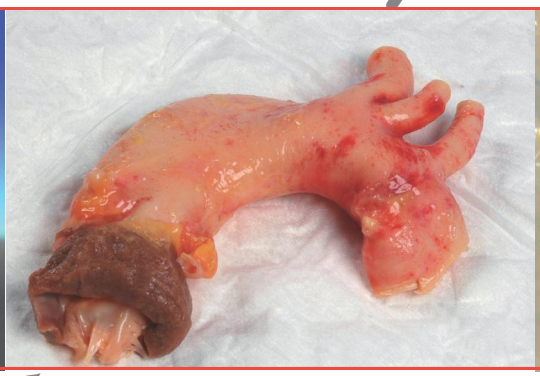
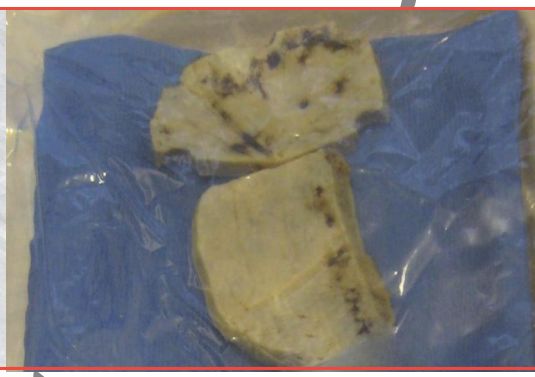
TRANSFUSIE REACTIES IN PATIËNTEN

TRIP

TRIP annual report 2009
Tissue vigilance





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The TRIP annual report 2009 regarding tissue vigilance reports in The Netherlands in 2009 is published under responsibility of the TRIP (Transfusion Reactions in Patients) Foundation.

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Foreword

The TRIP Annual Report 2009 concerning tissue vigilance is the second dedicated tissue vigilance report. As of last year the hemovigilance and the tissue vigilance reports are separate. In previous years the annual findings of hemovigilance and tissue vigilance were jointly published in the TRIP annual report. As medical professionals in the field of tissue vigilance are substantially different from medical professionals in the field of hemovigilance, it was decided to publish two independent reports.

The number of reports of adverse reactions and events occurring with application of human tissue and cells in 2009 is approximately equal to that of the reporting year 2008. However, there is an obvious increase in the number of serious reports that are mandatory reportable and included in the annual overview for the European Commission compared to the number of non-serious voluntary reports. In order to get a better understanding of the reports categories of adverse reactions and events have been developed.

By now tissue vigilance as required by the Dutch Law on Safety and Quality of Substances of Human Origin has been implemented by 60% of the users of human tissues and cells in hospitals and fertility clinics, as is shown by the participation figures. In many hospitals it is now known whether they transplant human tissues and cells. Participation of the distributors of human tissues and cells (tissue banks independent from hospitals) remains high.

In this report, once again a substantial number of reports concerns reproductive cells. The lead shown by the professional body of clinical embryologists in developing and implementing a guideline regarding reporting of adverse reactions and events has been instrumental in achieving this. Also figures of transplantation of reproductive cells are several times higher than that of transplantation of other human tissues and cells. Other medical professional bodies in the field of transplantation of human tissues and cells should follow suit in developing and implementing guidelines on reporting of adverse reactions and events. This is obviously preferable to an externally imposed guideline.

I warmly recommend this report to you and hope it will be an incentive to implement tissue vigilance on an even wider scale in order to contribute to the improvement of quality and safety of transplantation of human tissues and cells.

Prof. Dr. René R. P. de Vries
President, TRIP Foundation

Executive summary

The TRIP (Transfusion Reactions in Patients) National Hemovigilance Office introduced tissue vigilance in 2006 on request by the Ministry of Health with the aim to receive reports of adverse reactions and adverse events and report publicly on safety of human tissues and cells. On behalf of the Healthcare Inspectorate (IGZ), TRIP provides the yearly mandatory overview of serious adverse reactions and serious adverse events to be sumitted to the European Commission under the mandatory reporting requirement of the European Directive 2004/23/EC.

All reports are assessed by the TRIP office staff and if necessary additional information is sought. Before inclusion in the annual report all reports are assessed by an Advisory Committee consisting of experts in the field of transplantation of tissues and cells. In 2009 definitions were developed for categories of adverse reactions and adverse events.

Findings

Participation of transplanting institutions (hospitals and fertility clinics) of human tissues and cells, by submission to TRIP of numbers of transplanted tissues and cells and/or sending in reports, shows an increase from 37.0% in 2008 to 51.5% in 2009. A greater percentage (60.4%) has appointed a tissue vigilance officer or coordinator. Distributors of human tissues and cells (tissue banks/tissue establishments) show a good participation figure (93.8%). The closing date for inclusion in this report was May 1 2010.

Concerning the reporting year 2009 a total of 46 reports was received, of which 40 were assessed as serious and included in the overview for the European Commission. Subdivided according to implicated type of cells or tissue there were 28 reports regarding reproductive cells, nine reports regarding corneal transplants, six regarding hemopoietic stem cells, two regarding bone transplants an one regarding transplant of cardiovascular tissue. There were 41 reports of adverse events, of which 28 involved reproductive cells, and five adverse reactions. The large number of reports regarding reproductive cells is explained by the high number of applications of reproductive cells in conjunction with implementation of the professional guideline “Reporting of serious adverse events, reactions and calamities in the application of gametes and/or embryos in assisted reproduction”. According to this guideline all loss of tissue or cells is serious and thus in principle mandatory reportable.

Conclusion and recommendations

Participation of hospitals and tissue establishments shows an increase compared with 2008, but there is still incomplete information on distribution and application figures of human tissues and cells. Participation of hospitals and specialised clinics needs to be improved. Early in 2010 an online reporting system in pilot form was launched to facilitate reporting. Part of the 2009 reports were submitted online using this sysem. A joint circular by the Ministry of Health/Healthcare Inspectorate and TRIP should be drawn up to stress the legal requirement of tissue vigilance. Also the provision of numbers of distribution and application of human tissues and cells for the EU overview should be included with the requirements for mandatory accreditation.

A number of the reports demonstrate that abnormalities found in post-mortem tissues and organs have implications for other tissues and organs from the same post-mortem donor. They emphasize the importance of traceability and rapid reporting between organisations. Other reports have led to the instatement of fail-safe alarm systems for technical equipment to prevent loss of human tissues and cells in the event of malfunction or failur

1. | Introduction and TRIP working methods|

Regarding the reporting year 2009 as in 2008 a separate report concerning tissue vigilance has been published. Up to the year 2007 tissue vigilance reporting was included in the TRIP annual report concerning hemovigilance and tissue vigilance. As the medical professionals in the field of transplantation of human tissues and cells differ from the professionals involved in blood transfusion it was decided to publish two dedicated reports.

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 2005 at the request of the Ministry of Health TRIP initiated preparations for a reporting system for serious adverse events and serious adverse reactions associated with transplantation of human tissues and cells in accordance with the EU Directive 2004/23/EG that came into force in April 2006. The Directive defines standards for safety and quality for donating, procuring, testing, processing, storage and distribution of tissues and cells of human origin. Article 11 of this Directive is dedicated to reporting of serious adverse events and reactions and decrees that all member states should implement a reporting system.

In August 2006 all medical professional bodies, hospitals and clinics, tissue establishments and tissue banks were informed about the launch of a pilot reporting system. A paper form for reporting serious adverse events and serious adverse reactions was developed. On August 18 2006 the first report of a serious adverse reaction was registered by TRIP. Reporters were also asked to report non-serious reactions and events in order to provide insight in possible types of reactions and events in the field of human tissues and cells. Only serious reactions and events that meet the definition of the EU Directive are included in the overview of serious adverse events and reactions for the Ministry of Health and the Healthcare Inspectorate.

In January 2007 the Dutch Law on Safety and Quality of Substances of Human Origin (2003) was updated and adjusted to the EU Directive 2004/23/EG. This states that a tissue bank should appoint a responsible person who sees to a.o. reporting of serious adverse reactions and events, which is no longer voluntary with the coming into force of the law. Healthcare institutions are obliged to report to the tissue bank/tissue establishments any serious adverse reaction or serious adverse event that could possibly affect the safety and quality of human tissues and cells.

In 2007 an Advisory Committee was formed to counsel TRIP staff and board members 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 before inclusion in the TRIP annual report and the annual overview for the European Commission.

On the TRIP website (www.tripnet.nl) forms for reporting of reactions and events are available. In January 2010 an online pilot reporting system similar to that for hemovigilance was launched. Nineteen of the 2009 reports were submitted online. During 2009, in a tissue vigilance implementation project, continued efforts were made to further implementation of tissue vigilance particularly in hospitals and to stress the necessity of reporting in order to improve quality and safety in the use of substances of human origin. This project has been concluded; model documents, different models of tissue vigilance systems in hospitals and a roadmap for implementation are available on request to hospitals and clinics to help them in implementing tissue vigilance.

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.

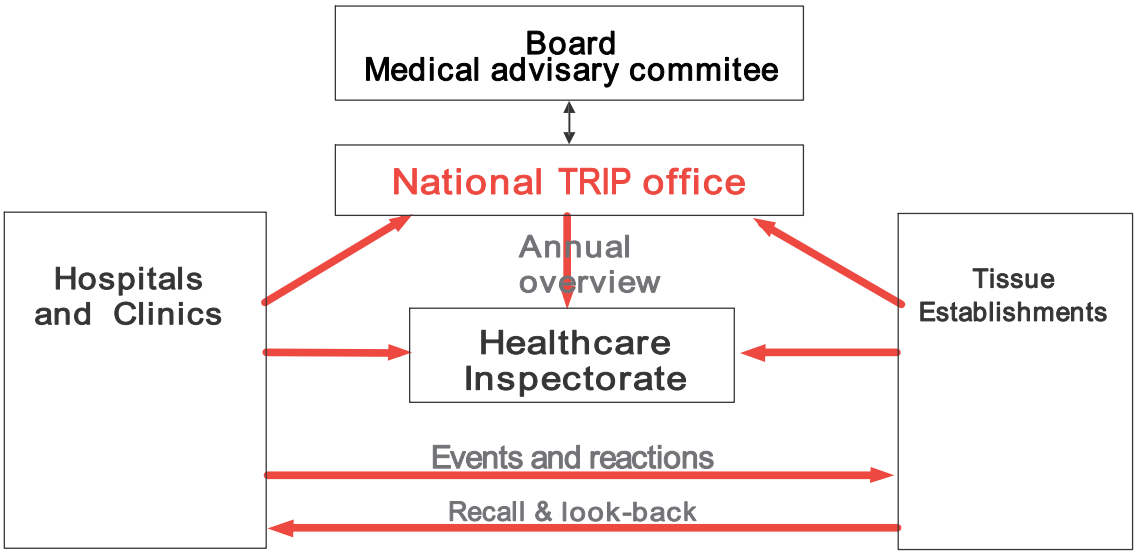


Figure 1 Flowchart of tissue vigilance reports

2. | Participation|

The participation of hospitals, tissue establishments and tissue banks in a reporting system for adverse reactions and events associated with transplantation of human tissues and cells is paramount for optimal registration and thus obtaining a clear picture of quality and safety of human tissues and cells. Also the comprehensiveness of reports is a determining factor. Participation is determined on the one hand by submission of reports and – if relevant – to the tissue bank involved and/or the Healthcare Inspectorate. On the other hand yearly numbers of distributed or applied human tissues and cells need to be submitted along with the number of transplanted patients.

In calculating participation rates TRIP distinguishes two categories of institutions: firstly suppliers of human tissues and cells: tissue establishments and tissue banks, and secondly the transplanting institutions, hospitals and fertility clinics. *Figure 2* and *Figure 3* show the participation of the two distinct categories of institutions in 2009.

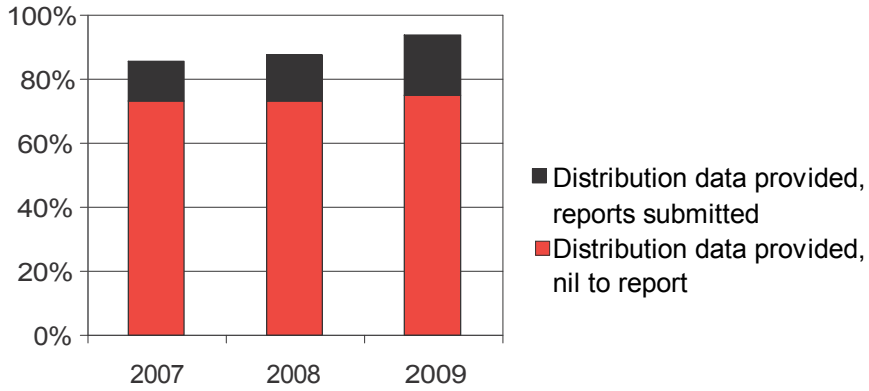


Figure 2. Participation by tissue establishments and tissue banks

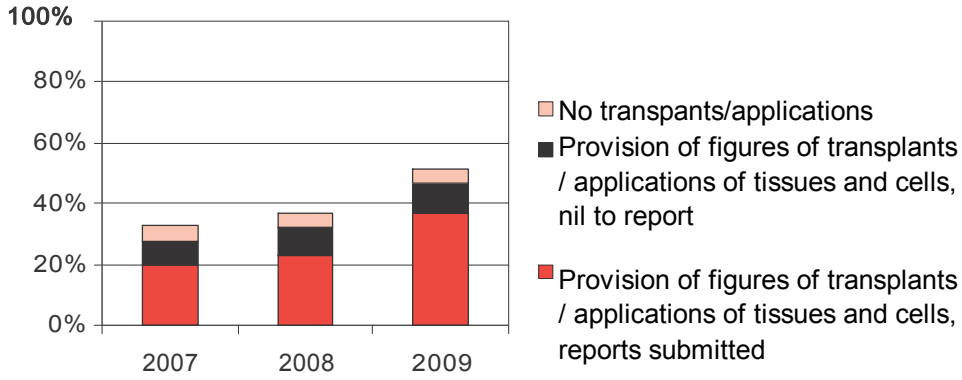


Figure 3. Participation by hospitals and ferility clinics

Hospitals are mainly transplanting tissues and cells. In some cases a hospital may also be a licensed tissue establishment if it pursues activities in preserving, processing, storage and distribution of human tissues and cells. For these activities a hospital a licence is obligatory. Licences of hospitals and clinics per tissue/cell type can be viewed on the website www.farmatec.nl. Many hospitals perform intra-uterine insemination (IUI); the processing of semen is one of the activities for which a licence from the Ministry of Health is required.

Many hospitals and fertility clinics have already appointed a tissue vigilance officer or coordinator. This is the case in 60.4% (60/101) of hospitals and clinics and in 100% (16/16) of tissue banks. TRIP has a contact in another 17.8% (18/101) of hospitals and fertility clinics who, however, is not formally appointed as a tissue vigilance officer.

Participation of hospitals and tissue banks has increased compared to 2008. The total number of hospitals and fertility clinics has decreased from 108 to 101 due to mergers or cessation of activities. The total number of tissue establishments and tissue banks was stable at 16. Three new tissue banks have been founded and three have ceased their activities.

Out of the 16 tissue establishments/tissue banks 15 (93.8%) participated in tissue vigilance in 2009: 15 submitted their distribution figures, three also sent report(s) to TRIP and ten stated that they had nil to report.

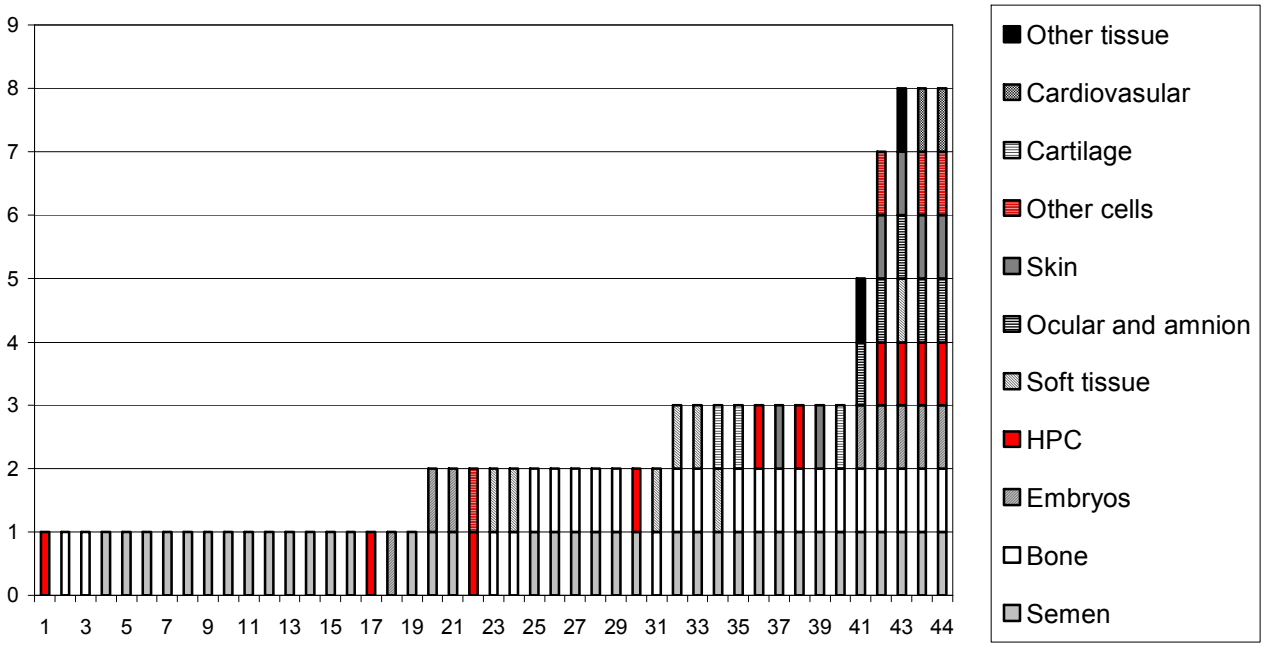
The situation is different in organisations responsible for human application of tissues and cells. Despite 61 of these 101 institutions (60.4%) having appointed a tissue vigilance officer, only 52 (51.5%) participated in the registration by stating to TRIP numbers of transplanted tissues and transplanted patients and/or sending in reports of adverse reactions and events. Out of these 52 transplanting institutions 42 stated they had nil to report and ten sent one or more reports to TRIP. Two institutions indicated that they were not able to submit annual numbers for 2009, but are planning to submit their figures in 2010. Five hospitals stated that they did not transplant any human tissue or cells in 2009.

Unfortunately it is still not known for all hospitals whether they are actually using human tissues and cells. Thirty-one hospitals have never submitted numbers despite yearly repeated requests. Five hold a licence for processing and/or storage of bone or semen. Presumably application figures must be available within these establishments. However if a hospital cannot provide annual figures or state that it is not transplanting human tissue or cells, the hospital board cannot be certain they are meeting their legal obligations with regard to licence, traceability and tissue vigilance reporting. TRIP recommends that the licensing organisation Farmatec reminds institutions requesting accreditation of the need to submit figures of transplanted tissues and cells and transplanted patients as well to report serious adverse reactions and events for the yearly compulsory overview for the European Commission. A question about participation and the reporting of SARE to TRIP is already part of inspections of laboratories and tissue banks.

3. | Distribution and transplantation |

All hospitals and tissue establishments/tissue banks in The Netherlands were requested to submit figures of distributed products and/or applications/transplantations of tissues and cells for the overview for the European Commission. With regard to the reporting year 2009 TRIP for the first time also requested numbers of transplanted patients and drew a distinction between distribution in The Netherlands, in the European Union and outside the European Union. These numbers are mandatory for each EU member state to submit to the European Commission accoding to directive 2004/23/EC and 2006/86/EC.

Figure 4 shows the type(s) of tissues and cells transplanted in hospitals which submitted information to TRIP in 2009.



Figuur 4. Types of tissue and cells per hospital

Table 1 shows available figures of distributed and transplanted human tissue and cells in The Netherlands in 2009. The table shows a discrepancy between numbers of distribution and transplantation for most types of tissues and cells. This is due to incomplete data, particularly because almost half of the hospitals failed to submit data or sent incomplete information. The reproductive cells account for by far the largest numbers. Here also the data are incomplete; eight out of 13 (62%) laboratories for in vitro fertilisation provided data to TRIP.

Table 1. Overview of distributed and transplanted units of human tissues and cells within The Netherlands in 2009

Type	Distributed by hospitals/ clinics*	Distributed by tissue bank**	Transplanted***	Recipients****
Skin				
Donor skin	20	1120	43	32
Cultured skin	93		93	9
Keratocytes	11		11	8
Bone				
Bone, whole		89	18	17
Bone chips/fragments	20	1233	227	156
Femoral heads (halved)	216	60	237	156
Femoral heads (whole)	64	2269	390	214
Cranial bone (autolog.)	36		43	43
Auditory ossicles			8	8
Demineralised bone		44	43	7
Cartilage		4	129	133
Soft tissue				
Tendons		216	19	11
Fascia		24	88	43
Other		42	5	
Ocular tissue				
Cornea		1002	165	165
Sclera		363	70	70
Amnion		66	6	6
Cardiovascular tissue				
Heart valves		82	9	9
Vessels and patches		27	29	29
Hematopoietic stem cells (unrelated donors)				
Bone marrow	15	59	19	19
Peripheral blood stem cells	65	164	101	94
Cord blood	11	70	41	18
Hematopoietic stem cells (related donors)				
Bone marrow			13	13
Peripheral blood stem cells	82		133	113
Hematopoietic stem cells (autologous)				
Bone marrow	84		127	126
Peripheral blood stem cells	1531		1314	344
Other cells				
Mesenchymal stem cells	20		11	11
Lymfocytes	123	47	228	136
Dendritic cells	6		6	2
Reproductive cells				
Semen (donor)	36		4062	410
Semen (partner)	6013		13739	5692
Oocytes	28967		23	
Embryos	8343		15864	7073
Other tissue				
Testicular tissue	5		5	5
Langerhans' islets	39		5	5

* Data submitted by 18 licensed hospitals/clinics
** Data submitted by 15 out of 16 tissue banks (94%)
*** Data submitted by 52 out of 101 hospitals and clinics (52%)
**** Figures from 31 out of 101 hospitals and clinics (31%)

Table 2 shows numbers of human tissues and cells distributed outside The Netherlands. These data are relevant as serious adverse reactions and events are reportable in the country of origin of the transplants.

Table 2. Human tissues and cells distributed outside The Netherlands in 2009

Type	Distributed within EU *	Distributed outside EU *
Skin		
Donor skin	10080	7500
Bone		
Bone, whole	12	
Bone chips/fragments	700	
Femoral heads (whole)	187	
Demineralised bone	159	486
Soft tissue		
Tendons	153	
Fascia	50	1
Other	80	10
Ocular tissue		
Cornea	283	24
Sclera	1	
Cardiovascular tissue		
Heart valves	59	
Vessels and patches	15	1
Hematopoietic stem cells (unrelated donors)		
Bone marrow	9	6
Peripheral blood stem cells	9	7
Cord blood	10	9
Other cells		
Lymfocytes	2	1
Reproductive cells		
Semen (donor)	104	
Semen (partner)	76	

* Data submitted by 15 out of 16 tissue banks (94%)

4. | Categories of adverse reactions and events |

Mandatory reports of adverse reactions for the overview for the European Commission[1] should be classified in six categories:

- Transmitted bacterial infection
- Transmitted viral infection
- Transmitted parasitical infection
- Transmitted malignant disease
- Other disease transmisions
- Other serious reactions

Serious adverse events should be classified in four categories:

- Tissues and cells defect
- Equipment failure
- Human error
- Other

As this classification is limited TRIP has elected to develop a more comprehensive set of categories of reactions and events to be able to get a more specific representation of the vigilance reports. These categories are listed below.

Categories of adverse reaction

- Anaphylactic reaction
- Other allergic reaction
- Hemolytic reaction
- TRALI (transfusion-related acute lung injury)
- Circulatory overload
- Post-transplant bacterial infection
- Post-transplant viral infection
- Post-transplant other infection
- Post-transplant malignancy
- Post-transplant febrile reaction
- Other reaction
- Donation complication

Categories of adverse events (incidents)

- Bacterial contamination of product
- Viral contamination of product
- Product incident
- Congenital abnormality
- Loss of tissues or cells
- Poor/failure of engraftment/growth
- Incorrect product transplanted
- Near miss
- Other incident

[1] European Directive 2004/23/ EC and 2006/86/EC

5. | Reports in 2009 |

Using the online reporting system for hemovigilance as a model, TRIP has adapted it to suit tissue vigilance. This online reporting system became available in pilot format shortly before the closing date for the 2009 report.

Regarding the reporting year 2009 TRIP received 46 reports of adverse reactions and events concerning transplantation of human tissues and cells. These reports came from three tissue establishments or tissue banks and nine hospitals. One hospital submitted a report for the first time. The number of reports per institution varies from one to 13. Nineteen of the 46 reports were submitted online.

The distribution of the reports per type of tissues and cells is shown in *Figure 5.*

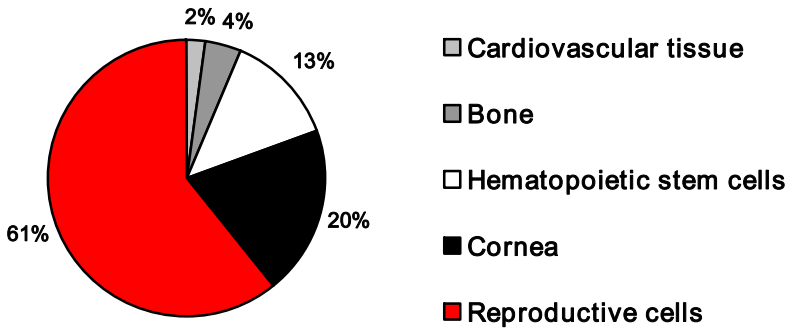


Figure 5. Percentage of reports in 2009 per tissue/cell type

No reports were received concerning skin or soft tissues. Forty reports were judged to be serious adverse reactions or events as shown in *Table 3.* A short description of the reports per type of tissue/cells follows.

Table 3. **Serious reports per tissue/cell type**

Type of tissue/cells	Total no of reports	Serious	Percentage serious reports
Cardiovascular tissue	1	1	100%
Bone	2	2	100%
Hematopoietic stem cells	6	6	100%
Cornea	9	8	89%
Reproductive cells	28	23	82%
Total	**46**	**40**	**87%**

Cardiovascular tissue

One report categorized as other incident was submitted: a routine culture of the storage solution of a postmorteml pulmonary valve became positive (Massilia Timonae) after 14 days. The patient experienced a febrile episode in the same period as the culture becoming positive. The patient received standard antibiotic prophylaxis after transplantation, all cultures in donor and recipient were negative. Considering the nature of the cultured bacterium it is possible that the storage solution was contaminated in the operating theatre at the time of transplantation of the valve.

Bone

In 2009 two reports were submitted concerning bone. In one other incident traceability could not be documented. An allogeneic femoral head that had been cleared for transplant disappeared from the freezer. All documentation about requesting specialist and recipient was lacking. Existing

procedures for transplant were not adhered to. The hospital could not establish who had removed the femoral head or whether it had been transplanted. The key for the freezer was available to all operating theatre staff. The other report was categorised as loss of tissues or cells. A hospital's central sterilisation department was asked to resterilise ten cranial bone segments. Six segments could no longer be identified as they were not properly labeled and for nine segments the shelf life had expired. No protocol was available for the sterilization and storage of autologous cranial bone segments. The irreplacable cranial bone had to be disposed of.

Hematopoietic stem cells

Peripheral blood stem cells

Three reports were submitted concerning peripheral blood stem cells: one adverse event and two reactions. The adverse event report, a product incident involved peripheral blood stem cells donated by a HLA-identical brother. On the second day of apheresis an slightly elevated number of B-cells. At immunophenotyping a "Hairy Cell Variant" was found. The apheresis products of the first and second day had already been infused. So far no sequelae for the recipient have been reported.

Two reports of adverse reactions were registered as other reaction. The first reported hypotension and decreased oxygenation at the beginning of reinfusion of autologous stem cells, that quickly resolved. The second reported acute dyspnea and diminished saturation during the last rapid reinfusion phase of allogeneic related stem cells. The patient recovered rapidly after oxygen supplementation; subsequently there was satisfactory engraftment. The chest X-ray at the time of the reaction was normal.

Cord blood

Two reports were received of hemolytic reactions after infusion of (allogeneic) cord blood. After the transplant elevevated hemolytic parameters were accompanied by transient renal compromise. Both cases were interpreted as non-immune hemolysis in the recipient.

Bone marrow

One report of an adverse event was submitted in the category poor/failure of engraftment/growth. After an autologous bone marrow transplant in a very ill patient there was engraftment failure. Prior to transplantation, evaluation of growth parameters had indicated moderate growth potential.

Cornea

Nine reports were received involving corneal transplants. There were eight advers events and one adverse reaction.

Product incidents

Four reports concerned the transplantation of a cornea from a donor for whom only at autopsy a contraindication for donation was found. A cornea can only be stored for a maximum of 28 days and will therefore be allocated and transplanted before the histologically confirmed autopsy report is available, usually six weeks weeks after the patient's death. Two reports regarded the two corneas from one donor found to have undiagnosed Kahler's disease. The third and fourth report mention abnormalities found at brain autopsy: incipient Alzheimer's disease and Lewy body disease respectively.

One submission concerns possible fungal contamination. At routine culture of the corneal storage solution a fungus was found two days after transplantation. The fungal colony, found at the edge of the culture dish, was initially deemed to be due to environmental contamination but proved to be relevant at fungal species determination. The patient had a suspicious lesion on the transplanted cornea and was already receiving antifungal therapy. It was decided to retransplant the patient to abolish the risk of fungal infection.

The last product incident report mentioned the discovery of a mucous plug from the storage solution at transplantation. The cornea was returned because of the minimal risk of systemic bacterial or fungal infection in the donor. As the recipient was already anesthetised in the operating

theatre an emergency cornea was supplied and transplanted. All cultures remained negative and extensive investigations of the donor revealed no systemic infection. Transplantation of the other cornea from the same donor was uneventful.

Bacterial contamination of product

One report was submitted in the category bacterial contamination of product. After transplantation of a cornea, revision histology of the heart valves from the same donor showed minimal endocarditis. There were no bacterial complications in the recipient.

Other incident

Polyoma virus was diagnosed in a transplanted kidney. From the same donor two corneas had been procured and transplanted. The recipients had no complications and showed no signs of polyoma virus infection. The heart valves from the donor were initially quarantined but later released for transplantation. It is impossible to determine whether the polyoma virus was latently present in the donor or due to a recent infection in an immunocompromised kidney recipient.

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Post-transplant bacterial infection

One post-transplant bacterial infection was registerd. After corneal transplant in another EU member state the recipient developed enterococcal infection involving a resistant strain. All cultures at the tissue bank were negative. Possibly this infection was hospital-induced at transplantation. There are no data available on the follow up of the recipient.

Reproductive cells

In 2009 there were 28 reports of adverse events during processing or transfer of gametes and/or embryos at assisted reproduction, a number comparable to that of 2008. Thirty reports were submitted in 2008 including six late reports. The late reports are briefly delineated in the next paragraph. In 2009 no adverse reactions were reported.

Figure 6 shows the distribution of adverse events per category. As in 2008 the largest category by number is loss of tissues or cells.

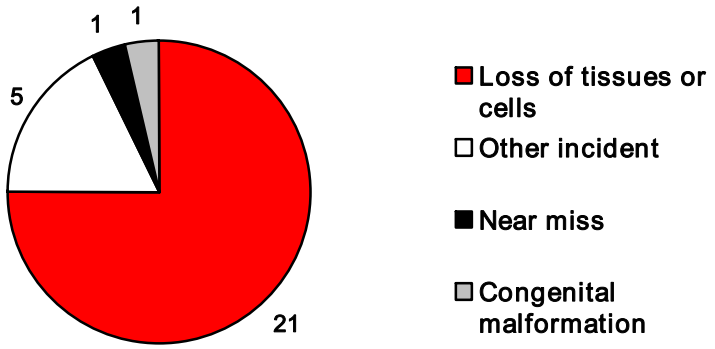

Figure 6. Categories of adverse events involving reproductive cells

Congenital malformation

This report concerned the transmission of a recessive disorder after donor insemination. The donor's history was negative for any genetic disorder. After birth the child was diagnosed with spinal muscular atrophy. Investigations showed donor and mother to be carriers of a recessive defect. The donor was deferred. Birth of a child affected by a recessive disorder, as in unassisted reproduction, is not preventable but it is important to monitor frequency.

Near miss

One near miss was reported. At in vitro fertilization (IVF) the label on the laboratory form accompanying the semen container was for the wrong person. All materials had been wrongly

labelled. This had not been noted at the procedural double check. At the start of the laboratory procedures the mistake was noted and corrected.

Other incident
Five reports were registered in this category. Two reports involved communication errors leading in one case to the transfer of one instead of two embryos and in the other case to an ICSI procedure being requested and performed instead of an IVF procedure.

One report described technical failure of an incubator holding 34 embryos from four couples. As the alarm system was not fail-safe the problem was discovered the next day. All embryos were morphologically normal and were transferred or frozen according to protocol.

Two reports deal with failure to follow standard operating procedures which may have led to less effective treatment. In one case semen was supplied in an unapproved container. Despite this the sample was processed and used for insemination. The other report concerned an emergency IVF procedure for fertility preservation. Only one embryo was obtained that by mistake was not frozen on the usual day according to protocol. An adapted freezing procedure for later freezing should have been used but unfortunately this was not done. In consequence the embryo has diminished viability to withstand storage and the thawing procedures.

Loss of tissues or cells
In total 21 reports were submitted concerning loss of tissues or cells. In *Figure 7* the distribution according to type of error is shown.

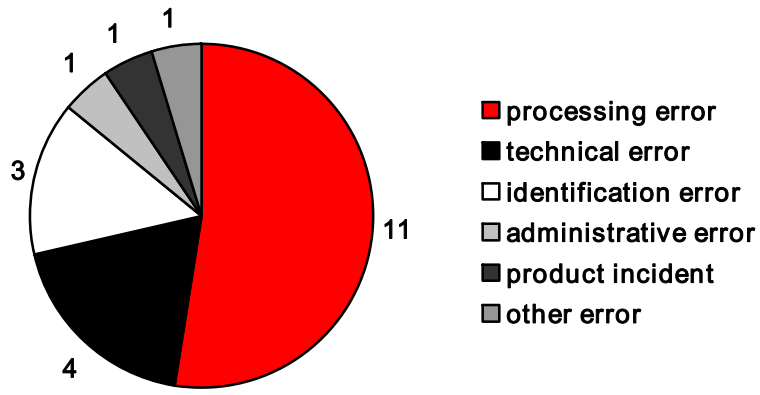

Figure 7. Type of error leading to loss of reproductive tissues and cells

Processing error
Most errors occurred during processing and were due to accidental mismanipulations or material being dropped (4 reports), failure of timely processing during an IVF procedure (also 4 reports) and mistakenly destroying embryos or a semen container. One report mentioned seeding[3] below the desired temperature leading to degeneration of a batch of embryos.

Technical error
Four reports were about a technical error leading to loss of reproductive tissues and cells. Two mentioned the absence of a fail-safe alarm system in freezers which forestalled timely intervention. In this case the manufacturer was contacted and modifications made to prevent repetition. One report regarded the incorrect preparation of a culture dish for fertilized oocytes. The fourth report described the loss of semen procured by an invasive procedure. It was transported in a cryocontainer that was found at retrospective validation to maintain the required conditions for less than the 24 hours stated in the specification.

Indentification error
Three reports concerned identification errors. One report described the possible mix-up of four embryos from two couples in a liquid nitrogen storage vat. All embryos were frozen and stored at

the same time. As identity could not be verified all the embryos were destroyed. The other two reports mentioned the loss of two embryos after an accidental switch of medical files.

Other error
One report mentioned the loss of a straw containing two embryos due to an administrative error. The straw belonging to another couple had been placed in the wrong position in a storage vat and was needlessly thawed. One report described a product defect: a positive culture (E. coli) was found in IVF culture solution. Culture of control solution was negative and semen culture was also found to be negative; in this report the non-fertilisation of the oöcytes could not be related to the possible bacterial infection. Another report described the unnecessary thawing of a second embryo after erroneously returning the patient's file to the pile of case notes "for embryo thawing".

Late reports from 2008

After the closing date for reports of adverse reactions and events in tissue and cells transplants in 2008 another six reports were received. The total number of reports in 2008 including these was brought to 47. All six reports were submitted by one hospital and concerned reproductive cells. Four were assessed to be serious adverse events. For the reporting year 2008 in total 33 (70%) reports were assessed to be serious.

The reports were five cases of loss of tissues or cells and one so-called other incident. Three reports of loss of tissues and cells involved technical errors because of defective micromanipulation pipettes and led to loss of embryos or an oocyte. One report described two embryo culture dishes accidentally falling and another the accidental destruction of a culture dish containing three oocytes. The other incident concerned IVF treatment being given instead of the intended ICSI treatment.

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

Table 4 shows an overview of the number of serious reactions and events reported in 2009.

Table 4 Overview of serious reports in 2009

	Oocytes	Embryos	Semen	Ocular	Bone	HPC	Cardio-vascular	Total
Serious reactions	0	0	0	1	0	4	0	**5**
Serious events	8	13	2	7	2	2	1	**35**
Serious reactions in donor	0	0	0	0	0	0	0	**0**
Total serious reports								**40**

7. | Conclusions and recommendations|

Actions and developments following the recommendations in the TRIP annual report 2008

1. TRIP recommends that the hospital governing boards should be officially reminded by letter of the mandatory nature of tissue vigilance. This could take the form of a joint circular from the healthcare ministry and inspectorate and TRIP.
   Action: TRIP has prepared a draft for a circular which can be sent jointly by the Ministry of Health, the Healthcare Inspectorate and TRIP. The Inspectorate and Ministry have yet to finalise the text.
2. The various groups of professionals who apply human tissues and cells should follow the example of the clinical embryologists and develop vigilance guidelines. This should give clear guidance on the types of adverse reactions and incidents which should be reported.
   Development: The Dutch working group of stem cell laboratories (Werkgroep Stamcellaboratoria Nederland, WSN) is preparing a guideline for reporting adverse reactions and events associated with hematopoietic stem cells.

Conclusions

1. Participation of hospitals and tissue establishments is growing but the percentage is still too low.
2. A tissue vigilance officer has been appointed in 60% of hospitals. Moreover another 18% have a contact for tissue vigilance.
3. Some specialized institutions do not submit numbers of transplanted tissues and cells, leading to a disparity between distribution and transplantation figures.
4. There is a large discrepancy between submitted numbers of distributed bone, soft tissue, skin and ocular tissue and figures for transplantation of these tissue types.
5. Many hospitals (46%) submit numbers of applied units of semen, but fail to give the number of recipients.
6. Of the total of 46 vigilance reports concerning 2009 19 (41%) were submitted through the online reporting system. From the start of the pilot in January 2010 19 out of 28 reports (68%) have been submitted online.
7. Abnormalities of different types of (postmortem) tissues and organs may have repercussions for tissues and organs procured from the same postmortem donor. Procedures of traceability and recall/look back should be well harmonised between organisations.
8. 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 of cells.

Recommendations

1. A joint circular from the Ministry of Health, the Healthcare Inspectorate and TRIP should point out the mandatory nature of tissue vigilance.
2. Participation of a healthcare instution requires the submission of information both on serious adverse reactions and events and on distribution and transplantations numbers.
3. At licensing inspections for tissue establishments and tissue banks the TRIP statement / certificate of participation should be formally reviewed. This certificate confirms receipt of the mandatory data for inclusion in the national data for the European Commission.

List of terms and abbreviations

Apheresis	Type of blood donation involving the selective mechanical withdrawal of specific blood components while reinfusing 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
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
HLA	Human Leucocyte Antigen
HPC	Hematopoietic stem cells
ICSI	Intra-Cytoplasmatic Sperm Injection (type of IVF)
IUI	Intra-Uterine Insemination
TRIP	TRIP Foudation (Transfusion Reactions in Patients)

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