TRIP REPORT 2023

BIOVIGILANCE

EXTENDED VERSION

TRIP
Hemo- en biovigilantie

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The TRIP 2023 Biovigilance report, extended version, is published under the responsibility of the TRIP (Transfusion and Transplantation Reactions in Patients) Foundation.

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1 INTRODUCTION

In this 2023 Biovigilance Report, TRIP presents reports of incidents and adverse reactions that occur in the chain from the donation to the clinical application of human tissues and cells. The report also provides an overview of figures for the processing, distribution and application of human tissues and cells and the number of recipients. These figures have been submitted by tissue establishments and healthcare centres participating in the national biovigilance network.

On 24 April 2024, the European Regulation on Substances of Human Origin (SoHO) was adopted by the European Parliament and the European Commission formally adopted this new Regulation on 27 May 2024. Following its publication in the EU's Official Journal, a three-year period has entered into force and the Regulation will apply directly to all European Member States on 7 August 2027. This Regulation will replace the current European Directives (2002/98 and 2004/23).

An important change is that all human blood products, tissues and cells and substances such as breast milk and faecal microbiota will be subject to the same regulation and thus become Substances of Human Origin (SoHO). The regulation also includes the new concept of a SoHO entity, encompassing all organisations involved in the chain from donation to the use of human body material in patients. All SoHO entities must register and declare their activities. This means that centres that only apply SoHO and have not been obliged to register until now must do so and are obliged to report their figures. This obligation should improve the traceability of SoHO. Exactly which figures will have to be reported is not yet known. Since 2007, TRIP has been receiving figures from both tissue establishments and applying centres. The participation of tissue establishments is high (> 95%), possible due to the mandatory nature that already exists under the Dutch Body Material (Safety and Quality) Act (WVKL). Similar to previous years – and in particular for other tissues and cells – the 2023 data indicates that application figures are incomplete or the number of recipients cannot be determined. This is a challenge for some of the future SoHO entities as well as for TRIP. Reporting serious incidents and adverse reactions is already mandatory and this requirement will remain in force and have wider application under the new Regulation. TRIP has also received this data since 2007. On average over the last ten years, TRIP received 104 reports annually (2014-2023; range 83-121). The participation of the tissue establishments and the reports overview demonstrate that TRIP has evolved into a robust biovigilance system in recent years. TRIP will continue to receive, analyse and process reports from the SoHO chain in accordance with the current system.

TRIP would like to thank all professionals who contributed to the preparation of this report.

2 BIOVIGILANCE IN 2023 AND RECOMMENDATIONS

2.1 Biovigilance in 2023

Similar to the year before, all tissue establishments known to TRIP that are active in the field of reproductive tissues and cells, hematopoietic stem cells and therapeutic cells declared their activities in 2023. Of the 24 tissue establishments that process, store and/or distribute other tissues and cells, 23 reported activity over the year 2023. Of the 136 applying centres known to TRIP, 115 centres submitted information on the application of other tissues and cells.

In 2023, a total of 94 reports (107 in 2022) were submitted to TRIP before the cut-off date for this report, 1 March 2024. Five reports were assessed as certainly unrelated to the transplant chain; These are excluded from the further report. In addition, there are seven late reports from an earlier reporting year that have been completed in 2023. Of the 89 reports, 32 reports (+2 late reports) were assessed as serious, based on the EU criteria. The previous year there were 44. The largest decrease in serious reports is in the other tissues and cells category. The two late reports that were assessed as serious are discussed in the relevant chapters.

— In 2023, there were eight serious incidents involving reproductive tissues and cells. Fourteen serious donation complications after treatment in the context of a fertility programme were also reported.
— In 2023, two serious incidents related to hematopoietic stem cells were recorded. In addition, four reports of serious adverse reactions were received.
— Four serious incidents were recorded in the category other tissues and cells, two involving bone tissue and two ocular tissue.

2.2 Recommendations

	Recommendation	Who
1	Taking note of the European Regulation on Substances of Human Origin (SoHO) and mapping the consequences for future SoHO entities.	Boards of Directors, tissue establishments, applying centres, TRIP
2	Emphasising that, following the finalisation of the European Regulation on Substances of Human Origin (SoHO), ensuring traceability and submission of figures will be mandatory for all entities in the SoHO chain.	Boards of Directors, tissue establishments, applying centres, TRIP

2.3 Follow-up to previous years

1 Attention to the development of circulatory overload in relation to stem cell transplants, so that risk factors can be identified

Development:

In 2022, there were four reports of circulatory overload in relation to stem cell transplants, two of which were serious adverse reactions. Last year, TRIP received one report of circulatory overload in relation to stem cell transplant; it has been assessed as not serious according to EU criteria. Follow-up in the coming years will show whether there is a decreasing trend of circulatory overload or whether additional recommendations and possible prevention tools need to be developed to prevent this adverse reaction.

2 Attention to ensuring the traceability of human body material in the applying centres

Development:

With the finalisation of the European Regulation on SoHO, last year's recommendation has become current. Ensuring traceability will help future SoHO entities collect the mandatory figures and is again included in the list of recommendations.

3 Ahead of the upcoming European Regulation: take note of upcoming legislative changes and their consequences for future SoHO entities

Development:

This recommendation also remains current with the finalisation of the SoHO Regulation. TRIP aims to assess the impact of the changes in legislation and has provided a link to the recently published European Regulation on SoHO on its website. In the near future, TRIP will keep the field informed of the impact of this European law on SoHO users and explore ways to support them until its entry into force.

3 REPRODUCTIVE TISSUES AND CELLS

3.1 Establishments and centres involved

In 2023, there were 16 registered IVF laboratories with an organ bank accreditation in the Netherlands. Furthermore, 51 semen laboratories had a tissue establishment or organ bank accreditation. Establishments with an organ bank accreditation are also authorised to receive donor semen after procurement. All IVF laboratories and semen laboratories provided data on the processing, distribution and application of reproductive tissues and cells in 2023.

3.2 Activities in 2023

Tables 1 and 2 show the figures for processing, distribution and application of reproductive tissues and cells based on the annual activity reports for 2023. Reproductive tissues and cells can be processed several times, not only after collection but also at a later time when processing cryopreserved tissue. The number of processing operations may therefore exceed the number of units distributed or applied. The processing figures below specify the origins of the material (from the Netherlands, from the EU, or from outside the EU). The columns under Distributed indicate whether material was distributed in the Netherlands or in the EU, or exported outside the EU.

Based on the European definition in current legislation, transport between tissue establishments is not registered as distribution. Units that were transported and delivered for use in the tissue establishment's own centre are included under Distributed.

Table 1a shows the figures for processing and distribution of semen and testicular tissue. An increase in the processing of donor sperm from the Netherlands has been observed in the last two years and a decrease in the processing of donor semen from Europe has been observed in 2023. The application of donor semen has remained fairly constant over the years (Figure 1a). Table 1c and Figure 1c show a decrease in ovarian tissue processing, with no reports of ovarian tissue application. The centres that reported application last year have (temporarily) stopped processing ovarian tissue for certain indications, or indicate that the processing and application of ovarian tissue varies from year to year. The difference between applications (Table 2) versus distributions (Table 1a) of donor semen is explained by centres that can apply donor semen without intervention from the tissue establishment. Table 2 shows an increase in both the number of applications and the number of recipients of embryos derived from donor oocytes and donor semen. This is attributed to the higher number of treatments performed. It is not the case that more embryos are used per embryo transfer.

Table 1a Processing and distribution of semen and testicular tissue in 2023

Type of semen or testicular tissue	Tissue establishments	Unit	Processed			Distributed		
			From NL	From EU	From Outside EU	In NL	In EU	Export Outside EU
Partner semen fresh and cryo	66	Sample/straws	39,315	14	0	24,936	0	0
Donor semen fresh and cryo	17	Sample/straws	10,310	3,752	0	8,233	0	0
Partner semen MESA/PESA/TESE	10	Puncture/biopsy	1,331	0	0	n/a	n/a	n/a
Donor semen MESA/PESA/TESE	0	Puncture/biopsy	0	0	0	n/a	n/a	n/a
Testicular tissue	2	Transplant	25	0	0	0	0	0

Table 1b Processing and distribution of oocytes and ovarian tissue 2023

Type of oocytes or ovarian tissue	Tissue establishment	Unit	Processed			Distributed		
			From NL	From EU	From Outside EU	In NL	In EU	Export Outside EU
Own oocytes, fresh and cryo	16	Oocyte	137,939	16	0	n/a	n/a	n/a
Donor oocytes, fresh and cryo	12	Oocyte	2,380	0	0	n/a	n/a	n/a
Ovarian tissue	4	Transplant	54	0	0	0	0	0

Table 1c Processing and distribution of embryos 2023

Type of embryo	Tissue establishment	Unit	Processed			Distributed in NL
			From NL	From EU	From Outside EU	
Embryos, own oocytes and partner semen	16	Embryo	63,133	6	2	26,801
Embryos, own oocytes and donor semen	14	Embryo	6,268	0	0	2,236
Embryos, donor oocytes and partner semen	12	Embryo	1,143	0	0	475
Embryos, donor oocytes and donor semen or donated	6	Embryo	596	0	0	226

Table 2 Application of reproductive tissues and cells 2023

Type	Recipients	Unit	Application
Partner semen	9,812	Insemination	25,170
Donor semen	2,976	Insemination	9,041
Embryos, own oocytes and partner semen	14,444	Embryo	26,801
Embryos, own oocytes and donor semen	1,117	Embryo	2,236
Embryos, donor oocytes and partner semen	226	Embryo	475
Embryos, donor oocytes and donor semen or donated	132	Embryo	226
Ovarian tissue	0	Transplant	0
Testicular tissue	0	Transplant	0

Figures 1a, 1b and 1b show the application data for the period 2019-2023.

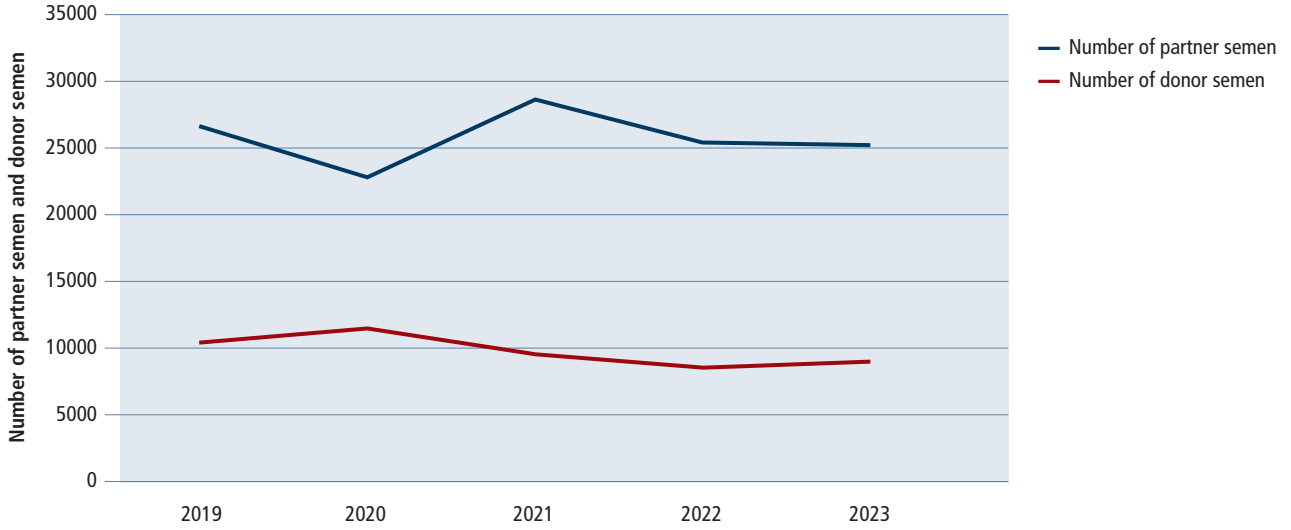

Figure 1a Number of inseminations with partner semen and donor semen, 2019-2023

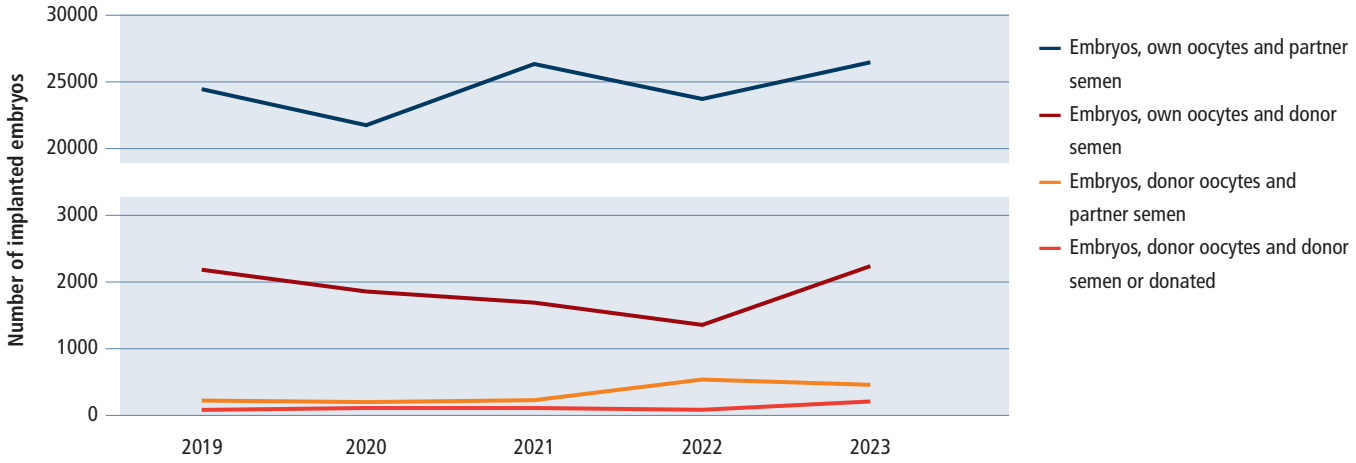

Figure 1b Number of embryos placed, 2019-2023

3.3 Reports

TRIP received 42 reports on the processing and application of gametes and embryos in medically assisted reproduction over the year 2023. Five reports were assessed as definitely not related to the medically assisted reproductive process and are not further considered in this biovigilance report.

The 37 reports can be subdivided into 23 incidents with or without adverse reactions and 14 donation complications (Table 3). Five late reports were also received of incidents that occurred before 2023 (Table 4). Where relevant, these reports were included in the figures for the years in which they occurred.

Figure 2 summarises all reports of incidents, adverse reactions and donation complications with unlikely, possible, probable or definite imputability, submitted in the period 2019-2023. The severity of incidents and the associated reporting obligation to the EU are determined on the basis of pre-established EU criteria (see TRIP website).

Case

Although the case is not part of a TRIP report, TRIP wants to present it with the aim of alerting everyone to the possibility of such a situation occurring. During a fertility journey, the prospective couple ends their relationship, but fails to inform the tissue establishment. Intracytoplasmic sperm injection (ICSI) treatment is carried out with frozen TESE semen, resulting in an embryo being implanted without the knowledge of the woman's ex-partner. While the storage agreements outline the responsibilities of the prospective parents, it is important to ensure that that both prospective parents consent to treatment and placement before embryos are created or transferred. This helps prevent a situation where a child develops from a procedure that one of the two prospective parents did not consent to.

Table 3 Reports of incidents and adverse reactions* concerning reproductive tissues and cells per type of fertility lab in 2023

Fertility laboratories	Number of centres	Establishments reporting	Total number of reports (serious EU)	Incidents (serious EU)	Adverse reactions (serious EU)	Donation complications (serious)
IVF laboratories	16	10	33 (22)	19 (8)	0	14 (14)
Semen laboratories	51	4	4 (0)	4 (0)	0	0
Total	**67**	**14**	**37 (22)**	**23 (8)**	**0**	**14 (14)**

* adverse reactions with definite, probable, possible or unlikely imputability

Table 4 Late reports of incidents involving reproductive tissues and cells per type of fertility laboratory

Year of occurrence	Type of tissue	Reporting category	Incidents (serious EU)	Description of serious incidentl
2019	Donor semen	Risk of transfer of condition	1 (1)	The donor reports carrying an autosomal dominant mutation.
2020	Donor semen	Congenital defect	1 (0)	
2022	Donor semen	Congenital defect	2 (0)	
Total			**4 (1)**	

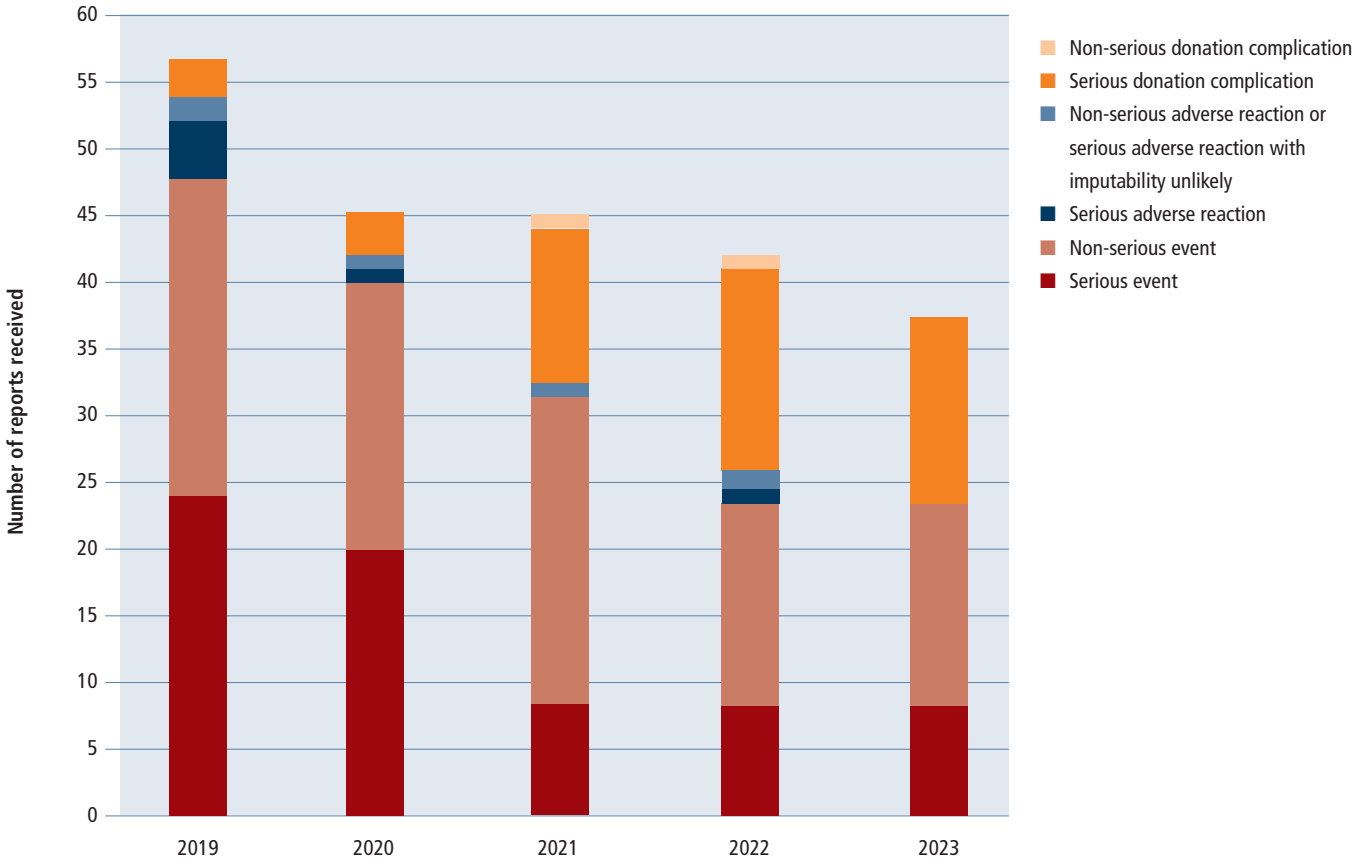

Figure 2 Reports of incidents and adverse reactions with definite, probable, possible or unlikely imputability concerning reproductive tissues and cells, classified by EU severity category, 2019-2023

Incidents

Figures 3a and 3b show the distribution of serious incidents in the period 2019-2023. Table 5 provides an overview of all incidents reported per type of tissue or cell. Serious incidents are discussed in the following sections.

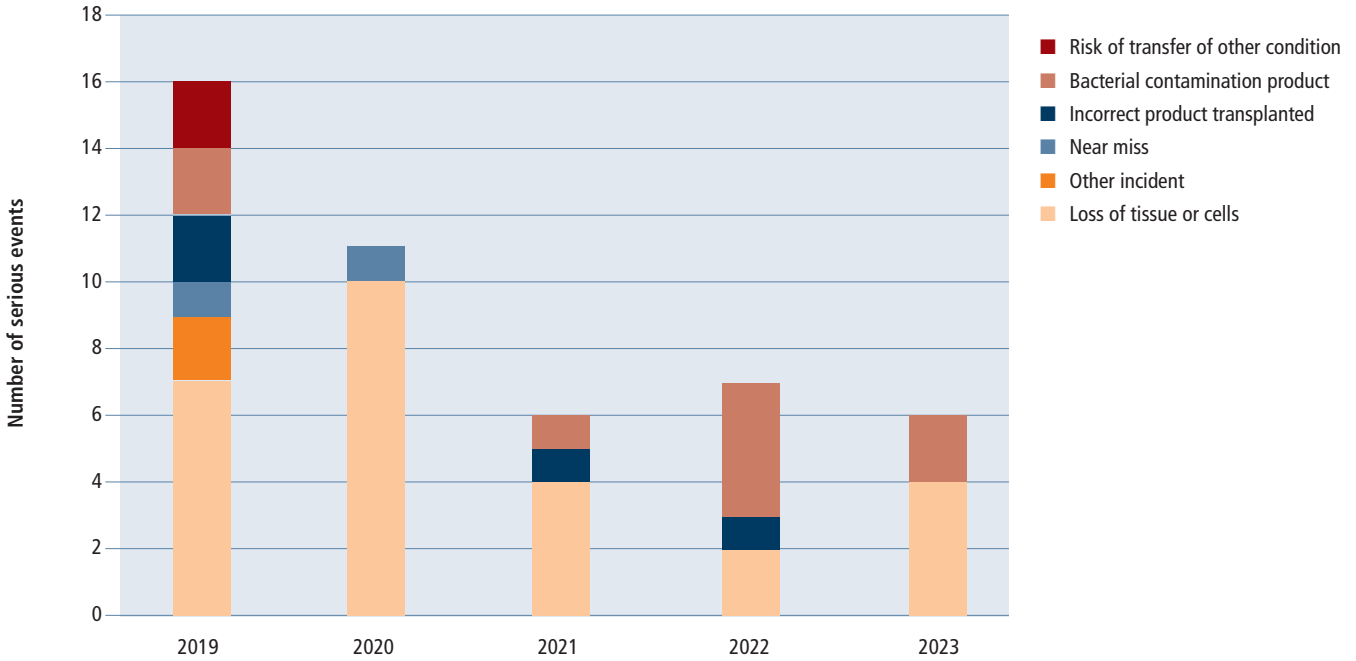

Figure 3a Number of reports of serious incidents per incident category concerning reproductive tissues and cells, 2019-2023

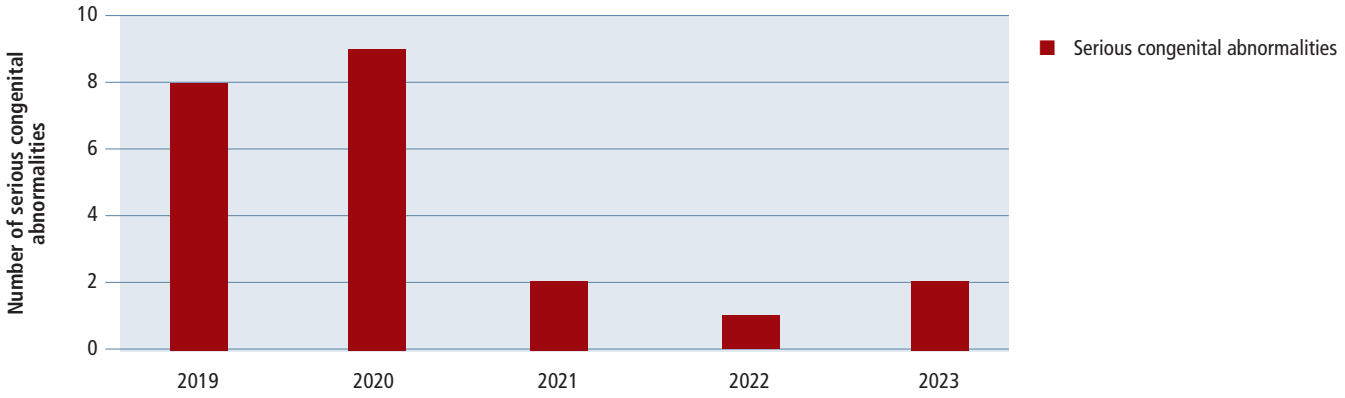

Figure 3b Number of reports of serious congenital abnormalities 2019-2023

Table 5 Overview of incidents in reproductive tissues and cells in 2023 and late reports

Type of tissue or cells	Incident category	Number of reports of incidents (serious EU)	Late reports (serious EU)
Semen	Bacterial contamination product	1 (1)	
	Congenital defect	8 (2)	3 (0)
	Other incident	4 (0)	
	Risk of transfer of condition		1 (1)
Oocytes	Loss of tissues or cells	7 (4)	
Embryos	Bacterial contamination product	1 (1)	
	Congenital defect	1 (0)	
	Other incident	1 (0)	

Loss of tissues or cells

In 2023, TRIP received four reports of serious incidents leading to the loss of oocytes. This involved the loss of a complete reproductive cycle (Table 6).

Table 6 Description of serious reports of loss of tissues or cells in 2023

Type of gamete or embryo	Phase in process	Description of incident
Oocyte	Procurement	After isolating the oocytes, a tube with the wrong name was found among the empty pick-up tubes. The use of the oocytes of the respective ovum pick-up is abandoned.
Oocyte	Processing	When transferring the oocyte after ovum pick-up, the pipette appears to be broken and the oocyte was lost.
Oocyte	Processing	After injecting oocytes, the culture dish was accidentally discarded, assuming that it had already been placed in the incubator by someone else.
Oocyte	Processing	During the processing of the oocytes, the culture dish fell and the oocytes were lost.

Congenital defects

In 2023, two reports were registered as serious congenital defects following the use of donor semen. In the first case, the neonate was diagnosed with a serious defect due to a chromosomal deletion. On examination, the semen donor was found to be mosaic for the same deletion. In the second case, an abnormal result was found from the heel puncture performed on the neonate. The semen donor is identified as a carrier of this autosomal recessive disorder. Figure 3b shows a decrease in the number of reports classified as serious congenital defects since 2021. One contributing factor is that, starting in

2018, imputability became a key factor in assessing the severity grade of congenital defects. Reports with an 'excluded' or 'unlikely' imputability are classified as not serious. The decline may also be influenced by advancements in genetic testing, which have made it easier to determine the extent to which donor sperm contributes to congenital defects.

Bacterial contamination of product

In 2023, two serious reports of 'Bacterial contamination product' were submitted by two different centres. One case involved bacterial contamination of an embryo, while the other involved contamination of semen that subsequently affected the embryo culture. In one case, the source of infection was traced to the partner semen. In the other case, the source was likely either the patient or the partner. These reports were classified as serious due to a complete loss of the reproductive cycle.

Adverse reactions

In 2023, TRIP did not receive any reports of serious adverse reactions following the application of reproductive tissues and cells with definite, probable or possible imputability. Figure 4 shows reports of serious adverse reactions with possible or higher imputability over the period 2019-2023.

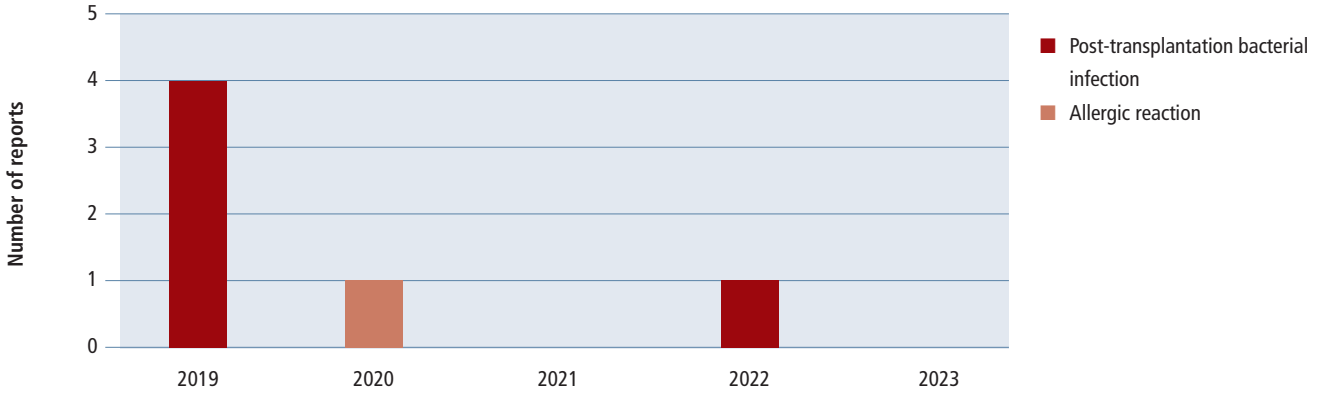

Figure 4 Reports of serious adverse reactions in medically assisted reproduction with definite, probable or possible imputability, 2019-2023

Donation complications

As described in previous annual reports, there is increasing international attention on donor health protection and the reporting of donor complications. The new regulation of the European Parliament and the European Commission (EU SoHO Regulation 2024/1938) has now been published. Under the new regulation, individuals from whom body material is collected for autologous use or use within a couple are no longer classified as (autologous) donors. Protecting their health during the process of material collection is considered part of their protection as recipients of SoHO, including ensuring informed consent for the entire procedure. For autologous use and 'within a couple' application, reporting serious adverse incidents and reactions is only mandatory if these affect the safety and quality of the material, as stipulated in the Safety and Quality of Body Material Act (WVKL). For example, an incident involving shared materials such as a gamete collection jar, where the incident results in material loss. For donations intended for a third party, reporting serious adverse incidents and reactions remains mandatory under the WVKL, and reporting serious adverse donation complications is now required under the new regulation.

Of the 67 centres, only three reported donation complications to TRIP. This suggests that the 14 reported donation complications likely represent underreporting of donation complications in the Netherlands. Consistent with previous years, the most commonly reported donation complication is ovarian hyperstimulation syndrome (OHSS). Thirteen of the 14 reports involved OHSS, with 12 cases requiring hospitalisation. One case involved ovarian torsion. One case concerns pain after a puncture with a suspected torsion. Torsion was not confirmed however, and the patient was discharged after one night of observation.

3.4 Summary of reproductive tissues and cells

All IVF and semen laboratories submitted data regarding the processing, distribution and application of reproductive tissues and cells in 2023. After a decline in the application of donor semen from the Netherlands in recent years, this has increased again over the past two years. The application of donor semen from Europe outside the Netherlands has steadily declined over the last five years (2019:6,138; 2023: 3,752). This year, there were no reports of ovarian tissue application.

In 2023, TRIP received 37 reports (+ four late reports) on the processing and application of gametes and embryos in medically assisted reproduction, compared to 45 reports in 2022. Of these, 22 reports were classified as serious according to EU criteria. This is comparable to 2022 (24). Eight serious incidents and 14 serious donation complications were reported in 2023. There have been no reports of adverse reactions in 2023. Among the four late reports of incidents completed in 2023, one was classified as serious according to EU criteria.

4 HEMATOPOIETIC STEM CELLS AND OTHER CELLS FOR THERAPEUTIC PURPOSES

4.1 Establishments and centres involved

In 2023, 16 tissue establishments in the Netherlands were authorised to collect, process, store and/or distribute hematopoietic stem cells (HSCs) and other cells for therapeutic purposes. These establishments include 12 centres that, besides the required licence as tissue establishment, also have a licence as an organ bank, allowing them to receive human tissues or cells after procurement elsewhere. Three of the 16 tissue establishments are exclusively active in the field of processing cells obtained from bone marrow or peripheral blood for the production of medicinal products. All tissue establishments active in the field of hematopoietic stem cells declared their activities in 2023.

Stem cell transplantation is performed in 12 transplant centres in the Netherlands. In four centres, this only concerns autologous stem cell transplants. Stem cell products from unrelated donors are delivered to eight academic transplant centres through the Matchis foundation, mostly via the stem cell laboratories of the respective hospitals. Peripheral blood stem cells (PBSCs), bone marrow and donor lymphocytes from unrelated Dutch donors are collected at two academic hospitals in the Netherlands. There is one tissue establishment that processes, stores and distributes unrelated cord blood units (CBU).

4.2 Activities in 2023

Table 7 shows the number of processed hematopoietic stem cell transplants obtained from peripheral blood, bone marrow, cord blood and donor lymphocytes for the purpose of DLI (donor lymphocyte infusion). The processing of a transplant occurs around the time of collection (e.g. by apheresis or bone marrow aspiration) and may also involve subsequent processing (e.g. after delivery of the transplant at the applying centre). Consequently, transplants may be counted multiple times in the processing figures. Table 8 shows the distribution and application of stem cell transplants and donor lymphocytes. Compared to the previous year, more bags were distributed and applied, despite involving fewer recipients. This discrepancy is likely due to one centre reporting figures by the number of transplants rather than bags. This was in contrast to 2022, when three centres reported their data in terms of transplants.

For the other cells for therapeutic purposes, the cells are in many cases obtained for processing into medicinal products: the production of Advanced Therapy Medicinal Products (ATMPs). Donation, procurement and testing of human tissues and cells that serve as starting material for these ATMPs fall under the Dutch Body Material (Safety and Quality) Act (WVKL). The manufacturing process falls under Good Manufacturing Practices (GMP) legislation and the product falls under the Medicines Act. Because of the responsibilities under the WVKL, TRIP wants to monitor the activities related to the procurement of the starting material in the coming years (see Table 9). The submission of data on distribution and final application of ATMPs (medicinal product) is optional, as this does not fall under the WVKL. This year, seven centres reported the application, compared to nine centres in 2022 (see Table 10). Reporting serious incidents and complications related to the procurement of human substances, without affecting the safety or quality of the tissues or cells, is not yet regulated by legislation, but TRIP wants to receive these reports, pending additional regulations. Reports of known adverse reactions in the application of medicines are not TRIP's responsibility. TRIP has worked with Lareb on a model for reporting, assessing and handling incidents and adverse reactions in the chain from donation to application of market registered ATMPs.

Table 7 Processing of hematopoietic stem cells and donor lymphocytes in 2023

Type of cells	Reporting tissue establishments	Transplant processing			
		From NL	From EU	Outside EU	Total
PBSC					
autologous	11	1,459	0	2	1,461
related	8	163	0	1	164
unrelated	8	311	229	40	580
Bone marrow					
autologous	2	7	0	0	7
related	7	45	0	0	45
unrelated	5	103	17	3	123
Cord blood					
related	1	1	0	0	1
unrelated	5	32	19	25	76
Donor lymphocytes					
related	8	48	0	1	49
unrelated	8	102	89	18	209

Table 8 Distribution and application of hematopoietic stem cells and donor lymphocytes in 2023

Type of cells	Reporting tissue establishments	Distributed/ delivered bags*	Reporting transplant centres	Transplanted bags*	Recipients
PBSC					
autologous	11	4,325	11	4,332	1,007
related	8	200	8	206	143
unrelated	8	558	8	541	392
Bone marrow					
autologous	1	1	1	1	1
related	7	47	7	47	45
unrelated	5	66	5	63	55
Cord blood					
related	0	0	0	0	0
unrelated	5	39	3	36	30
Donor lymphocytes					
related	8	67	8	65	63
unrelated	7	233	8	233	206

* One tissue establishments reported the number of transplants rather than the number of bags; 1 transplant was counted as 1 bag (compared to three tissue establishments in 2022)

Table 9 Processing of other cells for therapeutic purposes in 2023

Type of cells	Reporting tissue establishments	Transplants processed			
		From NL	From EU	Outside EU	Total
Mesenchymal stem cells allogeneic	0	0	0	0	0
Mononuclear cells from peripheral blood	8	139	0	782	921
Cells from umbilical cord blood	2	5	0	11	16
CAR T/TCR cells, autologous	2	26	0	0	26
Tumour tissue/cells	2	39	0	0	39
Granulocytes	1	7	0	0	7
Virus specific lymphocytes	1	1	0	0	1

Table 10 Processing of other cells for therapeutic purposes in 2023

Type of cells	Reporting centres	Distribution (unit = bag)	Reporting centres	Applied units	Number of recipients
Mesenchymal stem cells allogeneic	2	5	2	5	4
Dendritic cells, autologous	3	11	2	9	7
Mononuclear cells	4	85	2	22	14
Tumour infiltrating lymphocytes, autologous	2	9	3	45	45
CAR T/TCR cells, autologous	7	126	8	133	138
Expanded Natural Killer Cells from cord blood	2	25	2	25	4
Granulocytes	1	7	1	7	3
Virus specific lymphocytes	2	25	2	7	2

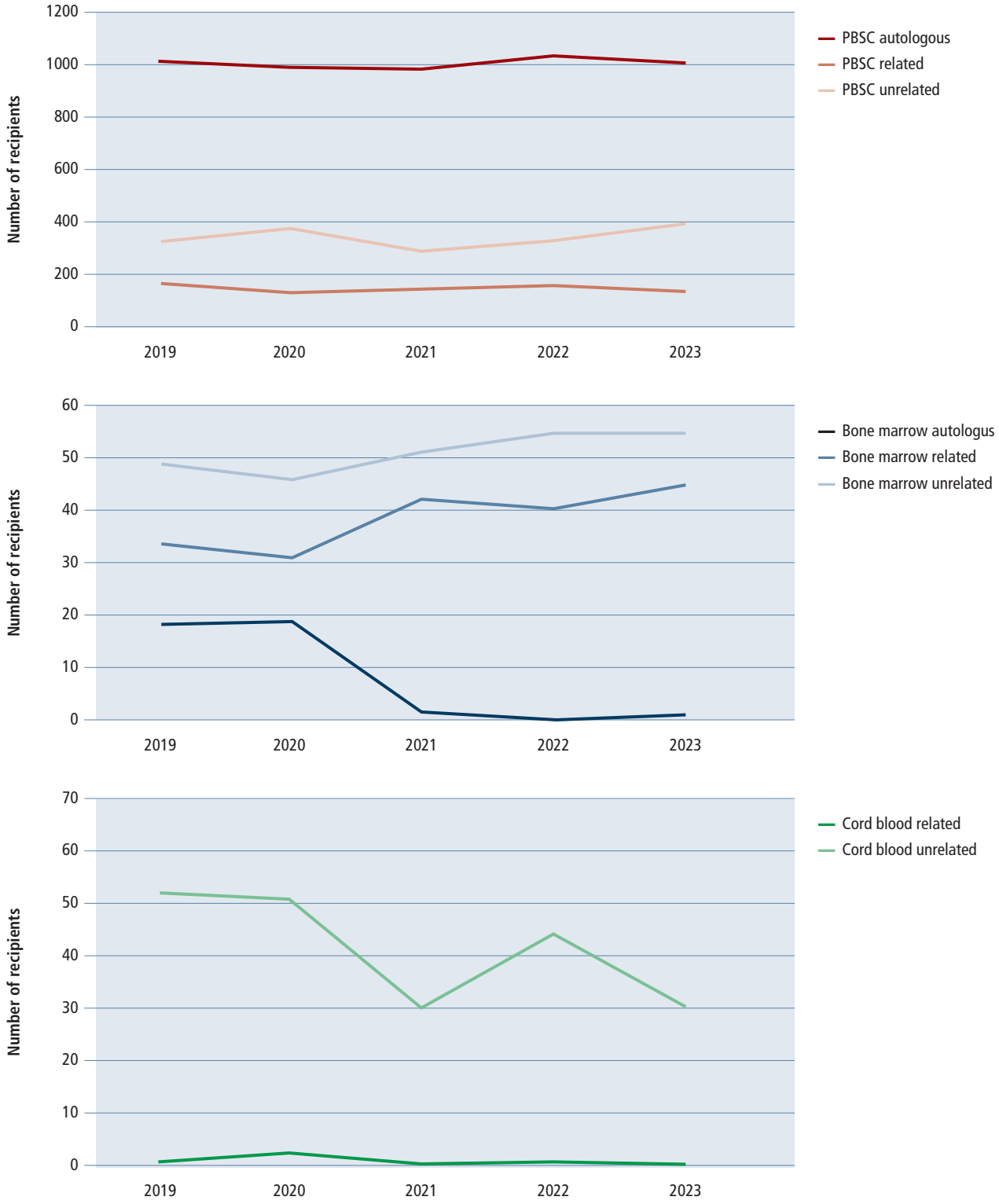

Figure 5a-b-c. Number of hematopoietic stem cell transplant recipients per transplant type, 2019-2023. In 2021, one centre did not report the number of recipients of PBSC and Bone marrow allogeneic related.

4.3 Reports

In 2023, a total of 42 reports relating to hematopoietic stem cells or other cells for therapeutic purposes were received from four reporting centres. Also, one late report from 2022. All reports have an unlikely, possible, probable or definite imputability. The reports mainly concern low-grade adverse reactions and incidents that are not serious according to EU criteria. Not all tissue establishments report these non-serious adverse reactions and incidents to TRIP. In 2023, six reports (four adverse reactions and two incidents) were assessed as serious in accordance with EU criteria and therefore mandatory to report to the competent authority, the IGJ (Figure 10). These reports can be made transparent to the IGJ via the TRIP reporting system. The late report from 2022 has also been assessed as serious in accordance with EU criteria.

See Table 11 for specifications of the reports. Figure 6 shows a multi-year overview of reports of HSCs and other cells for therapeutic purposes. The incidents defined as serious according to EU criteria (see TRIP website for criteria) and the adverse reactions with a severity grade of 2 or higher and definite, probable or possible imputability are described in Tables 12 and 13.

Table 11 Reports per tissue type, reporting category and severity (according to EU criteria), 2023 and one late report from 2022

Type of tissue or cells	Incident category	No. of reports (serious)*
Peripheral blood stem cells	Bacterial contamination of product	5 (0)
	Near miss#	1 (1)
	Loss of tissues or cells	2 (0)
	Other incident	1 (1)
Bone marrow	Bacterial contamination of product	6 (0)
Donor lymphocytes	Bacterial contamination of product	2 (0)
	Other incident	1 (0)
Tumour infiltrating lymphocytes	Bacterial contamination product	1 (1)
Type of tissue or cells	**Category of adverse reaction**	**No. of reports (serious)***
Peripheral blood stem cells	Post-transplant febrile reaction	1 (0)
	Post-transplant bacterial infection	1 (0)
	Hemolytic reaction	1 (0)
	Other reaction	9 (0)
Bone marrow	Post-transplant febrile reaction	1 (0)
	Hemolytic reaction	1 (0)
	Other reaction	4 (1)
Cord blood	Circulatory overload	1 (0)
	Other reaction	5 (3)

* Serious incidents according to EU criteria, serious adverse reactions ≥ grade 2 with definite, probable or possible imputability.

\# Late report

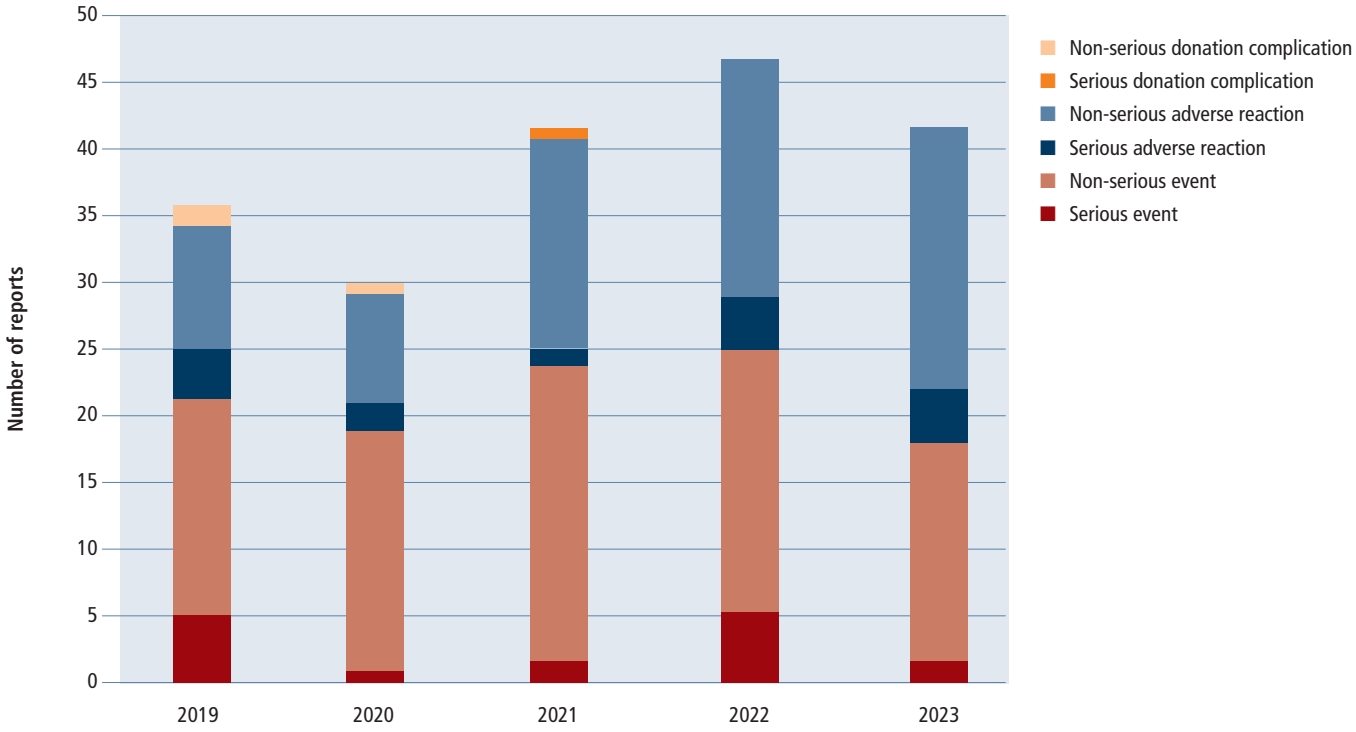

Figure 6 Total reports of hematopoietic stem cells and other cells for therapeutic purposes, 2019-2023

Loss of tissues or cells: one case of non-serious incident

During the stem cell apheresis of an allogeneic unrelated donor, a clot is found in the bag on the first day (at machine alarm). The clot could occur because the citrate bag connector was not broken properly, causing too little citrate to flow into the product. The clot was isolated, the apheresis product was filtered and extra citrate was added. Combined with a second apheresis, sufficient stem cells were obtained for application.

Breaking the connector is done manually; an incorrectly broken connector does not always sets off an alarm during donation. Due to the alertness of staff, the product was not lost and sufficient stem cells could be obtained with a second apheresis day. The above case shows that despite automation and digitisation, employees still need to be alert. In this case, the complete loss of apheresis was avoided and enough stem cells were obtained (together with the second apheresis day). If the second apheresis day had not been scheduled in advance and the donor had undergone an 'extra' admission day, this report would be a serious incident in accordance with EU criteria.

Table 12 Incidents (serious according to EU definition) relating to hematopoietic stem cells and other cells for therapeutic purposes in 2023 and one late report from 2022

Type of HSC	Incident (description)	Reporting category
PBSC, autologous	Assessment error during procurement Initially, after one apheresis procedure, it was assessed that the number of stem cells was sufficient. After cryo preservation, the number turned out to be too low. Therefore, the patient underwent a second stem cell mobilisation and apheresis, followed by a successful transplantation.	Other incident
Tumour infiltrating lymphocytes, autologous	Processing error after procurement Tumour tissue for TIL production was sent to the wrong department so that the tissue procured could no longer be used for the production of the ATMP. The intended treatment plan (for study purposes) was cancelled.	Loss of tissue, or cells + other cause
PBSC, allogeneic unrelated	Assessment error during testing The second HLA typing of a patient, which was done shortly before transplantation, did not correspond to the first HLA marker. As a result, a new unrelated stem cell donor had to be sought at a late stage.	Near miss

Table 13 Adverse reactions (severity grade ≥2, definite, probable or possible imputability) relating to hematopoietic stem cells in 2023

Type of HSC	Adverse reactions (description)	Interval v. transplant	Imputability	Severity
Bone marrow, allogeneic unrelated	Other reaction – Hypertension Complementary medical treatment with full recovery	During procedure	Probable	2
Cord blood, allogeneic, unrelated	Other reaction – Hypertension Complementary medical treatment with full recovery	During procedure	Probable	2
Cord blood, allogeneic, unrelated	Other reaction – Hypertension Complementary medical treatment with full recovery	During procedure	Probable	2
Cord blood, allogeneic, unrelated	Other reaction – Hypertension Complementary medical treatment and ICU admission for observation with full recovery	During procedure	Probable	2

4.4 Summary of hematopoietic stem cells and cells for therapeutic purposes

In 2023, TRIP received reports from all tissue establishments that are active in the field of hematopoietic stem cells. This year, one tissue establishment reported the number of transplants instead of the number of bags. There have been no reports of procedures involving mesenchymal stromal cells this year (two tissue establishments last year) and their distribution and application have also decreased.

In 2023, two serious incidents were registered compared to an average of four per year in the last five years (2018-2022: range 1-5). One serious incident from 2022 was reported late, bringing the number of serious events in 2022 to five. Four serious adverse reactions were registered compared to an average of 2,6 per year in the last five years (2018-2022: range 1-4). There have been no reports of donation complications in 2023.

The four serious adverse reactions involved one hypertensive reaction during bone marrow transplantation and three hypertensive reactions during cord blood transplantation. In all cases, complementary medical treatment was needed to normalise the blood pressure, with one patient briefly admitted to the ICU for observation. All recipients recovered completely from the adverse reaction.

5 OTHER TISSUES AND CELLS

Establishments and centres involved

In total, 71 hospitals and independent treatment centres are registered with TRIP, in addition 65 implantology practices applying other human tissues and cells in the Netherlands known to TRIP. In 2023, 65 hospitals reported application figures and two hospitals reported application figures only partially. Of the implantology practices known to TRIP (65), 53 reported application figures, among them were four that reported not to have applied human substances in 2023. It is not mandatory for establishments to report application figures. This is because the use of other tissues and cells is currently not a recognised activity under the WWKL. The 2006 Directive on Human Substances states that an applying centre "passes on all relevant information to the organ centre or tissue establishment from which the material originates, in order to facilitate traceability and to guarantee quality assurance and safety". The centres that provide information about possible reports and application figures will receive a participation statement from TRIP, which the IGJ may request during an inspection.

In the Netherlands, 24 tissue establishments are authorised to collect, process, store and/or distribute other tissues and cells, 23 of them have reported their annual figures. There are 14 establishments that, besides the required licence as tissue establishment, also have a licence as an organ bank, with which they are also authorised to receive tissue or cells direct after procurement. All have declared their activities in 2023 (Figure 7).

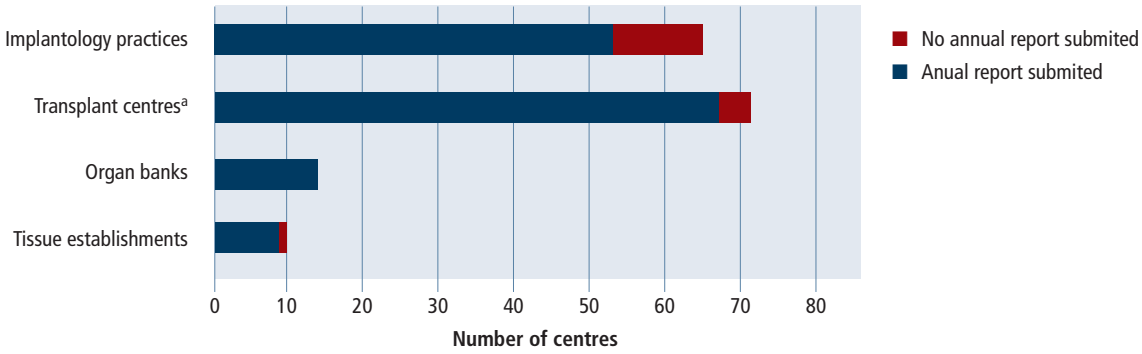

Figure 7 Participation relating to other tissues and cells in 2023

[a] Two applying centres submitted a partial report

5.1 Bone and other musculoskeletal tissues and cells

5.1.1 Establishments and centres involved

Bone and other musculoskeletal tissues include femoral heads from living and post-mortem donors, mineralised and demineralised bone filler, whole bones, cranial bones (autologous), tendons, bone-tendon-bone grafts, fascia, cartilage, (autologous) chondrocytes and menisci.

In total, 122 healthcare centres known to TRIP submitted reports of the application of musculoskeletal tissues, among them were two centres submitting figures partially and two hospitals and 12 implantology practices that did not provide information.

5.1.2 Activities 2023

Table 14 shows the processing of bone and other musculoskeletal tissues in 2023. Table 15 shows the distribution and application of the different tissues after processing.

The processing of bone into (demineralised) filler material by tissue establishments in the Netherlands has significantly decreased compared to last year. This decline could be due to high stock levels or an increase in the distribution of bone tissue processed or imported from within the EU.

While for cartilage processing a notable increase in 2022 was observed, it has now dropped by over 50%. The number of recipients has increased this year (from 17 to 24). This increase could be attributed to treatments using tissue that was in stock or with tissue from another supplier, outside the Netherlands.

In 2023, much less fascia were applied (nine), compared to 49 in 2022. Subsequent information from the supplying tissue establishment showed that at least 40 fascia were applied in one large centre. For femoral heads, bone filler, mineralised and demineralised, and tendons, the number of recipients was not reported in two cases. There is a significant discrepancy between the number of distributed bone products and the number of reported recipients, possibly because multiple transplants/units are used per recipient. Another reason is that some centres may struggle or are completely unable to track their inventory and the use of these products, leading to incomplete figures. Furthermore, not all users may be known to TRIP.

The storage and processing of autologous cranial bone have declined (from 157 in 2022) and are now conducted by three tissue establishments.

Autologous chondrocytes are cultivated and processed into Advanced Therapy Medicinal Products (ATMPs). Only the cartilage biopsy and the initial processing fall under the WVKL. Finally, not all establishments reported their application figures to TRIP, due to its non-mandatory nature.

Table 14 Processing of bone and other musculoskeletal tissues and cells in 2023

Type of tissues/cells	Reporting tissue establishments	Processing of tissue from donors from: NL	EU	Outside EU	Total
Femoral heads, living donor	7	3,266	270	0	3,536
Femoral heads, post-mortem donor	1	29	0	0	29
Bone filler, mineralised	1	2,307	0	0	2,307
Bone filler, demineralised	1	0	16	0	16
Bone, whole	2	183	6	0	189
Cranial bone (autologous)	3	107	1	1	109
Tendons	1	509	0	0	509
Bone-tendon-bone grafts	1	27	0	0	27
Fascia	2	115	0	0	115
Cartilage	1	12	0	0	12
Cartilage for chrondrocytes, autologous, for ATMP	1	94	0	0	94
Menisci	1	37	0	0	37

Table 15 Distribution and application of bone and other musculoskeletal tissues and cells in 2023

Type of tissue/cells	Reporting tissue establishments	Reporting healthcare centres	Distributed units				Applied units (from NL)	Recipients
			In NL	In EU	Export Outside EU	Total		
Femoral heads, living donor	7	48	1,686	615	7	2,308	1,201 (1,200)	1,129
Femoral heads, post-mortem	1		35	0	0	35		
Bone filler, mineralised	7	70	9,723	4,583	2,617	16,923	2,993 (2,667)	2,700
Bone filler, demineralised	7	21	667	10,417	11,232	22,316	643 (476)	616
Bone, whole	2	15	156	0	2	156	61 (61)	61
Cranial bone, autologous	3	10	59	1	0	53	42 (42)	42
Tendons	1	33	649	22	0	671	348 (348)	351
Bone-tendon-bone grafts	1	6	15	2	0	17	12 (12)	12
Fascia	2	4	101	0	0	101	14 (14)	9
Cartilage	1	6	12	0	0	12	24 (24)	24
Chondrocytes (ATMP)	1	1	89	0	0	89	37 (37)	37
Menisci	1	3	19	1	0	20	19 (19)	19

5.2 Cardiovascular tissues

5.2.1 Establishments and centres involved

Cardiovascular tissue includes aortic and pulmonary valves, vessels, patches and the pericardium. There is one tissue establishment in the Netherlands that is involved in the processing, storage and/or distribution of cardiovascular tissue. It submitted its annual report to TRIP.

Of the ten centres applying cardiovascular tissue known to TRIP, all reported the number of applications in 2023. In one case, one centre uses pericard from another supplier, which was not yet known to TRIP.

5.2.2 Activities 2023

There are no significant changes in the figures related to cardiovascular tissue compared to 2022 (Tables 16 and 17). In 2023, there were 242 post-mortem heart valve donors, which is slightly more than 2022 (215). However, the number of aortic or pulmonary valves deemed suitable for clinical applications after processing is much lower than the total number of donors who donated a heart for heart valve donation. This discrepancy is due to strict quality requirements (such as tissue structure and microbiological status). The distribution figures are therefore much lower for the pulmonary valves. In 2023, 84 pulmonary valves were distributed and 78 were applied from the Netherlands. However, the distribution of pulmonary valves exceeded their application in 2023 (Table 17). Given the stringent storage conditions, the question is whether some valves that remain "in stock" at applying centres – because, for example, a surgery schedule changes and the tissue cannot be used – should be classified as tissue loss. One centre did not specify the number of recipients when reporting the use of both patches and pericardium.

Table 16 Processing of cardiovascular tissues and cells in 2023

Type of tissue	Reporting tissue establishments	Processing of tissue from donors from			
		NL	EU	Outside EU	Total
Aortic valves	1	242	0	0	242
Pulmonary valves	1	242	0	0	242
Vessels	1	12	0	0	12
Patches	1	103	0	0	103

Table 17 Distribution and application of cardiovascular tissues in 2023

Type of tissue	Reporting tissue establishments	Reporting Healthcare centres	Distributed units In NL	In EU	Export	Total	Applied units (from NL)	Recipients
Aortic valves	1	3	6	4	0	10	6 (4)	6
Pulmonary valves	1	4	84	26	0	110	79 (76)	78
Vessels	1	1	1	0	0	1	1	1
Patches	1	4	32	9	0	41	36 (36)	35
Pericardium*	1	6					90 (40)	89

* Pericardium is ordered from distributors in or outside the Netherlands by the applying centres

5.3 Skin

5.3.1 Establishments and centres involved

Skin includes donor skin, acellular dermis, autologous skin and cultured skin.
Four tissue establishments in the Netherlands are involved in the processing, storage and/or distribution of skin tissue. All four submitted their annual reports to TRIP.
Of the ten centres applying skin known to TRIP, nine are hospitals and one is an implantology practice. Furthermore, four hospitals are known to use acellular dermis three have applied it in patients in 2023.
There are no hospitals anymore that report the use of autologous skin or cultured skin.

5.3.2 Activities 2023

The number of post-mortem skin donors from the Netherlands increased (in 2022 this was 389 donors). Fewer skin grafts were processed from EU donors (157 in 2022). The number of skin packages distributed in the Netherlands decreased compared to 2022 (2,364 packages). As in previous years, there is a discrepancy between the number of units distributed and the number applied, this is partly due to differences in reporting practices between tissue establishments and applying centres. Tissue establishments calculate annual figures based on an average number of cm^2 per container, while in practice, fewer containers with a higher cm^2 content are distributed, leading to consistent reporting discrepancies. Distribution in Europe has slightly decreased, while exports have shown a small increase compared to last year (Tables 18 and 19). There has been an increase in the distribution of acellular dermis packages, while the reported number of applications remains significantly lower. This is likely due to implantologists not reporting the application of pieces of acellular dermis to TRIP.

Table 18 Processing/import of skin in 2023

Type of tissue	Reporting tissue establishments	Processing of skin from donors from[a] NL	EU	Outside EU	Total
Donor skin	1	420	140	0	560
Acellular dermis	4	54	1	100[b]	155

[a] The processing of donor skin and acellular dermis is reported as the number of postmortem skin donors
[b] Import only, packaging with SEC

Table 19 Distribution and application of skin in 2023

Type of tissue	Reporting tissue establishments	Reporting healthcare centres	Distributed units In NL	In EU	Export	Total	Units applied (from NL)	Recipients
Donor skin	1	8	1,711	10,545	1,615	13,871	1,439 (1,405)	120
Acellular dermis	4	4	143	0	388	531	6[a] (6)	6

[a] The application of a large number of distributed acellular dermis grafts has not been reported

5.4 Ocular tissues

5.4.1 Establishments and centres involved

Ocular tissue includes corneal, scleral and limbal stem cells. The limbal stem cells are starting material for further processing into ATMP. Currently, it is not mandatory for tissue establishments to report their annual figures relating to starting material for ATMPs to TRIP, as there is no conclusive legislation yet. There are four Dutch establishments involved in the processing, storage and/or distribution of ocular tissue, all of which submitted their annual reports to TRIP. Of the 22 healthcare centres applying ocular tissue known to TRIP, one centre indicated that it would not be able to provide figures this year.

5.4.2 Activities in 2023

There is a discrepancy between the number of corneas and sclerae distributed and their applications. According to the annual figures of the Netherlands Transplant Foundation (NTS), 1,947 corneas were allocated in 2023. TRIP received reports from 13 centres detailing 1,798 cornea applications. This discrepancy between distribution and application is likely due to one applying centre not yet submitting their report and incomplete application figures from other centres. There is also a significant difference between distribution and application of sclera. Some application centres lack insight into their ordering and application data. It appears that the advice to verify these figures with the tissue establishment has been minimally followed.

Table 20 Processing of ocular tissues and cells in 2023

Type of tissues/cells	Reporting tissue establishments	Processing of tissue from donors from NL	EU	Outside EU	Total
Cornea	2	4,642	0	0	4,642
Sclera	1	566	0	0	566
Limbal stem cells	2	18	0	0	18

Table 21 Distribution and application of ocular tissues and cells in 2023

Type of tissues/cells	Reporting tissue establishments	Reporting health care centres	Distributed transplants In NL	In EU	Export	Total	Applied units (from NL)	Recipients
Cornea	2	13	1,944	588	117[a]	2,649	1,798 (1,789)	1,792
Sclera	1	13	2,077	82	0	2,159	1,203 (1,203)	1,124
Limbal stem cells	2	2	18	0	0	0	18	18

[a] The number of cornea exported is much higher compared to 2022 (47)

5.5 Miscellaneous tissues and cells

5.5.1 Establishments and centres involved

Miscellaneous tissues and cells include amniotic membranes, pancreatic islets and nerve tissue. In the Netherlands, three organ banks and one tissue establishment are involved in the processing, storage and/or distribution of these tissues and cells. Of the 10 centres known to TRIP that apply other cells and tissues, 8 reported their activities, while 2 centres indicated they were unable to supply figures for 2023.

5.5.2 Activities in 2023

Table 22 shows the number of processing operations involving miscellaneous tissues and cells. Some serve as starting material for further processing into ATMPs. Table 23 shows the distribution data, indicating that a portion of these tissues and cells was distributed to a centre outside the Netherlands. With the exception of nerve tissue, no miscellaneous tissues and cells were used that were not derived from Dutch donors.

For the first time, a centre reported the application of donated allogeneic breast milk. Although allogeneic breast milk is not yet classified as body material, it will fall under this category under the new SoHO regulation.

Table 22 Processing of miscellaneous tissues and cells in 2023

Type of tissue	Reporting tissue establishments	Processing of tissue from donors from NL	EU	Outside EU	Total
Amniotic membranes[a]	2	2	11	0	13
Pancreatic islets[b]	1	28	0	0	28
Salivary glands for ATMP	1	5	0	0	5

[a] Procured from placenta
[b] Procured from pancreas

Table 23 Distribution and application of miscellaneous tissues and cells in 2023

Type of tissues/cells	Reporting tissue establishments	Reporting healthcare centres	Distributed transplants In NL	In EU	Export	Total	Applied units (from NL)	Recipients
Amniotic membranes	2	7	266	32	0	298	112 (112)	110
Pancreatic islets	1	1	14	0	0	14	14 (14)	14
Salivary glands (ATMP)	1	1	5	0	0	5	5	5
Nervous tissue	1	1	0	26	0	26	6 (0)	5
Breast milk[a]		1					300	41

[a] Does not fall under the legislation on substances of human origin

5.6 Reports on other tissues and cells

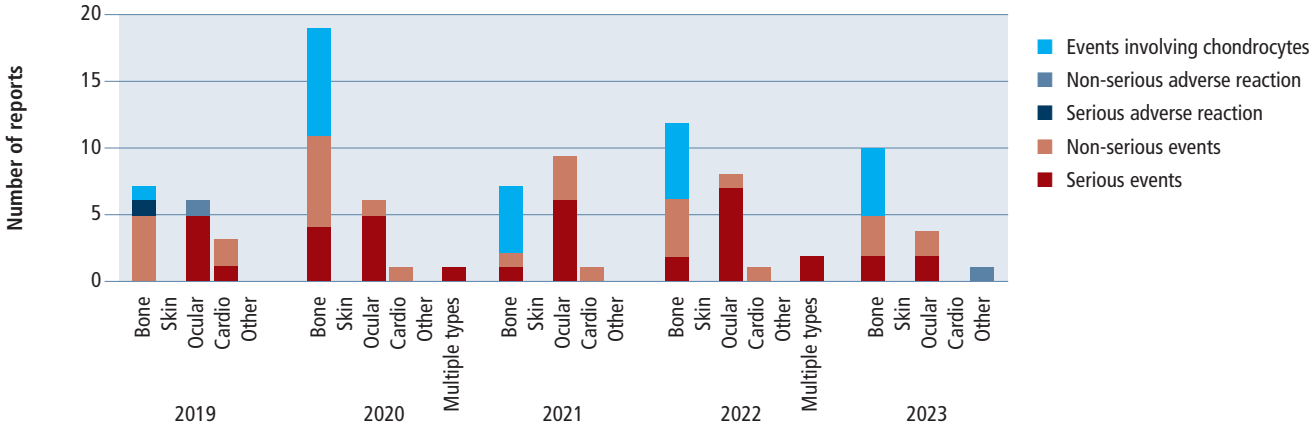

Figure 8 Reports relating to miscellaneous tissues and cells, 2019-2023

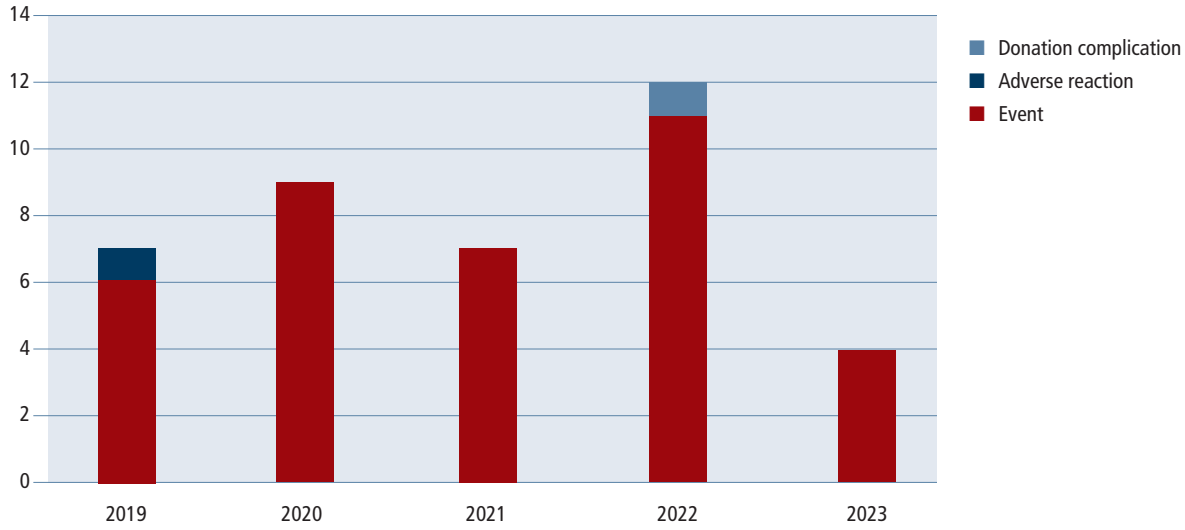

Figure 9 Number of reports (serious according to EU criteria) per year, 2019-2023

In 2023, TRIP received 15 reports concerning miscellaneous tissues and cells and two late reports from 2022. Five reports concern bone and five reports related to miscellaneous musculoskeletal tissues (cartilage). Four reports concern cornea (Figure 8) and one report pancreatic islets. In addition to the four cornea-related reports in 2023, one late report from 2022 detailed the loss of a cornea. In this case, the patient's vision was deemed sufficient, rendering the donor cornea unnecessary. The container with the cornea was kept too cold, which led to its eventually loss. The other late report concerned the loss of a pulmonary valve due to an unexpected situation; during the surgery, the valve could not be used on the patient.

The five cartilage-related reports involved the cultivation of chondrocytes for the production of an ATMP. In these incidents, the cartilage biopsy was lost due to insufficient growth of the correct cells during cultivation, making ATMP preparation (chondrocytes) impossible. As a result, the patient required another biopsy or had to pursue an alternative treatment. As mentioned earlier, there is currently no definitive regulation for reporting incidents during ATMP production involving human tissues and cells. The reports regarding ATMPs are included in Figure 8.

All reports were classified as incidents, with one incident having a direct impact on a patient. In this case, the surgery had to be postponed due to potential contamination during tissue processing. Of the 17 reports, four reports were assessed as serious according to EU criteria (Figure 9). They are summarised in Table 24.

Table 24 Serious incidents (according to EU definition, see Annex C) related to miscellaneous tissues and cells in 2023

Type of tissue	Incident (category and description)
Bone chips	Other incident. Due to a packaging error, a large number of products could no longer be guaranteed to be sterile at the time of application. A significant number of products had to be recalled, a lot of tissue was lost.
Bone, hip heads	Loss of tissues and cells. The containers for storing the hip heads were found to be contaminated. All hip heads stored in contaminated containers were removed from storage and destroyed.
Cornea	Near miss During surgery, the DMEK was found to be incorrectly marked and was reoriented and transplanted peri-operatively.
Cornea	Risk of transfer of condition After the results of the final donor autopsy report, a contraindication (neurodegenerative disorder) for tissue donation could not be ruled out, but the corneas were already transplanted.

In response to the report about the incorrect marking of a DMEK, the Advisory Committee recommended sending a photo of the cornea, in order to avoid confusion about orientation.

5.7 Summary of other tissues and cells

As last year, an assessment of the annual data reveals gaps in the application figures, particularly for musculoskeletal tissues and cornea/sclera, but also for acellular dermis. No information was received from several hospitals, while data from two hospitals was incomplete and a part was deemed incomplete upon closer examination. Like last year, an extra 'box' was added to the annual reporting form, allowing healthcare centres to indicate that they had not used humane substances. Four implantology practices ticked this box. Furthermore, a significant proportion (24%) of the implantologists known to TRIP did not respond to TRIP's request for annual figures.

In some reports, the number of recipients was not specified. A number of other health care centres of miscellaneous tissues and cells reported difficulties in obtaining application data, such as the number of treated patients. To support better data collection, a workshop was held during the biovigilance symposium 2024. It provided explanations and practical tips, such as requesting information from the supplying tissue establishments.

The European Regulation on SoHO now requires entities to register as a SoHO entity and submit annual figures. The health caresg centres still have until mid 2027 to optimise their reporting processes. TRIP will continue to provide support (through lectures, workshops, information on the TRIP website).

The number of reports concerning miscellaneous tissues and cells was lower compared to previous years. There were fewer serious reports in 2023, namely four (12 in 2022). There were no reports of errors during donor tissue retrieval leading to tissue loss, compared to five such reports in 2022.

Five of the reports regarding miscellaneous tissues and cells related to the cultivation of chondrocytes for ATMPs. Incidents during procurement or processing can have consequences for the donor, in this case autologous, as a new biopsy may be required. Recently, TRIP and Lareb have developed a model for the reporting, assessing and handling of incidents and adverse reactions in the chain from donation to application of market-registered ATMPs.

ANNEXES

A ABOUT TRIP

The TRIP (Transfusion and Transplantation Reactions in Patients) Foundation was established in 2001, with the aim to develop a national hemovigilance system. In 2006, at the request of the Ministry of Health, Welfare and Sport (VWS), a pilot project for biovigilance data registration was set up. Since 2012, biovigilance has been a formal task for the TRIP Foundation.

Biovigilance refers to the systematic monitoring of incidents and adverse reactions throughout the human substance transplantation chain, with the ultimate goal of achieving safer and more effective use of tissues and cells. European Directive 2004/23/EC obliges Member States to report serious adverse incidents and adverse reactions that may be related to the quality and/or safety of these human substances. This Directive was transposed into the Dutch Body Material (Safety and Quality) Act (WVKL) and the Body Material Requirements Decree 2006. The latter was amended in 2012, based on European Directive 2010/53/EC.

The TRIP reporting system for adverse incidents and adverse reactions related to the transplantation of human substances meets the requirements laid down in European and Dutch legislation. Figure 10 shows a flowchart of serious and non-serious biovigilance reports in Dutch healthcare. It is likely that the number of 'non-serious' incidents and adverse reactions is much higher than the number of serious cases, and that not all establishments submit the less serious reports to TRIP. This is consistent with the high percentage of serious incidents and reactions in reports to TRIP.

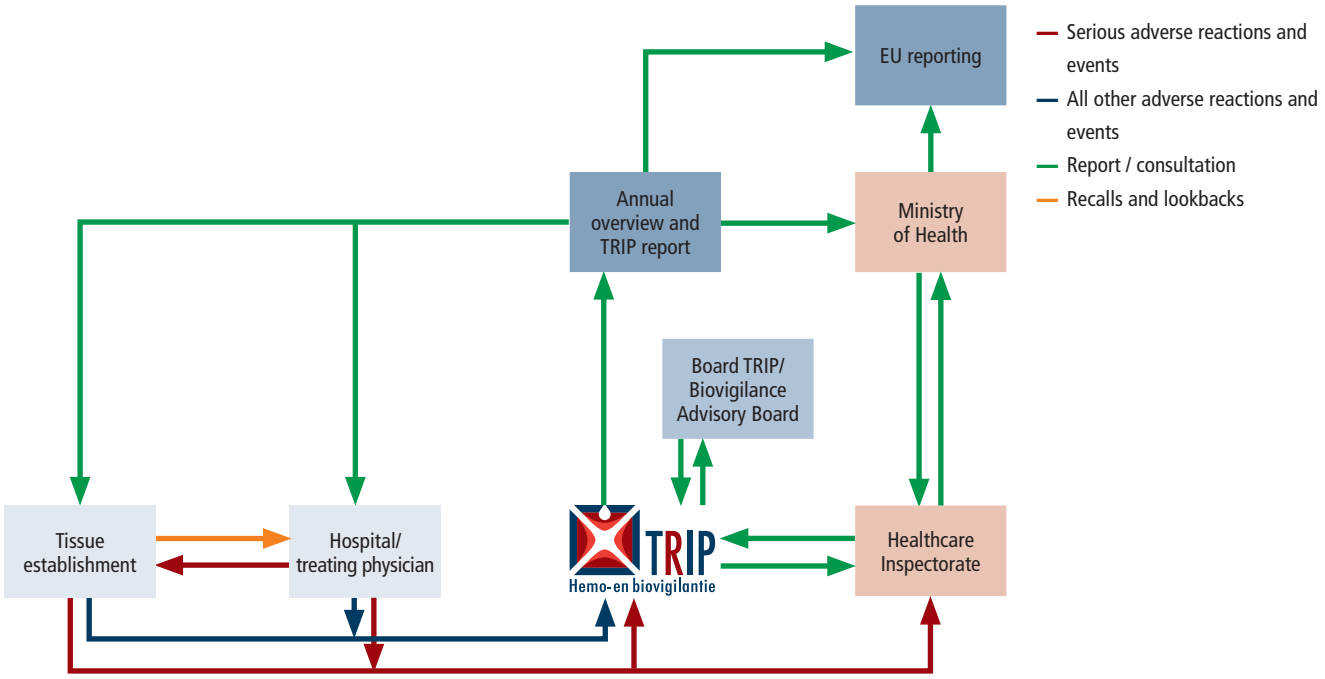

Figure 10 Flowchart of reports concerning human tissues and cells

All types of human substances, from both living and post-mortem donors, fall within the scope of the WVKL, with the exception of human substances removed and returned to the same person in the same surgical procedure. If autologous material is stored or processed in an area other than where the patient stays, the provisions of the WVKL do apply. Allogeneic applications of tissues fall under the scope of the WVKL in all cases.

Method

TRIP is an independent foundation that cooperates closely with the users of human substances and tissue establishments. All submitted reports are registered, analysed and reviewed by experts. The results and conclusions are published annually. TRIP also annually collects data on the numbers of processed, distributed and applied human substances by all Dutch tissue establishments, hospitals and other healthcare providers, in accordance with European regulations. The information is aggregated as a denominator for the data collected by TRIP on incidents and adverse reactions, as well as for the annual mandatory submission to the European Commission. TRIP compiles the required annual overview of serious adverse incidents and reactions for submission to the European Commission through the Ministry of Health, Welfare and Sport.

Tissue establishments, hospitals and other healthcare centres that provide figures on processing, distribution and/or application and information on incidents and/or adverse reactions to TRIP receive an annual participation certificate. This participation certificate promotes safety awareness in the application of substances of human origin and supports hospitals' safety management systems. The participation certificate may also be requested during inspections related to obtaining, renewing, or modifying a licence for tissue establishments or organ banks.

TRIP is supported by a Biovigilance Advisory Committee comprising representatives from relevant medical professional bodies and specialties. The Biovigilance Advisory Committee provides medical professional and strategic advice with regard to biovigilance to TRIP's board and staff members. The Biovigilance Advisory Committee also anonymously reviews all reports and advises with regard to the annual reports.

B REPORTING OF INCIDENTS AND ADVERSE REACTIONS

Tissue establishments

The reporting of serious adverse incidents and reactions relating to human substances is laid down in Article 8.1 of the Dutch Body Material Decree 2006 (see Annex 3). This article states that the tissue establishment is responsible for the reporting, investigation, registration and forwarding of information on serious adverse incidents and reactions that could influence the quality and safety of human substances or that are detected after clinical application and could be linked to the applied human substance. Adverse incidents and reactions should be reported to TRIP and also to the Health and Youth Care Inspectorate (IJG) if classified as serious. In case a report is assessed as serious by TRIP and has not been reported to the IGJ, the reporting party will be made aware of the obligations regarding reporting to the IGJ.

Hospitals, clinics and practices

Healthcare centres must report (possible) product-related serious adverse reactions or incidents to the supplying tissue establishment. They may also report these to TRIP. TRIP checks for duplicate reports and if any are found, merges them in consultation with the reporting healthcare centre and/or tissue establishment.

In the event of a 'calamity' (possible) caused by human substances, the hospital must also inform the IGJ in accordance with the Healthcare Quality, Complaints and Disputes Act (WKKGZ).

Reporting to the Health and Youth Care Inspectorate

In the Netherlands, the Health and Youth Care Inspectorate (IGJ) has been designated as the competent authority for receiving reports of serious incidents and adverse reactions. In agreement with the Ministry of Health, Welfare and Sport (VWS) and the Health and Youth Care Inspectorate (IGJ), TRIP takes care of the registration of all incidents and adverse reactions related to human substances. The TRIP digital reporting system facilitates the forwarding of serious incidents and adverse reactions reports to the IGJ. Reporting parties can choose to select the option of forwarding the report to the IGJ so they only need to submit information once.

The reporting of serious incidents and adverse reactions is different from the reporting of a calamity under the Healthcare Quality, Complaints and Disputes Act. Calamities have a different definition and the IGJ has its own specific procedure for dealing with calamities. Figure 11 shows a schematic presentation of the reporting route.

Serious incidents or adverse reactions within the scope of the Body Material (Safety and Quality) Act are best submitted to the Health and Youth Care Inspectorate through the TRIP reporting system. This channels the reports to the inspectors involved in enforcement of the Body Material (Safety and Quality) Act and reduces the likelihood of reports being (possibly incorrectly) treated as being within the scope of the Healthcare Quality, Complaints and Disputes Act. However, reports will always be assessed on healthcare quality aspects as well, and can, if required, be handled as a calamity.

Reports regarding ATMPs

In the production of ATMPs from human substances, human cells or tissues are used as starting material. The quality of this material may lead to adverse reactions in recipients of this type of medicine. Incidents can have consequences for both patient and donor, for example loss of tissues and cells.

Current vigilance systems provide part of the chain of tissue donation, ATMP production and administration, but certain adverse incidents are not yet addressed in existing regulations. To promote the safety and quality assurance of ATMPs, it is necessary to design a clear vigilance system that covers the entire ATMP chain from donation to follow-up after administration.

Based on international and national legislation, TRIP is collaborating with Lareb, the designated agency where serious and non-serious adverse reactions of medicines are reported under the Medicines Act, on the design of a comprehensive vigilance framework for ATMPs based on human substances. This creates a link between biovigilance and pharmacovigilance. Formalised cooperation between both vigilance systems is necessary to successfully implement the proposal and to increase knowledge of incidents and adverse reactions in the ATMP chain.

Definitions of categories of incidents and adverse reactions and reporting criteria

All definitions of the categories used for incidents and adverse reactions and reporting criteria for serious incidents or reactions can be found on the TRIP website.

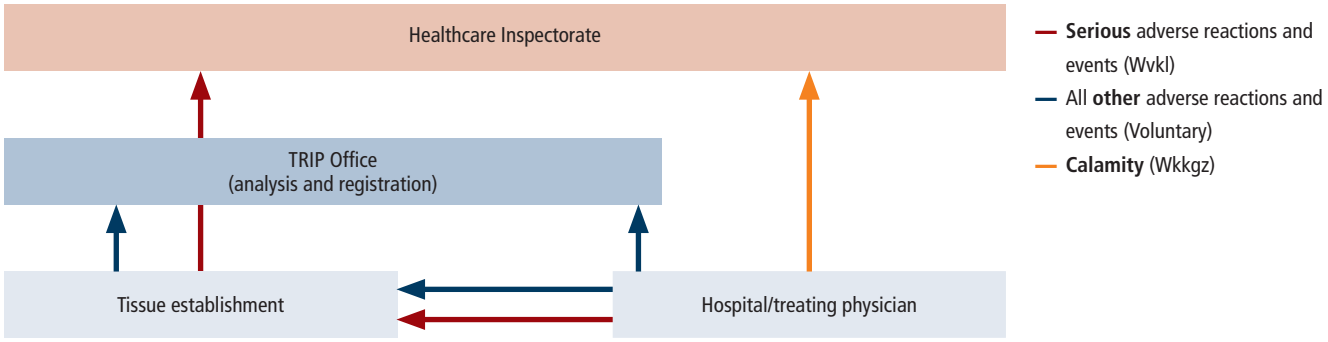

Figure 11 Flowchart of reports regarding human substances

C SUMMARY OF INCIDENTS AND ADVERSE REACTIONS REPORTED TO THE EU

Table 25 shows the number of serious incidents and adverse reactions related to human tissues or cells reported or concluded in 2023. In total, 32 reports (+ two completed in 2023) were assessed as serious. These are serious adverse reactions, serious incidents and serious donation complications.

Table 25 Overview of serious incidents and adverse reactions reported to the EU in 2023

Type	Serious adverse reaction	Serious incident*	Serious donation complication	Total serious reports
Semen	0	4	0	4
Oocytes	0	4	14	18
Embryos	0	1	0	1
HSC and therapeutic cells	4	3	0	7
Ocular tissue	0	2	0	2
Musculoskeletal tissue	0	2	0	2
Total	**4**	**16**	**14**	**34**

* TRIP classifies incidents followed by a serious adverse reaction or with a serious consequence as serious incidents. These reports are submitted to the European Commission (EC) as serious adverse reactions. These include proven and possible inheritance of a congenital abnormality when using donor gametes or embryos, post-transplantation contamination of a recipient with a micro-organism that requires treatment or prolonged hospitalisation, re-transplantation after transplantation with an incorrect product or additional mobilisation, apheresis or bone marrow aspiration for autologous stem cell transplantation(s) and an aborted procedure where the patient is already under anesthesia or has been conditioned for transplantation.

D LIST OF TERMS AND ABBREVIATIONS

Allogeneic	Originating from a donor (genetically non-identical person)
Apheresis	Type of blood donation involving the selective mechanical withdrawal of specific blood components while returning the remaining components (by infusion) to the donor or patient
ATMP	Advanced therapy medicinal product
Autologous	Originating from a person's own body or removed from and applied to the same person
CAR T-cells	Chimeric Antigen Receptor T-cells
CBU	Cord blood unit
Chondrocytes	Cartilage cells
Cryopreservation	The process of freezing and subsequent storage of frozen tissues and cells
Distribution	Transport and delivery of body material intended for human application
DLI	Donor lymphocyte infusion
DMEK	Descemet Membrane Endothelial Keratoplasty
EU	European Union
GMP	Good manufacturing practice
HSC	Hematopoietic stem cells
ICU	Intensive Care Unit
IGJ	Inspectorate for Healthcare and Youth
Imputability	Degree to which an adverse reaction can be attributed to an applied substance of human origin
IUI	Intrauterine insemination
IVF	In vitro fertilisation
Lareb	Dutch reporting and knowledge centre for adverse reactions to medicines, vaccines and other health products
Matchis	Dutch registry for stem cell donors
MESA	Microsurgical epididymal sperm aspiration
NL	The Netherlands
NTS	Netherlands Transplantation Foundation
Oocytes	Human egg cells
Organ bank	Tissue institution with licence to receive substances of human origin
PBSC	Peripheral blood stem cells
PESA	Microsurgical epididymal sperm aspiration
Procurement	Process by which body material or a donated organ becomes available
Semen	Sperm
SoHO	Substances of Human Origin
TCR	T-cell receptor (gene therapy)
TIL	Tumour infiltrating lymphocytes
TESE	Testicular sperm extraction
Tissue establishment	A tissue bank, hospital department or other centre that holds a licence for the processing, preservation, storage or distribution of human substances
VWS	Dutch Ministry of Health, Welfare and Sport
WKKGZ	Healthcare Quality, Complaints and Disputes Act
WVKL	Body Material (Safety and Quality) Act