TRIP report 2014

Biovigilance

TRIP
Hemo- en biovigilantie

TRIP report 2014

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Extended version

The TRIP report 2014 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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Introduction

The TRIP Biovigilance report 2014 is the 8th consecutive annual report describing adverse events and reactions related to processing and use of human tissues and cells. The number of submitted biovigilance reactions and events has remained stable over the last few years. Moreover participation by both tissue establishments and hospitals and clinics where tissues and cells are applied is stable and almost complete. This year therefore we have produced an overview of five years of adverse reactions and events and donor complications in relation to cycles of donations, processing and treatments using human tissues and cells. You will find this overview in Chapter 3. The trends which emerge can assist the various groups of healthcare professionals in improving quality and safety of human tissues and cells. It is not yet possible to make an international comparison of the findings in Chapter 3, but could be useful with regard to rare adverse reactions as well as the effect of differences in processing or treatment procedures. TRIP encourages other EU member states to review their data in this way.

After the closing date for the 2013 annual report a significant number of late cases were submitted. This report also describes these late submissions. After the 2013 recommendation with regard to the timely reporting of adverse reactions and events a considerable drop in the number of late reports has been seen. At the time of writing this report there were no late reports regarding 2014 that were submitted after the closing date.

With regard to hematopoietic stem cells, this report gives figures for processed grafts which were procured in The Netherlands, in other EU countries and outside the EU. It shows that many allogeneic unrelated transplants are obtained from donors outside The Netherlands. The data give a clearer picture of the cross-border traffic of stem cell transplants.

In 2014 the Health Council of The Netherlands published the report "Towards a sustainable tissue supply chain". This report is meant to inform the Dutch government and parliament as to whether the current tissue supply chain is sustainable. The main conclusion is that coordination of the national tissue supply has improved over the last few years but that there is room for further improvement. The two laws that relate to human tissues (the Law on organ donation and the Law on safety and quality of human tissues and cells) do not complement each other fully and do not accommodate new developments. In order to become future-proof a modified organisational model is proposed. TRIP's operations are specifically mentioned in this report as important for patient safety and shedding light on activities in the field of human tissues and cells.

TRIP Foundation wishes to acknowledge the indispensable part played by all the professionals who have contributed to the compiling of this report and hopes that it will be used to improve safety and quality of the chain of human tissues and cells.

Findings and recommendations

2014 findings

1. At the time of writing this 2014 report no late reports had been submitted after the closing date. This seems to be an improvement compared to 2013 when late reports were an issue.

2. The loss of reproductive cells is due to failure to perform a process step or activity (e.g. transfer of oocytes or embryos to another dish, insemination in IVF or ICSI, setting of temperature regulation) in 29% of reported cases.

3. There were two 2014 reports and one late 2013 report of a patient being inseminated with incorrect semen.

4. One report mentioned exceeding the recommended number of children (25) per semen donor due to failure to take into account future requests for siblings from the same donor.

5. Four late 2013 reports regarded stem cell transplants where failures in transport, labelling or sealing of the product were noted during shipment to another country or by a foreign tissue establishment. In one case an allogeneic stem cell transplant was lost.

6. Temporary storage of tissues in transplanting healthcare institutions led to loss of tissues and cells due to suboptimal storage conditions and expiration of shelf life of tissue held in stock.

7. Unforeseen circumstances in transplanting healthcare institutions lead to loss of corneas.

8. The reporting of a serious adverse event to the tissue establishment without returning explanted tissue (i.e. heart valve) seriously hampers adequate investigation by the tissue establishment.

9. Modification in composition of an additive solution can seriously affect the quality of tissue and cells; tissue establishments should not rely solely on the validation process of the manufacturer.

10. The number of serious reports in relation to the number of reproductive cell treatment cycles in the 2010-2014 period was low despite the complex processing procedures.

11. In the last five years there was a relatively large number of serious reports in relation to the number of treatment procedures with autologous cartilage and autologous cranial bone flaps.

12. In the 2010-2014 period serious donor complications were exclusively reported with hematopoietic stem cell donations (peripheral blood stem cells and bone marrow). The largest number of donor complications concerned subsequent diagnosis of an illness that is found fairly frequently in the general population and for which imputability to the donation is assessed as unlikely or at most possible.

2014 recommendations

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

2. Healthcare institutions applying human tissues and cells should review their tissue storage conditions in close cooperation with distributing tissue establishments and ensure that storage protocols and alarm systems are adequate and function as intended.

3. To avoid loss of tissue or cells due to expiration of shelf life, healthcare institutions should minimise the quantity of material kept in stock.

4. Cross-border traffic of tissue and cells requires close collaboration with foreign tissue establishments and courier companies as well as clear, detailed protocols.

5. It is recommended that transplanting healthcare institutions record whether, and if so how many corneas are lost due to unforeseen circumstances in order to determine how this loss could be prevented.

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.

Actions and developments following recommendations in the 2013 TRIP report

1. Adverse reactions and events need to be reported as soon as possible after detection and in any case before the closing date for the annual report in order to avoid incomplete analyses and conclusions in the TRIP annual report

   Development: There has been considerable improvement. At the time of writing no late 2014 reports of adverse reactions and events had been submitted after the closing date for this report.

2. Monitoring of reports of bacterial contamination of incubating embryos needs special attention by the Association of Clinical Embryologists and TRIP.

   Development: In 2014 two reports were registered in this category, one case leading to the loss of a complete fertility cycle.

3. The manual preparation of cryopreservation or other additive solutions by the tissue establishments must be carried out with the utmost care and include double check procedures to eliminate errors if they choose not to use commercially available solutions

   Development: No similar reports were registered in 2014. There was however an adverse event concerning a commercially available additive solution that was not validated by the tissue establishment.

4. Cryopreservation equipment needs frequent checking during the cryopreservation run and needs an effective alarm system.

   Development: This type of event was again reported in 2014. This recommendation is therefore still valid.

5. Transplanting healthcare institutions should notify the supplying tissue establishment or organ bank in a timely fashion if there is an adverse reaction or event relating to quality and safety of tissues and cells, so that appropriate actions (quarantine and investigations) can be undertaken.

   Development: This recommendation stays in place; the return of explanted allogeneic tissue with results of investigations (e.g. culture results) initiated by the transplanting institutions is essential.

6. To improve the completeness of application/transplantation data TRIP can collaborate with distributing tissue establishments so that transplanting healthcare institutions are provided with an overview of types of tissues and cells distributed to their facility.

   Development: At the annual inventory of numbers of transplanted or applied tissues and cells and numbers of recipients, all healthcare institutions were surveyed about their need for support in tracing transplanted/applied tissue and cells in their facility. Forty-seven percent replied that they did not need support and were able to inventory all tissues and cells. Thirty-eight percent would appreciate support whether or not on request.

Chapter 1. Reports to TRIP

1.1 Reports in 2014

Regarding reporting year 2014 there were 89 reports of adverse reactions and events related to human tissues and cells. The closing date for inclusion in the annual Biovigilance report 2014 and EU overview was 1 April 2015. Out of the total 29 reports (33%) were assessed as serious and included in the overview for the European Commission.

There has been a drop in the number of serious reports since 2013. This is mainly due to an adjustment in the European assessment criteria for serious adverse events regarding assisted reproductive technologies. Only the loss of a complete fertility cycle is assessed as serious whereas prior to 2013 a seriously reduced chance of pregnancy in a cycle due to loss of gametes, embryos or gonadal tissue was assessed as serious. Figure 1 shows the number of registered reports over the years, subdivided in serious and non-serious reports.

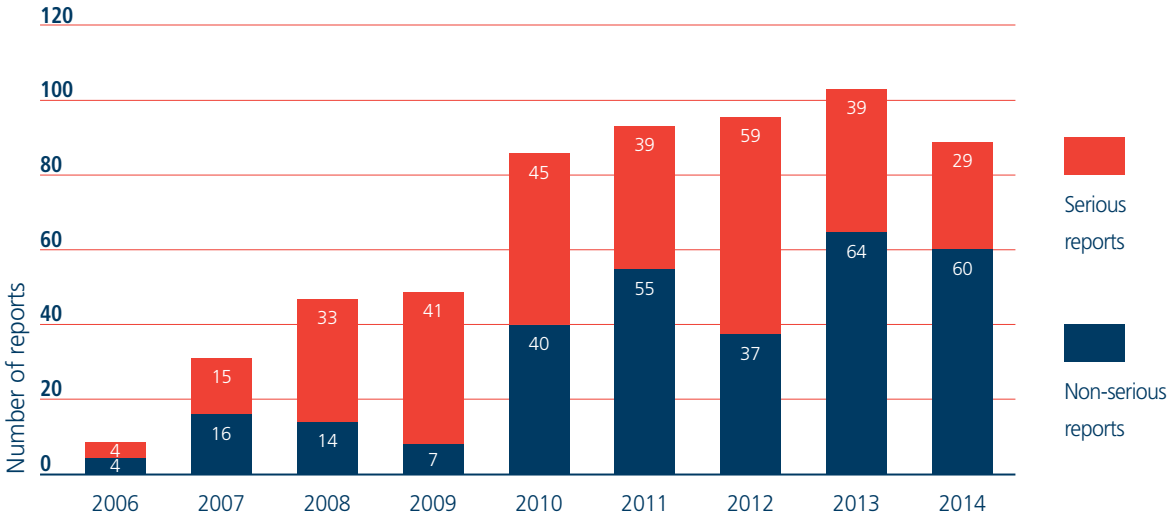

Figure 1. Reports to TRIP, 2006-2014

Table 1 gives an overview of the number of serious and non-serious reports in 2014 broken down by type of tissue or cells.

Table 1. Reports per type tissues and cells in 2014

	Total	Non-serious	Serious
Gametes, embryos and gonadal tissue	45	28	17
Hematopoietic stem cells and therapeutic cells	13	10	3
Bone and other musculoskeletal tissue	13	7	6
Skin	9	8	1
Ocular tissue	7	6	1
Cardiovascular tissue	2	1	1
Other tissue and cells	0	0	0
Total	**89**	**60**	**29**

Regarding reporting year 2013, a large number of reports (22) were submitted after the closing date. Many adverse events and reactions were submitted following the annual TRIP letter announcing the closing of the reporting year. Often reporters submit their adverse reactions and events for the entire year in one go. This is an undesirable situation leading to incomplete annual analyses. Also, serious adverse reactions and events cannot be included in the annual overview to the European Commission till the following year. In 2013 TRIP made a recommendation about late reporting and reporters were personally contacted regarding timely reporting. At the time of writing this annual report there were no late submissions about 2014. It could however still happen. Figure 2 shows the number of late reports per reporting year in the past eight years.

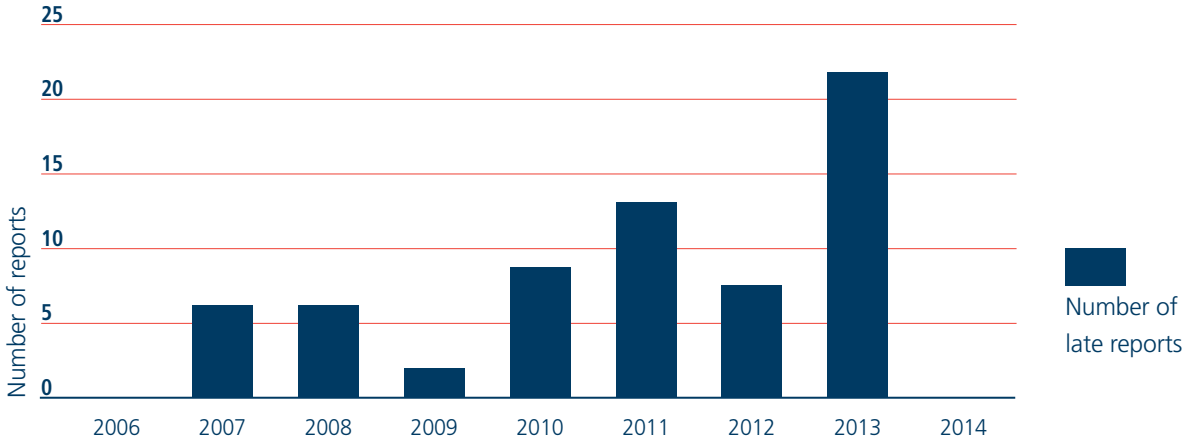

Figure 2. Number of late reports, 2006-2014

1.2 Late 2013 reports

After the closing date for the 2013 Biovigilance report another 22 reports were submitted, of which seven were serious. The total number of 2013 reports came to 103. All late reports have been included in the relevant figures and tables in this report and are also described in the chapters of specific tissue and cell types. Table 2 shows an overview of the late 2013 reports broken down per tissue and cell type.

Table 2. Overview of late 2013 reports per type of tissue or cells

	Total	Non-serious	Serious
Gametes, embryos en gonadal tissue	15	11	4
Hematopoietic stem cells and therapeutic cells	6	4	2
Bone and other musculoskeletal tissue	0	0	0
Skin	1	0	1
Ocular tissue	0	0	0
Cardiovascular tissue	0	0	0
Other tissue and cells	0	0	0
Total	**22**	**15**	**7**

1.3 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 (see Chapter 1.4).

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. 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.

1.4 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 so that 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. The Healthcare Inspectorate has a definition for a calamity (see Annex 3) and has specific procedures for this.

Chapter 2. Tissues and cells

In this chapter the processing/distribution and application data are presented per type of human tissue and cells. The 2014 reports and late 2013 reports for each type are discussed and analysed.

2.1 Gametes, embryos and gonadal tissue

Sometimes assisted reproductive technologies are needed to enable a woman to conceive. Three well-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 The Netherlands 13 laboratories (tissue establishments) perform IVF and ICSI treatment. They may also process gametes from patients treated in other clinics (so-called transport clinics). There are 61 licensed tissue establishments 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.

2.1.1 Processing, distribution and application

Tables 3 and 4 present the numbers of units of reproductive cells 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 difference 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 3. Processing and distribution of gametes, embryos and gonadal tissue in 2014

Cell/tissue type	No. of tissue establish-ments	Processed	Distributed in					
			Unit	NL onsite clinic	NL trans-port clinic	EU	Non EU	Total
Partner semen, fresh	74	36438	Donation	31651	0	47	0	31698
Partner semen, cryopreserved	17	2280	Straw	1443	276	361	0	2080
Donor semen, fresh	9	139	Donation	87	0	0	0	87
Donor semen, cryopreserved	16	5981	Straw	10217	276	791	0	11284
Partner semen MESA/PESA/ TESE, fresh	8	336	Aspiration or biopsy	79	0	0	0	79
Partner semen MESA/ PESA/ TESE, cryopreserved	9	588	Straw or biopsy	640	43	161	3	847
Donor semen MESA/ PESA/ TESE, fresh	0	0	Aspiration or biopsy	0	0	0	0	0
Donor semen MESA/PESA/ TESE, cryopreserved	1	1	Straw or biopsy	1	0	0	0	1
Oocytes, fresh	14	114357	Oocyte	109381	0	2314	0	111695
Oocytes, cryopreserved	11	2861	Oocyte	469	0	11	0	480
Oocytes for donation, fresh	13	2008	Oocyte	858	0	741	0	1599
Oocytes for donation, cryopreserved	2	246	Oocyte	108	0	0	0	108
Embryos, fresh	14	40833	Embryo	17681	0	0	0	17681
Embryos, cryopreserved	14	24004	Embryo	15197	19	27	0	15243
Embryos for donation, fresh	1	7	Embryo	7	0	0	0	7
Embryos for donation, cryopreserved	3	217	Embryo	63	8	0	0	71
Ovarian tissue	4	84	Transplant	13	0	0	0	13
Testicular tissue	2	17	Transplant	0	0	0	0	0

Table 4. Application of gametes, embryos and gonadal tissue in 2014

Cell/tissue type	Hospitals/ clinics	Recipients	Applications				
			Unit	From onsite lab	From NL	From EU	From non-EU	Total
Partner semen, fresh	75	10304	Donation	22745	228	0	0	22973
Partner semen, cryopreserved	18	147	Straw	1442	1077	368	0	2887
Donor semen, fresh	9	37	Donation	92	0	0	0	92
Donor semen, cryopreserved	15	2601	Straw	14454	798	556	0	15808
Embryos, fresh	14	9622	Embryo	14129	0	0	0	14129
Embryos, cryopreserved	14	6526	Embryo	11144	8	0	0	11152
Embryos for donation, fresh	1	6	Embryo	7	0	0	0	7
Embryos for donation, cryopreserved	2	37	Embryo	49	0	0	0	49
Ovarian tissue	1	2	Straw	13	0	0	0	13
Testicular tissue	0	0	Straw	0	0	0	0	0

Compared to previous years there is a remarkable increase of insemination with donor semen (42%) and a small decrease of insemination with fresh partner semen (10%). In 2014 there were fewer fresh (autologous) embryo transfers compared to 2012 and 2013. The number of donated embryo transfers was about the same.

2.1.2 Reports to TRIP

In 2014 TRIP registered 45 reports relating to procedures or application of gametes, embryos and/or gonadal tissue in assisted reproductive technologies. These represent, as in previous reporting years, half of all reports to TRIP. There were 44 adverse events, of which 16 were assessed as serious, and one serious adverse reaction. Table 5 shows the number of submitted 2014 reports and late 2013 reports in relation to the type of fertility laboratory.

Table 5. Overview of 2014 and late 2013 reports per type of fertility laboratory

Fertility laboratory	Number in NL	Reports submitted by	Number of 2014 reports	Number of late 2013 reports
13 IVF laboratories and 1 IVF preparatory lab	14	13 (93%)*	34	10
Semen laboratory	61	7 (11%)	10	5
Total	**75**	**20 (27%)**	**44**	**15**

** 1 IVF laboratory did not submit any reports*

Adverse reactions

There was one adverse reaction in the category post-transplantation bacterial infection. After IUI the patient developed acute salpingitis that led to laparoscopy. Adverse reactions in assisted reproductive technologies are seldom reported. In the past seven years there have been only three reports of adverse reactions.

Adverse events

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 adapted 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 lead 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 current Dutch Association of Clinical Embryologists (KLEM) guideline was followed for assessing the severity of an adverse event. The loss of reproductive tissues or cells was formerly assessed 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 6 shows the total number of reports alongside the numbers assessed as serious according to the new EU guidance and according to the clinical embryologists' guideline respectively. A revision of the clinical embryologists' guideline to implement the EU criteria is being prepared.

Table 6. Overview of adverse events concerning gametes, embryos and gonadal tissue in 2014

Tissue/cell type	Category of event	Total	Serious according to KLEM*	Serious according to EU**
Semen	Loss of tissues and cells	1	0	0
	Congenital malformation	0	0	0
	Incorrect product transplanted	2	2	2
	Other incident	8	1	1
	Bacterial contamination of product	1	1	1
Oocytes	Loss of tissues and cells	11	11	6
Semen and oocytes	Loss of tissues and cells	2	1	1
Embryos	Loss of tissues and cells	17	12	5
	Other incident	1	0	0
	Bacterial contamination of product	1	0	0
Total		**44**	**28**	**16**

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

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

In Figure 3 the registered reports in the period 2007-2014 are shown with serious reports according to the new EU criteria and according to the current Dutch Association of Clinical Embryologists' guideline.

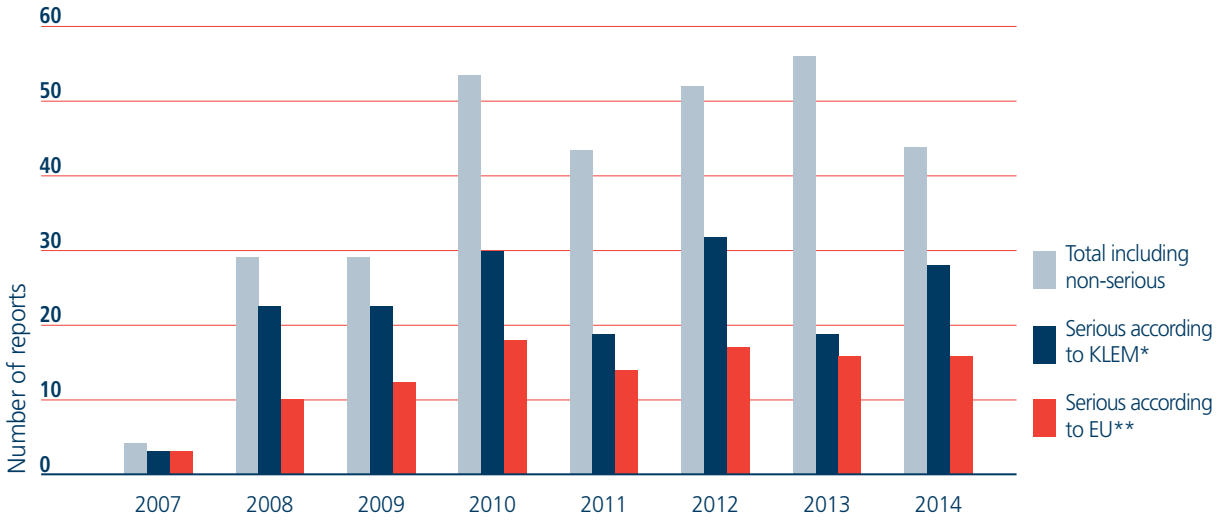

Figure 3. Number of reports of adverse events concerning gametes, embryos and gonadal tissue, 2007-2014

* *Serious according to the Dutch Association of Clinical Embryologists' guideline (KLEM): greatly 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 4 presents an overview of numbers and types of adverse event per cell or tissue type in 2014. As in previous years the category loss of tissues or cells represents the largest number of reported adverse events.

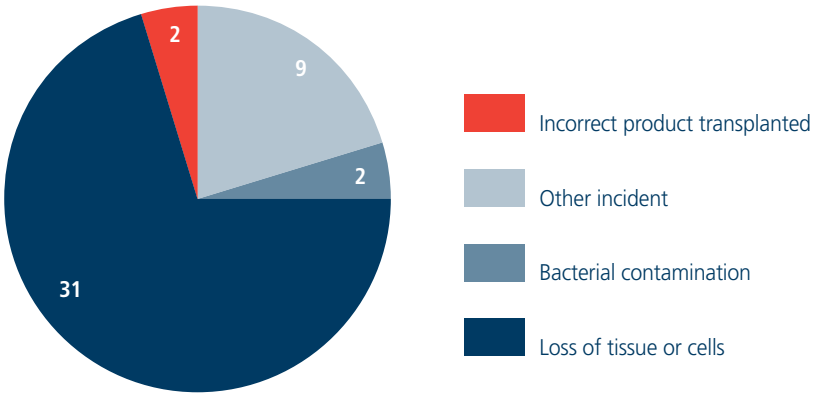

Figure 4. Reports concerning gametes, embryos and gonadal tissue per category of event in 2014

Loss of tissues or cells

In the period 2007-2014 the percentage of adverse events that was registered in the category loss of tissues or cells varied from 54% to 81% (2014: 69%). Loss of tissues or cells has serious consequences when it concerns reproductive tissues for fertility preservation or when a complete fertility cycle is lost. Table 7 presents a summary of adverse events in the category of loss of reproductive tissues or cells in 2014, broken down according to the type of error.

Table 7. Reports in category loss of tissues or cells concerning gametes, embryos and gonadal tissue in 2014

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Processing error	20	Retrieval	Oocytes	7 out of 11 oocytes degenerated due to failure to turn on the warming plate for follicles
		Insemination	Oocytes	1 out of 11 oocytes not inseminated
				10 out of 17 oocytes not inseminated
				Dish knocked: 4 out of 13 oocytes lost
				Single available oocyte lost due to error while drawing up processing solution
		Processing	Embryos	12 embryos discarded due to failure to transfer to another dish
			Oocytes	Dish knocked: 8 out of 16 injected oocytes lost
			Embryos	3 cryo-embryos lost due to error while using pipette
			Oocyte	1 out of 2 oocytes for ICSI lost by knocking dish
			Embryo	Loss of embryo from oocyte donor due to knocking pipette
			Oocyte	Injected oocyte not transferred to dish
			Embryos	6 oocytes not transferred to next dish
			Embryo	Pipette containing 1 embryo knocked and shattered
			Embryos	2 out of 5 embryos lost due to knocking pipette that had a label which was too large
		Incubation	Oocytes	Dish containing 4 (out of 7) oocytes thrown away in error
		PGD analysis	Embryos	1 out of 2 embryos lost while performing biopsy for preimplantation genetic diagnosis
		Cryopreservation	Embryos	1 out of 4 cryo-embryos not transferred to storage container
				Embryos from 4 couples cryopreserved without adding DMSO: 11 embryos degenerated
		Thawing	Embryos	Loss of only cryopreserved embryo, came into contact with mineral oil during thawing and was no longer to be found
				Embryos of two patients placed in same dish during thawing
Technical error	3	Semen processing	Semen	Semen tube shattered during centrifugation for IUI
		Retrieval	Oocytes	Transportation box for oocytes heated up to 48 ^{0}C: all oocytes lost.
		Transfer	Embryo	Pipette not airtight: 1 embryo lost
Assessment error	2	Cryopreservation	Embryo	Erroneously embryo with 3 pronuclei (PN) cryo-preserved together with good quality embryos
		Incubation	Embryo	Embryo incorrectly assessed as 3 PN (abnormal) instead of 2 PN
Identification error	1	Insemination	Oocytes/semen	Incorrect semen added. Complete fertility cycle lost
Selection error	1	Incubation	Oocyte	During assessment of fertilisation the only ferstilised oocyte was thrown away
Other error	4	Processing	Oocytes	After removal of surrounding cumulus cells all oocytes for ICSI proved to have degenerated
		Embryo transfer	Embryos	Transfer catheter bent: 2 embryos lost
		Distribution	Embryo	Twice a good quality 2PN embryo not found after incubation

The category loss of tissues of cells in reproductive cells has been numerically by far the largest year by year as shown in Figures 4 and 5. This can be explained by the large number of assisted reproductive technology procedures that are carried out annually as well as the good reporting discipline displayed by the clinical embryologists. The Association of Clinical Embryologists is the only professional body in the field of tissues and cells in The Netherlands that has implemented a guideline for the reporting of serious adverse reactions and events. Forgetting or omitting to carry out an action led in seven cases (29%) to complete or partial loss of a fertility cycle. In six reports the knocking of a dish or pipette was the cause of loss of reproductive tissues or cells. This cause cannot be completely eliminated as the process of IVF and ICSI involves multiple manual actions. In two cases there were mix-ups of semen and cryopreserved embryos respectively. A mix-up of reproductive tissue and cells is considered by both the EU directive and the Association of Clinical Embryologists' guideline to be a serious adverse event. In Chapter 3 the serious reports over the past five years are discussed in relation to the number of treatment cycles.

Table 8 gives an overview of late 2013 reports in the category loss of tissues or cells.

Table 8. Late 2013 reports in category loss of tissues or cells

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Processing error	4	Incubation	Oocytes	7 out of 14 oocytes erroneously not transferred to incubator
		Cryopreservation	Embryo	1 out of 6 embryos lost due to knocking of pipette
		Insemination	Oocytes	8 out of 12 oocytes not inseminated
		Incubation	Oocytes	The only 3 available fertilised oocytes placed in incorrect dish and thrown away
Technical error	1	Cryopreservation	Embryos	Stagnation of N_2 supply during cryopreservation led to loss of 14 embryos from 4 couples
Administrative error	1	Thawing	Embryos	Mix-up of cryopreservation papers of 2 couples, mix-up of embryos not ruled out therefore embryos destroyed

Figure 5 shows an overview of the category of loss of tissues and cells in the period 2007-2014.

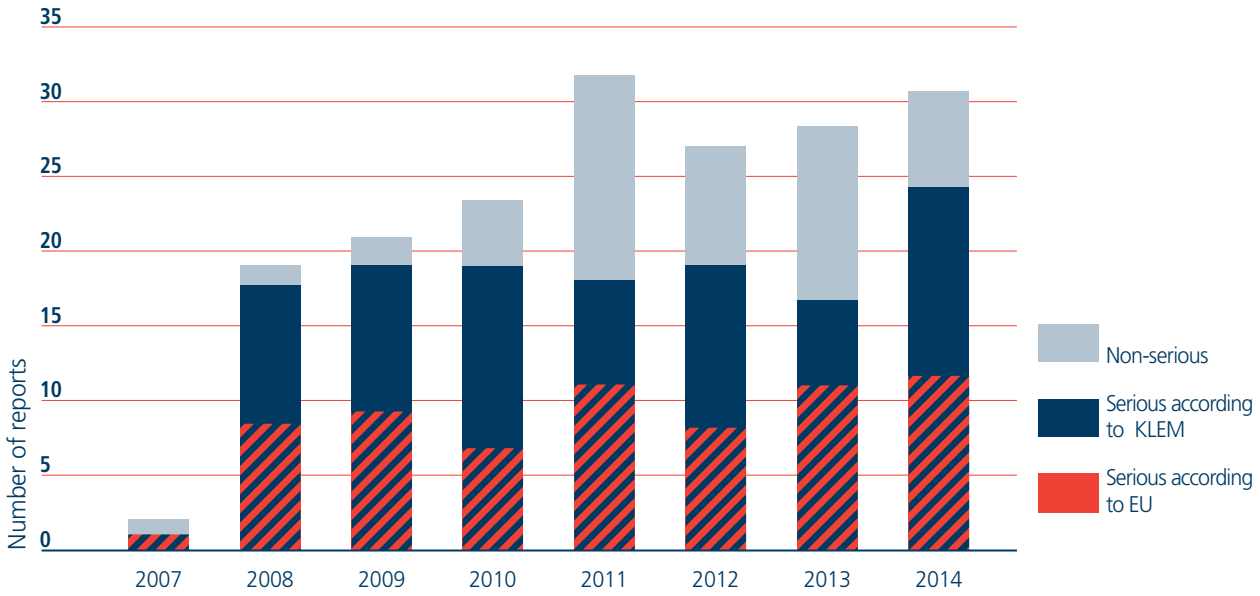

Figure 5. Reports of loss of reproductive tissues or cells, 2007-2014

Other incident

The category 'other incident' comprised mainly adverse events that led to possible loss of quality or volume of reproductive tissues or cells and events where a different procedure was carried out from the planned one. The annual percentage of adverse event reports in this category varied from 8 to 27%. In 2014 nine reports of other incidents were received, of which one was serious. Table 9 offers short descriptions of other incident reports in 2014.

Table 9. Reports of other incidents concerning gametes, embryos and gonadal tissue in 2014

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Storage error	3	Donation	Partner semen	2x semen for IUI collected in container that was past expiry date
		Storage	Donor semen	Straw of donor semen lost in storage container leading to delay of insemination
Processing error	2	Testing	Partner semen	Different tube used for semen analysis: shattered during spinning
		Distribution	Donor semen	Advised limit (25) of children per semen donor exceeded in 15 donors due to failure to allow for future requests for siblings from the same semen donor.
Administrative error	2	Donation	Partner semen	Container for semen provided without batch number
		Storage	Donor semen	Excel list not updated after relocating straws to another storage container
Communication error	1	Processing semen	Partner semen	Low semen count communicated for incorrect patient. Timely correction of error
Technical error	1	Cryopreservation	Embryos	Power cut led to disruption and restart of cryo-preservation run. Embryos thawed, possible quality loss of embryos

In addition there were seven late 2013 reports of other incident that are summarised in Table 10.

Table 10. Late 2013 reports of other incidents concerning gametes, embryos and gonadal tissue

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Administrative error	3	Distribution	Semen donor	2x administrative error in donor details of semen straws
		Storage	Semen donor	Administrative error in location in storage container (corrected)
Storage error	2	Storage	Semen donor	2x donor semen straw lost, eventually found at bottom of storage container
Technical error	2	All steps	Gametes and embryos	Power cut in lab. Timely switch to emergency power supply
		Incubation	Oocytes	pH of fertilisation solution too high due to stagnating gas flow and condensation

Figure 6 provides an overview of the number of reports of other incidents in the period 2008-2014.

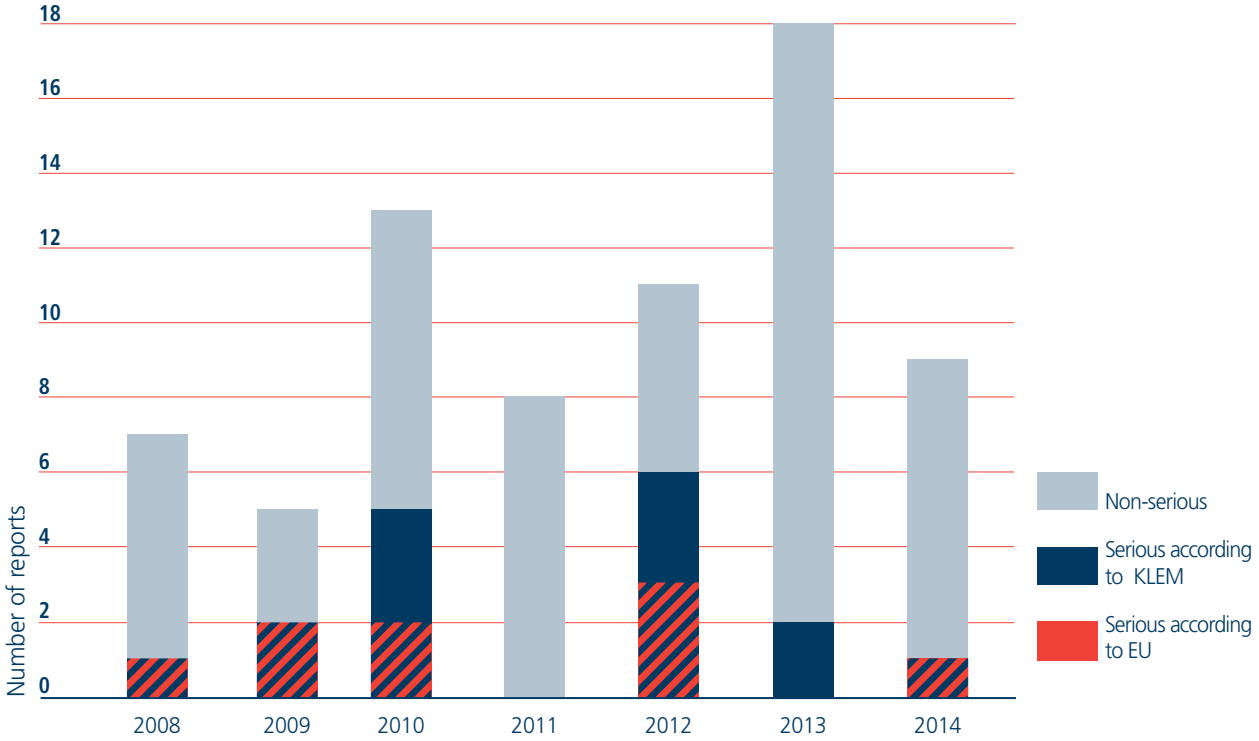

Figure 6. Reports of other incident concerning gametes, embryos and gonadal tissue, 2008-2014

The majority of reports concern (possible) loss of quality of reproductive tissues and cells. Another large part involved administrative errors or communication errors.

Near miss

In contrast to previous reporting years there were no reports of near miss relating to reproductive tissues and cells in 2014. The annual percentage of near miss events has varied from 4 to 10% (Figure 7). This category is comprised of mix-ups or other errors that, if undetected, could have led to transfer of embryo(s) or insemination of an incorrect recipient.

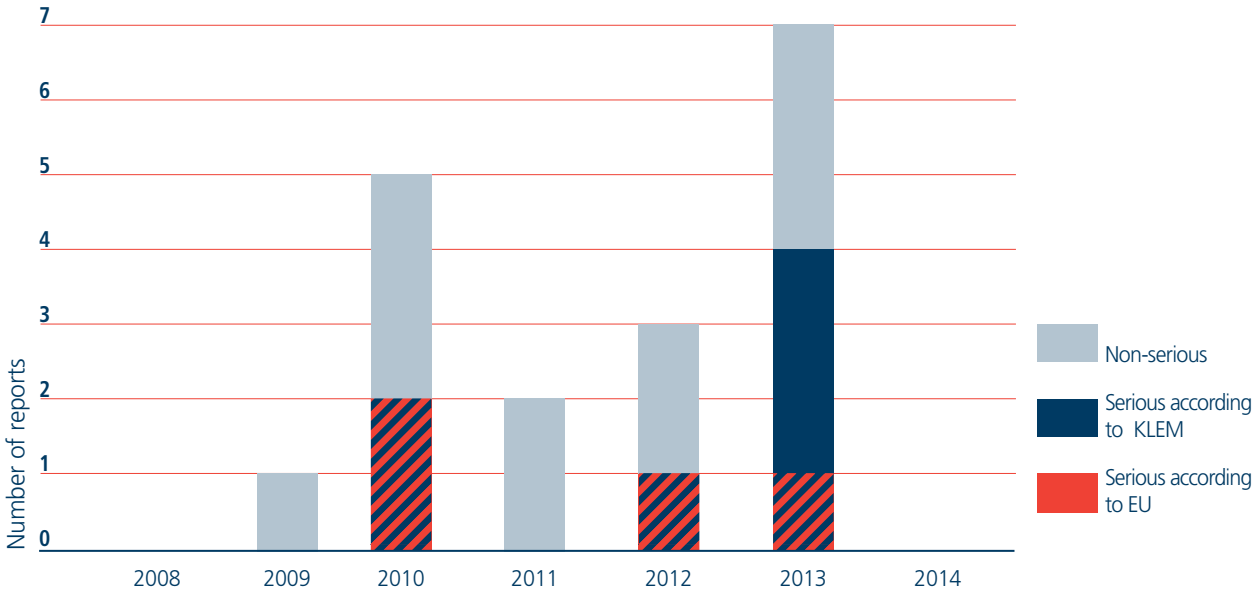

Figure 7. Reports of near misses concerning gametes, embryos and gonadal tissue, 2008-2014

Bacterial contamination

There were two reports in the category of bacterial contamination of product in 2014 that are summarised in Table 11. One report was serious due to the complete loss of a fertility cycle.

Table 11. Reports of bacterial contamination concerning gametes, embryos and gonadal tissue in 2014

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Other error	2	Insemination	Oocytes	Fertilisation failed and part of oocytes degenerated due to urinary tract infection in partner (enterococci and Pseudomonas)
		Transplantation	Embryo	Embryo culture contaminated by Proteus mirabilis, also detected in the partner semen. All cryo-preserved embryos lost

The numbers of reports of bacterial contamination in the period 2008-2014 are shown in Figure 8.

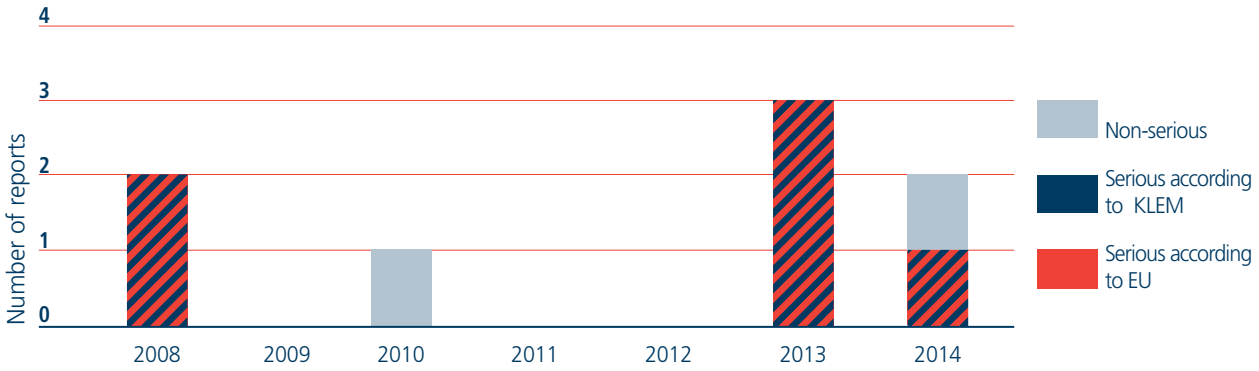

Figure 8. Reports of bacterial contamination concerning gametes, embryos and gonadal tissue, 2008-2014

Incorrect product transplanted

In 2014 there were two reports of transplanting/applying an incorrect product. One of the late 2013 reports came into the same category. This type of report is always assessed as serious. The reports are summarised in Table 12.

Table 12. Reports of incorrect product transplanted concerning gametes, embryos and gonadal tissue in 2014 and late 2013 reports

Type of error	Number of reports	Step in procedure	Type of gamete or embryo	Description
Identification error	1	Transplantation	Partner semen	Semen from incorrect partner inseminated
Communication error	1	Storage	Donor semen	Donor from EU member state found to be carrier of spinal muscular atrophy (SMA), failure to inform semen bank
2013 Identification error	1	Transplantation	Partner semen	Semen from incorrect partner inseminated

Figure 9 gives an overview of reports of incorrect product transplanted in the period 2008-2014.

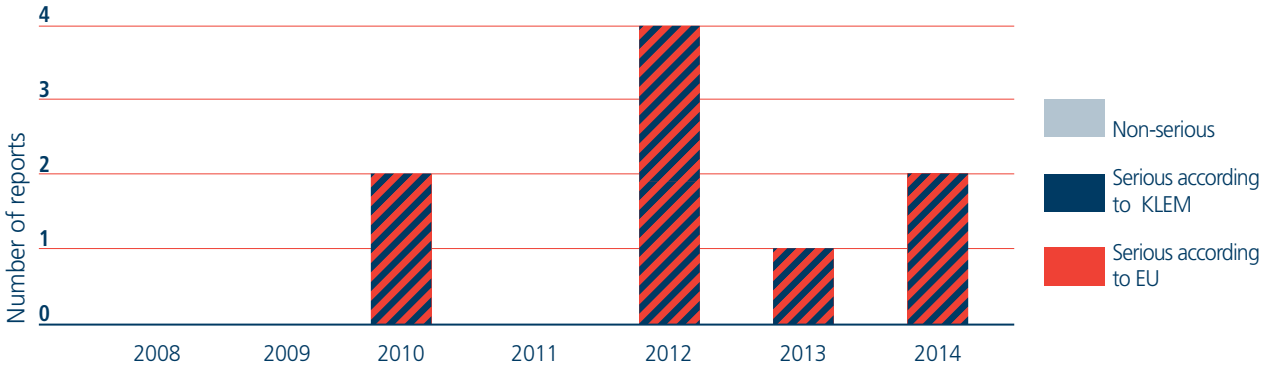

Figure 9. Reports of category incorrect product transplanted, 2008-2014

Congenital malformation

In reporting year 2014 there were no reports in the category of congenital malformation. Figure 10 presents an overview of this category in the period 2007-2014.

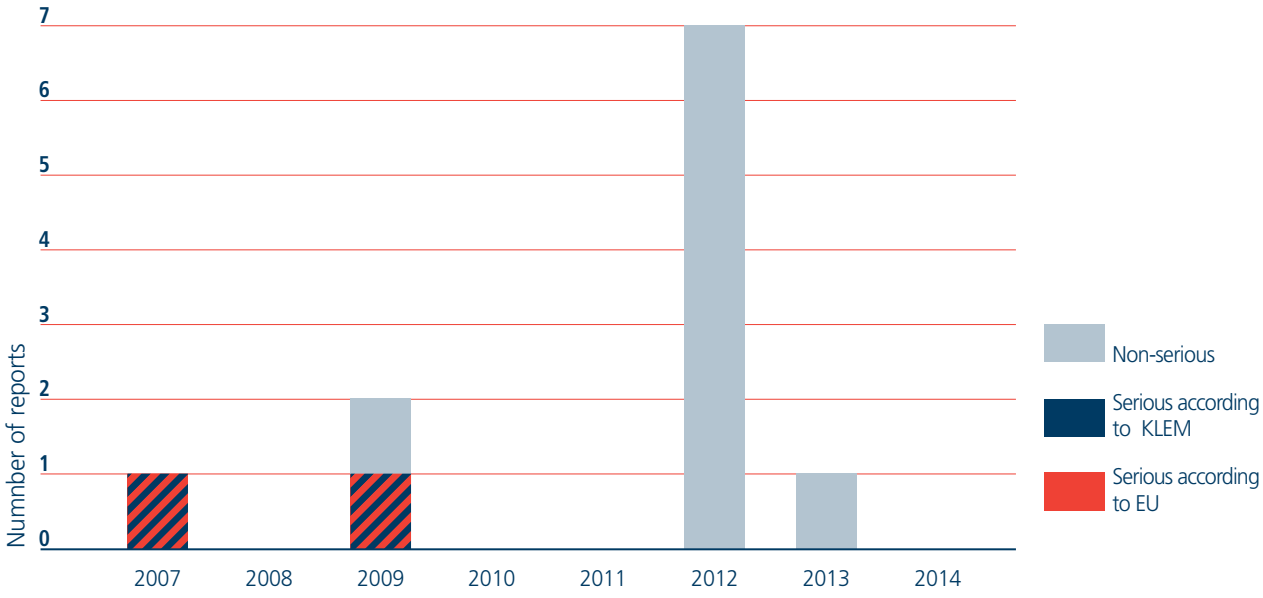

Figure 10. Reports of congenital malformation, 2007-2014

A pregnancy involving donated gametes or embryos (that are not derived 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 when a genetic abnormality is found in a donor (non partner) after donation of gametes or embryos.

In 2012 seven non-serious adverse events were submitted in the category of congenital malformation. They all involved a congenital malformation in a fetus or new-born that could not be related to the semen donor. Two serious reports in 2007 and 2009 concerned a baby with Spinal Muscular Atrophy (SMA) and a balanced translocation after use of donor semen that could have implications for the progeny of the child.

2.2 Hematopoietic stem cells and therapeutic cells

Hematopoietic stem cells (HPSC) can be transplanted into patients whose own blood production system needs replacing. The HPSC 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 HPSC 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 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 HPSC from autologous and related donors. Stem cell products from unrelated donors (including cord blood) are distributed by Europdonor Foundation (from January 2016: Matchis) to the eight academic transplant centres for specific recipients, usually via the stem cell laboratory. Unrelated stem cell transplants for Dutch patients usually derive from foreign volunteer donors (97% in 2014, see Table 15). In collaboration with Sanquin, Europdonor Foundation 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 Europdonor Foundation to foreign transplantation centres. In The Netherlands there is one public 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.

2.2.1 Processing, distribution and application

In Tables 13, 14 and 15 the figures for processing, distribution and transplantation of hematopoietic stem cells (HPSC) and therapeutic cells are presented with the number of institutions performing each activity.

Table 13. Processing of hematopoietic stem cells and therapeutic cells in 2014

Type of cells	No. of tissue establishments	Processed transplants or units			
		From NL	From EU	From outside EU	Total
HPSC unrelated					
Bone marrow	1	8	34	3	45
PBSC	6	125	150	19	294
Cord blood	4	205	59	20	284
HPSC related					
Bone marrow	5	29	0	0	29
PBSC	7	200	0	0	200
Cord blood	2	7	0	0	7
HPSC autologous					
Bone marrow	4	20	0	0	20
PBSC	10	2948	0	0	2948
Cord blood	2	461	7944	3728	12133
Therapeutic cells					
Mesenchymal stem cells, unrelated	4	27	0	0	27
Mesenchymal stem cells, autologous	1	2	0	0	2
Lymphocytes (DLI), unrelated	4	85	5	2	92
Lymphocytes (DLI), related	6	80	0	0	80
Dendritic cells, unrelated	1	1	0	0	1
Dendritic cells, related	1	3	0	0	3
Dendritic cells, autologous	2	52	0	0	52
Natural Killer cells, unrelated	2	2	0	0	2
Granulocytes, unrelated	1	6	0	0	6
Granulocytes, related	1	2	0	0	0
Granulocytes, autologous	1	20	0	0	20
TC-Til cells, autologous	1	7	0	0	7
Leucocytes, autologous	1	4	35	0	39

Table 14. Distribution of hematopoietic stem cells and therapeutic cells in 2014

Type of cells	No. of tissue establishments	Distributed units			
		In NL	In EU	Outside EU	Total
HPSC unrelated					
Bone marrow	1	41	1	2	44
PBSC	6	268	11	0	279
Cord blood	4	87	1	3	91
HPSC related					
Bone marrow	5	27	0	0	27
PBSC	7	206	0	0	206
Cord blood	2	1	0	0	1
HPSC autologous					
Bone marrow	4	17	0	0	17
PBSC	10	3394	0	0	3394
Cord blood	2	0	0	1	1
Therapeutic cells					
Mesenchymal stem cells, unrelated	4	121	16	2	139
Mesenchymal stem cells, autologous	1	2	0	0	2
Lymphocytes (DLI), unrelated	4	62	0	0	62
Lymphocytes (DLI), related	6	68	0	0	68
Dendritic cells, unrelated	1	3	0	0	3
Dendritic cells, related	1	9	0	0	9
Dendritic cells, autologous	2	55	0	0	55
Natural Killer cells, unrelated	2	4	0	0	4
Granulocytes, unrelated	1	6	0	0	6
Granulocytes, related	1	2	0	0	2
Granulocytes, autologous	1	20	0	0	20
TC-Til cells, autologous	1	4	0	0	4
Leucocytes, autologous	1	7	34	0	41

Table 15. Transplantation of hematopoietic stem cells and therapeutic cells in 2014

Type of cells	Transplant centres	Recipients	Transplanted units			
			From NL	From EU	From non EU	Total
HPSC unrelated						
Bone marrow	7	29	1	30	2	33
PBSC	8	269	11	236	34	281
Cord blood	6	55	2	64	19	101
HPSC related						
Bone marrow	5	29	29	0	0	29
PBSC	8	181	215	0	0	215
Cord blood	1	1	1	0	0	1
HPSC autologous						
Bone marrow	4	11	17	0	0	17
PBSC	11	711	2405	0	0	2405
Cord blood	0	0	0	0	0	0
Therapeutic cells						
Mesenchymal stem cells, unrelated	3	71	118	16	2	136
Mesenchymal stem cells, autologous	1	2	2	0	0	2
Lymphocytes (DLI), unrelated	4	50	2	53	7	62
Lymphocytes (DLI), related	5	55	66	0	0	66
Dendritic cells, unrelated	1	1	3	0	0	3
Dendritic cells, related	1	3	9	0	0	9
Dendritic cells, autologous	2	47	55	0	0	55
Natural Killer cells, unrelated	2	2	4	0	0	4
Granulocytes, unrelated	1	1	6	0	0	6
Granulocytes, related	1	1	2	0	0	2
Granulocytes, autologous	1	20	20	0	0	20
TC-Til cells, autologous	1	4	4	0	0	4
Leukocytes, autologous	1	13	3	33	0	36

There is a remarkable drop in the number of autologous bone marrow transplants. The number of recipients dropped from 41 (2012) and 56 (2013) to 11 in 2014. There is an increasing preference for harvesting autologous stem cells by an apheresis procedure. The total number of autologous stem cell transplants increased slightly from 659 (2012) and 596 (2013) to 711 in 2014.

2.2.2 Reports

In 2014 there were thirteen reports of adverse reactions and events concerning hematopoietic stem cells and therapeutic cells. Figure 11 presents the registered reports in the period 2007-2014. The number of hematopoietic stem cells reports halved compared to 2013. In particular there were no serious adverse events. In previous years leaking units were assessed to be 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.

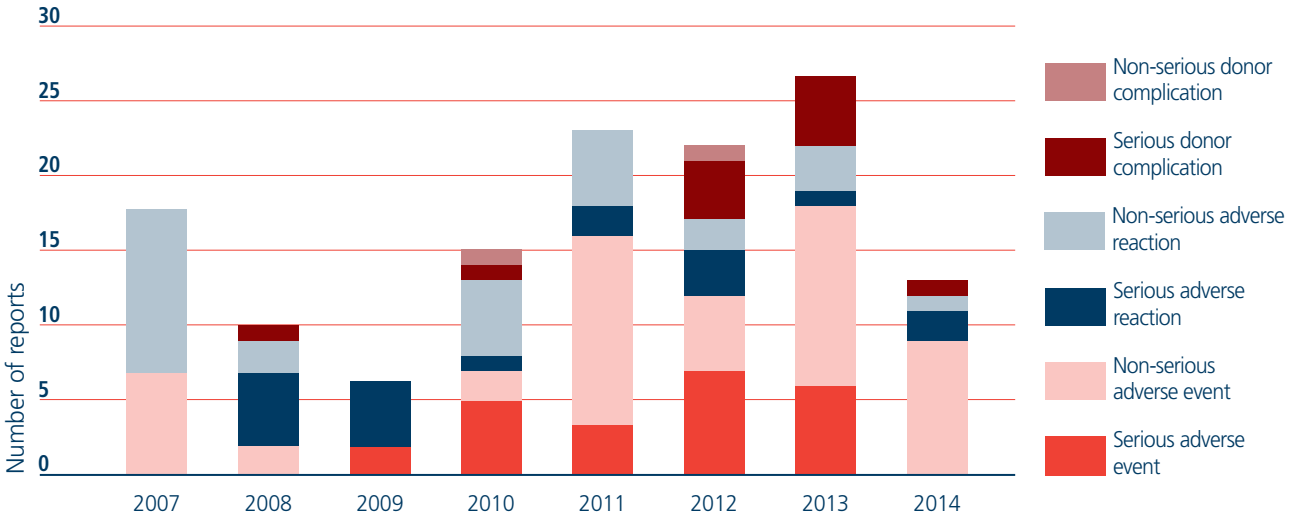

Figure 11. Reports concerning HPSC and therapeutic cells, 2007-2014

The reports in 2014 concerned nine adverse events (all non-serious) and four adverse reactions that included two serious adverse reactions in recipients and one serious reaction in a donor. The adverse events, subdivided according to type of HPSC, are summarized in Table 16.

Table 16. Overview of adverse event per type of HPSC or therapeutic cells in 2014

Type	Adverse event	Number
Peripheral blood stem cells (PBSC), autologous	Loss of tissues or cells	
	• Ruptured unit at thawing	1
	• Two units ruptured after drop from dryshipper	1
	Other incident	
	• Apheresis set ruptured after incorrect setup, loss of 150 ml whole blood	1
	• Incorrect seal in stem cell collection bag due to incorrect packaging for sterilisation	1
	• Incorrect access port in stem cell unit used at transplantation. Uncomplicated infusion	1
	Bacterial contamination of product	
	• Streptococcus agalactiae and Staphylococcus aureus after processing, reference sample negative. Uncomplicated Infusion with antibiotic prophylaxis	1
PBSC allogeneic, unrelated	Bacterial contamination of product	
	• Gram positive rods (further specification not possible). Negative recipient blood culture	1
Cord blood allogeneic, unrelated	Bacterial contamination of product	
	• Product from foreign stem cell bank: Staphylococcus epidermidis. Recipient received antibiotic prophylaxis	1
	• Streptococcus agalactiae. In error culture results were only reported after 20 days. Uncomplicated infusion with antibiotic prophylaxis	1
Total		**9**

Among the adverse events in 2014 there was only one case of a leaking unit. This presents a drop compared to previous years. The Stem Cell Laboratory Working Group initiated further investigations into leaking units. Analysis showed that reported cases occurred with various sizes of bags from different manufacturers, different batches

as well as different storage methods (in liquid and vapor phase nitrogen). No trend or common cause could be detected. Figure 12 gives an overview of the reports of leaking units and collection sets for stem cells in the period 2007-2014.

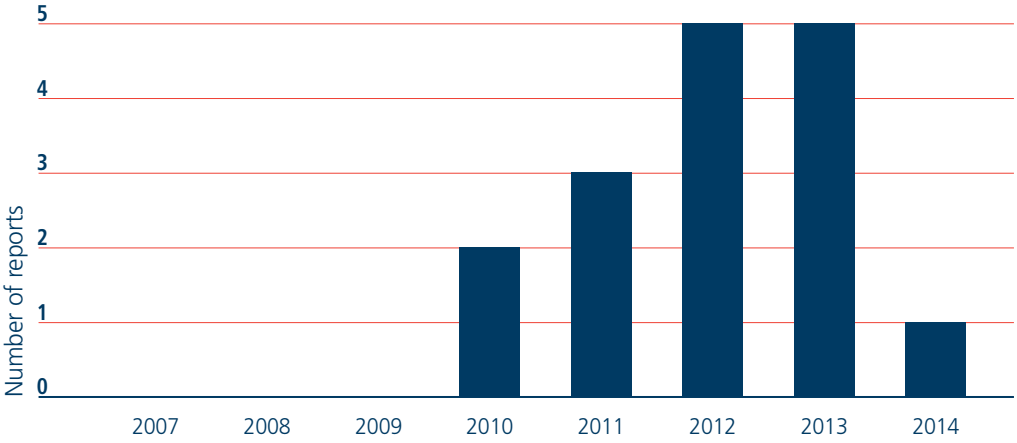

Figure 12. Reports of leaking or ruptured HPSC collection and storage bags, 2007-2014

In Table 17 the four adverse reaction reports are briefly described.

Tabel 17. Overview af adverse reactions per type HPSC or therapeutic cells in 2014

Type of cells	Adverse reaction	Number
Patient, autologous PBSC	Anaphylactic reaction* • Dyspnea and urticaria	1
Patient, allogeneic unrelated PBSC	Anaphylactic reaction • Stridor and erythema during infusion of ABO major incompatible product	1
	Other reaction* • Chest pain during infusion: myocardial infarction	1
Donor, related PBSC	Donor complication* • donor with mild mental retardation visited the emergency department in another hospital after 4th dose of G-CSF complaining of headache and vomiting. Uncomplicated donation procedure the next day. After 1 week increase of dyspnea from pre-existent asthma and radiating pain in leg with pre-existent back pain	1
Total		**4**

* *Serious*

In Table 18 an overview of donor complications reported to TRIP from 2007 to 2014 can be found. These include two donor complications from 2013 and 2014 respectively.

Table 18. Overview of donor complications associated with HPSC, 2007-2014

Type of cells	Number	Donor complication	Interval after donation	Imputability
PBSC, related	5	• Shoulder abcess (S. aureus)	12 days	possible
		• AML	7 years	possible
		• MDS-RAEB	5 years	possible
		• Transient rise of creatinine level	During procedure	probable
		• Benign paroxysmal positional vertigo	Immediate	probable
		• Exacerbation of asthma and back pain	7 days	probable
PBSC, unrelated	4	• Breast carcinoma	2 years	unlikely
		• Phlebitis	?	probable
		• CVA	2 months	unlikely
		• Rheumatoid arthritis	6 years	unlikely
		• Polyarthritis rheumatica	4 years	unlikely
Bone marrow, unrelated	2	• Breast carcinoma	2 years	unlikely
		• TIA	8 months	unlikely
PBSC, autologous	1	• Thrombopenia	During apheresis	certain

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.

2.2.3 Late 2013 reports concerning hematopoietic stem cells and therapeutic cells

After the closing date for the report another six reports were submitted from reporting year 2013: five adverse events and a donor complication. These reports have been included in Figure 11. For the sake of completeness they are summarized in Tables 19 and 20.

Table 19. Overview of late 2013 adverse event reports per type of hematopoietic stem cells and therapeutic cells

Type of cells	Adverse event	Number
PBSC allogeneic, unrelated	Other incident	
	• Unit from foreign bank distributed without removal of spike. Extra bacteriological screening negative	1
	Loss of tissues or cells	
	• Incorrect transportation by courier company (too cold) of transplant to foreign country	1
Bone marrow allogeneic, unrelated	Other incident	
	• Product from foreign bank not properly sealed. Extra bacteriological screening negative	1
	• Product from foreign bank distributed with incomplete and incorrect information on label	1
Donor lymphocytes (DLI)	Bacterial contamination of product	
	• DLI culture at cryopreservation was positive, but sample from thawed product negative. No adverse consequences for patient	1
Total		**5**

Table 20. Overview of late 2013 adverse reaction reports per type of hematopoietic stem cells

Type of cells	Adverse reaction	Number
PBSC allogeneic, unrelated	Donor complication • Polyarthritis rheumatica 4 years after donation	1

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, as filler for 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.

2.3.1 Bone

Processing, distribution and transplantation

In Table 21 the numbers of processed and distributed units of bone are presented. In Table 22 the numbers of bone tissue units are shown with the numbers of recipients. The data were submitted by 20 bone banks, 58 hospitals, three private clinics and 16 oral implantology practices.

Table 21. Processing and distribution of bone tissue in 2014

Type	Tissue-establishments*	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Bone, whole	2	51	Transplant	75	4	0	79
Bone filler, mineralised: chips, blocks and wedges	10	1365	Container	3524	6025	3546	13095
Bone filler, mineralized: whole and half femoral heads	12	4160	Transplant	2351	320	0	2671
Bone filler, demineralised	6	1770	Container	1528	13290	14410	29228
Auditory ossicles	1	47	Transplant	47	0	0	47
Cranial bone (autologous)	6	257	Transplant	174	0	0	174
Other	0	0	Transplant	0	0	0	0

* *Hospital bone banks (including cranial bone banks) and tissue establishments that hold a licence solely for distribution*

Table 22. Application of bone tissue in 2014

Type	Hospitals / clinics / practices	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Bone, whole	14	106	Bone	107	0	0	107
Bone filler, mineralised: chips, blocks and wedges	51	1837	Pack	1373	487	34	1894
Bone filler, mineralized: whole and half femoral heads	49	1453	Bone	1542	0	0	1542
Bone filler, demineralised	18	255	Pack	181	49	25	255
Auditory ossicles	2	17	Bone	3	14	0	17
Cranial bone (autologous)	12	122	Piece	122	1	0	123
Other	2	32	Piece	3	0	29	32

2.3.2 Reports

In 2014 there were eleven reports concerning bone tissue among which there were four serious adverse reactions and two serious adverse events. Figure 13 gives an overview of the number of bone tissue reports in the period 2006-2014. Possibly the rising trend in the number of reports is due to better reporting by the tissue establishments. 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 this period.

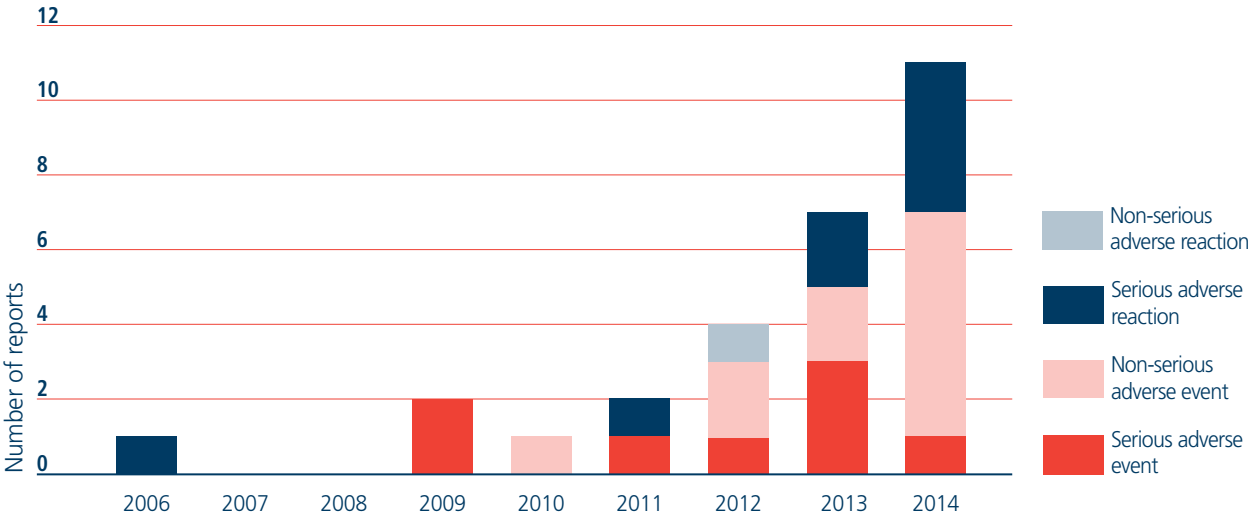

Figure 13. Reports concerning bone, 2006-2014

The reported adverse events and reactions are described briefly in Tables 23 and 24.

Table 23. Overview of adverse events concerning bone in 2014

Category of event	No. of reports	Description
Loss of tissues or cells	2	• Femoral head thawed but not needed
		• Fibula shaft stored in hospital not transplanted before expiry date, destroyed
Other incident	3	• Outer package of bone chips failed bubble leak test after 2 years after passing test at one year. Voluntary recall by TE. No adverse reactions in patients reported
		• Two autologous cranial bone flaps thawed due to failure to close freezer door properly. No fail safe alarm. One bone flap was transplanted without complications. The 2nd bone flap was not transplanted because the patient died.
		• At transplantation of auditory ossicles and temporal fascia in a single operation incorrect lot number recorded. Traceability failure
Risk of transmission of an other (non-infectious) disease/ condition	2	• After transplantation of femoral head the living donor is diagnosed with polycythemia vera (JAK-2 mutation) that was missed at donation. Recipient well and check for JAK-2 mutation negative
		• At the start of living donor procedure for second femoral head it was found that the donor had been treated for melanoma 26 years earlier. First femoral head had already been transplanted, no information available regarding recipient's condition. Transmission risk assessed as low

Tabel 24. Overview of adverse reactions concerning bone in 2014

Reaction	No. of reports	Description
Post-transplantation bacterial infection	1	• Infection (E. coli, E. coli ESBL and enterobacter) after revision surgery of shoulder prosthesis with application of bone tissue from living hip bone donor leading to prolongation of hospital stay and re-operations. Source of infection could not be found
	3	• Three patients developed infections after reimplantation of autologous cranial bone flap for which bone flap had to be removed. In all cases a causal relationship between infection and applied bone flap could neither be proven nor excluded

The largest risk in bone transplantation is transmission of pathogens. In this reporting year there were four reports of bacterial infection after bone transplantation, including three reports that mentioned infection after application of an autologous cranial bone flap and one late 2013 report concerning a similar case. These reports are all serious due to the fact that the patient needed a new operation for removal of the bone flap. In none of these cases could a causal relation with the transplanted tissue be established or excluded. Imputability was assessed as possible with exception of one improbable case where the patient had already had a second operation for a hemorrhage in the affected area before the infection became apparent.

There were two reports where a previous malignancy in the donor should have led to deferral of the donor. One donor failed to report a melanoma diagnosed 26 years previously and the other donor was subsequently diagnosed with a hematological malignancy following an abnormal blood count (thrombocytosis) which not pursued at donation. Both transplant procedures were uncomplicated and the recipients are well. The risk of transmission of a malignancy is assessed to be low. The treating physicians should make a note in the recipients' notes that in the unlikely event of transmission of malignancy in these recipients this should be reported to the tissue establishment and to TRIP.

2.3.2 Cartilage

Processing, distribution and application

In Tables 25 and 26 an overview of numbers of processed/distributed and applied units of cartilage is presented.

Table 25. Processing and distribution of cartilage in 2014

Type of tissues or cells	No. of tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cartilage	2	118	Transplant	120	0	0	120
Chondrocytes	1	235	Transplant	113	120	0	233

Table 26. Application of cartilage in 2014

Type of tissues or cells	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Cartilage	5	137	Transplant	136	1	0	137

Reports

In the reporting year 2014 there were no reports concerning cartilage. Figure 14 provides an overview of cartilage biovigilance reports in the period 2007-2014.

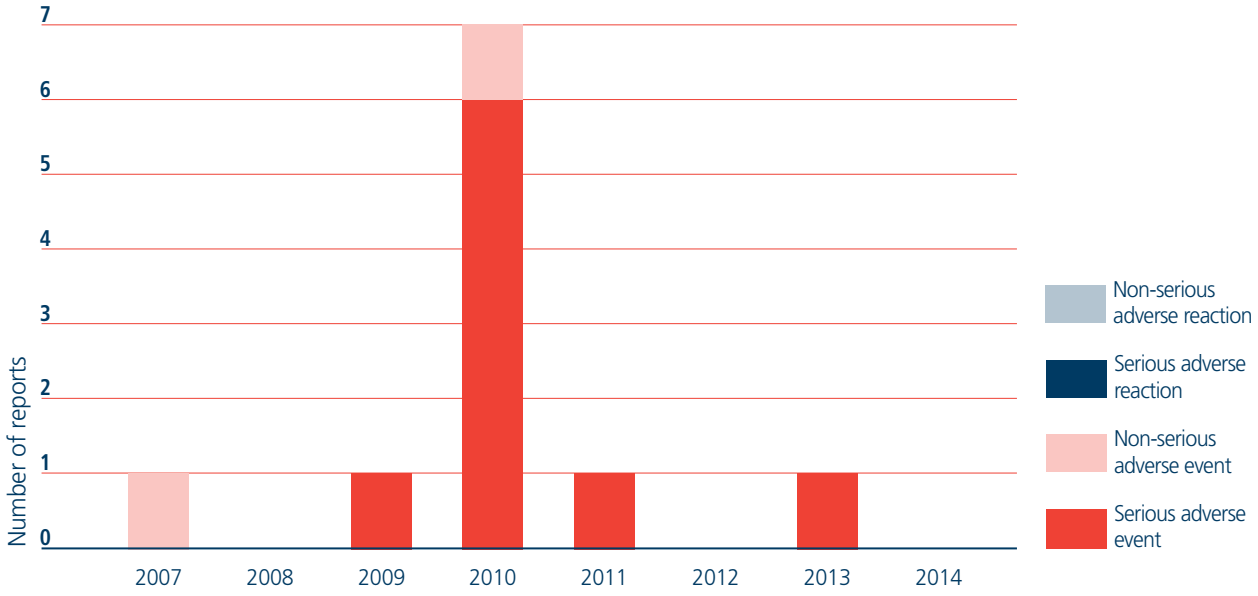

Figure 14. Reports concerning cartilage, 2007-2014

2.3.3 Tendons, ligaments, fascia and menisci

Processing, distribution and application

In Table 27 the data on processing and distribution of tendons, ligaments, fascia and menisci are presented followed by Table 28 with data on application of these tissues.

Table 27. Processing and distribution of tendons, ligaments, fascia and menisci in 2014

Type of tissue	No. of tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Tendons	2	533	Transplant	556	9	0	565
Ligaments and fascia	2	27	Transplant	36	182	0	218
Menisci	0	0	Transplant	0	0	0	0
Other	0	0	Transplant	0	0	0	0

Table 28. Application of tendons, ligaments, fascia and menisci in 2014

Type of tissue	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Tendons	28	287	Transplant	296	0	0	296
Ligaments and fascia	16	394	Transplant	410	21	0	431
Menisci	2	13	Transplant	0	13	0	13
Other	1	3	Transplant	3	0	0	3

Reports

In 2014 two reports regarding tendons were registered. Figure 15 presents an overview of the reports involving tendons in the years 2008-2014.

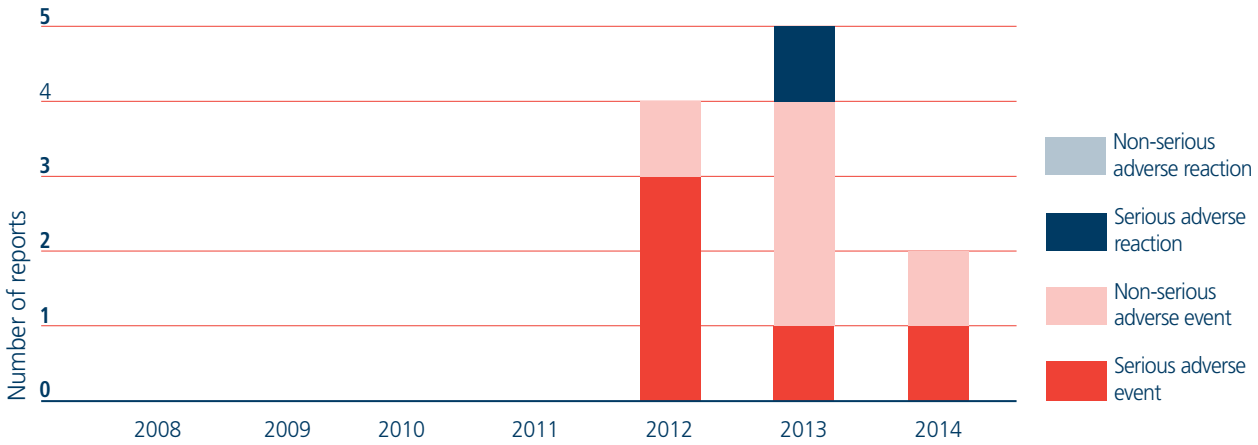

Figure 15. Overview of reports concerning tendons, 2008-2014

With regard to tendons there was one report of loss of tissues or cells and one other incident, briefly described in Table 29.

Tabel 29. Overview adverse events concerning tendons in 2014

Category of event	Reports	Description
Other incident	1	Tibialis anterior tendon at transplant surgery 'snotty' and of varying diameter. Tendon transplant and FU uncomplicated. Transplant procedures using other tendons of the same donor uneventful
Loss of tissues or cells	1	Seven tendons (2x Achilles tendon, 2x tibialis anterior tendon, 2x semitendinosus tendon and a bone-tendon-bone transplant) and 5 femoral heads lost. Freezer for temporary storage in transplanting hospital broke down and failsafe alarm failed (this case included under bone and tendinous tissue in Table 54)

The most noteworthy report regarded the loss of seven tendons and five femoral heads due to the break-down of a freezer and the failure of the failsafe alarm system. This led to the loss of scarce allogeneic tendons. Tissue establishments need a licence for storage of human tissues and cells. The responsibility for temporary storage in applying healthcare institutions is not specifically covered in the Law on safety and quality of substances of human origin. Healthcare institutions should minimize the quantity of tissues stored. In addition healthcare institutions should check their temporay storage facilities in cooperation with suppling tissue establishments and ensure they have a failsafe alarm system for the temperature control as well as adequate protocols.

2.4 Ocular tissue

Two parts of the eye can be transplanted: the cornea and the sclera. A corneal transplant is indicated when visual acuity is impaired due to corneal scarring or an opacity following infection or trauma. Annually around 1000 corneal transplants are carried out in The Netherlands. The shelf life of a cornea is limited: a cornea is in optimal condition 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. These are processed by two eye banks. Corneas and scleras are also exported and imported. The Dutch Society for Ophthalmology maintains a registry of all corneal transplants in The Netherlands.

2.4.1 Processing, distribution and application

In Table 30 the numbers of processed and distributed units of ocular tissue are shown. Table 31 presents the numbers of transplanted ocular tissue units as provided by the contacted hospitals, clinics and independent healthcare institutions. Out of 26 which transplant ocular tissue 24 provided data on transplanted corneas and scleras; this can explain the discrepancy between cornea distribution and transplantation figures. There is a larger discrepancy between distribution and transplantation of sclera. This may be explained by longer storage times for sclera. Sclera is also applied by ophthalmologists that do not perform corneal transplants and they might not be aware of the annual collection of data on applied tissues and the reporting of adverse events and reactions.

Table 30. Processing and distribution of ocular tissue in 2014

Type	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cornea	2	3202	Complete or lamella	1430	206	10	1646
Sclera	1	431	Complete or quadrant	1500	0	0	1500

Table 31. Application of ocular tissue in 2014

Type	Hospitals clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Cornea	17	1277	Complete or lamella	1281	4	0	1285
Sclera	13	972	Complete or quadrant	973	15	0	988

2.4.2 Reports

In 2014 seven adverse events with ocular tissue were reported. In Figure 16 an overview of reports in the period 2007-2014 is shown.

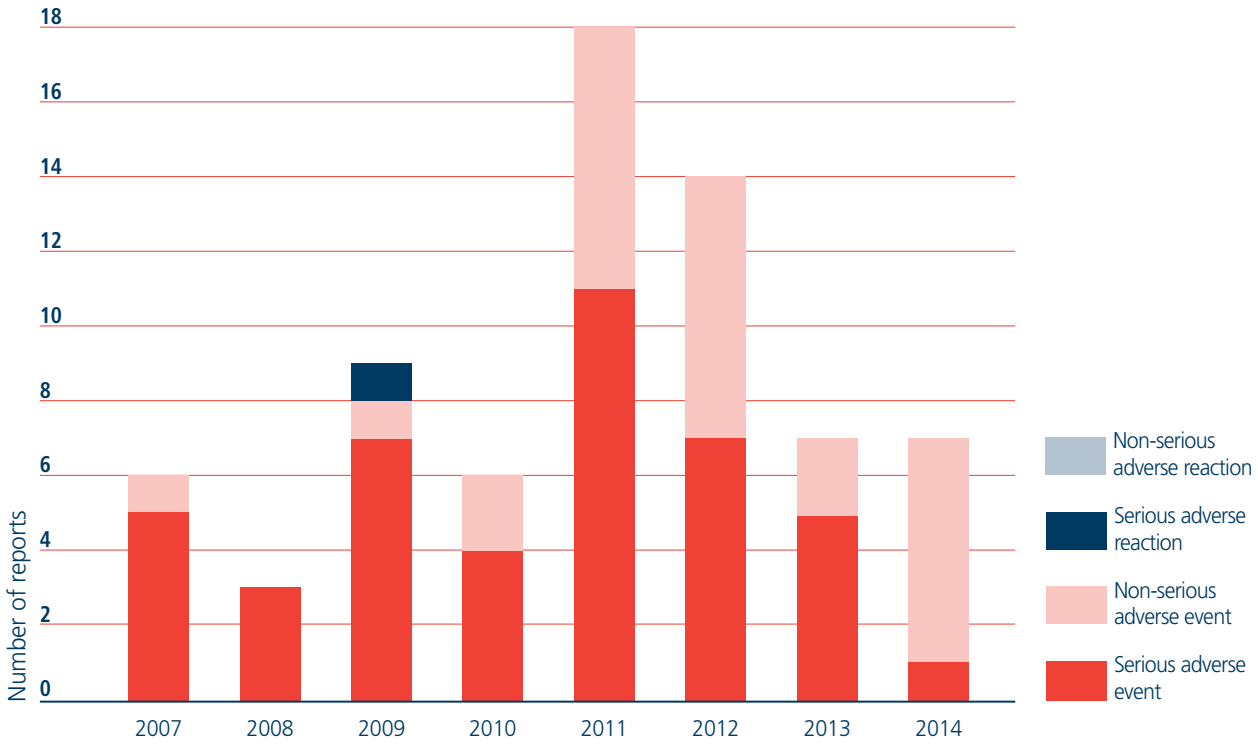

Figure 16. Reports concerning ocular tissue, 2007-2014

The seven adverse events in 2014 were submitted by one tissue establishment and one transplanting institution. The reports are briefly described in Table 32.

Table 32. Overview of adverse events in 2014

Category of event	Number of reports	Description
Loss of tissues or cells	4	• Two corneas lost in tissue establishment due to processing error at cutting of lamella. Two planned surgeries postponed
		• Two corneas lost in tissue establishment due to processing error following incorrect choice of blade for cutting lamella. Two planned surgeries postponed
		• Due to technical problem with hospital microscope two surgeries were postponed and two corneas lost
		• Due to processing error in hospital at cutting DMEK a second cornea intended for the next patient was cut and applied. The emergency cornea ordered for the next patient was unsuitable for the keratoconus operation, surgery postponed
Other incident	2	• At trephination in hospital an oversized trephine was chozen. Lamella had thickened edge and the surface did not align correctly. Patient had to have another operation
		• Insufficient adhesion of pre-cut lamella. Patient did not tolerate standard treatment (inserting air bubble) and chose to have full-thickness keratoplasty done. No relation to corneal quality
Near miss	1	• At slit lamp examination in tissue establishment L and R cornea switched. L cornea was rejected due to corneal scar, but mistakenly processed. The error was noted in time, R cornea was processed in time for transplant

Abbreviation: *DMEK= Descemet's Membrane Endothelial Keratoplasty*

In the previous three reporting years TRIP registered a total of eleven reports of a haze in the transplanted cornea. The cornea working party of the Dutch Ophthalmological Association initiated extensive investigations but could not determine a cause. No reports of haze were submitted in 2014.

2.5 Cardiovascular tissue

In The Netherlands heart valves, blood vessels and patches are used for transplantation purposes. 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 they are used for a small number of special 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 prepared 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.

2.5.1 Processing, distribution and application

In Tables 33 and 34 the data for processing/distribution and application of cardiovascular tissue are presented.

Table 33. Processing and distribution of cardiovascular tissues in 2014

Type	Tissue establishment	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Heart valves	1	3398	Transplant	90	18	0	108
Blood vessels	1	17	Transplant	1	0	0	1
Patches, pericardium, other	1	45	Transplant	21	17	0	38

Table 34. Application of cardiovascular tissue in 2014

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Heart valves	5	105	Transplant	90	15	0	105
Blood vessels	2	4	Transplant	1	2	1	4
Patches, pericardium, other	3	25	Transplant	21	2	2	25

2.5.2 Reports

There were two reports concerning cardiovascular tissue in 2014. In Figure 17 the numbers of reports are shown for the period 2006-2014. On average there was one serious adverse event per reporting year.

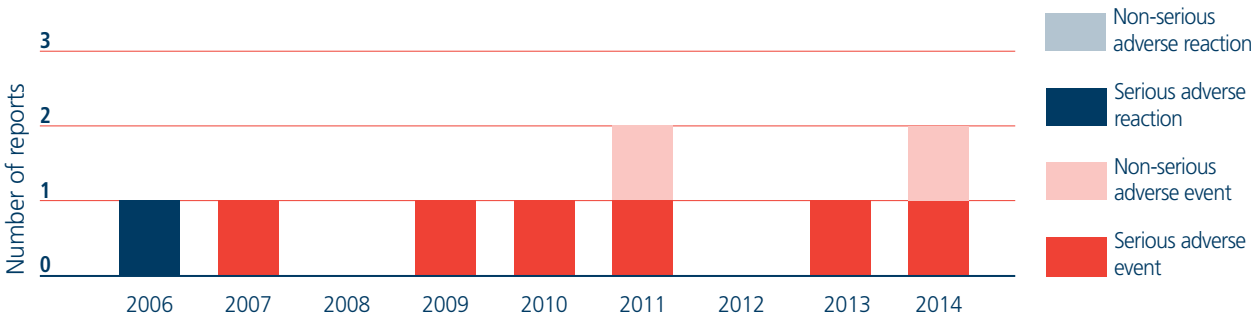

Figure 17. Reports concerning cardiovascular tissue, 2006-2014

All the reports concerning cardiovascular tissue in 2006-2014 involved heart valves, both aortic and pulmonary valves. In 2006 and 2007 an other reaction and an other incident were reported; in both cases the recipient died following complications that were not related to the transplanted tissue. The reports in 2009 and 2010 were in the category of bacterial contamination of product. Those in 2011 regard loss of tissues or cells due to a communication error and an other error respectively. In 2013 damage of a pulmonary valve due to dissection in the bank was found during surgery and was repaired without adverse consequences for the patient.

In 2014 two reports were submitted in the category of other incident:

- Aortic valve: report of Ehlers-Danlos disease (rare COL3A1 mutation) in the donor, discovered five years after transplantation. Ehlers-Danlos disease was diagnosed in relatives of the donor and subsequently demonstrated in retained splenic tissue from the donor. At the time of donation the donor's medical history revealed no symproms which could have been related to Ehlers-Danlos disease. Five years post-transplant the patient had no adverse sequelae (non-serious report).
- Pulmonary valve: two weeks after transplantation the valve ruptured and the recipient died despite surgical treatment (implantation of valve prosthesis). The pulmonary valve was lost during surgery and could not be examined by the tissue establishment. The relation to the transplanted tissue could not be assessed (serious adverse event, imputability possible).

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 bandage 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.

2.6.1 Processing, distribution and application

In Table 35 the numbers of processed and distributed units of skin in 2014 are shown.

Table 35. Processed and distributed skin units in 2014

Type	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Donor skin	1	556*	Pack	1265	8567	7648	17480
Autologous skin	0	0	Transplant	0	0	0	0
Cultured skin/skin cells	1	24	Transplant	12	0	0	12
Acellular dermis	3	41	Transplant	137	85	39	261

* *Donors*

In Table 36 the numbers of applied skin products in 2014 are shown.

Table 36. Applied skin in 2014

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Donor skin	4	66	Pack	309	7	0	316
Autologous skin	0	0	Transplant	0	0	0	0
Cultured skin/skin cells	1	1	Transplant	5	0	0	5
Acellular dermis	3	31	Transplant	20	11	0	31

2.6.2 Reports

In 2014 there were nine reports relating to skin tissue. The numbers of reports concerning skin tissue from year to year are shown in Figure 18.

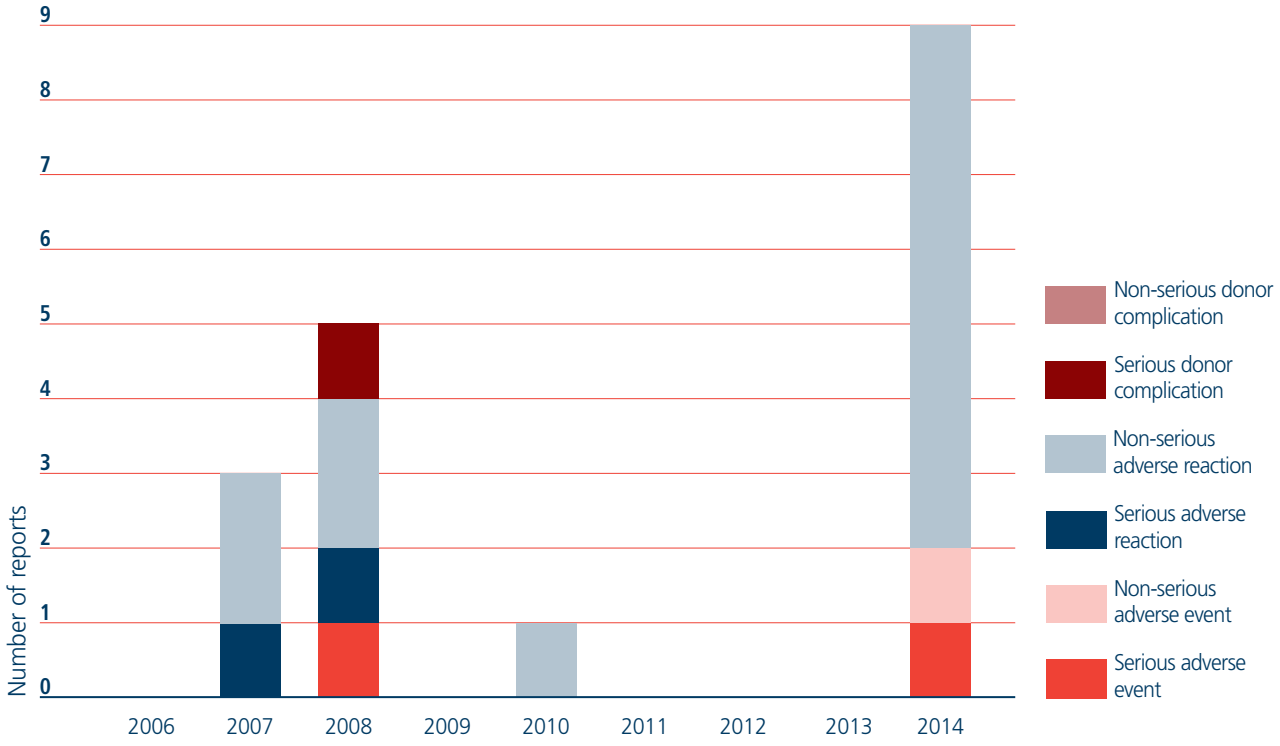

Figure 18. Reports concerning skin tissue or keratinocytes, 2006-2014

In 2008 there were five reports that related to the experimental phase of application of cultured skin. In the study setting all adverse events, including events not related to the skin product, had to be recorded and were also reported to TRIP.

The 2014 reports concerned seven adverse reactions and two adverse events. The seven reports of non-serious adverse reactions all concerned cases of complicated healing after application of a cultured autologous skin product in patients suffering from a chronic skin ulcer. Three reports of post-transplantation bacterial infection involved the same patient. In none of the reports was a causal relation with the quality of the applied skin established.

One report of near miss concerned a mix-up of culture results of donor skin and acellular dermis in the microbiology laboratory. The donor skin was erroneously released as a result. The error was found and corrected prior to distribution to an applying healthcare institution.

In addition there was an adverse event which resulted in loss of tissues and cells. The tissue establishment changed from glycerol to gamma irradiated glycerol (as method of sterilisation). According to the manufacturer's investigations irradiation does not affect composition of the glycerol solution. After processing however part of the donor skin was stiff and could not be used. Further analysis showed that irradiation produced strongly dehydrating substances (hydroxy-aceton, acetaldehyde, formaldehyde, acrolein) that could explain donor skin inflexibility. None of the hospitals which had been supplied with the skin processed in the solution had complained about the applied donor skin. The donor skin which was still in the bank was reprocessed and stiff parts were removed (0-10% per batch).

2.7 Other tissues and cells

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

2.7.1 Processing, distribution and application of other tissues and cells

In the following Tables 37 and 38 numbers of processed and distributed units and numbers of applied units of other tissues and cells are presented.

Table 37. Processing and distribution of other tissues and cells in 2014

Tissue or cell type	Tissue establishments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Amnion	1	2*	Container	94	14	0	108
Langerhans' islets	1	42	Transplant	42	0	0	42
Adipose tissue	1	0	Transplant	0	4	0	4
Cord blood tissue	1	7250	Transplant	0	0	0	0
Red blood cells**	1	82	Bag	81	0	0	81
Leukocytes**	1	120	Bag	119	0	0	119

* *Placentas*

***Radioactively labelled for diagnostic purposes*

Table 38. Application of other tissues and cells in 2014

Type tissue or cells	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Amnion	6	53	Container	54	0	0	54
Langerhans' islets	1	8	Transplant	42	0	0	42
Nerve tissue	1	2	Transplant	0	0	2	2

2.7.2 Reports

In 2014 there were no reports concerning other tissues and cells

Chapter 3. Five years of biovigilance

3.1 Introduction

During the past five years (2010-2014) the number of reports submitted to TRIP regarding adverse events and reactions concerning human tissues and cells has been stable (85-103).

Participation of tissue establishments was nearly complete (96-100%) and participation of hospitals and independent healthcare institutions was high (79-97%). The collected numbers of processed, distributed and applied tissues and cells are sufficiently complete to be used as denominators for a five-year overview (see Figures 29 and 30 in Chapter 4). Figure 19 presents an overview of reports per year for the different types of tissue and cells.

In the paragraphs of this chapter the numbers of reports of adverse reactions and events are placed in the context of numbers of processed or applied products of human origin. Each year the largest number of annual reports submitted to TRIP are adverse events associated with assisted reproductive technologies, however this should be seen in relation to the number of treatment cycles, which is much larger than e.g. hematopoietic stem cell transplants or application of cultured autologous cartilage.

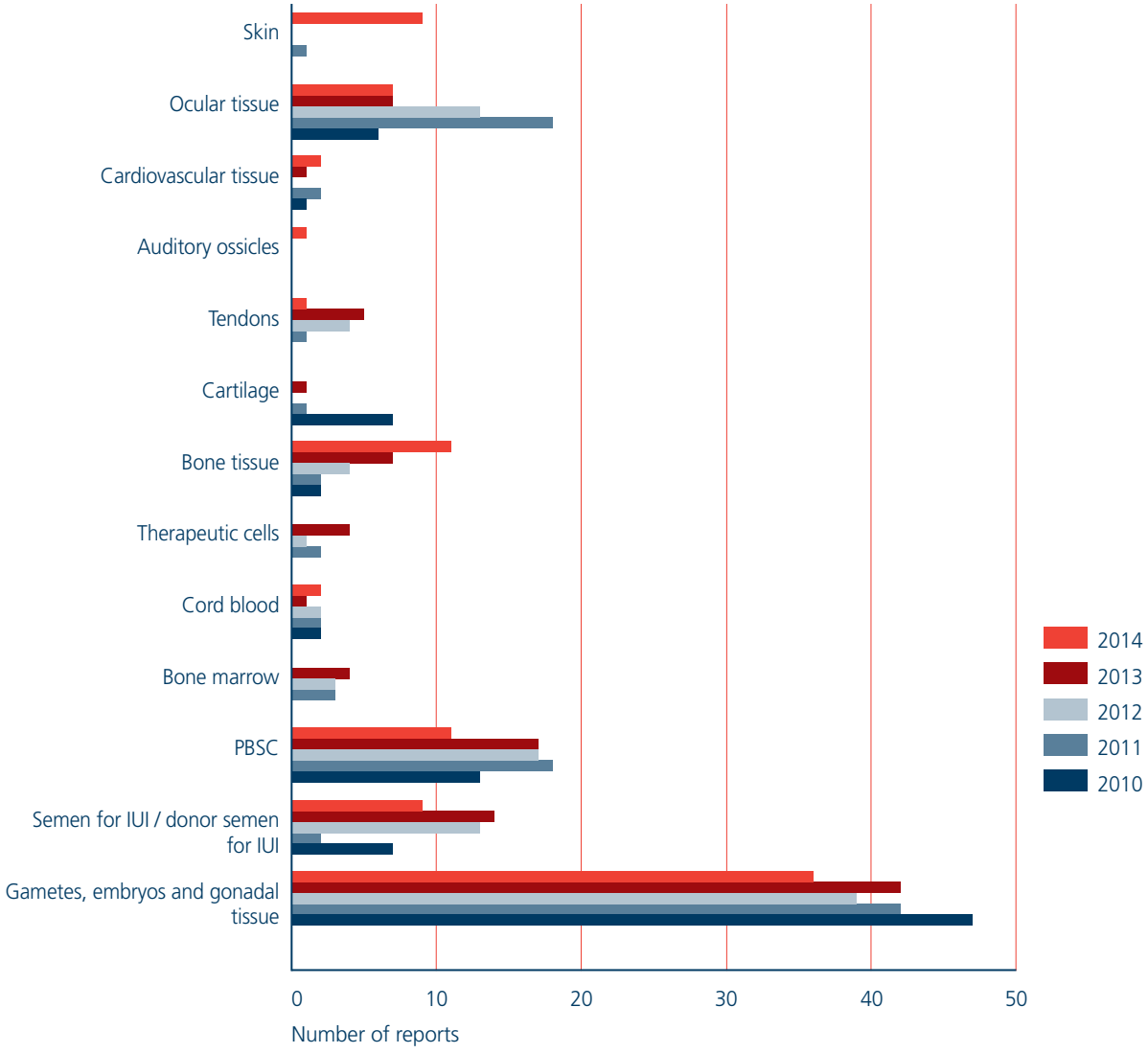

Figure 19 Annual number of reports per tissue or cell type, 2010-2014

3.2 Gametes, embryos and gonadal tissue

In the past five years the annual number of reports concerning reproductive tissues and cells has fluctuated between 43 and 56. The majority of these reports regarded IVF or ICSI treatment and all these reports were adverse events (Figure 20). A smaller number of reports related to partner or donor IUI (Figure 21). As procedures for these treatments are very different with regard to the various processing steps, they are considered separately.

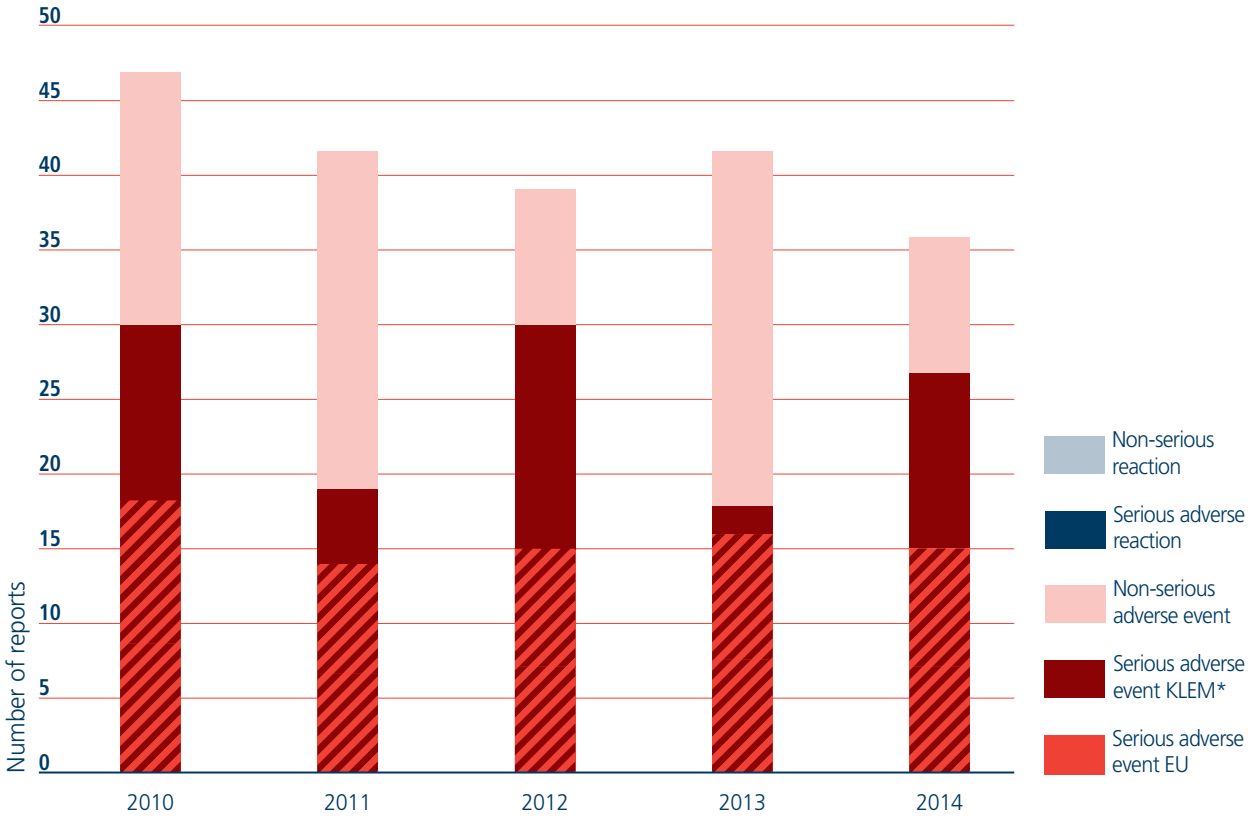

Figure 20. Reports relating to IVF and ICSI treatment, 2010-2014

* *According to Clinical Embryologists' guideline: significantly reduced chance of pregnancy due to loss of oocytes, embryos or irreplaceable semen*

In IVF/ICSI procedures there are many processing steps and actions:

- Collection of follicle fluid into containers
- In some cases transportation of gametes to distant 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
- Selection of well-developed embryos
- In some cases pre-implantation genetic diagnosis
- Transfer of fresh or cryopreserved embryo(s)
- Cryopreservation of (surplus) embryos, gametes and gonadal tissue
- Storage of embryos, gametes and gonadal tissue
- Thawing of embryos, gametes and gonadal tissue
- All administrative procedures

Adverse reactions following ovarian stimulation are reportable to Lareb (the National Registry for adverse drug reactions) through the pharmacovigilance system.

In Table 39 the numbers of adverse events in 2010-2014 are presented in relation to IVF/ICSI cycles in which oocyte retrieval was carried out.

Table 39. Adverse events reported with IVF/ICSI treatment procedures, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of oocyte retrieval IVF/ICSI cycles *	15621	15401	15392	13795	13150	73359	14672
No. of embryo transfers (fresh and cryo embryos)*	22494	21221	21623	21281	21078	107698	21540
No. of adverse events	47	42	39	42	36	206	41.2
No. of serious adverse events (EU)	18	14	15	16	15	78	15,6
Serious adverse events per 1000 cycles	1.2	0.9	1.0	1.2	1.1	1.1	1.1

* *NVOG (Dutch Society for Obstetrics and Gynaecology) IVF data 2010-2014*

Oocyte retrieval by aspiration of follicular fluid following ovarian stimulation (or during a regular menstrual cycle) is considered to be the start of the treatment procedure and is used as denominator since from this point adverse events and reactions may occur that come under the Law on safety and quality of substances of human origin. One or more embryo transfer procedures (fresh and cryopreserved) may follow. With regard to the complete IVF/ICSI treatment procedure there were on average 1.1 reported adverse events per 1000 follicle aspirations in IVF/ICSI cycles. The majority of adverse events were registered in the category loss of tissues or cells, accounting for 54-81% of reported adverse events in ART in that period. The reporting data regarding IVF/ICSI treatment are considered to be reliable due to the excellent reporting discipline of the members of the Association of Clinical Embryologists and their complete participation in the TRIP and NVOG (Dutch Society for Obstetrics and Gynaecology) registries.

Figure 21 shows the number of reports concerning IUI and donor semen IUI treatment.

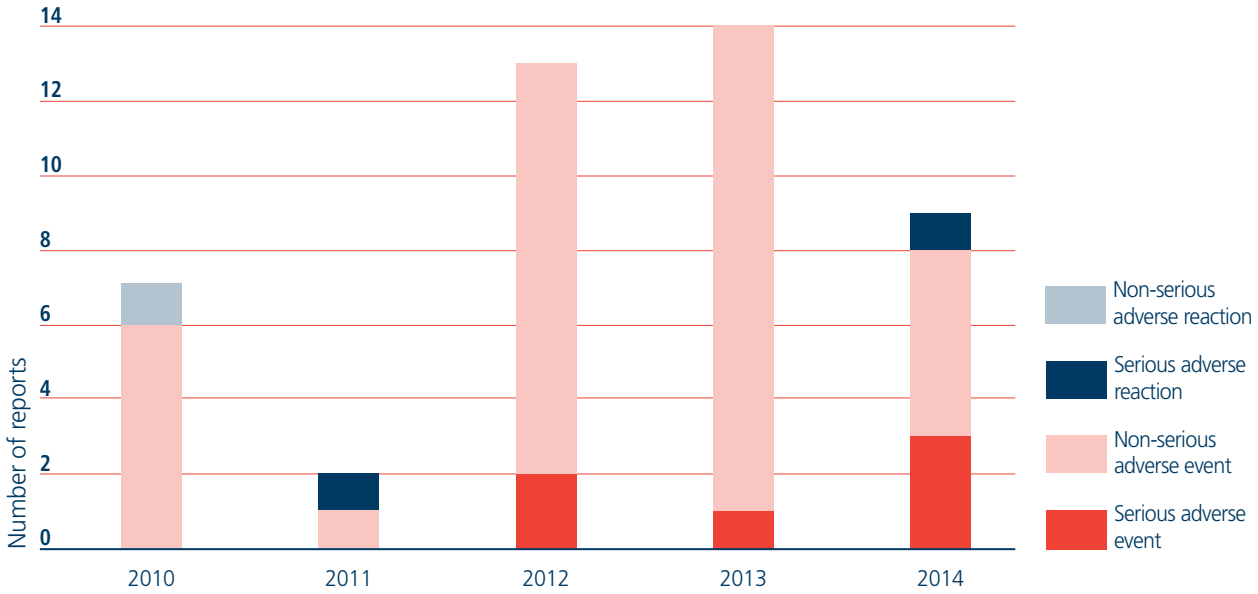

Figure 21. Reports concerning IUI and donor semen IUI treatment, 2010-2014

In IUI and donor semen IUI treatment there are significantly fewer processing steps:

- Collection of semen in container
- Transfer of semen to laboratory
- Semen analysis and motility assessment
- Semen processing
- Semen washing
- Cryopreservation
- Thawing
- Issue of semen in syringe
- Insemination
- All administrative procedures

Table 40 presents an overview of the number of IUI and donor semen IUI treatment procedures and the number of reported adverse reactions and events in the period 2010-2014.

Table 40. Adverse reactions and events concerning IUI and donor semen IUI treatment, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of IUI/donor semen IUI cycles	32306	39363	40507	38139	41760	192075	38415
No. of recipients	10549	16568	24109	12132	13089	76447	15289
No. of adverse events	6	1	13	14	8	42	8.4
No. of serious adverse events	0	0	2	1	3	6	0.8
Serious adverse events per 1000 cycles	0	0	0.05	0.03	0.07	0.03	0.03
No. of adverse reactions	1	1	0	0	1	3	0.6
No. of serious adverse reactions	0	1	0	0	1	2	0.4
Serious adverse reactions per 1000 cycles	0	0.03	0	0	0.02	0.01	0.01

In IUI and donor semen IUI there were 0.03 reported serious events per 1000 IUI and donor IUI cycles. Five of the six serious adverse events concerned mix-up of semen leading to IUI of incorrect partner or incorrect donor semen. There were 0.01 reported serious adverse reactions per 1000 cycles. The two serious adverse reactions were both infectious: salpingitis and hydrosalpinx with tubo-ovarian abscess.

3.3 Hematopoietic stem cells

In 2010-2014 there were 92 reports concerning hematopoietic stem cells from peripheral blood, bone marrow and cord blood. A overview of annual numbers of reports is presented in Figure 22.

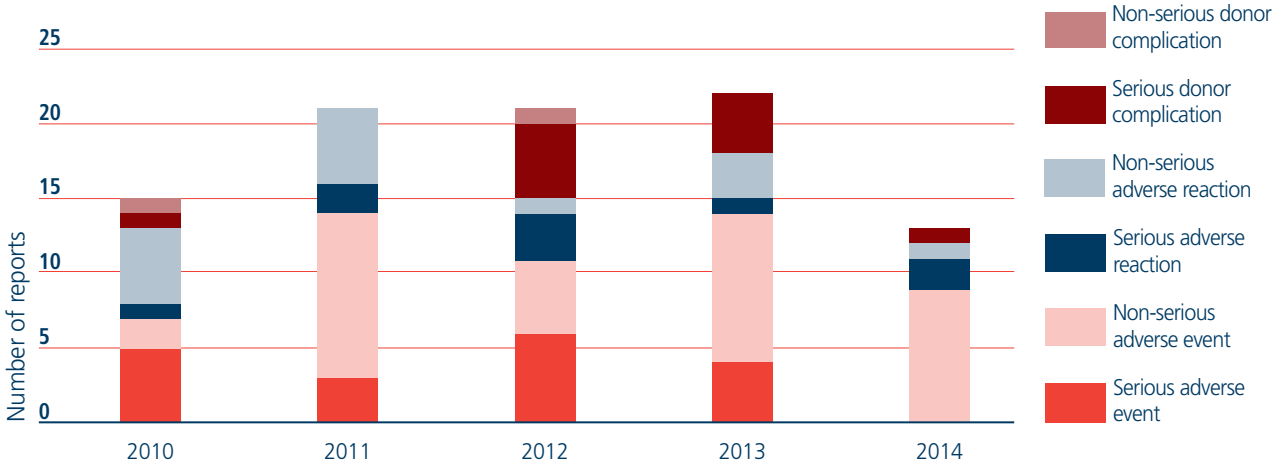

Figure 22. Reports concerning hematopoietic stem cells, 2010-2014

In Tables 41, 42, and 43 the reported reactions and events are presented in relation to the number of transplants or donations for the different types of stem cell donor: unrelated, related or autologous.

Table 41. Adverse events, reactions and donor complications in unrelated hematopoietic stem cel transplantion and donation, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of unrelated stem cell transplants*	356	374	421	456	415	2022	404
No. of adverse events	2	4	5	6	3	20	4
No. of serious adverse events	2	1	2	1	0	6	1.2
Serious adverse events per 1000 transplants	5.6	2.7	4.8	2.2	0	3.0	3.0
No. of adverse reactions	3	4	2	1	2	12	2.4
No. of serous adverse reactions	1	1	1	0	1	4	0.8
Serious adverse reactions per 1000 transplants	2.8	2.7	2.4	0	2.4	2.0	2.0
No. of unrelated stem cell donations**	53	26	35	32	47	193	38.6
No. of unrelated stem cell donor complications	1	0	3	3	0	7	1.4
No. of serious donor complications	1	0	3	3	0	7	1.4
Serious donor complications per 1000 donations***	18.9	0	85.7	93.8	0	36.3***	36.3***

* *Peripheral blood stem cells, bone marrow and cord blood*

** *Peripheral blood stem cells and bone marrow*

*** *All serious donor complications were late complications with low imputability (most unlikely, some possible)*

In unrelated stem cell transplantations 3.0 serious adverse events and 2.0 serious adverse reactions were reported per 1000 transplantations. In addition there were 36.3 serious donor complications per 1000 stem cell donations. All serious donor complications in unrelated stem cell donors concerned later diagnoses of illnesses that occur regularly in the general population; imputability of this type of donor complication to the stem cell donation procedure is judged to be unlikely or at most possible. Systematic long term follow-up is only provided for unrelated stem cell donors.

Table 42. Adverse events, reactions and donor complications in related stem cell transplantation and donation, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of related stem cell transplants*	177	188	190	211	245	1011	202
No. of adverse events	1	0	2	1	0	4	0.8
No. of serious adverse events	0	0	1	0	0	1	0.2
Serious adverse events per 1000 related stem cell transplants	0	0	5.3	0	0	1.0	1.0
No. of adverse reactions	1	1	1	1	0	4	0.8
No. of serious adverse reactions	0	0	1	0	0	1	0.2
Serious adverse reactions per 1000 related stem cell transplants	0	0	5.3	0	0	1.0	1.0
No. of related stem cell donations**	141	187	222	188	233	971	194
No. of donor complications	0	0	3	1	1	5	1
No. of serious donor complications	0	0	2	1	1	4	0.8
Serious donor complications per 1000 related donaties	0	0	9.0	5.3	4.3	4.1	4.1

* *Peripheral blood stem cells, bone marrow and cord blood*

** *Peripheral blood stem cells and bone marrow*

In related stem cell transplantation there were 1.0 serious advers events and 1.0 serious adverse reactions per 1000 stem cell transplants. The rate of reported serious donor complications per 1000 stem cell donations was 4.1.

Table 43. Adverse events, reactions and donor complications in autologous stem cell transplantation, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of autologous stem cell transplants*	1611	1538	2251	1894	2422	9716	1943
No. of adverse events	4	12	5	6	6	33	6.6
No. of serious adverse events	3	2	4	2	1	12	2,4
Serious adverse events per 1000 bags	1.9	1.3	1.8	1.1	0.4	1.2	1.2
No. of adverse reactions	2	2	1	2	1	8	1.6
No. of serious adverse reactions	0	1	1	1	1	4	0.8
Serious adverse reactions per 1000 bags	0	0.7	0.4	0.5	0.4	0.4	0.4
No. of autologous stem cell donations	495	504	700	652	722	3073	615
No. of donor complications	1	0	0	0	0	1	0.2
No. of serious donor complications	0	0	0	0	0	0	0
Serious donor complications per 1000 donations	0	0	0	0	0	0	0

* *Peripheral blood stem cells, bone marrow and cord blood*

** *Peripheral blood stem cells and bone marrow*

Autologous stem cell transplants are usually processed and stored in a number of bags. The EU data collection requests the number of distributed bags and this number is provided to TRIP and used as denominator in Table 42 as an adverse event or reaction may occur with a particular bag. There were 2.4 serious adverse reactions per 1000 autologous stem cell bags. No serious donor complications were reported.

3.4 Bone and other musculoskeletal tissues

3.4.1 Bone tissue

In the past five-year period there were 25 reports concerning bone tissue. Figure 23 shows an overview of reports in 2010-2014.

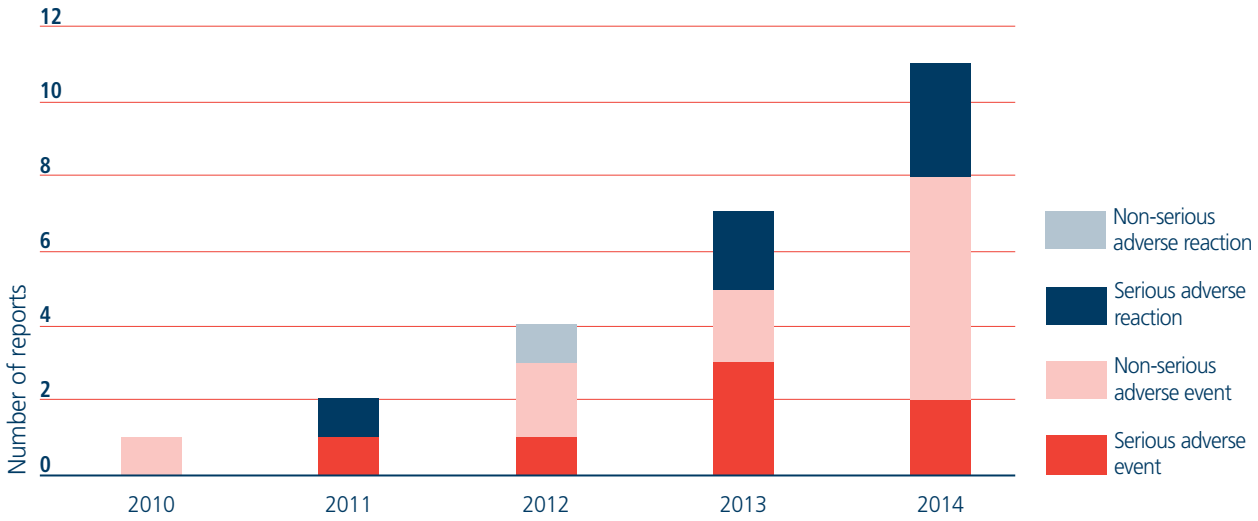

Figure 23. Reports concerning bone tissue, 2010-2014

Fifteen reports involved femoral heads and another six reports concerned autologous cranial bone flaps. The remaining four reports concerned whole bone (2) and cancellous bone chips (2). Large numbers of cancellous bone chips are distributed and transplanted (see Table 21 and 22 in chaper 2.3). As there have been very few reports regarding whole bone and bone chips these will not be discussed further. The data regarding femoral heads and autologous cranial bone flaps are presented in Tables 44 and 45.

Table 44. Adverse events and reactions concerning femoral bone heads, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of processed femoral heads	2494	3049	2528	4037	4160	16268	3254
No. of adverse events	1	1	2	4	3	11	2.2
No. of serious adverse events	0	1	1	1	1	4	0.8
Serious adverse events per 1000 processed	0	0.3	0.4	0.3	0.3	0.2	0.2
No. of distributed femoral heads	2336	2452	2706	2205	2351	12050	2410
No. of adverse reactions	1	1	1	0	1	4	0.8
No. of serious adverse reactions	0	1	0	0	1	2	0.4
Serious adverse reactions per 1000 distributed	0	0.4	0	0	0.4	0.2	0.2

The denominator chosen for the number of serious adverse reactions was the number of distributed femoral heads as these figures are more complete than those for transplanted femoral heads. In addition this figure is also requested by the EU as denominator for serious adverse reactions. In processing and application of femoral heads there were 0.2 serious adverse events and 0.2 serious adverse reactions per 1000 distributed femoral heads.

Table 45. Adverse events and reactions concerning autologous cranial bone flaps, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of processed cranial bone flaps	95	99	102	150	257	703	141
No. of adverse events	0	0	0	1	1	2	0.4
No. of serious adverse events	0	0	0	1	0	1	0.2
Serious adverse events per 1000 processed	0	0	0	6.7	3.9	1.4	1.4
No. of distributed cranial bone flaps	53	52	57	82	174	418	83.6
No. of adverse reactions	0	0	0	1	3	4	0.8
No. of serious adverse reactions	0	0	0	1	3	4	0.8
Serious adverse reactions per 1000 distibuted	0	0	0	12.2	17.2	9.6	9.6

There were 1.4 serious adverse events per 1000 processed cranial bone flaps and 9.6 serious adverse reactions per 1000 distributed cranial bone flaps. These serious adverse reactions were all post-transplantation bacterial infections but the transplanted tissue was never positively identified as the cause of infection.

3.4.2 Cartilage

In 2010-2014 there were 9 reports concerning cartilage. Figure 4 shows an overview of reports. All reports regarded adverse events and there were no reported adverse reactions.

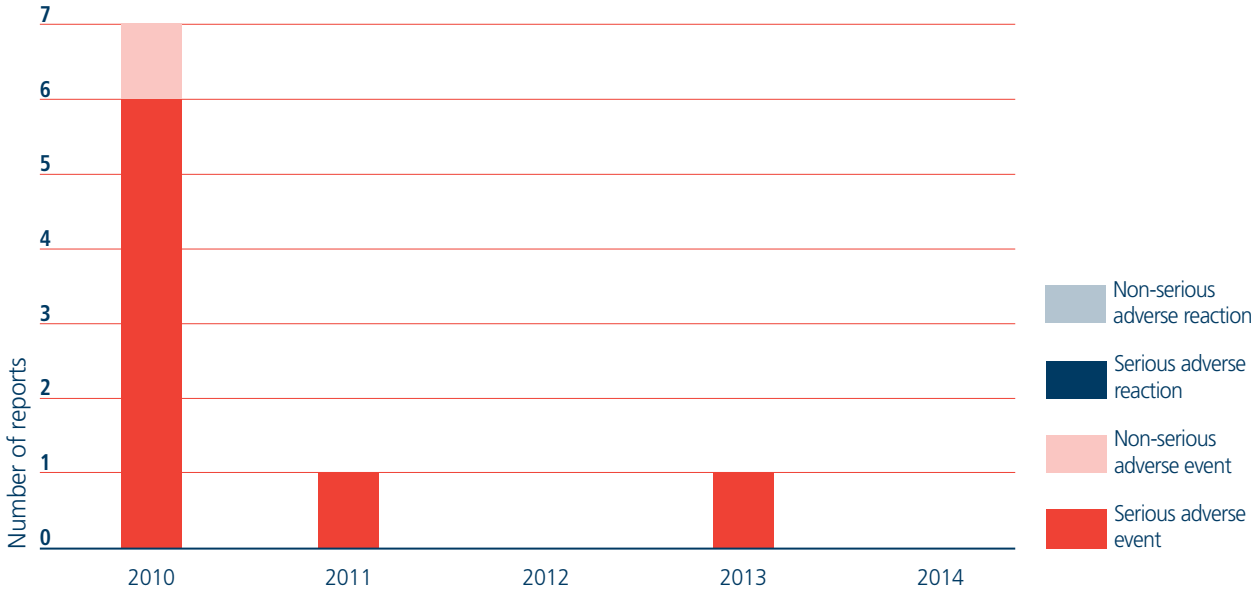

Figure 24. Reports concerning cartilage, 2010-2014

All cases related to the harvesting or culturing of autologous chondrocytes. Table 46 presents the reports in relation to the number of processing procedures.

Table 46. Adverse events concerning autologous chondrocytes, 2010-2014

	2010	2011	2012*	2013	2014	Total 2010-2014	Annual average
No. of processed chondrocyte biopsies	180	130	0	271	235	716	179
No. of adverse events	7	1	0	1	0	9	2.3
No. of serious adverse events	6	1	0	1	0	8	2
Serious adverse events per 1000 processed	33.3	7.7	0	3.7	0	11.2	11.2

* *No autologous chondrocyte culturing in The Netherlands*

Concerning autologous chondrocyte procedures there were 11.2 serious adverse events per 1000 processed biopsies. Four out of eight serious adverse events led to loss of the chondrocytes. In addition there was one case where a transplant was performed unintentionally using the chondrocyte culture product from another patient.

3.4.3 Tendons

There were 11 reports involving tendons 2010-2014 as shown in Figure 25.

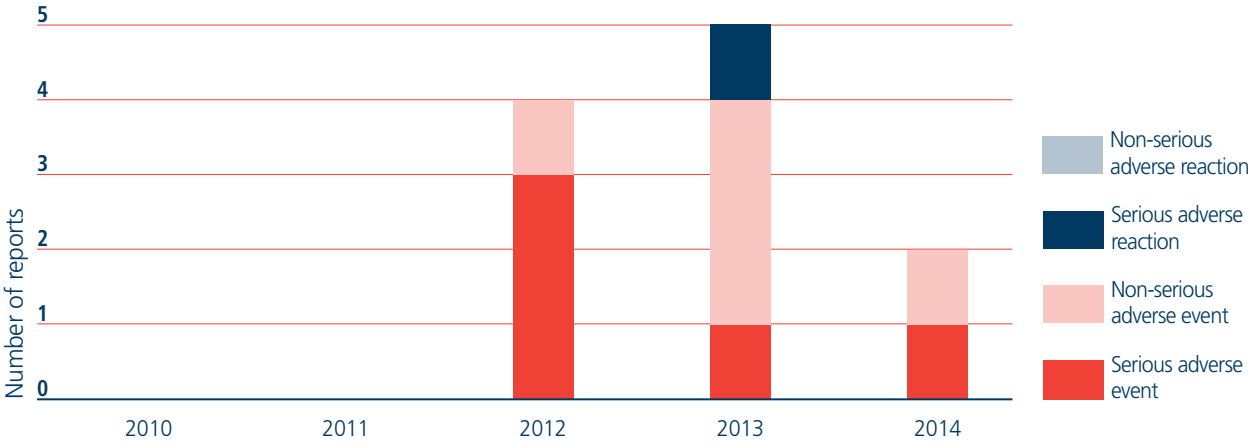

Figure 25. Reports concerning tendons, 2010-2014

There were 10 adverse events and one adverse reaction, presented in relation to the number of processed and distributed tendons in Table 47.

Table 47. Adverse events and reactions concerning tendons, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of processed tendons	220	488	581	742	533	2564	513
No. of adverse events	0	0	4	4	2	10	2
No. of serious adverse events	0	0	3	1	1	5	1
Serious adverse events per 1000 processed	0	0	5.2	1.4	1.9	2.0	2.0
No. of distributed tendons	136	389	472	532	556	2085	417
No. of adverse reactions	0	0	0	1	0	1	0.2
No. of serious adverse reactions	0	0	0	1	0	1	0.2
Serious reactions per 1000 distributed	0	0	0	1.9	0	0.5	0.5

There were 2.0 serious adverse events per 1000 processed tendons and 0.5 per 1000 distributed tendons.

3.5 Ocular tissue

Regarding ocular tissue 52 adverse events were reported to TRIP in 2010-2014. Only one report concerned sclera while 51 reports were about corneas. None of the reports reported an adverse reaction. The cornea reports are presented in Figure 26. Sclera reports are not analysed further because of the very low number of reports, although it should be mentioned that substantial numbers of scleras were processed and applied.

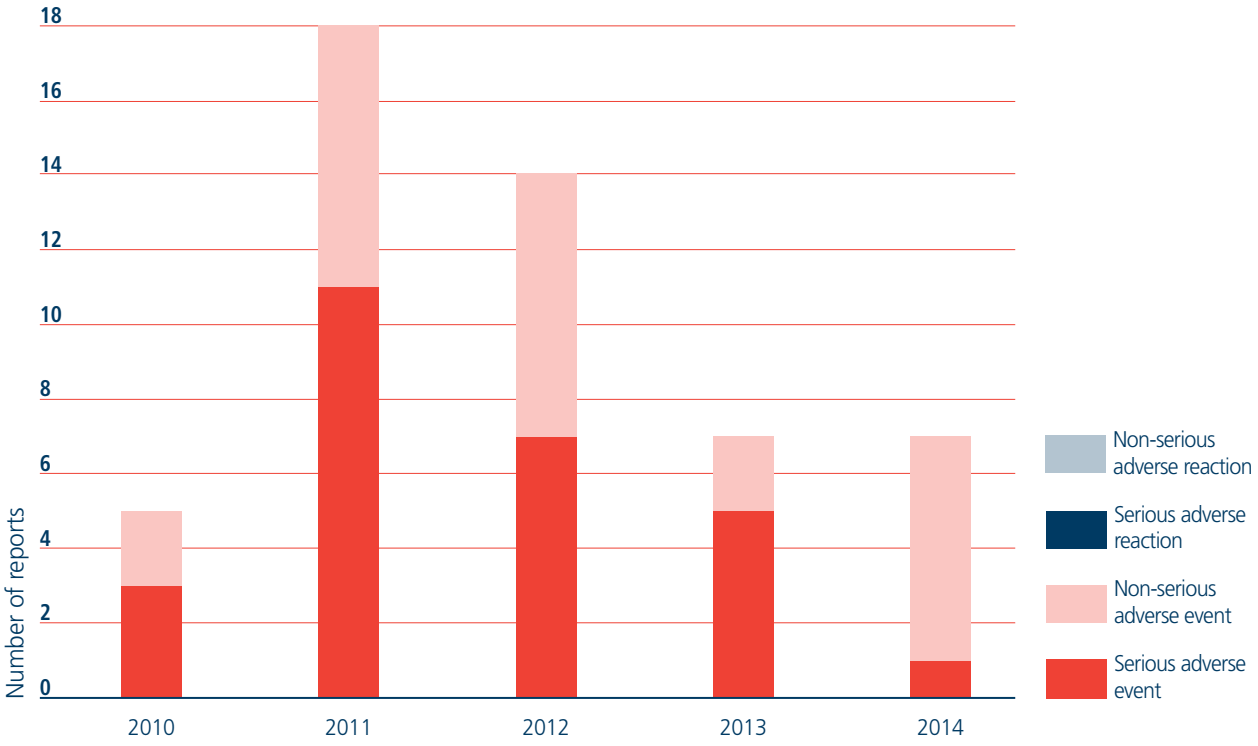

Figure 26. Reports concerning corneas, 2010-2014

In Table 48 the number of adverse events regarding corneas are presented in relation to the number of processed corneas.

Table 48. Adverse events concerning corneas, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of processed corneas	2707	3365	3282	3051	3202	15607	3121
No. of adverse events	5	18	14	7	7	51	10.2
No. of serious adverse events	3	11	7	5	1	27	5.4
Serious adverse events per 1000 processed	1.1	3.3	2.1	1.6	0.3	1.7	1.7

During the process from corneal donation up to and including transplantation there were 1.8 serious adverse events per 1000 processed corneas. Seven of the serious adverse events concerned a corneal haze.

3.6 Cardiovascular tissue

In 2010-2014 six reports were submitted concerning cardiovascular tissues. All were adverse events concerning aortic or pulmonary valves. Figure 27 gives an overview of reports concerning heart valves in the period 2010-2014.

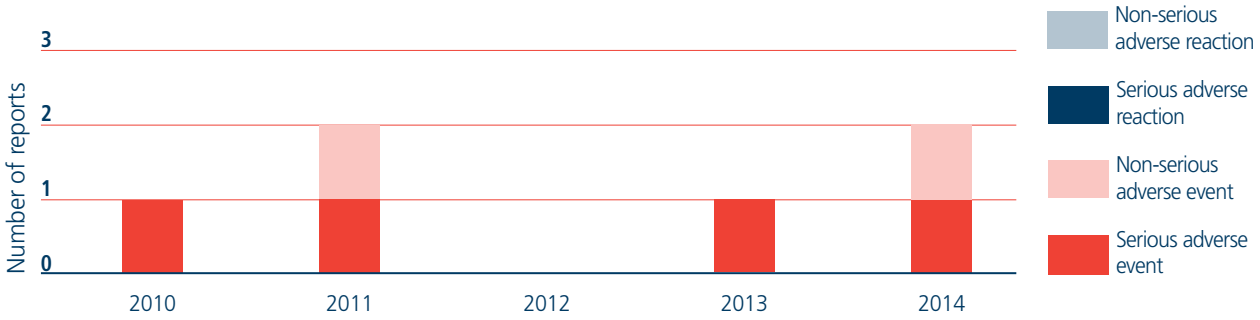

Figure 27. Reports concerning heart valves, 2010-2014

In Table 49 the number of serious adverse events is presented in relation to the number of processed heart valves. There were 2.3 serious adverse events per 1000 processed heart valves.

Table 49. Adverse events concerning heart valves, 2010-2014

	2010	2011	2012	2013	2014	Total 2010-2014	Annual average
No. of processed heart valves (aortic and pulmonary)	246	162	452	468	398	1726	345
No. of adverse events	1	2	0	1	2	6	1.2
No. of serious adverse events	1	1	0	1	1	4	0.8
Serious adverse events per 1000 processed valves	4.1	6.2	0	2.1	2.5	2.3	2.3

3.7 Skin

In the years 2010-2014 ten reports of adverse events and reactions involving donor skin and cultured skin were submitted. Only one report was judged to be serious and there were no serious adverse reactions. Due to the very low number of serious reports skin is not discussed further.

3.8 General discussion

The preceding paragraphs give an overview regarding serious adverse reactions and events and serious donation complications. TRIP stresses that the calculated number of reports per 1000 unit of processed tissues or cells, treatment cycles or donations cannot be directly interpreted as the chance of 'something going wrong'. In the first place the numbers of reports are small. Secondly, there are many steps and variables per processing or treatment cycle which make choosing a suitable denominator difficult. Thirdly, participation was not always 100% and therefore data were not complete. However the figures are sufficiently complete to provide the basis for a first impression of the risk of adverse reactions and events based on five years of biovigilance reporting. It should be borne in mind that biovigilance reporting is limited to unexpected serious adverse reactions that may be linked to the quality and safety of tissues and cells.

Tables 50, 51 and 52 give an overview of serious adverse events, reactions and donor complications in the past five years in relation to the best available denominators. Denominators differ according to tissue or cell type and the calculated results are not readily comparable.

Table 50. Serious adverse events in relation to numbers of tissues/cells processed, transplanted or per treatment cycle, 2010-2014

Tissue or cell type	Serious adverse event rate estimation	Per 1000
Gametes, embryos or gonadal tissue	1.1	IVF/ICSI cycles with follicle biopsy
	0.02	IUI/KID cycles
Hematopoietic stem cells	3.0	Unrelated stem cell transplants*
	1.0	Related stem cell transplants*
	1.2	Autologous stem cell transplants**
Bone and other musculoskeletal tissues	0.2	Processed femoral heads
	1.4	Processed autologous cranial bone flaps
	11.2	Autologous cartilage biopsies
	2.0	Processed tendons
Ocular tissue	1.7	Processed corneas
Cardiovascular tissues	2.3	Processed heart valves

* *Bone marrow, peripheral blood stem cells and cord blood*

** *Bone marrow, peripheral blood stem cells*

Tabel 51. Serious adverse reactions in relation to distribution data, transplantations or treatment cycles, 2010-2014

Tissue or cell type	Serious adverse reaction rate estimation	Per 1000
Gametes, embryos or gonadal tissue	0.01	IUI/donor insemination cycles
Hematopoietic stem cells	2.0	Unrelated stem cell transplants*
	1.0	Related stem cell transplants*
	0.4	Autologous stem cell transplants**
Bone and other musculoskeletal tissues	0.2	Distributed femoral heads
	9.6	Distributed autologous cranial bone flaps
	0.5	Distributed tendons

* *Bone marrow, peripheral blood stem cells and cord blood*

** *Bone marrow and peripheral blood stem cells*

Table 52. Serious donor complications per 1000 stem cell donations, 2010-2014

Tissue or cell type	Serious donor complication rate estimation	Per 1000
Hematopoietic stem cells	36.3*	Unrelated stem cell transplants*
	4.1	Related stem cell transplants*
	0	Autologous stem cell transplants**

* *All serious donor complications in unrelated stem cell donors were late complications of low imputability (unlikely or possible). Long term follow-up is only carried out in unrelated donors*

** *Bone marrow and peripheral blood stem cells*

In the above tables the following points stand out:

- In gametes, embryos and gonadal tissue the number of serious reports per treatment cycle was low despite the complex processing procedures in assisted reproductive technologies.
- In 2010-2014 there was a relatively high rate of serious reports concerning autologous cartilage and autologous cranial bone flap procedures compared to other musculoskeletal tissues.
- In the past five years serious donor complications all regarded hematopoietic stem cell donations. The higher number of donor complications in unrelated stem cell donors compared to related stem cell donors is explained by the systematic long term follow-up of unrelated donors whereas follow-up in related donors is limited to one year only. In autologous donors a complication of donation may not always be distinguishable from their underlying illness.

The trends in the data can be taken into account by the different groups of professionals in the surveillance and improvement of safety and quality in the processing, distribution and application of human tissues and cells.

To our knowledge other EU member states have not yet produced a five-year overview of serious adverse reactions and events in relation to processing procedures or treatment procedures. This provides a preliminary indication of the rates of adverse events and reactions based on Dutch data. International comparison of these data could be valuable for the detection of rare complications as well as for discerning the effects of possible differences in procedures.

Chapter 4. Participation

Participation of all stakeholders in the TRIP reporting system is essential for the quality of the biovigilance system. Participation is defined by submission of reports to TRIP or confirmation that there was nothing to report 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 suppliers (tissue establishments and organ banks) that procure, process, store and/or distribute human tissues and cells; and
2. the hospitals, clinics, independent healthcare institutions 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 substances 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 procure tissues and cells after donation without an additional licence. Procurement after harvesting of human tissues and cells is reserved for tissue establishments that are 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 53 presents an overview of licensed tissue establishments and organ banks in The Netherlands in 2014. Some hospitals house several tissue establishments and/or organ banks.

Table 53. Licensed tissue establishments and organ banks in 2014

	Tissue establishments	Organ banks	Total
Independent institution*	10	11	21
Located in hospital/clinic	60	38	98
Total	**70**	**49**	**119**

* *Excluding two independent institutions that are currently applying for a licence*

Figure 28 shows the number of licences issued by Farmatec for each type of human tissue and 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.

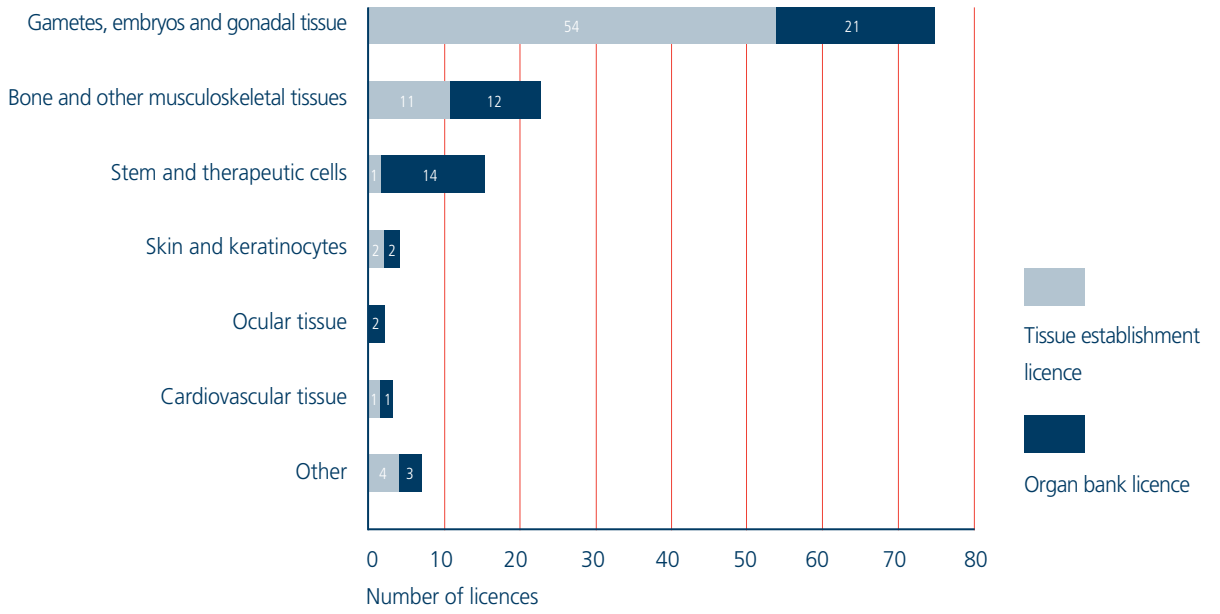

Figure 28. Number of licensed tissue establishments and organ banks in The Netherlands in 2014

Figure 29 shows the annual percentages of tissue establishments that provided data on processing and distribution and whether they submitted biovigilance reports. All tissue establishments submitted data on processing and distribution in 2014. One tissue establishment replied that it did not perform activities covered by the law on safety and quality in 2014. Participation was complete in 2014 (119 out of 119 tissue establishments).

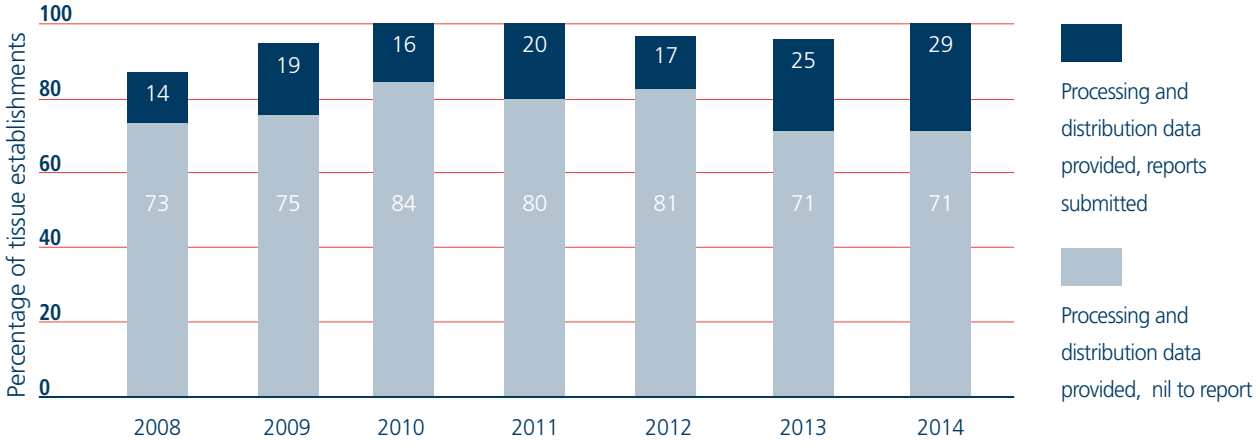

Figure 29. Participation by tissue establishments, 2008-2014
(in 2008-2011: n=20, 2012-2014*: n=118-119)

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

4.2 Users of substances of human origin

In all, in 2014 94 hospitals, 21 clinics and independent healthcare institutions and 36 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 independent healthcare institutions and oral implantology practices that had indicated in the 2013 survey that they applied tissues and cells were added to the database of applying institutions. Participation by hospitals, clinics and private healthcare institutions in 2014 was 96% (110 out of 115). The applying implantology practices were contacted for the second time and participation was 50% (18 out of 36). This constituted a 17% rise compared to 2013. Two hospitals, four independent healthcare institutions and four implantology practices replied they did not apply tissues or cells in 2014. In Figures 30 and 31 participation rates are shown from 2008 onwards.

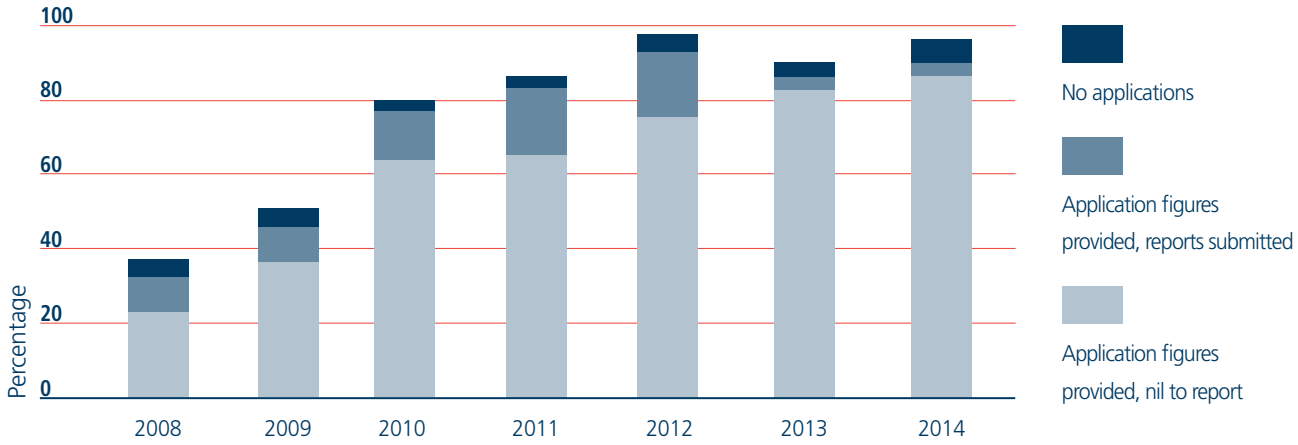

Figure 30. Participation by Dutch hospitals and clinics, 2008-2014 (n=101-115)

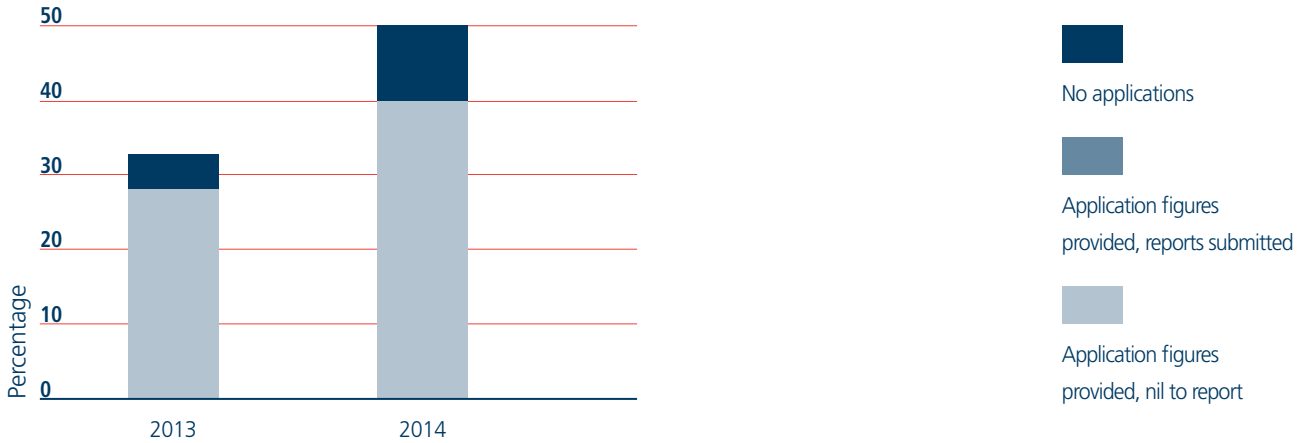

Figure 31. Participation by Dutch oral implantology practices, 2013-2014 (n=36)

4.3 Completeness of application information and need for assistance

In the annual request to hospitals, clinics and oral implantology practices for data on numbers of tissues and cells transplanted or applied and the number of reicipients treated, two questions were added in order to obtain insight into the completeness of data and awareness thereof as well as the institutions' need for support in identifying tissues and cells transplanted or applied in the institution. Figure 32 presents the responses to the question "Are the application data which you submitted complete?"

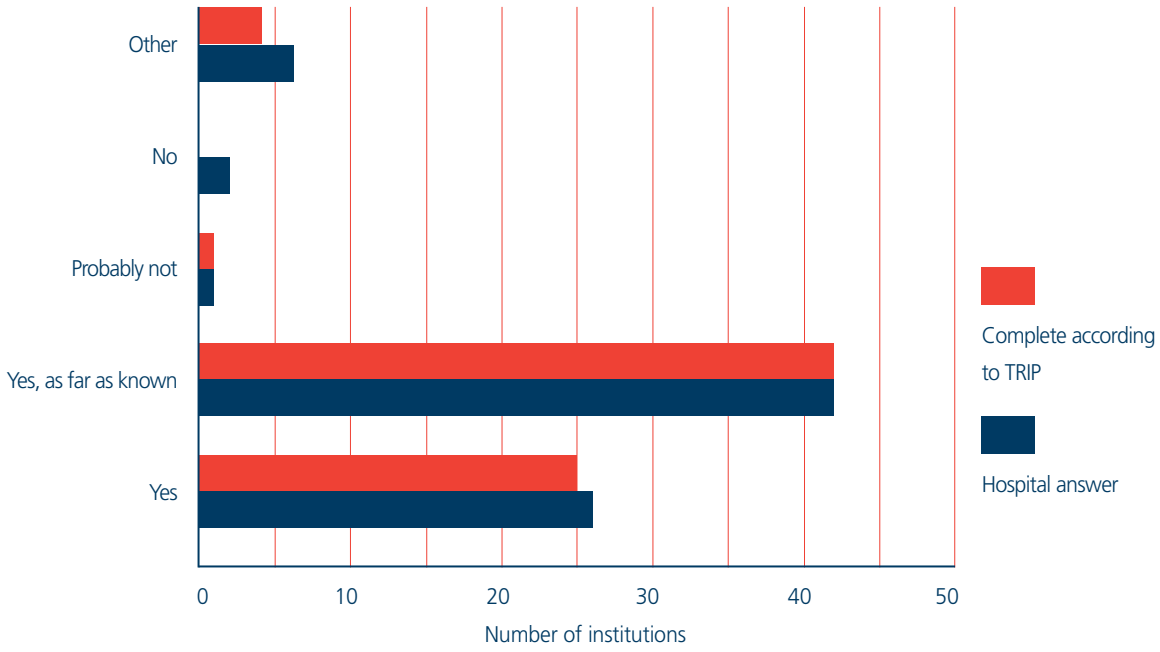

Figure 32. Reply to survey question: "Are the submitted application data complete?"

Sixty-eight out of 77 responding hospitals, clinics and oral implantology practices replied that they know or presume their provided figures to be complete. With only one exception this tallied with information known to TRIP regarding the types of tissues and cells applied. Responders answering 'other' often indicated that part of their data were provided by other departments, other staff members or in-house tissue establishments.

Figure 33 shows the responses about whether institutions would welcome a supporting role played by TRIP in identifying all types of applied tissues and cells in their institution.

Figure 33. Replies to survey question: "Would you like suppport by TRIP in identifying types of applied or transplanted tissues in your institution"

Seventy-four hospitals, clinics and oral implantology practices responded to this question. Thirty-five (47%) replied that they did not need support or they had already completed their inventory of applied tissues and cells. Twenty-eight (38%) indicated they would appreciate support, whether or not on request. Those that replied 'other' often indicated that they first wanted to be informed about the nature of the support.

Annex 1. About TRIP

The TRIP (Transfusion and Transplantation Reactions in Patients) Foundation was created in 2001 for the purpose of establishing national hemovigilance. 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 reporters 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 16 presents a flowchart of serious and non-serious Biovigilance reporting in Dutch healthcare.

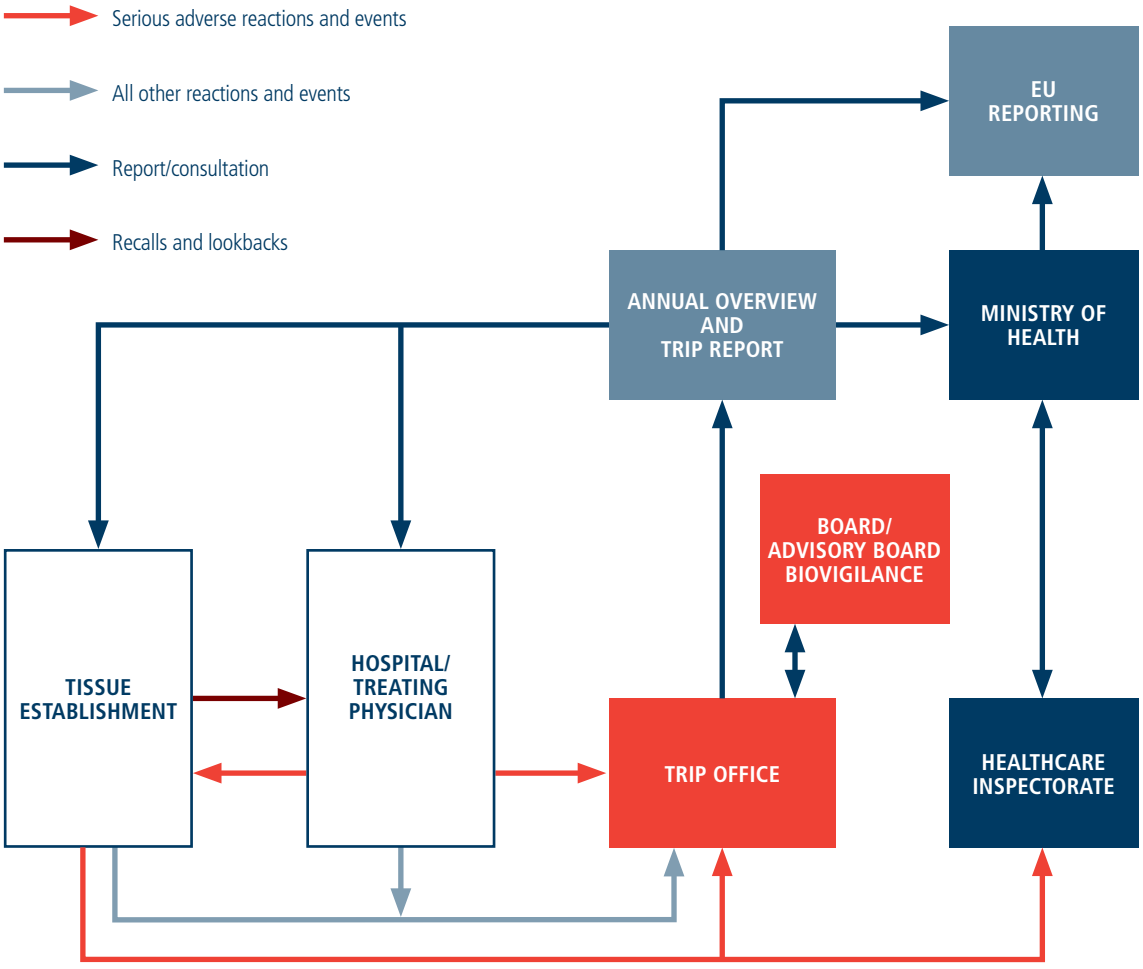

Figure 16. Flowchart of reporting

The scope of the Law on safety and quality of substances of human origin covers 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 to autologous tissues. 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 at 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.

Overview of mandatory reports of serious adverse reactions and events (in accordance with EU legislation)

Table 54 presents an overview of the number of serious adverse reactions and events relating to substances of human origin that were registered in 2014. In all, 29 reports were assessed as serious. These concerned 21 serious adverse events and eight serious adverse reactions, of which one was a serious adverse reaction in a donor.

Table 54. Overview of mandatory serious reports in 2014

Type of tissue or cells	Serious adverse reaction	Serious adverse event	Serious donor complication	Total serious reports
Semen	1	4	0	5
Oocytes	0	6	0	6
Semen and oocytes	0	1	0	1
Embryos	0	5	0	5
Ocular tissue	0	1	0	1
HPSC and therapeutic cells	2	0	1	3
Bone	4	1	0	5
Bone and tendons	0	1	0	1
Cardiovascular tissue	0	1	0	1
Skin	0	1	0	1
Total	**7**	**21**	**1**	**29**

Table 55 presents the 2013 overview of mandatory reports which has been updated to include the reports which were submitted after the closing date. TRIP registers reports according to the year in which a reaction or adverse event was observed. The total number of serious reports in 2013 came to 39.

Table 55. Overview of mandatory serious reports in 2013 including late submissions

Type of tissue or cells	Serious adverse reaction	Serious adverse event	Serious donor complication	Total serious reports
Semen	0	1	0	1
Oocytes	0	5	0	5
Embryos	0	10	0	10
Ocular tissue	0	5	0	5
HPSC and therapeutic cells	1	6	4	11
Bone	2	1	0	3
Cartilage	0	1	0	1
Tendon	1	1	0	2
Cardiovascular tissue	0	1	0	1
Total	**4**	**31**	**4**	**39**

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 56. 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 56. 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 event led to the loss of a complete reproductive cycle
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 57 shows the definitions of severity grades of adverse reactions. The definition of a serious adverse reaction corresponds to severity grade 2 or higher.

Table 57. Severity grade of adverse reactions

Grade 0	No morbidity
Grade 1	Minor morbidity, not life-threatening
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
Grade 4	Mortality following a transplantation 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

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

Calamity

A calamity is defined by the Dutch quality law for healthcare institutions 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. List of terms and abbreviation

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 myeloïd 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
Distribution	-	Transportation and delivery to end users
DLI	-	Donor lymphocyte infusion
DMSO	-	Dimethyl sulfoxide
EC	-	European Commission
ED	-	Europdonor Foundation (from 2016: Matchis)
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 in relation to pharmaceuticals, medical devices, blood products and substances of human origin
Gonadal	-	Belonging to sexual glands
HLA	-	Human leukocyte antigen
HPSC	-	Hematopoietic stem cells
ICSI	-	Intra cytoplasmic sperm injection (type of IVF)
IGZ	-	Healthcare Inspectorate
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
MESA	-	Microsurgucal epididymal sperm aspiration
NVOG	-	Dutch Society for Obstetrics and Gynaecology
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 diagnostis
Pharmacovigilance	-	Vigilance of pharmaceuticals
PN	-	Pro-Nuclei
Processing	-	All actions necessary for preparing, manupilating, 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
WMDA	-	World Marrow Donor Association
Wvkl	-	Dutch Law on safety and quality of substances of human origin

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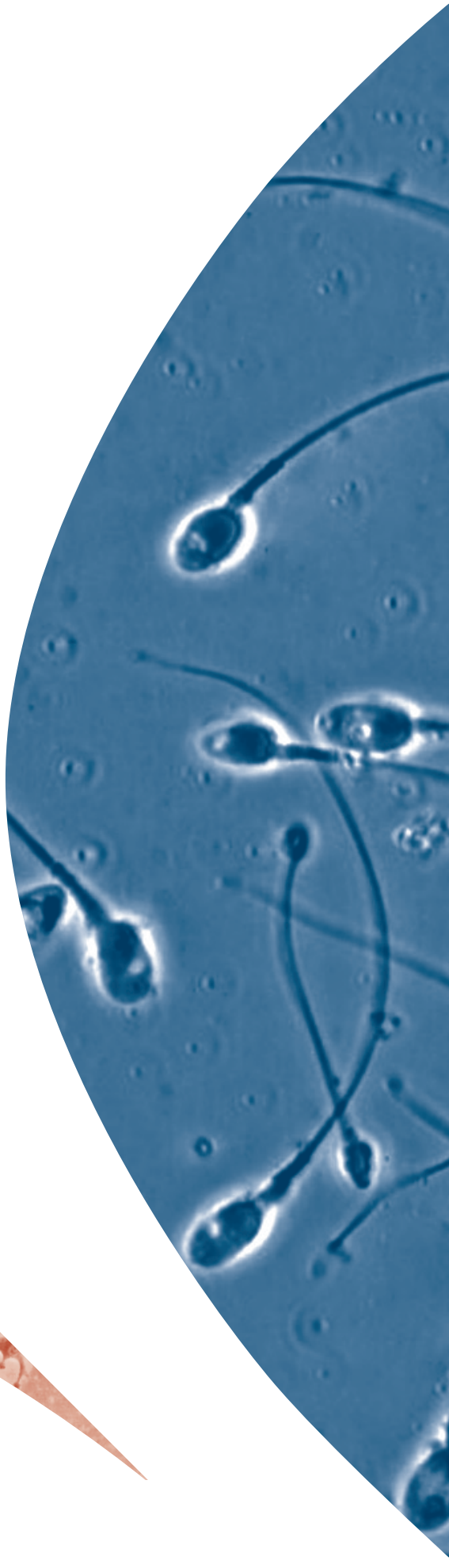

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