



Canadian Blood Services
Soci t  canadienne du sang

Safety of Organ and Tissue Transplantation

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Safety of Organ and Tissue Transplantation - Summary

Because organs and tissues come from human donors, there is inherent risk in their use. As a result, there are many safety measures in place, mandated by regulations and standards, to decrease the probability of transmission of diseases and infections. These include:

- Donor screening (medical and social history)
- Transmissible disease testing
- Bacterial testing
- Sterilization / disinfection procedures (tissues)
- Traceability requirements and surveillance mechanisms

However, there have been many instances where these measures have not prevented death and illness in recipients.

Generally, tissue allografts are safer than organs - few transmitted diseases have been reported given the number of allografts used. More time is available to test donors and most allografts go through a disinfectant or sterilization process. However, in cases where there is an intentional or unintentional breach in the regulations and standards, recalls can affect a larger number of recipients, as a tissue donor can provide over 80 allografts. Tissue disease transmissions (viral, bacterial or fungal) can be severe and can result in the death of the patient.

For organ donors, consequences of infection are significant, as organ recipients are receiving immunosuppressive drugs and are more susceptible to bacterial or viral infections. Transmission of malignancies also remains a risk, though it is difficult to quantify. When compared to tissue transplantation or blood transfusion, the higher risks associated with organ transplantation are tolerated, as the decision for an organ transplant is often based on urgent need and weighed against the possibility of the death of the patient. The safety risks also increase for those patients who receive transplant in third world countries (transplant tourism) where there are limited safety measures and regulations in place.

Much of the information in this document is taken from international sources, mainly from the United States. It is not known how closely this data compares to the Canadian situation. The lack of Canadian data severely limits calculation of risk associated with organ and tissue transplantation in this country.

Table 1: Canadian Organ and Tissue Safety Framework

Agency / Organization	Responsibilities Related to Safety
Health Canada Biologics and Genetic Therapies Directorate (BGTD)	<ul style="list-style-type: none"> ◆ Regulates cell tissue and organ establishments in reference to Canadian standards.
Health Canada Health Products and Food Branch Inspectorate	<ul style="list-style-type: none"> ◆ Registration of Canadian and international organ and tissue source establishments who distribute organs or tissues to Canadian hospitals and end users ◆ Inspection and audit of Canadian organ and tissue programs for regulatory requirements
Health Canada Therapeutic Products Directorate	<ul style="list-style-type: none"> ◆ Medical device licensure for cells and tissues which undergo more than minimal manipulation in processing for distribution (e.g. heart valves and demineralized bone)
Public Health Agency of Canada	<ul style="list-style-type: none"> ◆ Development of a Tissue and Organs Surveillance System (TOSS), a national registry to track identified adverse events in organs and tissue transplant recipients.
Canadian Institute for Health Information - Canadian Organ Replacement Registry (CORR)	<ul style="list-style-type: none"> ◆ Data collection on organ donation and transplant activity ◆ No data collection on tissue donation and transplant activity
Canadian Standards Association (CSA)	<ul style="list-style-type: none"> ◆ Contracted by Health Canada to maintain dynamic safety standards including safety standards for Cells, Tissues, and Organs
Accreditation Canada	<ul style="list-style-type: none"> ◆ Accredits Canadian hospitals in accordance with established standards. Organ and tissue donation and transplant accreditation standards under development.
Patient Safety Institute of Canada CPSI	<ul style="list-style-type: none"> ◆ Has a national mandate to build and advance a safer health system for Canadians. It does this by fostering collaboration between governments and stakeholders, supporting the development of patient safety initiatives.
Organ Procurement Organizations	<ul style="list-style-type: none"> ◆ Compliance with Health Canada regulations and CSA standards ◆ Informed consent for donation ◆ Traceability of organs to the transplanting centre ◆ Investigation of potential adverse events

Agency / Organization	Responsibilities Related to Safety
Organ Transplant Programs	<ul style="list-style-type: none"> ◆ Compliance with Health Canada regulations and CSA standards ◆ Informed consent of recipients to transplantation of organs ◆ Traceability of the donor organ from the procurement organization to the recipient ◆ Surveillance of the transplant recipient for potential adverse events and notification of the organ procurement organization of potential events
Eye, Tissue and Cell Banks/ Programs	<ul style="list-style-type: none"> ◆ Compliance with Health Canada regulations and CSA standards ◆ Traceability of tissues to the transplanting centre ◆ Investigation of potential adverse events
Eye, Tissue and Cell End Users: Hospitals, Surgeons, Hematologists, Periodontists and Dentists	<ul style="list-style-type: none"> ◆ Informed consent of recipients to the transplantation of the tissue graft ◆ Traceability of the allograft tissue to the transplant recipient ◆ Surveillance of the transplant recipient for potential adverse events ◆ Notification of the source tissue bank of potential adverse events
National Medical Associations	<ul style="list-style-type: none"> ◆ Communication with peer groups regarding standards and safety.
External Accrediting Organizations: Tissue	<ul style="list-style-type: none"> ◆ A number of tissue programs have sought external accreditations American Association of Tissue Banks, Eye Bank Association of America and International Standards Organization ISO to demonstrate their performance of peer established standards.
Centres For Disease Control Sentinel Network	<ul style="list-style-type: none"> ◆ The CDC is developing the Sentinel Network, a surveillance system for organs and tissue recipients. The role of this system in relation to US sourced allografts and organs imported into Canada and the implications to the TOSS system is to be determined.

Table 2: Safety Measures and Their Limitations

Safety Measure	Limitations
<p>Donor Screening – Medical and Social History:</p> <ul style="list-style-type: none"> Includes review of medical records and autopsy reports, physical examination and interview with donor (for living donation) or donor's family (deceased donation) 	<ul style="list-style-type: none"> For deceased donors, there could be high risk behaviours or medical conditions that are unknown to the family. Because of the short time lines involved in organ donation, information may not be obtained in a timely manner.
<p>Transmissible Disease (TD) Testing Required by Health Canada Regulations</p> <p><u>Mandatory</u></p> <ul style="list-style-type: none"> Anti-HIV 1 and 2 Anti-HCV Total Anti-HBc, HBsAG Anti-HTLV I and II Syphilis Toxoplasmosis (heart donors) Anti-CMV (stem cell donors) <p><u>Recommended</u></p> <ul style="list-style-type: none"> Anti-CMV (organ) Anti-EBV (organ) NAT HIV, HCV, WNV <p>Notes:</p> <ul style="list-style-type: none"> Syphilis and anti HTLV I and II are not required for ocular donors. Health Canada regulations require the assessment of all donor samples for hemodilution and the deferral of the donor if the sample is hemodiluted. 	<ul style="list-style-type: none"> A donor in the "window period", i.e. the time between infection and detectable seroconversion, will have a negative test result, but be able to transmit disease. NAT tests shorten the window period for HIV (from 22 to 11 days) and HCV (from 66 to 19 days) and reduce the risks of infection. While NAT testing is readily available in commercial labs, logistics and timeline requirements make NAT testing for organ donors challenging. NAT testing for tissue donors does not present the same logistical challenges or time restrictions as for organ donors. However, the cost of these tests has limited its use within some tissue programs. Health Canada requires TD testing for tissue donors using kits licensed for donor screening. These kits emphasize sensitivity (less false negatives) while diagnostic test kits emphasize specificity (less false positives). Donor screening testing is readily available in commercial laboratories but not in hospital or public health laboratories. Tissue banks are required to outsource their TD testing to commercial laboratories. A number of tissue banks have not resolved the fiscal and logistical challenges in outsourcing and continue to utilize diagnostic testing. The use of diagnostic testing increases the risk of false negative results. Health Canada does not require the use of donor screening testing for organ donors. Therefore most organ donors are tested using diagnostic tests, increasing the risk of false negative results. False negative results can be obtained as a result of hemodilution if the donor received large volumes of blood products or fluids, before the blood sample was obtained. There is no testing of less common pathogens, i.e. rabies, tuberculosis, Chagas, CJD, which have been shown to be transmitted through transplantation.

Safety Measure	Limitations
<p>Microbiologic Assessment</p> <p>Microbiologic cultures are performed on tissue at the time of procurement and at the time of processing (mandatory).</p> <ul style="list-style-type: none"> • Identification of bacteria prior to processing for baseline contamination data • Identification of microbiologic contamination after processing and disinfection 	<ul style="list-style-type: none"> • Tissue cultures of donated tissue have limitations and may not pick up all bacterial contaminations. The efficacy of bacterial swabs has been identified as a limiting factor. This can be mitigated by wash techniques. • There are inconsistent practices between tissue programs in relation to the discard practices and performance of procurement cultures.
<p>Sterilization/Disinfection Procedures</p> <p>Performed on tissue allografts:</p> <ul style="list-style-type: none"> • gamma or e-Beam irradiation • antibiotics • supercritical carbon dioxide • ethylene oxide gas • other proprietary methods 	<ul style="list-style-type: none"> • Tissues such as corneas, cardiac and soft tissue including tendons are not amenable to sterilization. • There is evidence that sterilization procedures impact the biologic efficacy of donor tissue such as bone. • While standards mandate the use of validated bio-burden reduction procedures for tissue, the scope and efficacy of these procedures vary significantly between programs. • The sterilization of tissue products is not a regulatory requirement in Canada or the United States. The use of sterilization procedures is dependent on the processor and end user preference. • There are currently no disinfection procedures for solid organs.
<p>Surveillance and Adverse Event Reporting</p> <p>Legal requirement in Canada to report adverse events or reactions to Health Canada, and take proper corrective action. This could include testing of affected recipients, recalls and withdrawals.</p> <p>The Public Health Agency of Canada is piloting a Tissue and Organs Surveillance System (TOSS) which provides a framework for adverse event surveillance and response.</p>	<ul style="list-style-type: none"> • Regulations which require reporting to Health Canada of adverse events/transmission of disease were only introduced in 2007. It is not known how effective these requirements have been in collecting data.

Table 3: Effectiveness of Safety Measures

Disease	Risk of Infection *	Reported Transmissions
HIV/AIDS	<ul style="list-style-type: none"> • Residual Risk of infection: <ul style="list-style-type: none"> – 1.82 per 100,000 donors (US data) – No Canadian data available • Blood data: 0.013 per 100,000 donors 	<ul style="list-style-type: none"> • No Canadian data found • 1986 - Donor tested negative due to hemodilution by blood transfusions and fluids. 2 recipients became HIV pos (3rd did not survive transplant) • Nov 2007 – HIV and HCV transmitted to all 4 organ recipients. Donor tested negative, though high risk behaviour identified through screening. (NAT testing not performed)
Hepatitis C	<ul style="list-style-type: none"> • Residual Risk of infection: <ul style="list-style-type: none"> – 2.37 per 100,000 donors (US data) – 2.17 per 100,000 donors (data from Northern Alberta) • Blood data: 0.004 per 100,000 donors 	<ul style="list-style-type: none"> • Many Canadian cases of HCV transmission with donors who tested HCV neg by 1st generation HCV test, retrospectively tested pos by 2nd generation test. • See HIV case above, Nov 2007 • 2000 – organ/tissue donor in US was HCV neg (no NAT testing) – 8 recipients became HCV pos – 3 organ, 5 tissue; 32 other tissue recipients were HCV neg
Hepatitis B	<ul style="list-style-type: none"> • Residual Risk of infection: <ul style="list-style-type: none"> – 2.96 per 100,000 donors (US data) – 3.90 per 100,000 donors (data from Northern Alberta) • Blood data: 0.65 per 100,000 donors 	<ul style="list-style-type: none"> • Many incidence of Hepatitis B transmission have been documented, though incidence rate has been decreasing due to improved testing. • Hepatitis B infection in the donor is not necessarily a restriction for transplantation as there is a high HBV prevalence in the patient population. • 2007 FDA tissue recall relating to two donors who tested HBsAg negative with diagnostic testing but when repeated with donor screening testing tested positive.
HTLV	<ul style="list-style-type: none"> • Residual Risk of infection: <ul style="list-style-type: none"> – 0.78 per 100,000 (US data) – No Canadian data available • Blood data: 0.023 per 100,000 donors** 	<ul style="list-style-type: none"> • A report from the US using UNOS data stated that between 1988 and 2000, 22 organs were transplanted from 3 donors who were HTLV positive – none of the recipients developed HTLV related disease

* US and Canadian data: Zahariadis et al

* CBS Blood data: O'Brien et al

**Note: use of leuko-reduction during blood processing brings risk of HTLV for blood close to zero.

Rates for blood donors have been included for comparative purposes. Rates for blood donors are lower for the following reasons:

- The majority of blood donors are repeat donors, who have been previously screened and cleared.
- Many high-risk donors are screened out by the medical/social questionnaire before they are tested.
- High risk behaviour information is solicited directly from the donor. For deceased organ and tissue donor this information comes from a family member who may not be aware of a donor's high risk behaviour.
- Blood donors are screened with NAT tests for HIV, HCV and WNV.

Disease	Risk of Infection	Reported Transmissions
West Nile Virus	<ul style="list-style-type: none"> No data found 	<ul style="list-style-type: none"> In 2002, in the US a patient received a transfusion with WNV infected blood. This patient became an organ donor and infected all recipients of the 4 organs donated.
Rabies	<ul style="list-style-type: none"> No data available 	<ul style="list-style-type: none"> In 2004, there was a confirmed transmission of rabies through organ transplantation in the US – all 3 patients died of rabies after receiving organs from this donor.
Bacterial Infections	<ul style="list-style-type: none"> No risk data available; however, bacterial or microbial infection/ colonization may be present in up to 60% of deceased organ donors** Transmission of Mycobacterium tuberculosis through organ donor accounts for approximately 4% of post-transplant TB cases** 	<ul style="list-style-type: none"> Donor to host transmission has been widely documented, though antibiotic treatment is generally effective. In 2001 –a 23 yr old man died from infection with Clostridium sordelli. This man had received a tendon from CryoLife.
Parasitic Infections	<ul style="list-style-type: none"> No data available 	<ul style="list-style-type: none"> Transmission widely documented in US including malaria, toxoplasmosis, Chagas FDA has issued a 2009 “Draft” non binding guidance document recommending serological screening for Chagas disease for all blood and tissue donors.
Creutzfeldt-Jakob Disease (CJD)	<ul style="list-style-type: none"> No data available 	<ul style="list-style-type: none"> CJD has been transmitted through cornea and duramater grafts.
Cancers	<ul style="list-style-type: none"> No Canadian data available Risk of 1.3% of having a donor with undetected malignancy and 0.2% risk for transmitting a cancer (Danish data)*** 	<ul style="list-style-type: none"> Studies indicate that transplant recipients have an increased risk of 1 – 2% per year of developing cancer in general and a 15 – 20 fold higher incidence of certain types of cancer. The general incidence of all malignancies after kidney transplantation increases with advancing time and seems to be dependent on both duration and intensity of immunosuppression**** (UNOS data).

** Tiessen et al

*** Birkeland et al

**** Kaufmann et al

Table 4: Known Tissue Recalls in Canada

Company/ Product	Year	Description
Tutoplast Dura	2002	<ul style="list-style-type: none"> • In April 2002, Health Canada suspended the license for Tutoplast Dura and monitored a recall of the product. This product, processed in Germany, was available in Canada between 1982 and 2002. • In 2003, a case of classical CJD was confirmed in a Canadian patient who received a graft in 1992.
Cryolife, Inc. (US)	2002	<ul style="list-style-type: none"> • In August, 2002, Health Canada issued notice of a risk of fungal and bacterial contamination of soft tissues for implantation processed and sold by CryoLife Inc. (Georgia). The FDA also initiated a recall due to infections having been reported with these implants and the occurrence of one confirmed death following knee allograft surgery. No cases of death or infection were reported in Canada.
B.C. Ear Bank	2003	<ul style="list-style-type: none"> • In February 2003, Health Canada began investigating the B.C. Ear Bank at St. Paul's Hospital, Vancouver. Their investigation revealed donor suitability and tissue processing documentation was incomplete. • All unused tissue was recalled and patients who were the recipients of bones or tissues supplied by the B.C. Ear Bank were advised to be tested for HIV, Hepatitis B and Hepatitis C. Thousands of patients across North America were affected, as the B.C. Ear Bank supplied tissue and bone to 87 hospitals and physicians across Canada and in two cities in the United States.
Biomedical Tissue Services Limited (BTS) (US)	2005	<ul style="list-style-type: none"> • In October of 2005, Health Canada advised Canadians of a voluntary recall in the United States of tissue products used in implants and grafts that were imported into Canada. • Tissues recovered by BTS were acquired without legal consent or proper screening. Funeral home operators accepted money from the company in exchange for ignoring forged death certificates and consent forms. BTS sold these tissues to several companies, including those that exported tissue to Canada. These companies initiated voluntary recalls for all products that were produced using tissues from BTS. About 10,000 people received product from BTS. Approximately 300 tissue products were imported into Canada, though no adverse effects have been reported from Canadian patients.
Donor Referral Services (DRS) (US)	2006	<ul style="list-style-type: none"> • In 2006 DRS, located in Raleigh, NC, was ordered by the FDA to cease all manufacturing operations because of serious deficiencies in its donor screening and record keeping practices. The owner allegedly used a local consumer group to procure material from a local funeral home's unsterilized embalming room. • The companies that received their tissues initiated voluntary recalls involving 2,400 allografts. Six implicated products were imported into Canada. None were transplanted, all were returned to the US.

Table 5. TD and HLA Testing - Organ Donation

Province / Programs	HLA Testing Lab	Transmissible Disease Testing Lab	NAT Testing
British Columbia <ul style="list-style-type: none"> All programs 	Immunology Lab, Vancouver General	BC Centre for Disease Control (BCCDC)	No HIV, HCV NAT testing WNV seasonally Apr-Nov
Alberta <ul style="list-style-type: none"> HOPE Program Calgary Alberta Children's Hospital, Calgary Foothills Medical Centre, Calgary 	Tissue Typing Diagnostic and Scientific Centre, Calgary	Provincial Lab, Calgary	High risk donor tested (Edmonton Lab)
<ul style="list-style-type: none"> HOPE Program Edmonton Capital Health Transplant Services, Edmonton 	Histocompatibility Lab, University of Alberta Hospital	Provincial Lab, Edmonton	High risk donor tested (Edmonton Lab); WNV done seasonally or if donor has travelled to an endemic area
Saskatchewan <ul style="list-style-type: none"> All programs 	HLA Laboratory, St. Paul's Hospital	Provincial Health Lab and Royal University Hospital Laboratory	Not performed
Manitoba <ul style="list-style-type: none"> All programs 	Transplant Immunology Lab, Diagnostic Services of Manitoba	Cadham Provincial Laboratory	Not performed
Ontario			
<ul style="list-style-type: none"> Kingston General Hospital 	Immunology Lab, Kingston General Hospital	Ottawa Hospital	Not performed
<ul style="list-style-type: none"> Multi Organ Transplant Program, London 	Transplantation Immunology Lab, London HSC	London HSC	Not performed
<ul style="list-style-type: none"> St. Joseph's Healthcare Hamilton 	Tissue Typing Hamilton HSC	Toronto Medical Lab, Mount Sinai	Not performed
<ul style="list-style-type: none"> Hospital for Sick Children St. Michael's Hospital Toronto Multi Organ Transplant Program, UHN 	Regional Histocompatibility Laboratory, UHN	Toronto Medical Lab, Mount Sinai	Not performed
<ul style="list-style-type: none"> The Ottawa Hospital University of Ottawa Heart Institute Transplant 	DNA/Tissue Typing Lab, Ottawa Hospital General Campus	Ottawa Hospital	Not performed

Province / Programs	HLA Testing Lab	Transmissible Disease Testing Lab	NAT Testing
Program			
Quebec			
<ul style="list-style-type: none"> CHUS Fleurimont 	HLA Lab, McGill	CHUM – Hôtel-Dieu de Montréal	Not performed
<ul style="list-style-type: none"> CHUM Notre Dame CHUM St. Luc Institute de cardiologie de Montreal L'Hopital Maisonneuve-Rosemont CHU Sainte-Justine 	INRS-Institut Armand-Frappier, Laval	CHUQ – CHUL	Not performed
<ul style="list-style-type: none"> CHUQ Hotel Dieu 	Departement Immunogenetique et Transplantation, Laurier	CHUQ – Hôtel-Dieu de Québec	Not performed
<ul style="list-style-type: none"> CHU Laval 	Departement Immunogenetique et Transplantation, Laurier	CHUQ – CHUL	Not performed
<ul style="list-style-type: none"> MUHC Montreal Children's MUHC Royal Victoria McGill 	HLA Laboratory, McGill	CHUM – Hôtel	Not performed
New Brunswick <ul style="list-style-type: none"> Organ and Tissue Procurement Program 	HLA Lab, QEII Halifax	George Dumont Hospital, Moncton or donor hospital site if testing available	Not performed
Nova Scotia <ul style="list-style-type: none"> All programs 	HLA Lab, QEII Halifax	QEII HSC Lab, Halifax	Not performed
Newfoundland and Labrador <ul style="list-style-type: none"> Organ Procurement & Exchange of NL (OPEN) 	Immunology & Genetics Laboratories, Eastern Health, St. John's	Public Health Lab, Diagnostic Testing	Not performed

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