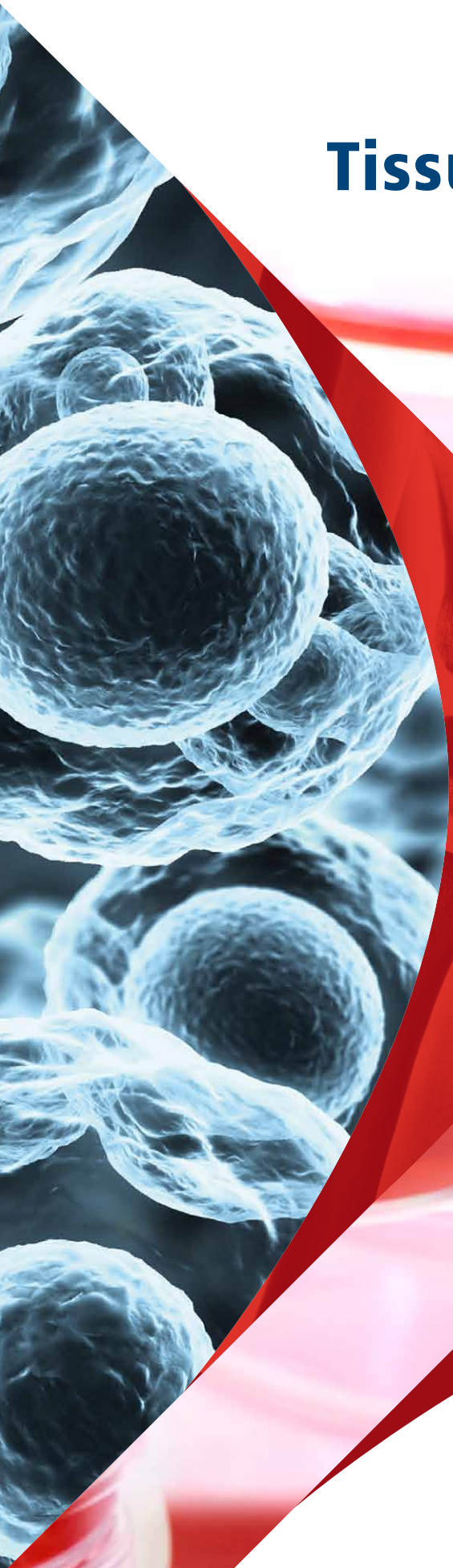
TRIP report 2011

Tissue vigilance



TRIP
Hemo-en biovigilantie

TRIP report 2011

Tissue vigilance

Extended version

The TRIP report 2011 regarding tissue vigilance in The Netherlands in 2011 is published under responsibility of the TRIP (Transfusion & Transplantation Reactions in Patients) Foundation.

TRIP
Hemo- en biovigilantie

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Foreword

Dear reader,

More than five years have passed since TRIP started to collect data on adverse reactions and events occurring with the application of tissues and cells of human origin. In cooperation with a growing number of tissue vigilance officers in the Dutch hospitals, TRIP can report a steady rise in the number of participating hospitals and consequently an increasing number of reports submitted. By now full participation of all the tissue processing institutions has been realised. Among the hospitals and clinics 87% now participate in the reporting system for adverse reactions and events in this field.

Obviously it is our aim to attain full participation by the hospitals. Moreover TRIP must now reach out to independent health care institutions and private clinics, as a number of these will undoubtedly transplant human tissues. Finally it is essential for tissue establishments that are solely involved in storage of human tissues, albeit after importing these, e.g. distributors of medical devices, to be made aware of the requirements of tissue vigilance.

In cooperation with this broad range of institutions involved in the application of human tissues and cells, it will eventually be possible to collate reliable data on the actual use. This insight is essential in assessment of risks related to the application of tissues and cells of human origin. This will enable the absolute number of reports and the trends therein to be evaluated in relation to denominator data in order to make a valid assessment of the quality and safety of transplantation of human tissues and cells.

The increase in submitted data from tissue establishments and hospitals will lead to a different reporting mode in future TRIP reports, in which the denominator data and reports will be presented and analysed per tissue or cell type.

With this tissue vigilance report we again hope to contribute to the insight in and quality and safety of the use of tissues and cells of human origin.

Dr. Martin R. Schipperus
President, TRIP Foundation

Summary

Under the mandatory reporting requirement of the European Directive 2004/23/EC TRIP provides the yearly mandatory overview of serious adverse reactions and events to the European Commission on behalf of the Health Care Inspectorate. At the request of the Ministry of Health, TRIP Foundation also collates, registers, analyses and reports on all voluntary reports of adverse reactions and events relating to human tissues and cells, even if they are assessed as non-serious. TRIP reports on all these safety aspects in the yearly TRIP report. The TRIP Office is assisted by an Advisory Committee of experts from the field of human tissues and cells.

Findings

There was a small increase in participation of transplanting institutions (hospitals and specialised clinics) of tissues and cells from 79% in 2010 to 85% in 2011. Participation is determined on the basis of institutions providing figures of processed, distributed and transplanted human tissues and cells as well as submission of reports of adverse reactions and events or confirmation that no such events occurred. A rising number (81%) of the transplanting institutions has appointed a tissue vigilance officer or coordinator. The independent tissue establishments continued to participate fully. The closing date for this annual report was April 1 2012.

Regarding the reporting year 2011 TRIP received 84 reports out of which 38 were assessed as serious and included in the annual overview for the European Commission. Broken down by tissue type, 36 reports related to gametes and embryos, 23 reports to hematopoietic stem cell transplants, 17 reports concerned ocular tissue, two heart valve transplantation, two bone transplants, two donor lymphocyte infusion, one report involved a skin transplant and one cartilage transplantation. There were nine adverse reactions and 75 adverse events, out of which 36 concerned gametes and embryos. This year 11 IVF laboratories and two semen laboratories sent in reports.

Conclusions and recommendations

Participation

Although a small increase was seen in the number of participating hospitals the submitted numbers of processed, distributed and transplanted human tissues and cells and the numbers of recipients do not tally. Hospitals should be aware that the registration and submission of numbers of recipients as well as full traceability of tissues and cells constitute essential parts of tissue vigilance.

Submission of data in units

For various tissue types there is a lack of agreement with regard to the units to be used as a measure for application of human tissues. In order to achieve a comprehensive registration the groups of professionals involved in the field of transplantation of human tissues and cells should reach consensus on the most appropriate units for registration purposes for each tissue type.

Reports on assisted reproduction

In assisted reproduction more than 50% of reports relate to potentially avoidable processing errors. It is recommended that processing errors should be studied further in order to find ways to avoid these errors.

Reports from semen laboratories

Three reports were submitted by two out of the 63 licensed semen laboratories (IUI) and licensed organ banks (IUI and DI). Fifty-one semen laboratories provided data on processing and distribution; it is not known how many semen laboratories have implemented the clinical embryologists' guideline on reporting of adverse reactions and events.

Reports on ocular tissue

A cluster of five reports related to a persistent central haze after corneal transplantation, where the recipient did not attain optimal visual acuity. Data on possible retransplantations were unavailable. Follow-up on visual

acuity and clinical outcome, including retransplant (if any) is needed for comprehensive tissue vigilance from donor to recipient. Since 2006 a total of thirteen reports concerned corneal transplants, where the donor was not eligible according to the definitive autopsy report which was not yet available at the time of transplant. This type of adverse event cannot be avoided because of the limited corneal shelf life. Research should be initiated to investigate the outcomes of recipients of a cornea that did not meet quality and safety requirements for donation according to subsequent autopsy report, in order to gain insight into possible long-term consequences.

Leaking units and equipment

Three reported adverse events related to leaking units or leaking equipment for apheresis of hematopoietic stem cells. These adverse events relating to leaking units or equipment for recipient-specific and potentially irreplaceable cells should be reported in order to assess the scope of this problem.

General recommendations

Every year the Boards of Healthcare Institutions should ascertain their compliance with all mandatory requirements with regard to human tissues and cells as new developments in the application of human tissues and cells may need licensing and implementation of appropriate tissue vigilance. More insight is needed into the importing of human tissues and cells. In particular, distributors should be included; independent health care institutions and private clinics should be identified and contacted. The participating institutions should be reclassified in order to be able to report separately on the rising number of licensed tissue establishments or organ banks that are part of hospitals.

1. Introduction and TRIP working methods

Tissue vigilance is the systematic monitoring of adverse events and adverse reactions throughout the chain from tissue or cell donor to recipient, and all other activities which can lead to safer and more effective use of tissues and cells.

In January 2007 the Dutch Law on Safety and Quality of Substances of Human Origin (2003) was updated and adapted to the EU Directive 2004/23/EC and the Decree on Substances of Human Origin (2006) specifies further requirements. This law states that a tissue establishment should appoint a responsible person whose tasks include the reporting of serious adverse reactions and events, which is no longer voluntary with the coming into force of this legislation (Article 8.1). Healthcare institutions are obliged to report to tissue establishments any serious adverse reaction or serious adverse event that could possibly affect the safety and quality of human tissues and cells.

At the request of the Ministry of Health, in 2007 TRIP developed a pilot reporting system for serious adverse events and reactions. From 2011 onwards tissue vigilance has been a formal task for the TRIP Office.

Forms for the reporting of adverse reactions and events are available on the TRIP website (www.tripnet.nl). In addition TRIP developed a network of tissue vigilance officers in the hospitals and tissue establishments whose task it is to detect and report adverse reactions and events relating to human tissues and cells. The pilot phase started with paper forms and in January 2010 online reporting was made available. The majority of reports in 2011 was submitted via the online reporting system. This online reporting system has an option allowing the reporter to simultaneously submit a serious report to the Competent Authority, the Healthcare Inspectorate. The TRIP Office is also concerned with the promotion of tissue vigilance in general and actively maintains its relations with all stakeholders. In order to assist hospitals in implementing tissue vigilance TRIP has developed a road map and model documents that are available on request.

In 2007 an Advisory Committee was formed to guide the TRIP office staff and the TRIP board in the setting up and consolidation of tissue vigilance. The members of the Advisory Committee are experts in the field of human tissues and cells representing various medical professional bodies and tissue establishments. The Advisory Committee assesses all reports and advises with regard to the annual report.

Figure 1 shows reporting communication lines. 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.

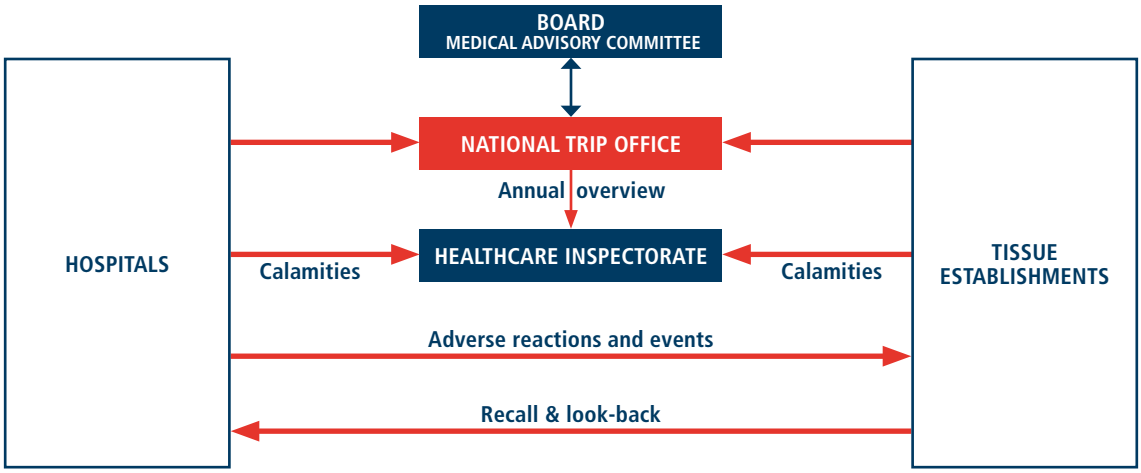


Figure 1. Flowchart of tissue vigilance reporting

2. Participation

A registration system in which all stakeholders actively participate is essential for effective tissue vigilance. Participation is determined on the one hand by submission of reports to TRIP and - if relevant - to the tissue establishment involved and/or the Healthcare Inspectorate. On the other hand annual numbers of distributed or transplanted human tissues and cells need to be submitted along with the numbers of recipients. The comprehensiveness of reports is also an important factor.

In calculating participation rates TRIP distinguishes two categories of institutions:

1. Tissue establishments that receive human tissues and cells after procurement from a donor and subsequently process, store and distribute human tissues and cells. These are named **organ banks**.
2. Tissue establishments that are licensed to perform one or more of the following activities: processing, storage, release and/or distribution, but do not procure tissue or cells from a donor. These are named **other tissue establishments**.

Both organ banks and other tissue establishments may operate as:

a. Independent tissue bank/establishment that holds a licence (via the licensing institution Farmatec) and that operates independently from a hospital or clinic.
b. Tissue establishment that are part of a hospital or clinic, where the latter holds a licence for human tissue or cell activities

Table 1 gives an overview of the number of institutions (TRIP contacts) per category. Figure 2 shows the number of licensed organ banks (total 37) per tissue type and figure 3 shows the number of licensed other tissue establishments.

Table 1. Number of licensed organ banks and tissue banks/establishments according to organisational category.

	Organ bank (1)	Other tissue establishments (2)	All tissue establishments
Independent institution (a)	11	9	**20**
Part of hospital or clinic (b)	26	50	**76**
Total	**37**	**59**	**96**

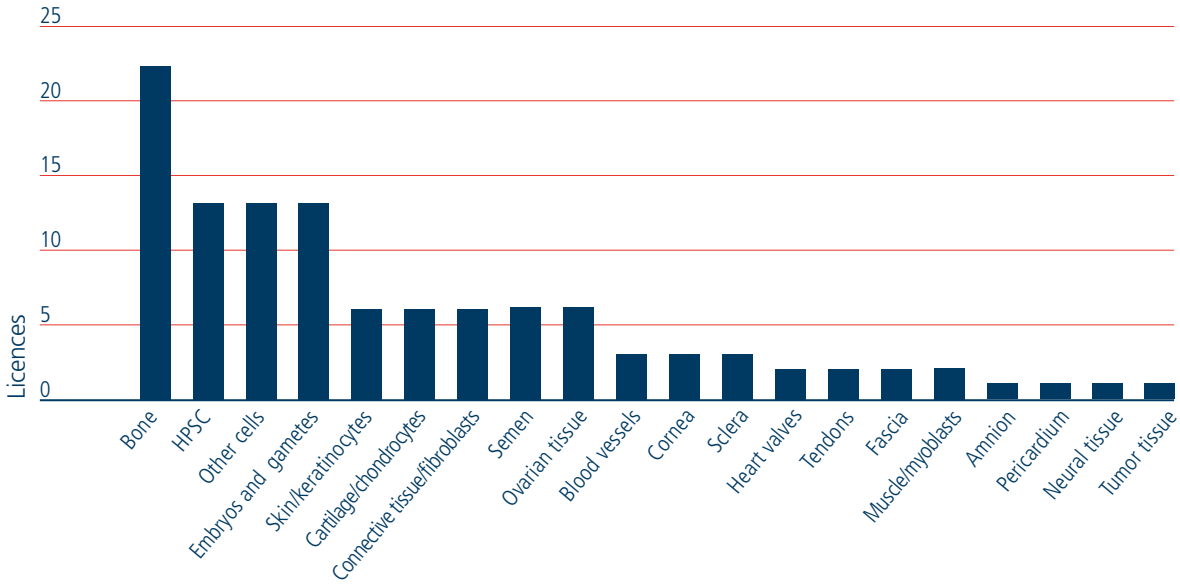


Figure 2. Number of licences granted to organ banks per tissue type*

** According to Farmatec website dated 27-7-2011*

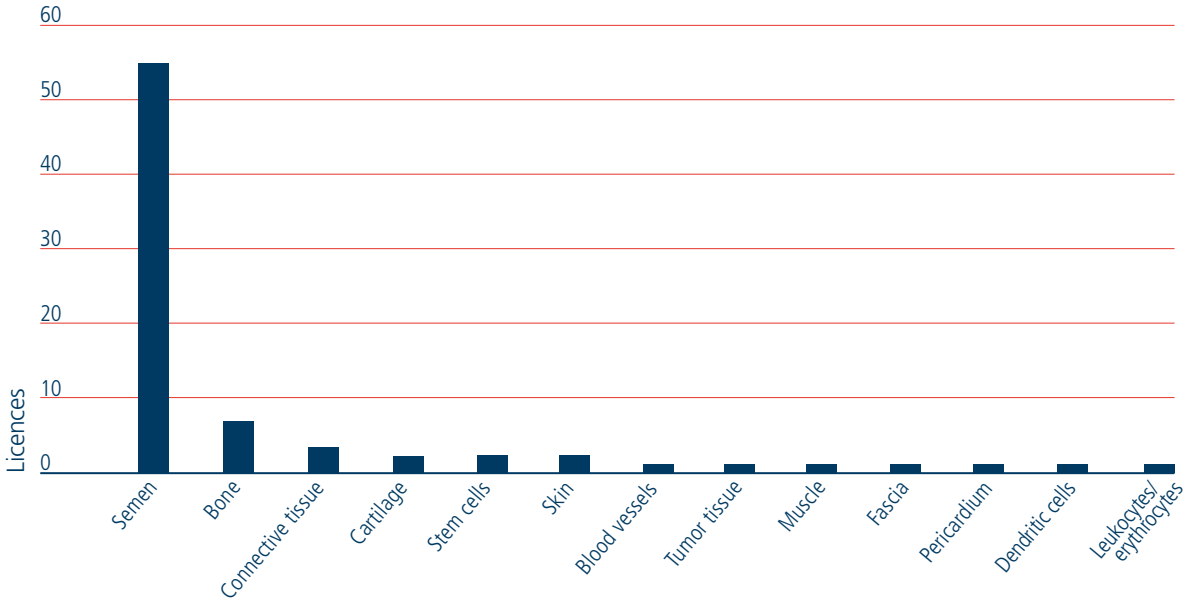


Figure 3. Number of licences granted to other tissue establishments affiliated to hospitals and clinics*

** According to Farmatec website dated 27-7-2011*

The number of independently operating tissue establishments rose from 19 to 20. Two new tissue banks were granted licences for processing or distribution of human tissue and cells and a merger of two tissue establishments was realised in 2011. Hospitals and clinics hold 76 licences for one or more types of tissue or cells: this concerns 26 organ banks and 50 other tissue establishments. The largest group of other tissue establishments in the clinical setting is involved with processing and storage of semen.

Figure 4 shows the participation of independent tissue establishments in providing processing and distribution data and in submitting vigilance reports. By now full participation of independent tissue establishments has been achieved. All submitted numbers for processing and distribution; four also sent reports to TRIP and the remaining 16 stated they had no serious reactions or events to report.

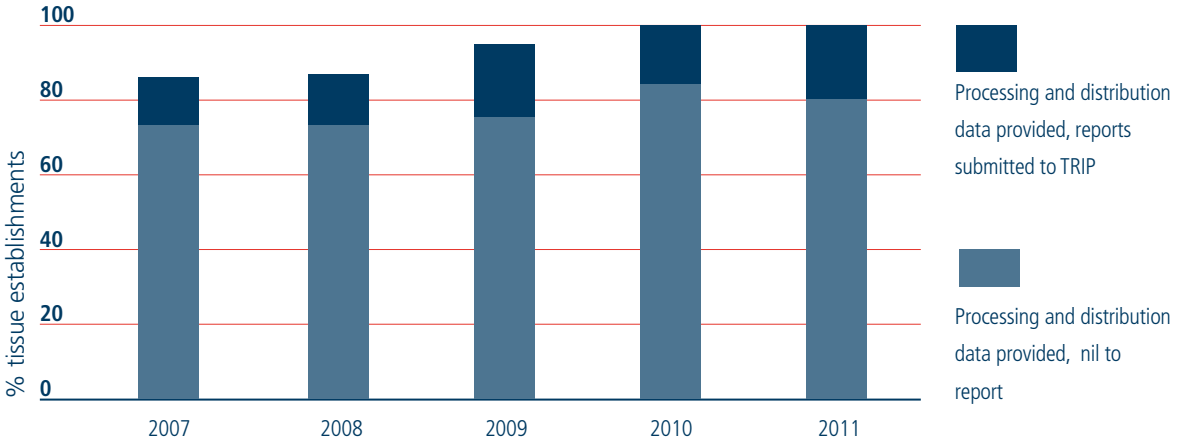


Figure 4. Participation by independent tissue establishments (n=20)

Figure 5 shows participation of hospitals and clinics from 2007 up to and including 2011. Here also a distinction was made between submission of denominator data and reporting of reactions and events. Participation of hospitals and clinics that transplant human tissues or cells shows a small increase. In 2011, 86 (85%) out of 101 hospitals/clinics participated in the registration by providing data on transplanted human tissues, number of recipients and the occurrence of serious adverse reactions and events. In 2010 79% of hospitals/clinics participated. Out of 86 hospitals/clinics in 2011, 65 stated that there were no reportable reactions or events; 18, including five new reporters, sent reports to TRIP. Three hospitals stated they did not transplant any human tissues or cells. The data on recipients of human tissues or cells are less incomplete than in previous years. Ten hospitals/clinics provided figures in 2011 for the first time and ten hospitals/clinics reported on the number of recipients for the first time. Also 13 organ banks that are part of a hospital started participating in 2011 by providing data on processing and distribution.

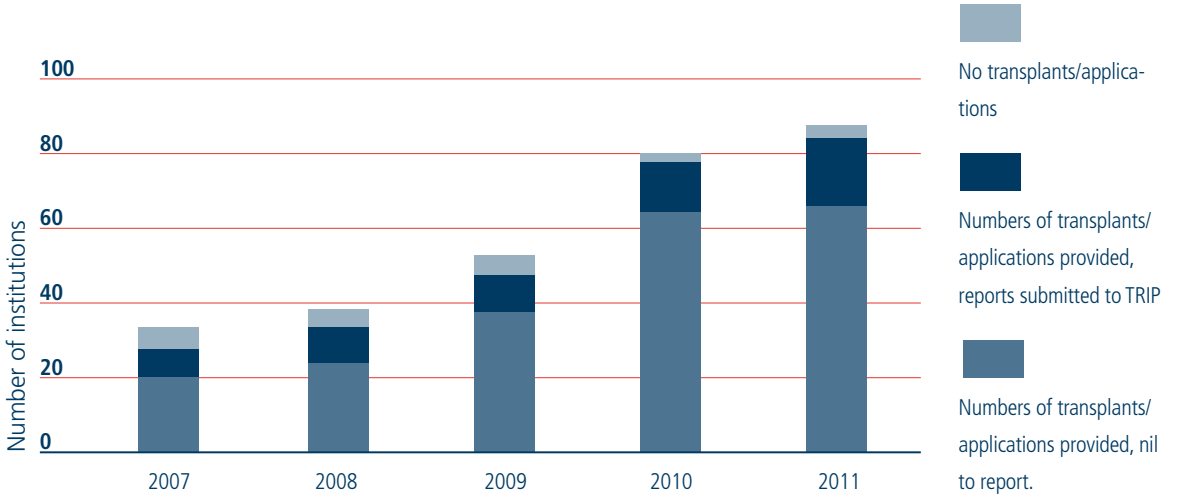


Figure 5. Number of Dutch hospitals/clinics that submitted data on transplantation of human tissues and number of hospitals that also reported adverse reactions and events (n=101)

Most hospitals (82) have appointed tissue vigilance officers. In another 14 hospitals/clinics TRIP does have a contact for tissue vigilance but this person has not been not formally appointed as tissue vigilance officer. In the remaining five hospitals TRIP communicates in writing with the Board of Directors. All of the 20 independent tissue establishments have appointed a tissue vigilance officer to be responsible for reporting to TRIP; in most cases this person is also the responsible person as laid down in EU Directive 2004/23/EC.

TRIP issues an annual certificate of participation to hospitals, clinics and tissue establishments to establishments which have provided data on processed, distributed and transplanted human tissues and cells as well as reports on serious adverse reactions and events or a statement of nil to report. This certificate of participation indicates the particular tissue type(s) and whether data were complete or incomplete. The Healthcare Inspectorate reviews this certificate at biannual inspections of tissue establishemnts. This formal review is not (yet) part of the inspections of hospitals, however it is included in various accreditation processes.

Table 2 presents the number of institutions that were issued a certificate of participation for the provision of data on processing/distribution or transplantation of human tissues.

Table 2. Certificate of participation issued regarding activities in 2011*

Type institution	No of institutions	Data	Percentage
Hospital/clinic	98 (101 minus 3 that stated no transplantation	85 (transplantation)	87%
Hospital/clinic holding licence as organ bank or other tissue establishment	76	65 (processing/ distribution)*	86%
Independent tissue establishment	20	20 (processing/ distribution)*	100%

** In a small number of cases the provision of data was incomplete as data for one or more specific tissue types was missing even though the institution did hold a licence.*

Unfortunately it is still not clear for all hospitals whether they actually transplant or apply human tissues. Three hospitals have never provided any data despite yearly repeated written requests; two of these however do hold a licence for semen processing. Fifteen hospitals/clinics sent incomplete information where e.g. the exact numbers of a specific tissue type or the number of recipients was lacking. These hospitals/clinics are included as participating institutions in the numbers shown above and figure 5. One hospital submitted reports but could not provide data on processing, distribution and transplantation. Only if a hospital can provide annual figures or state that it is not transplanting human tissue or cells can the board be sure that the institution is meeting its legal obligations with regard to licence, traceability and tissue vigilance reporting.

3. Processing and transplantation

All hospitals, clinics, tissue establishments and organ banks in The Netherlands were requested to provide data on activities regarding human tissues and cells. This request not only concerned processing and distribution of human tissues and cells, but also data on transplanted or applied human tissues and cells and the number of recipients of human tissues and cells in 2011. Regarding distribution a distinction was made between distribution in The Netherlands, within the European Union and outside the European Union. It is mandatory for each EU member to submit these data annually to the European Commission according to Directives 2004/23/EC and 2006/86/EC. It is not currently known how many imported human tissues and cells are actually transplanted in The Netherlands. This information is, however, relevant for the final risk assessment of transplantation of human tissues and cells.

In 2011 TRIP received data from 86 out of the 101 Dutch hospitals and clinics. Figure 6 shows the number of hospitals that apply a specific type of tissue or cells in 2011 in comparison to 2010 (data from 81 Dutch hospitals and clinics).

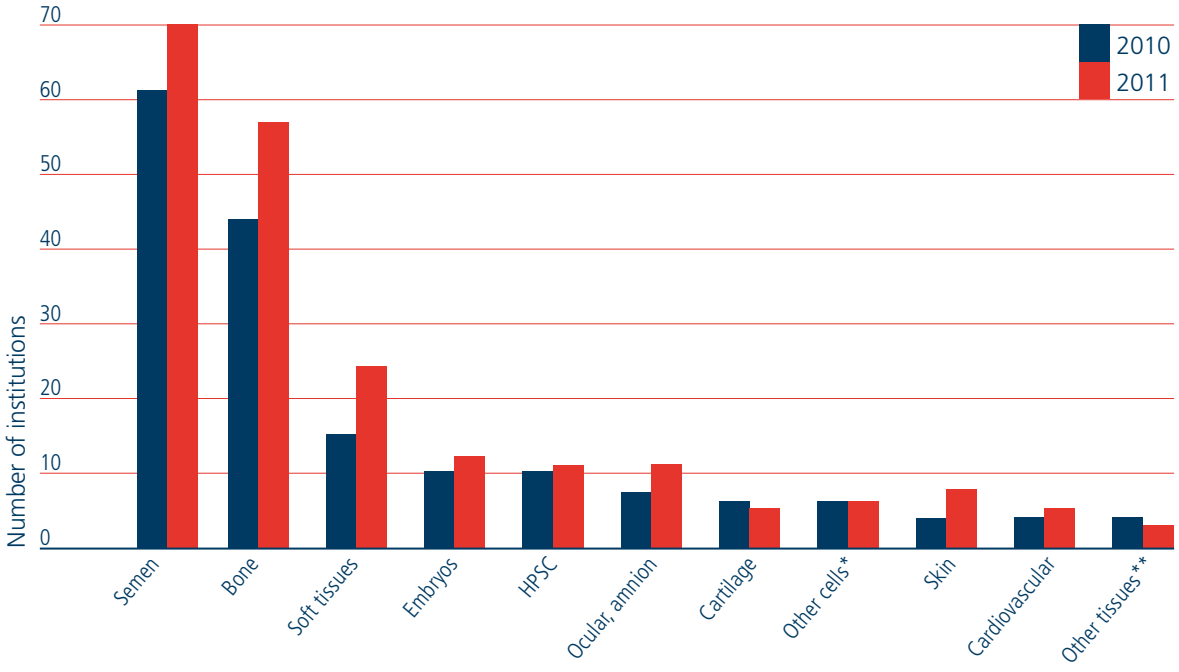


Figure 6. Number of hospitals transplanting/applying each tissue or cell type in 2011 compared to 2010

* *Other cells include mesenchymal stem cells, lymphocytes and dendritic cells*

** *Other tissues include: testicular and ovarian tissue, Langerhans' islets, umbilical cord tissue and adipose tissue*

Table 3 shows the numbers of processed and distributed tissues and cells within The Netherlands and numbers of exported tissues and cells.

Footnotes, table 3:

* *Data provided by 65 out of 72 hospitals and clinics holding a tissue establishment licence (90%) and 20 independent licensed tissue establishments (100%)*

** *Data provided by 20 independent licensed tissue establishments (100%) operating independently from a hospital or clinic and four hospitals with a tissue establishment licence for gametes and embryos.*

*** *Data provided by tissue establishment with licence for labelling of autologous erythrocytes and leukocytes*

Table 3. Processed and distributed tissues and cells in 2011

	Processed *	Distributed* in NL	Distributed in EU (excluding NL)**	Distributed outside EU**
Skin				
Donor skin (cm²/containers)	1872372	1013	9830	5453
Autologous skin				
Cultured skin				
Keratinocytes	12	12		
Bone				
Bone, whole	179	132	166	3
Bone chips or fragments	1933	2996	3186	1883
Femoral head (halved)	126	76	49	
Femoral head (whole)	2923	2376	265	
Cranial bone (autologous)	9	9		
Auditory ossicles		43		
Demineralised bone		1746	13148	2940
Bone miscellaneous			7	4
Cartilage				
Chondrocytes	130	127		
Cartilage		125		
Soft tissue				
Tendons		389	99	
Fascia	6	1716		
Other		148		
Ocular tissue				
Cornea	3365	1253	182	48
Sclera	506	348	15	
Amnion				
Amnion	2 placentas	62	10	
Cardiovascular tissue				
Heart valves	162	77	27	
Vessels and patches	59	23	5	
HPSC (unrelated donors)				
Bone marrow	28	37	4	1
Peripheral blood stem cells	290	294	15	14
Cord blood	270	96	7	4
HPSC (related donors)				
Bone marrow	33	26		
Peripheral blood stem cells	154	162		
HPSC (autologous procedures)				
Bone marrow	27	12		
Peripheral blood stem cells	2592	2252		
Cord blood	23397			
Other cells				
Mesenchymal stem cells	140	76		
Lymphocytes	213	150	1	
Dendritic cells	3	11		
Erythrocytes ***	63	63		
Leukocytes ***	156	153		
Gametes and embryos				
Semen (donor)	2752	8317	156	
Semen (partner)	39107	30946	963	
Oocytes (donated)	612	5		
Oocytes (autologous)	107054	31	745	
Embryos	52681	23251	4	8
Other tissues				
Testicular tissue	10			
Ovarian tissue	4			
Langerhans' islets	64	14		
Umbilical cord tissue	13176			
Adipose tissue	165		165	

HPSC = Hematopoietic stem cells

Table 4 shows the numbers of transplanted or applied tissues and cells and the number of recipients.

Tables 3 and 4 show a discrepancy between numbers of distributed tissues and cells and the number of recipients provided by hospitals and clinics. This can in part be explained by:

- missing or incomplete data on transplanted/applied tissues and cells from a quarter of the Dutch hospitals
- low participation by independent health care institutions and private clinics
- 12 out of 13 IVF laboratories provided data
- 52 out of 63 licensed semen laboratories provided data
- missing numbers of recipients although data on transplanted/applied tissues were provided by hospitals
- distribution is provided in units that differ from those used in transplantation (e.g. HPSC bags/containers versus grafts, skin cm^2 versus containers)

Finally the overall picture of production, distribution and transplantation is obscured by the lack of data on imported tissues and cells for Dutch recipients.

Footnotes table 4:

* *Data from 86 out of 101 hospitals and clinics (85%)*

** *Data from 79 out of 101 hospitals and clinics (78%)*

Table 4. Transplanted tissues and cells and numbers of recipients in 2011

	Transplanted tissues or cells*	Recipients**
Skin		
Donor skin (cm^2/containers)	740	
Autologous skin	106	87
Cultured skin		
Keratinocyte	12	12
Bone		
Bone, whole	122	106
Bone chips or fragments	779	619
Femoral head (halved)	69	44
Femoral head (whole)	1384	1228
Cranial bone (autologous)	74	74
Auditory ossicles	8	8
Demineralised bone	40	40
Bone miscellaneous	80	43
Cartilage		
Chondrocytes	107	107
Cartilage	9	9
Soft tissue		
Tendons	120	98
Fascia	134	131
Other	11	11
Ocular tissue		
Cornea	549	375
Sclera	120	128
Amnion		
Amnion	26	23
Cardiovascular tissue		
Heart valves	50	50
Blood vessels and patches	12	12
Hematopoietic stem cells (unrelated donors)		
Bone marrow	37	37
Peripheral blood stem cells	243	195
Cord blood	94	60
Hematopoietic stem cells (related donors)		
Bone marrow	26	26
Peripheral blood stem cells	162	121
Hematopoietic stem cells (autologous donors)		
Bone marrow	12	12
Peripheral blood stem cells	1526	492
Cord blood		
Other cells		
Mesenchymal stem cells	74	47
Lymphocytes	146	137
Dendritic cells	11	4
Erythrocytes		
Leukocytes		
Gametes and embryos		
Semen (donor)	8185	1415
Semen (partner)	31219	15153
Oocytes (donated)		
Oocytes (autologous)		
Embryos	22592	12335
Other tissues		
Testicular tissue		
Ovarian tissue		
Langerhans' islets	14	7
Umbilical cord tissue		
Adipose tissue		

4. Reports in 2011

4.1 Number of reports

TRIP received 84 reports of adverse reactions and events concerning reporting year 2011. This exactly equals the number of reports in 2010. The closing date for inclusion of reports in the 2011 annual report was April 1 2012. There were 75 reports of adverse events and 9 reports of adverse reactions; they were submitted by four independent tissue establishments and 18 hospitals/clinics (2010: 2 tissue establishments and 17 hospital/clinics).

Four hospitals and one independent tissue establishment sent in reports of adverse reactions and events for the first time in 2011. The number of reports per reporting institution varied from one to 11. The annual numbers of reports from 2006 up to and including 2011 are presented in figure 7, broken down according to whether they were submitted on paper forms or via the online reporting system.

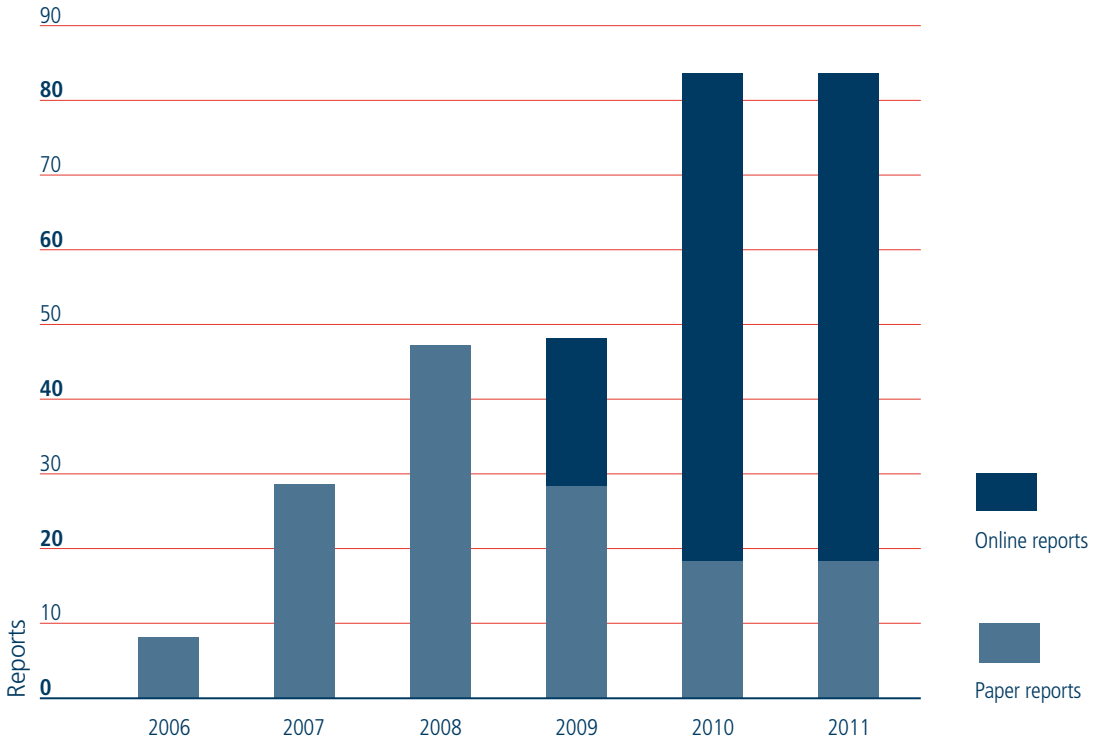


Figure 7. Number of reports per reporting year, 2006-2011

Figure 8 shows the distribution of reporting per tissue or cell type per reporting year. The large number of reports concerning gametes and embryos should be considered in relation to the large number of assisted reproduction treatments. Table 4 shows that according to provided data over 8,000 donor inseminations and over 29,000 IUI were performed in 2011. In 2010 15,660 follicular aspirations for IVF or ICSI (www.nvog.nl) were performed. These data are published by the Dutch Society for Obstetrics and Gynaecology when the outcome of ongoing pregnancies is available; the information about 2011 had not yet been published at the time this report going to press.

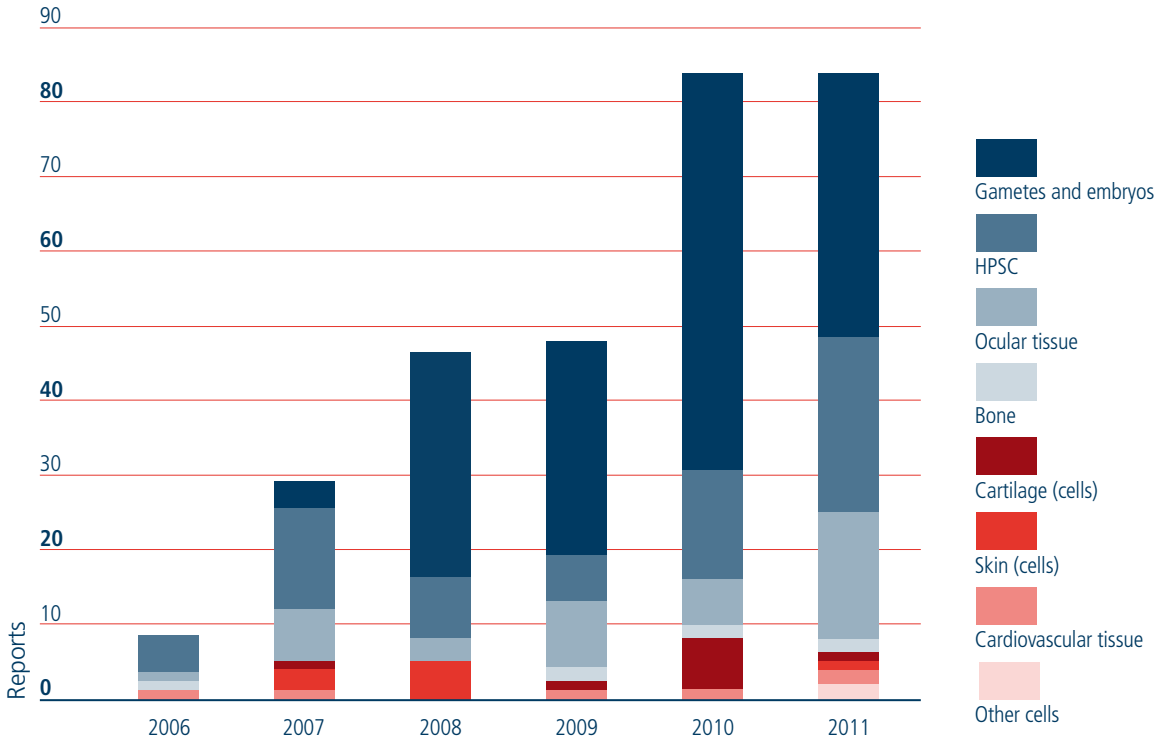


Figure 8. Reports per tissue or cell type, 2006-2011

Of all the reports, 38 (45%) were assessed in consultation with the medical advisory committee as serious according to criteria laid down in EU directive 2004/23/EC and the EUSTITE vigilance guideline. Reports concerning the avoidable loss of gametes and embryos are assessed as serious if a fertility cycle is lost, if 50% of oocytes or embryos are lost or if irreplaceable tissue is lost during a fertility preservation treatment. Table 5 presents an overview per tissue/cell type of the numbers of serious reports compared to the total number of reports. A slight drop is seen in the number of serious reports compared to previous reporting years (2010: 44, 2009: 40).

Table 5. Reports per tissue or cell type in 2011

	Number of reports	Number of serious reports
Skin (cells)	1	0
Cartilage (cells)	1	1
Other cells	2	0
Cardiovascular tissue	2	1
Bone	2	2
Ocular tissue	17	10
HPSC	23	5
Gametes and embryos	36	19
Total	**84**	**38 (45%)**

4.2 Types of reactions and events

Reports are classified in categories. These categories are more detailed and informative than the mandatory EU reporting categories. There are four EU reporting categories, namely:

- tissues or cell defect
- equipment failure
- human error
- other

The TRIP categories of adverse reactions and events with their definitions are available on the TRIP website (www.tripnet.nl). Tables 6 and 7 present the distribution per category per tissue or cell type in the TRIP categories of adverse events and reactions.

Table 6. Category of adverse event per tissue or cell type in 2011

Category adverse event	Cartilage (cells)	Other cells	Cardio-vascular	Bone	Ocular tissue	HPSC	Gametes & embryos	Total
Loss of tissues or cells	1		2		2	2	29	**36**
Poor/failure of engraftment/ growth						7		**7**
Bacterial contamination of product		2			1	3		**6**
Product incident					2			**2**
Incorrect product transplanted					1			**1**
Near miss							3	**3**
Other incident				1	11	4	4	**20**
Total	**1**	**2**	**2**	**1**	**17**	**16**	**36**	**75**

Table 7. Category of adverse reaction per tissue or cell type in 2011

Category of adverse reaction	Skin (cells)	Bone	HPSC	Total
Other reaction			3	**3**
Hemolytic reaction			2	**2**
Anaphylactic reaction			1	**1**
Circulatory overload			1	**1**
Post transplant bacterial infection		1		**1**
Post transplant other infection	1			**1**
Total	**1**	**1**	**7**	**9**

4.3 Gametes and embryos

In 2011 there were 36 reports of adverse events concerning procedures for application of gametes and/or embryos during assisted reproduction. The reports were submitted by 11 (out of 13) IVF laboratories and two (out of 63) hospitals with a licence for the processing of semen. In 2010 nine IVF laboratories and three semen laboratories sent reports to TRIP. The number of reports was smaller than in 2010 (see table 6). The drop in the number of reports could in part be explained by the fact that two IVF laboratories failed to report before the closing date of this report whereas they did report in 2010. All reports in 2011 regarded adverse events. Table 8 shows the number of reports in the adverse event categories in reporting years 2008-2011.

Table 8. Number of reported adverse events per category concerning gametes and embryos, 2008-2011

	2008	2009	2010	2011	Total
Loss of tissues or cells	19 (65%)	21 (72%)	32 (59%)	29 (81%)	**101 (68%)**
Other incident	7 (24%)	5 (17%)	12 (22%)	4 (11%)	**28 (19%)**
Near miss		1 (3%)	5 (1%)	3 (8%)	**9 (6%)**
Incorrect product transplanted			3(0,5%)		**3 (2%)**
Bacterial contamination of product	2 (7%)		1(0,2%)		**3 (2%)**
Congenital malformation		2 (7%)	1(0,2%)		**3 (2%)**
Viral contamination of product	1 (3%)				**1 (1%)**
Total	**29**	**29**	**54**	**36**	**148**

Figure 9 presents the distribution of adverse events in 2011. The category of loss of tissues or cells is numerically the largest; this was also found in 2010.

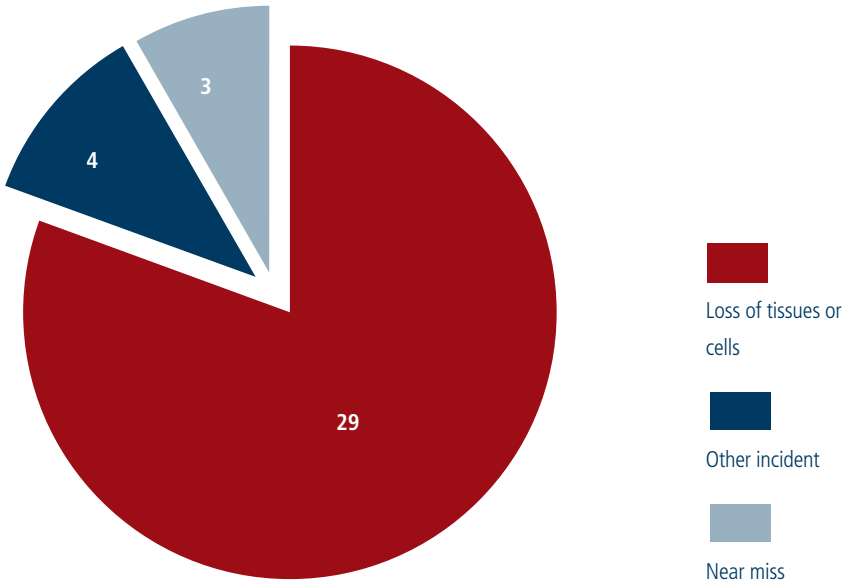


Figure 9. Number of reports concerning gametes and embryos per category of adverse event in 2011

In table 9,10 and 11 the reports relating to gametes and embryos are further subdivided according to the type of errors and the procedural step where the error occurred.

Table 9. Reports in the category loss of tissues or cells

Type of error	Step in procedure	Number of reports	Gametes or embryos	Number; event description
Processing error	Isolation	4	oocytes	• 3 x culture dish discarded in error • Culture dish dropped
	Insemination	3	oocytes	• 3 x no semen added
	Incubation	2	embryos	• Aspergillus contamination • 2 dishes left behind in incubator
	Transfer	7	oocytes	• 3 x oocytes lost in pipette • Not transferred to incubation dish • 2 x pipette/capillary knocked • 1 dish accidentally jolted
		1	embryos	• pipette knocked
	Assessment	1	oocytes	• Simultaneous assessment of oocytes of 2 couples at one workstation
	Cryo-preservation	2	embryos	• Insufficient liquid nitrogen in pressure vat • Straw not frozen by mistake
Identification error	Procurement	1	semen	• container not labelled
	Processing	1	semen	• Request entered for the wrong patient
	Cryo-preservation	2	embryos	• 2 x straws mixed up
	Thawing	1	embryos	• Wrong form filled out
Assessment error	Insemination	1	oocytes and semen	• Screening result overlooked
Communication error	Thawing	1	embryos	• Deviation from protocol regarding thawing frequency
Technical error	Transfer	1	oocytes	• Faulty pipette
Other	Insemination of patient	1	semen	• Syringe fell apart
	Embryo transfer (ET)	1	embryos	• ET deferred due to medical condition of patient

Table 10. Reports in the category of other incident

Type or error	Step in procedure	Number of reports	Gametes or embryos	Description
Processing error	Insemination	1	oocytes	• No semen added, procedure changed to ICSI next day
	Embryo transfer (ET)	1	embryos	• Mix-up of dishes of embryos for ET and remaining embryos for cryo-preservation
Identification error	Thawing	1	embryos	• Straw in visotube for research with-out patient consent
Other	Cryo-preservation	1	embryos	• Cryopreservation 1 day later than intended

Table 11. Near miss reports

Type of error	Step in procedure	Number of reports	Gametes or embryos	Description
Identification error	Procurement	1	semen	• container incorrectly labelled
	Transportation	1	semen	• visotube labelled with incorrect patient details in transportation cryo container
	Insemination	1	semen	• ICSI dish inadequately labelled

Figure 10 shows the proportions of the types of error. The number of reports recorded as processing errors is the largest and has been so for several years, accounting for more than half of the reports relating to gametes and embryos.

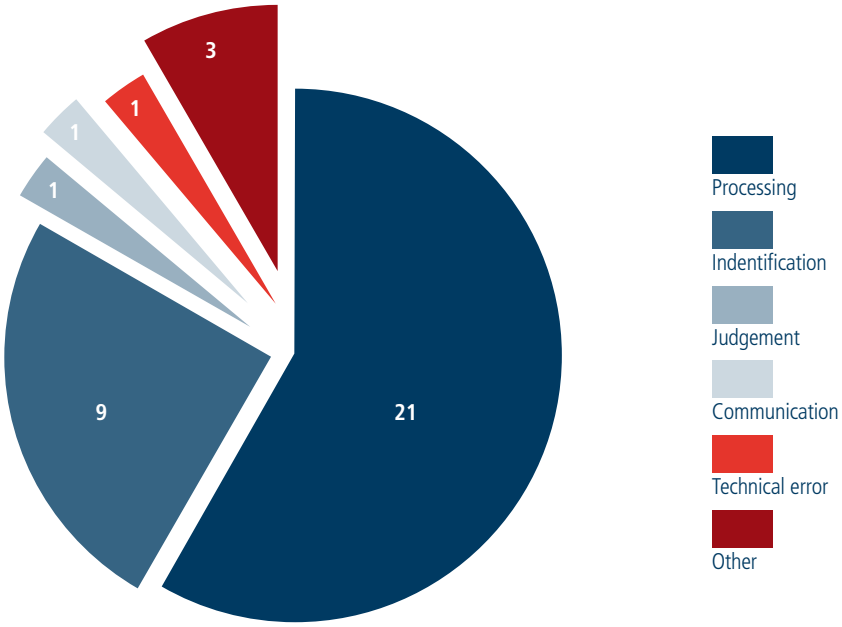


Figure 10. Type of error in reports concerning gametes and embryos in 2011

4.4 Musculoskeletal tissue

TRIP received two reports about bone: one adverse event and one adverse reaction. The adverse event concerned traceability failure of a femoral head. A tissue establishment found a femoral head to be missing and could not establish whether it was transplanted or (if it was) identify the recipient. The second report was classified as post-transplant bacterial infection after applying bone from an allogeneic femoral head for an ankle arthrodesis. Imputability was assessed as unlikely as bone cultures at procurement and transplantation were negative.

4.5 Cardiovascular tissue

There were two reports regarding cardiovascular tissue that are summarised in table 12.

Table 12. Reports about cardiovascular tissue

Tissue type	Event category	Type of error	Description
Pulmonary valve	Loss of tissues or cells	Communication error	Incorrect valve size ordered
Aortic valve	Loss of tissues or cells	Other	Procedure cancelled due to condition of recipient after transfer of valve to transport medium.

4.6 Skin

There was one report of an adverse reaction occurring after donor skin transplantation: fungal growth occurred on the donor skin in the recipient. All cultures taken by the tissue establishment remained negative.

4.7 Cartilage

One adverse event report was submitted relating to autologous chondrocytes. During tissue culture for expansion of chondrocytes an incorrect culture medium was added. This led to loss of the chondrocytes and the patient had to undergo another procedure for harvesting chondrocytes.

4.8 Hematopoietic stem cells (HPSC) and donor lymphocytes

There were 25 reports, submitted by six hospitals, concerning hematopoietic stem cells and donor lymphocytes. This constitutes a rise in the number of reports compared to 2010 (13 reports by four reporting establishments). The number of serious reports (five) however is comparable to 2009 and 2010 (six). Donor lymphocyte infusion (DLI) is an adjuvant therapy used in allogeneic blood stem cell transplantation; reports pertaining to DLI are therefore included in this chapter.

Among the total, two adverse reactions were assessed as serious. These were a hemolytic reaction that led to renal impairment requiring dialysis after cord blood transplant and an 'other reaction' (severe hypotension) during reinfusion of autologous stem cells. Furthermore three adverse events were assessed as serious: the loss of an autologous unit of peripheral blood stem cells due to a leak in the bag at thawing and two reports where the apheresis of autologous stem cells had to be aborted due to leakage of the apheresis set. In tables 13 and 14 the adverse events and reactions are summarised per stem cell type.

The number of adverse reactions after transplanting HPSC is largest among the types of tissues or cells. However only three hospitals sent in reports of adverse reactions. The professionals involved in HPSC transplantation unfortunately have not yet agreed on the types of adverse reactions that are relevant for systematic monitoring and thus for reporting to TRIP. There were three reports of adverse events concerning leaking bags or apheresis sets for recipient-specific or autologous materials. The extent of this problem should be investigated.

Table 13. Adverse events per type of hematopoietic stem cell product

	Description	Number of reports
PBSC autologous	Poor/failure of engraftment/growth, administered product met quality criteria in all cases	7
	Other incident • 2 x leaking apheresis set* • Transplant form belonging to another autologous unit distributed with an autologous unit despite double check	3
	Loss of tissues or cells* • 1 out of 4 bags leaked on thawing	1
	Bacterial contamination of product • Coagulase negative staphylococcus	1
PBSC, allogeneic unrelated	Loss of tissues or cells • Due to processing error MabCampath added before instead of after isolation of TC-T cells	1
Bone marrow, allogeneic unrelated	Bacterial contamination of product • 2 x coagulase negative staphylococcus, transplant uneventful	2
Cord blood	Other incident* • Small leak in unit from a non-EU stem cell bank, transplant and engraftment were uneventful, cultures negative	1
Donor lymphocytes, allogeneic related	Bacterial contamination of product • Staphylococcus hominis/gram negative rods, transfusion uneventful	2
Total		**18**

** serious report*

Table 14. Adverse reactions in recipients per type of hematopoietic stem cell

	Description of adverse reaction	Number
PBSC, autologous	Other reaction • Hypotension and low back pain possibly related to DMSO* • Patient died unexpectedly 13 days after SCT, product met all quality criteria, imputability unlikely	2
PBSC, allogeneic unrelated	Anaphylactic reaction • Drop in O_2 saturation and defecation urge with major ABO incompatible product	1
	Other reaction • Chills/rigors with minor ABO incompatible plasma-depleted product	1
PBSC, allogeneic related	Circulatory overload • Hypertension and dyspnea, chest X-ray consistent with circulatory overload	1
Bone marrow allogeneic unrelated	Hemolytic reaction • Mild hemolysis with major ABO incompatible product	1
Cord blood	Hemolytic reaction* • Double cord blood transplant, 1 major ABO incompatible, led to dialysis-dependent renal failure	1
Total		**7**

** serious report*

4.9 Ocular tissue

Seventeen reports of adverse events relating to ocular tissue were submitted by three licensed tissue establishments and one hospital. All of the reports related to corneal tissue and ten were assessed as serious. The reports in 2011 are summarised in table 15 with figures for similar reports in 2010 for comparison.

The reporting year 2011 shows an increase in the number of reports involving corneas (2010: 6). In particular this is due to a cluster of reports from two organ banks which reported a persistent central haze in five recipients. These cases originated from five different hospitals; a survey among ophthalmologists revealed one additional case that had not yet been reported to TRIP at the time of writing this report. Detailed analysis of the banks' processes did not bring to light any deviations. In the recipients retransplantation had not (yet) been undertaken. The age of donors eligible for cornea donation was recently raised from 76 to 85 years. In these cases the age of the donors varied and was not limited to older donors. Further study should determine if the increase in donor age is a possible factor in this issue of persistent haze.

Table 15. Reports concerning ocular tissue

Category of adverse event	Summary	Number of reports 2011	Number of reports 2010
Product incident	Penicillium chrysogenum at culture (non-pathogenic environmental fungus). No sequelae for recipient	1	-
	Assessment error of cornea in tissue establishment: scar missed, procedure deferred	1	-
Loss of tissues or cells	Storage error in hospital, corneas stored in fridge instead of at room temperature due to human error. Loss of 5 corneas	2	2
Bacterial contamination of product	Recall of cornea due to positive culture of preservation medium (paenibacillus lactus), transplant procedure deferred. Repeat cultures of recalled cornea negative.	1	1
Incorrect product transplanted	Donor assessment error: hematologic malignancy could not be ruled out. 2 corneas transplanted, no complications. Other tissues rejected.	1	-
Other incident	Donor information not yet available at time of transplant: autopsy revealed contraindication for donation. Corneas already transplanted due to limited shelf life. 1. M. Marfan, recipient showed astigmatism 2. Neurodegenerative disease, donor clinically normal. 3. Possible sepsis, no follow-up of recipient available	3	3
	Assessment ophthalmologist: possible keratoconus, procedure aborted	1	-
	Bacterial contamination of preservation medium, all other other cultures negative, recipient no complications, antibiotic prophylaxis	1	-
	Adverse outcome of transplant: persistent central haze, best corrected visual acuity 0.3 or less, no retransplantation	5	-
	Delayed epithelialisation. Survey among ophthalmologists revealed another 3 corneas with similar problem. Audit of tissue bank processes revealed no deviations. Donor age was relatively high.	1	-
Total		**17**	**6**

Some reports are due to the limited shelf life of corneas after procurement. In 2011 there were three such other incidents where relevant autopsy information only became available at a time when the cornea had already been transplanted. The number of this type of reports remains relatively stable.

4.10 Late 2010 reports

After the closing date for the 2010 TRIP tissue vigilance report another seven non-serious reports were submitted: two adverse reactions and five adverse events. This brings the total number of reports for 2010 to 84.

The late reports involved semen, embryos, oocytes, testicular tissue, a femoral head and peripheral blood stem cells.

The five adverse events were all in the category loss of tissues of cells. Two reports regarded processing errors with sealing of straws, leading to loss of one (out of many) semen straws and of a straw containing a testicular biopsy. Two embryos were not stored in time after cryopreservation and were found to have already thawed. Even though the embryos were cryopreserved again it must be assumed they have degenerated and should not be used. In two further reports an embryo was lost in the pipette on thawing and an incubation dish with a number of oocytes was discarded in error.

One of the adverse reaction reports concerned post-transplantation bacterial infection after applying bone from an allogeneic femoral head in an orthopaedic procedure. Imputability is unlikely as cultures of the grafted bone taken immediately before and during the operation remained negative. There was one other reaction with unlikely imputability. The recipient died unexpectedly 13 days after transplantation with autologous HPSC, probably due to (complications of) the underlying illness. Quality checks on the stem cell product were all within the normal range.

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

In table 16 an overview is presented of the number of serious adverse reactions and events reported to TRIP in reporting year 2011.

Table 16. Serious reports in 2011

Type of tissues or cells	Serious adverse reaction	Serious adverse event	Serious adverse reaction in donor	Total number of serious reports
Oocytes	0	10	0	10
Semen	0	2	0	2
Oocytes and semen	0	1	0	1
Embryos	0	6	0	6
Ocular tissue	0	10	0	10
Cartilage	0	1	0	1
Bone	1	1	0	2
HPSC	2	3	0	5
Cardiovascular tissue	0	1	0	1
Total	**3**	**35**	**0**	**38**

5. Conclusions and recommendations

5.1 Conclusions

1. Although there is a small increase in the number of participating hospitals the collected figures on processing, distribution and transplantation of human tissues and cells and the numbers of recipients do not yet tally.

2. The number of reports submitted by hospitals and tissue establishments has consolidated which indicates continued awareness of tissue vigilance.

3. There is lack of consensus regarding certain tissue and cell types on the most appropriate units for the collection of data.

4. More than 50% of reports concerning assisted reproduction techniques involve a potentially avoidable processing error.

5. There were only three reports from two of the 63 licensed tissue establishments (IUI) and organ banks (IUI and DI) involved in processing semen. Fifty-one semen laboratories provided figures on processing and distribution, however it is not known how many laboratories have implemented the clinical embryologists' guideline for the reporting of adverse reactions and adverse events.

6. From 2006 onwards thirteen reports involved corneal transplantation from a donor who was later found to have a contraindication for donation according to the definitive autopsy findings, which were not yet available at the time of transplantation due the limited shelf life of the cornea. This type of report is unavoidable.

7. A cluster of five reports mentioned a persistent central haze after corneal transplant with reduced visual acuity in the recipient. There is no information on retransplantation.

8. Three reports of adverse events concerned leaking bags or apheresis sets for hematopoietic stem cells.

5.2 Recommendations

1. Hospitals should be aware that provision of data on the number of recipients as well as full traceability of human tissue and cells constitute essential parts of tissue vigilance.

2. For a comprehensive and reliable registration professionals involved in various types of tissues and cells should reach agreement on the most appropriate units for registration purposes.

3. Further research should be initiated into processing errors occurring in assisted reproductive techniques and possible ways to avoid these errors.

4. The patient outcomes should be investigated following transplantation of corneas from donors who were later found to have a contraindication for donation according to the definitive autopsy findings. This will give insight into long term consequences (if any) for the recipient.

5. Follow-up on visual acuity and clinical outcome after corneal transplant, including the need for retransplantation, should be made available in order to complete the tissue vigilance chain from donor to recipient.

6. 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.

7. The boards of hospitals and clinics should ensure annually that all legal obligations regarding human tissues and cells are met as new developments in the field of transplantation of human substances may lead to new areas needing licensing and implementation of tissue vigilance.

8. More professionals involved in transplanting or applying human tissue and cells should be encouraged to also submit non-serious reports in order to contribute to the understanding of adverse reactions and events and possible ways to avoid these.

9. TRIP should collect further data on numbers of imported tissues and cells in collaboration with stakeholders. The importing and distributing institutions of tissue and cells should be involved in the reporting system and should be made aware of the legal obligations in this regard.

10. The requirements for vigilance in the form of reporting of adverse events and reactions and the submitting of data on processing, distribution, transplantation and recipients should specifically be pointed out to independent health care institutions and private clinics in order to increase participation of these groups.

5.3 Actions and developments following recommendations in the TRIP report 2010

1. The Boards of healthcare Institutions should ascertain that the medical specialists involved in transplantation of tissues and cells keep a comprehensive registry of number of transplantation procedures, tissue products, and adverse reactions and events.

   Development: There is improvement in the completeness of provided data on processing, distribution, transplantation and the number of recipients of human tissues and cells. Ten hospitals participated for the first time in 2011.

2. Identification of donors, recipients and tissues and cells should be carried out with the utmost care according to protocol at every step of the process. It can be included in the time-out protocol for an operative procedure.

   Development: In 2011 the number of identification errors amounted to nine which is equal to 2010. This recommendation remains in full force.

3. 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.

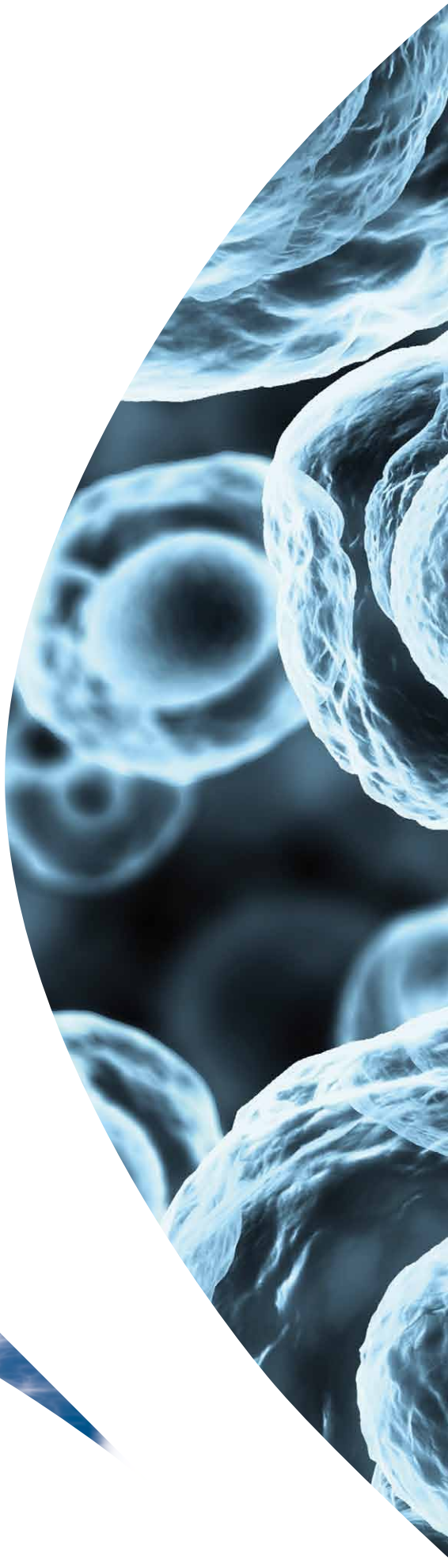
   Development: In 2011 no reports were registered concerning avoidable events that occurred with new techniques/transplants.

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

   Development: In 2011 no reports of adverse events related to maintenance or repair of equipment.

List of terms and abbreviations

Apheresis	-	Type of blood donation involving the selective mechanical withdrawal of specific blood components while infusing the remaining components to the donor or patient
Allogeneic	-	Originating from a donor (genetically non-identical person)
Autologous	-	Originating from a person's own body
DI	-	Donor insemination
DLI	-	Donor lymphocyte infusion
ET	-	Embryo Transfer
EU	-	European Union
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
HPSC	-	Hematopoietic stem cells
ICSI	-	Intra Cytoplasmic Sperm Injection (type of IVF)
IGZ	-	Healthcare Inspectorate
IUI	-	Intra Uterine Insemination
IVF	-	In Vitro Fertilisation
NVOG	-	Dutch Society for Obstetrics and Gynaecology
Organ bank	-	Tissue establishment that takes in human tissues and cells after procurement from a donor and subsequently processes, stores and distributes human tissues and cells (term used in Dutch law on quality and safety of substances of human origin).
PBSC	-	Peripheral blood stem cells
Tissue establishment	-	Institution which may be situated within a hospital of clinic or independent and holds a licence to perform one or more of the following activities: processing, storage, release and/or distribution. A tissue establishment may also be responsible for procurement or for testing of tissues and cells
TRIP	-	TRIP Foundation (Transfusion Reactions in Patients, from 2012: Transfusion and transplantation reactions in patients)
Tx	-	Transplantation



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