compared to 2014. This may be explained by an increase in number of institutions that provided data (2015: 73, 2014: 51). The number of processed and distributed cranial bone flaps decreased compared to 2014 (105 processed compared to 257 in 2014; 105 distributed compared to 174 in 2014). There was also a small decrease in the number of recipients of cranial bone (2015: 105, 2014: 122).

Reports

In 2015 two reports concerning bone tissue were submitted, both non-serious adverse events. In Figure 16 presents an overview of the number of reports concerning bone tissue in 2006-2015 and Table 19 provides short descriptions of the reported adverse events.

There are fewer reports than in previous years. Notably there were no reports concerning cranial bone whereas there were five reports in 2014 and one in 2013. Before the Law on safety and quality of substances of human origin came into force hospital neurosurgery departments managed their own explantation and reimplantation of autologous cranial bone. There are no national data on the frequency of bacterial infection after application of autologous cranial bone from that period.

The most feared risk in bone transplantation is transmission of bacterial pathogens as bone infections are difficult to eliminate. In 2015 there were no reports of bacterial infection after bone transplant.

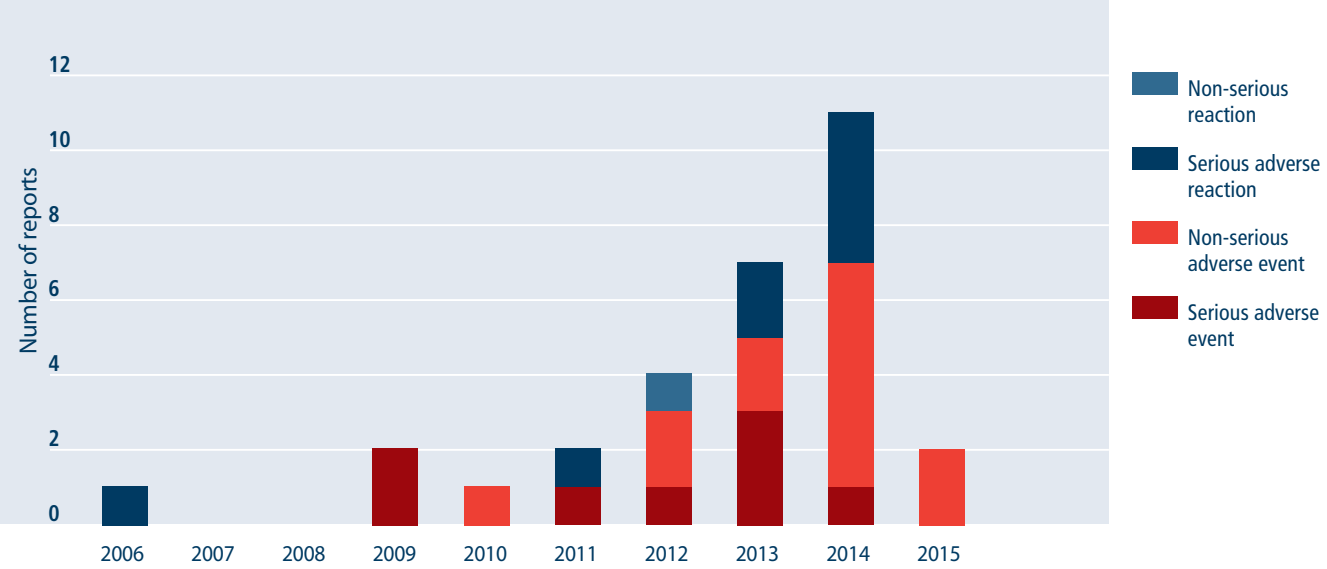


Figure 16. Reports involving bone, 2006-2015

Table 19. Adverse events involving bone in 2015

Category of event	Description	Reports
Other incident	• Mix-up of follow-up forms of two allogeneic femoral heads • Demineralised bone matrix did not mix with added bone marrow concentrate. No sequelae for the patient. Investigations by foreign tissue establishment are still ongoing	2

Cartilage

Processing, distribution and transplantation

In Tables 20 and 21 an overview of numbers of processed/distributed and applied units of cartilage is presented. In 2015 fewer cartilage transplants were processed than in 2014 (11 versus 118). The numbers of processed chondrocytes also decreased. The number of recipients decreased by 14%.

Table 20. Processing and distribution of cartilage in 2015

Type of tissue or cells	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cartilage	2	11	Graft	90	0	0	90
Chondrocytes	1	154	Graft	93	66	0	159

Table 21. Application of cartilage in 2015

Type of tissue or cells	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From non EU	Total
Cartilage	9	118	Graft	111	4	0	115

Reports

In reporting year 2015, as in 2014, there were no reports concerning cartilage. Figure 17 provides an overview of reports concerning cartilage during the period 2007-2015.

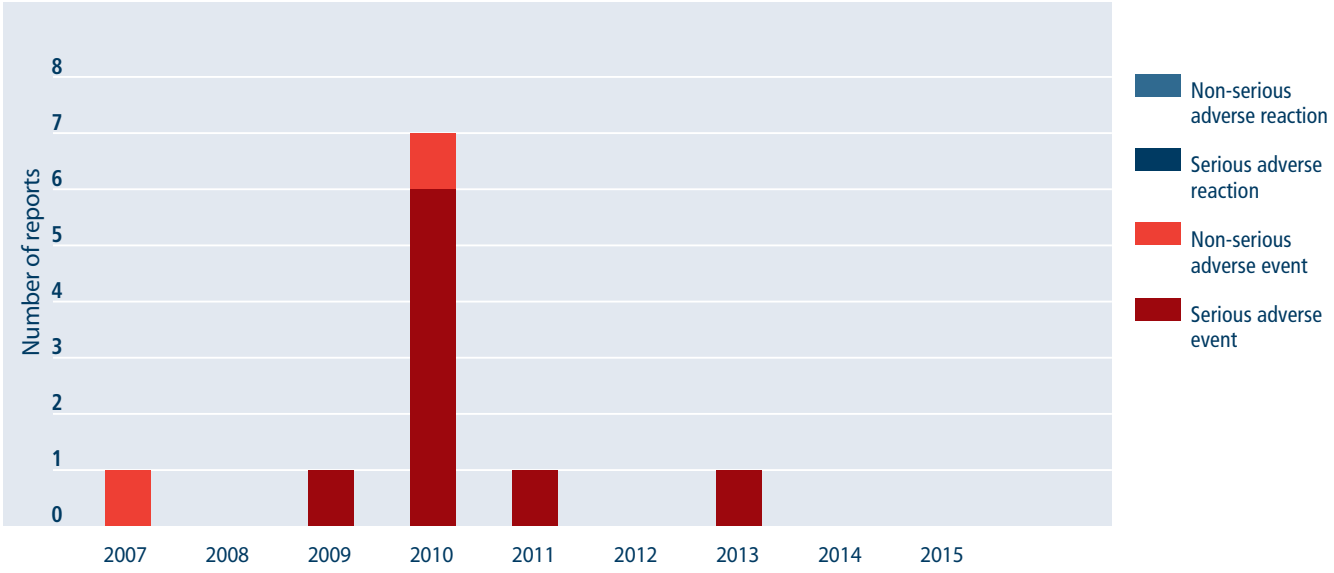


Figure 17. Reports concerning cartilage, 2007-2015

Tendons, ligaments, fascia and menisci

Processing, distribution and application

In Table 22 the data on processing and distribution of tendons, ligaments, fascia and menisci are presented followed by Table 23 with data on transplantation of these tissues. There were no relevant changes in the numbers of applications and recipients.

Table 22. Processing and distribution of tendons, ligaments, fascia and menisci in 2015

Type of tissue	Tissue establishments	Processed	Distributed				
			Eenheid	In NL	In EU	Outside EU	Total
Tendons	2	671	Graft	585	31	0	616
Ligaments and fascia	4	44	Graft	1598 *	168	0	1766
Menisci	0	0	Graft	0	0	0	0
Other	0	0	Graft	0	0	0	0

* *One tissue establishment started distribution of ligaments and fascia in 2015*

Table 23. Application of tendons, ligaments, fascia and menisci in 2015

Type of tissue	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Tendons	33	268	Graft	281	1	0	282
Ligaments and fascia	18	509	Graft	342	167	0	509
Menisci	1	15	Graft	0	15	0	15
Other	0	0	Graft	0	0	0	0

Reports

One non-serious adverse event involving a tendon was reported in 2015 (Table 24). Figure 18 gives an overview of reports involving tendons in the past few years.

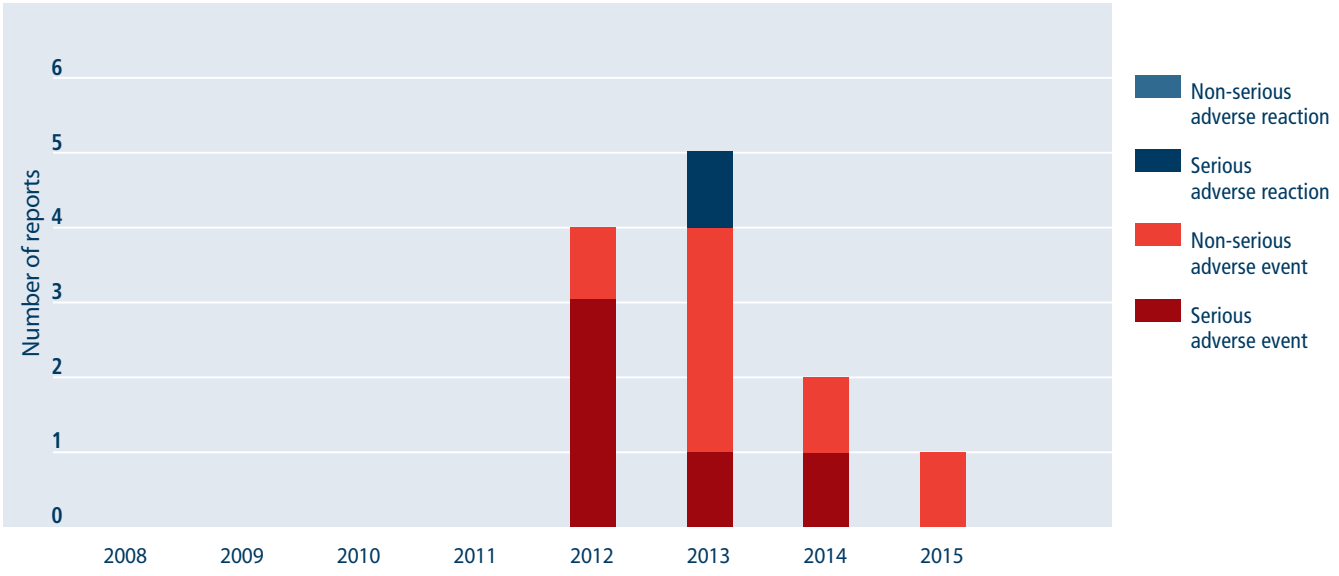


Figure 18. Overview of reports concerning tendons, 2008-2015

Table 24. Report concerning tendon in 2015

Category of event	Description
Other incident	Culture of tibialis tendon taken just before transplantation turned out to be positive: Staphylococcus warneri. Recipient's surgery and recovery were uneventful. All cultures in the tissue establishment were negative. The positive culture result was judged to result from contamination of the culture taken during surgery

2.4 Ocular tissue

Two parts of the eye can be transplanted: the cornea and the sclera. A corneal transplant is most often performed because visual acuity is impaired due to corneal disease, but may also be needed to save the eye or to relieve severe corneal pain. Common indications for corneal transplant include opacities, corneal deformity and scarring following infection or trauma. Each year around 1000 corneal transplants are carried out in The Netherlands. The shelf life of a cornea is limited: a cornea is in optimal condition in culture medium for up to four weeks after donation. Several corneal grafting techniques are available, among which penetrating (full thickness) and lamellar keratoplasty are most frequently carried out. A lamellar keratoplasty procedure can be done using an anterior or posterior technique.
Sclera is applied in reconstructive surgery of eyes and eyelids. Sclera can be preserved and stored for one year. Sclera is distributed whole or in segments or quadrants. In The Netherlands cornea and sclera are harvested from a post-mortem donor by enucleation of the complete eyeball which is then processed by one of the two eye banks. Corneas and scleras are also exported and imported.

Processing, distribution and application

In Table 25 the numbers of processed and distributed units of ocular tissue are shown. Table 26 presents the numbers of transplanted ocular tissue units as provided by the contacted hospitals and clinics.
Thirty-two hospitals and clinics transplant ocular tissue. Out of these, 26 are corneal transplant centres; 25 provided their data to TRIP, hence the difference between figures for distribution and transplantation of corneas. Fourteen out of 26 corneal transplant centres apply both cornea and sclera. There is a larger discrepancy between distribution and transplantation of sclera than cornea. This may be explained by longer storage times for sclera. Sclera is also applied by ophthalmologists who do not perform corneal transplants and who may not be aware of the annual collection of data on applied tissues and the reporting of adverse events and reactions.

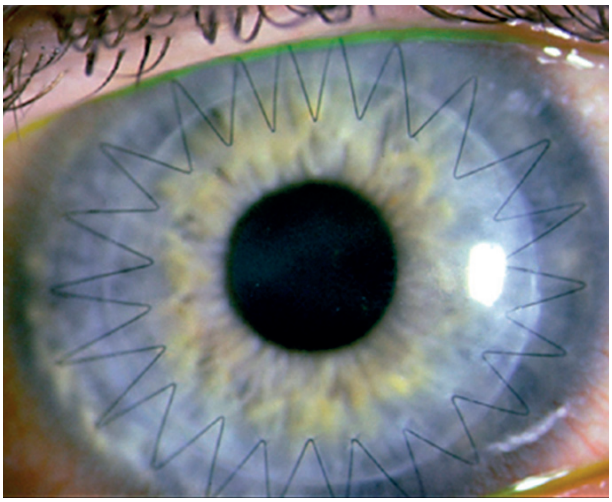


Table 25. Processing and distribution of ocular tissue in 2015

Type	Tissue establishment	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cornea	2	3288	Complete or lamella	1462	256	68	1786
Sclera	1	383	Complete or quadrant	1651	10	0	1661

Table 26. Transplantation of ocular tissue in 2015

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Cornea	19	1463	Complete or lamella	1460	16	0	1476
Sclera	16	1167	Complete or quadrant	1213	0	0	1213

Reports

In 2015 there were seven adverse events and two adverse reactions involving ocular tissue; all concerned cornea. Figure 19 gives an overview of reports concerning ocular tissue in 2007-2015.

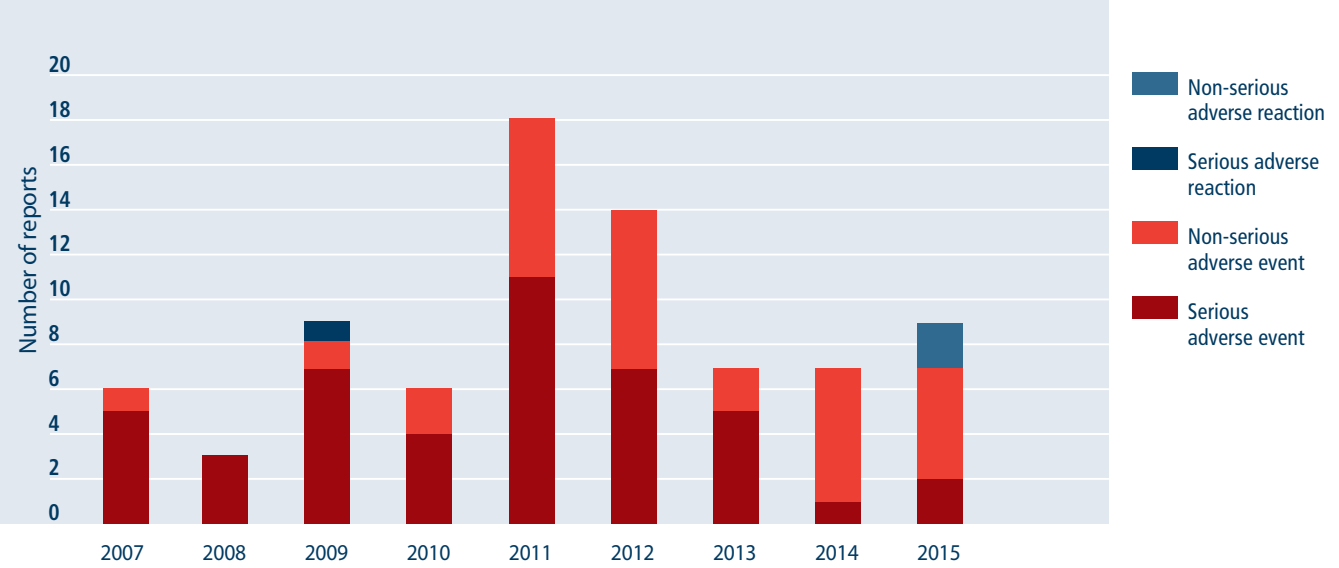


Figure 19. Reports concerning ocular tissue, 2007-2015

The seven adverse events in 2015 were submitted by two tissue establishments, one organisation responsible for allocation and one transplanting institution; three reports were judged to be serious. The reported adverse events are briefly described in Table 27 and the adverse reactions in Table 28..

Table 27. Overview of adverse events concerning ocular tissue in 2015

Category of event	Description	Reports
Incorrect product transplanted	• Instead of requested DSAEK a DMEK graft was distributed due to administrative error in the tissue establishment. Although the recipient was less suitable for a DMEK graft, surgery was performed. Patient had to be retransplanted*	1
Loss of tissues or cells	• During cutting of corneal lamellas a total of 22 corneas were lost due to various technical issues concerning the microkeratoma, in part also complicated by differences in elasticity of the corneal tissue* • At transplantation the lamella appeared to have a thick irregular edge and was removed. The tissue bank found no abnormality in returned lamella. Possiblity of mix-up of anterior and posterior lamella during surgery.	2
Risk of transmission of (non-infectious) other disease	• Relevant donor travel history to malaria region missed in release procedure for cornea, heart valves and bone. Corneas transplanted without complications in recipient. Bone and heart valves had not been distributed at time of discovery	1
Other incident	• At time of surgery, cornea container lid was found to have brown discoloration from surplus iodine. No adverse sequelae for patient • At procurement, failure to note information which meant that donor was not eligible for cornea donation • Corneal infiltrate suspect for fungal infection 1 week post-transplant. Similar problems after retransplantation, so it was concluded that problems were patient-related. Corneal culture: negative	3

** serious*

Abrreviations: DSAEK=Descemet's Stripping Automated Endothelial Keratoplasty, DMEK=Descemet's Membrane Endothelial Keratoplasty

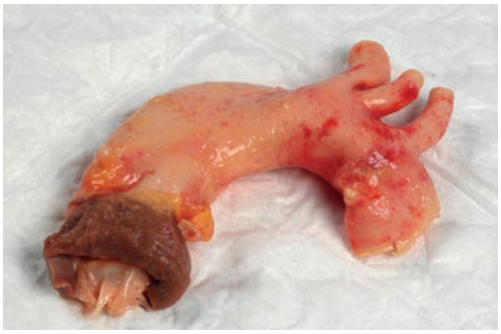
Table 28. Overview of adverse reactions concerning ocular tissue in 2015

Category of adverse reaction	Description	Reports
Other reaction	• 1 day after uncomplicated PKP for ulcer (Propionibacterium bacterium): corneal transplant edematous, hypopyon and Descemet folds. No indications of infection. On FU clear cornea and full healing • 1 day after second PKP for keratoconus: uveitis-like symptoms and signs. On FU: clear cornea and full healing	2

Abbreviations: PKP=penetrating keratoplasty, FU=follow up

2.5 Cardiovascular tissue

In The Netherlands heart valves, blood vessels and patches are applied in surgical procedures. Surgical heart valve replacement is an effective treatment for patients with damaged heart valves. For replacement of a damaged valve several options are available: a prosthetic (synthetic) valve or a biological valve of human or animal origin. Human post-mortem donor heart valves only account for a minority



of heart valve replacements and in a small number of clinical situations. In blood vessel transplantation only arteries are used. They are indicated for aortic disease with weakening of the vessel wall or in patients with an infected synthetic blood vessel prosthesis. Patches are taken from the pulmonary artery or aorta and are used for repair of congenital malformations in paediatric cardiac surgery. For the procurement of heart valves and aortic patches the complete human heart is retrieved and subsequently the heart valve bank performs dissection of the heart valves, aorta and pulmonary artery.

Processing, distribution and application

Tables 29 and 30 present data on processing/distribution and application of cardiovascular tissue.

Table 29. Processing and distribution of cardiovascular tissues in 2015

Tissue type	Tissue establishment	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Heart valves	1	374	Graft	71	16	0	87
Blood vessels	1	41	Graft	0	1	0	1
Patches, pericardium, other	1	38	Graft	20	3	0	23

Table 30. Application of cardiovascular tissue in 2015

Tissue type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Heart valves	5	90	Graft	70	20	0	90
Blood vessels	0	0	Graft	0	0	0	0
Patches, pericardium, other	3	20	Graft	20	8	0	28

Reports

There were no reports involving cardiovascular tissue in 2015. Figure 20 gives an overview of reports for cardiovascular tissue in 2006-2015. On average there was one serious adverse event per reporting year. All the reports concerning cardiovascular tissue in 2006-2015 involved heart valves, both aortic and pulmonary valves.

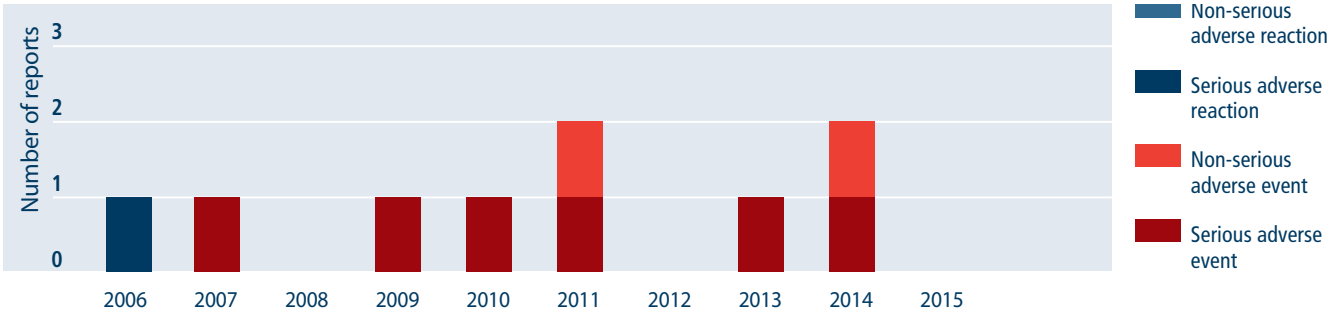


Figure 20. Reports concerning cardiovascular tissue, 2006-2015

2.6 Skin

Skin tissue can be subdivided into four categories: donor skin, autologous skin, cultured skin/skin cells and acellular dermis. The largest category is donor skin that is applied as a temporary dressing in burn patients. In The Netherlands one large organ bank is licensed for post-mortem donor skin processing, storage and distribution. Another three tissue establishments distribute imported skin products and one tissue establishment cultures keratinocytes.

Processing, distribution and application

Tables 31 and 32 show the numbers of processed, distributed and applied skin units. The numbers are similar to 2014. Hospitals and burn centres will keep some skin units in stock which contributes to the difference between numbers of distributed and transplanted units. One burn centre did not provide information on applied units of skin.

Table 31. Processed and distributed skin units in 2015

Type	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Donor skin	1	579 *	Pack	1500	7200	7940	16640
Autologous skin	1	10	Graft	5	0	0	5
Acellular dermis	3	101	Graft	187	92	38	317

* *Donors*

Table 32. Applied skin units in 2015

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Donor skin	5	77	Pack	512	1	0	513
Autologous skin	1	53	Graft	53	0	0	53
Cultured skin/ skin cells	1	5	Graft	5	0	0	5
Acellular dermis	3	10	Graft	2	4	6	12

Reports

Three non-serious reports of adverse events involving skin were submitted in 2015. They are summarised in Table 33..

Table 33. Reports concerning skin tissue in 2015

Category of event	Description	Number
Near miss	• Due to an identification error skin batches were released based on microbiology results of another donor	1
Loss of tissues or cells	• Due to an identification error incorrect skin batch discarded • Donor blood samples for infectious disease screening lost, donated skin had to be discarded	2

These reports again show that manual checks based on numbers may easily give rise to an error.

The numbers of reports concerning skin tissue from year to year are shown in Figure 21. The relatively high number of reports in 2014 is explained by reports concerning complications following application of cultured autologous skin in patients with a chronic ulcer. The complications were judged not to be related to the transplanted products.

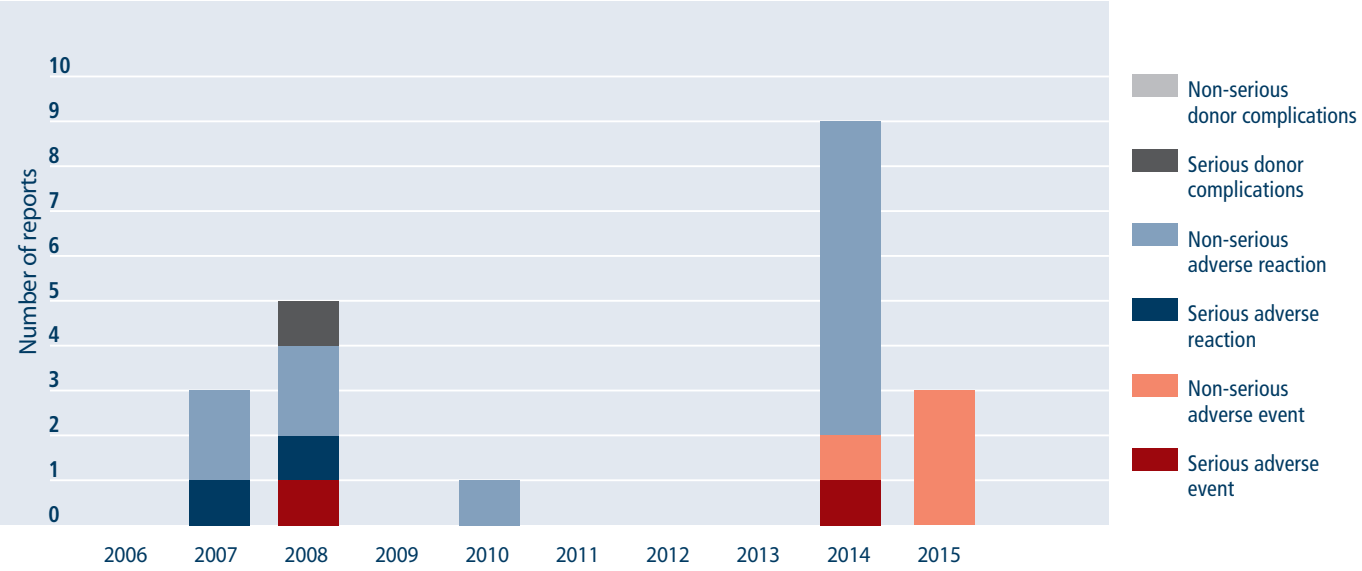


Figure 21. Reports concerning skin tissue or keratinocytes, 2006-2015

2.7 Other tissues and cells

A variety of tissues and cells are ranked in this category, including amniotic membrane, Langerhans' islets, umbilical cord tissue, adipose tissue and (autologous) radioactively labelled erythrocytes and leukocytes for diagnostic purposes.

Processing, distribution and transplantation

Tables 34 and 35 show numbers of processed and distributed units and applied units of other tissues and cells. Compared to 2014 there is an increase in the number of Langerhans' islets transplants (2015: 19 recipients, 2014: 8).

Table 34. Processing and distribution of other tissues and cells in 2015

Tissue or cell type	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Amnion	2	3 *	Pack	116	1	0	117
Langerhans' islets	1	40	Graft	40	0	0	40
Cord tissue	1	5756	Graft	0	0	0	0
Colonic tumour tissue	1	4	Graft	0	0	0	0
Glioma tumour tissue	1	16	Graft	16	0	0	16
Red blood cells**	1	79	Bag	79	0	0	79
Leukocytes**	1	146	Bag	135	0	0	135

* *Placentas*

***Radioactively labelled for diagnostic purposes*

Table 35. Application of other tissues and cells in 2015

Tissue or cell type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Amnion	8	51	Pack	57	0	0	57
Langerhans' islets	1	19	Graft	40	0	0	40

Reports

In 2015 one report concerning other tissues and cells was submitted: a non-serious adverse event regarding loss of amnion tissue. The distributing tissue establishment incorrect storage instructions on the container; the unit had to be discarded following storage at room temperature instead of in a fridge.

CHAPTER 3

Loss of gametes and embryos

3.1 Introduction: reports concerning assisted reproductive techniques

In 2008 the Dutch Association of Clinical Embryologists (KLEM) published its guideline "Reporting serious adverse events, reactions and calamities associated with application of gametes and embryos in assisted reproductive techniques". This guideline gives clear reporting criteria and is supported by all clinical embryologists. It was implemented retroactively to apply from 1 January 2008 and has since been revised twice. The KLEM starting point was to facilitate low-threshold reporting of adverse events according to clear criteria to TRIP as an independent body and this was always upheld. The guideline will be revised again in 2016 to incorporate the amended European Commission reporting guidelines with regard to reproductive cells.

From 2008 the percentage of reports concerning gametes, embryos and/or gonadal tissue has fluctuated between 48 and 63% (mean 57%) of the total number of reports. This should be seen in relation to the large number of assisted reproductive treatment procedures (around 15,000 IVF/ICSI cycles/year and 38,000 IUI/AID cycles/year). Each procedure comprises numerous processing steps and actions.
The number of adverse events in relation to the number of fertility cycles (1.1 per 1000 IVF/ICSI cycles) is not higher than the number of adverse events for other tissue or cell types (0.2-11.2 per 1000 processed transplants)[2].

Processing steps and actions in assisted reproductive techniques

IVF/ICSI

- Collection of follicle fluid into containers
- In some cases transportation of gametes to outside IVF laboratory
- Localising of oocytes in follicle fluid
- Removal of cumulus cells from oocytes
- Transfer to culture dishes
- Insemination (IVF and/or ICSI)
- Placement in incubator for embryo growth
- Daily check of embryo development (3-5 days)
- Selection of well-developed embryos
- In some cases pre-implantation genetic diagnosis
- Transfer of fresh (or cryopreserved) embryo(s)
- Cryopreservation of (surplus) embryos and gametes
- Storage of embryos and gametes
- Thawing of embryos or gametes
- All administrative procedures

IUI or donor sperm insemination

- Collection of semen in container
- Transfer of semen to laboratory
- Semen analysis and motility assessment
- Semen processing (including washing)

[2] See the 2014 TRIP biovigilance report, Chapter 3

- Cryopreservation
- Thawing
- Supply of semen in syringe
- Insemination
- All administrative procedures

Since 2008 the largest number of reports concerning assisted reproductive techniques has been registered in the category of loss of tissues or cells and regarded gametes and embryos. There have been no reports concerning gonadal tissues. The percentage of reports in the category loss of tissues or cells has fluctuated between 54 and 81% of the total number of reports relating to gametes, embryos and gonadal tissue. The Dutch Association of Clinical Embryologists' (KLEM) guideline uses a lower threshold for reporting of an adverse event compared to the European Commission and the Dutch Law on safety and quality of substances of human origin.

The KLEM guideline deems an adverse event reportable if there is (a. o.) a significantly reduced chance of pregnancy in that particular cycle whereas the European Commission and the Dutch Law on safety and quality of substances of human origin have used the complete loss of a fertility cycle as criterion since 2012. Consistent reporting according to clear criteria during several years offers the possibility of long term analysis. In this chapter the reports of loss of tissues or cells in ART will be analysed in depth.

3.2 Reports of loss of tissues or cells concerning gametes or embryos, 2007-2015

From 2007 up to and including 2015 a total of 387 adverse event reports concerning reproductive cells were submitted. Out of the total 59% (227 reports) were registered in the category loss of tissues or cells and concerned exclusively gametes and/or embryos.

The largest number of these reports involved embryos. Figure 22 presents the numbers of reports of loss of tissues or cells relating to assisted reproductive techniques in relation to the total number of ART reports. In Figure 23 the reports are subdivided in serious and non-serious reports per type of reproductive cell or embryo.

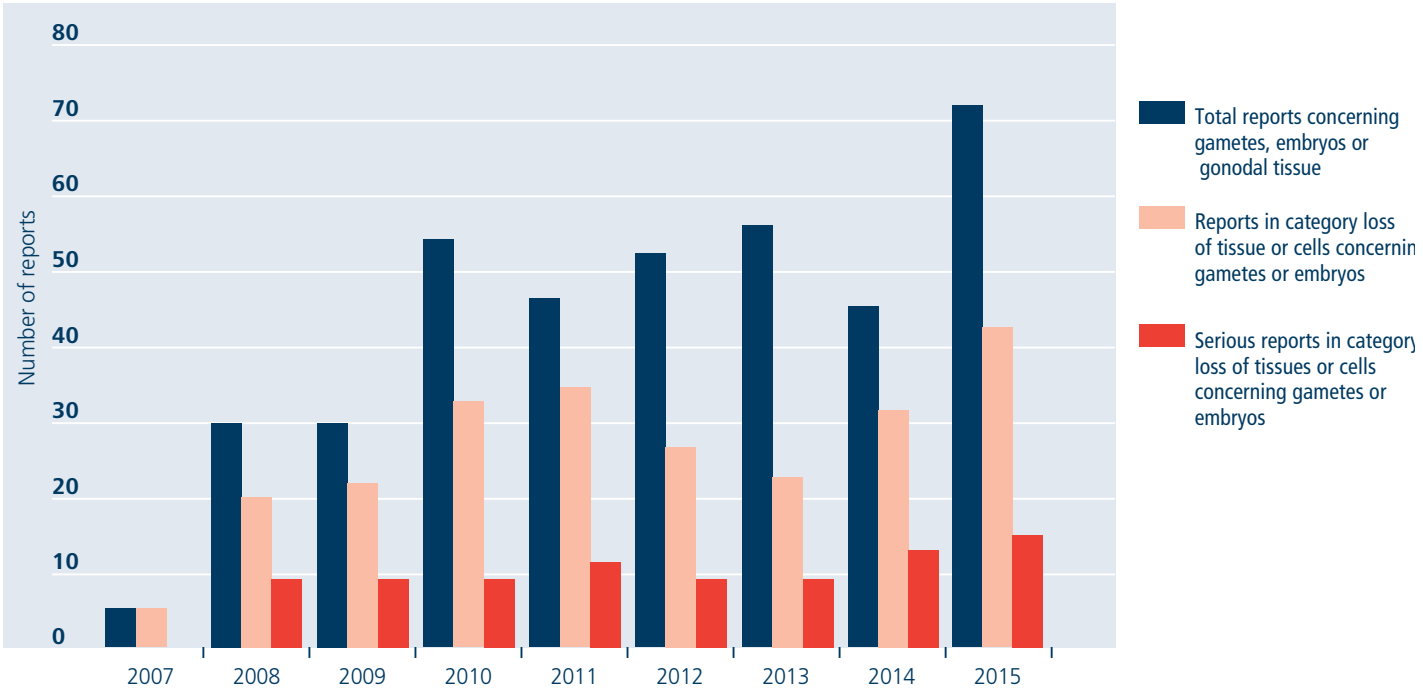


Figure 22. Reports of loss of reproductive cells in relation to all ART reports, 2007-2015

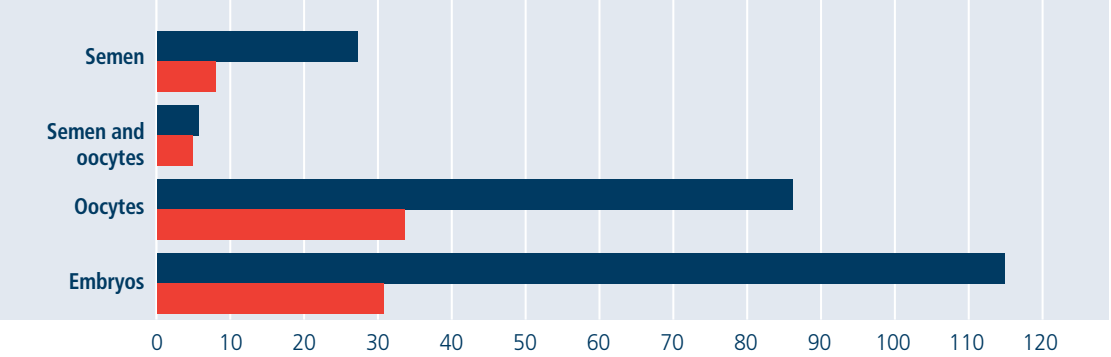


Figure 23. Reports of loss of tissues or cells per type of reproductive cell, 2007-2015

The step in the procedure where the adverse event occurred is shown in Figure 24. In 83% of reports the processing phase was involved. For the serious reports a similar picture is found. The number of reports per processing step is shown in Figure 25.

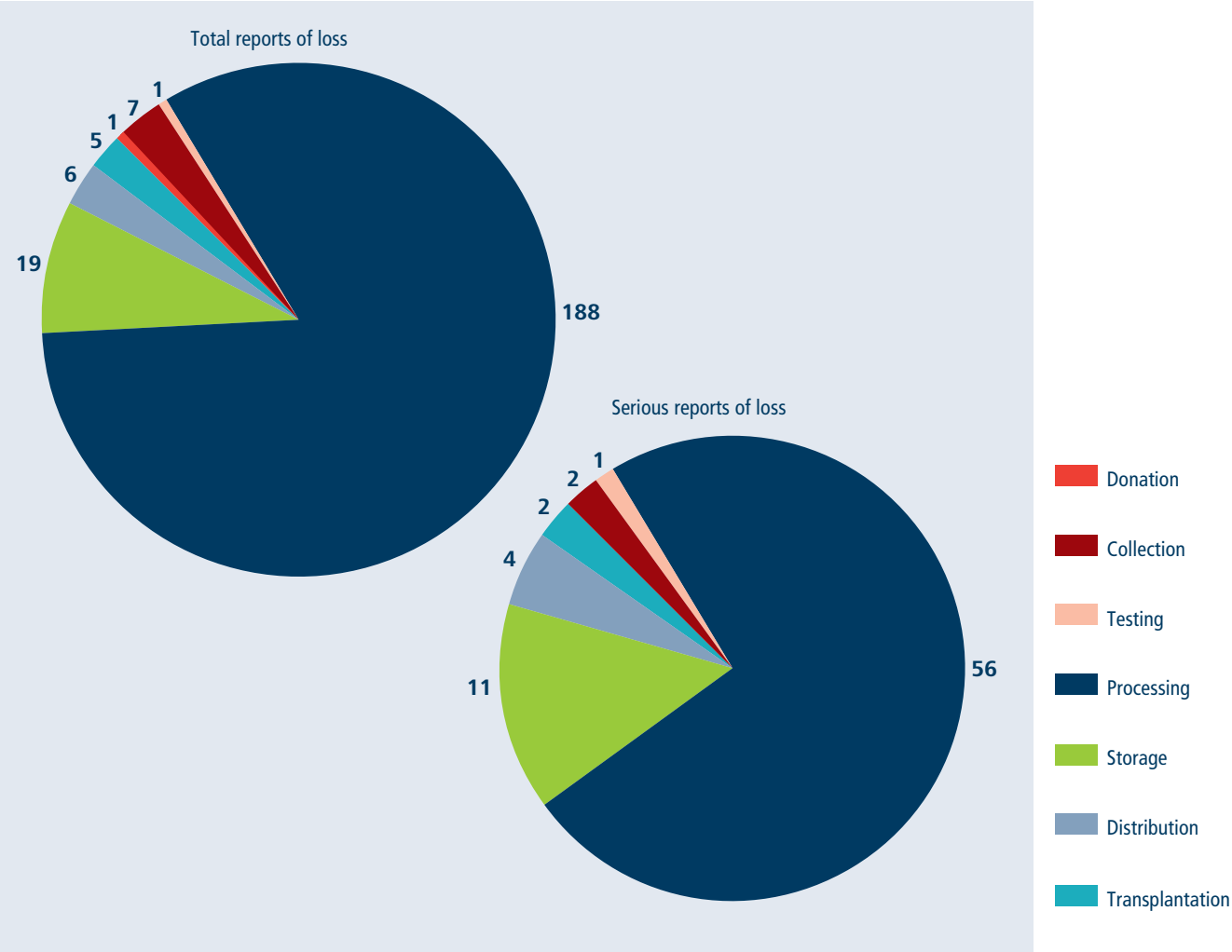


Figure 24. Stage of assisted reproduction where loss of gametes and embryos occurred, 2007-2015

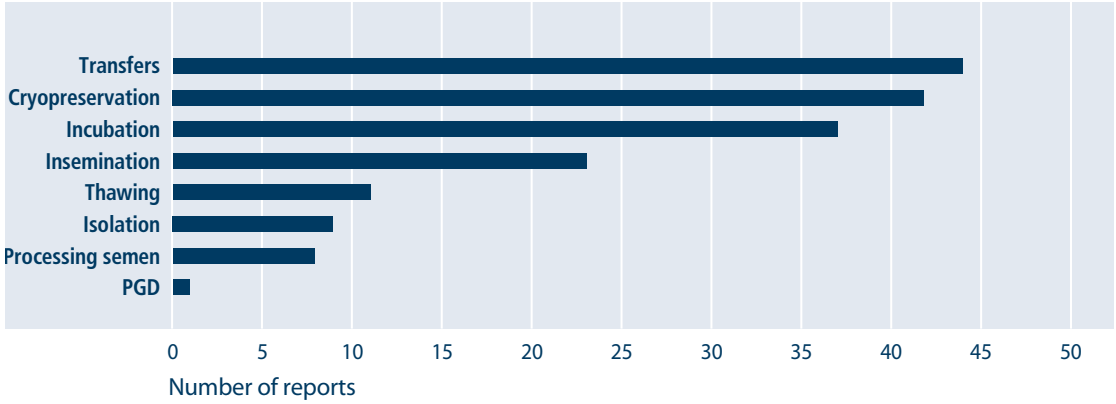


Figure 25. Loss of gametes and embryos, subdivided according to laboratory processing step, 2007-2015

The majority of events in the category loss of gametes and embryos occurred in the processing steps of transfers, cryopreservation, incubation and insemination: 85% (160 out of 188) of the reports. With regard to the serious reports a similar picture is found. Figure 26 presents the reports subdivided according to type of error and procedural step. In Figure 27 the processing errors are shown in more detail.

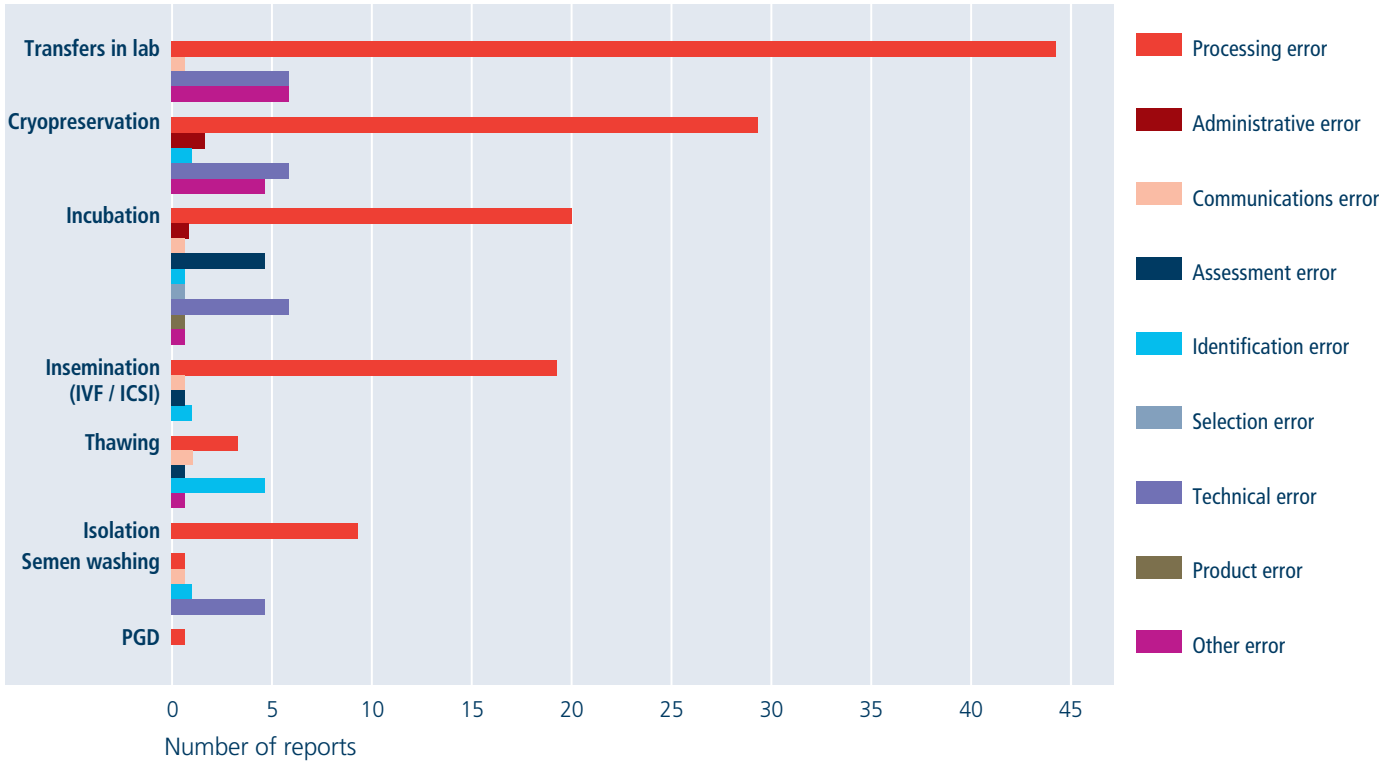


Figure 26. Reports of loss of gametes and embryos, subdivided according to type of error and processing step, 2007-2015

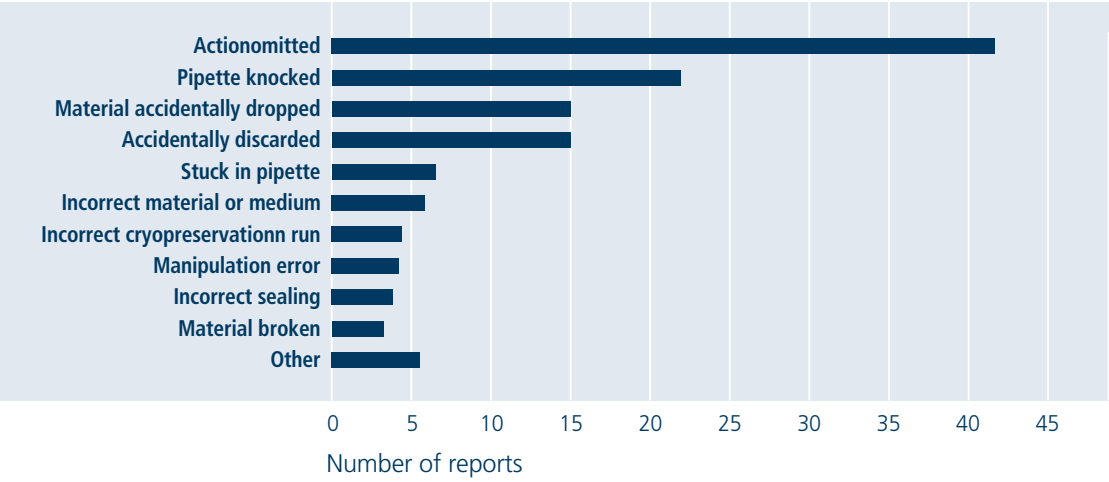


Figure 27. Reports of loss of gametes or embryos per type of processing error, 2007-2015

In 42 reports an action was accidentally omitted during processing. In 22 cases oocytes or embryos were lost due to accidentally knocking the pipette. In 15 reports gametes or embryos were accidentally dropped and lost and in another 15 reports gametes or embryos were erroneously discarded.

3.3 Conclusion

Adverse events leading to loss of gametes or embryos mainly occurred in the laboratory processing phase in the period 2007-2015. Omission of an action, knocking, dropping and erroneous discarding are the processing errors that were reported most frequently. This should be seen in relation to the large number of processing steps and actions that are necessary in assisted reproductive techniques. Errors like omitting a step or mistakenly discarding could (in part) be avoided by redesigning working procedures and protocols. TRIP recommends that all fertility laboratories evaluate their working procedures with this in mind and always perform a double check before discarding gametes or embryos.

CHAPTER 4

Participation

Participation of all stakeholders in the TRIP reporting system is essential for the quality of the biovigilance system. Participation is defined on the basis of both submission of reports to TRIP (or confirmation that there were no reportable reactions or events in a particular year) and provision of annual numbers of all types of processed, distributed and transplanted units of human tissues and cells along with the number of recipients. The quality and completeness of the submitted figures as well as of reports are also important.

In looking at participation rates TRIP distinguishes two categories of institutions:

1 the tissue establishments (this includes so-called "organ banks", see below) that procure, process, store and/or distribute human tissues and cells; and
2 the hospitals, clinics and oral implantology practices that apply or transplant human tissues and cells.

4.1 Tissue establishments

According to the definition in the Law on safety and quality of substances of human origin (Wvkl), article 1.1.k, a tissue establishment is a tissue bank, hospital department or other institution that performs activities in connection with processing, storage or distribution of human tissues and cells. A hospital can be a user of human tissues and cells and can also harbour one or more tissue establishments.

A tissue establishment cannot receive tissues and cells after procurement without an additional licence. Tissue establishments which receive human tissues and cellsafter harvesting of human tissues and cells must be licensed as so-called organ banks. Organ banks according to article 1.1.l of the Law on safety and quality are also licensed to subsequently process, store and distribute human tissue and cells and must be not-for-profit organisations. All organ banks are also tissue establishments; however, not all tissue establishments are organ banks. The scope of activities determines whether a licence as an organ bank or tissue establishment is necessary.

Table 36 presents an overview of licensed tissue establishments and organ banks in The Netherlands in 2015 (source: Farmatec). Some hospitals house several tissue establishments and/or organ banks.

Table 36. Licensed tissue establishments and organ banks in 2015

	Tissue establishments	Organ banks	Total
Independent institution*	10	11	21
Located in hospital or clinic	58	38	96
Total	**68**	**49**	**117**

** Excluding two independent institutions which have applied for but not yet received licences*

Figure 28 shows the number of licences issued by Farmatec for each type of human tissue or cells. Farmatec is an executive body that grants licences and permits with regard to pharmaceuticals, medical devices, blood components and substances of human origin on behalf of the Ministry of Health. Some tissue establishments and organ banks hold several licences.

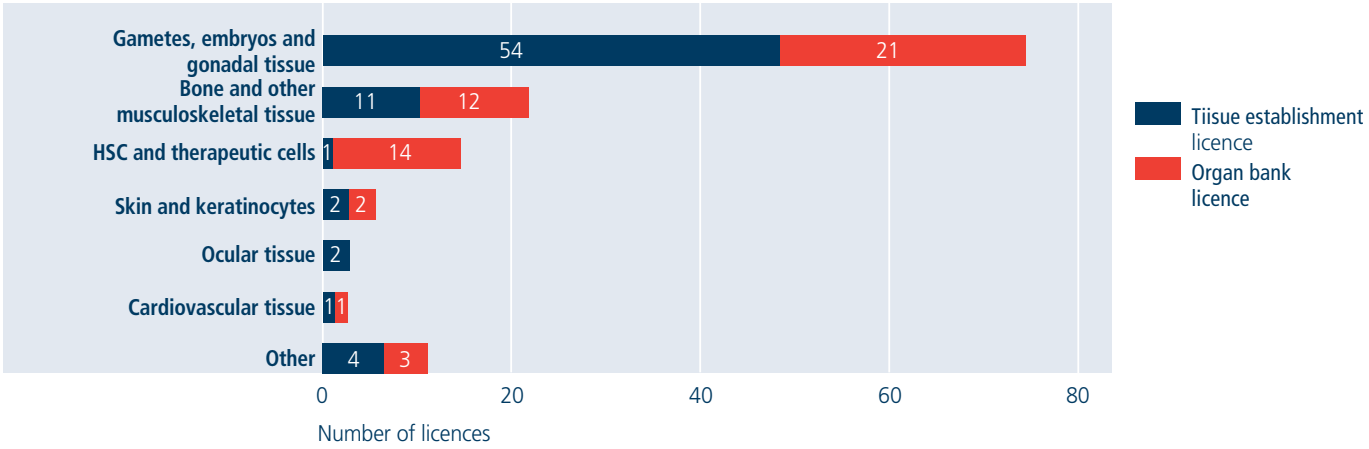
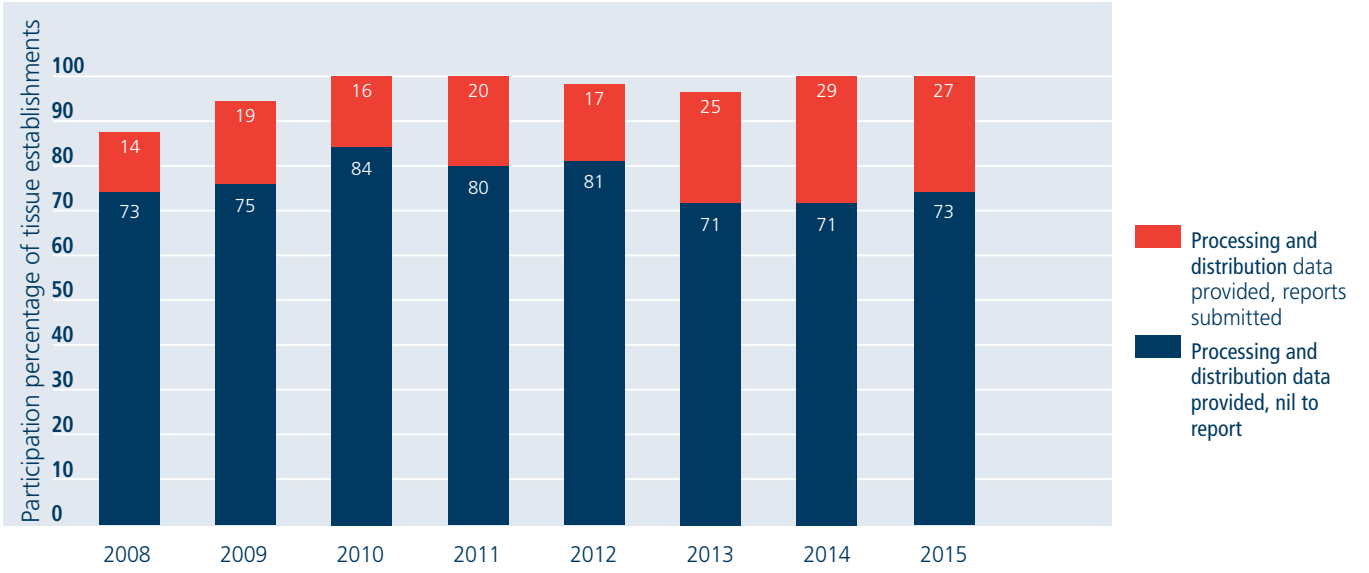


Figure 28. Number of licensed tissue establishments and organ banks in The Netherlands in 2015

Figure 29 shows the annual percentages of tissue establishments that provided data on processing and distribution and those submitting biovigilance reports. All tissue establishments submitted data on processing and distribution in 2015. Two tissue establishment replied that they did not perform activities covered by the law on safety and quality in 2015. All institutions participated in 2015 (118 out of 118 tissue establishments), although one tissue establishment provided incomplete data.



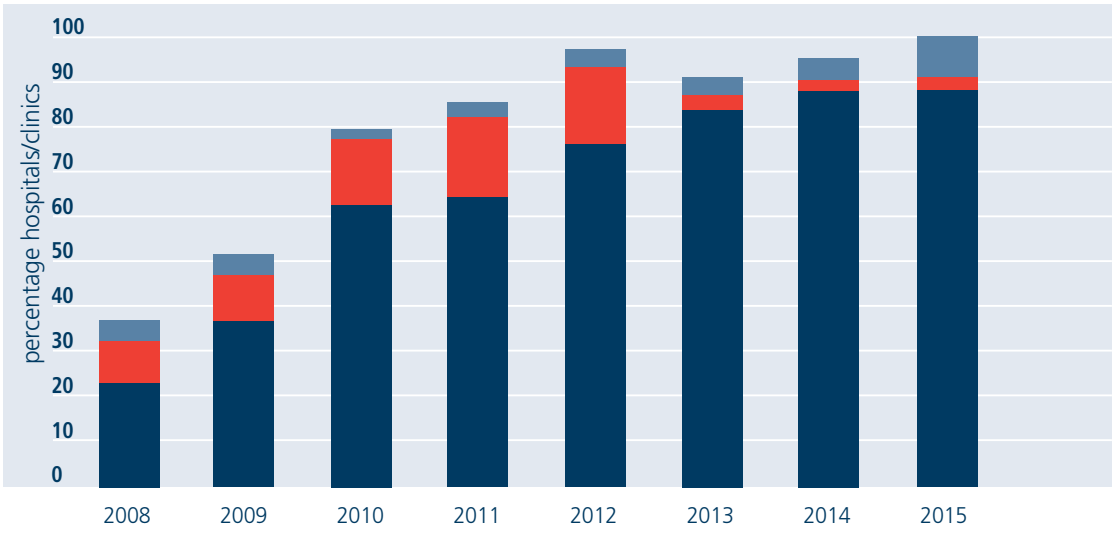
(in 2008-2011: n=20, 2012-2015*:n=118-120)

Figure 29. Participation by tissue establishments

** Up to 2012 tissue establishments located in hospitals or clinics were not considered under participation of tissue establishments.*

4.2 Organisations responsible for human application of tissues and cells

In 2015 92 hospitals, 20 clinics and 48 oral implantology practices were contacted for information on numbers of applied tissues and cells, the number of recipients and the reporting of adverse events and reactions. The clinics and oral implantology practices that indicated in a survey in 2013 that they applied human tissues and cells were added to the database of applying institutions and asked for their numbers of applied products in 2015. Participation by hospitals and clinics in 2015 was 100% (112 out of 112). In seven cases the data were incomplete. The implantology practices were contacted for the third time and their participation was 79% (38 out of 48). The number of oral implantology practices providing data on their use of tissues and cells rose from 36 to 48. This is due to a distributing tissue establishment informing users that they should provide data on applied tissues to TRIP. In all, two hospitals, seven clinics and four implantology practices replied they did not apply tissues or cells in 2015. The overall participation of organisations responsible for human application of tissues and cells in 2015 was 94% (150 out of 160). In Figures 30 and 31 participation rates are shown from 2008 onwards.



(n=101-115)

Figure 30. Participation by Dutch hospitals and clinics, 2008-2015

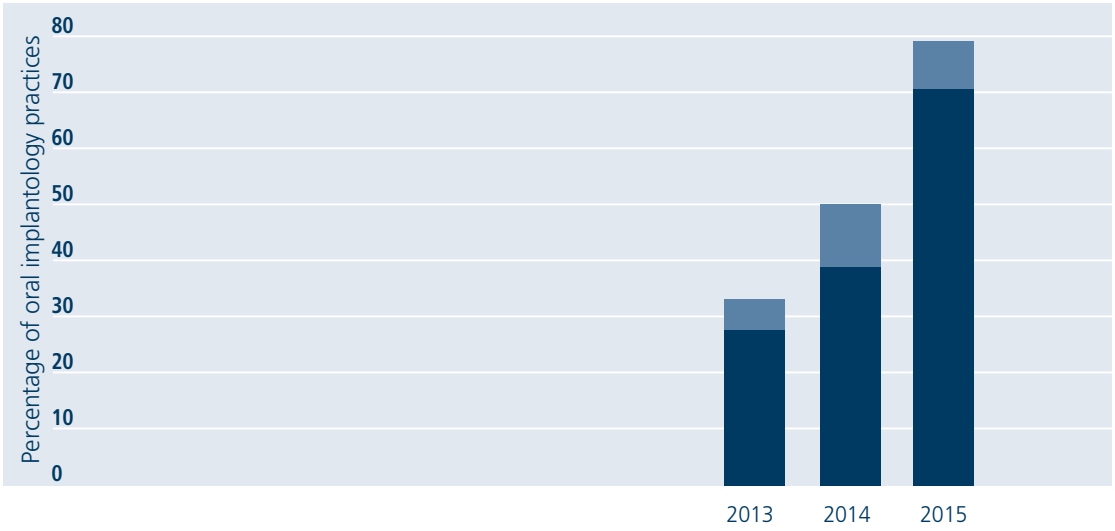


Figure 31. Participation by Dutch oral implantology practices, 2013-2015
(n=36-48)

ANNEX 1

About TRIP

TRIP (Transfusion and Transplantation Reactions in Patients) Foundation was created in 2001 for the purpose of establishing a national hemovigilance system. In 2006 at the request of the Ministry of Health a pilot project for biovigilance data registration was set up. Since 2012 biovigilance has been a formal task for the TRIP foundation.

The European law on safety and quality of human tissues and cells requires member states to have a system for the reporting of adverse reactions and events associated with the application of these substances of human origin (EU Directive 2004/23/EG). This is called biovigilance and refers to the systematic monitoring of (serious) unintended adverse reactions and events throughout the transplantation chain from donor to recipient of substances of human origin with the aim of achieving safer and more effective use of tissues, cells and organs.

The TRIP reporting system for adverse reactions and events related to the application and transplantation of substances of human origin meets the requirements laid down in Dutch and European legislation. The online reporting system allows those reporting to TRIP to simultaneously submit serious reactions and events to the Healthcare Inspectorate. The Healthcare Inspectorate is the competent authority on behalf of the Ministry of Health. The mandatory reporting of adverse reaction and events to the Healthcare Inspectorate applies to tissue establishments according to the Law on safety and quality of substances of human origin and the Decree on requirements for substances of human origin (2006). The Decree on requirements for substances of human origin was updated in 2012 in accordance with EU directive 2010/53/EG. Figure 32 presents a flowchart of serious and non-serious biovigilance reporting in Dutch healthcare.

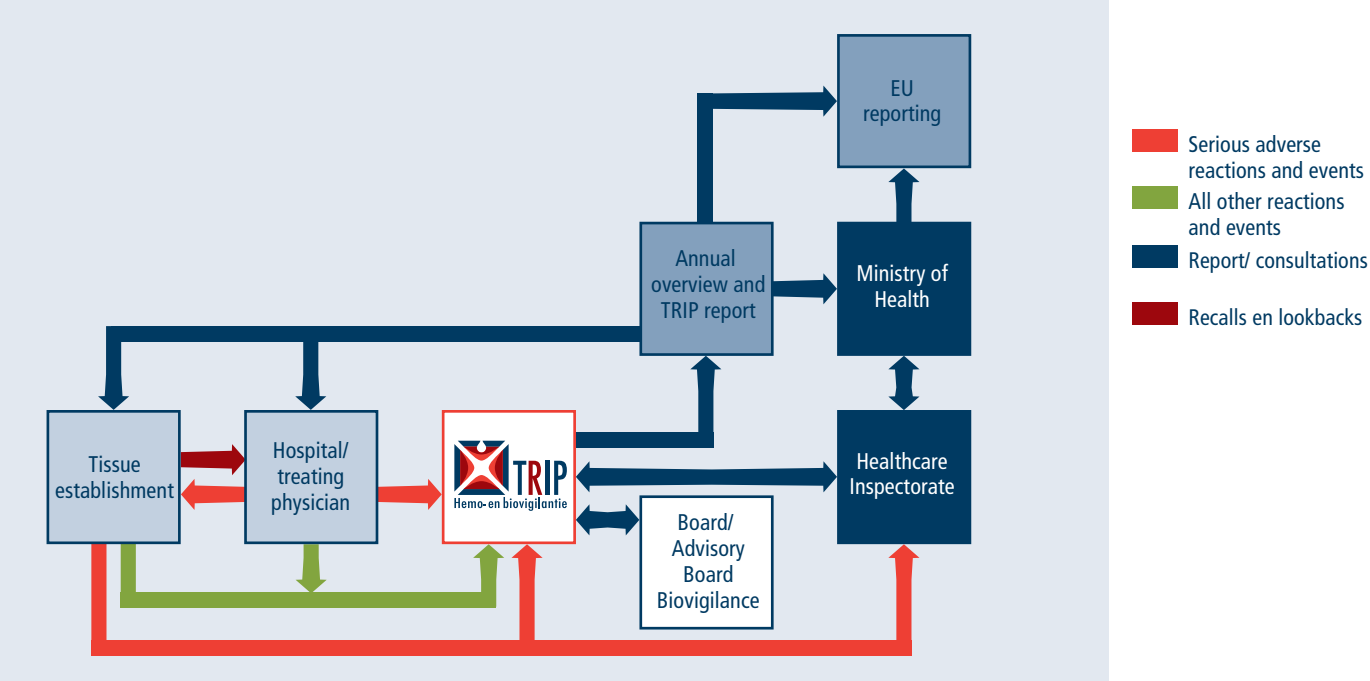


Figure 32. Flowchart of reporting

The scope of the Law on safety and quality of substances of human origin includes all substances of human origin (from living as well as deceased donors) with the exception of autologous material that is obtained and transplanted in the same procedure. If autologous tissues are preserved or processed (this includes preparation or processing in another location, distant from the patient) the Law on safety and quality does apply. The Law on safety and quality always applies to allogeneic application (derived from a human donor).

TRIP working method

TRIP is an independent foundation that cooperates closely with the users of human substances and tissue establishments. The TRIP reporting system has collected tissue and cell data from hospitals, clinics and licensed tissue establishments since 2006 and serves to support the monitoring and improvement of the quality and safety of substances of human origin. All submitted reports are registered, analysed and reviewed by experts. The results and conclusions are reported annually. TRIP also collects data annually on numbers of processed, distributed and applied substances of human origin in all Dutch hospitals, clinics and tissue establishments, in accordance with European regulations. The information is aggregated as a denominator for the TRIP data on adverse reactions and events and the annual mandatory data submission to the European Commission. On behalf of the Healthcare Inspectorate TRIP drafts the annual mandatory overview of serious adverse events and reactions to be forwarded to the European Commission.

Tissue establishments, hospitals and other institutions that provide processing, distribution and/or application figures and submit reports on adverse reactions and/or events to TRIP receive an annual participation certificate. This participation certificate contributes to safety awareness in the application of substances of human origin and to the safety management system. The participation certificate may also be formally reviewed by the Healthcare Inspectorate at the licensing procedures or licence renewal for tissue establishments.

TRIP is guided by a Biovigilance Advisory Committee representing relevant medical professional bodies and specialties as well as tissue establishments. The Biovigilance Advisory Committee provides medical professional and strategic guidance with regard to biovigilance, reviews all reports anonymously and advises with regard to the annual report.

ANNEX 2

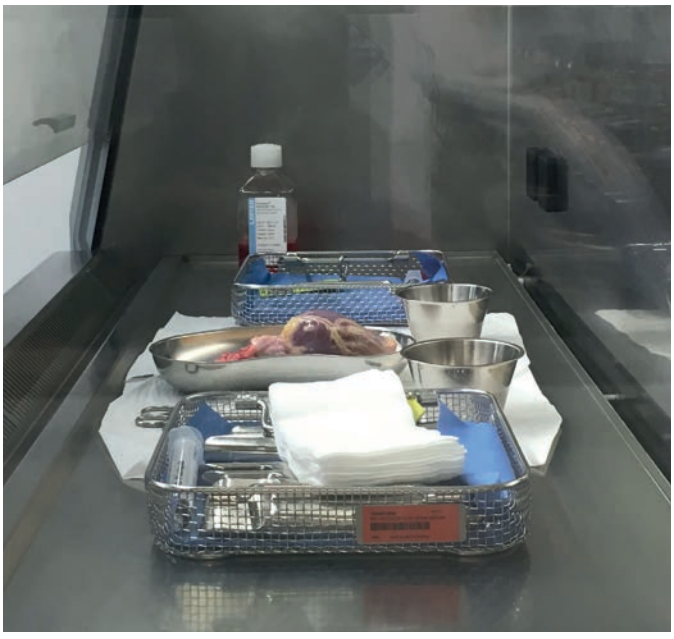
Reporting of serious adverse reactions and events

Reporting of serious adverse reactions and events relating to substances of human origin is laid down in article 8.1 of the Dutch Decree on Substances of Human Origin 2006 (see Annex 3). This article states that **the tissue establishment** is responsible for reporting, investigation, registration and forwarding of information on serious adverse reactions and events that could be related to quality and safety of substances of human origin or that are found after application and could be linked to the applied human tissues or cells. Adverse reactions and events should be reported to TRIP and also to the Healthcare Inspectorate if necessary.

Organisations responsible for human application of tissues and cells are responsible for reporting (possible) product-related serious adverse reactions and events to the supplying tissue establishment and may also report to TRIP. TRIP checks for duplicate reports and if any are found, merges them in consultation with the reporters. If a calamity has occurred which (possibly) has been caused by human tissue or cells the hospital must also report this to the Healthcare Inspectorate according to the Dutch quality law for healthcare institutions.

Reporting to the Healthcare Inspectorate

In The Netherlands the Healthcare Inspectorate is the designated competent authority to be notified of serious adverse reactions and events relating to human tissues and cells. In agreement with the Healthcare Inspectorate TRIP takes care of registration of all adverse reactions and events. The TRIP digital reporting system facilitates the forwarding of serious adverse reactions and events to the Healthcare Inspectorate: reporters can select the option of forwarding the report to the Healthcare Inspectorate so that they only need to submit information once. The reporting of serious adverse reactions and events differs from the reporting of a calamity according to the Dutch quality law for healthcare institutions (Law on Quality, Complaints and Disputes in Healthcare). The Healthcare Inspectorate has a definition for a calamity (see Annex 3) and has specific procedures for this. In November 2015 the Healthcare Inspectorate sent a letter to all tissue establishments clarifying the reporting of adverse reactions and events to the Healthcare Inspectorate and TRIP. Figure 33 shows the flowchart of reporting routes.



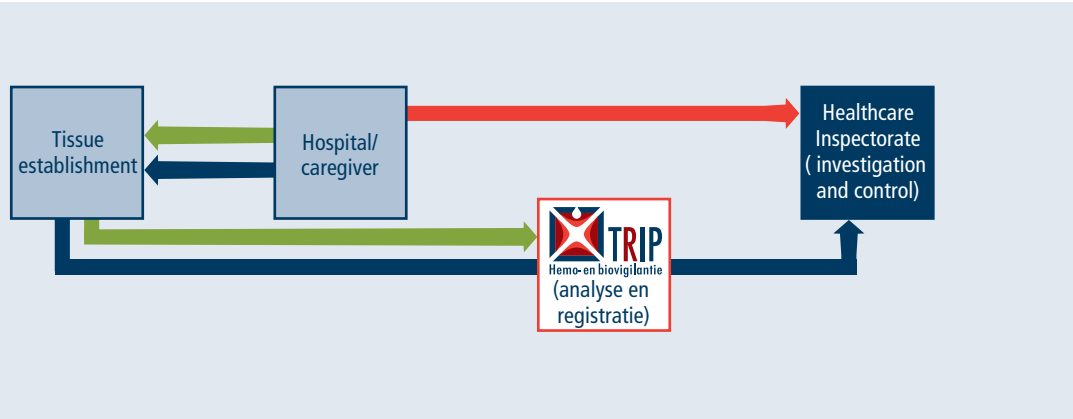


Figure 33. Flow chart of reports concerning substances of human origin

Serious adverse reactions or events within the scope of the Law on safety and quality of substances of human origin are best submitted to the Healthcare Inspectorate via the TRIP online reporting system. This channels the reports to the inspectors involved in enforcement of the Law on safety and quality of substances of human origin and avoids reports being (possibly incorrectly) treated as lying within the scope of the Law on quality in healthcare. However reports will always be assessed on healthcare quality aspects as well and full analysis will be required if an event is judged to be a calamity.

ANNEX 3

Definitions and reporting criteria

Serious adverse event

A serious adverse event is defined as follows (according EU Directive 2004/23/EC Article 3):

A serious adverse reaction is an unintended response, including a communicable disease, in the donor or in the recipient associated with procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity

The criteria used by the European Commission are presented in Table 37. These criteria were developed by the EU projects EUSTITE and SOHO V&S and adopted in the "Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC".

Table 37. Criteria for serious adverse event

- Inappropriate tissues or cells were distributed for clinical use, even if not used
- The event could have implications for other patients or donors because of shared practices, services, supplies or donors
- The event resulted in loss of any irreplaceable autologous tissues or cells or any highly matched (i.e. recipient-specific) allogeneic tissues or cells
- The event resulted in the loss of a significant quantity of unmatched allogeneic tissues or cells
- The event led to a serious adverse reaction (grade 2, 3 or 4)
- The event led to misidentification or switch of gametes or embryos
- The event led to birth of a child or abortion of a fetus with a transmitted genetic disease following assisted reproductive technologies with non-partner gametes or donated embryos
- The donor is diagnosed with a genetically transmissible disease after donation of gametes or embryos.

Serious adverse reaction

A serious adverse reaction is defined as follows ((EU Directive 2004/23/EC Article 3)

A serious adverse reaction is an unintended response, including a communicable disease, in the donor or in the recipient associated with procurement or human application of tissues and cells that is fatal, life-threatening, disabling incapacitating or which results in, or prolongs, hospitalisation or morbidity.

Table 38 shows the definitions of severity grades of adverse reactions with explanatory comment. The definition of a serious adverse reaction corresponds to severity grade 2 or higher.

Table 38. Severity grade of adverse reactions

Grade 0	• No morbidity. The reaction is only discovered later and/or through laboratory investigation or screening. Full recovery of the recipient or donor.
Grade 1	• Minor morbidity, not life-threatening Minor clinical effects without (prolongation of) need for hospital admission and without invalidity, incapacity or long-term consequences for the recipient.
Grade 2	• Moderate to serious morbidity, may or may not be life-threatening; or leading to hospitalisation or prolongation of illness; or associated with chronic disability or incapacity.
Grade 3	• Serious morbidity, directly life-threatening. A living donor or recipient needs medical or surgical intervention following harvesting or transplantation of the tissues or cells (vasopressor medication, intubation, transfer to intensive care) in order to prevent death; or a life-threatening infection is transmitted.
Grade 4	• Mortality following a transplantation adverse reaction NOTE Grade 4 does not apply if the patient recovers to a stable clinical condition after a transplantation reaction and subsequently dies of causes unrelated to the tissue or cell transplantation.

Donation complications can be graded for severity in the same manner. Serious donation complications are not yet subject to mandatory reporting to the EU. The EC however requests submission of these reports on a voluntary basis. TRIP collects donation complications for the annual overview of serious adverse reactions and events for the European Commission.

Calamity

A calamity is defined by the Dutch Law on Quality, Complaints and Disputes in Healthcare as follows:

A calamity is 'an unintended or unexpected adverse event related to the quality of healthcare and leading to death or serious adverse consequences for the patient or client of an institution

ANNEX 4

Overview of mandatory reports of serious adverse reactions and events

(IN ACCORDANCE WITH EU LEGISLATION)

Table 39 shows the numbers of serious adverse reactions and events relating to substances of human origin in 2015. In all, 40 reports were classified as serious. These concerned 20 serious adverse events and 20 serious adverse reactions, of which fifteen were serious adverse reactions in donors.

Table 39. Overview of serious adverse reactions and events in 2015

Tissue or cell type	Serious adverse reaction	Serious adverse event	Serious donation complication	Total serious reports
Semen	0	4	0	4
Oocytes	0	5	11	16
Semen and oocytes	0	1	0	1
Embryos	0	8	0	8
Ocular tissue	0	2	0	3
HSC and therapeutic cells	5	0	4	9
Total	**5**	**20**	**15**	**40**

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ANNEX 5

List of terms and abbreviations

Apheresis	Type of blood donation involving the selective mechanical withdrawal of specific blood components while returning (infusing) the remaining components to the donor or patient
Allogeneic	Originating from a donor (genetically non-identical person)
AML	Acute myeloid leukemia
Autologous	Originating from a person's own body
Cryopreservation	The process of freezing and subsequent storage of frozen tissues and cells
CVA	Cerebrovascular accident, stroke
Distribution	Transportation and delivery to end users
DLI	Donor lymphocyte infusion
DMSO	Dimethylsulfoxide
EC	European Commission
ET	Embryo Transfer
EU	European Union
EUSTITE	European Union Standards and Training in the Inspection of Tissue Establishments (EU project 2007-2009)
Farmatec	Organisation resorting under the Dutch Ministry of Health, responsible for accreditation and licensing of pharmaceuticals, medical devices, blood products and substances of human origin
GCSF	Granulocyte colony stimulating factor
GnRH	Gonadotrophin Releasing Hormone
Gonadotrophin	Hormone regulating sexual glands
HCG	Human chorionic gonadotrophin (stimulates ovulation)
HLA	Human leukocyte antigen
HSC	Hematopoietic stem cells
ICSI	Intra-cytoplasmic sperm injection (type of IVF)
Imputability	Degree to which an adverse reaction can be attributed to applied substances of human origin
IUI	Intra-uterine insemination
IVF	In vitro fertilisation
KLEM	Association of clinical embryologists
Lareb	Dutch national registry for adverse drug reactions
Luteal phase	Phase in menstrual cycle from ovulation to menstruation
MESA	Microsurgical epididymal sperm aspiration
Mono-zygotic	Deriving from one fertilised oocyte
NL	The Netherlands
NVOG	Dutch Society for Obstetrics and Gynaecology
OHSS	Ovarian hyperstimulaton syndrome
Organ bank	Tissue establishment with licence to receive substances of human origin after procurement
PBSC	Peripheral blood stem cells
PESA	Percutaneous epididymal sperm aspiration
PGD	Preimplantation genetic diagnosis

Pharmacovigilance	Vigilance of pharmaceuticals
PID	Pelvic inflammatory disease
PN	Pro Nuclei
Processing	All actions necessary for preparing, manipulating, preserving and packaging substances of human origin
Procurement	Process whereby donated substances of human origin become available
Semen	Sperm
SOHO V&S	Vigilance and Surveillance of Substances of Human Origin (EU project 2010-2013)
TESE	Testicular sperm extraction
TIA	Transient ischemic attack, temporary occlusion of a cerebral blood vessel
Tissue establishment	A tissue bank, a hospital department or another institution that holds a licence for processing, preserving, storage and/or distribution of substances of human origin
Vitrification	Rapid cryopreservation method mainly used for oocytes
WMDA	World Marrow Donor Association
Wkkgz	Law on healthcare quality, complaints and disputes (replaces former law on quality of healthcare institutions)
Wvkl	Dutch Law on safety and quality of substances of human origin
Zona pellucida	Protein coat around oocyte

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