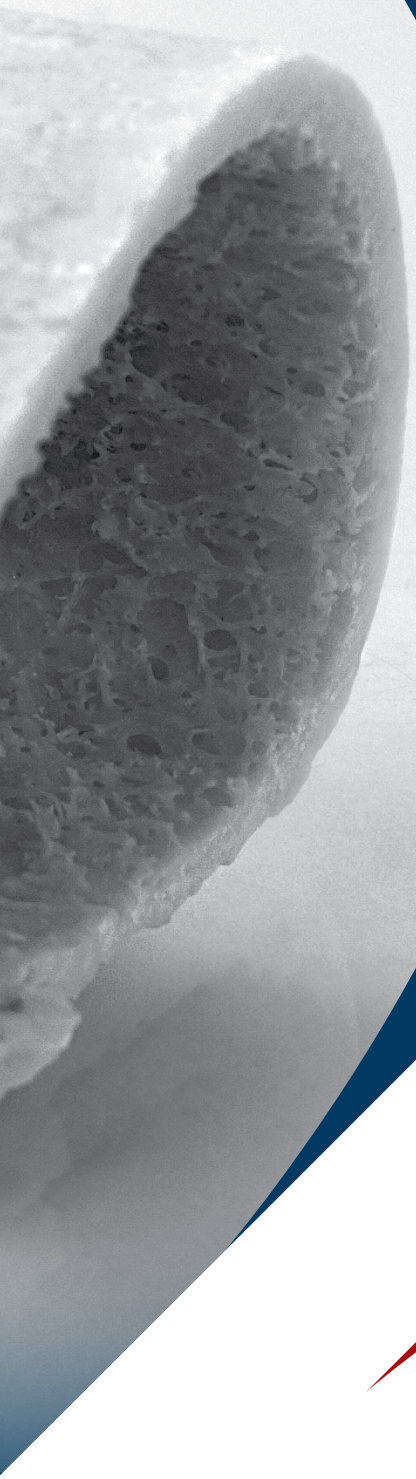
TRIP report 2013

Biovigilance



TRIP
Hemo-en biovigilantie

TRIP report 2013

Biovigilance

Extended version

The TRIP report 2013 regarding biovigilance in The Netherlands is published under responsibility of the TRIP (Transfusion & Transplantation Reactions In Patients) Foundation.

TRIP
Hemo- en biovigilantie

TRIP Governing Board	On behalf of
J.L.P. van Duijnhoven	Dutch Society for Clinical Chemistry and Laboratory Medicine, treasurer
M.R. Schipperus	President
J.W.P.H. Soons	Society for Hematological Laboratory Investigation, secretary

Advisory Board	
J.A. Bekkers	Dutch Society for Thoracic Surgery, vice-chairman
M. van den Bosch	Dutch Transplantation Foundation (till January 2014)
A. Brand	Dutch Society of Specialists in Internal Medicine
J.H.F. Falkenburg	Dutch Society for Haematology (till March 2013)
M. Grommé	Working Party Dutch Stem Cell Laboratories
P.M.W. Janssens	Dutch-Belgian Society for Artificial Insemination, chairman
J.H. Marcelis	Dutch Society for Medical Microbiology
D.J. van Rhenen	Dutch Society of Specialists in Internal Medicine (till September 2013)
C.D. Richters	Euro Tissue Bank, skin and cornea department
W.J. Rijneveld	Dutch Society for Ophthalmology (from April 2013)
B.J. van Royen	Dutch Orthopaedic Association (NOV) (from April 2013)
D.B.F. Saris	Scientific Committee of Dutch Orthopaedic Association (NOV) (till April 2013)
I. Schipper	Dutch Society for Obstetrics and Gynaecology
A. Tewarie	Dutch Transplantation Foundation (from January 2014)
S.M. Weima	Association of Clinical Embryologists
M.J. van Wijk	BISLIFE Foundation
M.L. Zandvliet	Dutch Society of Hospital Pharmacists
P.P.M. van Zuijlen	Dutch Society for Plastic Surgery (from April 2013)

Advisory Board	
J.M.M. Hansen (reading member)	Healthcare Inspectorate
R. Treffers	Dutch Association of Hospitals (till January 2014)
J.T. Tamsma	Dutch Federation of University Hospitals
H.J.C. de Wit	Sanquin Blood Supply

Patroness

E.J.G.M. Six - Barones van Voorst tot Voorst

TRIP Office	
A.G. Bokhorst	Director
J.C. Wiersum-Osselton	National coordinator
A.J.W. van Tilborgh-de Jong	Senior hemovigilance physician
P.Y. Zijlker-Jansen	Hemovigilance and biovigilance physician
M.J. Happel	Biovigilance Coordinator
M.S.E. Bergers	Staff member
I.C. van Veen-Rottier	Office Manager

Table of content

Introduction

This TRIP Biovigilance Report 2013 gives an overview of reports of adverse reactions and events occurring in the field of transplantation of human tissues and cells for the seventh consecutive year. The number of biovigilance reports seems to be stable in the last few years. However, this year a significant number of reports was submitted after the closing date for the 2013 report and consequently could not be included. The number of serious adverse events in assisted reproduction has dropped due to an adjustment of the European definitions of serious adverse events in this field.

The structure of this annual report is slightly different from previous years. Data on distribution and application together with adverse reactions and events are now presented per tissue type, giving the reader a more coherent picture per field of application. In addition, common trends and developments that are relevant to more than one tissue type are analysed thematically. This year's report focusses on adverse events due to so-called technical errors that involve equipment and material failures.

Technical errors do not only occur in essential equipment and materials, also preservation and transportation conditions have led to (unnecessary) loss of scarce substances of human origin. Analysis of reports in the last five years showed that attention to equipment management, alarm system and validation of critical processes after equipment repair or maintenance can contribute to a decrease in the number of (serious) events.

Also, the implementation of recommendations relating to identification of donor, recipient and human tissues and cells (Biovigilance report 2012) could contribute to a further drop in the number of reports. However, in 2013 the number of identification errors did not decrease.

To be able to quantify the risk of a specific adverse event or reaction it is crucial to have insight in numbers of applied tissues and cells in the Dutch hospitals and clinics. From the application data by Dutch hospitals and clinics it is clear that there still is a significant discrepancy in numbers of application and transplantation compared to numbers of distributed tissues and cells by tissue establishments. TRIP, in close collaboration with tissue establishments, will look into possibilities for supporting biovigilance professionals in participating hospitals and clinics in the collection of application data in their healthcare facility.

Based on chapter 4 of this report regarding participation of hospitals in the communal surveillance system of substances of human origin it can be concluded that almost 100% of relevant institutions are actively involved and contributing to biovigilance. In publishing this report TRIP not only would like to give an account of the state of affairs in biovigilance, but would also like to express appreciation for all the work and commitment of all those involved in biovigilance, without which this report could not be annually presented.

Conclusions and recommendations

Conclusions

1. In 2013 a total of 81 reports were registered, out of which 32 (40%) were assessed to be serious. The total number of reports in 2013 was comparable to previous reporting years.

2. A considerable time after the closing date for this report and the formal assessment by the Biovigilance Advisory Board another 20 reports were submitted. This amounts to 20% of the total number of reports in 2013. These reports could not be included in the 2013 report. This partially hinders analyses and conclusions.

3. In 2013 there were fewer reports assessed as serious. This is mainly due to an amendment in EU criteria for serious events in the field of assisted reproductive technologies, whereby an adverse event is only assessed to be serious if it has led to the loss of a complete fertility cycle.

4. There were three reports of bacterial contamination of incubating embryos. Only two comparable reports have been registered by TRIP to date, in 2008.

5. Two reports concerned the incorrect preparation of cryopreservation medium. This type of adverse event has not been previously reported to TRIP.

6. In the field of assisted reproductive technologies there were three reports of failing cryopreservation equipment, registered in the categories loss of tissues and cells and other incident. This problem was also reported in other European member states; and measures have been taken by the cryopreservation equipment manufacturer involved.

7. The transplanting healthcare facilities do not in all cases report to tissue establishments in a timely fashion, leading to investigations having to be aborted (cornea) or unnecessarily delayed (bone chips).

8. In 2013 there was a spontaneous drop in the number of reports concerning a corneal haze (2013: one report). In 2011 and 2012 a total of ten corneal haze reports were registered.

9. In 2013 participation of hospitals, private clinics and independent healthcare facilities was 92%. Participation of oral implantology practices was 33% and is expected to rise as in 2013 the oral implantology practices were contacted for the first time regarding application data.

10. Sixteen percent of registered reports in the past seven years concerned technical errors. These technical errors led to loss of tissues and cells or reduction in quality or volume of tissues and cells.

Recommendations

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.

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

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.

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

5. Transplanting healthcare institutions should notify the supplying tissue establishment or organ bank in 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.

6. To improve the completeness of application/transplantation data TRIP in close cooperation with distributing tissue establishments and organ banks will offer support by supplying an overview to transplanting healthcare institutions of types of tissues and cells that were distributed to their facility.

Actions and developments following recommendations in the 2012 TRIP report

1. In order to reach full participation TRIP should personally contact non-participating hospitals.

   Development: Contacts were established with a number of institutions. Although all non-participating institutions were contacted in writing, not all have been personally approached to date.

2. The gap between distributed and applied tissues and cells requires continued effort. By including private clinics that may use human tissues and cells as well as oral implantologists in the TRIP network part of the discrepancy could be resolved.

   Development: TRIP made the inventory forms for transplanting institutions as user-friendly as possible and actively encouraged the provision of application data by transplanting healthcare institutions.

3. Tissue establishments should advise hospitals or clinics that were (also) involved in an adverse event to report to TRIP. Full information from the complete chain of human tissues and cells could provide more insight into weak points in both tissue establishments and hospitals/clinics.

   Development: This did not result in any complementary 'chain' reports in 2013.

4. The issue of leaking units for collection of stem cell transplants needs further investigation and monitoring; the Stem Cell Laboratory Working Group will initiate further investigations.

   Development: Investigations have not yet been completed.

5. Validated transportation conditions are necessary for assuring the quality of transported tissues or cells. If validation of these processes has not been performed this should be undertaken.

   Development: In 2013 another report of failing transportation equipment was received. Technical equipment failures are further discussed in chapter 4.

6. Essential equipment like transportation boxes, incubators, cryopreservation devices and storage devices needs an adequate fail-safe alarm system to prevent quality loss or avoidable loss of tissues or cells in case of breakdown.

   Development: In 2013 three reports relating to failing cryopreservation equipment were registered. In one of these there was no back-up by a fail-safe alarm.

7. Congenital malformations that occur when using heterologous gametes are reportable adverse events. For confirmation of a genetic abnormality chromosomal and gene investigations of both parents (sperm donor and mother, or egg-cell donor and father) is necessary.

   Development: In 2013 a number of reports of congenital malformation using heterologous donors were received. Adequate genetic analysis was performed.

8. To decide if a poor outcome of a corneal graft needs reporting as an adverse event medical professionals should formulate criteria for follow-up time and parameters for determining whether an adverse event is to be classified as serious.

   Development: So far no action has been initiated.

9. In case of difficulties in preparing a cornea with a microkeratome in a transplanting institution a rejected cornea can be ordered to use as testing material.

   Development: It is not known whether any rejected corneas were ordered as testing material.

10. Double check identification procedures by two members of staff can reduce the number of errors and subsequent adverse outcomes.

11. Extra attention is needed when performing identification based on numerical codes of products or date of birth so that small differences will be noticed.

    Development: In 2013 TRIP received eight reports concerning identification or selection errors. This is a higher number compared to the annual average of six in the past six years.

Chapter 1. 2013 reports

1.1 Reports in 2013

TRIP registered 81 reports in 2013. The closing date for inclusion in the annual Biovigilance report 2013 and EU overview was April 1 2014. Out of the total number of reports 32 reports (40%) were assessed as serious. The annual overview of serious reports was sent to the European Commission.

There is a drop in the number of serious reports. This is mainly due to an adjustment in the European assessment criteria for serious adverse events regarding assisted reproductive technologies. Now only the loss of a complete fertility cycle is assessed as serious where previously loss of half (or more of) the gametes or embryos was assessed as serious. This is explained further in chapter 2.1. Figure 1 shows an overview of submitted reports from 2006 onwards subdivided in serious and non-serious reports.

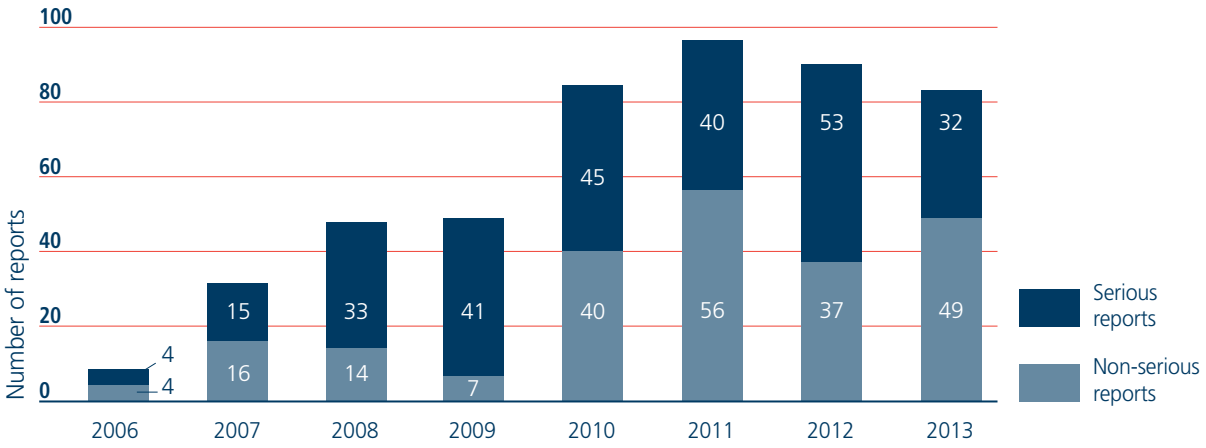


Figure 1. Number of reports 2006-2013

Table 1 gives an overview of serious and non-serious reports in 2013 broken down by type of human tissue and cells.

Table 1. Reports per type of tissue and cells in 2013

	Total	Non-serious	Serious
Gametes, embryos and gonadal tissue	41	29	12
Hematopoietic stem cells and therapeutic cells	20	11	9
Ocular tissue	7	2	5
Bone and other musculoskeletal tissue	12	7	5
Skin	0	0	0
Cardiovascular tissue	1	0	1
Other tissue and cells	0	0	0
Total	**81**	**49**	**32**

The drop in the total number of reports is explained by the large number of reports (20) that was submitted after the closing date for this report. Many adverse events and reactions were submitted only after 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 analysis. Also, serious adverse reactions and events can only be included in the annual overview to the European Commission

in the following year. Reports should preferably be submitted as soon as possible after detection and certainly no later than the closing date. Figure 2 shows the number of late reports per reporting year.

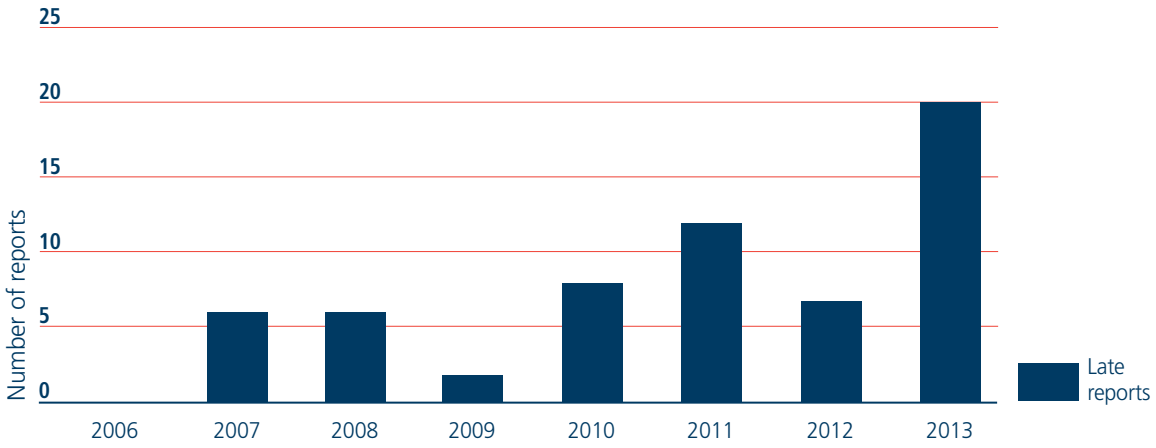


Figure 2. Number of late reports 2006-2013

1.2 Late reports from previous reporting years

After the closing date for the 2012 Biovigilance report another seven reports were submitted out of which four were serious. The total number of 2012 reports came to 97 reports. Late reports included two reports regarding ocular tissue, two reports regarding gametes and three reports regarding hematopoietic stem cells. One late report concerned hematopoietic stem cells in 2010. All late reports have been included in the relevant figures and tables in this report.

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. 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.

Hospitals and clinics 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 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 need to submit information only 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 and uses its specific procedure.

1.5 Definitions

Serious adverse event

A serious adverse event is defined as follows:

> *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. (EU Directive 2004/23/EC Article 3).*

The criteria used by the European Commission are presented in Table 2. These criteria were developed by the EU projects EUSTITE and SOHO V&S and were adopted by the *"Common approach for reportable serious adverse events and reactions as laid down in the tissues and cells Directive 2004/23/EC"*.

Table 2. 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 the loss of a complete cycle in assisted reproductive technologies

Serious adverse reaction

A serious adverse reaction is defined as follows:

> *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. (EU Directive 2004/23/EC Article 3).*

Table 3 shows the definitions of severity grades of adverse reactions. The definition of a serious adverse reaction corresponds to severity grade 2 or higher.

Table 3. 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 after a transplantation reaction to a stable clinical condition 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'.*

Chapter 2. Tissues and cells

In this chapter the trends in 2013 are discussed for each type of human tissue or cells. The processing/distribution and application data are presented separately per type of human tissue and cells and the corresponding biovigilance reports are analysed.

2.1 Gametes, embryos and gonadal tissue

To fulfil the desire for a child sometimes assisted reproductive technologies are needed. Three well-known techniques are: intra-uterine insemination (IUI), in vitro fertilisation (IVF) and intra-cytoplasmic sperm injection (ICSI). These reproductive techniques all increase the chance of the fertilisation of an egg 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 64 licensed tissue establishments that process semen (sperm) for IUI. Only semen laboratories holding an organ bank licence are authorised to process and store donor sperm. One clinic is licensed for processing of semen and oocytes but does not actually carry out IVF or ICSI treatments.

2.1.1 Processing, distribution and application

Tables 4 and 5 present the numbers of units of reproductive cells processed, distributed and applied. Some cryopreserved embryos are not viable after thawing, hence the difference between the numbers of distributed and applied cryopreserved embryos. The difference in semen distribution and applications arises from the figures for distribution. Some tissue establishments have included semen used in IVF treatment to their distribution numbers. In order to balance numbers the guidance for the 2013 inventory will give clearer instructions for the provision of data.

Table 4. Processing and distribution of gametes, embryos and gonadal tissue in 2013

Cell/tissue type	No of tissue establishments	Processed	Distributed in					
			Unit	NL onsite clinic	NL trans-port clinic	EU	Non EU	Total
Partner semen, fresh	76	37670	Donation	34788	1970	116	0	36874
Partner semen, cryopreserved	19	2769	Straw	2755	289	121	7	3172
Donor semen, fresh	7	766	Donation	263	0	0	0	263
Donor semen, cryopreserved	15	6897	Straw	18570	250	775	0	19595
Semen MESA/ PESA/ TESE, fresh	5	110	Aspiration or biopsy	103	0	24	0	127
Semen MESA/ PESA/ TESE, cryopreserved	9	772	Straw	642	97	273	0	1012
Oocytes for donation, fresh	13	2879	Oocyte	854	0	2007	0	2861
Oocytes for donation, cryopreserved	3	369	Oocyte	0	0	0	0	0
Oocytes, fresh	13	121111	Oocyte	113189	0	6049	0	119238
Oocytes, cryopreserved	13	2869	Oocyte	485	8	0	0	493
Embryos for donation, fresh	2	960	Embryo	34	0	0	0	34
Embryos for donation, cryopreserved	3	17	Embryo	18	4	0	0	22
Embryos, fresh	13	64854	Embryo	42067	0	0	0	42067
Embryos, cryopreserved	13	23518	Embryo	14088	17	13	0	14118
Ovarian tissue	3	170	Transplant	13	0	0	0	13
Testicular tissue	1	16	Transplant	0	0	0	0	0

Table 5. Application of gametes, embryos and gonadal tissue in 2013

Cell/tissue type	Hospitals/ clinics	Recipients	Applications				
			Unit	From NL	From EU	From non EU	Total
Partner semen, fresh	76	9506	Donation	25661	0	0	25661
Partner semen, cryopreserved	20	473	Straw	583	58	688	1329
Donor semen, fresh	7	30	Donation	69	0	0	69
Donor semen, cryopreserved	16	2123	Straw	9327	1753	0	11080
Embryos for donation, fresh	2	25	Embryo	34	0	0	34
Embryos for donation, cryopreserved	3	17	Embryo	22	0	0	22
Embryos, fresh	13	11398	Embryo	21451	0	0	21451
Embryos, cryopreserved	13	5634	Embryo	11486	0	0	11486
Ovarian tissue	2	3	Transplant	13	0	0	13
Testicular tissue	0	0	Transplant	0	0	0	0

2.1.2 Reports

In 2013 TRIP registered 41 reports relating to procedures or application of gametes, embryos and/or gonadal tissue in assisted reproductive technologies. This amounted to 50% of the total number of reports for 2013. The reports were submitted by 12 out of the 13 fertility clinics that are licensed for IVF and ICSI treatments, one fertility clinic that carries out the preparatory IVF treatments and five tissue establishments licensed for semen processing. One fertility clinic informed TRIP that no reportable adverse reactions or events occurred. All reports concerned adverse events and no adverse reactions were reported.

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. There is now a clear guideline for serious adverse events regarding assisted reproductive technologies. The change concerns the reporting of adverse events that led to the loss of a complete fertility cycle or the transmission of a genetic disease in (non-partner) gametes. 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 assessed as serious if there was a considerable reduction of the likelihood of pregnancy in that cycle (loss of ≥ 50% of tissues/ cells). Other criteria for serious adverse reactions and events remained unchanged (Tables 2 and 3). 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 and the numbers assessed as serious according to the new EU guidance and according to the clinical embryologists' guideline. The latter numbers are similar to previous years. A revision of the clinical embryologists' guideline to implement the EU criteria will be launched in 2014.

Table 6. Overview of adverse events concerning reproductive tissues and cells in 2013

Tissue or cell type	Type of event	Total	Serious according to KLEM*	Serious according to EU**
Semen	Loss of tissues or cells	1	0	0
	Congenital malformation	1	0	0
	Near miss	1	0	0
	Other incident	6	0	0
Oocytes	Loss of tissues or cells	10	5	4
	Other incident	1	0	0
Semen and oocytes	Other incident	1	0	0
Embryos	Loss of tissues or cells	11	7	4
	Other incident	3	2	0
	Bacterial contamination of product	3	3	3
	Near miss	3	2	1
Total		**41**	**19**	**12**

* *According to the Dutch Association of Clinical Embryologists' (KLEM) guideline: loss of ≥ 50% of oocytes, embryos or irreplaceable semen*

***According to EU criteria: loss of a complete fertility cycle*

In Figure 3 the reports from previous years are included and also broken down according to the amended EU criteria for a reportable serious event and compared to the current clinical embryologists' guideline (KLEM).

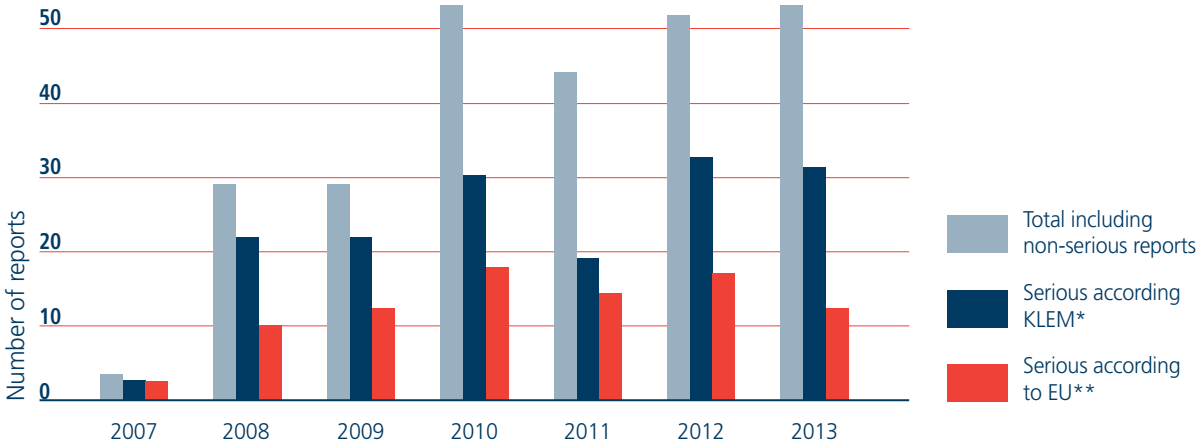


Figure 3. Reports concerning gametes, embryos and gonadal tissues 2007-2013

** According to the Dutch Association of Clinical Embryologists' guideline: loss of ≥ 50% of oocytes, embryos or irreplaceable semen*

***According to EU criteria: loss of a complete fertility cycle*

Figure 4 presents an overview of numbers and category of event per cell or tissue type in 2013. As in previous years the category of loss of tissues or cells represents the majority of reported adverse events.

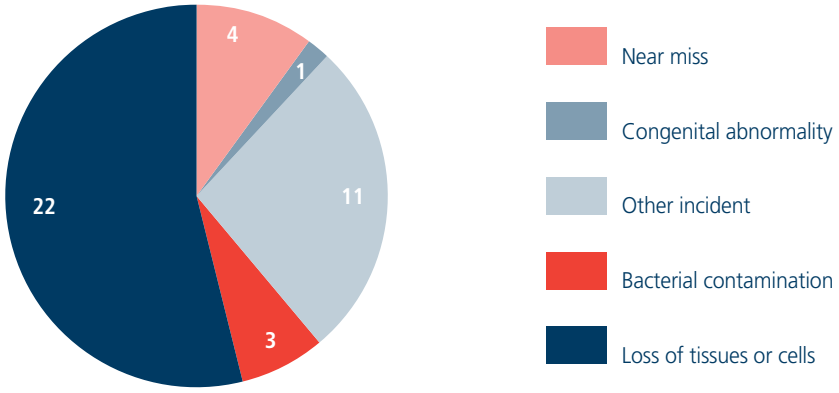


Figure 4. Reports per category of event in 2013

Loss of tissues or cells

Since the introduction of the Dutch Association of Clinical Embryologists' guideline for the reporting of adverse reaction and events in assisted reproductive technologies in 2008 the category of loss of tissues or cells has been the largest. The percentage varied from 54 to 81%. 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 2013, broken down according to the type of error.

Table 7. Reports in the category of loss of tissues or cells regarding gametes, embryos and gonadal tissues in 2013

Type of error	Number of reports	Step in procedure	Type gamete or embryo	Description
Processing error	16	Incubation	Oocytes	Dish of fertilised oocytes destroyed in error
				2x dish containing fertilised oocytes accidentally dropped
				Dish of fertilised oocytes knocked over
			Embryos	Dish containing embryos accidentally dropped
				Accidental switch of unfertilised oocytes and fertilised embryos
		Insemination	Oocytes	Oocytes 'inseminated' from tube that did not contain semen.
				Identification error when adding semen to oocytes in IVF
				1 out of 9 oocytes not injected in ICSI procedure
				At insemination dish of oocytes knocked over: 2 out of 9 oocytes lost
		Processing	Oocytes	Oocytes dropped from pipette
				Pipette accidentally knocked into container lid
			Embryo	Tip of pipette broke off at transfer to ET medium
		Cryopreservation	Embryos	2x incorrect composition of cryopreservation medium. All cryopreservation embryos for 4 and 12 couples respectively were lost
		Application	Embryo	Dish dropped with embryo for transfer
Technical error	3	Processing	Oocytes	Pipette breakage, all oocytes lost
			Partner semen	Tip of pipette shatters, semen could not be used
		Cryopreservation	Embryos	Cryopreservation device breaks down during cryopreservation run. Embryos of 2 couples lost
Assessment error	2	Incubation	Embryos	1 embryo erroneously assessed as unfit for cryopreservation
		Thawing		Straw containing 2 embryos mistaken for 1 embryo and thawed
Other	1	Cryopreservation	Embryos	Liquid nitrogen container incorrectly filled leading to pressure loss during cryopreservation run

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. Every year there are reports in this category, with a percentage varying from 8% to 27% regarding assisted reproductive technologies. Table 8 presents short descriptions of the other incident reports in 2013.

Table 8. Reports of other incidents regarding gametes, embryos and gonadal tissue in 2013

Type of error	Number of reports	Step in procedure	Type gamete or embryo	Description
Storage error	3	Donation	Partner semen	3x incorrect semen container used
Technical error	3	Cryopreservation	Embryos	Cryopreservation device broke down during cryopreservation run, no alarm
				Cryopreservation device error notification during cryopreservation run
		Transportation	Oocytes	Transportation box cooled down during transport
Identification error	2	Donation	Partner semen	Unlabelled semen sample presented and accepted
		Testing	Semen (autologous)	Switch of semen samples for analysis
Communication error	2	Processing	Partner semen	Semen for IUI destroyed in error
	1	Incubation	Semen and oocytes	Instead of combined IVF and ICSI procedure only IVF procedure carried out
Processing error			Embryos	Pronuclei score not determined

Near miss

TRIP has also received near miss reports concerning assisted reproductive technologies in every reporting year since 2008. Their percentage among the reports involving assisted reproductive technologies has varied from 4% to 10%. The near miss events in 2013 are summarised in Table 9.

Table 9. Reports of near miss concerning gametes, embryos and gonadal tissues.

Type of error	Number of reports	Step in procedure	Type gamete or embryo	Description
Identification error	3	Cryopreservation	Embryos	Possible misidentification of cryo embryo due to printing too many name labels
				Incorrect embryos taken for cryopreservation, error found at double check procedure
		Application		Switch of embryos for transfer for patients with identical name, error found at 1st check
Processing error	1	Processing	Partner semen	Semen for IUI moved to different work station leading to potential risk of switch

Bacterial contamination

Three adverse events were registered in the category of bacterial contamination in 2013 (Table 10). Reports were previously received in this category in 2008 (2), 2010 (1) and 2013 (3). This year's reports are summarised in Table 10.

Table 10. Reports of bacterial contamination concerning gametes, embryos or gonadal tissue in 2013

Type of error	Number of reports	Step in procedure	Type gamete or embryo	Description
Processing error	2	Incubation	Embryos	Incubating embryos of 5 couples contaminated by Staphylococcus epidermidis. 7 out of 20 embryos lost
				Incubating embryos of 2 couples contaminated by E. coli, all embryos lost
Other	1	Donation	Embryos	Incubating embryos of 1 couple contaminated by (ESBL-producing) E. Coli. Diagnosed after ET. Patient developed abdominal pain and fever, treated with antibiotics

Congenital abnormality

In 2007 (2), 2009 (1), 2012 (7) and 2013 (1) reports were received in the category of congenital abnormality. The 2013 report is described in Table 11.

Table 11. Report of congenital abnormality following application of reproductive cells

Type of error	Number of reports	Step in procedure	Type gamete or embryo	Description
Other	1	Donation	Semen (donor)	Tuberous sclerosis found in fetus, investigations revealed a de novo mutation

2.2 Hematopoietic stem cells and therapeutic cells

Hematopoietic stem cells (HPSC) can be transplanted in 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 collected 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 stem cell transplants.

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 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. In collaboration with Sanquin, Europdonor Foundation arranges collection of bone marrow and peripheral stem cells from Dutch volunteer donors in two university hospitals. In The Netherlands there is one (Sanquin) cord blood bank that processes and stores cord blood transplants, making them available for unrelated patients.

2.2.1 Processing, distribution and transplantation

Tables 12 and 13 show the figures for processing, distribution and transplantation of hematopoietic stem cells and numbers of institutions performing each activity.

Table 12. Processing and distribution of hematopoietic and therapeutic cells in 2013

Type	Establish-ment	Unit	Processed	Distributed				
				Unit	In NL	In EU	Outside EU	Total
HPSC unrelated								
Bone marrow	6	Transplant	27	Bag	27	15	4	46
PBSC	6	Transplant	173	Bag	269	28	11	308
Cord blood	7	Transplant	252	Bag	128	6	8	142
HPSC related								
Bone marrow	5	Transplant	39	Bag	37	0	0	37
PBSC	6	Transplant	149	Bag	160	0	0	160
Cord blood	3	Transplant	4	Bag	3	1	0	4
HPSC autologous								
Bone marrow	4	Transplant	56	Bag	56	0	0	56
PBSC	10	Transplant	2534	Bag	2561	0	0	2561
Cord blood	2	Transplant	14423	Bag	0	2	1	3
Other cells								
Mesenchymal stem cells, unrelated	3	Transplant	6	Bag	105	39	6	150
Lymphocytes (DLI), unrelated	3	Transplant	102	Bag	66	0	0	66
Lymphocytes (DLI), related	6	Transplant	92	Bag	58	0	0	58
Dendritic cells, related	1	Transplant	1	Bag	3	0	0	3
Dendritic cells, autologous	2	Transplant	60	Bag	105	0	0	105
Granulocytes, related	1	Transplant	20	Bag	20	0	0	20

Table 13. Application of hematopoietic stem cell and therapeutic cells in 2013

Type	Transplant centres	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total bags
HPSC unrelated							
Bone marrow	6	40	Bag	21	19	2	42
PBSC	6	251	Bag	115	137	32	284
Cord blood	7	73	Bag	25	63	42	130
HPSC related							
Bone marrow	5	32	Bag	32	0	0	32
PBSC	6	155	Bag	176	0	0	176
Cord blood	3	2	Bag	3	0	0	3
HPSC autologous							
Bone marrow	4	56	Bag	56	0	0	56
PBSC	10	596	Bag	1838	0	0	1838
Cord blood	2	0	Bag	0	0	0	0
Other cells							
Mesenchymal stem cells, unrelated	3	44	Bag	103	39	6	148
Lymphocytes (DLI), unrelated	3	113	Bag	49	56	8	113
Lymphocytes (DLI), related	6	53	Bag	58	0	0	58
Dendritic cells, related	1	1	Bag	3	0	0	3
Dendritic cells, autologous	2	59	Bag	63	0	0	63
Granulocytes, related	1	3	Bag	20	0	0	20

2.2.2 Reports

The reports with hematopoietic stem cells and therapeutic cells in 2013 concerned thirteen adverse event reports and seven adverse reactions. A summary is presented in Table 14 (adverse events) an Table 15 (adverse reactions).

Table 14. Overview of adverse events concerning hematopoietic stem cells and therapeutic cells in 2013

Type of error	Category of adverse event	Number
PBSC autologous	Loss of tissue or cells • Tear in 1 of 4 stem cell bags	1
	Other incident • Syringe used incorrectly at lab processing samples during apheresis leading to incorrect (lower) volume calculations (28 patients). No patient underwent an unnecessary second apheresis procedure	1
	• Injection port detached from bag, no bacterial contamination (1 of 6 bags)	1
	• Tear in 1 of 4 stem cell bags	1
	• Apheresis set ruptured due to incorrect setting up, no loss of stem cells	1
	• Temperature of cleanroom rose to 27°C due to technical malfunction, leading to poor recovery of stem cells	1
PBSC, allogeneic unrelated	Loss of tissue or cells • Injection port came away from bag (1 of 8)	1
	Other incident • Transplant product distributed by external donor centre with spike in corresponding plasma unit	1
Bone marrow, allogeneic related	Other incident • Collection of bone marrow in incorrect heparin bags; heparin washed out before application	1
Cord blood, allogeneic unrelated	Loss of tissue or cells • Bank supplied transplant with incorrectly stated (low) erythrocyte concentration, patient developed temporary macroscopic hematuria	1
Other cells	Loss of tissue or cells • Leakage of donor lymphocyte bag • Tube broken away from bag of mesenchymal stem cells, patients suffers worsening of GvHD	2
	Other incident • Luer connection loose on NK depletion set, sterility check OK	1
Total		**13**

Among the adverse events in 2013 there were another five reports of leaking or ruptured collection sets or storage bags. The Stem Cell Laboratory Working Group initiated further investigations that were not yet complete at the time of writing this report. Figure 5 presents an overview of reports of leaking or ruptured collection sets or storage bags in the period 2007-2013.

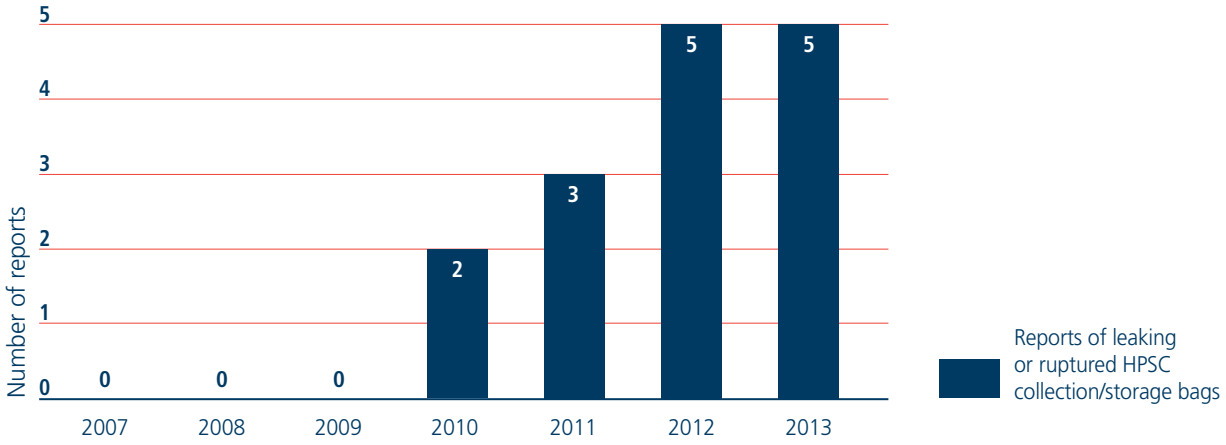


Figure 5. Reports of leaking or ruptured HPSC collection or storage bags 2007-2013

Table 15. Overview of adverse reactions per type hematopoietic stem cell or therapeutic cell in 2013

Type	Adverse reaction	Number
Donor: PBSC, allogeneic related	Donor complication • Donor developed hypertension and benign paroxysmal positional vertigo immediately after donation leading to prolonged absence from work	1
Donor: PBSC, allogeneic unrelated	Donor complication • Donor developed CVA 2 months after donation	1
Donor: bone marrow, allogeneic unrelated	Donor complication • Donor diagnosed with breast cancer 2 years after donation	1
Patient: PBSC, autologous	Other reaction • Brief loss of consciousness and tachycardia without hypotension; attributed to DMSO	1
	Anaphylactic reaction • Drop in blood pressure and O_2 saturation, neurologic deterioration during infusion of 2nd unit, bronchospasm during 3rd unit	1
Patient: PBSC, allogeneic related	Anaphylactic reaction • Hypotension, hypoxemia, somnolence and gasping; rapid recovery	1
Patient: PBSC, allogeneic unrelated	Other reaction • Chills and rigors, nausea and vomiting attributed to citrate toxicity	1
Total		**7**

In 2013 three donor complications were reported as well as three reports regarding donor complications in previous reporting years, two in 2012 and one in 2010. Two cases concerned an apheresis and a bone marrow donor who developed complications that were temporally related to donation (phlebitis and hypertension with benign paroxysmal positional vertigo respectively), where imputability was assessed as probable. The remaining donor complications concern major morbidity (breast cancer, rheumatoid arthritis, TIA and CVA) of the donor, where imputability is assessed to be unlikely. Table 16 presents an overview of all donor complications registered by TRIP in relation to stem cell donation.

Table 16. Overview of donor complications, 2007-2013

Type of HPSC	Number	Donor complication	Interval after donation	Imputability
PBSC, related	5	• Shoulder abscess (S. aureus)	12 days	possible
		• AML	7 years	possible
		• MDS-RAEB	5 years	possible
		• Transient rise of creatinine level	during apheresis	probable
		• Benign paroxysmal positional vertigo	immediately	probable
PBSC, unrelated	4	• Breast carcinoma	2 years	unlikely
		• Phlebitis	?	probable
		• CVA	2 months	unlikely
		• Rheumatoid arthritis	6 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 of unrelated donors is well organised, however follow-up of related donors is not yet fully established. 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.

Figure 6 shows the numbers of reports relating to hematopoietic stem cells and therapeutic cells in the years 2007-2013.

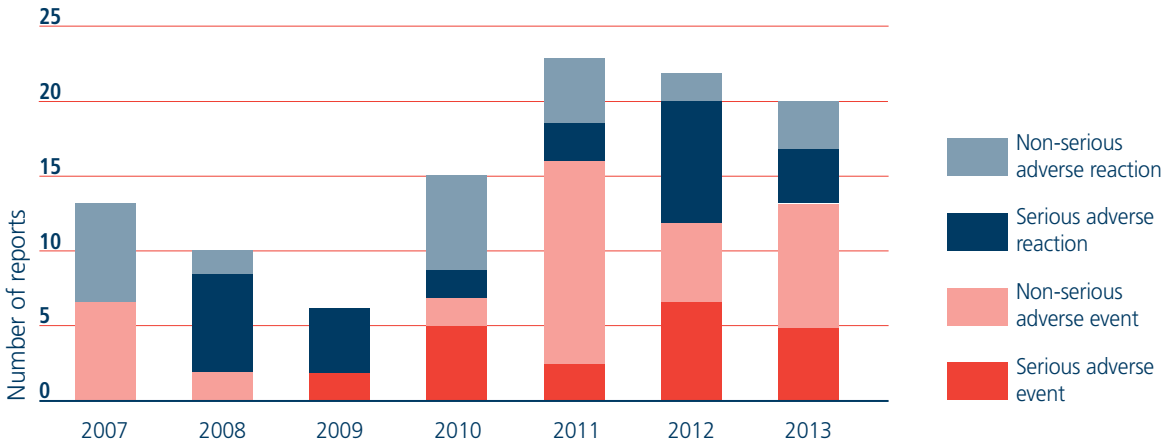


Figure 6. Reports concerning HPSC and therapeutic cells, 2007-2013

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 in reconstruction of bone 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 eleven 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. Two tissue establishments culture chondrocytes for autologous transplantation.

2.3.1 Bone

Processing, distribution and application

Table 17 shows the numbers of processed and distributed units of bone tissue. Table 18 shows the numbers of transplanted bone tissue units. These data were provided by 59 hospitals, six private clinics and nine oral implantology practices.

Table 17. Processing and distribution of bone in 2013

Type	Tissue establish-ments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Bone, whole	2	265	Transplant	95	6	1	102
Bone filler, mineralised: chips, cubes and wedges	9	2714	Container	3135	3564	4184	10883
Bone filler, mineralised: whole and halved femoral heads	12	4037	Transplant	2205	50	0	2255
Bone filler, demineralised	6	4860	Container	1405	17622	12595	31622
Auditory ossicles	1	32	Transplant	32	0	0	32
Cranial bone (autologous)	4	150	Transplant	82	1	0	83
Other	0	0	Transplant	0	0	0	0

Table 18. Application of bone tissue in 2013

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Bone, whole	11	57	Transplant	48	7	2	57
Bone filler, mineralised: chips, cubes and wedges	53	1419	Container	1311	156	20	1487
Bone filler, mineralised: whole and halved femoral heads	52	1213	Transplant	1264	14	0	1278
Bone filler, demineralised	12	100	Container	102	0	0	102
Auditory ossicles	2	15	Transplant	5	10	0	15
Cranial bone (autologous)	7	108	Transplant	107	1	0	108
Other	1	1	Transplant	1	0	0	1

Table 19. Distributed vs. applied bone tissue in The Netherlands in 2013

Type	Distributed in NL	Applied from NL	Discrepancy
Bone, whole	95	48	47
Bone filler, mineralised: chips, cubes and wedges	3135	1208	1927
Bone filler, mineralised: whole and halved femoral heads	2205	1264	941
Bone filler, demineralised	1405	102	1303
Auditory ossicles	32	5	27
Cranial bone (autologous)	82	107	-25
Other	0	1	-1

Even though more hospitals and clinics have submitted numbers of applied bone tissue, there remains a large discrepancy in number of distributed units of bone filler an auditory ossicles and the numbers of application. Bone filler, mineralised or demineralised, may not always be recognised in hospitals and clinics as a substance of human origin. The discrepancy in distributed and transplanted whole bones, however, was smaller compared to 2012. The negative discrepancy in autologous cranial bone is explained by temporary storage in hospitals pending the transplantation in neurosurgical patients. These cranial bone grafts are often not counted as distributed.

Reports

In 2013 six reports were registered concerning bone tissue, including one serious adverse reaction and two serious adverse events. The reports are summarised in Tables 20 and 21.

Table 20. Overview of adverse events concerning bone tissue in 2013

Category of event	Number	Description
Loss of tissue and cells	2	In a bone bank a femoral head with two identification numbers was found. Traceablility failure, femoral head destroyed
		Freezer alarm ignored, temperature of one femoral head rose to -17 ^{0}C
Bacterial contamination of product	2	From samples in theatre at transplant of allogeneic femoral head S. aureus was cultured (3 out 6 samples positive). Cultures from bone bank after donation negative. Patient treated with antibiotic prophylaxis, no infectious symptoms
		After reapplication of autologous cranial bone infection with Propioni and S. aureus. Autologous cranial bone was removed and sterilised. After second application reinfection necessitated second procedure for removal. Imputability unlikely
Other incident	1	Malfunction of storage freezer containing femoral heads. Due to timely installation of another freezer no loss of bone tissue

Table 21. Overview of adverse reactions concerning bone tissue in 2013

Category of adverse reaction	Number	Description
Post-transplant bacterial infection	1	Septic gonarthritis (staphylococcus aureus) after application of bone chips in reconstruction of tibial plateau fracture with local graze. Imputability unlikely

The largest risk in bone tissue transplantation is transmission of pathogens or malignancies. In 2013 there were two reports of bacterial contamination of product and one post-transplant bacterial infection. It is important to advise the distributing tissue establishment of a post-transplant bacterial infection immediately, so that adequate measures can be taken (i.e. quarantining tissues deriving from the donor concerned).

Figure 7 gives an overview of reports concerning bone tissue in 2006-2013.

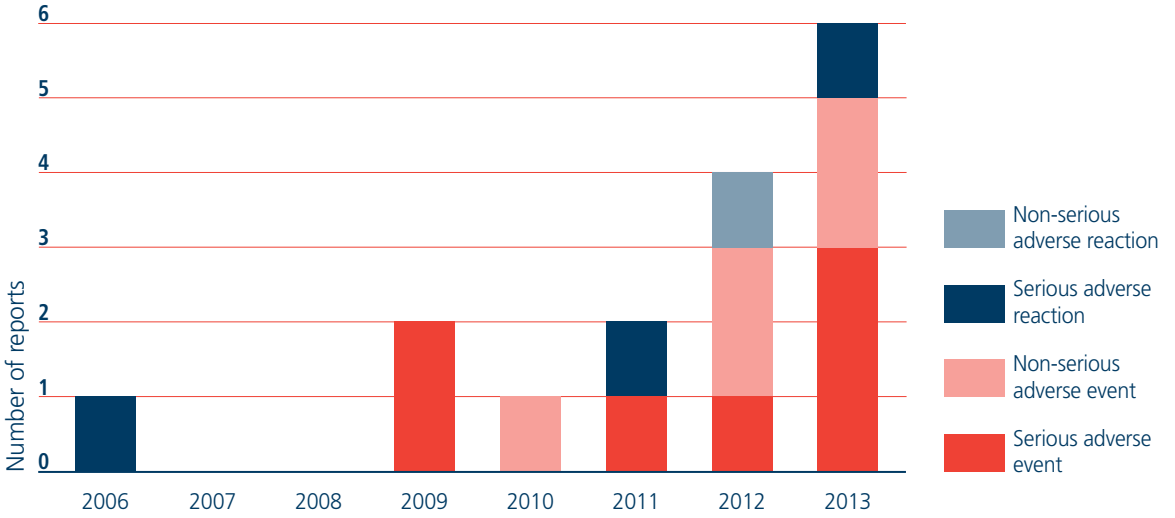


Figure 7. Reports concerning bone tissue, 2006-2013

2.3.2 Cartilage

Processing, distribution and application

Tables 22 and 23 present data on processed plus distributed cartilage and applied cartilage respectively.

Table 22. Processing and distribution of cartilage in 2013

Type	Tissue establish-ments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cartilage	3	98	Transplant	70	0	0	70
Chondrocytes	2	271	Transplant	64	106	0	170

Table 23. Application of cartilage in 2013

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Cartilage	5	91	Transplant	77	14	0	91

Reports

One report concerning cartilage was registered in 2013 in the category of other incident. An autologous cartilage biopsy was to be processed in a foreign tissue establishment. No chrondrocytes were found in the biopsy material. Investigations did not reveal a cause and the patient had to undergo a second biopsy. As this event occurred in a tissue establishment outside The Netherlands this event should be reported to the competent authority in the other country. Since a Dutch patient was affected the hospital decided to report to TRIP.

Figure 8 presents an overview of reports concerning cartilage in the period 2007-2013.

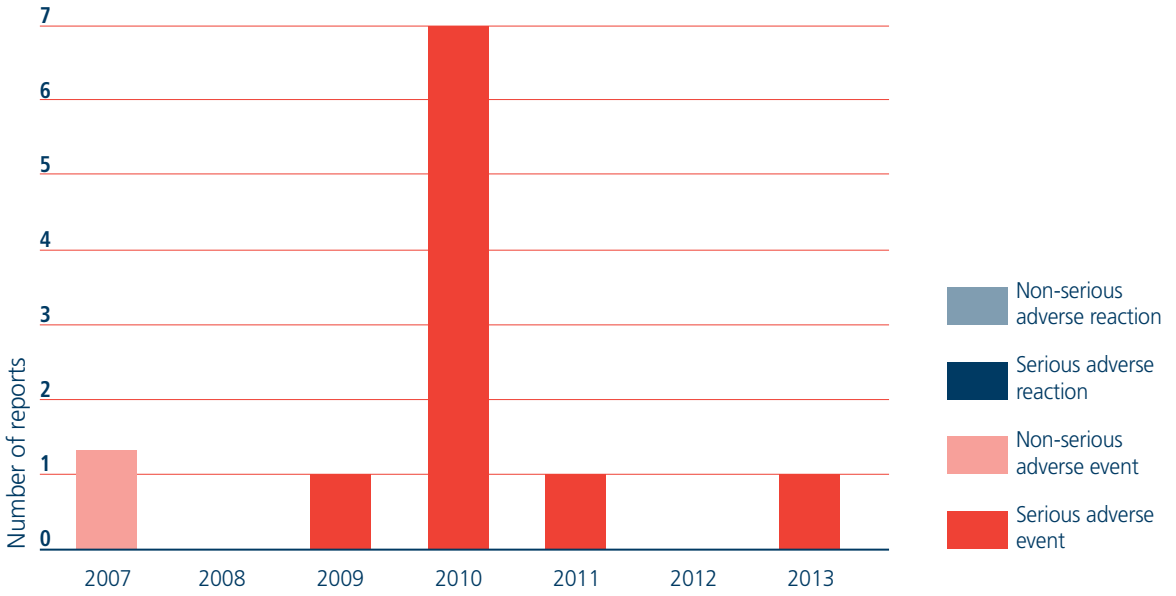


Figure 8. Reports concerning cartilage, 2007-2013

2.3.3 Tendons, ligaments, fascia and menisci

Processing, distribution and application

Table 24 presents numbers of processed and distributed tendons, ligaments, fascia and menisci and Table 25 gives an overview of application data of these tissues.

Table 24. Processing and distribution of tendons, ligaments, fascia and menisci in 2013

Type	Tissue establish-ments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Tendons	2	742	Transplant	532	45	0	577
Ligaments and fascia	3	1643	Transplant	1542	141	0	1683
Menisci	0	0	Transplant	0	0	0	0
Other	0	0	Transplant	0	0	0	0

Table 25. Application of tendons, ligaments, fascia and menisci 2013

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Tendon	27	310	Transplant	309	4	0	313
Ligaments and fascia	13	331	Transplant	268	69	0	337
Menisci	3	12	Transplant	0	9	11	20
Other	0	0	Transplant	0	0	0	0

As in the data regarding bone tissue there is a discrepancy between numbers of processed and distributed tendons, ligaments, fascia and menisci and the application data (Table 26).

Table 26. Distributed vs applied tendons, ligaments, fascia and menisci in The Netherlands in 2013

Type	Distributed in NL	Applied in NL	Discrepancy
Tendons	532	309	223
Ligaments and fascia	1542	268	1274
Menisci	0	0	0
Other	0	0	0

Reports

In 2013 there were five reports that all involved tendons. The reports are briefly described in Tables 27 and 28.

Table 27. Overview of adverse events concerning tendons in 2013

Category of event	Number	Description
Loss of tissues or cells	1	Tendon thawed too early due to communication error concerning date of surgery
Bacterial contamination of product	1	Peroperative culture specimen grew S. capitis and S. epidermidis. All processing cultures negative
Other incident	2	Dimensions of tendon incorrectly stated on label. Patient received thinner tendon than planned
		Surgeon trimmed tendon peroperatively, leading to weaker graft, instead of ordering required graft size. Tendon ruptured twice during transplant surgery

Table 28. Overview of adverse reactions concerning tendons in 2013

Category of adverse reaction	Number	Description
Post-transplantation bacterial infection	1	Severe postoperative wound infection from which 4 different micro-organisms were cultured after transplant of allogeneic tibial tendon in cruciate ligament reconstruction of knee. Imputability unlikely based on long time lag, large number of different micro-organisms and the fact that no other recipients from the donor were affected

Figure 9 presents an overview of reports concerning tendons in reporting years 2007-2013.

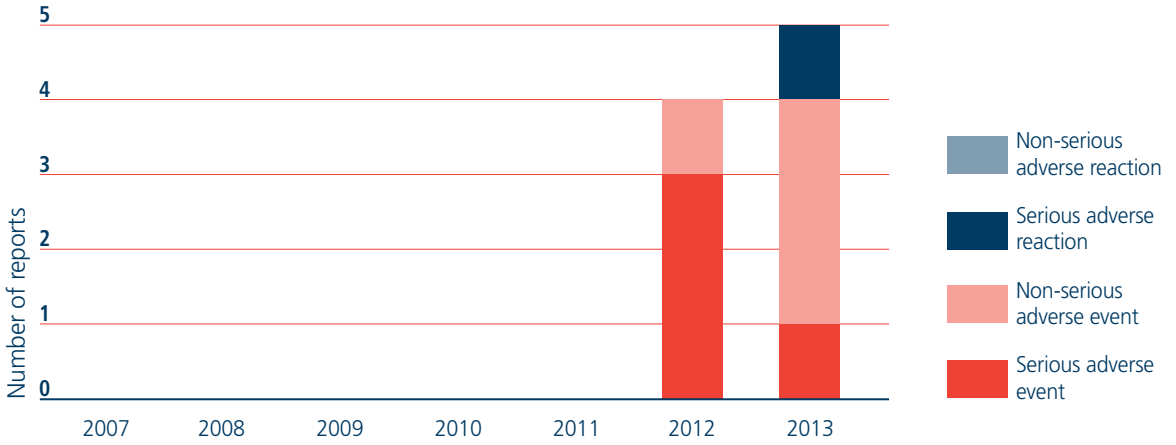


Figure 9. Overview of reports concerning tendons, 2007-2013

2.4 Ocular tissue

Two parts of the eye are used in transplant procedures: the cornea and the sclera. A corneal transplant is indicated when visual acuity is impaired due to a corneal scarring or 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. Two corneal grafting techniques are available, namely penetrating (full thickness) and lamellar keratoplasty. 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 29 the numbers of processed and distributed units of ocular tissue are presented. Table 30 gives data on application of ocular tissue as submitted by the hospitals and clinics. Eleven out of 17 hospitals and clinics that perform corneal transplants submitted data, which explains the difference between distribution and application data. Nine hospitals and clinics provided data on scleral transplants.

Table 29. Processing and distribution of ocular tissue in 2013

Type	Tissue establish-ments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Cornea	2	3051	Whole or lamella	1296	157	4	1457
Sclera	1	333	Whole or quadrant	996	1	0	997

Table 30. Application of ocular tissue in 2013

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Cornea	11	579	Whole or lamella	577	12	0	589
Sclera	9	293	Whole or quadrant	284	1	0	285

2.4.2 Reports

TRIP registered seven adverse events involving ocular tissue in 2013. The reports were submitted by one tissue establishment and one hospital. Five reports were assessed as serious. A summary of the reports is presented in Table 31.

Table 31. Overview of adverse events concerning ocular tissue in 2013

Category of event	Number	Description
Loss of tissues or cells	3	• Corneal lamella torn during pre-op dissection. Trephining by distributing tissue establishment was incomplete due to burr on microkeratome
		• Incomplete cutting of precut lamella due to erroneous re-use of disposable material on keratome. (Note: production of precut lamellae is relatively new technique for the TE)
		• Ophthalmologist decided to use different surgical technique from that indicated on cornea request. Cornea not suitable for the chosen technique
Other incident	2	• No donor consent for enucleation of eyeballs. Under time pressure consent for skin and eye donation was presumed whereas only consent for skin donation had been given
		• In operating theatre a corneal macula is noted during preparation. Surgery postponed. Cornea mistakenly not returned to tissue bank, rendering further evaluation impossible
Other contamina-tion of product	1	• Candida lipolytica, transplant postponed
Near miss	1	• At 2nd evaluation of corneas mix-up of L and R corneas noted. One cornea had already been distributed but was recalled for correction

Figure 10 presents an overview of reports concerning ocular tissue in 2007-2013.

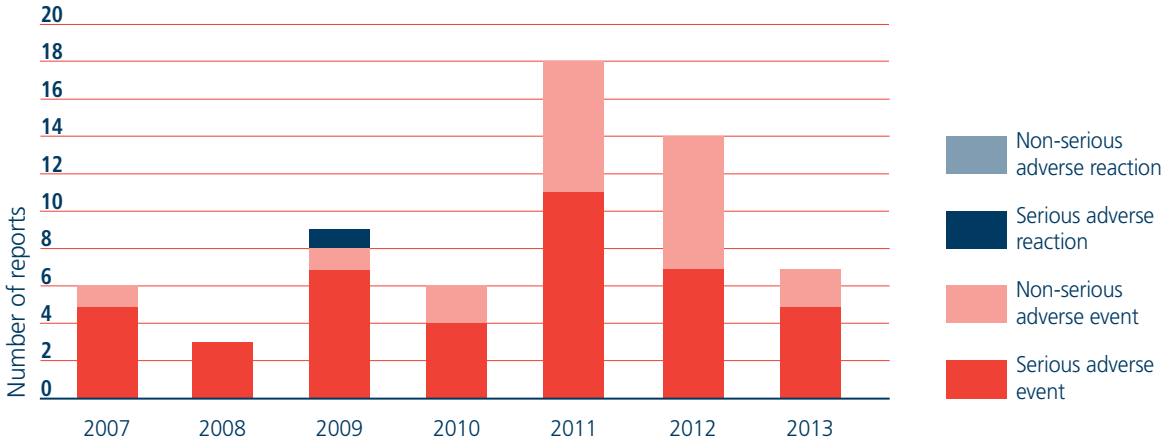


Figure 10. Reports concerning ocular tissue, 2007-2013

In reporting years 2011 and 2012 TRIP received ten reports that mentioned a haze in the transplanted cornea. The "cornea working group" of the Dutch Society for Ophthalmology, in collaboration with the tissue establishment, did not discover a cause despite extensive investigations. This type of report has subsequently dropped spontaneously. In 2013 there was just one report of an other incident that could be part of this cluster. The transplanting surgeon observed a corneal macula and decided not to use the cornea. Unfortunately the cornea bank's protocol that required return of the cornea to the tissue establishment was not followed. In the interests of safety of the chain of human tissue and cells transplanting surgeons should always urgently contact the distributing tissue establishment if there is an adverse event so that it can be properly investigated.

2.5 Cardiovascular tissue

In The Netherlands heart valves, blood vessels and patches are used for transplant 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 and 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

Tables 32 and 33 present figures of processing/distribution and application of cardiovascular tissue.

Table 32. Processing and distribution of cardiovascular tissue in 2013

Type	Tissue establish-ments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Heart valves	1	468	Transplant	72	9	0	81
Blood vessels	1	25	Transplant	1	8	0	9
Patches, pericardium and other	1	0	Transplant	13	9	0	22

Table 33. Application of cardiovascular tissue in 2013

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Heart valves	6	73	Transplant	70	3	0	73
Blood vessels	1	1	Transplant	1	0	0	1
Patches, pericardium and other	2	14	Transplant	13	1	0	14

2.5.2 Reports

In 2013 an other incident was reported that concerned a pulmonary valve which was found to have been damaged at dissection in the tissue establishment. The defect could be repaired during surgery and there were no adverse consequences for the patient. This report was assessed to be serious as a defective tissue product was distributed by the tissue establishment.

In Figure 11 an overview of reported adverse events and reactions concerning cardiovascular tissue is presented. On average there was one serious adverse event per reporting year.

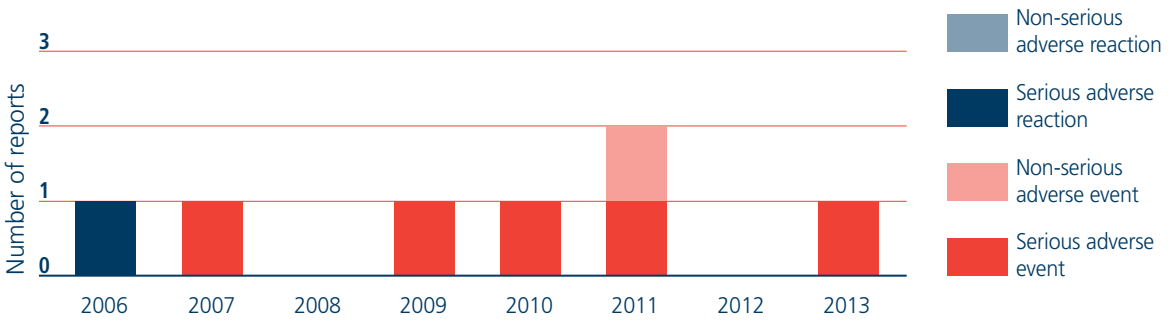


Figure 11. Reports regarding cardiovascular tissue, 2006-2013

All cardiovascular tissue reports in 2006-2013 concerned heart valves, both aortic and pulmonary valves. In 2006 and 2007 an other reaction and an other incident respectively were reported; in both cases the recipient died following complications that were not related to the transplanted tissue. The reports in 2009 and 2010 regarded bacterial contamination of products. In 2011 two adverse events were reported in the category loss of tissues and cells, caused by a communication error and an other error.

2.6 Skin

Skin tissue can be classified in four categories: donor skin, autologous skin, cultured skin/skin cells and non-cellular dermis. The largest category is donor skin that is applied as 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

Table 34 presents numbers of processed and distributed skin units and Table 35 gives numbers of applications of skin tissue.

Table 34. Processed and distributed skin units in 2013

Type	Establish-ments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Donor skin	2	440#	Pack	9075	81816	62876	153764
Autologous skin	0	0	Transplant	0	0	0	0
Cultured skin / skin cells	1	30	Transplant	15	0	0	15
Other*	3	0	Transplant	113	519	88	720

* *Non-cellular dermis derived from donor skin*

\# *Donors*

Table 35. Applied skin tissue in 2013

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Donor skin	5	61	Pack	460	5	0	5465
Autologous skin	3	240	Transplant	240	0	0	240
Cultured skin / skin cells	1	6	Transplant	65	0	0	65
Other	2	12	Transplant	12	0	0	12

2.6.2 Reports

As in 2011 and 2012 there were no reports concerning skin tissue in 2013. The numbers of reports per year are shown in Figure 12. In 2008 there were five reports that concerned the experimental phase of a cultured skin product. In the study setting all adverse events in patients, including events not related to the skin product, had to be recorded and were also reported to TRIP.

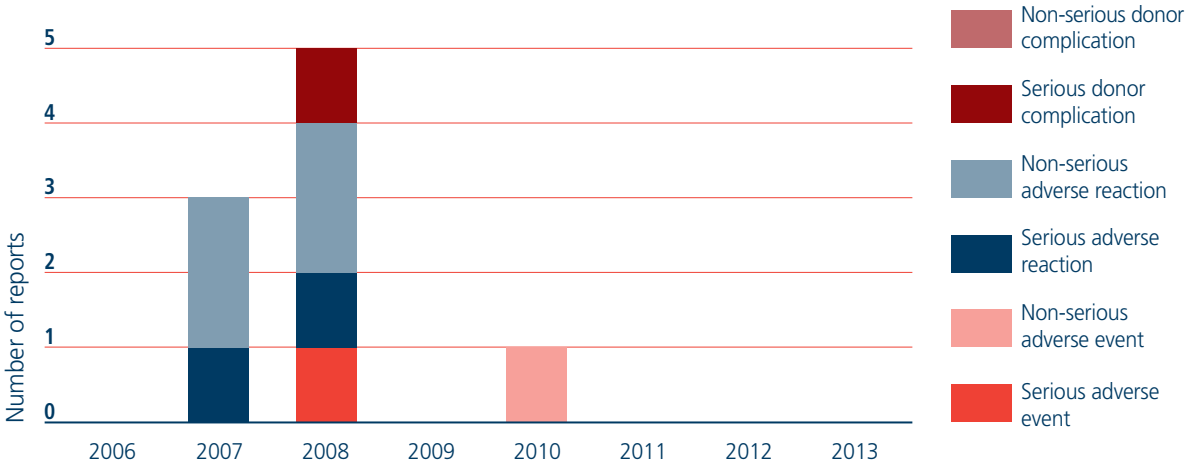


Figure 12. Reports concerning skin tissue or keratinocytes in 2006-2013

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) radio-active labelled erythrocytes and leukocytes for diagnostic purposes.

2.7.1 Processing, distribution an application

In the following Tables 36 and 37 numbers of processed and distributed units and numbers of applied units other tissues and cells are presented.

Table 36. Processing and distribution of other tissues and cells in 2013

Type	Establish-ments	Processed	Distributed				
			Unit	In NL	In EU	Outside EU	Total
Amniotic membrane	1	2*	Pack	71	51	0	122
Langerhans' islets	1	61	Transplant	9	0	0	9
Adipose tissue	1	0	Transplant	0	18	0	18
Umbilical cord tissue	1	9058	Transplant	0	0	0	0
Erythrocytes	1	78	Bag	78	0	0	78
Leukocytes	1	136	Bag	133	0	0	133

* *Placentas*

Table 37. Application of other tissues and cells in 2013

Type	Hospitals/ clinics	Recipients	Transplants				
			Unit	From NL	From EU	From non EU	Total
Amniotic membrane	3	22	Pack	23	0	0	23
Langerhans' islets	1	9	Transplant	7	2	0	9

2.7.2 Reports

In 2013 there were no reports of adverse events or reactions relating to these tissue and cell types.

Chapter 3. Technical errors

From 2007 up to and including 2013 TRIP registered 54 reports that were classified as technical errors or failures. This amounted to 11% of the total number of reports and 16% of adverse events in this period. This theme chapter takes a closer look at these errors.

The definition of a technical error:
All cases where the technical equipment or materials used for procurement, testing, processing, storage, transportation or application of the product was defective.

Table 38 shows the subdivision of these technical errors according to tissue type. Over half the technical error reports involved gametes, embryos and gonadal tissue.

Table 38. Technical errors subdivided by tissue type, 2007-2013

Tissue or cell type	Number of reports	Serious events
Bone	1	0
Cartilage	3	2
Ocular tissue	3	3
Hematopoietic stem cells	14	11
Gametes, embryos and gonadal tissue	31	18
Other tissues and cells	2	2
Total	**54**	**36**

In Table 39 the reports are subdivided according to the type of technical error and TRIP reporting category. The other incidents in all cases led to possible loss of quality or volume of the tissues or cells.

Table 39. Technical errors and TRIP category, 2007-2013

Description technical error	Total number of reports	Loss of tissues or cells	Other incident	Type of tissue or cells involved
Incorrect/defective storage material	15	11	4	Peripheral blood stem cells, therapeutic cells, semen and embryos
Incorrect/defective processing materials	10	9	1	Semen, oocytes, embryos
Failing/malfunctioning cryopreservation equipment	10	5	5	Semen, embryos, gonadal tissue
Incorrect composition of medium or additive solution	3	3	0	Cartilage (chondrocyte culture), embryos
Incorrect/defective collection material	3	0	3	Peripheral blood stem cells, cartilage
Defective processing equipment	3	3	0	Cornea
Failing/malfunctioning incubator	2	1	1	Embryos
Failing/malfunctioning transportation box	2	1	1	Semen, oocytes
Incorrect/defective collection container	2	1	1	Semen, oocytes
Failing/malfunctioning liquid nitrogen tank	1	1	0	Semen
Failing/malfunctioning of monitoring or alarm system	1	0	1	Semen, oocytes, embryos, gonadal tissue
Failing/malfunctioning freezer (-80°C)	1	0	1	Bone
Failing climate control in clean room	1	0	1	Peripheral blood stem cells
Total	**54**	**35**	**19**	

Technical errors are discussed further according to the type of material or equipment involved.

Storage material

The largest number of technical errors (15) concerned incorrect or defective storage material. In the case of peripheral blood stem cells, there were reports of tears in storage bags, fractures of attached ports and loosening of sealing caps. For semen and embryos there were reports describing a defective cryopreservation straw and a defect in a liquid nitrogen tank. Peripheral blood stem cells, therapeutic cells and embryos are all very difficult to replace or irreplaceable. Loss of these cells is therefore often assessed as a serious adverse event.

Processing material

Among the reports of incorrect or defective processing material, two reports mentioned rupture of semen tubes during spinning. Six reports described problems with pipettes used for transfer of embryos or gametes. Two reports concerned the use of incorrect dishes for embryo cultures.

Cryopreservation equipment

All nine reports of failing or malfunctioning cryopreservation equipment involved reproductive tissues or cells. Disruption of the cryopreservation run may well lead to quality loss or even complete loss of reproductive cells if viability is lost. For replacement of these cells a new treatment cycle will have to be started. Semen is usually easily replaced, but this is not the case for oocytes, embryos or gonadal tissue. Gametes, embryos or gonadal tissue for fertility preservation are irreplaceable; these were involved in two reports. One report concerned aspirated semen (PESA), which can only be replaced in another procedure. A fail-safe alarm system is able to detect failure or malfunctioning quickly and can limit adverse consequences. However, in two cases of malfunctioning cryopreservation the fail-safe system gave no alarm.

Composition of medium or additive solution

Two out of three reports in this group regarded media for sterility and endotoxin check, used at harvesting of autologous cartilage for chondrocyte culture. The third report concerned incorrect composition of mineral oil used for covering oocytes and embryos in culture.

Collection material

In two cases the collection set for peripheral stem cells leaked. A third report mentioned a defective collection kit for cartilage with an incorrect temperature registration.

Processing equipment

Three reports concerned a nick in the microkeratome used for preparing corneal lamellas. All reports involved the same microkeratome; the problem was found after loss of the third cornea.

Incubator

Two reports of malfunctioning incubators both involved embryo cultures. Failure or malfunctioning can result in failing temperature or atmospheric regulation and lead to quality loss or degeneration of the embryos.

Transportation box

Two reports involved transportation boxes for gametes. IVF laboratories cooperate with so-called transport clinics who carry out collection of oocytes and semen. The gametes are sent to the IVF laboratory using transportation boxes that keep temperature at 37°C. Often these boxes are equipped with a 9 volt battery. Malfunctioning of a transportation box can cause a drop in temperature which endangers quality and viability of the gametes. This happened in one case. Another type of transportation device uses liquid nitrogen for cryopreserved material. One report was of straws thawed due to evaporation of the liquid nitrogen, leading to loss of semen collected by aspiration (PESA).

Collection containers

Plastic containers are used for collection of semen and oocytes. These containers have to meet specific requirements. Two reports concern the use of an incorrect or defective container.

Liquid nitrogen storage containers

Many types of tissues and cells, like hematopoietic stem cells, heart valves, gametes, embryos and gonadal tissue are cryopreserved and stored in liquid nitrogen containers. Liquid nitrogen evaporates and has to be topped up regularly to prevent thawing of the stored tissues or cells. One report involved thawing of a semen storage container in the absence of a fail-safe alarm system.

Monitoring/alarm systems

Essential equipment is often monitored and secured by an alarm system. One report mentioned the malfunctioning of the alarm system.

Freezer (-80°C)

Musculoskeletal tissue is often stored in freezers maintaining temperature at -80°C. One report concerned malfunctioning of a freezer for femoral heads owing to leakage.

Temperature control in clean room

In one report the temperature went up too high in the cleanroom for processing peripheral blood stem cells.

Based on these reports TRIP has made the following recommendations in previous Biovigilance reports:

1. The introduction of new techniques or transplant procedures should be based on a standard operating procedure after careful guidance and training of staff in order to prevent avoidable adverse events.

2. Some technical equipment does not have a fail-safe alarm system leading to failure of timely detection of technical malfunction with the risk of loss of unique tissues or cells.

3. Particular alertness is advised after maintenance or repair of essential equipment. The recommissioning should be laid down in a standard operating procedure.

4. Adverse events concerning leakage of units of recipient-specific and potentially irreplaceable hematopoietic stem cells should be reported in order to gain insight into the extent of this problem.

5. The issue of leaking units for collection of stem cell transplants needs further investigation and monitoring; the Stem Cell Laboratory Working Group will initiate further investigations.

6. Validated transportation conditions are necessary for assuring the quality of transported tissues or cells. If validation of these processes has not been performed this should be undertaken.

7. Essential equipment like transportation boxes, incubators, cryopreservation devices and storage devices needs an adequate fail-safe alarm system to prevent quality loss or avoidable loss of tissues or cells in case of breakdown.

8. In case of difficulties in preparing a cornea with a microkeratome in a transplanting institution a rejected cornea can be ordered to use as testing material.

9. Cryopreservation equipment should be monitored during the cryopreservation run and should be equipped with an appropriate alarm system.

Summary

During the past seven years TRIP has registered 54 reports concerning some form of technical error. In 65% (35 out of 54) of the reports the error resulted in loss of tissues or cells. In the remaining 19 reports the error led to loss of quality or volume of the tissues or cells. Defective or incorrect storage or processing materials represented 46% (25 out of 54) of the reports. Failure or malfunctioning of cryopreservation equipment occurred in 19% (10 out 54) of reports. Technical errors can have major consequences for quality and viability of different types of tissues or cells, e.g. if they are cultured, preserved or stored in inappropriate conditions, if they are contaminated or if uncontrolled environmental factors have a deleterious effect.

Chapter 4. Participation

Participation of all stakeholders in the TRIP reporting system is essential for the quality of the Biovigilance system. Participation is determined on the one hand by submission of reports to TRIP and - if relevant - to the tissue establishment in question and/or the Healthcare Inspectorate. On the other hand annual numbers of all types of processed, distributed and transplanted units of human tissues and cells need to be provided along with the numbers 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 harvest and 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 like 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 which 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 activity determines the required licence type, as an organ bank or tissue establishment.

Table 40 presents an overview of licensed tissue establishments and organ banks in The Netherlands in 2013. A number of hospitals house several tissue establishments and/or organ banks.

Table 40. Licensed tissue establishments and organ banks in 2013*

	Tissue establishments	Organ banks	Total
Independent institution	10	10	20
Located in hospital/clinic	60	38	98
Total	**70**	**48**	**118**

* *Two further independent institutions are currently in the process of applying for a tissue establishment licence.*

Figure 13 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.

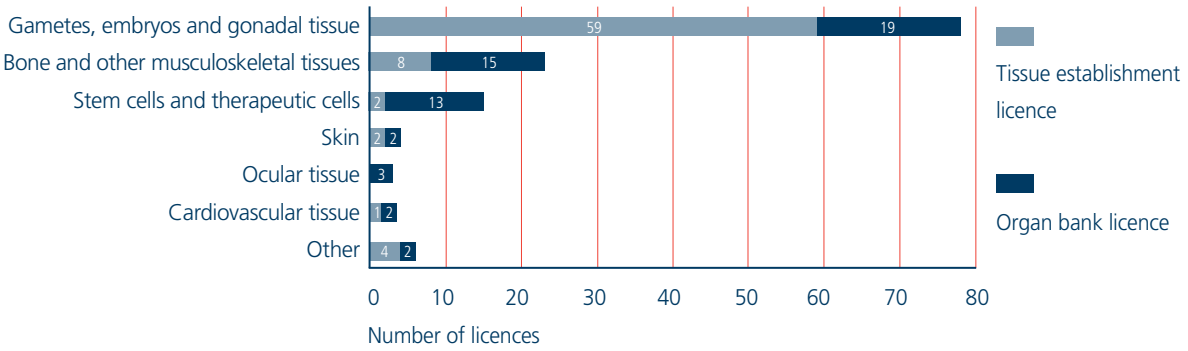


Figure 13. Number of licensed tissue establishments and organ banks in 2013

Figure 14 shows the percentage of tissue establishments that provided data on processing and distribution and whether they submitted biovigilance reports. Four tissue establishments did not provide data on processing and distribution. Two of these four hold a licence for semen processing and two hold a licence for distribution of musculoskeletal tissues. A total of three tissue establishments indicated that they did not perform any activities in 2013 that were within the scope of the Law on safety and quality of substances of human origin.

Participation of tissue establishments in 2013 amounted to 96% (114 out of 118) compared to 98% in 2012. Up till 2012 tissue establishments housed in a hospital or clinic were not included in participation figures for tissue establishments (but included in figures for participation by hospitals and clinics).

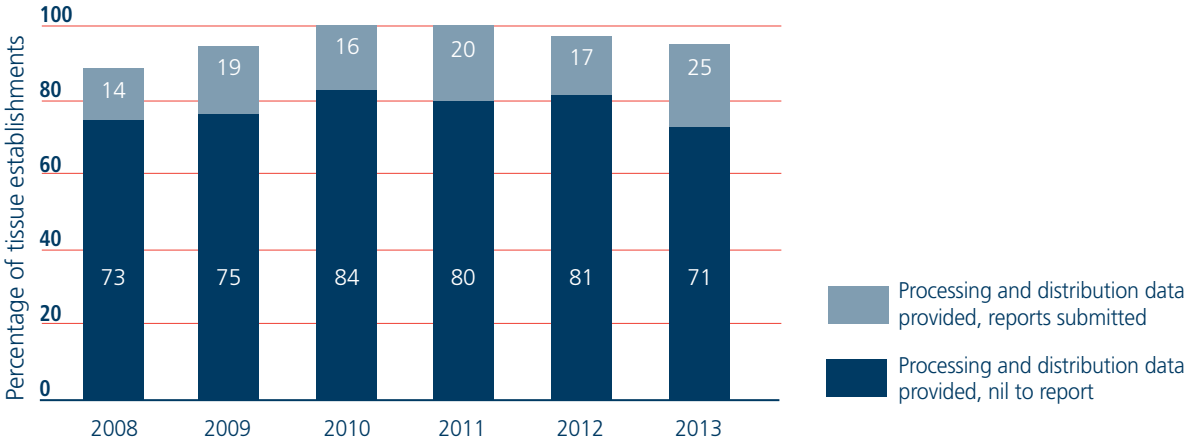


Figure 14. Participation of tissue establishments
(2008-2011: n=20, 2012-2013: n=118)

4.2 Users of substances of human origin

In all, in 2013 97 hospitals, 16 clinics and private healthcare institutions and 36 oral implantology practices were contacted for information on numbers of applied tissues and cells, the number of recipients and reports on adverse reactions and/or events. The private healthcare institutions and oral implantology practices were added to the database of users of substances of human origin on the basis of their response in the 2013 TRIP survey that they applied substances of human origin. The participation of hospitals, clinics and private health care institutions in 2013 was 92% (105 out of 113). The oral implantology practices were contacted for the first time in 2013 and their participation rate was 33% (12 out of 36). Figure 15 presents participation rates from 2008 onwards.

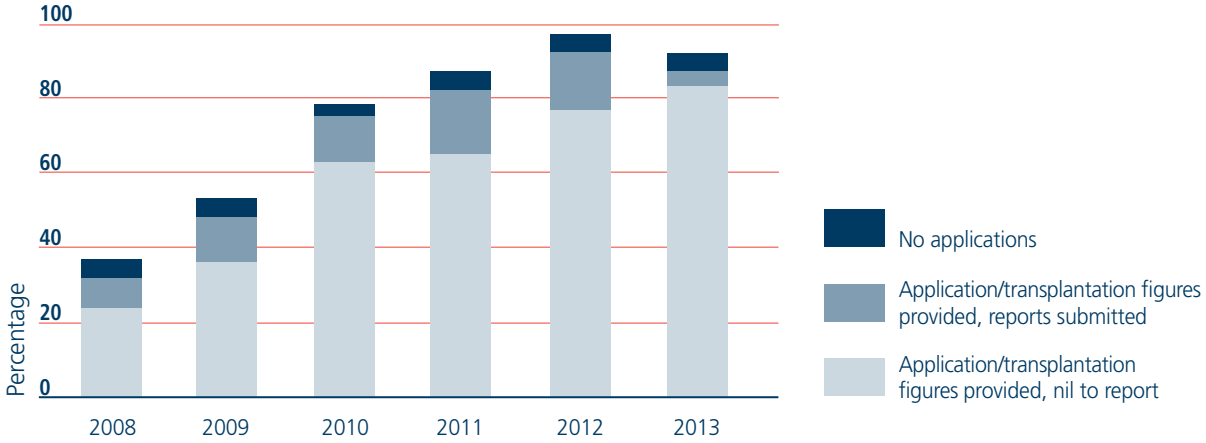


Figure 15. Participation of Dutch hospitals, clinics, private healthcare institutions and oral implantology practices, 2008-2013

(n=101-113)

Annex 1. About TRIP

The TRIP (Transfusion and Transplantation Reactions in Patients) Foundation was established 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.

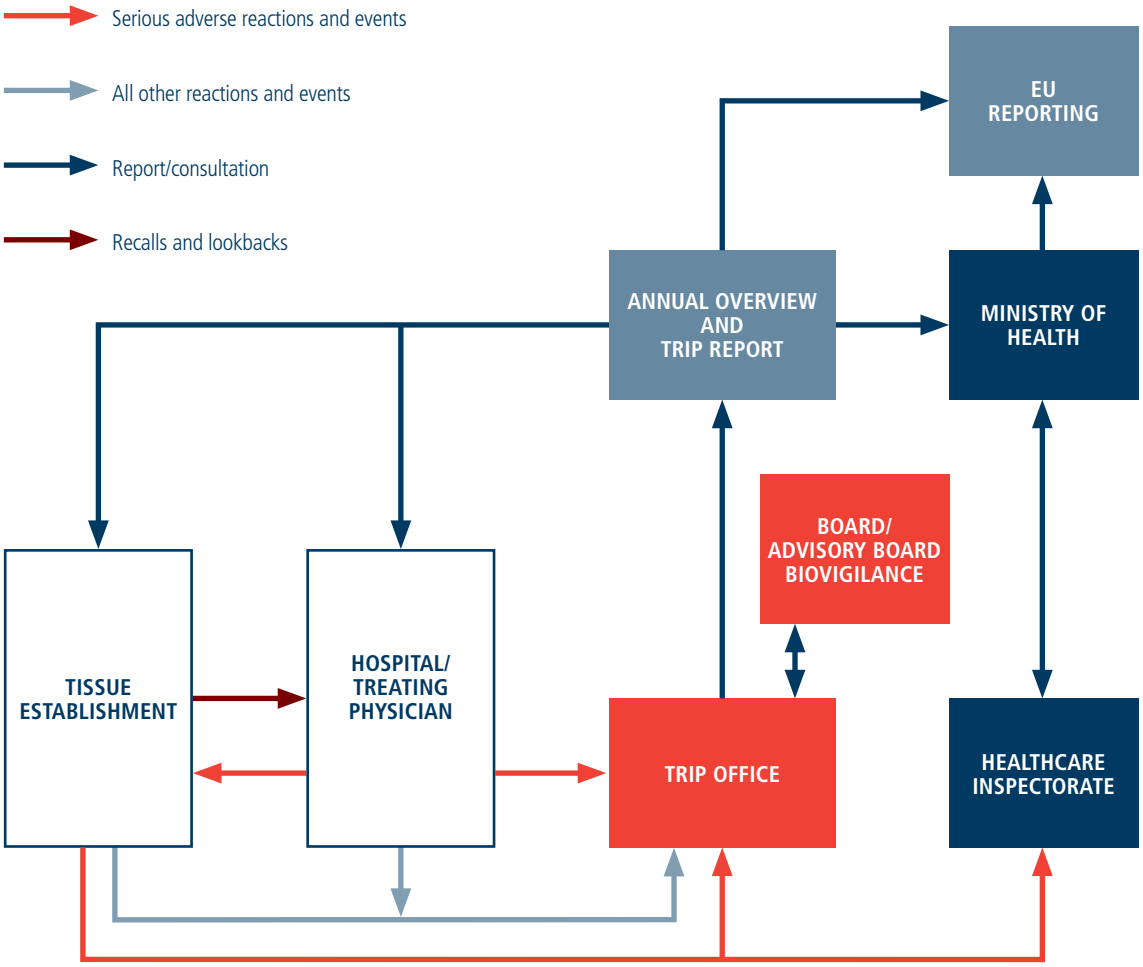


Figure 16. Flowchart of reporting

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 since 2006 from hospitals, private clinics and licensed tissue establishments 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 therefore can be part of 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 involved medical specialties, medical professional bodies and 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)

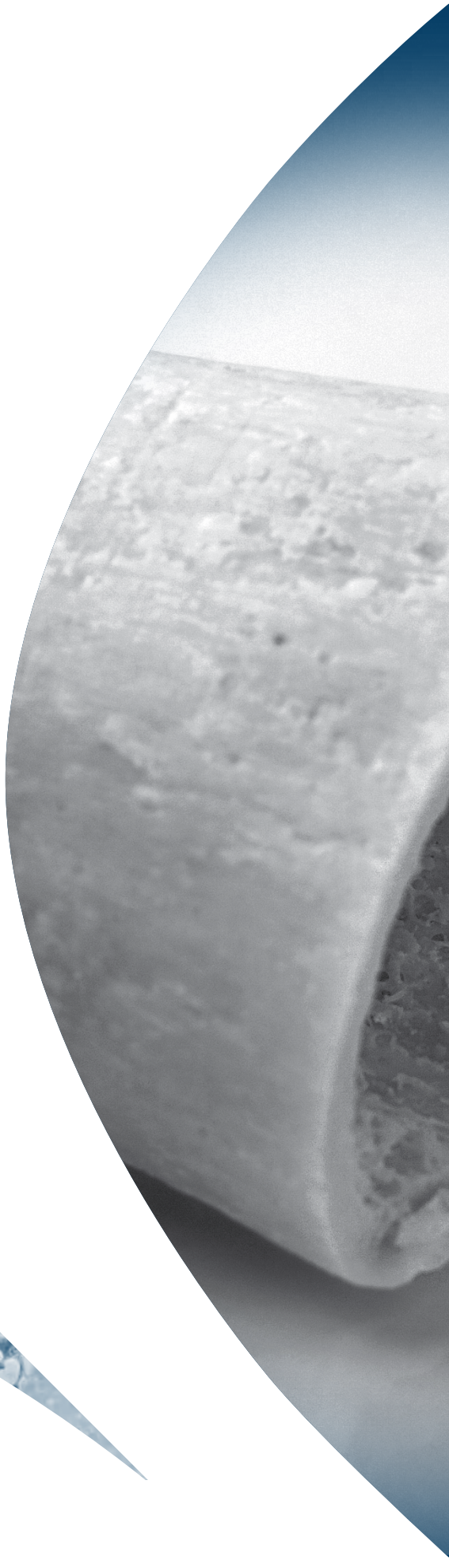
Table 41 presents an overview of the number of serious adverse reactions and events relating to substances of human origin that were registered in 2013. In all, 32 reports were assessed as serious. These concerned 26 serious adverse events and 6 serious adverse reactions, of which three concerned serious adverse reactions in donors.

Table 41. Overview of serious reports in 2013

Type	Serious adverse reaction	Serious adverse event	Serious donor complication	Total serious reports
Semen	0	0	0	0
Oocytes	0	4	0	4
Embryos	0	8	0	8
Gonadal tissue	0	0	0	0
Ocular tissue	0	5	0	5
HPSC and therapeutic cells	1	5	3	9
Bone	1	1	0	2
Cartilage	0	1	0	1
Tendons	1	1	0	2
Cardiovascular tissue	0	1	0	1
Total	**3**	**26**	**3**	**32**

Annex 3. List of terms and abbreviations

Apheresis	-	Type of blood donation involving the selective mechanical withdrawal of specific blood components while returning (infusing) the remaining components to the donor or patient
Allogeneic	-	Originating from a donor (genetically non-identical person)
AML	-	Acute myeloid leukaemia
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
ESBL	-	Extended-spectrum beta-lactamase
ET	-	Embryo Transfer
EU	-	European Union
EUSTITE	-	European Union Standards and Training in the Inspection of Tissue Establishments (EU project 2007-2009)
Farmatec	-	Organisation resorting under the Dutch Ministry of Health, responsible for accreditation and licensing of pharmaceuticals, medical devices, blood products and substances of human origin
Gonadal	-	Belonging to sexual glands
G-CSF	-	Granulocyte-colony stimulating factor
HLA	-	Human leukocyte antigen
HPSC	-	Hematopoietic stem cells
ICSI	-	Intra-cytoplasmic sperm injection (type of IVF)
Imputability	-	Degree to which an adverse reaction can be attributed to applied substances of human origin
IUI	-	Intra-Uterine Insemination
MESA	-	Microsurgical epididymal sperm aspiration
Organ bank	-	Tissue establishment with licence to receive substances of human origin after procurement
PBSC	-	Peripheral blood stem cells
PESA	-	Percutaneous epididymal sperm aspiration
Processing	-	All actions that necessary for preparing, manipulating, preserving and packaging of substances of human origin
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
Procurement	-	Process whereby donated substances of human origin become available
Tissue establishment	-	A tissue bank, a hospital department or another institution that holds a licence for processing, preserving, storage and/or distribution of human tissue or cells
WMDA	-	World Marrow Donor Association
Wwkl	-	Dutch Law on safety and quality of substances of human origin



TRIP Hemovigilance and biovigilance office
Schuttersveld 2 | 2316 ZA Leiden | Netherlands
Tel: 071 303 1540 | Email: info@tripnet.nl
www.tripnet.nl

TRIP
Hemo-en biovigilantie